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Article

Development and Validation of a Novel Nomogram for Predicting Perioperative Acute Kidney Injury Following Isolated Off-Pump Coronary Artery Bypass Grafting Surgery

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Abstract

Background: The aim of this work was to create a novel model for predicting acute kidney injury (AKI) after off-pump coronary artery bypass graft (OPCABG). **Methods**: The individuals who underwent OPCABG were randomly separated into a derivation group and a validation group, at a 7:3 ratio. The primary outcome was AKI under the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. To optimize feature selection and construct a nomogram, both least absolute shrinkage and selection operator regression (LASSO) and logistic regression analysis were utilized. The nomogram was assessed in various ways: with the C-index, calibration curve, decision curve analysis (DCA), and clinical impact curve analysis (CICA). **Results**: The use of an intra-aortic balloon pump (IABP), systolic blood pressure, smoking and baseline serum creatinine were identified as independent impact factors. The C-index of the nomogram was 0.733 (95% confidence interval (CI) = 0.669–0.791) and 0.786 (95% CI = 0.693–0.878) in the training and validation groups, respectively. The area under the curve (AUC) of the internal validation was 0.715 using bootstrapping with 1000 replicates. The calibration plot revealed that the predicted outcomes aligned well with the observations. DCA and CICA suggested that the model had clinical benefit. **Conclusion**: The nomogram that relied on clinical characteristics proved to be a dependable instrument to predict AKI after OPCABG. This model is conveniently applicable in clinical settings and will be a valuable resource for assessing timely medical measures to mitigate risk.

Keywords

off-pump coronary artery bypass grafting; prevention; acute kidney injury; nomogram

Introduction

The survival rates of individuals with coronary artery disease or myocardial infarction can be enhanced by undergoing coronary artery bypass graft (CABG) [1]. Acute kidney injury is frequently observed as a complication of CABG. Around 30% of patients who undergo CABG surgery develop acute kidney injury (AKI), up to 2% of whom require hemodialysis [2]. Patients with AKI, even of moderate grades, tend to have several adverse consequences [3–5]. Currently, in addition to continuous renal replacement therapy as a supportive measure [6], a variety of approaches (statins [7], fenoldopam [8], and remote ischemic preconditioning (RIPC) therapy [9]) have been proposed for postoperative AKI. Most of these strategies still require large-scale intervention experiments to prove their effectiveness [10]. Furthermore, AKI occurs soon after surgery (typically within the first 6 hours), which means that doctors have a short time to intervene [11]. This emphasizes the critical need for early screening to distinguish patients at high risk and to optimize perioperative care in everyday clinical practice [12].

Clinicians still face challenges even if they diagnose post-CABG AKI before loss of function occurs. Serum creatinine (Scr) does not sensitively detect kidney damage [13]. In recent years, a new approach has been tried for the early detection of AKI, which involves identifying biomarkers in blood or urine. These biomarkers are informative only a few hours before Scr is, and some of them are also affected by other conditions, leading to false-positive results [14]. Moreover, it is necessary to investigate whether the early detection of high-risk patients through the use of biomarkers can lead to improved patient outcomes or reduce the burden on the healthcare system [15].

A clinical risk model that relies on the patient's characteristics and clinical data accessible during the perioperative period can assist in clinical decision-making and optimizing treatment. Several renal risk-prediction scores have been published, such as the Cleveland Clinic score [16], Mehta

score [17], and a newly published model by Li *et al*. [18]. Each is limited by some factors. First, the incidence of AKI risk differs between various surgeries, so a model needs to aim at a group of patients for a particular surgical procedure [3,19]. Second, the multicollinearity between candidate independent variables is still a problem, and the models have not been calibrated and fit [20]. Third, race and sample source are still pivotal factors which indicates that models developed in Western populations would be challenging to adapt to Chinese patient populations [21]. There is no consensus scoring system to predict post-CABG AKI [22].

The purpose of developing off-pump CABG (OPCABG) was to prevent the possible risks associated with the utilization of cardiopulmonary bypass (CPB) during myocardial revascularization. The controversy surrounding the potential improvement of the outcome of CABG through the utilization of the off-pump persists [23]. Numerous studies have shown that off-pump CABG greatly diminishes the occurrence of postoperative AKI in comparison with OPCABG [24]. It is necessary to conduct a separate analysis of AKI after OPCABG.

Nomograms are a dependable visual scoring tool that can accurately predict postoperative complications [25]. Nomograms can assist clinicians in early detection and optimizing the management of higher risked individuals.

