

# Association Between Pulse Pressure With All-Cause and Cardiac Mortality in Acute Coronary Syndrome: An Observational Cohort Study

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Wang M, Su W, Jiang C-Y, Li W-P, Chen H and Li H-W (2022) Association Between Pulse Pressure With All-Cause and Cardiac Mortality in Acute Coronary Syndrome: An Observational Cohort Study. Front. Cardiovasc. Med. 9:930755. doi: 10.3389/fcvm.2022.930755 **Background:** Pulse pressure (PP) is a surrogate of aortic stiffness, and reflects cardiac performance and stroke volume. Previous studies have indicated that PP was a robust predictor of cardiovascular outcomes and mortality. However, results have been mixed, and very few studies have focused on the association of PP with mortality in acute coronary syndrome (ACS). Thus, we aimed to investigate the relationship between admission PP and the prognosis of patients with ACS.

**Methods:** This cohort study included 10,824 patients diagnosed with ACS from the Cardiovascular Center Beijing Friendship Hospital Database Bank (CBDBANK) from January 2013 to October 2018. Patients with cardiogenic shock, malignancy, severe trauma and, no PP at admission were excluded. Restricted cubic spline and Cox proportional hazards regression were used to evaluate the association between PP and 1-year all-cause and cardiac mortality.

**Results:** In the whole cohort, a total of 237 (2.19%) all-cause deaths were reported at 1-year follow-up. Restricted cubic spline analysis suggested a J-shaped relationship between PP and mortality. Among patients with ACS, both lower and higher PP levels were related to an increased risk of mortality ( $P_{non-linear} < 0.001$ ); with a PP level of 30 or 80 mmHg, as compared with 50 mmHg, the adjusted hazard ratios for 1-year all-cause mortality were 2.02 (95% CI, 1.27–3.22) and 1.62 (95% CI, 1.13–2.33), respectively, after adjustments for potential confounders. Similar results were observed for cardiac deaths. The J-shaped relationship between PP and mortality remained in a series of subgroup analyses.

**Conclusion:** Our results suggested that both low and high PP were associated with an increased risk of mortality in patients with ACS.

Keywords: pulse pressure, acute coronary syndrome, all-cause mortality, cardiac mortality, cohort study

# INTRODUCTION

Arterial hypertension is one of the well-known risk factors for atherosclerosis (1) and can increase the risk of death in patients with acute coronary syndrome (ACS). Currently, the criteria for diagnosis, treatment, and evaluation of therapeutic efficacy for hypertension are mainly based on the levels of systolic blood pressure (SBP) and/or diastolic blood pressure (DBP). Historically, a linear relationship between increasing SBP and the risk of adverse cardiovascular outcomes has been reported (2, 3). The famous SPRINT (Systolic Blood Pressure Intervention Trial) study conducted at 102 clinical sites in the United States, suggested an aggressive treatment of SBP (<120 mmHg) in highrisk non-diabetic patients (4). However, aggressive reduction of blood pressure, particularly DBP, may impair myocardial perfusion and lead to an adverse outcome, especially in patients with ischemic heart disease.

Pulse pressure (PP) calculated as SBP minus DBP, has been indicated as a more robust prognostic predictor of cardiovascular disease than SBP, DBP, or mean arterial pressure (MAP) by numerous previous population-based studies (5-11). However, results have been mixed, and most of these studies focused on PP measured in non-acute cardiovascular situations. Very few studies have focused on the association of mortality with PP in ACS patients, and the studies that have been performed show inconsistent results (12-17). The majority of these studies (12-15) indicated a substantial prognostic value of low PP in patients with ACS, which may provoke confusion since some other studies (16, 17) have shown that high, rather than low, PP was associated with higher mortality and risk of adverse outcomes. In light of this disparity, this study aimed to further explore the relationship between PP and clinical outcomes across the spectrum of ACS.

# MATERIALS AND METHODS

#### **Study Design**

This was an observational cohort study. The Cardiovascular Center Beijing Friendship Hospital Database Bank (CBDBANK) collected the medical records of inpatients diagnosed with ACS in the Department of Cardiology of Beijing Friendship Hospital. Patients were under standard medical and interventional management for ACS. Diagnostic criteria for ACS (including ST-segment elevation myocardial infarction [STEMI], non-STsegment elevation myocardial infarction [NSTEMI], and unstable angina unstable angina pectoris [UAP]) were based on relevant guidelines (18, 19). Acute myocardial infarction (AMI) was defined as a typical rise and/or fall of cardiac troponin values with at least one value above the 99th percentile upper reference limit (URL) and at least one of the following: symptoms of acute myocardial ischemia; new significant ST segment or T wave change or new-onset left bundle branch block; development of pathologic Q wave in  $\geq 2$  contiguous electrocardiogram leads; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; and identification of intracoronary lesion

by angiography. UAP was defined as myocardial ischemia at rest or on minimal exertion in the absence of acute cardiomyocyte injury/necrosis.

The study was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University and performed according to the guidelines of the Helsinki Declaration.

### Population

A total of 11,666 inpatients diagnosed with ACS were collected in CBDBANK from January 2013 to October 2018. Patients with cardiogenic shock (clinical criteria: SBP < 90 mmHg for  $\geq$ 30 min or catecholamines to maintain SBP > 90 mmHg, and clinical pulmonary congestion and impaired end-organ perfusion [altered mental status, cold/clammy skin and extremities, urine output <30 ml/h, or lactate >2.0 mmol/L], or a class IV rating according to the Killip classification) (20, 21), malignancy, and severe trauma; patients who recently underwent surgical operations; and patients with no PP at admission were excluded. Overall, 10,824 patients were included in this study (**Figure 1**).

## **Measurement of Blood Pressure**

Blood pressure was measured by cardiologists using the validated upper arm medical electronic (OMRON HBP-1300 blood pressure monitor) or mercury sphygmomanometer immediately when patients were admitted to the Cardiology Department of Beijing Friendship Hospital. Those who had STEMI were measured after reperfusion. All patients lay down for at least 5 minutes in a quiet room before the blood pressure measurement, and the patient's upper arms were kept at the heart level. Measurements on both arms were taken, and the arm with a higher value was used as the reference. PP was defined as SBP minus DBP.

#### Covariates

Demographic characteristics, medical history, laboratory test results, diagnoses, and medical therapy were collected by a standardized procedure. Based on prior knowledge, the following covariates were collected including: age, gender, body mass index (BMI), heart rate, medical history (hypertension, diabetes mellitus, myocardial infarction, chronic kidney disease [CKD], stroke, dyslipidemia, chronic heart failure, and smoking), medication used before admission (dual-antiplatelet therapy [DAPT], angiotensin-converting enzyme inhibitor [ACEI] or angiotensin receptor blocker [ARB], beta-blocker, and statins), laboratory results (fasting plasma glucose [FPG], glycosylated hemoglobin [HbA1c], total cholesterol, triglyceride, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol, high sensitivity C-reactive protein [hs-CRP], peak value of cardiac troponin I [cTnI], peak value of N-terminal pro-brain natriuretic peptide [NT-proBNP], and estimated glomerular filtration rate [eGFR]), Killip class, diagnosis of atrial fibrillation, angiography findings (left main coronary artery lesion, multi-vessel lesion, chronic total occlusion lesion), and in-hospital treatments (percutaneous coronary intervention [PCI], DAPT, ACEI/ARB, beta-blocker and statins). Medical history was identified according to the self-reported history of diagnosis. Overnight fasting blood samples were obtained and



tested in a central laboratory by standard methods. eGFR was calculated using the MDRD (The Modification of Diet in Renal Disease) formula: [eGFR (ml/min/1.73 m<sup>2</sup>) = 175 × (serum creatinine)<sup>-1.154</sup> × (Age)<sup>-0.203</sup> × (0.742 if female) × (1.212 if African American)] (22). Echocardiograms were performed by expert cardiologists or certified sonographers. Left ventricular ejection fraction (LVEF) was assessed with echocardiography using the Simpsons method, with LVEF ≤ 50% indicating left ventricular systolic dysfunction. The coronary angiography and PCI operation were performed according to the standard techniques by experienced cardiologists.

## **Study Outcomes**

Patients' outcomes during hospitalization were collected and confirmed based on their medical records. Follow-up information, particularly vital signs (and date of death whenever applicable) was collected for each participant at 1, 3, and 6 months, and every year after discharge until death. This information was obtained by phone calls or from medical records if patients came to the outpatient clinic for a followup examination. The primary endpoint was 1-year all-cause mortality during follow-up. 1-year cardiac mortality was a secondary outcome. Cardiac death was defined as death caused by AMI, heart failure, or documented sudden cardiac death.

## **Statistical Analysis**

Clinical characteristics were presented as proportions, mean (standard deviation) or median (interquartile range). Baseline characteristics were summarized according to vital status at 1-year follow-up and compared between survivors and decedents using the  $\chi^2$  test, *t*-test, or Mann–Whitney U test, as appropriate.

