Development and Validation of a Predictive Nomogram for Postoperative Acute Kidney Injury in Elderly Patients Undergoing Liver Resection

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Research

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Abstract

Background

Postoperative acute kidney injury (AKI) is associated with poor clinical outcomes. Early identification of high-risk patients of developing postoperative AKI can optimize perioperative renal management and facilitate patient survival. The present study aims to develop and validate a nomogram to predict postoperative AKI after liver resection in elderly patients.

Methods

Postoperative AKI was assessed in 850 patients undergoing liver resection in a single-center retrospective cohort between 2012 and 2019. We reviewed electronic medical records and collected patient information on perioperative variables. The data were randomly split into training and validation datasets (split ratio 0.7:0.3). Stepwise regression was applied to identify predictive factors associated with postoperative AKI based on Akaike's information criterion, and multivariate logistic regression was applied to establish the predictive nomogram. The receiver operating characteristic (ROC) curve and calibration curve were used to evaluate the discrimination and accuracy of the prediction. The decision curve analysis (DCA) was used to assess clinical usefulness. A summary risk score was also constructed for identifying postoperative AKI patients (ClinicalTrials.gov NCT 04922866).

Results

Postoperative AKI occurred in 156 (18.3%) patients and was highly associated with in-hospital mortality (5.1% vs. 0.7%, $P < 0.05$). Predictors selected and assembled into the nomogram included age, preexisting chronic kidney disease (CKD), non-steroidal anti-inflammatory drugs (NSAIDs), preoperative direct bilirubin values, intraoperative hepatic inflow occlusion, blood loss, and transfusion. The predictive nomogram performed well in terms of discrimination with area under ROC curve (AUC) in training (0.74, 95% CI: 0.69 - 0.79) and validation (0.72, 95% CI: 0.64 - 0.80) datasets. The nomogram was well-calibrated in the validation dataset with the Hosmer-Lemeshow χ^2 of 8.12 ($P = 0.62$). DCA demonstrated a significant clinical benefit. The summary risk score was calculated as the sum of points from the seven variables (one point for each variable) and performed as well as the nomogram in identifying the risk of AKI (AUC 0.73, 95% CI: 0.68 - 0.78).

Conclusions

This nomogram and summary risk score accurately predicted postoperative AKI using seven clinically accessible variables, with potential application in facilitating the optimized perioperative renal management in elderly patients undergoing liver resection.

Background

Despite the recent technical advances in surgical procedures, there have been considerably high rates of operative mortality and morbidity resulting from complex surgical procedures, especially in emergency surgery cases [1]. Among the various types of postoperative organ injuries, acute kidney injury (AKI) is particularly prevalent in 5 to 20% of patients undergoing major non-cardiac surgery and in 10 to 40% of high-risk patients with hepatic resection surgery [2–5]. Previous studies have confirmed AKI as an independent contributor to peri- and postoperative morbidity and mortality in both cardiac and non-cardiac surgeries [6–9]. It has been reported that postoperative AKI could increase the risk of death by twelve folds and extend the hospital stay by five days than usual [2], and may also contribute to the development of advanced chronic kidney disease (CKD), involving substantial healthcare burden [10].

In the older population, however, the incidence of postoperative CKD is significantly higher as the filtration capacity of the kidney decreases about 1% every year after the age of 40, even in the healthy population [11, 12]. Microstructural and functional changes in the kidney related to healthy aging are reportedly aggravated in the presence of postoperative CKD [11]. Aging reduces renal autoregulatory capacity due to physiological and functional changes, leading to different types of kidney diseases, such as vascular sclerosis [13], declining glomerular filtration rate (GFR) [14], thereby enhancing the susceptibility of the elderly population to the postoperative AKI. Notably, Chao *et al*. [15] found that almost 20% of patients in a cohort of 4000 elderly subjects developed postoperative AKI. Moreover, postoperative AKI cases can significantly increase during certain procedures, such as cardiac and vascular surgeries, up to 30% [16]. In contrast to cardiac or vascular surgery-associated postoperative AKI incidence, there are not enough studies on hepatic resection-related AKI onset and its risk factors and prognosis.

Therefore, in-depth knowledge of risk factors and identification of high-risk populations, who are predisposed to develop AKI is urgently warranted as a preventive measure to minimize operative mortality rate and to design efficient therapeutic strategies. Efficient preventive measures to reduce the risk of AKI include precise assessment of renal functions, careful administration of nephrotoxic drugs, minimizing procedural injuries, and an effective intravenous fluid regimen.

However, no validated model is currently available to predict the risk of postoperative AKI in elderly patients following liver resection surgery. Slankamena *et al.*[4, 17] has developed and updated predictive scores for identifying AKI in adult patients following liver resection, but the small sample size and complex algorithms limit the clinical usefulness of this model. Therefore, the present study aimed to establish and validate a predictive nomogram and a simple risk score assessment to identify the risk of developing postoperative AKI in elderly patients following liver resection.

Methods

Study Design and Population

This retrospective cohort study was conducted using the dataset of inpatient surgeries in a single tertiary care center (First Medical Center of Chinese People's Liberation Army General Hospital). Elderly patients (age ≥ 65 years) admitted to the hospital for elective hepatectomy between January 2012, and July 2019 were included in this cohort. While patients with no more than 65 years old, baseline GFR<15 ml/min per 1.73 m^2, emergency operation, concurrent operation, or liver transplantation surgery were excluded. The study protocol was approved by the Institutional Medical Ethics Committee (S2021-335-01) and registered at clinicaltrials.gov (NCT 04922866).

Data collection

Data acquisition from the electronic medical record (EMR) system was performed using SQL Server (Microsoft, USA). From the patient record integrated management system (PRIDE 2.1.2.193, Heren Health, China), we extracted the relevant patient demographics, including the age, sex, comorbidities, American Society of Anesthesiologists (ASA) physical score, laboratory findings, diagnoses, prescribed medication regimen, types of surgical procedures performed, length of hospital stay and in-hospital mortality incidence. From the anesthesia information management systems (DoCare 3.1.0 build 153, MEDICAL SYSTEM, China), we retrieved information on the duration of surgery and anesthesia procedures, the requirement for intraoperative infusion and transfusion, and volumes of blood loss and urine output. We also collected the patient's kidney function test results in terms of serum creatinine level before and 7 days postoperative period to determine whether that patient experienced postoperative AKI symptoms.