Materials and Methods

Study Population

We included individuals ≥18 years of age who were confirmed to have left main artery disease or severe triple branch disease by coronary angiography and needed simple OPCABG at The First Affiliated Hospital of Guangxi Medical University, China between January 2012 and December 2022. Patients with the following criteria were excluded: (1) Preexisting end-stage kidney disease; (2) Incomplete clinical data; (3) Scr concentration >1.5 mg/dL before surgery [26]. Fig. 1 displays the flow chart outlining the process of including and excluding patients.

This research complied with the Declaration of Helsinki and was conducted in accordance with the approval of the Ethics Committee at The First Affiliated Hospital of Guangxi Medical University (approval number: 2023-E480-01).

Data Collection

The data collected consisted of demographic characteristics, comorbidities, preoperative laboratory values, preoperative imaging characteristics, and operative and postoperative variables. The preoperative variables included demographic (sex, age, nation, blood pressure, heart rate, height, weight, body mass index, smoking, drinking), baseline renal function (Scr and Creatinine clear rate (Ccr)), comorbidities (diabetes mellitus, hypertension, previous myocardial infarct, peripheral vascular disease *etc*.), urine indicators (proteinuria, specific gravity and urinary potential of hydrogen (pH) value), cardiac function (aortic inner diameter, left ventricular diastolic dimension, left ventricular systolic diameter, left atrial diameter, ejection fraction, cardiac output, use of intra-aortic balloon pump (IABP) and left main stenosis >50%), and laboratory variables (hemoglobin, platelet count, neutrophil count, lymphocyte count, serum albumin, sodium, calcium, creatine kinase-MB, prothrombin time, fibrinogen, thrombin time, urea, Cystatin C (CysC)). Echocardiography was used to evaluate cardiac parameters before the operation. The intraoperative variables included red blood cell transfusion, plasma transfusion, dosage of adrenaline, dosage of norepinephrine, number of bridging vessels and operation time. Early postoperative variables included the dosage of levosimendan, dosage of natriuretic peptide, leukocyte count, hemoglobin, neutrophil count and lymphocyte count (within twenty-four hours postoperatively).

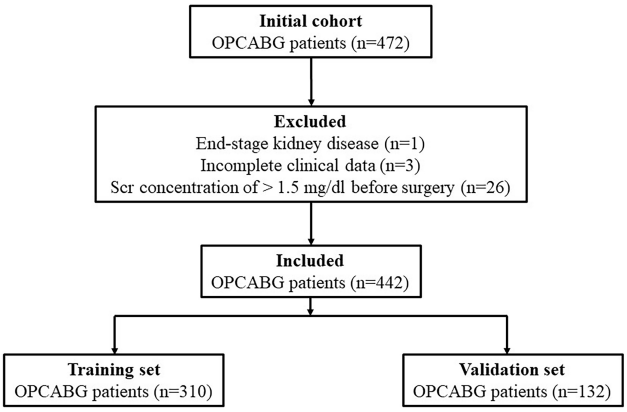

Fig. 1. Flow diagram of participant selection. Scr, serum creatinine; OPCABG, off-pump coronary artery bypass graft.

Definition

According to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, AKI was defined as either an increase in Scr by ≥0.3 mg/dL within forty-eight hours or an increase in Scr to ≥1.5 times the baseline level within seven days [27].

Statistical Analyses

Continuous variables are shown as average (SD) or median (interquartile range) and were analyzed using Student's *t* test or the Mann Whitney test. Categorical variables are shown as number (percentage), and were analyzed using the chi-square test or Fisher's exact test.

