Original Article

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J-curve relationship between admission SBP and 2-year cardiovascular mortality in older patients admitted for acute coronary syndrome

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Objective: To investigate the relationship between admission SBP and subsequent cardiovascular and all-cause mortality in older patients hospitalized for acute coronary syndrome (ACS).

Methods: This is a retrospective observational study. Data from the CBD Bank (Cardiovascular Center Beijing Friendship Hospital Database Bank) were used to analyze the cardiovascular and all-cause mortality during hospitalization and over the follow-up period in relation to admission SBP among patients aged at least 65 years admitted for ACS from December 2012 through July 2019. Results were presented according to SBP quartiles: Q1, less than 120 mmHg; Q2, from 120 to 129 mmHg; Q3, from 130 to 143 mmHg; and Q4, at or above 144 mmHg.

Results: A total of 6785 patients were included in this cohort study. Mean (SD) patient age was 74.0 (6.5) years, and 47.6% were women. Mean (SD) follow-up time was 2.54 (1.82) years. A nonlinear relation was observed between SBP at admission and cardiovascular and all-cause mortality during hospitalization and over the follow-up period using restricted cubic splines. After adjustment for potential confounders, patients in Q1 had higher risk for 2-year cardiovascular death by Cox proportional hazard model compared with patients in Q2 [hazard ratio, 1.58; 95% confidence interval (CI), 1.12–2.21, $P=0.009$], whereas patients in Q3 or Q4 exhibited a trend towards increased risk for 2-year cardiovascular death (hazard ratio, 1.33, 95% CI, 0.95–1.86, $P=0.094$, for Q3 vs. Q2; and hazard ratio, 1.28, 95% CI, 0.91–1.82, $P=0.160$, for Q4 vs. Q2). Meanwhile, when compared with patients in Q1, patients in Q2 had lower risk for 2-year cardiovascular death (hazard ratio, 0.64; 95% CI, 0.45–0.89, $P=0.009$) whereas patients in Q3 or Q4 had similar risk for cardiovascular death (hazard ratio, 0.85, 95% CI, 0.63–1.14, $P=0.272$, for Q3 vs. Q1; and hazard ratio, 0.82, 95% CI, 0.59–1.13, $P=0.221$, for Q4 vs. Q1). However, low-admission SBP was not an independent predictor of 2-year all-cause mortality in this population.

Conclusion: Among patients aged at least 65 years admitted for ACS, there is a J-curve relationship between supine admission SBP and risk for 2-year cardiovascular death, with a nadir at 120–129 mmHg.

Keywords: acute coronary syndrome, all-cause mortality, cardiovascular mortality, J-curve, older, SBP

Abbreviations: ACS, acute coronary syndrome; ACSIS, the Acute Coronary Syndrome Israel Survey; AMI, acute myocardial infarction; BNP, brain natriuretic peptide; BP, blood pressure; CBD Bank, Cardiovascular Center Beijing Friendship Hospital Database Bank; CI, confidence interval; CKD, chronic renal disease; cTnI, cardiac troponin I; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GRACE, the Global Registry of Acute Coronary Events; GUSTO, the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; NSTEMI, non ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; TIMI, the Thrombolysis in Myocardial Infarction

INTRODUCTION

Over the past decades, life expectancy has dramatically improved worldwide. It is projected that from the year 2000 to 2030, the proportion of people aged at least 65 years will increase from 12.4 to 19.6% in the United States [1]. As the second largest global economy, China is transforming rapidly into an aging nation and currently has the largest population of elderly in the world [2]. In 2010, there were 111 million (8.2% of the population) elderly aged at least 65 years, whereas by 2050 there will be 400 million (26.9% of the total population) aged at least 65 years [3,4]. The United States, China, as well as many other

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countries in the world, are encountering huge health challenges brought about by the problem of aging.

Ischemic heart disease is the leading cause of death in the world [5]. As an acute manifestation of ischemic heart disease, acute coronary syndrome (ACS) leads to substantial morbidity and mortality, especially in geriatric population. The risk stratification of ACS is important in helping clinicians guide the type and intensity of treatment and/or surveillance. However, although low SBP is suggested as an adverse prognostic factor in ACS, data on the predictive potential of admission SBP on short- and long-term outcomes in older patients with ACS are very limited [4]. Accordingly, we evaluated the relationship between SBP at admission and the subsequent cardiovascular and all-cause mortality during hospitalization and over the follow-up period in this population.

METHODS

Study design

This is a retrospective observational study based on the Cardiovascular Center Beijing Friendship Hospital Database Bank (CBD Bank), which includes data of consecutive patients admitted for ACS to the Cardiovascular Center Beijing Friendship Hospital, Capital Medical University. Patients were managed with standard medical and interventional treatments for ACS. Demographic, chronic and acute clinical data, baseline laboratory data, diagnoses, medical therapy, as well as in-hospital and out-of-hospital outcomes were recorded on prespecified forms for the enrolled patients. Admission blood pressure (BP) was defined as the measurement immediately obtained at admission to the cardiology department (not in the emergency room or the cath lab). This BP was recorded with the patient resting in the supine position for at least 5 min. Measurements on both arms were taken and the higher value was adopted as the reference. Patients were followed up at 1 month, 3 months, 6 months, and every year after discharge until death. The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University, with a waiver for informed consent (No. 2017-P2–123-01), and permission was granted to use data for analysis.

