Am J Transl Res 2025;17(6):4237-4246
www.ajtr.org /ISSN:1943-8141/AJTR0162221

Original Article

Association of heparin-binding protein with risk of in-hospital heart failure in patients with acute coronary syndrome

Xiao Liang, Qingxian Tu, Jie Zhang, Min Xu, Zhenglong Wang

Department of Cardiology, The Third Affiliated Hospital of Zunyi Medical University (The First People's Hospital of Zunyi), Zunyi 563000, Guizhou, The People's Republic of China

Received November 23, 2024; Accepted May 11, 2025; Epub June 15, 2025; Published June 30, 2025

Abstract: Objectives: To investigate the relationship between heparin-binding protein (HBP) levels and the risk of involving heart failure occurring during hospitalization in patients with acute coronary syndrome (ACS). Methods: This single-center retrospective study included 274 patients with ACS hospitalized at the Third Affiliated Hospital of Zunyi Medical University between June and December 2023. The primary outcome was the occurrence of in-hospital heart failure (HF). Multivariable logistic regression and restricted cubic spline (RCS) models were used to assess the relationship between HBP and HF. Receiver operating characteristic (ROC) curves were used to evaluate the predictive value of HBP for HF events. Results: During hospitalization, 56 patients (20.4%) developed HF. Patients with HF patients had higher HBP levels ($p < 0.01$). HBP was significantly associated with in-hospital HF risk (Model 3 OR = 4.232, $P < 0.001$). ROC analysis showed that HBP had a predictive value for HF events (AUC = 0.696, sensitivity = 55.36, specificity = 76.61, $P < 0.001$). The RCS model indicated a nonlinear dose-response relationship between HBP levels and in-hospital HF (P for nonlinearity = 0.007). Conclusion: HBP levels are associated with an increased risk of in-hospital HF in patients with ACS and serve as a superior predictor compared to traditional parameters and inflammatory markers.

Keywords: Heparin-binding protein, acute myocardial infarction, in-hospital heart failure, restricted cubic spline curve

Introduction

Acute coronary syndrome (ACS) is a clinical emergency that can lead to sudden cardiac death. According to the 2023 statistics by the American Heart Association, approximately 850,000 new and recurrent cases of acute myocardial infarction (AMI) occur yearly [1]. A recent systematic review and meta-analysis reported a global prevalence of AMI of 3.8% in individuals aged 60 years or less and 9.5% in those older than this age [2]. Despite advancements in percutaneous coronary intervention (PCI) techniques, many patients with ACS still experience varying degrees of heart failure (HF) symptoms during hospitalization [3]. Previous studies have indicated that up to 38% of patients with ACS experience HF events, representing nearly 1 million cases annually [4]. Data from Asian countries indicate that the incidence of HF following AMI is the highest during the initial hospitalization period and persists over the subsequent 1 to 6 years post-AMI [5]. Mechanisms leading to HF during hospitalization for myocardial infarction include myocardial damage from necrosis, myocardial stunning, and mechanical complications. Within the first 30 min of ischemia, myocardial cells swell and undergo structural changes, which lead to progressive cell death after 3 h. Reperfusion injury further damages myocardial cells [6]. Additionally, advanced age, hypertension, and diabetes increase the likelihood of developing HF following ACS (ACS-HF) [7]. Patients with ACS-HF have poor prognosis and higher hospital re-admission rates, which increases the healthcare burden [8]. It is thus essential to determine a reliable and straightforward mark-

https://doi.org/10.62347/LQLD9274

er to predict the likelihood of HF during hospitalization in patients with ACS and improve their short-term prognosis during their hospital stay.

ACS-HF is primarily caused by persistent coronary microcirculation disorders, which are important predictors of adverse cardiovascular events, including HF readmission and all-cause mortality [9, 10]. The incidence of microcirculation disorders in individuals with myocardial ischemia has been reported to be approximately 40-64% [11]. The main mechanisms underlying myocardial ischemia involve endothelial cell (EC) damage, intravascular microthrombosis formation, and coronary microvascular endothelial inflammation [12, 13]. Heparin-binding protein (HBP), also known as CAP37/azurocidin, is a granule protein located in neutrophils and among the initial inflammatory mediators released by neutrophils in response to infection [14-16]. HBP can bind to EC surface glycosaminoglycans, activate the PKC and Rho-kinase pathways, induce EC cytoskeletal rearrangement, disrupt the vascular endothelial barrier, increase vascular permeability, and promote the amplification of the inflammatory cascade, which contribute to tissue damage and microcirculation disorders [17, 18]. Previous studies have demonstrated that HBP levels above 11.46 ng/mL are a sensitive indicator for predicting AMI and are positively correlated with the Thrombolysis in Myocardial Infarction (TIMI) risk score [19]. Additionally, HBP has been confirmed as an independent risk factor in studies related to myocardial injury-associated cardiogenic shock (MIRCS) [20]. These studies indicated that HBP plays a crucial role in non-infectious inflammation, such as myocardial infarction. However, research exploring the relationship between HBP and the risk of in-hospital HF in patients with ACS remains limited.

In this study, we aimed at examining the relationship between HBP levels and the risk of developing HF during hospitalization in patients with ACS and to explore whether this relationship follows a dose-response pattern.

Methods

Study population

This single-center, retrospective observational study included 274 patients initially diagnosed with ACS and hospitalized in the Department of Cardiology at the Third Affiliated Hospital of Zunyi Medical University from June to December 2023. The Ethics Committee of the Third Affiliated Hospital of Zunyi Medical University approved the research (approval no. 2024-1-137), which adhered to the ethical requirements of the Declaration of Helsinki and its subsequent amendments. No interventions were performed with respect to the patients, and informed consent was waived due to the observational nature of the study. Inclusion criteria comprised patients diagnosed with ACS upon admission, including NSTEMI, STEMI, and unstable angina. The exclusion criteria were as follows: (1) patients with acute exacerbation of chronic HF; (2) patients who recently experienced acute infections; (3) patients with non-cardiac chest pain; (4) patients with severe valvular heart disease; (5) patients with malignant tumors; (6) patients with severe liver or spleen dysfunction; (7) pregnant women; and (8) cases with incomplete general clinical data or relevant examination data.

