The Prognostic Factors of Alcoholic Cardiomyopathy
A single-center cohort study

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Abstract
Background: Alcoholic cardiomyopathy (ACM) is considered one of the main causes of left ventricular dysfunction and is the leading cause of nonischemic dilated cardiomyopathy (DCM) in developed countries. However, very few studies have investigated the relationship between clinical characteristics and prognosis in ACM.

Aims: This study aimed to identify risk factors related to a poor outcome in ACM patients.

Study design: Retrospective cohort study.

Methods: This study included 321 patients with ACM admitted to our hospital between 2003 and 2013. This study aimed to investigate the clinical characteristics and outcomes of the patients with ACM, and the primary endpoint of the study was all-cause mortality, which was assessed through patient medical records (review of patient hospital records and periodic examination of patients in the outpatient clinic) and medical follow-up calls with trained personnel. All-cause mortality was assessed using Kaplan–Meier survival curves, and the risk factors were assessed using Cox regression. A receiver operating characteristic (ROC) curve analysis was performed to optimize the cutoff point for discriminating between the 2 risk groups.

Results: After a median follow-up period of 3.78 years (interquartile range: 2.08–6.52 years), 83 (27.7%) patients were dead. The independent predictors of all-cause mortality due to ACM were the QRS duration (HR: 1.014; 95% CI: 1.004–1.019; P = .003), systolic blood pressure (HR: 0.980; 95% CI: 0.963–0.997; P = .020), and New York Heart Association classification (HR: 1.596; 95% CI: 1.110–2.290; P = .011) at admission.

Conclusion: Our study indicated that the QRS duration, systolic blood pressure, and New York Heart Association classification at admission provided independent prognostic information in patients with ACM.

Abbreviations: $\chi^2$ = chi-square test, ACM = alcoholic cardiomyopathy, AF = atrial fibrillation, CT = coronary artery computed tomography, DBP = diastolic blood pressure, DCM = dilated cardiomyopathy, HF = heart failure, IQRS = interquartile ranges, LA = left atrium, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, NT-pro BNP = N-terminal probrain natriuretic peptide, NYHA = New York Heart Association, QRS = QRS duration, ROC = receiver operating characteristic, RV = right ventricle, SBP = systolic blood pressure.

Keywords: alcoholic cardiomyopathy, mortality, prognosis

1. Introduction
Excessive alcohol intake is a major health problem, especially in developed countries. Long-term excessive alcohol consumption has been determined to be the third leading cause of premature death in the United States, and the detrimental effects of alcohol consumption account for 3.8% of all deaths worldwide.\textsuperscript{[1,2]}
Individuals who consume more than 80 g of alcohol per day over a period of at least 5 years are at risk for the development of alcoholic cardiomyopathy (ACM) and heart failure (HF). Without complete abstinence, the 4-year mortality rate for ACM can be as high as 50%, and ACM is a common cause of death among long-term heavy drinkers. ACM is a form of dilated cardiomyopathy (DCM) and accounts for 40% of DCM cases. Similar to other causes of DCM, ACM is characterized by an increased left ventricular end-diastolic diameter (LVEDD) and a reduced left ventricular ejection fraction (LVEF); however, the diagnosis is usually one of exclusion in a patient with a long history of heavy alcohol abuse, as no specific clinical, or histological features have been identified.

Despite the key clinical importance of alcohol as a cause of DCM, little information has been published on the long-term outcome of patients with ACM in China. The aims of the present study were to define the long-term outcome of ACM, to compare the patient characteristics between the death and survival groups, and to determine prognostic markers.

2. Subjects and methods

2.1. Patients

This study was a retrospective, observational study of 299 patients admitted to our hospital from November 2003 to August 2013 due to physical signs of HF. These patients were diagnosed with ACM according to the definition proposed in the European Society Of Cardiology consensus document on the classification of cardiomyopathies, which states that ACM is classified among the acquired forms of DCM. Additionally, the level of alcohol consumption required to establish a diagnosis of ACM was more than 80 g per day over a duration of at least 5 years, and this alcohol abuse must have been continued until <3 months before the diagnosis of DCM. Patients with the following complications were excluded from the study: coronary heart disease, hypertension, thy rotoxic heart disease, diabetes, and congenital heart disease.

