

Case Series: Is Minimal Coronary Artery Disease a Prognostic Indicator in Dilated Cardiomyopathy?

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Abstract

Background The aim of this study was to study the prognostic implications of minimal coronary artery disease (CAD) in patients with dilated cardiomyopathy (DCMP) in terms of mortality and hospitalization due to heart failure.

Methods One-hundred sixty-three patients with DCMP were recruited for this study. Out of these, 61.9% ($n = 101$; 62.4% men) patients were without associated minimal CAD and 38% ($n = 62$; 66.1% men) with associated minimal CAD (stenosis $< 50\%$), and their risk factor profile was noted. These patients were followed for 30 months, with mortality being the primary endpoint, and hospitalization secondary to cardiac decompensation in the form of heart failure was denoted as the secondary endpoint.

Results In our study, independent significant predictors of CAD were age ($p = 0.002$), hypertension ($p = 0.001$), diabetes ($p < 0.001$), and smoking ($p = 0.023$). The presence of minimal CAD in DCMP patients as a predictor of mortality was not significant (odds ratio [OR]: 1.69, 95% confidence interval [CI]: 0.62–4.62, $p = 0.303$); however, it was a significant predictor of hospitalization secondary to cardiac decompensation (OR: 6.78, 95% CI: 2.28–20.13, $p = 0.001$).

Conclusions Minimal CAD was observed in 38% of DCMP patients. The risk factor profile predicting CAD in DCMP patients was the same as that of the general population. The presence of minimal CAD in DCMP patients was not associated with mortality. However, it was associated with hospitalization secondary to cardiac decompensation in the form of heart failure.

Keywords

- ▶ dilated cardiomyopathy
- ▶ coronary artery disease
- ▶ heart failure
- ▶ mortality

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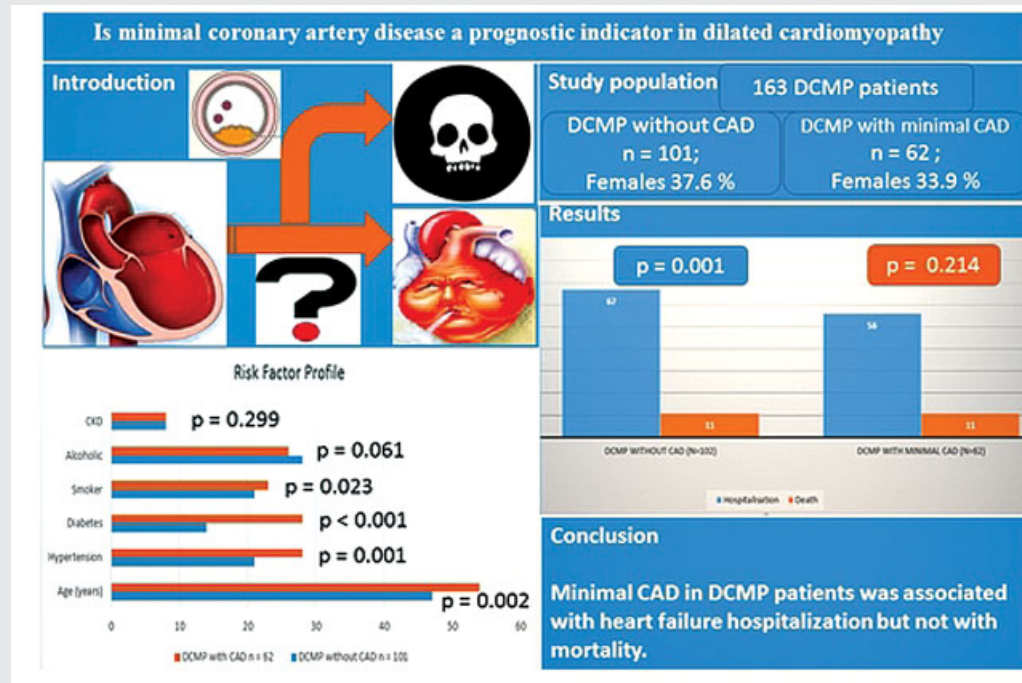
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Abstract Image



