Systolic blood pressure at admission and long-term clinical outcomes in patients hospitalized for heart failure

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Abstract

Aims The study sought to investigate the association between admission systolic blood pressure (SBP) and 1-year clinical outcomes in patients hospitalized for heart failure (HF) and in subgroups.

Methods This study was based on the China Patient-centred Evaluative Assessment of Cardiac Events Prospective Heart Failure Study, which prospectively enrolled patients hospitalized for HF in 52 hospitals from 20 provinces in China between August 2016 and May 2018. Patients were divided into four groups according to the quartiles of SBP at admission. The multivariable Cox proportional hazards regression models were fitted to examine the association between admission SBP and all-cause death and HF readmission within 1 year after the index hospitalization. Restricted cubic splines were used to explore the non-linear association between SBP and the clinical outcomes.

Results Among 4896 patients, those with lower admission SBP were younger, more likely to be male, have left ventricular ejection fraction <40%, and receive β-blockers, aldosterone antagonists, and diuretics. After adjustment for potential confounders, lower admission SBP was significantly associated with higher all-cause death and there is no threshold, while we only observed such an association with HF readmission when admission SBP was lower than 120 mmHg. Compared with the 4th SBP quartile, patients in the 1st SBP quartile had higher risk of all-cause death (hazard ratio, 1.85; 95% confidence interval 1.48–2.33; P < 0.001) and HF readmission (hazard ratio, 1.40; 95% confidence interval 1.19–1.65, P < 0.001). These associations were consistent in most subgroups, such as age, sex, and left ventricular ejection fraction.

Conclusions In patients hospitalized for HF, lower admission SBP portends an increased risk of 1 year all-cause death and HF readmission, and these associations were consistent among subgroups.

Keywords Heart failure; Blood pressure; Heart failure readmission; Death; China

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Introduction

Heart failure (HF) is a global major public health problem due to its high prevalence and poor prognosis.¹ Approximately 64.3 million people suffer from HF globally, and the prevalence is increasing with extended longevity, high prevalence of risk factors, and improved survival in those with cardiovascular disease.¹² High blood pressure is associated with an increased risk of the development of HF, and about 50% of patients admitted to hospital for HF have elevated systolic blood pressure (SBP).⁷,⁸ Patients hospitalized for HF are at high risk for all-cause death and HF readmission.⁹,¹⁰ It is important to understand the association between SBP at admission and long-term outcomes of HF patients.

Previous studies demonstrated that acute HF patients with lower admission SBP had higher risk of short-term death,; however, inconsistent results have been found in the association between admission SBP and long-term...
death, particularly whether the continuous relationship between lower admission SBP and higher mortality exists without upper threshold.6,13–16 Despite the high frequency of HF readmission, little is known about the association between admission SBP and HF readmission during the first year after the index hospitalization.14,17 Besides, patients with HF is a heterogeneous population and some studies indicated discrepancy in the association between admission SBP and prognosis among important subgroups [e.g. left ventricular ejection fraction (LVEF), diabetes, and age], which requires further investigation.6,14–17

To address this issue, we examined the association between admission SBP and 1 year clinical outcomes in a large prospective multicentre cohort of patients hospitalized for HF, and the associations in important subgroups as well.

Methods

Study design and population

We established a nationwide prospective cohort of acute HF, the China Patient-centered Evaluative Assessment of Cardiac Events Prospective Heart Failure Study (China PEACE 5p-HF Study), from 52 hospitals located in 20 provinces, covering all economic-geographic regions in China; the study design has been published before.18 Patients were eligible if they were aged 18 years or older, local residents, and hospitalized primarily for new-onset HF or decompensation of chronic HF. Between August 2016 and May 2018, we consecutively screened eligible patients and enrolled them if they signed informed consent to participate the study within 48 h of admission. We interviewed enrolled patients to collect data during the index hospitalization and at 1 month, 6 months, and 1 year after discharge.

The China PEACE 5p-HF study was approved by the ethics committees of Fuwai Hospital and all collaborating hospitals. The study protocol was registered on ClinicalTrials.gov (number: NCT02878811).

Data collection

We collected information on demographic characteristics, socio-economic characteristics, smoking status, and self-reported health status using a standardized questionnaire through face-to-face interview by trained local clinicians during index hospitalization. Data were directly entered into laptop computers equipped with a customized electronic data collection system to allow real-time off-line logic checks to verify the accuracy and completeness of entered data. We obtained clinical status, comorbidities, and medications through central medical record abstraction. LVEF was measured during hospitalization by trained clinicians according to the standard echocardiogram protocol. Laboratory test of serum creatinine, HbA1c, low-density lipoprotein cholesterol, and N-terminal pro-brain natriuretic peptide (NT-proBNP) were based on central laboratory tests (i.e. tests of blood and urine samples taken within 48 h of admission) or local laboratory tests at admission if central laboratory tests were unavailable (missing rate <7%); haemoglobin was based on local admission laboratory test results.

