

Risk Factors for Ileus After Radical Gastrectomy for Gastric Cancer and Construction of a Nomogram Prediction Model

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Objective: To construct a nomogram prediction model for ileus after radical gastrectomy for gastric cancer.

Methods: The 424 gastric cancer patients were assigned into a modeling group of 297 cases and a validation group of 127 cases. The modeling group was assigned into the ileus group of 54 cases and the non ileus group of 243 cases based on the occurrence of postoperative ileus. LASSO regression analysis and multivariate logistic regression analysis were used to screen the influencing factors of ileus after radical gastrectomy for gastric cancer. The nomogram model was constructed for predicting ileus after radical gastrectomy for gastric cancer. The calibration curve was used to evaluate the calibration degree of the model. ROC curve was used to evaluate the model discrimination. The clinical decision curve was used to analyze the clinical applicability of the model.

Results: LASSO regression analysis and multivariate logistic regression analysis showed that age (OR=4.999), previous abdominal surgery (OR=3.836), operative time (OR=3.541), IL-6 (OR=1.339), and TNF- α (OR=8.254) were all independent risk factors for ileus after radical gastrectomy for gastric cancer ($P < 0.05$). The deviation correction curves of the modeling group and the validation group were both close to the ideal curve, with Hosmer-Lemeshow test showed $\chi^2 = 7.785, 6.145, P = 0.236, 0.372$; the AUC of the ROC curve was 0.940 (95% CI: 0.898~0.981) and 0.904 (95% CI: 0.855~0.954). Both the modeling group and the validation group had high net returns within the threshold probability ranges of 0.02~0.86 and 0.02~0.80.

Conclusion: The nomogram prediction model constructed in this study can serve as an early warning indicator for ileus after radical gastrectomy for gastric cancer, guiding clinical decision-making.

Keywords: radical gastrectomy for gastric cancer, ileus, risk factors, nomogram

Introduction

Gastric cancer is a common malignant tumor of the digestive tract, which usually requires comprehensive surgery-based treatment.¹ Radical gastrectomy is usually extensive and traumatic, which hinders the recovery of gastrointestinal function.² Postoperative ileus is a common gastrointestinal dysfunction after abdominal surgery, characterized by weakened or absent bowel sounds, abdominal distension, constipation, and poor oral tolerance. Although most cases of postoperative ileus can be relieved within 3 days, some patients experience persistent or recurrent postoperative ileus.³ As a common complication after radical gastrectomy for gastric cancer, postoperative ileus is affected by various factors such as water and electrolyte imbalance, surgical trauma, inflammatory response, excessive sympathetic nerve activity, and drug effects. Its mechanism is complex and not yet fully understood.^{4,5} Postoperative ileus can lead to prolonged hospital stay, increased medical costs, and even increase the risk of other complications. By analyzing the related factors of postoperative ileus after radical gastrectomy for gastric cancer and establishing a model to predict the probability of postoperative ileus, early intervention and optimal preventive measures can be implemented, thereby benefiting more patients by improving outcomes and reducing medical costs.



However, there is currently a lack of simple and precise tools for individualized prediction of the risk of postoperative intestinal obstruction following radical gastrectomy. In this context, the present study aims to analyze the relevant risk factors for intestinal obstruction after radical gastrectomy for gastric cancer and to develop and validate an individualized nomogram model to quantify the probability of postoperative intestinal obstruction in patients.

Materials and Methods

General Information

This study followed the Declaration of Helsinki and obtained approval from the ethics committee. Patients who underwent radical gastrectomy for gastric cancer in our hospital from January 2022 to April 2025 were included as the study subjects. Inclusion criteria: ① adult patients with gastric cancer, pathologically confirmed as gastric cancer, and meeting the criteria;⁶ ② no neoadjuvant therapy before surgery; ③ no recent history of glucocorticoids or immunosuppressants. Exclusion criteria: ① incomplete or unanalyzable clinical, laboratory, or surgical data; ② death within 30 days after radical gastrectomy for gastric cancer; ③ severe hepatic or renal insufficiency or heart failure; ④ other malignant tumors; ⑤ Distant metastasis or peritoneal dissemination was confirmed intraoperatively or by postoperative pathology. The flowchart of case inclusion is shown in Figure 1. A total of 424 patients with gastric cancer were finally included, and they were divided into a modeling group of 297 cases and a validation group of 127 cases according to a ratio of approximately 7:3. The modeling group was further divided into an ileus group of 54 cases and a non-ileus group of 243 cases according to the occurrence of postoperative ileus.

