

# Nomogram for the Prediction of Intrahospital Mortality Risk of Patients with ST-Segment Elevation Myocardial Infarction Complicated with Hyperuricemia: A Multicenter Retrospective Study

Zhixun Bai<sup>1-4,\*</sup>Yi Ma<sup>2,3,5,\*</sup>Zhiyun Shi<sup>2,3,6,\*</sup>Ting Li<sup>2,3,7</sup>Shan Hu<sup>2-4,8</sup>Bei Shi<sup>2-4</sup>

<sup>1</sup>Department of Internal Medicine, The Second Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, People's Republic of China; <sup>2</sup>Department of Cardiology, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, People's Republic of China; <sup>3</sup>Affiliated Hospital of Zunyi Medical University Cross-Regional Specialized Alliance, Zunyi, Guizhou, People's Republic of China; <sup>4</sup>College of Medicine, Soochow University, Suzhou, Jiangsu, People's Republic of China; <sup>5</sup>Department of Cardiology, Affiliated Yijiang County People's Hospital of Zunyi Medical University, Tongren, Guizhou, People's Republic of China; <sup>6</sup>Department of Cardiology, Affiliated Qianxi County People's Hospital of Zunyi Medical University, Bijie, Guizhou, People's Republic of China; <sup>7</sup>Department of Cardiology, Affiliated Dafang County People's Hospital of Zunyi Medical University, Bijie, Guizhou, People's Republic of China; <sup>8</sup>Department of Cardiology, Affiliated Tongzi County People's Hospital of Zunyi Medical University, Zunyi, Guizhou, People's Republic of China

\*These authors contributed equally to this work

Correspondence: Bei Shi  
Department of Cardiology, Affiliated  
Hospital of Zunyi Medical University,  
Zunyi, Guizhou, People's Republic of  
China  
Email shibei2147@163.com

**Purpose:** This study aimed to establish an accurate and easy predictive model for ST-segment elevation myocardial infarction (STEMI) patients with hyperuricemia, using readily available features to estimate intrahospital mortality risk.

**Patients and Methods:** This was a multicenter retrospective study involving the development of risk prediction models for intrahospital mortality among all STEMI patients with hyperuricemia from Zunyi Medical University Chest Pain Center's specialized alliance between January 1, 2016 and June 30, 2020. The primary outcome was intrahospital mortality. A total of 48 candidate variables were considered from demographic and clinical data. The least absolute shrinkage and selection operator (LASSO) was used to develop a nomogram. Concordance index values, decision curve analysis, the area under the curve (AUC), and clinical impact curves were examined. In this study, 489 patients with STEMI were included in the training dataset and an additional 209 patients from the 44 chest pain centers were included in the test cohort. B-type natriuretic peptides,  $\alpha$ -hydroxybutyrate dehydrogenase ( $\alpha$ -HBDH), cystatin C, out-of-hospital cardiac arrest (OHCA), shock index, and neutrophil-to-lymphocyte ratio were associated with intrahospital mortality and included in the nomogram.

**Results:** The model showed good discrimination power, and the AUC generated to predict survival in the training set was 0.875 (95% confidence interval, 0.825–0.925). In the validation set, the AUC of survival predictions was 0.87 (95% confidence interval, 0.792–0.947). Calibration plots and decision curve analysis showed good model performance in both datasets. A web-based calculator (<https://bzxzmu.shinyapps.io/STEMI-with-Hyperuricemia-intrahospital-mortality/>) was established based on the nomogram model, which was used to measure the levels of OHCA, neutrophil-to-lymphocyte ratio, shock index,  $\alpha$ -HBDH, cystatin C, and B-type natriuretic peptides.

**Conclusion:** For practical applications, this model may prove clinically useful for personalized therapy management in patients with STEMI with hyperuricemia.

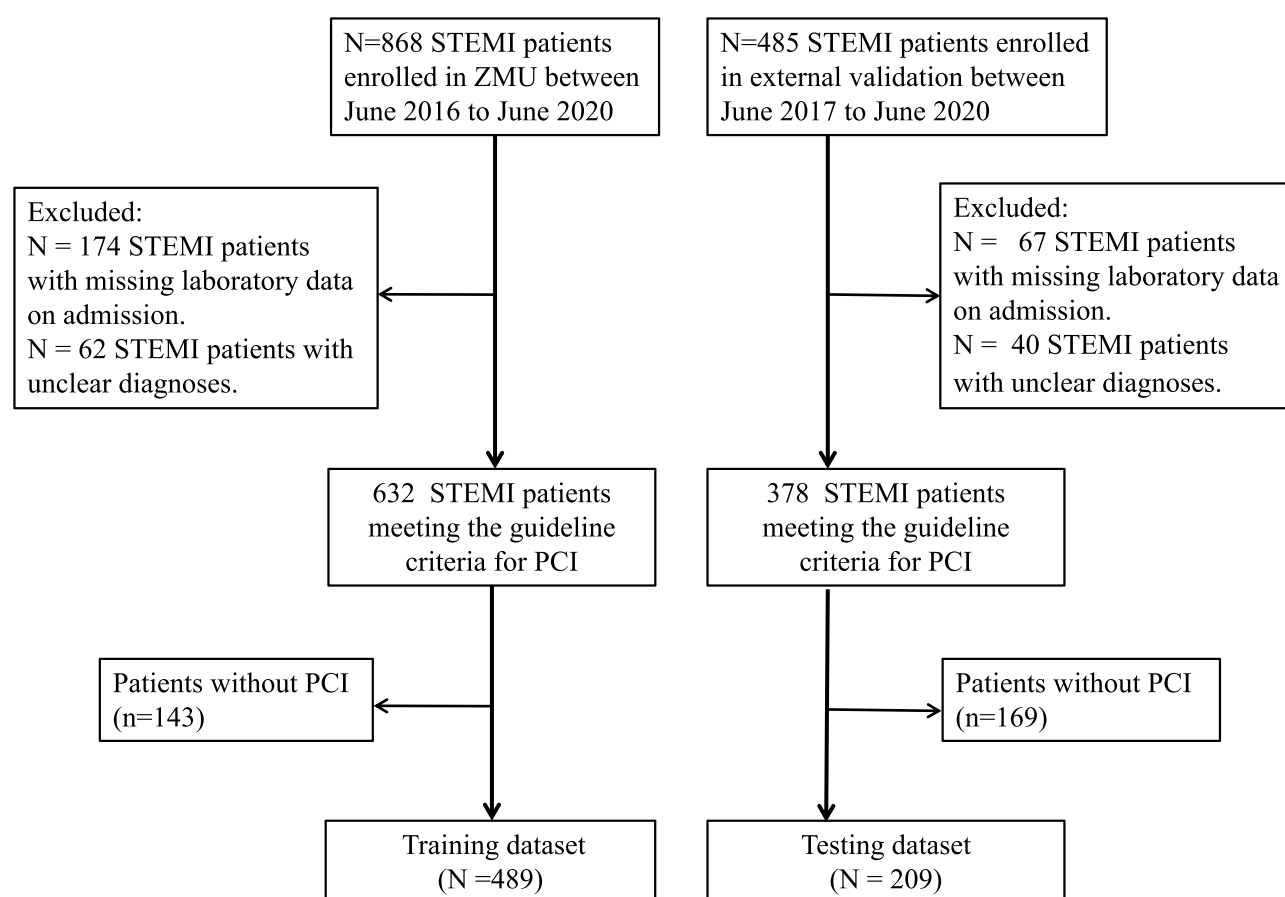
**Keywords:** hyperuricemia, STEMI, nomogram, mortality

