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ORIGINAL ARTICLE

Gender Differences in Prognostic Markers of All-Cause Death in Patients with Acute Heart Failure: a Prospective 18-Month Follow-Up Study

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Abstract

Acute heart failure (AHF) is a life-threatening condition with poor prognosis. Gender differences have been increasingly recognized in diverse cardiovascular diseases. The present study aimed to evaluate gender-specific prognostic markers of all-cause death in AHF patients based on a prospective 18-month follow-up study. Data were collected from 419 patients with AHF hospitalization who were followed up for 18 months using all-cause death as primary endpoint. The mean age of all patients was 60.9 ± 15.7 years old, 277 were males, and 142 were females. Females had higher rate of valvular heart disease (37.3%) and atrial fibrillation (45.8%) but lower rate of cardiomyopathy (30.3%) than males in this cohort. Based on multiple COX stepwise regression and ROC curve analysis, diastolic blood pressure (DBP), serum sodium, serum creatinine, and pulmonary artery systolic pressure (PASP) were identified as independent predictors of all-cause death in male AHF patients, while systolic blood pressure (SBP), serum aspartate transaminase (AST), serum creatinine, and serum D-dimer as independent predictors in females. Kaplan-Meier analysis showed a higher probability of all-cause death over time in male AHF patients with DBP ≤ 77 mmHg, serum sodium ≤ 138.5 mM, serum creatinine ≥ 126.2 μM, or PASP ≥ 52 mmHg, and in female AHF patients with SBP ≤ 129 mmHg, serum AST > 29.3 U/L, serum creatinine ≥ 102.7 μM, or serum D-dimer ≥ 1.76 mg/L. In conclusion, these data provide novel insights into gender differences in prognostic markers of outcomes of AHF patients.

Keywords Acute heart failure · Gender · All-cause death · Prognosis

Introduction

Heart failure (HF) is a common and complex clinical syndrome associated with structural and/or functional cardiac abnormality [1]. With the increasing life expectancy, the prevalence of HF increases to over 10% among people over 70 years old [2]. Compared to chronic heart failure, acute heart failure (AHF), usually caused by a rapid onset of new HF or acute exacerbation of preexisting myocardial dysfunction, is often a life-threatening condition and needs emergency hospitalization and clinical management [3]. Despite the improvement of pharmacological, interventional, and surgical therapies, the outcomes of HF patients still remain poor [4–6].

A great number of prognostic markers of death and/or HF hospitalization have been reported in HF patients such as age, blood pressure, blood sodium level, renal function, brain natriuretic peptide level, left ventricular ejection fraction, New York Heart Association functional class, diabetes, body mass index, and exercise capacity etc. [7, 8]. However, their clinical applicability still remains limited and their impact on clinical management of HF has not been well established [1, 9]. Men and women have different cardiac structure and physiology; thus, cardiac responses to cardiovascular and other systemic disorders may differ between men and women [10]. A large prospective population-based cohort study reported that the prevalence of HF was higher in men than in women; lifetime risk of HF was 33% for men and 29% for women at the age of

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55 years [11]. Female HF patients were likely to have higher rates of hypertension, atrial fibrillation, obesity, valvular abnormalities, and pulmonary hypertension but less ischemic heart diseases [12, 13]. Some studies reported that the mortality rate was similar between male and female HF patients [11–13]. But other studies reported that female HF patients had lower mortality rate [14–16]. To date, the results of HF prognosis among males and females remain controversial. Identifying gender differences in potential prognostic markers for outcomes of male and female HF patients is highly required.

The aim of the present study was to evaluate prognostic markers of all-cause death in patients with AHF hospitalization in both male and female patients based on a prospective 18-month follow-up study.

Methods

Study Population

This study was approved by the Ethic Committee of the First Affiliated Hospital of Nanjing Medical University. All participants gave written informed consent in accordance with the Declaration of Helsinki. This trial was registered at http://www.chictr.org/cn (Registration Number: ChiCTR-ONC-12001944). From March 2012 to October 2016, a total of 493 patients were prospectively enrolled and hospitalized for diagnosis of AHF in Cardiology Department of the First Affiliated Hospital of Nanjing Medical University, according to Chinese guidelines for the diagnosis and treatment of heart failure. The study population included new-onset AHF and acute exacerbation of chronic heart failure. The exclusion criteria included malignant tumor, cognitive dysfunction or dementia, severe mental illness, and uncontrolled systemic disease.

Data Collection

Data collection included demographic characteristics, medical history, etiology and comorbidity of AHF, and oral medications at time of hospitalization. Peripheral blood samples were collected from patients for biochemistry examinations, including serum levels of albumin, hemoglobin, sodium, potassium, uric acid, creatinine, N-terminal pro-brain natriuretic peptide (NT-proBNP), alanine aminotransferase (ALT), aspartate transaminase (AST), and D-dimer. All these biochemistry measurements were routinely analyzed by clinical laboratory in The First Affiliated Hospital of Nanjing Medical University. The first available 12-lead electrocardiogram (ECG) was examined at admission. Echocardiography was performed for measuring cardiac function and evaluating pulmonary artery systolic pressure (PASP) during hospitalization.

Follow-Up and Primary Endpoint

During 18 months follow-up, 74 (13.8%) patients were lost over time for giving the wrong telephone number or disconnecting the call. The primary endpoint was all-cause death, including in-hospital and out-hospital death. Patients were contacted by telephone every 3 months to evaluate the primary endpoint event after the initial clinical presentation, performed by a single trained researcher. The events were finally confirmed by the patients themselves, their families, or local hospital doctors.

Statistical Analysis

Continuous data were presented as mean ± standard deviation (SD) or interquartile range (median). Categorical variables were expressed as frequency (n) or proportion (%). Comparisons between groups were performed using Student t test, Mann-Whitney U test, and χ^2 test as appropriate. To investigate gender differences in the predictive factors of AHF prognosis, we divided male and female patients into survival and death subgroups, respectively. Multiple COX stepwise regression analysis (forward step, entry only if $P \leq 0.10$ and removal only if $P > 0.10$) was further performed to identify the independent predictors of all-cause death after 18-month follow-up in male and female AHF patients, respectively. Receiver operator characteristic (ROC) analysis was used to predict all-cause death in male and female AHF patients. Using cut-off values calculated from ROC analysis, Kaplan-Meier survival curves were performed to compare the cumulative survival proportion of male and female AHF patients, respectively. A P value of less than 0.05 was considered as significant. All statistical analyses were performed using SPSS software (version 22.0; SPSS Inc., Chicago, IL, USA) and MedCalc Software (version 18.11.3; MedCalc software, Mariakerke, Belgium).

Results

Gender Differences in Clinical Characteristics of AHF Patients

After 18-month follow-up, a total of 419 patients were finally enrolled in the present study (Table 1). The mean age of all patients was 60.9 ± 15.7 years old. Eighteen months after diagnosis of AHF, the rate of all-cause mortality was 21.7%. To evaluate gender differences in clinical characteristics of AHF patients, we divided patients into two groups: male ($n = 277$) and female ($n = 142$).

