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Development and validation of a prognostic nomogram for myocardial infarction patients in intensive care units: a retrospective cohort study

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ABSTRACT

Objectives: We aimed to develop and validate a prognostic nomogram in order to improve the prediction of 30-day survival of critically ill myocardial infarction (MI) patients.

Design: A retrospective cohort study.

Setting: Data were collected from the Medical Information Mart for Intensive Care (MIMIC)-III database, consisting of critically ill participants between 2001 and 2012 in the United States.

Participants: A total of 2031 adult critically ill patients with MI were enrolled from the MIMIC-III database.

Primary and secondary outcome: Thirty-day survival.

Results: Independent prognostic factors, including age, heart rate, white blood cell count, blood urea nitrogen, and bicarbonate, were identified by Cox regression model and used in the nomogram. Good agreement between the prediction and observation was indicated by the calibration curve for 30-day survival. The nomogram exhibited excellent discrimination [area under the receiver operating characteristic curve, 0.765, 95% (confidence interval) CI, 0.716-0.814] and calibration (C-index, 0.758, 95% CI, 0.712-0.804) in the validation cohort. Decision curve analysis demonstrated that the nomogram was clinically beneficial. Additionally, participants could be classified into two risk groups by the nomogram, and the 30-day survival probability was significantly different between them (P <0.001).

Conclusions: This five-factor nomogram can accurately predict 30-day survival in

critically ill MI patients and might be helpful for risk stratification and decision making for MI patients.

Keywords: myocardial infarction; 30-day survival; intensive care unit; nomogram; prognostic model

Article Summary

Strengths and limitations of this study

This is the first study to develop and validate a prognostic nomogram for Myocardial infarction (MI) patients in the intensive care unit (ICU).

This novel nomogram showed satisfactory performance in both the primary cohort and validation cohort as assessed by the area under the receiver operating characteristic curve, calibration curves, decision curve analysis and survival curves.

The prognostic nomogram developed by our study with five factors, including age, heart rate, white blood cell count, blood urea nitrogen level, and bicarbonate level, could be easily employed for risk stratification and decision making for MI patients undergoing clinical treatment.

Brain natriuretic peptide and troponin were not included in our analysis due to missing value.

Introduction

Myocardial infarction (MI) is a major health problem that causes high mortality and high economic costs worldwide.[1] A substantial proportion of MI patients are admitted to the intensive care unit (ICU).[2] However, not all MI patients benefit from ICU care.[3] It is necessary to perform risk stratification for MI to help clinicians make more efficient decisions, which provides benefits for more MI patients.

Nomograms are popular prognostic tools with the ability to predict clinical events by integrating potential risk factors.[4] Nomograms have been widely used for tumor prognosis, supporting the movement towards personalized oncology medicine.[5] Recently, a nomogram was effectively used to predict both short-term and long-term survival for asymptomatic adults undergoing screening for cardiac risk factors.[6] Thus, we hypothesized that a nomogram may also be feasible for the risk stratification of critically ill MI patients.

This study aimed to identify prognostic factors for the 30-day mortality of critically ill MI patients and establish a prognostic nomogram based on a multivariate Cox regression model in a primary cohort. Furthermore, the performance, discrimination capacity and clinical benefits of the nomogram were assessed in a validation cohort to validate the accuracy and utility of the prognostic nomogram model. The nomogram could be easily applied in clinical practice to identify high-risk patients and guide decision making.

Methods

Data source

The data were retrieved from the Medical Information Mart for Intensive Care (MIMIC-III) dataset. The MIMIC-III integrates the comprehensive clinical data of 53,423 stays of adult patients in the ICU between 2001 and 2012. An average of 4,597 charted observations and 380 laboratory measurements are available for individual hospital admissions. The overall information is saved as a relational database, consisting of patient demographics, laboratory tests, discharge summaries, electrocardiographs, imaging examinations, diagnostic information such as the International Classification of Disease (ICD)-9 code, and in-hospital and out-of-hospital mortality. The use of MIMIC-Ⅲ database was under the approval from the review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center.[7] All the patients in the database have been deidentified for privacy, and the need for informed consent was waived. This study was conducted in accordance with the recommendations of the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.[8]

Study cohort

Patients admitted to the ICU who were diagnosed with MI were eligible for inclusion. After screening of the MIMIC-III database, a total of 2,031 patients with MI were included for analysis. The cohort was randomly divided into the primary cohort and the validation cohort in a ratio of 7:3; the primary cohort was used to establish the nomogram, and the validation cohort was used for validation.

Data extraction

Structure Query Language was used for data extraction. For patients with multiple ICU

admissions, only the data of the patient's first ICU admission were used in this study. All data regarding baseline characteristics were collected in the initial 24 hours following admission. The variables for the following analysis included (1) basic demographics, including age, sex, weight, coronary care unit stay and private insurance; (2) vital signs, including heart rate, mean arterial pressure (MAP), temperature and central venous pressure (CVP); and (3) laboratory tests, including tests of white blood cell count (WBC), hemoglobin, platelets, serum creatinine, creatinine kinase, type B natriuretic peptide (BNP), blood urea nitrogen (BUN) level, bicarbonate level, pH, partial pressure of oxygen (pO_2), partial pressure of carbon dioxide (pCO_2), chloride, sodium, potassium, troponin and lactate.

In this study, we regarded 30-day survival as the outcome measure, which was also extracted from the MIMIC-III database.

Management of missing data

Variables with missing data are common in the MIMIC-III database. More than 20% of the data regarding CVP, pCO_2, pO_2, pH, BNP, troponin, and lactate were missing, and these parameters were not qualified for establishment of the nomogram (Supplementary Figure 1). A flag indicating whether these data were obtained is shown in the characteristics table. For variables that had missing data for less than 20% of patients, missing values were filled with predictors using multiple imputation to minimize the bias resulting from missing values.[9]

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation or median

(interquartile range, IQR), as appropriate. Categorical data are expressed as numbers (percentages). Continuous variables were compared using Student's *t* test or the rank-sum test, as appropriate. Categorical variables were compared by the chi-squared test. Univariate Cox regression was used to screen for variables that were significantly associated with 30-day survival in the primary cohort. Potential prognostic factors that were significant in the univariate Cox regression model were entered into the multivariable Cox proportional hazard model, in which the hazard ratio (HR) was also calculated. The backward stepwise process based on the Akaike information criterion was used to control the overfitting of the model.

A nomogram based on the results of previous multivariable analyses was constructed. The calibration, discrimination and clinical usefulness of the nomogram were calculated to evaluate its performance.[10] The area under the receiver operating characteristic curve (AUC) and Harrell's concordance index (C-index) were used to assess the predictive capacity of the prediction model. Confidence intervals (CIs) were obtained by creating 1000 bootstrap samples from the corresponding cohort and replicating the estimation process. The calibration curve was used to analyze the agreement between the nomogram and actual observation. Decision curve analysis was performed to assess the clinical usefulness of the prognostic nomogram by quantifying the standardized net benefits at different threshold probabilities. Survival curves were used to compare the survival probability between the low-risk group and the high-risk group defined by the nomogram.

A two-tailed *P* value < 0.05 was considered statistically significant in our study. SPSS

software (version 23.0, IBM, NY, USA) and R software (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis.

Patient and Public Involvement

Patients and/or the public were not directly involved in this study.

Results

Baseline characteristics of the primary cohort and validation cohort

The primary cohort and validation cohort consisted of 1,422 and 609 MI patients, respectively. In the primary cohort, the mean age was 67.6±14.2 years. The mean heart rate, WBC, BUN level, and bicarbonate level were 84.8±17.9 beats per minute (bpm), 12.6±5.6 K/μL, 18.0 (IQR: 13.8-27.0) mg/dL and 22.9±4.1 mg/dL, respectively. The 30-day mortality was 14.6% (208/1422). Regarding the validation cohort, the mean age was 68.5±14.1 years. The mean heart rate, WBC, BUN level, and bicarbonate level were 84.7±17.1 bpm, 12.7±5.5 K/μL, 19.7 (IQR: 14.0-28.0) mg/dL and 23.1±3.9 mg/dL, respectively. The 30-day mortality was 15.6% (95/609). There were no significant differences in the baseline characteristics between the primary cohort and validation cohort (all $P > 0.05$) (Table 1).

Prognostic factors in the primary cohort

Basic demographics, vital signs, and laboratory tests in the primary cohort were further examined by the univariate Cox regression model for the prediction of 30-day mortality (Supplementary Table 1). Variables including age, male sex, weight, private insurance, heart rate, MAP, hemoglobin WBC, BUN level, bicarbonate level, creatinine level, and potassium level were potential predictors of 30-day mortality in the univariate analysis

($P < 0.05$). All these candidate factors were entered into the multiple Cox proportional hazard model, and five prognostic factors, namely, age, heart rate, WBC, BUN level and bicarbonate level, were included in the final prediction model (each $P < 0.05$) (Table 2).

A prognostic nomogram for 30-day survival

A prognostic nomogram for 30-day survival was established with the five prognostic factors obtained from the multiple Cox proportional hazard model (Figure 1). The nomogram was generated by assigning a weighted score to each of the independent prognostic parameters. The scales of age, heart rate, WBC, BUN level, and bicarbonate level ranged from 10 to 100, 30 to 150, 0 to 75, 0 to 160, and 40 to 5, respectively. The highest total score was 300 points, and the scale of the 30-day survival probability ranged from 0.95 to 0.1. A higher score calculated from the sum of the assigned points for each prognostic factor in the nomogram corresponded to a lower probability of survival in 30 days. For instance, one MI patient with an age of 70 years old (57 points), a heart rate of 110 bpm (33 points), a WBC of 11 K/μL (10 points), a BUN level of 80 mg/dL (33 points) and a bicarbonate level of 10 mg/dL (85 points) had a total score of 218 points, which corresponded to an approximately 30% 30-day survival probability.

Performance evaluation of the prognostic nomogram

The AUC indicated that the predictive capacity of the prediction model was 0.803 (95% CI, 0.771-0.835) in the primary cohort and 0.765 (95% CI, 0.716-0.814) in the validation cohort (Figure 2A, B). The C-index was 0.787 (95% CI, 0.757-0.817) for the primary cohort and 0.758 (95% CI, 0.712-0.804) for the validation cohort. The

calibration plot demonstrated adequate fit of the nomogram for predicting 30-day survival, which was consistent with the Kaplan-Meier estimate in both the primary cohort and validation cohort (Figure 2C, D). The decision curve analysis showed the net benefits obtained from the application of our nomogram with threshold probabilities of 0.648 and 0.499 in the primary cohort and validation cohort, respectively (Figure 2E, F). Participants could be classified into low-risk and high-risk groups by the nomogram. Survival curves revealed a significantly lower survival probability in the high-risk group than in the low-risk group in both the primary cohort and validation cohort (P<0.001), which indicated the substantial discriminatory power of the nomogram to distinguish low-risk and high-risk MI patients in the ICU.

