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Research Article

Clinical Profile and Risk Factors of Dilated Cardiomyopathy with 10 Years Follow-Up: A Study from South India

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Abstract

Introduction: Dilated cardiomyopathy (DCM) is a disease of the heart muscle, causing ventricular dilation and systolic dysfunction.

Objective: To investigate the risk factors, clinical profile, mortality and long-term fellow up in dilated cardiomyopathy patients.

Methods We prospectively recruited 210 patients with dilated cardiomyopathy. All patients were evaluated for cardiac risk factors, thyroid profile, ECG, 2DEcho and were followed up at 6 months or one-year intervals.

Results: Out of 210 patients, men were 162(77.1%), mean age was 60.0±11.7 years, 142(67.6%) were in ≤64 years age group. Most common symptom was pedal edema 180(85.7%), while 125(59.5%) had chest paint, and 125(59.5%) had fatigue. On evaluation of comorbidities, 148(70.4%) had hypertension, 130(61.9%) had diabetes mellitus, 77(36.6%) had hypothyroidism, 30(14.2%) had chronic kidney disease (CKD). Mean follow up period was 6.5±3.4 in years with 68(32.3%) deaths. Age ≥65 years (p<0.0001), hypertension (p=0.01), diabetes mellitus (p=0.03), alcohol consumption (p<0.0001), CKD (p= 0.0005) and thyroid dysfunction (p=0.0008) were significantly associated with mortality on univariate analysis. Cox regression analysis showed significant association of age > 65 years (odds:2.51;95% CI: 1.81-4.56), hypertension (odds:1.81;95% CI:1.41-3.21), diabetes mellitus (odds:1.51;95%CI: 1.32-3.25), alcohol consumption (odds:3.72;95%CI: 1.98-7.82) and thyroid dysfunction (odds:2.41;95%CI: 1.54-4.59) with mortality.

Conclusion: DCM had mortality rate of 32.3% in our study. Age≥65 years, hypertension, diabetes mellitus, alcohol consumption, and thyroid dysfunction were independently associated with mortality.

Keywords

Dilated cardiomyopathy, Heart Disease, Risk Factors, LV dysfunction, Thyroid Hormone, Mortality.

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Introduction

Dilated cardiomyopathy (DCM) is characterised by cardiac muscle weakness, inability to pump blood to body and ventricular dilatation and reduced systolic left ventricular (LV) dysfunction and LV enlargement [1]. Prevalence of DCM in general population is around 36 cases per 100,000 [2]. Clinical symptoms include orthopnea, pedal edema, paroxysmal shortness of breath, nocturnal dyspnea, nonspecific symptoms such as fatigue, malaise, and weakness, etc. [3]. DCM has been associated with presence of non-modifiable cardiovascular risk factors such as family history, age, ethnicity, and sex, as well as modifiable risk factors such as hypertension, diabetes, smoking, alcohol consumption, dyslipidemia, physical inactivity, malnourishment, obesity [4], thyroid dysfunction in few studies [5]. Several studies have noted underlying etiology in 10-19% of patients [3]. The past few decades have seen increasing incidence rate of DCM in younger adults [6]. The prognosis in DCM patients is poor, with around half of all patients dying within 5 years of onset [4]. However, the prediction of mortality remains a challenge for cardiologists [6]. The current study to investigate risk factors and clinical profile and their association with mortality in DCM patients. Very few studies are available from Indian subcontinent.

Methods

Study Population and Design

This was a prospective observational study. This study was approved by the Institutional Ethics Committee (Yashoda Academy of Medical Education and Research). We screened 280 patients and 70 patients were excluded (40 patients did not fulfil criteria and the remaining patients (30) did not give consent). We recruited 210 consecutive patients with DCM from Department of Cardiology in Yashoda Hospital, Hyderabad, a tertiary medical care center and post-graduation teaching hospital in South India. Study period was between 2012 and 2022. On an average, 24 patients per year recruited. Consent was obtained from all patients. DCM was defined by European Society of Cardiology, the left ventricle (LV) dilation and reduced LV systolic function (Ejection Fraction (EF) < 45%), based on echocardiogram [6].