## Introduction

Acute myocardial infarction (AMI) covers a wide range of clinical manifestations, including ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI), that are associated with high morbidity and mortality rates. STEMI is the most severe type of AMI and has a poor prognosis.<sup>1-3</sup> It shows rapid progression and high risk of intrahospital mortality.<sup>4-6</sup> Therefore, a simple, easy, and rapid prognostic model

would have a huge clinical impact on the prognoses of patients with STEMI. Common risk factors for STEMI include dyslipidemia, hypertension, diabetes mellitus, and a family history of coronary artery disease. In recent years, elevated serum uric acid (UA) levels have become a well-known cardiovascular risk factor.<sup>7–12</sup> Although it is still controversial whether UA is an independent predictor of cardiovascular disease, recent retrospective studies have demonstrated that elevated UA levels are an independent predictor of short- and long-term mortality in patients with AMI.<sup>13,14</sup> Various prognostic models based on clinical and procedural variables have been established to predict the outcomes of STEMI, such as the Global Registry of Acute Coronary Events (GRACE) and Observatoire Regional Breton sur l'Infarctus (ORBI) scores.<sup>15,16</sup> Based on preprocedural factors (typically a combination of clinical and angiographic variables), several prognostic risk scores estimate the individualized risk for adverse outcomes after coronary revascularization.<sup>17–19</sup> However, for individualized prognosis prediction, these scores are limited by the categorization of continuous variables, such

as age and blood glucose levels, and the risk of delayed scoring until the angiographic variables can be collected and calculated. A nomogram is a graphical display tool that conveniently calculates and interprets predictive results. This device is essential to modern clinical decision-making that is used worldwide in various clinical applications, including cancer treatment, surgery, and other specialties.<sup>20–22</sup> However, to date, a nomogram model with adequacy to detect the probability of intrahospital mortality in STEMI patients with hyperuricemia is yet to be developed. Accurate prediction of adverse events after coronary revascularization is essential for preprocedural informed consent and appropriate therapy selection. Considering the number of related risk factors, an accurate prediction tool with early intervention could be the most effective way to treat STEMI patients with hyperuricemia. However, to the best of our knowledge, there is no research on this subject. This study aimed to establish an accurate and easy predictive model for STEMI patients with hyperuricemia, using readily available features to estimate intrahospital mortality risk.



**Figure 1** Flow chart outlining the patient inclusion process.

**Abbreviations:** ZMU, The affiliated Hospital of Zunyi Medical University; STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention.

**Table I** Demographics and Clinical Characteristics of the Training and Test Cohorts

Variables	Training Cohort (n = 489)	Test Cohort (n = 209)	P-value
<b>Demographic characteristics</b>			
Sex, n (%)			0.583
Female	22 (25)	57 (27)	
Male	367 (75)	152 (73)	
Age, y	64.0 (52.0, 74.0)	63.0 (53.0, 72.0)	0.216
Smoking, n (%)	314 (64)	132 (63)	0.857
Weekend on admission, n (%)	122 (25)	69 (33)	0.036
Delay, n (%)	119 (24)	50 (24)	0.984
<b>Vascular risk factors</b>			
Hypertension, n (%)	297 (61)	114 (55)	0.15
Diabetes mellitus, n (%)	98 (20)	45 (22)	0.731
Prior-Stroke, n (%)	30 (6)	8 (4)	0.294
CKD, n (%)	107 (22)	45 (22)	0.998
OHCA, n (%)	44 (9)	13 (6)	0.282
GRACE, score	128.0 (105.0, 154.0)	122.0 (102.0, 154.0)	0.363
<b>Clinical data</b>			
HR, beats/min	80.0 (73.0, 92.0)	84.0 (72.0, 94.0)	0.294
SBP, mmHg	126.0 (108.0, 140.0)	126.0 (110.0, 141.0)	0.4
DBP, mmHg	80.00 (72.00, 90.00)	80.00 (68.00, 90.00)	0.409
Shock index	0.7 (0.6, 0.8)	0.6 (0.5, 0.8)	0.965
Killip, n (%)			0.238
1	369 (75)	161 (77)	
2	54 (11)	16 (8)	
3	23 (5)	16 (8)	
4	43 (9)	16 (8)	
<b>Laboratory examinations on admission</b>			
WBC, *10 <sup>9</sup> /L	11.4 (8.6, 14.2)	11.3 (8.6, 14.0)	0.864
Neutrophil count, *10 <sup>9</sup> /L	8.9 (6.3, 11.8)	9.1 (6.1, 11.5)	0.898
NLR	6.8 (4.0, 10.7)	6.3 (3.5, 10.9)	0.735
PLR	152.4 (105.8, 228.7)	148.4 (100.5, 218.4)	0.325
MLR	0.5 (0.3, 0.8)	0.5 (0.4, 0.8)	0.28
SIRI	4.5 (2.6, 8.4)	3.9 (2.5, 7.4)	0.296
SII	1312.4 (789.4, 2256.4)	1307.8 (678.1, 2247.2)	0.545
HB, g/L	136.0 (121.0, 152.0)	139.0 (120.0, 152.0)	0.935
RBC, *10 <sup>12</sup> /L	4.5 (3.9, 5.0)	4.5 (4.0, 5.0)	0.504
PLT, *10 <sup>9</sup> /L	208.0 (165.0, 256.0)	212.0 (162.0, 248.0)	0.566
ALT, U/L	31.0 (22.0, 52.0)	34.0 (23.0, 56.0)	0.175
AST, U/L	69.0 (36.0, 163.0)	72.0 (34.0, 173.0)	0.647
GGT, U/L	42.0 (25.0, 73.0)	46.0 (29.0, 75.0)	0.197
BUN, mmol/L	6.7 (5.2, 9.1)	6.5 (5.2, 9.2)	0.379
Creatinine, umol/L	99.0 (80.0, 124.0)	97.0 (77.0, 123.0)	0.317
Uuric acid, umol/L	472.0 (437.0, 537.0)	473.0 (436.0, 523.0)	0.545
Cystatin C, mg/L	1.2 (1.0, 1.5)	1.1 (0.9, 1.5)	0.575
CK, U/L	453.0 (184.0, 1352.0)	501.0 (172.0, 1406.0)	0.588
CKMB, U/L	49.0 (24.0, 129.0)	48.0 (25.0, 126.0)	0.959
LDH, U/L	360.0 (264.0, 609.0)	390.0 (270.0, 657.0)	0.287
α-HBDH, U/L	251.0 (171.0, 459.0)	281.0 (183.0, 502.0)	0.325