Discussion

This study extracted clinical data and survival information of 2,031 MI patients from the MIMIC-III database. Five risk factors for 30-day mortality of MI, including age, heart rate, WBC, BUN level, and bicarbonate level, were identified by univariate and multivariate Cox regression models and used to establish a prognostic nomogram. To the best of our knowledge, this is the first study to develop and validate a prognostic nomogram for MI patients in the ICU. This novel nomogram showed satisfactory performance in both the primary cohort and validation cohort as assessed by the AUC, calibration curves, decision curve analysis and survival curves. Thus, this nomogram could be efficiently and effectively employed in clinical practice.

MI has been a global health problem with a high incidence and a high mortality, and it has led to economic and health burdens in patients.[1] The Thrombolysis in Myocardial

Infarction (TIMI) score and the Global Registry of Acute Coronary Events (GRACE) score are two common tools to predict short-term and long-term outcomes for acute MI patients.[11-13] Both the TIMI risk score and the GRACE score require more than five factors to calculate the probability of mortality. In addition, the Soroka Acute Myocardial Infarction (SAMI) risk score, which was used to predict 1-year and 5-year mortality of acute MI in Israel, consists of 10 risk factors.[14] Our nomogram uses five factors that can be collected at first-day admission, can be easily applied, and performs well in predicting short-term mortality of patients with MI. We hope that this short nomogram will be used for the quick identification of high-risk MI patients in the ICU. Nomograms are of great utility in predicting an individual's probability of a clinical event using individual variables, and they have become a common prognostic tool in oncology.[4] A nomogram was developed for the 5- to 15-year survival of asymptomatic adults undergoing coronary artery calcium scoring.[6] For the mortality of MI, our study is the first to provide a simple-to-use prognostic nomogram with five factors that are easily accessible on the first-day admission, and this nomogram might improve timely individualized risk stratification and the prevention of fatal outcomes. The satisfactory performance of this model was reflected by its moderate predictive ability, indicated by an AUC greater than 0.75 in both the primary cohort and validation cohort. Additionally, the calibration analysis performed in two cohorts revealed that the predicted 30-day mortality was similar to the actual 30-day mortality. Furthermore, decision curve analysis indicated that the net clinical benefits were positive in MI patients, with a probability of up to 50% in both cohorts. The survival curves also revealed the good

discriminative capacity to identify high-risk and low-risk patients in both the primary cohort and validation cohort.

It should be noted that only five prognostic factors were used in the final nomogram model. Age has been widely recognized as one of the most powerful risk factors in cardiovascular diseases, such as vascular senescence, cardiac remodeling, and atrial fibrillation.[15-17] Decreased expression of antioxidative factors and increased expression of oxidative molecular mediators occur in elderly patients, leading to aggravating ischemic injury.[15,18] Heart rate is also an important prognostic factor for cardiovascular mortality. A higher resting heart rate was reported to be positively related to a higher risk of MI and all-cause mortality.[19,20] These results were consistent with our study, in which heart rate was positively associated with mortality of MI.

Among lab tests, WBC has also been shown to be a potential risk factor and to be associated with myocardial perfusion and the severity of coronary artery disease.[21,22] A recent cohort study of triple-vessel coronary artery disease revealed the independent prognostic value of both total and differential white blood cell counts for predicting long-term mortality.[23] BUN level has also been demonstrated to be independently associated with mortality in patients with MI, even in patients with normal to mildly reduced glomerular filtration rates.[24,25] Bicarbonate is a central biomarker that reflects acid-base equilibrium and is affected by electrolyte disturbance. In this study, bicarbonate level was negatively related to 30-day mortality, which was consistent with another cohort study of cardiogenic shock patients hospitalized in the ICU.[26] In short, these five factors included in the nomogram were all credible prognostic factors for

cardiovascular mortality, and these factors could be used in clinical work.

One of the limitations of this study was that a few previously reported independent predictors for major cardiovascular events, including BNP and troponin, were not included to minimize the bias from excessive missing values.[27,28] Hence, the prognostic value of these factors for MI could not be estimated. Another limitation was that the model still required more samples to validate its viability. Although we performed random allocation to establish a validation cohort with 30% of the total sample size for the verification of the superiority of our model, a large external cohort would further enhance the credibility and effectiveness of our model in future studies.

In conclusion, our study developed a prognostic nomogram with five factors, including age, heart rate, WBC, BUN level, and bicarbonate level, for the prediction of 30-day survival in critically ill MI patients in the ICU. This nomogram performed well and might be helpful in risk stratification and decision making for MI patients undergoing clinical treatment.

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Author contributions

Qi Guo: Conceptualization, data analysis, Writing-original draft, Writing-review&editing. **Maoxiong Wu:** Conceptualization, Writing-original draft, Writing-review&editing. **Hongwei Li:** Writing-original draft, Data curation. **Huijun Ouyang:** Literature search, Data interpretation. **Runlu Sun:** Data collection, Data curation. **Junjie Wang:** Data collection, Data curation. **Zhaoyu Liu:** Literature search, Data interpretation. **Jingfeng Wang:** Conceptualization, Writing-review&editing, Data curation. **Yuling Zhang:** Conceptualization, Writing-review&editing, Data curation.

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Disclaimer

The funders had no roles in study design, data collection, data analysis, interpretation and writing of the report.

Declaration of Interests

All authors declare no potential conflicts of interest.

Data availability statement

The dataset analyzed to generate the findings for this study are available from the corresponding author on reasonable request.

References

1. Virani SS, Alonso A, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation* 2020: CIR0000000000000757.

2. Zhou L, Tao Z, Wu Y, et al. Individual and institutional factors affecting cardiac monitoring in coronary care units: a national survey of Chinese nurses. *Int J Nurs Stud* 2012; **49**(5): 570-8.

3. Valley TS, Iwashyna TJ, Cooke CR, et al. Intensive care use and mortality among patients with ST elevation myocardial infarction: retrospective cohort study. *BMJ* 2019; **365**: l1927.

4. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. *The Lancet Oncology* 2015; **16**(4): e173-e80.

5. Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. *J Clin Oncol* 2008; **26**(8): 1364-70.

6. B OH, Gransar H, Callister T, et al. Development and Validation of a Simple-to-Use Nomogram for Predicting 5-, 10-, and 15-Year Survival in Asymptomatic Adults Undergoing Coronary Artery Calcium Scoring. *JACC Cardiovasc Imaging* 2018; **11**(3): 450-8.

7. Johnson AEW, Pollard TJ, Shen L, et al. MIMIC-III, a freely accessible critical care database. *Sci Data* 2016; **3**: 160035.

8. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the

TRIPOD statement. *BMJ* 2015; **350**: g7594.

9. Zhang Z. Multiple imputation with multivariate imputation by chained equation (MICE) package. *Ann Transl Med* 2016; **4**(2): 30.

10. Alba AC, Agoritsas T, Walsh M, et al. Discrimination and Calibration of Clinical Prediction Models: Users' Guides to the Medical Literature. *Jama* 2017; **318**(14): 1377-84.

11. Antman EM CM, 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.

12. Morrow DA, Antman EM, Charlesworth A, et al. 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.

13. Granger CB GR, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KAA, Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. *Archives of internal medicine* 2003; **163**(19): 2345-53.

14. Plakht Y, Shiyovich A, Weitzman S, Fraser D, Zahger D, Gilutz H. A new risk score predicting 1- and 5-year mortality following acute myocardial infarction Soroka Acute Myocardial Infarction (SAMI) Project. *International journal of cardiology* 2012; **154**(2): 173-9.

15. Salazar G. NADPH Oxidases and Mitochondria in Vascular Senescence. *Int J Mol Sci* 2018; **19**(5).

16. Dhalla NS, Rangi S, Babick AP, Zieroth S, Elimban V. Cardiac remodeling and subcellular defects in heart failure due to myocardial infarction and aging. *Heart Fail Rev* 2012; **17**(4-5): 671-81.

17. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. *Circ Res* 2014; **114**(9): 1453-68.

18. Ham PB, 3rd, Raju R. Mitochondrial function in hypoxic ischemic injury and influence of aging. *Prog Neurobiol* 2017; **157**: 92-116.

19. Sharashova E, Wilsgaard T, Lochen ML, Mathiesen EB, Njolstad I, Brenn T. Resting heart rate trajectories and myocardial infarction, atrial fibrillation, ischaemic stroke and death in the general population: The Tromso Study. *Eur J Prev Cardiol* 2017; **24**(7): 748-59.

20. Dobre D, Kjekshus J, Rossignol P, et al. Heart rate, pulse pressure and mortality in patients with myocardial infarction complicated by heart failure. *International journal of cardiology* 2018; **271**: 181-5.

21. Barron HV CC, Murphy SA, Braunwald E, Gibson CM. Association between white blood cell count, epicardial blood flow, myocardial perfusion, and clinical outcomes in the setting of acute myocardial infarction: a thrombolysis in myocardial infarction 10 substudy. *Circulation* 2000; **102**(19): 2329-34.

22. Sabatine MS MD, Cannon CP, Murphy SA, Demopoulos LA, DiBattiste PM,

McCabe CH, Braunwald E, Gibson CM. Relationship between baseline white blood cell count and degree of coronary artery disease and mortality in patients with acute coronary syndromes: a TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy- Thrombolysis in Myocardial Infarction 18 trial)substudy. *J Am Coll Cardiol* 2002; **40**(10): 1761-8.

23. Zhao X, Jiang L, Xu L, et al. Predictive value of in-hospital white blood cell count in Chinese patients with triple-vessel coronary disease. *Eur J Prev Cardiol* 2019; **26**(8): 872-82.

24. Aronson D, Hammerman H, Beyar R, et al. Serum blood urea nitrogen and long-term mortality in acute ST-elevation myocardial infarction. *International journal of cardiology* 2008; **127**(3): 380-5.

25. Kirtane AJ, Leder DM, Waikar SS, et al. Serum blood urea nitrogen as an independent marker of subsequent mortality among patients with acute coronary syndromes and normal to mildly reduced glomerular filtration rates. *J Am Coll Cardiol* 2005; **45**(11): 1781-6.

26. Wigger O, Bloechlinger S, Berger D, et al. Baseline serum bicarbonate levels independently predict short-term mortality in critically ill patients with ischaemic cardiogenic shock. *Eur Heart J Acute Cardiovasc Care* 2018; **7**(1): 45-52.

27. Wang YP, Wang JH, Wang XL, et al. Roles of ST2, IL-33 and BNP in predicting major adverse cardiovascular events in acute myocardial infarction after percutaneous coronary intervention. *J Cell Mol Med* 2017; **21**(11): 2677-84.