Cox proportional hazards regression models were used to calculate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for PP and 1-year mortality. Our primary analysis was based on restricted cubic splines to facilitate detailed description of the dose-response curves between PP and all-cause mortality as well as cardiac mortality (23). Using spline regression, we calculated HRs and 95% CIs for specific admission PP values and depicted the shape of the overall doseresponse, and tested for linear and non-linear shapes of each association. Restricted cubic splines were fitted with 4 knots placed at the 5th, 35th, 65th, and 95th percentiles across the range of PP. The statistical significance (at the 0.05 level) of the overall association and the non-linearity of the risk curves was evaluated with Wald tests (23, 24). We enrolled the following confounders known to influence the prognosis of ACS in the spline Cox models: age, gender, BMI, previous diabetes mellitus, previous hypertension, previous myocardial infarction, current smoking, atrial fibrillation, previous DAPT, heart rate, LVEF < 50%, HbA1c, LDL-C, eGFR, the peak value of cTnI, angiography findings (left main coronary artery lesion, multi-vessel lesion, and chronic total occlusion lesion), and in-hospital treatments (PCI, DAPT, ACEI/ARB, and statins). Adjusted survival curves were calculated based on the final spline Cox model for 1-year all-cause and cardiac mortality at specific PP values (25).

In subgroup analyses, we examined results with separate splines in accordance with ACS types (UAP, AMI); age (<65 years,  $\geq$ 65 years); gender (male, female); BMI (<25 kg/m<sup>2</sup>,  $\geq$ 25 kg/m<sup>2</sup>); previous hypertension (with; without); previous diabetes mellitus (with; without); eGFR (<60 ml/min/1.73m<sup>2</sup>,  $\geq$ 60 ml/min/1.73m<sup>2</sup>); and smoking status (current smoker; non-smoker).

A *p*-value < 0.05 was considered statistically significant. All data analyses were carried out using the Stata software, version 17.0 (StataCorp LP, College Station, TX, United States), and R software, version 4.1.2 (R Foundation for Statistical Computing).

# RESULTS

The current study included 10,824 patients (Figure 1). Table 1 presents the summary of the baseline clinical characteristics and the laboratory test results according to vital status at 1-year follow-up. The PP levels were significantly higher in

