Fifteen-year mortality and prognostic factors in patients with dilated cardiomyopathy: persistent standardized application of drug therapy and strengthened management may bring about encouraging change in an aging society

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ABSTRACT

BACKGROUND   There is scarce data on the long-term mortality and associated prognostic factors in patients with dilated cardiomyopathy (DCM). The study aimed to investigate the all-cause mortality up to 15 years (mean 7.9 ± 5.7 years) in such patients, and the independent prognostic factors influencing their long-term mortality.

METHODS   One hundred and sixty-six consecutive patients with DCM were prospectively enrolled from 2002 to 2003. The mean age of patients was 59.5 ± 10.4 years, and approximately 57% were male. They were followed up by telephone or outpatient visit at least every three months until 2019 or all-cause death occurred. Predictors of mortality were identified using multivariate logistic regression analysis.

RESULTS   During the 15 years of follow-up, five patients were lost to follow-up, and the complete data records of 161 patients were included in the analysis. Patients were treated with angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin-receptor blocker (ARB), β-blockers, mineralocorticoid receptor antagonist (MRA), diuretics and digitalis from 2002 to 2004, and maintained at the maximum tolerated doses between 2004 and 2019. Our safety targets to maintain heart rate and blood pressure at 60-80 beats/min and 90-120/60-80 mmHg, respectively. All-cause mortality in the first five years was 55.9%. The independent risk factors for the 5-year mortality were age ≥ 70 years old (OR = 5.45, P = 0.006), systolic blood pressure (SBP) > 120 mmHg (OR = 3.63, P = 0.004), 6-minute walk distance (6MWD) < 450 m (OR = 3.84, P = 0.001). 15-year all-cause mortality was 65.8%. The independent risk factors for 15-year mortality were age ≥ 70 years old (OR = 16.07, P = 0.009), LVEF ≤ 35% (OR = 5.69, P = 0.003), and SBP > 120 mmHg (OR = 9.56, P < 0.001).

CONCLUSIONS   This study was the first to demonstrate the 15-year survival rate of 34% in DCM patients. The DCM patients' first five-year all-cause mortality decreased significantly after continuous standardized treatment and intensive management. The mortality then plateaued in the following 10 years. Age ≥ 70 years, LVEF ≤ 35%, and SBP > 120 mmHg were independent predictors of 15-year all-cause mortality.

Dilated cardiomyopathy (DCM) is characterized by ventricular dilatation and contractile dysfunction in the absence of abnormal loading conditions and coronary artery disease. As a common cause of heart failure (HF), sudden death can occur at any stage of the disease. In addition, DCM is currently the leading indication for heart transplantation.[1,2]

Risk stratification in patients with DCM remains challenging and represents a crucial part of disease management with implications for treatment and prognosis. Understanding the factors associated with mortality may help identify patients who need to be intensely monitored or treated in the hope of optimal blood pressure and heart rate. Previous studies have demonstrated that patients with DCM have a poor

prognosis, with one-year mortality rates of 25% to 30% and five-year mortality rates of approximately 50%.[3] Despite a large number of investigations on prognostic factors in heart failure, only a few have focused on non-ischemic DCM, and are almost limited to follow-up periods under five years. To our knowledge, no data are available to describe 15-year mortality in patients with DCM. Therefore, we conducted a study to investigate the mortality up to 15 years and the independent prognostic factors in patients with DCM.

METHODS

Study Population

One hundred sixty-six consecutive patients with DCM were enrolled in the study from January 2002 to December 2003. All patients received a standard and refined individualized medication regimen with long-term follow-up from 2004 to 2019.

A total of 166 eligible patients were screened during the study period, of whom five cases were lost to follow-up. Eventually, 161 patients with complete demographic, clinical, laboratory, echocardiographic and follow-up data were included in the analysis. The study was performed in compliance with the Declaration of Helsinki and was approved by the Ethics Committee. All the patients provided written informed consent before study entry.

