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Different prognostic association of systolic blood pressure at different time points with postdischarge events in patients hospitalized for decompensated heart failure

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Abstract

Background The association of systolic blood pressure (SBP) with mortality in heart failure (HF) patients is paradoxical, and the time points of baseline SBP are also different across prior studies. We hypothesized that the levels of SBP at admission and at discharge had different associations with postdischarge events. **Methods** The study population included patients hospitalized for decompensated HF in the Heart Failure Center of Fuwai Hospital from January 1, 2009 to December 31, 2014. The primary outcome was a composite of cardiovascular (CV) death and heart transplantation. Multivariate Cox proportional-hazards and restricted cubic spline analyses were used to assess the relationships between SBP at different time points and outcomes. **Results** In total, 2005 patients were included with a median follow-up of 48.4 months. The median age was 59 years, and 69.9% were male. Multivariate Cox analyses showed that compared with SBP < 105 mmHg, higher SBP at admission was associated with better long-term primary outcome (105–119 mmHg, HR = 0.764, $P = 0.005$; 120–134 mmHg, HR = 0.658, $P < 0.001$; ≥ 135 mmHg, HR = 0.657, $P = 0.001$). Patients whose discharge SBP was higher than 135 mmHg had a similar primary outcome as those with SBP < 105 mmHg (HR = 0.969, $P = 0.867$), and the results remained unchanged even after adjusting for admission SBP (HR = 1.235, $P = 0.291$). The results of restricted cubic spline analysis indicated similar associations. **Conclusions** Lower but not higher SBP at admission is associated with more CV deaths/heart transplantations (a reverse J-shaped curve). In contrast, there is a *U*-shaped association between discharge SBP and CV mortality/heart transplantation.

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Keywords: Admission; Discharge; Heart failure; Outcome; Systolic blood pressure

1 Introduction

Hypertension has been considered a common risk factor for heart failure (HF).[1,2] It is believed that the development of HF could be prevented by anti-hypertensive treatment in high-risk populations.[3–7] However, previous studies have found inconsistent results on the effects of systolic blood pressure (SBP) on mortality in HF patients. According to the Diet, Cancer and Health (DCH) cohort study, high baseline blood pressure was related to adverse outcomes in incident HF patients.[8] Conversely, other studies[9–14] showed that HF patients with high systolic blood pressure (SBP), even higher than 140 mmHg,[9,11,13] had a better prognosis than those with low blood pressure, regardless of the time of SBP measurements (at admission or the so-called baseline). The changes in SBP in HF patients have been confirmed,[15] suggesting that SBP drops significantly after admission and steadily increases thereafter. In OPTIMIZE-HF,[9] although HF patients with high SBP (> 140 mmHg at admission) had better outcomes, their mean SBP declined to 120–139 mmHg at discharge. Different SBP levels at different times may reflect various conditions in HF patients. For example, during the decompensated phase, SBP level usually reflects short-term "cardiovascular reserve", and SBP during the stable phase would have a long-term influence on outcomes. So far, it is unclear whether the SBP levels at different time-points have a similar association with adverse events. In this study, we hypothesized that the levels of SBP at admission and at discharge would have different associations with postdischarge outcomes in a cohort of HF patients hospitalized for decompensated HF.

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2 Methods

2.1 Study population

We retrospectively assessed patients hospitalized for decompensated HF at the Heart Failure Center of Fuwai Hospital from January 1, 2009 to December 31, 2014. For patients with multiple admissions, only the first admission was included in our analyses. The diagnosis of heart failure with reduced ejection fraction (HFrEF) was according to the 2012 European Society of Cardiology guidelines,[16] which was based on typical HF symptoms/signs and a left ventricular ejection fraction (LVEF) less than 40%. For those with LVEF ≥ 40%, in addition to typical symptoms/signs, the diagnosis of HF required one of the following conditions to be satisfied: elevated N-terminal pro B type natriuretic peptide (≥ 450 ng/L), HF history, left ventricular end-diastolic diameter ≥ 55 mm, left atrial diameter ≥ 45 mm, interventricular septal or left ventricular posterior wall thickness ≥ 12 mm, E/A< 1, and systolic/diastolic dysfunction, which was reported by qualitative assessment. Patients without any tumor, aortic dissection, stenosis of the renal artery or secondary hypertension were enrolled in this study. Additionally, those who were aged < 18 years, had no LVEF data, had no data on New York Heart Association (NYHA) classification at admission, died or had a heart transplant during the first hospitalization, were discharged with a left ventricular assistance device or continuous intravenous inotropic therapy, or transferred to another hospital for further treatment were excluded. All patients provided written informed consent, and the ethics committee of Fuwai Hospital approved this study.

2.2 Data collection

Data on blood pressure (BP) at admission were first recorded in the nursing notes from medical records, and data on BP at discharge were obtained from the electronic progress notes of the day of discharge. Both BPs were measured by an electronic sphygmomanometer in arm by nurses. The first record of BP was obtained before treatments for HF on the hospital floor in a supine position, and BP at discharge was measured in a supine position after resting for at least 10 minutes. SBP was categorized into four groups (quartile at admission: < 105, 105–119, 120–134 and ≥ 135 mmHg) for risk estimation.

Clinical variables at admission (the first record during hospitalization) and at discharge (the last record during hospitalization) included demographic characteristics (age, gender and body mass index), length of hospitalization, NYHA classification, SBP, DBP, heart rate, comorbidities (coronary heart disease, hypertension, atrial fibrillation/flutter, diabetes mellitus, dilated cardiomyopathy, anemia, cerebrovascular accident, myocardial infarction and pulmonary artery hypertension), laboratory data (hemoglobin, total protein, albumin, potassium, sodium, creatinine, blood urea nitrogen, uric acid, estimated glomerular filtration rate (eGFR), triglycerides, total cholesterol, high-density lipoprotein and low-density lipoprotein), LVEF and medications (angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), spironolactone, loop diuretics, digoxin, calcium channel blockers, statins and warfarin).

Adverse events with respect to all-cause death, cardiovascular (CV) death, and heart transplantation were ascertained every three months via electronic hospital record follow-up or conversation with patients or their families by telephone. The primary outcome of our study was a composite of CV death and heart transplantation. The secondary outcome was a composite of all-cause death and heart transplantation. CV death was defined as progressive heart failure death (progressive deterioration of HF in the absence of other causes), sudden death (unexpected and witnessed death in a stable patient without evidence of a special cause of death), death due to myocardial infarction or stroke, or other CV death (such as mortal complications of cardiac surgery, rupture of an aneurysm, pulmonary embolism, aortic dissection, etc.).

To categorize the potential effects of different doses of ACEIs/ARBs, beta blockers and loop diuretics on the renin-angiotensin-aldosterone system that would further affect the outcomes, we adjusted for some variables. Doses of ACEIs, ARBs and beta blockers were divided into four quartiles: 0, 1%–49%, 50%–99%, and ≥ 100% of the target dose.[16,17] Loop diuretics were converted to the furosemide-equivalent dose:[18] 1 mg of oral torsemide was considered equivalent to 2 mg of oral furosemide, and 1 mg of oral bumetanide was considered equivalent to 40 mg of oral furosemide. To evaluate the progression of heart failure, we introduced the variable ΔEF, which was defined as the difference between LVEF at discharge and LVEF at admission.

2.3 Statistical analyses

Continuous data are presented as median with interquartile range (IQR) and were compared by the Mann-Whitney *U* test or Kruskal-Wallis test. Categorical data are presented as percentages and were analyzed using the chi-square test or Fisher's exact test, as appropriate. Comparisons were also made between patients with and without follow-up information.

The Kaplan-Meier method was used to determine cumulative probabilities of endpoints from the time of discharge

throughout the follow-up period. Cumulative event rates were compared by the log-rank test.

We first examined the association of SBP at admission and outcomes in the total cohort. To explore the relationship between admission SBP (used as quartiles) and outcomes, variables at admission that had a P value < 0.05 in univariate Cox proportional-hazards analyses were introduced as covariates in a multivariate model with a stepwise forward method (four covariates, namely, the doses of ACEIs/ARBs, beta blockers, and spironolactone and ΔEF, were forced into in the final models). The adjusted hazard ratios (HRs) for each category of SBP were estimated in reference to the lowest quartile of SBP (< 105 mmHg). To examine the potential nonlinear relationship between SBP and outcomes, restricted cubic spline analyses were also used based on the same covariables in the multivariate Cox model. The incorporated knots used in the model were the 5th, 50th and 95th percentiles of SBP (at 90, 118, 153 mmHg for admission SBP and at 90, 110 and 130 mmHg for discharge SBP, respectively). The SBP level with the lowest risk of events was used as the reference in the restricted cubic spline model. The above-described method was repeated to evaluate the association of SBP at discharge and outcomes (covariates were those at discharge). In addition, we used SBP at admission as a covariate in all final models of discharge SBP. HRs are presented with 95% confidence intervals (CIs). We also explored the relationship between SBP and outcomes in subgroups. All statistical analyses were performed using SPSS version 22 and R 3.4.