Surgical and anesthetic management consisted of our well-defined standard processes that have been performed for the last ten years at our center [18, 19]. As such, special attention was given to fluid management to maintain a low central venous pressure (CVP) intraoperatively. Multidisciplinary perioperative cares were also routinely provided between the surgery, anesthesia, postanesthesia and intensive care conditions.

Primary outcome

The outcome event was postoperative AKI, defined as an absolute increase in serum creatinine level of 0.3 mg/dl within 48 hours or a 1.5-fold increase from preoperative baseline within seven days after surgery, according to the *Kidney Disease: Improving Global Outcomes (KDIGO)* criterion [20].

Study predictors

To facilitate the clinical use of predictors, we considered the inclusion of both preoperative and intraoperative parameters into the nomogram, which might closely affect renal function. We also considered restricting the numbers of predictive parameters to less than 10 to increase the model's applicability in case of over-fitting and taking sample size into account.

Therefore, candidate predictors included here were categorized as demographic, intra-, and perioperative variables and laboratory indexes. The demographic variables included gender, age, body mass index (BMI), hypertension, and preoperative CKD, which was defined as the GFR of less than 60 ml/min per 1.73 m^2 for adults based on the CKD Epidemiology Collaboration (CKD-EPI) equation [21]. Intraoperative variables were pathology diagnosis, the extent of liver resection, the volume of intraoperative blood loss, hepatic inflow occlusion, and duration of surgery. The extent of liver resection was categorized as a three-segment resection like right hemihepatectomy, left hemihepatectomy and partial hepatectomy. The perioperative variables were subcategorized into the use of medicines, intravenous fluid, and transfusion. While medication-associated variables included the use of dexamethasone, diuretics, non-steroid anti-inflammatory drugs (NSAIDs), and vasoactive drugs. The laboratory variables indicated preoperative concentrations of plasma hemoglobin, albumin, total bilirubin, direct bilirubin, and fasting glucose.

Statistical analysis and sample size

Missing data were complemented using the mean value imputation. The percentage of missing data ranged from 0 to 3.6%. Therefore, no multiple imputations were performed, as described elsewhere [22].

Continuous variables were tested for normality using the Skewness-Kurtosis All test. Normally distributed variables were reported as means and standard deviations and compared using the independent samples *t*-test. Abnormally distributed variables were reported as medians and interquartile ranges (IQR) and compared using Wilcoxon rank-sum test. Categorical data were reported as frequencies and percentages and compared using Fisher's χ^2 test.

The data were randomly split into training and validation datasets with a split ratio of 0.7: 0.3. The training dataset was used to develop the prediction model in the final logistic regression. Firstly, a bivariate analysis was performed using Wilcoxon rank-sum test for continuous variables and χ^2 test for categorical variables, with postoperative AKI as the outcome. Secondly, for the independent predictors included in the model, candidate variables that were clinically relevant to AKI and *P*-value < 0.1 in univariate analysis were included in the multivariate model. Additionally, the number of outcome events was considered, that is, at least ten outcome events per variable (EPV) generally [23]. Based on the EPV approach for determining sample size, our sample size could be expected to provide robust estimates. Thirdly, the forward stepwise approach was applied to select predictive variables in the final model, with Akaike's information criterion (AIC) value minimized with the minimum number of variables [24]. Finally, the multivariate logistic regression model was formulated to establish the prediction model, and a nomogram was further performed to predict postoperative AKI in the training dataset.

The predictive performance of the model was subsequently evaluated in patients from the validation cohort. The discrimination of the nomogram was assessed by calculating the area under the receiver operating characteristic (ROC) curve. The model calibration was evaluated using the Hosmer-Lemeshow goodness of fit test in the validation sample. Finally, the decision curve analysis (DCA) was performed to reveal the net benefits with each threshold probability [25]. Statistical analyses were performed using R 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria) and STATA 15.0 (StataCorp, College Station, TX) software. Statistical significance was accepted at the 0.05 level, and all tests were two-tailed.

Results

Patient characteristics

A total of 930 participants were screened for eligibility from January 2012 to July 2019. After the exclusion of 77 patients who undertook combined or multiple surgeries, 853 patients were selected with liver resection. Additionally, three subjects with missing serum creatinine values were excluded, thus leaving behind 850 individuals who were enrolled in the final analysis (Fig. 1). Patient characteristics for the overall population are listed in Table 1. Median (IQR) age at the time of surgery was 69 (66, 73) yr, where 556 (65%) patients were male, and 294 (35%) patients were female. The median (IQR) duration of operation was 205 (158, 270) min, and the median time to discharge was 10 (8, 13) days. Thirteen (1.5%) patients died before discharge.

Incidence of postoperative AKI and outcomes

Overall, 156 (18.3%) patients experienced postoperative AKI symptoms. Patients who underwent postoperative AKI were at a higher risk of death (5.1%) before discharge than those without AKI (0.7%) (Supplementary Table S1).

Development of a nomogram

The training dataset from 603 patients was used to establish the predictive nomogram. The validation dataset of the remaining 247 patients was used to evaluate the model's predictive performance.

The univariate analysis of factors associated with postoperative AKI is summarized in Table 2. Age, preexisting CKD, hepatic inflow occlusion, intraoperative blood loss and transfusion, perioperative use of NSAIDs, and preoperative direct bilirubin values were selected as the optimal subset for predicting postoperative AKI using the multivariate logistic regression model (Table 3). The nomogram comprising of these predictors is presented in Fig. 2a.

Validation of the nomogram

The nomogram had a satisfactory capacity with the areas under ROC curve (AUC) of 0.74 (95% CI: 0.69 - 0.79) and 0.72 (95% CI: 0.64 - 0.80) in the training and validation cohorts, respectively (Fig. 2b). Besides, the nomogram had a well-calibrated performance with Hosmer-Lemeshow χ^2 values of 8.30 ($P = 0.60$) and 8.12 ($P = 0.62$) in the training and validation cohorts, respectively (Fig. 2d and e). The DCA showed the overall net benefit that the patient could receive for the predictive nomogram. Fig. 2c indicated that the nomogram has a good net benefit in 10 to 40% of threshold probabilities.