All 299 patients underwent a routine evaluation including a physical examination, 12-lead electrocardiography, 2-dimen sional echocardiography, and a complete biochemical evaluation. Additional studies included 24-hour ECG monitoring and cardiac magnetic resonance imaging. Coronary angiography, coronary artery computed tomography (CT), or nuclear medicine testing was performed to rule out coronary heart diseases.

2.2. Follow-up and endpoints

Follow-up was performed until November 2016. The status of all patients was followed up by telephone interview, outpatient clinic attendance, or hospitalization during the follow-up period. Forty patients were lost to follow-up, and censored data were recorded. The only endpoint of the study was all-cause mortality. This study protocol was approved by the Ethics Commission of Fuwai Hospital.

2.3. Statistical analysis

Normally distributed variables are expressed as the means and standard deviations or percentages, whereas non-normally distributed variables are presented as the medians and interquartile ranges (IQRs). The t test was used to compare continuous variables between the 2 groups. The categorical variables were compared between groups using the chi-square (χ²) test.

To predict all-cause mortality from baseline variables, an initial screen of all parameter values at enrollment was performed with univariate Cox regression. For the forward/backward stepwise multivariable Cox proportional hazards analysis, we included only those variables with a P value <.05 in the univariate Cox regression.

Based on the multivariate Cox regression analysis, continuous variables were categorized. A receiver operating characteristic (ROC) curve analysis was performed to optimize the cutoff value of the continuous variables. Then, survival curves were calculated according to the Kaplan–Meier method, and the log-rank test was used to compare the groups based on the ROC curves. The level of statistical significance was defined as P < .05. All hypothesis tests were 2-tailed. The entire analysis was performed using SPSS version 17.0 software.

3. Results

3.1. Clinical features

Of the 299 hospitalized patients, 296 (98.9%) were men and 288 (96.3%) were members of the Han population. The age of the 299 patients ranged from 24 to 78 years (mean, 50.6 ± 10.7 years), and the duration of disease was 3 (IQR: 0.85–7) years. During the median follow-up period of 3.78 (IQR: 2.08–6.52) years, 83 ACM patients (27.7%) died.

The baseline clinical, ECG, and echocardiographic characteristics of the ACM patients are shown in Table 1. Among the ACM patients, no differences between the patients in the death and survival groups were observed at baseline with respect to age, disease duration, smoking status, presence of syncope, heart rate, gender, and blood test results. The frequencies of a high New York Heart Association (NYHA; class III/IV) classification, atrial fibrillation (AF) and atrioventricular block were higher in the death group than those in the survival group. The QRS duration, LVEDD, and diameter of the right ventricle (RV) and left atrium (LA) were higher in the death group than those in the survival group, but the LVEF and blood pressure (systolic [SBP] or diastolic [DBP]) were lower in the death group than those in the survival group.

3.2. Estimation of prognosis and risk factors in ACM

The univariate analysis indicated that NYHA classification, disease duration, SBP, DBP, QRS, AF, LVEDD, RV, LA, LVEF, and N-terminal probrain natriuretic peptide (NT-pro BNP) were prognostic predictors in ACM patients. Independent predictors of all-cause mortality in the multiple Cox regression analysis were QRS (HR: 1.014; 95% CI: 1.010–1.019; P = .003), SBP (HR: 0.980; 95% CI: 0.963–0.997; P = .020), and NYHA classification (HR: 1.395; 95% CI: 1.110–2.290; P = .011) at admission (Table 2).

3.3. Relationship between independent predictors and all-cause mortality

The Kaplan–Meier survival probability estimate was 96.3% at 1 year and 72.2% at 5 years. According to the ROC curve analysis, the optimal cutoff value was 109 ms for QRS duration and 112 mm Hg for SBP. The endpoint was reached by 58 patients with a QRS ≥ 109 and 25 patients with a QRS < 109; 57 patients with...
Table 1

