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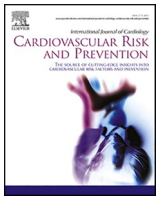

Enhanced predictive performance of the GRACE risk score by incorporating lipoprotein(a) for major adverse cardiac events in acute myocardial infarction patients undergoing PCI

Xuelin Cheng [a,b,1], Ming Liu [a,e,f,1], Qizhe Wang [a,b], Yaxin Xu [a,b], Ru Liu [a,b], Xiaopan Li [a], Hong Jiang [c,d,e,f,**], Sunfang Jiang [a,b,*]

[a] Department of Health Management Center, Zhongshan Hospital, Fudan University, Shanghai, 200032, China
[b] Department of General Practice, Zhongshan Hospital, Fudan University, Shanghai, 200032, China
[c] Department of Cardiology, Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, Shanghai, 200032, China
[d] National Clinical Research Center for Interventional Medicine, Zhongshan Hospital, Fudan University, Shanghai, 200032, China
[e] Innovative Center for New Drug Development of Immune Inflammatory Diseases, Ministry of Education, Fudan University, Shanghai, 201203, China
[f] Shanghai Engineering Research Center of AI Technology for Cardiopulmonary Diseases, Zhongshan Hospital, Fudan University, Shanghai, 200032, China

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ABSTRACT

Background: As scientific research advances, the landscape of detection indicators and methodologies evolves continuously. Our current study aimed to identify some novel perioperative indicators that can enhance the predictive accuracy of the Global Registry of Acute Coronary Events (GRACE) score for the in-hospital major adverse cardiovascular events (MACEs) in patients with acute myocardial infarction.

Methods: A total of 647 adult patients with AMI admitted to the emergency department were consecutively enrolled in the retrospective research starting from June 2016 to September 2019. The endpoint was in-hospital MACE. Stepwise regression analysis and multivariate logistic regression were performed to select the indicators for the union model established by nomogram. Bootstrap with 1000 replicates was chosen as the internal validation of the union model. The area under the receiver operating curve (AUC) and calibration plot were used to evaluate the discrimination and calibration. Decision curve analysis (DCA) was performed to evaluate the clinical sufficiency of the nomogram. Akaike's information criterion (AIC) and Bayesian Information Criterion (BIC) were used to evaluate the goodness of fit.

Results: Lipoprotein(a) combined with serum uric acid, fasting blood glucose, and hemoglobin could improve the GRACE risk score. The AUC of the union model was 0.86, which indicated a better discriminative ability than the GRACE risk score alone (AUC, 0.81; $P < 0.05$). The calibration plots of the union model showed favorable consistency between the prediction of the model and actual observations, which was better than the GRACE risk score. DCA plots suggested that the union model had better clinical applicability than the GRACE risk score.

Conclusion: Lipoprotein(a) has shown promise in augmenting the predictive capability of the GRACE risk score, however, it may be beneficial to integrate it with other commonly used indicators.

1. Introduction

Cardiovascular disease (CVD) stands as a primary contributor to mortality both in China and worldwide, with acute myocardial infarction (AMI) notably on the rise among younger populations [1]. The advent of percutaneous coronary intervention (PCI) has significantly decreased in-hospital mortality rates associated with AMI over the past several decades [2]. However, survivors of AMI confront an

* Corresponding author. Department of Health Management Center, Zhongshan Hospital, Fudan University, Shanghai, 200032, China.
** Corresponding author. Department of Cardiology, Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, Shanghai, 200032, China.
E-mail addresses: shirley17865198205@126.com (X. Cheng), mingliu14@fudan.edu.cn (M. Liu), qizhewang@163.com (Q. Wang), xuyaxin20@fudan.edu.cn (Y. Xu), rliu6510@163.com (R. Liu), xiaopanli0224@126.com (X. Li), jianghong_@fudan.edu.cn (H. Jiang), zsjkglzx@163.com (S. Jiang).
[1] These authors contributed to the work equally and should be regarded as co-first authors.