Summary risk score model

To promote the clinical application of the nomogram, variables selected for the predictive model were dichotomized and counted. Each parameter was divided into two subgroups with good or poor prediction based on the cut-off values determined by ROC analysis. One point was assigned to each of the following predictors: age above 67 years, preexisting CKD, NSAIDs medication, preoperative serum direct bilirubin ≥ 5.4 μmol/L, intraoperative hepatic inflow occlusion, intraoperative blood loss > 300 mL, and requirement for blood transfusion. The summary score for individual patients ranged from 0 to 7. The risk of AKI ranged from 3% with a score of 1, to 43%, with a score of 7. The summary scores were then grouped as low (0 to 3 points) and high-risk group (4 to 7 points), as shown in Fig. 3. AUC for predicting postoperative AKI was 0.73 (95% CI: 0.68 - 0.78) for the summary score model, which was not significantly different from the previous model (Supplementary Fig. S1).

Discussion

To the best of our knowledge, this study exploited the largest cohort of elderly patients to estimate the postoperative AKI risk following liver resection surgery. Comprehensive information from consecutive 850 patients with hepatic resection over the past eight years was thoroughly reviewed and analyzed. The results provided previously unexplored insights for exploring the potential therapeutic strategies for renal function protection in adults, especially elder subjects, in peri- and postoperative conditions.

Summary of key findings

The present study summarized the incidence rates, predictors, and mortality impact of AKI in an elderly population following liver resection surgery. Our findings indicated that the prevalence of postoperative AKI was high (18%) among older populations with any of the three different categories of liver resection, and associated with six-fold increased mortality rates compared with no occurrence of AKI, corroborating results from previous studies by Lim *et al*. [3] and Slankamenac *et al*. [17]. Furthermore, a predictive nomogram for postoperative AKI was established and subsequently validated with seven predictors readily available in clinical situations. A simple risk score scale was also developed based on the seven predictors, which predicted AKI as accurately as the nomogram and was more easily accessible in clinical use. Depending on this approach, we can speculate that the nomogram together with risk score assessment can help optimize decision-making in predicting and preventing postoperative renal dysfunction.

Predictors for postoperative AKI

Several prediction models for postoperative AKI have been developed in noncardiac surgeries [4, 17, 26]. Although AKI occurred in about 20% of patients following liver surgeries, the prediction of AKI in this subgroup population had been rarely concerned. Slankamenac *et al*. [17] have developed and validated a prediction score system for postoperative AKI in adult patients scheduled for liver resection. However, the model obtained from preoperative factors alone was subject to debate for accurately predicting postoperative AKI. Since postoperative AKI prediction can be affected by multiple factors resulting from the interactions between surgery, anesthesia procedure, and intensive care, therefore, therapeutic options to prevent and treat AKI following liver resection should involve pre-, intra-, and postoperative approaches. Considering these facts, Slankamenac *et al*. have updated their risk prediction models, including three additional intraoperative variables: blood transfusions, hepaticojejunostomy, and oliguria [4]. The updated risk scoring system was superior in identifying patients who would benefit from a special care unit stay in case of AKI onset, compared to the preoperative prediction score.

Based on the previous studies, here we explored the risk factors in elderly patients. Predictors identified in the present study included age, CKD, NSAIDs medication, direct bilirubin count, intraoperative hepatic inflow occlusion, the volume of blood loss, and transfusion. Thus, optimization of controllable factors such as preoperative renal dysfunction, NSAIDs usage, and blood transfusion due to substantial surgical bleeding may benefit patient's survival outcomes. Surgical variables such as intraoperative hepatic occlusion and blood loss remained significant predictors of postoperative AKI. A possible explanation could be the complexity of the procedures needed for hepatic inflow occlusion, the requirement of extensive hepatic excision, and severe blood loss [27, 28].

In this context, minimization of surgical trauma and bleeding were fundamental protective strategies for renal conservation and also equally crucial to restore liver function and minimize resection extent. Inflammatory responses to surgical stress and trauma lead to tubular injury and subsequent development of AKI, potentially due to microcirculatory dysfunction, oxidative stress, and endothelial cell injury [29]. This group of patients should be given special attention because of their exceptionally high-risk exposure to perioperative procedures. Reducing the duration of hepatic occlusion has been shown to be favorable to control trauma and alleviate ischemia-reperfusion injury [30], which might contribute to the risk of renal injury mediated by inflammatory mediators and microcirculatory dysfunction [31].

Low CVP was required during the hepatectomy to reduce bleeding complications and mortality. Hughes *et al*. [32] have consolidated reduced blood loss and transfusion requirement by maintaining CVP below 5 mmHg, by intravenous fluid restriction, and by applying diuretics. At the same time, the resultant hypovolemia and oliguria may increase the risks of renal impairment, as demonstrated by Myles *et al*. [5] in a study comparing restrictive and liberal fluid administration. Historically, whether restrictive or liberal fluid therapy benefits outcomes remained controversial. Surgeons expect a very low CVP, while anesthesiologists argue against the low fluid load. The prolonged fluid restriction may lead to possible renal hypoperfusion with resultant oliguria. Vasopressors to correct hypovolaemia could further aggravate oliguria. Therefore, the urine output criterion may result in an overestimation of AKI [33]. It has been suggested that intraoperative urine output of 0.3 ml/kg/h was the optimal threshold for oliguria, nevertheless a moderate association and poor predictive value for postoperative AKI [34-36]. In the present study, we found that postoperative AKI was associated with high urine output and more employment of diuretics. Numerous studies have established the negative bearing of diuretics usage in AKI in major abdominal surgeries [37]. However, the relationship between the predictive value of diuretics and urine output in AKI remained to discuss, and further studies are needed to confirm the associations.

Preoperative CKD is the most important patient-related risk factor. It was not a new finding regarding the associations between CKD and postoperative AKI and death. While Chaudery *et al.* [8] has illustrated that in patients with a history of previous CKD, low estimated GFR does not markedly increase the mortality in the absence of AKI, highlighting AKI is likely to be a pivotal event connecting preoperative CKD and survival outcomes.

Several studies have implied a higher risk resulting from disrupted renal autoregulation due to NSAIDs usage during the perioperative period [38, 39]. NSAIDs inhibit cyclooxygenase activity and reduce prostaglandin secretion, resulting in tubular toxicity, renal vasoconstriction, decreasing renal blood flow, and low GFR. A systemic review conducted by Lee *et al*. [40] has demonstrated that NSAIDs may cause a clinically transient reduction in renal function in the early postoperative period in patients with normal preoperative renal function. Therefore, it is reasonable to minimize the nephrotoxic NSAIDs exposure in elderly patients concerning postoperative renal function, especially in the case of those with persistent renal dysfunction.

