# The Variable Natural History of Idiopathic Dilated Cardiomyopathy

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**ABSTRACT:** **Background:** Determining the prognosis of patients with heart failure is essential for patient management and clinical trial conduct. The relative value of traditional prognostic criteria remains unclear and the assessment of long-term prognosis for individual patients is problematic.

**Objectives:** To determine the ability of clinical, hemodynamic and echocardiographic parameters to predict the long-term prognosis of patients with idiopathic dilated cardiomyopathy.

**Methods:** We investigated the ability of clinical, hemodynamic and echocardiographic parameters to predict the long-term prognosis of individual patients in a large, representative, contemporary cohort of idiopathic dilated cardiomyopathy (IDCM) patients referred to Johns Hopkins from 1997 to 2004 for evaluation of cardiomyopathy. In all patients a baseline history was taken, and physical examination, laboratory studies, echocardiogram, right heart catheterization and endomyocardial biopsy were performed.

**Results:** In 171 IDCM patients followed for a median 3.5 years, there were 50 long-term event-free survivors (LTS) (median survival 6.4 years) and 34 patients died or underwent ventricular assist device placement or transplantation within 5 years (NLTS; non-long-term survivors) (median time to event 1.83 years. Established risk factors (gender, race, presence of diabetes, serum creatinine, sodium) and the use of accepted heart failure medications (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers) were similar between the two groups. Although LTS had younger age, higher ejection fraction (EF) and lower New York Heart Association (NYHA) class at presentation, the positive predictive value of an EF ‹ 25% was 64% (95% CI 41%–79%) and that of NYHA class › 2 was 53% (95% CI 36–69%). A logistic model incorporating these three variables incorrectly classified 29% of patients.

**Conclusions:** IDCM exhibits a highly variable natural history and standard clinical predictors have limited ability to classify IDCM patients into broad prognostic categories. These findings suggest that there are important host-environmental factors still unappreciated in the biology of IDCM.

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**KEY WORDS:** cardiomyopathy, congestive heart failure, prognosis, epidemiology

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Cardiomyopathy is an important cause of heart failure and is largely due to idiopathic dilated cardiomyopathy [1,2]. Since the 1980s, many variables that predict survival in patients with idiopathic cardiomyopathy and congestive heart failure have been identified. These include increasing age [3], a low left ventricular ejection fraction [4], increasing New York Heart Association class [5], high left ventricular filling pressures [6], left ventricular dilation [6], marked intraventricular conduction delay (including a permanent pacemaker) [7], complex ventricular arrhythmias [4], atrial fibrillation [4], low left ventricular mass, the presence of moderate or greater mitral regurgitation [8], an increased left atrial size [9], right ventricular enlargement [10], and a reduced right ventricular ejection fraction [11]. It is believed that the natural history of the disease is tied to the measured parameters and that these variables can classify patients into risk strata. The ejection fraction and NYHA classification have emerged as dominant enrollment criteria for a broad array of clinical trials conducted over the past two decades.

The link between these prognostic factors and the biology of the disease remains incompletely understood and the use of these factors in managing individual patients is potentially misleading [12]. This can impair patient management as these patients have a poor prognosis with mortality rates of 25% to 30% at one year and approximately 50% at 5 years (range 35–6%) [13]. This is highly germane to the quest to develop and allocate new heart failure therapies. The treatment of heart failure and cardiomyopathy is rapidly evolving with the introduction of newer therapies that improve

NYHA = New York Heart Association

survival, such as beta blockers, cardiac resynchronization therapy, implantable defibrillators and emerging cell-based therapy. These issues make it difficult to translate the results of research studies to individual patients.

The clinical management of patients is also impaired by these factors since the highly variable outcomes possible for patients with heart failure due to cardiomyopathy may not be recognized. Most physicians believe that all heart failure syndromes are invariably progressive, that all patients will follow a similar trajectory, and that true recovery may not be achievable for a portion of the patient population. Accordingly, it is important to recognize the limitations of currently available diagnostic testing, and to appreciate the variable natural history of dilated cardiomyopathy.

In the present study we tested the hypothesis that current criteria offer only a poor estimation of prognosis for individual patients and may not reflect host-environment interactions in diseases of heart muscle. We investigated the ability of clinical, hemodynamic and echocardiographic parameters to predict the long-term prognosis of individual heart failure patients in the modern setting in a large, representative, contemporary cohort of patients with idiopathic dilated cardiomyopathy.