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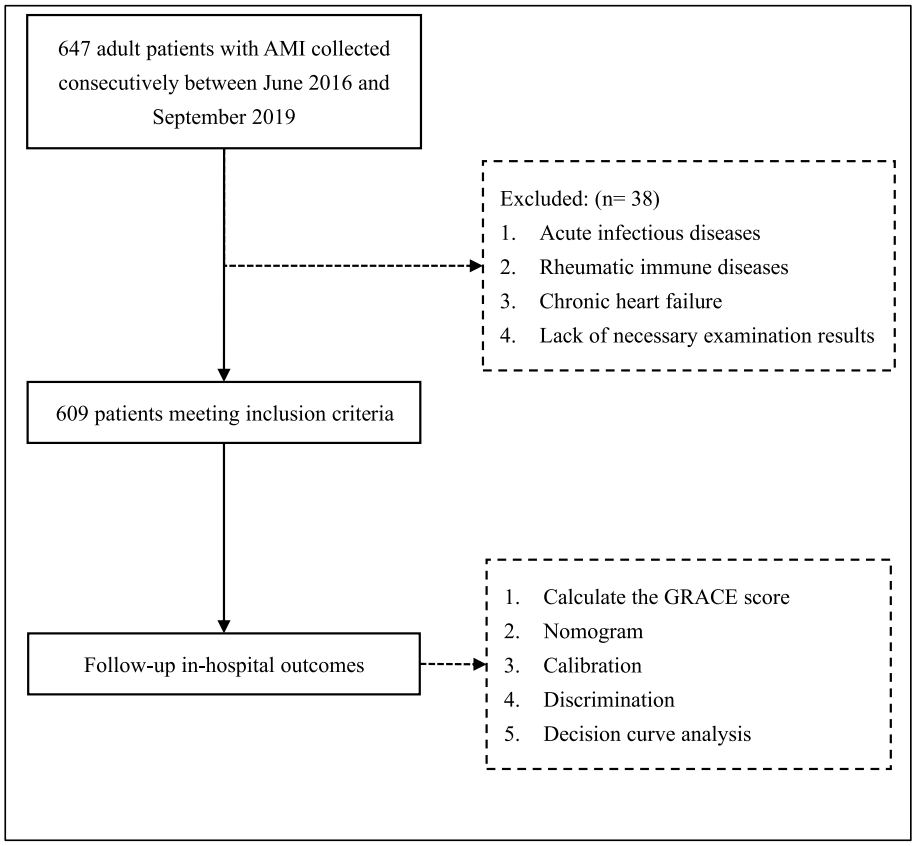

Fig. 1. Flow chart of the study.

increasing risk of subsequent cardiovascular events, including sudden cardiac death, and recurrent myocardial infarction [3].

The Global Registry of Acute Coronary Events (GRACE), launched in 1999, serves as a worldwide initiative aimed at monitoring in-hospital event rates, including death and recurrent myocardial infarction, as well as short-term and long-term prognosis among patients with acute coronary syndrome (ACS) [4]. Since the development of the GRACE risk score model in 2008, its exceptional predictive efficacy has been substantiated by numerous countries and researchers, particularly in comparison to analogous models, for both ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI). Consequently, international guidelines such as those from the European Society of Cardiology (ESC) and the American Heart Association (AHA) strongly advocate for the integration of the GRACE risk score into early risk assessments for AMI patients, serving as a reference for clinical decision-making [5].

The GRACE risk score model encompasses eight major risk factors, including age, heart rate, systolic blood pressure, serum creatinine, Killip class, presence of cardiac arrest at admission, elevated cardiac biomarkers, and ST-segment deviation on electrocardiogram. It primarily relies on vital sign indicators to forecast prognosis [6]. However, as scientific research progresses and technology advances, detection indicators and methodologies undergo continual refinement. Emerging indicators such as high-sensitivity C-reactive protein (hs-CRP), lipoprotein(a), and triglyceride-glucose (TyG) index have demonstrated relevance to myocardial infarction prognosis [7–10]. This study aimed to find potential perioperative indicators that could improve the GRACE risk score, thereby enhancing its ability to predict the short-term prognosis in AMI patients.