Implications for research priorities

Previous studies have indicated that preoperative hepatic dysfunction predisposes a patient to more medical complications such as renal insufficiency [3, 17]. Despite the multiple potential mechanisms necessitating further investigation, no effective treatment is available so far for this syndrome, apart from prophylactic measures. More importantly, it is critical to introduce close surveillance to raise early alarms for renal deterioration.

The application of novel biomarkers as clinical approaches for detecting early renal injury has been a matter of intense research. Though several biomarkers have been found promising in predicting postoperative AKI, the evidence has been controversial [41, 42]. For example, neutrophil gelatinase-associated lipocalin (NGAL) is not present in normal urine and plasma, and can be detected in urine during ischemic renal injury. Mishra *et al*. [43] have observed elevated NGAL in cardiac surgery-associated AKI within 2 hours and sustained high levels up to 24 hours. Inconsistent with these findings, subsequent studies in non-cardiac surgical cases have failed to correlate an association between NGAL and AKI onset [44, 45]. Urinary tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7 (TIMP2•IGFBP7) ratio has been proved to accurately detect high-risk surgical patients and enhance clinical prediction for imminent AKI [46]. These findings were further confirmed by Gocze *et al.* [47] in a randomized clinical trial evaluating the biomarker-triggered implementation of the KDIGO care bundle to prevent AKI. The study suggests that urinary TIMP2•IGFBP7 > 0.3 successfully allows for early initiation of renal protective interventions. Before these biomarkers are available in clinical settings, intense research is needed to explore the combined biomarker panels with agreeable predictive sensitivity and specificity.

It is of interest to develop target strategies for close monitoring of renal function. Previous studies have suggested that persistent intra- and postoperative low regional oxygen saturation (rSO_2) can be associated with postoperative renal dysfunction [48]. Unlike biomarkers, renal oxygenation measured by near-infrared spectroscopy (NIRS) enables noninvasive and real-time monitoring of renal function, indicating earlier alarms of renal injury than biomarkers such as NGAL. These potential targets are capable of implementing effective interventions to optimize renal function. Whether intraoperative renal desaturation predicts AKI and survival in noncardiac surgery remains to be investigated in our future studies.

Strengths of the study

The present nomogram and risk score assessment approach a landmark toward identifying strategies to reduce the prevalence of AKI following liver resection surgery. The general overview of the main highlights of this study is as follows. Firstly, we reviewed all relevant and eligible cases, acquired a few missing pieces of information. The large sample cohort allowed us the development and validation of a predictive model. Secondly, the estimated GFR was selected as a better predictor of outcome to define preexisting renal dysfunction instead of serum creatinine level. Thirdly, advanced statistical techniques such as the stepwise regression method increased the accuracy and applicability of the model. Finally, the simple summary risk score could be used to rapidly identify patients at high risk of developing AKI at the bedside without complex computation.

The prediction model was superior to the previous models, owing to the introduction of intraoperative variables. Notably, a patient assessed as the moderate risk of AKI preoperatively could still experience severe renal dysfunction mediated by the surgical insults (such as extended procedures and massive blood loss), which remained paramount in influencing renal function. Thus, it is considered to integrate risk scores with pre- and intraoperative parameters available throughout the entire perioperative process to precisely evaluate the risk of postoperative AKI.

Our findings shed light on a particular challenge faced by medical staff, including surgeons, anesthesiologists, and intensive care providers, which signify growing concerns that: (1) the incidence and prevalence of postoperative AKI is increasing as the number of the elderly population undergoing surgical procedures increases due to the aging population, proposing socio-economic and public health burdens; (2) early identification of AKI high-risk patients cannot be overemphasized to reduce the burden of postoperative complications and eventually the risk of death; (3) development of continuous surveillance (early identification) for renal dysfunction should be strengthened so that effective interventions could be started early rather than delayed.

Therefore, our attempts sought to provide a novel understanding of the disease to establish preventive strategies in perioperative patients, and promote potential targets for optimizing renal function in prospective clinical trials.

Limitations

Firstly, data were derived from a retrospective single-center cohort. The reproducibility and generalization of the model in other populations are unknown. Before the model is implemented in clinical applications, it is essential to be externally validated in open, prospective multicenter studies. Secondly, although intraoperative factors affecting renal function were incorporated into the model, the surrogate indicators did not obviously increase the model’s predictive performance. In combination with emerging biomarkers and novel specific monitoring, clinical risk predictive models may aid in future investigations of effective prevention and treatment strategies.

Conclusion

A nomogram and risk scoring system that accurately predicts postoperative AKI in elderly patients undergoing liver resection were established in this study. This model considered AKI based on seven conveniently available variables. It could provide guidance for both clinical decision-making and scheduling a tighter perioperative follow-up in AKI high-risk patients.

Abbreviations

AIC: Akaike's information criterion; AKI: acute kidney injury; ALB: albumin; ASA: American Society of Anesthesiologists; AUC: area under ROC curve; BMI: body mass index; CI: confidence interval; CKD: chronic kidney disease; CKD-EPI: CKD Epidemiology Collaboration; CVP: central venous pressure; DBIL: direct bilirubin; DCA: decision curve analysis; eGFR: estimated glomerular filtration rate; EMR: electronic medical record; EPV: events per variable; FBG: fasting blood glucose; HGB: hemoglobin; IGFBP7: insulin-like growth factor-binding protein 7; IQR: interquartile ranges; KDIGO: Kidney Disease: Improving Global Outcomes; HLOS: hospital length of stay; MAP: mean arterial pressure; NGAL: neutrophil gelatinase-associated lipocalin; NIRS: near-infrared spectroscopy; NSAIDs: non-steroid anti-inflammatory drugs; OR: odds ratio; ROC: receiver operating characteristic; rSO_2: regional oxygen saturation; Scr: serum creatinine; TBIL: total bilirubin; TIMP2: tissue inhibitor of metalloproteinases-2

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Medical Ethics Committee of the Chinese PLA General Hospital. Institutional review board approval (ref: S2021-335-01) was obtained for the data analysis of these collected data and signed patient consent was waived because no care interventions were mandated.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

YY: conceptualization, formal analysis, writing - original draft preparation. CSZ and FQZ: methodology, visualization, writing - original draft preparation. CL, HL and JSL: data curation, validation, project administration. ZPX: writing - review and editing. YHL and JBC: provision of study materials and data resources. WDM: writing - original draft preparation, funding acquisition, supervision. All authors read and approved the final manuscript.

