



Original Article

Long-term outcomes of non-ischemic dilated cardiomyopathy patients with left ventricular ejection fraction $\leq 19\%$ on medical therapy



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ARTICLE INFO

Article history:

Received 16 March 2020

Accepted 7 July 2020

Available online 21 July 2020

Keywords:

Dilated cardiomyopathy

Very low left ventricular ejection fraction

Outcomes

ABSTRACT

Background: Patients with heart failure and reduced ejection fraction in low resource settings may not have access to devices and expensive therapeutic options. We followed up a cohort of patients with non-ischemic dilated cardiomyopathy (DCM) with very low left ventricle ejection fraction (LVEF $\leq 19\%$) on low cost medical therapy alone. By selecting patients with such low LVEF, this study was restricted to patients with severe disease. We studied long-term transplant free survival of these patients.

Methods and results: The study enrolled 130 patients (83 men and 47 women) of DCM cohort with LVEF $\leq 19\%$ from April 2003–December 2018 on medical therapy alone. Mean age was 40.35 ± 13.9 years. Mean follow-up was 45.6 ± 39 months while median follow-up was 39 months (range: 0–176 months). Patients on devices (ICD/CRT) for heart failure management were excluded. Fifty-four patients died and three underwent transplant during the study. Median survival was 86 months (S.E. 22.38). 113 patients had follow-up till end of study. In the worst case scenario, if all 17 patients who were lost to final follow-up were assumed to be dead, the median survival was still 57 (S.E.9.28) months. Higher baseline NYHA class, recurrent heart failure hospitalizations, absence of treatment with beta-blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers and aldosterone antagonists were predictors of death on univariate analysis whereas none of these parameters were significant on multivariate analysis.

Conclusions: Median survival of our DCM cohort with LVEF $\leq 19\%$ on medical therapy was over 7 years.

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1. Introduction

Prognosis of idiopathic dilated cardiomyopathy (DCM) was considered ominous in the past, with a mortality of approximately 50% in the first 2 years following diagnosis.^{1–3} Introduction of beta-blockers, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blocker (ARB), neprilysin inhibitors and aldosterone antagonists had markedly improved survival of patients with heart failure and reduced ejection fraction.^{4–11} Recent studies have shown that around one-third patients of DCM on tailored medical therapy show improvement in left ventricular ejection fraction (LVEF).^{12–15}

Patients have variable presentations which range from asymptomatic left ventricular dysfunction to mild, moderate, or severe congestive heart failure. There are several studies on DCM patients that looked into prognosis and outcomes after insertion of devices like biventricular pacing, implantable cardioverter defibrillator and recently mitra clip which affect natural history.^{16–19} We have a large cohort of patients who had not received devices due to financial constraints or other reasons and were on guideline directed medical therapy. Many clinicians carry an impression that dilated cardiomyopathy patients with left ventricular ejection fraction (LVEF) $\leq 19\%$ have poor long-term outcomes. Outcomes of these patients are not well defined. The aim of this study was to define the long-term outcomes of DCM patients with LVEF $\leq 19\%$.

2. Methods

From April 2003 to December 2018, DCM patients with LVEF $\leq 19\%$ from DCM cohort of a tertiary care hospital, Postgraduate Institute