28. Jia X, Sun W, Hoogeveen RC, et al. High-Sensitivity Troponin I and Incident

Coronary Events, Stroke, Heart Failure Hospitalization, and Mortality in the ARIC Study. *Circulation* 2019; **139**(23): 2642-53.

Figure Legends

Figure 1. Nomogram to calculate risk score and predict 30-day survival probability in myocardial infarction patients.

Scores were assigned for age, heart rate, WBC, BUN level, and bicarbonate level by drawing a line upward from the corresponding values to the ‘‘Score’’ line. The sum of all these scores, plotted on the ‘‘Total score’’ line, corresponds to predictions of 30-day survival probability in myocardial infarction patients. WBC, white blood cell count; bpm, beats per minute; BUN, blood urea nitrogen.

Figure 2. Performance evaluation of the nomogram in the primary and validation cohorts.

Receiver operating characteristic curve analysis in the primary (a) and validation (b) cohorts. Calibration curve analysis in the primary (c) and validation (d) cohorts. The horizontal axis represents the nomogram-predicted probability of 30-day survival, and the vertical axis represents the actual observed 30-day mortality. Decision curve analysis for the primary (e) and validation (f) cohorts, implicating the net benefit with respect to the use of the nomogram. Survival curves for two groups classified by prognostic total score calculated from the nomogram in the primary (g) and validation (h) cohorts. AUC, area under the curve; CI, confidence interval.

Table 1 Comparison of basic demographics, vital signs, laboratory tests, and 30-day mortality between the primary cohort and the validation cohort

Variables	Primary cohort (n=1422)	Validation cohort (n=609)	*P*
Basic demographics			
Age, years	67.6±14.2	68.5±14.1	0.195
Male, n(%)	902 (63.4)	397 (65.2)	0.450
Weight, kg	80.8 ± 19.9	80.7 ±19.0	0.914
CCU stay, n(%)	931 (65.5)	390 (64.0)	0.535
Private insurance, n(%)	525 (36.92)	200 (32.84)	0.079
Vital signs			
Heart rate, bpm	84.8±17.9	84.7±17.1	0.910
MAP, mmHg	85.5±18.1	85.3±17.4	0.830
Temperature, ℃	36.3±0.9	36.3±0.9	0.619
CVP (tested)	525 (36.9)	228 (37.4)	0.825
Laboratory tests			
WBC, K/μL	12.6±5.6	12.7±5.5	0.813
Hemoglobin, g/dL	11.7±2.1	11.6±2.1	0.284
Platelet, K/μL	227.8±94.0	231.0±95.8	0.474
Creatinine, mg/dL	0.9(0.8-1.3)	1.0(0.8-1.4)	0.295
Creatinine kinase, U/L	338.0(67.0-988.6)	378.0(69.5-992.1)	0.510
BNP (tested)	14 (1.0)	5 (0.8)	0.726
BUN, mg/dL	18.0(13.8-27.0)	19.7(14.0-28.0)	0.165
Bicarbonate, mg/dL	22.9±4.1	23.1±3.9	0.421
pH (tested)	729(51.3)	326(53.5)	0.349
pO2 (tested)	719 (50.6)	319 (52.4)	0.453
pCO2 (tested)	719 (50.6)	319 (52.4)	0.453
Chloride, mg/dL	104.8±4.8	104.5±5.2	0.202
Sodium, mg/dL	137.8±3.8	137.7±3.9	0.672
Potassium, mg/dL	4.2±0.6	4.2±0.7	0.609
Troponin (tested)	757(53.2)	339(55.7)	0.314
Lactate (tested)	447 (31.4)	212 (34.8)	0.136
30-day mortality, n(%)	208 (14.6)	95 (15.6)	0.573

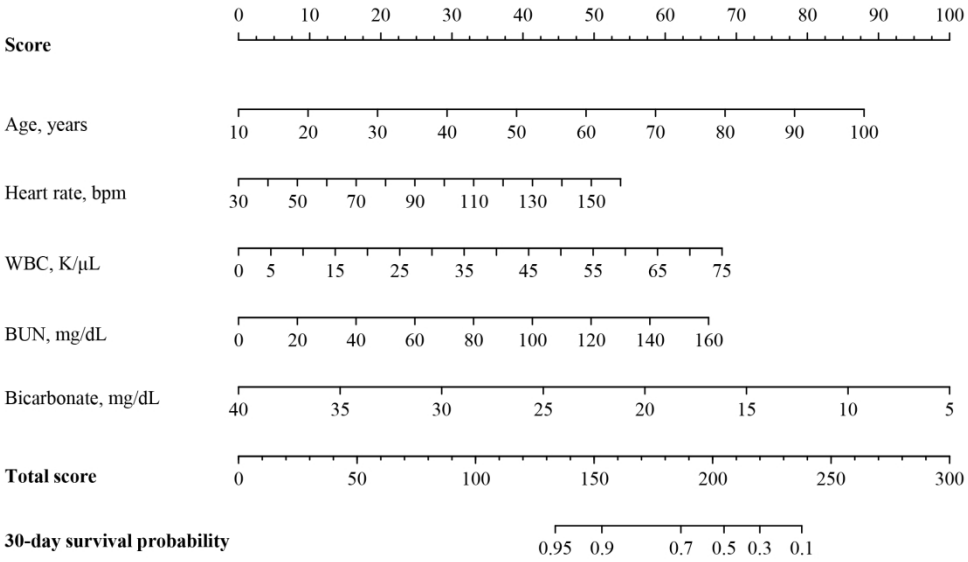
For each variable, the mean ± standard deviation, median (interquartile range) or frequency (percent) was reported as appropriate. For variables that had missing data for more than 20% of the patients in the current cohort, flags indicating whether these data were obtained were used as covariates. Continuous variables were compared using either Student's *t* test or the rank-sum test as appropriate. The chi-squared test was employed to compare the differences between categorical variables. CCU, cardiac care unit;

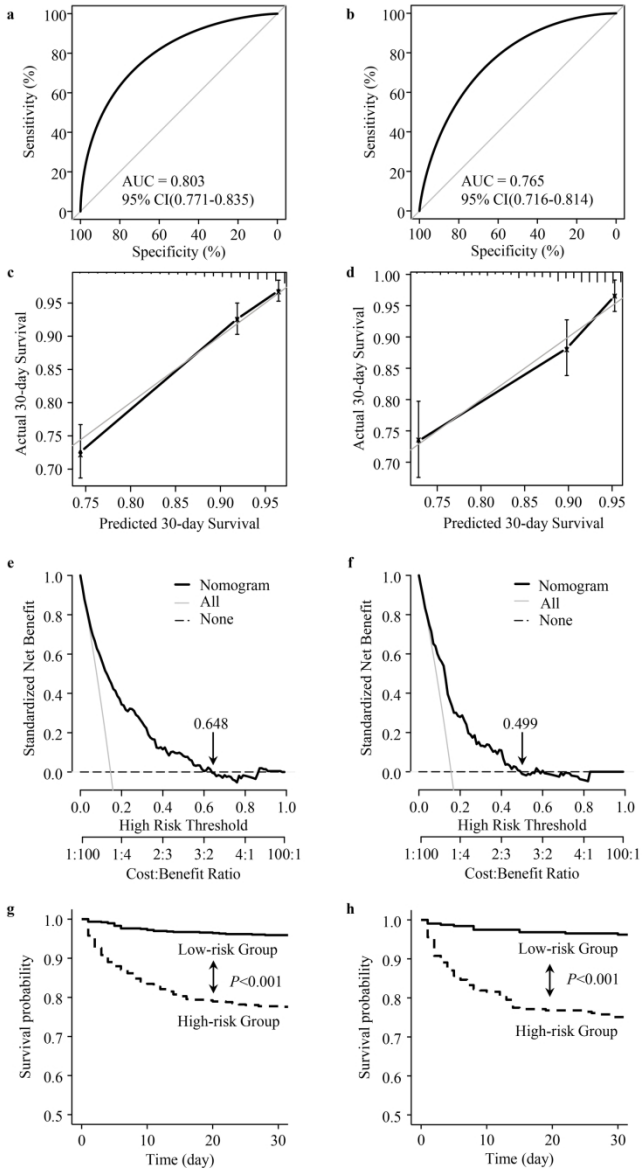
MAP, mean arterial pressure; bpm, beats per minute; CVP, central venous pressure; WBC, white blood cell count; BNP, brain natriuretic peptide; BUN, blood urea nitrogen.

Table 2 Univariate and multivariate analyses for the relationship between the candidate risk factors and 30-day mortality in the primary cohort

	Univariate model			Multivariate model		
Variables	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.042	1.031-1.053	<0.001	1.033	1.022-1.045	<0.001
Male	0.549	0.418-0.721	<0.001	0.763	0.574-1.015	0.063
Weight	0.989	0.981-0.996	0.002			
Private insurance	0.353	0.249-0.502	<0.001			
Heart rate	1.022	1.015-1.029	<0.001	1.016	1.008-1.023	<0.001
MAP	0.985	0.977-0.993	<0.001			
Hemoglobin	0.882	0.828-0.940	<0.001			
WBC	1.064	1.049-1.079	<0.001	1.029	1.014-1.044	<0.001
BUN	1.025	1.021-1.030	<0.001	1.014	1.008-1.020	<0.001
Bicarbonate	0.842	0.819-0.866	<0.001	0.904	0.875-0.933	<0.001
Creatinine	1.257	1.181-1.338	<0.001			
Potassium	1.394	1.193-1.630	<0.001	1.169	0.975-1.403	0.092

HRs were estimated by Cox proportional hazards regression. All statistical tests were two-sided. The selection of the final prediction model was performed with a backward stepwise selection process. HR, hazard ratio; CI, confidence interval; MAP, mean arterial pressure; WBC, white blood cell count; BUN, blood urea nitrogen.