| Patient characteristics categorized according to survival and death. | All patients (n = 299) | Death (n = 83) | Survival (n = 216) | P value |
|---|---|---|---|---|
| Mean age, y | 50.5 ±11 | 52.2 ±10.2 | 49.8 ±11.3 | .089 |
| Disease duration, y | 3 (0.85–7) | 4 (2–9) | 2 (0.5–6) | .105 |
| Smoking | 249 (83.2%) | 75 (90.4%) | 174 (80.6%) | .084 |
| Syncope | 21 (7%) | 9 (10.8%) | 12 (5.6%) | .109 |
| Heart rate | 80.8 ±17.8 | 77.8 ±18.5 | 81.±17.5 | .074 |
| Sex | Male 296 (99%) | 81 (97.6%) | 215 (99.5%) | .130 |
| Female 3 (1%) | 2 (2.4%) | 1 (0.5%) | |
| NYHA function class | I 4 (1.4%) | 1 (1.2%) | 3 (1.4%) | .01 |
| II 86 (29.1%) | 14 (17.1%) | 72 (33.6%) | |
| III 113 (38.2%) | 31 (37.8%) | 82 (38%) | |
| IV 93 (31.4%) | 36 (43.9%) | 57 (26.6%) | |
| Blood pressure | SBP, mm Hg 114.9 ±17.9 | 109.4 ±15.2 | 117.1 ±18.4 | .001 |
| DBP, mm Hg 74.9 ±12.4 | 72 ±11.2 | 76.1 ±12.7 | .011 |
| Blood test results | CR, μmol/L 95.4 ±32.5 | 101.5 ±37.6 | 93 ±30.2 | .081 |
| BUN, μmol/L 7.3 (5.7–9.27) | 7.3 (5.7–10.3) | 7.3 (5.7–9) | .688 |
| FBG, mmol/L 5.8 ±1.3 | 5.7 ±1.7 | 5.5 ±1.4 | .306 |
| NT-pro BNP, fmol/mL 1449 (768.2–2703.1) | 2179.9 (1187.8–3429.6) | 1269 (697.7–2280.3) | .058 |
| ECG test results | QRS duration, ms 119.5 ±32.3 | 132.1 ±32.9 | 114.8 ±30.8 | <.001 |
| AF 41 (13.7%) | 41 (49.4%) | 0 (0%) | <.001 |
| AVB 79 (26.4%) | 79 (95.2%) | 0 (0%) | .012 |
| Echocardiography results | LVEF, mm 34.6 ±10.6 | 32.5 ±10.1 | 35.4 ±10.7 | .043 |
| LV, mm 67.76 ±9.5 | 70.4 ±10.4 | 66.8 ±9.9 | .002 |
| RV, mm 23.9 ±5.7 | 25.6 ±7 | 23.4 ±5 | .024 |
| LA, mm 45.4 ±7.8 | 47.6 ±8.3 | 44.6 ±7.5 | .004 |

Data were expressed as means ± SD or medians (interquartile range) or as percentages. P values were calculated from independent samples t tests or χ² tests for categorical data. Bold data indicated P < .05.

Eighteen patients lacked LV data, 159 patients lacked a RV data, 22 lacked LA data, 16 patients lacked LVEF data, 105 patients lacked NT-pro BNP data, 28 patients lacked FBG data, 15 patients lacked CR data, 22 lacked BUN data, 3 patients lacked NYHA data, 6 patients lacked AVB data, and 1 patient lacked AF data at admission.

AF = atrial fibrillation, AVB = atrioventricular block, BUN = blood urea nitrogen, CR = creatinine, DBP = diastolic blood pressure, FBG = fasting blood glucose, LA = left atrium, LV = left ventricle, LVEF = left ventricular ejection fraction, NT-pro BNP = N-terminal pro-brain natriuretic peptide, NYHA = New York Heart Association, RV = right ventricle, SBP = systolic blood pressure.

an SBP < 112 and 26 patients with an SBP ≥112 mm Hg; and 67 patients classified as NYHA class III/IV and 15 patients classified as NYHA class III. Table 3 summarizes the baseline clinical characteristics of the 2 groups according to QRS, SBP, and NYHA classification. In our ACM cohort, patients with a QRS ≥109 ms, an SBP < 112 mm Hg, and an NYHA classification of class III/IV had a higher incidence of all-cause mortality than patients with a QRS < 109, an SBP ≥112 mm Hg, and an NYHA classification of class I/II, respectively [log-rank χ² = 23.945, P < .001; log-rank χ² = 11.109, P = .001; log-rank χ² = 8.176, P = .004; Fig. 1A–C].

4. Discussion

To our knowledge, our study determined prognostic factors for ACM outcome in the largest cohort of ACM patients described to date. Our data show that the variables most closely predicting a poor outcome in ACM are QRS duration, SBP and NYHA classification at admission.

