Nomogram for Predicting Risk of Intestinal Complications After Colorectal Cancer Surgery

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Background: Intestinal complications are a major cause of morbidity after colorectal cancer surgery. This study aimed to develop an effective nomogram for predicting risk of intestinal complications following colorectal cancer surgery.

Material/Methods: We retrospectively analyzed 1876 patients who underwent colorectal cancer surgery at Yangpu and Zhuji hospitals from January 2013 to October 2018. Intestinal complications were defined as intestinal obstruction, leakage or bleeding, or peritonitis within 30 days after surgery. A logistic regression model was used to identify the risk factors associated with postoperative intestinal complications, and a nomogram for intestinal complications was established. The predictive accuracy of the nomogram was assessed using area under the receiver operating characteristic curve (AUC) and calibration plot.

Results: A total of 164 patients (8.7%) developed intestinal complications after colorectal cancer surgery; 35 (21.3%) of whom died in the postoperative period. Multivariate logistic analysis showed that male gender, history of abdominal surgery, preoperative intestinal obstruction/perforation, metastatic cancer, and lower level of hemoglobin and prognostic nutrition index were independent risk factors ($P<0.05$ for all). A nomogram was then constructed, and it displayed good accuracy in predicting postoperative intestinal complications with an AUC of 0.76. The calibration plot also showed an excellent agreement between the predicted and observed probabilities.

Conclusions: We constructed a nomogram based on clinical variables, which could provide individual prediction of postoperative intestinal complications with good accuracy.

MeSH Keywords: Colorectal Neoplasms • Intestines • Nomograms • Postoperative Complications • Risk Factors

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Background

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the fourth leading cause of cancer death worldwide [1]. Surgical excision is the mainstay of treatment, and it is estimated that 80% of patients require some form of surgery [2,3]. Although recent evidence suggests a trend toward improved safety with CRC surgery, intestinal complications, which include intestinal obstruction, leakage and bleeding, and peritonitis, remain a major cause of morbidity after surgery, with a reported incidence of 5% to 15% [4–6]. These events not only result in prolonged hospitalization and increased healthcare costs, but also in higher mortality and impaired quality of life [4,6,7]. Therefore, it is important to identify significant risk factors for selection of patients at high risk of postoperative intestinal complications, so that appropriate and timely interventions can be applied to improve the outcome of these patients.

The pathogenesis of postoperative intestinal complications is complex and not fully understood [8,9]. Multiple factors may be involved, including patients' clinical characteristics, surgical technique and perioperative care [4,10]. Millan et al. [11] reported that male gender, respiratory comorbidity and ileostomy were independent risk factors for intestinal obstruction after CRC surgery. A study by Kørner et al. [12] indicated that increased C-reactive protein (CRP) level was associated with the development of intraabdominal infections after colorectal resection. In addition, Vasiliu et al. [13] found that male gender, obesity, preoperative anti-inflammatory drugs, longer duration of operation, surgical experience, and preoperative transfusion were contributive to detecting anastomotic leakage. It is believed that these postoperative intestinal complications are inter-related and often cluster together in their occurrence; for example, intestinal obstruction and leakage are often accompanied by peritonitis [14–16]. Thus, an integrated analysis may provide useful insights and better predictions. However, to date, few studies have focused on postoperative intestinal complications in CRC patients. Here, the purpose of this study was to investigate the incidence and risk factors of intestinal complications after CRC surgery, and provide recommendations for the prevention of intestinal complications according to a novel nomogram.

