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Original Article

Postoperative acute kidney injury following cardiac surgery with cardiopulmonary bypass: integration of circadian rhythm and anesthetic factors to develop and validate a predictive model at 7 days

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Abstract: Objective: To predict postoperative acute kidney injury (AKI) following cardiopulmonary bypass (CPB) surgery, we developed and validated a nomogram incorporating circadian rhythms and anesthesia-related variables to assist in predicting AKI occurrence. Methods: This retrospective analysis included clinical data from 298 patients who underwent cardiac surgery with extracorporeal circulation. All patients were randomly divided into two groups: one for model development (n = 209) and the other for internal validation (n = 89). Candidate variables were selected using least absolute shrinkage and selection operator (LASSO) regression. Independent predictors were identified through multivariable logistic regression, and a predictive nomogram was constructed. The model's discriminatory ability, calibration performance, and clinical utility were evaluated using receiver operating characteristic (ROC) curves, calibration plots, and decision curve analysis (DCA). Results: Among the 298 patients, 82 developed postoperative AKI, yielding an overall incidence rate of 27.52%. On multivariate logistic regression analysis, undergoing surgery in the afternoon was a protective factor (odds ratio [OR]: 0.482, P < 0.05), whereas preoperative circadian rhythm disturbance, prolonged CPB duration, and increased propofol infusion rate emerged as independent risk factors for postoperative AKI (OR: 3.081, 1.026, and 2.050, respectively; all P < 0.05). The nomogram showed satisfactory discrimination, with an area under the ROC curve (AUC) of 0.796 (95% CI: 0.728-0.864) in the training set and 0.776 (95% CI: 0.671-0.881) in the validation set. After bootstrap correction with 1,000 resamples, the optimism-corrected AUC was 0.793. At the optimal cutoff point, the sensitivity and specificity for the training cohort were 0.672 and 0.815, respectively, and for the validation cohort, 0.500 and 0.831. Both the training and validation sets showed adequate calibration on the Hosmer-Lemeshow test (P = 0.754 and P = 0.364, respectively). DCA further demonstrated that the nomogram provided a net positive clinical benefit over a wide range of clinically plausible threshold probabilities. Conclusion: The proposed nomogram combines chronobiological factors, anesthesia-related variables, and perfusion time during cardiac surgery. This tool shows potential as a practical means for assessing the risk of acute kidney injury after cardiac surgery, though external validation in independent multicenter cohorts is warranted before widespread clinical implementation. In clinical practice, with appropriate validation, this model may help with early risk stratification and aid in designing targeted perioperative intervention measures to reduce the risk of kidney injury in high-risk patients.

Keywords: Acute kidney injury, cardiac surgery, cardiopulmonary bypass, chronobiology, intravenous anesthesia, risk assessment, clinical prediction rule

Introduction

Although cardiopulmonary bypass is crucial for maintaining tissue perfusion during cardiac surgery, it can also cause severe pathophysiologic disturbances. This circulation method leads to systemic inflammation, non-pulsatile blood flow, and ischemia-reperfusion injury - all of which jointly expose patients to the risk of various complications during the surgery, with

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acute kidney injury (AKI) being the most prominent [1]. In surgeries performed under extracorporeal cardiac circulation, the incidence of acute kidney injury is approximately 30% to 40%, and 1% to 5% of patients require renal replacement therapy. Therefore, AKI remains a major challenge in cardiac surgery [2, 3].

In addition to prolonging the duration of ventilator support and increasing hospital costs, acute kidney injury also increases the risk of multiple organ dysfunction and may lead to the development of chronic kidney disease. Currently, clinicians still mainly rely on serum creatinine values for diagnosis, although this approach has several limitations - such as being susceptible to interference from other kidney-related factors, and the serum creatinine concentration typically reaches its peak within 48 to 72 hours after surgery. Because this delayed increase shortens the window for effective intervention [4], early identification of risks and optimization of perioperative modifiable factors are crucial for improving treatment outcome. To date, most studies on predictive models for acute kidney injury have focused on demographic and surgery-related variables [5], while the effects of circadian rhythms and anesthesia management on acute kidney injury have been largely understudied.

Circadian rhythm is of vital importance to the physiologic function of the kidneys, and its disruption - due to abnormal release of cortisol and melatonin - may interfere with renal tubule repair, hemodynamics, and metabolic homeostasis [6]. At the same time, anesthesia management is another modifiable factor affecting perioperative kidney injury. The choice of anesthetic drugs and their administration methods can influence perfusion and inflammatory signal transduction during surgery, and these factors may influence renal recovery [7]. This view is supported by a study of 317 nephrectomy cases: 27% of patients who received propofol developed acute kidney injury, while 23% of patients who received desflurane did so. This suggests a potential association between anesthesia choice and kidney protection [8]. These observations led us to conduct our own retrospective review of 298 consecutive CPB cases. Our main goal was to identify key risk factors for AKI following CPB - particularly chronobiological and anesthesia-related ones - and to incorporate them into an internally validated nomogram designed for early clinical risk stratification and tailored renoprotective decision-making.