According to the diagnostic guidelines of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies,[4] the diagnosis criteria of patients were: (1) left ventricular ejection fraction (LVEF) < 45% and left ventricular end-diastolic diameter (LVEDD) > 55 mm in men and (or) > 50 mm in women estimated by echocardiography, in the absence of ischemic heart disease, hypertension cardiomyopathy, viral myocarditis, valvular heart disease, alcohol-induced cardiomyopathy, peripartum cardiomyopathy, adriamycin toxicity and sarcoidosis; (2) patients were aged 18–80 years old; and (3) all patients achieved stable disease for ≥ 3 months and had no hospitalization records for nearly three months.

The exclusion criteria were the presence of any one of the following conditions: (1) heart rate 60 beats/min and blood pressure < 90/60 mmHg under the clearheaded quiescent state; (2) coronary angiography shows > 50% diameter luminal stenosis in one or more epicardial vessels; (3) a history of obstructive lung disease, or hepatic and renal dysfunction; (4) patients who were pregnant or lactating; and (5) patients with other end-stage diseases and an expected survival time < 5 years.

Persistent Treatment and Management

Standard and individualized treatment plan: the target dose was not defined for any medicines, and the safety target was defined as a heart rate of 60-80 beats/min, and a blood pressure of 90-120/60-80 mmHg. The digoxin serum concentration needs to be maintained at 0.5-0.9 ng/L to ensure patient safety for long-term use.

All patients were treated with a primary medication regimen according to chronic HF guidelines[3,4]: patients received angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin-receptor blocker (ARB), β-blockers, mineralocorticoid receptor antagonist (MRA), diuretics and digitalis from 2002 to 2004, then doses should be titrated up until the maximum tolerated dose and maintained from 2004 to 2019. Low-dose diuretics (furosemide and spironolactone remain the first choice of treatment); perindopril (an ACEI), was up-titrated over 2–4 weeks; the appropriate maintenance dosage of digoxin was 0.125-0.25 mg daily; it was recommended that the dose be doubled after each 2- or 4-week period until to a maximum tolerance dose of metoprolol. Patients were required to have their blood pressure, heart rate, liver and kidney function, digoxin concentrations and patient symptoms checked again at each follow-up visit, and the treatment regimen was adjusted according to their own condition.

Clinical Evaluation and Long-term Follow-up

The baseline variables were as follows: including heart rate (HR), blood pressure (BP), NYHA functional class, 6-minute walk test (6MWT), electrolytes and medication treatment. In addition, LVEF, left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD) were assessed by 2-dimensional echocardiography.

All patients were followed up by telephone or out-

patient visit at least every three months until 2019 or all-cause death occurred. Patient deaths during follow-up were reported and determined by the patients' family. Survival status was confirmed for all participants in this study.

Statistical Analysis

Continuous variables were presented as mean ± SD. Categorical variables were presented as counts with percentages. Student t tests was used for the comparison of the continuous variables; and the Chi-square test was used for the comparison of categorical variables between the two groups Logistic regression models were used to explore the associations between patients' baseline characteristics and all-cause mortality. The study used the stepwise and backward selection technique to select variables for the final model with a P value of 0.05. The final model was repeated using generalized estimating equations (GEE) to account for the correlation of data within the adjusted models.

Receiver operating characteristic (ROC) curve was used to determine the predictive ability, sensitivity and specificity of the prediction model. $P < 0.05$ was considered statistically significant. It is worth noting that patients' characteristics which are easily affected by long-term follow-up, such as biological or therapeutic characteristics, and were not considered as the candidate indicators for the model.

All analyses were performed using IBMSPSS V. 22.0 (IBM SPSS statistics for windows, IBM Corp).

RESULTS

Baseline Characteristics and Adverse Events

The enrolled patients' (n = 161) baseline characteristics were summarized in Table 1. The mean age

Table 1   Baseline characteristics of 161 patients with DCM.