Other factors associated with a poor prognosis have been proposed in previous ACM studies; however, those studies were hampered by a small patient sample size and had contradictory results. The first paper assessing the long-term prognosis of ACM was published by McDonald, who found that the only factors predictive of a bad outcome were the long-term, excessive intake of alcohol and the duration of HF symptoms before admission. Other authors also reported that the survival rates for cardiovascular events were improved among ACM patients who became abstinent, and the only independent predictors of cardiac death were alcohol abstinence and an increased left ventricular end-systolic diameter. Another paper reported that the prognosis for ACM patients who had reduced their alcohol consumption to moderate levels was similar to that for abstainers.

QRS prolongation is well known to occur in the general population, with an incidence that increases sharply with age, whereas patients with organic heart disease often have wide QRS complexes due to bundle branch blocks, and the presence of wide QRS complexes on ECG has been accepted as a traditional diagnostic marker for coronary artery disease. However, the presence of atrial fibrillation, a QRS duration ≥120 ms, a shorter distance in the 6-minute walking test, and the use of digoxin to be factors associated with the occurrence of major cardiac events (cardiovascular death or heart transplanta-
Echocardiography results

| Variable | Univariate analysis | | Multivariate analysis | |
|----------|---------------------|---|----------------------|---|
| NT-pro BNP | 1.000 | 1.000-1.018 | <.001 | 1.011 | 1.004-1.019 | .003 |
| AF | 2.497 | 1.516-4.112 | <.001 | 1.756 | 0.894-3.448 | .102 |
| AVB | 1.438 | 0.918-2.252 | | | | |
| LV | 1.034 | 1.012-1.056 | .002 | 1.004 | 0.968-1.041 | .835 |
| RV | 1.057 | 1.015-1.101 | .007 | 1.012 | 0.966-1.060 | .611 |
| LA | 1.051 | 1.021-1.08 | .001 | 1.022 | 0.977-1.070 | .338 |
| LVEF | 0.977 | 0.956-0.999 | .016 | 0.998 | 0.962-1.032 | .827 |
| NT-pro BNP | 1.000 | 1.000-1.000 | .047 | — | — | — |
| FBG | 1.101 | 0.96-1.264 | .169 | — | — | — |
| CR | 1.005 | 0.999-1.01 | .084 | — | — | — |

DBP and NT-pro BNP were not entered into multiple analysis, the former because of its significant collinearity with SBP (r = 0.641, P < .001) but NT-pro BNP for approximately one-third missing value. Bold data indicate P < .05.

AF = atrial fibrillation, AVB = atrioventricular block, CR = creatinine, DBP = diastolic blood pressure, FBG = fasting blood glucose, LA = left atrium, LV = left ventricle, LVEF = left ventricular ejection fraction, NT-pro BNP = N-terminal pro-brain natriuretic peptide, NYHA = New York Heart Association, QRS = QRS duration, RV = right ventricle, SBP = systolic blood pressure.

Many studies have investigated whether excessive alcohol consumption contributes to a higher baseline blood pressure (both systolic and diastolic). However, hypotension was a recognized predictor of poor prognosis in patients with HF, and patients with HF and a low SBP had a much higher incidence of in-hospital and postdischarge mortality. In a study by Meredith, HF patients with a low SBP (or DBP at baseline) had a greater risk of death from any cause. Recently, a study also indicated that patients with a wide QRS complex (≥109 ms) had a higher incidence of all-cause mortality and that QRS duration was one of the independent prognostic predictors in patients with ACM.