Data acquisition, handling, and outcome specification

Clinical features, historical medical data, and lab test outcomes were collected from the electronic medical records system upon the patients' admission and throughout their hospitalization. Upon admission, laboratory tests primarily comprised measurements of HBP, N-terminal pro-B-type natriuretic peptide (NT-proBNP), troponin levels, renal function, ion concentrations in serum, and cardiac enzymes. HBP detection was performed using an immunofluorescence dry quantitative method with an immunoassay analyzer (Jet-iStar 3000, Zhonghan Shengtai Biotechnology Co., Ltd., Shandong, China). Venous blood samples were taken after a minimum of 12 h of fasting, measuring indicators such as complete blood count, lipid profile, liver function, and C-reactive protein (CRP). Inflammatory markers, including monocyte-to-lymphocyte ratio (MHR), platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and systemic immune inflammation index (SII), were calculated based on these measurements. HBP was measured immediately after patient admission. A NT-proBNP value ≥ 300 pg/mL was defined as indicative of heart failure during hospitalization [21, 22].

Statistical analysis

Statistical analysis was conducted with SPSS version 22.0, MedCalc version 15.0, and R version 4.2.2. Categorical variables are presented as frequencies or percentages, while continuous variables are presented as the mean ± standard deviation for normally distributed data and as quartiles (median (25^{th} and 75^{th} percentiles) for non-normally distributed data. For normally distributed, continuous variables, *t*-tests or analysis of variance were used for comparisons across groups, while non-parametric tests were employed when normality was not met. For comparisons involving categorical data, Fisher's exact test or the Chi-square test was used. Receiver operating characteristic (ROC) curves were employed to determine the diagnostic accuracy of HBP. Multivariable logistic regression was used to evaluate the relationship between HBP and outcome events. Propensity score matching (PSM) was performed at a 1:2 ratio, with sex, age, BMI, SBP, and LDL-C included as matching variables, to further validate the robustness of the association between HBP and outcome events. Additionally, restricted cubic splines (RCS) were employed to assess the dose-response relationship between HBP levels and in-hospital HF. A *p*-value less than 0.05 was considered statistically significant.

Results

Sample characteristics

This retrospective study involved 274 patients with consecutive ACS, among whom 56 (20.4%) developed HF during the inpatient period. The mean age of patients in the HF group (69.679±10.357 years) was higher than that in the non-HF group (60.766±12.575 years). In the HF group, HBP levels were substantially greater than those in the non-HF group [24.905 (12.925, 45.125) vs. 12.555 (7.005, 23.278)]. Additionally, the HF group exhibited higher CTNT, CK-MB, CRP, NLR, and serum creatinine (Cre) levels, as well as higher neutrophil counts, than the non-HF group, with statistically significant differences ($P < 0.01$). Detailed information is presented in **Table 1**.

Association between HBP and the risk of heart failure during hospitalization in ACS patients

According to ROC curve analysis, the ideal cutoff value for HBP was 23.76. Accordingly, patients were categorized into two groups: a high HBP group (> 23.76) and a low HBP group (≤ 23.76). Logistic regression analysis was conducted to identify factors influencing in-hospital HF in patients with ACS. Univariate logistic regression analysis indicated that age, HBP, NLR, SII, CTNT, and SCR were associated with the risk of in-hospital HF in patients with ACS (**Figure 1**). To adjust for potential confounders and further investigate the association between HBP and the risk of in-hospital heart failure in ACS patients, multivariable logistic regression models were employed. Three models were established: Model 1 without adjustment for confounding factors, Model 2 adjusted for sex and age, and Model 3 adjusted based on Model 2 to account for hypertension, diabetes, CTNT, EF%, and the use of diuretics. Prior to performing multivariate logistic regression analysis, we performed a collinearity analysis of variables included in the final model (Model 3), which showed that all variables had a tolerance > 0.2 and variance inflation factors < 10, indicating no collinearity between the included variables, as detailed in Supplementary Table 1. The results of the multivariable logistic regression analysis demonstrated a significant association between elevated HBP levels and an increased risk of in-hospital HF in patients with ACS [Model 3 OR = 4.232 (1.718-10.429), $P < 0.001$]. We additionally conducted a sensitivity analysis based on PSM to further clarify whether the association between HBP and heart failure remains stable. The results indicated that after matching participants from both groups for sex, age, BMI, SBP, and LDL-C levels, HBP remained positively associated with heart failure (PSM: Model 3 = 4.161, 95% CI: 1.581-10.952, $P = 0.004$), further confirming the robustness of the association between HBP and heart failure (**Figure 2**). Finally, we conducted subgroup analyses and interaction tests based on patient sex, age, and comorbidities, as shown in **Figure 3**.