Materials and methods

Study subjects

We retrospectively enrolled patients who underwent cardiac procedures requiring CPB at our center from June 2022 to November 2025. We applied the following inclusion criteria: (1) presence of valid medical indications for cardiac surgery; (2) age ≥ 18 years; (3) normal or near-normal preoperative liver and kidney function - specifically, serum creatinine (Scr) < 133 μmol/L, and both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 120 U/L; and (4) availability of complete clinical documentation. Patients were excluded if they had: (1) a history of kidney transplantation, renal artery trauma, or chronic kidney disease, or those receiving renal replacement therapy; (2) preoperative renal insufficiency; (3) a history of nephrotoxic drug use; (4) undergone heart transplantation, emergency surgery, or cardiac assist device implantation surgery; (5) intraoperative death or postoperative death in the intensive care unit within 24 hours; (6) severe infection or autoimmune disease; (7) severe cognitive dysfunction making assessment of preoperative circadian rhythm status difficult. Applying the above criteria, we ultimately enrolled 298 patients - comprising 160 males and 138 females - with ages ranging from 22 to 78 years (mean 54.07±8.49).

Ethics statement: The Ethics Committee of General Hospital of Ningxia Medical University granted approval for this study (Approval No. KYLL-2026-0271). All procedures were performed in accordance with the Declaration of Helsinki.

Study grouping

Group assignment was determined according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [9], patients were assigned to the AKI group if they met ≥ 1 of the following criteria within 7 days post-surgery - (1) an increase in Scr to ≥ 1.5× baseline; (2) a ≥ 26.5 μmol/L increase in Scr within 48 hours after surgery; or (3) urine output < 0.5

mL/(kg·h) lasting ≥ 6 hours during the early postoperative period, with alternative causes of oliguria (e.g., dehydration or urinary tract obstruction) excluded. Patients who met none of these criteria formed the non-AKI group.

Data collection

Information was systematically gathered from the hospital's digital patient records. The collected variables fell into the following categories: (1) Demographic data - namely, sex, age, body mass index (BMI), history of hypertension and diabetes, plus American Society of Anesthesiologists (ASA) class; (2) Operative variables - including surgical type, CPB time, and aortic cross-clamp duration; and (3) Laboratory indices - ALT, AST, blood urea nitrogen (BUN), Scr, and estimated glomerular filtration rate (eGFR); (4) Circadian rhythm variables: the circadian timing of surgery/anesthesia and preoperative circadian rhythm status. Surgical timing was classified as morning (anesthesia induction between 8:00 and 12:00) or afternoon (induction between 14:00 and 18:00). Procedures occurring between 12:00-14:00 or after 18:00 were excluded for three reasons: (1) the 12:00-14:00 window represents the postprandial phase, during which hemodynamic and metabolic changes could confound circadian effect assessment; (2) surgeries after 18:00 at our institution are predominantly emergency or semi-emergency procedures with inherently different risk profiles; and (3) focusing on morning (8:00-12:00) and afternoon (14:00-18:00) allows clearer delineation of circadian phase effects, as previously recommended [8, 10]. Preoperative sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI) [11]. Nocturnal salivary melatonin concentration was assayed by enzyme-linked immunosorbent assay (ELISA) from samples obtained between 23:00 and 00:00. To provide a more comprehensive assessment of circadian rhythm disruption, we additionally measured salivary cortisol levels at 08:00 (morning) and 20:00 (evening) preoperatively. To assess circadian rhythm disruption (CRD), we used a composite index comprising: (1) PSQI ≥ 7; (2) peak salivary melatonin < 15 pg/mL; and (3) abnormal diurnal cortisol secretion (morning-to-evening ratio < 2.0 or > 3.0) [12, 13]. Using multiple hormonal and sleep metrics together, rather than a single indicator, allows a more precise evaluation of circadian status in surgical patients [11, 14]; (4) Data on anesthesia type (combined intravenous-inhalational vs. total intravenous anesthesia (TIVA)), propofol infusion rate [mg/(kg·h)], and the use of contrast media or renoprotective agents (N-acetylcysteine or sodium bicarbonate) in the 7 days preceding surgery were also collected. Every entry was extracted and cross-checked by two independent investigators for accuracy. Regarding the PSQI and melatonin assessments, missing data accounted for < 5%, and we addressed these with multiple imputation through chained equations based on 20 imputations - an accepted method to minimize bias due to incomplete data in retrospective studies.

Statistical methods

All statistical analyses were conducted using SPSS 26.0 and R 4.4.2 software. For continuous variables that followed a normal distribution, the data were presented as mean ± SD; while the differences between groups were evaluated through independent-samples t-tests. For categorical variables, they were expressed as counts (percentages), and comparisons were made using chi-square tests or Fisher's exact tests when appropriate. For model development, candidates with $P < 0.05$ by univariate analysis in the training set entered LASSO regression for dimension reduction. After that, the selected predictors underwent multivariate logistic regression to identify independent risk factors, which were then incorporated into the nomogram. We performed internal validation and optimism correction with *1,000* bootstrap resamples. The model's discrimination, calibration, and clinical use were evaluated by ROC curves, calibration plots, and DCA, respectively. To examine the effect of missing data on final findings, we conducted a sensitivity analysis comparing results with and without imputation. A two-sided $P < 0.05$ was deemed significant.

