2009-08-10

Pediatric Dilated Cardiomyopathy: Baseline Predictors of Outcomes in the Pediatric Cardiomyopathy Registry

Jorge Alex Alvarez
University of Miami, jalvarez1@med.miami.edu

UNIVERSITY OF MIAMI

PEDIATRIC DILATED CARDIOMYOPATHY: BASELINE PREDICTORS OF OUTCOMES IN THE PEDIATRIC CARDIOMYOPATHY REGISTRY

By

Jorge A. Alvarez

A DISSERTATION

Submitted to the Faculty
of the University of Miami
in partial fulfillment of the requirements for
the degree of Doctor of Philosophy

Coral Gables, Florida

August 2009

UNIVERSITY OF MIAMI

A dissertation submitted in partial fulfillment of
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Jorge A. Alvarez

Approved:

_____ David J. Lee, Ph.D. Associate Professor of Epidemiology and Public Health	_____ Terri A. Scandura, Ph.D. Dean of the Graduate School
_____ Steven E. Lipshultz, M.D. Professor of Pediatrics and Epidemiology and Public Health	_____ James D. Wilkinson, M.D., M.P.H. Professor of Pediatrics and Epidemiology and Public Health
_____ Lora E. Fleming, M.D., Ph.D., M.P.H. Professor of Epidemiology and Public Health	_____ E. John Orav, Ph.D. Associate Professor of Biostatistics Harvard School of Public Health

ALVAREZ, JORGE A. (Ph.D., Epidemiology)

Pediatric Dilated Cardiomyopathy: Baseline Predictors of Outcomes in the Pediatric Cardiomyopathy Registry (August 2009)

Abstract of a dissertation at the University of Miami.

Dissertation supervised by Professor David J. Lee
No. of pages in text. (126)

Background: Dilated Cardiomyopathy (DCM) is the most common functional type of cardiomyopathy in children with significant morbidity and the leading indication for cardiac transplant over 5 years of age. Identification of baseline risk factors for failing medical management by etiologic grouping remain to be elucidated in a large population-based study. The competing risk for heart death between all-cause mortality and heart transplantation is often overestimated in the literature and may obscure additional novel risk factors associated with poor clinical outcomes.

Methods: The National Heart Lung and Blood Institute Pediatric Cardiomyopathy Registry collected longitudinal data from 1731 children with DCM in North America from 1990 to 2007. Composite endpoint (CEP) was the earlier occurrence of death or heart transplant. Univariate and multivariate predictors were identified from demographic and echocardiographic data (expressed as z-scores) collected within 30 days of diagnosis. A competing risk analysis was performed calculating cumulative incidence and identifying novel prognostic factors. All analyses were performed by etiologic group.

Results: Multivariate Cox regression identified the highest mortality risk among children with idiopathic disease (N=1192, CEP: 41%) when diagnosed over age 6 years, and with congestive heart failure (CHF) and decreased left ventricular fractional shortening (FS). Risk factors for those with myocarditis (N=272, CEP: 26%) were older age, CHF, and increased left ventricular (LV) end-diastolic dimension (EDD); while for neuromuscular disease (N=139, CEP: 40%), it was a decreased FS and increased EDD. Only univariate predictors were identified for children with familial isolated cardiomyopathy (N=79, CEP: 44%) including: CHF, increased EDD, end-systolic dimension, or LV mass, and

decreased FS or ejection fraction), while for children with inborn errors of metabolism (N=43, CEP: 33%) risk factors included: a positive family history of cardiomyopathy or genetic syndromes. The group of children with malformation syndromes (N=6, CEP: 50%) was not large enough to model. Comparison of cause-specific event rates between Kaplan-Meier and cumulative incidence demonstrated an overestimation with the former method. Competing risk multivariate regression showed similar models to those for CEP, with the following exceptions: for neuromuscular disease, an increased EDD had a larger hazard ratio for transplant than for death; for idiopathic disease, an increased EDD was associated with transplant, but not with death, and growth retardation (height-for-age z-score) was associated with death but not transplant.

Conclusions: Within etiologic grouping, demographics and echocardiographic values at diagnosis have varying predictive value. Generally, the presence of symptomatic disease in the form of CHF, echocardiographic evidence of more severe DCM, and increased age were indicative of worse outcomes. These results help to validate those from conflicting studies; however, they suggest that etiology modifies the importance of particular factors. Analysis of competing risk provides an alternate interpretation of studies with composite endpoints and assists in the transfer of clinically relevant information. For children with idiopathic and neuromuscular disease, the degree of dilation had a differential effect that has gone unrecognized. The novel finding of reduced stature and its effect on mortality suggests a potential for treatment and mitigation of poor outcomes in idiopathic DCM. Both increased dilation and reduced stature could be used to improve the triage process and refer children to cardiac transplantation who otherwise might die prematurely and unnecessarily. Subsequent studies on the utility of these factors and their effect on improving survival are warranted.

DEDICATION

To my three greatest supporters throughout this process, Maria R. Alvarez, Jorge A. Alvarez, and Nathan T. Connell, I could not have made this journey without your memories, thoughts, words, and actions. I am everything I am because of you.

ACKNOWLEDGEMENTS

I would like to acknowledge the unwavering support of Drs. James D. Wilkinson and Steven E. Lipshultz. They provided incredible amounts of insight and direction. I have been very fortunate to have such great mentors who have dedicated time and effort in creating opportunities and assisting me to succeed in those endeavors. I am thankful for Dr. E. John Orav who provided a calm, reassuring approach to the incredible set of data on which I was privileged to work and for Drs. Lora E. Fleming and David J. Lee who each gave me invaluable feedback as part of my thesis committee.

I would like to thank the NHLBI-Pediatric Cardiomyopathy Registry and all of its investigators (Drs. Lynn Sleeper, Steve D. Colan, Charles E. Canter, Daphne T. Hsu, Gerald F. Cox, Steve A. Webber, and Jeffrey A. Towbin) and its staff (Natalya Bublik, Matthew Erxleben, Christina Cordero, Fahim Siddiqui, Natasha Gonzalez, Jane Messere, and JJ McGill). Working alongside them as part of a successful multi-center study group was inspiring and I am thankful for all of their collaborative efforts in creating and maintaining the premier database of children with this rare disease.

I would like to thank Heather Rose for all of her assistance in navigating all of the University's procedures and protocols.

The National Heart Lung and Blood Institute supported this research through a Ruth L. Kirschstein National Research Service Award (F31-HL-094100).

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Chapter 1. Introduction

1.1. General Summary and Significance

Dilated Cardiomyopathy (DCM) is a rare disease that afflicts children causing significant morbidity and mortality. This study analyzed the largest known dataset on children with DCM from the National Heart Lung and Blood Institute-sponsored Pediatric Cardiomyopathy Registry (PCMR) to determine predictors of outcomes by groupings based on the etiology of DCM (Idiopathic, Myocarditis, Neuromuscular Disease, Familial Isolated Cardiomyopathy, Inborn Errors of Metabolism, and Malformation Syndromes).

The PCMR has previously reported on the demographic and clinical features of children with pure DCM by etiology, as well as their clinical outcomes.[1] In that report, data from all available annual follow-up reports were used to classify the children into etiologic groups. Those analyses described the natural history by etiology in a retrospective fashion and presented predictors of the composite outcome of death or transplant, excluding the neuromuscular and inborn errors of metabolism etiologic groups and adjusting for the rest (idiopathic, myocarditis, familial isolated and malformation syndromes). While those analyses provided insight into what could be considered the "true" outcomes of the disease, their clinical application is limited. When a physician initially diagnoses a child with DCM, there is a need to structure their initial course of care based on information collected at the time of diagnosis. While sharing a common functional definition of cardiac disease, additional factors due to the etiology may impact the clinical course of DCM. With a clinical perspective in mind, this analysis uses data as they were gathered in a real-world clinical setting taking into consideration how a given

etiologic group was treated during the critical early period and how factors present at time of diagnosis affected long-term outcomes.

This analysis of the PCMR database characterized clinical outcomes and their predictors based on the etiology of DCM and risk factors recorded at the time of diagnosis. The use of competing risk methods assisted in elucidating novel risk factors previously undiscovered by traditional methods and composite endpoints. With the real-world considerations that clinicians face in providing optimal medical management or referring a child with DCM to heart transplantation, the appropriate triage of patients in a setting of limited resources is important. Ultimately, this analysis allows clinicians to provide more effective care to children with DCM and reduce morbidity and mortality.

1.2. Specific Aims and Hypotheses

Aim 1: To describe characteristics and outcomes of children with dilated cardiomyopathy at time of diagnosis by etiology.

Hypothesis 1a: At diagnosis, the majority of children with DCM will be of young age (<1 year old), have congestive heart failure, and no known etiology of DCM. In comparison to all other groups, children with neuromuscular disease will likely be older and more likely to be male with less severe disease at time of presentation.

Hypothesis 1b: Cardiac transplantation is more likely to occur among the idiopathic and myocarditis groups than among the groups with neuromuscular disease, malformation syndrome, or inborn errors of metabolism.

Aim 2: To identify factors measured at time of diagnosis which are prognostic of poor outcomes (death or transplant) utilizing the Cox proportional hazards regression method.

Hypothesis 2a: In each of the etiologic groups, at the time of diagnosis more severe symptoms (presence of congestive heart failure) and signs of systolic dysfunction (decreased left ventricular fractional shortening z-score) and impaired structure (increased left ventricular end-diastolic dimension) will predict poor outcomes.

Hypothesis 2b: Older age will be a risk factor in all etiologic groups, except those with neuromuscular disease who are expected to be older at time of presentation and thus will not show an effect of age on poor outcome.

Aim 3: To identify factors measured at time of diagnosis which are prognostic of poor outcomes (death or transplant) utilizing the competing risks method.

Hypothesis 3a: Kaplan-Meier methods will overestimate individual event rates when censoring for the competing risk.

Hypothesis 3b: Modified Cox proportional hazard regression taking into account death and transplant simultaneously will indicate the variable effect of prognostic factors across etiologic groups. The group with idiopathic DCM will show an interaction between outcome type and fractional shortening z-score and between outcome type and end-diastolic dimension z-score.

Chapter 2. Background

2.1. Overview

The World Health Organization classifies cardiomyopathy into four overarching functional categories: 1) dilated cardiomyopathy; 2) hypertrophic cardiomyopathy; 3) restrictive cardiomyopathy, and 4) arrhythmogenic right ventricular cardiomyopathy.[2] Among the four groups, dilated cardiomyopathy (DCM) is the most common in children.[3-5] The annual incidence is estimated to be between 0.34 to 0.73 per 100,000 children.[3-5] By comparison, this incidence is similar to estimated rates for Wilms Tumor and Acute Myeloid Leukemia in the United States.[6] Although rare, DCM is the most common indication for heart transplant among children older than 1year of age.[7, 8] Pediatric survival at one year after diagnosis from all forms of cancer in the US from 1990 to 2003 has ranged from 89.8 to 94.1%,[9] whereas the most recent report for children with DCM including cases diagnosed in the same period shows freedom from death of 87% and freedom from death or heart transplant at 69%.[1] Overall, pediatric DCM has substantial morbidity and mortality, and costs US society hundreds of millions of dollars annually.[10, 11]

According to the World Health Organization, DCM is "characterized by dilation and impaired contraction of the left ventricle or both ventricles… Presentation is usually with heart failure, which is often progressive."[2] Before this and its earlier 1980 definition,[12] DCM was viewed by the medical community in the context of primary myocardial diseases[13] or idiopathic non-obstructive cardiomyopathy. This is in contrast to the mainly ischemic causes of adult-onset DCM.[14] Although the majority of reported cases in children are a diagnosis of exclusion, in addition to idiopathic disease, primary

alterations to metabolic pathways; genetic dysfunction of the sarcomere, the building block of the heart; and sequelae of infectious or toxic exposure directed at those units, also result in the dilated physiology with the phenotypical description of this heterogeneous disorder.

The first reported large case series of primary myocardial disease, by Greenwood and colleagues in 1976, described 161 children.[15] On the basis of this study, the commonly cited natural history of DCM was that one-third of children would die, one-third would recover, and one-third would have chronic disease.[16-19] Poor clinical outcomes of DCM include death (usually either from congestive heart failure or sudden cardiac death), and heart transplant. Although transplant recipients continue to live, it is considered a poor outcome as the child is subjected to a lifetime of immunosuppressive therapy, re-transplantations (as the recipient outgrows it donor heart), associated co-morbidities and increased risk of death post-transplant. Nonetheless, there has been steady improvement in the reported survival rate from 1982 to 2006.[8] Median mortality post-transplantation is between 10 and 15 years, with differences by age at the time of transplantation (i.e. younger children having better survival) and cohort effects (i.e. more recent transplants having better survival). The risk of death is greatest in the first year after transplantation, and reports of median survival conditional on surviving the first year range from 18 years for the younger children to 15 years for the older children.

The ability to predict the outcomes of children presenting with DCM is crucial in an attempt to mitigate the difficult clinical course that they and their families endure. The search for predictive baseline factors has produced several studies over the past 30 years with a variety of results.

A previously published systematic review of the studies that sought to identify predictors of outcomes in children with DCM produced 32 articles published from 1976 to 2006.[20] These studies included children diagnosed with DCM between 1945 and 2004 (Table 2-1). The majority were reports from single institutions (28 of 32), and the two largest studies were published in 2006.[1, 21]

The median study sample size was 39 children (range: 13 to 1426). The average overall study mortality was 33% (range: 5% to 72%); 20 studies reported a 1-year overall survival rate between 41% and 90%; and 18 studies reported a 5-year overall survival rate between 20% and 83%. The most recent overall survival rates were from the Pediatric Cardiomyopathy Registry (PCMR), which utilized a large, population cohort: 1-year survival was 87% and 5-year survival was 77%.[1] Three studies, including the PCMR, reported the event-free survival (i.e. from death or transplant) at 1 year to be 70%, 72%, and 69% and at 5 years to be 58%, 63%, 54%.[1, 21, 22]

Of the 32 articles, 4 reported no associations between baseline factors and mortality: 1 was mainly descriptive with no modeling[23]; another emphasized baseline dysrhythmias and did not analyze other factors,[24] and the last two detected no significant univariate associations.[25, 26] One study found no "good" predictors, but identified two factors that were either "insensitive" or of "limited clinical value" in predicting survival (i.e. the presence of severe mitral regurgitation in only three subjects, all who ultimately died; and pre-diagnosis viral symptoms which had 78% sensitivity and 60% specificity).[16]

2.2. Cardiac Measurements

A routine diagnostic work up contains various measurements of the heart's structure and function in an attempt to recognize the pattern and to identify the source of dysfunction. Modalities of measurement include procedures that are non-invasive (electrocardiogram, trans-thoracic echocardiogram, and chest radiograph) and invasive (cardiac catheterization and angiography).

2.2.1. Electrocardiographic Measurements

Using electrocardiography (ECG), the first large study by Greenwood *et al.*[15] found extreme right or "NW" axis deviation to be a significant predictor of death. Subsequent studies have focused on arrhythmias or ECG patterns indicative of hypertrophy. Griffin *et al.*[17] found that all the children who died in their group (17 of 32) had ventricular arrhythmias. Wiles *et al.*[19] found that those who died (12 of 39) were more likely to have any arrhythmia at presentation: arrhythmias were present in 13% of survivors and in 50% of those who died (P=0.025). Lewis and Chabot[27] reported comparable results: arrhythmias were present in 16% of survivors and in 53% of those who died (P<0.05). Noguiera *et al.*[28] and Weng *et al.*[29] reported similar results, but Chen *et al.*[30], Friedman *et al.*[31], and Muller *et al.*[24] found no differences in the presence of arrhythmias between survivors and nonsurvivors.

Wiles *et al.*[19] also found that left ventricular hypertrophy (LVH), as indicated by ECG, was more common in those who survived (24 of 34) than in those who did not (2 of 12; P=0.002). They suggested that LVH may be a protective response which, in turn, decreases wall stress and enhances survival. Previously Taliercio *et al.* found no difference in mortality by baseline presence of LVH. Friedman *et al.*[31] found that left

atrial enlargement diagnosed by ECG was significantly associated with death (odds ratio = 5.3).

In a cohort of Korean children, Huh *et al.*[32] found that increased QT dispersion, a proposed marker of arrhythmogenicity, in children with DCM who died or had sustained CHF at last follow-up (mean 72 months) versus normal controls, but not when compared to those who had improved from baseline. However, they did find an increased mean QRS duration in the poor outcome groups as compared to those who showed improvement (84 vs 66 msec, $p < 0.05$), as well as normal controls (84 vs 67 msec, $p < 0.05$).

2.2.2. Echocardiographic Measurements

Qualitative patterns. Azevedo *et al.*[33] studied a large group of Brazilian children with DCM and found that moderate to severe mitral, tricuspid, or pulmonary regurgitation was associated with death. Only severe mitral regurgitation was an independent predictor of death in a multivariate survival analysis. Around 20 years prior to that, Taliercio *et al.* found that all 3 children who had severe mitral regurgitation at baseline died, but noted it was an insensitive, albeit specific, prognostic factor.[16] However, in this study the qualitative pattern was detected by angiography instead of the more common and less invasive echocardiography.

Table 2-1: Summary of Studies Reporting Analyses of Factors Potentially Predicting Outcomes in Children with Dilated Cardiomyopathy.

			Accrual (year)					Follow-up (months)		Survival (%)	
No.	Reference	Year	Start	End	Cases, N	Death, n	Mortality, %	Mean	Median	1-year	5-year
1	Greenwood[15]	1976	1945	1974	161	57	35	41	14	69	63
2	Taliercio[16]	1985	1973	1982	24	15	63	33		63	34
3	Schmaltz[25]	1987	1979	NR	13	5	38	41		77	69
4	Griffin[17]	1988	1975	1985	32	17	53	36		NR	NR
5	Chen[30]	1990	1970	1988	23	11	48	43		70	56
6	Bilgic[23]	1990	1984	1989	105	11	10	24		NR	
7	Akagi[34]	1991	1970	1989	25	18	72	12		41	20
8	Wiles[19]	1991	1966	1990	39	12	31	59	6.5	75	65
9	Lewis[27]	1991	1975	1990	81	30	37	42		80	64
10	Di Filippo[35]	1991	1970	1988	103	41	40	62		70	60
11	Friedman[31]	1991	NR		63	10	16	48		90	80
12	Matitiau[36]	1994	1982	1990	24	7	29	34		70	NR
13	Ciszewski[26]	1994	1981	1990	19	7	37	39		79	64
14	Burch[37]	1994	1979	1992	63	17	27	19		79	61
15	Lewis[38]	1994	1975	1992	72	18	25		NR	75	60
16	Muller[24]	1995	1964	1991	28	9	32	49		NR	
17	Carvalho[39]	1996	1989	1991	18	6	33	22		NR	
18	Venugopalan[40]	1998	1992	1997	18	3	17	42		94	NR
19	Arola[41]	1998	1980	1991	62	31	50	47		65	51
20	Noguiera[28]	2000	1985	1997	34	10	29	NR	30	77	71
21	Acar[42]	2001	NR		40	15	38	12		NR	
22	Nugent[43]	2001	1987	1997	34	7	21	34		NR	
23	Venugopalan[44]	2001	1980	1997	39	12	31	NR	36	69	69
24	Azevedo[33]	2004	1979	2003	148	35	24	45		NR	
25	Azevedo[45]	2004	1979	2003	152	43	28	43		NR	
26	Huh[32]	2004	NR		33	5	16	72	63	NR	
27	McMahon[46]	2004	1999	2002	54	3	6	NR	21	NR	
28	Tsirka[22]	2004	1990	1999	91	11	12		NR	90/70*	83/58*
29	Weng[29]	2005	1990	2004	18	13	72	NR	7	50	NR
30	Daubeney[21]	2006	1987	1996	184	75	41	38		72*	63*
31	Bostan[47]	2006	1995	2004	40	2	5	40		NR	
32	Towbin[1]	2006	1990	2003	1426	206	14	NR	19	87/69*	77/54*
Total					3046**	709**					
Median					39**						
Mean							33**				

* Survival from death or transplant; ** Calculations omit the duplicate study groups of Lewis, 1994, and Azevedo, 2004; NR = data not reported.

Fractional Shortening. Left ventricular fractional shortening (LVFS) is defined as the proportional change in LV dimension from the end of diastole to the end of systole in relation to the dimension at the end of diastole and is conceptualized as a marker of LV systolic function. Chen *et al.*[30] were the first to report a difference in mortality by this parameter: LVFS was 20.7% in 12 survivors and 11.5% in 11 non-survivors. Subsequent studies from 1991 to 1998 by Wiles,[19] Lewis,[27] and Arola[41] found no such difference. In 2000, Noguiera *et al.*[28] reported an association between lowered LVFS and mortality in a group of Portuguese children. In a study from a regional capture of DCM cases in West Scotland, Venugopalan *et al.*[44] found LVFS to be a significant predictor of death in univariate, but not multivariate analysis. Azevedo *et al.*[33] had similar findings. Tsirka *et al.*[22] found that LVFS was associated with death and transplant, and it remained a significant predictor of these events in a multivariate survival analysis. Two large population cohort studies (Daubeney *et al.*[21] in Australia and the PCMR[1] in North America) found that age-adjusted LVFS z-score at presentation was an independent predictor of death or transplant in multivariate survival analyses.

Ejection Fraction. Left ventricular ejection fraction is defined as the proportional change in LV volume from the end of diastole to the end of systole in relation to the volume at the end of diastole and is also conceptualized as a marker of LV systolic function. Among 25 children who presented with DCM after 2 years of age, Akagi *et al.*[34] found that the ejection fraction was lower at presentation among the 18 who died (40.0% vs. 31.3%; $P<0.05$). Matitiau *et al.*[36] reported similar findings, which included only children who presented with DCM before 2 years of age: LVEF was 29% in 17 survivors and 16% in 7 non-survivors. All children with an ejection fraction greater than

35% survived. Weng *et al.*[29] found that LVEF predicted death in 18 children in Taiwan, and Azevedo *et al.*[33] found it to be an independent predictor of death in a multivariate survival analysis.

McMahon *et al.*[46] prospectively measured tissue Doppler (TD) velocities in children with DCM and in healthy controls, as well as looked for baseline predictive factors. Children with DCM had significantly lower TD velocities than normal controls. For a composite primary end point of death, transplant, or hospitalization (which occurred in 30 of 54 children), LVEF along with RV total ejection isovolume index and tricuspid Ea (early diastole) velocity were predictive on univariate analysis; but only LVEF and Ea velocity were predictive on multivariate analysis. Similarly, when analyzing the death-or-transplant outcome (which occurred in 9 of the 30 children), LVEF, tricuspid Ea velocity, and RV fractional area change were significant predictors. The sensitivity and specificity for predicting death or transplant were 68% and 74%, respectively, for an LVEF less than 30%; 87% and 60% for a tricuspid Ea velocity less than 11.5 cm/s; and 100% and 44% for meeting both criteria.

Cardiac Dimensions. Matitiau *et al.*[36] calculated the ratio of the dimensions of the long axis to the short axis of the *left* ventricle in children with DCM presenting before 2 years of age. Children with more spherical ventricles (higher ratio) had a higher risk of death: the mean ratio was 0.74 in survivors and 0.86 in non-survivors. All those with a ratio below 0.75 survived.

In the Finnish population cohort, Arola *et al.*[41] found left atrial dilation to be the only echocardiographic predictor in a univariate survival analysis. Neither LVEDD nor LVESD were significant predictors. Azevedo *et al.*[33] studied 148 Brazilian children and

found several significant echocardiographic measurements that predicted death: left atrial dimension (LAD), LAD-to-aorta ratio, LAD-to-body-surface-area (BSA) ratio, LVESD, LVESD-BSA ratio, LVEDD, LVEDD-BSA ratio, LV mass, LV mass-BSA ratio, RV dimension, and calculated RV systolic and diastolic pressures. Of these, the LAD-aorta ratio remained predictive in a multivariate survival analysis. Tsirka *et al.*[22] found LVEDD and LVESD median z-scores to be associated with death and transplant, but neither was significant in multivariate analysis. Similarly, the PCMR group found BSA-adjusted LVEDD and LVESD z-scores, as well as LV Mass, to be significant predictors of death or transplant in univariate, but not multivariate, survival analyses.[1]

Kimball et al.[48] found that higher LV Mass was associated with symptoms, depressed contractility, and slightly higher wall stress in long-term survivors of DCM. (This study is not listed in the table because it focused on the post-diagnostic characteristics of long-term survivors, not on baseline predictors of mortality or transplant.)

Carvalho *et al.*[39] used M-Mode echocardiography which records the amplitude and rate of motion (M) in real time, yielding a monodimensional or "icepick" view of the heart in a study of M-Mode indices in 16 children with DCM who had LVFS less than 20% at presentation. They found an association between death or transplant and the ratio of LV posterior wall thickness (LVPWT) to LVEDD: the median ratio was 0.19 in survivors and 0.13 in those who died or received transplants. A ratio of 0.17 was determined to be a clinically useful cutoff. In the large North American cohort of the PCMR,[1] the LVPWT-LVEDD ratio was statistically significant in univariate, but not in

multivariate, analysis. Additionally, neither LVPWT nor LV septal wall thickness z-scores were significant in univariate modeling.

2.2.3. Chest Radiography

Several studies investigated the utility of radiographically determined cardiac measurements, ratios, and patterns to predict outcomes. The first study to review this association was Taliercio *et al.*[16] who found that cardiomegaly identified on chest radiographs was not predictive. In children who presented after age 2 years, Akagi *et al.*[34] found increased mortality among those with a cardiothoracic (CT) ratio greater than 65%. Nevertheless, four subsequent studies (Chen *et al.*[30] Wiles *et al.*[19] Venugopalan *et al.*[40] and Azevedo *et al.*[45]) found similar CT ratios between survivors and non-survivors. In one study, a univariate survival analsyis showed a 100% survival among those with absent cardiomegaly at baseline (median follow up 43 months, log-rank $p = 0.0189$).[45] However, using a factor that is commonly seen at presentation (between 88%[34] to 100%[19, 30] of all cases) severely limits the ability to discriminate outcomes at baseline and explain the larger number of negative study results.