(Continued)

**Table I** (Continued).

Variables	Training Cohort (n = 489)	Test Cohort (n = 209)	P-value
CTnT, ng/L	956.6 (204.5, 3291.0)	1014.0 (157.0, 3315.0)	0.767
BNP, pg/mL	1094.0 (265.6, 4087.0)	1013.0 (228.7, 4497.0)	0.718
Glucose, mmol/L	6.7 (5.6, 8.7)	6.7 (5.6, 9.0)	0.795
Myoglobin, ng/mL	375.7 (102.2, 961.6)	295.5 (91.7, 723.5)	0.08
<b>Procedural features</b>			
LM, n (%)	6 (1)	6 (3)	0.199
LAD, n (%)	149 (30)	79 (38)	0.071
LCX, n (%)	53 (11)	19 (9)	0.576
RCA, n (%)	118 (24)	51 (24)	1
<b>Intrahospital complications</b>			
Post-Ventricular fibrillation, n (%)	44 (9)	16 (8)	0.666
Post-Cardiogenic shock, n (%)	51 (10)	19 (9)	0.688
Intrahospital Mortality, n (%)	69 (14)	29 (13)	0.995
<b>Other</b>			
Total hospital duration stay, d	7.0 (5.0, 10.0)	6.0 (5.0, 9.0)	0.136

**Notes:** Values are expressed as medians with interquartile ranges for continuous data. Other values are presented as numbers and percentages.

**Abbreviations:** Shock index, ratio of HR to SBP; SIRI, systemic inflammatory response index; SII, systemic inflammatory reaction index; PLR, ratio of platelets to lymphocytes; NLR, the ratio of neutrophils to lymphocytes; MLR, ratio of monocytes to lymphocytes; OHCA, out-of-hospital cardiac arrest; GRACE, Global Registry of Acute Coronary Events score;  $\alpha$ -HBDH,  $\alpha$ -Hydroxybutyrate dehydrogenase; BNP, B-type natriuretic peptides.

## Materials and Methods

Training cohorts were selected from the affiliated hospital of Zunyi Medical University (ZMU), the tertiary medical institution of the Zunyi Cross-Regional Specialized Alliance of Chest Pain Center (ZMUCPC), between January 2016 and June 2020. ZMUCPC is a regional CPC association, including the affiliated hospital of ZMU (tertiary medical institution) and 44 other referral hospitals (secondary medical institutions) across 20 counties in the northern Guizhou Province, that serves 10 million people and was established in May 2017. Validation of the model was performed on a cohort of patients who underwent percutaneous coronary intervention (PCI) for STEMI between June 2017 and June 2020 at these 44 referral hospitals of the ZMUCPC. All patients met the diagnostic criteria of current guidelines for acute STEMI and underwent primary PCI.<sup>23</sup> Patients with STEMI who met the following inclusion criteria were included in the study: 1) increase or occurrence of ischemic chest discomfort at rest, 2) elevation of ST-segment  $\geq 0.1$  mV, 3) elevation of ST-segment in 2 consecutive leads, and 4) elevated levels of cardiac troponin I ( $\geq 0.03$   $\mu\text{g/L}$ ) or elevation of cardiac troponin T ( $\geq 42$  ng/L). The exclusion criteria were patients with STEMI who (1) did not undergo primary PCI, (2) were pregnant or lactating, and (3)

had allergies to the contrast agent. We also removed variables with  $> 20\%$  missing data to facilitate and ensure accuracy. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki. Research approval was obtained from the Ethics Committee of ZMU (approval no. KLL[2020]0144). ZMUCPC has a computerized database of all STEMI patients. Medical records pertaining to the demographic characteristics, clinical data, and outcomes were carefully obtained from the computerized database. The requirement for written informed consent from patients was waived because of the study's retrospective nature. As the data were susceptible to incorrect notation by the researcher; data cleansing and editing, that consisted of removing typographical errors and reviewing data integrity/quality in data reporting, were performed by a second researcher to avoid a flawed model training process. This researcher assessed all clinical endpoints blinded to the outcome of mortality. Additionally, a different researcher assessed the plausibility of the results regarding the outcome of mortality.