Additionally, to address the effect of omitting established AKI risk variables (intraoperative hypothermia, perioperative blood transfusion volume, aortic cross-clamp duration, and vasoactive drug use), we performed a sensitivity analysis using propensity score-matched analysis on the subset of patients with available

Table 1. Comparison of AKI incidence and clinical data between the training and validation sets

Clinical Data	Total (n = 298)	Training Set (n = 209)	Validation Set (n = 89)	t/χ^2	*P*
AKI (Yes/No)	82/216	58/151	24/65	0.019	0.890
Sex (male/female)	160/138	116/93	44/45	0.923	0.337
History of Hypertension (Yes/No)	132/166	96/113	36/53	0.761	0.383
History of Diabetes (Yes/No)	50/248	36/173	14/75	0.100	0.752
ASA Classification (II/III/IV)	127/162/9	88/115/6	39/47/3	0.151	0.927
Surgical Procedure (Valve/CABG/Aortic)	98/140/60	71/96/42	27/44/18	0.414	0.813
Circadian timing of surgery/anesthesia (Morning/Afternoon)	206/92	145/64	61/28	0.021	0.886
Preop CRD (Yes/No)	87/211	64/145	23/66	0.690	0.406
Anesthesia technique (Combined IV-inhalational/TIVA)	191/107	132/77	59/30	0.266	0.606
Age (years)	54.07±8.49	53.95±8.72	54.35±7.95	0.373	0.710
BMI (kg/m^2)	22.72±1.49	22.75±1.41	22.65±1.68	0.507	0.613
ALT (U/L)	41.84±6.33	41.76±6.16	42.02±6.74	0.328	0.743
AST (U/L)	57.07±8.57	56.82±8.57	57.63±8.58	1.167	0.244
BUN (mmol/L)	8.43±1.76	8.35±1.79	8.62±1.68	0.815	0.416
Scr (μmol/L)	81.13±13.22	80.69±12.38	82.16±15.03	0.815	0.416
eGFR ($mL/min/1.73\ m^2$)	114.71±21.88	114.91±21.94	114.26±21.85	0.235	0.814
CPB time (min)	110.23±27.32	110.45±28.41	109.71±24.70	0.213	0.832
Aortic Cross-Clamp Time (min)	73.51±14.29	73.20±14.00	74.25±15.02	0.580	0.562
Propofol Infusion Rate [mg/(kg·h)]	4.32±0.90	4.32±0.95	4.34±0.76	0.239	0.811

Note: CPB, cardiopulmonary bypass; Preop CRD, preoperative circadian rhythm disruption; AKI, acute kidney injury; ASA, American Society of Anesthesiologists; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; CABG, coronary artery bypass grafting.

data for these variables (n = 201). The AUC of the model was recalculated in this matched subset to evaluate whether the omission of these variables materially affected discriminative performance.

Results

Baseline characteristics and AKI incidence in the training and validation cohorts

Among the 298 enrolled patients, 82 (27.52%) had postoperative AKI. The rates were 27.76% for the training set and 26.97% for the validation set. There were no significant between-group differences in baseline variables (P > 0.05; **Table 1**). A sensitivity analysis that compared baseline characteristics and AKI incidence between the analytic cohort (n = 298) and the excluded patients (n = 43) found no significant differences across age, sex, BMI, preoperative renal function, or AKI incidence (all P > 0.05), suggesting that the exclusions did not introduce meaningful selection bias.

Sensitivity analysis comparing the imputed dataset with the complete-case dataset revealed consistent findings (all effect estimates within 10% of the original values), indicating that missing data did not substantially influence the final results.

In the propensity score-matched subset (n = 201), the AUC of the model was 0.783 (95% CI: 0.712-0.854), compared to 0.796 (95% CI: 0.728-0.864) in the full training set, indicating that the omission of intraoperative hypothermia, blood transfusion volume, aortic cross-clamp duration, or vasoactive drug use did not substantially alter the model's discriminative performance.

Univariate predictors of AKI in the training cohort

On univariate analysis of the training dataset, patients with AKI showed a higher prevalence of preoperative CRD, longer CPB time, and higher propofol infusion rates compared to the non-AKI group (all P < 0.05). In addition, afternoon procedures were significantly less frequent among AKI patients than among non-AKI patients (P < 0.05). The remaining clinical and laboratory variables did not differ significantly between the two groups (all P > 0.05; **Table 2**).

Table 2. Univariate analysis of factors associated with AKI occurrence in the training set

Clinical Data	Non-AKI Group (n = 151)	AKI Group (n = 58)	t/χ^2	*P*
Sex (male/female)	82/69	34/24	0.316	0.574
History of Hypertension (Yes/No)	68/83	28/30	0.177	0.674
History of Diabetes (Yes/No)	22/129	14/44	0.261	0.101
ASA Classification (II/III/IV)	63/83/5	25/32/1	-	1.000
Surgical Procedure (Valve/CABG/Aortic)	48/70/33	23/26/9	1.622	0.444
Circadian timing of surgery/anesthesia (Morning/Afternoon)	74/77	40/18	6.733	0.009
Preop CRD (Yes/No)	38/113	26/32	7.625	0.006
Anesthesia technique (Combined IV-inhalational/TIVA)	100/51	32/26	2.200	0.138
Age (years)	53.49±8.58	55.15±9.02	1.225	0.222
BMI (kg/m^2)	22.85±1.35	22.49±1.53	1.615	0.108
ALT (U/L)	41.26±6.31	43.05±5.58	1.892	0.060
AST (U/L)	56.35±8.48	58.06±8.74	1.301	0.195
BUN (mmol/L)	8.26±1.26	8.62±2.73	0.964	0.338
Scr (μmol/L)	80.16±12.06	82.09±13.19	1.009	0.314
eGFR ($mL/min/1.73\ m^2$)	115.26±22.08	113.98±21.74	0.380	0.704
CPB time (min)	104.65±27.46	125.57±25.26	5.040	< 0.001
Aortic Cross-Clamp Time (min)	72.36±14.29	75.36±13.08	1.389	0.166
Propofol Infusion Rate [mg/(kg·h)]	4.13±0.87	4.79±0.99	4.643	< 0.001

Note: CPB, cardiopulmonary bypass; Preop CRD, preoperative circadian rhythm disruption; AKI, acute kidney injury; ASA, American Society of Anesthesiologists; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; -, Fisher exact test.

