A Nomogram Based on Lactate to Predict Major Adverse Cardiovascular Events for Acute Coronary Syndrome after Percutaneous Coronary Intervention

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Abstract

Background

Accurate prediction of major adverse cardiovascular events (MACE) is very important for the management of acute coronary syndrome (ACS) patients. We aim to develop and validate effective prognostic nomogram for individualized risk estimate of MACE in patients with ACS after percutaneous coronary intervention (PCI).

Methods

We conducted a prospective assessment of patients with ACS after PCI from January 2013 to July 2019 (n = 1986). Based on the training set, single-factor and multi-factor Cox proportional hazard analysis method was used to determine the results of single-factor and multi-factor Cox proportional hazard analysis. The receiver operating characteristic (ROC) and calibration curve were used to evaluate the prediction accuracy and discriminability, we have compared nomogram with the classical cardiovascular risk scores. In the validation set, X-tile analysis and Kaplan-Meier curve were used to evaluate the value of clinical application.

Results

Independent prognostic factors included lactate, age, left anterior descending branch (LAD) stenosis ≥ 50%, right coronary artery (RCA) stenosis ≥ 50%, brain natriuretic peptide (BNP), and left ventricular ejection fraction (LVEF). The area under the ROC curve (AUC) of the training group were about 0.712 to 0.762. In the validation set, the nomogram still shows good differentiation (AUC were about 0.724 to 0.818). On the calibration plot, the predicted values of the statistical chart agree well with the actual observed values. In addition, participants can be divided into two different risk groups (low and high) according to the nomogram.

Background

According to the statistical results of the World Health Organization, coronary artery diseases such as acute coronary syndrome (ACS) have become one of the most important causes of death worldwide and also one of the diseases with the greatest social burden. [1] ACS includes acute ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA). [2] Percutaneous coronary intervention (PCI) remains the preferred treatment for ACS. [3] [4] However, the incidence of major adverse cardiovascular events (MACE) was approximately 5–6% at an average of 3.2 years after PCI, and about 29.8% after 10 years. [5] [6] The incidence of MACE in patients with different risk factors was vary.
A reliable method for predicting the risk of MACE may be valuable for selecting high-risk patients for new or aggressive treatment and for risk counseling with patients. A series of studies have shown that age, cardiac function indicators, coronary artery severity and laboratory testing indicators are independent prognostic factors for cardiovascular events to identify high-risk patients. Several cardiovascular disease risk and prognosis assessment tools have been established in different populations to guide clinical practice. Among them, GRACE and TIMI risk scores are recommended by the guidelines in predicting cardiovascular outcomes (short and medium term) for patients of ACS, especially NSTE-ACS(Class I, Level of Evidence: A). However, their indicators such as heart rate, systolic blood pressure, myocardial enzyme and creatinine are dynamic. Killip class and ST-segment depression require the judgment of experienced physicians. These reasons may lead to a deviation in the prediction score. Another question, their maximum prediction time is generally not more than one year, thus it is unable to say what the long-term prognosis would be.

New and reliable biomarkers need to be added to prognosis models. Several recent studies have shown in disease states, lactate is independent prognostic factor to be useful for identifying patients at high-risk. The increase of lactate concentration is the secondary cause of anaerobic glycolysis caused by tissue hypoperfusion, hypoxia or both, in addition, stress hyperlactataemia is actually due to increased production of aerobic lactate. Multifactor analysis of a latest study showed that for patients with ACS complicating refractory cardiogenic shock (CS) or refractory cardiac arrest (CA), level of lactate at extracorporeal life support implantation was the only independent predictor of survival. Another study showed that the peak of lactate under extracorporeal membrane oxygenation (ECMO) in the first 24 h predicted 30-day mortality in patients with ACS complicated with CS and CA. Therefore, the purpose of this study was to develop and validate a nomogram based on lactate for predicting short-term, mid-term and long-term MACE in patients of ACS after PCI.

**Methods**

**Patients selection**

The prospective study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University, eliminating the need for informed consent. From January 2013 to July 2019, a total of 2,465 patients in the Cardiovascular Department of the First Affiliated Hospital of Wenzhou Medical University were diagnosed with ACS and treated with PCI.

Inclusion criteria were: (1) coronary artery disease confirmed by coronary angiography; (2) symptoms of myocardial ischemia; (3) electrocardiographic changes consistent with ACS. Exclusion criteria were: (1) chronic coronary syndrome; (2) Tumor history; (3) significant comorbidity, trauma, or surgery; (4) incomplete follow-up data. According to these inclusion and exclusion criteria, 1,986 patients were included in the study. Patients followed for 4 years were randomly divided into a training set (n = 1324)
and a validated set (n = 662) based on a computer-generated randomly generated allocation sequence. All methods are carried out in accordance with approved guidelines.

**Clinical Outcomes Definitions**

MACE is defined as the end point of this study, which refers to all-cause mortality, clinically driven revascularization of target lesions, new or recurrent myocardial infarction, and ischemic cerebral infarction.