Characteristics	Value
Male	91 (56.5%)
Age, yrs	59.5 ± 10.4
HR, beats/min	82 ± 18
SBP, mmHg	113 ± 11
DBP, mmHg	72 ± 7
LVEDD, mm	63.1 ± 8.1
LVESD, mm	43.1 ± 9.2
LVEF	48.4% ± 11.4%
NYHA functional class	
I	45 (28.0%)
II	62 (38.5%)
III	34 (21.1%)
IV	20 (12.4%)
6MWT, m	420.0 ± 87.0
Potassium, mmol/L	4.1 ± 0.4
Medicines	
ACEI/ARB	114 (70.8%)
β-blockers	122 (75.8%)
MRA	137 (85.1%)
Diuretic	156 (96.9%)
Digitalis	122 (75.8%)

Data are presented as mean ± SD, or n (%) unless other indicated. ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blocker; DBP: diastolic blood pressure; HR: heart rate; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVEF: left ventricular ejection fraction; SBP: systolic blood pressure; 6MWT: 6-min walk test; MRA: mineralocorticoid receptor antagonists.

of the patients was 59.5 ± 10.4 years, and approximately 57% were male. The median LVEF was 48%. The mean distance of 6-min walk was approximately 420 m. About one-third of patients (*n* = 54, 33.5%) experienced severe heart failure symptoms (NYHA III and IV). 70.8%, 75.8%, 85.1%, 96.9% and 75.8% of the patients received ACEI or ARB, β-blockers, MRA, diuretics, and digitalis, respectively.

Primary Endpoints

The cumulative patient mortality over the 15-year follow-up time was 106, with 90 patients having died in the first five years. The first 5-year all-cause mortality rate was 55.9%, and the 15-year mortality rate was 65.8%. The follow-up results showed a significant decrease in the 15-year survival curve and reached a plateau 5 years before follow-up (Figure 1).

Prognostic Factors Associated with The First 5-year Mortality

According to univariate analysis (Table 2), age, heart rate, SBP, LVEF, and 6MWD were associated with mortality. Relevant variables presented statistical significance were used for multivariate logistic regression analysis. The results indicated that age ≥ 70 years, SBP > 120 mmHg, and 6MWT < 450 m were independent risk factors for 5-year mortality. The area under the curve (AUC) of the model for the first 5 years was 0.764 (95% CI: 0.691-0.838, *P* <
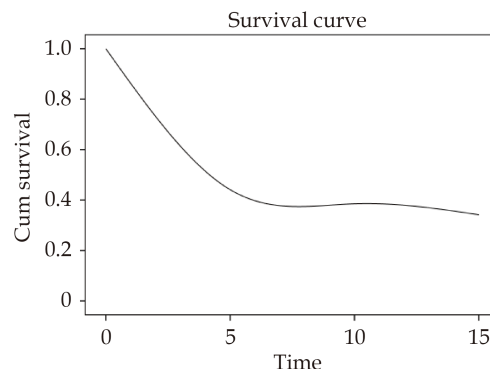

Figure 1   **15-year survival curve in patients with DCM.** A total of 161 patients completed the final analysis from January 2004 to January 2019. During the 15-year period, the survival rate of study patients was 44.1% at 5 years, 38.5% at 10 years, and 34.2% at 15 years. DCM: dilated cardiomyopathy.

0.001), indicating that these features were reliable for mortality prediction in the first five years (Figure 2).

Prognostic Factors Associated with 15-year Mortality

As shown in Table 3, age ≥ 70 years, heart rate > 80 beats/min, SBP > 120 mmHg, LVESD > 45 mm, LVEF ≤ 35%, NYHA classification ≥ III and 6MWT < 450 m were the related variables in 15-year mortality prediction. Age ≥ 70 years, LVEF ≤ 35%, and SBP > 120 mmHg were significant predictors of 15-year all-cause mortality after covariance adjustment.