Multivariate predictors of AKI in the training cohort

To screen variables from **Table 1**, we applied LASSO regression with ten-fold cross-validation, selecting lambda.min as the optimal value. Through this process, four variables with non-zero coefficients were retained (**Figure 1**) and included in the subsequent multivariable logistic analysis. We found that afternoon surgical timing conferred a protective effect against AKI (OR: 0.482, $P < 0.05$), whereas preoperative CRD, longer CPB time, and increased propofol infusion rate were independent predictors of heightened AKI risk (ORs: 3.081, 1.026, and 2.050, respectively; all $P < 0.05$; **Tables 3** and **4**).

Construction of the nomogram prediction model

The nomogram was based on the independent predictors from multivariate analysis. Points ranged from 0 to 200. The total score corresponded to AKI probabilities of 0.05-0.75. A higher score meant a higher AKI risk (**Figure 2**).

Nomogram performance evaluation and validation

We assessed the nomogram's discrimination using ROC curves. For the training set, the AUC was 0.796 (95% CI: 0.728-0.864), with sensitivity of 0.672 and specificity of 0.815; the corresponding figures for the validation set were 0.776 (95% CI: 0.671-0.881), 0.500, and 0.831, respectively (**Figure 3**). Bootstrap internal validation with 1,000 resamples gave an optimism-corrected AUC of 0.793, reflecting good model stability. Calibration was examined by calibration plots and the Hosmer-Lemeshow test, which showed adequate fit for both cohorts (training set: $\chi^2 = 5.036$, $P = 0.754$; validation set: $\chi^2 = 8.752$, $P = 0.364$) (**Figure 4**). DCA showed the nomogram provided a positive net clinical benefit over a wide range of clinically relevant thresholds, outperforming both "treat-all" and "treat-none" approaches in both datasets (**Figure 5**).

Discussion

Acute kidney injury (AKI) is diagnosed on the basis of an acute decline in renal function,

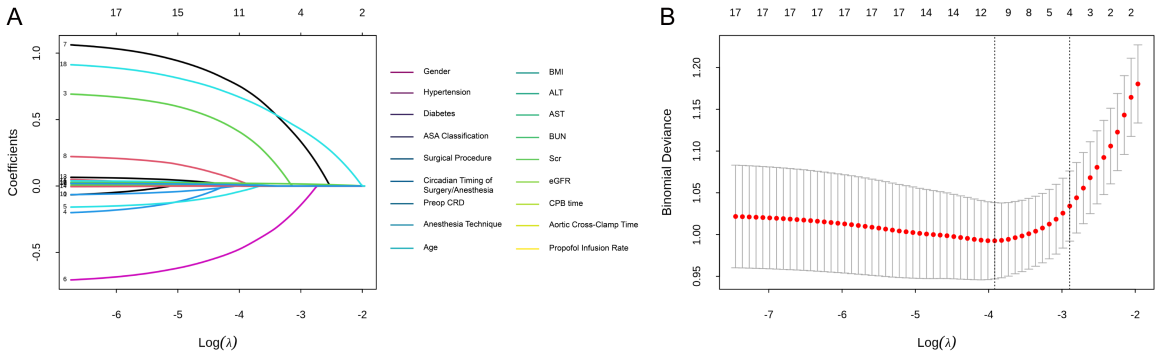

Figure 1. Process of variable selection via LASSO regression. A: Lambda fitting process; B: Cross-validation curve.

Table 3. Variable assignment table

Variable	Variable Type	Assignment
Circadian timing of surgery/anesthesia	Categorical	Morning timing = 0, Afternoon timing = 1
Preop CRD	Categorical	No = 0, Yes = 1
CPB time	Continuous	Original value entered
Propofol infusion rate	Continuous	Original value entered
AKI	Categorical	No = 0, Yes = 1

Note: CPB, cardiopulmonary bypass; Preop CRD, Preoperative circadian rhythm disruption; AKI, acute kidney injury.

Table 4. Multivariable analysis of AKI occurrence in the training set

Variable	β	SE	Z	*P*	OR (95% CI)	VIF
Circadian timing of surgery/anesthesia (Afternoon)	-0.729	0.366	-1.993	0.046	0.482 (0.235-0.988)	1.021
Preop CRD (Yes)	1.125	0.372	3.022	0.003	3.081 (1.485-6.392)	1.001
CPB time	0.026	0.007	3.770	< 0.001	1.026 (1.013-1.040)	1.060
Propofol infusion rate	0.718	0.202	3.551	< 0.001	2.050 (1.379-3.046)	1.052
Constant	-7.265	1.238	-5.868	< 0.001	0.001 (0.000-0.008)	-

Note: CPB, cardiopulmonary bypass; Preop CRD, Preoperative circadian rhythm disruption; AKI, acute kidney injury; VIF, variance inflation factor.

