A New Predictive Model for In-Hospital Major Adverse Cardiac and Cerebrovascular Events in Chinese Patients After Major Noncardiac Surgery

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Prediction tools focused on cardiovascular and cerebrovascular events after noncardiac surgery are lacking, particularly for Chinese patients. We developed and validated what we believe is a new predictive tool for postoperative major cardiovascular and cerebrovascular events (MACCEs) in Chinese patients in this study. Overall, 401 variables derived from 598 patients who received noncardiac surgery at our center were retrospectively analyzed to develop and validate the new predictive model for MACCEs during hospitalization. The 7 strongest predictors for MACCEs in the development cohort were chronic heart failure, age, atrial fibrillation, general anesthesia, history of coronary heart disease, high-risk procedures, and lymphocyte count. The area under the receiver operating characteristic curve was 0.698 (95% confidence interval 0.616 to 0.780) for the new predictive tool with the validation cohort. Receiver operating characteristic curve analysis showed the new predictive tool had better performance than the Revised Cardiac Risk Index and the American College of Surgeons National Surgical Quality Improvement Program scores. This new predictive tool is effective for the prediction of postoperative MACCEs in patients who undergo noncardiac surgery. **(Am J Cardiol 2022;00:1−7)**

Introduction

With the aging population and continuous advances in medical technology, patients are increasingly who underwent noncardiac surgery.[1] Moreover, the total number of patients who undergo major noncardiac surgery and those with cardiac complications is still increasing.[2] Accordingly, it is important to evaluate the risk of major adverse cardiovascular and cerebrovascular events (MACCEs) for patients scheduled for noncardiac surgeries. Guidelines recommended 3 risk prediction tools to predict the risk of perioperative major adverse cardiovascular events in patients who undergo noncardiac surgery,[3−5] including the Revised Cardiac Risk Index (RCRI), American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) Myocardial Infarction and Cardiac Arrest, and ACS NSQIP surgical risk calculator. These predictive tools are focused on adverse cardiovascular events, not cerebrovascular events. The RCRI was developed in 1999, and its predictive efficacy has been questioned.[6,7] NSQIP Myocardial Infarction and Cardiac Arrest only estimates myocardial infarction and cardiac arrest, which limits its application. Research showed that it also underestimates the actual risk.[8] The ACS NSQIP calculator may be too complicated to use in clinical settings.[9,10] Furthermore, the above predictive tools were mostly developed and validated in patients from Western countries. Therefore, in this study, we developed and validated a new predictive tool for postoperative MACCEs based on Chinese patients who underwent noncardiac surgeries and compared its predictive efficacy with the RCRI and ACS NSQIP scores.

Methods

We performed a single-center retrospective study including patients aged ≥18 years who underwent noncardiac surgeries at Beijing Chao Yang Hospital from January 1, 2018 to April 1, 2022. The study was conducted in accordance with the principles of patient research stipulated in the Declaration of Helsinki, and the study protocol was approved by the ethics committee of Beijing Chaoyang Hospital (2021-S-476). All data were anonymous, and the need for informed consent was waived owing to the retrospective study design. Excluded from the study were (1) patients who received low-risk procedures including breast surgery, dental surgery, endoscopic procedures, ophthalmic surgery, gynecological surgery, and plastic surgery,[11] or emergency surgery, transplantation, and trauma; (2) patients with American Society of Anesthesiologists (ASA) classification V or VI; (3) patients receiving palliative surgery for advanced malignant tumors; (4) patients with cardiomyopathy or congenital heart disease; (5) patients with a history of surgery within 4 months before inclusion; or (6) patients with incomplete data for the calculation of RCRI and ACS NSQIP scores.

The eligible patients were divided into development and validation cohorts based on the time of admission (dates of

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January 1, 2018 to January 1 2020 for development cohort and dates of January 2, 2020 to April 1, 2022 for validation cohort). Preoperative and intraoperative variables and clinical characteristics were extracted and analyzed from the medical charts. The putative predictors were chosen on the basis of previous studies and the clinical experiences of the investigators.

The primary outcome measure was MACCEs after surgery during hospitalization. MACCEs were defined as a composite outcome including all-cause death, acute myocardial infarction, heart failure, ventricular fibrillation, complete heart block, cardiac arrest, and ischemic stroke.