Study population and definitions

From December 2012 to July 2019, consecutive patients at least 65 years of age hospitalized for ACS were included in this study. ACS was defined as either acute myocardial infarction (AMI), with or without ST elevation, or unstable angina [6–8]. Chronic heart failure was defined as a documented diagnosis or when the patient was chronically prescribed relevant medications. Hypertension was defined as a documented diagnosis or when the patient was chronically prescribed antihypertensive medications. Diabetes mellitus was defined as a documented diagnosis or when the patient was chronically prescribed oral hypoglycemic medications or insulin. Chronic renal disease (CKD) was defined as documented medical chart diagnosis or when the calculated glomerular filtration rate of the patient was less than 60 ml/min per 1.73 m^2. Cardiogenic shock was defined as hypotension (a SBP of $<$90 mmHg for at least 30 min or the need for supportive measures to maintain a SBP of at least 90 mmHg) and evidence of end-organ hypoperfusion (cool extremities or a urine output of $<$30 ml per hour, and a heart rate of $\geqq$60 beats per minute), or a class IV rating according to the Killip classification [9,10].

Study outcomes

The primary outcome measure was cardiovascular death during hospitalization and over the follow-up period. All-cause death was a secondary outcome. Cardiovascular death was defined as any death with a demonstrable cardiovascular cause or any death that is not clearly attributable to a noncardiovascular cause [11]. Vital status (and date of death whenever applicable) was obtained for each participant at 1, 3, 6 months and every year after discharge until death. The vital status was obtained by contacting the patient or his/her family and/or reviewing hospital record. When the patient was deceased, the date and cause of death was obtained through the same method and was ascertained through registry data of Beijing Municipal Health Commission Information Center.

Statistical analysis

Clinical characteristics were presented as proportions or median (interquartile range) as appropriate, and categorical variables were presented as numbers and percentages. Intergroup comparison of continuous variables between SBP groups with quartile 2 was performed using the nonparametric rank test (Mann–Whitney *U*-test) and categorical variables were compared using the Pearson chi-square test or Fisher's exact test. We used restricted cubic splines with three knots at the 10th, 50th, and 90th centiles to flexibly model the association of admission SBP and 2-year cardiovascular and all-cause mortality. In the main statistical analyses, a Cox proportional hazards regression model was used. A model containing SBP in quartiles with quartile 2 as reference was mainly used, adjusted for age; sex; smoking; previous history of myocardial infarction, coronary revascularization, chronic heart failure, hypertension, diabetes, CKD, stroke, malignancy; diagnosis at discharge (AMI or unstable angina); cardiac function at admission; cardiogenic shock; diastolic BP; heart rate; BMI; hemoglobin; glucose; albumin; estimated glomerular filtration rate (eGFR); lactate; high-sensitivity C-reactive protein (hs-CRP), cardiac troponin I (cTnI); and brain natriuretic peptide (BNP). Predictors of clinical outcomes identified from univariate analysis ($P < 0.05$) were tested in a multivariate analysis. Hazard ratios, 95% confidence interval (CI), and *P* values were reported for significant predictors. In all the analyses, SBP was categorized in quartiles. Other ways of categorizing were considered but did not change the result regarding SBP in any substantial way. Intergroup comparison of continuous variables between SBP groups with quartile 2 was performed using the nonparametric rank test (Mann–Whitney *U*-test), and the Pearson chi-squared test or Fisher's exact test was used to compare categorical variables between SBP groups with quartile 2. *P*-value less than 0.05 was considered statistically significant and all tests were two-sided. All data analyses were carried out using the

Statistical Package for Social Sciences, version 20.0 (SPSS, Chicago, Illinois, USA) and R version 4.0.2.

RESULTS

The study cohort constituted 6785 patients (Fig. 1), of whom 866 (12.8%) with ST elevation myocardial infarction (STEMI), 1093 (16.1%) with non–ST elevation myocardial infarction (NSTEMI), and 4826 (71.1%) with unstable angina. Mean (SD) age of the cohort was 74.0 (6.5) years, and 47.6% were women. Among the 6785 patients, 43 (0.6%) presented with cardiogenic shock at admission; 787 (11.6%) died; and 474 (7.0%) died of cardiovascular diseases. Mean (SD) follow-up time was 2.54 (1.82) years.

The continuous relationship between admission SBP and cardiovascular and all-cause mortality, a nonlinear U-shaped trend, was assessed using restricted cubic splines (Fig. 2a and b). Table 1 listed patient characteristics and laboratory results in the cohort and in the quartiles of SBP at admission. SBP in the first quartile (Q1) was less than 120 mmHg; the second quartile (Q2) was from 120 to 129 mmHg; the third quartile (Q3), 130–143 mmHg; and the fourth quartile (Q4), at or above 144 mmHg. Compared with patients in Q2, patients in Q1 had higher rate of AMI, lower BMI, albumin and LVEF values, and higher glucose, lactate, cTNI and BNP values; whereas patients in Q4 were older, had higher rates of concomitant diseases including hypertension, diabetes and CKD, higher rate of AMI, lower albumin and eGFR values, and higher BMI, glucose, lactate, cTNI, and BNP values.

Among the total cohort, patients in Q1 had the highest in-hospital and overall cardiovascular mortality [4.0% (Q1) vs. 1.0% (Q2), 1.0% (Q3), and 1.0% (Q4), $P < 0.001$; and 10.6% (Q1) vs. 5.1% (Q2), 5.5% (Q3), and 7.5% (Q4), respectively, $P < 0.001$] and all-cause mortality [4.2% (Q1) vs. 1.1% (Q2), 1.0% (Q3), and 1.0% (Q4), $P < 0.001$; and 14.6% (Q1) vs. 9.7% (Q2), 10% (Q3), and 12.8% (Q4), respectively, $P < 0.001$]. No significant differences of in-hospital or overall cardiovascular or all-cause mortality rates were found between patients in Q3 and patients in Q2, whereas patients in Q4 had higher overall cardiovascular and all-cause mortality rates when compared with patients in Q2 [7.5% (Q4) vs. 5.1% (Q2), $P < 0.01$, and 12.8% (Q4) vs. 9.7% (Q2), respectively, $P < 0.01$].

