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Nomogram for predicting the development of pneumonia after colorectal cancer surgery

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The aim of this study was to analyze the factors contributing to the development of pneumonia after colorectal cancer (CRC) surgery and to develop a validated nomogram to predict the risk. We retrospectively collected information on patients who underwent radical CRC resection at a single clinical center from January 2011 to December 2021. The information was then randomly assigned to a training cohort and a validation cohort in a 7:3 ratio. Univariate and multivariate logistic regression analysis were performed on the training cohort to identify independent risk factors for the development of pneumonias, which were then included in the nomogram. Validation was performed in a validation cohort, area under the curve (AUC) and calibration curves were used to determine the predictive accuracy and discriminative power of the graphs, and decision curve analysis (DCA) was used to further substantiate the clinical efficacy of the nomogram. A total of 7130 patients were included in the study. Based on multivariate logistic regression analysis of the training cohort, age, sex, preoperative albumin, surgical methods, and surgical time were identified as independent risk factors for the development of pneumonia after CRC surgery, and a nomogram prediction model was established using the above five variables. The AUC was 0.745 in training cohort and 0.773 in validation cohort. This study established a nomogram that is a good predictor of the risk of developing pneumonia after CRC surgery and provided surgeons with a reference for personalized management of patients in the perioperative period.

Keywords Nomogram, Pneumonia, Colorectal cancer, Surgery, Risk factor

According to Global Cancer Statistics 2020, colorectal cancer (CRC) has become the third leading cause of new cancer diagnoses worldwide (10%) and the second leading cause of cancer-related deaths (9.4%) after lung cancer (18%).[1] Approximately 153,020 people are expected to be diagnosed with CRC and 52,550 people are expected to die from CRC in 2023[5] Current treatments for CRC include surgery, local radiotherapy and systemic therapy (chemotherapy, targeted therapy and immunotherapy),[7] however, radical surgical treatment remains the foundation for the treatment of CRC[9].

Postoperative complications of CRC have always been a hot topic in clinical researches. Due to the continuous improvements in surgical techniques and perioperative management, the incidence of postoperative complications of CRC has decreased significantly compared to the previous periods[14]. However, the incidence of postoperative pneumonia remains an important determinant of prognosis in patients with CRC, particularly following the global neocoronavirus epidemic, which has dramatically increased the incidence of postoperative pneumonia[15]. Previous studies of the factors that influenced the risk of developing pneumonia after heart surgery, hip surgery, lung cancer surgery, and oesophageal cancer surgery have shown that age, sex, preoperative hemoglobin and albumin, and the duration of the surgery may be the risk factors for the development of pneumonia in the postoperative period[18]. However, there are few studies on risk factors for the developing of pneumonia after CRC surgery.

In recent years, the application of nomogram prediction models has been widely recognised[24]. The probability of a medical event was estimated by integrating each predictor through a simple line graph, thus providing a good reference for patient management in clinical work[25] Therefore, the aim of this study was to analyze the factors contributing to the development of pneumonia after CRC surgery and to develop a validated nomogram to predict the risk.

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Materials and methods

Patient selection

The Clinical Research Ethics Committee of the First Affiliated Hospital of Chongqing Medical University reviewed and approved this study (2022-135-2), and all patients signed an informed consent form. In addition, this study was conducted in strict accordance with the Declaration of Helsinki. We retrospectively collected information on patients who underwent CRC surgery from January 2011 to December 2021 at a single clinical center.

The inclusion criteria were as follows: (1) Pathologically confirmed colorectal malignancy; (2) Undergoing CRC surgery. A total of 8152 Patients were included according to the inclusion criteria. The exclusion criteria were as follows: (1) Patients who underwent CRC surgery after recurrence ($n = 306$); (2) Patients with incomplete basic or clinical information ($n = 635$); (3) Patients with metastatic CRC ($n = 81$). Finally, 7130 patients were included.

Patient grouping

For the selection of training cohort and verification cohort, we adopted a simple random sampling method. Firstly, patients were numbered 1-7130, and then 4994 different random numbers were generated by random number generator. According to the generated random numbers, 4994 patients were selected from the data set as the training cohort, and the remaining 2136 patients were selected as the verification cohort. Regarding the ratio of training and validation cohort, the common ratio was 7:3, 8:2, 6:4. As the number of patients included in this study was sufficient, the most common ratio of 7:3 was selected in this study.