SPSS 23.0 for windows and R version 4.0.2 were used for data analysis. Continuous variables conforming to a normal distribution were presented as mean ± SD, and continuous variables not conforming to a normal distribution were presented as the median and interquartile range. Categorical variables were summarized as absolute values and percentages. To compare the differences between the 2 groups, the *t* test with normal distribution data, Mann-Whitney *U* test with tilt data, and chi-square test with classified data were applied separately. We used the adaptive least absolute shrinkage and selection operator to identify independent factors and to create the model for MACCE prediction after noncardiac surgeries. The final model was presented as a nomogram. We applied the receiver operating characteristic (ROC) curve to calculate the sensitivity and specificity of the model. The calibration plot was derived based on regression analysis. The areas under the ROC curves (AUCs) of the new prediction model, RCRI, and ACS NSQIP surgical risk calculator were calculated separately to compare the predictive efficacies of the 3 models in the validation cohort. The differences in the AUCs were also compared using the DeLong test. We used a random forest model to predict missing values. p Values were 2-sided, and $p < 0.05$ was identified as statistically significant.

Table 1
Demographics and baseline characteristics of the patients in the development and validation cohort

Characteristics	Development cohort	Validation cohort	$\chi 2$/Z value	p value
Men	186 (54.2)	123 (48.2)	2.103	0.147
Age (years)	65 (21)	71 (21)	−3.96	0.000
HLP	120 (35)	57 (22.4)	11.201	0.001
HBP	154 (44.9)	146 (57.3)	8.933	0.003
Stroke/TIA	49 (14.3)	44 (17.3)	2.415	0.299
Insulin treatment	26 (7.6)	34 (13.3)	5.363	0.021
CHF	9 (2.6)	13 (5.1)	4.703	0.095
AF	15 (4.4)	32 (12.5)	13.501	0.000
CAD	64 (18.7)	51 (20)	0.169	0.681
Chronic respiratory disease	24 (7)	18 (7.1)	0.745	0.689
Disseminated cancer	17 (5)	12 (4.7)	0.020	0.888
Current smoker within 1 year	88 (25.7)	53 (20.8)	1.926	0.165
High-risk type of surgery	140 (40.8)	110 (43.1)	0.324	0.569
General anesthesia	246 (71.7)	143 (56.1)	15.740	0.000
Cr > 2.0 mg/dL	10 (2.9)	9 (3.5)	0.919	0.632
Dialysis	3 (0.9)	5 (2.0)	1.307	0.253
PLT	218 (91)	195 (92)	−3.010	0.003
Neutrophil count	4.3 (3)	4.12 (3)	−0.055	0.956
Lymphocyte count	1.47 (1)	1.43 (1)	−1.506	0.132
N/L%	2.89 (3)	2.81 (4)	−0.790	0.429
ST-T changes on ECG	72 (21)	80 (31.4)	14.596	0.001
VHD	11 (3.2)	17 (6.7)	4.010	0.135
ASA class				
1	40 (11.7)	17 (6.7)	4.232	0.040
2	238 (69.4)	150 (58.8)	7.164	0.007
3	63 (18.4)	77 (30.2)	11.413	0.001
4	1 (0.3)	11 (4.5)	12.719	0.000
MACCEs				
AMI	13 (3.8)	7 (2.7)	0.494	0.482
HF	26 (7.6)	31 (12.2)	3.553	0.059
Death	12 (3.5)	14 (5.5)	1.395	0.238
Stroke	8 (2.3)	10 (3.9)	1.265	0.261

Data presented as mean (standard deviation) for continuous variables or n (%) for counting data. High-risk surgeries included intraperitoneal, intrathoracic or suprainguinal vascular procedures according to the modified RCRI score.

AF = atrial fibrillation; CAD = history of coronary heart disease; CHF = chronic heart failure; Cr > 2.0mg/dL = preoperative serum creatinine > 2.0 mg/dL; ECG = electrocardiogram; HBP = high blood pressure; HF = heart failure; HLP = hyperlipidemia; MACCEs = major adverse cardiovascular and cerebrovascular events; N/L% = neutrophil to lymphocyte ratio; PLT = platelets; VHD = valvular heart disease.