Congestion of the pulmonary vasculature, as determined by chest radiograph, was one of the first predictors reported by Greenwood *et al.*[15] and subsequently reported as a predictor by Azevedo *et al.*[45] Although Arola *et al.*[41] showed a worse outcome when pulmonary congestion was present, it was not statistically significant ($p = 0.06$).

2.2.4. Cardiac Catheterization

One of the initial findings by Greenwood *et al.*[15] was that a cardiac index, which is the measurement of cardiac output per unit time divided by body surface area, less than 3 L/min/m^2 was a risk factor for death. A subsequent study by Akagi *et al.*[34] found no

difference by mean cardiac index values at baseline between those who died and those who did not.

Taliercio *et al.* found that all 3 children who had severe mitral regurgitation at baseline died, but noted it was an insensitive, albeit specific, prognostic factor.[16] However, the invasive angiographic diagnosis used in his study is more commonly now made by non-invasive echocardiography at first examination.

Lewis and Chabot[27] found a difference in mortality based on LV end-diastolic pressure (LVEDP): mean pressure was 29.5 mm Hg in 22 survivors and 15.0 mm Hg in 13 non-survivors ($P < 0.001$). The authors considered an LVEDP greater than 25 mm Hg to be a clinically usefully cutoff for predicting death, with a clear separation of survival curves at 6 months (log rank, $P < 0.05$). Burch *et al.*[37] studied 17 children catheterized as part of a transplant evaluation, and found that those with an LVEDP above 20 mm Hg were more likely to die or to receive a transplant. Of catheterization values reported by Matitiau *et al.*[36] for 18 children (all of whom were under 2 years of age at presentation), none were prognostic. Likewise, no association between LVEDP or pulmonary artery pressure and mortality was found by Venugopalan *et al.*[44]

2.5. Baseline clinical factors

2.5.1. Age at Diagnosis

Griffin *et al.*[17] were the first to partition the data by age at diagnosis and to suggest a relationship between age and outcome. They compared outcomes by age at disease onset (birth to 2 years of age versus those older than 2 years), and found a worse outcome for older children. They recommended that all children diagnosed after 2 years

of age who survive at least 1 month be considered for transplant. This older group also had a higher proportion of children with a family history of CM and arrhythmias.

Although Taliercio *et al.*[16] reported age to be non-significant using the same data, Wiles *et al.* showed that more children over the age of 2 years died in that study (92% vs. 33%). However, Wiles' own data showed no significant differences by age: 40% of those more than 2 years old and 31% of those under 2 years old died.[19] Di Filippo *et al.*,[35] in 103 French children, also found a greater risk of death in children over 2 years old (57% vs. 33%). Similarly, Burch *et al.*[37] found age to be an independent predictor of death in multivariate analysis (hazard ratio [HR] for children more than 2 years old = 4.7; 95%Confidence Interval = 1.7 - 12.7). Carvalho *et al.*[39] found age greater than 2 years to predict poor outcome in children who presented with DCM and LVFS less than 20%.

Although there were only 2 deaths among 40 children (both over age 2), Bostan and Cil[49] showed that children presenting before the age of 2 years had a significantly greater rate of recovery (57% vs. 42%) as defined by the disappearance of symptoms with CT ratio <55% and normal LV function and ECG.

On the other hand, Tsirka *et al.*[22] identified two age groups at increased risk of death or transplant: those younger than 1 year of age at presentation (HR = 7.1) and those older than 12 years of age (HR = 4.5), relative to those between 1 and 12 years of age who did not suffer many poor outcomes and in fact recovered more so than the other two groups. In Australian children diagnosed between birth and 10 years of age, Daubeney *et al.*[50] found children older than 5 years at presentation to be at greater risk in a multivariate analysis (HR = 5.6). Similarly, the PCMR[1] found an age difference in event-free survival; however, the cutoff was age 6.

Despite the other positive findings, Chen *et al.*[30], Lewis and Chabot, [27] and Azevedo *et al.*[45] did not find an age-related difference in mortality at 2 years of age. Although they did not use the same age categorization, Akagi *et al.*[34] reported no baseline age difference in mortality. Likewise, Venugopalan *et al.* did not find an age difference when investigating mortality or disease progression with recovery in cohorts of children with DCM in Oman[40] or when reviewing overall mortality in West Scotland.[44]

2.5.2. Family History

Several studies have investigated family history of cardiomyopathy (CM) as a predictor. The first was Griffin *et al.*[17] who found increased mortality to be associated with a positive family history in children who were diagnosed after 2 years of age. Later, Chen *et al.*[30] reported that a positive family history of CM indicated a poor prognosis. However, his conclusion was based on a pair of brothers (among 23 children with DCM) with a family history of CM who ultimately died.

Di Filippo *et al.*[35] found a significant univariate association between a family history of CM and death or transplant (P=0.033), and Daubeney *et al.*[50], in the Australian population cohort, found a significant multivariate association (HR = 2.9). However, Venugopalan *et al.*[44] found no association with mortality, and the PCMR[1] found no significant difference between survivors and those who died or received transplants.

2.5.3. Myocarditis

Taliercio *et al.*[16] were the first to speculate that viral symptoms appearing within 3 months of the initial presentation of DCM may have a protective effect. In children under the age of 2 at presentation, Matitiau *et al.*[36] found that while histological evidence

of myocarditis in children alive at the time of myocarditis diagnosis resulted in some form of treatment, there was no association between myocarditis and survival.

Testing the association between certain ECG findings and myocarditis, Nugent et al.[43] studied 34 children, all of whom had biopsies and ECGs performed within 3 weeks of DCM diagnosis. The study showed poor predictive values of ECG for outcomes in children with myocarditis; however, children with a definite or probable diagnosis of myocarditis according to the Dallas Criteria[51] applied to endomyocardial biopsy samples fared better than those with non-specific histological findings. Event-free survival was 100% (15 of 15) in the definite/probable diagnosed group (mean follow-up 44 months) and 63% (12 of 19) in the non-specific group (mean follow-up 27 months).

Daubeney *et al.*[50] found in the Australian cohort 70 biopsy records of which 25 exhibited lymphocytic myocarditis. Twelve of those were performed at autopsy, of which 6 children presented with sudden death and the other 6 died within 3 days of presentation. When myocarditis was confirmed by biopsy during life, the authors detected improved event-free survival. They could not calculate a hazard ratio because all the children with confirmed cases were still alive at the time of analysis. However, a conditional analysis, based on the 39 biopsies of living children showed a significant difference in univariate event-free survival ($P = 0.01$). In the West Scotland cohort, of the 14 cases of myocarditis enumerated by Venugopalan *et al.*[44], their 1-year survival rate was reported to be worse than the 39 with idiopathic DCM (29% vs. 69%, log rank, $P < 0.01$). However, the analysis included 9 of 14 myocarditis cases diagnosed at autopsy. Analysis of PCMR[1] data indicated a greater risk of death or transplant in children with idiopathic disease relative to children with myocarditis (HR = 2.06).

Even without tissue diagnosis of myocarditis, Bostan and Cil[49] found that children with a recent viral illness at presentation recovered more frequently (81% vs. 26%) and more rapidly (mean duration: 11 months vs. 22 months) than those who did not.

2.5.4. Endocardial Fibroelastosis

In the first analysis to consider endocardial fibroelastosis (EFE), which is a pronounced, diffuse thickening of the ventricular endocardium, within the diagnosis of DCM, Chen *et al.*[30] found that children with EFE on biopsy had worse outcomes. All 5 children in their group with EFE died; however, only 2 were diagnosed before death. In children under the age of 2 at presentation, Matitiau *et al.*[36] found that EFE on biopsy was associated with death; of 6 children with EFE, 4 died, 2 of which were found at autopsy. In the Finnish population cohort, Arola *et al.*[41] found EFE to be the most highly statistically significant predictor of death or transplant in both univariate ($P<0.0001$) and multivariate survival analyses (HR = 5.24, $P<0.0001$). All children with EFE died.,However, EFE was diagnosed at autopsy in all cases.

2.5.5. Other Baseline Factors

Some significant prognostic factors have only been reported by a few studies. In the Finnish population cohort, Arola *et al.*[41] found that CHF and a duration of symptoms greater than 7 days at presentation to be significant predictors of mortality in univariate survival analyses; neither remained significant in the multivariate model. Similarly, the PCMR[1] found an increased risk of death or transplant when CHF was present at diagnosis; however, the increased risk of poor outcome was significant only within 1 year of diagnosis (HR = 3.67).

Also from the Finnish group[41], right ventricular failure, defined in the study as the presence of liver enlargement, peripheral edema, and distension of the jugular veins, was significant in both univariate and multivariate survival analyses.

A prospective study of children with DCM by Acar *et al.*[42] concluded that impaired cardiac adrenergic innervation, as measured by cardiac radiolabeled meta-iodobenzylguanidine imaging, led to worse outcomes. Their study group included several children with other specific causes of DCM (such as anthracycline use), but 23 of the 40 children were classified as having idiopathic DCM. One study by Tsirka *et al.*[22] has reported an increased risk of death or transplant in girls (HR = 3.0). However, this finding was not present when analyzed in other studies.[1, 30, 34, 45, 49] Lastly, Burch *et al.*[37] found mural thrombus to be a univariate predictor of mortality.

2.6. Summary

The search for prognostic factors over the past 30 years has identified several that have been sufficiently consistent in repeated studies to be useful. Age at diagnosis predicts risk of mortality, with older children having worse outcomes. Severe mitral regurgitation detected by echocardiography may be a symptom worth noting, specifically if the disease does not resolve early in its course. Severely reduced LVFS and, to a lesser extent, LVEF, may be important factors to consider on the initial echocardiogram.

The value of electrocardiography, namely to detect arrhythmias, is not as clear. Arrhythmias were statistically significant predictors in five studies and non-significant in 3 others, each study from a single-institution.

Although two studies found LVEDP to be associated with mortality, cardiac catheterization is not without risk, especially in infants and small children, and routinely

attempting the procedure in all children presenting with disease is not current practice standard. However, with data suggesting that biopsy-proven myocarditis may be protective, the acquisition of tissue for histological analysis may serve as a guide in treatment plans and may weigh in its favor. A Scientific Statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology suggest endomyocardial biopsy for children is "reasonable in the setting of unexplained cardiomyopathy in children."[52] The recommendation is given a IIa Class (conditions for which the weight of evidence/opinion is in favor of usefulness/efficacy) with Level of Evidence C (lowest; based on primarily expert consensus). Nevertheless, whether for determination of LVEDP or collection of a specimen, there is some level of risk. [For a review of the use, safety, and yield of catheterization for endomyocardial biopsy in children, see Webber *et al*.[53] and Pophal *et al*.[53, 54]]

The deleterious effect of EFE was observed in three studies, although all were heavily biased with the majority of diagnoses of EFE made at autopsy, limiting its clinical utility. These results were all produced after Dr. Paul Lurie's 1988 editorial in the American Journal of Cardiology, which proposed that EFE is not a disease in and of itself but the possible result of a myriad of diseases.[55] The editorial was written as a response to the study by Ino *et al.*[56], which classified EFE as its own disease, much as Greenwood *et al.*[15] in 1976 and the WHO which currently has EFE placed as an "unclassified" cardiomyopathy.[2] Recent investigations into EFE, however, have suggested that it might be a specific reaction to the Mumps virus.[57] Furthermore, the rarity of the finding in the US, most probably due to successful vaccination strategies make EFE less of an issue. Along the same line, childhood vaccination against

coxsackievirus B and adenovirus has been proposed as potential mitigation of myocarditis.[58]

Although several studies had been performed since Warren Guntheroth first stated that "It is good to have a forthright admission that apart from the most obvious indicators of severity, we do not even know how to predict outcome of the most common form of cardiomyopathy;"[59] the strongest predictors remain those that had already been identified at the time of his statement in 1990.

At the Idiopathic and Primary Cardiomyopathy in Children: Research Directions and Strategies Conference, in Bethesda, MD, (January 25-26, 2007), several participants previewed and provided feedback to an earlier presentation of this systematic review. They shared their belief that a comprehensive risk profile or algorithm that could stratify children for death, transplant, or recovery at the time of presentation would be clinically useful. The ability to create such an algorithm requires a robust dataset of a sufficiently large number of children, treated with modern medical care across multiple centers representing current clinical practice, and with sufficient follow-up to assess outcomes, both good and poor. The PCMR meets those requirements. Initial review and presentation of findings from the PCMR on children with DCM were published in *JAMA*[1] and corroborate some the suspected prognostic factors (older age at diagnosis and lower LVFS), but did so at the exclusion of two etiological groups originally recorded and included in the Registry. Despite that, the conference participants agreed that a more comprehensive predictive algorithm was needed with attention to the individual etiologic groups.

The overall prognosis of children with DCM has steadily improved over the past 30 years. Cardiac transplantation has provided an option when medical management fails. Although the most recently reported 1- and 5-year survival rates are high, three studies have reported event-free survival rates, or the absence of what some studies call "heart death" (i.e. freedom from death or transplant), similar to the earlier survival estimates before transplant was common.[1, 21, 22]

The 5-year survival of the 1995-1999 and 2000-2006 pediatric heart transplant cohorts in the International Society for Heart and Lung Transplantation registry were approximately 70% in their most recently report.[8] This rate is better than all but one of the 5-year survival rates reported in studies published between 1976 and 1998. Although this improvement is encouraging, we still need to understand the experience of children facing the "all-consuming therapy"[59] for dilated cardiomyopathy, from diagnosis through post-transplant survival.

From 32 studies published over 30 years including 3,046 children, several factors stand out across multiple studies as indicating a better prognosis: younger age at presentation of disease, higher left-ventricular fractional shortening and ejection fraction, and the presence of myocarditis. Although 1- and 5-year survival rates have steadily improved, more children with DCM are receiving cardiac transplants, and event-free survival (freedom from death or transplant) is similar to that of decades ago. A unified clinical risk algorithm is still needed to assess risk of mortality and transplant in light of the known and unknown causes of dilated cardiomyopathy.

Chapter 3. Methods

3.1. Study design

Predictors of outcome for death and heart transplantation were analyzed utilizing baseline data from the time of dilated cardiomyopathy diagnosis from the Pediatric Cardiomyopathy Registry (PCMR) database.[60]

3.2. The Pediatric Cardiomyopathy Registry

Children diagnosed with cardiomyopathy from January 1, 1990, were enrolled from 98 tertiary care centers across in the United States and Canada in three phases or Cohorts. Data included in the analysis included follow-up through January 3, 2008 on 49% of the overall cohort. The remaining 51% had follow-up through December 31, 2002, as the majority of clinical centers ceased follow-up activities at the conclusion of the second 5-year study period in anticipation of the third cycle which focused on a new set of study aims as described below.

3.2.1. Background

The Pediatric Cardiomyopathy Registry is a collaborative effort of five institutions serving as the premier repository of information on pediatric cardiomyopathy across many clinical centers in North America. In brief, these institutions and their responsibilities are as follows: 1. University of Miami; Steven E. Lipshultz, MD, principal investigator. This team forms the Administrative Coordinating Center and is responsible for the development of the PCMR, administration and coordination, financial aspects, accrual and retention of participating clinical centers, and quality assurance. Drs. Lipshultz and James D. Wilkinson, MD, MPH, oversee the data acquisition by the traveling data collection team and coordinate their activities, as well as fundamental

aspects of the day-to-day operational coordination. 2. New England Research Institutes (NERI); Lynn Sleeper, ScD, principal investigator. NERI forms the Data Coordinating Center and is responsible for development and revision of study forms and manuals, data management and coordination, development of registry brochures and newsletters, and data analysis. 3. Children's Hospital, Boston; Steven D. Colan, MD, principal investigator. This team formed one of two Clinical Coordinating Centers from the initial epidemiologic study aims and was responsible for the Northeast region's enrollment and data acquisition of prospective and retrospective data from hospitals within that region. They continue to provide leadership in the current PCMR. 4. Texas Children's Hospital; Jeffrey A. Towbin, MD, principal investigator. Dr. Towbin and his team formed the second Clinical Coordinating Center for the Central/Southwest region and similarly were responsible for its accrual and retention of participating clinical centers and patients. Similarly, the team remains involved in the current PCMR study aims processing biological samples for genetic and viral testing. 5. Brigham and Women's Hospital; E. John Orav, PhD, principal investigator. Dr. Orav was responsible for the functional assessment segment of the study and continues to provide statistical support.

The PCMR primarily collects data via chart review. The PCMR study design involves identification of potentially eligible patients by the cardiologists at each participating institution, followed by medical record reviews and enrollment of eligible patients by the PCMR's specially trained Data Analysts who travel to the various sites. Data are abstracted from the medical record, recorded on the case report forms (CRF), and then submitted electronically to the New England Research Institutes (NERI) for data

management and statistical analysis. NERI has developed a state of the art electronic data management system known as ADEPT (Advanced Data Entry and Protocol Tracking).

Originally two Registry cohorts were established. All cases presenting to pediatric cardiologists from 1990 to 2006 were eligible. One was a retrospective cohort of patients that were seen at large tertiary care centers in North America and who were diagnosed between January 1, 1990 and December 30, 1995. The other was a population-based prospective cohort of pediatric patients diagnosed with cardiomyopathy since January 1, 1996 at one of 98 pediatric cardiac centers. The focus of the PCMR at that time was complete capture of all new cases to estimate the incidence of cardiomyopathy in two geographic regions of the United States (New England and the Central Southwest). New England was defined as Maine, New Hampshire, Vermont, Massachusetts, Connecticut, and Rhode Island, and had 18 centers. The Central Southwest region consisted of Texas, Oklahoma, and Arkansas and had 20 centers. A survey of pediatric practices in these regions indicated that the clinic sites captured all diagnosed cases, with the possible exception of one center in Oklahoma (2-5 cases/year). The data collected from patients of each cohort have been previously compared and were found to be similar with respect to demographic and clinical characteristics.[1] The primary difference between the two cohorts was initially in the amount of clinical data that had been collected. Data collection of patients enrolled in the retrospective cohort had a greater volume of data collected for clinical tests and procedures. Since then an attempt was made to collect additional clinical data from children in the prospective cohort using additional case report forms. However, not all sites were available for this effort. Additionally, a third wave of children with cardiomyopathy were enrolled beginning July 24, 2006 from 10 of

the highest case-yielding sites to create a new cohort of incident and prevalent cases with extensive clinical and functional status survey data as well as blood and tissue specimens which will be analyzed for a specific genetic mutation and the presence of viral genetic material, respectively.

3.2.2. PCMR Patient Eligibility

To be eligible for the PCMR, a patient is required to be less than 18 years of age at diagnosis, and to meet one of 4 criteria:

1) Have echocardiographic evidence of cardiomyopathy, including at least 2 left ventricular measurements (fractional shortening, posterior wall thickness, or end-diastolic dimension or volume) exceeding 2 standard deviations for age (fractional shortening) or for body surface area (all other measurements); or

2) Have an echocardiographic pattern of cardiomyopathy (including localized ventricular hypertrophy or restrictive cardiomyopathy) or a contracted form of endocardial fibroelastosis; or

3) Have a pathologic diagnosis of cardiomyopathy on autopsy or endomyocardial biopsy; or

4) Have other clinical evidence of cardiomyopathy provided by the cardiologist.

There are 14 clinical exclusion criteria, including:

1) presence of a congenital heart defect not associated with a malformation syndrome;
2) endocrine disease known to cause myocardial damage;
3) chronic arrhythmia,;
4) pulmonary parenchymal or vascular disease;

5) immunologic disease;
6) history of rheumatic fever;
7) Kawasaki disease;
8) HIV infection of the child or mother;
9) invasive cardiothoracic procedures which may result in transient cardiomyopathy;
10) active or chronic uremia;
11) ischemic coronary vascular disease;
12) cancer;
13) toxic chemotherapy-associated cardiomyopathy (anthracyclines, iron overload, etc.); and/or,
14) drug use known to cause hypertrophy (corticosteroids, cocaine, etc.).

3.2.3. PCMR Data Collection

The PCMR Data Coordinating Center (NERI) along with the PCMR Administrative (Miami) and Clinical Coordinating Centers (Boston, Houston) work together to ensure regular review of patient medical records, with periodic collection of relevant clinical and demographic information.

3.2.4. Human Subject Protection

The initial phase of the PCMR, beginning in 1995, had all participating centers obtain institutional review board or ethics committee approval with a waiver of consent authorization. All data collected were obtained from chart review, and neither the patient nor their family was aware of study participation.

The current phase, beginning in 2006, with active enrollment for survey completion and blood acquisition, has all subjects enrolled with informed consent of the parents and age-appropriate assent as determined by the center's institutional review board or ethics committee.

3.2.5. PCMR Data Elements

The PCMR database contains only de-identified patient records. Each patient is assigned a unique study number, and the only linkage to patient identifiers is maintained on a roster at the participating clinical site. The only potential identifiers in the PCMR database are date of birth and zip code of residence. All patients have demographic data including race/ethnicity which is defined categorically as: White, Black, Hispanic, Native American, Asian/Pacific islander, Other or Unknown. Data elements are collected regarding presence of congestive heart failure, functional type (e.g. hypertrophic, dilated), etiology, health insurance and family history. Echocardiographic measures are collected at baseline and each annual follow up. Date of listing for cardiac transplantation and date of transplantation are recorded if applicable. Date of cardiac biopsy and results are recorded if applicable. Date and cause of death are recorded if applicable. Additionally, a subset of patients have extensive data on electrocardiogram, Holter study, blood and urine studies, cardiac catheterization, hospitalization, medication, and additional therapeutic procedures.

3.2.6. PCMR Data Management, Quality and Security

A customized data management system is currently in use for the PCMR using the New England Research Institute's (Watertown, MA) web-based, Advanced Data Entry and Protocol Tracking (ADEPT) system. This system integrates all aspects of study

data collection including: data entry, PCMR reporting, and quality control/validation checks on incoming data. All PCMR data are stored in an Oracle relational database at NERI. This system is specifically designed to support reliable and secure data entry for research purposes.

Unlike most Web-based data entry applications, ADEPT provides real-time field level validations and context-sensitive help at the time of data entry. Electronic data entry forms are formatted using HTML to closely resemble the paper-based study instruments. These forms are then enhanced with client side JavaScript code to ensure rapid data entry, proper validations of all data fields, and proper skip patterns within study data forms.

The Web-based components of the data management system utilize several levels of security to ensure the privacy and integrity of the study data including: Web access requires use of assigned user names and passwords; secure socket layer (SSL) data encryption; access controlled by Oracle database rights and privileges and protected by Oracle's extensive security features; and NERI firewalls.

Lastly, an NHLBI-appointed Observational Study Monitoring Board assists in data monitoring and reviews the progress of the study as well as any security issues semi-annually.

3.2.7. PCMR Data Collection Forms

All available data are recorded at the following PCMR study time points: (1) baseline measurements which cover the time period from diagnosis to 30 days post-diagnosis, and (2) annual measurements from the time of diagnosis through 1 year post diagnosis and annually thereafter with the date of diagnosis as the anniversary. If there is

no clinical contact with the patient during that annual period, the patient is still considered active. The annual forms are completed until one of several outcomes has been met: (1) death; (2) heart transplantation; (3) transfer to the care of a physician who is not participating in the PCMR; (4) discharge from clinical follow-up, which most commonly occurs for those children who have an acute presentation with subsequent resolution of all signs and symptoms; and (5) loss to follow-up, which is reserved for those who have not been seen at the site for at least three years and with whom the clinical team has lost all contact.

3.3. Case Classification

The source group of children diagnosed with dilated cardiomyopathy was defined by searching the PCMR database for all those who were documented as having met PCMR inclusion with no exclusion criteria and were defined as having "pure" DCM with no overlapping functional phenotype (i.e. hypertrophic, restrictive, or arrhythmogenic right ventricular dysplasia) during the baseline period. Additionally, children were excluded who were diagnosed at autopsy or had the following patterns recorded: concentric or local ventricular hypertrophy, contracted form of endocardial fibroelastosis, ventricular hyperplasia or Uhl's anomaly, or left ventricular noncompaction.

3.4. Etiologic Classification

The cases were further classified into 6 etiologic groups based on prior PCMR typology[1, 4] and published cardiomyopathy diagnosis guidelines[61]:

3.4.1. Inborn Error of Metabolism

Data from the medical record indicating any of the known metabolic diseases including: disorders of glycogen metabolism, degradation of mucopolysaccharides or

glycosphingolipids, and other cardiomyopathy associated disorders of energy metabolism.

3.4.2. Malformation Syndrome

Data from the medical record indicating any of the known malformation syndromes associated with cardiomyopathy which usually have characteristic dysmorphic features. For DCM, they include Leber's Congenital Amaurosis and Alstrom Syndrome.

3.4.3. Neuromuscular Disease

Data from the medical record indicating any of the known muscular dystrophies, congenital myopathies, or ataxias. This group is predominantly comprised of children with Duchenne or Becker muscular dystrophy who meet study criteria for cardiomyopathy.

3.4.4. Familial Isolated Cardiomyopathy

Data on family history as collected in the chart is used to determine this category. A previously published description by the PCMR study group[62] stated that it is a:

> "CM with no systemic features occurring in ≥2 family members, a single proband with an identified genetic defect, or a metabolic disorder known to cause isolated CM. The cause of familial isolated CM was considered to be known when a specific inheritance pattern could be inferred or when the genetic defect was identified and to be unknown when the relationship to affected relatives (e.g. non-first-degree relatives) precluded assignment of a conventional inheritance pattern (autosomal recessive, autosomal dominant, X-linked, or mitochondrial). When >1 inheritance pattern was theoretically possible, the more-conventional pattern was assumed. For example, if a brother and sister were affected and both parents had negative echocardiograms, then the inheritance pattern was described as autosomal recessive, although autosomal dominant with incomplete penetrance would be possible."