**Collection of demographic, clinical, and follow-up data**

All of the patient’s study data was extracted from the electronic medical record system. Demographic data included sex and age. Clinical indicators including left anterior descending branch (LAD) stenosis $\geq 50\%$, left circumflex artery (LCX) stenosis $\geq 50\%$, right coronary artery (RCA) stenosis $\geq 50\%$, Three vessel disease (LAD, LCX and RCA all stenosis $\geq 50\%$), serum lactate level, brain natriuretic peptide (BNP) level, estimated glomerular filtration rate (EGFR), serum creatinine level, hemoglobin (HB), serum uric acid level, left ventricular ejection fraction (LVEF), hypertension, diabetes, peripheral artery stenosis, atrial fibrillation, prior stroke, kidney disease. The stenosis of LAD, LCX and RCA was determined by coronary angiography during hospitalization. All laboratory tests and auxiliary examination were performed 7 days before coronary angiography. Lactate and BNP were the maximum during hospitalization. EGFR was calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. LVEF was obtained by echocardiography. Regular medical follow-up data were obtained by telephone or clinic visits. Patients with the training set and the validation set were followed up until 1 April 2020.

**Statistical analysis**

Median (1st quartile, 3rd quartile) were utilized to describe the characteristics of continuous variables, comparisons in the two sets were carried out with Mann–Whitney U test. The categorical variables were expressed in frequency (proportion) and compared using the Chi-square test or the Fisher's exact test. Univariate and multivariate Cox proportional hazards regression models were used to screen potential prognostic factors and estimate their weights. Multivariate Cox proportional hazard analysis was performed using forward step: LR. Results are reported as hazard ratios (HRs) and 95% CIs. Clinical variables with the P-value of $\leq 0.05$ were included in the model. The identified variables based on the results of multivariate analysis were incorporated to construct the nomogram to predict the risk of 6-month, 1-year and 4-year MACE after PCI using statistical software (rms in R, version 3.6.2; http://www.r-project.org). With the input of independent risk factors, the nomogram outputs a risk score for each patient.

To evaluate discrimination power of the nomogram, we calculated the area under the curve (AUC) of the time-dependent receiver operating characteristic (ROC) for both the training and validation sets of 6-month, 1-year and 4-year, then compared it with Grace risk score and CADILLAC risk score. And we evaluated the predictive ability the nomogram by plotting calibration curves. In addition, we analyzed the possibility of nominal mapping for MACE risk stratification in patients after PCI.
All data management and statistical analysis were performed using SPSS 20.0 and MedCalc 19.0.5 for windows. R 3.6.2, X-tile 3.6.1 and MedCalc 19.0.5 were used for analysis and mapping results. All tests were double-sided $P<0.05$ for the significant level.

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**Results**

**Baseline characteristics of patients and outcomes**

A total of 1,986 patients of ACS treated with PCI were included in this study. The training set comprised 1,324 patients with 662 patients in the validation set. Baseline characteristics of patients in the training and validation set are shown in Table 1. The baseline characteristics were similar between the two cohorts, except for gender. The male rate of the training set was higher than that of the validation set (81.3% vs. 76.4%, $P = 0.012$).
Table 1
Baseline demographics and clinical characteristics of patients in training set and validation set.

| Variables                                | Training set (N=1324) | Validation set (N=662) | P    |
|------------------------------------------|-----------------------|------------------------|------|
| **Discrete variables**                   |                       |                        |      |
| Gender                                   |                       |                        | 0.012|
| Men                                      | 1076(81.3)            | 506(76.4)              |      |
| Woman                                    | 248(18.7)             | 156(23.6)              |      |
| Three-vessel coronary artery disease     |                       |                        | 0.648|
| Yes                                      | 375(28.3)             | 194(29.3)              |      |
| No                                       | 949(71.7)             | 468(70.7)              |      |
| LAD stenosis (≥ 50%)                     |                       |                        | 0.346|
| Yes                                      | 1044(78.9)            | 534(80.7)              |      |
| No                                       | 280(21.1)             | 128(19.3)              |      |
| LCX stenosis (≥ 50%)                     |                       |                        | 0.775|
| Yes                                      | 639(48.3)             | 315(47.6)              |      |
| No                                       | 685(51.7)             | 347(52.4)              |      |
| RCA stenosis (≥ 50%)                     |                       |                        | 0.286|
| Yes                                      | 777(58.7)             | 405(61.2)              |      |
| No                                       | 547(41.3)             | 257(38.8)              |      |
| Hypertension                             |                       |                        | 0.773|
| Yes                                      | 741(56.0)             | 375(56.6)              |      |
| No                                       | 583(44.0)             | 287(43.4)              |      |
| Diabetes                                 |                       |                        | 0.564|
| Yes                                      | 293(22.1)             | 139(21.0)              |      |
| No                                       | 1031(77.9)            | 523(79.0)              |      |
| Peripheral artery stenosis               |                       |                        | 0.818|
| Yes                                      | 290(21.9)             | 148(22.4)              |      |