Material and Methods

Study population

The present study was a retrospective analysis of prospectively collected data from 1876 patients who underwent CRC surgery between January 2013 and October 2018. Among them, 979 patients were enrolled from Yangpu Hospital affiliated to Shanghai Tongji University School of Medicine, and 897 were recruited from Zhuji People's Hospital of Zhejiang Province. The inclusion criteria for this study were as follows: age ≥18 years, without gender or race restriction; complete clinico-pathological data available; histologically confirmed primary CRC that was treated by tumor resection. The exclusion criteria were as follows: patients who did not undergo CRC surgery, but related palliative treatment; and those who had no definitive pathological diagnosis of CRC. This study was approved by the Ethics Committee of Yangpu Hospital affiliated to Tongji University School of Medicine (LL-2018-SCI-002) and registered at Chinese Clinical Trial Registry (ChiCTR) site (*http://www.chictr.org*, No. ChiCTR1800019374). Written consent was obtained from all patients and their information was stored in the hospital database and used for research.

Data collection and variables definition

A series of demographic and clinical characteristics were abstracted from patients' medical records, including age, gender, history of smoking/drinking, basic disease, history of abdominal surgery, preoperative intestinal obstruction/perforation, operative method, operating time, and tumor location, differentiation, and stage. The continuous variables, such as age and operating time, were converted into dichotomous variables with cutoff points, such as 70 years and 4 hours, respectively. Basic disease was defined as the presence of cardiovascular/cerebrovascular diseases, hyperlipidemia, diabetes mellitus, or chronic obstructive pulmonary disease. Tumor location was categorized as right-sided colon (cecum, ascending colon, hepatic flexure and transverse colon), left-sided colon (splenic flexure and descending and sigmoid colon), and rectum (rectosigmoid junction and rectal ampulla). Tumor was staged according to the tumor-node-metastasis (TNM) classification and graded according to the World Health Organization system. In addition, 4 selected preoperative laboratory variables were recorded: serum albumin level, hemoglobin level, fasting blood glucose level, and absolute lymphocyte count. The prognostic nutrition index (PNI) was calculated as 10 x serum albumin (g/dL)+0.005×total lymphocyte count (per mL) [17], and was further classified into 3 degrees of severity (≥45, 35–45, and <35). Hemoglobin and fasting blood glucose levels were analyzed as dichotomous variables using the cutoff points of 110 g/L and 7.0 mmol/L, respectively.

Intestinal complications were defined as the presence of intestinal obstruction, leakage or bleeding, or peritonitis within 30 days after CRC surgery, and were determined by a combination of individual case note review and analysis of electronic blood bank records. Intestinal obstruction was defined based on clinical features (abdominal distension, vomiting, and constipation) in conjunction with plain abdominal radiography demonstrating at least 1 dilated bowel loop in order to exclude other

Table 1. Descriptive characteristics of study population (n=1876).

Characteristic	No. of patients (%)
Age (years)	
Median, range	64 (21–98)
Gender	
Female *vs.* Male	770 (41.0%) *vs.* 1106 (59.0%)
History of smoking/drinking	
Negative *vs.* positive	1370 (73.0%) *vs.* 506 (27.0%)
Basic disease	
Negative *vs.* positive	1231 (65.6%) *vs.* 645 (34.4%)
History of abdominal surgery	
Negative *vs.* positive	1578 (84.1%) *vs.* 298 (15.9%)
Preoperative intestinal obstruction/perforation	
Negative *vs.* positive	1740 (92.8%) *vs.* 136 (7.2%)
Operative method	
Open *vs.* laparoscopic	1135 (60.5%) *vs.* 741 (39.5%)
Operating time (h)	
Median, range	3.5 (2.5-7.2)

Characteristic	No. of patients (%)
Tumor location	
Right-sided colon *vs.* left-sided colon *vs.* rectum	423 (22.5%) *vs.* 461 (24.6%) *vs.* 992 (52.9%)
TNM stage	
I *vs.* II *vs.* III *vs.* IV	368 (19.6%) *vs.* 606 (32.3%) *vs.* 667 (35.6%) *vs.* 235 (12.5%)
Tumor differentiation	
Well differentiated *vs.* moderately differentiated *vs.* poorly differentiated	121 (6.4%) *vs.* 1281 (68.3%) *vs.* 474 (25.3%)
Hemoglobin level (g/L)	
Median, range	123 (42–193)
Fasting blood glucose level (mmol/L)	
Median, range	5.2 (2.0–45.0)
PNI value	
Median, range	45.6 (17.5–70.5)
Postoperative intestinal complications	
Negative *vs.* positive	1712 (91.3%) *vs.* 164 (8.7%)