3.4.5. Myocarditis

Data from the medical record indicating any indication of viral disease either through serologic or endomyocardial analysis, clinical history of active disease, or prodromal history of infection were included in this group. Although the World Health Organization classifies acute viral myocarditis as an inflammatory cardiomyopathy distinct from DCM,[2] it is included as an etiologic group within DCM because of their similar echocardiographic appearances.

3.4.6. Idiopathic DCM

By default, all those without an established etiology at baseline reside in this category. As reported previously,[1, 4] this group comprises the majority of cases at baseline. Although a small percentage are expected to have a diagnosis realized after continued testing and input from non-cardiology specialists, the baseline diagnosis was used for all analyses.

3.5. Data Elements and Considerations

3.5.1. Primary Outcome Variables

The first issue is the choice of primary outcome variables. A substantial percentage of children with DCM will go on to heart transplant. A limitation of this dataset is that there are no post-transplant follow-up data as part of the original PCMR study design. Nevertheless, the consideration of pre-transplant mortality is of interest in the setting of limited resources. The clinical terms “failure of medical management” or “heart death” have been applied to those children who either die or receive a heart transplant. These two outcomes, mortality and transplant, were the main considerations

for Kaplan-Meier and Cox proportional hazard models of the two separate outcomes as well as the combined outcome of "heart death."

Children who were noted as alive in this analysis included all those who were alive at last follow-up as well as a small group of children, mainly those with myocarditis, who were discharged from clinical follow-up by their physician.

3.5.2. Echocardiographic measures

The PCMR collected commonly recorded echocardiographic measures, at the time of diagnosis and annually. While raw values for echocardiographic measures are intuitive and common for analysis in the adult literature, they are impractical for pediatric studies since natural changes associated with age and growth make it difficult to determine whether, for example, a given value in fractional shortening is appropriate for a given age or whether the child has developed a functional abnormalities as indicated by a value that may seem abnormal in an adult. It is also inappropriate to combine the echocardiographic measures across a cohort of children since they will have different ages and body sizes. Therefore, all of the analyses will use echocardiographic measures that have been normalized to z-scores.

To calculate z-scores for fractional shortening, for example, the child's raw fractional shortening value is subtracted from the expected average fractional shortening that is appropriate for a normal child of the same age (or body surface area for some of the other echocardiographic measures), and then it is divided by the age-appropriate standard deviation. A fractional shortening z-score of 0 reflects a child whose fractional shortening is perfectly average for their age, while a fractional shortening z-score of –2 reflects a child whose fractional shortening has fallen 2 standard deviations below the

normal average for that age. Similar z-scores are calculated for other echocardiographic parameters, although, the remainder are normalized to the child's body-surface area.

3.5.3. Missing Data

The PCMR has a high rate of annual follow-up (approximately 90%). Nevertheless, with data collection relying on clinician input into the patients chart and subsequent chart review at the many participating clinics by the data collection team, there are a large number of children for whom some portion of baseline data at the time of diagnosis are simply not available. Children with incomplete baseline data were included in all analyses for which they could contribute data. However, multivariate analyses were limited to those with complete baseline data for the factors significant in univariate modeling.

3.5.4. Survival Analysis and Competing Risks

Semi-parametric Kaplan-Meier and Cox proportional hazard methods are common forms of survival data analysis where there is a single event of interest. Recently performed analyses in the DCM literature considered cardiac transplantation as well as mortality as outcomes of interest. Assumptions of independence of outcomes become questionable. Namely, when a child is doing poorly and is at risk of dying, he is considered for a heart transplant. If he receives a viable heart then he avoids the outcome of death. In an analysis of survival, the time to death, assuming sufficiently long follow-up is prolonged. If one is considering the time to "heart death," the event of a heart transplant is an artificial endpoint that while effectively producing a "heart death" is complicated if the recipient dies at any point prior to successful transplantation.

When multiple events of interest are involved, the competing risks method of analysis may be more appropriate. However, McGiffin *et al.*[63] stated that its usage is not a statement that one is "better" than the other, but that the two methods answer two different questions. The Kaplan-Meier method answers the question, "What is the probability of one outcome provided there is no opportunity for another competing outcome to occur?" Whereas the competing risks analysis asks, "What is the probability of actually experiencing a particular outcome?" Others have referred to this as "actuarial" versus "actual" estimates, respectively.[64, 65] The ability to extract the predictors for an outcome in the face of competing events can be compared to those derived from the Cox proportional hazard method. Such a comparison was performed using pediatric heart transplant data, for example, and found that the Kaplan-Meier method tended to over-estimate the percentage of children who experienced one of the several outcomes versus those who actually had the outcome using the competing risks method.[63] In that study at 6 months after listing for transplantation, the Kaplan-Meier estimate for freedom from death while waiting for a heart transplant, censoring other outcomes, was 60%, (event rate 40%), while the competing risk estimate of the event rate was 23%. Other examples of this overestimation have been shown for competing outcomes in patients with osteogenic sarcoma and failure of intrauterine devices.[66, 67]

Mathematically it can be shown that the Kaplan-Meier estimates of individual competing outcomes when the others outcomes are either censored or ignored do not sum to unity for a given point in time. In the study of pediatric heart transplant from above, the summation of the Kaplan-Meier estimates for the four outcomes at 6 months totaled to 156%, whereas the competing risk estimates totaled to 100%.[63]

The comparison of competing risk analyses by Tai et al[66] utilizes the data augmented Cox regression method of Lunn and McNeil[68] where each subject has his observation duplicated by the number of failure types and with an indicator variable for the failure type and its respective time and response variables. This approach lends itself to adaptation of existing SAS procedures. Tai also performed a visual analysis comparing the Kaplan-Meier and Lunn-McNeil for which a SAS macro was provided.

Other approaches to the competing risk problem have been suggested. Fine and Gray[69] had developed a similar semiparametric model of the subdistributions of the competing risks with an associated R macro. While McGiffin *et al.*[63] developed a parametric approached that partitioned the cause-specific hazard by time period into early and late phases.

3.6. Statistical Methods

Descriptive statistics are presented as a percentage or mean (standard deviation), with skewed continuous data summarized as median and quartiles. The distributions of categorical variables were compared using Fisher's exact test. Two groups of normally distributed variables were compared using *t* test, and analysis of variance was used to compare more than 2 groups. Skewed data were analyzed using the Wilcoxon rank-sum test and the Kruskal-Wallis test.

Left ventricular end-diastolic dimension, posterior wall thickness, septal thickness, and mass were measured and expressed conditional on body surface area.[70, 71] Fractional shortening (FS) is one measure of left ventricular contractility and is defined by the ratio of the difference between the end diastolic dimension (LVEDD) and end systolic dimension (LVESD) to the end diastolic dimension, and is expressed as

FS=LVEDD-LVESD/LVEDD x 100. FS is expressed conditional on age.[70] Quantitative right ventricular structure and function were not analyzed.

Outcome measures for univariate models were death, cardiac transplantation, and the composite endpoint of death or transplant. Due to varying times of follow-up, survival figures and estimates were calculated using the Kaplan-Meier method and were compared with the log rank test, with the time of DCM diagnosis as the origin. For multivariate models, the composite endpoint of death or transplant was used. Cox proportional hazards regression was used to identify multivariate predictors of outcomes within each etiologic group.

Competing risk analysis calculated the cumulative incidence for the outcomes of death, heart transplant, and alive without outcome. Predictors for each outcome were determined as per the data augmentation method described by Tai et al.[66] using the approach originally described by Lunn and McNeil.[68]

To control for the large number of subgroup analyses as well as multiple comparisons, only p values <0.01 were considered to be statistically significant. All analyses were conducted using the Statistical Analysis System version 9.1 (SAS, Cary, NC) and SAS macro for competing risk analysis as per Tai et al[66].

Chapter 4. Results

4.1. Demographics & Clinical Characteristics

4.1.1. Overall

Of the 1731 patients, only a small minority (125, 7%) did not have a record of meeting the strict echocardiographic measurement criteria for PCMR study inclusion. Of those, the vast majority were included as per the physician's assessment; in a review of associated comments, most were children with qualitative findings where the quantitative echocardiographic measurements were not recorded. A small number also had evidence of cardiomyopathy by endomyocardial biopsy (11).

Table 4-1 and Table 4-2 show the demographic data and Table 4-3 and Table 4-4 show the clinical data at baseline for the combined group of all DCM diagnoses (as well as each of the individual etiologic groups) in the PCMR meeting criteria for this analysis.

For the combined group of all DCM diagnoses (N=1731), males made up slightly over half of all cases (54%), with the largest age group represented by infants (< 1 year) at presentation (40%). A majority of children were white (55%), with black (20%) and Hispanic (16%) children also represented. The geographic representation was varied, with over half (60%) presenting to physicians outside of the Central-Southwest and New England regions, the source locations of the initial epidemiologic incidence study. Only a quarter of cases were from the Retrospective arm of the study (diagnoses between 1990 and 1995). The mean year of diagnosis was 1998 (range 1990 to 2007).

Growth parameters were slightly below normal for age. A large percentage of children presented with symptoms of congestive heart failure (71%). Echocardiographic parameters, which were recorded in 81% of cases, depicted left ventricles that were

enlarged in size (end-diastolic and end-systolic dimension z-scores) and mass, and had very poor systolic function (fractional shortening and ejection fraction z-scores). Septal and posterior wall thickness z-scores were, generally, within normal range.

Of the 1,005 children who had any family history of disease recorded in their medical records, slightly over a third had at least one of the following: cardiomyopathy (21%), sudden cardiac death (11%), genetic syndrome (9%), congenital heart disease (6%), or arrhythmia (4%).

4.1.2. Idiopathic DCM

The majority of the cases (1192, 68.5%) in this analysis were idiopathic, and did not have an etiology determined at baseline. Their baseline demographic and clinical characteristics, therefore, were similar to those described above for the combined DCM group. Of these, 157 (13%) subsequently were diagnosed with an etiology at some time point after baseline. The majority, 81 (52%) received a diagnosis during the first follow-up year. At 5 years, 90% of the 157 are classified with an etiology followed by an additional 1 to 2 cases per year after that. Overall, the additional etiologies reported are: Myocarditis (N=86), IEM (N=31), FDCM (N=25), NMD (N=6), MFS (N=5), and Other (N=4).

4.1.3. Inborn Error of Metabolism

This group was (N=43, 2.5%) based on the data from the medical record indicating any of the known metabolic diseases known to cause DCM (including disorders of glycogen metabolism, degradation of mucopolysaccharides or glycosphingolipids, etc.). The two largest sub-groups were those with a mitochondrial disorder, not otherwise specified, (11 of 43, 26%) and Barth syndrome (8 of 43, 19%).

There were more boys (74%) with presentation earlier in life (85% < 6 yr) when compared to the combined DCM group (67%). Racial composition was also different as there were more whites with IEM than the combined group (75% vs 56%). Hispanics made up the next largest group (19%) followed by "other" and black.

Children with IEM had the greatest proportion of positive family history (of any disease) documented (65%), consisting of family history of sudden death (35%), cardiomyopathy (33%), and genetic syndrome (21%).

4.1.4. Malformation Syndrome

The children were included in this group (N=6, 0.3%) based on data from the medical record indicating any of known malformation syndromes associated with cardiomyopathy (including one each of Leber's Congenital Amaurosis and Alstrom Syndrome). There were 3 cases with chromosomal defects not otherwise specified, and 1 case of autosomal recessive malformation not otherwise specified.

In this small group, only two were male, and all were under the age of 6 at diagnosis. Children in this group on average were significantly shorter than expected for their age (mean z-score, -2.8).

4.1.5. Neuromuscular Disease

This group (N=139, 8%) was based on data from the medical record indicating any of the known muscular dystrophies, congenital myopathies, or ataxias, and was predominantly comprised of children with Duchenne (117, 84%) or Becker (11, 8%) muscular dystrophy. All but 13 met study echocardiography criteria for cardiomyopathy at time of diagnosis. Of the 13 cases, all were described by clinicians as meeting clinical

criteria, and over the course of follow-up 10 of these cases had echocardiographic criteria recorded.

All but 5 children were male and were predominantly white (72%). All children presented with cardiomyopathy after 6 years of age with 83% presenting between ages 12 and 18. Only 28% had symptoms of congestive heart failure at diagnosis.

Of those with family history data, half had at least one condition documented with the most common being history of a genetic syndrome (42%) followed by cardiomyopathy (20%).

4.1.6. Familial Isolated Cardiomyopathy

This group (N=79, 4.6%) was based on family history data as recorded in the chart. The majority (89%) were considered to have an autosomal dominant inheritance pattern. The rest were autosomal recessive (N=1), X-linked (N=4), or mitochondrial (N=1).

These children were slightly older at presentation (median age, 5.94 years), with around half of them in congestive heart failure. There was a greater proportion with positive family history data than the other groups with the highest reported history of sudden death when compared to all the other groups (53%).

4.1.7. Myocarditis

Within the group of children with myocarditis (N=272, 15.7%), 112 had biopsy confirmation meeting the Dallas criteria for myocarditis,[51] whereas the majority (160, 59%) were classified as probable cases (i.e. either the endomyocardial biopsy did not meet Dallas criteria or the case was included due to clinical findings as reported by the physician and recorded in the medical record).

This group shared a similar profile of baseline characteristics as the idiopathic group, although a larger percentage (83%) presented with congestive heart failure.

Table 4-1: Demographics by Etiology at Baseline

		DCM (N = 1731)			Idiopathic (N = 1192)			IEM (N = 43)			MFS (N = 6)		
		n			n			n			n		
Male, %		939	54.3		593	49.8		32	74.4		2	33.3	
Age													
	Median, yr	1731	1.73		1192	1.2		43	0.87		6	0.4	
	IQR	(0	17.99)		(0	17.99)		(0	16.6)		(0.08	4.93)	
	Infant (< 1yr), %	692	40		558	46.8		22	51.16		4	66.67	
	1 to <6 yr, %	379	21.89		249	20.8		15	34.88		2	33.33	
	6 to <12 yr, %	246	14.21		167	13.95		3	6.98		0		
	12 to <18 yr, %	414	23.92		223	18.63		3	6.98		0		
Height for Age z-score, mean, SD		878	-0.35	1.62	629	-0.33	1.6	21	-0.85	1.68	3	-2.8	1.71
Weight for Age z-score, mean, SD		1041	-0.23	1.62	725	-0.26	1.61	27	-0.74	1.66	4	-0.9	2.72
Weight for Height z-score, mean, SD		542	-0.58	1.26	406	-0.64	1.17	11	0.07	1	2	0.8	3.68
Race, %													
	White	963	55.63		644	54.03		31	72.09		3	50	
	Black	350	20.22		251	21.06		1	2.33		0	0	
	Hispanic	280	16.18		197	16.53		8	18.6		1	16.67	
	Other	104	6.01		77	6.46		3	6.98		1	16.67	
	Missing	34	1.96		23	1.93		0	0		1	16.67	
Region, %													
	Central Southwest	417	24.09		273	22.9		8	18.6		2	33	
	New England	270	15.06		144	12.08		15	34.88		2	33	
	Other	1044	60.31		775	65.02		20	46.51		2	33	
Retrospective Cohort, %		480	27.73		307	25.76		11	25.58		1	16.67	

DCM: Dilated Cardiomyopathy, IEM: Inborn Errors of Metabolism, MFS: Malformation Syndrome, IQR: Interquartile Range

Table 4-2: Demographics by Etiology at Baseline, Continued

		NMD (N = 139)			FDCM (N = 79)			Myocarditis (N = 272)		
		n			n			n		
Male, %		134	96.4		44	55.7		134	49.3	
Age at Diagnosis										
	Median, yr	139	14.3		79	5.94		272	1.7	
	IQR	(7.78	17.99)		(0	17.91)		(0	17.98)	
	Infant (< 1yr), %	0			25	31.65		83	30.5	
	1 to <6 yr, %	0			15	18.99		99	36.7	
	6 to <12 yr, %	23	16.55		20	25.32		33	12.36	
	12 to <18 yr, %	116	83.45		19	24.05		53	19.85	
Height for Age z-score, mean, SD		56	-0.85	1.72	46	-0.32	2.06	126	-0.12	1.46
Weight for Age z-score, mean, SD		77	0.15	1.94	51	0.03	1.95	157	-0.29	1.30
Weight for Height z-score, mean, SD		12	1.08	2.47	27	-0.46	1.72	84	-0.67	1.07
Race, %										
	White	100	71.94		41	51.9		144	52.94	
	Black	19	13.67		12	15.19		67	24.63	
	Hispanic	14	10.07		17	21.52		43	15.81	
	Other	3	2.16		7	8.86		13	4.78	
	Missing	3	2.16		2	2.53		5	1.84	
Region, %										
	Central Southwest	32	23.02		20	25.32		82	30.15	
	New England	30	21.58		17	21.52		62	22.79	
	Other	77	55.4		42	53.16		128	47.06	
Retrospective Cohort, %		39	28.06		31	39.24		91	33.46	

NMD: Neuromuscular Disease, FDCM: Familial Isolated Dilated Cardiomyopathy IQR: Interquartile Range

Table 4-3: Clinical Characteristics by Etiology at Baseline

	DCM (N = 1731)			Idiopathic (N = 1192)			IEM (N = 43)			MFS (N = 6)		
	n			n			n			n		
Congestive Heart Failure, %	1236	71.4		894	75		27	62.79		4	66.7	
Echo z-score, mean, SD												
ED Dimension	1350	4.18	2.75	940	4.68	2.72	30	3.29	1.85	5	2.56	1.8
ED Posterior Wall	1072	-0.6	2.47	737	-0.65	2.48	25	-0.45	1.81	5	0.66	2.25
ED Septum	957	-0.91	1.92	663	-1.02	1.9	21	-0.51	2.09	5	-0.36	1.96
ES Dimension	1183	5.96	3.02	818	6.5	2.81	25	5.46	1.79	5	3.69	2.47
Fractional Shortening	1417	-8.46	3.73	963	-9.02	3.49	33	-7.85	3.35	5	-5.29	4.12
LV Mass	1055	2.18	2.8	726	2.48	2.83	25	1.73	1.9	5	1.8	2.93
Ejection Fraction	455	-6.08	2.42	310	-6.33	2.26	13	-4.39	3.82	1	-7.92	
PW-ED Dimension ratio, Median	1145	0.125		780	0.119		28	0.148		5	0.159	
(IQR)		(.1	.154)		(.096	.146)		(.13	.163)		(.15	.186)
Familial History, %												
Any Family History	353	35.1		198	27.5		11	61.1		2	50	
Cardiomyopathy	212	21.3		107	14.8		6	33.3		1	33.3	
Sudden Death	110	10.6		59	7.8		7	35		1	20	
Congenital Heart Dz	51	5.6		36	5.3		1	8.3		0		
Arrhythmia	37	4.1		26	3.9		0			0		
Genetic Syndrome	82	8.5		32	4.6		4	21.1		1	25	

DCM: Dilated Cardiomyopathy, IEM: Inborn Errors of Metabolism, MFS: Malformation Syndrome,
ED: End-Diastolic, ES: End-Systolic, PW: Posterior Wall, IQR: Interquartile Range, Dz: Disease

Table 4-4: Clinical Characteristics by Etiology at Baseline, Continued

		NMD (N = 139)			FDCM (N = 79)			Myocarditis (N = 272)		
		n			n			n		
Congestive Heart Failure, %		40	28.8		44	55.7		227	83.5	
Echo z-score, mean, SD										
	ED Dimension	101	1.63	1.96	60	3.42	2.49	214	3.56	2.49
	ED Posterior Wall	84	-1.70	2.2	51	-0.75	1.78	170	0.12	2.65
	ED Septum	78	-1.40	1.57	45	-0.68	1.46	145	-0.27	2.11
	ES Dimension	94	3.10	2.4	54	4.86	2.82	187	5.46	3.40
	Fractional Shortening	128	-5.56	3.3	64	-6.99	3.75	224	-8.31	4.11
	LV Mass	83	-0.19	1.85	51	1.67	2.26	163	2.45	2.82
	Ejection Fraction	24	-4.10	1.63	26	-5.26	2.24	81	-6.20	2.63
PW-ED Dimension ratio, Median		102	0.136		54	0.135		176	0.139	
	(IQR)		(.115	.16)		(.111	.156)		(.11	.167)
Familial History, %										
	Any Family History	36	52.9		76	98.7		30	25.4	
	Cardiomyopathy	12	20.7		76	98.7		10	8.5	
	Sudden Death	3	4.4		30	53.6		10	7.4	
	Congenital Heart Dz	1	2.0		7	16.3		6	5.3	
	Arrhythmia	3	6.0		5	11.6		3	2.7	
	Genetic Syndrome	32	42.7		5	11.1		8	6.4	

NMD: Neuromuscular Disease, FDCM: Familial Isolated Dilated Cardiomyopathy,
ED: End-Diastolic, ES: End-Systolic, PW: Posterior Wall, IQR: Interquartile Range, Dz: Disease

4.2. Outcomes

From the time of diagnosis of DCM, the median follow-up time for the entire group was 1.27 years (IQR, 0.24 – 4.0 years). For those who were alive at last clinical encounter, their median follow-up time was 2.87 years (IQR, 0.88 – 5.5 years) with the longest follow-up time of 16.6 years. Overall, 665 (39%) had some adverse outcome, of which the majority (77%) were cardiac transplantation. Of those listed for transplant, the median listing time across all groups was less than 8 months, however, almost a quarter (112, 22%) did not receive a transplant; of those, almost half were dead at last follow-up (46, 41%). Out of the 413 children who received a heart transplant, 29 did not have a date recorded for being placed on the transplant list. Survival rates varied by etiology for each outcome as well as by the composite endpoint. (Figures 1-3).

4.2.1. Idiopathic

Among those who died or received a heart transplant, median time to either event was 0.39 years. The majority received a transplant (326 of 491; 66%). Of those listed for a heart transplant, the idiopathic group had the largest number of observed of deaths while waiting and the third largest proportion (41, 47%) next to malformation syndromes (1, 100%) and neuromuscular disorder (1, 50%). At all time points up to 5 years, the children with idiopathic DCM had the worst survival experience when compared to the other groups, Table 4-6.

4.2.2. Inborn Error of Metabolism

A third of cases had a poor outcome, with the majority (71%) dying as opposed to receiving a transplant. Median time to death from diagnosis was three times as long as time to transplant (1.83 vs. 0.58 years).

4.2.3. Malformation Syndrome

Half of the children with MFS (3 of 6) died during follow up at 0.76, 0.99, and 2.15 years. One of those deaths was while waiting for heart transplantation. The remainder of the group was alive at last follow-up at 1.57, 6.0, and 7.0 years after diagnosis.

4.2.4. Neuromuscular Disease

Forty percent of children with NMD and CM failed medical management at a median time of 1.98 years after diagnosis. Of those, the majority died (84%), with only 9 receiving a heart transplant.

4.2.5. Familial DCM

When compared to the other etiologic groups, FDCM had the largest percentage of transplants with respect to all children in that group (28 of 79, 35%) and with respect to all the poor outcomes in that group (28 of 35, 80%). Most children in this group received a heart transplant within a year of diagnosis. Only 7 children with FDCM died (9%), also within a year of diagnosis (median time, 0.18 year).

4.2.6. Myocarditis

Children with myocarditis had the best outcomes (202 alive of 272, 74%) when compared to other etiologic groups. Only 26% of the group had a poor outcome, with two-third (46 of 70) receiving a heart transplant at a median time of 0.24 years from diagnosis. Those who died did so at a shorter median time from diagnosis (0.04 year).