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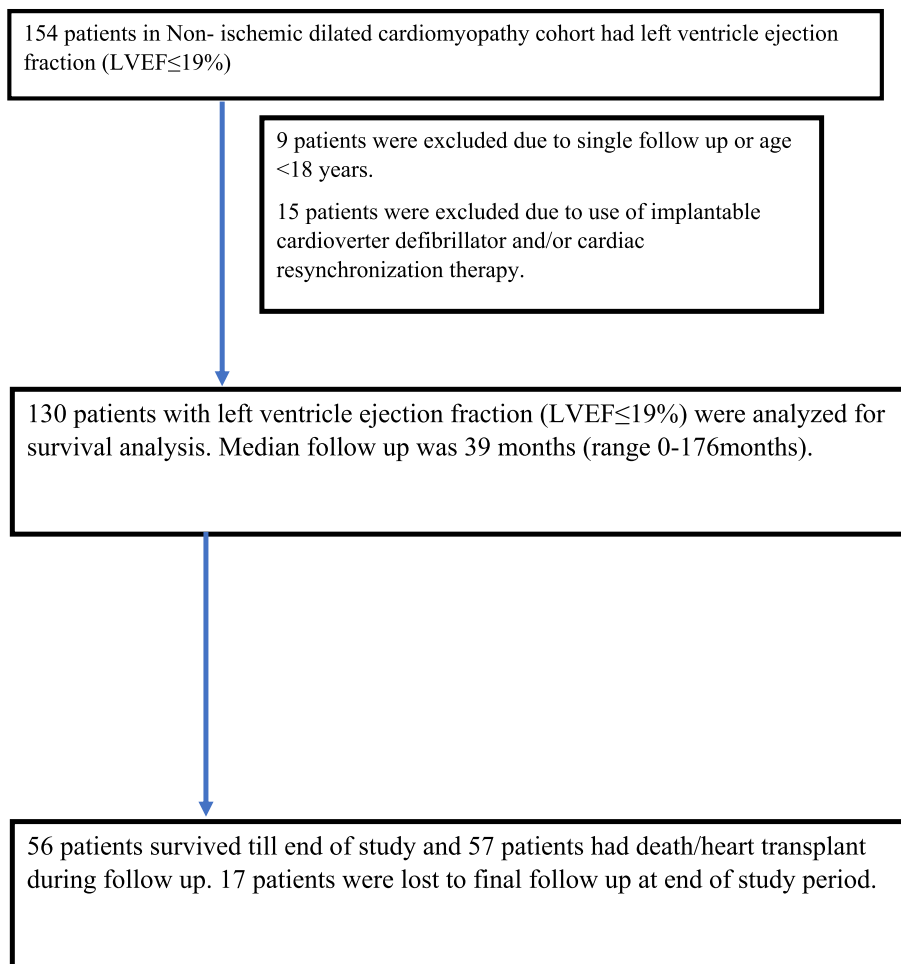


Fig. 1. Flow chart of patients in the study.

of Medical Education and Research, Chandigarh were enrolled in this study. It was a retrospective cohort analysis. The protocol was in accordance with the Helsinki Convention and was approved by the local ethics committee.

DCM was defined according to World Health Organization criteria.²⁰ Only the patients with left ventricular ejection fraction $\leq 19\%$ were included in the study. Patients recruited in the cohort from April 2003 to April 2017 were included in the study and followed till December 2018.

Inclusion criteria (all the following should be met) included.

- (i) Age above 18 years.
- (ii) No history of coronary artery disease or myocardial infarction.
- (iii) All patients ≥ 35 years of age underwent coronary angiography at diagnosis and had either normal coronaries or insignificant coronary artery disease ($< 50\%$ stenosis in any major coronary artery).
- (iv) Peripartum cardiomyopathy patients were included if their left ventricular ejection fraction was $\leq 19\%$ at least 1 year after delivery. Patients with history of less than 1 year were excluded.
- (v) LVEF on echocardiography $\leq 19\%$ by modified Simpsons method.

Exclusion Criteria (any of the following)

- (i) Patients with coronary artery disease including myocardial infarction in the past.
- (ii) Patients having significant coronary artery disease on coronary angiography.
- (iii) Reversible cause of DCM like thyrotoxicosis.
- (iv) Significant primary valvular heart disease.
- (v) Use of devices like biventricular pacing, implantable cardioverter defibrillator for heart failure management. Patients on single or dual chamber pacing for bradyarrhythmia pacing were however included in the study.

The study included all patients suffering from non-ischemic DCM with LVEF $\leq 19\%$ and retrospective analysis of all these patients was carried out. First record of LVEF $\leq 19\%$ was taken as an entry point into the study. For example, a patient was recorded to have LVEF of 35% at initial inclusion in 2008 into the cohort and developed LVEF of 18% two years later; that is 2010, entry point into this study would be taken as 2010. Clinical profile of each such patient studied for age of onset, presence or absence of symptoms of heart failure, NYHA class, risk factors and physical examination findings at time of diagnosis of ejection fraction ≤ 19 . Old investigations were reviewed including their blood investigations, thyroid and biochemical profile, baseline ECGs and echocardiographic characteristics. The primary endpoint was death or heart transplantation. Transplant free survival was analyzed.

Table 1
Baseline characteristics of study population (N = 130 patients).