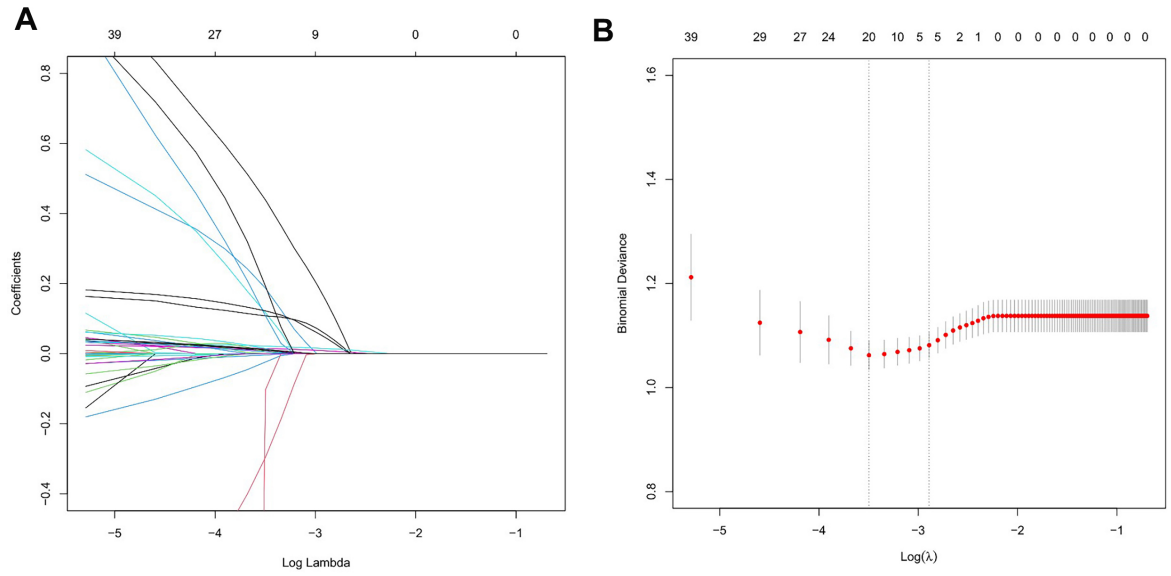

Fig. 2. Variable selection using least absolute shrinkage and selection operator (LASSO) regression. (A) Coefficient distribution map for the log λ sequence. (B) Cross validation plot for the penalty term.

The participants were allocated into a training group and a validation group using a random number generator, with a ratio of 7:3. A derivation set was utilized to build the nomogram, and the nomogram was tested in a validation group. Least absolute shrinkage and selection operator (LASSO) regression is a linear regression analytical method that uses an L1 regularization term to penalize coefficients with large absolute values, thereby controlling model complexity and variable selection. When using the lasso feature selection algorithm, it is necessary to carefully select the appropriate L1 regularization parameter and set the feature threshold to obtain the optimal feature variables, avoid overfitting the model, and improve the generalization ability of the model. To identify the ideal penalization coefficient (λ) in the derivation cohort, LASSO logistic regression was performed using the "glmnet" package of R (version 4.3.0, Statistics Department of the University of Auckland, Auckland, New Zealand). The parameter settings for the function were nlambda = 1000 and nfolds = 10. We chose the most suitable set of predictive features using the lambda.min criterion [28,29]. Variables with two-tailed $p < 0.05$ were selected as independent predictive factors for the model using multiple logistic regression analysis with forward stepwise selection.

A nomogram was made to score each patient's AKI risk. It provided a probability value that matched the cumulative risk scores of all predictors. To assess the nomogram's capacity to distinguish patients with and without OPCABG-AKI, the area under the curve (AUC) of the receiver operating characteristic (ROC) was computed [30]. The nomogram was subjected to 1000 bootstrap resamplings for internal validation of the training set. Calibration curves were generated to evaluate model calibration. We utilized decision curve analysis to evaluate the clinical usefulness of the nomogram by assessing the net benefits at various threshold probabilities [31]. A clinical impact curve (CIC) was drawn to demonstrate the value of the nomogram in a more intuitive way.

R software, version 4.3.0 for Windows, and SPSS 26.0 software (IBM Corp., Armonk, NY, USA) were used to perform statistical analyses. Statistical significance was indicated when p was <0.05.

Results

Patient Characteristics

The characteristics of the derivation and validation sets are summarized in Table 1. There were 310 patients in the derivation group, with an average age of 61. Of them, 261/310 (84.2%) were male. The validation cohort comprised 132 patients with a mean age of 62, and 108/132 (81.8%) were male. In the derivation cohort, the rate of AKI was 25.5% (79/310), whereas in the validation cohort, it was 20.5% (27/132).

Predictors of OPCABGAKI

In Fig. 2A, the variation in the regression coefficient of each independent variable is illustrated under different λ. In Fig. 2B, the mean-squared error (λ.min) is represented by the left vertical line, while the right vertical line represents the cross-validation mean-squared error within a standard error of the minimum (λ.lse). Here, λ.min was calculated to be the optimal value. A total of 20 variables were enrolled

Table 1. Patients data.