Table 4-5: Distribution of Outcomes and Time to Outcome from Diagnosis by Etiology

		Alive at last follow-up					Combined (Death or Transplant)					All time (Alive and Outcomes)				
	N	n	%	Median Time (yr)	IQR		n	%	Median Time (yr)	IQR		n	%	Median Time (yr)	IQR	
Idiopathic	1192	161	14%	0.39	0.05	1.34	326	27%	0.39	0.14	0.95	394	33%	0.13	0.02	0.54
IEM	43	10	23%	1.83	0.02	3.28	4	9%	0.58	0.32	0.79	5	12%	0.07	0.06	0.22
MFS	6	3	50%	0.99	0.76	2.15	0	0%				1	17%	0.66		
NMD	139	47	34%	2.31	1.30	4.05	9	6%	0.63	0.25	0.96	10	7%	0.11	0.06	0.49
FDCM	79	7	9%	0.18	0.16	0.87	28	35%	0.34	0.09	1.54	23	29%	0.25	0.01	1.11
Myocarditis	272	24	9%	0.04	0.01	0.19	46	17%	0.24	0.08	0.85	63	23%	0.05	0.02	0.44
Total	1731	252	15%	0.46	0.07	1.94	413	24%	0.39	0.12	0.96	496	29%	0.12	0.02	0.54

		Alive at last follow-up					Combined (Death or Transplant)					All time (Alive and Outcomes)				
	N	n	%	Median Time (yr)	IQR		n	%	Median Time (yr)	IQR		n	%	Median Time (yr)	IQR	
Idiopathic	1192	705	59%	2.75	0.81	5.64	487	41%	0.39	0.10	1.01	1192	100%	1.02	0.23	3.70
IEM	43	29	67%	4.06	1.22	7.07	14	33%	0.79	0.05	3.20	43	100%	3.00	0.57	6.07
MFS	6	3	50%	6.00	1.57	7.00	3	50%	0.99	0.76	2.15	6	100%	1.86	0.99	6.00
NMD	139	83	60%	3.74	1.52	5.54	56	40%	1.98	0.76	3.00	139	100%	2.66	1.05	5.00
FDCM	79	44	56%	4.26	1.81	6.98	35	44%	0.20	0.10	1.39	79	100%	1.83	0.21	5.02
Myocarditis	272	202	74%	1.95	0.74	4.67	70	26%	0.15	0.05	0.47	272	100%	1.12	0.17	3.98
Total	1731	1066	62%	2.81	0.88	5.54	665	38%	0.41	0.10	1.23	1731	100%	1.27	0.24	4.00

IEM: Inborn Errors of Metabolism, FDCM: Familial Isolated Dilated Cardiomyopathy, MFS: Malformation Syndrome, NMD: Neuromuscular Disease

Table 4-6: Survival from Death or Transplant by Etiologic Group at Specified Timepoints

Time (years)	Idiopathic	IEM	FDCM	MFS	Myocarditis	NMD
0.5	0.73	0.88	0.74	1.00	0.79	0.92
1	0.66	0.80	0.68	0.67	0.77	0.87
2	0.58	0.77	0.63	0.67	0.72	0.77
5	0.51	0.63	0.53	0.44	0.70	0.55
10	0.47	0.56	0.50		0.62	0.32
15	0.35		0.33			

IEM: Inborn Errors of Metabolism, FDCM: Familial Isolated Dilated Cardiomyopathy, MFS: Malformation Syndrome, NMD: Neuromuscular Disease

Figure 4-1: Survival for Children with DCM by Etiologic Group, with Cardiac Transplantation Censored

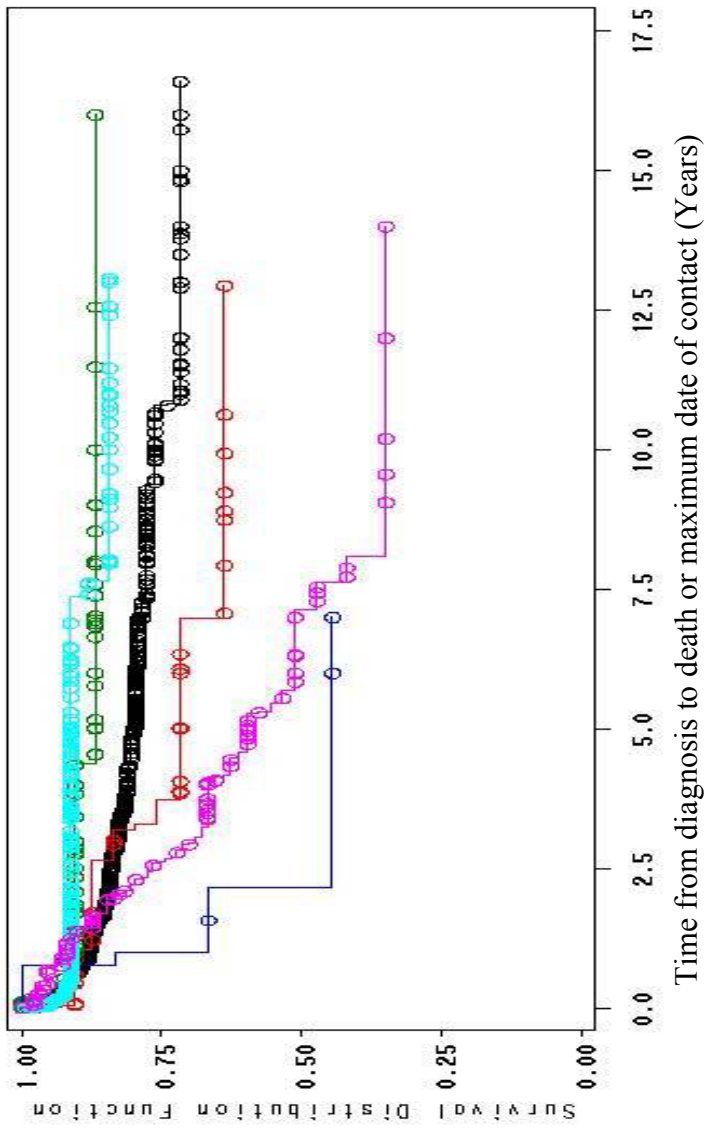


Figure 4-2: Freedom from Cardiac Transplantation for Children with DCM by Etiologic Group, with Death Censored

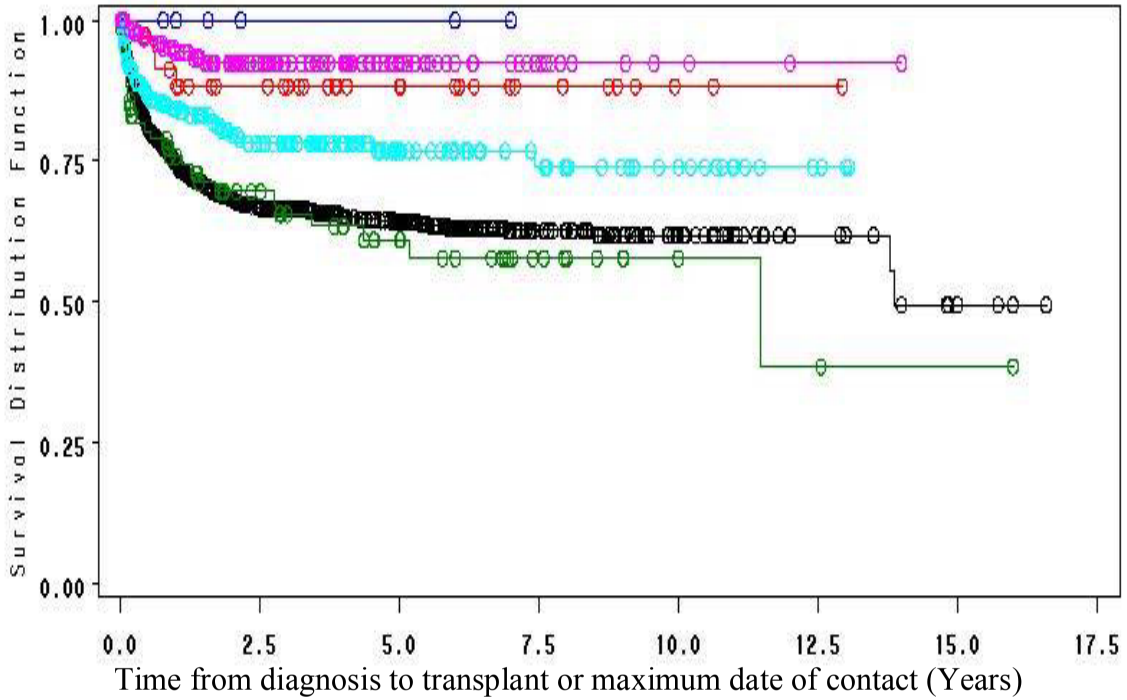
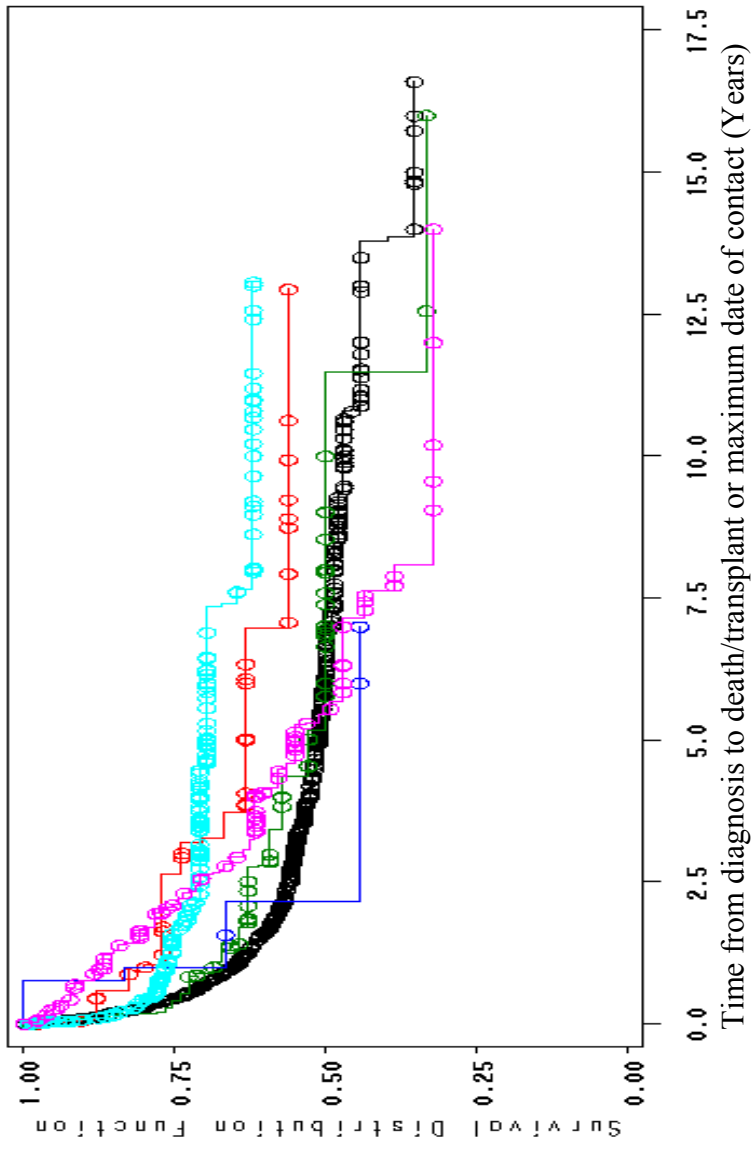


Figure 4-3: Freedom from Death or Transplantation for Children with DCM by Etiologic Group



4.3. Univariate Predictors of Outcome

The univariate survival analyses for each of the etiologic groups for the outcomes of death, transplant, and the composite endpoint of death or transplant, are presented below with accompanying tables. No results are shown for the MFS group as the number of patients within the group and the number of outcomes was too small for univariate modeling. Overall, in a model comparing each other etiologic group to idiopathic cases, the risk of death was significantly lower for those with myocarditis (HR=0.62; p=0.029) and higher for those with neuromuscular disease (HR=1.99; p<0.001).

Of note, in review of the pertinent study design characteristics, neither affiliation with the retrospective or prospective cohort nor affiliation with the sites that continued follow-up past 2003 showed a significant difference in any of the outcome groups (death/transplant), separate or combined in univariate analyses. Only regional location showed a significant difference as discussed below.

4.3.1. Death

For each of the groups, the univariate Cox regression analyses are displayed on Table 4-7 and Table 4-8 for demographic variables and Table 4-9, Table 4-10, and Table 4-11 for clinical variables.

Idiopathic: In children with unknown etiology of DCM, the strongest univariate risk factor for death, when data were censored for transplantation, was if they presented with the symptoms of congestive heart failure (HR=2.35; 95%CI: 1.51 to 3.60). There appeared to be an association with death if the child was seen at a center in the Central Southwest region when compared to other sites (HR=1.55; 95%CI: 1.11 to 2.16), but

with decreased risk if seen in New England (HR=0.47; 95%CI: 0.25 to 0.88). There are also several other factors associated with decreased risk of death: increased height or weight for age (z-score) and increased fractional shortening or ejection fraction (z-score). Also the posterior wall thickness to end-diastolic dimension (PWEDD) ratio appears to be significant when either the second or third quartile is compared to the first quartile, such that a higher PWEDD ratio was protective (HR=0.579 and 0.568, respectively), however, a significant HR is not seen when the fourth quartile is compared to the first (HR=0.619, p=0.069).

IEM: The only factors that approached significant association with death were family history of either cardiomyopathy (HR=12.4; 95%CI: 1.34 to 113; P=0.026) or genetic syndromes (HR=16.93; 95%CI: 1.72 to 166; P=0.015), each with very unstable estimates.

NMD: Children with neuromuscular disease and DCM were the group to have the most echocardiographic parameters as prognostic factors. Increased septal (HR=0.69; 95%CI: 0.49 to 0.81) and posterior wall thickness (HR=0.63; 95%CI: 0.57 to 0.86) z-scores, as well as fractional shortening z-score (HR=0.78; 95%CI: 0.70 to 0.86) were associated with decreased risk, while increased end-diastolic (HR=1.48; 95%CI: 1.21 to 1.82) and end-systolic (HR=1.5; 95%CI: 1.26 to 1.79) dimension z-score were associated with increased risk of death. Additionally, presence of CHF at diagnosis was associated with increased risk (HR=4.15; 95%CI: 2.32 to 7.4). Also the posterior wall thickness to end-diastolic dimension (PWEDD) ratio appears to significant across when each of three upper quartiles was compared to the first quartile, such that a higher PWEDD ratio was

protective as seen in the incremental benefits to the risk of death (q4 vs q1: HR=0.037; p=0.0017).

FDCM: In this group, there were no statistically significant univariate predictors of death. The only factors that approached significance are weight-for-height z-score (HR=0.25; p=0.054) and end-diastolic dimension z-score (HR=1.46; p=0.065)

Myocarditis: The only univariate predictor associated with increased risk of death for children with myocarditis that approached the P value cutoff was height for age z-score (HR=3.5; 95%CI: 1.22 to 10.24; P=0.02).

4.3.2. Transplant

Overall, in a model comparing each group to idiopathic cases, the risk of transplant is significantly lower for those with myocarditis (HR=0.62; p=0.002) as well as those with neuromuscular disease (HR=0.19 p<0.001) and IEM (HR=0.29; p=0.01). For each of the groups, the univariate Cox regression analyses are displayed on Table 4-12 and for demographic variables and Table 4-14, Table 4-15, and Table 4-16 for clinical variables.

Idiopathic: In children with idiopathic DCM at the time of presentation, some of the same factors associated with death remained. Increased fractional shortening or ejection fraction z-score was still associated with decreased risk (HR=0.71); in addition, other echocardiographic parameters became statistically significant predictors of increased risk of death, namely, increased EDD (HR=1.19), ESD (HR=1.21), and LV Mass (HR=1.14) z-scores (all P<0.0001). Presence of CHF at diagnosis was also associated with increased risk of death (HR=3.59), as was older age, either when included as a linear increase in age (HR=1.04, P<0.0001) or categorically when tertiles

were compared to infants (<1 year) as the reference group. The regional differences with the transplant outcome were still observed (NE (HR=0.57) and CSW (HR=0.52) better than "Other"; both P<0.001), although there was no significant height or weight association with transplant.

IEM: There were no significant univariate baseline predictors of transplant from the data reviewed.

NMD: Fewer of the echocardiographic parameters were predictors of transplant as an outcome: increased EDD (HR=4.48, P<0.001) and LV Mass (HR=1.63, P=0.007) z-score were associated with increased risk of transplant, while increased FS z-score was associated with decreased risk (HR=0.65, P<0.001). Family history of arrhythmia appeared to be associated with increased transplant risk (HR=9.65; 95%CI: 1.61 to 58.12). No demographic variables were significantly associated with transplant.

FDCM: Increased FS (HR=0.81, P=0.002) or EF (HR=0.53, P=0.003) z-score were associated with decreased transplant risk, while increased EDD (HR=1.27, P=0.008) and ESD (HR=1.27, P=0.007) z-scores were associated with increased risk. Presence of CHF at diagnosis was also associated with increased risk of death (HR=6.35; 95%CI: 2.19 to 18.41). No demographic variables were significantly associated with transplant.

Myocarditis: Older age appeared to be a factor associated with increased risk of transplant, either when included as a linear increase in age (HR=1.08, P=0.001) or categorically when tertiles were compared to infants (<1 year) as the reference group, specifically with the 12-18 year old group at greatest risk. Presence of CHF at diagnosis

approached significance (HR=11.41; 95%CI: 1.57 to 82; P=0.016), as did EDD z-score (HR=1.18; 95%CI: 1.02 to 1.37; P=0.029).

4.3.3. Composite Endpoint: Death or Transplant

Overall, in a model comparing each of the etiological group to idiopathic cases as the reference group, the risk of death or transplant was significantly lower for those with myocarditis (HR=0.62; p=0.0002). Those with neuromuscular disease also had a lower risk, but it did not reach statistical significance (HR=0.77; p=0.06). For each of the groups, the univariate Cox regression analyses are displayed on Table 4-17 and Table 4-18 for demographic variables and Table 4-19, Table 4-20, and Table 4-21 for clinical variables.

Idiopathic: As seen in the separate univariate analyses, the predictors of risk for the composite endpoint were reflected in the predictors for transplant. There was increased risk with the presence of CHF at diagnosis (HR=3.05, P<0.0001), older age (linear (HR=1.03, P<0.0001) or categorically (all P<0.001)), and increased EDD (HR=1.12, P<0.0001), ESD (HR=1.15, P<0.0001), or LV Mass (HR=1.07, P<0.001) z-scores. Decreased risk was seen with increased fractional shortening (HR=0.89) or ejection fraction (HR=0.75) z-score (both P<0.0001), as well as an association with regional differences where NE was better than "Other" (HR=0.56, P<0.001).

IEM: Identical to the predictors of death, the only factors associated that approached significance with death or transplant were family history of either cardiomyopathy (HR=5.38; 95%CI: 1.27 to 22.87; P=0.023) or genetic syndromes (HR=8.6; 95%CI: 1.41 to 52.49; P=0.02).

NMD: Also identical to the predictors of death, the factors associated with decreased risk death or transplant are increased septal (HR=0.65) and posterior wall (HR=0.75) thickness z-scores, as well as FS z-score (HR=0.75), while increased EDD (HR=1.71) or ESD (HR=1.68) z-scores or presence of CHF at diagnosis (HR=3.79) were associated with increased risk (all P<0.0001, except posterior wall: P<0.001). Additionally, there was a regional difference observed similar to that in the idiopathic group that approached significance, where the NE region had a decreased risk when compared to "Other" (HR=0.41, P=0.03).

FDCM: This group had the identical risk factors for the composite as it did for the transplant outcome: the presence of CHF at diagnosis was associated with an increased risk (HR=6.38, P<0.001). Echocardiographically, increased FS (HR=0.79, P<0.001) or EF (HR=0.53, P=0.003) z-score was associated with decreased transplant risk, while increased EDD or ESD z-scores was associated with increased risk (both HR=1.3, P=0.001). Additionally, increased LV Mass z-score approached significance (HR=1.21, P=0.048).

Myocarditis: This group had three of the same risk factors for the composite as it did for the transplant outcome: Older age at diagnosis approached significance with increased risk of transplant, either when included as a linear annual increase in age (HR=1.05, P=0.014) or categorically when the top tertile (12 to <18 years) was compared to infants (<1 year) as the reference group (HR=1.97, P=0.043). The presence of CHF at diagnosis was also associated with an increased risk of death (HR=5.52, P=0.004). However, increased EF z-score approached significance of decreased risk (HR=0.76, P=0.025).

Table 4-7: Univariate Demographic Predictors of Death, with Transplant Censored

	Idiopathic				IEM			
	HR	95% CI		P	HR	95% CI		P
Male vs Female	0.97	0.71	1.32	0.82	1.02	0.21	4.81	0.99
Age at diagnosis								
1 to <18 vs < 1	1.35	0.99	1.85	0.06	0.82	0.24	2.84	0.75
Per Year	1.02	0.99	1.04	0.19	1.02	0.89	1.16	0.83
1 to < 6 vs < 1	1.26	0.84	1.89	0.27	0.69	0.17	2.92	0.62
6 to <12 vs < 1	1.45	0.91	2.31	0.12	0.92	0.10	8.07	0.94
12 to <18 vs <1	1.39	0.92	2.11	0.12	1.40	0.16	12.10	0.76
Height for Age Z-score, per SD	**0.81**	**0.71**	**0.92**	**0.001**	0.97	0.52	1.81	0.93
Weight for Age Z-score, per SD	**0.86**	**0.75**	**0.98**	**0.027**	1.33	0.80	2.23	0.27
Weight for Height Z-score, per SD	0.82	0.62	1.08	0.16	2.12	0.71	6.34	0.18
Race vs White								
Black	1.30	0.89	1.88	0.17	.	.	.	.
Hispanic	0.87	0.55	1.38	0.57	1.54	0.38	6.22	0.54
Other	0.95	0.48	1.89	0.89	1.05	0.13	8.80	0.97
Region vs Other								
Central Southwest	**1.55**	**1.11**	**2.16**	**0.011**	3.67	0.74	18.29	0.11
New England	**0.47**	**0.25**	**0.88**	**0.019**	2.19	0.49	9.88	0.31
Retrospective vs Prospective Cohort	1.31	0.94	1.82	0.11	0.47	0.10	2.26	0.35

IEM: Inborn Errors of Metabolism, SD: Standard Deviation

Table 4-8: Univariate Demographic Predictors of Death, with Transplant Censored, Continued

	NMD				FDCM				Myocarditis			
	HR	95% CI		P	HR	95% CI		P	HR	95% CI		P
e	1.67	0.23	12.19	0.61	1.21	0.27	5.42	0.81	0.80	0.35	1.83	0.60
is												
1 to <18 vs < 1					1.20	0.23	6.20	0.83	1.34	0.53	3.40	0.54
Per Year	0.95	0.85	1.07	0.44	1.04	0.92	1.18	0.55	0.99	0.92	1.07	0.87
1 to < 6 vs < 1	.	.	.	.	.	.	.	.	1.48	0.54	4.08	0.45
6 to <12 vs < 1	1.06	0.50	2.28	0.87	2.13	0.39	11.67	0.38	1.64	0.46	5.82	0.45
12 to <18 vs <1	.	.	.	.	0.88	0.08	9.75	0.91	0.85	0.21	3.43	0.82
z-score, per SD	1.01	0.76	1.34	0.93	0.81	0.54	1.23	0.32	**3.54**	**1.22**	**10.24**	**0.02**
z-score, per SD	1.13	0.91	1.41	0.27	0.75	0.51	1.11	0.14	1.33	0.80	2.23	0.27
ght z-score, per SD	.	.	.	.	0.25	0.06	1.02	0.05	0.74	0.27	1.98	0.55
Black	1.79	0.88	3.67	0.11	3.07	0.56	16.85	0.20	1.60	0.64	3.98	0.31
Hispanic	1.04	0.37	2.95	0.95	0.40	0.08	6.29	0.75	1.14	0.36	3.58	0.82
Other	1.01	0.14	7.40	0.99	.	.	.	.	.	.	.	.
r												
Central Southwest	1.22	0.65	2.29	0.53	0.45	0.05	4.05	0.48	1.86	0.78	4.47	0.16
New England	0.44	0.18	1.08	0.07	1.32	0.24	7.27	0.75	0.41	0.09	1.91	0.26
s Prospective Cohort	1.40	0.77	2.55	0.27	3.59	0.69	18.54	0.13	1.22	0.51	2.92	0.65

NMD: Neuromuscular Disease, FDCM: Familial Isolated Dilated Cardiomyopathy, SD: Standard Deviation

Table 4-9: Univariate Clinical Predictors of Death, with Transplant Censored

	Idiopathic				IEM			
	HR	95% CI		P	HR	95% CI		P
CHF at Dx (present vs absent)	**2.35**	**1.53**	**3.60**	**<0.001**	1.04	0.29	3.72	0.95
Echocardiography z-score, per SD								
ED Dimension	1.02	0.96	1.09	0.53	0.88	0.64	1.21	0.44
ED Posterior Wall	0.97	0.89	1.05	0.44	0.81	0.51	1.27	0.36
ED Septum	0.96	0.86	1.07	0.48	0.78	0.48	1.26	0.31
ES Dimension	1.05	0.98	1.13	0.17	0.90	0.61	1.32	0.59
Fractional Shortening	**0.92**	**0.86**	**0.97**	**0.003**	0.99	0.80	1.22	0.90
LV Mass	1.01	0.94	1.08	0.81	0.78	0.53	1.16	0.22
Ejection Fraction	**0.83**	**0.70**	**0.98**	**0.024**	0.91	0.67	1.31	0.60
ED Post. Wall z-score, quartiles								
2 vs 1	0.78	0.45	1.34	0.37	1.15	0.16	8.26	0.89
3 vs 1	0.68	0.39	1.19	0.18	0.53	0.05	5.92	0.61
4 vs 1	0.77	0.44	1.32	0.34	0.41	0.04	4.53	0.47
ED Septum z-score, quartiles								
2 vs 1	0.78	0.45	1.35	0.37	0.50	0.03	8.53	0.63
3 vs 1	0.64	0.36	1.13	0.12	0.43	0.03	7.30	0.56
4 vs 1	0.71	0.41	1.25	0.24	.	.	.	.
Ratio of Posterior Wall to ED Dimension, quartiles								
2 vs 1	**0.58**	**0.34**	**0.98**	**0.041**	0.91	0.13	6.50	0.93
3 vs 1	**0.57**	**0.33**	**0.97**	**0.036**	0.45	0.04	4.97	0.45
4 vs 1	0.62	0.37	1.04	0.07	0.48	0.04	5.37	0.55
Familial History at Dx, present vs absent								
Any Family History	1.05	0.68	1.64	0.82	2.60	0.29	23.38	0.39
Cardiomyopathy	0.85	0.46	1.56	0.60	**12.40**	**1.36**	**113.4**	**0.026**
Sudden Death	1.69	0.92	3.11	0.09	2.00	0.28	14.20	0.49
Congenital Heart Dz	1.14	0.46	2.80	0.78	.	.	.	.
Arrhythmia	0.78	0.25	2.47	0.67	.	.	.	.
Genetic Syndrome	1.50	0.70	3.26	0.30	**16.93**	**1.72**	**166.8**	**0.015**

IEM: Inborn Errors of Metabolism, CHF: Congestive Heart Failure, Dx: Diagnosis, SD: Standard Deviation, ED: End-Diastolic, ES: End-Systolic, Dz: Disease

Table 4-10: Univariate Clinical Predictors of Death, with Transplant Censored, Continued