Introduction

Dilated cardiomyopathy (DCMP), as per the European Society of Cardiology 2008, is described as the dilatation and systolic dysfunction of the left ventricle, excluding conditions such as hypertension and valvular heart diseases that cause abnormal loading or coronary artery disease (CAD) sufficient to cause systolic dysfunction.¹ It is almost similar to the American Heart Association definition.² DCMP patients may have an associated CAD.³ The clinical profile of these patients is largely unknown. DCMP patients with associated CAD have been described on explanted hearts, that too, in a smaller group of studies.⁴⁻⁷ Presently, magnetic resonance imaging has evolved as a substitute for the coronary angiogram (CAG) for ruling out CAD.⁸ The amount of data about this issue other than these pathoanatomic studies has been of few case reports.^{9,10} The future risk and prognosis of an associated minimal CAD (stenosis <50%) in patients with DCMP are not clear. Some studies have shown a difference in outcome between patients with ischemic and nonischemic cardiomyopathy.^{11,12} In these studies, there appears some possibility of prognostic significance for associated minimal CAD (stenosis <50%) in DCMP patients. In our study, we tried to establish the risk factor profile and prognostic significance in terms of hospitalizations secondary to heart failure and mortality of DCMP patients with associated minimal CAD vis-à-vis normal coronaries in our cardiology department at Nizam's Institute of Medical Sciences (NIMS) hospital.

Aims and Objectives

The aim of this study was to study the effect of minimal CAD in DCMP patients on mortality and heart failure hospitalizations at follow-up of 30 months.

Materials and Methods

We enrolled a total of 163 patients with DCMP who had chronic systolic dysfunction in this study. Patients were admitted to the cardiology department of our institute for the evaluation of heart failure.

The study has local ethics committee approval.

Inclusion Criteria

1. DCMP patients with chronic systolic dysfunction.
2. Before undergoing CAG, patients were on required medical treatment for a minimum of 2 weeks.
3. CAG showed either normal coronaries or minimal CAD.
4. Minimal CAD was defined when angiographic luminal narrowing was <50%.

Exclusion Criteria

Following patients with a history of heart failure due to

- A. Diseases of pulmonary parenchyma/vasculature.
- B. Ischemic heart disease defined as having >50% lesion in any coronary artery on CAG or history of myocardial infarction or history of coronary intervention or history of coronary artery bypass surgery.

- C. Organic valvular heart disease.
D. Hypertrophic cardiomyopathy.

Determination of Cause of Heart Failure

Heart failure was diagnosed as the presence of symptoms consistent with the diagnosis and supported by the functional abnormality^{13,14} on two-dimensional (2D) echocardiography. The ischemic cause of heart failure was ruled out on CAG, which revealed either normal coronaries or minimal CAD.^{1,2,15–17} After that patients with normal coronaries were grouped as DCMP without CAD (normal coronaries) and DCMP with minimal CAD. DCMP with minimal CAD group patients had insignificant coronary artery stenosis (<50% luminal stenosis) in which the depressed left ventricular function could not be explained by the magnitude of stenosis.⁹

Patient Profile

History and physical examination of patients were done, and diagnostic testing, including detailed 2D echocardiography, was done in all patients during the initial workup. CAG was not done in the first admission for heart failure, as there was no evidence of ischemic heart disease. It was performed subsequently after a delay of 2 weeks of initial stabilization of heart failure. Comorbidities of the patient were noted.

Follow-Up and Outcome

The patients were followed up by scheduled visits to outpatient departments or by telephonic conversations to determine the survival status, as mortality was the primary endpoint of the study and cardiac decompensation in the form of heart failure requiring hospitalization was the secondary endpoint. All survivors of the cohort study were followed up for at least 30 months duration. None of the patients underwent cardiac transplantation or any other cardiac augmentation surgery during the follow-up period.

