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A severity index study of long-term prognosis in patients with chronic heart failure

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ABSTRACT

Aims: The present study describes the derivation and validation of the Chronic Heart Failure Severity Index (CHFSI).

Main methods: The CHFSI was derived using data obtained from a single-center prospective cohort study (2000–2014) that enrolled 756 patients. Logistic regression was used to identify independent predictors of mortality and quality of life over a 15-year follow-up period.

Key findings: The score was validated at the first 5-year (n = 644), second 5-year (n = 364), and third 5-year (n = 262). Independent predictors of mortality were older age (OR = 2.04, $P < 0.001$), etiology score (OR = 2.61, $P < 0.001$), faster heart rate (OR = 1.46, $P = 0.027$), higher systolic blood pressure (OR = 2.35, $P < 0.001$), and left ventricular ejection fraction ≤45% (OR = 1.97, $P = 0.018$). The derived CHFSI predicted the mortality, and the AUC for the logistic model was 0.78 (95% confidence interval = 0.74–0.81, $P < 0.001$). Based on the logistic model, an integer scoring system was derived. Patients were classified into three groups: low risk (0–7 points), intermediate risk (8–11 points) and high risk (≥12 points) groups. The cumulative mortality for 15 years was 45.5% (125/275), 84.0% (204/243), and 100% (99/99), respectively ($P < 0.001$). The 6-min walk test revealed a significant difference in quality of life among patients in the low, medium and high risk groups (all, $P < 0.0001$).

Significance: The CHFSI is a very useful clinical predictive tool that identifies patients at risk of future mortality and their quality of life across healthcare systems.

1. Introduction

Chronic heart failure (HF) is a worldwide epidemic, which continues to be associated with high morbidity and mortality [1]. The prognosis of HF remains poor, with reported survival estimates of 50% and 10% at five and 10 years, respectively [2]. It is noteworthy that in the chronic HF guidelines of the United States, Europe and China [3–5], a number of clinical studies have shown promising results, and some patients with left ventricular systolic dysfunction and near-normal left ventricular ejection fraction had a dramatic improvement [6–8]. Particularly, several predictive models have been reported in the outcomes of patients with acute HF [9,10]. As for chronic HF, several studies have also investigated risk factors that influence the prognosis of patients with chronic HF, including heart rate [11], body mass index, renal function [12] and cardiac biomarkers [13]. And Liu et al. [14] found that hypertension, QRS duration, LVEF and creatinine as independent predictors of mortalities for chronic HF after a median follow-up of 52 months. However, there is limited data on the continuity of the prognosis of patients with chronic HF for up to 15 years to further stratify this data according to severity scoring systems. Furthermore, there are also no risk stratification tools for all-cause mortality and quality of life in chronic HF patients in the short- or long-term.

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The primary objective of the present prospective study, which included 756 chronic HF patients with a 15-year follow-up, was to derivate and further validate the chronic heart failure severity index (CHFSI) using two important end points: all-cause mortality and health-related quality of life.

2. Methods

2.1. Study population

A total of 756 patients with stable chronic HF, a left ventricular ejection fraction (LVEF) of ≤45% and a heart failure duration of ≥6 months from 1998 to 2000 were studied, and a long-term clinical follow-up for at least 15 years from 1998 to 2014 was performed. The study complied with the Declaration of Helsinki, and was approved by the Ethics Committee and the Prescription and Therapeutic of Beijing Chao-yang Hospital-Affiliate of Capital University of Medical Sciences. All patients in the present study provided an informed consent prior to inclusion.

Before the introduction of long-term individual and refinement treatment, patients were ambulatory, clinically stable for ≥3 months, without recent (< 3 months) myocardial infarction or coronary revascularization, and admitted to the hospital.

Criteria for inclusion: (1) patients who were 18–80 years old; (2) patients with heart failure caused by dilated cardiomyopathy (DCM), coronary artery disease (CAD), or hypertensive heart disease (HHD); (3) patients with stable heart function, New York Heart Association (NYHA) II-III, and an LVEF of ≤45%; (4) patients evaluated by laboratory tests, including hemoglobin, creatinine, serum electrolytes and echocardiography at least once a year; (5) patients detected for digoxin serum concentration between the yearly follow-up points and any time, when necessary. HHD defined by the presence of left ventricular hypertrophy (LVH) and left ventricular systolic dysfunction in the absence of other causes other than arterial hypertension. CAD defined by the presence of atherosclerosis of coronary arteries leading to stenosis or blockage of the lumen, resulting in myocardial ischemia, hypoxia, or necrosis, with at least one major artery stenosis > 50% confirmed by coronary angiography.