Data elements and definition

The patient information included personal information, clinical information, and surgical information. Personal information included age, sex, body mass index (BMI), smoking and drinking, preoperative comorbidities, and previous abdominal surgery (PAS). Clinical information included neoadjuvant therapy, preoperative albumin and hemoglobin, tumor location, tumor stage and tumor size. Surgical information included surgical methods (open or laparoscopic), surgical time and blood loss.

Preoperative comorbidities included hypertension, type 2 diabetes mellitus (T2DM) and chronic heart disease (CHD). Tumor staging was comprehensively classified into stages I-IV according to TNM staging of tumors in the 8th edition of the AJCC guidelines[27]. Postoperative pneumonia was defined as the occurrence of postoperative symptoms of coughing and sputum with infection confirmed by sputum culture.

Patients with metastatic colorectal cancer were defined as those who, based on preoperative imaging, were determined to be unable to undergo radical surgery and therefore did not undergo surgical treatment. The stages displayed in the table incorporating patient information are pathological stages based on postoperative pathological results.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) using independent samples t-test, categorical variables are expressed as numbers or percentages using chi-squared test or Fisher's exact test. Univariate logistic regression analysis was performed on all variables to look for potential predictors of the development of pneumonia after CRC surgery. Multivariate logistic regression analysis was also performed on all variables with $p < 0.05$ to identify independent predictors of the development of pneumonia after CRC surgery. Variables with $P < 0.05$ in multivariate logistic regression analysis were included and a nomogram was created to predict the risk of developing pneumonia after CRC surgery.

A subject operating characteristic curve was used to calculate the optimal cut-off point for continuous variables and the area under the curve (AUC) was calculated to evaluate the predictive probability. Calibration curves were plotted comparing nomogram predicted probabilities to actual probabilities with the 45° line as a perfect model with 100% accuracy[28]. Decision curve analysis (DCA) was used to further confirm the clinical validity of the nomogram[29].

All data in this study were processed using SPSS (version 22.0) as well as R software (version 4.1.2).

Results

Baseline information

A total of 7130 patients who underwent surgery for CRC were finally included based on the above inclusion and exclusion criteria. The 7130 patients were randomized in a 7:3 ratio to a training cohort and a validation cohort, with 4994 patients in the training cohort and 2136 patients in the validation cohort.

Baseline information was compared between the two groups of patients and there was no statistical difference in the baseline information ($p > 0.05$), including age, sex, BMI, smoking and drinking, preoperative comorbidities, PAS, neoadjuvant therapy, preoperative hemoglobin, tumor location, tumor stage, tumor size, surgical methods, and blood loss, except for preoperative albumin ($p = 0.021$) and surgical time ($P = 0.027$). (Table 1)

Nomogram variable screening

As shown in Table 2, we performed univariate and multivariate logistic regression analysis of 18 potential factors to identify risk factors for the development of pneumonia after CRC surgery. The results of univariate logistic regression analysis suggested that age ($p < 0.01$, OR = 1.070, 95% CI = 1.056–1.083), sex ($p < 0.01$, OR = 0.484, 95% CI = 0.359–0.654), BMI ($p = 0.014$, OR = 0.948, 95% CI = 0.909–0.989), smoking ($p < 0.01$, OR = 1.651, 95% CI = 1.268–2.150), drinking ($p < 0.01$, OR = 1.624, 95% CI = 1.241–2.125), hypertension ($p = 0.011$, OR = 1.443, 95% CI = 1.088–1.914), CHD ($p < 0.01$, OR = 2.116, 95% CI = 1.318–3.397), PAS ($p = 0.015$, OR = 1.426, 95%