Inclusion Criteria

Patients of all age groups and both genders presenting with clinical features of DCM and admitted in hospital, whose 2D ECHO showed left ventricle' ejection fraction < 45%, Global hyokinesia of LV, dilatation of all chambers of heart, left ventricle end diastolic dimension > 3 cm / body surface area were included in the study after obtaining consent.

Exclusion Criteria

Patients eligible for heart transplantation, those with coexisting COPD (chronic obstructive pulmonary disease), any malignancy, rheumatological disorder, drug abuse, history of radiation to thorax, congenital cardiac diseases, resuscitated cardiac arrest (rCA), pericardial disease, corpulmonale with CHF, hypertrophic cardiomyopathy, restrictive cardiomyopathy, congenital heart disease, clinical history of untreated myocardial infarction, significant untreated coronary artery disease (defined as >70% luminal stenosis in a major coronary artery or >50% in the left main coronary artery) or the presence of sub-endocardial late gadolinium enhancement (LGE) at cardiac magnetic resonance (CMR), systemic hypertension (>160/100 mm Hg), heart rate < 60 beats/min and blood pressure < 90/60 mmHg, sustained supraventricular tachycardia, history of, liver disease, renal dysfunction, patients who were pregnant or lactating, patients with other end-stage diseases, an expected survival time < 5 years, chronic anemia <6 g/dl and those who refused consent were excluded from study.

Evaluation

Detailed medical history was taken and physical examination was done by a senior cardiologist in all patients. All underwent laboratory investigations (complete blood count, blood sugar, renal function, lipid profile etc) for assessing rest of the organs.

Assessment of ECG and 2DEcho

All patients had 12 leads electrocardiography (ECG) taken by a senior technician, and 2 dimensional echocardiography (2DEcho) performed by a cardiologist. ECGs and 2DEcho were interpreted by the same person.

Evaluation of New York Heart Association (NYHA) functional score

All patient were assessed using the NYHA I to IV scale,

NYHA I: No limitations of physical activity, does not cause undue fatigue, palpitation or shortness of breath.

NYHA II: Less limitation of physical activity and comfortable for rest. Patients have fatigue, palpitation, shortness of breath or chest pain.

NYHA III: Remarked limitation of physical activity less than ordinary activity causes fatigue, palpitation, shortness of breath or chest pain.

NYHA IV: Symptoms of heart failure, patients have performed physical activity causes further discomfort. These assessments were done by a senior cardiologist.

Risk Factors Evaluation

Hypertension was defined as a patient's self-reported history of hypertension and antihypertensive medications or systolic blood pressure ≥ 140 mm Hg and/or a diastolic blood pressure ≥ 90 mm Hg, alcoholics were defined as those who took alcohol more than 50 g/day (equivalent to 500 mL [2 drinks] of wine, 1000 mL of beer, or 5 drinks [units] of spirits). Diabetes mellitus was defined as fasting plasma glucose ≥ 110 mg/dL or patient was on antidiabetic medications. Dyslipidaemia was considered as one or more of the following: total cholesterol more than 200 mg/dL, low-density lipoprotein-cholesterol (LDL-C) more than 130 mg/dL, high-density lipoprotein-cholesterol (HDL-C) below 40 mg/dL, very-low-density lipoprotein-cholesterol (VLDL-C) more than 30 mg/dL, triglycerides more than 150 mg/dL. Smokers were defined as those reporting daily smoking. Ex-smokers and occasional smokers were classified as non-smokers and thyroid dysfunction

was defined by lab parameters as discussed in previous studies [7].

Patients' Follow-up

Follow-up visits were conducted at outpatient department. Patient medical history was collected and physical examination was performed in all by senior cardiologist. Patients came approximately every 6 months or 12 months based on patient condition. The duration of the follow-up was calculated starting from the first diagnosis of DCM. Survival status was confirmed by physical follow-ups or telephonic follow-up (if patient was unable to come due to varies reasons).

Statistical Analysis

Statistical analysis was done by SPSS 17.0 (Statistical Package for the Social Sciences, SPSS Inc statistical package Chicago IL USA). Continuous variables were presented in titer of mean ± standard deviation. Chi-square test was applied to study the difference between two groups (Survival vs deaths). Multiple logistic regression analysis was performed before and after adjustment and survival assessment done by Kaplan Meier. All tests were two-sided and $p < 0.05$ was considered statistically significant.