	HR	NMD 95% CI		P
CHF at Dx (present vs absent)	**4.15**	**2.32**	**7.40**	**<0.0001**
Echocardiography z-score, per SD				
ED Dimension	**1.48**	**1.21**	**1.82**	**<0.001**
ED Posterior Wall	**0.70**	**0.57**	**0.86**	**<0.001**
ED Septum	**0.63**	**0.49**	**0.81**	**<0.001**
ES Dimension	**1.50**	**1.26**	**1.79**	**<0.0001**
Fractional Shortening	**0.78**	**0.70**	**0.86**	**<0.0001**
LV Mass	1.06	0.84	1.32	0.66
Ejection Fraction	0.84	0.53	1.33	0.46
ED Post. Wall z-score, quartiles				
2 vs 1	0.45	0.17	1.22	0.12
3 vs 1	**0.16**	**0.04**	**0.62**	**0.008**
4 vs 1	0.37	0.11	1.22	0.10
ED Septum z-score, quartiles				
2 vs 1	0.78	0.31	1.94	0.59
3 vs 1	0.33	0.10	1.07	0.06
4 vs 1	**0.09**	**0.01**	**0.69**	**0.021**
Ratio of Posterior Wall to ED Dimension, quartiles				
2 vs 1	**0.32**	**0.13**	**0.76**	**0.01**
3 vs 1	**0.22**	**0.08**	**0.61**	**0.003**
4 vs 1	**0.04**	**0.01**	**0.29**	**0.002**
Familial History at Dx, present vs absent				
Any Family History	0.55	0.27	1.16	0.12
Cardiomyopathy	0.38	0.13	1.11	0.08
Sudden Death	1.93	0.45	8.30	0.38
Congenital Heart Dz	.	.	.	.
Arrhythmia	1.28	0.17	9.67	0.81
Genetic Syndrome	0.54	0.26	1.12	0.10

NMD: Neuromuscular Disease, CHF: Congestive Heart Failure, Dx: Diagnosis, SD: Standard Deviation, ED: End-Diastolic, ES: End-Systolic, Dz: Disease

Table 4-11: Univariate Clinical Predictors of Death, with Transplant Censored

	FDCM				Myocarditis			
	HR	95%CI		P	HR	95%CI		P
CHF at Dx (present vs absent)	6.50	0.78	54.07	0.08	2.46	0.58	10.53	0.23
Echo Z-score, per SD								
ED Dimension	1.46	1.00	2.18	0.06	1.02	0.84	1.23	0.87
ED Posterior Wall	1.21	0.68	2.15	0.53	1.05	0.83	1.34	0.68
ED Septum	0.48	0.11	2.04	0.32	1.29	0.94	1.77	0.11
ES Dimension	1.49	0.96	2.30	0.08	1.03	0.84	1.25	0.80
Fractional Shortening	0.72	0.50	1.06	0.10	0.93	0.81	1.07	0.29
LV Mass	1.28	0.81	2.02	0.30	1.10	0.87	1.38	0.43
Ejection Fraction	.	.	.	.	0.53	0.25	1.10	0.09
ED Post. Wall z-score, quartiles								
2 vs 1	.	.	.	.	0.58	0.10	3.52	0.56
3 vs 1	0.97	0.06	15.48	0.98	1.21	0.27	5.43	0.81
4 vs 1	0.93	0.06	15.13	0.96	1.12	0.25	5.04	0.89
ED Septum z-score, quartiles								
2 vs 1	.	.	.	.	0.27	0.03	2.63	0.26
3 vs 1	.	.	.	.	0.35	0.04	3.35	0.36
4 vs 1	.	.	.	.	1.46	0.34	6.22	0.61
Ratio of Posterior Wall to ED Dimension, quartiles								
2 vs 1	.	.	.	.	0.15	0.02	1.17	0.07
3 vs 1	0.50	0.05	5.50	0.57	0.59	0.16	2.10	0.41
4 vs 1	0.45	0.04	5.05	0.52	0.58	0.16	2.06	0.58
Familial History at Dx, present vs absent								
Any Family History	.	.	.	.	1.17	0.40	3.49	0.77
Cardiomyopathy	.	.	.	.	2.01	0.54	7.50	0.30
Sudden Death	0.37	0.07	2.05	0.25	0.74	0.10	5.64	0.77
Congenital Heart Dz	.	.	.	.	1.56	0.20	12.08	0.67
Arrhythmia	.	.	.	.	.	.	.	.
Genetic Syndrome	.	.	.	.	.	.	.	.

FDCM: Familial Isolated Dilated Cardiomyopathy, CHF: Congestive Heart Failure, Dx: Diagnosis, SD: Standard Deviation, ED: End-Diastolic, ES: End-Systolic, Dz: Disease

Table 4-12: Univariate Demographic Predictors of Transplant, with Death Censored

		Idiopathic				IEM			
		HR	95% CI		P	HR	95% CI		P
Male vs Female		1.22	0.98	1.52	0.07	0.27	0.04	1.91	0.19
Age at diagnosis									
	1 to <18 vs < 1	**1.42**	**1.14**	**1.77**	**0.002**	2.46	0.26	23.65	0.44
	Per Year	**1.04**	**1.02**	**1.06**	**<.0001**	1.11	0.95	1.30	0.18
	1 to < 6 vs < 1	0.95	0.68	1.31	0.75	1.18	0.07	18.86	0.91
	6 to <12 vs < 1	**2.04**	**1.52**	**2.74**	**<.0001**	5.96	0.37	95.69	0.21
	12 to <18 vs <1	**1.53**	**1.15**	**2.03**	**0.004**	4.89	0.31	78.31	0.26
Height for Age Z-score, per SD		1.019	1.02	0.92	1.13	0.71	2.04	0.46	9.10
Weight for Age Z-score, per SD		1.036	1.04	0.95	1.13	0.42	1.25	0.56	2.76
Weight for Height Z-score, per SD		1.125	1.13	0.96	1.32	0.15	0.23	0.00	25.09
Race versus white									
	Black	1.05	0.80	1.38	0.70	.	.	.	.
	Hispanic	**0.71**	**0.51**	**0.99**	**0.044**	.	.	.	.
	Other	1.01	0.65	1.59	0.95	.	.	.	.
Region vs Other									
	Central Southwest	**0.52**	**0.38**	**0.71**	**<.0001**	3.29	0.21	52.56	0.40
	New England	**0.60**	**0.42**	**0.84**	**0.004**	3.37	0.31	37.18	0.32
Retrospective vs Prospective Cohort		0.951	0.95	0.74	1.22	0.69	0.75	0.08	7.26

IEM: Inborn Errors of Metabolism, SD: Standard Deviation

Table 4-13: Univariate Demographic Predictors of Transplant, with Death Censored, Continued

	NMD				FDCM				Myocarditis			
	HR	95% CI		P	HR	95% CI		P	HR	95% CI		P
Male vs Female	0.31	0.04	2.45	0.26	1.48	0.69	3.19	0.31	1.15	0.64	2.05	0.64
Age at diagnosis												
1 to <18 vs < 1	.	.	.	.	1.12	0.49	2.56	0.79	1.78	0.88	3.59	0.11
Per Year	0.90	0.68	1.18	0.43	1.04	0.97	1.10	0.28	**1.08**	**1.03**	**1.13**	**0.001**
1 to < 6 vs < 1	.	.	.	.	1.05	0.34	3.20	0.94	1.01	0.43	2.38	0.98
6 to <12 vs < 1	1.44	0.30	6.92	0.65	0.55	0.17	1.82	0.33	2.42	0.98	5.69	0.05
12 to <18 vs <1	.	.	.	.	2.06	0.80	5.28	0.13	**2.87**	**1.30**	**6.33**	**0.01**
Height for Age Z-score, per SD	1.36	0.75	2.48	0.31	1.20	0.79	1.82	0.39	0.83	0.65	1.08	0.16
Weight for Age Z-score, per SD	0.86	0.61	1.22	0.39	1.09	0.80	1.49	0.58	0.79	0.59	1.07	0.13
Weight for Height Z-score, per SD	.	.	.	.	1.05	0.63	1.74	0.85	0.89	0.52	1.53	0.67
Race versus white												
Black	0.62	0.08	4.97	0.65	2.22	0.78	6.29	0.13	0.63	0.29	1.38	0.25
Hispanic	.	.	.	.	1.34	0.51	3.53	0.56	0.65	0.27	1.57	0.34
Other	.	.	.	.	1.60	0.45	5.63	0.47	2.06	0.72	5.87	0.18
Region vs Other												
Central Southwest	0.30	0.04	2.40	0.25	0.56	0.20	1.52	0.25	0.54	0.26	1.12	0.10
New England	0.29	0.04	2.38	0.25	0.88	0.35	2.25	0.79	0.58	0.27	1.24	0.16
Retrospective vs Prospective Cohort	2.30	0.62	8.56	0.22	1.22	0.57	2.61	0.61	0.87	0.47	1.61	0.65

NMD: Neuromuscular Disease, FDCM: Familial Isolated Dilated Cardiomyopathy, SD: Standard Deviation

Table 4-14: Univariate Clinical Predictors of Transplant, with Death Censored

	Idiopathic				IEM			
	HR	LL	UL	p	HR	LL	UL	p
CHF at Dx (present vs absent)	**3.59**	**2.53**	**5.01**	**<0.0001**	2.39	0.25	23.03	0.45
Echo Z-score, per SD								
ED Dimension	**1.19**	**1.13**	**1.25**	**<0.0001**	0.88	0.45	1.75	0.72
ED Posterior Wall	1.11	0.95	1.09	0.583	1.18	0.54	2.58	0.67
ED Septum	0.98	0.89	1.07	0.658	0.93	0.35	2.49	0.88
ES Dimension	**1.21**	**1.14**	**1.28**	**<0.0001**	0.59	0.21	1.67	0.32
Fractional Shortening	**0.88**	**0.84**	**0.92**	**<0.0001**	0.91	0.66	1.27	0.59
LV Mass	**1.14**	**1.07**	**1.21**	**<0.0001**	0.97	0.47	1.98	0.93
Ejection Fraction	**0.71**	**0.63**	**0.81**	**<0.0001**	1.06	0.62	1.79	0.84
ED Post. Wall z-score, quartiles								
2 vs 1	1.19	0.77	1.84	0.44	.	.	.	.
3 vs 1	1.19	0.78	1.83	0.42	.	.	.	.
4 vs 1	1.30	0.85	1.99	0.23	.	.	.	.
ED Septum z-score, quartiles								
2 vs 1	0.93	0.59	1.47	0.77	.	.	.	.
3 vs 1	0.94	0.60	1.47	0.78	.	.	.	.
4 vs 1	0.99	0.63	1.54	0.96	.	.	.	.
Ratio of Posterior Wall to ED Dimension, quartiles								
2 vs 1	**0.59**	**0.41**	**0.86**	**0.006**	.	.	.	.
3 vs 1	**0.54**	**0.36**	**0.80**	**0.002**	.	.	.	.
4 vs 1	**0.40**	**0.26**	**0.61**	**<0.0001**	.	.	.	.
Familial History at Dx, present vs absent								
Any Family History	0.94	0.70	1.26	0.68	.	.	.	.
Cardiomyopathy	1.05	0.73	1.51	0.80	1.77	0.16	19.66	0.64
Sudden Death	1.05	0.66	1.66	0.84	.	.	.	.
Congenital Heart Dz	0.96	0.54	1.72	0.89	.	.	.	.
Arrhythmia	0.58	0.26	1.31	0.19	.	.	.	.
Genetic Syndrome	0.70	0.35	1.42	0.32	.	.	.	.

IEM: Inborn Errors of Metabolism, CHF: Congestive Heart Failure, Dx: Diagnosis, SD: Standard Deviation, ED: End-Diastolic, ES: End-Systolic, Dz: Disease

Table 4-15: Univariate Clinical Predictors of Transplant, with Death Censored , Continued

	NMD				FDCM			
	HR	95% CI		P	HR	95% CI		P
CHF at Dx (present vs absent)	2.41	0.65	8.97	0.19	**6.35**	**2.19**	**18.41**	**0.0007**
Echo Z-score, per SD								
ED Dimension	**4.48**	**2.04**	**9.85**	**0.0002**	**1.27**	**1.06**	**1.51**	**0.008**
ED Posterior Wall	0.88	0.63	1.23	0.44	1.14	0.86	1.50	0.3619
ED Septum	0.72	0.46	1.11	0.13	1.08	0.79	1.46	0.6344
ES Dimension	**2.79**	**1.65**	**4.73**	**0.0001**	**1.27**	**1.07**	**1.50**	**0.007**
Fractional Shortening	**0.65**	**0.51**	**0.83**	**0.0006**	**0.81**	**0.70**	**0.93**	**0.002**
LV Mass	**1.63**	**1.14**	**2.31**	**0.007**	1.20	0.97	1.48	0.09
Ejection Fraction	0.37	0.04	3.31	0.37	**0.53**	**0.35**	**0.80**	**0.003**
ED Post. Wall z-score, quartiles								
2 vs 1	0.55	0.09	3.31	0.52	0.69	0.12	4.12	0.68
3 vs 1	0.28	0.03	2.65	0.26	1.66	0.39	7.00	0.49
4 vs 1	0.68	0.11	4.04	0.67	1.35	0.31	5.79	0.69
ED Septum z-score, quartiles								
2 vs 1	0.91	0.13	6.40	0.92	0.72	0.12	4.32	0.72
3 vs 1	0.45	0.04	4.94	0.51	2.67	0.67	10.67	0.16
4 vs 1	0.87	0.12	6.20	0.89	0.94	0.19	4.66	0.94
Ratio of Posterior Wall to ED Dimension, quartiles								
2 vs 1	**0.10**	**0.01**	**0.81**	**0.031**	0.59	0.16	2.25	0.45
3 vs 1	**0.10**	**0.01**	**0.83**	**0.033**	0.61	0.15	2.56	0.50
4 vs 1	**4.48**	**2.04**	**9.85**	**0.0002**	0.60	0.15	2.35	0.47
Familial History at Dx, present vs absent								
Any Family History	1.00	0.18	6.00	0.90	.	.	.	.
Cardiomyopathy	1.50	0.27	8.20	0.64	.	.	.	.
Sudden Death	2.81	0.34	23.40	0.34	0.86	0.40	1.87	0.71
Congenital Heart Dz	.	.	.	.	1.21	0.35	4.20	0.77
Arrhythmia	**9.68**	**1.61**	**58.12**	**0.013**	.	.	.	.
Genetic Syndrome	1.13	0.23	5.59	0.88	1.03	0.24	4.45	0.97

NMD: Neuromuscular Disease, FDCM: Familial Isolated Dilated Cardiomyopathy, CHF: Congestive Heart Failure, Dx: Diagnosis, SD: Standard Deviation, ED: End-Diastolic,
ES: End-Systolic, Dz: Disease

Table 4-16: Univariate Clinical Predictors of Transplant, with Death Censored, Continued

	Myocarditis			
	HR	LL	UL	p
CHF at Dx (present vs absent)	**11.41**	**1.57**	**82.80**	**0.016**
Echo Z-score, per SD				
ED Dimension	**1.18**	**1.02**	**1.37**	**0.029**
ED Posterior Wall	0.92	0.77	1.11	0.38
ED Septum	0.86	0.65	1.14	0.31
ES Dimension	1.16	0.99	1.35	0.06
Fractional Shortening	0.95	0.86	1.05	0.29
LV Mass	1.11	0.93	1.32	0.27
Ejection Fraction	0.81	0.63	1.05	0.11
ED Post. Wall z-score, quartiles				
2 vs 1	0.66	0.22	2.02	0.47
3 vs 1	1.09	0.41	2.91	0.86
4 vs 1	0.58	0.19	1.79	0.35
ED Septum z-score, quartiles				
2 vs 1	0.53	0.17	1.64	0.27
3 vs 1	0.44	0.12	1.67	0.23
4 vs 1	0.35	0.09	1.31	0.12
Ratio of Posterior Wall to ED Dimension, quartiles				
2 vs 1	0.93	0.37	2.34	0.87
3 vs 1	0.68	0.24	1.91	0.46
4 vs 1	0.22	0.05	1.01	0.05
Familial History at Dx, present vs absent				
Any Family History	0.78	0.28	2.13	0.63
Cardiomyopathy	0.78	0.18	3.32	0.73
Sudden Death	1.29	0.39	4.30	0.68
Congenital Heart Dz	0.92	0.13	6.85	0.93
Arrhythmia	.	.	.	.
Genetic Syndrome	0.61	0.08	4.53	0.63

CHF: Congestive Heart Failure, Dx: Diagnosis, SD: Standard Deviation, ED: End-Diastolic, ES: End-Systolic, Dz: Disease

Table 4-17: Univariate Demographic Predictors of Composite Endpoint (Death/Cardiac Transplant) at Baseline by Etiology

	Idiopathic				IEM			
	HR	95% CI		P	HR	95% CI		P
Male vs Female	1.13	0.95	1.35	0.18	0.64	0.20	2.06	0.46
Age at diagnosis								
1 to <18 vs < 1	**1.40**	**1.17**	**1.67**	**0.0003**	1.09	0.38	3.16	0.87
Per Year	**1.03**	**1.02**	**1.05**	**<0.0001**	1.05	0.95	1.16	0.33
1 to < 6 vs < 1	1.06	0.82	1.36	0.67	0.78	0.22	2.76	0.70
6 to <12 vs < 1	**1.84**	**1.44**	**2.36**	**<0.0001**	1.65	0.33	8.34	0.21
12 to <18 vs <1	**1.48**	**1.17**	**1.88**	**0.0013**	2.08	0.42	10.36	0.37
Height for Age Z-score, per SD	0.94	0.87	1.02	0.15	1.14	0.65	1.98	0.66
Weight for Age Z-score, per SD	0.98	0.91	1.06	0.60	1.31	0.85	2.01	0.22
Weight for Height Z-score, per SD	1.04	0.90	1.19	0.60	1.41	0.57	3.53	0.46
Race versus white								
Black	1.12	0.90	1.40	0.30	.	.	.	.
Hispanic	**0.76**	**0.58**	**0.99**	**0.043**	0.92	0.25	3.36	0.90
Other	0.99	0.68	1.44	0.96	0.65	0.08	5.10	0.68
Region vs Other								
Central Southwest	0.81	0.65	1.01	0.06	3.55	0.89	14.26	0.07
New England	**0.56**	**0.41**	**0.76**	**0.0002**	2.48	0.70	8.86	0.16
Retrospective vs Prospective Cohort	1.06	0.87	1.29	0.56	0.54	0.15	1.96	0.35

IEM: Inborn Errors of Metabolism, SD: Standard Deviation

Table 4-18: Univariate Demographic Predictors of Composite Endpoint (Death/Cardiac Transplant) at Baseline by Etiology, Continued

	NMD				FDCM				Myocarditis			
	HR	95% CI		P	HR	95% CI		P	HR	95% CI		P
Male vs Female	0.99	0.24	4.07	0.99	1.42	0.72	2.81	0.31	0.99	0.62	1.58	0.96
Age at diagnosis												
1 to <18 vs < 1	.	.	.	.	1.14	0.54	2.38	0.74	1.52	0.88	2.62	0.13
Per Year	0.95	0.85	1.05	0.31	1.04	0.98	1.10	0.22	**1.05**	**1.01**	**1.09**	**0.014**
1 to < 6 vs < 1	.	.	.	.	0.85	0.29	2.48	0.76	1.12	0.59	2.13	0.72
6 to <12 vs < 1	1.12	0.57	2.23	0.74	0.87	0.34	2.21	0.77	2.00	0.97	4.11	0.06
12 to <18 vs <1	.	.	.	.	1.83	0.77	4.36	0.17	**1.97**	**1.02**	**3.80**	**0.043**
Height for Age Z-score, per SD	1.08	0.84	1.39	0.56	1.06	0.79	1.43	0.71	0.96	0.76	1.22	0.74
Weight for Age Z-score, per SD	1.05	0.88	1.26	0.59	0.97	0.76	1.25	0.83	0.91	0.71	1.17	0.47
Weight for Height Z-score, per SD	.	.	.	.	0.77	0.47	1.26	0.30	0.83	0.52	1.31	0.42
Race versus white												
Black	1.54	0.79	3.01	0.21	2.41	0.99	5.85	0.05	0.90	0.50	1.62	0.73
Hispanic	0.80	0.28	2.23	0.67	1.19	0.49	2.87	0.71	0.79	0.94	1.58	0.50
Other	0.81	0.11	5.86	0.83	1.23	0.36	4.20	0.74	1.81	0.71	4.61	0.21
Region vs Other												
Central Southwest	1.03	0.57	1.85	0.93	0.54	0.22	1.33	0.18	0.88	0.52	1.50	0.63
New England	**0.41**	**0.18**	**0.93**	**0.033**	0.96	0.43	2.18	0.93	0.59	0.31	1.14	0.12
Retrospective vs Prospective Cohort	1.52	0.88	2.62	0.13	1.50	0.77	2.95	0.24	1.01	0.62	1.67	0.96

NMD: Neuromuscular Disease, FDCM: Familial Isolated Dilated Cardiomyopathy, SD: Standard Deviation

Table 4-19: Univariate Clinical Predictors of Composite Endpoint (Death/Cardiac Transplant) at Baseline by Etiology

	Idiopathic				IEM			
	HR	95% CI		P	HR	95% CI		P
CHF at Dx (present vs absent)	**3.06**	**2.33**	**4.01**	**<0.0001**	1.30	0.44	3.91	0.64
Echo Z-score, per SD								
ED Dimension	**1.12**	**1.08**	**1.17**	**<0.0001**	0.88	0.66	1.18	0.40
ED Posterior Wall	1.00	0.95	1.06	0.91	0.89	0.61	1.31	0.54
ED Septum	0.97	0.90	1.05	0.47	0.81	0.53	1.24	0.33
ES Dimension	**1.15**	**1.10**	**1.20**	**<0.0001**	0.85	0.60	1.22	0.38
Fractional Shortening	**0.89**	**0.86**	**0.93**	**<0.0001**	0.96	0.80	1.15	0.68
LV Mass	**1.07**	**1.05**	**1.15**	**0.0002**	0.82	0.59	1.15	0.26
Ejection Fraction	**0.75**	**0.68**	**0.83**	**<0.0001**	0.95	0.71	1.27	0.73
ED Post. Wall z-score, quartiles								
2 vs 1	**1.00**	**0.72**	**1.41**	**0.98**	**1.05**	**0.15**	**7.57**	**0.96**
3 vs 1	**0.97**	**0.69**	**1.35**	**0.84**	**1.55**	**0.26**	**9.36**	**0.64**
4 vs 1	**1.08**	**0.78**	**1.51**	**0.64**	**0.40**	**0.03**	**4.42**	**0.45**
ED Septum z-score, quartiles								
2 vs 1	0.88	0.62	1.25	0.48	0.51	0.03	8.50	0.64
3 vs 1	0.81	0.57	1.15	0.24	0.82	0.07	9.50	0.87
4 vs 1	0.88	0.62	1.24	0.46	.	.	.	.
Ratio of Posterior Wall to ED Dimension, quartiles								
2 vs 1	**0.58**	**0.43**	**0.79**	**0.0005**	1.33	0.22	7.99	0.75
3 vs 1	**0.55**	**0.40**	**0.75**	**0.0002**	0.48	0.04	5.25	0.54
4 vs 1	**0.47**	**0.34**	**0.65**	**<0.0001**	1.39	0.23	8.36	0.72
Familial History at Dx, present vs absent								
Any Family History	0.97	0.76	1.24	0.82	1.85	0.36	9.63	0.46
Cardiomyopathy	0.99	0.72	1.35	0.95	**5.38**	**1.27**	**22.87**	**0.023**
Sudden Death	1.22	0.85	1.76	0.28	1.08	0.20	5.91	0.93
Congenital Heart Dz	1.01	0.62	1.64	0.98	.	.	.	.
Arrhythmia	0.64	0.33	1.24	0.64	.	.	.	.
Genetic Syndrome	0.93	0.55	1.57	0.79	**8.60**	**1.41**	**52.49**	**0.02**

IEM: Inborn Errors of Metabolism, CHF: Congestive Heart Failure, Dx: Diagnosis, SD: Standard Deviation, ED: End-Diastolic, ES: End-Systolic, Dz: Disease

Table 4-20: Univariate Clinical Predictors of Composite Endpoint (Death/Cardiac Transplant) at Baseline by Etiology, Continued

	NMD			
	HR	95% CI		P
CHF at Dx (present vs absent)	**3.79**	**2.33**	**6.45**	**<0.0001**
Echo Z-score, per SD				
ED Dimension	**1.71**	**1.41**	**2.06**	**<0.0001**
ED Posterior Wall	**0.75**	**0.63**	**0.89**	**0.001**
ED Septum	**0.65**	**0.53**	**0.81**	**<0.0001**
ES Dimension	**1.66**	**1.41**	**1.95**	**<0.0001**
Fractional Shortening	**0.75**	**0.69**	**0.83**	**<0.0001**
LV Mass	1.19	0.98	1.45	0.08
Ejection Fraction	0.80	0.51	1.23	0.30
ED Post. Wall z-score, quartiles				
2 vs 1	0.48	0.20	1.14	0.10
3 vs 1	**0.19**	**0.06**	**0.59**	**0.0043**
4 vs 1	0.44	0.17	1.19	0.11
ED Septum z-score, quartiles				
2 vs 1	0.81	0.35	1.84	0.61
3 vs 1	0.35	0.12	1.01	0.05
4 vs 1	**0.22**	**0.06**	**0.80**	**0.021**
Ratio of Posterior Wall to ED Dimension, quartiles				
2 vs 1	**0.25**	**0.12**	**0.54**	**0.0005**
3 vs 1	**0.18**	**0.07**	**0.44**	**0.0002**
4 vs 1	**0.03**	**0.00**	**0.20**	**0.0004**
Familial History at Dx, present vs absent				
Any Family History	0.61	0.31	1.21	0.16
Cardiomyopathy	0.52	0.21	1.26	0.15
Sudden Death	2.16	0.65	7.15	0.21
Congenital Heart Dz	.	.	.	.
Arrhythmia	2.97	0.87	10.09	0.08
Genetic Syndrome	0.61	0.31	1.18	0.14