If patients had HF for some time and chronic stable HF deterioration led to the admission, they were considered as decompensation of chronic HF; others were considered as new-onset HF. Coronary heart disease, hypertension, diabetes, chronic obstructive pulmonary disease, valvular heart disease, stroke, atrial fibrillation, reduced renal function, and anaemia were defined according to medical history, discharge diagnosis, or positive laboratory test results. The diagnosis criteria of laboratory tests of anaemia (haemoglobin <120 g/L in men or <110 g/L in women), reduced renal function (estimated glomerular filtration rate <60 mL/min/1.73 m²), and diabetes (HbA1c ≥ 6.5%) were defined. Self-reported health status was evaluated during index hospitalization by the summary score of the short version of the Kansas City Cardiomyopathy Questionnaire, with scores ranging from 0 to 100 (lower score indicating poorer health status).

Outcomes

Two clinical outcomes were evaluated: all-cause death and HF readmission within 1 year after the index hospitalization. We collected information on clinical outcomes through follow-up interviews and searching the national death cause database in China. Potential outcome events were centrally adjudicated based on medical records by trained clinicians at the national coordinating centre.

Statistical analysis

Patient characteristics were described using mean ± standard deviation, median (interquartile range), or frequency (percentage) as appropriate. Patients were categorized into quartiles by admission SBP (<117, 117–130, 131–148, and >148 mmHg). We evaluated the differences in baseline characteristics of patients among the SBP groups using the one-way analysis of variance for normal distributed continuous variables, the Kruskal–Wallis test for skewed distributed continuous variables, and the chi-square test for categorical variables.

Kaplan–Meier survival analysis was used to compare cumulative risk of outcomes. Differences in outcomes across SBP groups were evaluated using the log-rank test. The associations between SBP and outcomes were estimated with Cox
proportional hazards regression models, adjusting demo-
graphic characteristics (age and sex), socio-economic status
(marital status and education level), clinical characteristics
at admission (body mass index, heart rate, New York Heart
Association functional class, LVEF, and HF type), current
smoking, comorbidities (coronary heart disease, hyperten-
sion, diabetes, chronic obstructive pulmonary disease, valvu-
lar heart disease, stroke, atrial fibrillation, reduced renal
function, and anaemia), laboratory test results at admission
(low-density lipoprotein cholesterol, NT-proBNP), medications
before admission [angiotensin-converting enzyme in-
hibitors (ACEIs), angiotensin receptor blockers (ARBs),
β-blockers, aldosterone antagonists, and diuretics], medica-
tions during hospitalization (ACEIs, ARBs, β-blockers, aldoste-
rone antagonists, diuretics, digoxin, and nitrates), and Kansas
City Cardiomyopathy Questionnaire sum score. Restricted cu-
ic splines were used to explore the non-linear association
between SBP and the clinical outcomes. Four knots were
placed at the 5th, 35th, 65th, and 95th percentiles (at 97,
121, 140, and 180 mmHg, respectively).

We conducted subgroup analyses to assess the homogene-
ity of the association between SBP and outcomes in clinical
important subgroups, including sex (male or female), age (<65 or
≥65 years), LVEF (<40%, 40–49%, or ≥50%), HF type (new-onset
HF or decompensation of chronic HF), NT-proBNP (<median or ≥median), diabetes (yes or no), atrial fibrillation (yes or no), coronary heart disease (yes or no), valvular heart dis-
ease (yes or no), prescriptions of ACEIs/ARBs (yes or no),
β-blockers (yes or no), and aldosterone antagonists (yes or no).

Variables with missing values (e.g. NT-proBNP and Kansas
City Cardiomyopathy Questionnaire score) were imputed
using the multiple imputation method with 20 imputations,
and the final imputed value was the average of the 20 impu-
tations. NT-proBNP had the highest missing rates (112, 2.3%).

All analyses were performed with SAS (9.4, SAS institute,
Cary, North Carolina, USA). All the tests of significance were
two sided, and an alpha level of less than 0.05 indicated sta-
tistical significance for all analysis.