The predictive model showed an AUC of 0.801 (95% CI: 0.726-0.875, *P* < 0.001), which suggested that it could

Table 2   **Prognostic factors associated with the first 5-year mortality.**

	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Male	1.12 (0.60-2.10)	0.717		
Age ≥ 70 years	3.07 (1.07-8.76)	0.036	5.45 (1.64-18.09)	0.006
HR > 80 beats/min	2.30 (1.21-4.36)	0.011		
SBP > 120 mmHg	6.59 (2.93-14.84)	0.000	3.63 (1.50-8.79)	0.004
DBP > 80 mmHg	1.09 (0.57-2.12)	0.784		
LVEDD > 65 mm	1.02 (0.98-1.06)	0.453		
LVESD > 45mm	1.02 (0.99-1.06)	0.216		
LVEF ≤ 35%	3.03 (1.27-17.22)	0.012		
NYHA ≥ III	1.68 (0.84-3.36)	0.143		
6MWD < 450 m	3.44 (1.79-6.62)	0.000	3.84 (1.72-8.57)	0.001
Potassium < 4.0 mmol/L	0.86 (0.43-1.70)	0.657		

The univariate analysis shows that age, heart rate, SBP, LVEF, and 6MWD were associated with mortality. Meanwhile, multivariate analysis demonstrated that age ≥ 70 years, SBP > 120 mmHg and 6MWT < 450 m were independent risk factors for 5-year mortality. DBP: diastolic blood pressure; HR: heart rate; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVEF: left ventricular ejection fraction; SBP: systolic blood pressure; 6MWT: 6-min walk test.
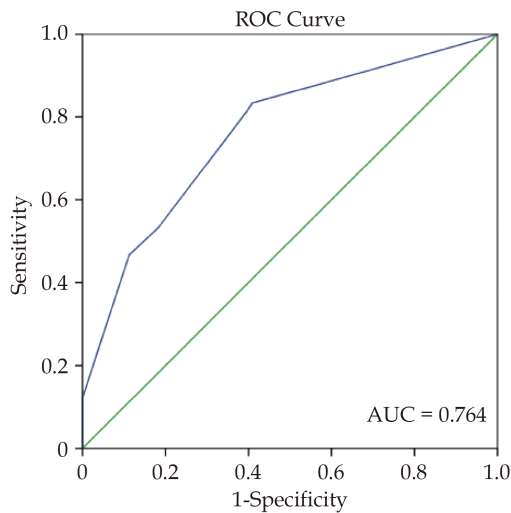
Figure 2 Receiver operator curve (ROC) of the predictive factors for 5-year mortality. The area under the curve (AUC) for predictors in the first 5 years was 0.764 (95% CI: 0.691-0.838, *P* < 0.001), the result suggested that predictors were reliable for mortality of the first five years.

more accurately predict long-term mortality in such patients (Figure 3).

DISCUSSION

This study is the first to investigate 15-year mortality and prognostic factors in patients with DCM. We found that a 55.9% mortality rate in such patients in the first five years, and a 65.8% mortality rate at 15 years. Patients with dilated cardiomyopathy have a poor prognosis, so more accurate risk stratification and personalized therapy may considerably improve outcomes. Most current studies on mortality prediction are usually limited to a follow-up period of less than five years. There is a lack of data on the long-term mortality and associated prognosis of DCM. Interestingly, our results indicated that the all-cause mortality significantly declined from 2004 to 2019, with a nearly 46% reduction after 10-year mortality (2009–2019) compared with the first 5-year (2004–2008). The results of the present study also showed that the 5-, 10-, and 15-year survival rates of the patients were 44.1%, 38.5%, and 34.2%, respectively. A prospective study (EPICAL) enrolling a total of 352 French inpatients with systolic HF reported 5-, 10-, 15- year survival rates of 34.5%, 19.7%, and 12.3%, respectively.[5] The survival rate obtained in our study is higher than this data from previous studies, which may be related to the population of selected patients, etiology of HF, and baseline status of cardiac function. Our findings also suggest that regular follow-up and management contribute to the prognosis of HF patients. The significantly improved 15-year survival of such patients is very encouraging. That means that most patients who survive after receiving 5 years of standardized treatment will have relatively long-term event free survival.

In terms of impact factor exploration, our results

Table 3 Prognostic factors associated with the total 15-year mortality.