	Derivation cohort (n = 310)	Validation cohort (n = 132)	*p* value
Preoperative variables			
Demographic			
Sex, male	261 (84.2)	108 (81.8)	0.538
Age, years	60.83 (8.35)	62.27 (7.42)	0.086
Nation, the Han nationality	214 (69.0)	86 (65.2)	0.424
Systolic blood pressure	131.10 (20.51)	130.58 (19.03)	0.803
Diastolic blood pressure	75.63 (12.39)	73.44 (11.38)	0.082
Heart rate	74.81 (11.51)	74.38 (11.28)	0.715
Height, cm	163.98 (7.08)	163.96 (7.57)	0.98
Weight, kg	65.54 (10.67)	64.54 (11.92)	0.386
Body mass index, kg/m^2	24.28 (3.17)	23.96 (3.98)	0.367
Smoke	150 (48.4)	65 (49.2)	0.869
Drink	84 (27.1)	44 (33.3)	0.186
Baseline renal function			
Serum creatinine, μmol/L	86.27 (17.08)	86.72 (18.63)	0.807
Ccr, mL/min/1.73 m^2	80.54 (19.67)	76.24 (20.36)	0.038
Comorbidities			
Diabetes mellitus	92 (29.7)	33 (25.0)	0.318
Hypertension	181 (58.4)	73 (55.3)	0.548
Previous myocardial infarct	83 (26.8)	31 (23.5)	0.469
Peripheral vascular disease	28 (9.0)	21 (15.9)	0.035
Chronic obstructive pulmonary disease	10 (3.2)	4 (3.0)	0.307
Urine indicators			
Proteinuria	22 (7.1)	13 (9.8)	0.327
Specific gravity	1.02 (0.01)	1.02 (0.01)	0.243
Urinary pH value	5.88 (0.68)	6.08 (0.73)	0.008
Cardiac function			
Aortic inner diameter, mm	29.33 (2.93)	29.35 (3.84)	0.946
Left ventricular diastolic dimension, mm	53.57 (7.26)	53.86 (7.01)	0.692
Left ventricular systolic diameter, mm	35.42 (8.12)	35.77 (8.02)	0.674
Left atrial diameter, mm	37.52 (15.88)	38.59 (26.66)	0.602
Ejection fraction, %	62.05 (10.93)	60.85 (11.90)	0.303
Cardiac output, L/min	6.45 (7.41)	5.73 (1.65)	0.266
Use of IABP	106 (34.2)	42 (31.8)	0.628
Left main stenosis >50, %	148 (47.7)	63 (47.7)	0.998
Laboratory variables			
Hemoglobin, g/L	129.49 (14.86)	129.79 (14.62)	0.846
Platelet count, 10^9/L	234.50 (63.68)	238.52 (73.32)	0.562
Neutrophil count, 10^9/L	4.16 (1.49)	4.26 (1.49)	0.536
Lymphocyte count, 10^9/L	5.33 (59.02)	1.98 (0.69)	0.515
Serum albumin, g/L	39.64 (3.65)	39.62 (3.62)	0.968
Sodium, mmol/L	140.23 (2.74)	139.62 (2.92)	0.038
Calcium, mmol/L	2.26 (0.11)	2.26 (0.11)	0.602
Creatine kinase-MB, U/L	15.32 (9.04)	16.42 (12.35)	0.298
Prothrombin time, s	11.17 (1.66)	11.34 (3.16)	0.479
Fibrinogen, g/L	4.04 (1.01)	3.95 (1.05)	0.398
Thrombin time, s	12.65 (7.40)	12.45 (1.53)	0.765
Urea, mmol/L	5.33 (1.59)	5.47 (2.05)	0.413
CysC, mg/L	1.00 (0.23)	1.07 (0.31)	0.006
Intraoperative variables			
Red blood cells transfused, U	4.42 (1.89)	4.33 (1.65)	0.624
Plasma transfused, dL	5.30 (2.35)	4.84 (1.37)	0.038
Adrenaline, mg	0.62 (0.29)	0.66 (0.25)	0.129

Table 1. Continued.

	Derivation cohort (n = 310)	Validation cohort (n = 132)	*p* value
Norepinephrine, mg	1.54 (1.45)	1.35 (1.20)	0.194
Bridging vessel	2.78 (0.61)	2.73 (0.62)	0.377
Operation time, h	5.14 (1.16)	5.15 (1.07)	0.93
Postoperative variables			
Levosimendan, mg	2.21 (5.35)	2.27 (5.31)	0.91
Natriuretic peptide, mg	0.31 (0.95)	0.32 (0.94)	0.913
Leukocyte count, 10^9/L	15.76 (4.66)	15.71 (4.46)	0.928
Hemoglobin, g/L	113.60 (17.57)	112.25 (22.26)	0.498
Neutrophil count, 10^9/L	13.87 (4.42)	13.90 (4.12)	0.953
Lymphocyte count, 10^9/L	0.79 (0.32)	0.77 (0.37)	0.69
Prognosis			
Acute kidney injury	79 (25.5)	27 (20.5)	0.257

Data are average (standard deviation) or count (percentage). IABP, intra-aortic balloon pump; Ccr, Creatinine clear rate; CysC, Cystatin C.