A standardized case-report form was used to collect demographic and clinical data, including procedural information. Intrahospital mortality was defined as all-cause mortality during hospitalization. Hyperuricemia was defined as UA levels

**Table 2** Comparison of Characteristics of Patients with and without Mortality in the Training Cohort

Variables	Survival (n=420)	Death (n=69)	P-value
<b>Demographic characteristics</b>			
Sex, n (%)			0.059
Female	98 (23)	24 (35)	
Male	322 (77)	45 (65)	
Age, y	64.0 (51.8, 73.0)	70.0 (61.0, 77.0)	< 0.001
Smoking, n (%)	273 (65)	41 (59)	0.447
Weekend on admission, n (%)	108 (26)	14 (20)	0.415
Delay, n (%)	92 (22)	27 (39)	0.003
<b>Vascular risk factors</b>			
Hypertension, n (%)	256 (61)	41 (59)	0.914
Diabetes mellitus, n (%)	83 (20)	15 (22)	0.827
Prior-Stroke, n (%)	26 (6)	4 (6)	1
CKD, n (%)	85 (20)	22 (32)	0.044
OHCA, n (%)	16 (4)	28 (41)	< 0.001
GRACE, score	122.0 (102.0, 145.0)	178.0 (142.0, 213.0)	< 0.001
<b>Clinical data</b>			
HR, beats/min	79.0 (72.0, 90.0)	86.0 (76.0, 110.0)	< 0.001
SBP, mmHg	128.0 (110.0, 142.0)	109.0 (89.0, 130.0)	< 0.001
DBP, mmHg	80.00 (68.00, 92.00)	73.00 (58.00, 85.00)	< 0.001
Shock_index	0.6 (0.5, 0.7)	0.8 (0.7, 1.1)	< 0.001
Killip, n (%)			< 0.001
1	343 (82)	26 (38)	
2	47 (11)	7 (10)	
3	14 (3)	9 (13)	
4	16 (4)	27 (39)	
<b>Electrocardiographic data</b>			
Inferior_wall, n (%)	196 (47)	23 (33)	0.053
Anterior_wall, n (%)	205 (49)	41 (59)	0.133
Other, n (%)	13 (3)	4 (6)	0.28
Right_ventricular, n (%)	5 (1)	1 (1)	0.601
<b>Laboratory examinations on admission</b>			
WBC, *10 <sup>9</sup> /L	11.2 (8.4, 13.5)	13.6 (10.0, 18.1)	< 0.001
Neutrophil_count, *10 <sup>9</sup> /L	8.6 (6.2, 11.1)	11.3 (7.8, 15.1)	< 0.001
NLR	6.3 (3.9, 9.8)	9.7 (5.9, 14.8)	< 0.001
PLR	152.0 (107.8, 223.3)	155.6 (87.2, 278.2)	0.93
MLR	0.5 (0.3, 0.8)	0.8 (0.4, 1.1)	0.003
SIRI	4.2 (2.5, 7.4)	7.9 (4.1, 14.1)	< 0.001
SII	1236.8 (778.3, 2094.1)	2009.1 (1074.2, 2940.4)	0.005
HB, g/L	138.00 (122.00, 153.00)	126.00 (115.00, 147.00)	0.018
RBC, *10 <sup>12</sup> /L	4.52 (3.98, 4.98)	4.17 (3.74, 4.85)	0.027
PLT, *10 <sup>9</sup> /L	209.5 (167.5, 256.2)	197.0 (157.0, 254.0)	0.286
ALT, U/L	30.0 (22.0, 48.0)	50.0 (26.0, 129.0)	< 0.001
AST, U/L	63.0 (35.0, 139.2)	178.0 (64.0, 399.0)	< 0.001
GGT, U/L	41.0 (25.8, 69.2)	55.0 (25.0, 83.0)	0.403
BUN, mmol/L	6.4 (5.1, 8.2)	10.2 (7.7, 13.1)	< 0.001
Creatinine, umol/L	96.0 (79.0, 116.0)	135.0 (100.0, 181.0)	< 0.001

(Continued)

**Table 2** (Continued).

Variables	Survival (n=420)	Death (n=69)	P-value
Uuric acid, umol/L	470.0 (436.0, 527.0)	515.0 (449.0, 601.0)	0.003
Cystatin C, mg/L	1.2 (0.9, 1.5)	1.6 (1.2, 2.2)	< 0.001
CK, U/L	423.0 (166.5, 1297.8)	744.0 (303.0, 1639.0)	0.006
CKMB, U/L	45.0 (23.0, 118.5)	86.0 (39.0, 182.0)	0.002
LDH, U/L	343.5 (253.0, 523.8)	655.0 (381.0, 1057.0)	< 0.001
$\alpha$ -HBDH, U/L	233.5 (166.0, 404.5)	451.0 (276.0, 739.0)	< 0.001
CTnT, ng/L	747.1 (175.7, 2914.2)	2590.0 (1140.0, 5476.0)	< 0.001
BNP, pg/mL	870.1 (212.3, 2878.5)	6279.0 (2061.0, 21,400.0)	< 0.001
Glucose, mmol/L	6.6 (5.6, 8.4)	7.9 (6.3, 10.6)	< 0.001
Myoglobin, ng/mL	332.5 (94.4, 893.2)	677.1 (191.0, 1908.0)	< 0.001
<b>Procedural features</b>			
LM, n (%)	6 (1)	0 (0)	1
LAD, n (%)	129 (31)	20 (29)	0.882
LCX, n (%)	47 (11)	6 (9)	0.683
RCA, n (%)	102 (24)	16 (23)	0.964
<b>Intrahospital complications</b>			
Post-Ventricular fibrillation, n (%)	19 (5)	25 (36)	< 0.001
Post-Cardiogenic shock, n (%)	16 (4)	35 (51)	< 0.001
<b>Other</b>			
Total hospital duration stay, d	7.0 (5.0, 10.0)	2.0 (1.0, 4.0)	< 0.001

**Notes:** Values are expressed as medians with interquartile ranges for continuous data. Other values are presented as numbers and percentages. Shock index ratio of HR to SBP.