Methods

Collection and Definition of Clinical Data

Clinical data of gastric cancer patients were collected, including age (<60 years or ≥ 60 years), gender, body mass index (BMI) (weight/height²), smoking (continuous or cumulative smoking for 6 months or more is defined as a history of smoking), alcohol consumption (at least once a month, including social occasions, or drinking for more than half a year is defined as a history of drinking), diabetes mellitus (1. Having symptoms of diabetes with random venous plasma glucose concentration ≥ 11.1 mmol/L;

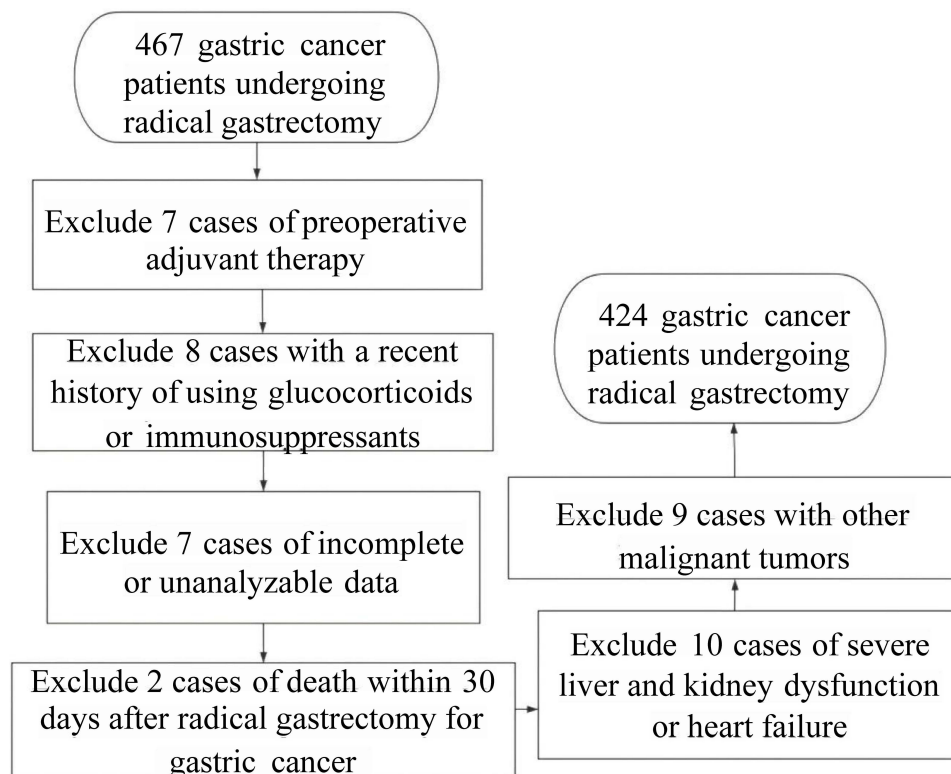


Figure 1 Flowchart of case inclusion.

2. Venous plasma glucose concentration ≥ 11.1 mmol/L 2 hours after oral administration of 75 g glucose in an oral glucose tolerance test; 3. Fasting venous plasma glucose concentration ≥ 7.0 mmol/L), hypertension (without the use of antihypertensive drugs, blood pressure measured 3 times on different days with systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg), tumor size (< 5 cm or ≥ 5 cm), tumor location (gastric antrum or gastric body), previous abdominal surgery, surgical method (laparoscopic or open), TNM stage (III or IIIIV), differentiation degree (moderate/high differentiation or low differentiation), operation time (< 400 min or ≥ 400 min), intraoperative blood loss (< 500 mL or ≥ 500 mL), IL-2, IL-4, IL-6, TNF- α , IL-10, CRP, WBC. Among them, IL-2, IL-4, IL-6, TNF- α , and IL-10 were detected using an Aixkang AE120 fully automatic enzyme immunoassay analyzer, CRP was detected by immunoturbidimetry, and WBC was detected by a Sysmex 800 blood analyzer. The cutoff values for age, tumor size, intraoperative blood loss, and operative time were set at the median values of each respective variable.

Evaluation of Postoperative Ileus

The definition of postoperative ileus referred to the criteria proposed in recent systematic reviews and global surveys,⁷ specifically including the diagnosis of postoperative ileus if the patient met two or more of the following five criteria on or after the 4th postoperative day: ① nausea or vomiting within the first 12 hours; ② no passage of gas or stool within the first 24 hours; ③ inability to tolerate oral diet within the first 24 hours; ④ abdominal distension; ⑤ radiological confirmation. The diagnosis of postoperative ileus was made independently by two experienced surgeons.

Statistical Methods

Measurement data were expressed as ($\bar{x} \pm s$), all of which conformed to a normal distribution, and were analyzed using the *t*-test (two-tailed); count data were expressed as [n (%)], and were analyzed using the Pearson χ^2 test; LASSO regression analysis and multivariate logistic regression analysis were used to screen the influencing factors of postoperative ileus after radical gastrectomy for gastric cancer; a nomogram model was constructed to predict postoperative ileus after radical gastrectomy for gastric cancer, and calibration curves were used to evaluate the model's calibration, ROC curves were used to evaluate the model's discrimination, and clinical decision curve analysis was used to analyze the model's clinical applicability. Nomograms, LASSO regression analysis feature variable selection plots, calibration curves, and decision curves were drawn using R software (R 4.3.3), ROC curves were drawn using SPSS software (version 25.0), and $P < 0.05$ indicated a statistically significant difference.