Table 2. Predictive factors of AKI in OPCABG.

Variables	Multivariable analysis		
	β	Odds ratio [95% CI]	*p*
Use of IABP	0.846	2.331 [1.242, 4.411]	0.009
Systolic blood pressure	0.028	1.028 [1.008, 1.050]	0.006
Smoking	0.647	1.910 [1.017, 3.652]	0.046
Scr	0.031	1.032 [1.010, 1.055]	0.004

β, Regression coefficient; AKI, acute kidney injury; Scr, Serum creatinine; CI, Confidence interval.

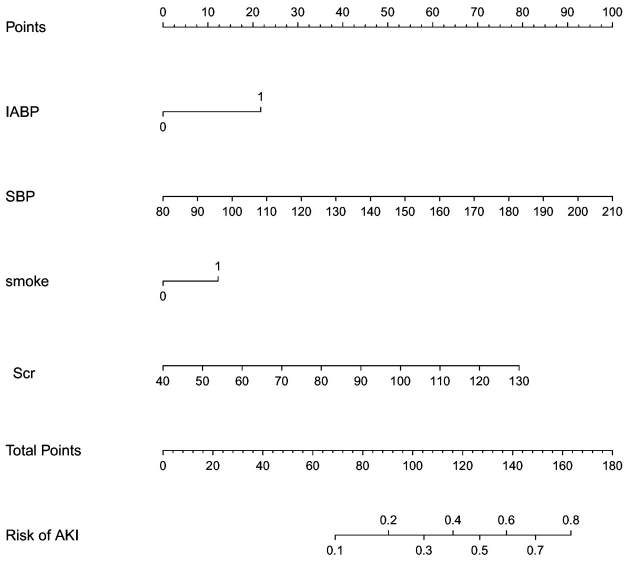

Fig. 3. The nomogram of AKI after OPCABG. SBP, systolic blood pressure; Scr, serum creatinine.

for further analysis according to the minimum criterion. Afterward, the multivariate logistic regression analysis with forward stepwise selection was constructed by filtering out the remaining 20 variables. Variables with two-tailed $p < 0.05$ were selected. As shown in Table 2, significant predictors of postoperative AKI included Scr, IABP use, smoking and systolic blood pressure. Table 2 contains a comprehensive list of the variables of the multiple logistic regression.

Nomogram Construction and Validation

This nomogram included four crucial risk factors (Fig. 3). Each variable value corresponded to a score on the dot scale axis. The sum of individual scores determined the total score. Following this, we estimated the probability of AKI.

Fig. 4 displays the outcomes of the ROC curve analyses. The AUC was 0.733 (95% confidence interval (CI) = 0.669–0.791) for the derivation set and 0.786 (95% CI = 0.693–0.878) for the validation set. The AUC of the internal validation was 0.715 using bootstrapping with 1000 replicates, signifying a strong level of recognition by the model. The optimal cutoff point on the two ROC curves was 0.304 (sensitivity 0.595 and specificity 0.762) in the derivation set, and 0.266 (sensitivity 0.741 and specificity 0.714) in the validation set.

The calibration plots in both groups demonstrated that the new nomogram outperformed previous models in terms of performance (Fig. 5). We also ran the Hosmer–Lemeshow goodness-of-fit test. The OPCABG-AKI score demonstrated strong performance when tested in both the training (χ^2 statistic = 4.336, df = 8, $p = 0.8256$) and validation sets (χ^2 statistic = 5.02, df = 8, $p = 0.7546$). The risk for OPCABG-AKI predicted by the OPCABG-AKI score was similar to the observed risk.

Decision curves demonstrated that the new nomogram exhibited a greater clinical net gain in both the derivation and validation datasets, when the threshold probability ranged from 0.15 to 0.8 (Fig. 6A,C). The clinical impact curve (Fig. 6B,D) was used to predict the stratifica-