TNM – tumor-node-metastasis; PNI – prognostic nutrition index.

causes of abdominal distension such as ascites or constipation. Anastomotic leakage was defined as anastomotic dehiscence confirmed by clinical symptoms, including the appearance of fecal material from drains, development of colo-cutaneous fistula, and development of systemic sepsis associated with peritonitis and/or contrast radiography. Intestinal bleeding was defined as an episode of overt bleeding (hematemesis, melena, or hematochezia), accompanied by a change in hematocrit of 10 points or the need for blood transfusion. Peritonitis was defined on the basis of clinical features (abdominal tenderness, rebound tenderness, guarding, and absent bowel sounds), with cloudy peritoneal effluent containing >100 leukocytes/mL, with >50% neutrophils.

Statistical analysis

Statistical analysis was performed with SPSS version 22.0 statistical software (IMB-SPSS Inc., Armonk, NY, USA) and EmpowerStats software (Boston, MA, USA). Continuous data were described as median and range, and categorical variables as frequencies and percentages. Comparisons between 2 categories were made using Pearson's χ^2 test or Fisher's exact test. Variables with $P<0.05$ in univariate analysis were subsequently included in a multivariate logistic regression model with a stepwise selection process. The odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for risk factors. The nomogram was developed based on the results of multivariate logistic analysis and its predictive accuracy was quantified with the area under the receiver operating characteristics (ROC) curve (AUC). Calibration, agreement between predicted probabilities and observed frequencies, was tested with the Hosmer-Lemeshow test, where $P>0.05$ reflected good agreement. Bootstraps with 1000 resamples were applied to these activities. All tests were 2-tailed, and statistical significance was set at $P<0.05$.

Results

Patient characteristics and incidence of intestinal complications

The clinical characteristics of the 1876 CRC patients were summarized in Table 1. Of these, 41.0% of patients were females

Table 2. Univariate and multivariate analyses for risk factors of intestinal complications after colorectal cancer surgery.

Variable	Group	Univariate			Multivariate	
		ICs (n=164)	Non-ICs (n=1712)	P value	OR (95% CI)	P value
Age (years)	<70	80 (48.8%)	1103 (64.4%)			
	≥70	84 (51.2%)	609 (35.6%)	<0.001		
Gender	Female	52 (31.7%)	718 (41.9%)		1 (Reference)	
	Male	112 (68.3%)	994 (58.1%)	0.012	2.08 (1.43–3.02)	<0.001
History of smoking/ drinking	Negative	119 (72.6%)	1251 (73.1%)			
	Positive	45 (27.4%)	461 (26.9%)	0.927		
Basic disease	Negative	119 (72.6%)	1112 (65.0%)			
	Positive	45 (27.4%)	600 (35.0%)	0.058		
History of abdominal surgery	Negative	122 (74.4%)	1456 (85.0%)		1 (Reference)	
	Positive	42 (25.6%)	256 (15.0%)	0.001	1.88 (1.25–2.83)	0.003
Preoperative intestinal obstruction/perforation	Negative	120 (73.2%)	1620 (94.6%)		1 (Reference)	
	Positive	44 (26.8%)	92 (5.4%)	<0.001	4.31 (2.77–6.71)	<0.001
Operative method	Open	97 (59.1%)	1038 (60.6%)			
	Laparoscopic	67 (40.9%)	674 (39.4%)	0.738		
Operating time (h)	<4	84 (51.2%)	1091 (63.7%)			
	≥4	80 (48.8%)	621 (36.3%)	0.002		
Tumor location	Right-sided colon	44 (26.8%)	379 (22.1%)			
	Left-sided colon	49 (29.9%)	412 (24.1%)			
	Rectum	71 (43.3%)	921 (53.8%)	0.036		
TNM stage	I	20 (12.2%)	348 (20.3%)		1 (Reference)	
	II	49 (29.9%)	557 (32.5%)		1.08 (0.62–1.90)	0.778
	III	62 (37.8%)	605 (35.3%)		1.29 (0.74–2.23)	0.141
	IV	33 (20.1%)	202 (11.8%)	0.003	1.94 (1.05–3.59)	0.036
Tumor differentiation	Poorly differentiated	50 (30.5%)	424 (24.8%)			
	Moderately differentiated	100 (61.0%)	1181 (69.0%)			
	Well differentiated	14 (8.5%)	107 (6.2%)	0.108		
Hemoglobin level (g/L)	≥110	90 (54.9%)	1252 (73.1%)		1 (Reference)	
	<110	74 (45.1%)	460 (26.9%)	<0.001	1.54 (1.06–2.23)	0.025
Fasting blood glucose level (mmol/L)	<7.0	129 (78.7%)	1499 (87.6%)			
	≥7.0	35 (21.3%)	213 (12.4%)	0.002		
PNI value	≥45	46 (28.0%)	964 (56.3%)		1 (Reference)	
	35–45	81 (49.4%)	658 (38.4%)		2.12 (1.42–3.14)	<0.001
	<35	37 (22.6%)	90 (5.3%)	<0.001	4.91 (2.84–8.50)	<0.001