Among a total of 419 AHF patients, 66% were males ($n = 277$) and 34% were females ($n = 142$). There was no difference in systolic blood pressure (SBP), heart rate, body mass

Table 1 Baseline clinical characteristics of patients

	Male patients ($n = 277$)	Female patients ($n = 142$)	P value
Demographic characteristics			
Age, years	59.5 ± 15.3	63.6 ± 16.1	0.011
SBP, mmHg	123.7 ± 20.2	126.8 ± 20.6	0.141
DBP, mmHg	78.6 ± 13.6	75.8 ± 13.4	0.046
Heart rate, beat/min	85.1 ± 19.5	86.9 ± 24.2	0.435
BMI, kg/m^2	24.6 ± 4.3	23.8 ± 4.5	0.159
18-month mortality, *n* (%)	55 (19.9%)	36 (25.4%)	0.197
Etiology, *n* (%)			
CHD	74 (26.7%)	32 (22.5%)	0.352
VHD	56 (20.2%)	53 (37.3%)	<0.001
Cardiomyopathy	126 (45.5%)	43 (30.3%)	0.003
Comorbidity, *n* (%)			
Hypertension	139 (50.2%)	64 (45.1%)	0.322
Diabetes mellitus	58 (20.9%)	33 (23.2%)	0.589
Atrial fibrillation	87 (31.4%)	65 (45.8%)	0.004
Pulmonary infection	60 (21.7%)	25 (17.6%)	0.320
NYHA class, *n* (%)			
NYHA class II	51 (18.4%)	16 (11.3%)	0.262
NYHA class III	144 (52.0%)	83 (58.5%)	
NYHA class IV	82 (29.6%)	43 (30.3%)	

SBP systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *CHD* coronary heart disease, *VHD* valvular heart disease, *NYHA* New York Heart Association

Table 3 Oral medication at admission

	Male patients ($n = 277$)	Female patients ($n = 142$)	P value
Aldosterone antagonists, *n* (%)	254 (91.7%)	133 (93.7%)	0.627
Digoxin, *n* (%)	109 (39.4%)	65 (45.8%)	0.228
Loop diuretics, *n* (%)	263 (94.9%)	134 (94.4%)	0.565
ACEI/ARB, *n* (%)	223 (80.5%)	117 (82.4%)	0.745
β-Blockers, *n* (%)	222 (80.1%)	109 (76.8%)	0.343
Aspirin, *n* (%)	127 (45.8%)	60 (42.3%)	0.445

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker

index (BMI), and 18-month mortality between male and female AHF patients. The mean age of patients was 59.5 ± 15.3 years old for male vs. 63.6 ± 16.1 years old for female ($P < 0.05$). Although diastolic blood pressure (DBP) was statistically different between male and female patients (78.6 ± 13.6 mmHg for male vs. 75.8 ± 13.4 mmHg for female, $P < 0.05$), the average value of DBP is within the normal range for both male and female patients (Table 1).

Cardiomyopathy (40.3%), coronary heart disease (CHD, 25.3%), and valvular heart disease (VHD, 26.0%) represent the major etiologies of AHF. Etiology comparisons between males and females showed that females had higher rate of valvular heart disease (37.3%) and lower rate of cardiomyopathy (30.3%) than

Table 2 Biochemistry examination and device inspection of patients

	Male patients ($n = 277$)	Female patients ($n = 142$)	P value
Biochemistry examination			
Albumin, g/dL	3.70 ± 0.49	3.68 ± 0.51	0.687
Hemoglobin, g/dL	13.9 ± 1.9	12.2 ± 2.1	< 0.001
Sodium, mM	139.6 ± 3.8	140.0 ± 4.1	0.347
Potassium, mM	4.0 ± 0.5	3.9 ± 0.5	0.166
Creatinine, μM	76.0–108.1 (89.6)	64.1–94.4 (76.7)	< 0.001
NT-proBNP, pg/mL	1259.0–5265.3 (2142.5)	1176.0–5132.0 (2292.0)	0.802
Uric acid, μM	494.0 ± 168.1	451.6 ± 162.1	0.015
ALT, U/L	19.0–50.9 (30.5)	14.4–35.0 (21.2)	< 0.001
AST, U/L	22.4–42.7 (28.8)	21.1–40.8 (26.4)	0.118
D-dimer, mg/L	0.3–1.5 (0.7)	0.4–1.6 (0.8)	0.440
Device inspection			
LVEF, %	28.9–47.5 (34.9)	35.4–62.7 (48.1)	< 0.001
LVEDd, mm	65.4 ± 11.5	55.0 ± 11.3	< 0.001
LVEDs, mm	53.1 ± 13.1	41.9 ± 12.8	< 0.001
QRS duration, ms	133.9 ± 40.2	120.8 ± 38.8	0.002
QTc, ms	453.1 ± 88.5	424.6 ± 99.9	0.003
PASP, mmHg	42.2 ± 14.3	47.6 ± 19.8	0.007

NT-proBNP N-terminal pro-brain natriuretic peptide, *ALT* alanine aminotransferase, *AST* aspartate transaminase, *LVEF* left ventricular ejection fraction, *LVEDd* left ventricular end-diastolic dimension, *LVEDs*, left ventricular end-systolic dimension, *PASP* pulmonary artery systolic pressure

Table 4 Characteristics of male patients between survival and death subgroups

	Male patients ($n = 277$)	Survival ($n = 222$)	Death ($n = 55$)	P value
Demographic characteristics				
Age, years	59.5 ± 15.3	58.4 ± 15.6	63.9 ± 13.4	0.017
SBP, mmHg	123.7 ± 20.2	125.9 ± 20.1	114.8 ± 18.0	<0.001
DBP, mmHg	78.6 ± 13.6	80.5 ± 13.6	71.0 ± 10.7	<0.001
Heart rate, beat/min	85.1 ± 19.5	86.0 ± 20.0	81.5 ± 16.9	0.125
BMI, kg/m^2	24.6 ± 4.3	24.5 ± 4.5	24.8 ± 3.7	0.159
Biochemistry examination				
Albumin, g/dL	3.70 ± 0.49	3.71 ± 0.44	3.67 ± 0.65	0.623
Hemoglobin, g/dL	13.9 ± 1.9	14.0 ± 1.9	13.3 ± 1.9	0.012
Sodium, mM	139.6 ± 3.8	140.0 ± 3.4	138.0 ± 4.8	0.007
Potassium, mM	4.0 ± 0.5	4.0 ± 0.5	4.0 ± 0.5	0.388
Uric acid, μM	494.0 ± 168.1	478.1 ± 147.7	556.7 ± 222.7	0.017
Creatinine, μM	76.0–108.1 (89.6)	75.7–103.1 (87.2)	82.4–142.0 (99.3)	<0.001
NT-proBNP, pg/mL	1259.0–5265.3 (2142.5)	1190.0–4855.0 (1969.0)	1648.0–8251.0 (2777.0)	0.002
ALT, U/L	19.0–50.9 (30.5)	20.4–50.8 (31.1)	16.1–50.9 (25.5)	0.283
AST, U/L	22.4–42.7 (28.8)	22.5–41.8 (28.8)	22.4–44.0 (31.3)	0.351
D-dimer, mg/L	0.3–1.5 (0.7)	0.3–1.4 (0.6)	0.5–1.9 (1.0)	0.023
Device inspection				
LVEF, %	28.9–47.5 (34.9)	28.9–47.6 (35.3)	28.5–47.1 (33.8)	0.893
LVEDd, mm	65.4 ± 11.5	65.0 ± 11.1	67.0 ± 13.3	0.272
LVEDs, mm	53.1 ± 13.1	52.9 ± 12.9	54.2 ± 14.3	0.507
QRS duration, ms	133.9 ± 40.2	132.3 ± 40.9	140.6 ± 36.6	0.171
QTc, ms	453.1 ± 88.5	449.4 ± 92.5	467.8 ± 69.0	0.167
PASP, mmHg	42.2 ± 14.3	40.7 ± 13.5	47.4 ± 15.9	0.003
Etiology, n (%)				
CHD	74 (26.7%)	59 (26.6%)	15 (27.3%)	0.917
VHD	56 (20.2%)	42 (18.9%)	14 (25.5%)	0.280
Cardiomyopathy	126 (45.5%)	103 (46.4%)	23 (41.8%)	0.542
Comorbidity, n (%)				
Hypertension	139 (50.2%)	116 (52.3%)	23 (41.8%)	0.166
Diabetes mellitus	58 (20.9%)	43 (19.4%)	15 (27.3%)	0.197
Atrial fibrillation	87 (31.4%)	65 (29.3%)	22 (40.0%)	0.125
Pulmonary infection	60 (21.7%)	43 (19.4%)	17 (30.9%)	0.065
NYHA class, n (%)				
NYHA class II	51 (18.4%)	45 (20.3%)	6 (10.9%)	0.095
NYHA class III	144 (52.0%)	117 (52.7%)	27 (49.1%)	
NYHA class IV	82 (29.6%)	60 (27.0%)	22 (40.0%)	

