One-year survival cohort of patients with reduced ejection fraction heart failure in Iranian population: A single center study

Mahdi Abdollahi-Karizno[(1)] **Neda Partovi**[(2)] **, Vahid Noferesti**[(1)]**, Naeem Ravanbakhsh**[(3)]**, Toba Kazemi**[(4)]**, Saeede Khosravi-Bizhaem**[(5)]

Original Article

Abstract

BACKGROUND: Cardiovascular diseases (CVDs) are one of the main concerns of health care systems. The aim of this study was to investigate the most important prognostic factors of heart failure (HF) and their survival outcomes in patients in Birjand, East of Iran.

METHODS: A total of 194 systolic HF patients hospitalized in Birjand Valiasr hospital were followed up for 12 months in 2016, and those with reduced left ventricle ejection fraction (LVEF < 50%) were included in this study. Kaplan-Meier and Cox proportional hazard analysis were used to determine the association of each factor with events.

RESULTS: The mean age of patients was 68.23 ± 13.40 (27-95) years, and 57.2% (111 out of 194) were women. Mean survival time was 294.7 ± 9.924 days. Pervious history of myocardial infarction (MI) [2.141 (1.101-4.161)] increased the risk of cardiovascular hospitalization. Elevated blood levels of potassium [2.264 (1.438-3.564)] was found to be a risk factor for all-cause and cardiovascular mortality. Moreover, there was a reverse relationship between body height [0.942 (0.888-0.999)] and cardiovascular death. Patients with opium addiction [4.049 (1.310-12.516)] are at a higher risk of cardiovascular mortality. Lower levels of LDL-C [0.977 (0.960-0.996)] and living in rural areas [3.052 (1.039-8.964)] increased all-cause mortality levels. Lack of pervious history of chronic obstructive pulmonary disease (COPD) decreased cardiovascular hospitalization [0.265 (0.062-1.122)].

CONCLUSION: In our study, serum potassium, LDL-C, and uric acid levels in patients with HF were identified as prognostic factors. The height of patients, which can be an indicator of the functional state of their respiratory system, and the history of COPD were also recognized as prognostic factors. Opium use and rural living were identified as social factors influencing patients' prognosis.

Keywords: Systolic Heart Failure; Prognostic Factors; Follow-Up Study

Introduction

Heart failure (HF) is considered a global health problem worldwide. This chronic disorder is the cause of many mortalities in the world and imposes many burdens on the community.[1] Any factor that changes the ventricular function can make the patient susceptible to HF, these factors include coronary artery disease (CAD), myocardial infarction (MI), hypertension (HTN), abnormal heart valves, dilated cardiomyopathy, hypertrophic cardiomyopathy, inflammation (myocarditis) or congenital heart disease.[2] HF is generally divided into systolic HF with reduced ejection fraction

1- Medical Student, Student Research Committee, Birjand University of Medical Sciences, Birjand, Iran
2- Assistant Professor, Cardiovascular Diseases Research Center AND Department of Cardiology, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran
3- General Practitioners, Student Research Committee, Birjand University of Medical Sciences, Birjand, Iran
4- Professor, Razi Clinical Research Development Unit (RCRDU) AND Department of Cardiology, Cardiovascular Diseases Research Center, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran
5- Cardiovascular Diseases Research Center, Birjand University of Medical Sciences, Birjand, Iran
Address for correspondence: Neda Partovi; Assistant Professor, Cardiovascular Diseases Research Center AND Department of Cardiology, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran; Email: partovin99@gmail.com

(EF < 50%) and diastolic HF with preserved EF.[1] Today, left ventricular EF (LVEF) is considered as an essential factor in the classification of patients with HF.[3] Various studies have shown that 30-40% of patients with HF will die within 1 year after diagnosis and 60-70% will die within 5 years, for which a function class (FC) ≥ III is the most important predictor.[4,5] Factors affecting the prognosis of the disease should be identified due to the importance of this issue. Some prognostic factors such as age, sex, EF, C-reactive protein (CRP), functional capacity, brain type natriuretic peptide (BNP), electrocardiogram abnormalities (such as arrhythmias, voltage changes, etc.), comorbidities [such as HTN, diabetes mellitus (DM), CAD, chronic kidney disease (CKD), and chronic obstructive pulmonary disease (COPD)], body mass index (BMI), blood hemoglobin, and uric acid have been considered in the literature.[6] Cardiovascular diseases (CVDs) are the prime cause of death in Iran.[7] Long-term outcome data of HF patients remain scarce in developing countries such as Iran.[8] Therefore, this study was designed to evaluate survival outcomes in HF and investigate the prognostic factors of HF patients.

Materials and Methods

A total of 194 consecutive patients diagnosed with LVHF and hospitalized in Vali-e-Asr Hospital in Birjand, Iran, from July 2016 to March 2017 were enrolled in this prospective survival cohort study. The diagnosis was based on echocardiography results (LVEF < 50%) and clinical examinations.[9] After explaining the goals of the study to the participants, they were asked to provide a written informed consent for the use of their data. Demographic, electrocardiographic, echocardiographic, and laboratory data and past medical history were recorded in a data collection checklist.