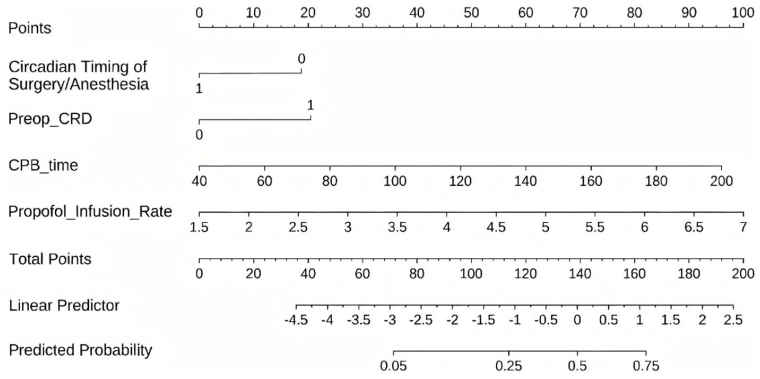

Figure 2. Nomogram for predicting the risk of AKI occurrence.

which classically presents with elevated blood urea nitrogen and creatinine, a reduced glomerular filtration rate, and serum electrolyte disturbances. During the perioperative period, inflammation, tissue hypoperfusion, and neuroendocrine changes act in concert to promote the onset and progression of acute kidney injury. Aortic cross-clamping, hypothermia, hemodilution, and non-pulsatile perfusion - all inherent to cardiac surgery - place these patients at a particularly high risk of AKI. Our nomogram, developed to predict the likelihood of AKI following CPB, intentionally incorporates two clinically modifiable variables: the choice of anesthetic and the circadian timing of surgery. On the whole, this nomogram exhibits good discriminative capacity and calibration, along with stable clini-

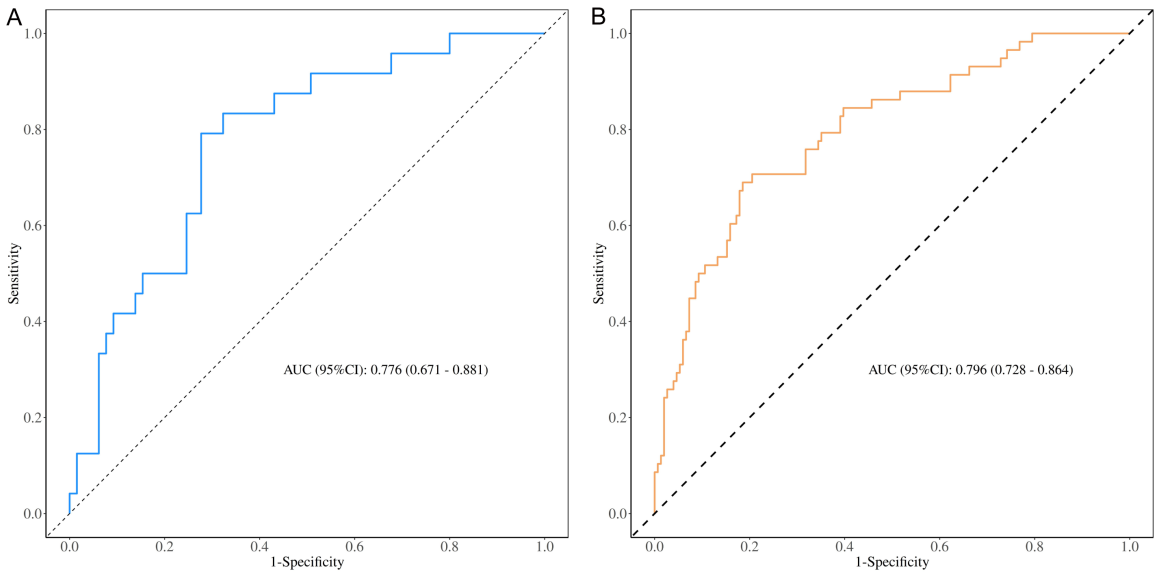

Figure 3. ROC curves of the nomogram for predicting AKI risk. A: Training set; B: Validation set.

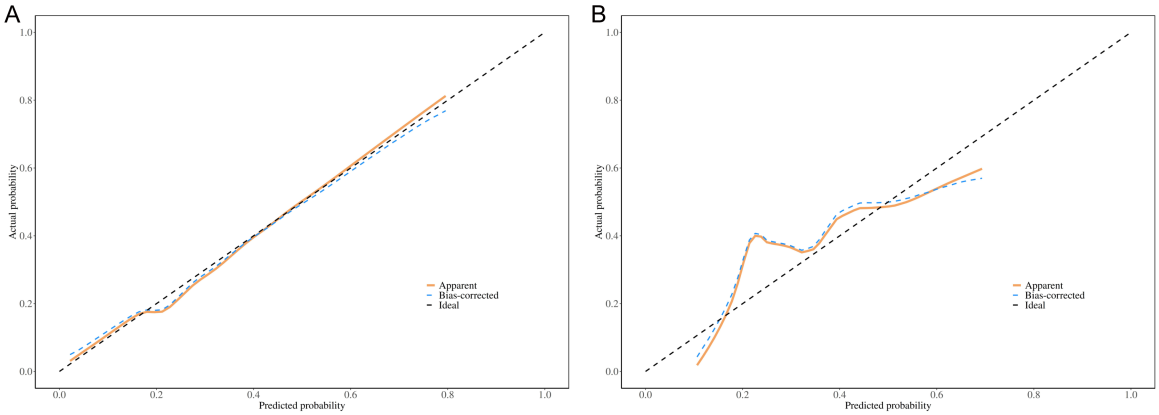

Figure 4. Calibration curves of the nomogram for predicting AKI risk. A: Training set; B: Validation set.