NMD: Neuromuscular Disease, CHF: Congestive Heart Failure, Dx: Diagnosis, SD: Standard Deviation, ED: End-Diastolic, ES: End-Systolic, Dz: Disease

Table 4-21: Univariate Clinical Predictors of Composite Endpoint (Death/Cardiac Transplant) at Baseline by Etiology, Continued

	FDCM				Myocarditis			
	HR	95% CI		P	HR	95% CI		P
CHF at Dx (present vs absent)	**6.38**	**2.47**	**16.52**	**0.0001**	**5.52**	**1.74**	**17.56**	**0.004**
Echo Z-score, per SD								
ED Dimension	**1.30**	**1.11**	**1.52**	**0.001**	**1.13**	**1.01**	**1.27**	**0.037**
ED Posterior Wall	1.15	0.90	1.48	0.27	0.99	0.86	1.15	0.93
ED Septum	1.04	0.77	1.40	0.82	1.02	0.81	1.28	0.90
ES Dimension	**1.30**	**1.11**	**1.52**	**0.001**	1.12	1.00	1.27	0.06
Fractional Shortening	**0.79**	**0.70**	**0.91**	**0.001**	0.94	0.86	1.02	0.11
LV Mass	**1.21**	**1.00**	**1.47**	**0.048**	1.13	0.98	1.30	0.09
Ejection Fraction	**0.53**	**0.35**	**0.80**	**0.003**	**0.76**	**0.59**	**0.97**	**0.025**
End Dias Post Wall z, quartiles								
2 vs 1	0.50	0.09	2.73	0.42	0.63	0.24	1.63	0.34
3 vs 1	1.49	0.42	5.30	0.54	1.12	0.49	2.54	0.79
4 vs 1	1.24	0.34	4.49	0.74	0.82	0.35	1.94	0.65
ED Septum z-score, quartiles								
2 vs 1	0.53	0.10	2.90	0.47	0.46	0.17	1.25	0.13
3 vs 1	1.94	0.55	6.82	0.30	0.22	0.18	1.48	0.22
4 vs 1	0.69	0.16	3.12	0.63	0.66	0.27	1.66	0.38
Ratio of Posterior Wall to ED Dimension, quartiles								
2 vs 1	0.43	0.13	1.49	0.18	0.60	0.27	1.34	0.21
3 vs 1	0.58	0.17	1.99	0.39	0.64	0.29	1.45	0.29
4 vs 1	0.55	0.17	1.82	0.33	0.44	0.18	1.09	0.08
Familial History at Dx, present vs absent								
Any Family History	.	.	.	.	0.93	0.45	1.95	0.85
Cardiomyopathy	.	.	.	.	1.21	0.47	3.15	0.70
Sudden Death	0.74	0.37	1.49	0.39	1.09	0.39	3.05	0.87
Congenital Heart Dz	0.89	0.26	3.03	0.86	1.16	0.28	4.84	0.84
Arrhythmia	.	.	.	.	.	.	.	.
Genetic Syndrome	0.81	0.19	3.44	0.77	0.36	0.05	2.60	0.31

FDCM: Familial Isolated Dilated Cardiomyopathy, CHF: Congestive Heart Failure, Dx: Diagnosis, SD: Standard Deviation, ED: End-Diastolic, ES: End-Systolic, Dz: Disease

4.4. Multivariate Predictors of "Heart Death"

The results of a multivariate model utilizing the composite endpoint of the earlier of death or transplant, also termed "Heart Death" appear in Table 4-22 for the three largest groups (idiopathic, NMD, and Myocarditis). Each model was fit to include all significant univariate variables to achieve the best fit. The remaining three etiologic groups did not produce any multivariate models with two or more statistically significant predictors beyond their univariate regressions and, therefore, are not presented in this section.

Children with idiopathic disease when diagnosed over age 6 when compared to infants (6 to <12: HR=2.98; 12 to <18: HR=2.78), with congestive heart failure present (HR=3.01), and decreased FS z-score (HR=0.87) were at greatest risk for death or transplant (all P<0.0001).

In the myocarditis group, risk factors identified were older age (per year: HR=1.01, P<0.0001), CHF as presentation (HR=5.96, P=0.01), and increased EDD z-score (HR=1.20, P=0.005). Adjusting by whether the myocarditis was confirmed by biopsy versus diagnosed clinically does not appreciably affect the other factors nor is it independently statistically significant (HR=1.16, P=0.61).

For the children with NMD and DCM, decreased FS (HR=0.84, P=0.01) and increased EDD z-scores (HR=1.41, P=0.007) were independent predictors of heart death. Further adjustment for subtype of neuromuscular disease using three categories (Duchenne, Becker, and Other) did not appreciably affect the magnitude of the hazard ratios of the other predictors nor was the contrast by subtype of NMD independently predictive. Excluding the Other group and comparing the Duchenne to the Becker group

did not show a significant effect either (HR=0.53; p=0.22). Nevertheless, the results presented are adjusted for the three sub-groups.

Table 4-22: Multivariate Predictors of Death or Transplant by Etiology

Group	Factor	HR	95% CI		P
Idiopathic	Age at diagnosis				
n=959	1 to <6 vs. Infants (<1)	1.18	0.88	1.58	0.27
	6 to <12 vs. Infants (<1)	**2.98**	**2.21**	**4.01**	**<0.0001**
	12 to <18 vs. Infants (<1)	**2.78**	**2.06**	**3.75**	**<0.0001**
	Congestive Heart Failure at diagnosis (present vs. absent)	**3.01**	**2.18**	**4.17**	**<0.0001**
	Fractional Shortening z-score (per SD increase)	**0.87**	**0.84**	**0.91**	**<0.0001**
Neuromuscular Disease*					
n=98	ED Dimension z-score (per SD increase)	**1.41**	**1.1**	**1.81**	**0.007**
	Fractional Shortening z-score (per SD increase)	**0.84**	**0.73**	**0.96**	**0.01**
Myocarditis					
n=214	Congestive Heart Failure at diagnosis (present vs. absent)	**5.96**	**1.43**	**24.89**	**0.01**
	Age at diagnosis (per year increase)	**1.10**	**1.05**	**1.16**	**<0.0001**
	ED Dimension z-score (per SD increase)	**1.20**	**1.06**	**1.36**	**0.005**

*Adjusted for subgroup of NMD (Duchenne, Becker or Other)
ED: End-Diastolic

4.5. Sub-Group Analyses

Additional prognostic factors described in prior studies, for which the PCMR had substantial data were used for sub-group analyses separate from the main univariate and multivariate analyses due to the large number of missing data (50 to 90% for some variables). Due to the smaller sample sizes, all analyses were performed using the composite death/heart transplant outcome.

4.5.1. Mitral and Tricuspid Regurgitation

Data were available in the greatest proportion for the idiopathic (325, 27%) and neuromuscular disease (38, 27%) groups. For the idiopathic group, the presence of mitral regurgitation (MR) or tricuspid regurgitation (TR) as detected by echocardiography was each a significant predictor of increased risk in the univariate models for the composite endpoint of death or transplant (HR 1.9, 95%CI: 1.3 to 2.9; HR 1.6, 95%CI: 1.2 to 2.3; respectively). In order to detect a response by degree of severity, regurgitation was grouped into mild, moderate, and severe (as specified by the clinical center). A model comparing each category to absence of regurgitation was not significant. In order to see if there was a categorization less coarse than the dichotomous model, the reference group of normal mitral or tricuspid blood flow was compared to two different pairing strategies: first to a combined severe/moderate and to mild, and second to severe and combined moderate/mild. Both models were statistically significant, where the group that included the severe cases was just slightly worse than the group below it; however, with each group had HR estimates around 2 with overlapping 95% confidence intervals.

After adding each variable to the multivariate models for death/transplant, only MR remained as an independent predictor in the full model with the other predictors stable in value and statistically significant.

The effect size of MR for the neuromuscular group was larger (HR 3.4, 95%CI: 1.4 to 7.9) and TR (HR 4.9, 95%CI: 1.7 to 14.1), but the confidence intervals were much wider than for the idiopathic group. Constructing models of MR and TR grouped by severity revealed that the only significant model was for severe/moderate and mild versus normal mitral valve performance. Even then, the estimated HRs had substantially larger 95% confidence intervals. Neither MR nor TR added additional information to the final multivariate model for the composite endpoint.

4.5.2. Cardiac Catheterization

Two parameters measured during cardiac catheterization have been cited in the literature: left ventricular end-diastolic pressure (LVEDP) and cardiac index (CI). The idiopathic (127, 11%) and myocarditis (66, 25%) groups had the largest numbers of catheterizations performed. For the idiopathic group, there was a significant difference in the mean CI when comparing those who reached the heart death (P=0.016); independently the difference was not significant for either death or transplant. Univariate models for the combined endpoint using the previously described cutoff of 3 L/min/m^2 were not significant, while a model for the linear effect was significant (HR 0.53; P=0.0009). Mean LVEDP was significantly different when comparing heart death or transplant, but not death. Univariate models for the combined endpoint using the previously described cutoff of 25 mmHg were not significant (P=0.21). The cutoff of 18

mmHg produced a significant model (HR 1.92; P=0.016) as did a model for the linear effect (HR 1.06; P=0.012).

For the myocarditis group, there was a significant difference in mean CI when comparing those who reached heart death (P=0.04), but independently the difference was not significant for either death or transplant. Univariate models for the combined endpoint with a cutoff of 3 L/min/m^2 were not significant (P=0.13), and had an extremely large model parameter, as did the model for the linear effect (P=0.045). Mean LVEDP was not significantly different between outcome groups. Neither a univariate model for the combined endpoint using the cutoff of 25 mmHg was significant (P=0.37), nor was the model for the per mmHg increase (P=0.16).

4.5.3. Viral Serology

The assessment of viral infection at time of presentation is important in the diagnosis of myocarditis. At time of diagnosis, the two largest groups with viral serology performed were idiopathic (166, 14%) and myocarditis (69, 26%). Those with a positive result for any virus tested were at greater risk of heart death with a greater effect in the myocarditis group (HR 5.6; 95%CI: 2.5 to 12.2) than in the idiopathic group (HR 1.7; 95%CI: 1.1 to 2.7). In each group, when separate models are made for death or transplant, the HR for transplant was greater than death; and for the idiopathic group, the transplant outcome was significant, while for death it was not.

4.5.4. Electrocardiography

The results from electrocardiography (ECG) can be interpreted into various patterns as can each parameter by quantified and used for prognostication. The largest two groups with initial ECG were idiopathic (410, 33%) and myocarditis (130, 49%). In

the idiopathic group, the corrected QT interval (QTc) was not associated with any outcome, nor were any survival models significant either in linear form or dichotomized at a cutoff of 440 msec (considered the upper limit of normal). The increased duration of the QRS interval was associated with lower risk of transplant using the 80 msec cutoff (HR 0.69, P=0.007) and approached significance with a per msec increase (HR 1.01; P=0.029).

For the myocarditis group, QTc was not associated with any outcome nor were any survival models significant either in linear form or dichotomized at a cutoff of 440 msec. The QRS interval was associated with transplant in linear form (HR 1.02; p=0.009), but not for the 80 msec cutoff.

For both groups the deviation of the QRS axis into left, right, and intermediate directions were reviewed; there were no associations when tested individually or in various groupings when compared to those with normal QRS axis.

4.5.5. Holter Study

In the idiopathic group (111, 9%), Holter studies were reviewed to assess the association of various pathologic patterns with poor outcomes. The following had the most recorded responses and positive results: supraventricular tachycardia (18 of 90), ventricular tachycardia (31 of 77), and ventricular couplets (31 of 76). None of them showed an association with a poor outcome, nor where they significant in subsequent survival models.

4.6. Competing Risk Analysis: Event Probabilities

The results of the competing risk analysis are summarized below by etiologic group, first with the accompanied cumulative incidence competing risk (CICR) plots for each group, and then the risk factor analysis for the three largest groups.

4.6.1. Idiopathic

For children with idiopathic DCM (Figure 4-4), the majority of events are for cardiac transplant. By 2 years, 1/3 of idiopathic cases have received a transplant Similarly, the rate of death, by the end of the first year post-diagnosis was approximately 20%.

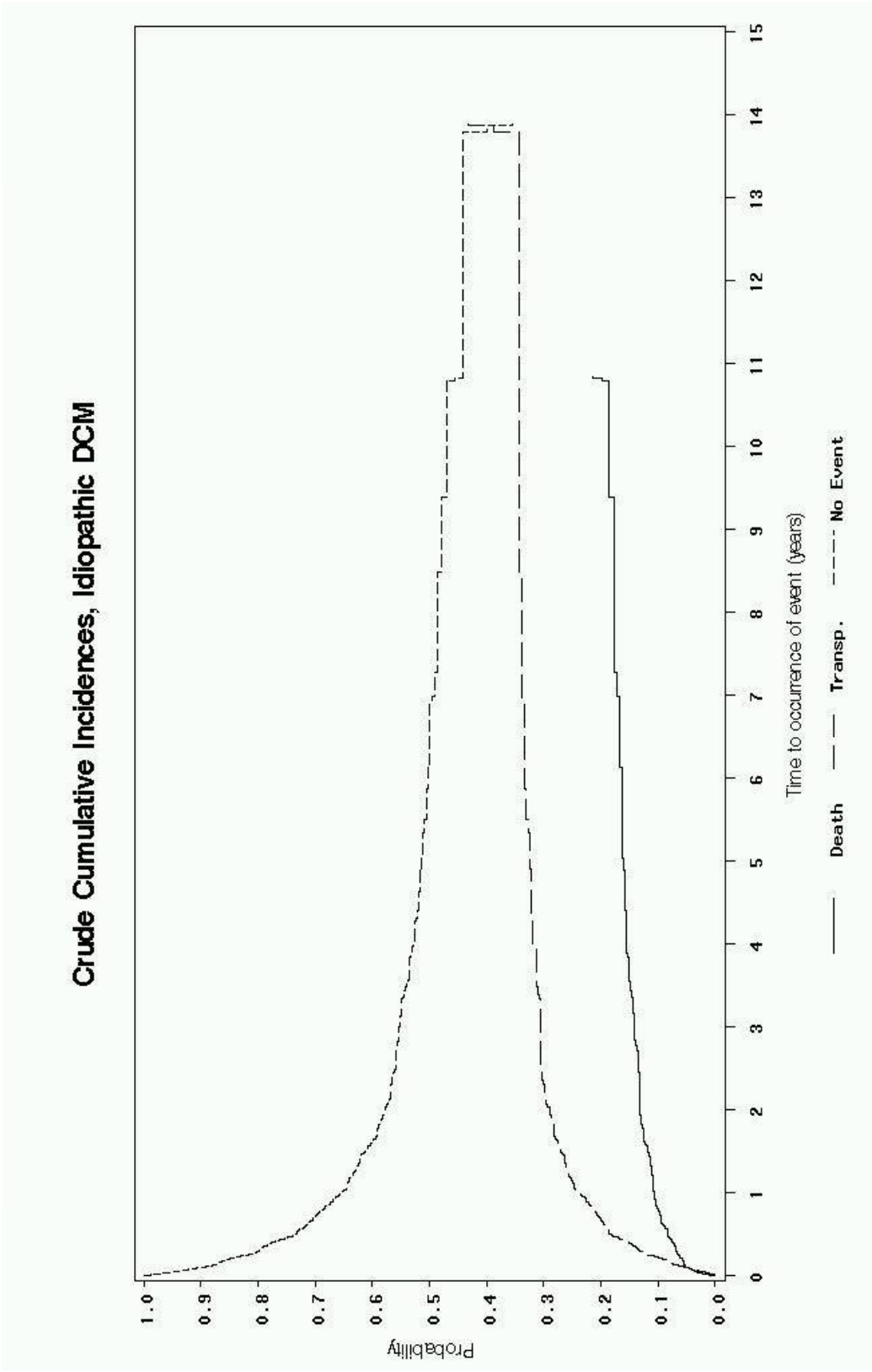


Figure 4-4: Competing Risk Estimates of Death, Transplant, and Alive Rates for Idiopathic DCM

Comparison to the event rate estimates for cause-specific death using Kaplan-Meier (KM) estimation showed an overestimation for each event when compared to the cumulative incidence in context of the competing risk (CICR), see Figure 4-5 and Figure 4-6. For death, early on there was relatively little difference between the two estimates (less than one percentage point); after 2 years there is a 3 percentage point difference, see Table 4-23. For transplant, at less than a year, the difference was greater than what is observed for death (1.4 vs 0.5 percentage point); after a year the difference went from a 3.2 to 7 percentage point difference.

Table 4-23: Comparison of Competing Risk and Kaplan Meier Estimates of Event Rates

Time	Death (n=161)		Transplant (n=326)	
(years)	CICR	KM	CICR	KM
0.5	0.082	0.087	0.183	0.197
1	0.107	0.120	0.236	0.254
2	0.131	0.154	0.290	0.316
5	0.161	0.199	0.325	0.359
10	0.185	0.240	0.344	0.382
15	0.213	0.240	0.432	0.506

CICR = Cumulative Incidence Competing Risk,
KM = Kaplan Meier

Figure 4-5: Comparison of Competing Risk and Kaplan-Meier Estimates of Transplant Rates

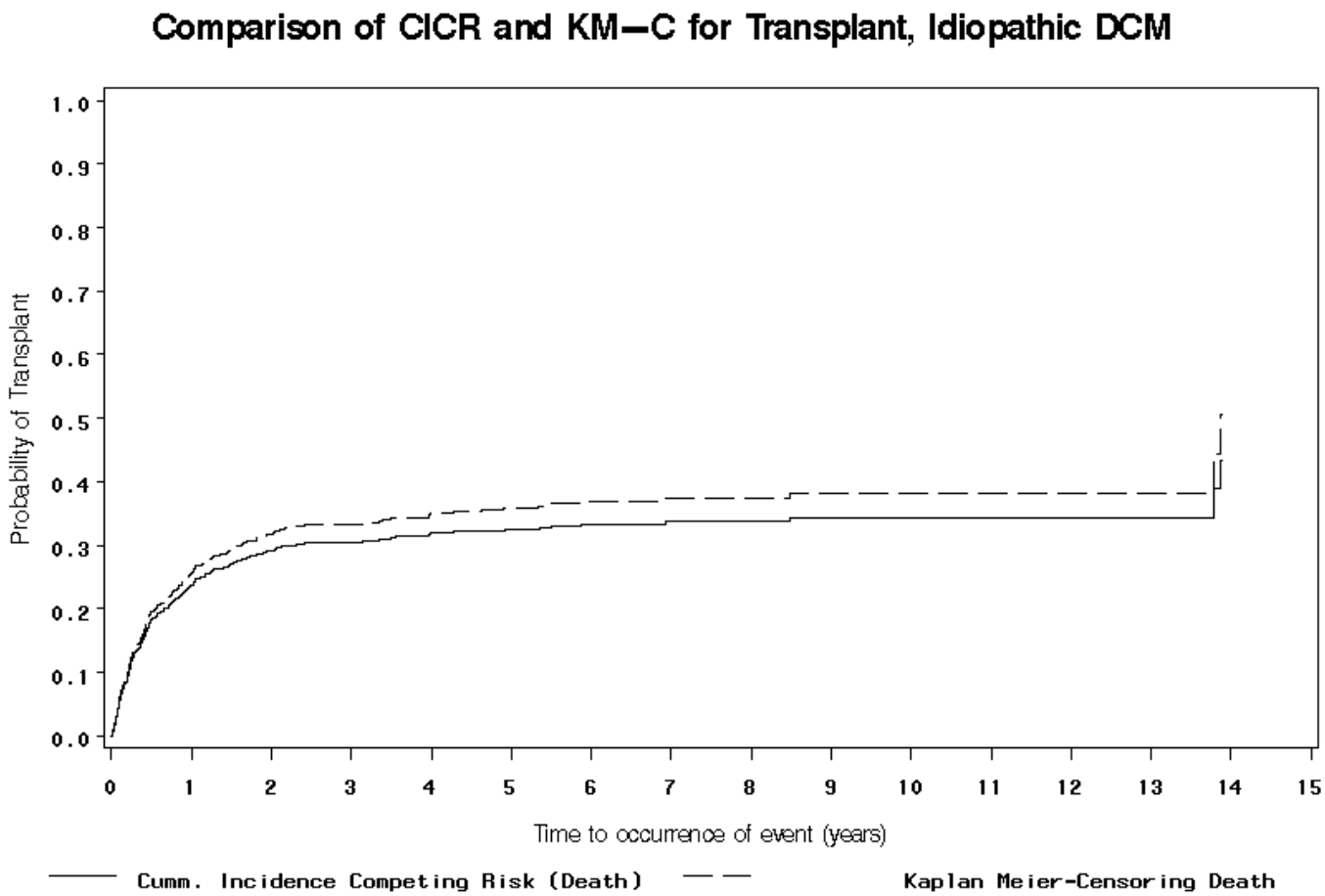
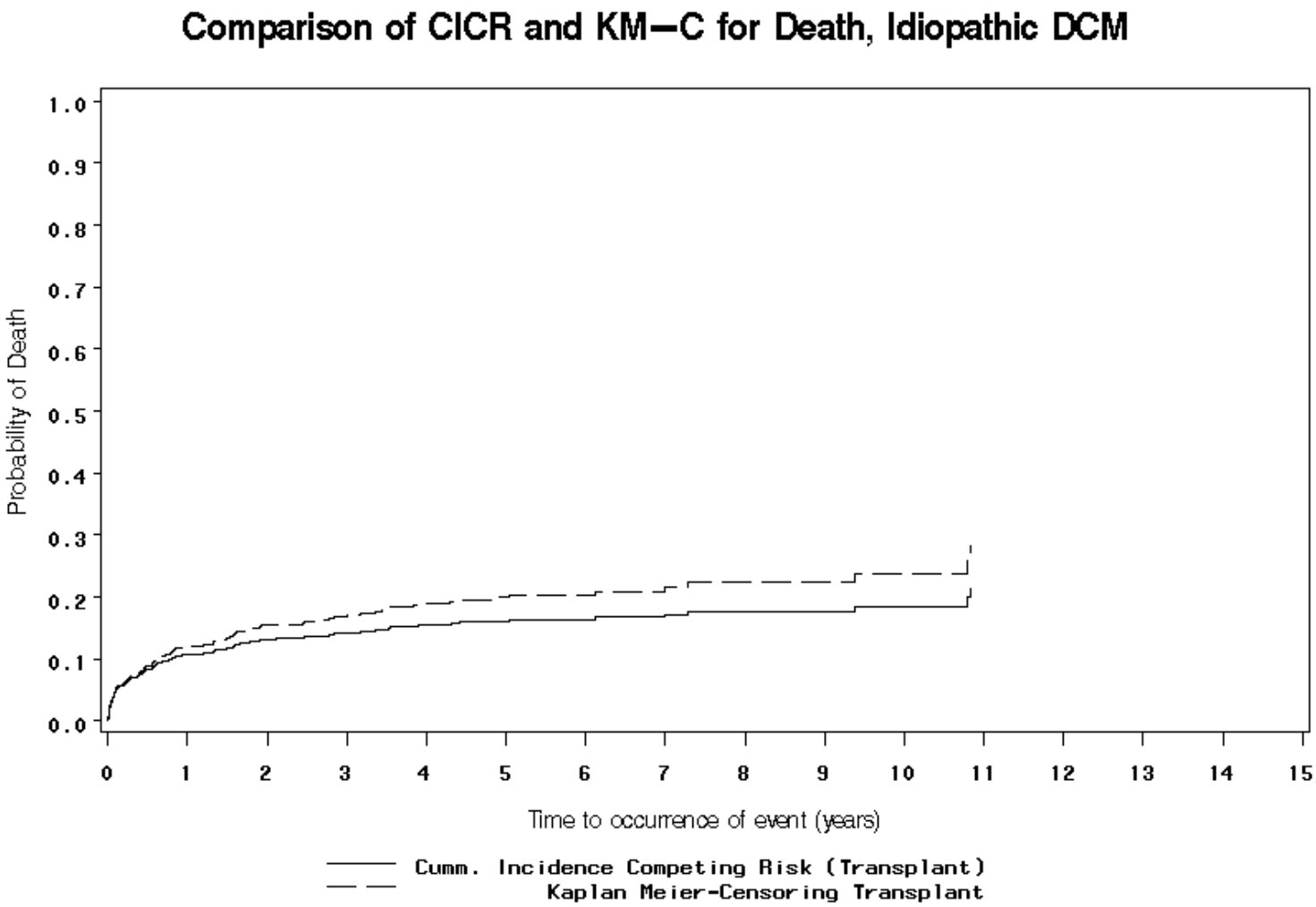


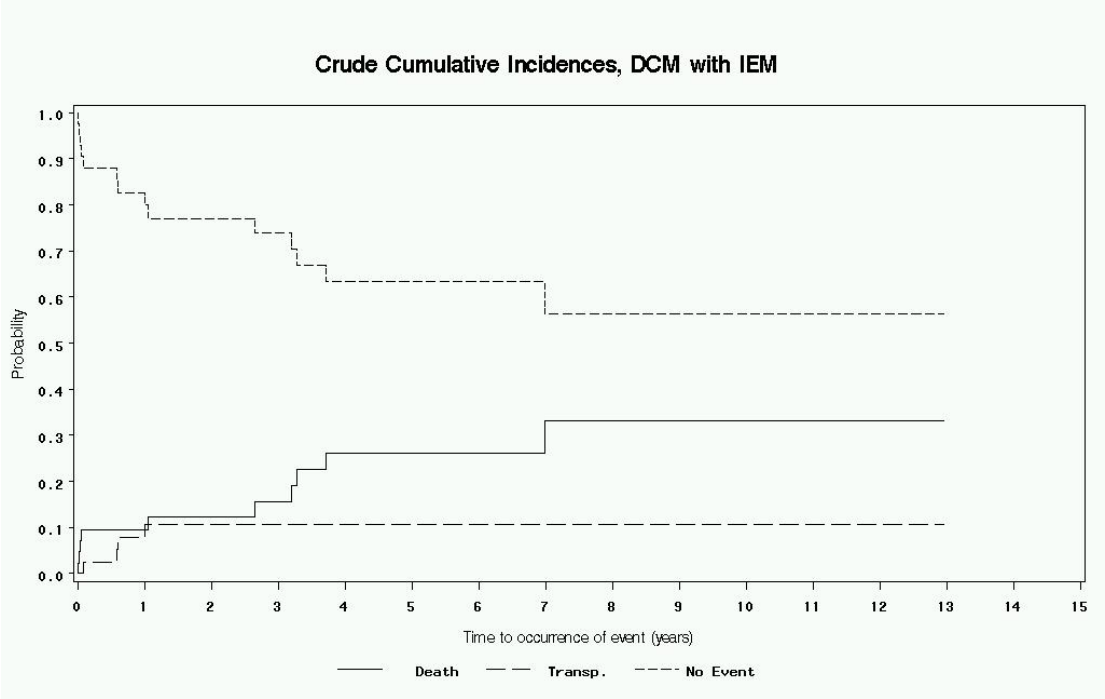
Figure 4-6: Comparison of Competing Risk and Kaplan-Meier Estimates of Death Rates



4.6.2. Inborn Errors of Metabolism

Over the course of follow-up, there are more deaths than transplants. Mortality rose steeply within the first 6 months after diagnosis, after which it evened out with the transplantation rate at one year. After 2.5 years mortality continued to be observed, however, this may have been an issue of selection bias as the median follow-up was 3 years for this subpopulation.