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Tables

Table 1 Patient characteristics and perioperative variables stratified by datasets.

Variables	All Patients (n=850)	Training dataset (n=603)	Validation dataset (n=247)	*P* value
Age (years)	69 (66, 73)	69 (66, 72)	69 (66, 73)	0.44
Gender (n, %)				0.27
Male	556 (65.4%)	387 (64.2%)	169 (68.4%)	
Female	294 (34.6%)	216 (35.8%)	78 (31.6%)	
BMI (kg/m^2)	23.6 (21.5, 25.9)	23.6 (21.6, 25.7)	23.5 (20.9, 26.0)	0.66
Hypertension (n, %)				0.70
No	530(62.4%)	373 (61.9%)	157 (63.6%)	
Yes	320 (37.6%)	230 (38.1%)	90 (36.4%)	
Diabetes mellitus (n, %)				0.70
No	693 (81.5%)	494 (81.9%)	199 (80.6%)	
Yes	157 (18.5%)	109 (18.1%)	48 (19.4%)	
CKD (n, %)				0.24
No	818 (96.2%)	577 (95.7%)	241 (97.6%)	
Yes	32 (3.8%)	26 (4.3%)	6 (2.4%)	
ASA physical status, n (%)				0.77
I-II	699 (82.2%)	494 (81.9%)	205 (83.0%)	
III-IV	151 (17.8%)	109 (18.1%)	42 (17.0%)	
Pathology (n, %)				0.13
Hepatoma	539 (63.4%)	385 (63.8%)	154 (62.3%)	
Cholangiocarcinoma	129 (15.2%)	82 (13.6%)	47 (19.0%)	
Hepatic Metastasis	24 (2.8%)	16 (2.7%)	8 (3.2%)	
Benign lesions	158 (18.6%)	120 (19.9%)	38 (15.4%)	
Resection extent (n, %)				0.59
Right hemihepatectomy	120 (14.1%)	86 (14.3%)	34 (13.8%)	
Left hemihepatectomy	227 (26.7%)	155 (25.7%)	72 (29.1%)	
Partial hepatectomy	503 (59.2%)	362 (60.0%)	141 (57.1%)	
Hepatic inflow occlusion (n, %)				0.78

No	332 (39.1%)	238 (39.5%)	94 (38.1%)	
Yes	518 (60.9%)	365 (60.5%)	153 (61.9%)	
Duration of occlusion (min)	14 (0, 29)	14 (0, 30)	14 (0, 27)	0.87
	205 (158, 270)	204 (160, 270)	205 (155, 280)	0.95
Duration of operation (min)				
	300 (200, 550)			0.97
Blood loss (ml)		300 (200, 600)	300 (200, 500)	
	3100 (2600, 3600)			0.70
Total infusion volume (ml)				
	400 (200, 650)	3100 (2600, 3600)	3100 (2600, 3600)	0.51
Urine output (ml)				
				0.07
MAP<60 mmHg (n, %)		400 (200, 650)	400 (200, 650)	
	298 (35.1%)			
No				
	552 (64.9%)			
Yes				
	5 (0, 20)	223 (37.0%)	75 (30.4%)	0.06
Duration of MAP<60 mmHg (min)		380 (63.0%)	172 (69.6%)	0.93
Blood transfusion (n, %)	657 (77.3%)	5 (0, 20)	10 (0, 20)	
No	193 (22.7%)			
Yes		465 (77.1%)	192 (77.7%)	0.15
Vasoactive drugs (n, %)	452 (53.2%)	138 (22.9%)	55 (22.3%)	
None	248 (29.2%)			
Hyperensort	94 (11.1%)	328 (54.4%)	124 (50.2%)	
Hypotensor	56 (6.6%)	168 (27.9%)	80 (32.4%)	
Both		62 (10.3%)	32 (13.0%)	0.63
Glucocorticoid (n, %)	226 (26.6%)	45 (7.5%)	11 (4.5%)	
None	239 (28.1%)			
Dexamethasone	385 (45.3%)	159 (26.4%)	67 (27.1%)	
Methylprednisolone		165 (27.4%)	74 (30.0%)	0.20
Diuretics (n, %)	668 (78.6%)	279 (46.3%)	106 (42.9%)	
No	182 (21.4%)			
Yes		481 (79.8%)	187 (75.7%)	0.53
NSAIDs (n, %)	84 (9.9%)	122 (20.2%)	60 (24.3%)	
No	766 (90.1%)			
Yes	131 (120, 142)	57 (9.5%)	27 (10.9%)	0.28

Preoperative HGB (g/L)	39 (36.2, 41.5)	546 (90.5%)	220 (89.1%)	0.72
Preoperative ALB (g/L)	12.9 (9.3, 19.8)	131 (120, 142)	130 (119, 140)	0.93
Preoperative TBIL (μmol/L)	4.3 (3.0, 7.6)			0.86
Preoperative DBIL (μmol/L)	5.06 (4.58, 5.87)	39 (36.1, 41.5)	39 (36.8, 41.4)	0.55
Preoperative FBG (μmol/L)		13.1 (9.2, 19.7)	12.7 (9.7, 19.8)	
Preoperative eGFR	89.9 (82.0, 94.6)			0.07
		4.3 (3.0, 7.5)	4.3 (3.0, 7.8)	
(ml/min per 1.73 m^2)	68.0 (58.9, 78.8)			0.20
			5.13 (4.62, 5.96)	
Preoperative Scr (μmol/L)		5.04 (4.58, 5.84)		1.00
Postoperative AKI (n, %)	694 (81.6%)			
No	156 (18.4%)		90.3 (84.6, 95.3)	
Yes	10 (8, 13)	89.8 (80.6, 94.4)		0.74
			65.9 (58.2, 76.8)	
HLOS (days)		68.4 (59.0, 79.2)		0.22
Death before discharge (n, %)	837 (98.5%)			
	13 (1.5%)		202 (81.8%)	
No		492 (81.6%)		
			45 (18.2%)	
Yes		111 (18.4%)		
			10 (8,13)	
		10 (8,13)		
			241 (97.6%)	
		596 (98.8%)		
			6 (2.4%)	
		7 (1.2%)		

AKI acute kidney injury, ALB albumin, ASA American Society of Anesthesiologists, BMI body mass index, CKD chronic kidney disease, DBIL direct bilirubin, eGFR estimated glomerular filtration rate, FBG fasting blood glucose, HGB hemoglobin, HLOS hospital length of stay, IQR interquartile range, MAP mean arterial pressure, NSAIDs non-steroidal anti-inflammatory drugs, Scr serum creatinine, TBIL total bilirubin. Continuous data are shown as median (IQR) and compared using Wilcoxon rank-sum test. Categorical variables are shown as frequencies (percentages) and compared using Fisher's χ^2 test.