Score
0 10 20 30 40 50 60 70 80 90 100
Age, years
10 20 30 40 50 60 70 80 90 100
Heart rate, bpm
30 50 70 90 110 130 150
WBC, K/μL
0 5 15 25 35 45 55 65 75
BUN, mg/dL
0 20 40 60 80 100 120 140 160
Bicarbonate, mg/dL
40 35 30 25 20 15 10 5
Total score
0 50 100 150 200 250 300
30-day survival probability
0.95 0.9 0.7 0.5 0.3 0.1



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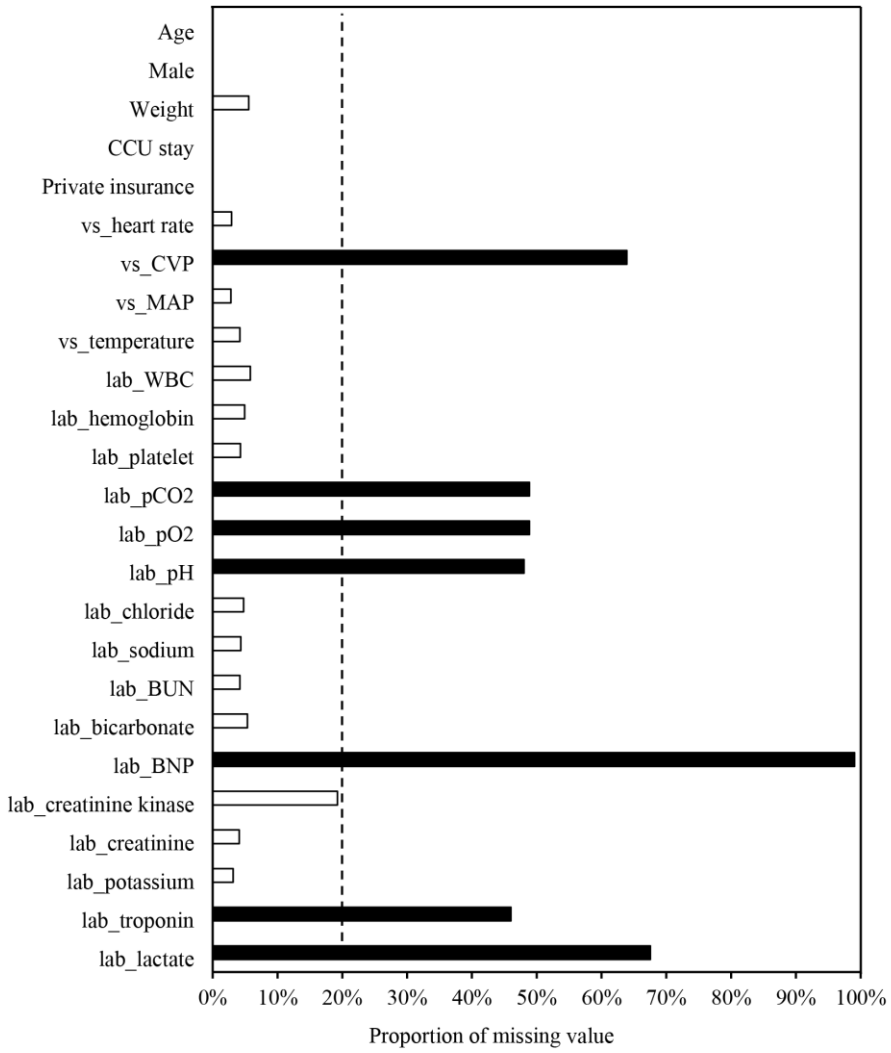

Supplementary Figure 1. Summary of missing data.

Black bars indicate variables with missing data for more than 20% of patients. CCU, cardiac care unit; MAP, mean arterial pressure; CVP, central venous pressure; WBC, white blood cell count; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; vs, vital signs; lab, laboratory tests.

Supplementary Table 1. Univariate analyses for the relationship between the candidate risk factors and 30-day mortality in the primary cohort

Variables	HR	95% CI	*P*
Basic demographics			
age	1.042	1.031-1.053	<0.001
male	0.549	0.418-0.721	<0.001
Weight	0.989	0.981-0.996	0.002
CCU	0.818	0.618-1.081	0.158
Private insurance	0.353	0.249-0.502	<0.001
Vital signs			
Heart rate	1.022	1.015-1.029	<0.001
MAP	0.985	0.977-0.993	<0.001
Temperature	0.877	0.768-1.002	0.054
Laboratory tests			
Hemoglobin	0.882	0.828-0.940	<0.001
Platelet	1.000	0.999-1.002	0.707
Creatinine kinase	1.000	1.000-1.000	0.518
WBC	1.064	1.049-1.079	<0.001
Chloride	1.018	0.988-1.048	0.241
Sodium	0.998	0.962-1.036	0.922
BUN	1.025	1.021-1.030	<0.001
Bicarbonate	0.842	0.819-0.866	<0.001
Creatinine	1.257	1.181-1.338	<0.001
Potassium	1.394	1.193-1.630	<0.001

HRs were estimated by Cox proportional hazards regression. All statistical tests were two-sided. HR, hazard ratio; CI, confidence interval; CCU, cardiac care unit; MAP, mean arterial pressure; WBC, white blood cell count; BUN, blood urea nitrogen.

TRIPOD Checklist: Prediction Model Development

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	5
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5
	5b	Describe eligibility criteria for participants.	5
	5c	Give details of treatments received, if relevant.	NA
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	6
	6b	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	6
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	Explain how the study size was arrived at.	NA
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	6
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	7
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	7
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	7
Risk groups	11	Provide details on how risk groups were created, if done.	7
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	8
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	8
Model development	14a	Specify the number of participants and outcome events in each analysis.	8
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	8
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	9
	15b	Explain how to the use the prediction model.	9
Model performance	16	Report performance measures (with CIs) for the prediction model.	10
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	12
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	10
Implications	20	Discuss the potential clinical use of the model and implications for future research.	11
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	6
Funding	22	Give the source of funding and the role of the funders for the present study.	14

We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

BMJ Open

Development and validation of a prognostic nomogram for myocardial infarction patients in intensive care units: a retrospective cohort study

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Development and validation of a prognostic nomogram for myocardial infarction patients in intensive care units: a retrospective cohort study

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Word count: 2845

ABSTRACT

Objectives: We aimed to develop and validate a prognostic nomogram and evaluate the discrimination of the nomogram model in order to improve the prediction of 30-day survival of critically ill myocardial infarction (MI) patients.

Design: A retrospective cohort study.

Setting: Data were collected from the Medical Information Mart for Intensive Care (MIMIC)-III database, consisting of critically ill participants between 2001 and 2012 in the United States.

Participants: A total of 2031 adult critically ill patients with MI were enrolled from the MIMIC-III database.

Primary and secondary outcome: Thirty-day survival.

Results: Independent prognostic factors, including age, heart rate, white blood cell count, blood urea nitrogen, and bicarbonate, were identified by Cox regression model and used in the nomogram. Good agreement between the prediction and observation was indicated by the calibration curve for 30-day survival. The nomogram exhibited reasonably accurate discrimination [area under the receiver operating characteristic curve, 0.765, 95% (confidence interval) CI, 0.716-0.814] and calibration (C-index, 0.758, 95% CI, 0.712-0.804) in the validation cohort. Decision curve analysis demonstrated that the nomogram was clinically beneficial. Additionally, participants could be classified into two risk groups by the nomogram, and the 30-day survival probability was significantly different between them (P <0.001).

Conclusions: This five-factor nomogram can achieve a reasonable degree of accuracy

to predict 30-day survival in critically ill MI patients and might be helpful for risk stratification and decision making for MI patients.

Keywords: myocardial infarction; 30-day survival; intensive care unit; nomogram; prognostic model

Article Summary

Strengths and limitations of this study

This is the first study to develop and validate a prognostic nomogram for myocardial infarction (MI) patients in the intensive care unit (ICU).

The area under the receiver operating characteristic curve, calibration curves, decision curve analysis and survival curves were enrolled to evaluate the performance of this novel nomogram model in both the primary cohort and validation cohort.

Multiple imputation was used to handle the covariates with less than 20% missing to minimize the bias resulting from missing values.

ST elevation, oliguria, and ventricular arrhythmias, were not accessible in this study, and this might lead to reduced effectiveness of this nomogram.

We could not compare the performance of nomogram model with existing model, such the Thrombolysis in Myocardial Infarction (TIMI) score and the Global Registry of Acute Coronary Events (GRACE) score.

Introduction

Myocardial infarction (MI) is a major health problem that causes high mortality and high economic costs worldwide.[1] A substantial proportion of MI patients are admitted to the intensive care unit (ICU).[2] However, not all MI patients benefit from ICU care.[3] It is necessary to perform risk stratification for MI to help clinicians make more efficient decisions, which provides benefits for more MI patients.

Nomograms are popular prognostic tools with the ability to predict clinical events by integrating potential risk factors.[4] Nomograms have been widely used for tumor prognosis, supporting the movement towards personalized oncology medicine.[5] Recently, a nomogram was effectively used to predict both short-term and long-term survival for asymptomatic adults undergoing screening for cardiac risk factors.[6] Thus, we hypothesized that a nomogram may also be feasible for the risk stratification of critically ill MI patients.

This study aimed to identify prognostic factors for the 30-day mortality of critically ill MI patients and establish a prognostic nomogram based on a multivariable Cox regression model in a primary cohort. Furthermore, the performance and clinical benefits of the nomogram were assessed in a validation cohort to validate the accuracy and utility of the prognostic nomogram model. The nomogram could be easily applied in clinical practice to identify high-risk patients and guide decision making.

Methods

Data source

The data were retrieved from the Medical Information Mart for Intensive Care

(MIMIC-III) dataset. The MIMIC-III integrates the comprehensive clinical data of 53,423 stays of adult patients in the ICU between 2001 and 2012. An average of 4,597 charted observations and 380 laboratory measurements are available for individual hospital admissions. The overall information is saved as a relational database, consisting of patient demographics, laboratory tests, discharge summaries, electrocardiographs, imaging examinations, diagnostic information such as the International Classification of Disease (ICD)-9 code, and in-hospital and out-of-hospital mortality. The use of MIMIC-Ⅲ database was under the approval from the review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center.[7] All the patients in the database have been deidentified for privacy, and the need for informed consent was waived. This study was conducted in accordance with the recommendations of the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.[8]

Study cohort

Patients admitted to the ICU who were diagnosed with MI were eligible for inclusion. After screening of the MIMIC-III database, a total of 2,031 patients with MI were included for analysis. The cohort was randomly divided into the primary cohort and the validation cohort in a ratio of 7:3; the primary cohort was used to establish the nomogram, and the validation cohort was used for validation.

Data extraction

Structure Query Language was used for data extraction. For patients with multiple ICU admissions, only the data of the patient's first ICU admission were used in this study.

All data regarding baseline characteristics were collected as the first value in the initial 24 hours following admission. The variables for the following analysis included (1) basic demographics, including age, sex, weight, coronary care unit stay and private insurance; (2) vital signs, including heart rate, mean arterial pressure (MAP), temperature and central venous pressure (CVP); and (3) laboratory tests, including tests of white blood cell count (WBC), hemoglobin, platelets, serum creatinine, creatinine kinase, type B natriuretic peptide (BNP), blood urea nitrogen (BUN) level, bicarbonate level, pH, partial pressure of oxygen (pO_2), partial pressure of carbon dioxide (pCO_2), chloride, sodium, potassium, troponin and lactate.

In this study, we regarded 30-day survival as the outcome measure, which was also extracted from the MIMIC-III database.