3 Results

A total of 2144 patients fulfilled the inclusion criteria. After excluding those patients who had no follow-up data (n = 139), a total of 2005 patients were included in our analyses. The median age was 59 years (IQR: 48–69 years), and 69.9% were male. Their characteristics were compared with those of the patients who had no follow-up data. Patients without follow-up data were more likely to have cerebrovascular accidents, worse renal function (reflected by blood urea nitrogen and eGFR), worse heart function (reflected by LVEF and NYHA classification), and lower SBP at discharge (Supplement Table 1).

3.1 SBP at admission and patient characteristics

The characteristics of the patients categorized by admission SBP are listed in Table 1. Patients with higher admission SBP were older and were more likely to have coronary heart disease, hypertension, diabetes mellitus and cerebrovascular accidents but less likely to have dilated cardiomyopathy or pulmonary artery hypertension. They were also less likely to suffer from hyponatremia, had lower levels of blood urea nitrogen and uric acid levels, and had better heart function on admission. ΔEF was not significantly different across the SBP categories. Patients with higher SBP were more likely to use higher doses of ACEIs/ARBs, calcium channel blockers and statins. However, they were less likely to be prescribed beta blockers, spironolactone, loop diuretics and digoxin. Most patients had experienced a process of SBP decline or maintenance, except for those in the lowest quartile.

3.2 SBP at discharge and patient characteristics

The characteristics of the patients categorized by discharge SBP are shown in Table 2. Patients with higher SBP at discharge were also older and were more likely to have coronary heart disease, hypertension, diabetes mellitus and cerebrovascular accidents but less likely to have dilated cardiomyopathy. They were also less likely to have hyponatremia. However, they experienced more anemia at discharge. Patients with higher discharge SBP also had higher BMI, worse renal function (reflected by creatinine, blood urea nitrogen and eGFR) and better heart function (reflected by LVEF and NYHA classification) on admission. They were more likely to use a higher dose of ACEI/ARB but less likely to be prescribed spironolactone.

3.3 Relationship between SBPs and outcomes

During the follow-up period, 837 patients had reached an endpoint, of whom 778 had died (709 were due to cardiovascular reasons), and 59 had undergone heart transplantation. The median follow-up time of our patient cohort was 48.4 months (interquartile range 20.9–72.4 months). The unadjusted survival curves for patients by SBP quartile are shown in Figure 1.

In univariate Cox proportional-hazards analyses for SBP at admission, patients in the highest quartile of SBP (≥ 135 mmHg) had a lower risk of CV death/heart transplantation (HR = 0.452, 95% CI: 0.366–0.559, P < 0.001) compared with SBP < 105 mmHg, and the survival of patients with SBP from 105 to 134 mmHg was between the two (105–119 mmHg, HR = 0.656, 95% CI: 0.548–0.786, P < 0.001; 120–134 mmHg HR = 0.481, 95% CI: 0.395–0.586, P < 0.001). According to the multivariate Cox model, compared with SBP < 105 mmHg, higher SBP was also associated with better long-term primary outcome (105–119 mmHg, HR = 0.764, 95% CI: 0.634–0.921, P = 0.005; 120–134 mmHg, HR = 0.658, 95% CI: 0.532–0.813, P < 0.001; ≥ 135 mmHg, HR = 0.657, 95% CI: 0.515–0.837; P = 0.001).

Table 1. Characteristics of the patients by admission SBP categories.

	< 105 mmHg (*n* = 478)	105–119 mmHg (*n* = 571)	120–134 mmHg (*n* = 520)	≥ 135 mmHg (*n* = 436)	*P* value
Male	67.4%	70.4%	73.7%	67.4%	0.099
Age, yrs	56 (44, 66)	57 (47, 66)	61 (50, 71)	64 (53, 72)	< 0.001
Hospitalization days	13 (10, 20)	12 (8, 17)	12 (8, 18)	12 (8, 18)	< 0.001
CHD	28.5%	37.7%	46.0%	46.8%	< 0.001
HTN	21.5%	33.1%	50.8%	72.5%	< 0.001
AF or atrial flutter	38.7%	33.5%	35.0%	32.6%	0.202
DM	16.1%	21.7%	31.0%	35.1%	< 0.001
DCM	36.4%	30.6%	23.8%	11.9%	< 0.001
PH	20.1%	13.0%	14.0%	12.8%	0.004
CE	10.3%	10.2%	11.9%	17.2%	0.003
MI	23.0%	29.2%	28.5%	29.1%	0.089
At admission					
NYHA classification					< 0.001
II	11.7%	20.5%	25.6%	25.5%	
III	49.6%	50.3%	52.5%	52.3%	
IV	38.7%	29.2%	21.9%	22.2%	
SBP, mmHg	97 (91, 101)	112 (108, 116)	126 (123, 130)	145 (139, 152)	< 0.001
DBP, mmHg	64 (58, 70)	70 (63, 77)	76 (68, 83)	80 (69, 90)	< 0.001
Heart rate, beats/min	80 (71, 92)	82 (71,96)	80.5 (70, 93)	80 (69, 91)	0.097
Hb, g/L	136 (124, 149)	139 (127, 151)	139 (124, 152)	135 (119, 150)	0.008
Hypoproteinemia	11.3%	8.6%	6.7%	9.2%	0.088
Hypoalbuminemia	18.0%	14.4%	10.8%	14.9%	0.014
Hypokalemia	11.1%	12.1%	10.2%	11.2%	0.804
Hyponatremia	28.2%	21.0%	16.2%	12.6%	< 0.001
Cr, μmol/L	95.85 (80.83, 116.1)	93.3 (79, 112.1)	92.8 (79.23, 115.8)	92.44 (76.6, 116.4)	0.571
Cr ≥ 225 μmol/L	1.5%	0.8%	1.8%	2.6%	0.154
eGFR, mL/min per 1.73 m^2	65.38 (50.05, 87.13)	70.93 (51.98, 93.38)	71.40 (50.94, 92.72)	67.42 (48.33, 91.77)	0.045
eGFR < 60 mL/min per 1.73 m^2	42.5%	37.0%	34.4%	39.0%	0.062
BUN, mmol/L	7.74 (5.84, 10.16)	7.36 (5.80, 9.70)	7.29 (5.60, 9.64)	7.19 (5.51, 9.22)	0.049
UA, μmol/L	444.1 (361.2, 552.2)	426.6 (335.4, 538.2)	403.4 (321.6, 507.6)	384.8 (303.2, 491.0)	< 0.001
TG, mmol/L	1.195 (0.910, 1.643)	1.360 (1.000, 1.900)	1.410 (1.073, 2.053)	1.400 (1.053, 1.960)	< 0.001
TC, mmol/L	3.98 (3.31, 4.77)	4.13 (3.39, 4.99)	4.22 (3.52, 5.06)	4.27 (3.63, 5.12)	< 0.001
HDL, mmol/L	0.95 (0.76, 1.16)	0.97 (0.79, 1.19)	0.98 (0.82, 1.18)	1.00 (0.83, 1.26)	0.001
LDL, mmol/L	2.42 (1.90, 3.02)	2.46 (1.90, 3.17)	2.52 (2.02, 3.15)	2.52 (2.01, 3.14)	0.154
LVEF, %	33 (26, 48)	36 (28, 48)	40 (30, 55)	44.5 (34, 58)	< 0.001
LVEF ≥ 40%	36.8%	41.3%	52.1%	62.4%	< 0.001
At discharge					
BMI, kg/m^2	21.63 (19.20, 24.22)	22.49 (20.20, 25.16)	24.04 (21.51, 26.49)	24.14 (21.53, 26.73)	< 0.001
Hb, g/L	133 (115, 149)	136 (120, 150)	135.5 (114, 153)	132 (110, 150)	0.031
Anemia	24.3%	19.3%	26.4%	31.0%	< 0.001
Hypoproteinemia	6.7%	7.4%	9.2%	9.6%	0.271
Hypoalbuminemia	20.3%	17.5%	17.7%	16.7%	0.515
Hyponatremia	21.5%	18.2%	13.3%	13.8%	0.001
Cr, μmol/L	91.55 (75.0, 112.51)	95.6 (77.76, 113.18)	98.0 (80.53, 117.28)	102.55 (82.05, 129.8)	< 0.001
Cr > 225 μmol/L	1.0%	1.6%	2.2%	3.4%	0.042
eGFR, mL/min per 1.73 m^2	67.47 (48.62, 88.48)	68.95 (47.32, 90.69)	67.22 (47.57, 90.16)	60.17 (40.29, 83.05)	< 0.001
eGFR < 60 mL/min per 1.73 m^2	38.9%	40.8%	39.6%	49.8%	0.003
BUN, mmol/L	8.16 (6.19, 11.01)	8.40 (6.50, 11.10)	8.50 (6.78, 11.18)	9.50 (7.00, 13.27)	< 0.001

Table 1. Cont.