Statistical Analysis

A chi-squared analysis was performed to compare the frequencies between the two groups. Two-sample Wilcoxon's

test and Student's *t*-test were used to test significant differences between means. Univariable and multivariable logistic regression was performed using the status of the coronary artery as independent variable, and death and hospitalization secondary to cardiac decompensation in the form of heart failure as a dependent variable and the results in the form of the unadjusted odds ratio (OR). Subsequently, the OR was adjusted for age and sex and then adjusted for age, sex, hypertension, diabetes, and smoking. Finally, the *p*-value was determined. Cox regression analysis was done for both the endpoints. All tests used for the statistical analysis of the study were two-tailed, and a *p*-value < 0.05% was considered significant. The demographic data were described as mean ± standard deviation wherever it was deemed feasible.

Results of the Study

The final study population included were 163 patients out of which 101 had normal coronaries, classified as “DCMP without CAD group (normal coronaries)”, and 62 patients with insignificant CAD as “DCMP with minimal CAD group.”

There was no difference in sex distribution, alcohol consumption, and history of chronic kidney disease (CKD) between both groups. Patients with DCMP with minimal CAD differed from patients with DCMP without CAD (normal coronaries) in the risk factor profile prototypical for CAD such as age, hypertension, diabetes, and smoking (►Table 1).

Investigation parameters such as hemoglobin, creatinine, sodium, potassium, and mean ejection fraction between the two groups were compared as enumerated in ►Table 2. However, the difference was found to be insignificant.

The total study population was followed up for 30 months, and it was found that 11 (10.9%) patients expired in the DCMP without CAD (normal coronaries) group and 11 (17.7%) patients in the DCMP with minimal CAD group. The results of the study revealed that 67 patients (66.3%) in the DCMP without CAD (normal coronaries) group and 56 patients (90.3%) in the DCMP with minimal CAD group

Table 1 Comparisons of demographic features in both groups

	Without CAD (<i>n</i> = 101) <i>n</i> %		With CAD (<i>n</i> = 62) <i>n</i> %		<i>p</i> -Value ^a
Age (mean, SD)	47.1, 14.13		54.0, 12.02		0.002+
Male sex	63	62.4	41	66.1	0.628
Hypertension	21	20.8	28	45.2	0.001
DM	14	13.9	28	45.2	<0.001
Smoker	21	20.8	23	37.1	0.023
Alcoholic	28	27.7	26	41.9	0.061
CKD	8	7.9	8	12.9	0.299

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; SD, standard deviation.

^aChi-squared test unless specified; + unpaired *t*-test.

Table 2 Two-sample *t*-test comparing the various investigative parameters between the two groups denoted by mean values \pm standard deviation. The *p*-value was calculated to observe for statistical significance

Investigation parameters (mean values)	DCMP without CAD	DCMP with minimal CAD	<i>p</i> -Value
Hemoglobin	13.4 \pm 3.2	12.8 \pm 2.8	0.211
Creatinine	1 \pm 0.2	0.98 \pm 0.3	0.643
Sodium	135 \pm 10	136 \pm 11	0.561
Potassium	3.8 \pm 0.6	3.6 \pm 0.7	0.064
Mean ejection fraction (%)	30 \pm 8	29 \pm 8	0.44

Abbreviations: CAD, coronary artery disease; DCMP, dilated cardiomyopathy.

Table 3 Comparison of hospitalization and death rate between the two groups

Parameters	DCMP without CAD (<i>n</i> = 102)	DCMP with minimal CAD (<i>n</i> = 62)	<i>p</i> -Value
Hospitalization	67	56	0.001
Death	11	11	0.214

Abbreviations: CAD, coronary artery disease; DCMP, dilated cardiomyopathy.

developed acute decompensated heart failure requiring hospitalization during the follow-up period (**Table 3**; **Fig. 1**).

Prognostic Implications of Minimal CAD

It was found that minimal CAD was not a significant predictor of mortality in univariable analysis. (OR: 1.76, 95% confidence interval [CI]: 0.71–4.36, *p* = 0.218). The result

remained insignificant even after multivariable correction using logistic regression analysis with death (yes/no) as the dependent variable and CAD as the independent variable (OR: 1.69, 95% CI: 0.62–4.62, *p* = 0.303) (**Table 4**).

However, minimal CAD was found to predict cardiac decompensation in the form of heart failure requiring hospitalization, and the result was statistically significant (OR: 4.74, 95% CI: 1.85–12.70, *p* = 0.001). It remained significant even after multivariable correction (OR: 6.78, 95% CI: 2.28–20.13, *p* = 0.001) (**Table 5**).