Management of missing data

Variables with missing data are common in the MIMIC-III database. More than 20% of the data regarding CVP, pCO_2, pO_2, pH, BNP, troponin, and lactate were missing, and these parameters were not qualified for establishment of the nomogram (Supplementary Figure 1). A flag indicating whether these data were obtained is shown in the characteristics table. For variables that had missing data for less than 20% of patients, missing values were filled with predictors using multiple imputation to minimize the bias resulting from missing values.[9]

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation or median (interquartile range, IQR), as appropriate. Categorical data are expressed as numbers

(percentages). Continuous variables were compared using Student's *t* test or the rank-sum test, as appropriate. Categorical variables were compared by the chi-squared test.

In this study, the objective was to develop a fast-to-use prognostic model for 30-day mortality in critically ill MI patients. And Cox proportional hazards model was the most frequently used regression model for survival analysis and thus was enrolled in this study. Univariate Cox regression was used to screen for variables that were significantly associated with 30-day survival in the primary cohort. The proportional hazards assumption was checked based on the scaled Schoenfeld residuals using *survival* package in R tool. Potential prognostic factors that were significant in the univariate Cox regression model were entered into the multivariable Cox proportional hazard model, in which the hazard ratio (HR), which was used to approximate risk of event, was also calculated. To avoid too many variables entering into the final model and influencing the practicality of model, a strict cut-off value of 0.05 was chosen. The backward stepwise process based on the Akaike information criterion was used to control the overfitting of the model.

A nomogram based on the results of previous multivariable analyses was constructed. The calibration, discrimination and clinical usefulness of the nomogram were calculated to evaluate its performance.[10] The area under the receiver operating characteristic curve (AUC) and Harrell's concordance index (C-index) were used to assess the predictive capacity of the prediction model. Confidence intervals (CIs) were obtained by creating 1000 bootstrap samples from the corresponding cohort and replicating the estimation process. The calibration curve was used to analyze the

agreement between the nomogram and actual observation. Decision curve analysis was performed to assess the clinical usefulness of the prognostic nomogram by quantifying the standardized net benefits at different threshold probabilities. Survival curves were used to compare the survival probability between the low-risk group and the high-risk group defined by the nomogram.

A two-tailed *P* value < 0.05 was considered statistically significant in our study. SPSS software (version 23.0, IBM, NY, USA) and R software (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis.

Patient and Public Involvement

Patients and/or the public were not directly involved in this study.

Results

Baseline characteristics of the primary cohort and validation cohort

The primary cohort and validation cohort consisted of 1,422 and 609 MI patients, respectively. All baseline characteristics of the primary cohort and validation cohort were shown in Table 1. There were no significant differences in the baseline characteristics between the primary cohort and validation cohort (all $P > 0.05$).

Prognostic factors in the primary cohort

Basic demographics, vital signs, and laboratory tests in the primary cohort were further examined by the univariate Cox regression model for the prediction of 30-day mortality (Supplementary Table 1). Variables including age, male sex, weight, private insurance, heart rate, MAP, hemoglobin WBC, BUN level, bicarbonate level, creatinine level, and potassium level were potential predictors of 30-day mortality in the univariate analysis

($P < 0.05$). All these candidate factors were entered into the multivariable Cox proportional hazard model, and five prognostic factors, namely, age, heart rate, WBC, BUN level and bicarbonate level, were included in the final prediction model (each $P < 0.05$) (Table 2).

A prognostic nomogram for 30-day survival

A prognostic nomogram for 30-day survival was established with the five prognostic factors obtained from the multivariable Cox proportional hazard model (Figure 1). The nomogram was generated by assigning a weighted score to each of the independent prognostic parameters. The scales of age, heart rate, WBC, BUN level, and bicarbonate level ranged from 10 to 100, 30 to 150, 0 to 75, 0 to 160, and 40 to 5, respectively. The highest total score was 300 points, and the scale of the 30-day survival probability ranged from 0.95 to 0.1. A higher score calculated from the sum of the assigned points for each prognostic factor in the nomogram corresponded to a lower probability of survival in 30 days.

For instance, one MI patient with an age of 70 years old (57 points), a heart rate of 110 bpm (33 points), a WBC of 11 K/μL (10 points), a BUN level of 80 mg/dL (33 points) and a bicarbonate level of 10 mg/dL (85 points) had a total score of 218 points, which corresponded to an approximately 30% 30-day survival probability (Supplementary Figure 2).

Another MI patient who had an age of 50 years old (39 points), a heart rate of 70 bpm (17 points), a WBC of 11 K/μL (10 points), a BUN level of 60 mg/dL (25 points) and a bicarbonate level of 18 mg/dL (63 points) had a total score of 154 points. Then this

MI patient was predicted to suffer 90% 30-day survival probability (Supplementary Figure 3).

Performance evaluation of the prognostic nomogram

The AUC indicated that the predictive capacity of the prediction model was 0.803 (95% CI, 0.771-0.835) in the primary cohort and 0.765 (95% CI, 0.716-0.814) in the validation cohort (Figure 2A, B). The C-index was 0.787 (95% CI, 0.757-0.817) for the primary cohort and 0.758 (95% CI, 0.712-0.804) for the validation cohort. The calibration plot demonstrated adequate fit of the nomogram for predicting 30-day survival, which was consistent with the Kaplan-Meier estimate in both the primary cohort and validation cohort (Figure 2C, D). The decision curve analysis showed the net benefits obtained from the application of our nomogram with threshold probabilities of 0.648 and 0.499 in the primary cohort and validation cohort, respectively (Figure 2E, F). Participants could be classified into low-risk and high-risk groups by the nomogram. Survival curves revealed a significantly lower survival probability in the high-risk group than in the low-risk group in both the primary cohort and validation cohort (P<0.001), which indicated the substantial discriminatory power of the nomogram to distinguish low-risk and high-risk MI patients in the ICU (Figure 3).

Discussion

This study extracted clinical data and survival information of 2,031 MI patients from the MIMIC-III database. Five risk factors for 30-day mortality of MI, including age, heart rate, WBC, BUN level, and bicarbonate level, were identified by univariate and multivariable Cox regression models and used to establish a prognostic nomogram. To

the best of our knowledge, this is the first study to develop and validate a prognostic nomogram for MI patients in the ICU. This novel nomogram showed satisfactory performance in both the primary cohort and validation cohort as assessed by the AUC, calibration curves, decision curve analysis and survival curves. Thus, this nomogram could be efficiently and effectively employed in clinical practice.

MI has been a global health problem with a high incidence and a high mortality, and it has led to economic and health burdens in patients.[1] The Thrombolysis in Myocardial Infarction (TIMI) score and the Global Registry of Acute Coronary Events (GRACE) score are two common tools to predict short-term and long-term outcomes for acute MI patients.[11-13] Both the TIMI risk score and the GRACE score require more than five factors to calculate the probability of mortality. In addition, the Soroka Acute Myocardial Infarction (SAMI) risk score, which was used to predict 1-year and 5-year mortality of acute MI in Israel, consists of 10 risk factors.[14] Comparing with other existing models of which the AUC ranged from 0.66 to 0.90, the nomogram model showed an acceptable AUC of 0.80 (Supplementary Table 2). Our nomogram uses five factors that can be collected at first-day admission, can be easily applied, and performs well in predicting short-term mortality of patients with MI. We hope that this short nomogram will be used for the quick identification of high-risk MI patients in the ICU. Nomograms are of great utility in predicting an individual's probability of a clinical event using individual variables, and they have become a common prognostic tool in oncology.[4] A nomogram was developed for the 5- to 15-year survival of asymptomatic adults undergoing coronary artery calcium scoring.[6] For the mortality of MI, our study

is the first to provide a simple-to-use prognostic nomogram with five factors that are easily accessible on the first-day admission, and this nomogram might improve timely individualized risk stratification and the prevention of fatal outcomes. The satisfactory performance of this model was reflected by its moderate predictive ability, indicated by an AUC greater than 0.75 in both the primary cohort and validation cohort. Additionally, the calibration analysis performed in two cohorts revealed that the predicted 30-day mortality was similar to the actual 30-day mortality. Furthermore, decision curve analysis indicated that the net clinical benefits were positive in MI patients, with a probability of up to 50% in both cohorts. A difference in threshold probability between primary and validation cohort was observed in our study. This difference may be due to the potential heterogeneity between these two cohorts, such as the level of variables or mortality rate, although which had not shown significant differences in statistical analyses. Overall, both two decision curves indicated a net benefit with respect to the use of nomogram model. The survival curves also revealed the good discriminative capacity to identify high-risk and low-risk patients in both the primary cohort and validation cohort.

It should be noted that only five prognostic factors were used in the final nomogram model. Age has been widely recognized as one of the most powerful risk factors in cardiovascular diseases, such as vascular senescence, cardiac remodeling, and atrial fibrillation.[15-17] Decreased expression of antioxidative factors and increased expression of oxidative molecular mediators occur in elderly patients, leading to aggravating ischemic injury.[15,18] Heart rate is also an important prognostic factor for cardiovascular

mortality. A higher resting heart rate was reported to be positively related to a higher risk of MI and all-cause mortality.[19,20] These results were consistent with our study, in which heart rate was positively associated with mortality of MI.

Among lab tests, WBC has also been shown to be a potential risk factor and to be associated with myocardial perfusion and the severity of coronary artery disease.[21,22] A recent cohort study of triple-vessel coronary artery disease revealed the independent prognostic value of both total and differential white blood cell counts for predicting long-term mortality.[23] BUN level has also been demonstrated to be independently associated with mortality in patients with MI, even in patients with normal to mildly reduced glomerular filtration rates.[24,25] Bicarbonate is a central biomarker that reflects acid-base equilibrium and is affected by electrolyte disturbance. In this study, bicarbonate level was negatively related to 30-day mortality, which was consistent with another cohort study of cardiogenic shock patients hospitalized in the ICU.[26] In short, these five factors included in the nomogram were all credible prognostic factors for cardiovascular mortality, and these factors could be used in clinical work.

Several limitations should be pointed out. Firstly, a few previously reported independent predictors for major cardiovascular events, including BNP and troponin, were not included to minimize the bias from excessive missing values.[27,28] Hence, the prognostic value of these factors for MI could not be estimated. Secondly, ST elevation, oliguria, and ventricular arrhythmias, were not accessible in this study, and this might lead to reduced effectiveness of this nomogram. GRACE score and TIMI score could not be obtained, and thus the comparison between nomogram model and these two

score models could not be made. Thirdly, the model still required more samples to validate its viability. Although we performed random allocation to establish a validation cohort with 30% of the total sample size for the verification of the superiority of our model, a large external cohort would further enhance the credibility and effectiveness of our model in future studies.

In conclusion, our study developed a prognostic nomogram with five factors, including age, heart rate, WBC, BUN level, and bicarbonate level, for the prediction of 30-day survival in critically ill MI patients in the ICU. This nomogram performed well and might be helpful in risk stratification and decision making for MI patients undergoing clinical treatment.