Results

Comparison of Clinical Data Between the Modeling and Validation Groups

There were no statistically significant differences in age, gender, BMI, smoking, alcohol consumption, diabetes mellitus, hypertension, tumor size, tumor location, previous abdominal surgery, surgical approach, TNM stage, differentiation degree, operation time, intraoperative blood loss, IL-2, IL-4, IL-6, TNF- α , IL-10, CRP, and WBC between the modeling and validation groups ($P > 0.05$). See Table 1.

Table 1 Comparison of Clinical Data Between Modeling Group and Validation Group [n (%)]/($\bar{x} \pm s$)

Index	Modeling Group (n=297)	Validation Group (n=127)	χ^2/t	P
Age (years old)			0.260	0.61
<60	151 (50.84)	68 (53.54)		
≥ 60	146 (49.16)	59 (46.46)		
Gender [n (%)]			0.872	0.35
Male	210 (70.71)	84 (66.14)		
Female	87 (29.29)	43 (33.86)		
BMI (kg/m ²)	22.78 \pm 2.97	23.01 \pm 3.09	0.722	0.47
Smoke [n (%)]	186 (62.63)	81 (63.78)	0.051	0.82
Drink [n (%)]	43 (14.48)	25 (19.69)	1.791	0.18

(Continued)

Table 1 (Continued).

Index	Modeling Group (n=297)	Validation Group (n=127)	χ^2/t	P
Diabetes [n (%)]	41 (13.80)	15 (11.81)	0.308	0.58
Hypertension [n (%)]	67 (22.56)	35 (27.56)	1.217	0.27
Tumor size (cm)			3.035	0.08
<5	149 (50.17)	52 (40.94)		
≥5	148 (49.83)	75 (59.06)		
Tumor site [n (%)]			2.686	0.10
Gastric antrum	224 (75.42)	86 (67.72)		
Gastric body	73 (24.58)	41 (32.28)		
Previous abdominal surgery [n (%)]			1.758	0.19
No	260 (87.54)	105 (82.68)		
Yes	37 (12.46)	22 (17.32)		
Surgical procedure [n (%)]			0.173	0.68
Laparoscope	280 (94.28)	121 (95.28)		
Open	17 (5.72)	6 (4.72)		
TNM stage [n (%)]			1.036	0.31
I~II	154 (51.85)	59 (46.46)		
III~IV	143 (48.15)	68 (53.54)		
Degree of differentiation [n (%)]			1.030	0.31
Medium/high differentiation	169 (56.90)	79 (62.20)		
Low differentiation	128 (43.10)	48 (37.80)		
Operative time (min)			2.961	0.09
<400	199 (67.00)	74 (58.27)		
≥400	98 (33.00)	53 (41.73)		
Intraoperative bleeding volume (mL)			0.032	0.86
<500	182 (61.28)	79 (62.20)		
≥500	115 (38.72)	48 (37.80)		
IL-6 (pg/mL)	15.51±4.56	16.38±4.67	1.787	0.08
IL-2 (pg/mL)	1.80±0.42	1.77±0.42	0.674	0.50
IL-4 (pg/mL)	2.20±0.51	2.25±0.54	0.908	0.36
TNF- α (pg/mL)	2.55±0.65	2.61±0.63	0.879	0.38
IL-10 (pg/mL)	5.91±1.30	5.82±1.35	0.645	0.52
CRP (mg/L)	31.22±7.49	32.06±7.54	1.056	0.29
WBC ($\times 10^9/L$)	5.89±1.46	5.76±1.51	0.831	0.41

Univariate Analysis of Postoperative Ileus After Radical Gastrectomy for Gastric Cancer in the Modeling Group

There were no statistically significant differences in gender, BMI, smoking, alcohol consumption, diabetes mellitus, hypertension, tumor location, TNM stage, differentiation degree, intraoperative blood loss, IL-2, and IL-4 between the ileus group and the non-ileus group ($P > 0.05$). The proportions of patients aged ≥ 60 years, with tumor size ≥ 5 cm, with previous abdominal surgery, undergoing open surgery, with operation time ≥ 400 min, and the levels of IL-6, TNF- α , IL-10, CRP, and WBC were significantly higher in the ileus group than in the non-ileus group ($P < 0.05$). See [Table 2](#).

Variable Screening for Postoperative Ileus After Radical Gastrectomy for Gastric Cancer

Age, tumor size, previous abdominal surgery, surgical approach, operation time, IL-6, TNF- α , IL-10, CRP, and WBC from the univariate analysis in 2.2 were included in the LASSO regression analysis for variable screening.