Adjusted 2-year cardiovascular mortality rate by Cox proportional hazards model showed that compared with patients in Q2, patients in Q1 had higher risk for 2-year cardiovascular death [hazard ratio, 1.58, 95% confidence interval (CI), 1.12–2.21, $P = 0.009$]; whereas patients in Q3 or Q4 exhibited a trend towards increased risk for 2-year cardiovascular death (hazard ratio, 1.33, 95% CI, 0.95–1.86, $P = 0.094$, for Q3 vs. Q2; and hazard ratio, 1.28, 95% CI, 0.91–1.82, $P = 0.160$, for Q4 vs. Q2) (Table 2 and Fig. 3). Meanwhile, when compared with patients in Q1, patients in Q2 had lower risk for 2-year cardiovascular death (hazard ratio, 0.64, 95% CI, 0.45–0.89, $P = 0.009$); whereas patients

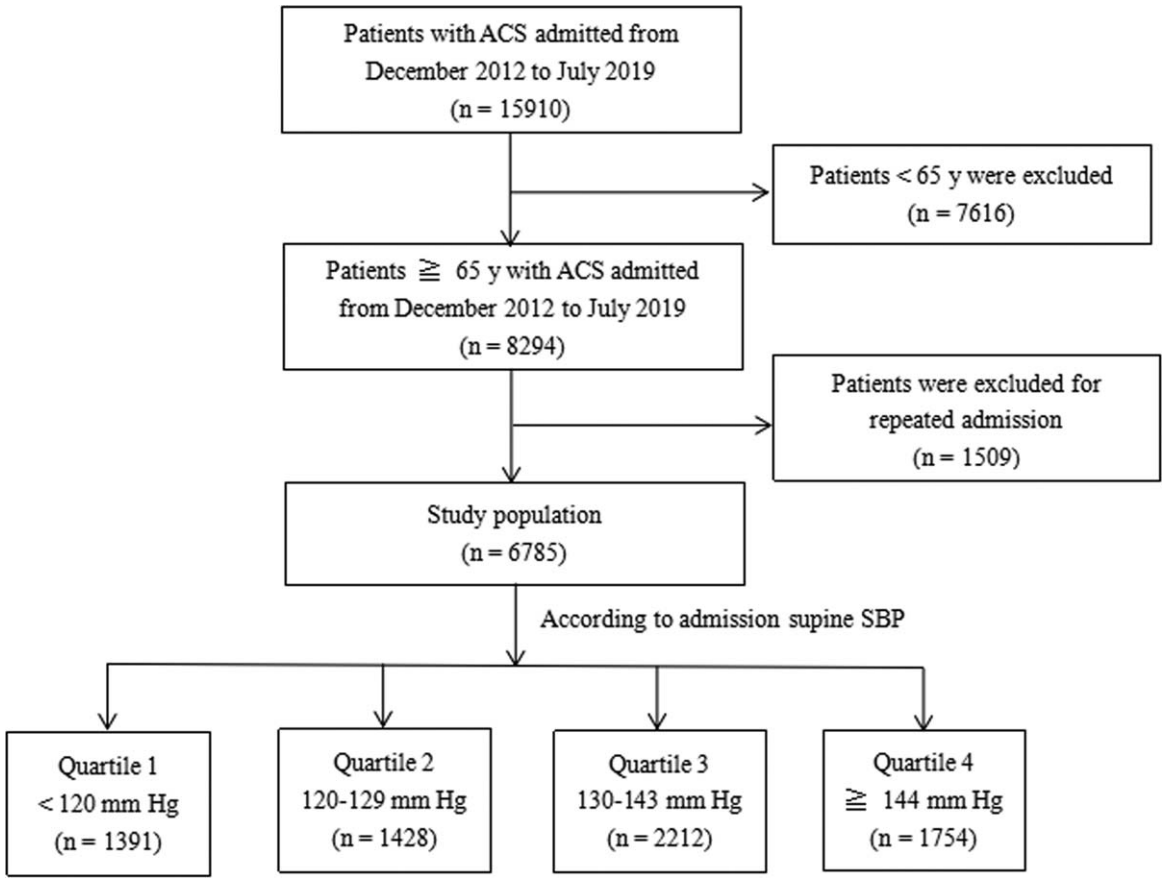

FIGURE 1 Study population and selection.