	< 105 mmHg (*n* = 478)	**105–119 mmHg (*n* = 571)**	**120–134 mmHg (*n* = 520)**	**≥ 135 mmHg (*n* = 436)**	***P* value**
UA, μmol/L	406.0 (297.9, 493.3)	406.1 (317.0, 502.9)	405.8 (306.4, 505.7)	399.4 (306.1, 495.8)	0.808
LVEF, %	34% (26%, 47%)	35% (28%, 50%)	40% (30%, 56%)	45% (35%, 58%)	< 0.001
LVEF ≥ 40%	37.9%	40.1%	52.5%	64.4%	< 0.001
ΔEF, %	0 (–3, 3)	0 (–2, 3)	0 (–2, 3)	0 (–1, 4)	0.215
SBP quartile					< 0.001
< 105 mmHg	58.2%	34.5%	19.2%	7.8%	
105–119 mmHg	31.8%	48.9%	47.5%	38.3%	
120–134 mmHg	9.6%	15.9%	29.8%	41.5%	
≥ 135 mmHg	0.4%	0.7%	3.5%	12.4%	
ΔSBP, mmHg	6 (–2, 14)	–5 (–11,3)	–13 (–21, –5)	–28 (–36, 19)	< 0.001
DBP, mmHg	64 (60, 70)	67 (60, 70)	70 (62, 74)	70 (62, 75)	< 0.001
Heart rate, beats/min	72 (65, 80)	72 (65, 80)	71 (65, 78)	70 (63, 77)	< 0.001
ACEI/ARB					< 0.001
None	62.6%	44.5%	38.8%	35.1%	
< 50%	30.8%	38.9%	30.8%	27.1%	
50%–99%	5.9%	14.0%	21.3%	22.0%	
≥ 100%	0.8%	2.6%	9.0%	15.8%	
Beta-blocker					0.003
None	16.7%	15.1%	15.2%	22.0%	
< 50%	60.3%	58.8%	55.8%	47.0%	
50%–99%	17.8%	21.5%	23.3%	24.1%	
≥ 100%	5.2%	4.6%	5.8%	6.9%	
Spironolactone	80.1%	72.5%	70.4%	62.4%	< 0.001
Loop diuretics	94.6%	91.9%	91.2%	86.0%	< 0.001
Furosemide equivalent	40 (20, 40)	40 (20, 40)	30 (20, 40)	30 (20, 40)	< 0.001
CCB	2.7%	3.7%	9.6%	25.9%	< 0.001
Thiazide diuretic	2.1%	3.3%	4.2%	3.7%	0.292
Digoxin	72.8%	62.0%	55.6%	45.2%	< 0.001
Warfarin	29.3%	24.9%	25.0%	26.1%	0.352
Statin	25.5%	40.5%	49.6%	52.1%	< 0.001

Continuous data are presented as median with interquartile range; categorical data are presented as percentages. ACEI: angiotensin-converting enzyme inhibitor; AF: atrial fibrillation; ARB: angiotensin receptor blocker; BMI: body mass index; BUN: blood urea nitrogen; CCB: calcium channel blocker; CE: cerebrovascular accident; CHD: coronary heart disease; Cr: creatinine; DBP: diastolic blood pressure; DCM: dilated cardiomyopathy; DM: diabetes mellitus; EF: ejection fractions; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; HDL: high-density lipoprotein; HTN: hypertension; LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PH: pulmonary hypertension; SBP: systolic blood pressure; TC: total cholesterol; TG: triglyceride; UA: uric acid.

The results of survival analyses for SBP at discharge were dramatically different. In univariate Cox analyses, patients in the highest quartile of SBP (≥ 135 mmHg) had a lower risk of CV death and transplantation compared with SBP < 105 mmHg (HR = 0.688, 95% CI: 0.485–0.976, *P* = 0.036). However, the multivariate Cox model showed that these patients all had similar primary outcomes (HR = 0.969, 95% CI: 0.667–1.407, *P* = 0.867). This remained unchanged even after adjusting admission SBP (HR = 1.235, 95% CI: 0.835–1.826, *P* = 0.291). Detailed results of multivariate analyses (CV death/heart transplantation or all-cause death/heart transplantation) are shown in Tables 3 & 4.

Restricted cubic spline graphical representations of the relationship between SBP and the outcomes of interest are shown in Figure 2. There was a reverse J-curve relationship between admission SBP and outcomes. Patients whose SBP

Table 2. Characteristics of the patients by discharge SBP categories.

	< 105 mmHg (*n* = 609)	105–119 mmHg (*n* = 845)	120–134 mmHg (*n* = 473)	≥ 135 mmHg (*n* = 78)	*P* value
Male	68.1%	69.9%	72.1%	69.2%	0.575
Age, yrs	55 (43, 65)	60 (50, 69)	62 (52, 71)	64 (52, 72)	< 0.001
Hospitalization days	12 (9, 17)	12 (8, 19)	13 (8, 20)	11 (7, 14)	0.014
CHD	31.5%	42.4%	44.6%	42.3%	< 0.001
HTN	25.0%	42.5%	62.6%	83.3%	< 0.001
AF or atrial flutter	33.2%	35.5%	37.2%	28.2%	0.310
DM	19.2%	25.0%	32.3%	43.6%	< 0.001
DCM	36.8%	23.4%	20.3%	9.0%	< 0.001
PH	18.9%	14.4%	10.8%	14.1%	0.003
CE	9.9%	12.3%	12.9%	24.4%	0.003
MI	25.9%	29.7%	24.7%	33.3%	0.115
At admission					
SBP quartile					< 0.001
< 105 mmHg	45.6%	18.0%	9.7%	2.6%	
105–119 mmHg	32.3%	33.0%	19.2%	5.1%	
120–134 mmHg	16.4%	29.2%	32.8%	23.1%	
≥ 135 mmHg	5.6%	19.8%	38.3%	69.2%	
NYHA classification					< 0.001
II	15.5%	23.4%	22.2%	25.6%	
III	48.4%	52.7%	52.0%	50.0%	
IV	36.1%	23.9%	25.8%	24.4%	
At discharge					
BMI, kg/m^2	21.80 (19.46, 24.51)	23.11 (20.56, 25.81)	24.22 (21.67, 27.05)	24.35 (22.19, 27.06)	< 0.001
Hb, g/L	137 (122, 151)	133 (112, 149)	132 (113.5, 150)	132 (110, 149)	0.007
Anemia	17.1%	27.6%	28.3%	34.6%	< 0.001
Hypoproteinemia	5.7%	8.9%	10.4%	6.4%	0.034
Hypoalbuminemia	16.1%	18.8%	19.7%	15.4%	0.374
Hyponatremia	17.4%	18.8%	13.5%	9.0%	0.022
Cr, μmol/L	92.5 (76.4, 111.5)	96.0 (78.0, 117.1)	100.4 (83.7, 121.8)	114.7 (82.4, 176.2)	< 0.001
Cr > 225 μmol/L	1.3%	1.2%	2.8%	11.3%	< 0.001
eGFR, mL/min per 1.73 m^2	68.96 (48.54, 89.43)	66.00 (46.35, 89.25)	64.38 (44.61, 86.15)	55.94 (36.16, 80.83)	0.016
eGFR < 60 mL/min per 1.73 m^2	38.4%	42.0%	44.2%	56.4%	0.013
BUN, mmol/L	8.10 (6.22, 10.70)	8.52 (6.65, 11.72)	9.27 (6.90, 12.4)	9.75 (6.98, 13.5)	< 0.001
UA, μmol/L	413.0 (322.4, 509.3)	395.4 (288.2, 488.6)	399.1 (318.0, 500.4)	431.3 (342.8, 488.1)	0.017
LVEF, %	33% (26%, 45%)	40% (30%, 55%)	43% (34%, 58%)	45% (35%, 56%)	< 0.001
LVEF ≥ 40%	33.2%	50.3%	60.9%	62.8%	< 0.001
ΔEF	0 (–2%, 2%)	0 (–3%, 3%)	0 (–2%, 5%)	0 (–2%, 3%)	0.094
SBP, mmHg	97 (92, 100)	110 (108, 112)	121 (120, 127)	140 (138, 147)	< 0.001
ΔSBP, mmHg	–10 (–21, –1)	–9 (–20, 2)	–5 (–19, 5)	–2 (–16, 10)	< 0.001
DBP, mmHg	60 (59, 66)	70 (62, 70)	70 (68, 80)	73 (67, 82)	< 0.001
Heart rate, beats/min	72 (64, 80)	72 (65, 78)	70 (65, 80)	70 (64, 76)	0.135
ACEI/ARB					< 0.001
None	53.7%	43.8%	38.5%	37.2%	
< 50%	35.8%	33.0%	29.0%	16.7%	
50%–99%	8.5%	16.0%	23.3%	23.1%	
≥ 100%	2.0%	7.2%	9.3%	23.1%	

Table 2. Cont.