The demographic variables of gender, place of residence, age, and education were collected via self-declaration and medical records, height was measured using a stadiometer with an accuracy of 0.5 cm after removal of shoes, weight was measured using a digital balance with an accuracy of 0.1 kg after removal of shoes and with light clothing, waist circumference (WC) was measured using a fabric tape in standing position with measurements made between the lower border of the lowest rib crossing the belly button, and the iliac crest in the horizontal plane, body mass index (BMI) was calculated as weight (kg)/height (m)^2 which were extracted from medical records. Electrocardiographic variables included rhythm, axis, p wave, PR interval (PR int), QRS, right bundle branch block (RBBB), left bundle branch block (LBBB), QT interval (QT int. was corrected using the Hodge formula[10]) and were confirmed by 2 cardiologists. Echocardiographic variables, including ejection fraction, mitral stenosis, mitral regurgitation, aortic insufficiency, aortic stenosis, and tricuspid regurgitation, were measured using an echocardiogram (EKO 7, Samsung Electronics Co., Seoul, South Korea) and were confirmed by 2 cardiologists. Blood samples (5 cc) were collected immediately after admission after 12 hours of fasting and were sent to the hospital laboratory for testing. Laboratory variables included hemoglobin (Hb), high density lipoprotein (HDL), low density lipoprotein (LDL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting blood sugar (FBS), urea, creatinine, acid uric, cholesterol, triglyceride (TG), troponin, sodium, and potassium. The medical history variables extracted from medical records included the New York Heart Association (NYHA) classification, HTN, DM, COPD, CKD, dyslipidemia, heart valve diseases, MI, cerebrovascular accident (CVA), Ischemic heart disease (IHD), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), prosthetic heart valves, smoking, and opium addiction. Blood pressure (BP) was measured early in the morning (8 A.M); patients had rested for at least 5 minutes and they were in a seated position during the measurement. Pre-HTN was defined as systolic blood pressure (SBP) within the range of 120-139 mmHg and diastolic blood pressure (DBP) within the range of 80-89 mmHg. HTN was defined as SBP of above 140 mmHg and DBP of higher than 90 mmHg. Pre-diabetes and diabetes were defined as FBS within the range of 100-125 mg/dl and FBS of equal to or higher than 126 mg/dl, respectively.[11]

Patients were excluded from the study if they were unwilling to provide informed consent and if no way for follow-up was available. In the follow-up phase, outcomes of participants, including mortality and re-hospitalization, were obtained at 3, 6, and 12 months after discharge via telephone interviews by a registered nurse. The protocol of this study was approved by Birjand University of Medical Sciences (Ir.bums.REC.1395.203).

Statistical analysis: Data were analyzed using SPSS (Version 21.0.; IBM Corp., Armonk, NY, USA) and R (V.3.6.3) software. Continuous data were reported as median (IQR) and categorical variables

were reported as number (frequency).

The events used in the Cox model were all-cause mortality, cardiovascular mortality, and HF hospitalization. The univariate Cox regression models were applied separately to discriminate each significant factor. Adjusted survival and hazard functions were estimated using a multiple Cox regression model. Factors with P-values of less than 0.20 in the previous stage (univariate Cox models) were candidates for multiple analysis. In all models, factors with P-values of less than 0.050 were considered to be significant.

Results

Of the 194 HF patients, 111 (57.2%) and 83 (42.8%) individuals were women and men, respectively. The mean age of patients was 68.23 ± 13.40 (27-95) years. There was no statistical difference between men (69 ± 14.14 years) and women (67.63 ± 12.86 years) in terms of mean age (P = 0.480). Demographic characteristics, medical history, cardiac and laboratory parameters, and electrograph and echocardiography findings of the study population are presented in table 1. Of the initial 194 patients, 23 subjects were lost to follow-up, 44 patients died during the 1-year follow-up (40 patients died due to cardiovascular causes), and 37 patients were re-hospitalized during the 1-year follow-up (27 patients were re-hospitalized due to cardiovascular cause). The Kaplan-Meier survival curve for defined endpoints is show in figure 1. One-year survival rate for cardiovascular mortality, all-cause mortality, and cardiovascular hospitalization was 0.776, 0.757, and 0.865, respectively.

In the univariate Cox-PH model for cardiovascular mortality, age [1.031 (1.005-1.058)], EF [0.966 (0.935-0.997)], SBP [0.983 (0.967-1.00)], TG [0.992 (0.985-0.999)], uric acid [1.222 (1.073-1.391)], urea [1.009 (1.002-1.016)], potassium [1.727 (1.29-2.312)], and previous MI [1.947

(1.039-3.649) were significant at P < 0.050. In the univariate Cox-PH model for all-cause mortality, age [1.036 (1.01-1.062)], SBP [0.984 (0.968-1.00)], TG [0.991 (0.984-0.998)], uric acid [1.178 (1.037-1.338)], urea [1.009 (1.002-1.015)], and potassium [1.605,95 (1.191-2.162)] were significant at P < 0.050 (Table 2).