Results

Baseline Characteristics of Study Patients

Out of 210 DCM patients, 162(77.1%) were men and mean age was 60.0±11.7years (age range 32-86 years), ≤64 years age group were 142(67.6%) and ≥ 65 years age group were 68(32.3%).

Among the clinical profile, most common presentation was with NYHA-I class seen in 92(43.8%) followed by NYHA-II in 60(28.5%) and NYHA-III/IV in 58(27.6%). Fatigue was seen in 125(59.5%), pedal edema in 180(85.7%) and orthopnea in 120(57.1%). Risk factors assessment in DCM patients revealed hypertension in 148(70.4%), diabetes in 130(61.9%), smoking among 79(37.6%), alcohol consumption in 52(24.7%), dyslipidemia in 38(18%), hypothyroidism in 77(36.6%), CKD in 30(14.2%), previous myocardial infarction/coronary artery bypass graft/percutaneous coronary intervention in 39(18.5%). Mean follow up was for 6.5±3.4 years and 68 patients died (mortality 32.3%) (Table 1).

Table 1: Baseline characteristics.

Parameters	Number (n=210) (%)
Men	162(77.1%)
Mean age	60.0±11.7
≤64 years age group	142(67.6%)
≥ 65 years age group	68(32.3%)
Age range (years)	32-86
Hypertension	148(70.4%)
Diabetes Mellitus	130(61.9%)
Smoking	79(37.6%)
Alcoholic consumption	62(29.5%)
Dyslipidemia	38(18%)
Hypothyroidism	77(36.6%)
CKD	30(14.2%)
Previous MI/CABG/PCI	39(18.5%)
fellow up range (in years)	1-10
Mean fellow up (in years)	6.5±3.4
Mortality (in 10 years duration)	68(32.3%)
Shortness of breath NYHAI	92(43.8%)
Shortness of breath NYHAII	60(28.5%)
NYHA III/IV	58(27.6%)
Fatigue	125(59.5%)
pedal edema	180(85.7%)
Orthopnea	120(57.1%)
Chest paint	125(59.5%)
Basal crepitations	48(22.8%)
SBP < 100 mmhg	9(13.3%)
Ectopicbeats	40(19%)
atrial fibrillation	10(4.7%)

Medications

In our cohort, 60 % received beta-blockers, 20% received calcium channel antagonist, 15% received ACE inhibitor and 90% received diuretics or nitrates. Warfarin was prescribed to 8% of DCM patients while 2% received novel anticoagulants and all patients (100%) received antiplatelets.

Underlying Cause of Death in Dilated Cardiomyopathy

As per the details given by patient attendants, 52(76.4%) patients had sudden cardiac death, 6 (8.8%) patients had stroke and cause was unknown in 10(14.7%) patients (Table 2).

Table 2: Underlying cause of death in dilated cardiomyopathy.

Year of Death	sudden cardiac death (n=52)	Stroke (n=6)	Unknown cause (n=10)
1st year	10(19.2%)	0	1(10%)
2nd year	3(5.7%)	0	0
3rd year	5(9.6%)	0	1(10%)
4th year	6(11.5%)	0	0
5th year	8(15.3%)	2(33.3%)	2(20%)
6th year	5(9.6%)	3(66.6%)	2(20%)
7th year	5(9.6%)	0	0
8th year	4(7.6%)	1(16.6%)	1(10%)
9th year	5(9.6%)	0	1(10%)
9.5 years	1(1.9%)	0	1(10%)

Association of Various Risk Factors with Mortality

Table 3 shows the association of various risk factors with mortality. Mean age ($p<0.0001$), age ≥65 years ($p<0.0001$), hypertension ($p=0.001$), diabetes mellitus ($p=0.02$), alcohol consumption ($p <0.0001$), hypothyroidism ($p=0.0008$), CKD ($p=0.0005$), NYHA III/IV ($p<0.0001$) were significantly associated with mortality.