Results

Baseline characteristics

In this study, we excluded patients without admission SBP
(n = 2) or patients discharged alive but not attending follow
up interview (n = 9), and a total of 4896 patients were in-
cluded in the current study (Figure 1). The mean age of pa-
tients was 65.2 ± 13.5 years, 37.6% were female, and 70.7%
were decompensated chronic HF. Compared with patients
with higher admission SBP, those with lower admission SBP
were younger, more likely to be male, LVEF <40%, and have
lower creatinine; while they were less likely to be new-onset
HF, and have history of coronary heart disease, hypertension,
diabetes, reduced renal function, and stroke. Prescriptions of
β-blockers, aldosterone antagonists, diuretics, and digoxin
during hospitalization were more often observed in the lower
SBP quartiles, whereas ACEIs/ARBs and nitrates were less
prescribed (Table 1).

Admission systolic blood pressure and clinical
outcomes

Within 1 year after the index hospitalization, 856 (17.5%) pa-
tients died and 1560 (31.9%) had HF readmission. Cumulative
risks for 1 year all-cause death and HF readmission by SBP
groups were shown in Figure 2. Of patients with SBP in the
Table 1  Baseline characteristics of patients by systolic blood pressure quartiles

|                      | Total      | Q1 (SBP <117 mmHg) | Q2 (SBP 117–130 mmHg) | Q3 (SBP 131–148 mmHg) | Q4 (SBP >148 mmHg) | P value |
|----------------------|------------|---------------------|-----------------------|-----------------------|--------------------|---------|
| **Demographics**     |            |                     |                       |                       |                    |         |
| Age (years)          | 65.2 ± 13.5| 61.3 ± 13.8         | 65.3 ± 12.7           | 66.6 ± 12.9           | 67.5 ± 13.5        | <0.001  |
| Female               | 1843 (37.6)| 416 (33.7)          | 358 (35.3)            | 560 (40.1)            | 509 (40.7)         | <0.001  |
| **Socio-economic status** |          |                     |                       |                       |                    |         |
| Education level      |            |                     |                       |                       |                    | 0.043   |
| Illiterate/primary school | 519 (10.6)| 161 (13.1)          | 98 (9.7)              | 143 (10.2)            | 117 (9.4)          |         |
| Junior/senior high school | 2185 (44.6)| 554 (44.9)         | 476 (46.9)            | 599 (42.9)            | 556 (44.4)         |         |
| College/postgraduate | 2041 (41.7)| 481 (39.0)          | 408 (40.2)            | 614 (44.0)            | 538 (43.0)         |         |
| Unknown              | 151 (3.1)  | 36 (2.9)            | 33 (3.3)              | 41 (2.9)              | 41 (3.3)           |         |
| Marital status       |            |                     |                       |                       |                    | <0.001  |
| Married              | 3830 (78.2)| 1007 (81.7)         | 809 (79.7)            | 1079 (77.2)           | 935 (74.7)         |         |
| Divorced/separated/widowed | 838 (17.1)| 161 (13.1)          | 158 (15.6)            | 261 (18.7)            | 258 (20.6)         |         |
| Single               | 228 (4.7)  | 64 (5.2)            | 48 (4.7)              | 57 (4.1)              | 59 (4.7)           |         |
| **Clinical status**  |            |                     |                       |                       |                    |         |
| Medical history      |            |                     |                       |                       |                    |         |
| Hypertension         | 2857 (58.4)| 382 (31.0)          | 491 (48.4)            | 898 (64.3)            | 1086 (86.7)        | <0.001  |
| Coronary heart disease | 2840 (58.0)| 571 (45.9)          | 582 (57.3)            | 875 (62.6)            | 812 (64.9)         | <0.001  |