In conclusion, the presence of minimal CAD in DCMP patients had more frequent hospitalization due to heart failure (90.3 vs. 66.3%), which was statistically significant, but not the increase in mortality even though number-wise mortality was more (17.7 vs. 10.9%).

Discussion

In our study, the risk factor profile to predict CAD in DCMP patients was noted. The prognostic implications of associated minimal CAD in DCMP patients on mortality and

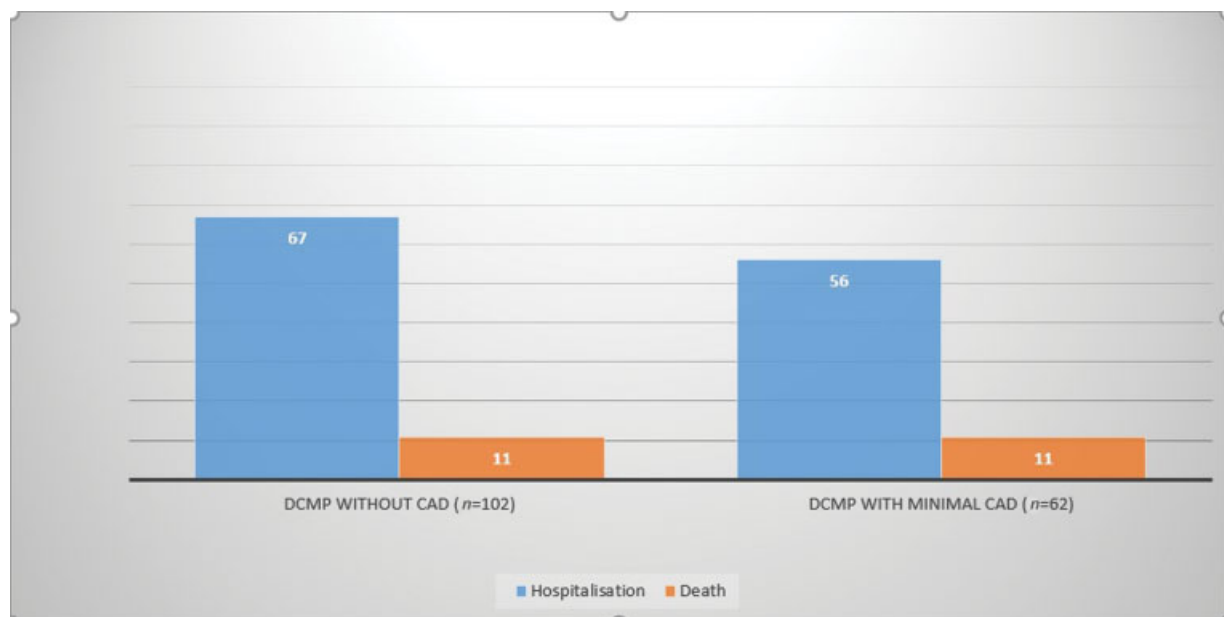
**Fig. 1** Bar diagram comparing hospitalization and mortality between the two groups. CAD, coronary artery disease; DCMP, dilated cardiomyopathy.

Table 4 Logistic regression analysis with death as the dependent variable and CAD as an independent variable

	Unadjusted OR	OR adjusted for age and sex	OR adjusted for age, sex, hypertension, diabetes, and smoking
OR	1.76	1.56	1.69
95% CI	0.71–4.36	0.61–3.96	0.62–4.62
p-Value	0.218	0.351	0.303

Abbreviation: CAD, coronary artery disease; CI, confidence interval; OR, odds ratio.