Predictive value of HBP for the risk of in-hospital HF in patients with ACS

We used ROC curves to evaluate the predictive performance of HBP and other inflammatory markers for the accuracy of heart failure occurrence. The results indicate that HBP had the highest predictive ability for heart failure occurrence in patients with ACS [area under the curve (AUC) = 0.696, 95% CI: 0.637-0.749, $P < 0.001$]. The optimal cutoff value for HBP was

Table 1. Baseline data of each group

Variables	Total N = 274	Heart failure group N = 56	Non-heart failure group N = 218	P
Age (years)	62.588±12.660	69.679±10.357	60.766±12.575	< 0.01
Height (cm)	167.00 (160.00, 173.00)	165.00 (160.00, 173.00)	168.00 (160.00, 173.00)	0.637
Weight (kg)	70.00 (62.00, 80.00)	69.50 (61.25, 75.00)	70.00 (62.00, 80.00)	0.482
HR (BPM)	78.00 (66.00, 86.00)	80.00 (65.00, 96.00)	78.00 (66.00, 84.00)	0.343
BMI (kg/m^2)	24.977 (22.818, 27.548)	24.655 (22.770, 27.497)	25.007 (22.818, 27.548)	0.606
Sex				0.850
Male/[n, (%)]	145 (52.92)	29 (51.79)	116 (53.21)	
Female/[n, (%)]	129 (47.08)	27 (48.21)	102 (46.79)	
Past history				
Hypertension/[n, (%)]	162 (59.12)	41 (73.21)	121 (55.50)	0.016
Diabetes/[n, (%)]	98 (35.77)	28 (46.48)	70 (32.35)	0.013
Heart Failure Indicators				
NYHA III or IV/[n, (%)]	18 (6.57)	18 (25.35)	1 (0.49)	< 0.01
WMA	51 (18.61)	31 (43.66)	21 (10.29)	< 0.01
Biochemical indicators				
HBP (ng/mL)	14.535 (7.830, 27.030)	24.905 (12.925, 45.125)	12.555 (7.005, 23.278)	< 0.01
NT-proBNP	108.250 (99.025, 128.875)	1013.450 (678.32, 45.125)	105.050 (96.700, 109.900)	< 0.01
cTnT (ug/L)	0.004 (0.002, 0.023)	0.027 (0.008, 1.367)	0.003 (0.002, 0.007)	< 0.01
CK-MB (ug/L)	0.900 (0.600, 1.600)	1.650 (1.125, 5.600)	0.800 (0.600, 1.325)	< 0.01
CRP (mg/L)	1.470 (0.618, 3.933)	3.965 (1.435, 12.740)	1.270 (0.570, 2.713)	< 0.01
SII	398.799 (264.162, 578.068)	540.312 (340.222, 1021.704)	379.657 (249.897, 529.681)	< 0.01
NLR	1.918 (1.430, 2.506)	2.815 (1.933, 4.309)	1.784 (1.379, 2.308)	< 0.01
Neutrophils (10^9/L)	3.325 (2.615, 4.488)	4.245 (3.383, 5.863)	3.130 (2.578, 4.153)	< 0.01
Lymphocytes (10^9/L)	1.785 (1.380, 2.233)	1.520 (1.050, 1.963)	1.830 (1.448, 2.278)	0.01
Monocyte (10^9/L)	0.380 (0.310, 0.490)	0.490 (0.375, 0.618)	0.360 (0.308, 0.440)	< 0.01
PLT (10^9/L)	210.000 (176.000, 247.000)	199.500 (165.500, 245.750)	212.500 (178.000, 247.000)	0.424
TC (mmol/L)	4.370 (3.590, 5.225)	4.105 (3.330, 5.398)	4.495 (3.740, 5.188)	0.424
TG (mmol/L)	1.400 (0.978, 1.933)	1.270 (0.950, 1.750)	1.410 (0.978, 1.983)	0.351
HDL-C (mmol/L)	1.015 (0.870, 1.220)	1.000 (0.883, 1.208)	1.020 (0.868, 1.220)	0.883
LDL-C (mmol/L)	2.590 (2.018, 3.293)	2.520 (1.943, 3.333)	2.650 (2.055, 3.293)	0.585
Cre (ml/min)	68.890 (58.393, 80.723)	77.795 (63.525, 99.405)	67.265 (56.858, 77.975)	< 0.01
ALT (U/L)	19.655 (14.213, 29.645)	22.920 (15.800, 31.998)	18.730 (13.708, 29.143)	0.041
AST (U/L)	20.020 (16.445, 26.033)	27.320 (17.015, 41.495)	19.435 (16.103, 24.003)	< 0.01

Abbreviations: HR, heart rate; BMI, body mass index; WMA, wall motion abnormal; HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mid-range-also called mildly reduced EF; HFrEF, heart failure with reduced EF; HBP, heparin-binding protein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CTNT, cardiac troponin T; CK-MB, creatine kinase-MB; CRP, C-reactive protein; SII, systemic immune inflammation index; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Cre, creatinine; EF%, ejection fraction; ALT, alamine aminotransferase; AST, aspartate aminotransferase.

23.76, with a sensitivity of 55.36% and a specificity of 76.61%. The AUCs for other inflammatory markers such as SII, MLR, and PLR were 0.679, 0.649, and 0.605, respectively (**Table 2**). Subsequently, we combined HBP with CTNT or EF to evaluate whether this combination could improve predictive performance. The results showed that the AUC increased significantly when HBP was combined with CTNT or EF. Notably, the combination of HBP and EF achieved the highest accuracy in predicting in-hospital heart failure among ACS patients (AUC = 0.859, 95% CI: 0.812-0.898), as detailed in **Figure 4**.

Dose-response analysis of HBP levels and the incidence of in-hospital HF in patients with ACS

The dose-response relationship between HBP levels and the occurrence of in-hospital HF in patients with ACS was evaluated using RCS analysis. The results revealed a non-linear

Variables	OR(95%CI)	P
Age (years)	1.069(1.038-1.100)	<0.01
EF(%)	0.599(0.510-0.703)	<0.01
HBP (ng/mL)	1.020(1.006-1.033)	<0.01
cTnT (ug/L)	1.060(1.020-1.102)	<0.01
CK-MB (ug/L)	1.011(1.001-1.021)	0.038
CRP (mg/L)	1.076(1.036-1.117)	<0.01
SII	1.001(1.001-1.002)	<0.01
NLR	1.349(1.161-1.566)	<0.01
Neutrophils (10^9/L)	1.402(1.194-1.646)	<0.01
Lymphocytes (10^9/L)	0.512(0.310-0.845)	<0.01
Monocyte (10^9/L)	2.062(0.832-5.110)	0.118
CR (ml/min)	1.021(1.009-1.034)	<0.01
ALT (U/L)	1.013(1.013-1.023)	0.015
AST (U/L)	1.017(1.006-1.028)	<0.01