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Author contributions

Qi Guo: Conceptualization, data analysis, Writing-original draft, Writing-review&editing. **Maoxiong Wu:** Conceptualization, Writing-original draft, Writing-review&editing. **Hongwei Li:** Writing-original draft, Data curation. **Huijun Ouyang:** Literature search, Data interpretation. **Runlu Sun:** Data collection, Data curation. **Junjie Wang:** Data collection, Data curation. **Zhaoyu Liu:** Literature search, Data interpretation. **Jingfeng Wang:** Conceptualization, Writing-review&editing, Data curation. **Yuling Zhang:** Conceptualization, Writing-review&editing, Data curation.

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Disclaimer

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Declaration of Interests

All authors declare no potential conflicts of interest.

Data availability statement

The dataset analyzed to generate the findings for this study are available from the corresponding author on reasonable request.

References

1. Virani SS, Alonso A, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation* 2020: CIR0000000000000757.

2. Zhou L, Tao Z, Wu Y, et al. Individual and institutional factors affecting cardiac monitoring in coronary care units: a national survey of Chinese nurses. *Int J Nurs Stud* 2012; **49**(5): 570-8.

3. Valley TS, Iwashyna TJ, Cooke CR, et al. Intensive care use and mortality among patients with ST elevation myocardial infarction: retrospective cohort study. *BMJ* 2019; **365**: l1927.

4. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. *The Lancet Oncology* 2015; **16**(4): e173-e80.

5. Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. *J Clin Oncol* 2008; **26**(8): 1364-70.

6. B OH, Gransar H, Callister T, et al. Development and Validation of a Simple-to-Use Nomogram for Predicting 5-, 10-, and 15-Year Survival in Asymptomatic Adults Undergoing Coronary Artery Calcium Scoring. *JACC Cardiovasc Imaging* 2018; **11**(3): 450-8.

7. Johnson AEW, Pollard TJ, Shen L, et al. MIMIC-III, a freely accessible critical care database. *Sci Data* 2016; **3**: 160035.

8. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the

TRIPOD statement. *BMJ* 2015; **350**: g7594.

9. Zhang Z. Multiple imputation with multivariate imputation by chained equation (MICE) package. *Ann Transl Med* 2016; **4**(2): 30.

10. Alba AC, Agoritsas T, Walsh M, et al. Discrimination and Calibration of Clinical Prediction Models: Users' Guides to the Medical Literature. *Jama* 2017; **318**(14): 1377-84.

11. Antman EM CM, 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.

12. Morrow DA, Antman EM, Charlesworth A, et al. 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.

13. Granger CB GR, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KAA, Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. *Archives of internal medicine* 2003; **163**(19): 2345-53.

14. Plakht Y, Shiyovich A, Weitzman S, Fraser D, Zahger D, Gilutz H. A new risk score predicting 1- and 5-year mortality following acute myocardial infarction Soroka Acute Myocardial Infarction (SAMI) Project. *International journal of cardiology* 2012; **154**(2): 173-9.

15. Salazar G. NADPH Oxidases and Mitochondria in Vascular Senescence. *Int J Mol Sci* 2018; **19**(5).

16. Dhalla NS, Rangi S, Babick AP, Zieroth S, Elimban V. Cardiac remodeling and subcellular defects in heart failure due to myocardial infarction and aging. *Heart Fail Rev* 2012; **17**(4-5): 671-81.

17. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. *Circ Res* 2014; **114**(9): 1453-68.

18. Ham PB, 3rd, Raju R. Mitochondrial function in hypoxic ischemic injury and influence of aging. *Prog Neurobiol* 2017; **157**: 92-116.

19. Sharashova E, Wilsgaard T, Lochen ML, Mathiesen EB, Njolstad I, Brenn T. Resting heart rate trajectories and myocardial infarction, atrial fibrillation, ischaemic stroke and death in the general population: The Tromso Study. *Eur J Prev Cardiol* 2017; **24**(7): 748-59.

20. Dobre D, Kjekshus J, Rossignol P, et al. Heart rate, pulse pressure and mortality in patients with myocardial infarction complicated by heart failure. *International journal of cardiology* 2018; **271**: 181-5.

21. Barron HV CC, Murphy SA, Braunwald E, Gibson CM. Association between white blood cell count, epicardial blood flow, myocardial perfusion, and clinical outcomes in the setting of acute myocardial infarction: a thrombolysis in myocardial infarction 10 substudy. *Circulation* 2000; **102**(19): 2329-34.

22. Sabatine MS MD, Cannon CP, Murphy SA, Demopoulos LA, DiBattiste PM,

McCabe CH, Braunwald E, Gibson CM. Relationship between baseline white blood cell count and degree of coronary artery disease and mortality in patients with acute coronary syndromes: a TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy- Thrombolysis in Myocardial Infarction 18 trial)substudy. *J Am Coll Cardiol* 2002; **40**(10): 1761-8.

23. Zhao X, Jiang L, Xu L, et al. Predictive value of in-hospital white blood cell count in Chinese patients with triple-vessel coronary disease. *Eur J Prev Cardiol* 2019; **26**(8): 872-82.

24. Aronson D, Hammerman H, Beyar R, et al. Serum blood urea nitrogen and long-term mortality in acute ST-elevation myocardial infarction. *International journal of cardiology* 2008; **127**(3): 380-5.

25. Kirtane AJ, Leder DM, Waikar SS, et al. Serum blood urea nitrogen as an independent marker of subsequent mortality among patients with acute coronary syndromes and normal to mildly reduced glomerular filtration rates. *J Am Coll Cardiol* 2005; **45**(11): 1781-6.

26. Wigger O, Bloechlinger S, Berger D, et al. Baseline serum bicarbonate levels independently predict short-term mortality in critically ill patients with ischaemic cardiogenic shock. *Eur Heart J Acute Cardiovasc Care* 2018; **7**(1): 45-52.

27. Wang YP, Wang JH, Wang XL, et al. Roles of ST2, IL-33 and BNP in predicting major adverse cardiovascular events in acute myocardial infarction after percutaneous coronary intervention. *J Cell Mol Med* 2017; **21**(11): 2677-84.

28. Jia X, Sun W, Hoogeveen RC, et al. High-Sensitivity Troponin I and Incident

Coronary Events, Stroke, Heart Failure Hospitalization, and Mortality in the ARIC Study. *Circulation* 2019; **139**(23): 2642-53.

Figure Legends

Figure 1. Nomogram to calculate risk score and predict 30-day survival probability in myocardial infarction patients.

Scores were assigned for age, heart rate, WBC, BUN level, and bicarbonate level by drawing a line upward from the corresponding values to the ‘‘Score’’ line. The sum of all these scores, plotted on the ‘‘Total score’’ line, corresponds to predictions of 30-day survival probability in myocardial infarction patients. WBC, white blood cell count; bpm, beats per minute; BUN, blood urea nitrogen.

Figure 2. Performance evaluation of the nomogram in the primary and validation cohorts.

Receiver operating characteristic curve analysis in the primary (A) and validation (B) cohorts. Calibration curve analysis in the primary (C) and validation (D) cohorts. The horizontal axis represents the nomogram-predicted probability of 30-day survival, and the vertical axis represents the actual observed 30-day mortality. Decision curve analysis for the primary (E) and validation (F) cohorts, implicating the net benefit with respect to the use of the nomogram. AUC, area under the curve; CI, confidence interval.

Figure 3 Survival curves classified by high-risk and low-risk group.

Survival curves for two groups classified by prognostic total score calculated from the nomogram in the primary(A) and validation(B) cohort. For each survival curve, 95% confidence intervals and number at risk for each group were also presented.

Table 1 Comparison of basic demographics, vital signs, laboratory tests, and 30-day mortality between the primary cohort and the validation cohort

Variables	Primary cohort (n=1422)	Validation cohort (n=609)	*P*
Basic demographics			
Age, years	67.6±14.2	68.5±14.1	0.195
Male, n(%)	902 (63.4)	397 (65.2)	0.450
Weight, kg	80.8 ± 19.9	80.7 ±19.0	0.914
CCU stay, n(%)	931 (65.5)	390 (64.0)	0.535
Private insurance, n(%)	525 (36.92)	200 (32.84)	0.079
Vital signs			
Heart rate, bpm	84.8±17.9	84.7±17.1	0.910
MAP, mmHg	85.5±18.1	85.3±17.4	0.830
Temperature, ℃	36.3±0.9	36.3±0.9	0.619
CVP (tested)	525 (36.9)	228 (37.4)	0.825
Laboratory tests			
WBC, K/μL	12.6±5.6	12.7±5.5	0.813
Hemoglobin, g/dL	11.7±2.1	11.6±2.1	0.284
Platelet, K/μL	227.8±94.0	231.0±95.8	0.474
Creatinine, mg/dL	0.9(0.8-1.3)	1.0(0.8-1.4)	0.295
Creatinine kinase, U/L	338.0(67.0-988.6)	378.0(69.5-992.1)	0.510
BNP (tested)	14 (1.0)	5 (0.8)	0.726
BUN, mg/dL	18.0(13.8-27.0)	19.7(14.0-28.0)	0.165
Bicarbonate, mg/dL	22.9±4.1	23.1±3.9	0.421
pH (tested)	729(51.3)	326(53.5)	0.349
pO2 (tested)	719 (50.6)	319 (52.4)	0.453
pCO2 (tested)	719 (50.6)	319 (52.4)	0.453
Chloride, mg/dL	104.8±4.8	104.5±5.2	0.202
Sodium, mg/dL	137.8±3.8	137.7±3.9	0.672
Potassium, mg/dL	4.2±0.6	4.2±0.7	0.609
Troponin (tested)	757(53.2)	339(55.7)	0.314
Lactate (tested)	447 (31.4)	212 (34.8)	0.136
30-day mortality, n(%)	208 (14.6)	95 (15.6)	0.573

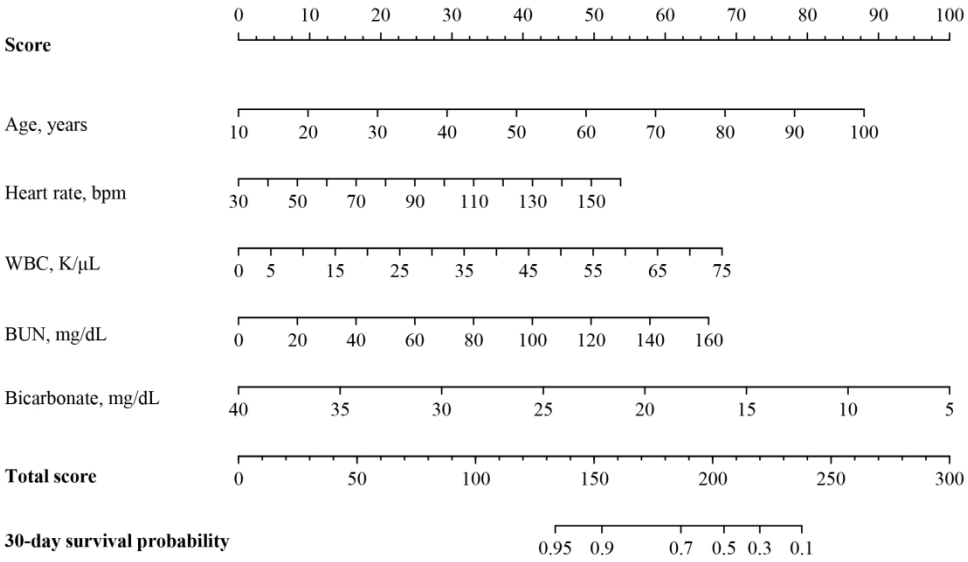
For each variable, the mean ± standard deviation, median (interquartile range) or frequency (percent) was reported as appropriate. For variables that had missing data for more than 20% of the patients in the current cohort, flags indicating whether these data were obtained were used as covariates. Continuous variables were compared using either Student's *t* test or the rank-sum test as appropriate. The chi-squared test was employed to compare the differences between categorical variables. CCU, cardiac care unit;

