Published in final edited form as:

Prog Pediatr Cardiol. 2007 September 1; 23(1): 25–32. doi:10.1016/j.ppedcard.2007.05.009.

Outcome Predictors for Pediatric Dilated Cardiomyopathy: A Systematic Review

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Abstract

Dilated cardiomyopathy comprises the largest group of pediatric cardiomyopathy functional types and is the most common indication for heart transplant in children over 5 years old. Prognostic factors for this condition have long been sought by many researchers. In a systematic review of these factors, we found 32 relevant articles published since 1976. Four studies report finding no predictive factors. In the remaining 28 studies, several factors indicating better prognosis stand out across multiple articles: younger age at diagnosis, higher left-ventricular fractional shortening and ejection fraction, and the presence of myocarditis. Results for other factors conflict across studies: severe mitral regurgitation, arrhythmias, and a family history of cardiomyopathy. Elevated left-ventricular end diastolic pressure was statistically significant in two studies, but it may be of limited utility as a result of its invasiveness. Although most children have congestive heart failure at presentation, only two studies found it to be a significant predictor of mortality. The largest study of this factor qualified the increased risk to 1 year after presentation. Other significant predictors that have not been analyzed or reported by more than one study group, are right ventricular failure and impaired cardiac adrenergic innervation, as detected by radiolabeled meta-iodobenzylguanidine imaging. Although 1- and 5-year survival rates have steadily improved, as more children with DCM receive cardiac transplants, event-free survival rates (the absence of “heart death” resulting in death or transplant) are similar to those from decades ago. A unified risk algorithm may assist in clinical decision-making but requires more studies. Other studies are needed to assess the post-transplant survival experience.

Keywords

Dilated Cardiomyopathy; Predictors; Heart Transplant

INTRODUCTION

The World Health Organization classifies cardiomyopathy into four categories: 1) dilated cardiomyopathy; 2) hypertrophic cardiomyopathy; 3) restrictive cardiomyopathy, and 4) arrhythmogenic right ventricular cardiomyopathy.¹ Among the four groups, dilated cardiomyopathy (DCM) is the most common in children.^{2–4} The annual incidence is between 0.34 to 0.73 per 100,000 children.^{2–4} Although rare, DCM is the most common indication for

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heart transplant among children older than 5 years of age.⁵ It has substantial morbidity and mortality and costs US society several billion dollars annually.⁶

According to the World Health Organization, DCM is “characterized by dilatation and impaired contraction of the left ventricle or both ventricles... Presentation is usually with heart failure, which is often progressive.”¹ Before this and its earlier 1980 definition⁷, DCM was viewed by the medical community in the context of primary myocardial diseases⁸ or idiopathic non-obstructive cardiomyopathy.⁹ The first large case series, by Greenwood and colleagues in 1976, described 161 children.¹⁰ 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.^{11–13} To predict the outcomes for children with DCM is crucial for mitigating the tumultuous 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. Here, we systematically review the studies that have attempted to identify predictors of outcomes in children with DCM.

METHODS

We searched OVID MEDLINE from 1966 to February, 2007, with MeSH terms and key words including: dilated cardiomyopathy, congestive heart failure, prognosis, predictors, and risk factors. The search was limited to studies performed in children with idiopathic or primary DCM, including myocarditis. Studies were also limited to those systematically analyzing patients; case reports and small case series were excluded. Reference lists of appropriate studies were reviewed for articles not identified in the MEDLINE search. Abstracted data included the dates of the accrual period, sample size, follow-up time, and univariate and multivariate predictors of mortality or “heart death,” a composite endpoint of death or heart transplant.

RESULTS

There were 712 articles initially identified through the MEDLINE search. Of those 26 articles met the inclusion criteria and an additional 6 were found from searching reference lists within those articles. They included children diagnosed with DCM between 1945 and 2004 (Table). The majority were reports from single institutions (28 of 32), and the two largest studies were published in 2006.^{14, 15}

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 are from the Pediatric Cardiomyopathy Registry (PCMR), which covers a large population cohort: 1-year survival is 87% and 5-year survival is 77%.¹⁵ Three studies, including the PCMR, reported event-free survival (i.e. from death or transplant) at 1-year survival to be 70%, 72%, and 69% and 5-year survival to be 58%, 63%, 54%.^{14–16}

Of the 32 articles, 4 reported no associations between baseline factors and mortality: 1 was mainly descriptive with no modeling¹⁷; another emphasized baseline dysrhythmias and did not analyze other factors,¹⁸ and the last two detected no significant univariate associations.^{19, 20} One study found no “good” predictors but identified two factors that were either “insensitive” or of “limited clinical value” in predicting survival (the presence of severe mitral regurgitation in only three subjects who ultimately died; and pre-diagnosis viral symptoms had 78% sensitivity and 60% specificity).¹¹

We review the evidence for specific predictors below.