#### TABLE 1 | Baseline characteristics by vital status at 1-year follow-up.

Ape, years65.2 (0.9)65.0 (0.8)7.5 (0.9)7.5 (0.9)7.5 (0.9)BMI, kop'n25.6 5.025.8 0.923.9 (0.4)0.001BMI, sop'n25.6 5.025.8 0.923.9 (0.4)0.001BMI, sop'n75.5 (11.3)75.6 (1.2)7.5 (11.2)0.001BMI, sop'n75.5 (11.3)75.6 (1.2)7.5 (11.2)0.001BMI, sop'n75.5 (11.3)75.6 (1.2)7.5 (11.2)0.001BMI, sop'n75.6 (1.2)7.5 (11.2)7.5 (11.2)0.001Heat rate, sop'n71.6 (2.0)7.6 (1.0)0.0020.001Modeal Bistory, No. (N)74.6 (10.5)9.6 (1.0)0.001Modeal Bistory, No. (N)74.6 (10.5)9.6 (1.0)0.001Modeal Bistory, No. (N)9.002 (2.2)9.7 (1.9)0.6 (0.0)Chronic Minifer Gine3008 (2.2)9.7 (1.9)0.6 (0.0)Stoke438 (0.4)402 (3.8)3.6 (3.4)0.001Chronic Minifer Gine73.0 (2.0)6.6 (0.0)6.6 (0.0)0.007Stoke30.8 (0.1)7.7 (2.5)0.20.20.2Chronic Martine73.6 (7.6 (3.6)7.7 (2.5)0.20.2Stoke30.8 (0.1)9.6 (1.0)0.0070.0070.007Loboter admission, No. (%)1.6 (1.0,2)7.7 (2.5)0.20.2Chronic Martine2.6 (2.6)7.6 (2.6)7.6 (2.6)0.007Loboter admission, No. (%)1.6 (1.0,2)1.1 (0.2)1.0 (0.1)0.001Chronic Martine2.6 (0		Total population (n = 10,824)	Survivors ( <i>n</i> = 10,587)	Decedents ( <i>n</i> = 237)	P-value
Maie, No. (%)GSB (SA7)G722 (S3.8)117 (202)0.5.8SBP, mmHg131 (16.8)131 (17.8)(32.9.4.1)-0.001SBP, mmHg131 (16.8)151 (17.8)(56.01 (56.0)60.2 (21.2)-0.001Mear Lab, Nom7.17 (12.9)7.15 (12.7)7.07.71 (8.2)-0.001Mear Lab, Nom7.58 (17.3)7.66 (16.6)60.2 (21.3)-0.001Medra Labstory, No. (%)8309 (52.2)3710 (50.0)9.04 (13.0)-0.001More Labstory, No. (%)3209 (52.2)3710 (50.0)9.04 (13.0)-0.001More Labstory, No. (%)435 (12.0)440 (10.0)45 (10.0)-0.001More Labstory, No. (%)435 (12.0)440 (10.0)45 (13.0)-0.001Stroke138 (17.4)45 (16.0)48 (17.4)50 (21.1)-0.001Stroke138 (12.0)470 (12.0)86 (15.0)85 (15.0)-0.001Stroke138 (12.0)3008 (4.1)300 (4.	Age, years	65.2 (10.9)	65.0 (10.8)	73.5 (11.2)	<0.001
BML gon BDR, mody28.8 (8.6)28.8 (8.6)28.8 (8.6)28.8 (8.6)28.9 (8.6)4.0001DBR, mody75.5 (11.3)75.6 (11.2)75.2 (24.0)0.403DBR, mody75.5 (11.3)75.6 (11.2)79.7 (18.2)0.001Haat rate, bpm71.7 (12.9)71.5 (12.7)79.7 (18.2)0.001Madcal fastory, No. (%)77.7 (12.9)71.7 (12.9)79.7 (18.2)0.001Mocardial finatcion92.6 (92.2)97.7 (8.9)45 (19.0)0.002Mocardial finatcion92.6 (92.2)97.7 (8.9)45 (19.0)0.001Mocardial finatcion92.6 (92.2)97.7 (8.9)45 (19.0)0.001Stroke163.9 (17.5)19.6 (17.4)0.021.1)0.11Opcardial finatcion73.0.765 (6.9)8.3.4)0.001Stroke73.0.765 (6.9)8.3.4)0.001Stroke29.67 (25.7)0.4260.0010.001Stroke29.67 (25.7)0.4260.0010.001Stroke29.67 (25.7)0.4260.0010.001Stroke29.67 (25.7)0.4260.0010.001Stroke29.67 (25.7)0.4260.0010.001Date table29.67 (25.7)0.0010.0010.001Stroke29.67 (25.7)0.266 (15.0)7.7 (25.9)0.001Loberta durission, No. (%)51.67 (25.0)0.0010.0010.001Date table29.67 (25.1)0.016 (15.0)0.0010.001Date table29.67 (	Male, No. (%)	6899 (63.7)	6752 (63.8)	147 (62.0)	0.58
SBP, mm/sj(131,6116,8)(134,6116,8)(136,6112)(75,0112,3)(0.03)PP, mm/sj(54,115,8)(56,015,6)(0.22,13,3)(0.01)Medical history, No. (%)(71,512,7)(73,710,50,3)(73,700,75,9)(0.02,710,70,73,9)Pypertosion(766,610,7)(74,76,70,50)(99,94,14,8)(0.02,70,70,73,9)(0.02,70,70,73,9)Mocardial infraction(92,92,9,2)(94,76,8)(13,11,8),1)(0.01,70,10,10,10,10,10,10,10,10,10,10,10,10,10	BMI, kg/m <sup>2</sup>	25.8 (3.6)	25.8 (3.6)	23.9 (4.1)	< 0.001
DBP, mmlig75.6 (11.3)76.0 (11.2)70.7 (19.2)0.48Hear rate, bpm71.7 (12.9)71.5 (12.7)79.7 (18.2)<0.001	SBP, mmHg	131.6 (18.8)	131.6 (18.6)	135.2 (24.4)	0.003
PP, mmlg66 (16.8)7.7 (12.9)7.7 (12.7)7.7 (12.9)7.0 (12.7)7.7 (12.9)7.0 (12.7)7.7 (12.9)	DBP, mmHg	75.5 (11.3)	75.6 (11.2)	75.0 (12.9)	0.48
Heart alpon71,7 (7.2.9)71,7 (7.2.7)70,7 (18.2)-0.001Mycerclai linkay, No. (%)7056 (70.7)7476 (70.6)180 (75.6)0.074Diabetes mellitus389 (85.2)3710 (35.0)94 (1.9.0)0.032Mycerclai linkarcbion982 (9.2)947 (8.9)45 (10.4)0.032Okorabi1833 (17.3)450 (2.1)45 (10.4)0.011Chronic kidney disease433 (4.0)442 (3.8)311(3.1)-0.001Okorabi1833 (17.4)65 (0.6)8.6.4)0.008Chronic kidney disease73 (0.7)65 (0.0)8.6.4)0.009Smoking393 (9.4.1)3030 (4.3)82 (6.2)0.009Smoking3765 (15.0)3708 (35.0)77 (2.5)0.42Satura256 (22.5)2468 (22.6)50 (21.1)0.009ACEI/ARB3765 (15.0)3708 (35.0)77 (2.5)0.42Beta-blocker256 (22.5)2468 (22.6)50 (21.1)0.001ACEI/ARB3765 (15.0)3708 (35.0)70 (3.1)0.001ACEI/ARB43 (1.0)4.41 (1.0)1.01.010.0010.001ACEI/ARB4.51 (1.0)1.01.010.0010.0010.001ACEI/ARB3705 (15.0)4.41 (1.0)0.0100.0010.001ACEI/ARB4.51 (1.0)1.01.010.0010.0010.001ACEI/ARB4.51 (1.0)1.01.010.0010.0010.001ACEI/ARB4.51 (1.0)1.01.010.0010.001ACEI/AR	PP, mmHg	56.1 (15.8)	56.0 (15.6)	60.2 (21.3)	< 0.001
Medical history, No. (%)         TAGE (70.7)         747 (70.6)         190 (74.5)         0.074           Hypertension         3609 (85.2)         3710 (85.0)         99 (41.6)         0.032           Myceardial infarction         92 (9.2)         947 (8.9)         451 (9.0)         <0.001	Heart rate, bpm	71.7 (12.9)	71.5 (12.7)	79.7 (18.2)	< 0.001
Hypertension768 (707)7476 (708)100 (75.9)0.074Disbetes mellins3390 (55.2)3710 (55.0)96 (41.6)0.032Myccardial infarction92 (9.2)947 (8.3)45 (19.0)-0.001Chronic kidney disease4381 (4.0)442 (5.3)311 (3.1)-0.001Stroke1838 (17.5)1843 (17.4)50 (2.1)0.141Dyslipciemia4852 (44.8)4766 (45.0)8.6.4)-0.001Smoking0380 (34.1)0380 (43.3)03.06.4)0.008Smoking2546 (23.5)2466 (23.6)50 (21.1)0.029DAPT1708 (15.8)1656 (15.6)50 (21.1)0.37Statins2546 (23.5)2466 (23.6)50 (21.1)0.37Statins2546 (23.5)2466 (23.6)50 (21.1)0.37Statins64 (1.3)64 (1.3)67 (1.9)-0.001TC, mmol/L64 (1.3)64 (1.3)67 (1.9)0.009Libotacy values11 (0.3)11 (0.3)11 (0.3)0.010TC, mmol/L24 (0.8)24 (0.8)24 (0.9)0.40Lib-C, mmol/L24 (0.8)24 (0.8)0.0010.001Lib-C, mmol/L11 (0.3)11 (0.3)11 (0.3)0.001Lib-C, mmol/L20 (0.8, 51)20 (0.8, 59)55 (2.0, 17.2)-0.001Lib-C, mmol/L20 (0.8, 51)20 (0.8, 59)55 (2.0, 17.2)-0.001Lib-C, mmol/L10 (0.0, 0.1)0.1 (0.0, 1.4)-0.001-0.001Lib-C, mmol/L20 (0.8, 51)	Medical history, No. (%)				
Diabetes meliticaB300 (B5.2)B71 (B3.0)B94 (1.8)C.002Myocardial infarction992 (D.2)947 (B3)45 (10.3)<.0001	Hypertension	7656 (70.7)	7476 (70.6)	180 (75.9)	0.074
Myceardial infarction992 (b2)947 (8.3)45 (19.0)-0.001Chronic kidney disease433 (4.0)402 (3.8)31 (13.1)-0.001Dysibic1880 (17.5)1843 (17.4)50 (21.1)0.14Dysibic4862 (44.8)4766 (46.0)88 (86.3)-0.001Chronic heart failure73 (8.7)65 (0.8)8.13 (4.0)-0.001Smoking3080 (4.1)3080 (4.3)65 (21.9)0.002Smoking3080 (65.1)156 (15.6)52 (21.9)0.002ACEL/ARB3766 (5.6)22.9 (2.5)0.42Bata-blocker254 (62.3)2496 (23.6)50 (21.1)0.37Statins2867 (67.2)24.2850 (21.1)0.37Statins2867 (67.2)6.4 (1.3)6.4 (1.3)6.001HbA1c,%6.4 (1.3)6.4 (1.0)4.2 (1.2)0.008TG, mmol/L1.4 (1.0, 2.0)1.4 (10, 2.0)1.3 (0.9, 1.5)-0.001HbA1c,%6.4 (1.3)6.4 (1.3)6.4 (1.3)6.1020.001HbA1c,%6.4 (1.3)1.1 (0.3)1.1 (0.3)1.1 (0.3)0.101HbA1c,%6.4 (1.3)1.1 (0.3)1.1 (0.3)0.0010.001HbA1c,%6.4 (1.9.4)2.4 (0.8)2.4 (0.8)2.4 (0.8)2.4 (0.9)0.001HbA1c,%0.0 (0.0, 0.1)0.0 (0.0, 0.1)0.1 (0.0, 1.1)0.0010.0010.001HbC-GRP mg/L2.0 (0.8, 0.1)2.0 (0.8, 0.1)2.0 (0.8)2.9 (0.8)2.9 (0.8)2.9 (0.8)HbA1c,%	Diabetes mellitus	3809 (35.2)	3710 (35.0)	99 (41.8)	0.032
Chronic kidney disease433 (4,0)402 (2.8)31 (1.3,1)-0.01Stroke1930 (7.5)1943 (7.4)60 (2.1)0.141Dysipiderina4352 (4.8)4766 (45.0)86 (6.3)0.008Chronic heart failure77 (0.7)65 (0.8)8 (3.4)-0.001Smoking2983 (4.4)2803 (4.3)62 (2.1)0.013Medication used before admission, No. (%)0.0020.013Medication used before admission, No. (%)0.0230.0230.021ACEL/ARB3766 (6.5)77 (82.5)0.4240.003ACEL/ARD2847 (2.5)249 (9.25.3)50 (2.1.1)0.370Statins2877 (6.7.)2424 (2.8.3)45 (15.0)0.007Laboratory values4.1 (3.2)6.4 (1.3)6.7 (1.5)-0.001Laboratory values4.3 (1.0)4.3 (1.0)4.3 (1.0)4.0 (1.5)-0.001TG, mmol/L1.4 (0.3)1.4 (0.3)1.4 (0.3)0.010-0.001LDL-C, mmol/L2.4 (0.8)2.4 (0.8)2.4 (0.8)0.010LDL-C, mmol/L1.4 (0.3)1.0 (0.3)1.1 (0.3)0.010-0.001LDL-C, mmol/L2.0 (0.8.6.1)2.0 (0.8.5.9)5.5 (2.0, 17.2)-0.001LDL-C, mmol/L2.0 (0.8.6.1)2.0 (0.8.5.9)5.5 (2.0, 17.2)-0.001LDL-C, mmol/L2.0 (0.8.6.1)2.0 (0.8.5.9)5.5 (2.0, 17.2)-0.001LDL-C, mmol/L1.4 (0.3)2.0 (0.8.1)0.0 (0.1, 0.1.4)-0.001LDL-C, m	Myocardial infarction	992 (9.2)	947 (8.9)	45 (19.0)	< 0.001