## PATIENTS AND METHODS

The Institutional Review Board of Johns Hopkins Hospital approved this study. The study was conducted in a cohort of patients referred to Johns Hopkins from 1997 to 2004 for evaluation of cardiomyopathy. All patients underwent a history taking (which included a comprehensive family and social history), physical examination, laboratory studies, echocardiogram, right heart catheterization and endomyocardial biopsy at baseline. After this evaluation, consenting patients in whom no cause of cardiomyopathy was found were classified as having idiopathic dilated cardiomyopathy and were included in the study (n=180). These patients were followed to assess vital status using the Social Security Death Index. In addition, hospital databases were reviewed to assess if the patient had undergone cardiac transplantation or implantation of a ventricular assist device. Complete follow-up was available in 171 patients (median duration of follow-up was 3.5 years).

### STATISTICAL ANALYSIS

To assess associations between covariates, categorical variables were tested using the chi-square test or the Fisher exact test if the number of observations in a cell was < 5. All continuous variables were compared by the *t*-test if the variable showed a normal distribution (tested visually using a histogram and a Quantile-Quantile plot of the candidate variable against the inverse normal). Those continuous variables that were not normally distributed were tested using the Wilcoxon rank-sum test.

To determine the most useful predictors in the cohort, a Cox-regression model was developed. Due to the large number of predictable variables, we were concerned about the possibility of model over fitting. This can occur when substantially fewer than 10 events per variable are considered [14]. Therefore, we used serial bootstrapping to reduce the number of candidate variables in an unbiased way. Bootstrapping involves the generation of many new datasets by random sampling and replacement of the main cohort set [15]. We generated 1000 bootstrap re-sampled datasets with replacement and performed a stepwise Cox regression analysis on each one. Variables had to achieve a $P$ value < 0.05 to enter the model stepwise Cox model. Those variables that enter at least 50% of the models were considered for a second set of 1000 bootstrap-based analyses. The resulting variables that enter at least 50% of these models are likely to be the most robust predictors in this dataset.

The utility of these variables was then assessed by determining how accurate these variables are at predicting whether a patient will have > 5 years of event-free survival. The variables were assessed individually and in combination using logistic regression models. Receiver-operator curves were drawn, and as a measure of the correct classification of patients the area under the curve was calculated for each variable as well as for combinations of variables. All analyses were conducted using STATA 8.0 for windows. A $P$ value < 0.05 was considered statistically significant.

## RESULTS

### PATIENT CHARACTERISTICS

The clinical characteristics of the patients are outlined in Table 1. The majority of patients were male and Caucasian, distributed over a wide age range. Patients were symptomatic for an average of 11 months and 44% were classified as NYHA class 1 or 2. A number of patients had comorbidities such as hypertension (47%) and diabetes (22%). Most patients were on either an angiotensin-converting enzyme inhibitor or angiotensin receptor blockers, over half of them were on beta blockers (58%), and 11% of patients had an implantable cardioverter defibrillator. The use of beta blockers varied with time: before 1999, 30% of patients were on beta blocker; from 1999 to 2002, 58%; and after 2002, 77%.

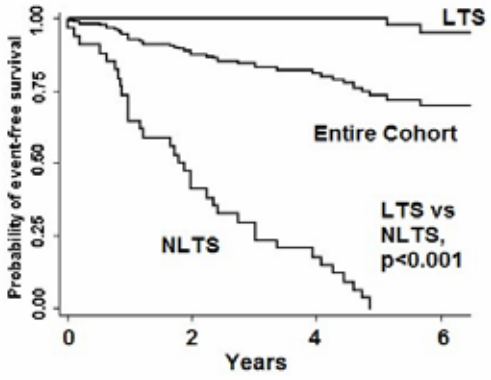
Of 171 patients with idiopathic dilated cardiomyopathy, there were 50 long-term event-free survivors (29%) (median survival 6.4 years) and 34 patients (20%) sustained an event within 5 years (median time to event 1.83 years). Eighty-seven patients did not sustain an event but had less than 5 years of follow-up and therefore did not fall in either category. Of the patients with events (non-long-term survivors), 26 patients