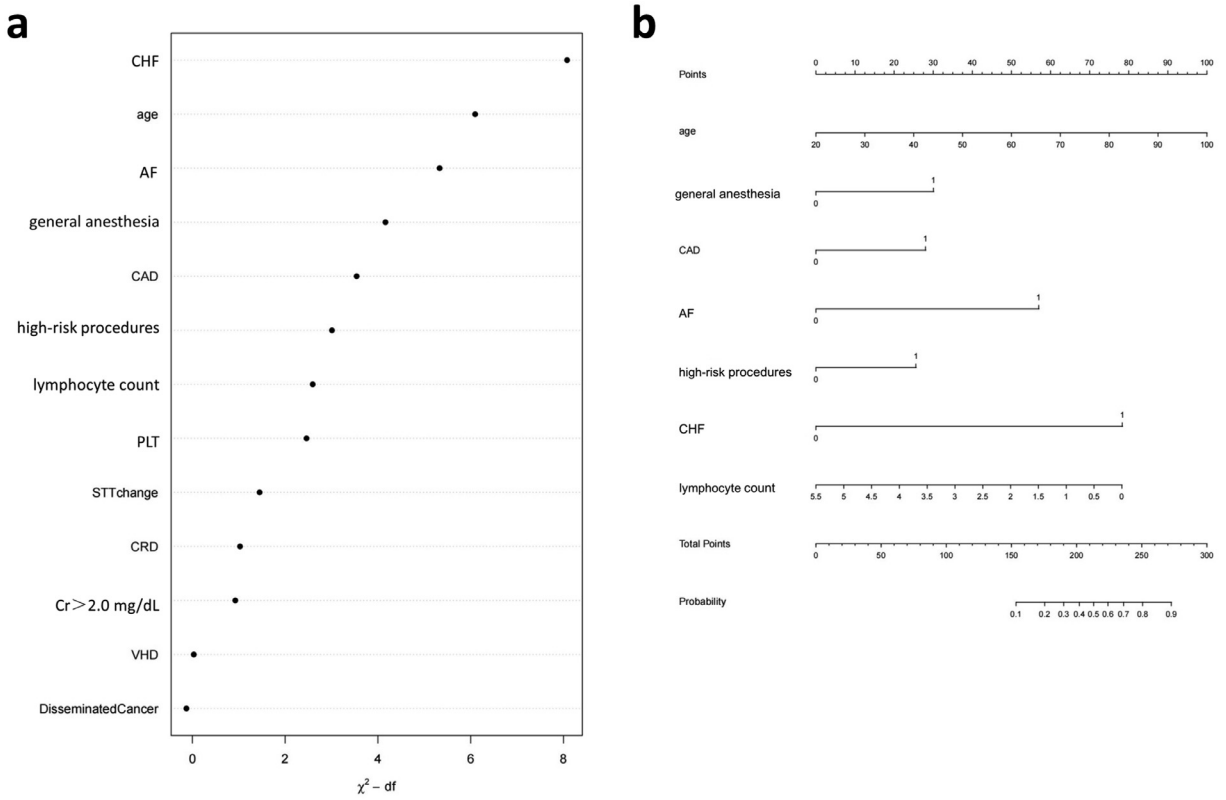

Figure 1. Importance and the nomogram of variables of the prediction model. (*A*) Images indicating the importance of each variable in the full model as measured with the partial Wald chi-square minus the predictor degrees of freedom; (*B*) Images indicating the nomogram for each variable of the prediction model. Cr = creatinine**;** PLT = platelets.

Results

From January 1, 2018 to April 1, 2022, a total of 25,969 surgeries were performed in our hospital, and 14,124 cases were excluded according to the predefined criteria. In the remaining 11,845 cases, MACCEs occurred in 124 cases. In the 124 cases, 18 cases were excluded for the following reasons: 1 patient died unexpectedly because of an unrelated accident; 8 patients were classified as ASA grade 5; and 9 patients received advanced palliative surgery for malignant tumors. Matched by the surgery type, 492 patients with no events after noncardiac surgeries were randomly selected, resulting in a total of 598 patients in this study (Supplementary Figure 1). These patients were divided into development and validation cohorts based on the dates of admission. The baseline characteristics of patients from the 2 cohorts are shown in Table 1.