Stroke1893 (17.5)1843 (17.4)50 (21.1)0.14Dysipciemia4852 (44.8)4766 (45.0)86 (65.3)0.008Ornoic heart failure73 (0.7)65 (0.6)68 (4.3)0.008Smoking0863 (3.1)0850 (3.4.3)63 (26.5)0.009Medication used before admission, No. (%)7700 (15.8)1666 (15.6)52 (1.9)0.009OEI/ARS2766 (5.0)3708 (55.0)3708 (55.0)570 (2.1)0.37Statins2867 (26.7)2496 (23.6)50 (21.1)0.37Statins2867 (26.7)2496 (23.6)50 (21.1)0.37Statins2647 (3.3)64 (1.4)69 (3.3)<0.001The, mmol/L6.1 (2.2)6.1 (2.2)6.9 (3.3)<0.001The, mmol/L6.1 (1.2)1.4 (1.0, 2.0)1.4 (1.0, 2.0)1.3 (0.9, 1.5)<0.001The, mmol/L1.4 (1.0, 2.0)1.4 (1.0, 2.0)1.3 (0.9, 1.5)<0.001The, mmol/L2.4 (0.8)2.4 (0.8)5.2 (1.72)<0.001DL-C, mmol/L2.4 (0.8)6.4 (2.0.1)6.4 (1.0.0)<0.010Desk value of Th, ng/mL2.0 (0.8, 6.1)2.0 (0.8, 5)5.2 (1.72)<0.001Pesk value of Th, ng/mL0.00 (0.0.0.1)0.00 (0.0.1)0.00 (0.0.1)0.00 (0.0.1)0.00 (0.0.1)Pesk value of Th, ng/mL2.0 (0.51)5.0 (2.0.12)<0.001<0.001Desk value of Th, ng/mL2.0 (2.5)7.0 (0.01)<0.001<0.001Current Strest2.0 (0.51)5.0 (2.0.1)<0.001<	Chronic kidney disease	433 (4.0)	402 (3.8)	31 (13.1)	< 0.001
Dysliperini4852 (44.8)4766 (45.0)86 (64.3)0.008Chronic heart failure73 (0.7)65 (0.6)8 (3.4)-0.001Smoking3683 (34.1)3633 (34.3)653 (26.5)0.018Medication used before admission, No. (%)I1656 (15.6)52 (21.9)0.002DAPT708 (15.6)2708 (35.0)77 (82.5)0.422ACEL/ARB2786 (62.3)2496 (23.6)270 (21.1)0.37Statins2897 (26.7)2842 (28.2)45 (19.0)0.007Laboratory valuesF77787970FPG, mmo/L4.3 (1.0)4.4 (1.3)6.7 (1.5)<0.001HAA15,%6.4 (1.3)6.4 (1.3)6.4 (1.3)6.7 (1.5)<0.001Cho, mmo/L1.4 (1.0, 2.0)1.4 (1.0, 2.0)1.5 (0.9, 1.5)<0.001LD-C, mmo/L1.4 (1.0, 2.0)1.1 (0.3)1.1 (0.3)0.018HD-C, mmo/L1.4 (1.0, 2.0)1.1 (0.3)0.010<0.010LD-C, mmo/L2.4 (0.8)2.4 (0.8)2.4 (0.8)2.4 (0.8)0.010LD-C, mmo/L1.0 (3.0)1.1 (0.3)1.1 (0.3)0.011<0.010LD-C, mmo/L1.4 (1.0, 2.0)1.4 (1.0, 2.0)5.5 (2.0, 17.2)<0.001LD-C, mmo/L2.4 (0.8)2.6 (2.6, 1)5.6 (2.0, 17.2)<0.001Desk value of Thi, ng/mL0.0 (0.0, 0.1)0.0 (0.0, 0.1)0.0 (0.0, 0.1)0.0 (0.0, 0.1)LD-C, mmo/L2.0 (0.01)0.0 (0.0, 0.1)0.0 (0.0, 0.1)0.0 (0.0, 0.1)0.0 (0.0, 0.1) <td>Stroke</td> <td>1893 (17.5)</td> <td>1843 (17.4)</td> <td>50 (21.1)</td> <td>0.14</td>	Stroke	1893 (17.5)	1843 (17.4)	50 (21.1)	0.14
Chrone heart failure73 (0.7)65 (0.6)8 (2.4)-0.001Smoking3630 (34.1)3630 (34.3)63 (26.5)0.013Medication used before admission, No. (%)1708 (15.8)1565 (15.6)52 (21.9)0.009DAPT1708 (15.8)3766 (50.6)57 (22.5)0.42Beta-blocker2546 (23.5)2496 (23.6)50 (21.1)0.37Statins287 (26.7)2496 (23.6)50 (21.1)0.37Laboratory valuesFPG, mmol/L6.4 (1.3)6.4 (1.3)6.7 (1.5)<0.001	Dyslipidemia	4852 (44.8)	4766 (45.0)	86 (36.3)	0.008
Sneking3693 (34.1)3630 (34.3)652 (26.9)0.013Medication used before admission, No. (%)7708 (15.6)1656 (15.6)52 (21.9)0.009ACEI/ARB3756 (52.0)3706 (52.0)77 (82.5)0.42Beta-block2546 (25.2)2469 (23.6)455 (19.0)0.007Laboratory values57 (25.7)242 (26.8)45 (19.0)0.007Indoratory values6.1 (2.2)6.1 (2.2)6.9 (3.3)-0.001HbA1c, %6.4 (1.3)6.4 (1.3)6.7 (1.5)-0.001TC, mmol/L1.4 (1.0, 2.0)1.4 (10, 2.0)1.3 (0.9, 1.5)-0.001DL-C, mmol/L1.4 (1.0, 2.0)1.4 (10, 2.0)1.3 (0.9, 1.5)-0.001DL-C, mmol/L1.1 (0.3)1.1 (0.3)1.1 (0.3)-0.001DL-C, mmol/L0.0 (0.0, 0.1)0.0 (0.0, 1.1)-0.001DL-C, mmol/L0.0 (0.0, 0.1)0.0 (0.0, 1.1)-0.001DL-C, mmol/L0.0 (0.0, 0.1)0.0 (0.0, 1.1)-0.001DL-C, mmol/L0.0 (0.0, 0.1)0.0 (0.0, 0.1)-0.001DL-C, mmol/L0.0 (0.0, 0.1)0.0 (0.0, 0.1)0.0 (0.0, 0.1)DL-C, STEM (SC	Chronic heart failure	73 (0.7)	65 (0.6)	8 (3.4)	< 0.001
Medication used before admission, No. (%)708 (15.6)52 (21.9)0.042DAPT3786 (35.0)3708 (35.0)77 (32.5)0.42Beta-blocker2546 (23.5)2408 (23.6)50 (21.1)0.37Statina2887 (26.7)2408 (23.6)50 (21.1)0.37Laboratory values6.1 (2.2)6.9 (3.3)<0.001	Smoking	3693 (34.1)	3630 (34.3)	63 (26.6)	0.013
DAPT1708 (15.8)1656 (15.6)52 (21.9)0.009ACE/ARB3785 (35.0)3708 (35.0)77 (22.3)0.42Bata-blocker2566 (23.5)2469 (25.6)50 (21.1)0.37Statins2887 (26.7)2842 (26.8)45 (19.0)0.007Laboratory valuesFFG, mm0/L6.1 (2.2)6.1 (2.2)6.9 (3.3)<0.001	Medication used before admission, No. (%)				
ACE/ARB3785 (35.0)3708 (35.0)77 (32.5)0.42Beta-blocker2564 (23.5)2496 (23.6)50 (21.1)0.377Statins2576 (23.5)2492 (26.8)45 (19.0)0.007Labractory values </td <td>DAPT</td> <td>1708 (15.8)</td> <td>1656 (15.6)</td> <td>52 (21.9)</td> <td>0.009</td>	DAPT	1708 (15.8)	1656 (15.6)	52 (21.9)	0.009
Beta-blocker2546 (2.5.)2496 (23.6.)50 (21.1)0.37Statins2687 (26.7.)2492 (26.8.)450 (19.0.)0.07Statins2887 (26.7.)2842 (26.8.)451 (19.0.)0.07FPG, mmol/L6.1 (2.2)6.1 (2.2)6.9 (3.3.)-0.001HbAtc,%6.4 (1.3)6.4 (1.3.)6.7 (1.5.)-0.001Cr, mmol/L4.3 (1.0.)4.3 (1.0.)4.2 (1.2.)0.089TG, mmol/L1.4 (1.0.2.0)1.4 (1.0.2.0)1.3 (0.9, 1.5)-0.001LDL-C, mmol/L2.0 (0.8, 6.1)2.0 (0.8, 5.9)5.5 (2.0, 17.2)-0.001LDL-G, mmol/L0.0 (0.0, 0.1)0.0 (0.0, 0.1)0.1 (0.0, 1.4)-0.001Peak value of Thi, ng/mL0.0 (0.0, 0.1)0.0 (0.0, 0.1)0.1 (0.0, 1.4)-0.001Peak value of Thi, ng/mL287 (119, 844)287 (116, 770)4346 (755, 16066)-0.001Initial diagnosis, No. (%)	ACEI/ARB	3785 (35.0)	3708 (35.0)	77 (32.5)	0.42
Stains2887 (26.7)2842 (26.8)45 (19.0)0.007Laboratry valuesFPG, mmo/L6.1 (.2.)6.1 (.2.)6.9 (3.3)0.001HbA1c,%6.4 (1.3)6.4 (1.3)6.4 (1.3)6.7 (1.5)<0.001TG, mmo/L4.3 (1.0)4.3 (1.0)4.4 (1.0. 2.0)1.3 (0.9, 1.5)<0.001LDL-C, mmo/L2.4 (0.8)2.4 (0.8)2.4 (0.8)2.4 (0.9)0.40HDL-C, mmo/L0.00 (0.0, 1)0.1 (0.3, 1.5)<0.001LDC-R, mmo/L0.00 (0.0, 0.1)0.00 (0.0, 0.1)0.10 (0.1, 4.0)<0.001PecR value of rTn, ng/mL0.0 (0.0, 0.1)0.0 (0.0, 0.1)0.10 (0.1, 4.0)<0.001Pesk value of rTn, ng/mL0.0 (0.0, 0.1)0.0 (0.0, 0.1)0.10 (0.1, 4.0)<0.001Pesk value of rTn, ng/mL0.0 (0.0, 0.1)0.0 (0.0, 0.1)0.10 (0.1, 4.0)<0.001Pesk value of rTn, ng/mL0.0 (0.0, 0.1)0.0 (0.0, 0.1)0.10 (0.1, 4.0)<0.001Pesk value of rTn, ng/mL0.0 (0.0, 0.1)0.0 (0.0, 0.1)0.10 (0.1, 4.0)<0.001Pesk value of rTn, ng/mL0.0 (0.0, 0.1)0.0 (0.0, 0.1)0.10 (0.1, 4.0)<0.001Pesk value of rTn, ng/mL0.0 (0.0, 0.1)0.0 (0.0, 0.1)0.10 (0.1, 4.0)<0.001Pesk value of rTn, ng/mL0.0 (0.0, 0.1)0.0 (0.0, 0.1)0.10 (0.1, 4.0)<0.001Pesk value of rTn, ng/mL0.0 (0.0, 0.1)0.0 (0.0, 0.1)0.10 (0.1, 4.0)<0.001Pesk value of rTn, ng/mL0.0 (0.0)0.0 (0.0)0.0 (0.0)<0.001<	Beta-blocker	2546 (23.5)	2496 (23.6)	50 (21.1)	0.37
Laboratory values         FPG, mmol/L         6.1 (2.2)         6.4 (1.2)         6.9 (3.3)         <0.001           FPG, mmol/L         6.4 (1.3)         6.4 (1.3)         6.4 (1.3)         6.9 (3.3)         <0.001	Statins	2887 (26.7)	2842 (26.8)	45 (19.0)	0.007
FPG, mmol/L         6.1 (2.2)         6.1 (2.2)         6.9 (3.3)         <0.001           HbAtc,%         6.4 (1.3)         6.4 (1.3)         6.7 (1.5)         <0.001	Laboratory values				
HbAte,%         6.4 (1.3)         6.4 (1.3)         6.7 (1.5)         <0.001           TC, mmol/L         4.3 (1.0)         4.3 (1.0)         4.2 (1.2)         0.089           TG, mmol/L         1.4 (1.0, 2.0)         1.4 (1.0, 2.0)         1.3 (0.9, 1.5)         <0.001	FPG, mmol/L	6.1 (2.2)	6.1 (2.2)	6.9 (3.3)	< 0.001
TC, mmol/L         4.3 (1.0)         4.3 (1.0)         4.2 (1.2)         0.089           TG, mmol/L         1.4 (1.0, 2.0)         1.3 (0.9, 1.5)         <0.001	HbA1c,%	6.4 (1.3)	6.4 (1.3)	6.7 (1.5)	<0.001