Multivariate Cox regression analysis revealed that LVEF [0.951 (0.908-0.997)], potassium [1.700 (1.150-2.154)], serum LDL-C [0.977 (0.960-0.996)], and residence in rural areas [3.052 (1.039-8.964)] were significant predictors of all-cause mortality (Table 3). Moreover, in the multivariate Cox-PH model for cardiovascular mortality, LVEF [0.945 (0.893-0.999)], potassium levels [2.264 (1.438-3.564)], body height [0.942 (0.888-0.999)], and opium consumption [4.049 (1.310-12.516)] were significantly associated with 1-year mortality (Table 3). Furthermore, MI of 2.456 (1.120-5.386) was found to be a significant predictor of cardiovascular re-hospitalization (Table 3).

Discussion

Our data revealed that only 1 out of 4 (25.4%) HF patients died within 1 year. In India, Harikrishnan et al. reported that one-third of patients (30.8%) died due to HF during their 1-year follow-up.[12] In England, Goldberg et al. found that 37.3% of hospitalized HF patients died within the first year after discharge and 78.5% during a follow-up period of 5 years.[13] It seems that our results are in line with that of previous studies.

In the present study, the risk of all-cause mortality was higher in rural areas than in urban areas, which may be due to access to hospitals and more health services. In a study by Singh et al., the rate of CAD and its risk factors among urban populations were 2-3 times higher than rural populations, which may be due to more sedentary behaviors and greater alcohol consumption among urban residents.[14]
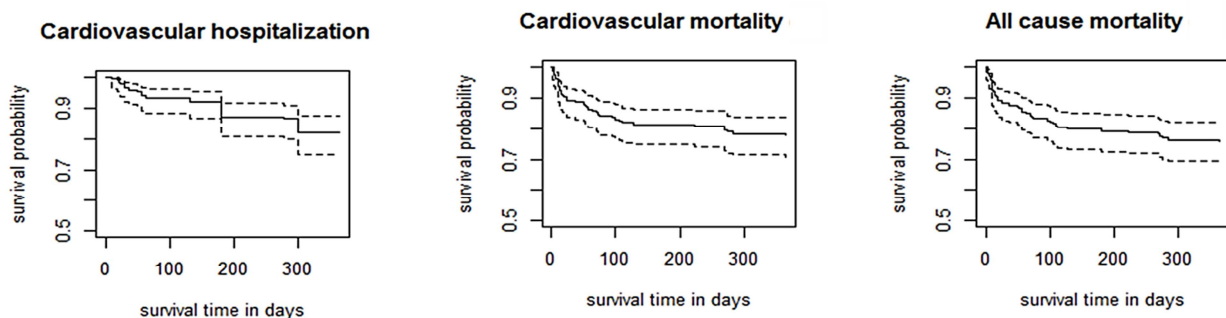
Figure 1. Kaplan-Meier survival curve