Table 2 Univariate Analysis of Postoperative Ileus After Radical Gastrectomy for Gastric Cancer in the Modeling Group [n (%)]/($\bar{x} \pm s$)

Index	Non Ileus Group (n=243)	Ileus Group (n=54)	χ^2/t	P
Age (years old)			18.921	<0.001
<60	138 (56.79)	13 (24.07)		
≥60	105 (43.21)	41 (75.93)		
Gender [n (%)]			1.106	0.29
Male	175 (72.02)	35 (64.81)		
Female	68 (27.98)	19 (35.19)		
BMI (kg/m ²)	22.81±3.05	22.62±2.93	0.417	0.68
Smoke [n (%)]	156 (64.20)	30 (55.56)	1.410	0.24
Drink [n (%)]	33 (13.58)	10 (18.52)	0.870	0.35
Diabetes [n (%)]	32 (13.17)	9 (16.67)	0.454	0.50
Hypertension [n (%)]	50 (20.58)	17 (31.48)	3.008	0.08
Tumor size (cm)			5.927	0.02
<5	130 (53.50)	19 (35.19)		
≥5	113 (46.50)	35 (64.81)		
Tumor site [n (%)]			0.908	0.34
Gastric antrum	186 (76.54)	38 (70.37)		
Gastric body	57 (23.46)	16 (29.63)		
Previous abdominal surgery [n (%)]			14.203	0.00
No	221 (90.95)	39 (72.22)		
Yes	22 (9.05)	15 (27.78)		
Surgical procedure [n (%)]			4.875	0.03
Laparoscope	233 (95.88)	47 (87.04)		
Open	10 (4.12)	7 (12.96)		
TNM stage [n (%)]			0.363	0.55
I-II	128 (52.67)	26 (48.15)		
III-IV	115 (47.33)	28 (51.85)		
Degree of differentiation [n (%)]			0.150	0.70
Medium/high differentiation	137 (56.38)	32 (59.26)		
Low differentiation	106 (43.62)	22 (40.74)		
Operative time (min)			15.192	<0.001
<400	175 (72.02)	24 (44.44)		
≥400	68 (27.98)	30 (55.56)		
Intraoperative bleeding volume (mL)			2.472	0.12
<500	154 (63.37)	28 (51.85)		
≥500	89 (36.63)	26 (48.15)		
IL-6 (pg/mL)	14.65±3.91	19.37±4.82	7.674	<0.001
IL-2 (pg/mL)	1.79±0.41	1.82±0.43	0.482	0.63
IL-4 (pg/mL)	2.19±0.50	2.22±0.54	0.393	0.70
TNF- α (pg/mL)	2.41±0.60	3.15±0.83	7.598	<0.001
IL-10 (pg/mL)	5.80±1.24	6.42±1.45	3.219	<0.001
CRP (mg/L)	30.25±7.31	35.59±8.15	4.753	<0.001
WBC ($\times 10^9/L$)	5.75±1.42	6.53±1.57	3.580	<0.001

The relationship between binomial deviance and $\text{Log}(\lambda)$ is plotted in Figure 2. When the λ value was 0.0142, only 5 variables (which may have the greatest impact on the occurrence of postoperative ileus) were retained in the model.