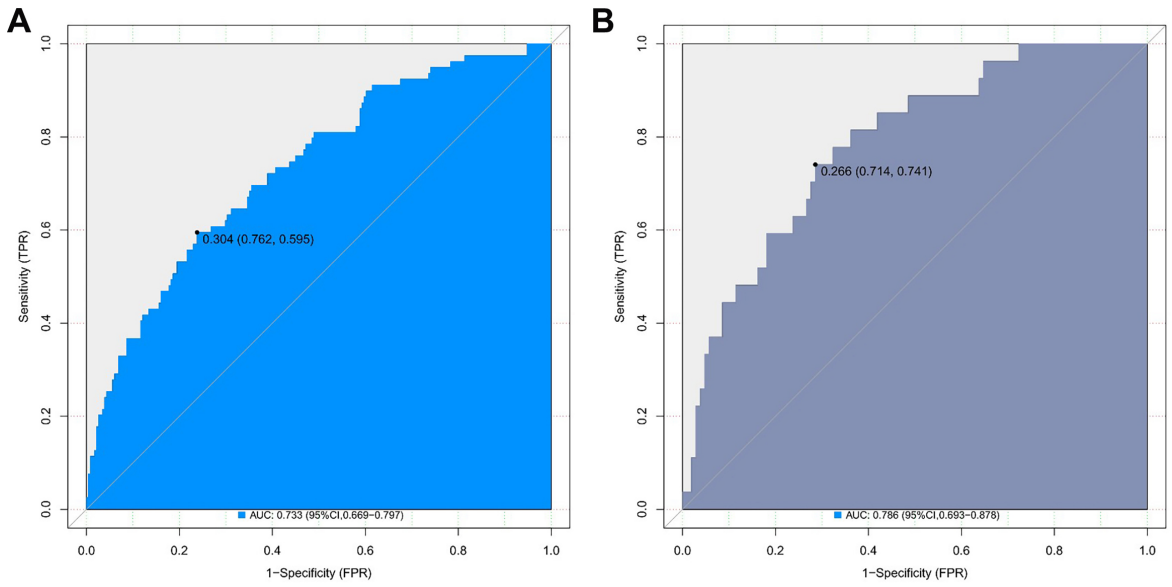

Fig. 4. Receiver operating characteristic (ROC) curves of the model in the training group (A) and validation group (B).

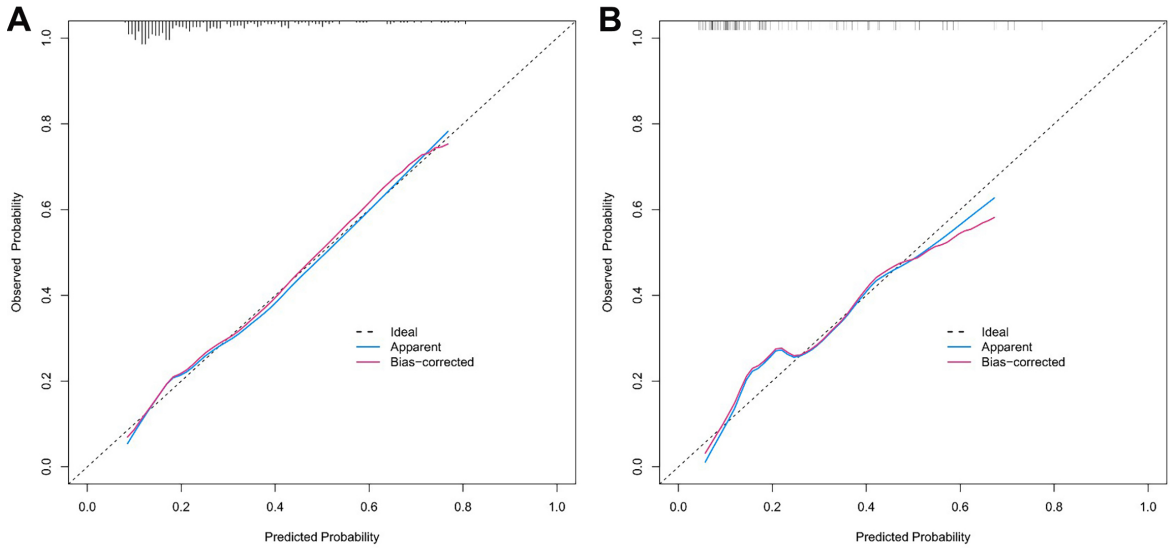

Fig. 5. The calibration curves of the model in the training group (A) and validation group (B).

tion of AKI probability for 1000 samples. When the threshold probability exceeded 0.40, the predicted number closely matched the actual number of AKI cases.

Discussion

Researchers have increasingly emphasized the timely identification and classification of AKI that occurs after cardiac surgery, with the aim of delivering tailored prevention and treatment plans to patients. In this work, we created a risk prediction model with four variables to forecast the occurrence of AKI following OPCABG. This model demonstrated excellent performance. AKI occurred in 22.4% of our patients, which aligns well with the reported incidence in published data (12% to 48.5%) [32]. This means that the off-pump technique does not provide significant renal protection to patients undergoing CABG.