**Table 1.** Baseline characteristics of patients

| Demographics/History | Entire cohort (n=171) | Patients with long-term events (NLTS) (n=34) | Survivors (LTS) (n=50) | *P* value |
|---|---|---|---|---|
| Male (%) | 100 (58%) | 23 (68%) | 30 (60%) | 0.5 |
| Caucasian | 113 (66%) | 23 (68%) | 34 (68%) | 0.97 |
| Age (yrs, mean ± SD) | 48.6 ± 15 | 53.6 ± 19 | 45.4 ± 14 | 0.02 |
| Symptom duration (months, mean ± SD) | 11 ± 20 | 15 ± 24 | 10 ± 19 | 0.3 |
| NYHA 1 | 9 (11%) | 1 (3%) | 8 (16%) | |
| NYHA 2 | 39 (46%) | 14 (41%) | 25 (50%) | 0.03 |
| NYHA 3 | 31 (37%) | 14 (41%) | 17 (34%) | |
| NYHA 4 | 5 (6%) | 5 (15%) | 0 (0%) | |
| Hypertension | 80 (47%) | 14 (44%) | 28 (56%) | 0.3 |
| Diabetes mellitus | 35 (21%) | 9 (26%) | 12 (24%) | 0.8 |
| Hypercholesterolemia | 37 (22%) | 9 (26%) | 11 (22%) | 0.6 |
| End-stage renal disease | 11 (6%) | 3 8%) | 3 (6%) | 0.7 |
| History of ventricular tachycardia | 18 (11%) | 6 (18%) | 5 (10%) | 0.3 |
| Never smoked | 83 (49%) | 14 (41%) | 24 (48%) | 0.5 |
| Family history | 19 (11%) | 3 (9%) | 4 (8%) | 0.9 |
| **Medications/treatment** | | | | |
| Beta blocker | 99 (58%) | 17 (50%) | 23 (47%) | 0.8 |
| ACE inhibitor or ARB | 145 (85%) | 30 (88%) | 42 (86%) | 0.7 |
| Digoxin | 81 (47%) | 20 (59%) | 27 (55%) | 0.7 |
| Spironolactone | 26 (15%) | 9 (26%) | 2 (4%) | 0.004 |
| Loop diuretic | 121 (71%) | 29 (85%) | 33 (67%) | 0.06 |
| ICD | 19 (11%) | 6 (17%) | 4 (8%) | 0.2 |
| Pacemaker | 11 (6%) | 1 (3%) | 2 (4%) | 0.9 |
| **Physical exam** | | | | |
| Body mass index | 28 ± 6 | 26 ± 6 | 28 ± 6 | 0.2 |
| Heart rate (bpm) | 85 ± 16 | 88 ± 19 | 82 ± 16 | 0.2 |
| Systolic BP (mmHg) | 129 ± 25 | 124 ± 26 | 132 ± 27 | 0.2 |
| Diastolic BP (mmHg) | 75 ± 15 | 71 ± 13 | 79 ± 15 | 0.001 |
| **Investigations** | | | | |
| Sodium (mean ± SD) | 138 ± 3.5 | 137 ± 4.9 | 138 ± 2.7 | 0.12 |
| Potassium | 4.3 ± 0.6 | 4.5 ± 0.5 | 4.3 ± 0.6 | 0.05 |
| Creatinine | 1.5 ± 1.8 | 1.7 ± 2.1 | 1.4 ± 1.6 | 0.5 |
| Ejection fraction (mean ± SD) | 25 ± 11 | 21 ± 10 | 28 ± 12 | 0.004 |
| LV diastolic dimension# | 6.1 ± 1.1 | 6.5 ± 1.5 | 6.2 ± 0.9 | 0.2 |
| No mitral regurgitation+ | 42 (32%) | 3 (11%) | 15 (42%) | |
| Mild mitral regurgitation+ | 44 (33%) | 11 (39%) | 12 (33%) | 0.03 |
| Moderate mitral regurgitation+ | 34 (25%) | 10 (36%) | 7 (19%) | |
| Severe mitral regurgitation+ | 13 (10%) | 4 (14%) | 2 (6%) | |
| Sinus rhythm | 137 (80%) | 31 (91%) | 38 (76%) | |
| Mean QRS duration* | 111 ± 31 | 116 ± 36 | 107 ± 24 | 0.2 |
| QRS > 120 ms* | 41 (28%) | 16 (47%) | 18 (37%) | 0.3 |
| PA systolic (mmHg) | 38 ± 15 | 43 ± 17 | 38 ± 15 | 0.15 |
| PA diastolic (mmHg) | 18 ± 9 | 20 ± 10 | 18 ± 9 | 0.4 |
| Pulmonary capillary wedge pressure (mmHg) | 16 ± 9 | 17 ± 9 | 16 ± 9 | 0.6 |
| Cardiac output (L/min) | 4.36 ± 1.4 | 3.9 ± 1.5 | 4.5 ± 1.3 | 0.05 |