Characteristics	Development (4994)	Validation (2136)	*P* value
Age, year	62.7 ± 12.3	63.0 ± 12.3	0.416
Sex			0.572
Male	2917 (58.4%)	1263 (59.1%)	
Female	2077 (41.6%)	873 (40.9%)	
BMI, kg/m^2	22.6 ± 3.2	22.6 ± 3.2	0.767
Smoking	1850 (37.0%)	809 (37.9%)	0.507
Drinking	1540 (30.8%)	636 (29.8%)	0.372
Hypertension	1255 (25.1%)	543 (25.4%)	0.795
T2DM	572 (11.5%)	246 (11.5%)	0.939
CHD	217 (4.3%)	103 (4.8%)	0.373
PAS	1216 (24.3%)	544 (25.5%)	0.315
Neoadjuvant therapy	324 (6.5%)	147 (6.9%)	0.539
Albumin, g/L	39.7 ± 5.5	40.0 ± 23.9	0.021*
Hemoglobin, g/L	120.9 ± 24.0	121.3 ± 23.9	0.479
Tumor location			0.776
Colon	2361 (47.3%)	1002 (46.9%)	
Rectum	2633 (52.7%)	1134 (53.1%)	
TNM stage			0.346
I	945 (18.9%)	392 (18.4%)	
II	1991 (39.9%)	864 (40.4%)	
III	1779 (35.6%)	781 (36.6%)	
IV	279 (5.6%)	99 (4.6%)	
Tumor size			0.529
< 5 cm	3002 (60.1%)	1301 (60.9%)	
≥ 5 cm	1992 (39.9%)	835 (39.1%)	
Surgical methods			0.604
Open	630 (12.6%)	279 (13.1%)	
Laparoscopic	4364 (87.4%)	1857 (86.9%)	
Surgical time, min	227.8 ± 86.2	223.0 ± 80.0	0.027*
Blood loss, mL	107.1 ± 179.7	101.1 ± 143.1	0.170
Pneumonia	155 (3.1%)	73 (3.4%)	0.409

Table 1. Baseline information between the development and validation cohorts. Note: Variables are expressed as the mean ± SD, n (%), *P-value < 0.05. Abbreviations: T2DM, type 2 diabetes mellitus; BMI, body mass index; CHD, chronic heart disease; PAS, previous abdominal surgery.

CI = 1.073–1.895), neoadjuvant therapy ($p = 0.018$, OR = 0.374, 95% CI = 0.165–0.846), preoperative albumin ($p < 0.01$, OR = 0.902, 95% CI = 0.881–0.923), preoperative hemoglobin ($p < 0.01$, OR = 0.991, 95% CI = 0.986–0.996), tumor location ($p = 0.019$, OR = 1.373, 95% CI = 1.053–1.790), tumor size ($p = 0.011$, OR = 1.410, 95% CI = 1.083–1.837), surgical methods ($p < 0.01$, OR = 2.426, 95% CI = 1.785–3.296), surgical time ($p < 0.01$, OR = 1.002, 95% CI = 1.001–1.004) and blood loss ($p < 0.01$, OR = 1.001, 95% CI = 1.000-1.001) were potential risk factors for the development of pneumonia after CRC surgery.

Further multivariate logistic regression analysis revealed that age ($p < 0.01$, OR = 1.057, 95% CI = 1.043–1.072), sex ($p < 0.01$, OR = 0.595, 95% CI = 0.408–0.868), preoperative albumin ($p < 0.01$, OR = 0.940, 95% CI = 0.914–0.966), surgical methods ($p = 0.014$, OR = 1.540, 95% CI = 1.093–2.168), and surgical time ($p < 0.01$, OR = 1.002, 95% CI = 1.001–1.004) were independent risk factors for the development of pneumonia after CRC surgery.

Nomogram construction and validation

Based on five independent risk factors identified by multivariate logistic regression analysis, we constructed a nomogram model to predict the risk of pneumonia in patients after CRC surgery. As shown in Fig. 1, the corresponding points of each factor was obtained according to the patient's own situation, and the five points were added to obtain the total points, and then the risk of pneumonia after CRC surgery was determined according to the corresponding risk of the total points.

We use the following three approaches to validate the effectiveness of the nomogram model. Firstly, after time-dependent receiver operating characteristic (ROC) curve analysis, the time-dependent AUC for the training cohort was 0.745, and the AUC for the validation cohort was 0.773, suggesting that the model has a high predictive potential. (Fig. 2) Secondly, a bootstrap resampling procedure was applied to plot the calibration curves for the training and validation cohorts respectively, as shown in Fig. 3, which shows that there is a good agreement between the predicted probabilities and observed probabilities of the nomogram model constructed in this study. DCA curves are used to assess clinical utility, and as shown in Fig. 4, the model multi curve is