Table 2 Results of bivariate analyses of study variables versus postoperative AKI for the training dataset.

Variables	Non-AKI Patients (n=492)	AKI Patients (n=111)	*P* value
Age (years)	68 (66, 72)	69 (67, 74)	0.03
Gender (n, %)			0.66
Male	318 (64.6%)	69 (62.2%)	
Female	174 (35.4%)	42 (37.8%)	
BMI (kg/m^2)	23.7 (21.8, 25.7)	23.2 (21.0, 25.9)	0.27
Hypertension (n, %)			0.07
No	313 (63.6%)	60 (54.1%)	
Yes	179 (36.4%)	51 (45.9%)	
Diabetes mellitus (n, %)			0.07
No	410 (83.3%)	84 (75.7%)	
Yes	82 (16.7%)	27 (24.3%)	
CKD (n, %)			0.02
No	476 (96.7%)	101 (91%)	
Yes	16 (3.3%)	10 (9%)	
ASA status (n, %)			0.04
I-II	411 (83.5%)	83 (74.8%)	
III-IV	82 (16.5%)	28 (25.2%)	
Pathology (n, %)			0.17
Hepatoma	312 (63.4%)	73 (65.8%)	
Cholangiocarcinoma	63 (12.8%)	19 (17.1%)	
Hepatic Metastasis	12 (2.4%)	4 (3.6%)	
Benign lesions	105 (21.3%)	15 (13.5%)	
Resection extent (n, %)			< 0.01
Right hemihepatectomy	54 (11.0%)	32 (28.8%)	
Left hemihepatectomy	136 (27.6%)	19 (17.1%)	
Partial hepatectomy	302 (61.4%)	60 (54.1%)	
Hepatic inflow occlusion (n, %)			0.04
No	204 (41.5%)	34 (30.6%)	
Yes	288 (58.5%)	77 (69.4%)	

Duration of occlusion (min)	13 (0, 29)	18 (0, 32)	0.04
Duration of operation (min)	195 (152, 257)	240 (180, 305)	< 0.01
Blood loss (ml)	300 (200, 500)	500 (300, 800)	< 0.01
Total infusion volume (ml)	3100 (2600, 3600)	3460 (2700, 4100)	< 0.01
Urine output (ml)	400 (200, 600)	500 (250, 700)	0.04
MAP<60 mmHg (n, %)			0.45
No	186 (37.8%)	37 (33.3%)	
Yes	306 (62.2%)	74 (66.7%)	
Duration of MAP<60 mmHg (min)	5 (0, 15)	10 (0, 25)	0.05
Blood transfusion (n, %)			< 0.01
No	402 (81.7%)	63 (56.8%)	
Yes	90 (18.3%)	48 (43.2%)	
Vasoactive drugs (n, %)			< 0.01
None	276 (56.1%)	52 (46.8%)	
Hyperensort	129 (26.2%)	39 (35.1%)	
Hypotensor	56 (11.4%)	6 (5.4%)	
Both	31 (6.3%)	14 (12.6%)	
Glucocorticoid (n, %)			0.57
None	129 (26.2%)	30 (27.0%)	
Dexamethasone	139 (28.3%)	26 (23.4%)	
Methylprednisolone	224 (45.5%)	55 (49.5%)	
Diuretics (n, %)			0.02
No	402 (81.7%)	79 (71.2%)	
Yes	90 (18.3%)	32 (28.8%)	
NSAIDs (n, %)			< 0.01
No	54 (11.0%)	3 (2.7%)	
Yes	438 (89.0%)	108 (97.3%)	
Preoperative HGB (g/L)	133 (122, 142)	124 (112, 137)	< 0.01
Preoperative ALB (g/L)	39.2 (36.2, 41.7)	38.0 (34.1, 41.0)	< 0.01
Preoperative TBIL (μmol/L)	13 (9.3, 19.0)	13.8 (9.1, 27.2)	0.21

Preoperative DBIL (μmol/L)	4.2 (2.9, 7.3)	5.5 (3.2, 16.4)	< 0.01
Preoperative FBG (μmol/L)	5.02 (4.58, 5.78)	5.30 (4.56, 6.26)	0.10
Preoperative eGFR (ml/min per 1.73 m^2)	89.7 (81.0, 94.4)	90.2 (79.2, 95.6)	0.86
Preoperative Scr (μmol/L)	68.9 (59.1, 79.4)	66.6 (58.5, 77.6)	0.38
HLOS (days)	10 (8, 13)	11 (8, 16)	0.02
Death before discharge (n, %)			
No	489 (99.4%)	107 (96.4%)	0.02
Yes	3 (0.6%)	4 (3.6%)	

AKI acute kidney injury, ALB albumin, ASA American Society of Anesthesiologists, BMI body mass index, CKD chronic kidney disease, DBIL direct bilirubin, eGFR estimated glomerular filtration rate, FBG fasting blood glucose, HGB hemoglobin, HLOS hospital length of stay, IQR interquartile range, MAP mean arterial pressure, NSAIDs: non-steroidal anti-inflammatory drugs, Scr serum creatinine, TBIL total bilirubin. Continuous data are shown as median (IQR) and categorical variables are shown as frequencies (percentages). Bivariate analyses were conducted using either Fisher's χ^2 test or Wilcoxon rank-sum test. *P* value is derived from the bivariate association analyses between each study variable and postoperative AKI.

Table 3 Predictors for postoperative AKI after liver resection in final regression model for training dataset.