| Diabetes             | 1539 (31.4)| 305 (24.7)          | 296 (29.2)            | 473 (33.9)            | 465 (37.2)         | <0.001  |
| Chronic obstructive pulmonary disease | 953 (19.5) | 207 (16.8)          | 202 (19.9)            | 305 (21.8)            | 239 (19.1)         | 0.013   |
| Valvular heart disease | 800 (16.3)| 252 (20.4)          | 201 (19.8)            | 215 (15.4)            | 132 (10.6)         | <0.001  |
| Stroke               | 1002 (20.4)| 196 (15.9)          | 172 (17.0)            | 297 (21.3)            | 337 (26.9)         | <0.001  |
| Atrial fibrillation  | 1783 (36.4)| 484 (39.3)          | 416 (41.0)            | 521 (37.3)            | 362 (28.9)         | <0.001  |
| Anaemia              | 1150 (23.5)| 276 (22.4)          | 219 (21.6)            | 323 (23.1)            | 332 (26.5)         | 0.025   |
| Reduced renal function | 1419 (29.0)| 311 (25.2)          | 262 (25.8)            | 387 (27.7)            | 459 (36.7)         | <0.001  |
| SBP at admission (mmHg) | 133.2 ± 24.7 | 104.5 ± 8.7       | 122.3 ± 3.3           | 137.1 ± 5.3           | 165.9 ± 16.6       | <0.001  |
| DBP at admission (mmHg) | 81.0 ± 16.0 | 69.5 ± 10.0        | 76.5 ± 11.0           | 83.0 ± 12.7           | 93.8 ± 17.5        | <0.001  |
| HR at admission (beats/min) | 89.3 ± 22.4 | 89.8 ± 23.2       | 88.2 ± 21.7           | 89.7 ± 22.2           | 89.5 ± 22.4        | 0.285   |
| NYHA class at admission |            |                     |                       |                       |                    | <0.001  |
| II                   | 705 (14.4) | 152 (12.3)          | 172 (16.9)            | 203 (14.5)            | 178 (14.2)         |         |
| III                  | 2163 (44.2)| 519 (42.1)          | 498 (49.1)            | 640 (45.8)            | 506 (40.4)         |         |
| IV                   | 2028 (41.4)| 561 (45.5)          | 345 (34.0)            | 554 (39.7)            | 568 (45.4)         |         |
| LVEF type            |            |                     |                       |                       |                    | <0.001  |
| LVEF<40%             | 1850 (37.8)| 641 (52.0)          | 390 (38.4)            | 494 (35.4)            | 325 (26.0)         |         |
| LVEF 40–49%          | 1041 (21.3)| 229 (18.6)          | 226 (22.3)            | 296 (21.2)            | 290 (23.2)         |         |
| LVEF ≥50%            | 1706 (34.8)| 297 (24.1)          | 341 (33.6)            | 518 (37.1)            | 550 (43.9)         |         |
| Unmeasured           | 299 (6.1)  | 65 (5.3)            | 58 (5.7)              | 89 (6.4)              | 87 (6.9)           |         |
| HF type              |            |                     |                       |                       |                    | <0.001  |
| New-onset HF         | 1440 (29.4)| 277 (22.5)          | 250 (24.6)            | 428 (30.6)            | 485 (38.7)         |         |
| Decompensated chronic HF |          |                     |                       |                       |                    |         |
| Hospitalized in prior half year | 458 (9.4) | 143 (11.6)          | 106 (10.4)            | 115 (8.2)             | 94 (7.5)           |         |
| Without hospitalization in prior half year | 2998 (61.3)| 812 (65.9)        | 659 (64.9)            | 854 (61.1)            | 673 (53.8)         |         |
| Body mass index (kg/m²) |            |                     |                       |                       |                    | <0.001  |
| <18.5                | 343 (7.0)  | 127 (10.4)          | 65 (6.4)              | 86 (6.2)              | 65 (5.2)           |         |
| 18.5–23.9            | 1954 (39.9)| 541 (43.9)          | 430 (42.4)            | 549 (39.3)            | 434 (34.7)         |         |