Electrocardiographic Measurements

Using electrocardiography (ECG), the first large study by Greenwood *et al.*¹⁰, found “NW” axis deviation to be a significant predictor of death. Subsequent studies have focused on arrhythmias or ECG indications of hypertrophy. Griffin *et al.*¹² found that all the children who died in their group (17 of 32) had ventricular arrhythmias. Wiles *et al.*¹³ 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 Chabot²¹ reported identical results: arrhythmias were present in 16% of survivors and in 53% of those who died ($P<0.05$). Noguiera *et al.*²² and Weng *et al.*²³ reported similar results, but Chen *et al.*²⁴, Friedman *et al.*²⁵, and Muller *et al.*¹⁸ found no difference in the presence of arrhythmias between survivors and non-survivors.

Wiles *et al.*¹³ 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 that, 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.*²⁵ 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.*²⁶ found 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, $p < 0.05$).

Echocardiographic Measurements

Qualitative patterns—The first study published after Greenwood, by Taliercio *et al.*, found all 3 children who had severe mitral regurgitation at baseline died, but noted that it was an insensitive, albeit specific, prognostic factor.¹¹ However, the diagnosis was made by angiography, not by echocardiography as would be more commonly detected at first examination. Almost 20 years later, Azevedo *et al.*²⁷ studied a large group of Brazilian children 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.

Fractional Shortening—Chen *et al.*²⁴ were the first to find a difference in mortality by fractional shortening: LVFS was 20.7% in 12 survivors and 11.5% in 11 non-survivors. Subsequent studies from 1991 to 1998 by Wiles,¹³ Lewis,²¹ and Arola²⁸ found no such difference. In 2000, Noguiera *et al.*²² reported an association between lowered LVFS and mortality in a group of Portuguese children. In a study from a regional capture in West Scotland, Venugopalan *et al.*²⁹ found LVFS to be a significant predictor of death in univariate, but not multivariate, analysis. Azevedo *et al.*²⁷ had similar findings. Tsirka *et al.*¹⁶ 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.*¹⁴ in Australia and the PCMR¹⁵ 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—Among 25 children who presented with DCM after age 2 years, Akagi *et al.*³⁰ found that the ejection fraction was lower at presentation among the 18 who died (40.0% vs. 31.3%; $P<0.05$). Matitau *et al.*³¹ 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.*²³ found that LVEF predicted death in 18 children in Taiwan, and Azevedo *et al.*²⁷ found it to be an independent predictor of death in a multivariate survival analysis.

McMahon *et al.*³² 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), RV total ejection isovolume index, LVEF, and tricuspid Ea (early diastole) velocity were predictive on univariate analysis, and the latter two measures 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—Matitau *et al.*³¹ calculated the ratio 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 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.*²⁸ found left atrial dilatation to be the only echocardiographic predictor in a univariate survival analysis. Neither LVEDD nor LVESD was significant predictors. Azevedo *et al.*²⁷ 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.*¹⁶ found LVEDD and LVESD median z-scores to be associated with death and transplant, but neither were 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.¹⁵

Kimball *et al.*³³ 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 characteristics of long-term survivors and not on predictors of mortality or transplant.)

Carvalho *et al.*³⁴ studied 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,¹⁵ 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.

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.*¹¹ who found that cardiomegaly identified on chest radiographs was not predictive. In children who presented after age 2 years, Akagi *et al.*³⁰ found increased mortality among those

with a cardiothoracic (CT) ratio greater than 65%. Nevertheless, four subsequent studies (Chen *et al.*²⁴ Wiles *et al.*¹³ Venugopalan *et al.*³⁵ and Azevedo *et al.*³⁶) found similar CT ratios between survivors and non-survivors. In one study, a univariate survival analysis showed a 100% survival among those with absent cardiomegaly at baseline (median follow up 43 months, log-rank $p = 0.0189$).³⁶ However, using a factor that is commonly seen at presentation (between 88%³⁰ to 100%^{13, 24} of all cases) extinguishes the ability to discriminate outcomes at baseline and explain the larger number of negative study results.

Pulmonary vascular congestion, as determined by chest radiograph, was one of the first predictors reported by Greenwood *et al.*¹⁰ and subsequently reported as a predictor by Azevedo *et al.*³⁶ Although Arola *et al.*²⁸ showed a worse outcome when pulmonary congestion was present, it was not statistically significant ($p = 0.06$).