P values were calculated by Mann-Whitney U test, Chi-square test or Fisher's exact test. BNP, Brain natriuretic peptide; CPR, Cardio-pulmonary resuscitation; EGFR, Estimated glomerular filtration rate; LAD, Left anterior descending branch; LCX, Left circumflex artery; LVEF, Left ventricular ejection fraction; RCA, Right coronary artery.
| Variables                  | Training set (N= 1324) | Validation set (N= 662) | P    |
|---------------------------|------------------------|-------------------------|------|
| No                        | 1034(78.1)             | 514(77.6)               | 0.900|
| Atrial fibrillation       |                        |                         |      |
| Yes                       | 90(6.8)                | 46(6.9)                 |      |
| No                        | 1234(93.2)             | 616(93.1)               |      |
| Prior stroke              |                        |                         | 0.275|
| Yes                       | 104(7.9)               | 43(6.5)                 |      |
| No                        | 1220(92.1)             | 619(93.5)               |      |
| Kidney disease            |                        |                         | 0.695|
| Yes                       | 55(4.2)                | 30(4.5)                 |      |
| No                        | 1269(95.8)             | 632(95.5)               |      |
| Killip class              |                        |                         | 0.356|
| I                         | 989(74.7)              | 485(73.3)               |      |
| II                        | 187(14.1)              | 91(13.7)                |      |
| III                       | 52(3.9)                | 23(3.5)                 |      |
| IV                        | 96(7.3)                | 63(9.5)                 |      |
| TIMI flow grades          |                        |                         | 0.190|
| I                         | 91(6.9)                | 56(8.5)                 |      |
| II                        | 12(0.9)                | 11(1.7)                 |      |
| III                       | 45(3.4)                | 17(2.6)                 |      |
| IV                        | 1176(88.8)             | 578(87.3)               |      |
| Prior CPR                 |                        |                         | 0.183|
| Yes                       | 58(4.4)                | 38(5.7)                 |      |
| No                        | 1266(95.6)             | 624(94.3)               |      |

**Continuous variables**

| Age, year                  | 64.0(54.0,73.0)       | 64.0(53.0,73.0)         | 0.8513 |

*P values were calculated by Mann-Whitney U test, Chi-square test or Fisher's exact test. BNP, Brain natriuretic peptide; CPR, Cardio-pulmonary resuscitation; EGFR, Estimated glomerular filtration rate; LAD, Left anterior descending branch; LCX, Left circumflex artery; LVEF, Left ventricular ejection fraction; RCA, Right coronary artery.*
| Variables           | Training set (N= 1324) | Validation set (N= 662) | P   |
|---------------------|------------------------|-------------------------|-----|
| Lactate, mmol/L     | 2.80(2.20,3.70)        | 2.80(2.10,3.70)         | 0.687 |
| BNP, pg/ml          | 277.0(103.0,671.5)     | 270.5(109.0,755.0)      | 0.6686 |
| Uric acid, umol/L   | 361.0(300.0,438.5)     | 369.0(305.0,447.0)      | 0.0871 |
| LVEF, %             | 48.0(43.0,55.8)        | 49.0(43.0,55.0)         | 0.9864 |
| EGFR, ml/min/1.73m² | 82.8(61.0,100.8)       | 83.7(58.8,100.8)        | 0.6192 |
| Creatinine, µmol/L  | 83.0(71.0,102.0)       | 82.0(70.0,105.0)        | 0.4397 |
| Hemoglobin, g/L     | 133.0(120.0,144.0)     | 132.0(119.0,143.0)      | 0.5253 |

*P values were calculated by Mann-Whitney U test, Chi-square test or Fisher’s exact test. BNP, Brain natriuretic peptide; CPR, Cardio-pulmonary resuscitation; EGFR, Estimated glomerular filtration rate; LAD, Left anterior descending branch; LCX, Left circumflex artery; LVEF, Left ventricular ejection fraction; RCA, Right coronary artery.*

During follow-up, MACE occurred in 201 (15.1%) cases in the training data set, but not in 1,123 cases. For the training set, after 6 months, 1 year and 4 years, the MACE rate was respectively 3.1%, 3.8% and 74.4%. For the validation set, MACE occurred in 96 (14.5%) cases, but not in 566. The MACE rate in validation set, 6-month, 1 year and 4 years later was 3.9%, 4.1% and 66.4%, respectively. During the period of follow-up, there was no significant difference in MACE probability between the two groups (P = 0.751).

**Nomogram screening depending on the training set**

According to the single factor survival analysis, a total of 15 factors statistically significant in the single factor survival analysis. (Table 2). According to the multivariate. The multivariate Cox regression analysis indicated age, LAD stenosis (≥ 50%), RCA stenosis (≥ 50%), lactate, BNP and LVEF as independent prognostic factors in the training dataset (P < 0.05), and were used to construct the nomogram. (Fig. 1) Each predictor corresponds to a specific point by drawing the straight line upwards to the point axis (e.g. Age ≥ 75) and corresponds to 75 points on the integral axis. The sum represents the incidence of MACE, and a straight line is plotted down to the total point axis.
Table 2
Univariate and multivariable Cox hazards analysis of the training cohort.