SBP systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *ALT* alanine aminotransferase, *AST* aspartate transaminase, *LVEF* left ventricular ejection fraction, *LVEDd* left ventricular end-diastolic dimension, *LVEDs* left ventricular end-systolic dimension, *PASP* pulmonary artery systolic pressure, *CHD* coronary heart disease, *VHD* valvular heart disease, *NYHA* New York Heart Association

males (20.2% and 45.5%, respectively) (Table 1). For comorbidities of AHF, female patients had higher rate of atrial fibrillation (45.8%) than males (31.4%) ($P < 0.01$), while other comorbidities including hypertension, diabetes mellitus, and pulmonary infection were not different between males and females (Table 1). A total of 84% AHF patients had NYHA functional class III-IV. No difference was found in NYHA class between male and female AHF patients (Table 1).

Serum samples of patients were collected and submitted to biochemistry examinations, and the 12-lead ECG and

Table 5 Characteristics of female patients between survival and death subgroups

	Female patients ($n = 142$)	Survival ($n = 106$)	Death ($n = 36$)	P value
Demographic characteristics				
Age, years	63.6 ± 16.1	63.3 ± 15.3	64.4 ± 18.5	0.724
SBP, mmHg	126.8 ± 20.6	129.5 ± 20.8	119.0 ± 18.3	0.008
DBP, mmHg	75.8 ± 13.4	77.3 ± 13.6	71.4 ± 12.1	0.023
Heart rate, beat/min	86.9 ± 24.2	87.1 ± 23.4	86.5 ± 26.7	0.905
BMI, kg/m^2	23.8 ± 4.5	24.2 ± 5.0	22.8 ± 2.7	0.084
Biochemistry examination				
Albumin, g/dL	3.68 ± 0.49	3.75 ± 0.46	3.47 ± 0.61	0.006
Hemoglobin, g/dL	12.2 ± 2.1	12.4 ± 2.0	11.7 ± 2.2	0.066
Sodium, mM	140.0 ± 4.1	140.4 ± 4.0	138.6 ± 4.1	0.020
Potassium, mM	3.9 ± 0.5	3.9 ± 0.5	3.9 ± 0.5	0.858
Uric acid, μM	451.6 ± 162.1	433.5 ± 147.2	506.9 ± 193.1	0.021
Creatinine, μM	64.1–94.4 (76.7)	63.1–90.3 (73.0)	67.2–113.1 (88.1)	0.009
NT-proBNP, pg/mL	1176.0–5132.0 (2292.0)	1075.3–4457.3 (2116.5)	1667.0–7235.0 (3316.0)	0.006
ALT, U/L	14.4–35.0 (21.2)	13.8–31.4 (19.1)	15.7–54.7 (29.9)	0.010
AST, U/L	21.1–40.8 (26.4)	20.2–34.2 (25.6)	24.6–69.8 (36.0)	<0.001
D-dimer, mg/L	0.4–1.6 (0.8)	0.3–1.4 (0.7)	0.5–3.3 (1.0)	0.003
Device inspection				
LVEF, %	35.4–62.7 (48.1)	35.3–61.6 (47.5)	38.1–66.0 (57.1)	0.075
LVEDd, mm	55.0 ± 11.3	55.1 ± 10.8	53.4 ± 12.8	0.367
LVEDs, mm	41.9 ± 12.8	42.5 ± 12.3	39.9 ± 14.4	0.315
QRS duration, ms	120.8 ± 38.8	119.8 ± 38.9	123.4 ± 38.9	0.643
QTc, ms	424.6 ± 99.9	431.4 ± 97.7	405.5 ± 104.9	0.183
PASP, mmHg	47.6 ± 19.8	46.2 ± 17.2	51.4 ± 25.6	0.282
Etiology, n (%)				
CHD	32 (22.5%)	23 (21.7%)	9 (25.0%)	0.682
VHD	53 (37.3%)	44 (41.5%)	9 (25.0%)	0.077
Cardiomyopathy	43 (30.3%)	33 (31.1%)	10 (27.8%)	0.705
Comorbidity, n (%)				
Hypertension	64 (45.1%)	48 (45.3%)	16 (44.4%)	0.930
Diabetes Mellitus	33 (23.2%)	25 (23.6%)	8 (22.2%)	0.867
Atrial fibrillation	65 (45.8%)	53 (50.0%)	12 (33.3%)	0.083
Pulmonary infection	25 (17.6%)	20 (18.9%)	5 (13.9%)	0.498
NYHA class, n (%)				
NYHA class II	16 (11.3%)	12 (11.3%)	4 (11.1%)	0.673
NYHA class III	83 (58.5%)	64 (60.4%)	19 (52.8%)	
NYHA class IV	43 (30.3%)	30 (28.3%)	13 (36.1%)	

SBP systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *ALT* alanine aminotransferase, *AST* aspartate transaminase, *LVEF* left ventricular ejection fraction, *LVEDd* left ventricular end-diastolic dimension, *LVEDs* left ventricular end-systolic dimension, *PASP* pulmonary artery systolic pressure, *CHD* coronary heart disease, *VHD* valvular heart disease, *NYHA* New York Heart Association

echocardiography were available during hospitalization (Table 2). Male patients had higher serum levels of hemoglobin, creatinine, uric acid, and alanine aminotransferase (ALT) than females. Results from 12-lead ECG and echocardiography showed that male patients had longer QRS duration and QTc ($P < 0.01$), but lower left ventricular ejection fraction (LVEF) and larger left ventricular end-diastolic and end-systolic dimension (LVEDd and LVEDs) than females ($P < 0.001$). Moreover, pulmonary artery systolic pressure (PASP) was higher in female patients based on echocardiography measurement ($P < 0.01$).

At admission, aldosterone antagonists, loop diuretics, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), and β-blockers were used in 92.4%, 94.7%, 81.1%, and 79.0% of all patients, respectively. Digoxin and aspirin were used in 41.5% and 44.6% of all patients, respectively. There was no difference in oral medication at admission between male and female patients (Table 3).