The new risk score was developed based on 343 patients (55 with MACCEs) in the development cohort. We evaluated 401 variables, including clinical variables, electrocardiogram ST-T ischemic changes, cardiac ultrasound parameters, and laboratory tests, to construct a new model. Using Lasso logistic regression, we screened 13 predictors from the 401 potential variables. The predictors were history of chronic heart failure (CHF), age, atrial fibrillation (AF), general anesthesia, history of coronary heart disease (CAD), high-risk procedures, lymphocyte count, platelet count, ST-T ischemic change of electrocardiogram, chronic respiratory disease, serum creatinine >2.0 mg/100 ml (creatinine >2.0 mg/100 ml), valvular heart disease, and disseminated cancer. The weights of all predictive variables are shown in Figure 1. Only the 7 strongest predictors (CHF, age, AF, general anesthesia, history of CAD, high-risk procedures, and lymphocyte count) based on the likelihood ratio were selected and used to construct the final model. Integrating the 7 variables, we were able to build a nomogram for predicting in-hospital MACCEs in patients who underwent major noncardiac surgery (Figure 2). The sum of the corresponding scores of each variable in the nomogram is the total score of the patient, and a vertical line is made at the total score. The corresponding prediction probability is the perioperative incidence of MACCE in the patient with noncardiac surgery. The regression equation of the new prediction model is the following: L = age + CHF × 2.872/0.043 + AF × 2.116/0.043 + general anesthesia × 1.809/0.043 + history of CAD × 1.080/0.043 + high-risk procedures × 0.905/0.043 − lymphocyte count × 0.499/0.043. Multivariate logistic analysis of risk factors for perioperative MACCE is shown in Table 2.

The ROC curve for the new risk score is shown in Figure 2. The AUC was 0.804 (95% confidence interval 0.737 to 0.871). The calibration plot for the new prediction model is shown in Figure 2.

We validated the new risk score in the validation cohort. The ROC curves are shown in Figure 3**,** and the AUC was 0.698 (95% confidence interval 0.616 to 0.780) for the

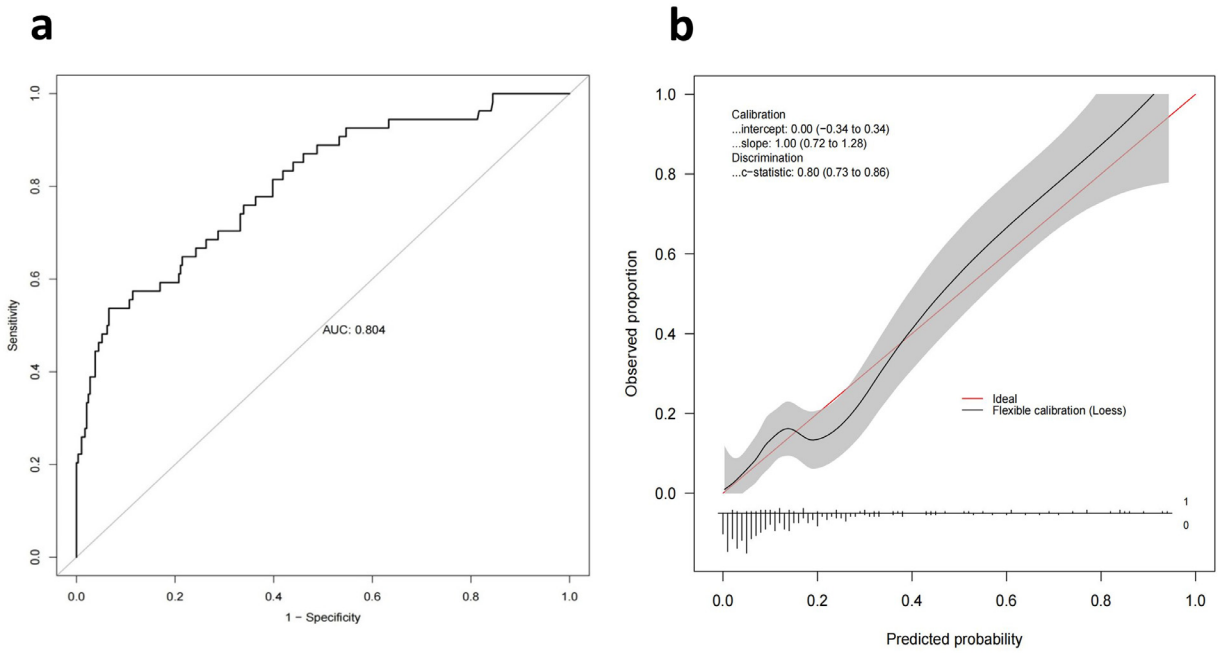

Figure 2. ROC curves and calibration plots for the new prediction model in the development cohort. (*A*) ROC curves of the new prediction model with the development cohort; (*B*) Calibration plots for the new prediction model.