	< 105 mmHg (*n* = 609)	105–119 mmHg (*n* = 845)	120–134 mmHg (*n* = 473)	≥ 135 mmHg (*n* = 78)	*P* value
Beta blocker					0.004
None	11.8%	19.3%	19.5%	17.9%	
< 50%	62.6%	53.6%	50.7%	57.7%	
50%–99%	20.0%	21.5%	24.1%	20.5%	
≥ 100%	5.6%	5.6%	5.7%	3.8%	
Spironolactone	82.4%	68.9%	64.5%	59.0%	< 0.001
Loop diuretics	95.6%	90.3%	86.7%	91.0%	< 0.001
Furosemide equivalent	40 (20, 40)	30 (20, 40)	30 (20, 40)	35 (20, 40)	< 0.001
CCB	2.1%	8.0%	16.1%	51.3%	< 0.001
Thiazide diuretic	1.3%	4.3%	4.7%	1.3%	0.004
Digoxin	69.5%	57.0%	51.4%	51.3%	< 0.001
Warfarin	25.0%	26.2%	29.2%	19.2%	0.203
Statin	34.3%	41.8%	49.3%	55.1%	< 0.001

Continuous data are presented as median with interquartile range; categorical data are presented as percentages. ACEI: angiotensin-converting enzyme inhibitor; AF: atrial fibrillation; ARB: angiotensin receptor blocker; BMI: body mass index; BUN: blood urea nitrogen; CCB: calcium channel blocker; CE: cerebrovascular accident; Cr: creatinine; CHD: coronary heart disease; DBP: diastolic blood pressure; DCM: dilated cardiomyopathy; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; HTN: hypertension; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PH: pulmonary hypertension; SBP: systolic blood pressure; UA: uric acid.

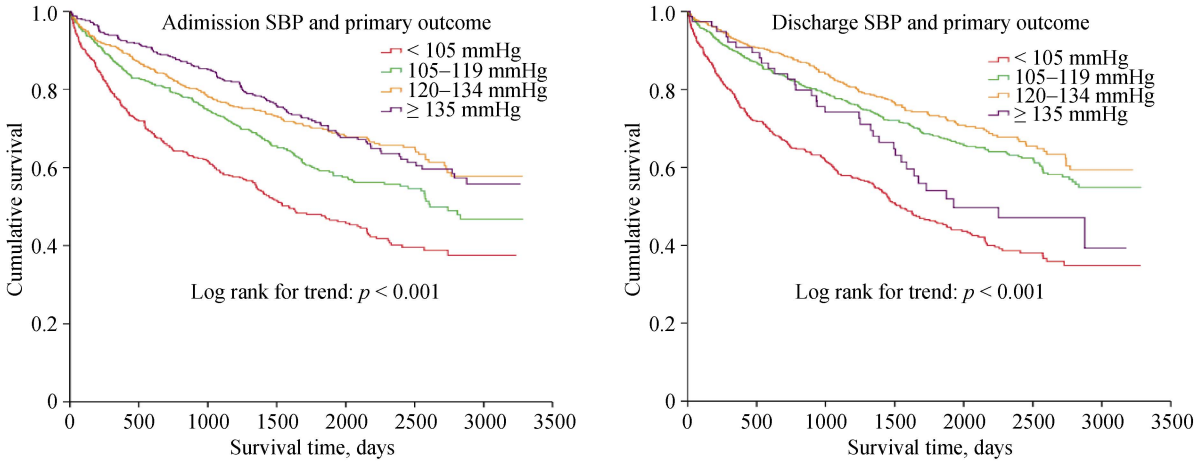

Figure 1. Kaplan-Meier curve by SBP quartile. SBP: systolic blood pressure.

Table 3. Adjusted hazard ratios for quartile of SBP at admission.

SBP at admission, mmHg	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
	*Cardiovascular mortality and heart transplantation		#All-cause mortality and heart transplantation	
< 105	Reference		Reference	
105–119	0.764 (0.634, 0.921)	0.005	0.801 (0.669, 0.960)	0.016
120–134	0.658 (0.532, 0.813)	< 0.001	0.707 (0.577, 0.867)	0.001
≥ 135	0.657 (0.515, 0.837)	0.001	0.655 (0.519, 0.827)	< 0.001

Covariates in the models were consistent with the results of multivariable Cox analysis with a stepwise forward method, and ACEIs/ARBs, beta blockers, spironolactone and ΔEF were forced into the models. *Adjusted for age, hospitalization days, hypertension, atrial fibrillation/flutter, myocardial infarction, hemoglobin, hypoalbuminemia, blood urea nitrogen, uric acid, estimated glomerular filtration rate, triglyceride, LVEF, NYHA classification, furosemide-equivalent dose, warfarin, ACEIs/ARBs, beta blockers, spironolactone and ΔEF. #Adjusted for age, hospitalization days, hypertension, atrial fibrillation/flutter, myocardial infarction, hemoglobin, hypoalbuminemia, blood urea nitrogen, uric acid, estimated glomerular filtration rate, triglyceride, high-density lipoprotein, low-density lipoprotein, LVEF, NYHA classification, hydrochlorothiazide, warfarin, ACEIs/ARBs, beta blockers, spironolactone and ΔEF. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; EF: ejection fraction; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SBP: systolic blood pressure.

Table 4. Adjusted hazard ratios for quartile of SBP at discharge.

SBP at discharge, mmHg	Adjusted HR (95% CI)	*P* value	Admission SBP Adjusted HR (95% CI)	*P* value
*Cardiovascular mortality and heart transplantation				
< 105	Reference		Reference	
105–119	0.617 (0.518, 0.734)	< 0.001	0.663 (0.554, 0.793)	< 0.001
120–134	0.598 (0.475, 0.752)	< 0.001	0.684 (0.538, 0.870)	0.002
≥ 135	0.969 (0.667, 1.407)	0.867	1.235 (0.835, 1.826)	0.291
#All-cause mortality and heart transplantation				
< 105	Reference		Reference	
105–119	0.600 (0.507, 0.710)	< 0.001	0.641 (0.539, 0.761)	< 0.001
120–134	0.553 (0.443, 0.691)	< 0.001	0.621 (0.493, 0.783)	< 0.001
≥ 135	0.747 (0.510, 1.093)	0.134	0.913 (0.616, 1.353)	0.650

Covariates in the models were consistent with the results of multivariable Cox analysis with a stepwise forward method, and ACEIs/ARBs, beta blockers, spironolactone and ΔEF were forced into the models. *Adjusted for age, hospitalization days, atrial fibrillation/flutter, hypoalbuminemia, hyponatremia, estimated glomerular filtration rate, uric acid, LVEF, diastolic blood pressure, NYHA classification, furosemide-equivalent dose, warfarin, ACEIs/ARBs, beta blockers, spironolactone and ΔEF. #Adjusted for age, hospitalization days, hypertension, atrial fibrillation/flutter, hemoglobin, hypoalbuminemia, hyponatremia, creatinine, uric acid, LVEF, NYHA classification, diastolic blood pressure at discharge, furosemide-equivalent dose, hydrochlorothiazide, warfarin, ACEIs/ARBs, beta blockers, spironolactone and ΔEF. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; EF: ejection fraction; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SBP: systolic blood pressure.