Table 6 COX stepwise regression analysis (forward step, entry only if $P \leq 0.10$ and removal only if $P > 0.10$) of mortality on the significant ($P < 0.05$) variables in baseline characteristics of male patients

	β value	Std. error	HR	95%CI	*P* value
DBP	− 0.042	0.015	0.959	0.930~0.988	0.006
Sodium	− 0.081	0.037	0.922	0.858~0.992	0.029
lgCreatinine	2.935	0.984	18.824	2.734~129.628	0.003
PASP	0.024	0.011	1.024	1.003~1.046	0.024

DBP diastolic blood pressure, *PASP* pulmonary artery systolic pressure

Clinical Characteristics of Male and Female AHF Patients Between Survival and Death Subgroups

To investigate gender differences in the predictive factors of AHF prognosis, we divided male and female patients into survival and death subgroups, respectively (Tables 4 and 5).

A total of 277 male AHF patients were divided into two subgroups: survival ($n = 222$) vs. death ($n = 55$) (Table 4). The male death subgroup had lower systolic and diastolic blood pressure than survival subgroup ($P < 0.001$), although the average blood pressure is within the normal range. Serum biochemistry examinations showed that the male death subgroup had statistically lower levels of hemoglobin and sodium but higher levels of uric acid, creatinine, NT-proBNP, and D-dimer than survival subgroup. Although cardiac function was not significantly different between survival and death male patients, pulmonary artery systolic pressure (PASP) was higher in death subgroup ($P < 0.01$).

A total of 142 female AHF patients were divided into two subgroups: survival ($n = 106$) vs. death ($n = 36$) (Table 5). The female death subgroup had lower systolic and diastolic blood pressure than survival subgroup, although the average blood pressure is within the normal range. Serum biochemistry examinations showed that the female death subgroup had statistically lower levels of albumin and sodium but higher levels of uric acid, creatinine, NT-proBNP, ALT, aspartate transaminase (AST), and D-dimer than survival subgroup. Echocardiography and 12-lead ECG results were not significantly different between survival and death female patients.

For both male and female AHF patients, no difference was found in the etiology, comorbidity, and NYHA class between survival and death subgroups (Tables 4 and 5).

COX Regression Analysis for Independent Predictors of All-Cause Death in Male and Female AHF Patients

Multiple COX stepwise regression analysis (forward step, entry only if $P \leq 0.10$ and removal only if $P > 0.10$) was further performed to identify the independent predictors of all-cause death after 18 months follow-up in male and female AHF patients, respectively.

For male AHF patients, diastolic blood pressure (DBP), serum sodium, serum lgCreatinine, and pulmonary artery systolic pressure (PASP) were identified as independent prognostic markers for all-cause death (Table 6). For female AHF patients, systolic blood pressure (SBP), lgAST, lgD-dimer, and lgCreatinine were identified as independent prognostic markers for all-cause death (Table 7).

DBP, Serum Sodium, Serum Creatinine, and PASP as the Prognostic Markers of All-Cause Death in Male AHF Patients

ROC curve analysis was further performed to compare the ability of DBP, serum sodium, serum creatinine, and PASP to predict all-cause death in male AHF patients (Fig. 1). For male AHF patients, the AUC of DBP (AUC_{DBP} 0.709, 95%CI 0.652–0.762), sodium (AUC_{Sodium} 0.638, 95%CI 0.578–0.695), creatinine ($AUC_{Creatinin}$ 0.658, 95%CI 0.598–0.713), and PASP (AUC_{PASP} 0.638, 95%CI 0.573–0.699) indicated that these factors could significantly predict all-cause death in male AHF patients after 18-month follow-up (Fig. 1a–f). The combine of DBP with sodium ($AUC_{DBP + Sodium}$ 0.727, 95%CI 0.670–0.779), creatinine ($AUC_{DBP + Creatinine}$ 0.756, 95%CI 0.701–0.806), or PASP ($AUC_{DBP + PASP}$ 0.754, 95%CI 0.693–0.807) could significantly enhance the AUC compared to AUC_{Sodium}, $AUC_{Creatinine}$, and AUC_{PASP}, respectively ($P < 0.01$) (Fig. 1a–c). Moreover, the combine of four factors could further enhance the AUC ($AUC_{DBP + Sodium + Creatinine + PASP}$ 0.784, 95%CI 0.725–0.835), which was statistically significant compared to the AUC of either single factor (Fig. 1g). The sensitivity and specificity of the combined four factors to predict all-cause death in male AHF patients were 62.75% and 85.64%, respectively.

Using the cut-off values of DBP, serum sodium, serum creatinine, and PASP, Kaplan-Meier survival curves were performed to compare the cumulative survival proportion of male AHF patients during 18 months follow-up. Kaplan-Meier analysis showed a significantly lower probability of all-cause death over time in male AHF patients with DBP > 77 mmHg, serum sodium

Table 7 COX stepwise regression analysis (forward step, entry only if $P \leq 0.10$ and removal only if $P > 0.10$) of mortality on the significant ($P < 0.05$) variables in baseline characteristics of female patients

	β value	Std. error	HR	95%CI	*P* value
SBP	−0.022	0.011	0.978	0.958~0.999	0.038
lgAST	1.463	0.519	4.317	1.562~11.932	0.005
lgCreatinine	2.211	0.929	9.125	1.478~56.347	0.017
lgD-dimer	0.731	0.368	2.076	1.010~4.267	0.047