#Data available for 141 patients, +data available for 133 patients, *data available for 145 patients
ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blockers, ICD = implantable cardioverter defibrillator, LV = left ventricular, PA = pulmonary artery

**Figure 1.** Actuarial event-free survival of patients with idiopathic dilated cardiomyopathy evaluated from 1997 to 2004 with superimposed survival curves of LTS and NLTS by the Kaplan-Meier method. The actuarial survival of the entire cohort is comparable to that of other large contemporary cohorts of idiopathic dilated cardiomyopathy such as the DEFINITE [16] and SCD-HEFT [17] trials. In the cohort, there were 50 long-term event-free survivors (LTS) (29%) and 34 patients (20%) died or underwent ventricular assist device placement or transplantation within 5 years (NLTS). As depicted by the Kaplan-Meier curves, there is a marked contrast in prognosis of LTS and NLTS patients within the cohort ($P < 0.001$) and the curves diverge widely (median event-free survival 6.4 years for LTS compared to 1.83 years for NLTS).




died, 4 received cardiac transplant and 4 received a ventricular assist device. The difference in survival of these groups is highlighted by the Kaplan-Meier curves [Figure 1]. The clinical characteristics of these patients are described in Table 1.

LTS were significantly younger than NLTS. Established risk factors including gender, race, diabetes, serum creatinine or serum sodium were not different between these groups. There was no difference in presence of sinus rhythm, hypertension, diabetes, hypercholesterolemia, smoking, family history, end-stage renal disease (defined as the need for renal replacement therapy, hemodialysis or peritoneal dialysis), or body mass index. The use of ACE inhibitors, ARB and beta blockers was identical in the two groups. There was lower spironolactone use in LTS. Serum potassium was slightly lower in LTS (4.3 ± 0.6 compared to 4.5 ± 0.5, $P = 0.04$). LTS had significantly higher mean arterial pressure (97 ± 18 compared to 89 ± 15, $P = 0.03$). Patients with LTS had a higher ejection fraction (28% vs. 21%, $P = 0.008$), less mitral regurgitation ($P = 0.03$) and lower NYHA class ($P = 0.01$) compared to NLTS.

LTS = long-term event-free survivors
NLTS = non-long-term survivors
ACE = angiotensin-converting enzyme
ARB = angiotensin receptor blockers

### PREDICTORS OF OUTCOME

The results of the stepwise Cox models in the bootstrapped datasets showed that the most consistent predictors of outcome were age (entered 95% models), NYHA class (entered 78% models) and ejection fraction (entered 77% models). In a Cox model on the original dataset that included the three variables, a 10 year increase in age was associated with a hazard ratio of 1.31 (95% confidence interval 1.06–1.63, $P = 0.014$), increase in NYHA class was associated with a hazard ratio of 2.27 (95% CI 1.32–3.91, $P = 0.003$) and a 10% increase in EF was protective with a hazard ratio of 0.65 (95% CI 0.44–0.95, $P = 0.027$).

### PROGNOSTIC ABILITY

The only independent predictors of LTS versus NLTS were age, EF and NYHA class, as expected from the stepwise models. Kaplan-Meier curves based on strata of these variables are shown in Figure 2. Using ejection fraction alone, 66% of the patients could be correctly classified as LTS. The positive predictive value of an EF < 25% was 64% (95% CI 41–79%) and the AUC for EF was 0.68. NYHA class > 2 had a positive predictive value of 53% (95% CI 36–69%). Using age alone, we could correctly classify 69% of patients and the AUC for age was 0.64. A logistic model incorporating age, ejection fraction and NYHA class correctly classified only 71% of the patients as NLTS versus LTS. The AUC for the model was 0.75 [Figure 3]. In addition, those patients who were identified as having a poor prognosis based on the logistic model of age, NYHA and EF had a median survival of 4.9 years [Figure 2D], as compared to the median survival of 1.8 years of NLTS [Figure 1]. The results of these analyses did not change significantly when restricted to the years after 1999, when the major beta blocker trials were published.