	N = 130
Age, years	40.35 ± 13.9
Sex, n (%)	
Male	83 (63.8%)
Female	47 (34.5%)
Etiology, n (%)	
Idiopathic	114 (87.6%)
Familial	6 (4.6%)
Peripartum	10 (7.7%)
NYHA functional class, n (%)	
NYHA I	5 (3.8%)
NYHA II	61 (46.9%)
NYHA III	38 (29.2%)
NYHA IV	26 (20%)
Mean NYHA at baseline	2.65 ± 0.84
Duration of symptoms, (months)	12 (2–36)
Comorbidities, n (%)	
Diabetes mellitus	30 (23.1%)
Hypertension	20 (15.4%)
Smoking	30 (23.1%)
Alcohol	9 (6.92%)
Chronic kidney disease	5 (3.8%)
Hypothyroid	9 (6.9%)
Hyperthyroid	1 (0.8%)
Systolic BP (mmHg)	107.7 ± 22.9
Diastolic BP (mmHg)	70.6 ± 16.58
Hemoglobin (g/dl)	12.7 ± 2.36
Electrocardiography, n(%)	
QRS 120–150 ms	33(25.4%)
QRS>150 ms	23(17.7%)
QRS duration (milliseconds)	121.75 ± 32.31
LBBB	50(38.5%)
IVCD	12(9.2%)
RBBB	5(3.8%)
Atrial fibrillation	12(9.2%)
Complete heart block	2(1.5%)
Echocardiography, n(%)	
Baseline LVEF	14.65 ± 3.33%
LVIDd (mm)	63 ± 11.77
Left atrial dimension (mm)	42.7 ± 8.81
Significant MR (%)	47(36.2%)
Treatment, n(%)	
Diuretics	128(98.5%)
Beta-blockers	114(87.7%)
ACEI/ARB	120(92.3%)
Aldosterone receptor antagonists	117(90%)
Digoxin (%)	81(62.3%)
Death/heart transplant	57(43.84%)
Heart transplant	3
Death	54(41.5%)
Heart failure death (%)	19(14.6%)
SCD (%)	19(14.6%)
Other death (%)	16(12.3%)

ACEI/ARB: Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; NYHA: New York heart association; BP: Blood Pressure; LVEF: Left ventricle ejection fraction; LVIDd: Left ventricle internal diameter in diastole; LBBB: left bundle branch block; RBBB: Right bundle branch block; IVCD: Intraventricular conduction delay; SCD: sudden cardiac death. Values are expressed as mean ± SD or %; for parametric distribution; and median (IQR) for non-parametric distribution.

2.1. Statistical analysis

Categorical data were expressed as percentages and compared using the chi-square test or Fisher's exact test. Normally distributed continuous variables were expressed as means and standard deviations, whereas non-normally distributed variables were given as medians and interquartile ranges or range from minimum to maximum. For statistical analysis, independent *t* test were used in 2-group comparisons.

To look for predictors of mortality from baseline variables, univariate variables with $p < 0.05$ were taken and analyzed by binomial logistic regression analysis (Enter method). Finally, the

survival curve was calculated according to the Kaplan-Meier method. Death or heart transplantation was taken as an event and the rest of the patients were censored during survival analysis. The level of statistical significance was $p < 0.05$. All hypothesis tests were 2-sided. The entire analysis was performed using SPSS version 23.0 software (IBM, Armonk, New York).

3. Results

A total of 154 patients were initially included in this cohort study. 9 patients were excluded due to incomplete information (lost to follow up after single visit) and age <18 years, 15 patients were excluded due to having devices including biventricular pacing, implantable cardioverter defibrillator (Fig. 1). A total of 130 patients were included in this cohort study, of which 54 died on follow up and 3 underwent heart transplant. Raw data of these patients is provided in [Supplementary Tables 1 and 2](#).

The mean age of DCM patients who participated in study was 40.35 ± 13.9 years. 114 (87.6%) patients had idiopathic DCM, 6 (4.6%) patients had familial dilated cardiomyopathy and 10 (7.7%) patients had peripartum cardiomyopathy. The mean duration of symptoms was 22.9 ± 30.19 months. The baseline clinical, ECG and electrocardiographic characteristics of patients are shown in [Table 1](#).

The mean follow up was 45.6 ± 39 months while the median follow up was 39 months (range 0–176months). During this follow up period 54 (41.7%) patients died: 19 (14.6%) from progressive heart failure, 19 (14.6%) from sudden cardiac death and 16 (12.3%) from other causes. Survival of the three patients who underwent heart transplant was considered only till the date of the transplant. The baseline characteristics were compared between with and without outcome (death or heart transplantation) are shown in [Table 2](#). There was no significant difference in age, gender, etiology of DCM, duration of symptoms, comorbidities, systolic blood pressure, diastolic blood pressure, mean haemoglobin levels, echocardiographic parameters between these two groups. Factors associated with the occurrence of primary outcome in DCM patients with LVEF ≤ 19% were higher baseline NYHA functional class, recurrent heart failure hospitalizations, QRS duration and absence of treatment with beta-blockers, ACEI/ARB and aldosterone antagonists. None of the parameters were statistically significant in binary logistic regression analysis.