SBP systolic blood pressure, *AST* aspartate transaminase

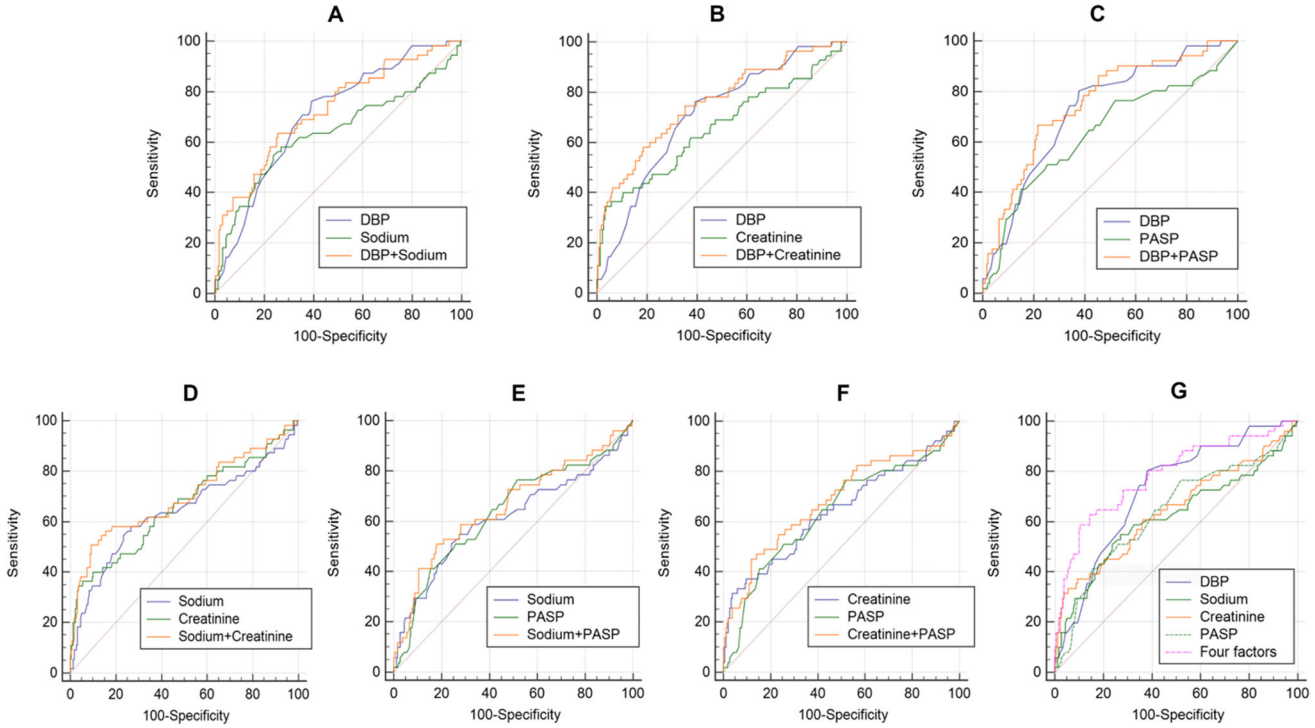

Fig. 1 Receiver operator characteristic curves of DBP, serum sodium, serum creatinine, and PASP for predicting 18-month all-cause death in male AHF patients. AUC_{DBP} 0.709, 95%CI 0.652–0.762, sensitivity = 76.36%, specificity = 60.81%, cut off point 77 mmHg; AUC_{Sodium} 0.638, 95%CI 0.578–0.695, sensitivity = 58.18%, specificity = 73.06%, cut off point 138.5 mM; $AUC_{Creatinine}$ 0.658, 95%CI 0.598–0.713, sensitivity = 34.55%, specificity = 96.38%, cut off point 126.2 μM; AUC_{PASP} 0.638, 95%CI 0.573–0.699, sensitivity = 41.18%, specificity = 84.86%, cut off point 52 mmHg. **a** $AUC_{DBP+Sodium}$ 0.727, 95%CI 0.670–0.779, sensitivity = 63.64%, specificity = 74.43%; AUC_{DBP} vs. $AUC_{DBP+Sodium}$, $P = 0.3328$; AUC_{Sodium} vs. $AUC_{DBP+Sodium}$, $P = 0.0067$. **b** $AUC_{DBP+Creatinine}$ 0.756, 95%CI 0.701–0.806, sensitivity = 58.18%, specificity = 81.45%; AUC_{DBP} vs. $AUC_{DBP+Creatinine}$, $P = 0.1169$; $AUC_{Creatinine}$ vs. $AUC_{DBP+Creatinine}$, $P = 0.0026$. **c** $AUC_{DBP+PASP}$ 0.754, 95%CI 0.693–0.807, sensitivity = 66.7%, specificity = 78.4%; AUC_{DBP} vs. $AUC_{DBP+PASP}$, $P = 0.2183$; AUC_{PASP} vs. $AUC_{DBP+PASP}$, $P = 0.0055$. **d** $AUC_{Sodium+Creatinine}$ 0.697, 95%CI 0.638–0.751, sensitivity = 50.91%, specificity = 90.83%; AUC_{Sodium} vs. $AUC_{Sodium+Creatinine}$, $P = 0.1988$; $AUC_{Creatinine}$ vs. $AUC_{Sodium+Creatinine}$, $P = 0.1777$. **e** $AUC_{Sodium+PASP}$ 0.660, 95%CI 0.595–0.721, sensitivity = 50.98%, specificity = 81.87%; AUC_{Sodium} vs. $AUC_{PASP+Sodium}$, $P = 0.2927$; AUC_{PASP} vs. $AUC_{PASP+Sodium}$, $P = 0.4821$. **f** $AUC_{PASP+Creatinine}$ 0.684, 95%CI 0.621–0.743, sensitivity = 45.1%, specificity = 88.0%; $AUC_{Creatinine}$ vs. $AUC_{PASP+Creatinine}$, $P = 0.1494$; AUC_{PASP} vs. $AUC_{PASP+Creatinine}$, $P = 0.2598$. **g** $AUC_{DBP+Sodium+Creatinine+PASP}$ 0.784, 95%CI 0.725–0.835, sensitivity = 62.75%, specificity = 85.64%; AUC_{DBP} vs. $AUC_{Four\ factors}$, $P = 0.0456$; AUC_{Sodium} vs. $AUC_{Four\ factors}$, $P < 0.001$; $AUC_{Creatinine}$ vs. $AUC_{Four\ factors}$, $P = 0.0012$; AUC_{PASP} vs. $AUC_{Four\ factors}$, $P = 0.0015$

> 138.5 mM, serum creatinine < 126.2 μM, or PASP < 52 mmHg ($P < 0.001$) (Fig. 2). Collectively, these data indicated DBP, serum sodium, serum creatinine, and PASP as independent predictors of all-cause death in male AHF patients.

SBP, Serum AST, Serum Creatinine, and Serum D-Dimer as the Prognostic Markers of All-Cause Death in Female AHF Patients

ROC curve analysis was further performed to compare the ability of SBP, serum AST, serum creatinine, and serum D-dimer to predict all-cause death in female AHF patients (Fig. 3). For female AHF patients, the AUC of SBP (AUC_{SBP} 0.657, 95%CI 0.572–0.734), AST (AUC_{AST} 0.708, 95%CI 0.626–0.782), creatinine ($AUC_{Creatinin}$ 0.646, 95%CI 0.562–0.725), and D-dimer ($AUC_{D\text{-}dimer}$ 0.671, 95%CI 0.583–0.751) indicated that these factors could significantly predict all-cause death in female AHF patients after 18 months follow-up (Fig. 3a–f). The combination of either two factors could not significantly enhance the AUC compared to a single factor (Fig. 3a–f). However, the AUC of combined four factors was significantly different from that of either single factor ($AUC_{SBP+AST+Creatinine+D\text{-}dimer}$ 0.773, 95%CI 0.691–0.842) (Fig. 3g). The sensitivity and specificity of the combined four factors to predict all-cause death in female AHF patients were 52.94% and 95.79%, respectively.

Using the cut-off values of SBP, serum AST, serum creatinine, and serum D-dimer, Kaplan-Meier survival curves were performed to compare the cumulative survival proportion of female AHF patients during 18-month follow-up. Kaplan-Meier analysis showed a significantly lower probability of all-cause death over time in female AHF patients with SBP > 129 mmHg, serum AST ≤ 29.3 U/L, serum creatinine < 102.7 μM, or serum D-dimer < 1.76 mg/L ($P < 0.001$)