2. Methods

2.1. Study population

This was a retrospective and observational research conducted at Zhongshan Hospital of Fudan University in Shanghai, China. A total of 647 adult patients were consecutively enrolled in this research, including STEMI and NSTEMI, from the same medical group. All patients were admitted to the emergency department for AMI from June 2016 to September 2019. Inclusion criteria mandated that patients had their first diagnosis of AMI. Exclusion criteria: (1) chronic heart failure, severe arrhythmia, severe valvular disease, and myocarditis; (2) acute infectious diseases, rheumatic diseases, and hematological disease; and (3) recent major surgery and severe trauma. The sample size was determined using the MedSci Sample Size tools (MSST), with an expected sensitivity of 0.85, an expected specificity of 0.80, an allowable error for sensitivity of 0.05, an allowable error for specificity of 0.05, and α of 0.05 (two-sided test), resulting in a calculated sample size of N = 348.

2.2. Data collection and study variables

Demographic data and baseline characters were obtained from the electronic medical record systems of the hospital, including age, sex, height, weight, blood pressure, heart rates, types of AMI, comorbidities, medical history, biochemical indicators, and GRACE risk score-associated factors. Most of the biochemical indicators were collected promptly upon admission. Blood glucose and glycosylated hemoglobin A1c, total cholesterol, triglyceride, low density lipoprotein cholesterol (LDL-c), and Lipoprotein (a) were tested early in the morning of the second day post-admission, with patients in a fasting state. The GRACE risk score was computed using version 1.0 of the GRACE risk score model app, which incorporates factors such as age, heart rate, systolic

Table 1
Comparison of Characteristics Between the MACE Group and the non-MACE Group.

Characteristics	MACE (n = 70)	non-MACE (n = 539)	*P* value
AMI (STEMI)	42 (60.0 %)	262 (48.6 %)	0.07
Demographics			
Age (year)	72.76 ± 1.16	62.66 ± 1.22	<0.01*
Men (n, %)	55 (78.6 %)	447 (82.9 %)	0.37
clinical data			
BMI (kg/m^2)	23.66 (21.64–26.73)	24.54 (22.60–26.62)	0.05
SBP (mmHg)	124.5 (103.0–144.0)	128.0 (114.0–146.0)	0.04*
DBP (mmHg)	70.0 (64.0–85.0)	77.0 (69.0–88.0)	0.03*
Killip class III/IV	14 (20.0 %)	13 (2.4 %)	<0.01*
LVEF (%)	45.00 (40.00–48.00)	55.00 (49.00–60.00)	<0.01*
Comorbidities			
Diabetes (%)	25 (36.8 %)	134 (24.9 %)	0.04*
Hyperlipidemia (%)	9 (12.9 %)	35 (6.5 %)	0.08
current smoke (%)	22 (31.4 %)	214 (39.7 %)	0.19
Laboratory data			
Hemoglobin (g/L)	125.00 (110.00–140.00)	136.00 (125.00–148.00)	<0.01*
White blood cell (10^9)	10.04 (7.20–12.80)	9.02 (7.22–11.26)	0.06
Platelets count (10^9)	196.50 (156.00–245.00)	206.50 (173.00–248.00)	0.07
Alanine aminotransferase (U/L)	33.50 (22.50–50.00)	32.00 (20.00–48.00)	0.67
Serum creatinine (μmol/L)	106.0 (84.0–145.0)	81.0 (69.0–97.0)	<0.01*
Serum uric acid (mmol/L)	381.0 (337.0–525.0)	342.0 (290.0–401.0)	<0.01*
Fasting blood glucose (mmol/L)	8.10 (6.40–11.70)	6.50 (5.60–8.70)	<0.01*
HbA1c (g/L)	6.60 (5.90–7.30)	6.10 (5.50–6.90)	0.06
Total cholesterol (mmol/L)	3.98 (3.29–4.81)	4.24 (3.59–4.82)	0.23
Triglyceride (mmol/L)	1.15 (0.92–1.50)	1.38 (1.01–1.98)	0.02*
LDL-C (mmol/L)	2.33 (1.70–3.09)	2.41 (1.84–3.05)	0.70
Lipoprotein (a) (nmol/L)	192.0 (99.0–436.0)	139.0 (58.5–294.5)	0.02*
TyG index	8.99 ± 0.68	9.00 ± 0.71	0.93
cTnT (ng/L)	3.49 (1.67–7.92)	1.43 (0.42–3.64)	<0.01*
Albumin (g/L)	37.0 (34.0–40.0)	40.0 (37.0–42.0)	<0.01*
CRP (mg/L)	19.20 (5.00–73.80)	7.00 (2.30–27.80)	<0.01*