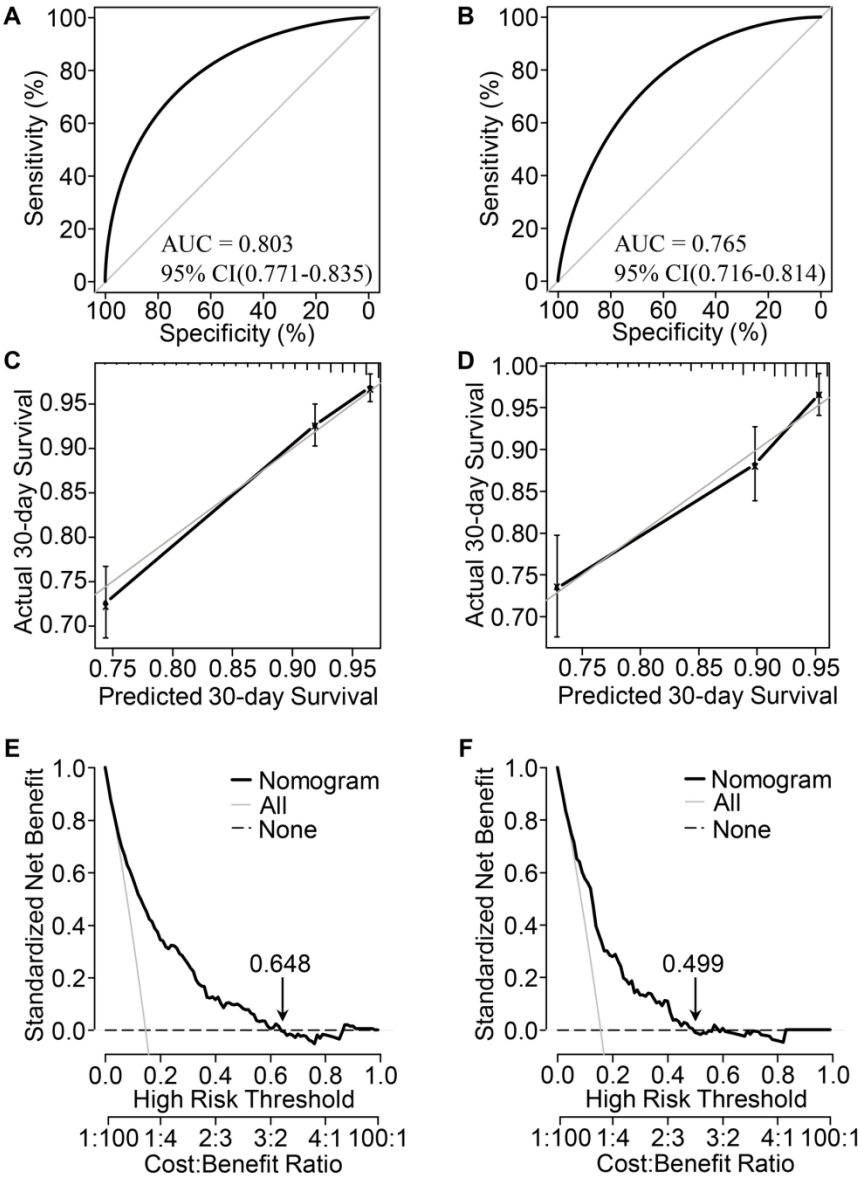
MAP, mean arterial pressure; bpm, beats per minute; CVP, central venous pressure; WBC, white blood cell count; BNP, brain natriuretic peptide; BUN, blood urea nitrogen.

Table 2 Univariate and multivariable analyses for the relationship between the candidate risk factors and 30-day mortality in the primary cohort

	Univariate model			Multivariable model		
Variables	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.042	1.031-1.053	<0.001	1.033	1.022-1.045	<0.001
Male	0.549	0.418-0.721	<0.001	0.763	0.574-1.015	0.063
Weight	0.989	0.981-0.996	0.002			
Private insurance	0.353	0.249-0.502	<0.001			
Heart rate	1.022	1.015-1.029	<0.001	1.016	1.008-1.023	<0.001
MAP	0.985	0.977-0.993	<0.001			
Hemoglobin	0.882	0.828-0.940	<0.001			
WBC	1.064	1.049-1.079	<0.001	1.029	1.014-1.044	<0.001
BUN	1.025	1.021-1.030	<0.001	1.014	1.008-1.020	<0.001
Bicarbonate	0.842	0.819-0.866	<0.001	0.904	0.875-0.933	<0.001
Creatinine	1.257	1.181-1.338	<0.001			
Potassium	1.394	1.193-1.630	<0.001	1.169	0.975-1.403	0.092

HRs were estimated by Cox proportional hazards regression. All statistical tests were two-sided. The selection of the final prediction model was performed with a backward stepwise selection process. HR, hazard ratio; CI, confidence interval; MAP, mean arterial pressure; WBC, white blood cell count; BUN, blood urea nitrogen.


Score
0 10 20 30 40 50 60 70 80 90 100
Age, years
10 20 30 40 50 60 70 80 90 100
Heart rate, bpm
30 50 70 90 110 130 150
WBC, K/μL
0 5 15 25 35 45 55 65 75
BUN, mg/dL
0 20 40 60 80 100 120 140 160
Bicarbonate, mg/dL
40 35 30 25 20 15 10 5
Total score
0 50 100 150 200 250 300
30-day survival probability
0.95 0.9 0.7 0.5 0.3 0.1



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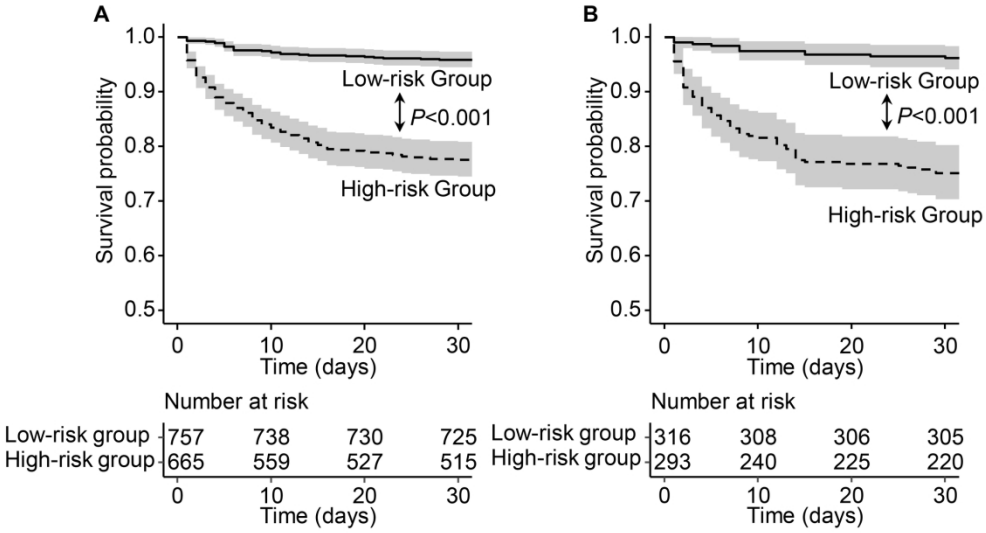