Risk factors	Univariate logistic regression analysis		Multivariate logistic regression analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, year	1.070 (1.056–1.083)	< 0.01*	1.057 (1.043–1.072)	< 0.01*
Sex (female/male)	0.484 (0.359–0.654)	< 0.01*	0.595 (0.408–0.868)	< 0.01*
BMI, Kg/m^2	0.948 (0.909–0.989)	0.014*	0.986 (0.943–1.031)	0.528
Smoking (yes/no)	1.651 (1.268–2.150)	< 0.01*	1.242 (0.858–1.799)	0.250
Drinking (yes/no)	1.624 (1.241–2.125)	< 0.01*	1.253 (0.879–1.786)	0.213
Hypertension (yes/no)	1.443 (1.088–1.914)	0.011*	1.078 (0.795–1.462)	0.629
T2DM (yes/no)	1.129 (0.759–1.679)	0.549		
CHD (yes/no)	2.116 (1.318–3.397)	< 0.01*	1.276 (0.772–2.110)	0.341
PAS (yes/no)	1.426 (1.073–1.895)	0.015*	1.319 (0.981–1.775)	0.067
Neoadjuvant therapy (yes/no)	0.374 (0.165–0.846)	0.018*	0.466 (0.202–1.076)	0.074
Albumin, g/L	0.902 (0.881–0.923)	< 0.01*	0.940 (0.914–0.966)	< 0.01*
Hemoglobin, g/L	0.991 (0.986–0.996)	< 0.01*	0.999 (0.993–1.006)	0.846
Tumor location (colon/ rectum)	1.373 (1.053–1.790)	0.019*	0.988 (0.734–1.331)	0.939
Tumor stage (IV/III/II/I)	0.922 (0.785–1.081)	0.317		
Tumor size (≥ 5/<5), cm	1.410 (1.083–1.837)	0.011*	1.034 (0.777–1.377)	0.819
Surgical methods (open/ laparoscopic)	2.426 (1.785–3.296)	< 0.01*	1.540 (1.093–2.168)	0.014*
Surgical time, min	1.002 (1.001–1.004)	< 0.01*	1.002 (1.001–1.004)	< 0.01*
Blood loss, mL	1.001 (1.000-1.001)	< 0.01*	1.000 (1.000-1.001)	0.138

Table 2. Univariate and multivariate logistic regression analysis of the pneumonia. Note: *P-value < 0.05. Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; T2DM, type 2 diabetes mellitus; BMI, body mass index; CHD, chronic heart disease; PAS, previous abdominal surgery.

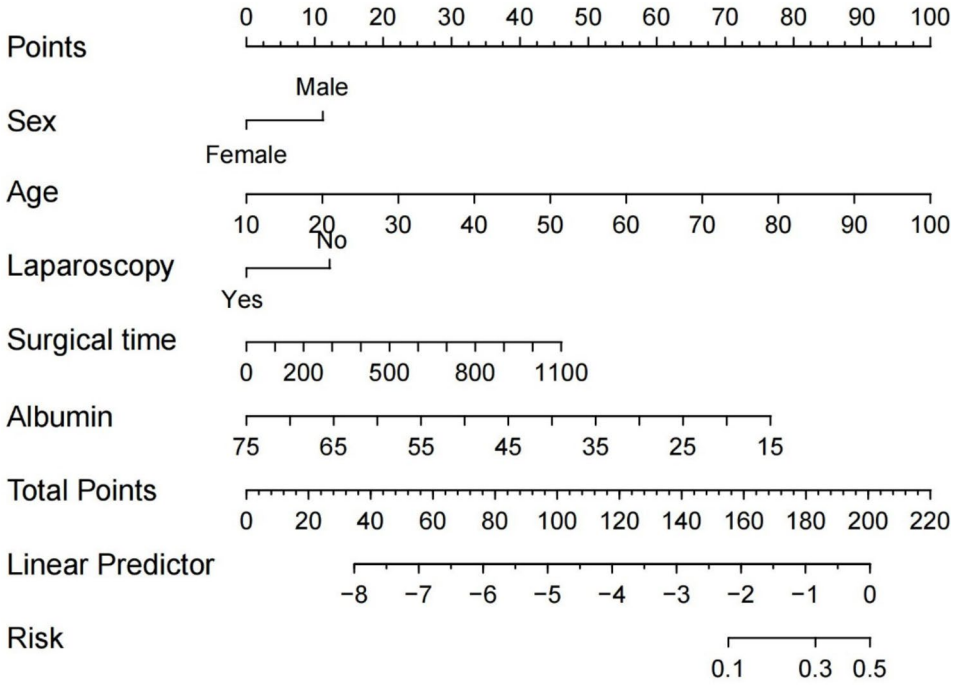

Fig. 1. Nomogram for predicting the development of pneumonia after colorectal cancer surgery.

higher than the none and all curves for certain threshold ranges, indicating that the model's predictions within these threshold ranges are useful for clinical decision making.