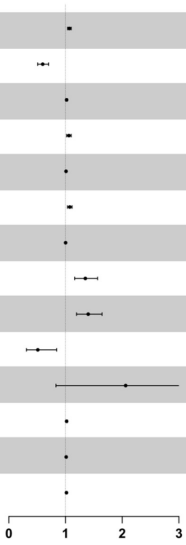

Figure 1. Univariate logistic regression analysis. Abbreviations: OR, odds ratio; CI, confidence interval; EF%, ejection fraction; HBP, heparin-binding protein; CTNT, cardiac troponin T; CK-MB, creatine kinase-MB; CRP, C-reactive protein; SII, systemic immune inflammation index; NLR, neutrophil-to-lymphocyte ratio; CR, creatinine; ALT, alamine aminotransferase; AST, aspartate aminotransferase.

Multivariate Logistic Regression	OR(95%CI)	P
Model 1	4.06(2.199-7.496)	<0.001
Model 2	4.247(2.203-8.191)	<0.001
Model 3	4.232(1.718-10.429)	<0.001
PSM	**OR(95%CI)**	**P**
Model 1	3.963(1.900-8.266)	<0.001
Model 2	4.037(1.925-8.468)	<0.001
Model 3	4.161(1.581-10.952)	0.004

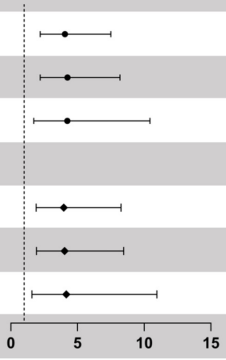

Figure 2. The associations between HBP and in-hospital heart failure in ACS Patients. Note: Model 1 was unadjusted. Model 2 included adjustments for sex and age. Model 3 further adjusted for sex, age, hypertension, diabetes, diuretics, CTNT, EF%. Abbreviations: ACS, acute coronary syndrome; PSM, propensity score matching; OR, odds ratio; CI, confidence interval; CTNT, cardiac troponin T; EF%, ejection fraction; HBP, heparin-binding protein.

dose-response relationship between HBP levels and the risk of in-hospital HF in patients with ACS without adjusting for confounding factors (*p* for non-linearity = 0.007). This nonlinear relationship remained significant even after accounting for potential confounding factors, as in Model 3 (*p* for non-linearity = 0.007; **Figure 5**).

Discussion

In this retrospective study, we included 274 patients with ACS and investigated the relationship between HBP and the risk of in-hospital HF. Multivariable logistic regression analysis demonstrated a strong relationship between elevated HBP levels and the risk of in-hospital HF in patients with ACS [Model 3 OR = 4.232 (1.718-10.429), *P* < 0.001]. ROC curve analysis indicated that HBP can accurately predict the occurrence of in-hospital HF in patients with ACS. Additionally, we for the first time explored the dose-response relationship between HBP and the risk of in-hospital HF in patients with ACS using the RCS model. The results revealed a nonlinear relationship, suggesting that as HBP levels increase, the risk of developing HF during hospitalization increases as well.

Post-ACS occurrence, the incidence of ACS-related HF ranges from 7 to 38% [3]. Some ACS patients with pre-existing HF may experience acute HF with relatively minor ischemic events, while others without prior heart dysfunction may develop transient or permanent HF following severe myocardial ischemia [23]. Persistent microvascular obstruction contributes significantly to ACS-related HF [24]. Survey data indicated that nearly half of the patients undergoing direct PCI exhibit microcirculatory dysfunction [25], which is associated with worse clinical outcomes. Current indices for assessing cardiac function during hospitalization in patients with ACS include clinical signs, cardiac troponins, echocardiography, B-type natriuretic peptide, and NT-proBNP [26-28]. However, due to limitations

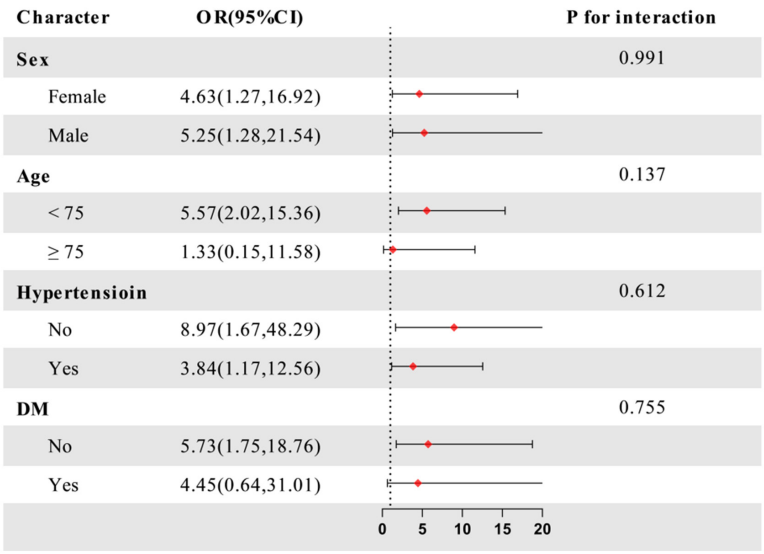

Figure 3. Subgroup analysis and interaction test. Abbreviations: DM, diabetes mellitus.

Table 2. ROC analysis for HBP and other inflammatory markers

Variable	AUC	SE	95% CI	P
HBP	0.696	0.040	0.637-0.749	< 0.0001
SII	0.679	0.043	0.620-0.734	< 0.0001
MLR	0.649	0.044	0.589-0.705	0.001
PLR	0.605	0.046	0.545-0.663	0.015

Abbreviations: AUC, area under curve; SE, standard error; CI, confidence interval; HBP, heparin-binding protein; SII, systemic immune inflammation index; MLR, monocyte-to-lymphocyte ratio; PLR, platelet to lymphocyte ratio.