Intercept and Variable	*β* Coefficient	OR (95% CI)	*P* value
Intercept	-8.067	NA	NA
Age in years	0.063	1.065 (1.014-1.118)	0.013
CKD	0.985	2.677 (1.123-6.381)	0.026
NSAIDs	1.176	3.240 (0.975-10.770)	0.055
DBIL (per 10 μmol/L)	0.075	1.078 (1.001-1.161)	0.047
Hepatic inflow occlusion	0.521	1.684 (1.053-2.693)	0.030
Blood loss (per 100 ml)	0.069	1.071 (1.022-1.123)	0.004
Blood transfusion	0.654	1.923 (1.101-3.358)	0.022
Area under ROC curve			
Training dataset		0.74 (0.69-0.79)	
Validation dataset		0.72 (0.64-0.80)	

CI confidence interval, CKD chronic kidney disease, DBIL direct bilirubin, NA not applicable, NSAIDs non-steroidal anti-inflammatory drugs, OR odds ratio, ROC receiver operating characteristic.

Figures

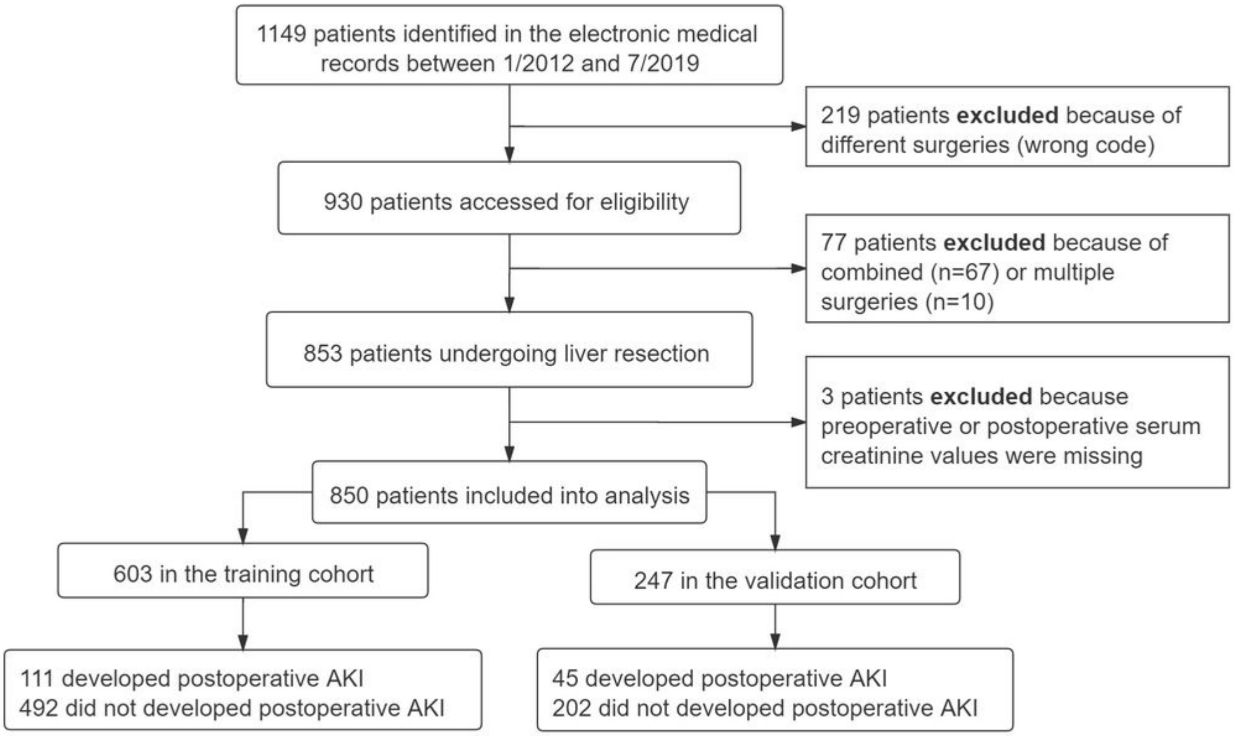

Figure 1

Study population enrolled and outcomes in the training and validation datasets. AKI acute kidney injury.