Discussion

A total of 7130 patients who underwent CRC surgery at a single clinical center was included in this retrospective study and randomly assigned to a training cohort and a validation cohort in a ratio of 7:3, with 4994 in the

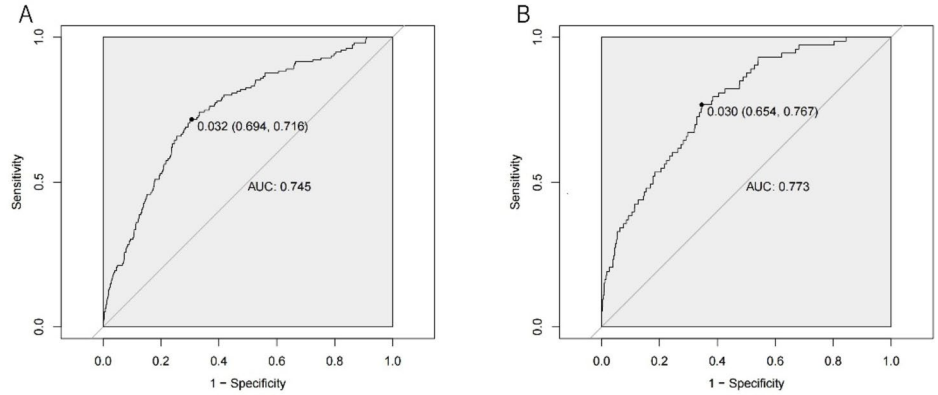

Fig. 2. ROC curves of the nomogram. (**A**) training cohort; (**B**) validation cohort. Note: ROC, receiver operating characteristic; AUC, area under the curve.

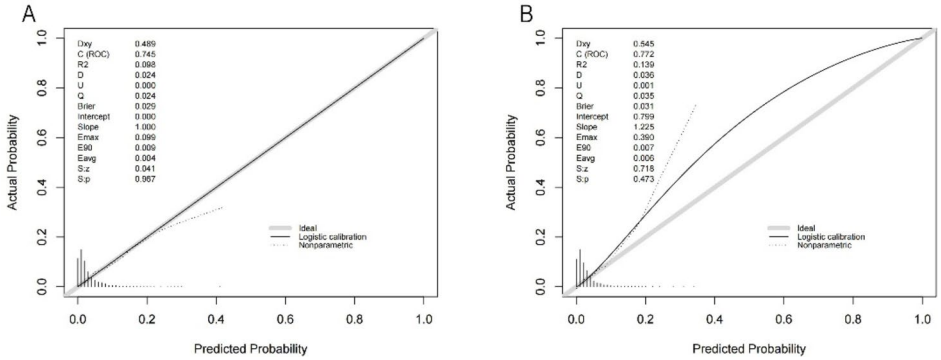

Fig. 3. Calibration curves for the nomogram. (**A**) training cohort; (**B**).

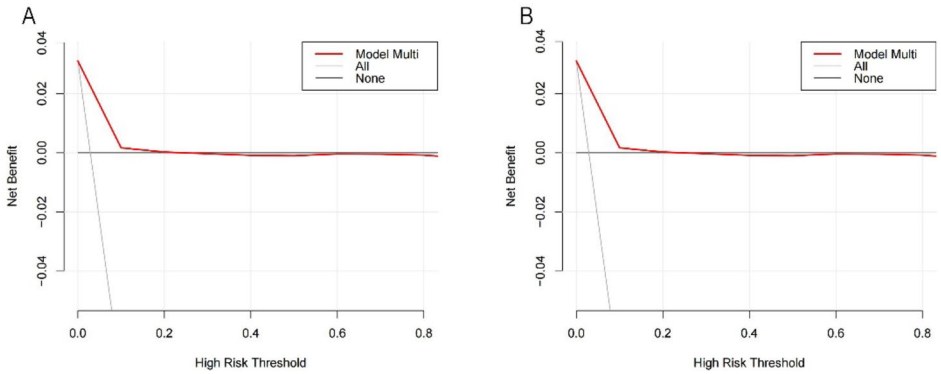

Fig. 4. DCA for the nomogram. (**A**) training cohort; (**B**). Note: DCA, decision curve analysis.

training cohort and 2136 in the validation cohort. Multivariate logistic regression analysis showed that age, sex, preoperative albumin, surgical methods and surgical time were independent risk factors for the development of pneumonia after CRC surgery. Based on five independent risk factors identified by multivariate logistic regression analysis, we constructed a nomogram model to predict the risk of postoperative pneumonia in patients with CRC.