ICs – intestinal complications; TNM – tumor-node-metastasis; PNI – prognostic nutrition index; OR – odds ratio; CI – confidence interva.
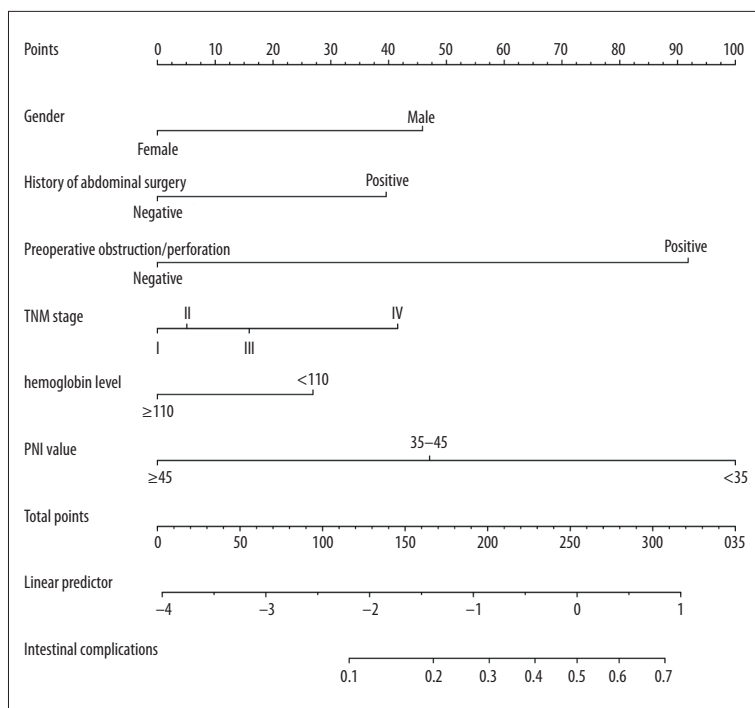
Figure 1. Nomogram for predicting risk of intestinal complications after colorectal cancer surgery. TNM – tumor-node-metastasis; PNI – prognostic nutrition index.

and 59.0% of patients were males, with a median age of 64 years. All the patients underwent colorectal resection, and 7.2% of the patients underwent emergency surgery because of intestinal obstruction or perforation. Tumor staging revealed that 19.6% of the cases were stage I, 32.3% stage II, 35.6% stage III, and 12.5% stage IV. The median preoperative hemoglobin level and PNI value of the study population were 123 g/L and 45.6, respectively. A total of 164 patients (8.7%) developed intestinal complications within 30 days after CRC surgery; 35 (21.3%) of whom died in the hospital. In addition, 48.2% of the patients (79 out of 164) developed 2 or more intestinal complications during the postoperative period. All the cases of anastomotic leakage and over half of the cases of intestinal obstruction were accompanied by peritonitis. The incidence of postoperative peritonitis, and intestinal leakage, obstruction and bleeding was 5.0, 2.4, 2.3, and 0.8%, respectively.