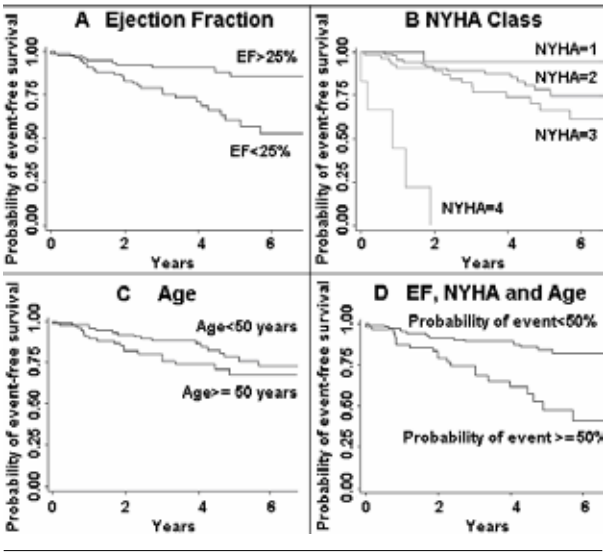
## DISCUSSION

The major new finding of this study was the strong heterogeneity of prognosis in IDCM in the current era, as highlighted by the two extremes of phenotypes LTS and NLTS, and the limited ability of clinical predictors to differentiate between these two groups. The strongest independent predictors of outcome were, as previously recognized, age, EF and NYHA class. However, despite their strong independent association with mortality, these clinical predictors were not capable of clearly differentiating these two groups. Even when using a combination of the predictors we found that 29% of the patients were incorrectly classified. These findings have important clinical and biological implications, given the importance of assessing prognosis for individual patients and the ongoing quest to develop and appropriately target new therapies. The characteristics of the patients in our cohort and the event rates were similar to other series of non-ischemic cardiomyopathy patients. For example, the actuarial survival of the patients in our study with EF < 36% was almost identical to that of the DEFINITE [16] and SCD-HEFT [17] trials. Our event rate was also comparable to an Italian cohort that reported 76% transplant-free survival at 5 years [18].

Our results are consistent with previous reports that found strong associations between age [3], NYHA class [4] and EF [5] and outcomes in patients with IDCM. Although prior attempts to develop prognostic models have used different variables from those described above, the AUC for these models is remarkably similar to that found in the present study. For example, Aaronson et al. [19] report an AUC of 0.74 for a model that included clinical variables, invasive measurements as well as peak oxygen consumption ($VO_2$). Similarly, Levy et al. [20] found an AUC of 0.729 in the Seattle Heart Failure model that included novel predictors such as uric acid and lymphocyte count. While we too found comparably strong associations between clinical predictors and mortality using a relatively simple model (AUC 0.75), our data suggest that the clinical utility for an individual patient seems to be limited as these variables were unable to correctly classify patients into broad prognostic categories.

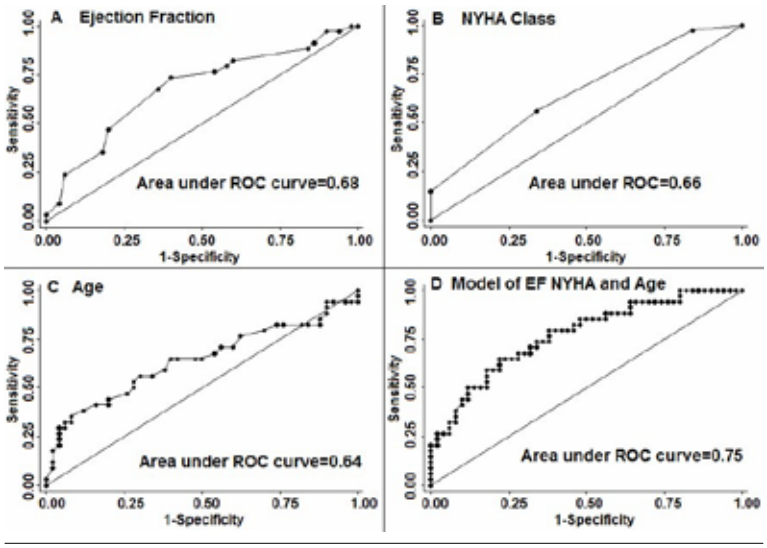
Our findings on the limitations of clinical parameters for predicting the prognosis of individual patients with IDCM have important clinical and research implications. Clinical decisions are made on the basis of these parameters and must be weighed carefully, keeping in mind the limitations of these factors. Prognosis is often conveyed to a patient on the basis of EF, NYHA class and other clinical parameters, and this discussion should be tempered by the fact that these parameters have limitations when applied to the individual patient. In addition, the design of randomized controlled

**Figure 2.** Kaplan-Meier survival curves among strata of predictive variables. The curves were drawn based on the strongest conventional predictors of outcome in the cohort generated from a bootstrapped stepwise cox proportional hazards regression analysis of all the variables in Table 1. These were **[A]** EF, **[B]** NYHA class, **[C]** age, and **[D]** a combination of these in a logistic regression model. As depicted, these variables are associated with differences in survival within the cohort ($P < 0.01$ for all comparisons), but they do not identify the same contrast in prognosis seen in the Kaplan-Meier curves of NLTS vs. LTS in Figure 1.