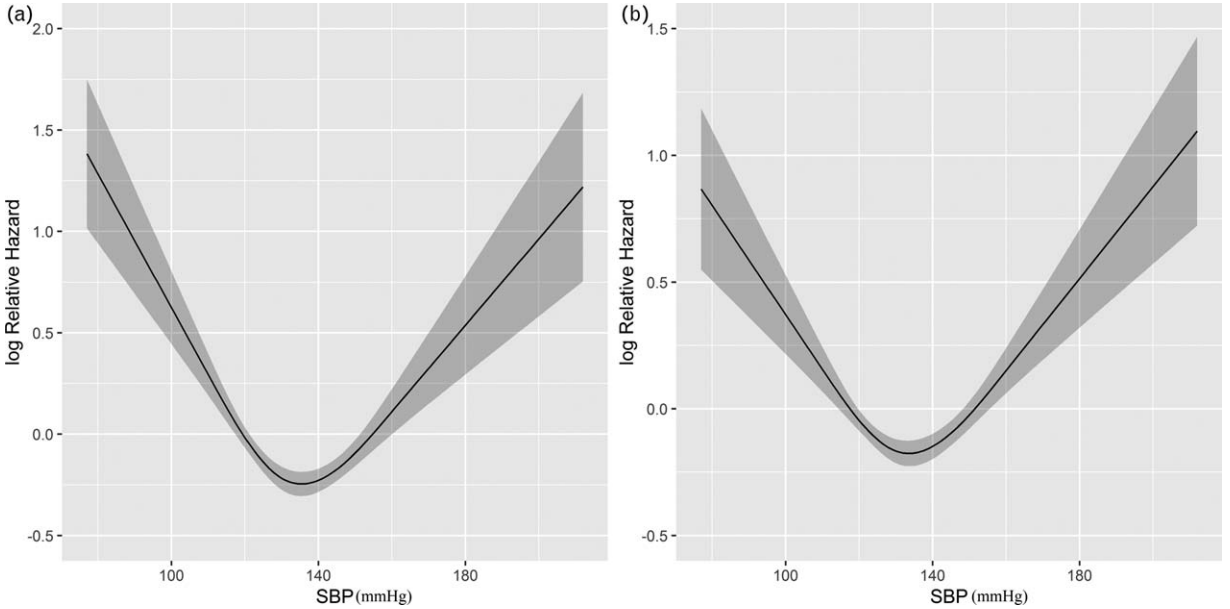

FIGURE 2 (a) Nonlinear relation between continuous admission SBP and cardiovascular mortality was assessed using restricted cubic splines. (b) Nonlinear relation between continuous admission SBP and all-cause mortality was assessed using restricted cubic splines.

in Q3 or Q4 had similar risk for cardiovascular death (hazard ratio, 0.85, 95% CI, 0.63–1.14, $P = 0.272$, for Q3 vs. Q1; and hazard ratio, 0.82, 95% CI, 0.59–1.13, $P = 0.221$, for Q4 vs. Q1), indicating a J-curve relationship between admission SBP and 2-year cardiovascular mortality in older patients after ACS, with a nadir at 120–129 mmHg. The findings of the highest risk for 2-year cardiovascular death in patients in Q1 and the lowest risk for 2-year cardiovascular death in patients in Q2 was unaffected when data were adjusted for presence of history of MI and coronary revascularization, chronic heart failure, hypertension, diabetes, stroke, and malignancy, and it persisted when data for patients who died in the hospital ($n = 113$) were removed (hazard ratio, 1.56, 95% CI, 1.06–2.28, $P = 0.023$, Q1 vs. Q2; hazard ratio, 1.28, 95% CI, 0.89–1.85, $P = 0.191$, Q3 vs. Q2; hazard ratio, 1.39. 95% CI, 0.95–2.04, $P = 0.089$, Q4 vs. Q2; hazard ratio, 0.64, 95% CI, 0.44–0.94, $P = 0.023$, Q2 vs. Q1; hazard ratio, 0.82; 95% CI, 0.58–1.16, $P = 0.258$, Q3 vs. Q1; hazard ratio, 0.90, 95% CI, 0.62–1.29, $P = 0.557$, Q4 vs. Q1; in the remaining data set).

In addition to lower admission SBP, men, older age, prior myocardial infarction, diagnosis of AMI, worse cardiac function, lower levels of BMI, hemoglobin, albumin and eGFR, and higher levels of glucose and lactate all had higher risk for 2-year cardiovascular death. Of note, among these variables, cardiac function was the strongest predictor for higher risk of cardiovascular death (Killip II hazard ratio, 1.82, and 95% CI, 1.38–2.40; Killip III hazard ratio, 3.41, and 95% CI, 2.43–4.80; Killip IV hazard ratio, 9.51, and 95% CI, 6.63–13.64), followed by older age (hazard ratio, 3.37, and 95% CI, 1.29–8.77) and diagnosis of AMI (hazard ratio, 2.62, and 95% CI, 2.02–3.39).

No similar relationship between admission SBP in quartiles and 2-year all-cause mortality was found. Patients in Q1, Q3, and Q4 of SBP had similar risk for 2-year all-cause death with an adjusted hazard ratio of 1.20 (95% CI, 0.93–1.55), 1.23 (95% CI, 0.97–1.55), and 1.22 (95% CI, 0.95–1.57), respectively, compared with patients in Q2, indicating that admission SBP alone was not an independent predictor of 2-year all-cause mortality in older patients admitted for ACS (Table 3). However, variables including men, older age, older age, prior myocardial infarction, diagnosis of AMI, worse cardiac function, lower levels of BMI, hemoglobin, albumin and eGFR, and higher levels of heart rate, glucose, lactate, and hs-CRP were associated with higher risks for 2-year all-cause death. And also, cardiac function was the strongest predictor for higher risk of 2-year all-cause death (Killip II hazard ratio, 1.79, and 95% CI, 1.47–2.19; Killip III hazard ratio, 3.28, and 95% CI, 2.55–4.22; Killip IV hazard ratio, 6.68, and 95% CI, 5.00–8.93), followed by diagnosis of AMI (hazard ratio, 1.87, and 95% CI, 1.54–2.27) and prior myocardial infarction (hazard ratio, 1.48, and 95% CI, 1.20–2.83).

DISCUSSION

In this population-based study in patients at least 65 years of age admitted for ACS, there is a J-curve or U-curve, which is defined by an increase in cardiovascular outcomes below or above a certain BP with the trough BP representing the point where the lowest risk of cardiovascular events is noted, relationship between supine admission SBP and 2-year cardiovascular mortality in older patients after ACS, with a nadir at 120–129 mmHg [12,13]. This association persisted even after adjustment for potential confounders or with exclusion of patients who died in the hospital. To the best of our knowledge, this is the first study to investigate the association between admission SBP and long-term cardiovascular and all-cause mortality in older patients with ACS in a real-world setting. Our data indicated an increased risk of cardiovascular death in older patients admitted for ACS with lower admission SBP (<120 mmHg)