Table 1. Baseline characteristics of patients

Baseline Characteristics	Cardiovascular Hospitalization (n = 22)	All-cause mortality (n = 44)	Cardiovascular mortality (n = 40)	All patients (n = 194)
Age (year)	68.00 [54.50-74.50]	77.00 [70.25-81.00]	77.00 [65.50-80.75]	70.00 [58.00-79.00]
Height (cm)	163.53 [153.75-171.25]	161.50 [152.00-167.00]	160.00 [150.50-167.00]	164.00 [155.75-170.00]
Weight (kg)	72.50 [57.00-80.00]	63.00 [52.25-70.00]	62.50 [52.25-68.93]	65.70 [54.00-73.25]
Waist circumstance (cm)	90.00 [80.55-103.50]	74.50 [66.25-88.18]	73.50 [66.25-88.18]	82.73 [70-96.25.00]
Body mass index (kg/m^2)	26.29 [23.54-29.14]	24.23 [20.94-26.53]	24.43 [20.94-26.67]	24.42 [21.29-26.84]
PRI	130.00 [120.00-170.00]	160.00 [160.00-200.00]	160.00 [160.00-200.00]	160.00 [160.00-162.78]
Urban	18 (81.8)	29 (65.9)	27 (67.5)	148 (76.3)
Male	9 (40.9)	24 (54.5)	22 (50.0)	83 (42.8)
Medical history				
NYHA Classification				
Class I	5 (22.7)	4 (9.5)	4 (10.5)	29 (15.4)
Class II	4 (18.2)	5 (11.9)	5 (13.2)	25 (13.3)
Class III	2 (9.1)	9 (21.4)	9 (23.7)	46 (24.5)
Class IV	11 (12.5)	24 (57.1)	20(52.6)	88 (46.8)
History of hypertension	13 (59.1)	16 (36.4)	15 (37.5)	88 (45.4)
History of diabetes	7 (31.8)	14(32.6)	13 (33.3)	64 (33.3)
History of COPD	1 (4.5)	8 (19)	6 (15.8)	42 (21.7)
History of CKD	3 (13.6)	9 (20.9)	7 (17.9)	30 (15.5)
History of dyslipidemia	11 (50.0)	8 (18.6)	8 (20.5)	56 (28.9)
Heart valve diseases	3 (15.0)	4 (9.3)	3 (15.0)	20 (10.3)
MI	10(45.5)	20 (46.5)	19 (48.7)	65 (33.5)
Stroke	2 (9.1)	5 (11.6)	5 (12.8)	21 (10.8)
IHD	11 (50.0)	19 (45.2)	17 (44.7)	69 (35.6)
PCI	8 (36.4)	11 (26.2)	10 (26.3)	57 (29.4)
CABG	2 (9.1)	6 (14)	6 (15.4)	22 (11.3)
Prosthetic heart valves	1 (4.5)	1 (2.4)	1 (2.7)	4 (2.1)
Diabetes	7 (33.3)	19 (48.7)	17 (48.6)	78 (40.2)
Hypertension	15 (12.8)	23 (54.8)	21 (55.3)	117 (61.3)
Low HDL	119 (61.3)	21 (61.8)	24 (63.2)	17 (14.3)
Abdominal obesity	62 (32.0)	8 (20.0)	9 (20.5)	10 (45.5)
Smoke	44 (22.7)	8 (20.5)	8 (19.0)	1 (11.1)
Opium	46 (23.7)	13 (34.2)	14 (33.3)	5 (22.7)
EKG findings				
Rhythm (AF)	13 (8.1)	1 (3.0)	1 (2.8)	3 (15.8)
Axis (LAD)	32(20.5)	7 (21.9)	9 (25.7)	2 (11.8)
RAD	14(9.0)	4 (12.5)	4 (11.4)	2 (11.8)
LAHB	16 (9.6)	2 (5.9)	4 (10.8)	0
LPHB	3(1.5)	1 (2.9)	1 (2.7)	0
P wave				
RAE	10(6.0)	2 (5.9)	2 (5.4)	0
LAE	13(7.8)	1 (2.9)	2 (5.4)	2 (10.5)
Normal	117 (70.5)	27 (79.4)	28 (75.7)	13 (68.4)
No P wave	26 (15.7)	4 (11.8)	5 (13.5)	4 (21.1)
Education (illiterate)	108 (67.5)	26 (72.2)	29 (72.5)	13 (8.6)
QRS				
RBBB	5 (3)	1 (2.9)	1 (2.7)	0
LBBB	25(15.1)	6 (17.6)	8 (21.6)	1 (5.3)
NO QRS	17 (10.2)	24 (70.6)	3 (8.1)	15 (78.9)

Table 1. Baseline characteristics of patients (continue)

Baseline Characteristics	Cardiovascular Hospitalization (n = 22)	All-cause mortality (n = 44)	Cardiovascular mortality (n = 40)	All patients (n = 194)
Av block	6 (3.1)	2 (5.9)	2 (5.4)	2 (10.5)
Echocardiography findings				
MS	10 (5.2)	1(2.5)	2(4.5)	1 (4.5)
MR	143 (73.7)	30 (75.0)	33 (75.0)	15(68.2)
AI	47 (25.3)	15 (40.5)	17 (41.5)	5(22.7)
AS	4 (2.2)	2 (5.6)	2 (5.0)	0
TR	137 (70.6)	29 (72.5)	33 (75.0)	16 (72.7)
QT int (ms)	410.00[389.00-426.00]	417.00 [386.00-457.00]	416.50 [375.00-457.00]	390.00 [351.10-442.50]
Cardiac parameters				
Heart rate	80.00 [75.00-90.00]	80.00 [73.75-100.00]	80.00 [72.50-100.00]	77.50 [73.75-100.00]
Systolic blood pressure (mm Hg)	126.34 [110.00-140.00]	120.00 [107.75-130.00]	120.00 [107.75-131.50]	130.00 [116.50-140.00]
Diastolic blood pressure (mm Hg)	74.38 [65.00-82.25]	70.00 [60.00-80.00]	70.00 [60.00-80.00]	80.00 [70.00-90.00]
Ejection fraction (%)	33.07 [27.50-40.63]	32.50 [22.50-40.00]	32.50 [22.50-40.00]	32.50 [29.38-40.00]
Laboratory parameters				
Hb (g/dl)	12.91 [11.90-14.33]	12.55 [11.50-13.60]	12.40 [11.18-13.60]	13.00 [11.88-15.65]
Fasting blood sugar (mg/dl)	112.00 [86.00-126.25]	109.00 [83.25-123.85]	10.90[83.25-125.46]	104.00 [86.75-135.25]
Urea (mg/dl)	44.00 [35.00-56.25]	53.00[42.25-68.5]	52.50[42.00-68.50]	49.00 [32.50-58.75]
Creatinine (mg/dl)	1.00 [0.90-1.20]	1.00 [0.83-1.28]	1.00 [0.83-1.30]	1.00 [0.88-1.20]
Acid uric (mg/dl)	6.00 [5.00-8.28]	6.68 [6.68-8.40]	6.68 [6.68-7.60]	6.68 [6.66-7.68]
Cholesterol (mg/dl)	153.81 [132.00-175.00]	148.00 [129.25-167.00]	148.00 [127.50-168.50]	154.41 [136.50-197.75]
Triglyceride (mg/dl)	94.50 [73.00-131.75]	85.00 [61.75-118.01]	84.00 [61.25-117.26]	121.53 [78.00-191.25]
HDL (mg/dl)	38.60 [32.00-42.00]	38.59 [32.00-46.75]	38.60 [32.00-47.00]	38.59 [32.00-46.75]
LDL-C (mg/dl)	89.18 [71.75-101.25]	87.00 [68-92.75.00]	87.00 [65.00-96.00]	87.00 [68-92.75.00]
AST (IU/l)	67.52 [29.00-67.52]	66.76 [35.00-67.52]	66.76 [35.00-67.52]	49.00 [24.75-67.52]
ALT (IU/l)	37.99 [23-37.99.00]	37.99 [25.50-37.99]	37.98 [27.00-37.98]	27.50 [16.00-37.99]
Troponin (ng/ml)	1.70 [0.07-4.65]	1.11 [0.01-5.96]	1.40 [0.01-5.96]	0.10 [0.01-3.26]