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricle ejection fraction; HbA1c, glycosylated hemoglobin A1c; LDL-C, low density lipoprotein cholesterol; TyG, triglyceride glucose; cTnT, cardiac troponin T; CRP, C reactive protein. *$P < 0.05$.

pressure, serum creatinine, Killip class, cardiac enzymes or markers, ST-segment deviation, and the event of cardiac arrest at admission. The app was accessible on the official website (https://www.outcomes-umassmed.org/grace/). The primary endpoint was the occurrence of MACE during the hospitalization period.

Table 2
Univariate and multivariate logistic regression analysis for the risk factors associated with MACEs.

Variable	Univariate analysis			Multivariate analysis		
	OR	95%CI	*P* Value	OR	95%CI	*P* Value
Hemoglobin	0.29	0.17–0.49	<0.001	0.37	0.18–0.77	<0.001
Serum uric acid	2.37	1.86–2.88	<0.001	3.71	1.89–7.28	<0.001
Fasting blood glucose	1.13	1.07–1.19	<0.001	1.13	1.04–1.22	<0.01
Lipoprotein (a)	1.88	1.14–2.63	<0.05	1.01	1.01–1.02	<0.01
the GRACE risk score	1.04	1.03–1.04	<0.001	1.03	1.02–1.04	<0.001

2.3. Clinical definitions

The diagnosis of AMI in this study was based on the fourth universal definition of myocardial infarction [11] that patients should have clinical evidence of acute myocardial ischemia, changes in cardiac troponin (cTn) and at least one of the following: symptoms of myocardial ischemia; new ischemic electrocardiogram (ECG) changes; development of pathological Q waves; imaging evidence; and identification of coronary thrombus (not for types 2 or 3 MIs). The upper reference limit of cardiac troponin T (cTnT) in Zhongshan Hospital was 0.03 ng/ml. We calculated triglyceride-glucose (TyG) index as Ln [triglycerides (mg/dl) * fasting glucose (mg/dl)/2]. MACEs were defined in this study as all-cause death and re-myocardial infarction.

2.4. Statistical analysis

Continuous variables were presented as mean ± SD or medians with interquartile ranges, and categorical variables were expressed as n (%). Differences in baseline characteristics between groups were analyzed using Student's *t*-test and Mann-Whitney *U* tests for continuous variables, and chi-squared test or Fisher's exact for categorical variables, as appropriate.

Stepwise regression analysis was performed first to screen risk factors of MACEs and factors with $P < 0.2$ were further analyzed by multivariate logistic regression. The nomogram was established using the multivariate model including the GRACE risk score. Bootstrap with 1000 replicates was used as the internal validation of the nomogram. The area under the receiver operating characteristic curve (AUC) and calibration were performed to represent the prediction accuracy and prediction consistency of the nomogram model. The AUC of the GRACE risk score model and nomogram model were compared using the Delong method. Decision curve analysis (DCA) was performed to evaluate the validity of the nomogram. Comparison of nested and non-nested models including the GRACE risk score, or its combination with other potential indicators was performed by calculating Akaike's information criterion (AIC) and Bayesian Information Criterion (BIC). All statistical analyses were performed using Stata 17 and R software (version 4.30, www.R-project.org/). All *P*-values were two-sided, and statistical significance was set at $P < 0.05$.