validation cohort. The calibration plot for the new prediction model is shown in Figure 3, and the Brier score was 0.122.

Because the end point of the RCRI does not include ischemic stroke, we removed 10 cases with ischemic stroke as the end point in the validation cohort. The final 245 cases (41 cases with MACCE and 204 cases without MACCE) were subjected to subgroup analysis. Comparisons between the new risk score and RCRI with AUCs are presented in Figure 4, which showed a better predictive efficacy for the new risk score than that of the RCRI.

The end point of ACS NSQIP calculator also does not include cerebral infarction, so we also removed 10 cases in the validation cohort with cerebral infarction as the end point. In contrast, because the ACS NSQIP calculator does not include the operation type for 32 cases in the validation cohort, the actual number of cases analyzed in the comparison between the new risk score and the ACS NSQIP calculator was 213 (36 cases with MACCE and 177 cases without MACCE). Comparisons between the new risk score and the ACS NSQIP calculator with AUCs are presented in Figure 4, which revealed a better predictive efficacy for the new risk score than that of the ACS NSQIP calculator.

Discussion

In this study, we developed and validated what is, to the best of our knowledge, a new risk score for the prediction of MACCEs in patients who underwent major noncardiac surgery. The results showed that the new risk score based on 7 variables (history of CHF, age, AF, general anesthesia, history of CAD, high-risk procedures, and lymphocyte count) was associated with better predictive performance than that of the RCRI and ACS NSQIP scores for MACCEs after noncardiac surgery. The predictive efficacy of the new risk score was further validated in an independent cohort. Taken together, these results suggested that the nomogram showed satisfactory discriminative ability in development and validation cohorts comprising Chinese patients receiving noncardiac surgery.

Table 2
Multivariate logistic analysis of risk factors for perioperative MACCE

Variables	B	SE	Wald	p value	OR	95% CI
Age	0.043	0.016	7.145	0.008	1.044	1.012−1.077
CHF	2.872	0.895	10.305	0.001	17.679	3.061−102.119
AF	2.116	0.666	10.092	0.001	8.301	2.249−30.632
General anesthesia	1.089	0.491	4.919	0.027	2.972	1.135−7.782
History of CAD	1.080	0.397	7.420	0.06	2.945	1.354−6.408
High-risk procedures	0.905	0.390	5.388	0.020	2.473	1.151−5.312
Lymphocyte count	−0.499	0.289	2.987	0.044	0.607	0.345−1.069
Constant	−5.701	1.443	15.067	0.000	0.003	