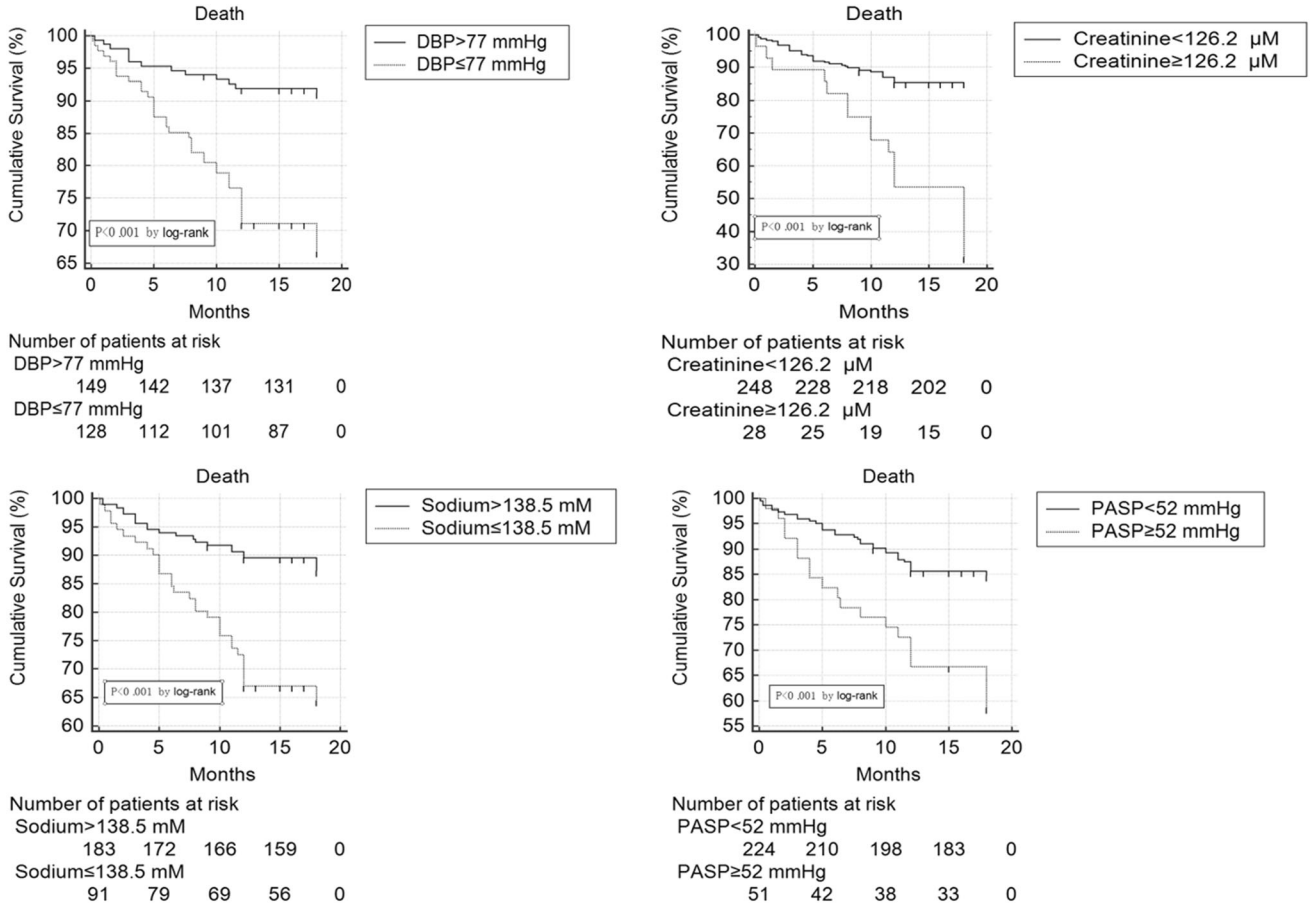

Fig. 2 Kaplan-Meier survival curves to compare the cumulative survival proportion of male AHF patients during 18 months follow-up

(Fig. 4). Collectively, these data indicated SBP, serum AST, serum creatinine, and serum D-dimer as independent predictors of all-cause death in female AHF patients.

Discussion

In this prospective 18-month follow-up study, we analyzed the gender differences in prognostic markers of outcomes of AHF patients. Our main results indicate that DBP, serum sodium, serum creatinine, and PASP are potential predictors of all-cause death among male AHF patients, while SBP, serum AST, serum creatinine, and serum D-dimer are potential predictors of all-cause death among female AHF patients.

Among a total of 419 AHF patients, 66% were males and 34% were females. Etiology and comorbidity comparisons between males and females showed that females had higher rate of valvular heart disease and atrial fibrillation but lower rate of cardiomyopathy than males. Additionally, males were more likely to have lower LVEF and larger LVEDd and LVEDs, while females were more likely to have higher PASP. These data were in consistent with previous studies which reported that female HF patients more frequently had valvular heart disease, atrial fibrillation, and pulmonary hypertension and less frequently had cardiomyopathy [12, 13]. Although previous studies also reported higher rate of hypertension and diabetes but lower rate of coronary heart disease among female HF patients than males [12, 13], no difference was found in these etiology or comorbidity of HF between males and females in the present study. Moreover, all-cause mortality during 18-month follow-up was not significantly different between male and female AHF patients.

Due to an under-representation of women in cardiovascular clinical trials, gender-specific prognostic markers for HF are far from explored [17]. To identify gender-specific predictors of outcomes of AHF patients, we further divided males and females into survival and death subgroups. Using COX stepwise regression and ROC curve analysis, independent prognostic markers were identified and compared to predict all-cause death in male and female AHF patients, respectively.

For male AHF patients, DBP, serum sodium, serum creatinine, and PASP were identified as independent prognostic markers for all-cause death. Kaplan-Meier analysis showed a higher probability of all-cause death over time in male AHF patients with DBP ≤ 77 mmHg, serum sodium ≤ 138.5 mM, serum creatinine ≥ 126.2 μM, or PASP ≥ 52 mmHg. Increasing