| Variables                        | Univariate            | Multivariate         |
|----------------------------------|------------------------|----------------------|
|                                  | HR(95% CI)             | P-value              | HR(95% CI)             | P-value              |
| Statistically significant factors|                        |                      |                        |                      |
| Men                              | 0.508(0.375,0.689)     | < 0.001              | 1.342(1.124,1.603)     | 0.001                |
| Age, year                        | 1.675(1.418,1.978)     | < 0.001              | 1.342(1.124,1.603)     | 0.004                |
| LAD stenosis(≥ 50%)              | 2.192(1.445,3.327)     | < 0.001              | 1.871(1.223,2.863)     | 0.004                |
| LCX stenosis (≥ 50%)             | 1.394(1.051,1.848)     | 0.021                | 1.872(1.364,2.568)     | < 0.001              |
| RCA stenosis(≥ 50%)              | 1.969(1.444,2.684)     | < 0.001              | 1.872(1.364,2.568)     | < 0.001              |
| Hypertension                     | 1.523(1.137,2.040)     | 0.005                |                        |                      |
| Diabetes                         | 1.310(0.952,1.803)     | 0.097                |                        |                      |
| Atrial fibrillation              | 1.841(1.223,2.771)     | 0.003                |                        |                      |
| Kidney disease                   | 2.284(1.367,3.814)     | 0.002                |                        |                      |
| Lactate, mmol/L                  | 1.604(1.096,2.347)     | 0.015                | 1.595(1.080,2.356)     | 0.019                |
| BNP, pg/ml                       | 1.858(1.584,2.179)     | < 0.001              | 1.501(1.259,1.790)     | < 0.001              |
| LVEF, %                          | 2.138(1.585,2.885)     | < 0.001              | 1.608(1.171,2.207)     | 0.003                |
| EGFR, ml/min/1.73m²              | 2.149(1.618,2.855)     | < 0.001              |                        |                      |
| Creatinine, µmol/L               | 2.402(1.566,3.684)     | < 0.001              |                        |                      |
| Hemoglobin, g/L                  | 1.831(1.370,2.448)     | < 0.001              |                        |                      |
| Statistically non-significant factors|                      |                      |                        |                      |
| Peripheral artery stenosis       | 1.290(0.928,1.793)     | 0.129                |                        |                      |
| Prior stroke                     | 1.419(0.924,2.179)     | 0.109                |                        |                      |
| Prior CPR                        | 1.193(0.611,2.331)     | 0.605                |                        |                      |
| Uric acid, umol/L                | 1.310(0.926,1.854)     | 0.128                |                        |                      |

BNP, Brain natriuretic peptide; CPR, Cardio-pulmonary resuscitation; EGFR, Estimated glomerular filtration rate; LAD, Left anterior descending artery; LCX, Left circumflex artery; LVEF, Left ventricular ejection fraction; RCA, Right coronary artery.

We reported a case of 75 years old (75 points), The degree of LAD stenosis is 50% (78 points), The degree of RCA stenosis is 10% (0 point), lactate 1 mmol/L (0 point), BNP 100 pg/ml(0 point) and LVEF 38%(58
points). The total score is 211 points, and the MACE rate after 6 months, 1 year and 4 years is 3%, 4% and 30% respectively.

**Validation of nomogram**

In training set, the 6-month area under ROC curve (AUC) is 0.712 (95% CI, 0.621–0.803) for the prognostic nomogram, the 1-year AUC is 0.741 (95% CI, 0.665–0.817), the 4-year AUC is 0.762 (95% CI, 0.692–0.831), indicating that this model can correctly predict the 6-month, 1-year and 4-year MACE rates of 71.2%, 74.1% and 76.2% respectively. In validation set, AUC of 6-month is 0.811 (95% CI, 0.730–0.891), 1-year AUC is 0.818 (95% CI, 0.739, 0.897), and 4-year AUC is 0.724 (95% CI, 0.631–0.816) (Fig. 2).

We compared the discrimination of the nomogram with that of other already available risk scores such as CADILLAC score and GRACE score in the training and validation sets. The time-dependent ROC curve was found to be consistently more favorable in both training and validation sets. (Table 3)

**Table 3**
Comparisons of AUC of the risk scores to predict MACE.

| Risk scores | Training set | Validation set |
|-------------|--------------|----------------|
|             | AUC          | 95%CI          | AUC          | 95%CI          |
| 6 months    |              |                |              |                |
| Nomogram    | 0.712        | 0.621–0.803    | 0.811        | 0.730–0.891    |
| CADILLAC score | 0.674      | 0.582–0.766    | 0.715        | 0.605–0.825    |
| GRACE score | 0.653        | 0.556–0.751    | 0.75         | 0.659–0.842    |
| 1 year      |              |                |              |                |
| Nomogram    | 0.741        | 0.665–0.817    | 0.818        | 0.739–0.897    |
| CADILLAC score | 0.699      | 0.622–0.775    | 0.725        | 0.617–0.833    |
| GRACE score | 0.662        | 0.578–0.746    | 0.761        | 0.672–0.850    |
| 4 years     |              |                |              |                |
| Nomogram    | 0.762        | 0.692–0.831    | 0.724        | 0.631–0.816    |
| CADILLAC score | 0.572      | 0.496–0.648    | 0.629        | 0.534–0.724    |
| GRACE score | 0.629        | 0.549–0.710    | 0.622        | 0.522–0.722    |

AUC, Area under the curve; CADILLAC, The controlled abciximab and device investigation to lower late angioplasty complications; CI, Confidence interval; GRACE, The global registry of acute coronary events; MACE: Major adverse cardiovascular events.