Tô, mmol/L         1.4 (10, 2.0)         1.4 (10, 2.0)         1.3 (0.9, 1.5)         <0.001           LDL-C, mmol/L         2.4 (0.8)         2.4 (0.8)         2.4 (0.9)         0.40           HDL-C, mmol/L         1.1 (0.3)         1.1 (0.3)         1.1 (0.3)         0.11 (0.3)         0.018           hs-CRP, mg/L         2.0 (0.8, 6.1)         2.0 (0.8, 5.9)         5.5 (2.0, 17.2)         <0.001           LVEF,%         64.0 (9.3)         64.2 (9.1)         54.4 (13.0)         <0.001           Peak value of cTnl, ng/mL         0.0 (0.0, 0.1)         0.0 (0.0, 0.1)         0.1 (0.0, 1.4)         <0.001           Peak value of NT-proBNP, pg/mL         287 (118, 844)         287 (116, 77)         4346 (785, 1606)         <0.001           UAP         7705 (71.2)         7626 (72.0)         79 (33.3)          <0.001           UAP         3119 (28.5)         2951 (28.0)         158 (66.7)         <0.001           STEMI         1611 (14.9)         1520 (14.4)         91 (38.4)         <0.001           JTEMI         1611 (14.9)         1520 (14.4)         91 (38.4)         <0.001           JTEMI         1611 (14.9)         1520 (14.4)         91 (38.4)         <0.001           JTEMI         6516 (6.5)         5125 (52.1	TC, mmol/L	4.3 (1.0)	4.3 (1.0)	4.2 (1.2)	0.089
LDC, mmol/L         2.4 (0.8)         2.4 (0.8)         2.4 (0.9)         0.40           HDL-C, mmol/L         1.1 (0.3)         1.1 (0.3)         1.1 (0.3)         0.018           hs-CRP, mg/L         2.0 (0.8, 6.1)         2.0 (0.8, 5.9)         5.5 (2.0, 17.2)         <0.001	TG, mmol/L	1.4 (1.0, 2.0)	1.4 (1.0, 2.0)	1.3 (0.9, 1.5)	<0.001
HDL-C, mmol/L         1.1 (0.3)         1.1 (0.3)         1.1 (0.3)         1.1 (0.3)         0.018           hs-GRP, mg/L         2.0 (0.8, 6.1)         2.0 (0.8, 5.9)         5.5 (2.0, 17.2)         <0.001           LVEF,%         64.0 (9.3)         64.2 (9.1)         54.4 (13.0)         <0.001           Peak value of Tr1, ng/mL         0.0 (0.0, 0.1)         0.0 (0.0, 0.1)         0.1 (0.0, 1.4)         <0.001           Peak value of Tr-proBNP, pg/mL         287 (119, 844)         287 (116, 770)         4346 (785, 16066)         <0.001           Peak value of Tr-proBNP, pg/mL         287 (119, 844)         287 (116, 770)         4346 (785, 16066)         <0.001           Uap         7705 (71.2)         7626 (72.0)         79 (33.3)           <0.001           UAP         7705 (71.2)         7626 (72.0)         79 (33.4)           <0.001           UAP         7705 (71.2)         7626 (72.0)         79 (33.3)              MII         3119 (28.8)         2961 (28.0)         158 (66.7)               MII         1008 (13.9)         1441 (13.6)         67 (28.3)                <	LDL-C, mmol/L	2.4 (0.8)	2.4 (0.8)	2.4 (0.9)	0.40
hs-CRP, mg/L         2.0 (0.8, 6.1)         2.0 (0.8, 5.9)         5.5 (2.0, 17.2)         <0.001           LVEF,%         64.0 (0.3)         64.2 (9.1)         54.4 (13.0)         <0.001	HDL-C, mmol/L	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	0.018
LVEF, %         64.0 (9.3)         64.2 (9.1)         54.4 (13.0)         <0.001           Peak value of CTnl, ng/mL         0.0 (0.0, 0.1)         0.0 (0.0, 0.1)         0.1 (0.0, 1.4)         <0.001	hs-CRP, mg/L	2.0 (0.8, 6.1)	2.0 (0.8, 5.9)	5.5 (2.0, 17.2)	<0.001
Peak value of cTnl, ng/mL         0.0 (0.0, 0.1)         0.0 (0.0, 0.1)         0.1 (0.0, 1.4)         <0.001           Peak value of NT-proBNP, pg/mL         287 (119, 844)         287 (116, 770)         4346 (785, 16066)         <0.001	LVEF.%	64.0 (9.3)	64.2 (9.1)	54.4 (13.0)	<0.001
Peak value of NT-proBNP, pg/mL         287 (119, 844)         287 (116, 77)         4346 (785, 16066)         <0.001           eGFR, ml/min/1.73m <sup>2</sup> 80.3 (21.4)         80.8 (21.0)         59.9 (25.5)         <0.001	Peak value of cTnl, ng/mL	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	0.1 (0.0, 1.4)	<0.001
eGFR, ml/min/1.73m <sup>2</sup> 80.3 (21.4)         80.8 (21.0)         59.9 (25.5)         <0.001           Initial diagnosis, No. (%)         -         -         -         -         -         -         -         0.001           UAP         7705 (71.2)         7626 (72.0)         79 (33.3)         -	Peak value of NT-proBNP, pg/mL	287 (119, 844)	287 (116, 770)	4346 (785, 16066)	<0.001
Initial diagnosis, No. (%)         -0.001           UAP         7705 (71.2)         7626 (72.0)         79 (33.3)           AMI         3119 (28.8)         2961 (28.0)         158 (66.7)           NSTEMI         1611 (14.9)         1520 (14.4)         91 (38.4)           STEMI         1601 (14.9)         1520 (14.4)         91 (38.4)           STEMI         1500 (51.5)         5125 (52.1)         65 (28.5)           II         4230 (42.0)         4113 (41.8)         117 (51.3)           III         651 (6.5)         605 (6.1)         46 (20.2)           Atrial fibrillation         671 (6.2)         624 (5.9)         47 (19.8)         <0.001	eGFR, ml/min/1.73m <sup>2</sup>	80.3 (21.4)	80.8 (21.0)	59.9 (25.5)	<0.001
UAP         7705 (71.2)         7626 (72.0)         79 (33.3)           AMI         3119 (28.8)         2961 (28.0)         158 (66.7)           NSTEMI         1611 (14.9)         1520 (14.4)         91 (38.4)           STEMI         1508 (13.9)         1441 (13.6)         67 (28.3)           Killip class, No. (%)              I         5190 (51.5)         5125 (52.1)         65 (28.5)           II         4230 (42.0)         4113 (41.8)         117 (51.3)           III         651 (6.5)         605 (6.1)         46 (20.2)           Atrial fibrillation         671 (6.2)         624 (5.9)         47 (19.8)         <0.001           Angiography findings, No. (%)           <0.001         <0.001           LM lesion         940 (8.7)         915 (8.6)         25 (10.5)         0.30           Multi-vessel lesion         7130 (65.9)         7026 (66.4)         104 (43.9)         <0.001           Chronic total occlusion lesion         291 (21.2)         2238 (21.1)         53 (22.4)         0.65           In-hospital treatments, No. (%)           S949 (55.0)         5834 (55.1)         115 (48.5)         0.001           DAPT         59	Initial diagnosis, No. (%)		( ),		<0.001
AMI         3119 (28.)         2961 (28.0)         158 (66.7)           NSTEMI         1611 (14.9)         1520 (14.4)         91 (38.4)           STEMI         1508 (13.9)         1441 (13.6)         67 (28.3)           Killip class, No. (%)              I         5190 (51.5)         5125 (52.1)         65 (28.5)           II         4230 (42.0)         4113 (41.8)         117 (51.3)           III         651 (6.5)         605 (6.1)         46 (20.2)           Atrial fibrillation         671 (6.2)         605 (6.1)         46 (20.2)           Angiography findings, No. (%)              LM lesion         940 (8.7)         915 (8.6)         25 (10.5)         0.30           Multi-vessel lesion         7130 (65.9)         7026 (66.4)         104 (43.9)         <0.001	UAP	7705 (71.2)	7626 (72.0)	79 (33.3)	
NSTEMI         1611 (14.9)         1520 (14.4)         91 (38.4)           STEMI         1508 (13.9)         1441 (13.6)         67 (28.3)           Killip class, No. (%)              I         5190 (51.5)         5125 (52.1)         65 (28.5)           II         4230 (42.0)         4113 (41.8)         117 (51.3)           III         651 (6.5)         605 (6.1)         46 (20.2)           Atrial fibrillation         671 (6.2)         624 (5.9)         47 (19.8)         <0.001           Angiography findings, No. (%)         U         U         U         0.001           LM lesion         940 (8.7)         915 (8.6)         25 (10.5)         0.30           Multi-vessel lesion         7130 (65.9)         7026 (66.4)         104 (43.9)         <0.001           Chronic total occlusion lesion         2291 (21.2)         2238 (21.1)         53 (22.4)         0.65           In-hospital treatments, No. (%)         PCI         5567 (51.4)         5490 (51.9)         77 (32.5)         <0.001           DAPT         5949 (55.0)         5834 (55.1)         115 (48.5)         0.044           ACEL/ARB         6034 (55.7)         5926 (56.0)         108 (45.6)         0.001	AMI	3119 (28.8)	2961 (28.0)	158 (66.7)	