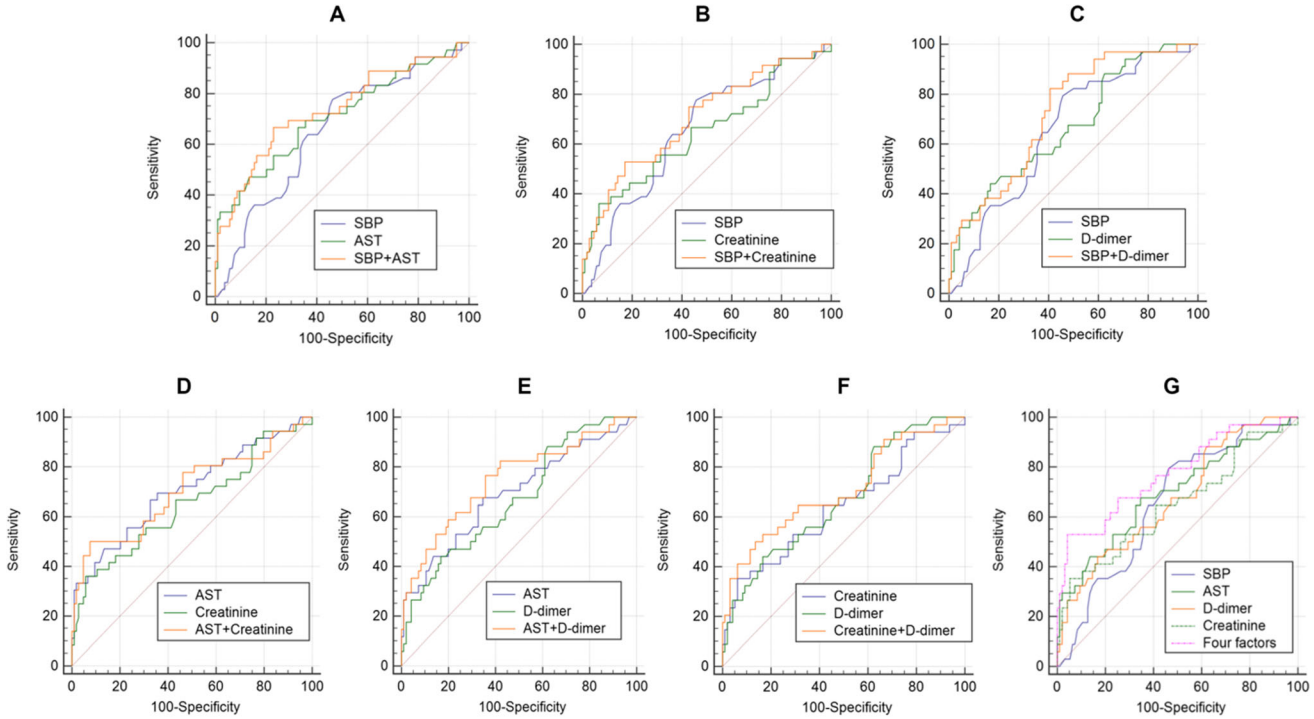

Fig. 3 Receiver operator characteristic curves of SBP, serum AST, serum creatinine, and D-dimer for predicting 18-month all-cause death in female AHF patients. AUC_{SBP} 0.657, 95%CI 0.572–0.734, sensitivity = 77.8%, specificity = 53.8%, cut off point 129 mmHg; AUC_{AST} 0.708, 95%CI 0.626–0.782, sensitivity = 66.7%, specificity = 67.3%, cut off point 29.3 U/L; $AUC_{Creatinine}$ 0.646, 95%CI 0.562–0.725, sensitivity = 36.1%, specificity = 93.3%, cut off point 102.7 μM; $AUC_{D\text{-}dimer}$ 0.671, 95%CI 0.583–0.751, sensitivity = 44.1%, specificity = 83.3%, cut off point 1.76 mg/L. **a** $AUC_{SBP+AST}$ 0.736, 95%CI 0.655–0.807, sensitivity = 66.67%, specificity = 76.92%; AUC_{SBP} vs. $AUC_{SBP+AST}$, $P = 0.0811$; AUC_{AST} vs. $AUC_{SBP+AST}$, $P = 0.3150$. **b** $AUC_{SBP+Creatinine}$ 0.704, 95%CI 0.621–0778, sensitivity = 52.78%, specificity = 82.86%; AUC_{SBP} vs. $AUC_{SBP+Creatinine}$, $P = 0.2968$; $AUC_{Creatinine}$ vs. $AUC_{SBP+Creatinine}$, $P = 0.1901$. **c** $AUC_{SBP+D\text{-}dimer}$ 0.728, 95%CI 0.643–0.803, sensitivity = 82.35%, specificity = 59.38%; AUC_{SBP} vs. $AUC_{SBP+D\text{-}dimer}$, $P = 0.1281$; $AUC_{D\text{-}dimer}$ vs. $AUC_{SBP+D\text{-}dimer}$, $P = 0.1184$. **d** $AUC_{AST+Creatinine}$ 0.706, 95%CI 0.624–0.780, sensitivity = 50.00%, specificity = 92.31%; AUC_{AST} vs. $AUC_{AST+Creatinine}$, $P = 0.9368$; $AUC_{Creatinine}$ vs. $AUC_{AST+Creatinine}$, $P = 0.2345$. **e** $AUC_{AST+D\text{-}dimer}$ 0.749, 95%CI 0.665–0.821, sensitivity = 76.47%, specificity = 64.21%; AUC_{AST} vs. $AUC_{D\text{-}dimer+AST}$, $P = 0.1260$; $AUC_{D\text{-}dimer}$ vs. $AUC_{D\text{-}dimer+AST}$, $P = 0.0828$. **f** $AUC_{D\text{-}dimer+Creatinine}$ 0.709, 95%CI 0.623–0.786, sensitivity = 50.00%, specificity = 86.46%; $AUC_{D\text{-}dimer}$ vs. $AUC_{D\text{-}dimer+Creatinine}$, $P = 0.2930$; $AUC_{Creatinine}$ vs. $AUC_{D\text{-}dimer+Creatinine}$, $P = 0.0831$. **g** $AUC_{SBP+AST+Creatinine+D\text{-}dimer}$ 0.773, 95%CI 0.691–0.842, sensitivity = 52.94%, specificity = 95.79%; AUC_{SBP} vs. $AUC_{Four\ factors}$, $P = 0.0287$; AUC_{AST} vs. $AUC_{Four\ factors}$, $P = 0.0391$; $AUC_{Creatinine}$ vs. $AUC_{Four\ factors}$, $P = 0.0153$; $AUC_{D\text{-}dimer}$ vs. $AUC_{Four\ factors}$, $P = 0.0446$

evidence suggests that preexisting hypertension and higher SBP and DBP reactivity are inversely associated with cardiovascular mortality in HF patients, which may be related to better cardiovascular regulation capacity upon stress [18, 19]. However, greater blood pressure change during hospitalization or long-term follow-up was associated with worse prognosis for HF patients [20, 21]. A large amount of studies suggests that hyponatremia (< 135 mM) and even low-normal range (≥ 135 and < 140 mM) of serum sodium level could increase the risk of long-term mortality or rehospitalization in AHF patients [22–24]. In this study, we observed that male AHF patients with admission serum sodium ≤ 138.5 mM had a higher probability of all-cause death during 18-month follow-up. Meanwhile, serum creatinine ≥ 126.2 μM was also identified as a potential predictor of all-cause death in male AHF patients. As renal failure was significantly more frequent among male HF patients, renal salt sensing and neurohormonal regulation of sodium-conserving pathway may play essential roles in influencing the outcomes of male AHF patients [12, 13]. Pulmonary hypertension in HF patients has been proved to be associated with worse prognosis [25–27]. Instead of invasive right heart catheterization, echocardiographic measurement of PASP is used as an alternative method for routine pulmonary hypertension detection [28]. Elevated PASP was previously reported to predict increased risk of death, heart transplantation, and rehospitalization in HF patients [29, 30]. However, gender-specific prognostic value of PASP for HF patients is largely unclear. Here, we identified PASP ≥52 mmHg as an independent predictor of 18-month all-cause death in male AHF patients. In fact, pulmonary artery pressure-guided HF management was shown to efficiently reduce total HF hospitalization and all-cause 30-day readmission [31].

For female AHF patients, SBP, serum AST, serum creatinine, and serum D-dimer were identified as independent