The calibration curves for the MACE probability at 6 months, 1 year and 4 years after PCI showed favorable agreement between the predicted probability and actual observation, demonstrating good calibration of the nomogram (Fig. 3)
Performance of the prognostic nomogram in stratifying risk

The total prognostic scores calculated by the nomogram were categorized into two risk groups to predict MACE: ‘low-risk’ (score ≤ 285.1) and ‘high-risk’ (score > 285.1) based on the cut-off value calculated using the X-tile software (Fig. 4).

The Kaplan-Meier curves for both sets clearly show that nomogram is stable in differentiating between high-risk and low-risk patients (Fig. 5). The HR for ‘high-risk’ category was found to be 4.11 (95%CI,3.08–5.49) compared to the ‘low-risk’ category in the training set and 4.01 (95%CI,2.68–6.00) in the validation set.

Discussion

The long-term clinical outcomes of ACS patients after PCI vary, so an accurate predictive model is required for identification. Risk prediction can help clinicians identify high-risk groups, guide follow-up and individualized treatment. In addition, the prediction contributes to the development of health care and clinical guidelines for ACS. Nomogram is evidence-based and fully personalized tool to regulate clinical decision-making and provides patient friendly, accurate and repeatable predictions without the need for computer software to interpret. [31] Therefore, we have developed and validated a nomogram with satisfying stability and accuracy. The most important 6 factors—lactate, age, LAD stenosis, RCA stenosis, BNP and LVEF—contained most of the prognostic information has been included.

Harjola et al. found lactate level (≥ 2 mmol/L) independently associated with an increased short-term mortality in patients with cardiogenic shock [32] A meta-analysis showed a greater reduction in lactate concentrations in survivors than in non-survivors, whether following cardiac surgery, cardiogenic shock, or cardiac arrest. [33] In STEMI patients, higher lactate levels were independently associated with 30-day mortality and overall adverse reactions to PCI (in particular, lactate ≥ 1.8 mmol/L). [34] Besides, in a study of 1,865 patients with ACS, elevated lactate levels (≥ 1.8 mmol/L) at admission were an independent predictor of 30-day and 180-day all-cause mortality. [26] In terms of energy supply for heart, in a normal heart, at rest, β-oxidation of fatty acids provides about 60%-90% of energy while pyruvate produces 10%-40%. [35] Lactate produced by dehydrogenation of pyruvate which synthesized from glycolysis, is also an important fuel for the stressed heart. [36] [37] During exercise, the uptake and use of lactate in the myocardium increases, as does the stimulation of β-adrenergic stimulation and shock. [27] Hyperlactatemia can be seen as part of the stress response, including increased metabolic rate, sympathetic nervous system activation, accelerated glycolysis, and improved bioenergy supply. [38] Hyper-lactate after ACS may be caused by hypoxia following hemodynamic disorders or by catecholamine-induced aerobic glycolysis in response to stress. [27, 39] These studies suggest that lactate may play an important role in the course of ACS. To the best of our knowledge, however, there has
been no such risk prediction tool for MACE containing lactate so far. Therefore, it is significant to set up this risk model.

For the other five variables, TIMI flow grades reported significant coronary stenosis as an independent predictor. [24] In a study of 6,755 patients after PCI, Iqbal et al. found that in patients with multivessel disease, untreated proximal LAD and RCA were associated with increased mortality. [7] BNP level was a strong independent predictor of short-term postoperative mortality.[8] Grabowski et al. have improved their predictive power by adding BNP to the Killip class and TIMI flow grades. [40] The possible explanation is that the elevated BNP level reflects a larger infarct size and progressive left ventricular remodeling, thus more obviously reflecting the degree of cardiac insufficiency.[41] The same to BNP, LVEF also serves as a reference index for cardiac function, to supply important prognostic information and should be included in approaches for stratifying risk after myocardial infarction. [9] Many studies have reported that age is a significant risk factor for clinical events (cardiac death, target vessel myocardial infarction, and clinically driven target vessel revascularization) after PCI. [10] [42] The predictive ability of simple age cutoff points of 65 and 75 are similar to that of a more complex model age as a continuous variable. [24]

The COX regression analysis results of our study consistent with the above results, that is, lactate, LAD stenosis, RCA stenosis, BNP, LVEF and age were important predictors. In order to overcome or avoid the limitations of a single predictor and achieve high prediction accuracy, we combined six detected predictors to construct a nomogram model. Because of dynamic, the nomogram did not include clinical symptoms and signs, such as Killip class, heart rate, and systolic blood pressure, which are significantly associated with ACS mortality.[22] [24] [43] [21] And Killip class may result in information bias by the judgment error of the clinician's supervisor. Nomogram is easy to recall and clinically useful.