STEMI         1508 (13.9)         1441 (13.6)         67 (28.3)           Killip class, No. (%)           <0.001	NSTEMI	1611 (14.9)	1520 (14.4)	91 (38.4)	
Killip class, No. (%)	STEMI	1508 (13.9)	1441 (13.6)	67 (28.3)	
Image: Normal State         5190 (51.5)         5125 (52.1)         65 (28.5)           II         4230 (42.0)         4113 (41.8)         117 (51.3)           III         651 (6.5)         605 (6.1)         46 (20.2)           Atrial fibrillation         671 (6.2)         624 (5.9)         47 (19.8)         <0.001	Killip class, No. (%)				<0.001
II         4230 (42.0)         4113 (41.8)         117 (51.3)           III         651 (6.5)         605 (6.1)         46 (20.2)           Atrial fibrillation         671 (6.2)         624 (5.9)         47 (19.8)         <0.001           Angiography findings, No. (%)         III         525 (10.5)         0.30           LM lesion         940 (8.7)         915 (8.6)         25 (10.5)         0.30           Multi-vessel lesion         7130 (65.9)         7026 (66.4)         104 (43.9)         <0.001           Chronic total occlusion lesion         2291 (21.2)         2238 (21.1)         53 (22.4)         0.65           In-hospital treatments, No. (%)         PCI         5567 (51.4)         5490 (51.9)         77 (32.5)         <0.001           DAPT         5949 (55.0)         5834 (55.1)         115 (48.5)         0.044           ACEI/ARB         6034 (55.7)         5926 (56.0)         108 (45.6)         0.001           Beta-blocker         7464 (69.0)         7330 (69.2)         134 (56.5)         <0.001           Statins         9535 (88.1)         9371 (88.5)         164 (69.2)         <0.001	1	5190 (51.5)	5125 (52.1)	65 (28.5)	
III         651 (6.5)         605 (6.1)         46 (20.2)           Atrial fibrillation         671 (6.2)         624 (5.9)         47 (19.8)         <0.001           Angiography findings, No. (%)         U         U         U         U         U           LM lesion         940 (8.7)         915 (8.6)         25 (10.5)         0.30           Multi-vessel lesion         7130 (65.9)         7026 (66.4)         104 (43.9)         <0.001           Chronic total occlusion lesion         2291 (21.2)         2238 (21.1)         53 (22.4)         0.65           In-hospital treatments, No. (%)         PCI         5567 (51.4)         5490 (51.9)         77 (32.5)         <0.001           DAPT         5949 (55.0)         5834 (55.1)         115 (48.5)         0.044           ACEI/ARB         6034 (55.7)         5926 (56.0)         108 (45.6)         0.001           Beta-blocker         7464 (69.0)         7330 (69.2)         134 (56.5)         <0.001           Statins         9535 (88.1)         9371 (88.5)         164 (69.2)         <0.001	н	4230 (42.0)	4113 (41.8)	117 (51.3)	
Atrial fibrillation         671 (6.2)         624 (5.9)         47 (19.8)         <0.001           Angiography findings, No. (%)                 0.001           LM lesion         940 (8.7)         915 (8.6)         25 (10.5)         0.30           Multi-vessel lesion         7130 (65.9)         7026 (66.4)         104 (43.9)         <0.001	Ш	651 (6.5)	605 (6.1)	46 (20.2)	
Angiography findings, No. (%)         LM lesion       940 (8.7)       915 (8.6)       25 (10.5)       0.30         Multi-vessel lesion       7130 (65.9)       7026 (66.4)       104 (43.9)       <0.001	Atrial fibrillation	671 (6.2)	624 (5.9)	47 (19.8)	<0.001
LM lesion         940 (8.7)         915 (8.6)         25 (10.5)         0.30           Multi-vessel lesion         7130 (65.9)         7026 (66.4)         104 (43.9)         <0.001           Chronic total occlusion lesion         2291 (21.2)         2238 (21.1)         53 (22.4)         0.65           In-hospital treatments, No. (%)         PCI         5567 (51.4)         5490 (51.9)         77 (32.5)         <0.001           DAPT         5949 (55.0)         5834 (55.1)         115 (48.5)         0.044           ACEI/ARB         6034 (55.7)         5926 (56.0)         108 (45.6)         0.001           Beta-blocker         7464 (69.0)         7330 (69.2)         134 (56.5)         <0.001           Statins         9535 (88.1)         9371 (88.5)         164 (69.2)         <0.001	Angiography findings, No. (%)				
Multi-vessel lesion         7130 (65.9)         7026 (66.4)         104 (43.9)         <0.001           Chronic total occlusion lesion         2291 (21.2)         2238 (21.1)         53 (22.4)         0.65           In-hospital treatments, No. (%)         PCI         5567 (51.4)         5490 (51.9)         77 (32.5)         <0.001           DAPT         5949 (55.0)         5834 (55.1)         115 (48.5)         0.044           ACEI/ARB         6034 (55.7)         5926 (56.0)         108 (45.6)         0.001           Beta-blocker         7464 (69.0)         7330 (69.2)         134 (56.5)         <0.001           Statins         9535 (88.1)         9371 (88.5)         164 (69.2)         <0.001	LM lesion	940 (8.7)	915 (8.6)	25 (10.5)	0.30
Chronic total occlusion lesion         2291 (21.2)         2238 (21.1)         53 (22.4)         0.65           In-hospital treatments, No. (%)                 0.001          0.65              0.65                          0.65   <	Multi-vessel lesion	7130 (65.9)	7026 (66.4)	104 (43.9)	< 0.001
In-hospital treatments, No. (%)       PCI       5567 (51.4)       5490 (51.9)       77 (32.5)       <0.001	Chronic total occlusion lesion	2291 (21.2)	2238 (21.1)	53 (22.4)	0.65
PCI         5567 (51.4)         5490 (51.9)         77 (32.5)         <0.001           DAPT         5949 (55.0)         5834 (55.1)         115 (48.5)         0.044           ACEI/ARB         6034 (55.7)         5926 (56.0)         108 (45.6)         0.001           Beta-blocker         7464 (69.0)         7330 (69.2)         134 (56.5)         <0.001           Statins         9535 (88.1)         9371 (88.5)         164 (69.2)         <0.001	In-hospital treatments, No. (%)	- ( )			
DAPT         5949 (55.0)         5834 (55.1)         115 (48.5)         0.044           ACEI/ARB         6034 (55.7)         5926 (56.0)         108 (45.6)         0.001           Beta-blocker         7464 (69.0)         7330 (69.2)         134 (56.5)         <0.001           Statins         9535 (88.1)         9371 (88.5)         164 (69.2)         <0.001	PCI	5567 (51.4)	5490 (51.9)	77 (32.5)	< 0.001
ACEI/ARB         6034 (55.7)         5926 (56.0)         108 (45.6)         0.001           Beta-blocker         7464 (69.0)         7330 (69.2)         134 (56.5)         <0.001           Statins         9535 (88.1)         9371 (88.5)         164 (69.2)         <0.001	DAPT	5949 (55.0)	5834 (55.1)	115 (48.5)	0.044
Beta-blocker         7464 (69.0)         7330 (69.2)         134 (56.5)         <0.001           Statins         9535 (88.1)         9371 (88.5)         164 (69.2)         <0.001	ACEI/ARB	6034 (55.7)	5926 (56.0)	108 (45.6)	0.001
Statins         9535 (88.1)         9371 (88.5)         164 (69.2)         <0.001	Beta-blocker	7464 (69.0)	7330 (69.2)	134 (56.5)	< 0.001
	Statins	9535 (88.1)	9371 (88.5)	164 (69.2)	< 0.001