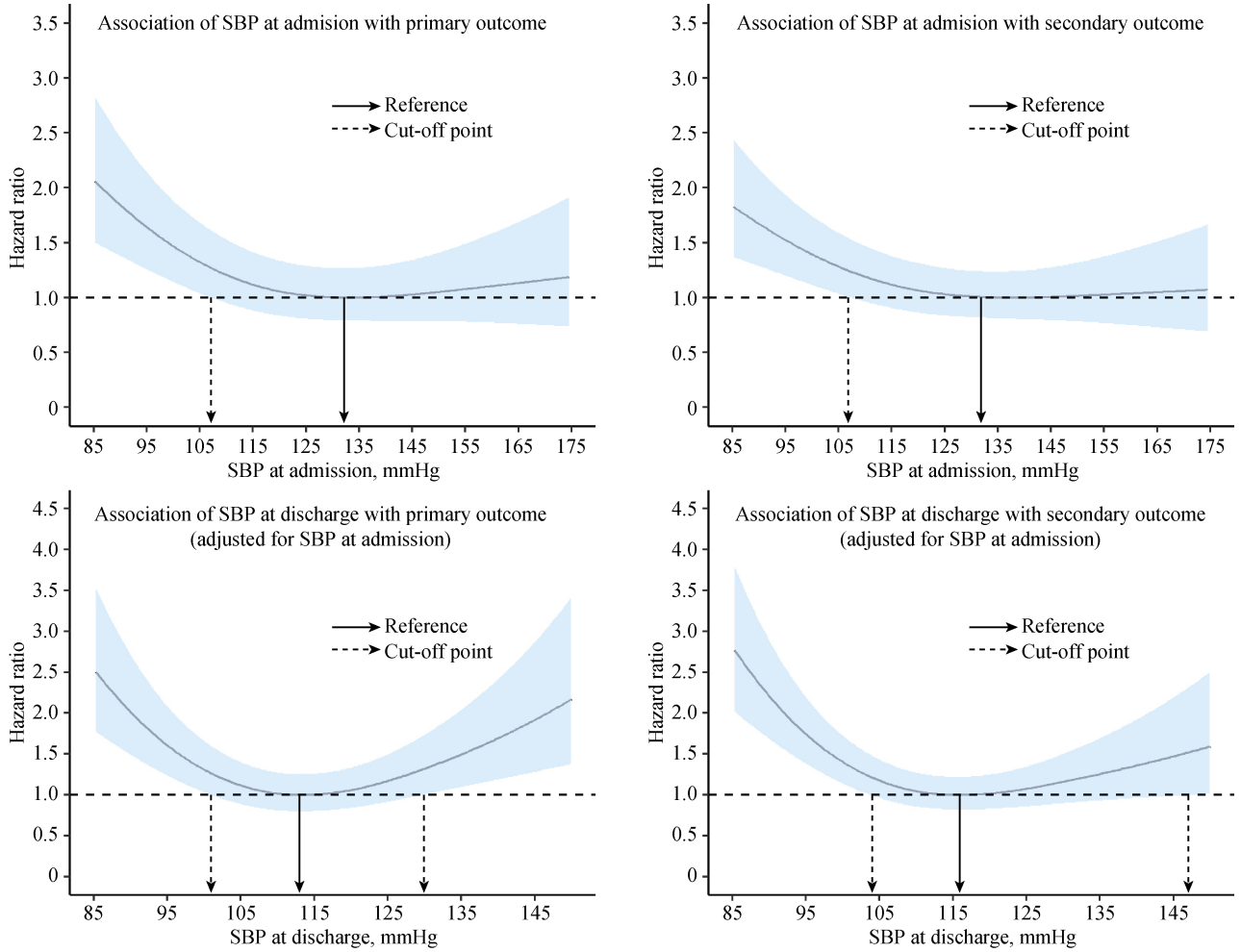

Figure 2. Restricted cubic spline models for outcomes according to SBP. Covariables in models were consistent with those in the corresponding multivariate Cox models. LVEF: left ventricular ejection fraction; SBP: systolic blood pressure.

at admission was lower than 107 mmHg had a higher risk of adverse events. Additionally, we observed a U-shaped association between discharge SBP and CV death/heart transplantation. Those with SBP at discharge lower than 101 mmHg and higher than 130 mmHg both shared a higher risk of CV death/heart transplantation. These results were mostly consistent with those in multivariate Cox analysis.

In subgroup analysis, the associations of SBP at different time points with outcomes in HF patients with or without coronary heart disease, hypertension, diabetes, myocardial infarction, atrial fibrillation/flutter, eGFR < 60 mL/min per 1.73 m^2 and LVEF < 40% were also consistent with the overall cohort results (Figure 3, Figure 4, Supplemental Figures 1 and 2).

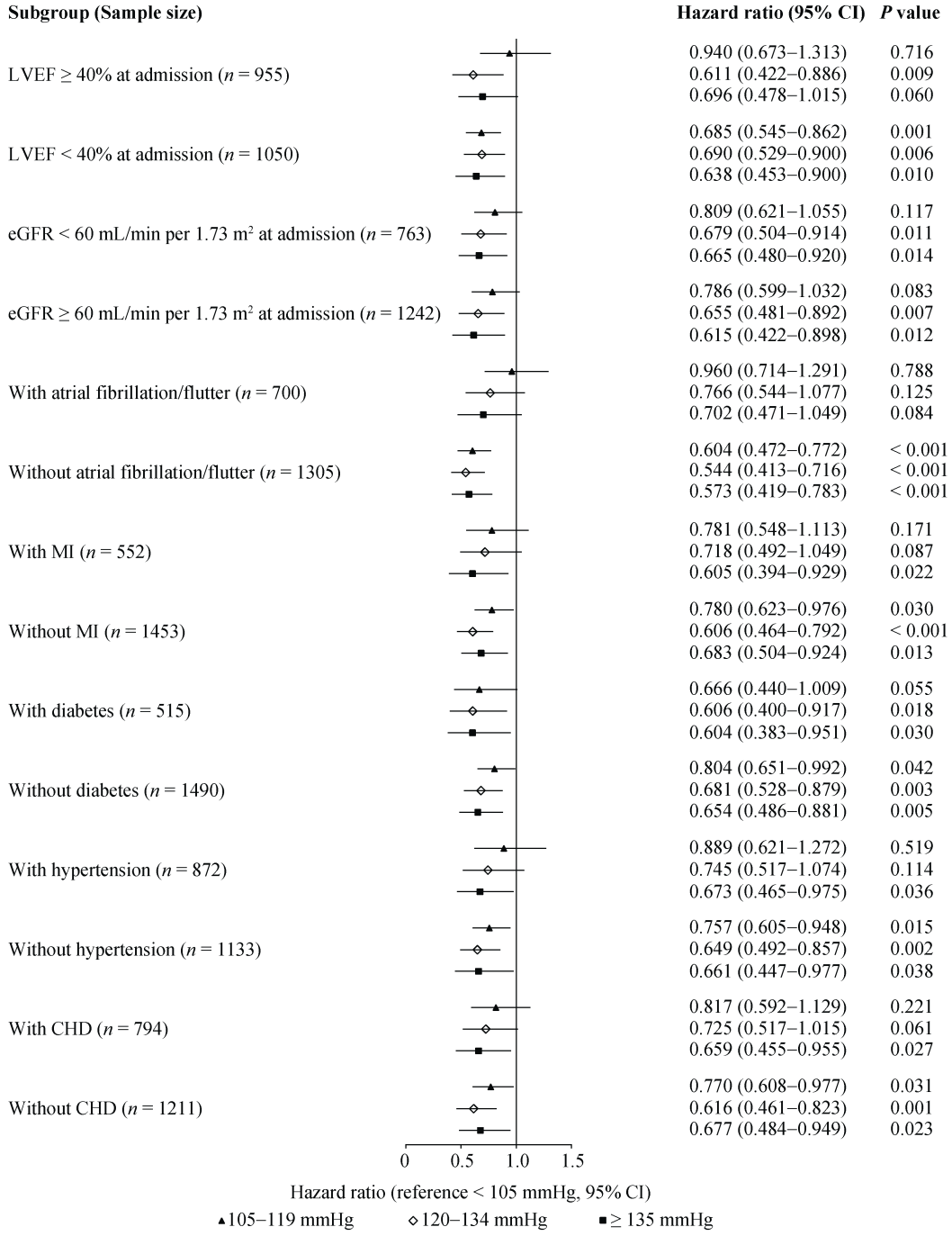

Figure 3. Association between SBP at admission and cardiovascular mortality/heart transplantation. Covariables in models were consistent with those in the corresponding multivariate Cox models. CHD: coronary heart disease; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; MI: myocardial infarction; SBP: systolic blood pressure.