Family History

Several studies have investigated family history of cardiomyopathy (CM) as a predictor. The first was Griffin *et al.*¹², 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.*²⁴ 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.*³⁷ found a significant univariate association between a family history of CM and death or transplant ($P=0.033$), and Daubeney *et al.*³⁸, in the Australian population cohort, found a significant multivariate association ($HR = 2.9$). However, Venugopalan *et al.*²⁹ found no association with mortality and the PCMR¹⁵ found no significant difference between survivors and those who died or received transplants.

Age at Diagnosis

Griffin *et al.*¹² 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.*¹¹ 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.¹³ Di Filippo *et al.*³⁷, in 103 French children, also found a greater risk of death in children over 2 years old (57% vs. 33%). Similarly, Burch *et al.*³⁹ 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%CI = 1.7 to 12.7).

Carvalho *et al.*³⁴ found age over 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 Cil⁴⁰ 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.

In a break from the trend, Tsirka *et al.*¹⁶ 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 ($HR = 4.5$). In Australian children diagnosed between birth and 10 years of age, Daubeney *et al.*³⁸ found children older than 5 years at presentation to be at greater risk in

a multivariate analysis (HR = 5.6). Similarly, the PCMR¹⁵ found an age difference in event-free survival; however, the cutoff was age 6.

Despite the other positive findings, Chen *et al.*²⁴, Lewis and Chabot,²¹ and Azevedo *et al.*³⁶ did not find an age-related difference in mortality using the 2 year cutoff. Although they did not use the 2-year mark, Akagi *et al.*³⁰ reported no baseline age difference in mortality. Likewise, Venugopalan *et al.* did not find an age difference when comparing mortality or disease progression with recovery in Oman³⁵ or in West Scotland²⁹ when reviewing overall mortality.

Cardiac Catheterization

One of the initial findings by Greenwood *et al.*¹⁰ was that a cardiac index higher than 3 L/min/m² was a risk factor for death. A subsequent study by Akagi *et al.*³⁰ found no difference by mean cardiac index values at baseline between those who died and those who did not.

Lewis and Chabot²¹ 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 useful cutoff for predicting death, with a clear separation of survival curves at 6 months (log rank, $P < 0.05$). Burch *et al.*³⁹ 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.*³¹ 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.*²⁹

Myocarditis

Taliercio *et al.*¹¹ was 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.*³¹ 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.*⁴¹ 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 myocarditis; however, children with a definite or probable diagnosis of myocarditis according to the Dallas Criteria⁴² fared better than those with non-specific histologic findings. Event-free survival was 100% (15 of 15) in the 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.*³⁸ found in the Australian cohort 70 biopsy records of which 25 exhibited lymphocytic myocarditis. 12 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 West Scotland, of the 14 cases of myocarditis enumerated by Venugopalan *et al.*²⁹ 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 includes 9 of 14 myocarditis cases diagnosed at autopsy. The most recent

finding on the matter from the PCMR¹⁵ showed that children with idiopathic disease were worse off than those with myocarditis (HR = 2.06).

Even without tissue diagnosis, indicating the potentially protective effect of myocarditis, Bostan and Cil⁴⁰ 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.

Endocardial Fibroelastosis

In the first analysis to consider endocardial fibroelastosis (EFE) within the diagnosis of DCM, Chen *et al.*²⁴ 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, Matitau *et al.*³¹ 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.*²⁸ 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.

Other Baseline Factors

Some significant prognostic factors have only been reported by a few studies. Burch *et al.*³⁹ found mural thrombus to be a univariate predictor of mortality. In the Finnish population cohort, Arola *et al.*²⁸ found CHF and 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 PCMR¹⁵ 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 group²⁸, 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.*⁴³ concluded that impaired cardiac adrenergic innervation, as measured by cardiac radiolabeled meta-iodobenzylguanidine imaging, led to worse outcomes. However, 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.*¹⁶ has reported an increased risk of death or transplant in girls (HR = 3.0). However, this finding has not been present in several other studies.^{15, 24, 30, 36, 40}

Longitudinal Factors

There has also been speculation about factors that can predict survival when observed longitudinally. Griffin *et al.*¹² were the first to report that persistent cardiomegaly as indicated by chest radiography (defined as a CT ratio of greater than 70%) was a risk factor for death. However, their follow-up measurements were taken at a mean of 4 years from presentation. Azevedo *et al.*³⁶ also reviewed longitudinal CT ratio figures and found a separation of groups based on mortality within 3 months using a CT ratio limit of 68%.