Risk factors associated with intestinal complications

The comparison between individuals with and without intestinal complications after CRC surgery suggested that patients with intestinal complications were more likely to be older, male, and have colon-specific, advanced-stage tumor, and have a history of abdominal surgery. In addition, they had a prolonged operating time, more frequent preoperative intestinal obstruction/perforation, higher level of fasting blood glucose, and lower level of hemoglobin and PNI ($P<0.05$ for all). Multivariate logistic analysis identified that male gender ($P<0.001$), history of abdominal surgery ($P=0.003$), preoperative intestinal obstruction/perforation ($P<0.001$), tumor stage IV ($P=0.036$) and

hemoglobin level <110 g/L ($P=0.025$) were independent risk factors for postoperative intestinal complications. Moreover, compared with patients with PNI ≥45, those with PNI 35–45 and <35 showed a 2.12-fold (95% CI: 1.42–3.14, $P<0.001$) and 4.91-fold (95% CI: 2.84–8.50, $P<0.001$) increased risk of developing intestinal complications, respectively (Table 2).

Development of the nomogram for intestinal complications

A nomogram that incorporated the 6 significant risk factors was established (Figure 1). The total points were used to assess the risk for postoperative intestinal complications. For example, a male patient receives 46 points for his gender. His history of abdominal surgery, preoperative intestinal perforation, metastatic CRC, hemoglobin level 100 g/L, and PNI 38 contribute 40+92+42+27+47=248 additional points, for a total of 294 risk points. This patient had a 65% probability of developing intestinal complications after CRC surgery. The overall predictive accuracy of the nomogram, as measured by the bootstrap corrected ROC curve, was 0.76 (95% CI: 0.72–0.80), indicating good discrimination (Figure 2). The calibration plot revealed that the nomogram was well calibrated, with no significant difference between the predicted and observed probabilities (Hosmer-Lemeshow test, $P=0.348$) (Figure 3).

Discussion

Postoperative intestinal complications, including intestinal obstruction, leakage and bleeding, and peritonitis, are always
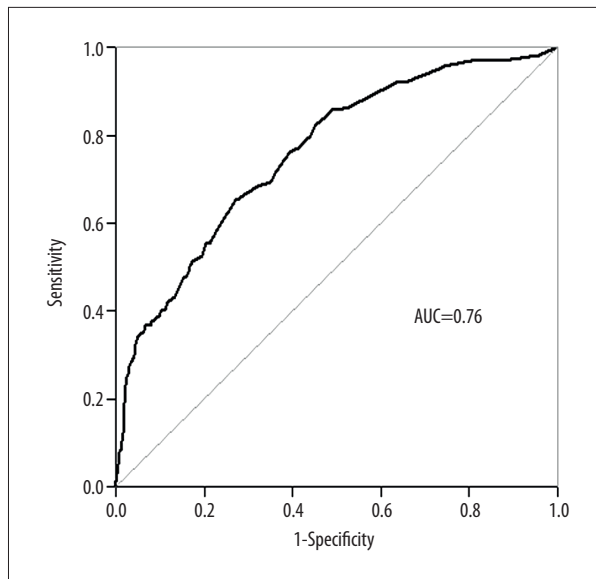
Figure 2. ROC analysis of the nomogram for intestinal complications after colorectal cancer surgery. AUC – area under curve; ROC – receiver operating characteristic.
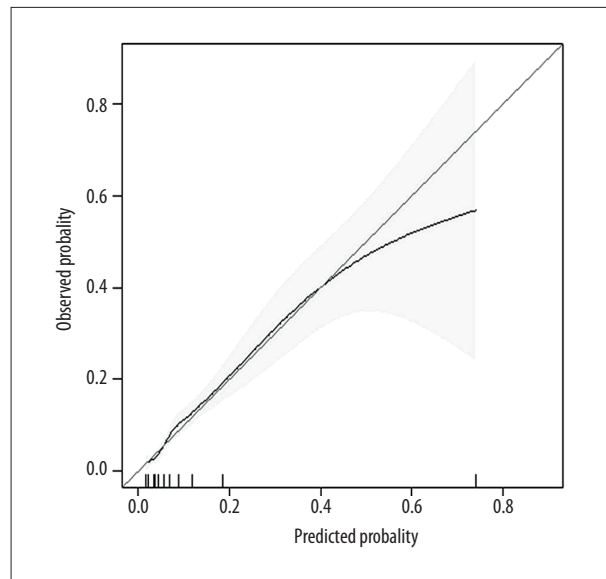