3. Results

3.1. Baseline characteristics

Among the 647 adult patients with AMI enrolled consecutively between June 2016 and September 2019, nine patients were experiencing acute infectious diseases; four patients were inflicted with rheumatic immune disease; 11 patients had chronic heart failure; and 14 patients lacked necessary examination results such as ECG. The remaining 609 patients who met the inclusion criteria were followed up until discharge (Fig. 1).

Of the 609 patients, 70 (11.5 %) MACEs occurred, including 27 (4.4 %) deaths, and 43 (7.1 %) recurrence of myocardial infarction. We assigned included patients into either MACE (70, 11.5 %) or non-MACE (539, 88.5 %) group according to the baseline characteristics which are shown in Table 1. There was no significant difference in the proportions of STEMI and non-STEMI in the two groups (STEMI 60.0 % vs 48.6 %, $P = 0.07$). The mean age of the MACE group was 62.66 ± 1.22 years and the non-MACE group was 72.76 ± 1.16 years ($P < 0.01$). Patients in the MACE group exhibit higher levels of serum uric acid (median, 381.0 vs. 342.0 mmol/L; $P < 0.01$), fasting blood glucose (median, 8.10 vs. 6.50 mmol/L; $P < 0.01$), lipoprotein (a) (median, 192.0 vs. 139.0 nmol/L; $P < 0.05$), and CRP (median, 19.20 vs. 7.00, $P < 0.01$), as well as low levels of hemoglobin (median, 125.0 vs. 136.0 g/L; $P \leq 0.01$), and albumin (median, 30.0 vs. 40.0, $P \leq 0.01$). TyG index (median, 8.99 vs. 9.00 g/L; $P = 0.93$) was not significantly different between the two

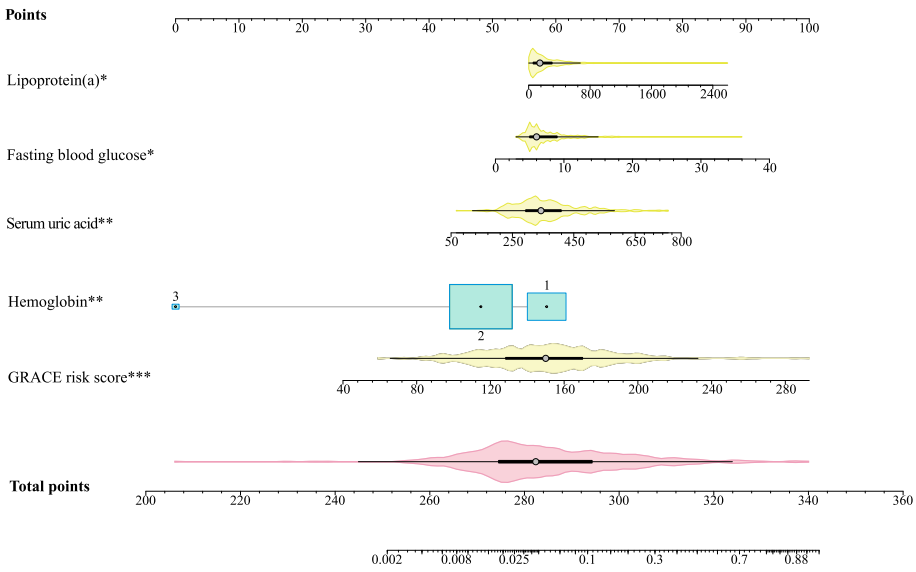

Fig. 2. Nomogram to predict the occurrence of MACEs in the hospital, consisting of GRACE risk score, lipoprotein(a), serum uric acid, fasting blood glucose, and hemoglobin. Hemoglobin: 1, below the lower limit of the medical reference range; 2, Within the normal range of medical reference values; 3, exceed the upper limit of medical reference range.