Follow-up LVEF data till end of study was available for 113 patients (86.9%). At the last follow up, 11 patients showed LVEF >40% among which 1 patient died due to sudden cardiac death. Ten patients had substantial cardiac recovery (LVEF absolute improvement of ≥10% with final LVEF of >40%).

3.1. Survival analysis

130 patients were included in the final survival analysis. The median survival of DCM patients with left ventricular ejection fraction EF ≤ 19% was 86 (S.E. 22.38) months ([Fig. 2](#)). Since 17 patients were lost to follow up till the end of study in December 2018, a worst-case scenario was assumed. Even if all patients who lost to final follow up were assumed to be dead at last follow up, the median survival was 57 (S.E.9.08) months.

4. Discussion

We have a large population of patients in whom devices including biventricular pacemakers and implantable defibrillators are not used largely due to financial reasons. These patients are thus managed with drug therapy alone with an attempt to optimize the therapy. Results of this study thus reflect outcomes of patients on guideline directed medical therapy alone. The small number of

Table 2

Comparison of clinical, electrocardiographic, and echocardiographic characteristics of patients who died or underwent heart transplant with those who survived.

Characteristic	Patients who died or underwent heart transplant (N = 57)	Survivors (N = 56)	P value
Mean age, years	39.3 ± 15.3	40.9 ± 12.9	0.534
Sex (N)			
Male (N)	40	34	0.290
Female (N)	17	22	
Etiology (N)			
Idiopathic	51	48	0.132
Familial	4	1	
Peripartum	2	7	
Baseline NYHA functional class (N)			
NYHA I/NYHA II	26	32	0.001
NYHA III	13	20	
NYHA IV	18	4	
Duration of symptoms (months)	12 (1.5–36)	7.5(2–29.75)	0.633
Heart failure hospitalizations (N)	34	24	0.074
Comorbidities (N)			
Diabetes	18	12	0.741
Hypertension	9	8	0.730
Smoking	14	12	0.579
Alcohol	4	3	0.661
Chronic kidney disease	2	3	0.677
Hypothyroid	1	6	0.096
Hyperthyroid	0	1	
History of syncope	6	6	0.947
Systolic BP (mmHg)	106.2 ± 23.7	112.1 ± 17.9	0.132
Diastolic BP (mmHg)	68.8 ± 16.7	73.5 ± 14.8	0.114
Hemoglobin (g/dl)	12.5 ± 2.8	12.5 ± 1.8	0.988
Electrocardiography (N)			
Sinus rhythm	50	52	
Atrial fibrillation	6	4	0.566
QRS 120–150 ms	20	10	0.037
QRS>150 ms	9	9	
QRS duration (milliseconds)	126.7 ± 28.89	117.9 ± 35.82	0.168
LBBB	23	20	0.612
IVCD	8	4	0.120
RBBB	3	1	0.662
Echocardiography (N)			
Baseline LVEF	14.6 ± 3.2	14.7 ± 3.4	0.969
LVIDd (mm)	63.6 ± 13.79	61.4 ± 12.28	0.579
LA dimension (mm)	43.9 ± 8.7	41.2 ± 8.93	0.106
Significant MR	19	19	0.901
Significant MR on follow up	13	16	0.447
Treatment (N)			
Diuretics	55	56	0.146
Beta-blockers	46	54	0.010
ACEI/ARB	49	55	0.007
ARA	46	53	0.005
Digoxin	38	29	0.133

ACEI/ARB: Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, ARA: Aldosterone receptor antagonists, NYHA: New York heart association, BP: Blood Pressure, LVEF: Left ventricle ejection fraction, LVIDd: Left ventricle internal diameter in diastole, LBBB: Left bundle branch block, RBBB: Right bundle branch block, IVCD: Intraventricular conduction delay. Values are expressed as mean ± SD for parametric distribution; and median (IQR) for non-parametric distribution.

patients in the cohort with devices including biventricular pacemakers and implantable defibrillators were excluded from this study. With increasing use of devices in our setting such a cohort may not be available for a long follow up in future. We thus looked at patients with very low ejection fraction (LVEF ≤ 19%). This value was empirically selected since this ensured that only patients with the poorest LVEF were selected. There are no studies looking specifically at this subset of patients. This is the largest cohort of DCM patients with such poor LVEF in the modern era of heart failure medical management to look for outcomes of these patients.