Table 3

| Variable | QRS<109 (125) | QRS=109 (149) | QRS>112 (148) | QRS>112 (151) | NYHA=3 (206) | NYHA=3 (90) |
|----------|--------------|---------------|---------------|---------------|--------------|--------------|
| Mean age, y | 51.2±10.9* | 48.7±10.8 | 52.4±11.4* | 48.6±11.3 | 49.8±11.6 | 51.9±9 |
| Disease duration, y | 4 (1-10)* | 2 (0.34-5) | 3 (0.59-7) | 3 (0.98-7) | 3 (0.9-7) | 3 (0.97-8) |
| Smoking | 125 (100%) | 149 (100%) | 129 (87.2%) | 120 (70.5%) | 173 (84%) | 73 (81.1%) |
| Syncope | 13 (10.4%) | 7 (4.7%) | 9 (6.1%) | 12 (7.9%) | 14 (6.8%) | 7 (7.8%) |
| Heart rate | 80.2±16.8 | 83±18.3 | 81.2±15.5 | 80.4±19.8 | 83.7±18.4* | 74.3±14.6 |
| Sex | 124 (99.2%) | 148 (99.3%) | 148 (100%) | 148 (98%) | 205 (99.5%) | 88 (97.8%) |
| Female | 1 (0.8%) | 1 (0.7%) | 0 (0%) | 3 (2%) | 1 (0.5%) | 2 (2.2%) |
| Blood test results | | | | | | |
| CR, μmol/L | 98.3±38 | 92.3±23.8 | 96±37.7 | 94.7±26.3 | 98.9±34.9* | 23.2±2.5 |
| FBG, mmol/L | 5.5±1.3* | 5.7±1.6 | 5.6±1.4 | 5.5±1.5 | 5.6±1.4 | 5.6±1.3 |
| ECG test results | | | | | | |
| AF | 24 (19.2%) | 12 (8.1%) | 17 (11.5%) | 24 (15.9%) | 27 (13.1%) | 13 (14.4%) |
| AVB | 37 (29.6%) | 36 (24.2%) | 38 (25.7%) | 41 (27.2%) | 62 (30.1%) | 17 (18.9%) |
| Echocardiography results | | | | | | |
| LVEF, mm | 32.4±9.8* | 36.4±11.1 | 36.4±10.9* | 32.7±19.8 | 32.9±9* | 40±10 |
| LV, mm | 71±10.2* | 64±7.5 | 66.4±9.6* | 68.9±9.2 | 68.8±9.6* | 64.6±8.4 |
| RV, mm | 24.8±6.5* | 23±4.8 | 22.9±5.2* | 25±6 | 24.7±6.1* | 22.2±4.3 |
| LA, mm | 47±7.8* | 43.4±7.3 | 44.7±8.6* | 46.6±7.7 | 46.9±7.5* | 41.7±7.1 |

Data were expressed as means±SD or medians (interquartile range) or as percentages. P values were calculated from independent samples t tests or χ² tests for categorical data. Data with ** indicated P < .05.

Eighteen patients lacked LV data, 159 patients lacked a RV data, 22 lacked LA data, 18 patients lacked LVEF data, 28 patients lacked FBG data, 15 patients lacked CR data, 3 patients lacked NYHA data, 6 patients lacked AVB data, and 1 patient lacked AF data at admission.

AF = atrial fibrillation, AVB = atrioventricular block, CR = creatinine, DBP = diastolic blood pressure, LA = left atrium, LV = left ventricle, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, QRS = QRS duration, RV = right ventricle, SBP = systolic blood pressure.
demonstrated that patients with a lower SBP had a higher prevalence of ventricular arrhythmias, a lower EF, higher natriuretic peptide concentrations, and a wider QRS duration.\cite{25} The author of that study further noted that SBP was an independent clinical predictor of morbidity and mortality after initial therapy during hospitalization for HF in patients with a reduced EF.\cite{25} In our study, patients with an SBP < 112 mm Hg had a higher incidence of all-cause mortality than those with an SBP ≥ 112 mm Hg, and SBP was an independent prognostic predictor in ACM patients.

The NYHA classification is a widely used method for assessing disease severity among patients with chronic HF and provides clinicians with an objective method of describing functional capacity limitations.\cite{26} As early as 1996, Prazak et al\cite{6} reported that the assessment of a patient as NYHA functional class III/IV was a predictive factor of a bad prognosis over a follow-up time of 10 years in 23 ACM patients. Other studies have indicated that the association between higher NYHA functional classes and poorer outcomes in HF patients was widely recognized.\cite{27,28} In recent years, several studies have argued that the NYHA class assessment demonstrated prognostic value among individuals with acute HF and emerged as a significant independent predictor of all-cause mortality in patients with DCM.\cite{29} In our study, patients assessed as NYHA class III/IV had a higher death rate than those assessed as having a lower NYHA classification, and NYHA was one of the predictors of all-cause mortality in the multivariate Cox regression analysis.

4.1. Study limitations

This cohort of patients was included in a single-center study in our hospital. Although our hospital is the largest cardiovascular disease hospital that admits patients from all areas of China, the data described herein cannot be extrapolated to the entire ACM population. In addition, because the present study was a retrospective analysis, we did not collect precise information on medication use and alcohol abstinence in the patients with ACM. Therefore, we did not include medication use and alcohol abstinence as evaluation indices in this study, although these factors may influence all-cause mortality.

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