Table 5 Logistic regression analysis with hospitalization secondary to cardiac decompensation as dependent variable and CAD as an independent variable

	Unadjusted OR	OR adjusted for age and sex	OR adjusted for age, sex, hypertension, diabetes, and smoking
OR	4.74	4.86	6.78
95% CI	1.85–12.10	1.86–12.70	2.28–20.13
p-Value	0.001	0.001	0.001

Abbreviations: CAD, coronary artery disease; CI, confidence interval; OR, odds ratio.

hospitalization secondary to cardiac decompensation in the form of heart failure were determined. However, in many studies, cardiomyopathy secondary to nonischemic cause and DCMP does not connote the same entity. Alternately, the degree of CAD might predict more regarding future events than the assigned cause.^{18–20} This would mean that the presence of an associated minimal CAD would not be of significant value in predicting future events in DCMP patients. However, some studies show worse outcomes for DCMP patients with associated CAD than those with normal coronaries in terms of heart failure hospitalization and death rates.

There has been only scarce data regarding DCMP with associated CAD. One of the recent studies²¹ concluded that concomitant CAD is frequent in DCMP patients. However, it does not predict mortality or hospitalization secondary to cardiac decompensation in these patients. ATLAS trial revealed that ischemia accounted for 9% of DCMP patients admitted in the hospital because of ischemia, and 19 patients died from myocardial infarction on follow-up out of a total of 1,129 patients.²² Similarly, in the SOLVD trial,²³ 164 patients out of 586 patients with DCMP had

ischemic events. Explanted hearts were studied to determine whether the initial cause leading to cardiomyopathy was correctly defined or not.^{4–7} The results obtained from this study showed a prevalence of significant CAD of around 23 to 27% in these specimens. Repetto et al,⁶ in his study, revealed that the prevalence of CAD in DCMP patients was around 65%. However, our study revealed a prevalence of around 38%. Repetto et al⁶ studied the presence and severity of CAD in his study population as predicted by the clinical factors (– **Table 6**). In our study, we evaluated the effect of age, sex, hypertension, diabetes, smoking, alcohol, and CKD as a predictor of CAD in DCMP patients. The results were almost the same as those in the general population.

In one of the case reports, cardiac decompensation in long-standing DCMP patients was linked to CAD.¹⁰ It appears quite possible as chronic heart failure is atherogenic in itself.²⁴

In our study, we found a significant association of CAD with cardiac decompensation in the form of heart failure requiring hospitalization. However, there was no association of associated insignificant CAD in DCMP patients related to mortality. Usually, the outcome of ischemic cardiomyopathy is worse than idiopathic

Table 6 Studies of concomitant CAD in DCMP patients

Trials	Conclusion
Frankenstein et al ²¹	Concomitant CAD is common in DCMP patients. However, it is not a predictor of mortality or heart failure
Cleland et al ²²	9% of DCMP patients had ischemia, 19 out of 1,129 patients died from MI on follow-up
Yusuf et al ²³	164 out of 586 DCMP patients had ischemic events
Repetto et al ⁶	65% prevalence of CAD in DCMP patients

Abbreviations: CAD, coronary artery disease; DCMP, dilated cardiomyopathy; MI, myocardial infarction.

DCMP.^{25,26} Moreover, both impairments in the coronary reserve²⁷ or positron emission tomography stress denoting perfusion–metabolism mismatch²⁸ are related to a poor prognosis even in idiopathic DCMP patients. The result may be explained as the CAD in our study group was just a bystander (not the cause of cardiomyopathy) as opposed to ischemic heart disease in which it is the causal factor; thus, it does not bear the same prognostic significance. The second explanation for no significant difference in mortality may be strict follow-up and adherence to mortality benefit drugs, particularly beta-blockers.

The possible explanation for the association of minimal CAD in DCMP patients with an increase in hospitalization secondary to heart failure is that CAD in these patients may actively contribute to the diastolic abnormalities. The second explanation may be that the associated comorbidities such as hypertension, diabetes, older age, and smoking, which are higher in the DCMP with minimal CAD group, may impair diastolic function and thus increase in heart failure rates as compared with DCMP with normal coronaries group.

Conclusion

The risk factor profile predicting CAD in DCMP patients is the same as that in the general population. In our study, the presence of minimal CAD in DCMP patients was not associated with mortality. However, it is associated with hospitalization secondary to cardiac decompensation in the form of heart failure.

Audio 1

Audio file for this article is available at: <https://doi.org/10.1055/s-0041-1739127>.

Conflict of Interest

None.

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