(Continues)
Table 1 (continued)

|                          | Total     | Q1 (SBP <117 mmHg) | Q2 (SBP 117–130 mmHg) | Q3 (SBP 131–148 mmHg) | Q4 (SBP >148 mmHg) | P value |
|--------------------------|-----------|--------------------|-----------------------|-----------------------|-------------------|---------|
| ≥24                      | 2206 (45.1)| 470 (38.1)         | 445 (43.8)            | 647 (46.3)            | 644 (51.5)        | -       |
| Unmeasured               | 393 (8.0) | 94 (7.6)           | 75 (7.4)              | 115 (8.2)             | 109 (8.7)         | -       |
| Current smoking          | 1224 (25.0)| 323 (26.2)         | 252 (24.8)            | 354 (25.3)            | 295 (23.6)        | 0.483   |
| Central laboratory tests |           |                    |                       |                       |                   |         |
| NT-proBNP (pg/mL)        | 1487.0 (605.4, 3325.5)| 1901.0 (881.0, 3821.0) | 1323.0 (565.6, 3212.0) | 1369.0 (549.1, 3130.0) | 1321.0 (544.2, 3181.0) | <0.001  |
| Creatinine (μmol/L)      | 102.4 ± 63.2| 94.9 ± 39.6         | 96.3 ± 53.0           | 100.3 ± 57.4          | 117.2 ± 88.4      | <0.001  |
| Medication before admission |        |                    |                       |                       |                   |         |
| ACEIs/ARBs               | 1720 (35.2)| 434 (35.2)         | 338 (33.3)            | 503 (36.0)            | 445 (35.6)        | 0.560   |
| β-blockers               | 2080 (42.5)| 617 (50.1)         | 458 (45.1)            | 581 (41.6)            | 424 (33.9)        | <0.001  |
| Aldosterone antagonists  | 1820 (37.2)| 681 (55.2)         | 422 (41.6)            | 455 (32.6)            | 262 (20.9)        | <0.001  |
| Diuretics                | 999 (20.4)| 370 (30.0)         | 237 (23.3)            | 250 (17.9)            | 142 (11.4)        | <0.001  |
| Medication during hospitalization |        |                    |                       |                       |                   |         |
| ACEIs/ARBs               | 3288 (67.2)| 741 (60.1)         | 636 (62.7)            | 967 (69.2)            | 944 (75.5)        | <0.001  |
| β-blockers               | 3609 (73.7)| 949 (77.0)         | 760 (74.9)            | 1017 (72.8)           | 883 (70.5)        | 0.002   |
| Aldosterone antagonists  | 4075 (83.2)| 1076 (87.3)        | 855 (84.2)            | 1163 (83.2)           | 981 (78.4)        | <0.001  |
| Diuretics                | 4302 (87.9)| 1119 (90.8)        | 885 (87.2)            | 1224 (87.6)           | 1074 (85.8)       | 0.001   |
| Digoxin                  | 1640 (33.5)| 546 (44.3)         | 373 (36.7)            | 425 (30.4)            | 296 (23.7)        | <0.001  |
| Nitrates                 | 3039 (62.1)| 655 (53.1)         | 600 (59.1)            | 936 (67.0)            | 848 (67.7)        | <0.001  |
| Self-reported health status |        |                    |                       |                       |                   |         |
| KCCQ score               | 44.0 ± 22.8| 42.7 ± 22.5         | 44.5 ± 22.7           | 43.7 ± 23.1           | 45.2 ± 22.8       | 0.038   |

Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; LDL-C, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.
Figure 2. Kaplan–Meier plots for all-cause death (A) and heart failure readmission (B) by systolic blood pressure quartiles. This study assessed the association of admission systolic blood pressure with outcomes in patients hospitalized with heart failure. Patients were categorized into quartiles by admission systolic blood pressure (<117, 117–130, 131–148, >148 mmHg) for analysis. During 1 year follow up, patients in the 1st systolic blood pressure quartile had higher event rates of all-cause death and heart failure readmission than those in other systolic blood pressure quartiles.

After adjusting covariates, the associations between SBP and 1-year clinical outcomes were slightly attenuated but still significant (Table 2). Compared with the 4th SBP quartile, the adjusted hazard ratios (HR) for all-cause death were 1.85 [95% confidence interval (CI) 1.48–2.33; \( P < 0.001 \)] for the 1st SBP quartile, 1.50 [95% CI 1.19–1.89; \( P < 0.001 \)] for the 2nd SBP quartile (SBP of 117–130 mmHg), and 1.30 [95% CI 1.05–1.60; \( P = 0.015 \)] for the 3rd SBP quartile (SBP of 131–148 mmHg). For HF readmission, patients in the 1st admission SBP quartile were more likely to be readmitted for HF than those in the 4th SBP quartile (adjusted HR, 1.40; 95% CI: 1.19–1.65; \( P < 0.001 \)), and the 2nd and 3rd quartiles had no significant difference in the risk of HF readmission.

Restricted cubic splines for the association between SBP and outcomes were shown in Figure 3. Lower admission SBP was associated with significantly higher all-cause death, and this association persisted even at rather high SBP levels. The risk of HF readmission was higher in patients with a lower SBP; however, above a SBP of approximately 120 mmHg, the relationship between SBP and HF readmission got flattened and was not significant.