PRI: PR Interval; NYHA: New York Heart Association; COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease; MI: Myocardial Infarction; IHD: Ischemic Heart Disease; PCI: Percutaneous Coronary Intervention; CABG: Coronary artery bypass grafting; LDL-C: Low density lipoprotein; EKG: Electrocardiography; AF: Atrial Fibrillation; LAD: Left-axis deviation; RAD: Right-axis deviation; LAHB: Left anterior hemiblock; LPHB: Left posterior hemiblock; RBBB: Right Bundle Branch Block; LBBB: Left Bundle Branch Block; RAE: Right Atrial Enlargement; LAE: Left Atrial Enlargement; QTint: QT interval; MS: Mitral stenosis; MR: Mitral Regurgitation; AI: Aortic Insufficiency; AS: Aortic Stenosis; TR: Tricuspid Regurgitation; Hb: hemoglobin; HDL: high density lipoprotein; AST: Aspartate Aminotransferase; ALT: alanine aminotransferase
Continues variables were reported as median (IQR), and categorical variables were reported as number (percentage).

In line with previous studies, our findings showed that elevated blood potassium levels were associated with increased risk of all-cause mortality [P < 0.008; 1.70 (1.150-2.154)] and cardiovascular mortality [P < 0.001; 2.264 (1.438-3.564)]. Tromp et al. observed a linear univariate relationship between serum potassium levels and mortality (hazard ratio of 2.36; 95% confidence interval (CI): 1.07-5.23; P = 0.034). However, in a multiple model, it was not associated with mortality.[15] In HF patients with preserved EF, both hypokalemia and hyperkalemia are associated with an increased risk of death.[16] Aldahl et al. reported that serum potassium levels outside the normal range were associated with increased risk of mortality in chronic HF patients.[17] Patel et al. noticed a U-shaped relationship between blood potassium levels and the risk of cardiovascular death in acute coronary syndrome (ACS) patients.[18] They also found that the risk of arrhythmia increased at both ends of the blood potassium concentration spectra, and the best range for blood potassium concentration was 3.5-4.5 mmol/l.

Table 2. Univariate Cox regression analysis of baseline factors with risk for all-cause mortality, cardiovascular mortality, and cardiovascular hospitalization