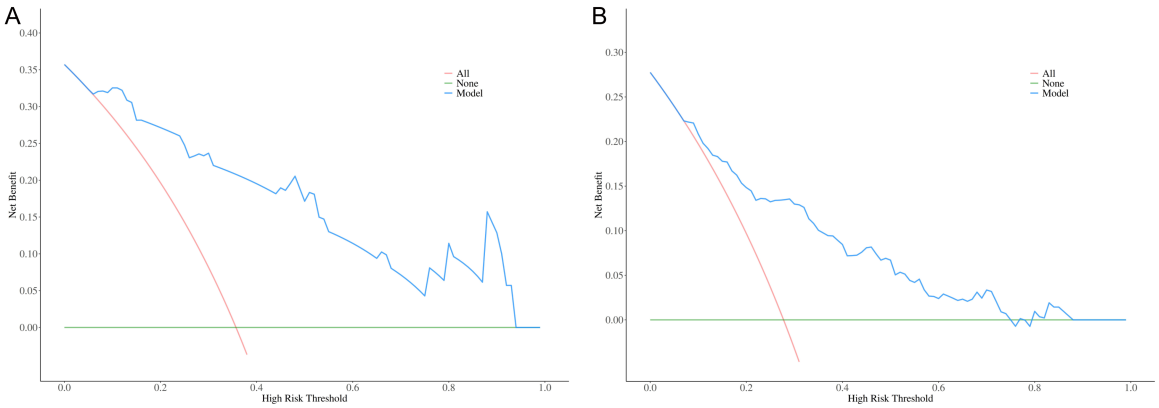

Figure 5. Clinical decision curves of the nomogram for predicting AKI risk. A: Training set; B: Validation set.

cal utility in practice. It provides clinicians with an evidence-based reference for early identification of high-risk patients and for delivering individualized perioperative care.

Through the LASSO-logistic regression model, we found that afternoon surgery was associated with a lower AKI risk, whereas three factors emerged as risk factors - preoperative circadian rhythm disturbance, prolonged CPB duration, and increased propofol infusion rate. We defined CRD using a composite of PSQI, melatonin, and cortisol - broader than relying on any single index. Circadian biology may be involved. The kidney has an intrinsic daily rhythm and responds to circadian signals. Renal blood flow, tubular reabsorption, and the renin-angiotensin-aldosterone system all fluctuate over the course of the day. This rhythmic pattern relies on the regulation of rhythmically secreted hormones (e.g., melatonin, cortisol) and the control of core clock genes [15]. The molecular clock, comprising BMAL1, CLOCK, PER, and CRY, relies on a transcriptional-translational feedback architecture to synchronize nearly half of the mammalian genome. In the kidney, BMAL1-driven rhythmicity regulates pathways essential for xenobiotic metabolism, redox homeostasis, and electrolyte flux. Compromising this timing apparatus exacerbates ischemia-reperfusion injury by impaired Nrf2 antioxidant responses [6]. Moreover, circadian timing orchestrates ferroptosis (a recently characterized iron-dependent cell death pathway) through Rev-Erbα/β-dependent coordination of lipid peroxidation and iron homeostasis [14]. Shi et al. [16] observed that when mice were exposed to abnormal light cycles, the acute kidney injury caused by cholesterol crystals showed time-dependent changes. This phenomenon was mainly attributed to impaired neutrophil recruitment. Patients with CRD before the surgery had a higher risk of developing acute kidney injury after the surgery, which might be due to suppressed melatonin secretion and sleep disturbances. Since melatonin can inhibit oxidative stress, alleviate inflammatory responses, and prevent excessive immune activation, melatonin deficiency before surgery may make the kidneys more susceptible to surgical damage [12]. To assess the dysregulation of the neuroendocrine system, we measured the changes in cortisol levels throughout the day. Usually, cortisol reaches its peak in the morning and drops to its lowest level at night. However, during the surgery, this rhythm is often disrupted - the morning-to-evening cortisol ratio is lower than 2.0 or higher than 3.0. The decrease in cortisol levels indicates an imbalance in the hypothalamic-pituitary-adrenal axis, which may lead to serious health problems. The inflammatory response in surgical patients may be enhanced, and the defense capacity against surgical stress may be reduced [12, 13]. Poor sleep quality will disrupt the balance of the autonomic nervous system - vagal tone decreases, while the activity of the sympathetic nervous system increases. Subsequently, renal perfusion deteriorates, vasoconstriction occurs, the renin-angiotensin system is activated, and a series of conditions that may lead to acute kidney injury are triggered.

Why might the surgery conducted in the afternoon be beneficial for protecting the kidneys? One possible explanation is that the kidneys have an inherent circadian rhythm. In the morning, the kidney function is relatively stable, while in the afternoon, the blood flow to the kidneys increases, the activity of the renal tubules intensifies, and the cortisol level reaches its peak. Iron loss and abnormal iron metabolism are the key factors leading to acute kidney injury caused by ischemia-reperfusion [13]. In contrast, the increase in cortisol levels during the afternoon surgery may exert its effect through another mechanism - namely, inhibiting inflammation and stabilizing vascular tone. The decrease in the expression of the Rev-Erbα/β genes in the afternoon may help prevent damage caused by iron loss [10], which might explain why patients undergoing afternoon surgery have a lower risk of developing acute kidney injury compared to those undergoing morning surgery.

Propofol has two important effects: free radical clearance and inflammation inhibition. These properties may protect the kidneys during surgery, thereby reducing the risk of acute kidney injury after surgery. Although propofol is widely used in cardiac surgery with CPB, its potential renoprotective effect has not been fully confirmed [17, 18]. However, in pediatric research, the situation is different - continuous use of propofol leads to a higher incidence of AKI compared to other anesthetics [19]. Similarly, our data also indicates a correlation

between the infusion rate of propofol and the risk of acute kidney injury. What explains this discrepancy? High-dose propofol may inhibit the central nervous system and sympathetic nervous system activity, resulting in hypotension and renal artery constriction. When renal perfusion decreases, renal function is impaired, and acute kidney injury is triggered.