TABLE 1. Characteristics of the study population at admission

Characteristic	Total cohort ($N=6785$)	Quartile[a]					
		1 ($n=1391$)	*P* value[b]	2 ($n=1428$)	3 ($n=2212$)	*P* value[b]	4 ($n=1754$)	*P* value[b]
Age, mean (SD), (years)	74.0 (6.5)	73.8 (6.6)	0.191	73.4 (6.5)	74.0 (6.4)	0.020	74.8 (6.4)	<0.001
Women, No. (%)	3231 (47.6)	609 (43.8)	0.373	649 (45.4)	1116 (50.5)	0.003	857 (48.9)	0.055
Medical history, No. (%)								
Myocardial infraction	721 (10.6)	160 (11.5)	0.784	169 (11.8)	224 (10.1)	0.105	168 (9.6)	0.040
PCI	1254 (18.5)	265 (19.1)	0.179	301 (21.1)	397 (17.9)	0.019	291 (16.6)	0.001
CABG	230 (3.4)	40 (2.9)	0.345	50 (3.5)	66 (3.0)	0.385	74 (4.2)	0.298
Chronic heart failure	110 (1.6)	35 (2.5)	0.047	21 (1.5)	31 (1.4)	0.864	23 (1.3)	0.702
Hypertension	5191 (76.5)	855 (61.5)	<0.001	1038 (72.7)	1756 (79.4)	<0.001	1542 (87.9)	<0.001
Diabetes mellitus	2607 (38.4)	497 (35.7)	0.468	529 (37.0)	846 (38.2)	0.466	735 (41.9)	0.005
Chronic kidney disease	403 (5.9)	64 (4.6)	0.772	69 (4.8)	117 (5.3)	0.541	153 (8.7)	<0.001
Stroke	1589 (23.4)	324 (23.3)	0.546	319 (22.3)	513 (23.2)	0.550	433 (24.7)	0.121
Malignancy	419 (6.2)	88 (6.3)	0.428	101 (7.1)	139 (6.3)	0.349	91 (5.2)	0.026
Smoking, No. (%)[d]	2713 (40.0)	624 (44.9)	0.040	586 (41.0)	847 (38.3)	0.098	656 (37.4)	0.037
Diagnosis of AMI, No. (%)	1959 (28.9)	604 (43.4)	<0.001	315 (22.1)	503 (22.7)	0.631	537 (30.6)	<0.001
Killip class, No. (%)[e]								
I	2581 (38.0)	571 (41.0)	0.007	502 (35.2)	865 (39.1)	0.010	643 (36.7)	0.706
II	3018 (44.5)	561 (40.3)	<0.001	651 (45.6)	971 (43.9)	0.376	835 (47.6)	0.609
III	635 (9.4)	127 (9.1)	0.120	151 (10.6)	191 (8.6)	0.056	166 (9.5)	0.204
IV	196 (2.9)	84 (6.0)	<0.001	35 (2.5)	36 (1.6)	0.083	41 (2.3)	0.753
Clinical characteristics								
SBP, median (IQR) (mmHg)	130 (120–144)	110 (104–115)	<0.001	122 (120–125)	135 (130–140)	<0.001	154 (150–163)	<0.001
DBP, median (IQR) (mmHg)	72 (66–80)	65 (60–70)	<0.001	70 (66–80)	75 (70–80)	<0.001	80 (71–89)	<0.001
PP, median (IQR)) (mmHg)	59 (49–70)	43 (38–50)	<0.001	50 (45–58)	60 (54–68)	<0.001	76 (68–86)	<0.001
MAP, median (IQR) (mmHg)	93.3 (85.7–100.0)	79.7 (74.7–83.3)	<0.001	88.3 (85.3–93.3)	95.7 (90.0–100.0)	<0.001	105.0 (99.3–112,1)	<0.001
Heart rate, median (IQR), beats/min	70 (62–78)	70 (62–80)	0.123	69 (62–77)	70 (63–77)	0.198	70 (63–80)	0.003
BMI, median (IQR)[f] ($n=6763$)	25.15 (22.89–27.54)	24.67 (22.34–27.23)	0.016	25.14 (22.83–27.43)	25.34 (23.12–27.68)	0.009	25.34 (23.18–27.68)	0.041
Hemoglobin, median (IQR), (g/l) ($n=6650$)	129.0 (118.0–140.0)	129.0 (117.8–140.0)	0.294	129.0 (119.0–140.0)	130.0 (118.0–141.0)	0.461	129.0 (118.0–139.0)	0.408
Albumin, median (IQR), (g/l) ($n=6689$)	38.0 (35.5–40.6)	37.2 (34.5–39.9)	<0.001	38.2 (35.9–40.8)	38.5 (36.0–41.0)	0.118	37.8 (35.2–40.5)	0.001
Creatinine, median (IQR), μmmol/l ($n=6699$)	80.60 (68.40–95.90)	79.70 (68.00–94.65)	0.659	81.00 (68.90–94.00)	79.40 (68.00–94.28)	0.313	82.70 (68,60–100.20)	0.002
eGFR, median (IQR), (ml/min per 1.73 m^2) ($n=6699$)	72.99 (59.76–85.72)	75.28 (61.57–87.35)	0.437	73.50 (60.92–86.86)	73.13 (60.83–85.26)	0.286	70.43 (56.06–84.37)	<0.001
Glucose, median (IQR) (mmol/l) ($n=6689$)	5.45 (4.81–6.74)	5.50 (4.80–6.98)	0.024	5.40 (4.79–6.54)	5.41 (4.79–6.57)	0.705	5.52 (4.85–7.04)	0.001
Lactate, median (IQR) (mmol/l) ($n=6512$)	1.93 (1.57–2.44)	1.99 (1.61–2.53)	<0.001	1.91 (1.54–2.35)	1.90 (1.56–2.39)	0.786	1.94 (1.58–2.48)	0.028
cTnI, median (IQR) (ng/ml) ($n=6501$)	0.007 (0.002–0.106)	0.015 (0.002–0.549)	<0.001	0.005 (0.002–0.039)	0.006 (0.002–0.045)	0.233	0.011 (0.003–0.124)	<0.001
BNP, median (IQR) (pg/ml) ($n=5767$)	460 (148–2504)	995 (188–4876)	<0.001	316 (115–1875)	353 (133–1563)	0.375	595 (189–2836)	<0.001
LVEF, median (IQR) ($n=6523$)	0.66 (0.60–0.70)	0.64 (0.55–0.69)	<0.001	0.66 (0.60–0.70)	0.66 (0.61–0.70)	0.928	0.66 (0.60–0.70)	0.277
In-hospital death, No. (%)								
Cardiovascular	110 (1.6)	56 (4.0)	<0.001	14 (1.0)	22 (1.0)	0.966	18 (1.0)	0.897
All-cause	113 (1.7)	58 (4.2)	<0.001	15 (1.1)	22 (1.0)	0.870	18 (1.0)	0.947