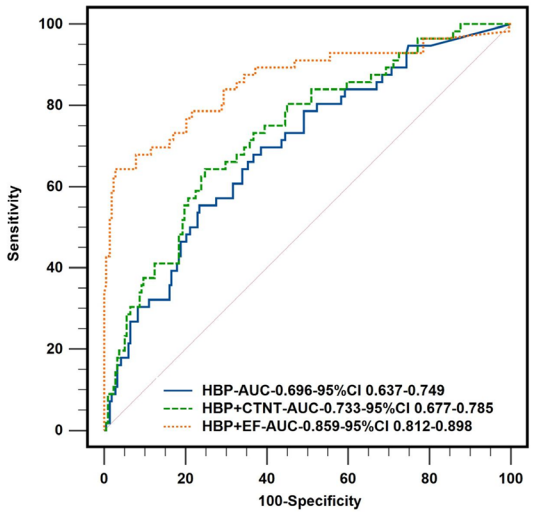

Figure 4. ROC curve analysis for HBP, HBP+CTNT, and HBP+EF in predicting the risk of in-hospital heart failure among ACS patients. Abbreviations: ROC, receiver operating characteristic; HBP, heparin-binding protein; CTNT, cardiac troponin T; EF, ejection fraction.

in hospitalization time, these indicators may not accurately reflect the cardiac function status of patients with ACS within a short period. ACS represents the extreme manifestation of a long-standing low-grade inflammatory response in coronary plaques [29]. In recent years, emerging inflammatory markers such as CRP, SII, NLR, PLR, MLR, and the systemic inflammation response index have been considered independent predictors of ACS severity [30-33]. However, these markers primarily focus on the relationship with the severity of vascular lesions and less on the degree of cardiac dysfunction following acute coronary events. Moreover, patients with ACS-related HF have significantly higher mortality rates than those without HF [34]. Therefore, identifying a timely and accurate method for assessing the likelihood of post-ACS HF is crucial, as it is essential for clinical treatment and improving prognosis, ultimately serving as a foundation for ACS management.

HBP, secreted by neutrophils, is a multifunctional protein composed of α-helices and β-sheets. It features cationic regions formed by arginine and lysine residues, along with multiple binding sites. These cationic regions interact with anionic molecules during intercellular communication, enhancing cell adhesion and signal transduction [35]. Studies have shown that HBP significantly reduces EC resistance and increases protein permeability. This effect is mediated through elevated intracellular Ca^{2+} levels, leading to cytoskeletal reorganization and stress fiber formation in ECs, ultimately increasing vascular permeability [36, 37]. HBP is considered a reliable prognostic factor for evaluating the severity of inflammation and has shown better predictive value than CRP and PCT in various infectious diseases [38]. In non-infectious inflammations, such as myocardial infarction, Ipek et al. [19] found that a HBP threshold of > 11.46 ng/mL predicted myocardial infarction with a sensitivity of 74% and specificity of 58% (ROC AUC = 0.713; $P = 0.018$), and that HBP levels were significantly correlated with the TIMI score ($P < 0.001$). Pan et al.

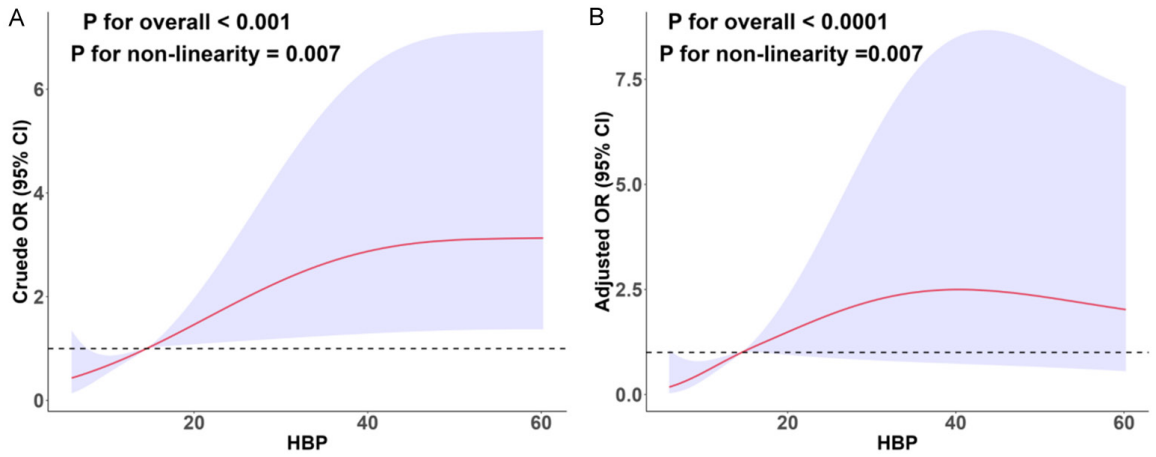

Figure 5. The dose-response relationship between HBP levels and in-hospital heart failure in ACS patients. A: Crude model OR; B: Adjusted model. Abbreviations: OR, odds ratio; HBP, heparin-binding protein.