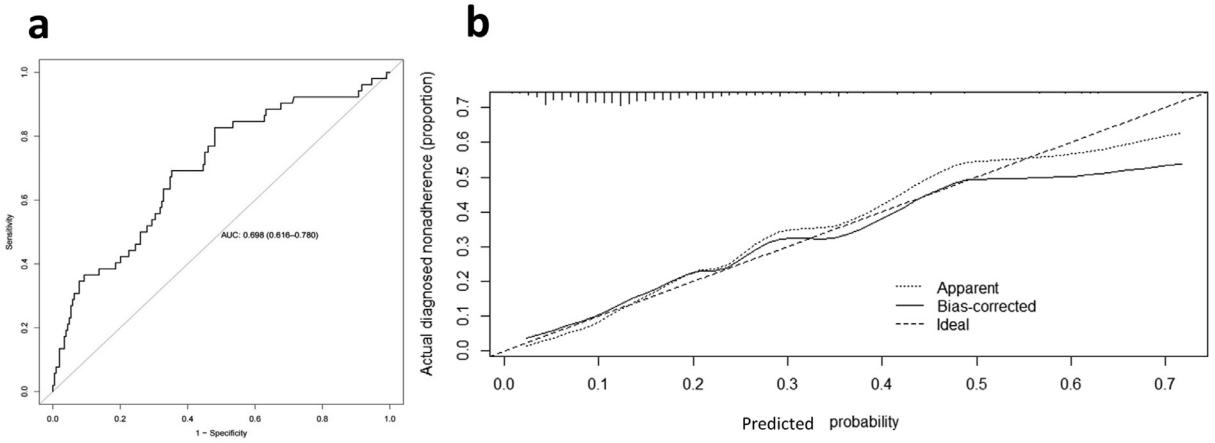

Figure 3. Calibration plots for the new prediction model in the validation cohort. (*A*) ROC curves of the new prediction model with the validation cohort; (*B*) Calibration plots for the new prediction model with the validation cohort.