Table 3
Comparison of prognostic value and goodness-of-fit of the different models.

Model	ROC		Goodness of fit	
	AUC(95%CI)	*P*	AIC	BIC
GRACE risk score	0.81 (0.77–0.89)	Ref.	355.11	363.92
GRACE risk score + Lp(a)	0.83 (0.77–0.89)	0.27	277.90	290.56
GRACE risk score + Hb + UA + FBG	0.83 (0.74–0.88)	0.16	284.76	306.17
GRACE risk score + Lp(a) + Hb + UA + FBG	0.86 (0.79–0.92)	<0.05	224.34	248.99

Lp(a), lipoprotein(a); Hb, hemoglobin; UA, uric acid; FBG, fasting blood glucose; AIC, Akaike's information criterion; BIC, Bayesian Information Criterion.

groups.

3.2. Nomogram development and assessment

Based on the results from Table 1, potential variables were selected for univariate regression analysis and then those with $P < 0.2$ were further analyzed using multivariable regression analysis. Elevated levels of serum uric acid (odds ratio [OR], 3.71; 95%CI, 1.89–7.28; $P < 0.001$), lipoprotein(a) (OR, 1.01; 95%CI, 1.01–1.02; $P < 0.01$), fasting blood glucose (OR, 1.13; 95%CI, 1.04–1.22; $P < 0.01$), and the GRACE score (OR, 1.03; 95%CI, 1.02–1.04; $P < 0.001$)were risk factors for MACEs, and higher levels of hemoglobin (OR, 0.37; 95%CI, 0.18–0.77; $P < 0.001$) served as protective factor (Table 2). A union model based on those four variables and the GRACE risk score was then established to predict the risk of in-hospital MACEs (Fig. 2).

Suppose there is a female patient with AMI who has been admitted to the hospital. Upon admission, the patient's serum uric acid level was measured at 471 μmol/L, lipoprotein(a) level at 170 g/L, fasting blood glucose at 8.0 mmol/L, and hemoglobin at 120 g/L. The patient's GRACE risk score was determined to be 64 points, indicating a low-risk status. The union model yielded a score of 67 points, corresponding to an approximate probability of around 3 % for in-hospital MACE occurrence.

The discrimination was assessed by plotting receiver operating characteristic curves, with AUCs of 0.81, 0.83, 0.83, and 0.86 for the GRACE risk score, GRACE risk score with Lp(a), GRACE risk score with Hb, UA and FBG, and GRACE risk score with Lp(a), Hb, UA, and FBG (union model), respectively (*P*, 0.27, 0.16 and < 0.05; Table 3 and Fig. 3A). The AICs of the four models were 355.11, 277.90, 284.76, and 224.34, and the BICs were 363.92, 290.56, 306.17, and 248.99, respectively (Table 3). The calibration of the union model and GRACE risk score model is shown in Fig. 3C and D. The DCA curves demonstrated the performance of both models in clinical usefulness (Fig. 3B). The net benefit of the union model was greater than the "treat all" and "treat none" strategies. When the risk threshold exceeded approximately 20 %, the net benefit of the union model surpasses that of the GRACE risk score model. When the risk threshold exceeded approximately 50 %, the net benefit of the GRACE risk score model was inferior to the strategy of "treat none".

4. Discussion

In our study, we observed that perioperative indicators like lipoprotein(a) when combined with hemoglobin, fasting blood glucose, and uric acid, could enhance the predictive accuracy of the GRACE risk score for in-hospital MACEs in patients with AMI. The calibration and discrimination of the composite model surpassed that of the GRACE risk score alone.

When the risk threshold surpassed approximately 50 %, the net benefit derived from the GRACE risk score fell short of that from the "treat none" strategy, indicating a possible overestimation of patient risk by the GRACE risk score model. The union model that the GRACE risk score combined with lipoprotein(a), serum uric acid, fasting blood glucose, and hemoglobin, however, could mitigate this deficiency. We found that lipoprotein(a) alone did not significantly enhance the predictive power of the GRACE risk score and must be combined with other common perioperative indicators. The GRACE risk score, established at the onset of the 21st century, should be revitalized as research progresses and testing methodologies evolve.