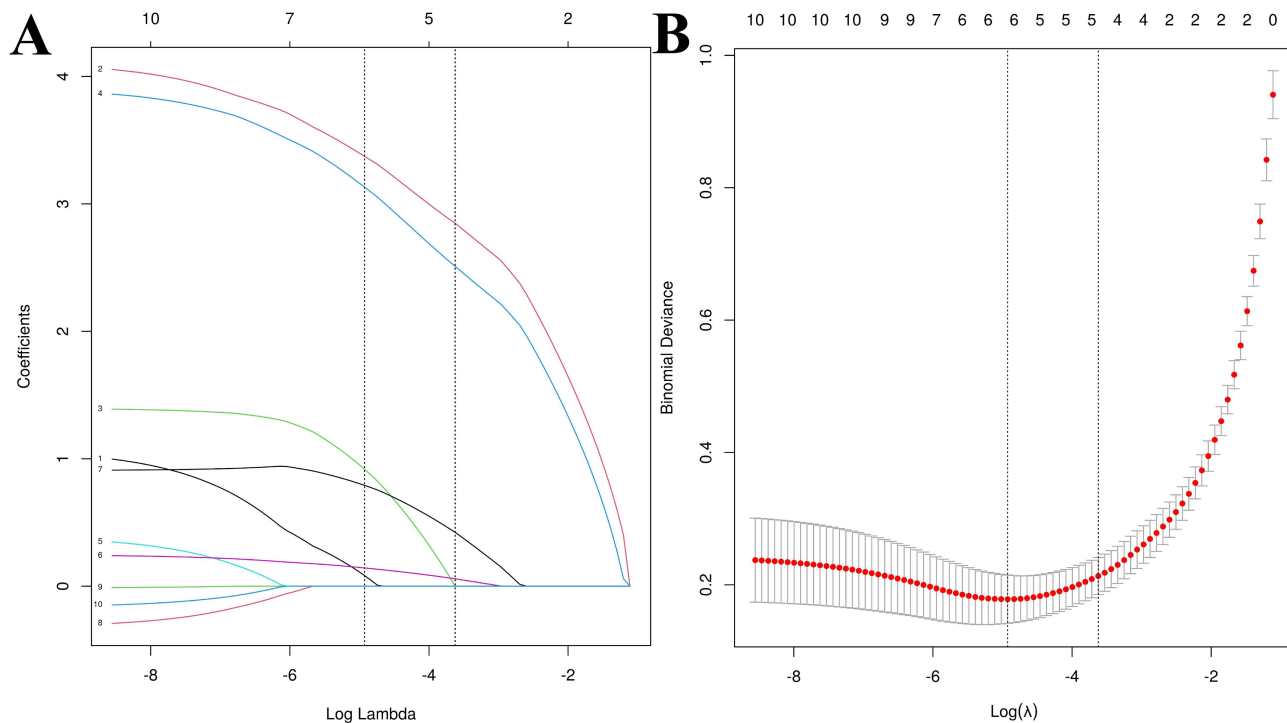


Figure 2 LASSO Regression Analysis for Screening Characteristic Variables of Postoperative Ileus After Radical Gastrectomy for Gastric Cancer (A) Variable screening plot; (B) Selection process plot of the optimal parameter λ .

Multivariate Logistic Regression Analysis of Postoperative Ileus After Radical Gastrectomy for Gastric Cancer

The characteristic variables screened by LASSO regression analysis were used as independent variables, and the occurrence of postoperative ileus was used as the dependent variable. The assignment of variables is shown in Table 3. The results of multivariate logistic regression analysis showed that age (OR=4.999), previous abdominal surgery (OR=3.836), operation time (OR=3.541), IL-6 (OR=1.339), and TNF- α (OR=8.254) were independent risk factors for postoperative ileus after radical gastrectomy for gastric cancer ($P < 0.05$). See Table 4.

Construction of a Nomogram Model for Predicting Postoperative Ileus After Radical Gastrectomy for Gastric Cancer

The results of multivariate logistic regression analysis were used to generate a nomogram to predict the occurrence of postoperative ileus after radical gastrectomy for gastric cancer. See Figure 3. The nomogram scores 5 independent risk factors: age, previous abdominal surgery, operation time, IL-6, and TNF- α , with each factor assigned a score ranging from 0 to 100.

Table 3 Assignment Table of Variables for Multivariate Logistic Regression Analysis

Variable	Assignment
Age	≥ 60 years old=1, < 60 years old=0
Previous abdominal surgery	Yes=1, No=0
Operative time	≥ 400 min=1, < 400 min=0
IL-6	Continuous variable
TNF- α	Continuous variable
Dependent variable	Ileus=1, Non ileus=0

Table 4 Multivariate Logistic Regression Analysis of Postoperative Ileus After Radical Gastrectomy for Gastric Cancer

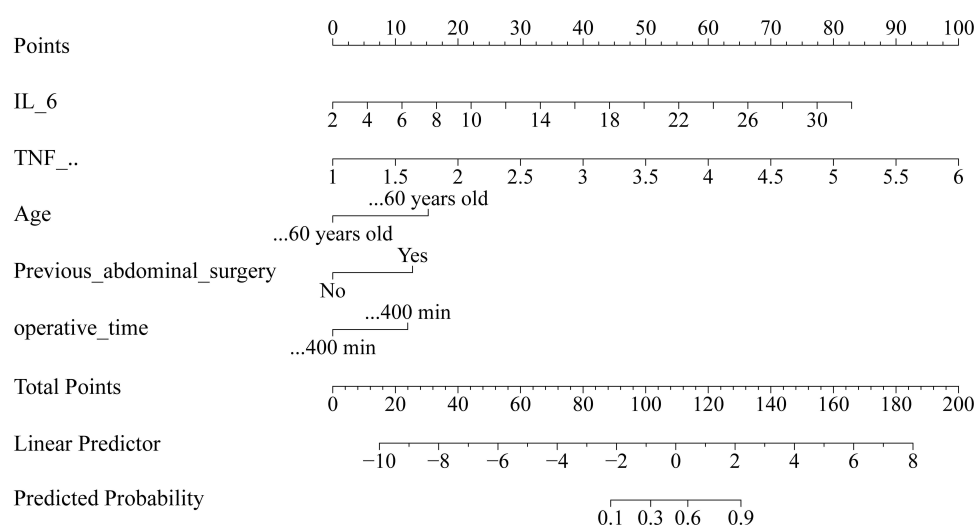
Influence Factor	β	SE	Wald χ^2	OR	95% CI	P
Age	1.609	0.531	9.198	4.999	1.767~14.144	0.002
Previous abdominal surgery	1.344	0.580	5.365	3.836	1.230~11.965	0.02
Operative time	1.264	0.489	6.698	3.541	1.359~9.224	0.01
IL-6	0.292	0.061	22.949	1.339	1.188~1.508	<0.001
TNF- α	2.111	0.377	31.273	8.254	3.939~17.296	<0.001
Constant	-14.265	1.880	57.577	0.000	-	<0.001

Calibration Curve and ROC Curve Analysis of the Nomogram in the Modeling and Validation Groups

Calibration curve analysis in the modeling group showed that the bias-corrected curve was close to the ideal curve, and the Hosmer-Lemeshow test $\chi^2=7.785$, $P=0.236$, indicating good calibration of the nomogram model. ROC curve analysis showed that the AUC of the nomogram model was 0.940 (95% CI: 0.8980.981), indicating good discrimination of the nomogram model. Calibration curve analysis in the validation group showed that the bias-corrected curve was close to the ideal curve, and the Hosmer-Lemeshow test $\chi^2=6.145$, $P=0.372$, indicating good calibration of the nomogram model. ROC curve analysis showed that the AUC of the nomogram model was 0.904 (95% CI: 0.8550.954), indicating good discrimination of the nomogram model. See [Figure 4](#).