A longer CPB duration has also been shown to be another risk factor. Inoue et al. [20] also found a similar finding. We found that the longer the CPB duration, the lower the oxygen delivery, and it will also aggravate reperfusion injury, thereby damaging kidney function. The OR was 1.026 (95% CI: 1.013-1.040).

This nomogram performed very well in both cohorts. In the training set, its AUC reached 0.796 (95% confidence interval: 0.728-0.864); and in the validation set, the value was 0.776 (95% confidence interval: 0.671-0.881). The corresponding sensitivity and specificity values were 0.672/0.815 and 0.500/0.800. The optimism-corrected AUC obtained through bootstrap validation was 0.793. The calibration curve and DCA results also supported the model's performance - the predicted results of the model were very consistent with the observed outcomes, and showed good clinical utility at different thresholds. This nomogram enables clinicians to quickly and simply grade the AKI risk of CPB patients. If high-risk individuals can be identified before the surgery, corresponding preventive measures can be taken. To prevent postoperative AKI, clinicians can consider restoring the normal circadian rhythm, performing surgeries in the afternoon, controlling the infusion rate of propofol, and shortening the operation time.

Previous risk assessment tools have had certain limitations [21-23]. Our model is innovative because it takes into account modifiable factors such as circadian rhythms and anesthesia techniques, which were rarely considered in earlier tools. Since the graphical interface does not require specialized statistical knowledge, it simplifies the risk assessment process; this ease of use can accelerate clinical decision-making and enhance the practicality of the tool in routine practice.

We are aware that this study had some limitations. First, the single-center retrospective design may have introduced selection bias. Because consistent electronic record data could not be obtained, clock gene expression (BMAL1, CLOCK, PER, CRY) and 24-hour urine rhythm could not be evaluated. To address this limitation, we combined PSQI, melatonin, and cortisol measures to construct a comprehensive CRD definition - this method better reflects circadian status than a single indicator [11, 14]. Future prospective studies should incorporate clock gene profiling and continuous circadian monitoring to enhance the molecular specificity of CRD assessment. Second, our model does not include some widely recognized perioperative variables such as intraoperative hypothermia, aortic cross-clamp duration, blood transfusion volume, and vasoactive drug use. The absence of these variables may affect the accuracy of predictions. However, our propensity score-matched sensitivity analysis (n = 201) showed that the AUC remained stable (0.783 vs. 0.796), suggesting that the omission of these variables did not substantially alter the model's discriminative performance. Nevertheless, future studies should prospectively collect these variables to further refine the model. Third, the study only performed single-center internal bootstrap validation and lacked independent multicenter external cohort validation. The sensitivity of the validation set was only 0.500, indicating a limited ability to distinguish positive cases. Recent evidence has demonstrated that cardiac surgery-associated acute kidney injury (CSA-AKI) prediction models may exhibit substantial performance attenuation in external populations - one study reported an AUC decrease from 0.709 to 0.548 in an independent validation cohort due to population heterogeneity and differences in pathophysiologic milieu [8]. Therefore, the current model requires external validation before widespread clinical implementation. Fourth, this study focused only on the short-term outcomes of 7-day postoperative KDIGO-defined AKI and did not evaluate the predictive value of the model for long-term renal endpoints, including persistent renal dysfunction, progression of chronic kidney disease, renal replacement therapy, and all-cause mortality. Recent evidence shows that CSA-AKI is associated with a significantly greater decline in eGFR, increased mortality, and more rapid CKD progression within 5 years [9]. In future

translational research, we plan to conduct a multicenter prospective cohort study with standardized collection of circadian biological specimens (including clock gene expression and serial salivary melatonin/cortisol measurements) and a complete set of perioperative clinical indicators, with extended follow-up of 1-3 years to evaluate the predictive performance of the model for both short-term and long-term kidney-related outcomes. Finally, measurement bias is also a concern, as the sleep score is based on patient self-reporting, while melatonin levels are obtained through laboratory testing. Although we used strict imputation methods, these issues could not be completely resolved. We excluded surgeries performed between 12:00 and 14:00 and after 18:00 to minimize the influence of circadian rhythms on the results. Therefore, our findings may not be applicable to patients undergoing surgery at these times. Larger-scale prospective multicenter studies with longer follow-up and a broader patient population are needed to further validate and refine our model.

Conclusions

We constructed a nomogram based on three variable categories: circadian factors (related to the selection of surgery time and preoperative CRD), anesthesia factors (propofol infusion rate), and CPB duration. This model performed well in predicting the occurrence of AKI after cardiac surgery. In practical applications, this model may be useful, enabling clinicians to identify high-risk patients early and formulate personalized strategies for preventing complications. However, given the single-center retrospective design and the lack of external validation, the current model should be regarded as a preliminary tool that requires validation in independent multicenter cohorts before widespread clinical adoption. Future prospective studies incorporating standardized circadian biological specimen collection and long-term renal endpoint assessment are warranted to further establish the model's clinical utility.

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Disclosure of conflict of interest

None.

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References

[1] Pérez-Fernández X, Ulsamer A, Cámara-Rosell M, Sbraga F, Boza-Hernández E, Moret-Ruíz E, Plata-Menchaca E, Santiago-Bautista D, Boronat-García P, Gumucio-Sanguino V, Peñafiel-Muñoz J, Camacho-Pérez M, Betbesé-Roig A, Forni L, Campos-Gómez A and Sabater-Riera J; SIRAKI02 Study Group. Extracorporeal blood purification and acute kidney injury in cardiac surgery: the SIRAKI02 randomized clinical trial. JAMA 2024; 332: 1446-1454.