	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Male	1.13 (0.59-2.18)	0.716		
Age ≥ 70 years	13.34 (1.74-102.08)	0.013	16.07 (2.01-128.59)	0.009
HR > 80 beats/min	2.12 (1.08-4.16)	0.029		
SBP > 120 mmHg	10.96 (3.70-32.50)	0.000	9.56 (3.12-29.32)	0.000
DBP > 80 mmHg	2.04 (0.98-4.25)	0.058		
LVEDD > 65 mm	1.34 (0.68-2.65)	0.391		
LVESD > 45 mm	3.49 (1.55-7.86)	0.003		
LVEF ≤ 35%	4.80 (1.59-14.48)	0.005	5.69 (1.78-18.16)	0.003
NYHA ≥ III	3.19 (1.45-7.01)	0.004		
6MWT < 450 m	2.79 (1.41-5.51)	0.003		
Potassium < 4 mmol/L	1.77 (0.83-3.77)	0.141		

By univariate analysis, age ≥ 70 years, heart rate > 80 beats/min, SBP > 120 mmHg, LVESD > 45 mm, LVEF ≤ 35%, NYHA classification ≥ III and 6MWT < 450 m were associated with mortality. After adjusting for covariates, age ≥ 70 years, LVEF ≤ 35% and SBP > 120 mmHg were significant predictors of 15-year all-cause mortality. DBP: diastolic blood pressure; HR: heart rate; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVEF: left ventricular ejection fraction; SBP: systolic blood pressure; 6MWT: 6-min walk test.
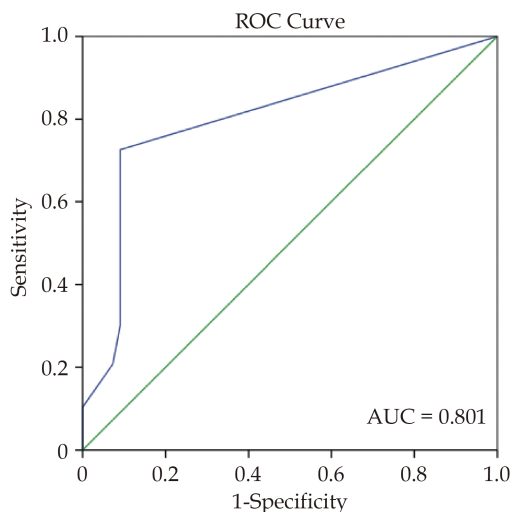
Figure 3 Receiver operator curve (ROC) of the predictive factors for 15-year mortality. The area under the curve (AUC) for these predictors was 0.801(95% CI: 0.726-0.875, *P* < 0.001), indicating excellent predicting capacity of mortality for the total 15 years.

showed that age ≥ 70 years, SBP > 120 mmHg and 6MWT < 450 m were strongly related to 5-year mortality. The predictors identified in the study affecting long-term mortality were consistent with the results of previous studies.[6,7] These predictors that we identified may also be of value for long-term prognosis in stable DCM. In our study, age ≥ 70 years, LVEF ≤ 35% and SBP > 120 mmHg were independent predictors of 15-year all-cause mortality. The AUC of this prediction model was 0.801, indicating that the predictive ability of this model for 15-year mortality was excellent.

The age of DCM onset is usually concentrated at 30 or 40 years, therefore, older age is an independent risk factor for mortality. A study from Parakh, *et al.*[6] showed that a 10-year increase in patient's age was associated with a 31% increased 5-year mortality risk. Agrinier, *et al.*,[5] found that age older than 65 years was an independent risk predictor of 15-year mortality in patients with systolic heart failure. In our study, we observed that age ≥ 70 years old was an independent risk factor for both 5- and 15-year all-cause death. It suggests that the prognosis of older patients with DCM requires more attention.

Functional status assessment is the cornerstone of DCM prognosis and management. LVEF, NYHA class, and 6MWT as commonly used assessment tools have shown their value in predicting short - and long-term outcomes in many studies. Our results

showed that 6MWT < 450 m was associated with 5-year mortality, and LVEF ≤ 35% was associated with 15-year outcome.