Baseline Characteristics	Cardiovascular mortality		All-cause mortality		Cardiovascular Hospitalization	
	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)
Age	0.019	1.031 (1.005,1.058)	0.006	1.036 (1.010,1.062)	0.666	0.994 (0.965,1.023)
Sex (male/female)	0.108	0.600 (0.322,1.119)	0.102	0.610 (0.337,1.104)	0.519	0.780 (0.366,1.66)
BMI	0.528	0.981 (0.924,1.041)	0.312	0.970 (0.915,1.029)	0.461	1.024 (0.962,1.089)
BMI classification						
Severely underweight	ref	1	ref	1	ref	1
Underweight	0.224	0.179 (0.011,2.865)	0.049	0.089 (0.008,0.987)	0.011	0.043 (0.004,0.49)
Normal	0.776	0.747 (0.100,5.587)	0.231	0.412 (0.096,1.759)	0.003	0.092 (0.019,0.442)
Overweight	0.763	0.729 (0.094,5.656)	0.189	0.364 (0.08,1.644)	0.031	0.180 (0.038,0.857)
Obese*	0.452	0.431 (0.048,3.866)	0.077	0.216 (0.039,1.179)	0.012	0.109 (0.019,0.614)
Residence (urban/rural)	0.109	1.719 (0.887,3.333)	0.053	1.849 (0.991,3.450)	0.936	1.038 (0.419,2.572)
Education (Yes/No)	0.522	0.788 (0.38,1.634)	0.474	0.776 (0.388,1.553)	0.244	0.555 (0.206,1.495)
Cardiac parameters						
Ejection fraction	0.032	0.966 (0.935,0.997)	0.060	0.971 (0.942,1.001)	0.731	0.993 (0.955,1.033)
SBP	0.049	0.983 (0.967,1.000)	0.048	0.984 (0.968,1.000)	0.643	1.004 (0.987,1.022)
DBP	0.224	0.985 (0.962,1.009)	0.304	0.988 (0.966,1.011)	0.287	1.015 (0.987,1.043)
Heart rate	0.401	1.007 (0.991,1.023)	0.522	1.005 (0.989,1.021)	0.396	1.009 (0.989,1.029)
Laboratory parameters						
Creatinine (mg/dl)	0.672	0.906 (0.574,1.431)	0.639	1.080 (0.783,1.49)	0.580	0.842 (0.458,1.547)
Hb (g/dl)	0.320	0.929 (0.803,1.074)	0.244	0.921 (0.803,1.058)	0.777	1.025 (0.862,1.219)
Fasting Blood Sugar(mg/dl)	0.356	0.997 (0.991,1.003)	0.753	0.999(0.994,1.004)	0.784	1.001 (0.995,1.007)
Triglyceride (mg/dl)	0.020	0.992 (0.985,0.999)	0.010	0.991 (0.984,0.998)	0.733	1.001 (0.996,1.006)
Cholesterol (mg/dl)	0.514	0.997 (0.988,1.006)	0.287	0.995 (0.987,1.004)	0.212	1.007 (0.996,1.017)
Uric acid* (mg/dl)	0.003	1.222 (1.073,1.391)	0.012	1.178 (1.037,1.338)	0.142	1.141 (0.957,1.36)
Urea (mg/dl)	0.017	1.009 (1.002,1.016)	0.010	1.009 (1.002,1.015)	0.840	0.999 (0.986,1.012)
AST (IU/l)	0.487	1.002 (0.997,1.007)	0.117	1.003 (0.999,1.008)	0.609	0.998 (0.99,1.006)
ALT (IU/l)	0.854	0.999 (0.985,1.013)	0.628	1.003 (0.991,1.015)	0.679	0.996 (0.98,1.013)
HDL (mg/dl)	0.075	1.016 (0.998,1.033)	0.091	1.015 (0.998,1.032)	0.067	1.021 (0.999,1.044)
LDL-C (mg/dl)	0.124	0.990 (0.978,1.003)	0.057	0.988 (0.977,1.000)	0.579	1.004 (0.990,1.018)
Troponin (ng/dl)	0.808	1.005 (0.965,1.047)	0.770	1.006 (0.967,1.046)	0.316	0.967 (0.905,1.033)
Sodium (mmol/l)	0.224	0.965 (0.910,1.022)	0.368	0.974 (0.918,1.032)	0.545	1.030 (0.935,1.135)
Potassium* (mmol/l)	<0.001	1.727 (1.290,2.312)	0.002	1.605 (1.191,2.162)	0.801	0.928 (0.521,1.655)
Medical history						
NYHA	ref	--	ref	--	ref	--
NYHA (II)	0.532	1.520 (0.408,5.661)	0.533	1.519 (0.408,5.655)	0.879	1.107 (0.297,4.124)
NYHA (III)	0.535	1.453 (0.447,4.717)	0.535	1.451 (0.447,4.713)	0.310	0.506 (0.136,1.885)
NYHA (IV)	0.326	1.712 (0.585,5.009)	0.182	2.057 (0.714,5.93)	0.978	1.015 (0.365,2.818)
History of hypertension (no/yes)	0.187	0.649 (0.342,1.232)	0.125	0.618 (0.334,1.143)	0.712	1.153 (0.542,2.453)
History of diabetes (no/yes)	0.808	0.921 (0.473,1.792)	0.717	0.889 (0.47,1.682)	0.540	0.773 (0.338,1.765)
History of COPD (no/yes)	0.264	0.609 (0.254,1.456)	0.495	0.765 (0.354,1.652)	0.048	0.234 (0.056,0.99)
History of CKD (no/yes)	0.733	1.153 (0.509,2.613)	0.381	1.389 (0.666,2.896)	0.871	0.915 (0.316,2.649)
History of dyslipidemia (no/yes)	0.079	0.498 (0.229,1.085)	0.037	0.442 (0.205,0.953)	0.161	1.716 (0.807,3.652)
History of heart valve diseases (no/yes)	0.463	0.643 (0.198,2.089)	0.655	0.791 (0.283,2.213)	0.655	1.274 (0.440,3.684)
MI (no/yes)	0.038	1.947 (1.039,3.649)	0.059	1.781 (0.978,3.244)	0.062	2.053 (0.965,4.369)
Stroke (no/yes)	0.806	1.125 (0.440,2.876)	0.986	1.009 (0.397,2.562)	0.926	0.944 (0.284,3.137)
IHD (no/yes)	0.401	1.315 (0.694,2.494)	0.340	1.344 (0.732,2.469)	0.045	2.176 (1.018,4.654)
PCI (no/yes)	0.699	0.867 (0.421,1.785)	0.668	0.860 (0.432,1.712)	0.595	1.243 (0.558,2.766)
CABG (no/yes)	0.363	1.498 (0.627,3.575)	0.514	1.333 (0.563,3.159)	0.987	1.010 (0.304,3.355)