[2] Schurle A and Koyner JL. CSA-AKI: incidence, epidemiology, clinical outcomes, and economic impact. J Clin Med 2021; 10: 5746.

[3] Tseng PY, Chen YT, Wang CH, Chiu KM, Peng YS, Hsu SP, Chen KL, Yang CY and Lee OK. Prediction of the development of acute kidney injury following cardiac surgery by machine learning. Crit Care 2020; 24: 478.

[4] Li Y, Bie D, Xiong C, Shi S, Fang Z, Lu Z and Wang J. The clinical outcomes of acute kidney injury substages based on serum cystatin C in pediatric patients undergoing cardiac surgery. Ren Fail 2025; 47: 2466114.

[5] Permeisari D. Future insights of pharmacological prevention for AKI post cardiopulmonary bypass surgery (based on PK/PD approach). Front Pharmacol 2022; 13: 975641.

[6] Yang S, Ye Z, Chen L, Zhou X, Li W and Cheng F. Circadian clock gene Bmal1: a molecular bridge from AKI to CKD. Biomolecules 2025; 15: 77.

[7] Franzén S, DiBona G and Frithiof R. Anesthesia and the renal sympathetic nervous system in perioperative AKI. Semin Nephrol 2022; 42: 151283.

[8] Yoon SH, Kim YJ, Seo JH, Lim H, Lee HJ, Kwak C, Kim WH and Yoon HK. Influence of the type of anaesthesia on acute kidney injury after nephrectomy: a randomised controlled trial. Anaesthesia 2025; 80: 278-287.

[9] Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012; 120: c179-c184.

[10] Montaigne D, Marechal X, Modine T, Coisne A, Mouton S, Fayad G, Ninni S, Klein C, Ortmans S, Seunes C, Potelle C, Berthier A, Gheeraert C, Piveteau C, Deprez R, Eeckhoute J, Duez H, Lacroix D, Deprez B, Jegou B, Koussa M, Edme JL, Lefebvre P and Staels B. Daytime variation of perioperative myocardial injury in cardiac surgery and its prevention by Rev-Erbα antagonism: a single-centre propensity-matched cohort study and a randomised study. Lancet 2018; 391: 59-69.

[11] Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR and Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res 1989; 28: 193-213.

[12] Melone MA, Becker TC, Wendt LH, Ten Eyck P, Patel SB, Poston J, Pohlman AS, Pohlman M, Miller A, Nedeltcheva A, Hall JB, Van Cauter E, Zabner J and Gehlbach BK. Disruption of the circadian rhythm of melatonin: a biomarker of critical illness severity. Sleep Med 2023; 110: 60-67.

[13] Chen B, Yuan S, Wei P, Jing F, Zhu M, Zhang X, Zhang Y, Zhang Y, Wang H, Su Z, Yang J, Luo Y, Liu Y, Ning H, Li Z, Guo X, Song Y and Yang Z. The feasibility of salivary melatonin in assessing perioperative circadian rhythm in surgical patients: study protocol for a multicentre prospective study in China. BMJ Open 2025; 15: e105679.

[14] Sun SY and Chen GH. Treatment of circadian rhythm sleep-wake disorders. Curr Neuropharmacol 2022; 20: 1022-1034.

[15] Mercan M, Şehirli AÖ, Chukwunyere U and Abacıoğlu N. Acute kidney injury due to COVID-19 and the circadian rhythm. Med Hypotheses 2021; 146: 110463.

[16] Shi C, Zhao D, Lyubenov L, Motrapu M, Li N, Steiger S, Mammadova-Bach E, Yang L, Liu D and Anders HJ. Neutrophil circadian rhythm is associated with different outcomes of acute kidney injury due to cholesterol crystal embolism. Front Cardiovasc Med 2022; 9: 974759.

[17] Franzén S, Frithiof R and Hultström M. Postoperative acute kidney injury after volatile or intravenous anesthesia: a meta-analysis. Am J Physiol Renal Physiol 2023; 324: F329-F334.

[18] Fan T, Zhao Z, Liu J, Ma W, Tian J and Ma G. A randomized controlled trial on the impact of anesthetic agents on renal function in cardiac surgery with cardiopulmonary bypass. Mol Cell Biochem 2025; 480: 5399-5410.

[19] Li H, Weng Y, Yuan S, Liu W, Yu H and Yu W. Effect of sevoflurane and propofol on acute kidney injury in pediatric living donor liver transplantation. Ann Transl Med 2019; 7: 340.

[20] Inoue T, Kohira S, Ebine T, Shikata F, Fujii K and Miyaji K. Monitoring of intraoperative femoral oxygenation predicts acute kidney injury after pediatric cardiac surgery. Int J Artif Organs 2022; 45: 981-987.

[21] Lin X, Xiao L, Lin W, Wang D, Xu K and Kuang L. A model for predicting AKI after cardiopulmonary bypass surgery in Chinese patients with normal preoperative renal function. BMC Surg 2024; 24: 383.

[22] Wang K, Lin L, Zheng R, Nan S, Lu X and Duan H. Leveraging large language models for preoperative prevention of cardiopulmonary bypass-associated acute kidney injury. Ren Fail 2025; 47: 2509786.

[23] Peng W, Yang B, Qiao H, Liu Y and Lin Y. Prediction of acute kidney injury following coronary artery bypass graft surgery in elderly Chinese population. J Cardiothorac Surg 2023; 18: 287.