Table 2. Unadjusted and adjusted risk for outcomes according to systolic blood pressure quartiles

|                | All-cause death | Heart failure readmission |
|----------------|-----------------|----------------------------|
|                | Hazard ratio (95% CI) | \( p \) value | Hazard ratio (95% CI) | \( p \) value |
| Unadjusted     |                 |               |                       |               |
| <117 mmHg      | 1.99 (1.64–2.41) | <0.001        | 1.61 (1.40–1.85)     | <0.001        |
| 117–130 mmHg   | 1.41 (1.14–1.75) | 0.001         | 1.16 (0.99–1.35)     | 0.062         |
| 131–148 mmHg   | 1.27 (1.03–1.55) | 0.022         | 1.10 (0.95–1.27)     | 0.188         |
| >148 mmHg      | 1.00            |               |                       |               |
| Adjusted       |                 |               |                       |               |
| <117 mmHg      | 1.85 (1.48–2.33) | <0.001        | 1.40 (1.19–1.65)     | <0.001        |
| 117–130 mmHg   | 1.50 (1.19–1.89) | <0.001        | 1.09 (0.92–1.29)     | 0.303         |
| 131–148 mmHg   | 1.30 (1.05–1.60) | 0.015         | 1.04 (0.89–1.20)     | 0.641         |
| >148 mmHg      | 1.00            |               |                       |               |

Abbreviations: CI, confidence interval.

1st quartile (SBP < 117 mmHg), 293 (23.8%) died compared with 161 (12.9%) of those with SBP in the 4th quartile (SBP > 148 mmHg) \( (P < 0.001) \). There were 474 (38.4%) patients in the 1st SBP quartile having HF readmission compared with 355 (28.4%) patients in the 4th SBP quartile \( (P < 0.001) \).

After adjusting covariates, the associations between SBP and 1-year clinical outcomes were slightly attenuated but still significant (Table 2). Compared with the 4th SBP quartile, the adjusted hazard ratios (HR) for all-cause death were 1.85 [95% confidence interval (CI) 1.48–2.33; \( P < 0.001 \)] for the 1st SBP quartile, 1.50 [95% CI 1.19–1.89; \( P < 0.001 \)] for the 2nd SBP quartile (SBP of 117–130 mmHg), and 1.30 [95% CI 1.05–1.60; \( P = 0.015 \)] for the 3rd SBP quartile (SBP of 131–148 mmHg). For HF readmission, patients in the 1st admission SBP quartile were more likely to be readmitted for HF than those in the 4th SBP quartile (adjusted HR, 1.40; 95% CI: 1.19–1.65; \( P < 0.001 \)), and the 2nd and 3rd quartiles had no significant difference in the risk of HF readmission.
Admission systolic blood pressure and clinical outcomes in subgroups

The association between SBP and all-cause death was consistent across various clinically relevant subgroups of patients, such as age, sex, and LVEF type; although there is an interaction between prescription of aldosterone antagonists and SBP, the directions of the associations in the subgroups were the same (Figure 4A). The association between SBP and HF readmission was also consistent across subgroups, except those with diabetes; but the directions were the same (Figure 4B).

Discussion

This study demonstrates an independent association between lower admission SBP and higher risk of 1-year all-cause death in patients hospitalized for the entire spectrum of HF, and there is no threshold; while we only observed such an association with 1-year HF readmission when admission SBP was lower than 120 mmHg. These associations were consistent across subgroups such as age, sex, LVEF, HF type, and coronary heart disease, and the consistency was not affected by the use of important medications for HF, which have blood pressure-lowering effect, such as ACEIs/ARBs and β-blockers. Our findings could help physicians to stratify the risk of patients hospitalized for HF very early and improve their management of HF patients.

We demonstrate a continuous relationship between lower admission SBP and higher 1-year death without upper threshold in the whole HF cohort and various subgroups. This finding is consistent with that in old HF patients, HF patients with reduced ejection fraction, and a Gulf cohort of HF.8,14,19 Previous studies reported heterogeneous results among subgroups. Barsheshet et al found that among the elderly, the association between SBP and death was inverse linear; in contrast, in patients younger than 75 years, there was a J shape curve.16 Núñez et al demonstrated that in HF patients with reduced ejection fraction, SBP has an inverse linear relationship with death, while in HF patients with preserved ejection fraction, the relationship showed a J shape curve.15 The inconsistency may be related to different study populations, sample sizes, and confounders. In this study, we collected comprehensive information on potential confounders in a large cohort. Besides demographic and clinical characteristics, we also adjusted socio-economic status and self-reported health status and the association between low SBP and high risks of 1-year death persisted without upper threshold. Our findings indicate that SBP measurement at admission for HF patients can help to identify the patients at high risk of 1-year death at a very early time, and to provide intensive care to HF patients with low admission SBP may improve their long-term survival.