Favorable discrimination power of the nomogram has been ascertained by drawing the time-dependent ROC of nomogram in the training set (AUC = 0.712–0.762) and validation set (AUC = 0.724–0.818). The calibration curve showed consistency between the predicted MACE after 6 months, 1 year and 4 years and the actual results.

TIMI Risk Score, published in 2000, predicted primary end point (all-cause mortality, MI, or severe recurrent ischemia requiring urgent revascularization) through 14 days after randomization for UA/ NSTEMI. [44] GRACE risk score has been established to predict the risk of death during hospitalization and at 6 months in patients with ACS. [11] To predict 30-day and 1-year mortality risk after PCI in AMI, PAMI risk score and CADILLAC risk score established successively. [21] [22] Several studies has proved that in predicting the 30-day and 1-year mortality, CADILLAC risk score showed slight superiority than Grace, TIMI, and PAMI risk scores. [45]

The probable reason is CADILLAC risk score considers LVEF and three-vessel disease. [46] Our nomogram also takes LVEF and specific coronary angiography results into account. Furthermore, data from both our training set and validation set confirmed that nomogram was superior in predicting the MACE in ACS patients after PCI than the above several risk scores.
In order to achieve better results in the actual prediction, we used the nomogram to calculate the total score of MACE risk. ACS Patients after PCI can be classified into the "high risk" group (score ≥ 285.1) and the "low risk" group (score < 285.1) based on the cutoff values determined by X-tile analysis. Kaplan-Meier analysis showed that the incidence of MACE was statistically different between the two groups. It helps more accurately monitoring of high-risk patients to personalized health management and increase cost-effectiveness.

Several strengths could be found in the study. In the past, risk scores were almost based on western populations, while the population of patients with ACS after PCI in the East, especially in China, was much larger, requiring a specialized prediction model. Our nomogram uses the latest clinical data from the past 7 years to reflect current cardiovascular medical standards. Between PCI, drug therapy, and coronary bypass surgery, our study evaluated patient outcomes solely treated with PCI, with fewer uncontrolled variables and more stability and accuracy. Our nomogram has combined an independent and new risk factor, lactate, that is an easily accessible indicator. Unlike traditional forecasting models, a follow-up period of up to 4 years, which is conducive to the evaluation of both short-term and long-term prognosis. The most attractive aspect of the nomogram is its good discrimination and calibration power.

Limitations also existed in this study. Our data came from the same medical center. Independent external validation is required to confirm the performance of the nomogram before the clinical application. Although lactate has certain predictive ability, the detection time and collection method of lactate are not unified and clear. Some clinical drugs may cause changes in lactate without the improvement of the prognosis.

**Conclusions**

In conclusion, a novel prognostic nomogram based on lactate with other five easily determined and objective variables were developed and validated to predict short-term and long-term MACE in ACS patients after PCI. The nomogram can distinguish high-risk patients for precise individualized management.

**Abbreviations**

ACS: Acute coronary syndrome; AUC: Area under the receiver operating characteristic curve; BNP: Brain natriuretic peptide; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; ECMO: Extracorporeal membrane oxygenation; EF: Ejection fraction; HB: Hemoglobin; HR: Hazard ratio; LAD: Left anterior descending branch; LCX: Left circumflex artery; LVEF: Left ventricular ejection fraction; MACE: Major adverse cardiovascular events; NSTEMI: Non-ST-segment elevation myocardial infarction; PCI: Percutaneous coronary intervention; RCA: Right coronary artery; ROC: Receiver operating characteristic; STEMI: ST-segment elevation myocardial infarction; UA: Unstable angina.

**Declarations**
Ethics approval and consent to participate:
The prospective study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University, eliminating the need for informed consent.

Consent for publication
Not applicable.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests.

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Authors' contribution:
1 Shuting Kong: study conceptualization and design, collected the clinical data, statistical analysis, drafted the manuscript and figures. 1 Changxi Chen: collected the clinical data. 1 Gaoshu Zheng: collected the clinical data. 1 Hui Yao: collected the clinical data and follow-up data. 1 Junfeng Li: searched relevant literatures. 2 Hong Ye: edited the manuscript. 3 Xiaobo Wang: statistical analysis. 1 Xiang Qu: data curation. 1 Xiaodong Zhou: study conceptualization and design. 4 Yucheng Lu: collected the clinical data. Hao Zhou: study conceptualization and design, reviewed and edited the manuscript. All authors read and approved the final manuscripts.

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References
1. Global health estimates 2016: deaths by cause, age, sex, by country and by region, 2000–2016, 2018 [https://www.who.int/healthinfo/global_burden_disease/en/].
2. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD. Fourth Universal Definition of Myocardial Infarction (2018). 2018, 72(18):2231–2264.
3. Keeley EC, Boura JA, Grines CL: **Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials.** Lancet (London, England) 2003, 361(9351):13–20.

4. Zijlstra F, Hoornanje JC, de Boer MJ, Reiffers S, Miedema K, Ottervanger JP, van ‘t Hof AW, Suryapranata H. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. N Engl J Med. 1999;341(19):1413–9.