Friedman *et al.*²⁵ reported a significant association between mortality and the persistence from baseline to follow-up of CHF symptoms (OR = 11.7) and ST or T wave changes, or both, on ECG (OR = 16.6). The length of time between ECG measurements is reported to be ≥ 6 months,

however, it is unclear about the last ascertainment of CHF symptoms. Additionally, uncontrolled atrial fibrillation or flutter was associated with death in this group of children.

Although Lewis and Chabot²¹ originally did not find a statistical difference in survival based on LVFS at presentation, a subsequent study⁴⁴ with roughly the same patients (81 of 96 patients) showed that among those who survived more than 1 month ($n = 53$), a follow-up LVFS of less than 15% was associated with worse survival: in the low LVFS group, 1-year survival was 46% and 5-year survival was 29% ($P < 0.05$).

In the Finnish population cohort, Arola *et al.*²⁸ found that use of intravenous inotropic or vasodilative therapy anytime during follow-up was a significant predictor of mortality in univariate survival analyses, but not in multivariate analysis. However, anticoagulant therapy administered during follow-up was statistically significant in multivariate survival analyses.

In the study by Azevedo *et al.*²⁷, repeated-measures analyses were performed on the echocardiographic values collected from 148 children over 477 visits. In comparison to the longer list of univariate predictors cited above, they found that mortality could be predicted by several factors followed longitudinally: LAD, LAD-Aorta ratio, LVESD, LVEDD, LV Mass, LVEF, LVFS, and RV dimension. Additionally, in survivors, mitral and tricuspid regurgitation remained absent or mild, whereas among those who died, regurgitation progressed from mild to moderate or severe. The groups were clearly distinct from within several months after presentation until 72 months of observation. In the same study group,³⁶ CT ratio is also seen to become clearly distinct between survivors and non-survivors within 3 months at a mean CT ratio of 68%.

In the Australian population cohort, Daubeney *et al.*³⁸ found that changes in LVFS from presentation, both as raw percentages and z-scores, were associated with death or transplant. From their multivariate model, z-score change was a beneficial independent predictor (HR = 0.68 per unit z-score).

DISCUSSION

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 more 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 may be prohibitive. However, with data suggesting that biopsy-proven myocarditis may be protective, the acquisition of tissue for histological analysis to guide treatment plans will weigh in on the consideration. 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.*⁴⁵ and Pophal *et al.*^{45, 46}

The deleterious effect of EFE was observed in three studies, although all had a heavy bias of diagnosis at autopsy, limiting its clinical utility. These results were all produced after Paul

Lurie's editorial, which proposed that EFE is not a disease in and of itself but the possible result of a myriad of diseases.⁴⁷ The editorial was written as a response to the study by Ino *et al.*⁴⁸, which classified EFE as its own disease, much as Greenwood *et al.*¹⁰ in 1976 and the WHO placing EFE as an "unclassified" cardiomyopathy, currently.¹ Recent investigations into EFE, however, have suggested that it might be a specific reaction to the Mumps virus.⁴⁹ 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 lines, childhood vaccination against coxsackievirus B and adenovirus was proposed as potential mitigators of myocarditis.⁵⁰

Although several studies have been performed since 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;"⁵¹ the strongest predictors remain those that had already been identified at the time of his statement.

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 would 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 has that dataset and can provide the needed information. The initial findings were published in *JAMA*¹⁵ and corroborate some other findings (older age at diagnosis and lower LVFS); however, a more comprehensive predictive algorithm is needed.

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). These studies show that the current prognosis of heart death is similar to the earlier survival estimates before transplant was common.

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 was approximately 70% in their most recently reported Kaplan-Meier plot.⁵ 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"⁵¹ for dilated cardiomyopathy, from diagnosis through post-transplant survival.

CONCLUSION

From 32 studies published over 30 years and including 3046 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. A unified clinical risk algorithm is still needed to stratify mortality, transplant, and recovery. 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. New studies are needed to assess the post-transplant survival experience and to identify pre-transplant prognostic factors.

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

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

No.	Reference	Year	Accrual		N	Death (n)	Mortality (%)	Follow-up (months)		Survival (%)	
			Start	End				Mean	Median	1-year	5-year
26	Huh ²⁶	2004		NR	33	5	16	72	63		NR
27	McMahon ³²	2004	1999	2002	54	3	6	NR	21		NR
28	Tsirka ¹⁶	2004	1990	1999	91	11	12		NR	90/70*	83/58*
29	Weng ²³	2005	1990	2004	18	13	72	NR	7	50	NR
30	Daubeney ¹⁴	2006	1987	1996	184	75	41	38		72*	63*
31	Bostan ⁴⁰	2006	1995	2004	40	2	5	40			NR
32	Towbin ¹⁵	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, 1994,¹ and Azevedo, 2004,²

NR = data not reported.