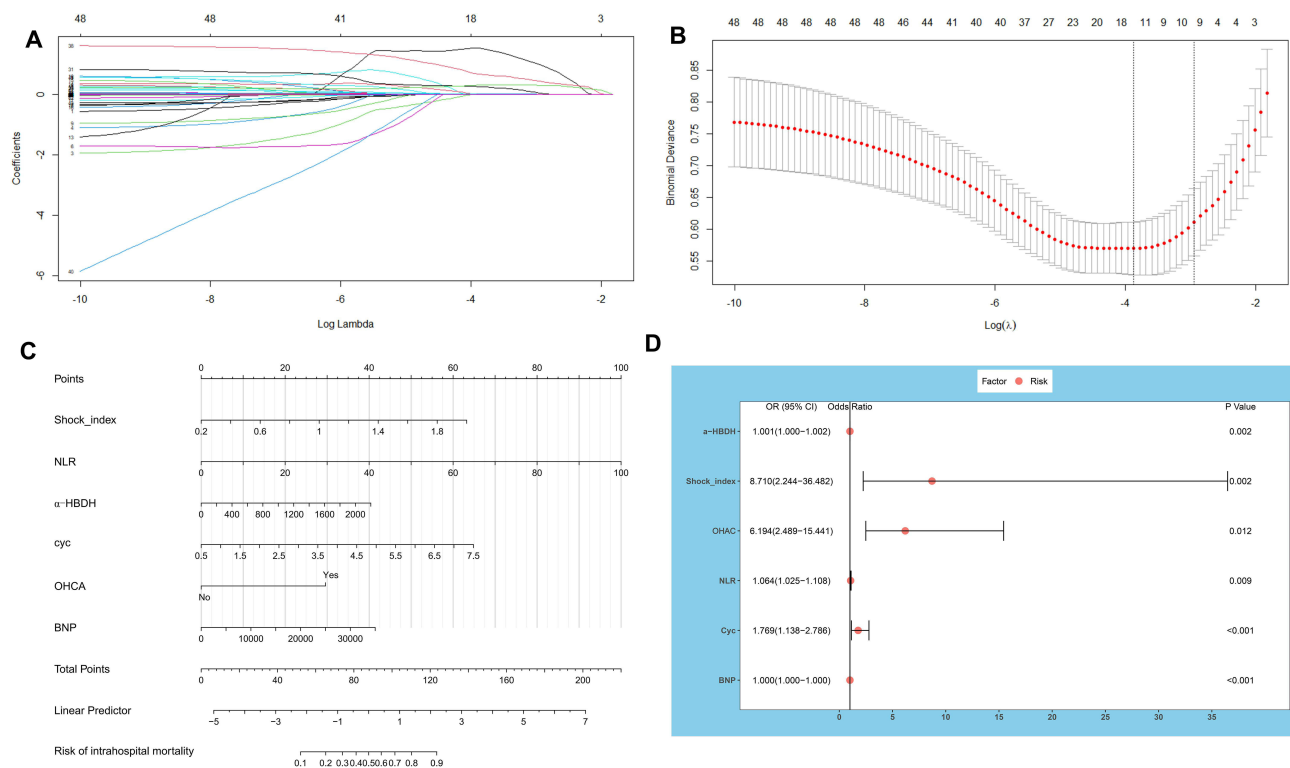
**Abbreviations:** SIRI, systemic inflammatory response index; SII, systemic inflammatory reaction index; PLR, ratio of platelets to lymphocytes; NLR, the ratio of neutrophils to lymphocytes; MLR, ratio of monocytes to lymphocytes; OHCA, out-of-hospital cardiac arrest; GRACE, Global Registry of Acute Coronary Events score;  $\alpha$ -HBDH,  $\alpha$ -Hydroxybutyrate dehydrogenase; BNP, B-type natriuretic peptides.

>7 mg/dL (420 mmol/L) in males and >6 mg/dL (360 mmol/L) in females, as described in previous studies.<sup>24</sup> Patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m<sup>2</sup> for more than three months were defined as having chronic kidney disease (CKD). Delay was defined as and when patient's first medical contact exceeded 12 hours from symptom onset. Weekend (Saturday and Sunday) or nonweekend exposure (Monday to Friday) was categorized according to the admission calendar. To enrich the dataset, we computed "index" variables, such as shock index (SI), which was defined as the ratio of heart rate and systolic blood pressure, systemic inflammatory response index, systemic inflammatory reaction index, platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio (NLR), and monocyte-to-lymphocyte ratio.

Continuous variables were presented as the medians (interquartile ranges [IQR]) and categorical variables as the numbers (%). Differences in baseline characteristics between groups were analyzed using independent sample *t*-tests, with Mann–Whitney *U*-tests used for continuous

variables and chi-squared or Fisher's exact tests used for categorical variables, as appropriate. All statistical analyses were performed using R software (Version 4.0.2; <https://www.R-project.org>). We used the LASSO approach with the Akaike information criterion (AIC) to select the best predictive features of mortality using the backward selection method that included variables with *P*<0.05. The characteristic of the nonzero coefficient in the cable regression model was selected, and these risk factors were considered based on odds ratios (ORs) with 95% confidence intervals (CIs) and *P*-values. A vertical line needs to be delineated to the point raw to assign a point value for significant predictors to use the nomogram, and then it needs to be added to generate a total score and converted into an individual probability of intrahospital mortality. The nomogram was programmed using the ZMU data and externally validated using the test cohort. The discriminative performance was measured by the concordance index (C-index). Calibration was tested using





**Figure 2** Demographic and clinical feature selection using the LASSO. **(A)** The minimum criterion of 10-fold cross-validation selects the optimal parameter ( $\lambda$ ) in the LASSO model. **(B)** LASSO coefficient profiles of the 45 features. The coefficient profiles are drawn as a function of  $\log(\lambda)$ . **(C)** Intrahospital mortality nomogram. **(D)** Forest plot of odds ratio (OR) with confidence intervals.

a calibration plot with bootstraps of 1000 resamples, which described the degree of fit between actual and nomogram-predicted mortality. Decision curve analysis (DCA) was conducted to assess the predictive nomogram's clinical usefulness by quantifying the net benefits at different threshold probabilities. Finally, the clinical impact curve (CIC) was plotted to evaluate the model's clinical usefulness and applicability with net benefits with the best diagnostic value.