5. Park D, Ahn J, Park H, Yun S, Kang D, Lee P, Kim Y, Lim D, Rha S, Park G, et al: **Ten-Year Outcomes After Drug-Eluting Stents Versus Coronary Artery Bypass Grafting for Left Main Coronary Disease: Extended Follow-Up of the PRECOMBAT Trial.** 2020, 141(18):1437–1446.

6. Sud M, Han L, Koh M, Abdel-Qadir H, Austin P, Farkouh M, Godoy L, Lawler P, Udell J, Wijeysundera H, et al: **Low-Density Lipoprotein Cholesterol and Adverse Cardiovascular Events After Percutaneous Coronary Intervention.** 2020, 76(12):1440–1450.

7. Iqbal MB, Smith RD, Lane R, Patel N, Mattar W, Kabir T, Panoulas V, Mason M, Dalby MC, Grocott-Mason R, et al. The prognostic significance of incomplete revascularization and untreated coronary anatomy following percutaneous coronary intervention: An analysis of 6,755 patients with multivessel disease. Catheter Cardiovasc Interv. 2018;91(7):1229–39.

8. Grabowski M, Filipiak KJ, Karpinski G, Wretowski D, Rdzanek A, Huczek Z, Horszczaruk GJ, Kochman J, Rudowski R, Opolski G. Serum B-type natriuretic peptide levels on admission predict not only short-term death but also angiographic success of procedure in patients with acute ST-elevation myocardial infarction treated with primary angioplasty. Am Heart J. 2004;148(4):655–62.

9. Singh M, Reeder GS, Jacobsen SJ, Weston S, Killian J, Roger VL. Scores for post-myocardial infarction risk stratification in the community. Circulation. 2002;106(18):2309–14.

10. Hwang D, Lee JM, Yang S, Chang M, Zhang J, Choi KH, Kim CH, Nam CW, Shin ES, Kwak JJ, et al. Role of Post-Stent Physiological Assessment in a Risk Prediction Model After Coronary Stent Implantation. JACC Cardiovasc Interv. 2020;13(14):1639–50.

11. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van de Werf F, Avezum Á, Goodman SG, Flather MD, et al. Predictors of Hospital Mortality in the Global Registry of Acute Coronary Events. Arch Intern Med. 2003;163(19):2345–53.

12. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743–53.

13. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetière P, Jousilahti P, Keil U, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24(11):987–1003.

14. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. Bmj. 2007;335(7611):136.
15. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):49–73.

16. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, Giugliano RP, McCabe CH, Braunwald E. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation. 2000;102(17):2031–7.

17. Morrow DA, Antman EM, Giugliano RP, Cairns R, Charlesworth A, Murphy SA, de Lemos JA, McCabe CH, Braunwald E. A simple risk index for rapid initial triage of patients with ST-elevation myocardial infarction: an InTIME II substudy. Lancet. 2001;358(9293):1571–5.

18. Dorsch MF, Lawrance RA, Sapsford RJ, Oldham J, Greenwood DC, Jackson BM, Morrell C, Ball SG, Robinson MB, Hall AS. A simple benchmark for evaluating quality of care of patients following acute myocardial infarction. Heart. 2001;86(2):150–4.

19. Vernon ST, Coffey S, D'Souza M, Chow CK, Kilian J, Hyun K, Shaw JA, Adams M, Roberts-Thomson P, Brieger D, et al. ST-Segment-Elevation Myocardial Infarction (STEMI) Patients Without Standard Modifiable Cardiovascular Risk Factors-How Common Are They, and What Are Their Outcomes? Journal of the American Heart Association. 2019;8(21):e013296–6.

20. Huynh T, Kouz S, Yan AT, Danchin N, O'Loughlin J, Schampaert E, Yan RT, Rinfret S, Tardif JC, Eisenberg MJ, et al. Canada Acute Coronary Syndrome Risk Score: a new risk score for early prognostication in acute coronary syndromes. Am Heart J. 2013;166(1):58–63.

21. Addala S, Grines CL, Dixon SR, Stone GW, Boura JA, Ochoa AB, Pellizzon G, O'Neill WW, Kahn JK. Predicting mortality in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention (PAMI risk score). Am J Cardiol. 2004;93(5):629–32.

22. Halkin A, Singh M, Nikolsky E, Grines CL, Tcheng JE, Garcia E, Cox DA, Turco M, Stuckey TD, Na Y, et al. Prediction of mortality after primary percutaneous coronary intervention for acute myocardial infarction: the CADILLAC risk score. J Am Coll Cardiol. 2005;45(9):1397–405.

23. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum A, Goodman SG, Flather MD, Anderson FA Jr, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). Bmj. 2006;333(7578):1091.

24. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. Jama. 2000;284(7):835–42.

25. Amsterdam EA, Wenger NK, Brindis RG Jr, Ganiats CD, TG, Jr HD, Jaffe, Jneid AS, Kelly H, Kontos RF MC: 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: Duke University Press; 2014.
26. Liang D, Zhou X, Hong X, Feng X, Shan P, Xie Q, Xu T, Cai M, Zhou J, Wang S, et al. Association between admission lactate levels and mortality in patients with acute coronary syndrome: a retrospective cohort study. Coron Artery Dis. 2019;30(1):26–32.