The prognosis of the non-ischemic DCM patients has improved with better adherence to guideline-directed medical therapy.^{21–23} However, most studies have looked at patients with a higher LVEF and cannot be compared to the current study. Data on survival of patients with such low LVEF are sparse.^{21,23}

We have reported the median survival of DCM patients with LVEF ≤ 19% has improved to median of 86 months. It was often presumed that patients with such low ejection fraction have worse prognosis. This survival is similar to that of patients in the medical therapy arm of the DEFINITE trial, despite our patients having a lower LVEF.¹⁷ Multiple studies have demonstrated that poor compliance to anti-heart failure medications is an important factor behind lack of LVEF improvement and such patients have poorer outcomes.^{22,24} An older study found a 3 year mortality of 74% in HF patients with LVEF ≤ 20%.²⁵ Angiotensin converting enzyme inhibitors were the only disease modifying drugs mentioned in this study. 92.3% of the patients in our study were on angiotensin converting enzyme inhibitors/angiotensin receptor blockers, 87.7% patients were on beta-blockers, and over 90% patients were on spironolactone/eplerenone. This high proportion of the patients on

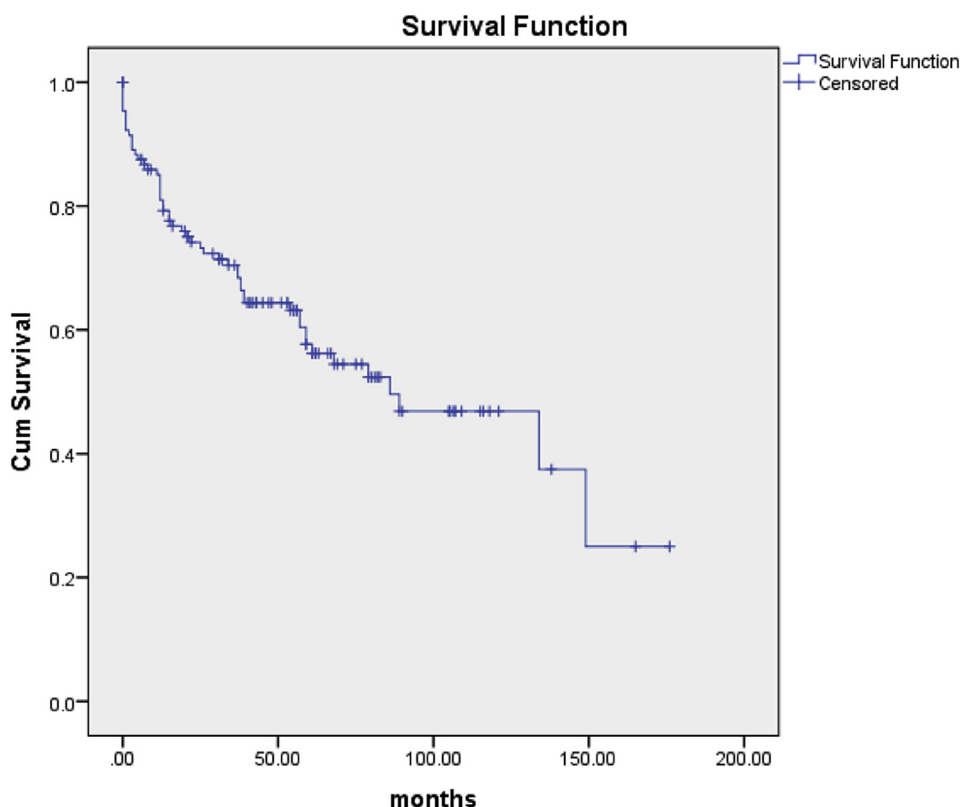


Fig. 2. Kaplan–Meier curve for the primary outcome of all cause death or heart transplantation.

optimal medical therapy can be explained by regular follow-up of these patients with emphasis on drug compliance. Neprilysin inhibitors were not available commercially for most of the study period. Even when available, their use was minimal largely due to high cost.

4.1. Limitations of the study

The current study population was enrolled in a tertiary care center, thus imposing a selection bias with respect to the characteristics of DCM in the general population. Another limitation could be the shorter follow-up of the patients who were enrolled in the later part of the study period. Our population included only patients with non-ischemic dilated cardiomyopathy; therefore, the results should not be extrapolated to patients with ischemic left ventricular dysfunction. Cardiac MRI was not carried out therefore specific etiologies including some ischemic cardiomyopathies may have been missed. However, this study provides useful data on long term outcomes in a real-world setting.

5. Conclusions

Prognosis of DCM patients has improved in last two decades. The median survival of our DCM cohort with LVEF \leq 19% on guideline directed medical therapy alone was 86 (S.E. 22.38) months.

Grant support

Nil.

Declaration of competing interest

Nil.

Acknowledgements

Nil.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.ihj.2020.07.016>.

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