Decision Curve Analysis of the Nomogram

The results of decision curve analysis showed that the nomogram had high net benefit within the threshold probability range of 0.020.86 and 0.020.80 in the modeling and validation groups, respectively, confirming good clinical applicability of the nomogram in predicting postoperative ileus after radical gastrectomy for gastric cancer. See [Figure 5](#).

**Figure 3** Nomogram Model for Predicting Postoperative Ileus After Radical Gastrectomy for Gastric Cancer.

Note: For an individual patient, sum the scores for each of the 5 risk factors to obtain a total score. Then, draw a vertical line down from the total score axis to obtain the corresponding probability of postoperative ileus after radical gastrectomy for gastric cancer.

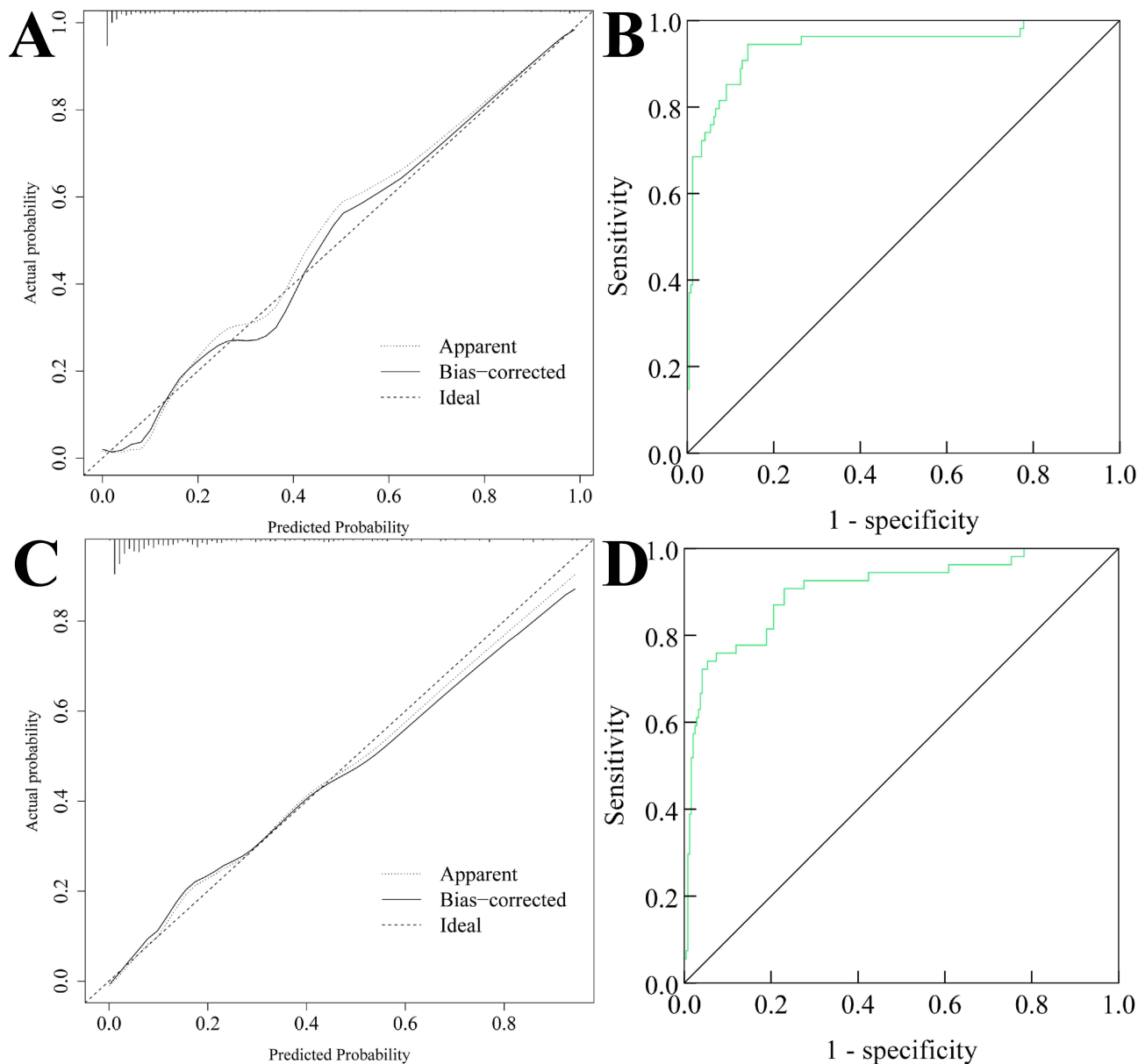


Figure 4 Calibration Curve and ROC Curve Analysis of the Nomogram in the Modeling and Validation Groups **(A)** Calibration curve for the modeling group; **(B)** ROC curve for the modeling group; **(C)** Calibration curve for the validation group; **(D)** ROC curve for the validation group.