27. Garcia-Alvarez M, Marik P, Bellomo R. Stress hyperlactataemia: present understanding and controversy. Lancet Diabetes Endocrinol. 2014;2(4):339–47.

28. Porto I, Mattesini A, D'Amario D, Sorini Dini C, Della Bona R, Scicchitano M, Vergallo R, Martellini A, Caporusso S, Trani C, et al. Blood lactate predicts survival after percutaneous implantation of extracorporeal life support for refractory cardiac arrest or cardiogenic shock complicating acute coronary syndrome: insights from the CareGem registry. Internal and emergency medicine 2020.

29. Rigamonti F, Montecucco F, Boroli F, Rey F, Gencer B, Cikirikcioglu M, Reverdin S, Carbone F, Noble S, Roffi M, et al. The peak of blood lactate during the first 24 h predicts mortality in acute coronary syndrome patients under extracorporeal membrane oxygenation. Int J Cardiol. 2016;221:741–5.

30. A New Equation to Estimate Glomerular Filtration Rate. 2009, 150(9):604–612.

31. Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2008;26(8):1364–70.

32. Harjola VP, Lassus J, Sionis A, Køber L, Tarvasmäki T, Spinar J, Parissis J, Banaszewski M, Silva-Cardoso J, Carubelli V, et al. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. Eur J Heart Fail. 2015;17(5):501–9.

33. Vincent JL, Quintairos ESA, Couto L Jr, Taccone FS. The value of blood lactate kinetics in critically ill patients: a systematic review. Crit Care. 2016;20(1):257.

34. Vermeulen RP, Hoekstra M, Nijsten MW, van der Horst IC, van Pelt LJ, Jessurun GA, Jaarsma T, Zijlstra F, van den Heuvel AF. Clinical correlates of arterial lactate levels in patients with ST-segment elevation myocardial infarction at admission: a descriptive study. Crit Care. 2010;14(5):R164.

35. Beadle RM, Frenneaux M. Modification of myocardial substrate utilisation: a new therapeutic paradigm in cardiovascular disease. Heart. 2010;96(11):824–30.

36. Kubiak GM, Tomasik AR, Bartus K, Olszanecki R, Cерановић P. Lactate in cardiogenic shock - current understanding and clinical implications. Journal of physiology pharmacology: an official journal of the Polish Physiological Society. 2018;69(1):15–21.

37. Hütter JF, Schweickhardt C, Piper HM, Spieckermann PG. Inhibition of fatty acid oxidation and decrease of oxygen consumption of working rat heart by 4-bromocrotonic acid. J Mol Cell Cardiol. 1984;16(1):105–8.

38. Lazzeri C, Valente S, Chiostri M, Gensini GF. Clinical significance of lactate in acute cardiac patients. World J Cardiol. 2015;7(8):483–9.

39. Kraut JA, Madias NE. Lactic acidosis. N Engl J Med. 2014;371(24):2309–19.

40. Grabowski M, Filipiak KJ, Malek LA, Karpinski G, Huczek Z, Stolarz P, Spiewak M, Kochman J, Rudowski R, Opolski G. Admission B-type natriuretic peptide assessment improves early risk
stratification by Killip classes and TIMI risk score in patients with acute ST elevation myocardial infarction treated with primary angioplasty. Int J Cardiol. 2007;115(3):386–90.

41. Eggers KM, Lagerqvist B, Venge P, Wallentin L, Lindahl B. Prognostic value of biomarkers during and after non-ST-segment elevation acute coronary syndrome. J Am Coll Cardiol. 2009;54(4):357–64.

42. Zheng YY, Wu TT, Gao Y, Guo QQ, Ma YY, Zhang JC, Xun YL, Wang DY, Pan Y, Cheng MD, et al: A Novel ABC Score Predicts Mortality in Non-ST-Segment Elevation Acute Coronary Syndrome Patients Who underwent Percutaneous Coronary Intervention. Thromb Haemost 2020.

43. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, et al. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med. 2003;163(19):2345–53.

44. Antman EM, Cohen M, Bernink PJLM, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI Risk Score for Unstable Angina/Non–ST Elevation MIA Method for Prognostication and Therapeutic Decision Making. JAMA. 2000;284(7):835–42.

45. Lev EI, Kornowski R, Vaknin-Assa H, Porter A, Teplitsky I, Ben-Dor I, Brosh D, Fuchs S, Battler A, Assali A. Comparison of the predictive value of four different risk scores for outcomes of patients with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention. Am J Cardiol. 2008;102(1):6–11.

46. Kao Y-T, Hsieh Y-C, Hsu C-Y, Huang C-Y, Hsieh M-H, Lin Y-K, Yeh J-S. Comparison of the TIMI, GRACE, PAMI and CADILLAC risk scores for prediction of long-term cardiovascular outcomes in Taiwanese diabetic patients with ST-segment elevation myocardial infarction: From the registry of the Taiwan Society of Cardiology. PloS one. 2020;15(2):e0229186–6.