Values are presented as mean (SD), median (IQR) or number (%).

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AMI, acute myocardial infarction; BMI, body mass index; cTnI, cardiac troponin I; CCB, calcium channel blocker; DAPT, dual-antiplatelet therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LM, left main coronary artery; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NSTEM, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; PP, pulse pressure; SD, standard deviation; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction; TC, total cholesterol; TG, triglyceride; UAP, unstable angina pectoris.

**TABLE 2** | Risk of 1-year all-cause mortality associated with PP levels in whole cohort, UAP patients, and AMI patients.

PP levels	Hazard ratio (95% CI)*				
	Whole cohort	UAP	AMI		
30 mmHg	2.02 (1.27–3.22)	1.61 (0.59–4.41)	1.80 (1.07–3.03)		
40 mmHg	1.30 (1.10–1.55)	1.28 (0.88–1.87)	1.19 (0.98–1.43)		
50 mmHg	1.00 [reference]	1.00 [reference]	1.00 [reference]		
60 mmHg	1.10 (0.87–1.39)	0.80 (0.53–1.20)	1.26 (0.95–1.67)		
70 mmHg	1.33 (0.93–1.90)	0.82 (0.44–1.53)	1.61 (1.05–2.46)		
80 mmHg	1.62 (1.13–2.33)	1.04 (0.56–1.93)	1.91 (1.22–2.98)		
90 mmHg	1.99 (1.37–2.89)	1.41 (0.76–2.64)	2.21 (1.37–3.56)		
100 mmHg	2.43 (1.56–3.79)	1.92 (0.94–3.93)	2.55 (1.44–4.54)		
P for Non-linearity	<0.001	0.030	0.010		

\*Estimates were adjusted for age, gender, BMI, previous diabetes mellitus, previous hypertension, previous MI, current smoking, atrial fibrillation, previous DAPT, heart rate, LVEF < 50%, HbA1c, LDL-C, eGFR, peak value of cTnl, angiography findings (LM lesion, multi-vessel lesion, and chronic total occlusion lesion), and in-hospital treatments (PCI, DAPT, ACEI/ARB, and statins). Abbreviations see **Table 1**.

decedents than those in survivors. Decedents also tended to be older, with lower levels of BMI, with higher prevalence of previous diabetes, myocardial infarction, CKD, and chronic heart failure, and with higher levels of heart rate, FPG, HbA1c, hs-CRP, the peak value of cTnI, and peak value of NT-proBNP. In addition, decedents were prone to have lower levels of eGFR and LVEF. Notably, decedents showed a lower rate of receiving PCI, DAPT, ACEI/ARB, beta-blockers, and statins during hospitalization.

A total of 237 (2.19%) all-cause deaths were reported, including 79 (1.03%) of the 7,705 UAP patients and 158 (5.07%) of the 3,119 AMI patients during 1-year follow-up. Associations between PP levels and 1-year all-cause mortality were shown in **Table 2** and **Figure 2**. The multivariable-adjusted spline Cox models were shown in **Supplementary Table 1**. In the whole cohort, the risk of all-cause mortality increased with both lower or higher PP levels ( $P_{non-linear} < 0.001$ ), which indicated a J-shaped relationship between PP and all-cause mortality. For a PP

level of 30 mmHg, as compared with 50 mmHg, the adjusted HR for 1-year all-cause mortality was 2.02 (95% CI, 1.27–3.22). While, for a PP level of 80 mmHg, the adjusted HR for 1-year all-cause mortality was 1.62 (95% CI, 1.13–2.33). Moreover, among AMI patients, lower and higher PP levels were also associated with increased 1-year all-cause mortality ( $P_{non-linear} = 0.010$ ). The adjusted HRs for a PP level of 30 mmHg and 80 mmHg were 1.80 (95% CI, 1.07–3.03) and 1.91 (95% CI, 1.22–2.98), respectively.

Similar results were observed for the association between PP and 1-year cardiac mortality (Table 3 and Figure 3). The multivariable-adjusted spline Cox models were shown in Supplementary Table 2. In the whole cohort, the risk of cardiac mortality was higher in both lower or higher PP levels  $(P_{\rm non-linear} < 0.001)$ . For a PP level of 30 mmHg, as compared with 50 mmHg, the adjusted HR for 1-year cardiac mortality was 2.30 (95% CI, 1.34-3.93). While, for a PP level of 80 mmHg, the adjusted HR for 1-year cardiac mortality was 1.98 (95% CI, 1.28-3.08). A similar relationship between PP and cardiac mortality  $(P_{\text{non-linear}} = 0.017)$  was observed in AMI patients that the adjusted HRs for a PP level of 30 mmHg and 80mmHg were 1.87 (95% CI, 1.03-3.39) and 1.99 (95% CI, 1.19-3.33), respectively. However, among UAP patients, PP was no longer significantly associated with 1-year all-cause or cardiac mortality, although patients with higher PP showed a trend toward increased risk for mortality.

Covariates-adjusted survival curves of time until all-cause and cardiac mortality were shown in **Figure 4**. Patients with both lower and higher levels of PP were associated with a higher mortality rate at 1-year follow-up. Subgroup analyses were performed for all-cause and cardiac mortality outcomes by the following variables: age, gender, BMI, previous hypertension, previous diabetes mellitus, eGFR, and smoking status (**Figure 5**). The J-shaped relationship between PP and all-cause mortality was more pronounced among patients aged  $\geq 65$  years, female, patients with BMI < 25 kg/m<sup>2</sup>, patients with previous hypertension, patients without previous diabetes, patients with eGFR < 60 ml/min/1.73m<sup>2</sup>, and both current smokers and non-smokers. The results did not significantly change between PP and cardiac mortality.



**FIGURE 2** | Restricted cubic spline analysis for association of PP and 1-year all-cause mortality. Adjusted model included age, gender, BMI, previous diabetes mellitus, previous hypertension, previous MI, current smoking, atrial fibrillation, previous DAPT, heart rate, LVEF < 50%, HbA1c, LDL-C, eGFR, peak value of cTnl, angiography findings (LM lesion, multi-vessel lesion, chronic total occlusion lesion), and in-hospital treatments (PCI, DAPT, ACEI/ARB, statins).

**TABLE 3** | Risk of 1-year cardiac mortality associated with PP levels in whole cohort, UAP patients, and AMI patients.