Discussion

Postoperative ileus is a common complication after radical gastrectomy for gastric cancer. Yu et al⁸ reported its incidence to be as high as 22.54%, while Pan et al⁹ showed an incidence of 10.9% after gastrectomy for gastric cancer, and Fan et al¹⁰ found an incidence of 38.0% after colorectal cancer surgery. In the present study, the incidence of postoperative ileus in the modeling group was 18.18% (54/297), which falls between the incidence rates reported in the above studies. This indicates that there is some heterogeneity in the incidence of postoperative ileus across different studies, which may be related to the surgeon's technique, surgical conditions, and the patient's own condition. Current research has limitations, and there is still a lack of predictive models for postoperative ileus in patients undergoing radical surgery. Therefore, the purpose of this study was to identify independent risk factors for postoperative ileus and establish a nomogram prediction model.

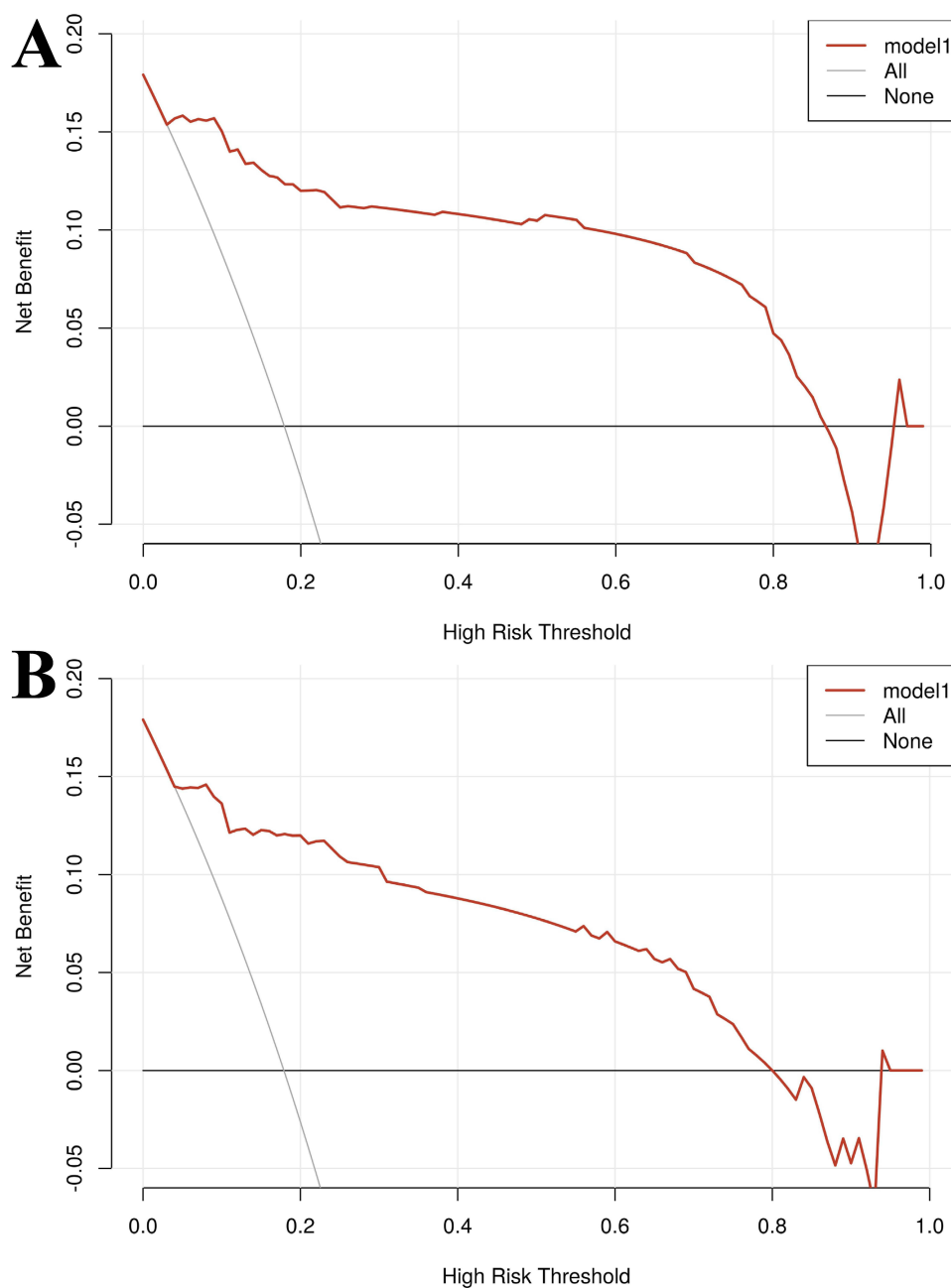


Figure 5 Decision Curve Analysis of the Nomogram **(A)** Decision curve for the modeling group; **(B)** Decision curve for the validation group.