Table 2. Univariate Cox regression analysis of baseline factors with risk for all-cause mortality, cardiovascular mortality, and cardiovascular hospitalization (continue)

Baseline Characteristics	Cardiovascular mortality		All-cause mortality		Cardiovascular Hospitalization	
	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)
Prosthetic valve (<u>no</u>/yes)	0.948	1.069 (0.146,7.796)	0.969	0.961 (0.132,6.991)	0.768	1.352 (0.183,9.998)
DM (no)	ref	--	ref	--	ref	--
Pre-DM	0.703	0.861 (0.398,1.861)	0.716	0.871 (0.415,1.831)	0.653	1.224(0.507,2.954)
DM	0.505	0.752 (0.325,1.737)	0.695	0.856 (0.393,1.864)	0.725	0.831 (0.296,2.334)
BP (normal)	ref	--	ref	--	ref	--
Pre-Hypertension	0.055	0.461 (0.209,1.016)	0.042	0.454 (0.212,0.970)	0.857	1.109 (0.358,3.44)
Hypertension	0.079	0.481 (0.212,1.090)	0.093	0.516 (0.238,1.116)	0.678	1.274 (0.406,4.002)
Low HDL (<u>no</u>/yes)	0.068	0.524 (0.262,1.048)	0.080	0.555 (0.287,1.074)	0.899	0.942 (0.374,2.373)
Abdominal obesity (<u>no</u>/yes)	0.056	0.469 (0.216,1.018)	0.051	0.483 (0.232,1.004)	0.468	1.329 (0.617,2.864)
Smoking						
Smoking (no)	ref	--	ref	--	ref	--
Smoking (yes)	0.668	0.826 (0.345,1.98)	0.524	0.754 (0.317,1.797)	0.443	1.432 (0.572,3.587)
Recently quitted smoking	0.700	0.755 (0.181,3.155)	0.611	0.691 (0.166,2.874)	0.868	1.131 (0.263,4.858)
Opium (<u>no</u>/yes)	0.073	1.846 (0.944,3.610)	0.081	1.771 (0.932,3.365)	.835	0.902 (0.341,2.383)

HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; Hb: Hemoglobin; AST: Aspartate Aminotransferase; ALT: Alanine aminotransferase; HDL: High density lipoprotein; LDL-C: Low density lipoprotein; NYHA: New York Heart Association; COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease; MI: Myocardial Infarction, IHD: ischemic heart disease. PCI: percutaneous coronary intervention. CABG: Coronary artery bypass grafting; DM: Diabetes mellitus; BP: Blood pressure

Finally, patients with blood potassium levels of above 4.5 mmol/l were at a higher risk for cardiovascular death within a year.[18] Collins et al. also reported a U-shaped relationship between blood potassium levels and CVD.[19] The study by Hughes-Austin et al. indicated that blood potassium concentrations of above 4.5 mmol/l led to a 41% increase in risk of all-cause mortality compared to concentrations of 4-4.5 mmol/l.[20] In a study by McDonald et al., it was found that high concentrations of extracellular potassium impaired platelet aggregation.[21]

Our findings revealed a reverse relationship between serum LDL-C levels and all-cause mortality, which is similar to the findings of others. Similarly, in a Swedish Apolipoprotein Mortality Risk (AMORIS) study on 84,740 individuals, hazard ratios for LDL-C level were 2.18 (1.98–2.40) for men and 1.68 (1.45–1.95) for women.[22] A Uppsala Longitudinal Study of Adult Men (ULSAM) study also revealed higher risk of HF in those with higher levels of cholesterol and TG;[22] however, Varbo and Nordestgaard reported that LDL-C was not a risk factor for HF.[23] They noted that this might be due to adequate lipid-lowering therapy after the study, because participants were informed of test results.[24]

Table 3. Multivariate Cox regression analysis for all-cause mortality, cardiovascular mortality, and cardiovascular hospitalization

Baseline Characteristics	Cardiovascular mortality		All-cause mortality		Cardiovascular Hospitalization	
	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)
MI (<u>no</u>/yes)	-	-	-	-	0.025	2.456 (1.120-5.386)
History of COPD (<u>no</u>/yes)	-	-	-	-	0.071	0.265 (0.062-1.122)
Potassium (mmol/l)	< 0.001	2.264 (1.438-3.564)	0.008	1.70 (1.150-2.154)	-	-
Ejection fraction (LVEF%)	0.046	0.945 (0.893-0.999)	0.038	0.951 (0.908-0.997)	-	-
Height (cm)	0.047	0.942 (0.888-0.999)	-	-	-	-
Opium (<u>no</u>/yes)	0.015	4.049 (1.310-12.516)	-	-	-	-
Residence	-	-	0.042	3.052 (1.039- 8.964)	-	-
LDL-C (mg/dl)	-	-	0.015	0.977 (0.960- 0.996)	-	-