This study for the first time shows that lower admission SBP is only associated with increased HF readmission in the range of 117 mmHg and below. HF readmission very frequently occurred after a hospitalization for HF;17,20 patients with admission SBP below 120 mmHg should be particularly given more attention and more aggressive care to reduce their risk of HF readmission. The association between admission SBP and HF readmission is similar to, but weaker than, that between admission SBP and all-cause death. Compared with the 4th SBP quartile, the 2nd and 3rd quartiles show...
Figure 4  Forest plots for subgroup analyses of all-cause death (A) and heart failure readmission (B) by systolic blood pressure quartiles. Forest plots displaying hazard ratios and 95% confidence intervals for all-cause death and heart failure readmission in subgroups of patients hospitalized with heart failure by the 1st systolic blood pressure quartile vs. 4th systolic blood pressure quartile. Abbreviation: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.

### Subgroup Analyses: All-Cause Death

| Subgroup                  | Hazard Ratio (95% CI) | P for interaction |
|---------------------------|-----------------------|-------------------|
| Overall                   | 1.88 (1.48, 2.35)     | 0.196             |
| Sex                       |                       |                   |
| Male                      | 2.16 (1.61, 2.90)     |                   |
| Female                    | 1.64 (1.08, 2.48)     |                   |
| Age                       |                       |                   |
| >65 yrs                   | 2.06 (1.33, 3.19)     | 0.893             |
| ≤65 yrs                   | 1.94 (1.44, 2.51)     |                   |
| LVEF type                 |                       |                   |
| IEF                       | 2.16 (1.41, 3.29)     | 0.401             |
| IIHCEF                    | 2.16 (1.41, 3.29)     |                   |
| IIIHCEF                   | 2.16 (1.41, 3.29)     |                   |
| BP type                   |                       |                   |
| Normol                    | 2.01 (1.23, 3.26)     | 0.926             |
| Chronic                   | 1.82 (1.40, 2.39)     |                   |
| Quadrant NT-proBNP        |                       |                   |
| < median                  | 1.71 (1.18, 2.43)     | 0.299             |
| > median                  | 1.94 (1.48, 2.54)     |                   |
| Diabetic                  |                       |                   |
| Yes                       | 1.08 (1.33, 2.94)     | 0.507             |
| No                        | 1.07 (1.40, 2.49)     |                   |
| Anterior/Posterior         |                       |                   |
| Yes                       | 1.26 (1.27, 2.71)     | 0.371             |
| No                        | 1.09 (1.42, 2.52)     |                   |
| Coronary heart disease    |                       |                   |
| Yes                       | 1.79 (1.24, 2.79)     | 0.790             |
| No                        | 1.09 (1.22, 2.99)     |                   |
| Pulmonary heart disease   |                       |                   |
| Yes                       | 2.11 (1.17, 3.73)     | 0.719             |
| No                        | 1.08 (1.48, 2.31)     |                   |
| ACEIs/ARBs                |                       |                   |
| Yes                       | 1.78 (1.31, 2.41)     | 0.718             |
| No                        | 1.08 (1.32, 2.50)     |                   |
| J-blockers                |                       |                   |
| Yes                       | 1.08 (1.24, 2.43)     | 0.179             |
| No                        | 2.13 (1.44, 3.08)     |                   |
| Alleles tumorigenic       |                       |                   |
| Yes                       | 1.99 (1.18, 3.32)     | 0.010             |
| No                        | 1.12 (0.71, 1.79)     |                   |