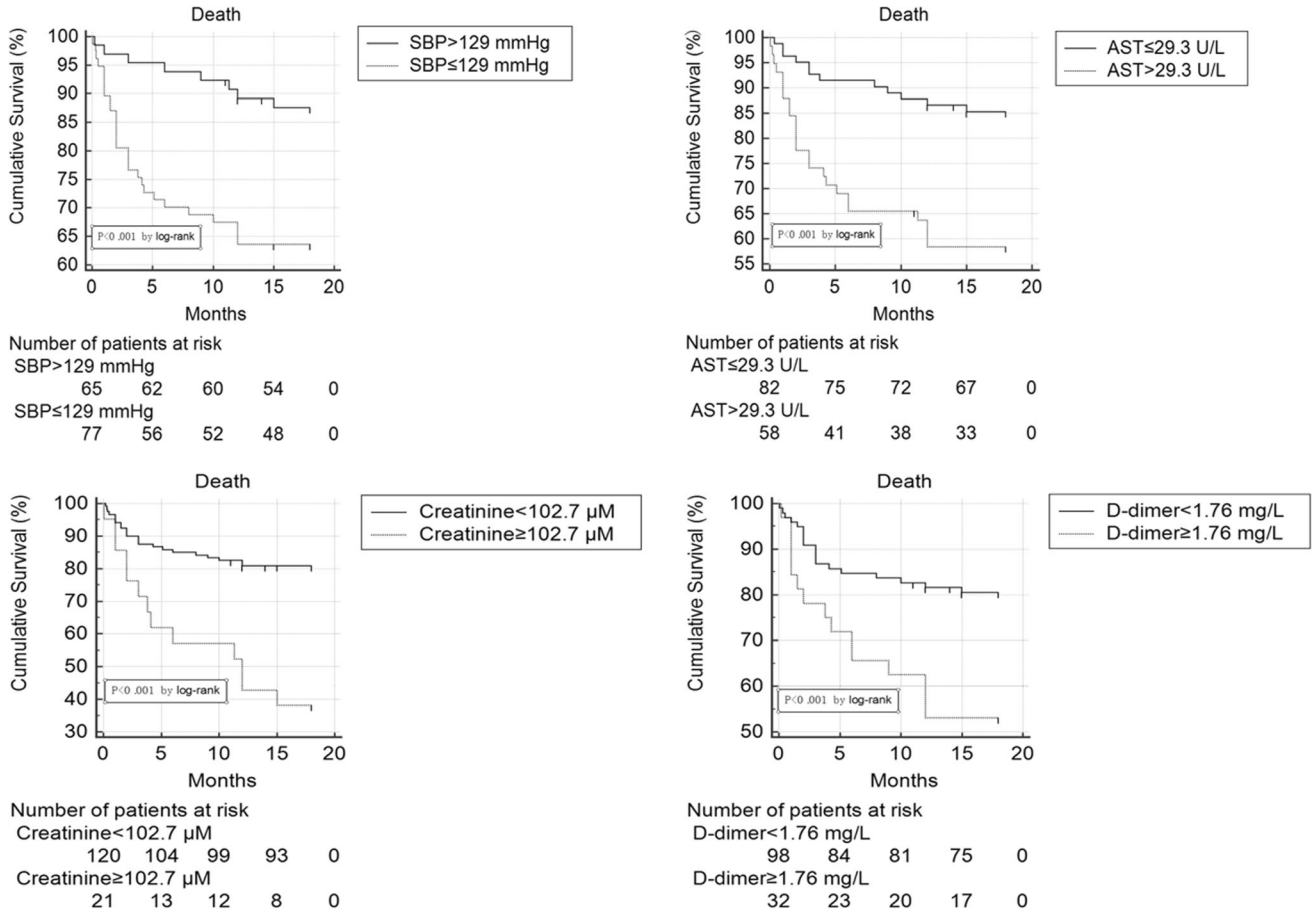

Fig. 4 Kaplan-Meier survival curves to compare the cumulative survival proportion of female AHF patients during 18 months follow-up

prognostic markers for all-cause death. Kaplan-Meier analysis showed a higher probability of all-cause death over time in female AHF patients with SBP ≤ 129 mmHg, serum AST > 29.3 U/L, serum creatinine ≥ 102.7 μM, or serum D-dimer ≥ 1.76 mg/L. Although blood pressure control is critical in clinical management, how much the blood pressure needs to be lowered is still a matter of debate [32–34]. SBP < 125 mmHg was reported to be associated with increased cardiovascular death in myocardial infarction patients with HF, although this may be a reverse causality phenomenon [35]. Lower SBP was also identified as a strong predictor of rehospitalization in HF patients [36]. In contrast, other studies reported that targeting blood pressure < 120 mmHg, rather than < 140 mmHg, was more efficient to reduce AHF events [37]. In this study, we identified that female AHF patients with SBP ≤ 129 mmHg had higher risk of long-term mortality; however, the blood pressure control and the threshold to which blood pressure should be lowered in female HF patients needs further investigation. Here, we also identified serum AST > 29.3 U/L as a predictive marker of all-cause death in female AHF patients. Patients receiving surgery for infective endocarditis who had higher baseline ALT and AST levels were previously reported to have higher 30-day mortality [38]. Liver fibrosis, as determined by non-alcoholic fatty liver disease fibrosis score (NFS), was associated with higher all-cause mortality in HF patients [39]. The reduced arterial perfusion and increased central venous pressure during HF may cause liver congestion, leading to liver fibrosis [40, 41]. The increased central venous pressure could also enhance cholestatic abnormalities and hepatocyte dysfunction in HF patients [42]. These studies, together with our data, suggest that liver dysfunction may be a potential predictor of worse prognosis of HF patients, and the gender-specific prognostic value of serum AST in female AHF patients needs further study. Additionally, we also identified serum creatinine ≥ 102.7 μM as a predictor of all-cause death in female AHF patients. Noteworthy, multiple-organ dysfunction including kidney, liver, and myocardium was suggested to predict long-term mortality in AHF patients [43]. These results implicate a need to further assess the clinical relevance of serum AST and serum creatinine each or combined in the prognosis of AHF patients. In female AHF patients, we also found that serum D-dimer ≥ 1.76 mg/L was a predictor of 18-month all-cause death. Increased serum D-dimer is a marker of hypercoagulable state usually caused by neurohormonal activation in HF [44, 45]. Elevated serum D-dimer was previously reported to predict cardiovascular

mortality in HF patients [46]. In this study, D-dimer ≥ 1.76 mg/L was identified to predict worse prognosis in female AHF patients, which emphasized that these patients may need more intensive follow-up after hospital discharge.

Several limitations should be considered for this study. First, prognostic markers of HF were not separately examined for heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) due to a relatively small sample size of male and female HF patients. Second, pulmonary artery pressure was estimated using non-invasive echocardiography in the present study, while right-heart catheterization results should be further examined and compared to determine the gender-specific prognostic value of elevated pulmonary artery pressure in long-term mortality of HF patients, especially for male AHF patients. Third, medication changes during follow-up were not available in the present study which may also influence the prognosis of AHF patients. Fourth, a combination of the identified gender-specific prognostic markers of all-cause death deserve further investigation, which may further improve their predictive values and guide long-term follow-up and medication of male and female AHF patients. Fifth, mechanistic explanation for gender differences in prognostic markers of all-cause death in AHF patients was not provided in our study. The differences in hormone levels, psychological stress, gender-specific molecular mechanisms, and risk factors unique to female patients such as pregnancy and menopause may contribute to gender differences in prognostic markers of all-cause death in patients with AHF [47–50]. Further studies are needed to elucidate their roles in the pathophysiology of HF. Finally, although this is a prospective 18-month follow-up study, larger number of male and female patients from multiple centers will further enhance the strength of the study to identify gender-specific prognostic markers of AHF [51].

In conclusion, this prospective study indicates that DBP, serum sodium, serum creatinine, and PASP predict all-cause death in male AHF patients, while SBP, serum AST, serum creatinine, and serum D-dimer predict all-cause death in female AHF patients. Our study provides novel insights into gender differences in prognostic markers of outcomes of AHF patients, which will be useful to improve clinical management and follow-up in male and female AHF patients.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Research Involving Human Participants and/or Animals This study was approved by the Ethic Committee of the First Affiliated Hospital of Nanjing Medical University and registered at http://www.chictr.org/cn (Registration Number: ChiCTR-ONC-12001944). From March 2012 to October 2016, a total of 493 patients were prospectively enrolled and hospitalized for diagnosis of AHF in Cardiology Department of the First Affiliated Hospital of Nanjing Medical University, according to Chinese guidelines for the diagnosis and treatment of heart failure. Data collection included demographic characteristics, medical history, etiology and comorbidity of AHF, oral medications at admission, laboratory examination, 12-lead ECG, and echocardiography. Patients with AHF hospitalization were followed up for 18 months using all-cause death as primary endpoint.

Informed Consent All participants gave written informed consent in accordance with the Declaration of Helsinki.

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