AMI, acute myocardial infarction; BNP, brain natriuretic peptide; CABG, coronary artery bypass surgery; cTnI, cardiac troponin I; eGFR, estamated glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; PCI, percutaneous coronary intervention; PP, pulse pressure; SD, standard deviation.
[a]SBP in quartile 1 was less than 120 mmHg; in quartile 2, 120–129 mmHg; in quartile 3, 130–143 mmHg; and in quartile 4, at least 144 mmHg.
[b]*P* values are for comparisons with quartile 2.
[c]Known diseases at admission.
[d]Sum of ex-smokers and current smokers.
[e]Degree of heart failure present on admission categorized by Killip class.
[f]Calculated as weight in kilograms divided by height in meters squared.

TABLE 2. Cumulative 2-year cardiovascular death hazard ratios in comparison with quartile 2 of systolic BP in the total cohort (adjusted)[a]

	Univariate regression			Multivariate regression		
Variable	**HR**	**95% CI**	***P* value**	**HR**	**95%CI**	***P* value**
Quartile 1 (SBP <120 mmHg)	2.22	1.68–2.94	<0.001	1.58	1.12–2.21	0.009
Quartile 3 (SBP 130–143 mmHg)	1.08	0.81–1.44	0.625	1.33	0.95–1.86	0.094
Quartile 4 (SBP at least 144 mmHg)	1.54	1.16–2.05	0.003	1.28	0.91–1.82	0.160
Sex[b]	0.91	0.76–1.09	0.293	0.68	0.55–0.85	0.001
Age	1.13	1.11–1.15	<0.001	3.37	1.29–8.77	0.013
Prior myocardial infraction	1.60	1.26–2.04	<0.001	1.54	1.17–2.03	0.002
Diabetes mellitus	1.25	1.05–1.50	0.015	1.08	0.84–1.37	0.560
Diagnosis of AMI[c]	4.50	3.73–5.42	<0.001	2.62	2.02–3.39	<0.001
Killip class[d]						
II	1.75	1.37–2.23	<0.001	1.82	1.38–2.40	<0.001
III	4.64	3.49–6.16	<0.001	3.41	2.43–4.80	<0.001
IV	21.23	15.95–28.26	<0.001	9.51	6.63–13.63	<0.001
DBP	0.99	0.98–1.00	0.007	1.00	0.99–1.01	0.785
Heart rate	1.03	1.03–1.04	<0.001	1.01	1.00–1.01	0.067
BMI[e]	0.90	0.88–0.92	<0.001	0.94	0.92–0.97	<0.001
Hemoglobin	0.97	0.96–0.97	<0.001	0.99	0.99–1.00	0.003
Glucose	1.11	1.09–1.13	<0.001	1.05	1.01–1.09	0.011
Albumin	0.84	0.83–0.86	<0.001	0.97	0.94–0.99	0.016
Lactate	1.11	1.06–1.15	<0.001	1.09	1.05–1.120	<0.001
eGFR[f]	0.96	0.96–0.97	<0.001	0.99	0.98–0.99	<0.001
hs-CRP	1.05	1.04–1.06	<0.001	1.01	1.00–1.02	0.072

AMI, acute myocardial infarction; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; SP, blood pressure.
[a]Adjusted for age; sex; concomitant diseases; diagnosis of AMI; Killip class grade; cardiac shock at admission; DBP; heart rate; BMI; hemoglobin; glucose; albumin; lactate; eGFR; and hsCRP. Quartile 2 had a SBP of 120–129 mmHg. $n = 5696$ with data on all covariates.
[b]Sex was set as 1 for men, 2 for women, in the statistical analysis.
[c]Diagnosis of AMI was set as 0 for unstable angina, 1 for AMI.
[d]Degree of heart failure present on admission categorized by Killip class; *P* values were for comparisons with group of Killip class I.
[e]Calculated as weight in kilograms divided by height in meters squared.
[f]Calculated with Chronic Kidney Disease Epidemiology (CKD-EPI) equation.

when compared with those with admission SBP of 120–129 mmHg, regardless of a history of hypertension. Meanwhile, patients admitted with higher SBP (at least 130 mmHg) exhibited a trend towards increased risk for 2-year cardiovascular death. Moreover, our data showed that lower admission SBP (<120 mmHg) was an independent predictor of 2-year cardiovascular mortality in older patients after ACS.