CI = confidence interval
EF = ejection fraction
AUC = area under the curve
IDCM = idiopathic dilated cardiomyopathy

**Figure 3.** Receiver-operator characteristic (ROC) curves for the predictive variables. The ROC curves were drawn for the strongest conventional predictors of outcome in the cohort generated from a bootstrapped stepwise cox proportional hazards regression analysis of all the variables in Table 1. These were **[A]** EF, **[B]** NYHA class, **[C]** age, and **[D]** a combination of these in a logistic regression model. The four graphs show that these variables are predictive of outcome to some degree, but there is still significant misclassification of patients; for example, based on the logistic model incorporating age, ejection fraction and NYHA class **[D],** approximately 29% of the patients would be incorrectly classified as having 5 year event-free survival.




trials involves using clinical criteria in patient selection, with the intention of enrolling a homogeneous group and then randomizing these patients to the intervention or control arm. However, as our data highlight, clinical predictors have limitations, indicating that patients enrolled in the randomized controlled trials may actually be heterogeneous, introducing a source of inaccuracy in the study. This study emphasizes the need for continued research into this area to develop better predictors of outcome in these patients, and in this regard we recently reported on the use of transcriptomic based biomarkers that may address this issue [21].

There are new attempts to develop biomarkers with genomic [22] and proteomic technology to refine diagnosis and prognosis of cardiomyopathy. Given the variable natural history and the limitations of clinical predictors as found in our study, these efforts are justified. In addition, these markers appear to be more closely related to the pathophysiology of the disease, and exploring these avenues may provide insights into the reasons for the variable natural history of the disease suggested in our study. For example, the variable natural history observed may be due to different underlying etiologies of the disease which have a common final pathway leading to the appearance of a more homogeneous condition that we call IDCM [23,24].

This study has some limitations. There may be referral bias as this was a hospital-based cohort of patients; however, this allowed us to capture a larger number of patients than we would otherwise have. Also, while we attempted to collect a broad number of clinical variables, we were unable to collect data on every variable associated with long-term outcomes including peak oxygen consumption and pro-brain natriuretic peptide. Finally, family history in this cohort was not obtained using current guidelines, which include a three to four-generation family history and clinical screening of first-degree family members. This might have resulted in a relatively low prevalence of patients identified as having a familial cardiomyopathy. The impact of genetic influence on prognosis will require ongoing study. We believe, however, that we captured the more important variables routinely used in clinical practice to evaluate these patients. Also, as described above, these variables provided prognostic information comparable to previous reports.

In addition, as reported in previous studies, we used the same dataset to develop predictor variables as to test them, which results in the over-estimation of prognostic ability of these variables [5]. We used bootstrapping to help overcome this limitation, but in spite of this it is likely that we overestimated the ability of these variables to correctly classify patients. Therefore, even though in our study 71% of patients were appropriately identified to have a poor outcome, in clinical practice the discriminatory value of clinical predictors is likely to be even less than this. In addition, even patients who were identified as having a poor prognosis based on their age, NYHA and EF had a median survival of 4.9 years compared to the median survival of 1.8 years of NLTS [Figure 1], which highlights the degree of misclassification. This reinforces our belief that even the limited ability of clinical variables to predict long-term outcomes is probably over-estimated. Finally, only patients who underwent endomyocardial biopsy were enrolled in this study and this may have introduced selection bias. However, endomyocardial biopsy is helpful in determining the etiology of cardiomyopathy [25] and is often included in the workup of patients with cardiomyopathy; therefore, we believe our strategy reduced misclassification of the etiology of cardiomyopathy.

Our data highlight the variable natural history of idiopathic dilated cardiomyopathy and the limitations of clinical predictors in correctly identifying patients with good long-term prognosis. Ongoing attempts to develop biomarkers of disease prognosis are warranted for the management of individual patients with heart failure and for the conduct of clinical trials.

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