[20] evaluated patients who developed MIRCS after cardiac surgery and found that HBP had an AUC of 0.85 (95% CI: 0.81-0.89), with a threshold of 220 ng/mL, a sensitivity of 92%, and a specificity of 70% for predicting MIRCS. After adjusting for various confounding factors, HBP emerged as an independent risk factor for MIRCS (OR: 7.65, 95% CI: 4.86-12.06, $P < 0.01$). Additionally, HBP levels showed a positive correlation with CTNT ($P < 0.01$). Pesonen et al. [39] studied 30 patients undergoing aortic valve replacement and found that local HBP concentrations increased in the coronary sinus after reperfusion, which was accompanied by myocardial injury and neutrophil adhesion in coronary vessels. This suggests that HBP plays a specific role in myocardial reperfusion injury. Vincent et al. [40] found that mediators of the inflammatory response might be central to microcirculatory dysfunction in septic patients, likely due to the interaction between activated neutrophils and ECs. This aligns with our initial hypothesis that sustained inflammation triggers ACS, leading to HBP release from activated neutrophils and interaction with ECs, which ultimately causes microcirculatory dysfunction and promotes HF occurrence. Our study confirmed a significant correlation between HBP levels and the incidence of in-hospital HF in patients with ACS. We also found a correlation between HBP and wall motion abnormalities following myocardial infarction, supporting the conclusion that HBP can induce microcirculatory dysfunction. Nevertheless, additional studies are necessary to confirm these results. Although numerous studies have investigated the role of HBP in infectious inflammation, its function under non-infectious inflammatory conditions remains underexplored. Many cardiovascular diseases are associated with inflammation, and HBP, as a crucial regulator of the inflammatory response, holds significant clinical potential. Its application may offer novel therapeutic avenues for inflammation-related cardiovascular diseases. Our study indicates that monitoring HBP levels can help identify high-risk patients prone to developing HF following ACS. HBP can be utilized as an effective tool for risk stratification, enabling optimized pharmacological treatment and personalized cardiac rehabilitation strategies, which will ultimately improve patient outcomes [41-43].

This study had certain limitations: First, the limited sample size may have increased the risk of type II errors, indicating that certain associations may have existed but not reached statistical significance. Additionally, the limited sample size may have led to the sparse effect, which primarily affects subgroup analyses as the sample size within different subgroups is further reduced. Second, a smaller sample size limits the number of confounding variables that can be adjusted for in the multivariable regression model. Finally, a small sample size may affect the representativeness of the results, indicating that our conclusions require further validation in larger cohorts. Despite these limitations, we applied PSM, with sex, age, BMI, SBP, and LDL-C as matching variables, to enhance the robustness of our study findings and reduce potential biases. The rationale for

choosing PSM was that it helps balance key confounding factors (age, sex, BMI, SBP, and LDL-C), thereby minimizing systematic differences between the two investigated groups. This allows for a more accurate estimation of the association between hypertension and outcomes while reducing potential biases. Moreover, PSM enhances the robustness of our findings by ensuring that observed associations are not driven solely by confounding variables. Notably, we measured HBP levels only at the early stage of patient admission, without monitoring dynamic changes during hospitalization. Therefore, we were unable to assess the variation in HBP during hospitalization or determine whether this trend affected the risk of HF. As an inflammatory biomarker, HBP may fluctuate with disease progression or resolution. However, due to the lack of dynamic monitoring, we cannot ascertain whether changes in this biomarker during hospitalization influence its value as a predictor of HF. Consequently, relying solely on baseline HBP levels to evaluate the association of HBP with HF risk may lead to either an overestimation or underestimation of this relationship. Future studies should consider employing multi-time-point dynamic monitoring strategies to comprehensively assess the impact of HBP level variations on HF occurrence. Despite these limitations, our study is the first to reveal an association between HBP and the risk of in-hospital HF in ACS patients, providing a new direction for future research to further explore its potential pathophysiological mechanisms.

Conclusions

Our findings revealed that elevated HBP levels (> 23.76) were positively correlated with a higher risk of in-hospital HF in patients with ACS. Furthermore, a nonlinear dose-response relationship was observed between HBP levels and the risk of in-hospital HF in these patients. HBP has also been associated with wall motion abnormalities in patients with ACS. Therefore, clinicians can use HBP to risk-stratify hospitalized patients with ACS, potentially reducing the risk of HF during hospitalization.

Acknowledgements

This study was funded by the Regional Fund Project of the National Natural Science Foundation of China (81760072), Guizhou Provincial Science and Technology Foundation Key Project (ZK [2024] Key 085), and 2023 Science and Technology Fund of Guizhou Provincial Health Commission (ZSKH HZ No. [2024] 43).

This study was exempted from informed consent under the approval of the Ethics Committee of the Third Affiliated Hospital of Zunyi Medical University.

Disclosure of conflict of interest

None.

Address correspondence to: Zhenglong Wang, Department of Cardiology, The Third Affiliated Hospital of Zunyi Medical University, No. 98 Fenghuang North Road, Zunyi 563000, Guizhou, The People's Republic of China. Tel: +86-0851-23235011; E-mail: Wangzhenglong@zmu.edu.cn

References

[1] Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, Baker-Smith CM, Beaton AZ, Boehme AK, Buxton AE, Commodore-Mensah Y, Elkind MSV, Evenson KR, Eze-Nliam C, Fugar S, Generoso G, Heard DG, Hiremath S, Ho JE, Kalani R, Kazi DS, Ko D, Levine DA, Liu J, Ma J, Magnani JW, Michos ED, Mussolino ME, Navaneethan SD, Parikh NI, Poudel R, Rezk-Hanna M, Roth GA, Shah NS, St-Onge MP, Thacker EL, Virani SS, Voeks JH, Wang NY, Wong ND, Wong SS, Yaffe K and Martin SS. Heart disease and stroke statistics-2023 update: a report from the American Heart Association. Circulation 2023; 147: e93-e621.

[2] Salari N, Morddarvanjoghi F, Abdolmaleki A, Rasoulpoor S, Khaleghi AA, Hezarkhani LA, Shohaimi S and Mohammadi M. The global prevalence of myocardial infarction: a systematic review and meta-analysis. BMC Cardiovasc Disord 2023; 23: 206.