## Results

The flow chart of patient inclusion is presented in Figure 1. The baseline characteristics of the training and validation sets are described in Table 1. The training and test cohort included 489 (median age, 64 years; 24.9% female) and 209 (median age, 63 years; 27.2% female) patients, respectively. No difference in intrahospital mortality was detected between the cohorts (14.1% versus 13.8%;  $P=0.995$ ). According to LASSO analysis, in the training cohort, the SI index, out-of-hospital cardiac arrest (OHCA), neutrophil count, NLR, and  $\alpha$ -hydroxybutyrate dehydrogenase ( $\alpha$ -HBDH), B-type

natriuretic peptides (BNP), LDH, Killip, and cystatin C levels were potential predictors for intrahospital mortality ( $P<0.01$ ; Table 2, Figure 2A and B). Figure 2C shows the nomogram diagram including six significant predictors. Baseline BNP (OR, 1.000; 95% CI, 1.000–1.000;  $P<0.001$ ),  $\alpha$ -HBDH (OR, 1.001; 95% CI, 1.000–1.002;  $P=0.012$ ), and cystatin C (OR, 1.769; 95% CI, 1.137–2.786;  $P=0.009$ ) levels; OHCA (OR, 6.194; 95% CI, 2.489–15.441;  $P<0.001$ ), SI (OR, 8.71; 95% CI, 2.244–36.482;  $P=0.002$ ), and NLR (OR, 1.063; 95% CI, 1.025–1.108;  $P=0.002$ ) were detected by AIC as predictors of intrahospital mortality (Table 3, Figure 2D). To facilitate the clinical application of our findings, we established a model to predict the risk of intrahospital mortality among patients with STEMI with hyperuricemia according to the nomogram (Figure 3). For example, a patient with a circulating cystatin C level of 2 mg/L, BNP level of 20,000 pg/mL,  $\alpha$ -HBDH level of 800 U/L, SI of 1, and NLR of 10 would have a total of 91 points (14 points for cystatin C, 24 points for BNP, 15 points for  $\alpha$ -HBDH, 28 points for SI, and 10 points for NLR). Intrahospital mortality was

**Table 3** Multivariate Logistic Regression Analysis for the Risk Factors Associated with Mortality in the Training Cohort

	Multivariate Analysis OR(95% CI)	P-value	AIC Adjusted OR(95% CI)	P-value
(Intercept)	0.001(0.000–0.006)	< 0.001	0.002(0.001–0.008)	< 0.001
Shock_index	8.661(2.07–39.641)	0.003	8.710(2.244–36.482)	0.002
Neutrophil count	1.04(0.956–1.131)	0.352		
NLR	1.048(1.001–1.101)	0.053	1.063(1.025–1.108)	0.002
BUN	1.032(0.946–1.122)	0.466		
LDH	1.000(0.998–1.001)	0.901		
Cystatin C	1.548(0.892–2.687)	0.109	1.769(1.137–2.786)	0.009
$\alpha$ -HBDH	1.000(0.998–1.002)	0.451	1.001(1.000–1.002)	0.012
OHCA	3.054(0.460–19.378)	0.236	6.194(2.489–15.441)	< 0.001
Killip1	Reference			
Killip2	1.0193(0.313–2.817)	0.972		
Killip3	2.344(0.655–7.593)	0.169		
Killip4	2.334(0.3462–15.158)	0.376		
BNP	1.000(1.000–1.000)	0.007	1.000(1.000–1.000)	< 0.001

approximately 31.9% (95% CI, 14.8–55.6%) among the study cohort.

Discrimination of the nomogram was measured by calculating the C-index, which was 0.875 (95% CI, 0.825–0.925), indicating good predictive power in the training cohort (Figure 4A). The C-index of all training and test cohorts was 0.866 by 10-fold cross-validation. The test cohort also confirmed the nomogram's calibration with a C-index of 0.87 (95% CI, 0.792–0.947; Figure 4B). As a C-index >0.75 is generally considered to indicate reliable discrimination, this nomogram performed well in terms of discrimination and calibration in both the training and test cohorts.<sup>25</sup> We further compared the DCA of the new nomogram with the previously published GRACE score. The nomogram's DCA was superior to that of the GRACE scores in the training and test cohorts (Figure 4C and D). Similar significant associations were also observed in the receiver operating characteristic curves (Figure 4E and F). The DCA demonstrated that when the threshold probabilities ranged between 1.0% and 99.0% and 2.0% and 99% in the training and test cohorts, respectively, the use of nomogram to predict intrahospital mortality versus the strategy of “assuming all” or “assuming

no” shows different results for categorizing patients as “at high mortality risk”. For example, if the individual threshold probability of a patient is 30% (the patient would opt for further treatment if his probability of mortality were >30%), the net benefit is 0.44 in the training cohort and 0.43 in the test cohort. The CIC is another type of plot produced based on the decision curve. For this risk model, Figure 5 shows the estimated number who would be declared as high risk for each risk threshold and shows the proportion of cases (true positives). In this example, if a 20% of risk threshold was used, then of the 1000 patients screened, about 180 would be deemed at high risk, about 100 of which would experience mortality. Similar plots have been used in the literature.<sup>26</sup>

## Discussion

Previous studies have confirmed that baseline renal dysfunction and acute kidney injury are strong predictors of in-hospital adverse cardiovascular outcomes after STEMI.<sup>27,28</sup> Our study has shown that hyperuricemia on admission was frequently observed in patients with AMI who underwent PCI similar to previous studies.<sup>1,8</sup> The nomogram shows that the SI may be the critical individual



## A Dynamic Nomogram



Graphical Summary Numerical Summary Model Summary

Shock\_Index NLR alpha\_HBDH Cystatin\_C OHCA BNP Prediction Lower bound Upper bound