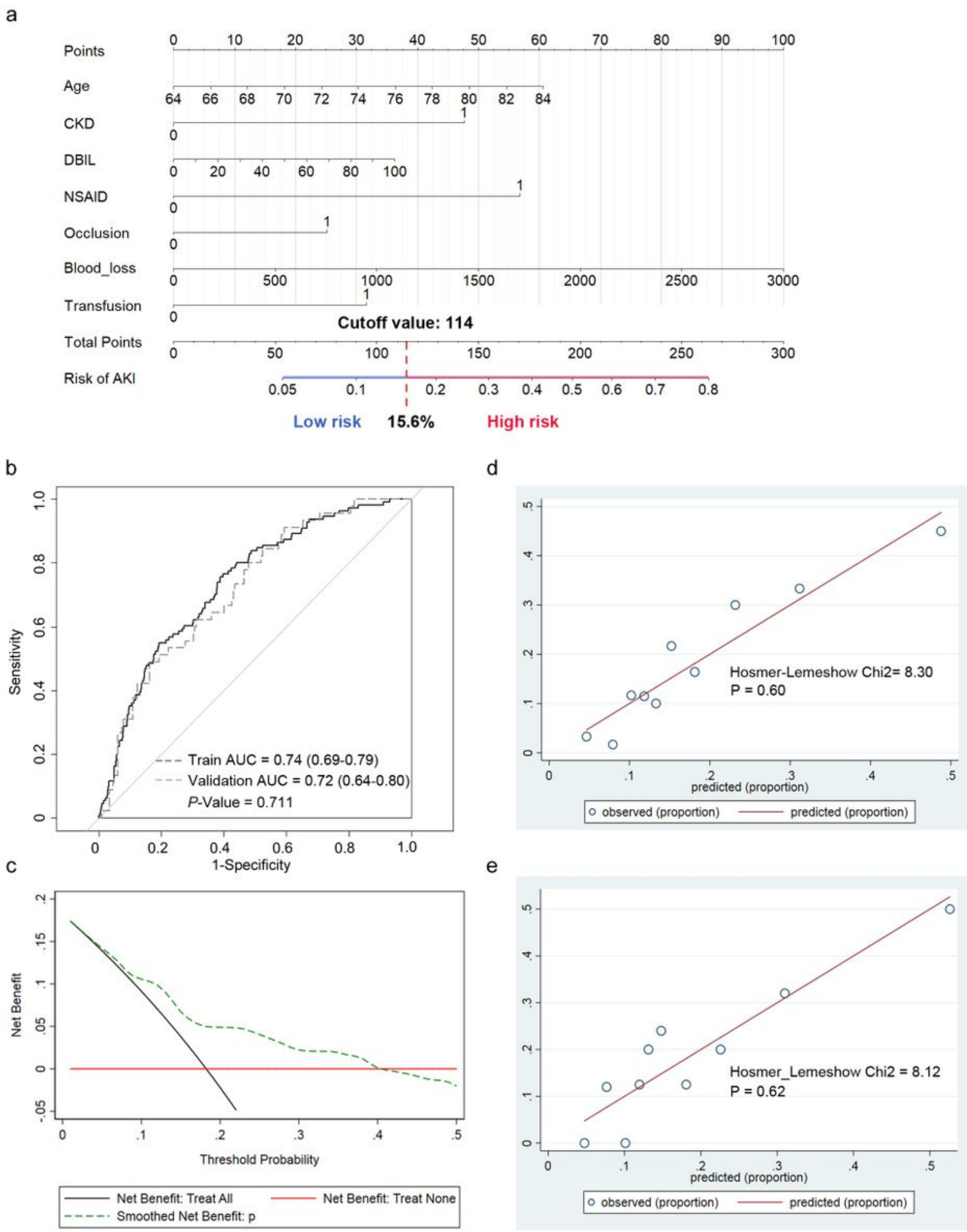

Figure 2

Developed and validated nomogram to estimate the probability of postoperative AKI. (a) This nomogram was developed with seven perioperative predictors. Find each predictor's point on the uppermost point scale and add them up. The total point projected to the bottom scale indicates the % probability of postoperative AKI. (b) Receiver operating characteristic (ROC) curves of the nomograms in training and validation cohorts. (c) Decision curve analysis (DCA) for the nomogram. The green line represents the nomogram and the y-axis indicates the net benefit. The DCA showed that if the threshold probability is 10 to 40%, using the nomogram to predict postoperative AKI adds more benefit than treat-all or treat-none scheme. (d, e) Calibration curves for predicting postoperative AKI by the nomogram in the training (d) and validation (e) cohorts. The y-axis represents the actual rate of postoperative AKI, the x-axis represents the predicted probability of postoperative AKI. The Hosmer-Lemeshow goodness-of-fit test is preferred to compare the significant difference between the predictive probability and actual occurrence, with P > 0.05 indicating no statistically significant difference and good predictive accuracy.

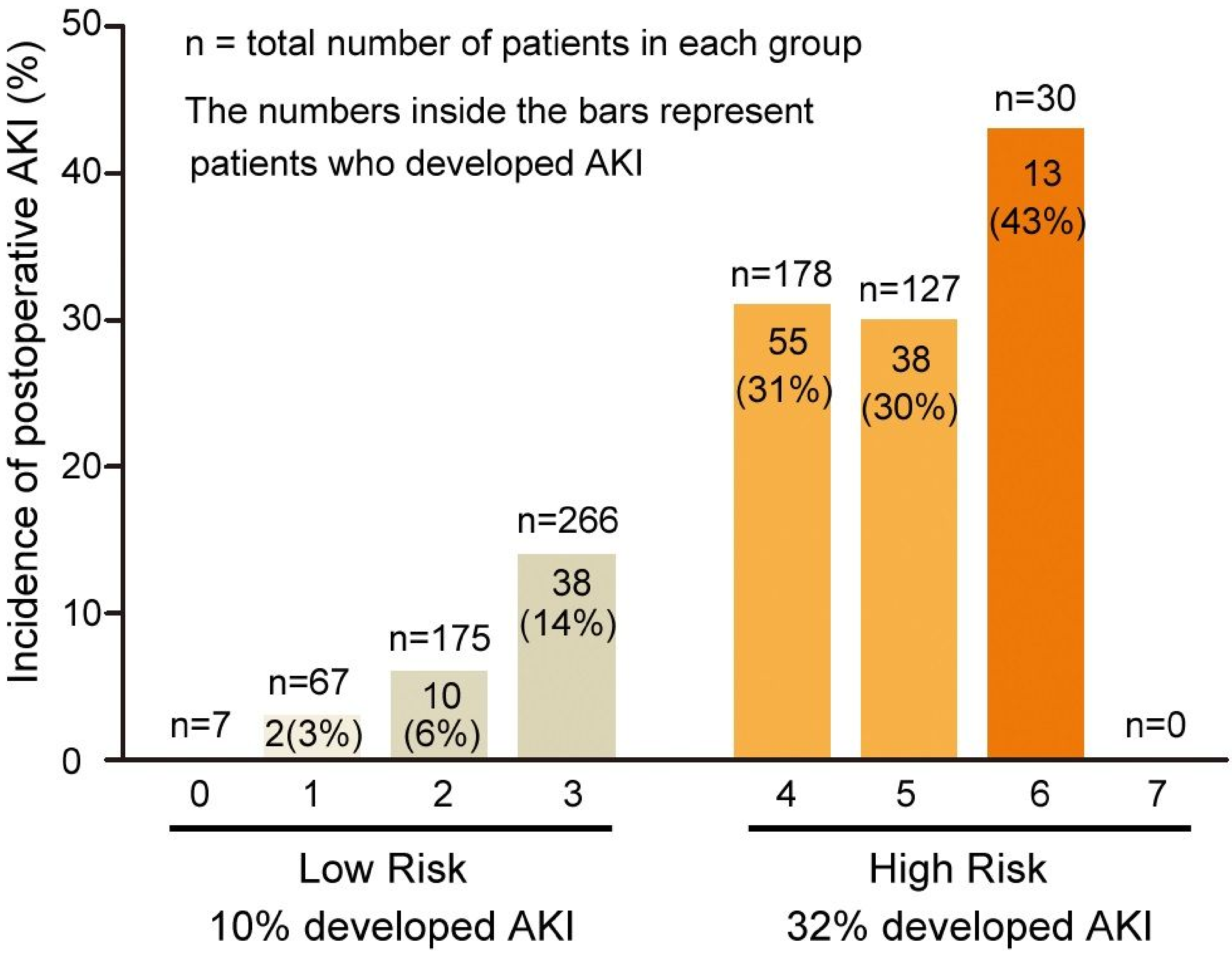

Figure 3

Association of the summary risk score with development of postoperative AKI. One point is assigned to each of the seven predictors: age above 67 years, CKD, NSAIDs use, preoperative direct bilirubin ≥ 5.4 μmol/L, intraoperative hepatic inflow occlusion, intraoperative blood loss > 300 mL, and requirements for blood transfusion.

Supplementary Files

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- SupplementaryFigureS1.tif
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