Note: “All” refers to the assumption that all patients will develop postoperative ileus after radical gastrectomy for gastric cancer; “None” refers to the assumption that no patients will develop postoperative ileus.

Studies by Sun et al¹¹ and Xiu et al¹² have shown that older age is associated with a higher risk of postoperative ileus in patients undergoing radical cystectomy or colorectal cancer surgery. The above studies mainly focused on tumors at other sites, while our study focused on gastric cancer and found that age ≥ 60 years was also a risk factor for postoperative ileus after gastrectomy for gastric cancer, which is consistent with the results of Yu et al.⁸ The analysis suggests that older patients may have a history of various previous surgeries or medication use, which may damage the gastrointestinal neuromuscular system. In addition, as basal metabolism slows down with age, general anesthesia drugs may remain in the body for a longer time, thereby inhibiting the recovery of gastrointestinal function and increasing the risk of ileus.¹³ The results of this study also showed that previous abdominal surgery was an independent influencing factor for postoperative ileus, which is basically consistent with the findings of Pan et al.⁹ During abdominal surgery, the intestines

are generally exposed to the external environment and are susceptible to mechanical stimulation and injury. Postoperatively, adhesions may occur in the abdominal cavity, and the inflammatory response in the surgical area can cause fibrin exudation, leading to adhesions between adjacent intestinal segments and the abdominal wall, thereby causing ileus.^{14,15} Some studies have examined the relationship between operation time and postoperative ileus, confirming that longer operation time is a risk factor for early small bowel obstruction after right colectomy.¹⁶ Our results are consistent with this, and an operation time ≥ 400 min was associated with a 3.541 times higher risk of postoperative ileus compared to patients with an operation time < 400 min (OR=3.541). The possible reason is that as the operation time prolongs, the anesthesia time will also be prolonged, which may increase the risk of infection or elevate the level of inflammation. Local inflammation can increase tissue edema and fibrin exudation, leading to adhesive ileus. This study found that inflammation-related factors IL-6 and TNF- α were associated with the occurrence of postoperative ileus, which is similar to the results of Sui et al.¹⁷ Their study showed that the inflammatory response is an important stage in the progression of postoperative ileus, during which various inflammatory factors are secreted in large quantities, directly or indirectly leading to gastrointestinal motility disorders. Significant increases in cytokines such as IL-6 and TNF- α are considered favorable evidence for the development of postoperative ileus.¹⁸

Nomogram models have been widely used in risk assessment and prognostic studies of gastric cancer patients. Compared with traditional regression models, nomograms can provide convenient and accurate risk assessments for different patients by creating user-friendly charts.^{19,20} There are numerous predictive models for postoperative intestinal obstruction after colorectal surgery and cystectomy, but nomogram-based predictive models for intestinal obstruction following radical gastrectomy for gastric cancer remain to be further developed and validated. In this study, a risk nomogram prediction model was constructed using clinical data including age, previous abdominal surgery, operation time, and inflammatory markers IL-6 and TNF- α as variables. The prediction AUCs were 0.940 and 0.904, which are higher than the predictive AUCs of postoperative intestinal obstruction models in previous studies on other tumors.^{12,18} Medical staff can use the nomogram model to calculate the risk of postoperative ileus after radical gastrectomy for gastric cancer, identify high-risk patients early, and implement key monitoring. For high-risk patients, fluid management can be optimized, the use of opioid drugs can be reduced, and early ambulation can be encouraged. Furthermore, in this study, the measured values of the model calibration curve were basically consistent with the predicted values, suggesting that the nomogram model constructed in this study has high discrimination and calibration, and good predictive performance. In addition, the decision curve analysis showed that the nomogram model had high net benefit values, indicating good clinical applicability.

However, this study still has some limitations. First, although we have tried to maximize the sample size, errors due to selection bias may still occur due to the inclusion and exclusion criteria. Second, this study is a single-center data study, and perioperative management of patients may differ from other institutions. Third, although this study has been validated with data outside the modeling group, it is still data from our center and external validation has not been completed. Fourth, this study included a limited number of inflammatory markers. In future research, more inflammatory markers will be incorporated for comparative analysis to further refine the predictive model.

Conclusions

In summary, age, previous abdominal surgery, operation time, IL-6, and TNF- α are independent risk factors for postoperative ileus after radical gastrectomy for gastric cancer, and the nomogram model constructed with these factors has important predictive value for postoperative ileus. The nomogram model constructed in this study provides surgeons with a simple method for calculating the risk of ileus, which may be beneficial for them to counsel and treat patients with potential risks.

Research Involving Human Participants

The study was in accordance with Changzhi People's Hospital ethics review board and with the 1964 Helsinki Declaration. Written informed consent to participate in this study was provided by the participants.

Data Sharing Statement

The original contributions presented in the study are included in the article.

Funding

This work was supported by the Fundamental Research Program of Shanxi Province (Grant No. 202203021212011).

Disclosure

No potential conflicts of interest were reported by the authors.

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