Not only does the prognosis of AKI vary with the etiology and clinical situation, but it is also influenced by the extent of renal function impairment. Even a slight increase in Scr in cardiac surgery patients showed a tight correlation with poor outcomes [33]. Therefore, developing a prediction model for AKI following OPCABG would be extremely beneficial for clinicians. The nomogram showed that the use of IABP, higher systolic blood pressure at admission, smoking habit and higher serum creatinine would increase the risk of AKI. These four factors should be considered when advising patients preoperatively of their risk

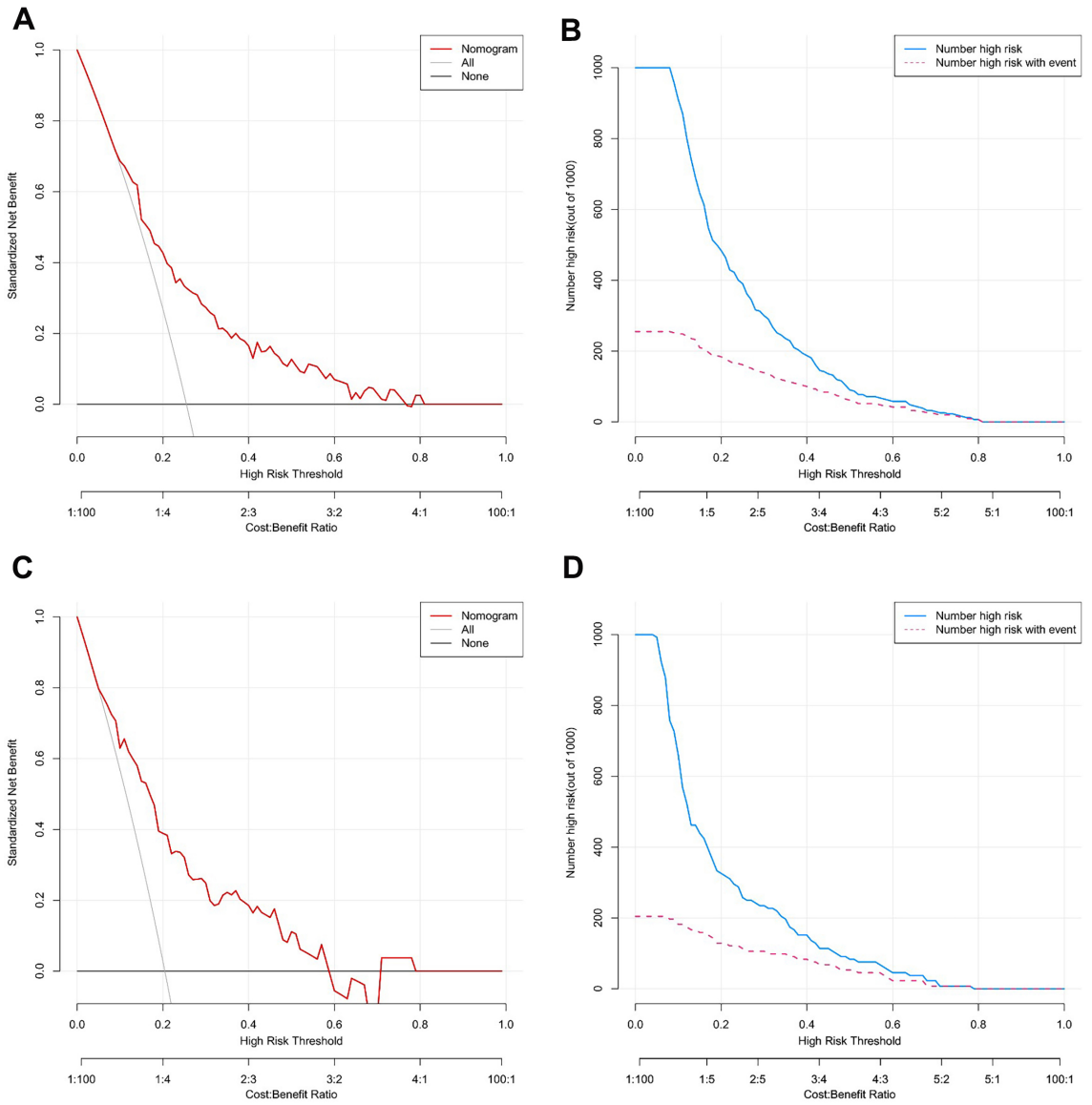

Fig. 6. Decision curve analysis and clinical impact curve analysis of the model in the training group (A,B) and the validation group (C,D). Illustration: In the decision curve of the model, the net benefit is represented by the y axis, while the high risk thresholds chosen here vary from 0 to 1 on the x axis. The assumption that no one has AKI is depicted by the horizontal gray line, while the diagonal gray line signifies that everyone has AKI.