Lipoprotein(a) is a form of low-density lipoprotein particle that contains apolipoprotein (a) and apolipoprotein B-100 moieties, and it promotes atherosclerosis, thrombosis, and inflammations [12–14]. Lipoprotein(a) levels are primarily genetically determined, and many guidelines and statements consider lipoprotein(a) to be a high-risk factor for cardiovascular disease when its concentration exceeds approximately 100 nmol/L [15–17]. A prospective study involving 10,424

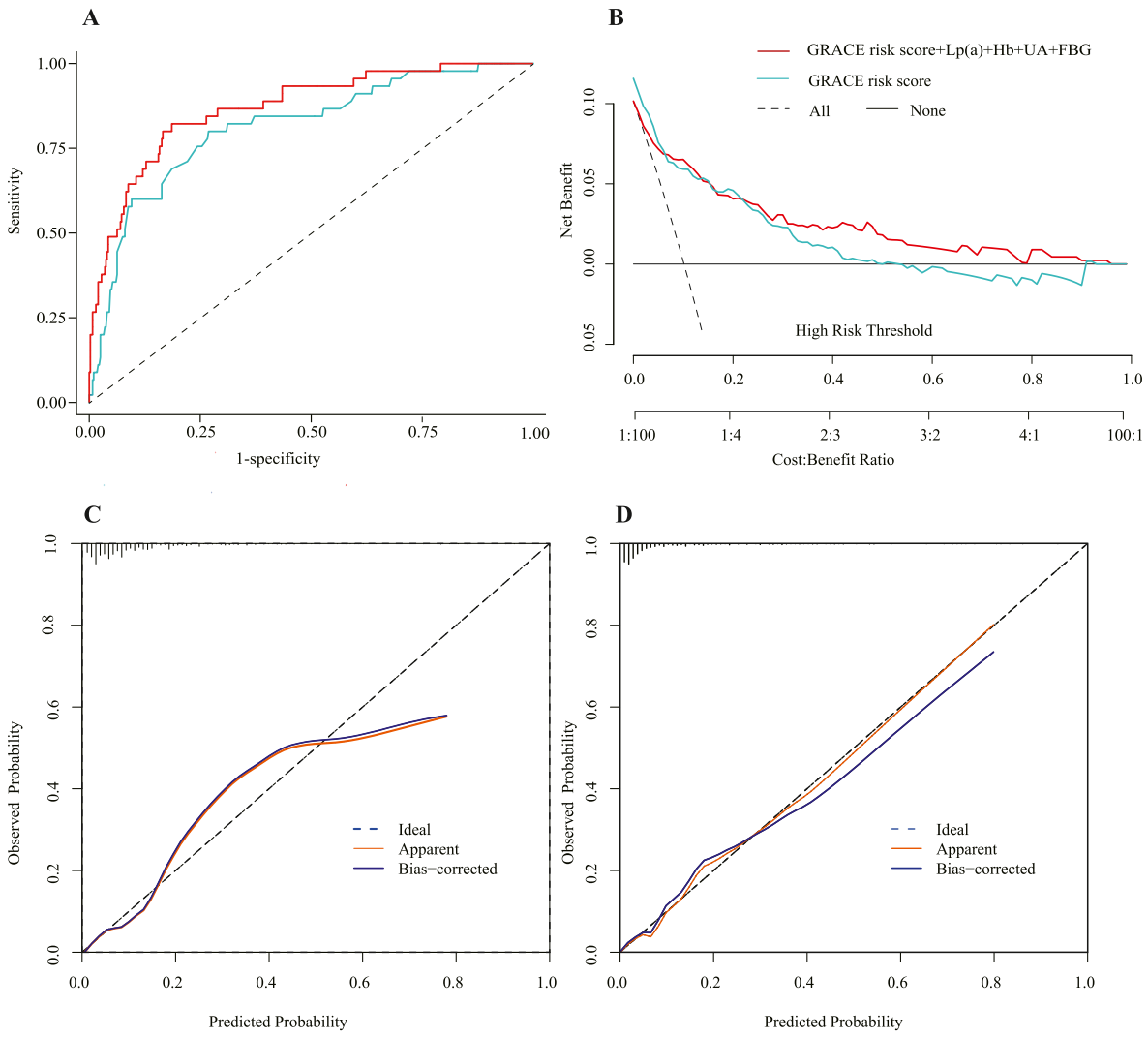

Fig. 3. Receiver operating characteristic (ROC) curves of the GRACE risk score, and GRACE risk score with Lp(a), Hb, UA, and FBG **(A)**, decision curves of the union model and the GRACE risk score **(B)**, calibration plot of the GRACE risk score **(C)** and the union model **(D)**. AUC indicates the area under the curve.

individuals showed that elevated lipoprotein(a) was associated with adverse outcomes in patients with coronary artery disease undergoing PCI [10]. In our study, participants exhibited lipoprotein(a) levels exceeding 100 nmol/L, with those in the MACE group notably surpassing those in the non-MACE group. There are still no effective and widely recognized drugs or methods to lower lipoprotein(a) especially, and further research is needed in the future [14].

Indeed, several studies, akin to our own, have demonstrated a correlation between low hemoglobin levels and adverse outcomes in patients with AMI [18,19]. This association is likely attributable to hemoglobin's vital role in oxygen transport [20,21], suggesting that reduced hemoglobin levels may exacerbate myocardial hypoxia and contribute to poorer outcomes in AMI patients. Serum uric acid levels are associated with endothelial dysfunction, inflammation, and oxidative stress [22], and elevated levels may be linked to adverse outcomes in AMI patients. Additionally, some researchers noted that the GRACE risk score model exhibits improved predictive accuracy for all-cause mortality in AMI patients with high serum uric acid levels [23].