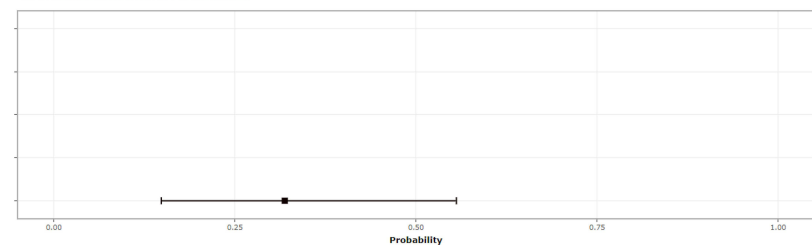
1 1 10 799 2 0 20,000 0.318 0.148 0.556

## B Dynamic Nomogram



Graphical Summary Numerical Summary Model Summary

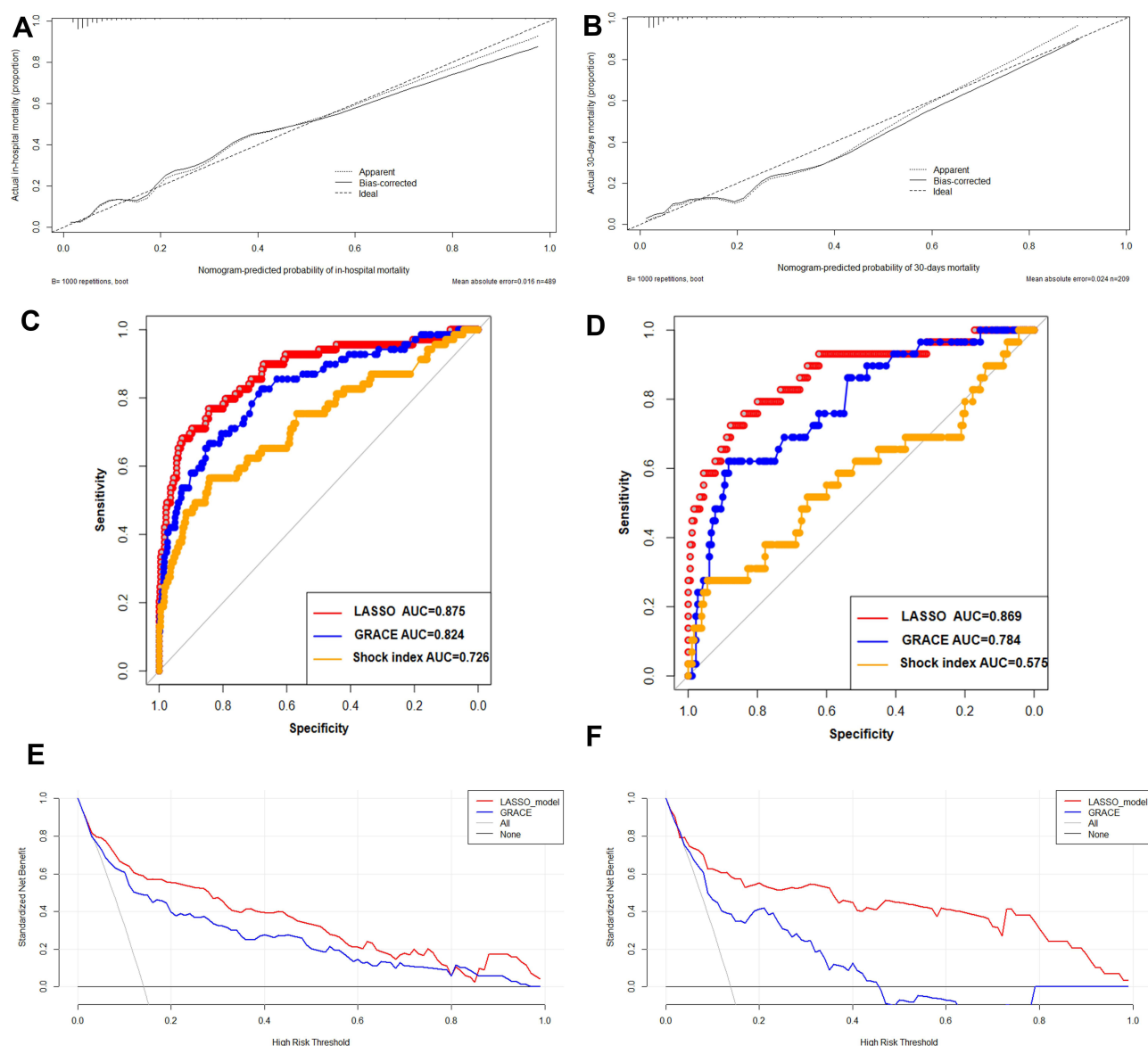
95% Confidence Interval for Response



**Figure 3** Construction of a web-based calculator (<https://bzxzmu.shinyapps.io/STEMI-with-Hyperuricemia-intrahospital-mortality/>) for predicting intrahospital mortality based on the nomogram model. (A) Web mortality risk calculator. (B) 95% confidence interval of the web mortality rate.

factor determining intrahospital mortality in STEMI patients with hyperuricemia on admission. UA acts as a direct modulator of inflammation, sub-intimal lipid accumulation, oxidative stress, and tissue injury, contributing to atherosclerosis, plaque composition, and vascular instability.<sup>9</sup> UA is strongly associated with cardiovascular disease. This study developed an accurate nomogram based on the baseline SI, NLR, OHCA, and circulating  $\alpha$ -HBDH, cystatin C, and BNP levels that can predict the probability of intrahospital mortality for STEMI patients with hyperuricemia. The nomogram's excellent capacity to

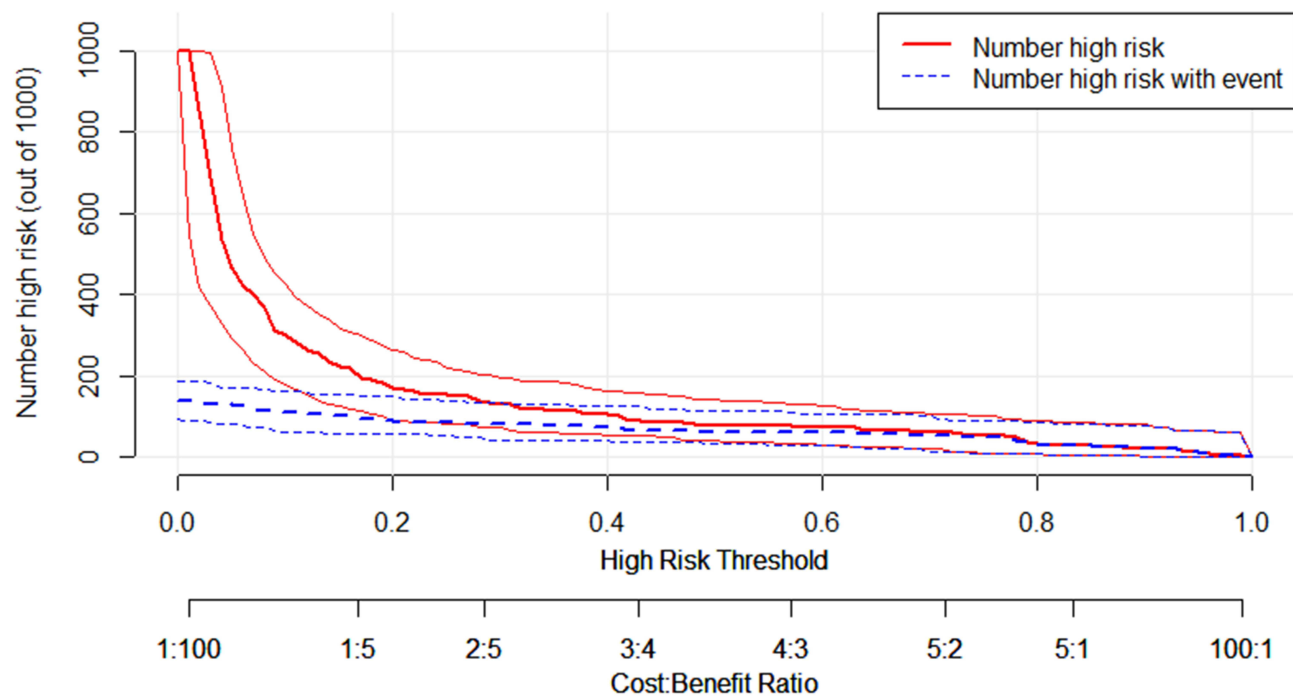
discriminate and calibrate the mortality risk was demonstrated in the training cohort and further confirmed through external validation. LASSO regression results in a full shrinkage of a subset of variables, which effectively operates as a form of variable selection. This leads to a more stable model with better predictability, mainly when applied to external datasets.<sup>29</sup> Integrating risk factors for clinical data and laboratory measurements on admission into an easy-to-use nomogram facilitates individualized prediction of mortality development in STEMI patients with hyperuricemia via the creation of a risk nomogram.