[34]. We have preliminarily used this nomogram for risk prediction by applying it to electronic medical records, guiding the cardiac surgery team to develop personalized plans for high-risk patients, such as monitoring urine volume, controlling fluid balance, maintaining hemodynamic stability, and avoiding using kidney injury drugs during the perioperative period.

Contrary to our findings, a meta-analysis indicated that preoperative IABP placement can have a beneficial effect on postoperative AKI incidence [35]. An IABP cannot induce AKI directly, and they are mostly put in patients with poor heart function before surgery. Its use can reflect the inadequate perfusion of organs [18]. Some studies have indicated that IABP reflects unstable hemodynamics and is closely linked to AKI [36,37]. The presence of an IABP could hinder the organ perfusion supplied by the aorta below the IABP balloon [38]. Therefore, the evaluation of perfusion pressure beyond the balloon should be a priority whenever an IABP is employed.

Extensive research has been conducted on the correlation between hypertension and kidneys. Elevated blood pressure that persists will result in fibrosis of the glomerulus and sclerosis of the blood vessels. Renal parenchymal ischemia and nephron reduction can occur even if renal function is normal prior to surgery [39]. In 2018, a cross-sectional study involving 3473 patients was performed by Barkhordari *et al.* [40]. The findings indicated a significant association between hypertension and the occurrence

of AKI following CABG. Our study found that high admission systolic blood pressure was a risk factor for postoperative AKI, while a history of hypertension was not. According to reports, there are many masked hypertension patients and hypertensive patients with poor medication compliance in the Chinese population [41]. Our research indicates that for patients with a history of hypertension, we need to evaluate the current antihypertensive regimen and their compliance with it. Similarly, for patients without a history of hypertension, continuous blood pressure testing is still necessary to detect masked hypertension.

Several possible mechanisms could be responsible for the decline in kidney function caused by smoking. Sympathetic overactivity and a transient increase in blood pressure have been linked to kidney injury [42,43]. Due to the connection between inflammation, oxidative stress in the lungs, and its impact on the circulatory system, smoke-induced respiratory reactive oxidative species could cause kidney damage by increasing systemic oxidative stress [44]. Preoperative smoking cessation is beneficial for patients.

Baseline serum creatinine has been correlated with renal perfusion [45,46]. Preoperative hidden or slight renal dysfunction, which is widely recognized as a contributing factor to postoperative AKI, is highly prevalent (49.1%) among patients undergoing cardiac surgery with normal Scr levels [47]. Our study indicates that despite the delayed detection of a significant rise in Scr, it remains a reliable predictor of AKI [48].

It is important to consider the limitations of this study when interpreting our findings. First, compared to other studies that have established robust and widely used models, ours had a relatively small sample. Furthermore, these observations come from a single cardiac center. Due to differences in the research population and definition of AKI, comparing different models can result in a biased evaluation of each model's ability to predict outcomes. Thus, it would be more reliable to validate our model prospectively or at least in another database. Due to the unavailability of urine volume data, our study may have underestimated the incidence of AKI. Last, this retrospective study exhibited some unavoidable bias, which would negatively impact the predictive accuracy of the model. For example, information regarding the amount of bleeding, estimated glomerular filtration rate and partial medication use, such as anesthesia, was not available and thus was not included in our model. We also excluded some patients whose Scr during the procedures was lost, which could have caused a serious selection bias. In the future, we will include patients from other centers to optimize the model. We will also apply the existing model to patients in other heart centers to test its clinical utility in a wider range of patients.

Conclusion

The novel nomogram predicted AKI in patients undergoing OPCABG better than earlier models. It can help with perioperative risk assessment, prevention, early diagnosis and improving patients' renal and overall prognosis.

Abbreviations

AKI, acute kidney injury; OPCABG, off-pump coronary artery bypass grafting surgery; KDIGO, Kidney Disease, Improving Global Outcomes; IABP, intra-aortic balloon pump; Scr, serum creatinine; LASSO, least absolute shrinkage and selection operator regression.

Availability of Data and Materials

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

Author Contributions

SC and CL conceived and designed the study, data analysis and article writing. CF, YL, XC, GL, HS and SF contributed to data curation, writing - original draft; LM, SZ, and BZ were responsible for the acquisition, and interpretation of data. All persons designated as the authors have participated sufficiently in the work to take public responsibility for the content of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The studies involving human participants were reviewed and approved by the Ethics Committee of The First Affiliated Hospital of Guangxi Medical University (approval number: 2023-E480-01). All patients have signed informed consent forms.

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Conflict of Interest

The authors declare no conflict of interest.

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