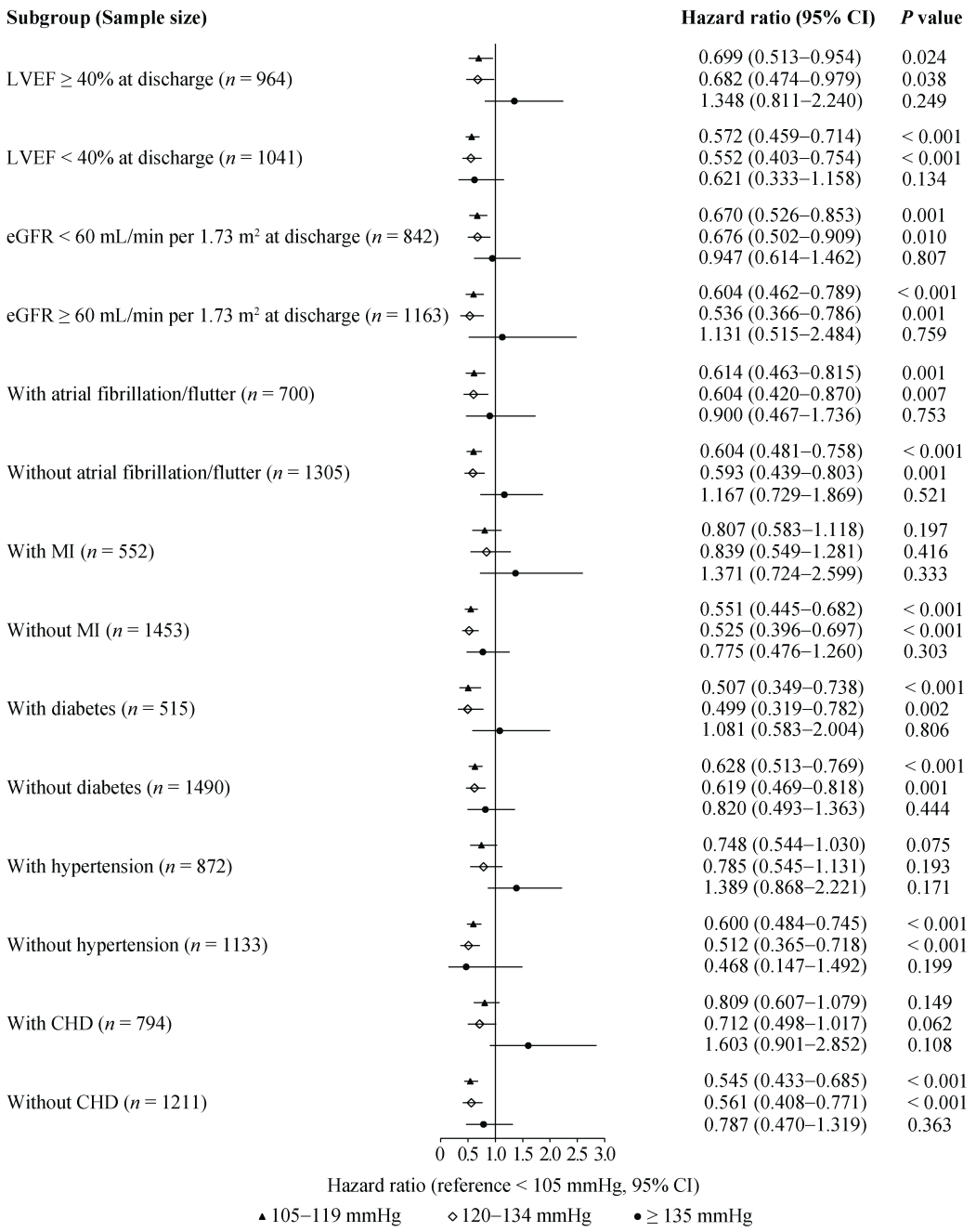

Figure 4. Association between SBP at discharge and cardiovascular mortality/heart transplantation. Covariables in models were consistent with those in the corresponding multivariate Cox models. CHD: coronary heart disease; LVEF: left ventricular ejection fraction; MI: myocardial infarction; SBP: systolic blood pressure.

4 Discussion

Our study was the first to use a hospitalized HF cohort to explore the association of SBP measured at different time points (at admission and at discharge) with long-term post-discharge mortality. Doses of ACEIs/ARBs and beta blockers were used as covariates in multivariate analyses. The characteristics of our cohort were different across SBP categories. In spite of better heart function and higher doses of ACEIs/ARBs, patients with higher SBP at admission suffered from more coronary heart disease, hypertension, diabetes mellitus and cerebrovascular accidents. Consistent with previous studies, our study also showed that HF patients with higher SBP at admission had better outcomes. However, when we assessed the effect of SBP at discharge, we found dramatically different results from the results of

admission SBP. Although patients with higher SBP at discharge were less likely to have dilated cardiomyopathy and more likely to have better heart function and to receive higher doses of ACEIs/ARBs, they tended to have higher rates of poor renal function, coronary heart disease, hypertension, diabetes mellitus and cerebrovascular accidents. After multivariate adjustment, we found that patients with SBP ≥ 135 mmHg shared a similar risk of adverse outcomes as patients with SBP < 105 mmHg (CV death/heart transplantation HR = 0.969, P = 0.867; all-cause death/heart transplantation HR = 1.235, P = 0.291). Restricted cubic spline analyses also showed that patients with discharge SBP < 101 mmHg and ≥ 130 mmHg had higher risks of CV death and heart transplantation.

Like hypertension,[1,2] high-normal SBP (130–139 mmHg)[19] is associated with an increased risk of cardiovascular disease (including HF). Previous clinical trials[3,20,21] have shown that anti-hypertensive treatments can reduce the risk of HF. A recent meta-analysis[5] with stringent criteria of including RCTs with no baseline heart failure also showed a large and highly significant reduction of "new-onset" heart failure after blood pressure lowering. Moreover, the results from the Systolic Blood Pressure Intervention Trial (SPRINT)[4] demonstrated that intensive treatment (SBP less than 120 mmHg) in a non-diabetic population reduced the risk of developing heart failure.

However, in patients who have suffered from HF, the effect of SBP on outcomes remains unclear. The time points of SBP measurement are also different across prior studies. Real-world evidence showed that low SBP at admission was associated with in-hospital death.[22,23] However, the long-term relationship between SBP and mortality is controversial. In a group of incident HF patients,[8] the highest quartile of baseline SBP was associated with a higher rate of adverse events (composite of stroke, major bleeding or death), and restricted cubic spline analysis indicated a slightly U-shaped association for SBP regarding death. OPTIMIZE-HF[9] found that lower SBP at admission was an independent predictor of postdischarge mortality in patients with HF. The results of other studies[10–14] also showed that higher baseline SBP was associated with better outcomes. Recently, Lee, *et al*.[15] discovered that the relationship between on-treatment SBP and all-cause mortality followed a reversed J-curve relationship, and SBP < 100 mmHg at discharge and during follow-up were associated with worse survival in HF patients. However, all these studies did not adjust for the doses of ACEIs/ARBs and beta blockers, which would affect SBP and heart function at the same time.

It is recommended by the current guidelines of the European Society of Cardiology[16] to treat heart failure patients with reduced EF with the maximum tolerated doses of ACEIs/ARBs and beta blockers. Studies showed the superiority of higher doses of ACEIs/ARBs and beta blockers compared with lower doses.[24–26] Physicians may be more aggressive in using ACEIs/ARBs and beta blockers, which also have anti-hypertensive effects in patients with higher blood pressure. In addition, patients with higher SBP may better tolerate higher doses of these agents, which could improve their prognosis. Therefore, in addition to the high rate of use of ACEIs/ARBs and beta blockers, different doses of these agents may mask the effect of SBP on mortality in HF patients, especially in those with high SBP. Notably, ACEIs/ARBs and beta blockers were introduced in previous studies as binary variables. Previous studies ignored the importance of the doses of these agents, which might be a potential confounder between SBP and prognosis in heart failure. We were the first to introduce ACEIs/ARBs and beta blockers as dose-based covariates into a multivariate Cox model, and we found a U-shaped association between discharge SBP and CV mortality/heart transplantation, which was different from the reverse J-shaped relationship between admission SBP and outcomes.

The mechanism of these opposite relationships between the different SBPs and mortality and whether these relationships were consequences or etiological factors for outcomes are unclear. Higher SBP at admission may be related to greater short-term "cardiovascular reserve". This makes such patients able to receive ACEIs/ARBs or beta blockers and tolerate higher doses of these drugs. The effect of these treatments and the better heart function drive an improved prognosis. In contrast, after adjustment for variables at discharge, there was a U-shaped association between discharge SBP and outcomes. It was independent of patient characteristics and was consistent in subgroup analyses. This meant that even high-normal SBP at discharge may also be associated with an increased risk of postdischarge mortality in HF patients. Our result was consistent with the results of a postanalysis of the COMET (Carvedilol Or Metoprolol European Trial) study.[27] In multivariable analysis, the SBP at four months played a more important role in prognosis than baseline SBP, and patients with SBP > 140 mmHg had a similar risk of mortality as those with SBP < 110 mmHg. This phenomenon may be due to heavy afterload on the heart over a long period of time. Notably, we found that the SBP of most patients in the highest quartile at admission declined to 105–134 mmHg (79.8%) at discharge from the hospital, and only 12.4% stayed at ≥ 135 mmHg. This was consistent with the data of OPTIMIZE-HF,[9] where the mean SBP at discharge was 128 mmHg in the third admis-

sion SBP quartile (140–161 mmHg) and 138 mmHg in the highest quartile (> 161 mmHg). Obviously, the majority of patients with high SBP at admission eventually had their SBP decline to a normal range. This may explain the different associations with outcomes between high admission SBP and high discharge SBP.