Predictors of Mortality with Risk Factors

After adjustment using multiple logistic regression analysis, age ≥65 years (odds:2.51;95%CI:1.81-4.56), ($p<0.0001$), hypertension (odd: 1.81;95%CI:1.41-3.21), ($p=0.01$) diabetes mellitus (odds:1.51;95%CI:1.32-3.25), ($p=0.03$), alcohol consumption (odds: 3.72;95%CI:1.98-7.82), ($p<0.0001$), and thyroid dysfunction

(odds:2.41:95%CI:1.54-4.59), (p<0.0001) were independently associated with mortality in DCM patients (table 4). Kaplan Meier survival curve showed better survival prognosis in present study (Figure 1).

Table 3: Association of various risk factors with mortality.

Parameters	Survival (n=102)	Deaths (n=68)	P value
Men	76(74.5%)	54(84.3%)	0.6
Mean age	54.1±10.8	65.5±11.4	<0.0001
≤64 years	92(90.1%)	12(18.7%)	<0.0001
≥65 years	10(9.9%)	56(82.3%)	<0.0001
Age range (years)	32-64	46-85	
Hypertension	59(57.8%)	53(77.9%)	0.001
Diabetes Mellitus	50(49%)	50(73.5%)	0.02
Smoking	35(34.3%)	22(32.3%)	0.9
Alcoholic consumption	19(18.6%)	36(52.9%)	<0.0001
Dyslipidemia	20(19.6%)	13(19.1%)	0.9
Hypothyroidism	27(26.4%)	38(55.8%)	=0.0008
CKD	9(8.8%)	16(23.5%)	=0.0005
Previous MI/CABG/PCI	23(22.5%)	8(11.7%)	0.
Shortness of breath NYHAI	80(78.4%)	0	<0.0001
Shortness of breath NYHAII	22(21.5%)	4(5.8%)	<0.0001
NYHA III/IV	0	64(94.2%)	<0.0001
Fatigue	51(50%)	30(44.1%)	0.4
pedal edema	75(73.5%)	43(63.2%)	0.5
Orthopnea	59(57.8%)	35(51.4%)	0.4
Chest paint	50(49%)	30(44.1%)	0.5
Basal crepitations	12(11.7%)	6(8.8%)	0.4
SBP < 100 mmhg	0	1(1.4%)	0.9
Ectopicbeats	2(1.9%)	6(8.8%)	0.08
atrial fibrillation	1(0.9%)	4(5.8%)	0.1

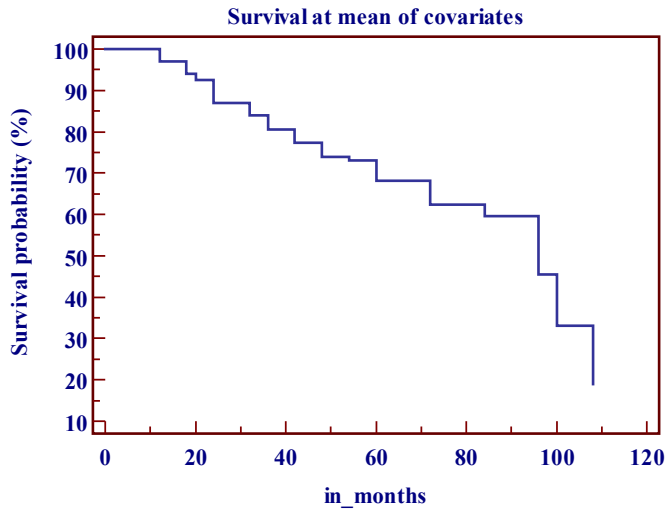

Figure 1: Kaplan Meier survival curve showed better survival prognosis.

Table 4: Predictors of mortality with risk factors.

Parameters	Before adjustment		After adjustment		p value
	Odds	95%CI	Odds	95% CI	
≥65 years	4.9	2.53-9.76	2.51	1.81-4.56	<0.0001
Hypertension	2.4	1.70-5.15	1.81	1.41-3.21	0.01
Diabetes Mellitus	2.2	1.62-4.32	1.51	1.32-3.25	0.03
Alcoholic consumption	5.6	2.78-11.3	3.72	1.98-7.82	<0.0001
Smoking	1.9	1.62-2.45	1.0	0.5-1.57	0.1
Thyroid dysfunction	3.1	1.73-6.03	2.41	1.54-4.59	<0.0001
CKD	1.9	1.52-2.12	*	*	*

*Number of patients insufficient for statistical analysis

Discussion

In our study, most common symptom associated with DCM was pedal edema, seen in 85.7%, followed by fatigue (59.5%) and orthopnea (57.1%), most had mild to moderate shortness of breath while NYHA III/IV was seen in 27.6%, similar findings were noted by others [4,8,9]. Several studies have established that men are more affected than women [10]. In the current study too, men were more affected 77.1%, of patients with DCM were men which is similar to the gender prevalence seen in others [9,10].