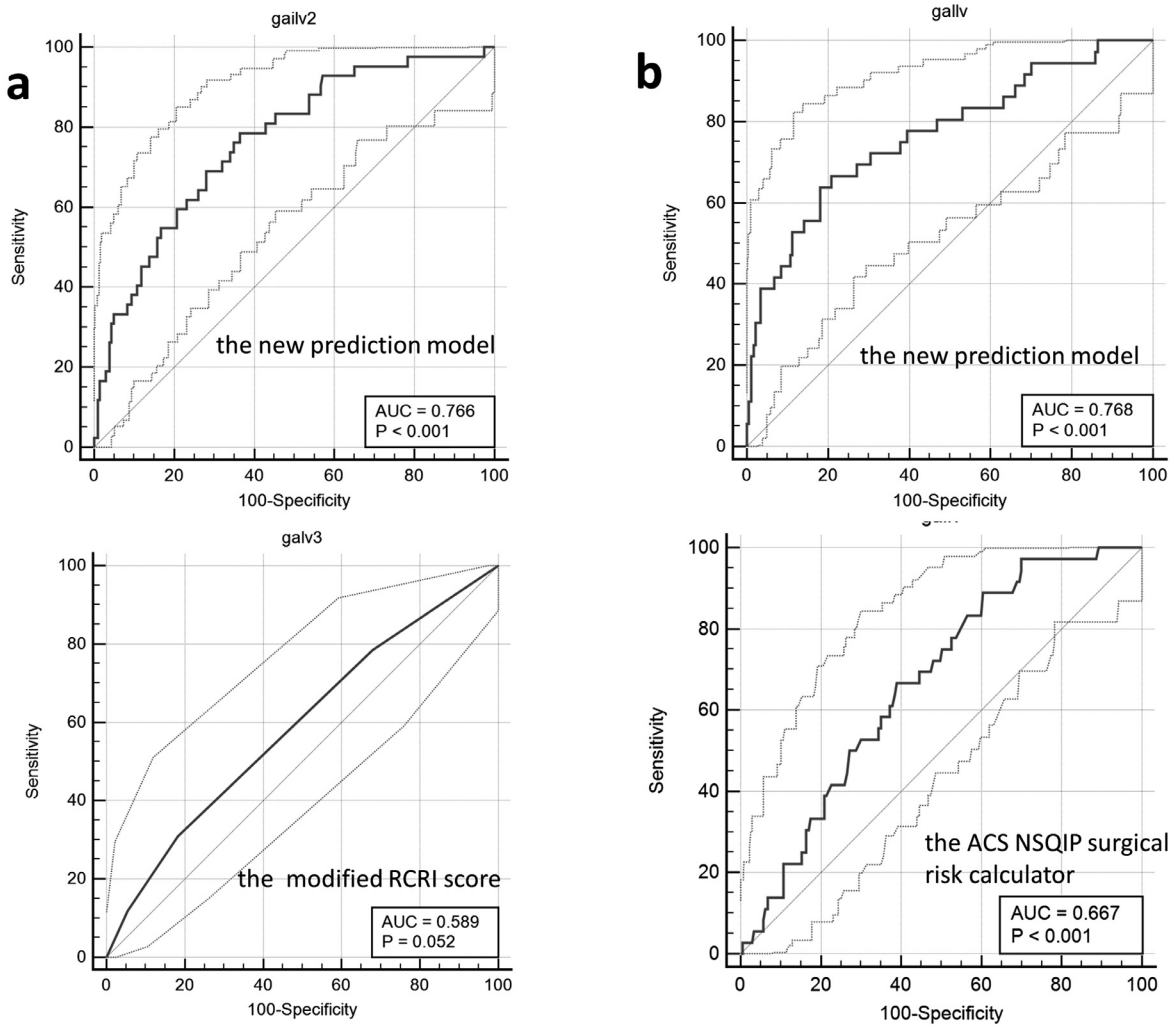

Figure 4. ROC curves for the efficacy of the new prediction model, the modified RCRI score, and the ACS NSQIP surgical risk calculator. (*A*) ROC curves for the efficacy of the new prediction model and the modified RCRI score in the subgroup analysis; (*B*) ROC curves for the efficacy of the new prediction model and the ACS NSQIP surgical risk calculator in the subgroup analysis.

The results of the study showed that a history of CHF, age, general anesthesia,[12–14] history of CAD, high-risk procedures, and lymphocyte count[15–17] were common risk factors related to MACCEs. Notably, the clinical implications of preoperative AF are being recognized.[18] Recent studies have shown that preoperative AF is an independent risk factor for MACCEs, and postoperative cardiovascular events such as heart failure and stroke are more common in patients with a preoperative history of AF who undergo noncardiac surgery[19–21] than in those without a history of AF.

Several risk factors that were identified in other risk prediction models, including ASA class, diabetes, current smoking status, and body mass index, were also included and analyzed in our study, but were not correlated with complications in our study. The absence of these factors in our risk score should not be considered an indication that these factors are not significantly correlated with postoperative MACCEs in other populations.

The nomogram had higher accuracy and better clinical practicability than did the RCRI and the ACS NSQIP surgical risk calculator. The RCRI was developed early. Its ability to predict perioperative MACCEs in modern noncardiac surgery is limited. The ACS NSQIP calculator did not show better discrimination ability or clinical practicability than that of the new prediction model, possibly owing to differences in nationality, disease type, disease characteristics, medical technology, and surgical methods. Serious complications in the ACS NSQIP calculator include, but are not limited to, the end point of our study, which may be another reason for the better predictive ability of our risk score.

The advantages of this new risk score mainly include the simple and practical use. Firstly, it can be immediately implemented in clinical settings using the nomogram. Secondly, surgical details were not part of the new risk score, unlike the ACS NSQIP calculator. Another advantage of the new prediction model is that it is based on data for the Chinese population. China has a large population and a large volume of surgeries, but there is no risk prediction tool based on Chinese patients. It is hoped that the construction of our prediction model can provide an effective prediction tool for Chinese patients and surgeons.

This study was not a multicenter study, which limited the generalization of its results. External validation is still needed to ensure the generality of the model. Furthermore, the study is subject to the limitations of a retrospective review. Some biomarkers that may have predictive ability could not be systematically monitored during the perioperative period and therefore could not be incorporated into this model. Consequently, further prospective studies are needed. Another limitation of our study was that the influence of preoperative prophylactic measures on the outcome of MACCE was not analyzed, which may also affect the predictive efficacy of the new model.

In conclusion, we developed, validated, and calibrated a new nomogram to predict MACCEs after major noncardiac surgery using data for Chinese patients. The risk predictors of the nomogram were history of CHF, age, AF, general anesthesia, history of CAD, high-risk procedures, and lymphocyte count. Using a cohort of Chinese patients, our evaluation score showed better discrimination and practicability than those of the RCRI and the ACS NSQIP calculator. Taken together, although further validation is needed, this risk score may become an effective assistant and informed consent tool for clinical decision-making regarding patients with noncardiac surgery.

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Author Contributions

Xuejiao Wua and Xinchun Yang conceived and designed this study. Xuejiao Wua and Mei Hua collected the data. Xuejiao Wua and Kuibao Lib performed statistical analysis and interpretation of data. Xuejiao Wua wrote the manuscript. Jianjun Zhanga, Kuibao Lib, and Xinchun Yang revised the manuscript. All authors read and approved the final manuscript.

Disclosures

The authors have no conflicts of interest to declare.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author (Dr. Yang). The data are not publicly available because they contain information that could compromise research participant privacy/consent.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.09.028.

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