Our study provides new insights into the relationship between SBP and mortality in HF patients. First, the SBP at admission usually reflects the "cardiovascular reserve" in the decompensated phase (the higher SBP at admission, the greater "cardiovascular reserve"). This explains why HF patients with higher SBP at admission have a better prognosis.

Second, HF patients with uncontrolled hypertension at discharge (in our study SBP ≥ 135 mmHg) also had a similar risk of mortality as those with the lowest quartile SBP (in our study SBP < 105 mmHg). In patients with systolic dysfunction and/or heart failure, higher SBP has been associated with higher stroke risk.[14] The harm of hypertension in HF patients was likely to be immerged into those with high admission SBP because most of these patients had normal SBP at discharge (in our study SBP 105–134 mmHg).

We should be aware of the necessity of anti-hypertension treatment in HF patients during hospitalization and after discharge from the hospital. The proposed anti-hypertension strategy was geared toward preserving systolic function in HFrEF or toward improving diastolic dysfunction in heart failure with preserved ejection fraction (HFpEF) and heart failure with mid-range reduced ejection fraction (HFmrEF). ACEIs/ARBs, beta blockers, angiotensin receptor–neprilysin inhibitors, MRAs and diuretics are the first-line agents to control blood pressure in HFrEF.[7] Nondihydropyridine CCBs and moxonidine should be avoided in patients with HFrEF. If blood pressure was not controlled with an ACEI/ARB, a beta blocker, an MRA and a diuretic, then hydralazine and amlodipine (or felodipine) are recommended agents that have been shown to be safe in HFrEF.[16] Circumstantial evidence has shown that treating hypertension is important in HFmrEF/HFpEF.[16] ACEIs/ARBs, MRAs and diuretics all appear to be appropriate agents, but beta blockers might be less effective in reducing SBP.[16] Patients with HFrEF and hypertension should attain a blood pressure of less than 130/80 mmHg, and SBP of less than 130 mmHg was a recommend for patients with HFpEF and persistent hypertension.[7]

Several limitations of this study should be acknowledged. First, this was a single-center, retrospective study, and many unmeasured variables could have had residual confounding bias. Second, the exclusion of those patients without follow-up data might have affected our results. Third, despite adjustment of the doses of ACEIs/ARBs and beta blockers, the doses of these agents might change after discharge, and the SBP during follow-up could vary as the treatment and patient condition change. Additionally, the BP measurement was not strictly measured at standardized time intervals), and this might have affected the results of our study. Last, the results of our study were based on hospitalized patients with decompensated HF, and they might not be generalizable to ambulatory patients who manifest with acute decompensation or chronic HF with good titration of ACEIs/ARBs and beta blockers.

In conclusion, SBP measured at different time points (at admission and at discharge) has different associations with postdischarge outcomes. Lower but not higher SBP at admission is associated with more cardiovascular deaths/heart transplantations (a reverse J-shaped curve). In contrast, there is a U-shaped association between discharge SBP and cardiovascular deaths/heart transplantations. Patients with SBP ≥ 135 mmHg have a similar risk of cardiovascular death/heart transplantation as patients whose SBP < 105 mmHg. Blood pressure management remains an important issue to be addressed, and further studies are needed to evaluate the relationship among blood pressure, doses of drugs that would reduce blood pressure but improve the prognosis, and outcomes in HF patients.

Acknowledgment

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Supplementary materials

Table 1. Characteristics of patients with follow-up and without follow-up.

	Follow-up (*n* = 2005)	Without Follow-up (*n* = 139)	*P* value
Male	69.9%	77%	0.076
Age, years	59 (48, 69)	59 (47, 68)	0.802
Hospitalization days	12 (9, 18)	12 (8, 17)	0.620
CHD	39.6%	41%	0.743
HTN	43.5%	41%	0.568
AF or atrial flutter	34.9%	38.1%	0.442
DM	25.7%	30.9%	0.173
DCM	26.2%	26.6%	0.910
PH	14.9%	12.9%	0.528
CE	12.2%	19.4%	0.013
MI	27.5%	31.7%	0.294
At admission			
NYHA classification			0.015
II	20.8%	16.5%	
III	51.1%	43.9%	
IV	28.1%	39.6%	
SBP, mmHg	118 (105, 132)	117 (103, 131)	0.350
SBP quartile			0.510
< 105 mmHg	23.8%	28.1%	
105–119 mmHg	28.5%	29.5%	
120–134 mmHg	25.9%	20.9%	
≥ 135 mmHg	21.7%	21.6%	
DBP, mmHg	71 (63, 80)	71 (61, 80)	0.646
Heart rate, beats/min	81 (70, 94)	82 (68, 96)	0.825
Hb, g/L	137 (124, 151)	140 (125, 154)	0.344
hypoproteinemia	8.9%	8.6%	0.922
hypoalbuminemia	14.4%	15.1%	0.822
hypokalemia	11.2%	13.7%	0.369
hyponatremia	19.7%	24.5%	0.170
Cr, umol/L	93.5 (79.25, 115.12)	100.1 (78.8, 122.0)	0.088
eGFR, mL/min per 1.73 m^2	67.2 (49.16, 89.35)	63.27 (45.47, 80.43)	0.078
eGFR < 60 mL/min per 1.73 m^2	39.5%	48.2%	0.043
BUN, mmol/L	7.4 (5.7, 9.765)	8.0 (6.3, 10.6)	0.048
UA, μmol/L	417.3 (327.55, 519.45)	475.0 (323.9, 581.3)	0.019
TG, mmol/L	1.35 (1.00, 1.89)	1.48 (1.05, 1.80)	0.283
TC, mmol/L	4.15 (3.435, 4.98)	4.18 (3.44, 4.98)	0.627
HDL, mmol/L	0.97 (0.81, 1.19)	0.95 (0.76, 1.18)	0.244
LDL, mmol/L	2.48 (1.96, 3.12)	2.57 (2.08, 3.15)	0.390
LVEF, %	38 (30, 53)	36 (28, 49)	0.028
LVEF ≥ 40%	47.6%	39.6%	0.660
At discharge			
BMI, kg/m^2	23.05(20.44, 25.78)	22.64(19.24, 25.56)	0.054
Hb, g/L	134 (115, 150)	137 (121, 151)	0.252
Anemia	24.9%	19.4%	0.150
hypoproteinemia	8.2%	9.4%	0.627
hypoalbuminemia	18.1%	18.0%	0.984

Table 1. Cont.

	Follow-up (*n* = 2005)	Without Follow-up (*n* = 139)	*P* value
hyponatremia	16.8%	18.7%	0.553
Cr, umol/L	96.4 (78.5, 117.85)	96.8 (79.8, 129.7)	0.225
eGFR [mL/(min·1.73 m^2)]	67.32 (47.50, 89.51)	61.79 (43.28, 84.11)	0.115
eGFR < 60 mL/(min·1.73 m^2)	40.2%	46.0%	0.179
BUN, mmol/L	8.6 (6.6, 11.64)	9.8 (6.92, 13.61)	0.004
UA, umol/L	403.7 (308.45, 500.55)	449.5 (327.35, 567.9)	0.004
LVEF, %	38 (30, 55)	36 (28, 50)	0.033
LVEF ≥ 40%	48.1%	41.0%	0.106
ΔEF, %	0 (–2, 3)	0 (–2, 5)	0.581
SBP, mmHg	110 (101, 120)	109 (100, 118)	0.025
SBP quartile			0.026
< 105, mmHg	30.4%	41.7%	
105–119 mmHg	42.1%	33.8%	
120–134 mmHg	23.6%	23.0%	
≥ 135 mmHg	3.9%	1.4%	
DBP, mmHg	68 (60, 70)	68 (60, 70)	0.932
Heart rate, beats/min	71 (65, 79.5)	72 (65, 80)	0.223
ACEI/ARB			0.866
None	45.3%	44.6%	
< 50%	32.3%	35.3%	
50%–99%	15.7%	13.7%	
≥ 100%	6.7%	6.5%	
Beta blocker			0.612
None	17.0%	14.4%	
< 50%	55.8%	59.7%	
50%–99%	21.6%	22.3%	
≥ 100%	5.5%	3.6%	
Spirolactone	71.6%	71.2%	0.930
Loop diuretics	91.1%	92.1%	0.684
Furosemide equivalent, mg/day	40 (20, 40)	40 (20, 40)	0.125
CCB	9.8%	7.2%	0.310
Thiazide diuretic	3.3%	2.9%	0.768
Digoxin	59.3%	64.0%	0.267
Warfarin	26.2%	19.4%	0.076
Statin	41.8%	38.8%	0.496