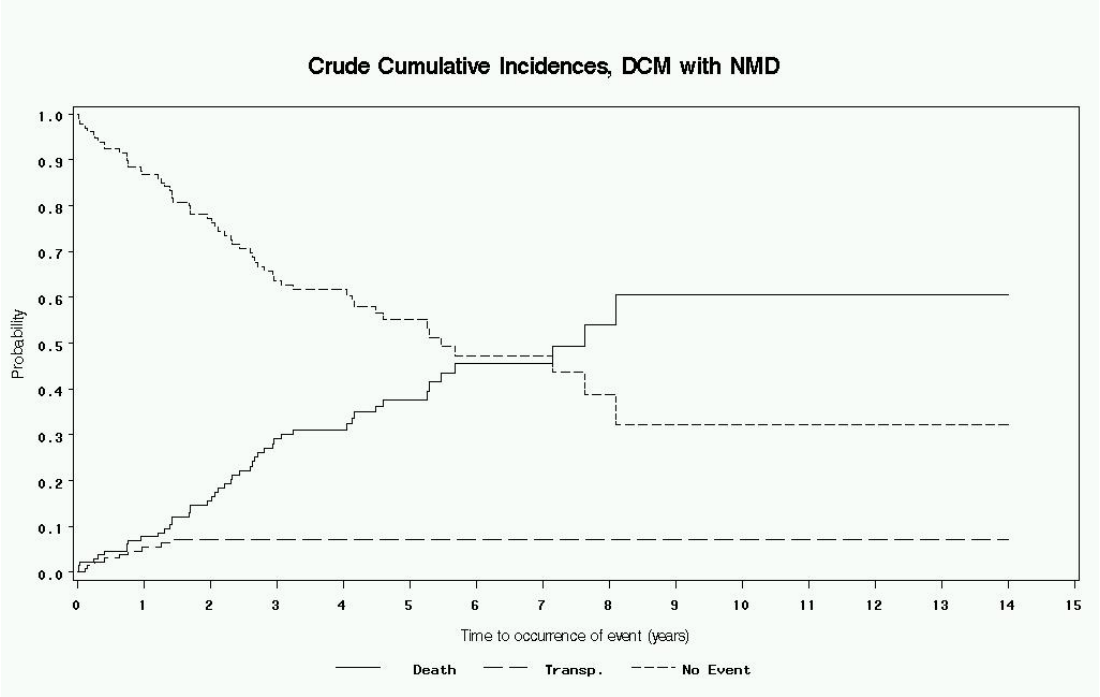
Figure 4-7: Competing Risk Estimates of Death, Transplant, and Alive Rates for Inborn Errors of Metabolism with DCM



4.6.3. Neuromuscular Disease

The rates for death and transplant tracked together through the first year after diagnosis of DCM. Mortality continued to rise, but transplant plateaued. After 7 years, mortality and survival crossed. This would coincide with the time that most patients would be entering young adulthood.

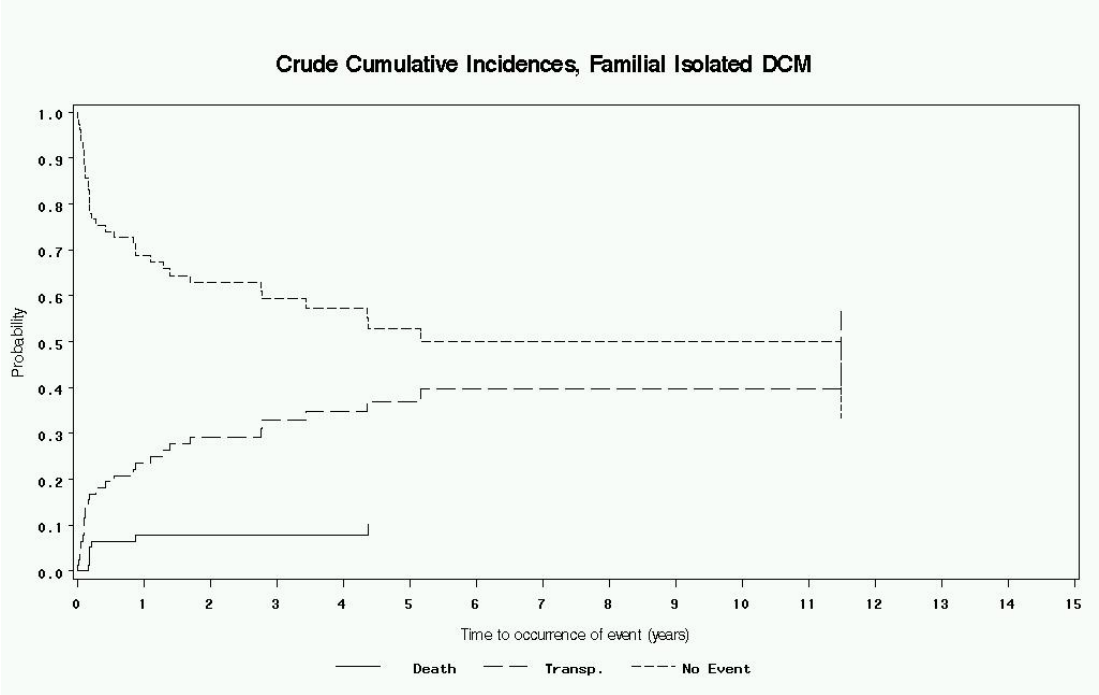
Figure 4-8: Competing Risk Estimates of Death, Transplant, and Alive Rates for Neuromuscular Disease with DCM



4.6.4. Familial Cardiomyopathy

As a whole, the rate of transplant was greater than death. The steep rise in transplantation within first year after diagnosis continued steadily increasing through the first five years. After the first few deaths occurred within first year, a plateau was observed; again, this may be an issue of selection bias as the median follow-up time was less than 2 years.

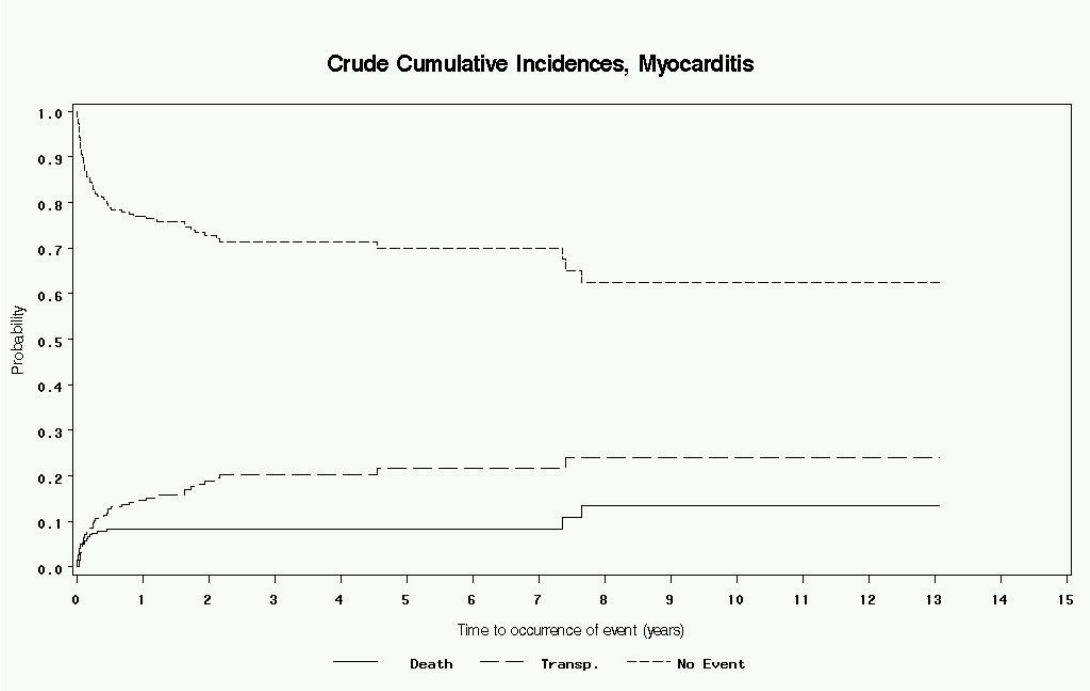
Figure 4-9: Competing Risk Estimates of Death, Transplant, and Alive Rates for Familial Isolated DCM



4.6.5. Myocarditis

Within the first six months after diagnosis of myocarditis, death and transplantation tracked together, after which the rate of transplantation surpassed mortality and continued with a steady increase through the middle of the second year. In contrast, death plateaued in the middle of the first year, and remained constant, although at 7 years there was an increase and then continued plateau.

Figure 4-10: Competing Risk Estimates of Death, Transplant, and Alive Rates for Myocarditis with DCM



4.7. Competing Risk Analysis: Risk Factors

The investigation of risk factors for death and transplantation in the face of competing events is detailed below for the three largest groups:

4.7.1. Idiopathic

For children with idiopathic DCM at time of diagnosis, the competing risk univariate models showed significant interaction for height-for-age and weight-for-age z-score, PCMR-pre-specified region, as well as EDD, ESD and LV Mass z-scores (Table 4-24). The final competing risk multivariate model for death or transplant outcomes was found to accommodate additional factors that the multivariate model for heart death did not (Table 4-25). The model included the previously observed factors (age, FS, and presence of CHF), as well as EDD, height-for-age z-score (HAZ), and the PCMR specific Region variable. The hazard ratios for age, FS, and CHF were similar to those of the model for heart death. The additional variables were included with an interaction term which, as seen in the table, produced two hazard ratios, one for each outcome. In this full model, increased age, decreased FS, and the presence of CHF were predictors of either death or transplant. Decreased HAZ was associated with an increased risk of death, but was not significantly associated with transplantation. Increased EDD was associated with increased risk of transplantation, but, paradoxically, it was significantly associated with a decreased risk of death. The region variable, specifically the comparison of children in the Central-Southwest region, had a decreased risk of transplantation when compared to "Other" parts of North America. There was not a significant association with death, nor was the comparison of New England to "Other" for either outcome.

A reduced model was calculated and shown below the full model out of concern for the decrease in sample size due to the smaller number of patients who have the HAZ variable collected. In the reduced model, age, FS, and CHF were included, as was EDD. Only EDD was found to have a significant interaction with outcome and is presented with separate HRs. Each of the HRs in this model was identical to either the heart death HRs for age, FS, and CHF, or the cause-specific HRs for EDD.

Table 4-24: Competing Risk Univariate Models for Idiopathic DCM

Variable	Death/Transplant			Death			Transplant			
	HR	95% CI		HR	95% CI		HR	95% CI		P*
Male vs Female	1.13	0.95	1.35							0.25
Age at diagnosis										
1 to <18 vs < 1	**1.40**	**1.17**	**1.67**							0.81
Per Year	**1.03**	**1.02**	**1.05**							0.09
1 to < 6 vs < 1	1.06	0.82	1.36							0.25
6 to <12 vs < 1	**1.84**	**1.44**	**2.36**							0.23
12 to <18 vs <1	**1.48**	**1.17**	**1.88**							0.65
Height for Age z-score, per SD	0.94	0.87	1.02	**0.81**	**0.71**	**0.92**	1.02	0.92	1.13	0.005
Weight for Age z-score, per SD	0.98	0.91	1.06	0.85	0.73	1.00	1.04	0.96	1.13	0.037
Weight for Height z-score, per SD	1.04	0.90	1.19							0.055
Race (vs White)										
Black	1.12	0.90	1.40							0.45
Hispanic	0.76	0.58	0.99							0.52
Other	0.99	0.68	1.44							0.85
Region (vs Other)										
Central Southwest	0.81	0.65	1.01	**1.54**	**1.10**	**2.16**	**0.52**	**0.38**	**0.71**	<.0001
New England	**0.56**	**0.41**	**0.76**	**0.47**	**0.26**	**0.88**	**0.60**	**0.42**	**0.84**	0.53
Retrospective vs Prospective	1.06	0.87	1.29							0.07
CHF at Dx (present vs absent)	**3.06**	**2.33**	**4.01**							0.13
Echo Z-score, per SD										
ED Dimension	**1.12**	**1.08**	**1.17**	1.02	0.95	1.09	**1.19**	**1.13**	**1.24**	0.0002
ED Posterior Wall	1.00	0.95	1.06							0.47
ED Septum	0.97	0.90	1.05							0.98
ES Dimension	**1.15**	**1.10**	**1.20**	1.05	0.98	1.12	**1.21**	**1.15**	**1.27**	0.0004
Fractional Shortening	**0.89**	**0.86**	**0.92**							0.20
LV Mass	**1.07**	**1.05**	**1.15**	1.02	0.94	1.11	**1.14**	**1.08**	**1.21**	0.033
Ejection Fraction	**0.75**	**0.68**	**0.83**							0.14
Ratio of Posterior Wall to ED Dimension, quartiles										
2 vs 1	**0.58**	**0.43**	**0.79**							0.98
3 vs 1	**0.55**	**0.40**	**0.75**							0.90
4 vs 1	**0.47**	**0.34**	**0.65**							0.13
Familial History at Dx, present vs absent										
Any Family History	0.97	0.76	1.24							0.72
Cardiomyopathy	0.99	0.72	1.35							0.59
Sudden Death	1.22	0.85	1.76							0.22
Congenital Heart Dz	1.01	0.62	1.64							0.86
Arrhythmia	0.64	0.33	1.24							0.74
Genetic Syndrome	0.93	0.55	1.57							0.13

SD: Standard Deviation, ED: End-Diastolic, ES: End-Systolic, Dx: Diagnosis, Dz: Disease, *Interaction

Table 4-25: Multivariate Model of Competing Risks of Death and Heart Transplantation for Idiopathic DCM

Group	Factor	HR	95% CI		P
Idiopathic					
	Full Model, n=536				
		Age at Diagnosis				
		1 to <6 vs. Infants (<1)	1.17	0.74	1.86	0.49
		6 to <12 vs. Infants (<1)	4.39	2.92	6.58	<.0001
		12 to <18 vs. Infants (<1)	3.59	2.42	5.33	<.0001
		Region				
		For Death				
		Central Southwest v Other	1.56	0.92	2.67	0.10
		New England v Other	0.46	0.19	1.12	0.09
		For Transplant				
		Central Southwest v Other	0.50	0.28	0.89	0.019
		New England v Other	0.77	0.49	1.22	0.27
		CHF (present vs. absent)	3.34	2.16	5.18	<.0001
		ED Dimension z-score (per SD increase)				
		For Death	0.86	0.76	0.98	0.019
		For Transplant	1.10	1.02	1.20	0.02
		Fractional Shortening z-score (per SD)	0.85	0.8	0.91	<.0001
		Height-for Age z-score (per SD increase)				
		For Death	0.77	0.66	0.89	0.0005
		For Transplant	0.98	0.88	1.09	0.69
	Reduced Model, n=855					
		Age				
		1 to <6 vs. Infants (<1)	1.11	0.79	1.57	0.56
		6 to <12 vs. Infants (<1)	3.15	2.32	4.28	<.0001
		12 to <18 vs. Infants (<1)	3.15	2.31	4.30	<.0001
		CHF (present vs. absent)	2.99	2.11	4.23	<.0001
		ED Dimension z-score (per SD increase)				
		For Death	0.95	0.87	1.03	0.21
		For Transplant	1.12	1.05	1.19	0.0003
		Fractional Shortening z-score (per SD)	0.88	0.84	0.92	<.0001

CHF: Congestive Heart Failure, SD: Standard Deviation, ED: End-Diastolic

4.7.2. Neuromuscular Disease

For children with neuromuscular disease and DCM, the competing risk univariate models showed significant interaction for EDD, ESD, Ejection Fraction and LV Mass z-scores (Table 4-26). The final competing risk multivariate model included the same two factors were as in the multivariate model for heart death; however, for EDD the interaction with outcome was present (Table 4-27). For a similar increase in EDD, there was a greater risk for transplant than death, the HRs were identical to their cause-specific HRs, but different from the all-cause HR of heart death. The HR for FS is identical to that of the HR for heart death showing an increased risk of either death or transplant with decreased FS.

Table 4-26: Univariate Competing Risk Model for Neuromuscular Disease

Variable	Death/Transplant			Death			Transplant			
	HR	95% CI		HR	95% CI		HR	95% CI		P*
Male vs Female	0.99	0.24	4.07							0.23
Age at diagnosis										
Per Year	0.95	0.85	1.05							0.63
Height for Age z-score, per SD	1.08	0.84	1.39							0.42
Weight for Age z-score, per SD	1.05	0.88	1.26							0.14
Weight for Height z-score, per SD	.	.	.							.
Race (vs White)										
Black	1.54	0.79	3.01							.
Hispanic	0.80	0.28	2.23							.
Other	0.81	0.11	5.86							.
Region (vs Other)										
Central Southwest	1.03	0.57	1.85							0.18
New England	0.41	0.18	0.93							0.66
Retrospective vs Prospective	1.52	0.88	2.62							0.82
CHF at Dx (present vs absent)	3.79	2.33	6.45							0.72
Echo Z-score, per SD										
ED Dimension	**1.71**	**1.41**	**2.06**	**1.45**	**1.19**	**1.78**	**1.27**	**1.06**	**1.51**	**0.001**
ED Posterior Wall	0.75	0.63	0.89							0.58
ED Septum	0.65	0.53	0.81							0.86
ES Dimension	**1.66**	**1.41**	**1.95**	**1.48**	**1.24**	**1.76**	**1.27**	**1.08**	**1.50**	**0.002**
Fractional Shortening	0.75	0.69	0.83							0.058
LV Mass	1.19	0.98	1.45	1.05	0.83	1.31	**1.64**	**1.16**	**2.33**	**0.017**
Ejection Fraction	0.80	0.51	1.23	0.86	0.54	1.36	**0.53**	**0.37**	**0.75**	**0.016**
Ratio of Post. Wall to ED Dimension, quartiles										
2 vs 1	0.25	0.12	0.54							.
3 vs 1	0.18	0.07	0.44							.
4 vs 1	0.03	0.003	0.20							.
Familial History at Dx, present vs absent										
Any Family History	0.61	0.31	1.21							0.63
Cardiomyopathy	0.52	0.21	1.26							0.32
Sudden Death	2.16	0.65	7.15							0.57
Congenital Heart Dz	.	.	.							.
Arrhythmia	2.97	0.87	10.1							0.054
Genetic Syndrome	0.61	0.31	1.18							0.10

CHF: Congestive Heart Failure, SD: Standard Deviation, ED: End-Diastolic, ES: End-Systolic, Dx: Diagnosis, Dz: Disease, * Interaction

Table 4-27: Multivariate Model of Competing Risks of Death and Heart Transplantation for Neuromuscular Disease and Dilated Cardiomyopathy

Group	Factor	HR	95% CI		P
Neuromuscular Disease*					
n=98	ED Dimension z-score (per SD increase)				
	For Death	1.23	0.96	1.59	0.10
	For Transplant	3.45	1.74	6.84	0.0004
	Fractional Shortening z-score (per SD increase)	0.85	0.74	0.97	0.016

*Adjusted for subgroup (Duchenne, Becker or Other)
ED: End-Diastolic, SD: Standard Deviation

4.7.3. Myocarditis

The univariate models for competing risk in the myocarditis group showed three significant interactions: height-for-age, weight-for-age z-score and PCMR-pre-specified regions (Table 4-28). However, none of the variables maintained statistical significance when partitioned into either the death or transplant outcomes. Ultimately, the final model had identical hazard ratios to the heart death model (Table 4-22).

Table 4-28: Univariate Competing Risk Models for Myocarditis

Variable	Death/Transplant			Death			Transplant			
	HR	95% CI		HR	95% CI		HR	95% CI		P*
Male vs Female	0.99	0.62	1.58							0.40
Age at diagnosis										
1 to <18 vs < 1	1.52	0.88	2.62							0.69
Per Year	1.05	1.01	1.09							0.07
1 to < 6 vs < 1	1.12	0.59	2.13							0.54
6 to <12 vs < 1	2.00	0.97	4.11							0.70
12 to <18 vs <1	1.97	1.02	3.80							0.15
Height for Age z-score, per SD	**0.96**	**0.76**	**1.22**	**4.08**	**1.00**	**16.7**	**0.83**	**0.64**	**1.07**	**0.029**
Weight for Age z-score, per SD	**0.91**	**0.71**	**1.17**	**1.43**	**0.92**	**2.21**	**0.79**	**0.56**	**1.13**	**0.041**
Weight for Height z-score, per SD	0.83	0.52	1.31							0.50
Race (vs White)										
Black	0.90	0.50	1.62							.
Hispanic	0.79	0.94	1.58							.
Other	1.81	0.71	4.61							.
Region (vs Other)										
Central Southwest	**0.89**	**0.52**	**1.50**	**1.91**	**0.80**	**4.58**	**0.53**	**0.26**	**1.08**	**0.026**
New England	**0.59**	**0.31**	**1.14**	**0.39**	**0.08**	**1.87**	**0.59**	**0.28**	**1.26**	**0.64**
Retrospective vs Prospective	1.01	0.62	1.67							0.48
CHF at Dx (present vs absent)	5.52	1.74	17.6							0.25
Echo Z-score, per SD										
ED Dimension	1.13	1.01	1.27							0.21
ED Posterior Wall	0.99	0.86	1.15							0.49
ED Septum	1.02	0.81	1.28							0.63
ES Dimension	1.12	1.00	1.27							0.30
Fractional Shortening	0.94	0.86	1.02							0.76
LV Mass	1.13	0.98	1.30							0.92
Ejection Fraction	0.76	0.59	0.97							0.37
Ratio of Post. Wall to ED Dimension, quartiles										
2 vs 1	0.60	0.27	1.34							.
3 vs 1	0.64	0.29	1.45							.
4 vs 1	0.44	0.18	1.09							.
Familial History at Dx, present vs absent										
Any Family History	0.93	0.45	1.95							0.53
Cardiomyopathy	1.21	0.47	3.15							0.27
Sudden Death	1.09	0.39	3.05							0.64
Congenital Heart Dz	1.16	0.28	4.84							0.73
Arrhythmia	.	.	.							.
Genetic Syndrome	0.36	0.05	2.60							.

CHF: Congestive Heart Failure, SD: Standard Deviation, ED: End-Diastolic, ES: End-Systolic, Dx: Diagnosis, Dz: Disease

Chapter 5. Conclusions

The analysis of risk factors for poor outcomes at the time of diagnosis by etiologic grouping demonstrated the differences across the groups. This was the first study of competing risk analysis in the largest database of longitudinal follow-up in children with dilated cardiomyopathy. It demonstrated the ability of a different analytical model to highlight novel and important clinical differences in particular groups that may have real-life impacts on the initial assessment and the ultimate treatment and survival.

5.1. Outcomes

After the initial report from the PCMR on the incidence of DCM in children and its outcomes,[1] this analysis carried the inquiry forward to answer what role etiology plays in the risk of poor outcomes and what, if any, prognostic factors exist for a given etiology at time of diagnosis, especially in light of competing risks.

The role of etiology shows that for a given outcome, risk is heterogeneous. When analyzing the risk of each outcome as well as the composite endpoint by etiologic group with the idiopathic group as the reference, the differences observed in single group analysis were apparent. Myocarditis had the lowest overall proportion of poor outcomes (26%) and had the lowest rates of poor outcomes when compared to the idiopathic group (death: 9 vs 14%, transplant: 17 vs 27%). For a single endpoint, the only other groups to exhibit a lower rate when compared to the idiopathic group (27%) were inborn errors of metabolism (9%) and neuromuscular disease (6%) (both in the case of transplant where death was censored). However, the NMD group had an increased rate of death compared to the idiopathic group when transplant was censored (34 vs 14%), which explained the similar rates for the combined endpoint (40 vs 41%, respectively).

The univariate regression models for each outcome individually showed some overlap in statistically significant factors observed, but also contrasted with the predictors of the composite endpoint, Table 5-1.