**Figure 4** Calibration plot of the nomogram in the training (A) and test cohorts (B). The dotted line represents the nomogram's performance, whereas the solid line corrects any bias in the nomogram. The dashed line represents the reference line where an ideal nomogram would lie. Predictive accuracy of the LASSO model, GRACE model, shock index model for intrahospital mortality in the training (C) and test cohorts (D). Decision curve analysis of the nomogram in the training (E) and test cohorts (F). The x-axis indicates the threshold probability. The y-axis measures the net benefit. The gray line displays the net benefit of the strategy of treating all patients. The black line illustrates the net benefit of the strategy of treating no patients. The red line indicates the nomogram. Decision curve analysis is a specific method developed for evaluating the prognostic value of nomogram strategies. The net benefit of using a model to predict intrahospital mortality versus the strategies of "assuming all" or "assuming no" patients would be at high risk is shown for a different decision. The LASSO nomogram model (red) demonstrated an improved net benefit compared with the GRACE model.

OHCA is a leading cause of mortality worldwide. The primary cause of OHCA is coronary artery disease, in particular ACS. The survival rate of OHCA patients in Asia is 3.0%.<sup>30,31</sup> Urgent coronary angiography and PCI are essential to post-resuscitation care. Inflammatory and oxidative stress play a major role in the pathogenesis of cardiovascular disease. As an easily available

inflammatory marker, the role of NLR in cardiovascular disease has been widely studied in the past few years. NLR has been shown to predict short-term mortality in patients with AMI. It has a good correlation with AMI risk prediction models such as GRACE and SYNTAX scores.<sup>32</sup> Consistent with previous reports,<sup>33–37</sup> NLR, OHCA and cystatin C were significant predictors of mortality in our



**Figure 5** Clinical impact curve for the LASSO nomogram model. The heavy red solid line shows the total number of patients out of 1000 who would be deemed high risk for each risk threshold. The blue dashed line shows how many of those would be true positives cases.

nomogram. These factors indicate that it is challenging to rescue patients with STEMI who were hypoperfused at the time of admission. Except for other laboratory variables on admission like cystatin C, BNP,  $\alpha$ -HBDH, and NLR, SI was shown to be the strongest predictor in the nomogram. Previous studies have used it to predict mortality of AMI and found that an increased SI can predict short-term mortality in patients with STEMI.<sup>38–41</sup> Our current research has some strengths. First, the nomogram was developed from a largely homogeneous population of patients with STEMI analyzed using the LASSO approach and achieved improved model performance over traditional regression methods. This method also results in a better final prediction model without sacrificing the interpretability of the relationship between risk factors and the outcome of interest. Second, a high risk of bias will overestimate model efficacy. The risk of bias assessment is an essential step in any prediction model study. Based on the prediction model risk of the bias assessment tool (PROBAST), the risk of bias is low when predictions are made without knowing the outcome status.<sup>42</sup>

Based on the patients' clinical and laboratory examinations on admission, the proposed LASSO risk model

of intrahospital mortality was constructed to ensure a low ROB. Additionally, there was no risk of delayed calculation caused by waiting for the available procedural results. Despite these strengths, our study had certain limitations. First, as the nature of the study was exploratory, the findings should have been interpreted with caution, as this study excluded several patients because of missing laboratory data. Second, our study focused on STEMI patients with hyperuricemia, and therefore, may not be applicable to all patients with STEMI or NSTEMI. Third, not all possible factors that influence mortality were included among the risk factors studied. For example, lactate was not routinely recorded among our patients and could not be tested as a potential predictor of mortality.

## Conclusion

In summary, the nomogram, composed of OHCA, NLR, SI, circulating  $\alpha$ -HBDH, cystatin C, and BNP levels, may predict the risk of intrahospital mortality in patients with STEMI with hyperuricemia. Further studies are warranted to validate our findings in other STEMI populations in other regions and countries.

## Abbreviations

SI, Shock index; SIRI, systemic inflammatory response index; SII, systemic inflammatory reaction index; PLR, ratio of platelets to lymphocytes; NLR, the ratio of neutrophils to lymphocytes; MLR, ratio of monocytes to lymphocytes; OHCA, out-of-hospital cardiac arrest; GRACE, Global Registry of Acute Coronary Events score;  $\alpha$ -HBDH,  $\alpha$ -Hydroxybutyrate dehydrogenase; BNP, B-type natriuretic peptides.

## Data Sharing Statement

The datasets are available from the corresponding author upon reasonable request.

## Ethical Approval and Informed Consent

The Ethics Committee of the Affiliated Hospital of Zunyi Medical University (approval no KLL[2020]0144) approved the study. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki.

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## Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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