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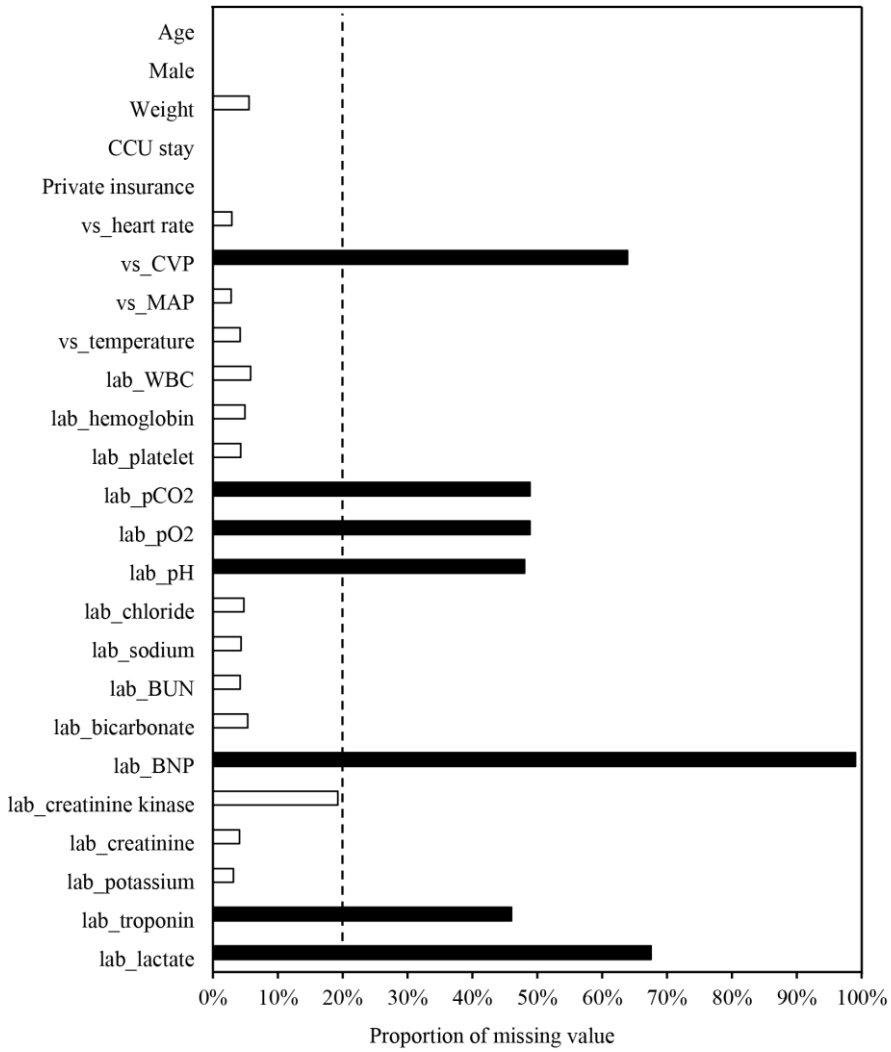
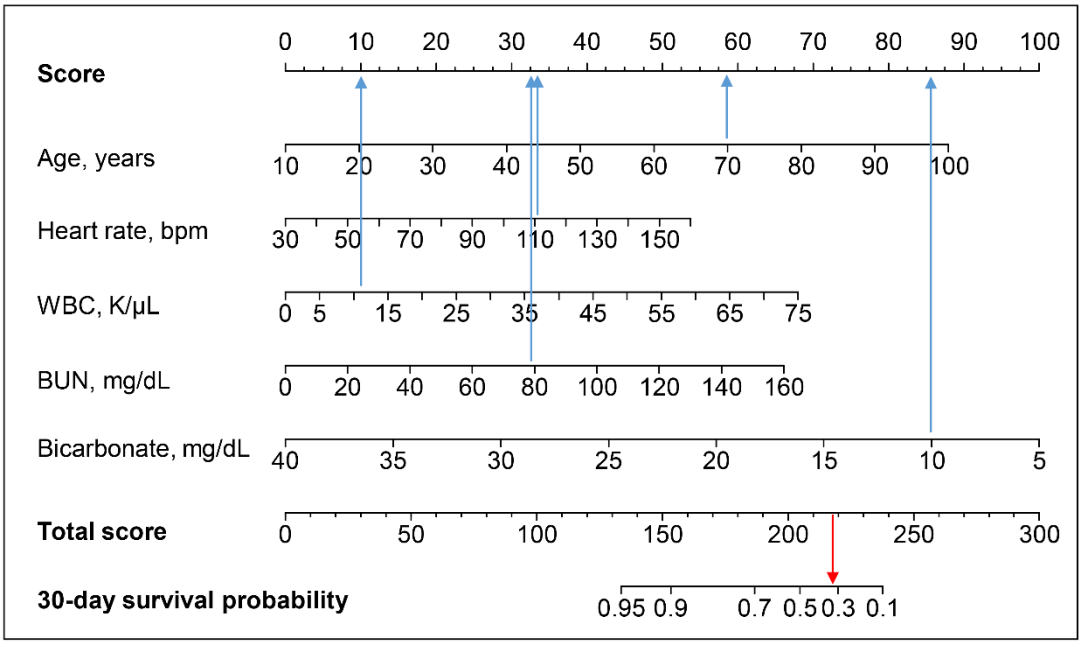
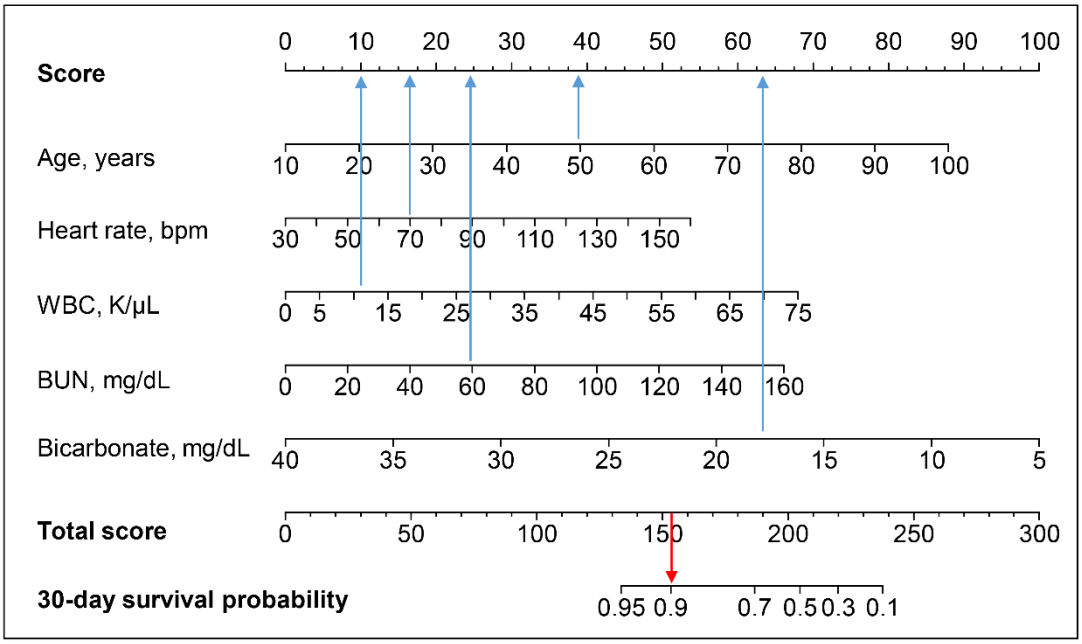


Supplementary Figure 1. Summary of missing data.

Black bars indicate variables with missing data for more than 20% of patients. CCU, cardiac care unit; MAP, mean arterial pressure; CVP, central venous pressure; WBC, white blood cell count; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; vs, vital signs; lab, laboratory tests.



Supplementary Figure 2. A high-risk sample predicted by nomogram model.
Score was assigned for age, heart rate, WBC, BUN, and bicarbonate, by drawing a line upward from the corresponding values to the "Score" line. The sum of all these scores, plotted on the "Total score" line, corresponds to predictions of 30-day survival probability in myocardial infarction patients. WBC, white blood cell count; bpm, beats per minute; BUN, blood urea nitrogen.



Supplementary Figure 3. A low-risk sample predicted by nomogram model.
Score was assigned for age, heart rate, WBC, BUN, and bicarbonate, by drawing a line upward from the corresponding values to the "Score" line. The sum of all these scores, plotted on the "Total score" line, corresponds to predictions of 30-day survival probability in myocardial infarction patients. WBC, white blood cell count; bpm, beats per minute; BUN, blood urea nitrogen.

Supplementary Table 1. Univariate analyses for the relationship between the candidate risk factors and 30-day mortality in the primary cohort

Variables	HR	95% CI	*P* for Cox model	*P* for proportional hazards assumption
Basic demographics				
age	1.042	1.031-1.053	<0.001	0.146
male	0.549	0.418-0.721	<0.001	0.902
Weight	0.989	0.981-0.996	0.002	0.904
CCU	0.818	0.618-1.081	0.158	0.915
Private insurance	0.353	0.249-0.502	<0.001	0.155
Vital signs				
Heart rate	1.022	1.015-1.029	<0.001	0.004
MAP	0.985	0.977-0.993	<0.001	0.318
Temperature	0.877	0.768-1.002	0.054	0.612
Laboratory tests				
Hemoglobin	0.882	0.828-0.940	<0.001	0.764
Platelet	1.000	0.999-1.002	0.707	0.325
Creatinine kinase	1.000	1.000-1.000	0.518	0.596
WBC	1.064	1.049-1.079	<0.001	0.728
Chloride	1.018	0.988-1.048	0.241	0.458
Sodium	0.998	0.962-1.036	0.922	0.615
BUN	1.025	1.021-1.030	<0.001	0.791
Bicarbonate	0.842	0.819-0.866	<0.001	0.640
Creatinine	1.257	1.181-1.338	<0.001	0.926
Potassium	1.394	1.193-1.630	<0.001	0.976

HRs were estimated by Cox proportional hazards regression. The proportional hazards assumption was checked based on the scaled Schoenfeld residuals. All statistical tests were two-sided. HR, hazard ratio; CI, confidence interval; CCU, cardiac care unit; MAP, mean arterial pressure; WBC, white blood cell count; BUN, blood urea nitrogen.

Supplementary Table 2. Comparison among nomogram model and other existing models for 30-day mortality in MI patients

Author	Year	Model	Disease	Number of subjects	Observed 30-day mortality, %	AUC
Qi Guo et al	2020	Five-factor nomogram	MI	2031	14.9	0.80
Harlan M. Krumholz et al	2015	Twenty-seven variables administrative claims model	Acute MI	140120	18.0	0.71
Sorin J. Brener et al	2019	Eight variables risk score	MI patients after percutaneous coronary intervention	24532	0.5	0.85
Meng H. Hsieh et al	2019	Decision tree model	Acute MI patients after percutaneous coronary intervention	3421	3.7	0.90
Batric Popovic et al	2016	TIMI score	ST elevation MI with left ventricular dysfunction	2486	2.4	0.66
Roni Shouval et al	2017	GRACE score	ST elevation MI	2482	4.5	0.87

MI, myocardial infarction; AUC, the area under the receiver operating characteristic curve; TIMI, Thrombolysis in Myocardial Infarction; GRACE, Global Registry of Acute Coronary Events.

[1] Krumholz HM, Wang Y, Mattera JA, et al. An administrative claims model suitable for profiling hospital performance based on 30-day mortality rates among patients with an acute myocardial infarction. Circulation. 2006;113(13):1683-1692.

[2] Brener SJ, Leon MB, Serruys PW, et al. Derivation and external validation of a novel risk score for prediction of 30-day mortality after percutaneous coronary intervention. EuroIntervention. 2019;15(6):e551-e557.

[3] Hsieh MH, Lin SY, Lin CL, et al. A fitting machine learning prediction model for short-term mortality following percutaneous catheterization intervention: a nationwide population-based study. Ann Transl Med. 2019;7(23):732.

[4] Popovic B, Girerd N, Rossignol P, et al. Prognostic Value of the Thrombolysis in Myocardial Infarction Risk Score in ST-Elevation Myocardial Infarction Patients With Left Ventricular Dysfunction (from the EPHESUS Trial). Am J Cardiol. 2016;118(10):1442-1447.

[5] Shouval R, Hadanny A, Shlomo N, et al. Machine learning for prediction of 30-day mortality after ST elevation myocardial infraction: An Acute Coronary Syndrome Israeli Survey data mining study. Int J Cardiol. 2017;246:7-13.

TRIPOD Checklist: Prediction Model Development

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	5
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5
	5b	Describe eligibility criteria for participants.	5
	5c	Give details of treatments received, if relevant.	NA
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	6
	6b	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	6
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	Explain how the study size was arrived at.	NA
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	6
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	7
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	7
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	7
Risk groups	11	Provide details on how risk groups were created, if done.	7
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	8
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	8
Model development	14a	Specify the number of participants and outcome events in each analysis.	8
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	8
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	9
	15b	Explain how to the use the prediction model.	9
Model performance	16	Report performance measures (with CIs) for the prediction model.	10
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	12
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	10
Implications	20	Discuss the potential clinical use of the model and implications for future research.	11
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	6
Funding	22	Give the source of funding and the role of the funders for the present study.	14

We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.