Table 5-1: List of Univariate Predictors for Death, Transplant, and Death/Transplant

	Both (Death/Trapnsplant)	Death	Transplant
Idiopathic = 1192 Dead = 161 Transplant = 326 Both = 491	Age: Infant, Per Year 6-12 v 1, 12-18 v 1 +New England v Other CHF ED Dimension ES Dimension +Fractional Shortening LVMass +Ejection Fraction +Post.Wall to EDD +quartiles +2v1, 3v1 *MR/TR, *LVEDP, +CI, viral	 +Height for Age z-score +Weight for Age z-score -Central Southwest v Other +New England v Other CHF +Fractional Shortening +Ejection Fraction +Post.Wall to EDD +quartiles +2v1, 3v1 *TR	Age: Infant, Per Year 6-12 v 1, 12-18 v 1 -Central Southwest v Other +New England v Other CHF ED Dimension ES Dimension +Fractional Shortening LVMass +Ejection Fraction +Post.Wall to EDD +quartiles +2v1, 3v1, 4v1 *MR *LVEDP, viral, QRS
IEM = 43 Dead = 10 Transplant = 4 Both = 14	Family Hx: Cardiomyopathy Family Hx: Genetic Synd.	Family Hx: Cardiomyopathy Family Hx: Genetic Synd.	
MFS = 6 Dead = 3 Transplant = 0	None	None	None
NMD = 139 Dead = 47 Transplant = 9 Both = 56	+New England v Other CHF ED Dimension +ED Posterior Wall +ED Septum ES Dimension +Fractional Shortening +Post.Wall to EDD +quartiles, 3v1 +Septum q, 4v1 +quartiles, 4v1 +Post. Wall to EDD +quartiles +2v1, 3v1, 4v1 *MR/TR	 CHF ED Dimension +ED Posterior Wall +ED Septum ES Dimension +Fractional Shortening +Post.Wall to EDD +quartiles, 3v1 +Septum q, 4v1 +quartiles, 4v1 +Post. Wall to EDD +quartiles +2v1, 3v1, 4v1	 ED Dimension +Fractional Shortening LVMass +Post Wall to EDD +quartiles Family Hx: Arrhythmia *TR
FDCM = 79 Dead = 7 Transplant = 28 Both = 35	CHF ED Dimension ES Dimension +Fractional Shortening LVMass +Ejection Fraction		CHF ED Dimension ES Dimension +Fractional Shortening +Ejection Fraction
Myocarditis = 267 Dead = 22 Transplant = 44 Both = 70	Age: Per Year, 12-18 v 1 CHF ED Dimension +Ejection Fraction *viral, QRS	 Height for Age z-score *viral	Age: Per Year, 12-18 v 1 CHF ED Dimension *viral, QRS

+ Decreased risk of outcome with increase of factor, *From sub-group analyses
ED: End-Diastolic, ES: End-Systolic, Hx: History, CHF: Congestive Heart Failure, q: quartile, MR: Mitral Regurgitation, TR: Tricuspid Regurgitation, Infant: <1 vs >1year of age at diagnosis, viral: positive viral serology, QRS: duration of QRS on surface ECG, LVEDP: Left Ventricular End-Diastolic Pressure, CI: Cardiac Index

For the idiopathic group, the effect of older age was predominantly driven by the transplant outcome, as were EDD, ESD, and LV Mass. The growth parameters (height- and weight-for-age) only achieved significance in the model for death with transplant censored. This may reflect the role that failure to thrive has on the symptomatic child that dies prior to receiving a heart transplant. However, in the multivariate model for the composite endpoint, older age, echocardiographic parameters indicative of worse structure and systolic function, and symptomatic disease stood out as independent predictors.

5.2. Age

One explanation of the effect of age is that as children who are older present with more symptomatic disease, they are the product of a disease process that has had sufficient time to cause damage to cardiomyocytes. The effect of long-term insults due to an undiscovered source may diminish the reserves of the maturing heart, and ultimately make it more difficult for the child with significant structural and functional problems to recover.

Prior studies had debated the exact cut off for the observed age effect. Using 2 years at the cut off, a significant hazard ratio is observed for the composite outcome (HR1.57, 1.32-1.88). While the effect is larger, it is not significantly different than the HR observed using 1 year of age as cutoff. Given that the two older age groups appear to have similar HRs, a model using 6 years of age at presentation produced a HR of 1.60 (CI 1.34 to 1.92). Again, very similar, however, comparing each age cutoff, the greatest statistical difference was seen with the 4 categories.

The myocarditis group also exhibited an age effect, mainly through its role in modifying the risk of transplantation where the older children were seen to be at greater risk. In contrast to idiopathic group, attempting to include age as a categorical variable did not improve the fit of the model, and the linear effect of age was observed to provide a better model. The age effect was accompanied in the multivariate model for the composite outcome by the presence of CHF and increased EDD at diagnosis.

Overall, older age, which in previous studies has shown varying cutoffs for significance, in general is indicative of worse outcome, but in different etiologic groups age exhibited a heterogeneous effect.

5.3. Myocarditis

While a much lower percentage of children died or required transplant when the myocarditis group was compared to the idiopathic group (26 vs 41%), the ratio of death to transplantation was similar (0.52 vs 0.49). Nevertheless, the absence of the functional component in the role of fractional shortening from the multivariate model, as well as all three univariate models, may have had to do with the manner in which inflammation acts in the disease process. The acute phase of the infection brings about the temporary circulation of pro-inflammatory cytokines, like TNF and IL-6, which the body produces in response to the offending organism, predominantly viral in the cases of myocarditis collected by the PCMR which excluded toxic exposure as per study design. Animal models have shown the time-dependent effects of these cytokines in response to coxsackievirus in acute and chronic inflammatory models.[72] One hypothesis is that the transient nature of the infection and cytokine release affects systolic function of a majority of cases, however, it is those that exhibit significant structural damage that face

the worse outcomes. Therapeutic studies using anti-inflammatory agents, like intravenous immunoglobulin (IVIG) or steroids, have shown some promise in small cases series of children,[73] even long-term results in a larger Italian cohort with 13 years of follow-up,[74] but no randomized trial data have been published. While there is still debate on the efficacy of treatment, especially with equivocal findings in adult trials and a similar lukewarm recommendation by Cochrane,[75] an inflammatory process may explain the particular constellation of predictors uncovered by this analysis.

Other thoughts from a recent review by Cooper[76] include the hypothesis that myocardial damage during infection may occur that is independent of immune reactions and inflammation. Viral proteases might cleave myocardial structural proteins, like dystrophin, which may lead to cardiomyopathy. The review stated that data from experimental models indicated that coxsackievirus B may persist in the myocardium with a partially deleted genome, leading to a low-grade, noncytolytic, chronic infection in the heart. Duplication of results in patients with DCM might help to explain how a viral infection can progress to chronic DCM, especially in cases without of myocarditis.

5.4. Neuromuscular Disease

The children who have some form of neuromuscular disease and go on to develop DCM appear to have a variation of what has been observed in the idiopathic group, namely worse structure and function predict worse outcomes. The absence of age as a factor is not surprising since as a whole, the children with NMD who present with DCM tend to do so at a much later age, usually during adolescence. As a group there is not much heterogeneity in risk based on age as a factor at time of diagnosis. Arguably, there may be some bias as those children with NMD observed in the PCMR may have more

severe disease than the general population of children with NMD. However, only 29% of this group recorded having congestive heart failure at the time of diagnosis, which is significantly less than any of the other etiologic groups which exhibited proportions of 50% or more. The symptomatic burden of disease was less prevalent in contrast to the other groups at time of diagnosis. Nevertheless, the pervasive effects of NMD presented a paradox in which those children who showed the most significant cardiovascular decline also tended to have concurrent respiratory problems that ultimately make them less suitable as a candidate for a heart transplant than children with other etiologies of DCM.[77]

One univariate predictor shared only by the NMD and the idiopathic groups was the effect of increasing ratio of posterior wall thickness to end diastolic dimension (PWEDD). PWEDD has been observed to remain within a range of 0.25 to 0.29 though out childhood and into adulthood.[78, 79] During acute dilation, the ratio is expected to decrease relative to normal as the posterior wall has normal to decreased thickness and has not been able to adequately hypertrophy in response to dilation of the left ventricle. Similarly, in a chronic condition, the dilation would be attributable to the decreased wall thickness allowing the LV to dilate. Not surprisingly, median PWEDD was observed to be below normal across all groups. Posterior wall thickness was decreased more in the NMD than the idiopathic group (-1.7 vs -0.7 z-score) as was EDD (1.63 vs 4.7 z-score). A normal PWEDD in the face of dilation would indicate a very thick posterior wall that would contribute to an increased LV Mass, however, despite the relatively larger PWEDD of the NMD group (0.14 vs 0.12), LV Mass was actually lower (-0.19 vs 2.39 z-score) than the idiopathic group.

With this calculated echocardiographic parameter, relatively thicker walls, according to Carvalho *et al.*,[39] may serve as a proxy to indicate those whose left ventricular mass is relatively preserved and potentially able to recover function. Carvalho suggested 0.17 as a prognostic cutoff, and for these groups those with PWEDD greater than or equal to 0.17 fared better (Idiopathic: HR=0.65, P=0.03, and NMD: HR=unstable, >0.17: 0 of 17 death/transplant vs. <0.17: 42 of 85 death/transplant). Another idea posited by Carvahlo was that the relatively thicker wall reflects myocardial edema, a sign of active inflammation with the capacity to improve. However, PWEDD did not appear as a significant predictor in any of the models for the group with myocarditis, nor in a model with a 0.17 cutoff for PWEDD. The significant role of relatively increased PWEDD in the idiopathic and the neuromuscular disease groups may reflect the relative sparing of cardiomyocytes to provide sufficient short-term hypertrophy and maintain adequate systolic function. In the NMD group it would be compensatory mechanism in the face of the dystrophin defect, while for the idiopathic group it may be an unrecognized inflammatory process. That relatively increased septal thickness and posterior wall thickness, both in linear and categorical form, were also significantly associated with improved outcomes is consistent with this hypothesis. However, given the relative short follow-up time, the long term effects of the below-normal, relatively increased PWEDD is unclear.

5.5. Familial Isolated CM and IEM

The groups with familial isolated cardiomyopathy and IEM showed a similar trend where all of the univariate predictors were driven by their majority outcome: transplantation and death, respectively. Data from neither group produced a multivariate

model for risk of death or transplant. For the FDCM group, echocardiographic parameters and symptomatic CHF acted as predictors, whereas, for IEM, only family history of CM or genetic syndromes predicted death. It is unclear if the familial cases that did not have a putative cause identified as a specific genetic defect were susceptibility to common environmental factors which produced the dilation and systolic dysfunction seen in DCM in multiple family members. The similarity in 5-year survival from heart death for children with either familial or "non-familial" DCM has been observed in an earlier study by Michels et al.[80]

For children with IEM, the different insults to the regulation of energy metabolism are the main source of disease and functional impairment, and for some can be possibly treated directly with enzyme replacement therapy to improve the defect and reduce the morbidity and risk of mortality. Not surprisingly, in this study, this group had the second best overall survival, however, it had the third highest proportion of death out of combined endpoints from among the 6 groups (10 of 14, 71%). As the second smallest group, the lack of predictors may be attributable to the small sample size and as a result did not lend itself to much statistical manipulation. The key to improving outcomes for this group is early diagnosis of the underlying cause. It is unclear if heart transplantation in a child with an underlying systemic disease would be appropriate.

The majority of cases in this group had Barth syndrome, an X-linked genetic disorder that results in cardiomyopathy, neutropenia, muscle hypoplasia and weakness, growth retardation, cardiolipin deficiency, and 3-methylglutaconic aciduria.[81, 82] Currently the thought is that mutations in the tafazzin gene (TAZ, also called G4.5, located on Xq28), which are closely associated with Barth syndrome, is the underlying

defect in this sydrome.[83] The tafazzin gene product functions as an acyltransferase in lipid metabolism involving cardiolipin, which is a mitochondrial lipid. Its connection with the electron transport chain proteins and the mitochondrial membrane structure may be the link to the constellation of symptoms. There is no current treatment, although supplementation with carnitine has shown mixed results.[84, 85]

5.6. Malformation Syndromes

Malformation syndromes with associated DCM are an especially rare group with only 6 cases out of 1731 with DCM. As such, regression modeling to predict outcomes was not possible. This group had three deaths with one while waiting for transplantation. The two known causes identified in this group, Leber's Congenital Amaurosis[86] and Alstrom Syndrome,[87, 88] are both associated blindness and are incredibly rare. Regardless, the difficulty lies in providing appropriate screening and symptom management.

5.7. Subgroup Analyses

The additional sub-group analyses utilized other factors that have been reviewed in the literature but not previously analyzed by the PCMR. Mitral valve regurgitation (MR) and tricuspid valve regurgitation (TR) have been associated with poor outcomes, namely death. Only TR was found to be associated with death in the idiopathic group, whereas MR and TR were associated with transplantation. It is unclear why a similar association was not found for MR and death and why both were associated with transplantation, given previous studies.[16, 33]

The association of positive viral serology and death or transplant in myocarditis (HR 5.6; 95% CI, 2.5 to 12.2) was as large as that for the presence of CHF (HR 5.96; 95% CI, 1.43 to 24.89) with similarly large confidence intervals. Cases of myocarditis

can arise from inflammation secondary to bacterial, fungal, and toxic exposure as well as viral. The PCMR excludes toxic exposure etiologies, and the majority of cases are presumed to be viral, but not certain. Given the small sample size this could be a spurious finding. For those with idiopathic disease, the finding is still interesting in that myocarditis has been reported to have better outcomes. It is unclear if a positive viral serology can be equated to viral myocarditis. The presence of viremia may have other multi-organ impacts that predispose a patient to worse outcomes.

The finding from the catheterization parameters (LV end-diastolic pressure [LVEDP] and Cardiac Index [CI]) analyses showed that LVEDP while associated with poor outcomes was mainly derived from its effects on transplantation. Additionally, CI was only associated with the combined endpoint but not death or transplant separately. It is unclear why neither would have an association with death, given previous studies.[15, 27, 37]

Lastly, of the three ECG parameters (QTc QRS, Axis deviation) analyzed only QRS was associated with a poor outcome. For both the idiopathic and myocarditis groups, prolonged QRS was associated with an increased risk of transplant. This continues the trend of subgroup analysis parameters associated with transplant, but not with death. The potential for fatal arrhythmia would lead to placement a pacemaker or an automated implantable cardiodefibrillator or ablation of an errant pathway or node. Failure to prevent such a rhythm could result in sudden death, which may explain an increase toward preventive transplantation, although it seems extreme. A similar argument could be made for the other subgroup analysis parameters. Severity that would

have previously led to death could have been met by increase utilization of heart transplantation.

5.8. Competing Risk Analysis

In comparing the graphs for event rates of either death or transplant independently and the cumulative incidence competing risk (CICR), the event rates under the Kaplan-Meier method where the competing risk was censored (KM-C) were overestimates at each time point. This finding has been present in multiple other studies.[63, 66, 67]

While the survival estimates in this particular case were similar, the additional information for event rates increased the utility of the CICR. The KM-C for heart death did not communicate to the observer the relative difference that each event contributed to the overall event rate. This information was lost, and the event rate overestimated in the presence of competing risks.

The competing risk regression (CRR) highlighted the strength of the approach as well as a drawback of this dataset. When compared to the univariate Cox regression (UCR) and the multivariate Cox regression (MCR), the CCR for myocarditis did not communicate any additional information that was not already gained from the MCR. For the neuromuscular disease group, CRR showed the differential effect of EDD on death as compared to transplant in a single regression. While one could have performed the various UCR for each outcome and then the combined outcome and then compared all the results, this one model in the CRR conveyed all the information simultaneously and parsimoniously. Similarly, the CRR for the idiopathic group showed the additional information for the risk of transplant that EDD provided, as well as the potential role of growth retardation on death via the height-for-age z-score.

For the two groups with significant interactions, novel risk factors appeared, namely the effect of growth retardation and enlarged left ventricle at the time of diagnosis. The height-for-age z-score, which previously did not maintain significance in the multivariate model for heart death, showed its differential effect in the competing risk model. Namely, the effect of growth retardation was influential on mortality, but did not appear to have an impact on risk of transplantation. The association of growth retardation and congestive heart failure had been documented previously and had been recommended as an indication for heart transplantation by the American Heart Association since 1995 and again in 2007.[89, 90] Here, we presented the association of reduced stature at time of DCM diagnosis with mortality in the context of the competing risk of transplant as an independent predictor.

Several studies have investigated the role of growth retardation, through growth hormone insufficiency and supplementation in cardiac disease. One trial of GH in adults with idiopathic DCM showed a reduction in the circulating TNF system and soluble apoptosis mediators.[91] They hypothesized that these GH-induced anti-apoptotic effects may have been associated with the concurrent improvement in exercise capacity, as well as with the reverse of LV remodeling.

A 6-month trial of GH in 8 children with idiopathic DCM showed an improvement in LV functional indices, as well as a sustained increase in IGF-1 activity, 6 months after terminating GH treatment.[92] The authors hypothesized that the sustained IGF-1 may have indicated continued improvement. However, another study investigated the long-term effects of GH on children treated with anthracyclines for cancer (predominantly acute lymphoblastic leukemia). Anthracycline exposure has significant

impact on cardiomyocytes and subsequent cardiac dysfunction.[93] They showed that although with treatment there were concurrent improvement with cardiovascular indices, after 10 years the effects on several indices diminished and dysfunction continued, despite treatment.[94] It is unknown if similar long-term effects would be seen in children with DCM who did not share the severely toxic exposures of anthracycline or cranial radiation, but may have had undiagnosed alterations to their somatotrophic axis.

The ability to utilize reduced stature as an indicator to recommend transplantation at most could improve survival for 50% of those children who are below 2 standard deviations of height for age (HR 1.5; 95% CI, 1.03 to 2.18) who would have died but may benefit from transplantation.

The other variable to show interaction with outcome was EDD. The effect of EDD was observed to have a significant increase for the risk of transplant with increasing EDD z-score, but either a protective effect or no effect on the risk of death with increasing EDD z-score when viewed in the full or reduced models, respectively. LV dilation is by definition part of the disease physiology; however, relatively increased dilation appears to be a significant factor in the decision and follow-through on successful heart transplantation. This effect may be biased by either center- or physician-specific factors that are unmeasured by the study. However, the use of significantly increased EDD as a factor to determine the utilization of heart transplantation may improve the ultimate survival of children with idiopathic DCM.

An analysis of data from a subset of children from the PCMR with DCM (n=261) who go on to transplant and have post-transplant survival data as collected by another group (Pediatric Heart Transplant Study Group) showed that an increased EDD at time of

listing for transplant was a significant predictor of mortality after listing and during a 6 month post-transplant period.[95] LV fractional shortening, mass and wall thickness were not associated with outcome. The implication for timing of transplantation based on the degree of dilation, among other clinical and demographic factors, may have a beneficial effect on post-transplantation mortality.

5.9. Limitations

There are several limitations to this analysis. The cases analyzed here were possibly more severe than what can be found along the spectrum of DCM pathophysiology as all children were identified by physicians in a clinical setting, through a combination of clinical signs and symptoms, and thus excluded the majority of asymptomatic cases. On the other hand, this analysis also excluded some of the most severe cases where the first presentation of disease was death.

Although the high percentage of children with idiopathic disease is cited as an impediment to the development of etiology specific prognostic factors, the PCMR has the largest groupings of specific etiologies. Nevertheless, the power to detect statistically significant differences between factors is limited by the small sample size for certain subpopulations. Increased diagnostic rigor as well as the availability of genetic testing may continue to shed more light on etiologic-specific differences in prognostic factors in the future.

The observational nature of the study via review of medical records also limited the ability to study a given clinical factor if that factor was either not measured or recorded by the provider at time of measurement. Nevertheless, this was also a strength

as it reflects the real world practice and the factors at time of presentation ought to be the most relevant and useful for the physician encountering DCM in the clinical setting.

In terms of the competing risk analysis, the drawback to the PCMR dataset lies in the lack of post-transplant survival data. The lack of interaction for many variables may be due to this particular detail in the design of data collection where follow-up customarily ends at time of transplantation. Nevertheless, for a small subset of 21 patients with idiopathic disease post-transplant information with date of death was recorded as the death occurred within the annual reporting visit of their transplantation. Re-analyzing the idiopathic competing risk regressions provided no new significant interactions; however, it did substantially change the magnitude of one of the predictors: the effect of EDD on death in the full model ceased to be significant. Originally this was intriguing as the full model showed an association with increased dilation and decreased mortality ($p=.019$) which was not significant in the reduced model. It is suggestive that additional follow-up time with the involvement of cases of post-transplant death as well as post-transplant time may create a different model. However, the CRR model showed what actually happened, as compared to the actuarial estimates which indicated the probability of the occurrence of an outcome ignoring or censoring any competing outcomes.

The addition of post-transplant data would answer a different question than what the data currently was designed to answer. Pre-transplant data treats the heart as a machine that is capable of failure with two poor outcomes: either the heart fails (the child dies) or it is replaced (equivalent to the heart dying, but without the concomitant death of the child). Post-transplant data would treat the heart similarly to a replaced machine

where the question is which fails first the new machine or the child. The replacement of the heart, while prolonging life, causes the child to enter a new and different period of hazard where the factors influencing death or heart failure, including rejection, and the need for another transplant are different from those prior to his first transplant.

Lastly, the interpretation and generalization of conclusions should be weighed carefully in the context of the data collection process and potential selection bias, namely the relatively short period of follow-up among those who were alive and without an event at time of last follow-up. Given that majority of events do occur relatively rapidly within the first year, the overall conclusions are reasonable, but with half of those alive having a follow-up of just less than 3 years, extrapolation to longer follow-up time should be cautioned against. Nevertheless, this is to our knowledge the largest cohort of children with DCM with the longest period of follow-up.

5.10. Public Health Impact and Future Directions

Dilated cardiomyopathy in children has significant morbidity and mortality. With relatively low event-free survival at one and two years from presentation (66% and 51% for idiopathic DCM), improvements in prognosis provide a meaningful impact in the care of these children. This study has provided additional information on the effect of etiology and presented novel risk factors for the largest group (idiopathic DCM), one of which is the common and easy to acquire measurement of height. The simple task of assess height for age may save the lives of 23% of children with idiopathic DCM. Furthermore, whether height, as a product of nutrition and growth, can be modified is open to future research. As is access to care and the influence on transplant as an

endpoint with respect to the availability of tertiary care programs as well as the availability of bridge therapy and of donor hearts.

Future analyses would include increased follow-up time, as well as ascertainment of clinically important outcomes such as normalization. Additional ascertainment of post-transplant would be beneficial, but any conclusions from a competing risk analysis would need to be carefully understood for context prior to making recommendations to the general medical community.

Continued follow-up is warranted to establish more accurate predictors of long-term events. Additionally, more detailed analysis of cause of death could further stratify a competing-risk analysis by partitioning non-cardiac related deaths and sub-dividing sudden death from death due to congestive heart failure.

5.11. Summary

Within etiologic grouping, demographics and echocardiographic values at presentation have varying predictive value. Generally, the presence of symptomatic disease in the form of CHF, greater echocardiographic evidence of DCM, and increased age were indicative of worse outcome. In the idiopathic group, at time of diagnosis age above 6 years, the presence of CHF and decreased fractional shortening where predictive. For the group with neuromuscular disease and DCM, the presence of CHF and increased EDD were predictive. For the group with myocarditis, each year of increased age, presence of CHF, and increased EDD were predictive. These results help to validate those from conflicting studies; however, they suggest that etiology of DCM modifies the importance of certain factors. Improved prognostication of failure of medical

management may result from an increase in establishing etiology and further study of those groups.

Lastly, the usage of competing risk analysis contributes information about component outcomes that are overestimated in analyses that ignore the other events, making it difficult to interpret analyses that combine the competitors into a composite endpoint. Using a composite endpoint may lose the interaction a given predictor may have with the competing outcomes. Interaction was found between the effect of two predictors and the outcomes of death or transplantation. For reduced stature in those with idiopathic DCM, it was found that the risk of death was significantly increased while it was not for transplant. Although already a recommended criteria for heart transplantation, this analysis shows that there are still more children dying than might be necessary and who could potentially benefit from a heart transplant as a result of a simple to perform office procedure. The potential benefit for up to 50% of children presenting with low height for age would be profound. Increased LV dilation was found to have an increased risk of transplantation for both idiopathic and neuromuscular disease, and increased risk of death, albeit smaller in magnitude, only in the neuromuscular disease group. For each of these groups, the increased risk of transplant reflected the utilization of transplantation in children with severely dilated and failing hearts. The associated finding linking dilation to post-transplant mortality showed that the degree of dilation appeared to be vital throughout the triage process in deciding when to proceed with transplantation, the success of both medical and surgical management, and the avoidance of premature death.

The novel finding of reduced stature and its effect on mortality suggests a potential for treatment and mitigation of poor outcomes in idiopathic DCM. Together with the findings on increased dilation, this analysis presented the opportunity for new investigations and interventions which ultimately will improve the lives of children with DCM. Subsequent studies on the utility of these factors and their effect on improving survival are warranted.

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VITA

Jorge Alex Alvarez was born in New York City, New York, on January 31, 1979. Along with his parents, Jorge and Teresa Alvarez, he moved to Miami, Florida, in 1981 and completed elementary education at St. Timothy Catholic School and secondary education at Christopher Columbus High School. He graduated from Harvard University with the A.B. degree in Biology *cum laude* in June, 2001. After a year as a Research Assistant at Brigham and Women's Hospital in Boston, he matriculated at the University of Miami School of Medicine. In his second year of medical school, he applied and was accepted into the combined M.D./Ph.D. program where he was granted the degree of Doctor of Philosophy in August 2009. He will be granted the degree of Doctor of Medicine in May 2011, after successful completion of medical school.