6MWT is a simple and widely used method to measure of functional status of patients with chronic heart failure (CHF).[8] Kinga, *et al.*[9] indicated that the mortality hazard ratio in HF patients with a 6-min walk distance ≤ 468 m was 3.22 at one year and 2.18 at three years. A systematic review showed a negative correlation between 6MWD and NYHA II-IV, and patients with chronic heart failure had a worse prognosis, shorter walking distance, and higher NYHA class. Our results showed that 6MWT < 450 m was a risk factors for 5-year all-caused death.[10]

LVEF remains the most commonly used parameter of cardiac function and is related to prognosis in patients with heart failure.[11,12] Karatolios, *et al.*,[13] showed that LVEF < 35% was a multivariable risk predictor of 5-year outcome in patients with DCM. Recent PARADIGM-HF study reported that the risk of all outcomes increased with decreasing LVEF, each 5-point reduction in LVEF was associated with a 9% increased risk of cardiovascular death or HF hospitalization, and a 7% increased risk in all-cause mortality.[14] Agrinier, *et al.*,[5] showed that each quartile increase in LVEF was associated with 12% reduction in 15-year mortality risk. Survival analysis from Japan revealed that significantly higher composite cardiac event free survival in patients with left ventricular reverse remodeling.[15] Therefore, our results indicated that LVEF ≤ 35% was associated with 15-year all-cause death.

In HFREF, higher HR and lower systolic and diastolic BP were associated with higher mortality and hospitalization rates.[16] A Korean acute heart failure study showed the relationship between on-treatment BP and all-cause mortality followed a reversed J-curve relationship. Systolic and diastolic BPs < 130/70 mmHg at discharge and during follow-up was associated with worse survival in HF patients. These data suggest that the lowest BP might not be an optimal target for acute HF patients.[17]

The results of a previous single-center prospective study by our team demonstrated a significant increase in mortality with SBP. The lowest mortality was within 90–110 mmHg, followed by 111–120 mmHg and 121–130 mmHg, and > 130 mmHg. When SBP > 130 mmHg, the mortality increased by four times,

when compared with 90–110 mmHg.[18]

However, few previous studies have focused on the prognostic relationship between SBP and DCM. The optimal BP level for patients following treatment is controversial. Our results showed that SBP > 120 mmHg was an independent risk predictor for both 5- and 15- year mortality. We speculate that our study population was idiopathic dilated cardiomyopathy with systolic dysfunction, and SBP > 120 mmHg increased afterload compared with SBP ≤ 120 mmHg further impairs their systolic function, which is related to adverse outcome. The above results might provide valuable guidance for clinical practice. Besides, our study population was small，and the appropriate BP target (maybe 100–120 mmHg) for DCM patients' needs further validated by other large cohort studies.

It can be seen that although the first 5-year mortality rate of DCM patients was very high, the mortality rate decreased significantly after the standardized treatment and reached a plateau in the last 10 years, and the survival rate of DCM patients improved at the end.

National and international guidelines for DCM and heart failure[19−20] emphasize the importance of removing the cause and enhancing follow-up management (such as drugs, lifestyle intervention, cardiac rehabilitation) on patient outcomes. We suggest that more attention should be paid to the prognosis of older patients with DCM.

Patient compliance was improved to some extent by regular follow-up with physicians and care team, and intensive management with continuous standardized medical therapy for optimal blood pressure and heart rate. Our findings are very encouraging and provide some valuable reference for optimal treatment targets for DCM.

LIMITATION

Still, this study has some limitations. Firstly, we performed a very long-term follow-up study, but the number of patients was relatively small to exclude moderate relations of some factors with a certain outcome. Secondly, the predictors identified in our study are clinically intuitive and relatively simple. Thirdly, we only assessed the long-term prognostic value of baseline characteristics, susceptible features such as biological or therapeutic, were not incorporated into the model. Fourthly, these predictors in our study need to be further validated by other cohort studies.

CONCLUSION

This study was the first to demonstrate a 15-year survival rate for DCM as high as 34%. Although the mortality rate was very high in patients with DCM in the first five years, it significantly decreased after continuous standardized treatment and strengthened heart rate and blood pressure target management, their mortality rate significantly decreased and then entered a plateau after 10 years. Age ≥ 70 years, LVEF ≤ 35%, and SBP > 120 mmHg were independent predictors of 15-year all-cause mortality.

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