[3] Harrington J, Jones WS, Udell JA, Hannan K, Bhatt DL, Anker SD, Petrie MC, Vedin O, Butler J and Hernandez AF. Acute decompensated heart failure in the setting of acute coronary syndrome. JACC Heart Fail 2022; 10: 404-414.

[4] Sulo G, Sulo E, Jørgensen T, Linnenberg A, Prescott E, Tell GS and Osler M. Ischemic heart failure as a complication of incident acute myocardial infarction: Timing and time trends: a national analysis including 78,814 Danish patients during 2000-2009. Scand J Public Health 2020; 48: 294-302.

[5] Choi H, Seo JY, Shin J, Choi BY and Kim YM. A long-term incidence of heart failure and pre-

dictors following newly developed acute myocardial infarction: a 10 years retrospective cohort study with Korean national health insurance data. Int J Environ Res Public Health 2021; 18: 6207.
[6] Jenča D, Melenovský V, Stehlik J, Staněk V, Kettner J, Kautzner J, Adámková V and Wohlfahrt P. Heart failure after myocardial infarction: incidence and predictors. ESC Heart Fail 2021; 8: 222-237.
[7] Costa R, Trêpa M, Oliveira M, Frias A, Campinas A, Luz A, Santos M and Torres S. Heart failure incidence following ST-elevation myocardial infarction. Am J Cardiol 2022; 164: 14-20.
[8] Cahill TJ and Kharbanda RK. Heart failure after myocardial infarction in the era of primary percutaneous coronary intervention: mechanisms, incidence and identification of patients at risk. World J Cardiol 2017; 9: 407-415.
[9] de Waha S, Patel MR, Granger CB, Ohman EM, Maehara A, Eitel I, Ben-Yehuda O, Jenkins P, Thiele H and Stone GW. Relationship between microvascular obstruction and adverse events following primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: an individual patient data pooled analysis from seven randomized trials. Eur Heart J 2017; 38: 3502-3510.
[10] Montone RA, Niccoli G, Minelli S, Fracassi F, Vetrugno V, Aurigemma C, Burzotta F, Porto I, Trani C and Crea F. Clinical outcome and correlates of coronary microvascular obstruction in latecomers after acute myocardial infarction. Int J Cardiol 2017; 236: 30-35.
[11] Chen C, Wei J, AlBadri A, Zarrini P and Bairey Merz CN. Coronary microvascular dysfunction - epidemiology, pathogenesis, prognosis, diagnosis, risk factors and therapy. Circ J 2016; 81: 3-11.
[12] Paulus WJ and Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013; 62: 263-71.
[13] Kibel A, Selthofer-Relatic K, Drenjancevic I, Bacun T, Bosnjak I, Kibel D and Gros M. Coronary microvascular dysfunction in diabetes mellitus. J Int Med Res 2017; 45: 1901-1929.
[14] Pereira HA, Shafer WM, Pohl J, Martin LE and Spitznagel JK. CAP37, a human neutrophil-derived chemotactic factor with monocyte specific activity. J Clin Invest 1990; 85: 1468-76.
[15] Pierrakos C and Vincent JL. Sepsis biomarkers: a review. Crit Care 2010; 14: R15.
[16] Tapper H, Karlsson A, Mörgelin M, Flodgaard H and Herwald H. Secretion of heparin-binding protein from human neutrophils is determined by its localization in azurophilic granules and secretory vesicles. Blood 2002; 99: 1785-93.
[17] Honore PM, De Bels D, Barreto Gutierrez L, Redant S and Spapen HD. Heparin-binding protein in sepsis: player! predictor! positioning. Ann Intensive Care 2019; 9: 71.
[18] Bentzer P, Fisher J, Kong HJ, Mörgelin M, Boyd JH, Walley KR, Russell JA and Linder A. Heparin-binding protein is important for vascular leak in sepsis. Intensive Care Med Exp 2016; 4: 33.
[19] Ipek E, Yolcu M, Yildirim E, Altinkaynak K, Ozbek Sebin S, Kalkan K, Gulcu O, Ermis E and Ozturk M. A novel marker of inflammation: azurocidin in patients with ST segment elevation myocardial infarction. Int J Mol Sci 2018; 19: 3797.
[20] Pan T, Long GF, Chen C, Zhang HT, Wang JX, Ahaskar A, Chen HB and Wang DJ. Heparin-binding protein measurement improves the prediction of myocardial injury-related cardiogenic shock. BMC Cardiovasc Disord 2020; 20: 124.
[21] Bayes-Genis A, Docherty KF, Petrie MC, Januzzi JL, Mueller C, Anderson L, Bozkurt B, Butler J, Chioncel O, Cleland JGF, Christodorescu R, Del Prato S, Gustafsson F, Lam CSP, Moura B, Pop-Busui R, Seferovic P, Volterrani M, Vaduganathan M, Metra M and Rosano G. Practical algorithms for early diagnosis of heart failure and heart stress using NT-proBNP: a clinical consensus statement from the Heart Failure Association of the ESC. Eur J Heart Fail 2023; 25: 1891-1898.
[22] McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F and Skibelund AK. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021; 42: 3599-3726.
[23] Conti CR. The stunned and hibernating myocardium: a brief review. Clin Cardiol 1991; 14: 708-12.
[24] McCartney PJ, Eteiba H, Maznyczka AM, McEntegart M, Greenwood JP, Muir DF, Chowdhary S, Gershlick AH, Appleby C, Cotton JM, Wragg A, Curzen N, Oldroyd KG, Lindsay M, Rocchiccioli JP, Shaukat A, Good R, Watkins S, Robertson K, Malkin C, Martin L, Gillespie L, Ford TJ, Petrie MC, Macfarlane PW, Tait RC, Welsh P, Sattar N, Weir RA, Fox KA, Ford I, McConnachie A and Berry C. Effect of low-dose intracoronary