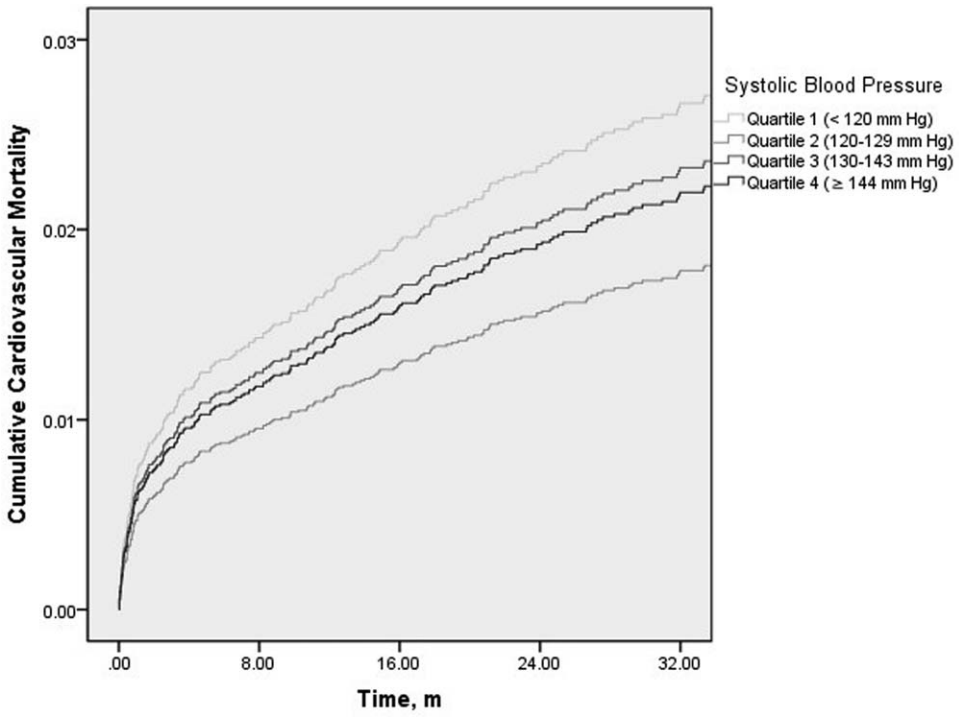

FIGURE 3 Adjusted multivariate COX regression cumulative 2-year cardiovascular mortality risk by quartile of SBP.

TABLE 3. Cumulative all-cause death hazard ratios in comparison with quartile 2 of SBP in the total cohort (adjusted)[a]

	Univariate regression			Multivariable regression		
Variable	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Quartile 1 (SBP <120 mmHg)	1.63	1.31–2.02	<0.001	1.20	0.93–1.55	0.154
Quartile 3 (SBP 130–143 mmHg)	1.03	0.83–1.28	0.775	1.23	0.97–1.55	0.095
Quartile 4 (SBP at least 144 mmHg)	1.43	1.15–1.76	0.001	1.22	0.95–1.57	0.114
Sex[b]	0.90	0.78–1.03	0.119	0.69	0.59–0.81	<0.001
Age	1.12	1.11–1.13	<0.001	1.27	1.07–1.51	0.006
Prior myocardial infraction	1.49	1.23–1.81	<0.001	1.48	1.20–1.83	<0.001
Diabetes mellitus	1.21	1.05–1.39	0.010	1.07	0.89–1.28	0.486
Diagnosis of AMI[c]	3.21	2.79–3.70	<0.001	1.87	1.54–2.27	<0.001
Killip class[d]						
II	1.77	1.48–2.22	<0.001	1.79	1.47–2.19	<0.001
III	4.56	3.69–5.65	<0.001	3.28	2.55–4.22	<0.001
IV	14.87	11.72–18.87	<0.001	6.68	5.00–8.93	<0.001
DBP	0.99	0.98–1.00	0.004	1.00	0.99–1.01	0.800
Heart rate	1.03	1.02–1.03	<0.001	1.01	1.00–1.01	0.005
BMI[e]	0.91	0.89–0.93	<0.001	0.95	0.93–0.97	<0.001
Hemoglobin	0.97	0.97–0.98	<0.001	0.99	0.99–0.99	<0.001
Glucose	1.09	1.07–1.11	<0.001	1.04	1.00–1.07	0.028
Albumin	0.86	1.85–0.88	<0.001	0.97	0.95–0.99	0.013
Lactate	1.10	1.06–1.14	<0.001	1.08	1.05–1.11	<0.001
eGFR[f]	0.97	0.96–0.97	<0.001	0.99	0.99–0.99	<0.001
hs-CRP	1.05	1.04–1.05	<0.001	1.01	1.01–1.02	<0.001

AMI, acute myocardial infarction; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein.
[a]Adjusted for age; sex; concomitant diseases; diagnosis of AMI; Killip class grade; DBP; heart rate; BMI; hemoglobin; glucose; albumin; lactate; eGFR; and hsCRP. Quartile 2 had a SBP of 120–129 mmHg. $n = 5696$ with data on all covariates.
[b]Sex was set as1 for men, 2 for women, in the statistical analysis.
[c]Diagnosis of AMI was set as 0 for unstable angina, 1 for AMI.
[d]Degree of heart failure present on admission categorized by Killip class; *P* values were for comparisons with group of Killip class I.
[e]Calculated as weight in kilograms divided by height in meters squared.
[f]Calculated with Chronic Kidney Disease Epidemiology (CKD-EPI) equation.

High BP has been well studied and established as a major risk factor for cardiovascular outcomes in different clinical settings. In the last century, large epidemiology studies exposed the health dangers of high BP, followed by large landmark clinical trials demonstrating the benefits of BP reduction to a target of 140/90 mmHg for most adults. Meanwhile, BP-related variables have been included in many risk scores in patients with ACS. In the Thrombolysis in Myocardial Infarction (TIMI) risk score for unstable angina/NSTEMI, a set of at least three risk factors including hypertension, hypercholesterolemia, diabetes, smoking, and family history of coronary artery disease receives one point with an odds ratio of 1.54 (1.16–2.06) in the multiple regression model [14]. Whereas in the TIMI risk score for STEMI, SBP less than 100 mmHg is a strong risk factor for mortality and receives three points with a 40-fold graded increase in mortality at 30 days between those with a TIMI risk score of 0 and those with a score greater than 8 [15]. In the Global Registry of Acute Coronary Events (GRACE) postdischarge risk score, a validated prediction model for predicting 6-month mortality of patients with all forms of ACS, emphasis is also placed on lower SBP at presentation and a value of less than 100 mmHg provides 22 points [8,16]. The GRACE score can also accurately provide long-term (up to 4 years) prognostic information for patients at the time of discharge from the initial ACS [17]. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) risk model for predicting 30-day mortality of patients with AMI, five characteristics including age, SBP, Killip class, heart rate, and infarct location contained 90% of the prognostic information in the baseline clinical data, whereas diabetes, smoking, and history of hypertension accounted for only 2.5% of the risk of 30-day mortality [18]. These risk stratification scores indicate BP-related variables, especially BP levels at presentation, are important predictors for outcomes in patients with ACS [19]. Moreover, in the presence of cardiogenic shock, SBP is a main prognostic determinant with a reversed correlation for values under 80 mmHg on admission [20,21].