The results of this study showed that older age, male patients, lower preoperative albumin, open surgery, and longer surgical time were independent risk factors for the development of postoperative pneumonia. Several previous studies have shown that older age and male sex are important influences on poor postoperative prognosis (including postoperative pneumonia)[36]. With age, swallowing and immune dysfunction occuring, leading to increased airway inflammation, decreased lung volume and a decline in baseline lung function, which

increases the risk of post-operative pneumonia[37]. Male patients may have a higher risk of developing pneumonia after surgery, possibly due to different lifestyles and behaviors as well as socio-economic differences[40].

Low preoperative albumin was an independent risk factor for developing pneumonia in the postoperative period. Low preoperative albumin indicates a reduction in the organism's organ reserve function, which in turn reduces the organism's ability to withstand a major blow such as surgery[41]. Secondly, low albumin in patients would reduce the number of lymphocytes in the body, weaken phagocytosis and reduce the activity of antibody synthase, thus reducing the body's immune function and increasing the risk of lung infection[42]. In addition, low blood albumin can reduce plasma osmolality and destroy vascular endothelial growth factor, leading to interstitial oedema and further impairment of lung function[45].

Numerous studies have shown that laparoscopic surgery was significantly better than open surgery for radical CRC, both in terms of surgical time, short-term complications and prognosis[47]. Open surgery has often been the main cause of postoperative pain, leading to inadequate cough expectoration, which increases the risk of postoperative pneumonia[24]. It has been suggested that aspiration of secretions that accumulated in the subglottic space during general anesthesia might lead to postoperative pneumonia, which might be an important reason why the prolonged duration of surgery increases the risk of postoperative pneumonia[50].

Despite many advances in anesthetic techniques and surgical approaches, and increasingly standardized perioperative management, postoperative pneumonia remains a major complication after surgery[51]. To the best of our knowledge, this is the first attempt to construct a nomogram prediction model for the risk of developing postoperative pneumonia after CRC using clinically significant risk factors screened by multivariate logistic regression analysis.

Although the present study has a large amount of data and a good efficacy of the nomogram prediction model, the present study still has some limitations. First, this was a single-center retrospective study, and although the data were divided into a training cohort and a validation cohort at a ratio of 7:3, selection bias could not be completely avoided. Second, this was a retrospective study, and it was not possible to track patients' preoperative lung function because pulmonary function testing was not routine. Furthermore, regarding certain general condition indicators of patients, such as ECOG PS and ASA, were not included in the present study because of the difficulty in collecting comparative data, so they could not be included in this study. However, this model has certain limitations when the risk threshold for pneumonia after colorectal surgery is considered 0.2 or higher, and later models that are more capable of assessing postoperative complications need to be developed. Therefore, prospective, multicenter and more comprehensive risk assessment is needed in the future.

In conclusion, this study established a nomogram that is a good predictor of the risk of developing pneumonia after CRC surgery and provided surgeons with a reference for personalized management of patients in the perioperative period.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due but are available from the corresponding author upon reasonable request.

Received: 31 January 2024; Accepted: 25 February 2025
Published online: 03 March 2025

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Acknowledgements
We acknowledge all the authors whose publications are referred in our article.

Author contributions
Peng D and Liu XY contributed to the conception and design of the study. Hai ZX organized the database. Peng D performed the statistical analysis. Peng D and Liu XY wrote the first draft of the manuscript. Lv Q, Zhang W and Liu XR wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version. Finally, XiangYC and Wen GX made excellent contributions to the article revision process.

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and informed consent
The study was approved by the ethics committee of our institution (The First Affiliated Hospital of Chongqing Medical University, 2022-135-2), and all patients signed informed consent.

Consent for publication
Not applicable.

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