In the current study, we also observed that CRP as well as albumin were significantly different between the MACE and non-MACE groups, both of which are markers associated with inflammation. CRP is an acute-phase inflammatory response biomarker, which is an independent prognostic marker of poor outcomes in patients with AMI [7,24,25]. Serum albumin has some physiological properties, including anti-inflammatory, antioxidant, anticoagulant, and anti-platelet aggregation activities, which may be related to cardiovascular diseases [26,27]. This study showed that either CRP or albumin alone could serve as predictors of AMI prognosis. However, interestingly, the significance of risk assessment appears to diminish when both factors are explored simultaneously, which is similar to other studies [27].

This study is subject to several limitations. Firstly, due to the difficulty in obtaining external cohort data, external validation couldn't be performed. However, internal validation was conducted diligently, and we compared the performance of the union model with the GRACE risk score model in terms of discrimination and clinical application. Secondly, considering the differing evaluation criteria and performance of the GRACE risk score model between short-term and long-term prognosis prediction in patients with AMI, ongoing patient follow-up is necessary to evaluate the union model's ability to predict long-term prognosis accurately.

In conclusion, this study establishes a composite model based on the GRACE risk score model, incorporating lipoprotein(a), serum uric acid, fasting blood glucose, and hemoglobin. It could predict in-hospital MACE occurrence in patients with AMI more effectively than the GRACE risk score model alone, particularly in identifying high-risk individuals.

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Ethics approval

This research involves human participants and was approved by the ethics committee of Zhongshan Hospital of Fudan University (B2021-219). All participants gave informed consent at admission.

CRediT authorship contribution statement

Xuelin Cheng: Writing – original draft, Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Ming Liu:** Writing – original draft, Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Qizhe Wang:** Data curation. **Yaxin Xu:** Data curation. **Ru Liu:** Data curation. **Xiaopan Li:** Methodology. **Hong Jiang:** Writing – review & editing. **Sunfang Jiang:** Funding acquisition.

Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

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