alteplase during primary percutaneous coronary intervention on microvascular obstruction in patients with acute myocardial infarction: a randomized clinical trial. JAMA 2019; 321: 56-68.
[25] Wu KC, Zerhouni EA, Judd RM, Lugo-Olivieri CH, Barouch LA, Schulman SP, Blumenthal RS and Lima JA. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. Circulation 1998; 97: 765-72.
[26] Jolly SS, Shenkman H, Brieger D, Fox KA, Yan AT, Eagle KA, Steg PG, Lim KD, Quill A and Goodman SG. Quantitative troponin and death, cardiogenic shock, cardiac arrest and new heart failure in patients with non-ST-segment elevation acute coronary syndromes (NSTE ACS): insights from the Global Registry of Acute Coronary Events. Heart 2011; 97: 197-202.
[27] Carvalho LSF, Bogniotti LAC, de Almeida OLR, E Silva JCQ, Nadruz W, Coelho OR and Sposito AC. Change of BNP between admission and discharge after ST-elevation myocardial infarction (Killip I) improves risk prediction of heart failure, death, and recurrent myocardial infarction compared to single isolated measurement in addition to the GRACE score. Eur Heart J Acute Cardiovasc Care 2019; 8: 643-651.
[28] Khot UN, Jia G, Moliterno DJ, Lincoff AM, Khot MB, Harrington RA and Topol EJ. Prognostic importance of physical examination for heart failure in non-ST-elevation acute coronary syndromes: the enduring value of Killip classification. JAMA 2003; 290: 2174-81.
[29] Henein MY, Vancheri S, Longo G and Vancheri F. The role of inflammation in cardiovascular disease. Int J Mol Sci 2022; 23: 12906.
[30] Al Aseri ZA, Habib SS and Marzouk A. Predictive value of high sensitivity C-reactive protein on progression to heart failure occurring after the first myocardial infarction. Vasc Health Risk Manag 2019; 15: 221-227.
[31] Li Y, Bai G, Gao Y, Guo Z, Chen X, Liu T and Li G. The systemic immune inflammatory response index can predict the clinical prognosis of patients with initially diagnosed coronary artery disease. J Inflamm Res 2023; 16: 5069-5082.
[32] Li Y, Chen X, Huang L and Lu J. Association between neutrophil-lymphocyte ratio and arterial stiffness in patients with acute coronary syndrome. Biosci Rep 2019; 39: BSR20190015.
[33] Li Q, Ma X, Shao Q, Yang Z, Wang Y, Gao F, Zhou Y, Yang L and Wang Z. Prognostic impact of multiple lymphocyte-based inflammatory indices in acute coronary syndrome patients. Front Cardiovasc Med 2022; 9: 811790.
[34] Jeger RV, Pfister O, Radovanovic D, Eberli FR, Rickli H, Urban P, Pedrazzini G, Stauffer JC, Nossen J and Erne P. Heart failure in patients admitted for acute coronary syndromes: a report from a large national registry. Clin Cardiol 2017; 40: 907-913.
[35] Iversen LF, Kastrup JS, Bjørn SE, Rasmussen PB, Wiberg FC, Flodgaard HJ and Larsen IK. Structure of HBP, a multifunctional protein with a serine proteinase fold. Nat Struct Biol 1997; 4: 265-8.
[36] Gautam N, Olofsson AM, Herwald H, Iversen LF, Lundgren-Akerlund E, Hedqvist P, Arfors KE, Flodgaard H and Lindbom L. Heparin-binding protein (HBP/CAP37): a missing link in neutrophil-evoked alteration of vascular permeability. Nat Med 2001; 7: 1123-7.
[37] Soehnlein O and Lindbom L. Neutrophil-derived azurocidin alarms the immune system. J Leukoc Biol 2009; 85: 344-51.
[38] Xue H and Yu F. Changes in heparin-binding protein, procalcitonin, and C-reactive protein within the first 72 hours predict 28-day mortality in patients admitted to the intensive care unit with septic shock. Med Sci Monit 2023; 29: e938538.
[39] Pesonen E, Passov A, Salminen US, Ilmakunnas M, Vento A, Aittomäki J, Andersson S and Schramko A. Heparin binding protein in adult heart surgery. Ann Thorac Surg 2019; 107: 1154-1159.
[40] Vincent JL and De Backer D. Microvascular dysfunction as a cause of organ dysfunction in severe sepsis. Crit Care 2005; 9 Suppl 4: S9-12.
[41] Damluji AA, Forman DE, Wang TY, Chikwe J, Kunadian V, Rich MW, Young BA, Page RL 2nd, DeVon HA and Alexander KP. Management of acute coronary syndrome in the older adult population: a scientific statement from the American Heart Association. Circulation 2023; 147: e32-e62.
[42] Thakker R, Khan M and Al-Hemyari B. Cardiac rehabilitation after hospitalization for acute coronary syndrome. Curr Cardiol Rep 2023; 25: 1699-1703.
[43] Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, Claeys MJ, Dan GA, Dweck MR, Galbraith M, Gilard M, Hinterbuchner L, Jankowska EA, Jüni P, Kimura T, Kunadian V, Leosdottir M, Lorusso R, Pedretti RFE, Rigopoulos AG, Rubini Gimenez M, Thiele H, Vranckx P, Wassmann S, Wenger NK and Ibanez B; ESC Scientific Document Group. 2023 ESC guidelines for the management of acute coronary syndromes. Eur Heart J 2023; 44: 3720-3826.

Supplementary Table 1. Collinearity analysis among variables

Variable	VIF	Tolerance
HBP	1.07438	0.93077
Age	1.10454	0.90535
Sex	1.09724	0.91138
cTnT	1.03372	0.96738
Hypertension	1.18464	0.84414
Diabetes	1.14764	0.87135
EF	2.01488	0.49631
Diuretics	2.00754	0.49812

Abbreviations: VIF, variance inflation factor; HBP, heparin-binding protein; CTNT, cardiac troponin T; EF, ejection fraction.