CHD, coronary heart disease; HTN, hypertension; AF, atrial fibrillation; DM, diabetes mellitus; DCM, dilated cardiomyopathy; PH, pulmonary hypertension; CE, cerebrovascular accident; MI, myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; Cr, creatinine; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; UA, uric acid; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

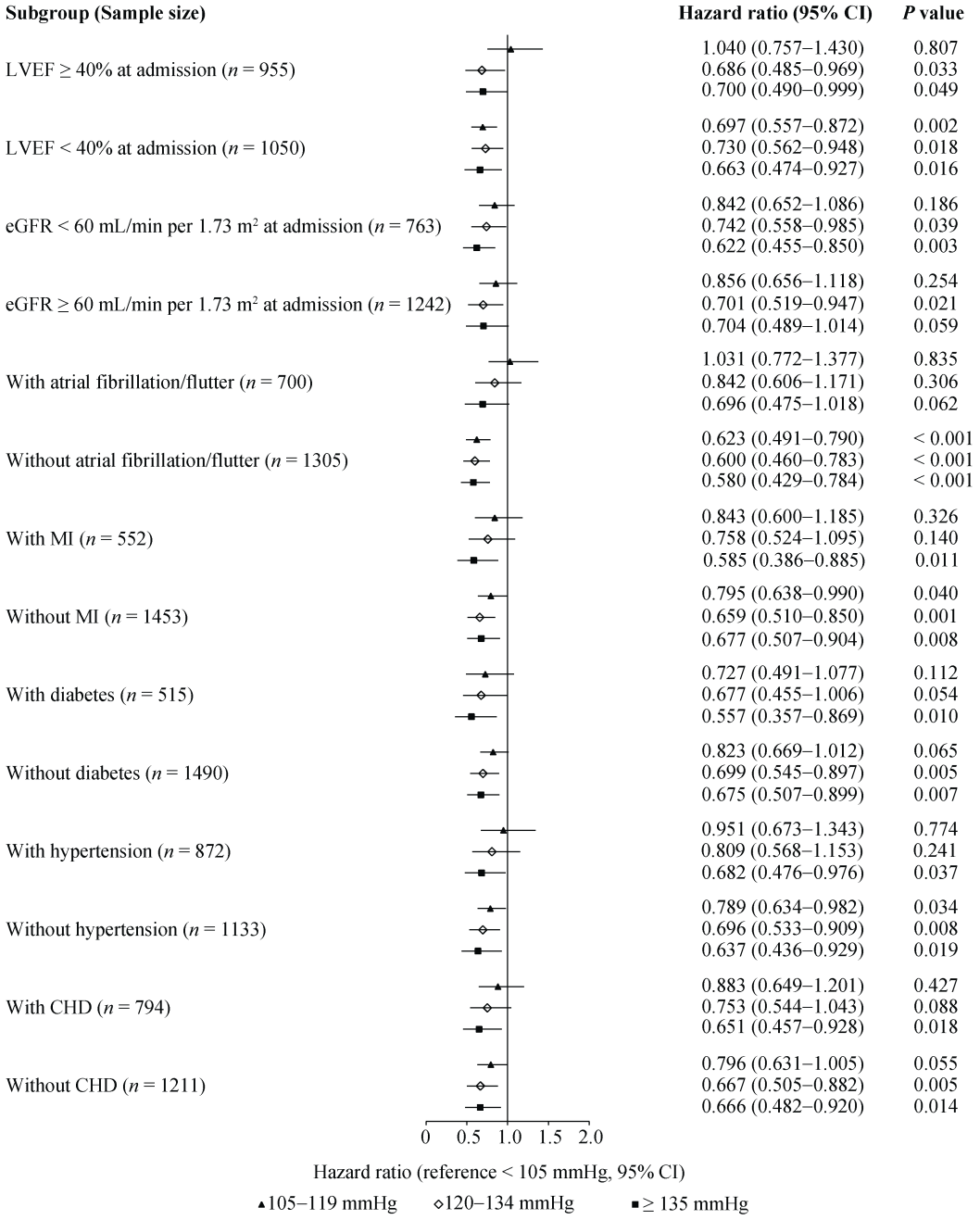

Figure 1. Association between SBP at admission and all-cause mortality/heart transplantation. SBP, systolic blood pressure.

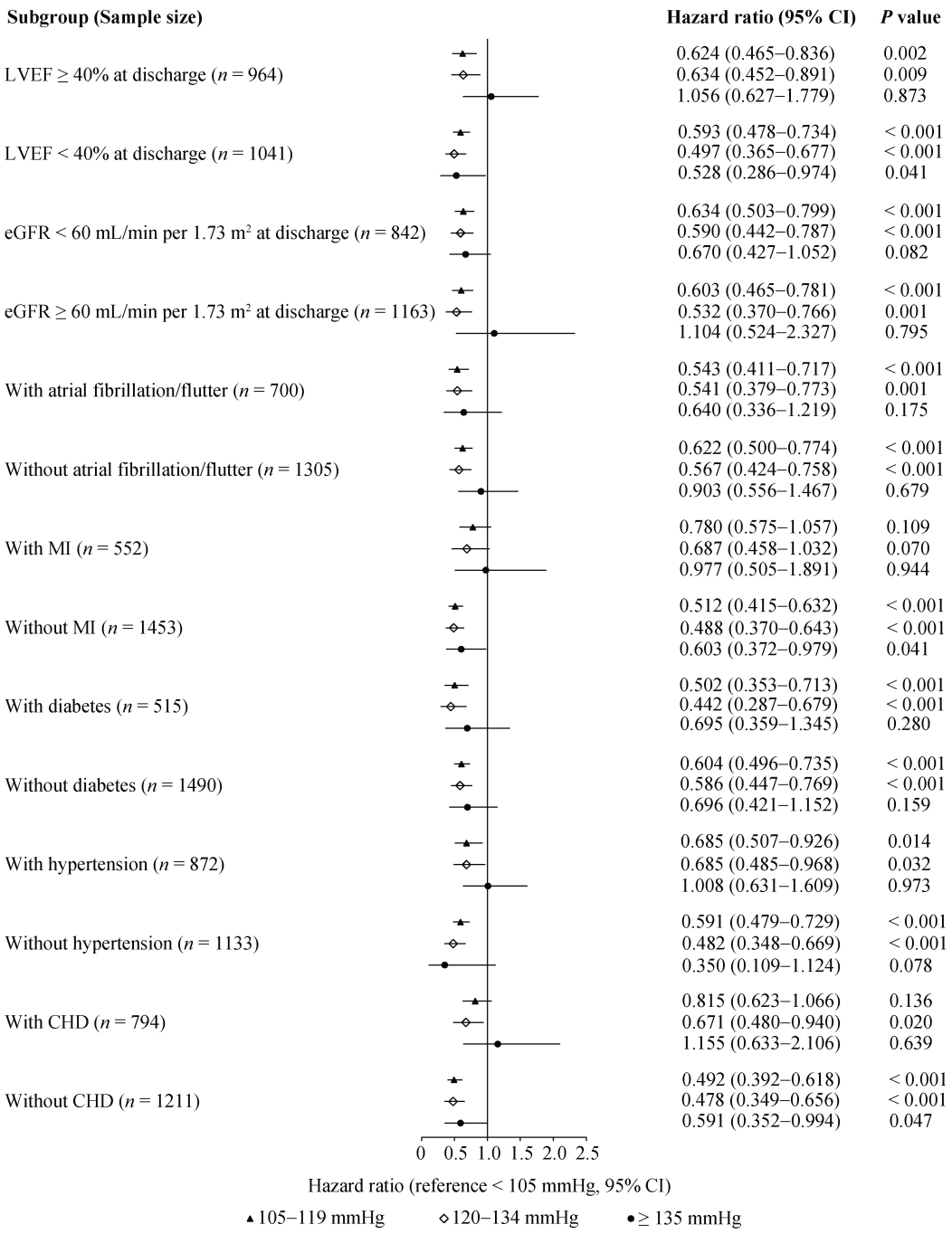

Figure 2. Association between SBP at discharge and all-cause mortality/heart transplantation.