### Subgroup Analyses: Heart Failure Readmission

| Subgroup                  | Hazard Ratio (95% CI) | P for interaction |
|---------------------------|-----------------------|-------------------|
| Overall                   | 1.40 (1.19, 1.61)     | 0.009             |
| Sex                       |                       |                   |
| Male                      | 1.35 (1.08, 1.69)     |                   |
| Female                    | 1.44 (1.16, 1.80)     | 0.552             |
| Age                       |                       |                   |
| >65 yrs                   | 1.44 (1.08, 1.94)     |                   |
| ≤65 yrs                   | 1.38 (1.13, 1.70)     | 0.105             |
| LVEF type                 |                       |                   |
| IEF                       | 1.41 (1.07, 1.85)     |                   |
| IIHCEF                    | 2.29 (1.16, 3.05)     | 0.151             |
| IIIHCEF                   | 2.19 (1.06, 4.48)     |                   |
| BP type                   |                       |                   |
| Normol                    | 1.88 (1.17, 2.92)     | 0.551             |
| Chronic                   | 1.33 (1.10, 1.55)     |                   |
| Quadrant NT-proBNP        |                       |                   |
| < median                  | 1.32 (0.96, 1.87)     | 0.249             |
| > median                  | 1.41 (1.26, 1.68)     |                   |
| Diabetic                  |                       |                   |
| Yes                       | 1.33 (0.85, 2.06)     | 0.259             |
| No                        | 1.54 (1.25, 1.89)     |                   |
| Anterior/Posterior         |                       |                   |
| Yes                       | 1.68 (1.22, 2.31)     | 0.242             |
| No                        | 1.29 (1.05, 1.59)     |                   |
| Coronary heart disease    |                       |                   |
| Yes                       | 1.29 (1.04, 1.59)     | 0.214             |
| No                        | 1.32 (1.15, 1.52)     |                   |
| Pulmonary heart disease   |                       |                   |
| Yes                       | 1.17 (0.77, 1.78)     | 0.280             |
| No                        | 1.44 (1.21, 1.75)     |                   |
| ACEIs/ARBs                |                       |                   |
| Yes                       | 1.35 (1.06, 1.70)     | 0.160             |
| No                        | 1.40 (1.05, 1.85)     |                   |
| J-blockers                |                       |                   |
| Yes                       | 1.39 (1.15, 1.68)     | 0.601             |
| No                        | 1.51 (1.16, 1.97)     |                   |
| Alleles tumorigenic       |                       |                   |
| Yes                       | 1.40 (1.17, 1.67)     | 0.061             |
| No                        | 1.36 (0.99, 1.87)     |                   |
weak but not significant tendencies towards higher risk of HF readmission. There are two possible explanations for the weak and non-significant associations. First, a more modest relative risk of HF readmission may be due to the substantial competing risk of death, that is, patients in lower SBP quartiles may have less opportunity to be readmitted because of increased mortality. Second, apart from disease severity, other factors (e.g. medical resource accessibility and availability) could influence the occurrence of HF readmission. We noted that there was a significant interaction between admission SBP and diabetes for HF readmission and no significant association was found between SBP and HF readmission in diabetic patients. These findings may be explained by high rates of HF readmission across all admission SBP quartiles in diabetic patients and the little extra risk added by decreased SBP (Table S1).

The association between admission SBP and clinical outcomes remained after adjustment for potential confounders (including demographic and clinical characteristics of patients, proved beneficial medications for HF patients with reduced ejection fraction, socio-economic status, and self-reported health status), although we are uncertain whether the association is causality. Some people argued that patients with lower SBP tend to be older and weaker. However, in this study, old age could not explain the worse prognosis because patients with lower admission SBP were even younger. Although LVEF was lower in patients with lower SBP levels, indicating a worse systolic function, the association between admission SBP and death remained significant after adjustment for LVEF. The differences in comorbidities may explain the results, which is however unlikely because patients with higher SBP also have high proportion of comorbidities; even after adjustment for these comorbidities, the associations persisted. In terms of medications, some people stated that physicians may be reluctant to use ACEIs/ARBs or β-blockers in HF patients with lower SBP and tend to treat those with higher SBP more aggressively; however, this study found that even in the lowest SBP quartile, most patients used these medications during hospitalization.

The results should be interpreted in the context of limitations. First, patients with different admission SBP may receive different medications during follow up, but we did not collect comprehensive data about the follow-up medications, which could be confounders. Second, although we minimized the risk of confounding by a thorough multivariate adjustment, other unknown confounders could have been missed, which is inevitable for observational studies.

In conclusion, lower admission SBP was significantly associated with higher risk of all-cause death and there is no threshold, while such an association with HF readmission was only observed when admission SBP was lower than 120 mmHg. These associations were consistent among various clinically important subgroups. These findings can improve risk stratification at very early stage and facilitate more effective management strategies for patients hospitalized for HF.

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Conflict of interest

Dr Li reported receiving research grants, through Fuwai Hospital, from the People’s Republic of China for work to improve the management of hypertension and blood lipids and to improve care quality and patient outcomes of cardiovascular disease; receiving research agreements, through the National Center for Cardiovascular Diseases and Fuwai Hospital, from Amgen for a multicentre clinical trial assessing the efficacy and safety of omecamtiv mecarbil and for dyslipidaemic patient registration; receiving a research agreement, through Fuwai Hospital, from Sanofi for a multicentre clinical trial on the effects of sotagliflozin; receiving a research agreement, through Fuwai Hospital, with the University of Oxford for a multicentre clinical trial of empagliflozin; receiving a research agreement, through the National Center for Cardiovascular Diseases, from AstraZeneca for clinical research methods training outside the submitted work; and receiving a research agreement, through the National Center for Cardiovascular Diseases, from Lilly for physician training outside the submitted work.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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