Gender

Male gender is an important risk factor for developing heart failure in a number of cardiovascular conditions. Studies have showed that men with DCM had higher levels of apoptosis-related protein expression compared to women [4]. In DCM patients, there is twofold increase of myocardial fibrosis in men compared to women and fibrosis plays a vital role in the pathogenesis of DCM. Sex hormones also play a major role in cardiac inflammation, and several genes are affected by estrogen response elements in heart, which is a main factor that leads to dilatation and heart failure.

In the current study, 32.3% of patients had age ≥ 65 years, our findings are similar to the prevalence seen in previous studies [8,10]. Dudharejia et al, had 38% of their patients older than 60 years [10], while Mishra et al, had 44% patients in the >60-year age group 44% [8].

Risk Factors

Hypertension, one of the major risk factors for cardiac diseases, was seen in 70.4% of our patients, other studies have showed similar findings [11,12]. Diabetes mellitus is a well-established risk factor for cardiac disease and plays a vital role in in the pathogenesis of DCM [8]. In our study, we noted diabetes mellitus among 61.9%, our findings were advocated by others with percentages ranging from 12-70% [8-11].

Smoking and alcohol consumption increase risk of DCM, in our study, established smokers were 37% and alcohol consumption was present in 24.7%, other studies have shown similar results

[4,5,8-10]. Dyslipidemia plays a vital role in cardiac diseases, in our study we found a relatively lower prevalence of 18%, compared to others who have noted significant higher prevalence in DCM patients [13]. This low percentage can be explained by the fact that many patients had already received intermittent treatment with lipid lowering medications. Thyroid dysfunction is associated with DCM patients, studies have suggested significant association with mortality [4]. The present study, we found thyroid dysfunction in 36%, these finding were advocated by others [4], ranging from around 4-40% [4,5]. Cardiac diseases can coexist with chronic kidney disease. The present study showed 14% of DCM patients also had CKD, similar findings were noted by others [14]. The association between CKD and DCM is complex with common risk factors and both the diseases increasing the others risk.

Mortality

DCM is associated with high risk of mortality, occurring in almost a third of our patients (32.3%) over 10 years, this is similar to other studies Dziewiecka et al., (17.2%) [6], Fadl et al. (30% in children) [15], Komajdo et al., (27.8%) [16], Demming et al., (29.3%) [17], and Li et al., (47%) [5]. The risk factors for mortality were assessed, in our study, age≥65 years was independently associated with mortality (odds:2.51;95%CI:1.81-4.56), our findings are advocated by others [5,18,19,].

We also found hypertension to be independently associated with mortality in DCM patients (odds:1.81;95%CI: 1.41-3.21), this was similar to other population studies [18], though a recent study showed no significant association of hypertension with mortality in DCM patients [19]. The presence of hypertension during course of heart failure increases the workload on the heart worsening the performance. Systemic arterial hypertension can occur as a result of increased sympathetic activity and overactive renin angiotensin system, especially in the initial stages of DCM as a compensatory mechanism. Although it does help in the initial maintenance of blood perfusion, it worsens the heart failure as the disease progresses. Systemic hypertension with systolic or diastolic cardiac dysfunction causes a chronic increase in pressure in left atrium, which in turn leads to increased pulmonary venous pressure. Initially there is a passive increase of pulmonary artery pressure which is potentially reversible after correction/improvement of left heart hemodynamic. As heart failure progresses, there is a reduction in left atrium compliance and these further increases pulmonary artery pressure irreversibly and further leads to HF [20].