Criteria for exclusion: (1) patients with a heart rate of < 60 bpm and a blood pressure < 90/60 mmHg under a clear-headed and quiescent state; (2) patients with first-degree atrioventricular block, sick sinus syndrome, and cardiogenic shock; (3) patients with obstructive lung disease, and hepatic and renal dysfunction; (4) patients who are pregnant or lactating, and have a terminal disease with a predicated survival of < 5 years.

2.2. Standard and refined individualized pharmacological regimen

Standard and individualized treatment plan: first, a target dose of any medication was not set, but a safety target of 60–70 bpm and 90–130/60–80 mmHg was set up for heart rate and blood pressure, respectively; second, serum digoxin concentration was maintained at 0.5–0.9 ng/L to ensure patient safety following the long-term use of medicine.

According to the guidelines of chronic HF [3–5], as well as its pathological and pharmacological mechanism, all patients received the main pharmacological regimen: low-dose diuretics (10–20 mg day^{-1} of furosemide and spironolactone remains as the first choice drugs; 2 mg day^{-1} (2 mg, *qd*) of angiotensin-converting enzyme (ACE) inhibitor perindopril, which was up-titrated over 2–4 weeks (4 mg, *qd*); 0.125–0.25 mg day^{-1} (0.125–0.25 mg, *qd*) of digoxin, among the above drugs from 1998 to 2014; 12.5 mg day^{-1} (6.25 mg, *bid*) of β1-receptor blocker metoprolol was selected, which was up-titrated over a 2–4 week period by doubling the twice-daily amount to a maximum tolerance dose from 2000 to 2014. As for HF patients caused by CAD, standard secondary prevention for CAD was administered, including asprin and statins. We gave the patients the optimized drug regimen to minimize the effect of drug factors on the experimental results.

2.3. Clinical evaluation and long-term follow-up

All patients were evaluated by collecting the detailed clinical history, physical examination, 12-lead electrocardiogram (ECG), 24-h ambulatory ECG, chest radiography, and transthoracic echocardiography (M-mode, 3D, Doppler) at baseline. These patients were clinically followed up for at least 15 years, or until interventional therapy or death. Repeat echocardiography was performed at least once a year after entering the study, when possible.

Patients were encouraged to schedule interim appointments, when needed, and the diuretic dose was self-adjusted based on symptoms and the daily intake and output. Data were collected during the patient's examination, including heart rate, blood pressure, weight, the presence of rales through a pulmonary exam, cardiac function, the presence of peripheral edema, and dosage of each drug. Then, these patients were questioned and examined for the presence of any adverse drug reaction. The follow-up examinations were performed at least once per month for the first year after the initiation of the study, and subsequently every 3–6 months up to the first 5-year follow-up period (2000–2004), every 6–12 months up to the second 5-year follow-up period (2005–2009), and at the third 5-year follow-up period (2010–2014) through a full-time nurse, or through outpatient clinical visit or a telephone link to the patient. Each patient was assigned to no more than two designated study investigators from whom the patient received follow-up examinations.

2.4. End-points

2.4.1. Mortality

During the follow-up period, all mortality was reported and determined through the death records linked to the patient's family. The cause of death was identified and assigned as cardiovascular death or all-cause death after the individual case review. The cardiovascular death included acute coronary syndrome (including unstable angina pectoris and acute myocardial infarction), arrhythmia (including ventricular tachycardia and ventricular fibrillation), heart failure, sudden death (sudden death due to illness within 1 h) and stroke (including transient ischemic attack, cerebral infarction and cerebral hemorrhage). We finally counted all-cause death because other causes unrelated to cardiovascular are less. Survival status was confirmed in 100% of the participants.

2.4.2. Quality of life

Patients completed the 6-min walk test (6-MWT) to measure of the quality of life at baseline. Classification criteria for 6-MWT: I, < 300 m; II, 300–374 m; III, 375–449 m; IV ≥450 m [15].

2.4.3. Data analysis and derivation of the clinical prediction tool

In order to facilitate the statistics and comparison, all long-term follow-up data up to 15 years were divided as follows: first 5-year (2000–2004), second 5-year (2005–2009), and third 5-year (2010–2014). In each 5-year, the last record was used for modeling and validating.

Quantitative variables, which followed a normal distribution, were presented as mean ± standard deviation (SD), while non-normally distributed data were presented as median with interquartile. Chi-squared test was used for contingency tables. *t*-test and ANOVA was used for data comparison. Levene's test was used for the homogeneity test of variance.

Data discretization was used to improve the sensitivity of the multivariate model through the following strategies. Age was grouped at the following intervals: < 40 years old, 40–59 years old, 60–69 years old, and ≥ 70 years old. Heart rate was classified into the following