Few studies have investigated if admission BP levels per se influence outcomes in patients with ACS [22]. The Acute Coronary Syndrome Israel Survey (ACSIS) studied 7645 patients admitted with AMI and investigated the association between admission SBP and total mortality as well as cardiovascular events. In contrast to those with normal admission SBP (defined as 110–140 mmHg), patients with low SBP (<110 mmHg) displayed significantly increased hazard ratio for 7-day and 1-year all-cause mortality as well as 30-day major adverse cardiovascular events. Conversely, patients with high admission SBP (>140 mmHg) presented with a lower risk for the same end points [23]. In another study including 3943 patients with AMI treated at an Austrian tertiary care hospital, admission SBP 120 mmHg or less was associated with the worst outcome compared with normal SBP defined as 121–140 mmHg, whereas admission SBP greater than 160 mmHg was associated with the best outcome compared with normal admission BP. A 70% relative risk reduction for 1-year mortality in the highest vs. the lowest SBP category was documented [24]. Similar inverse association between admission supine SBP and 1-year total mortality was found by Stenestrand

et al. [25] who found that mortality of patients admitted for chest pain to be the lowest when admission SBP was in excess of 163 mmHg. However, this study included only patients admitted to the ICU because of chest pain, and AMI was only studied as a subgroup. Unlike the adult patients with AMI included and the inverse relation between admission SBP and 1-year all-cause mortality shown in these studies, our study included older patients with ACS and displayed J-curve association between admission SBP and 2-year cardiovascular mortality, but not all-cause mortality, suggesting the prognostic value of admission SBP may exhibit slight differences with respect to different population or ACS type.

Our findings concur with a study on patients with non-ST elevation ACS published by Lee *et al.* [26], who found an independent correlation between lower SBP and in-hospital mortality, whereas history of hypertension or use of antihypertensive medications did not affect these associations. On the other hand, in a prospective study on 11 292 Korean patients with STEMI, patients with normal SBP (defined as 100–139 mmHg) had a higher risk for in-hospital death compared with those with high BP (at least 140 mmHg), and higher rates of all-cause death and MACE during a median of 330 days of follow-up [27]. In a retrospective analysis on 7033 STEMI patients, comparison of admission SBP, DBP, pulse pressure, and mean arterial pressure showed that only SBP and pulse pressure were significantly associated with 30-day all-cause mortality, and patients with low admission SBP (defined as <110 mmHg) had a greater cumulative 30-day mortality [28]. More recently, in a prospective population-based study in 814 elderly French patients aged more than 75 years admitted for AMI, low average SBP (<125 mmHg) within the first 48 h after admission was an independent and powerful predictor of 1-year cardiovascular mortality [29]. Our results suggest a J-curve relationship between admission SBP and 2-year cardiovascular mortality in older patients admitted for ACS, with admission SBP of 120–129 mmHg representing the lowest risk of cardiovascular events and an increase in cardiovascular death below or above admission SBP of 120–129 mmHg. Furthermore, our data support admission SBP measurement could help to improve risk stratification in this particular population.

Early risk stratification of older patients with ACS is important in clinical decision regarding subsequent treatment and surveillance. Our study revealed that older patients admitted for ACS with the lowest quartile of SBP (<120 mmHg) had a greater cumulative 2-year cardiovascular mortality than those with quartile of SBP from 120 to 129 mmHg, regardless of a history of hypertension. Meanwhile, older patients admitted for ACS with higher quartiles of SBP (at least 130 mmHg) exhibited a trend towards increased risk for 2-year cardiovascular death. In addition, worse cardiac function, older age, diagnosis of AMI, and prior myocardial infarction are also independent predictors for 2-year cardiovascular mortality in this particular population. Our results support the feasibility of incorporating admission SBP in risk scoring models, such as the TIMI risk score for STEMI, the GRACE score, and the GUSTO risk model, and suggest low admission SBP should serve as a warning sign in older patients admitted for ACS.

Limitations

This study is a retrospective observational study and the reported relationship applies to BP measured after hospital admission for ACS, thus the results presented here could only be used to provide prognostic information in this particular context and are not applicable to the long-term (before or after the acute event) management of these patients. We did not adjust our analyses for some potential confounders, such as frailty, socioeconomic status, and mental health. Frailty is defined as a state of increased vulnerability to poor resolution of homoeostasis after a stress or event, which increases the risk of adverse outcomes, such as falls, delirium, and disability, and therefore, provides significant prognostic value for mortality and adverse events in elderly patients [30]. Also, socioeconomic status and dementia may be associated with increased mortality in older patients with ACS. Moreover, the underlying mechanisms for the association between increased risk of 2-year cardiovascular mortality and low admission SBP are not completely clear, may be multifactorial, and cannot be extrapolated from our observational findings.

In conclusion, in this population-based observational study in older patients hospitalized for ACS, a J-curve association existed between supine admission SBP and the risk of 2-year cardiovascular death, with a nadir at 120–129 mmHg. Moreover, low admission SBP (<120 mmHg) was an independent predictor of 2-year cardiovascular mortality in this particular population.

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Conflicts of interest

There are no conflicts of interest.

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