HR: Hazard ratio; CI: Confidence interval; MI: Myocardial infarction; COPD: Chronic obstructive pulmonary disease; LVEF: Left ventricle ejection fraction; LDL-C: Low density lipoprotein

As suggested by Velavan et al., there is a "reverse epidemiology" in HF patients in whom higher cholesterol levels are associated with better outcomes.[25] Charach et al. also supported this reverse epidemiology as low cholesterol level was a poor prognostic factor in their study.[26] Rauchhaus et al. observed hypercholesterolemia in patients with severe HF, and attributed this to factors such as endotoxins, inflammation, adrenergic activation, oxidative stress, cachexia, and tissue injury.[27] All these factors can increase resting energy consumption and lead to a catabolic state in which lipids are preferably used to produce energy. According to Witte and Clark, low cholesterol level is associated with poorer prognosis of diseases.[28] They have suggested that low levels of cholesterol are caused by malnutrition, which may be due to reduced food intake or intestinal malabsorption because of bowel edema.[28]

In our study, past medical history of MI was associated with elevated risk of cardiovascular re-hospitalization [P < 0.025; hazard ratio (HR) = 2.456 (1.120-5.386)]. CADs are the most common cause of systolic HF. Mechanical complications and ventricular remodeling that occur after MI are predisposed to HF.[11] Pathogens caused by EF reduction in HF are mainly due to the occurrence of an index event, such as MI, that decreases cardiac pumping capacity.[11] In a study on 2596 patients for over 2 decades (1990-2010), Gerber et al. reported that HF significantly increased the risk of death after MI, mostly in patients who developed HF.[29] Similar to our findings, Jackson et al. examined 628 patients admitted with a decompensated HF in a 1.5-year follow-up study in the multivariable Cox model and reported that previous MI history significantly increased mortality [HR = 1.49 (1.12-1.89)].[30] In a 1-year follow-up study on 1205 people in India, Harikrishnan et al. found that non-ischemic causes of HF led to higher mortality than ischemic causes [HR = 1.54 (1.13-2.08)].[12] They claimed that those who present with ischemic causes and pectoralis angina are more likely to undergo coronary revascularization, which improves the prognosis.

In this study, patients with coexistence of COPD and HF presented increased risk of cardiovascular re-hospitalization, but this had no effect on mortality. However, Jacob et al. studied patients with acute HF and reported that short-term risk of re-hospitalization increased in people with a history of COPD, while there was no association between COPD and prolonged re-hospitalization.[31]

In a study by Cuthbert et al., all patients complaining of breathlessness were evaluated for HF and COPD using specialized tests (echocardiography, NTproBNP, and spirometry) with regard to the overlap between COPD and HF symptoms.[32] Half of the HF patients were found to have COPD, but in HF patients, high BNP levels were a predictor of mortality, not the presence or absence of COPD. However, as many COPD patients are not diagnosed with HF, it is recommended that COPD and bronchodilator medications be considered.[32] There is a great deal of evidence that coexistence of COPD and HF does not increase the risk of mortality. Most well-detailed studies examining true HF and true COPD reported that, although many people with HF had COPD, it had no effect on the overall mortality rate.

In line with previous studies, the present observations revealed an inverse relationship between height and cardiovascular death [P = 0.047; HR = 0.942 (0.888-0.999)]. Short stature has recently been suggested as a cardiovascular risk factor in studies. In 2012, a meta-analysis of 300 cohort studies found that shorter stature was associated with greater cardiovascular risk, which was justified by racial and genetic differences. Sofer et al. examined polygenic risk scores (PSR) and Mendalian randomization in European populations, and detected a direct/mediated reverse relationship between PSR and the forced expiratory value in one score (FEV1)/forced vital capacity (FVC) ratio.[33] FEV1 and FVC alone did not have any relationship with PSR, indicating that pulmonary functional genes are in a different position than the FEV1 and FVC genes alone. These PSRs were also associated with total cholesterol level.[33] Height, regardless of weight and body mass index (BMI), was a significant predictor in our study. This may be due to the stronger respiratory power and better metabolic status of patients with higher height.

Although all-cause mortality rate was significantly higher in addicted patients than non-addicted patients in our study, Harati et al. reported that there were no major differences in mortality rates between addicted and non-addicted patients with MI.[34] Khodneva et al. reported that patients who used opiate derivatives to relieve pain were at higher risk of CVD than those using non-opioid analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs).[35] Davoodi et al. also stated that opium can have specific effects on lipid profile and enhance atherosclerosis in the vessels.[36] In the 1970s, endogenous ligands were identified as opioid

peptides that play important roles in cardiovascular problems, including HTN, bradycardia, peripheral vasodilatation, and, in some cases, tachycardia.[37]

Incomplete hospital records limited the authors' access to some data.

Conclusion

In conclusion, our findings confirmed the prognostic role of blood potassium levels, LVEF, serum LDL-C levels, history of MI, height, and history of COPD in patients with HF, which can be considered in the management of HF patients.

Acknowledgments

Conflict of Interests

Authors have no conflict of interests.

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