The second killer in DCM is diabetes mellitus. In the current study too, diabetes mellitus was independently associated with mortality (odds:1.51;95%CI:1.32-3.25), which emphasises the findings of others [21,22]. Diabetes mellitus has been shown to cause impairment of myocardial relaxation, enlarged myocardial fibrosis, and mitochondrial degeneration in DCM causing death [17]. Smoking is one of the various risk factors for heart disease, however in our study we did not find an association with mortality in DCM, these finding are supported by Li et al. [23].

Alcohol consumption is a major predictor of cardiac death. Among various abnormalities caused by high levels of use of alcohol, direct effect on heart can lead to alcoholic cardiomyopathy, which is characterized by a dilation and impairment of left ventricle [24]. Further associated complications thiamine deficiency, liver dysfunction etc can exacerbate the heart failure and thus contribute to mortality. The present study reiterated the independent association of alcohol consumption with mortality (odds:3.72;95%CI:1.98-7.82), our findings were advocated by Li et al., (HR:0.95:95%CI:0.67–1.35) [23].

Thyroid diseases have been known to cause numerous changes in heart (functions and structure) [7], and direct or indirect effects on cardiac function and may be regulated by both genomic and nongenomic mechanisms. In a recent study, Zhao et al., showed low FT3 levels was significantly associated with increased mortality rate in DCM patients [24]. In a large cohort study by Kannan et al., thyroid dysfunction was significantly associated with mortality in DCM [25]. Similarly, in the current study, we established thyroid dysfunction to increase the risk of mortality in DCM patents (odds:3.72;95%CI:1.98-7.82). Both hyperthyroidism and hypothyroidism produce changes in cardiac contractility, myocardial oxygen consumption, cardiac output, blood pressure, and systemic vascular resistance. Diastolic dysfunction is a common abnormality reported in hypothyroidism. Although alterations in myosin heavy chain isoform expression have been documented, hypothyroidism-induced DCM is an uncommon phenomenon [26].

Another process which has been seen as a contributor is the locally impaired thyroid hormone signalling in DCM myocardium. End-stage heart failure due to DCM could exhibit a local hypothyroid state due to disordered THRs expression. Reduced expression of not only THRs (1 and 2), but also adrenergic receptors (1 and 2) at both gene and protein levels have been seen in cardiomyocytes isolated from the end-stage DCM subjects. Importantly, T3 is able to enhance the expression of 1-adrenergic receptors and some of their downstream targets. Thus, local cardiac hypothyroidism could potentiate detrimental consequences of myocardial 1-adrenergic receptor downregulation accompanying end-stage heart failure caused by DCM, thereby contributing to an adverse outcome [22].

The heart and kidney are closely associated and kidneys play a vital role to maintain salt water homeostasis and normal blood pressure. Cardiac dysfunction can decrease kidney perfusion and lead to kidney failure. Chronic kidney disease associated cardiomyopathy is characterised by structural remodelling of the heart. Widespread interstitial fibrosis and cardiac hypertrophy give rise to cardiac electromechanical dysfunction and increased risk of death. In our study, we found CKD to be significantly associated with mortality on univariate analysis. We were unable to do logistic regression analysis due to small numbers but recent studies have found independent association with mortality [27]. In the current study during follow-up, mortality rate was 32.3% and 19% were lost to follow-up during 10 years. These finding are similar to other

studies [28]. A longer follow up study by Xu et al., showed a lower survival rate of 34% during 15 years follow-up [18].

Strengths and Pitfalls of Study

The current study was performed in a single center with a long term (10 years) follow up. Physical, clinical examination and 2DEcho was done by one senior cardiologist avoiding inter rater bias.

In current study, demerits were that the population was from one urban tertiary centre and may not apply to the diverse population. Around one fifth of the patients were lost to follow up. We were unable to analyse (missed data) the differences between non-ischemic DCM and ischemic DCM. Due to logistic problems, we were unable to assess the cardiac inflammation markers in all. We were not able to perform sub-analysis of T3 T4 and Thyroid-stimulating hormone (TSH) with DCM. Due to small number, we were unable to perform multiple logistic regression analysis in CKD patients.

Conclusion

In our study, mortality rate was 32.3% in DCM patients over 10 years follow up. The present study established, older age, hypertension, diabetes mellitus, alcohol consumption, and thyroid dysfunction to be independently associated with mortality. Further large-scale studies are required to confirm these findings.

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