PP levels	Hazard Ratio (95% CI)*				
	Whole Cohort	UAP	AMI		
30 mmHg	2.30 (1.34–3.93)	3.35 (0.98–11.44)	1.87 (1.03–3.39)		
40 mmHg	1.34 (1.10–1.63)	1.58 (1.00–2.48)	1.20 (0.97–1.49)		
50 mmHg	1.00 [reference]	1.00 [reference]	1.00 [reference]		
60 mmHg	1.24 (0.93–1.66)	1.17 (0.66–2.08)	1.28 (0.92–1.76)		
70 mmHg	1.62 (1.05–2.50)	1.51 (0.63–3.60)	1.65 (1.01–2.70)		
80 mmHg	1.98 (1.28–3.08)	1.89 (0.80–4.48)	1.99 (1.19–3.33)		
90 mmHg	2.38 (1.50–3.76)	2.35 (0.98–5.62)	2.34 (1.35–4.05)		
100 mmHg	2.85 (1.66–4.89)	2.91 (1.07–7.94)	2.75 (1.43–5.29)		
P for Non-linearity	< 0.001	0.046	0.017		

\*Estimates were adjusted for age, gender, BMI, previous diabetes mellitus, previous hypertension, previous MI, current smoking, atrial fibrillation, previous DAPT, heart rate, LVEF < 50%, HbA1c, LDL-C, eGFR, peak value of cTnl, angiography findings (LM lesion, multi-vessel lesion, and chronic total occlusion lesion), and in-hospital treatments (PCI, DAPT, ACEI/ARB, and statins). Abbreviations see **Table 1**.

## DISCUSSION

In this study of patients across the spectrum of ACS, a J-shaped relationship between PP and 1-year all-cause and cardiac mortality was observed with increased mortality in patients with lower and higher PP levels. Subgroup analyses confirmed the significance of the relationship in patients with AMI, which was attenuated in patients with UAP.

The robust cardiovascular prognostic value of PP has been identified in numerous population-based studies (5–10, 26–28). One study including 2,152 individuals aged over 65 years showed that higher PP was an independent predictor of incident coronary heart disease and heart failure among the community elderly (8). In the PROCAM study of 5,389 men aged 35–65, increased PP was shown to be an important independent determinant of coronary risk (10). The REasons for Geographic And Racial Differences in Stroke (REGARDS) study found that PP was an independent risk factor for acute coronary heart disease in the national cohort of 30,239 black and white participants aged

over 45 years old (28). However, these findings were discovered in non-acute cardiovascular situations. Investigations of the association of PP with the outcome within one year in patients with ACS are scarce and somewhat contradictory. Here for the first time, we provide evidence from a population-based realworld cohort of ACS and use PP as a continuous variable to reveal the association between PP and the prognosis of ACS using spline regression.

We postulated that higher PP may be associated with worse outcomes, since it had been reported in multiple non-acute situation studies and also some ACS studies (16, 17). However, our study also showed a strong association between lower PP and worse prognosis in patients with ACS, which indicated a J-shaped relationship between PP and mortality. The J-shaped relationship was defined as an increase in adverse cardiovascular outcomes below or above a certain blood pressure, with the trough representing the point that had the lowest risk of adverse events (29). This phenomenon has also been mentioned in studies of ACS patients. In a five-year follow-up of 353 ACS patients aged at least 80 years, the mortality rate increased in patients with PP < 50 mmHg or >70 mmHg (13). A more recent study by Gjin Ndrepepa et al. (30) suggested a U-shaped relationship between central PP and 8-year all-cause or cardiac mortality in patients with STEMI undergoing PCI. However, after adjustment of demographic and clinical variables such as infarct size, postprocedural TIMI flow grade, age, sex, diabetes, smoking, and hypercholesterolemia, the association between central PP and the long-term prognosis was attenuated. In contrast, the association remained after adjustment for potential confounders in our study, which indicated PP as an independent prognostic predictor.

The mechanism underlying the J-shaped phenomenon was unclear and debated, especially for the explanation for the adverse prognosis of lower PP. Warren J. et al. (31), on the other hand, suggested that a lower PP in the setting of PCI independently predicted lower long-term mortality. This study emphasized the protective role of high DBP in coronary perfusion for a long-term prognosis in patients undergoing PCI. Whereas, there was no difference between PP groups in the rate of cardiac and all-cause mortality at 1-year post-procedure. Conversely, a previous study





FIGURE 4 | Adjusted survival curves for 1-year all-cause and cardiac mortality according to different PP levels. Adjusted model included age, gender, BMI, previous diabetes mellitus, previous hypertension, previous MI, current smoking, atrial fibrillation, previous DAPT, heart rate, LVEF < 50%, HbA1c, LDL-C, eGFR, peak value of cTnl, angiography findings (LM lesion, multi-vessel lesion, chronic total occlusion lesion), and in-hospital treatments (PCI, DAPT, ACEI/ARB, statins).

by El-Menyar et al. (12) has shown that lower PP was an independent predictor of stroke and in-hospital mortality in overall ACS. A multicenter study involving 14,514 ACS patients showed that PP < 49 mmHg was independently associated higher in-hospital mortality compared with PP > 76 mmHg (OR = 2.57, 95% CI, 1.80-3.67) (14). In fact, PP is not only associated with the degree of aortic stiffness but also the ventricular stroke volume (32). When the patient's stroke volume decreases (as a decrease in LVEF in clinical), PP is no longer the marker of arteriosclerosis (33). One study of the SPUM-ACS cohort indicated that the J-shaped relationship disappeared after the exclusion of patients with LVEF  $\leq$  40%, indicating that LVEF is a very powerful confounder that has specific statistical interaction with mortality (16). In the present study, as was shown in the Kaplan-Meier survival curve according to PP categories in patients with PP < 50 mmHg (Supplementary Table 3 and **Supplementary Figure 1**), patients with SBP < 120 mmHg were associated with higher mortality regardless of DBP. Thus, from our perspective, lower PP might help identify patients with a high risk of mortality because of reduced cardiac functional reserve. In addition, in our subgroup analyses, the J-shaped relationship was more obvious in patients with a diagnosis of AMI, aged  $\geq$ 65 years, previous hypertension, and eGFR  $< 60 \text{ ml/min/1.73m}^2$ . The

adverse prognosis of lower PP might be affected by the severity of the disease and chronic condition.

The mechanism underlying the relationship between PP and mortality remains unclear. Physiologically, there is a linear rise in both SBP and DBP until age 60 after which SBP continues to rise and DBP begins to decrease. The subsequent increase in PP is consistent with the increased large artery stiffness (34). Blood pressure is a complicated variable but can be broken down into two components: the steady-state (e.g., MAP) and the pulsatile (e.g., PP). PP is determined by stroke volume, wave reflections and arterial stiffness (35). Aging and diseases (e.g., hypertension, CKD, diabetes, and atherosclerosis) could cause structural changes in blood vessels, exacerbating arterial stiffness. Fragmentation of elastin and increased deposition of collagen change the patient's collagen to elastin ratio and cause arterial calcification. Glycation of both elastin and collagen fibers and crosslinking of collagen molecules by advanced glycation endproducts can compromise vessel compliance (36-38). The loss of elastic recoil and earlier timing of reflected pressure waves in late systole reduce the DBP. Therefore, the "de-stiffening" strategy based on the antihypertrophic effect on vascular smooth muscle cells by blocking angiotensin and/or aldosterone system is proposed to reduce cardiovascular risk (39). It is possible





to selectively reduce central SBP and PP by decreasing arterial stiffness and/or wave reflections. In most studies focusing on therapeutic efficacy, the renin-angiotensin system inhibition combined with diuretics or calcium antagonists (40, 41) were recommended, whereas the renin-angiotensin system inhibition combined with classic beta-blockers was not, because the beta-blockers are shown to have little or no effect on central PP (42). Because cardiovascular risk reduction is mainly associated with the management of central SBP and PP, this strategy should be extensively evaluated in the future.

Our study had several limitations. First, despite the fact that all data in this study were collected prospectively, our study was limited by its retrospective design. Second, the long-term monitoring of blood pressure was insufficient, and admission PP only partially reflected the status of patients' blood pressure management. Third, the severity of myocardial ischemia or infarct size was not included in this research. Finally, the underlying mechanisms for the association between adverse outcomes and lower PP were not completely clear, and further investigations were needed in the future.

# CONCLUSION

In summary, PP is an independent prognostic factor for 1-year all-cause and cardiac mortality in patients with ACS. The present study demonstrates a J-shaped relationship between PP and the prognosis of ACS, especially in patients with AMI. Further prospective cohort studies are needed to confirm these findings and elucidate the underlying mechanisms.

# DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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# ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Beijing Friendship Hospital affiliated to Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

# **AUTHOR CONTRIBUTIONS**

H-WL designed the protocol of the study. MW drafted the manuscript. MW, WS, C-YJ, W-PL, HC, and H-WL participated in the collection, interpretation, and analysis of the data. All authors approved the final version for publication.

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# SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm. 2022.930755/full#supplementary-material

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