Figure 3. Calibration plot of the nomogram for intestinal complications after colorectal cancer surgery. Hosmer-Lemeshow test, *P*=0.348.

a major issue in the management of CRC that not only threaten patients' lives but also put surgeons in a dilemma between prevention and treatment [4,7,18]. According to some previous studies, the incidence of intestinal complications after colorectal resection varies from 5% to 15% [4–6]. A comparable result was observed in our study, in which 164 patients (8.7%) of 1876 CRC patients developed intestinal complications within 30 days after surgery. Of the complications, peritonitis was the most frequent (5.0%), followed by intestinal leakage (2.4%) and obstruction (2.3%), and bleeding was less common. Previous studies suggested that postoperative intestinal complications were closely correlated, and often contributed to the development of another intestinal complication [14,16,19]. This was confirmed in our study, where we found that the majority of patients with intestinal leakage or obstruction developed peritonitis concomitantly. In addition, we observed that 21.3% (35 out of 164) of the patients with intestinal complications died during the postoperative period, indicating a high threat to life. Thus, it is particularly important to investigate the risk factors associated with postoperative intestinal complications and provide suggestions for preventing them.

The etiology of postoperative intestinal complications is considered multifactorial [9,10,20]. By the univariate and multivariate analysis, 6 independent risk factors were identified in the current study. Our results showed that male patients were more likely to experience intestinal complications with an OR of 2.08. The increased operative difficulty in the narrower male pelvis and the recently shown hormonal differences that influence the intestinal microcirculation could be the possible

explanation for this phenomenon [21,22]. Male gender is the risk factor deserving increased attention, particularly as reports also suggest that it is a strong predictor of poor survival after complications [23]. We also found that a history of prior abdominal surgery was associated with an increased incidence of postoperative intestinal complications. This relationship may account for a greater degree of adhesions, making the operation more difficult [24]. Various studies have indicated that CRC patients who underwent emergency surgery for intestinal obstruction or perforation have a significantly higher risk of developing intestinal complications [25,26], and this was confirmed in our study. During emergency surgery, the bowel status might be suboptimal and technical problems more commonly encountered. In addition, it is recognized that preoperative nutritional status is not only closely associated with the incidence of postoperative complications [27], but also with the long-term outcomes of patients with malignant tumors [28]. Hemoglobin and PNI are commonly used markers for assessing patients' nutritional status, and our study confirmed that anemia and malnutrition contributed significantly to the development of intestinal complications after CRC surgery [17,29]. Furthermore, we observed that patients with metastatic cancer tended to have a higher risk for intestinal complications, which was probably related to patients' poor general condition. A similar finding was reported by Davis et al. [10] and Bot et al. [30]. In addition to these factors, age [31], operating time [13], tumor location [32], smoking and alcohol abuse [33] have also been reported to be associated with postoperative intestinal complications, but no significant correlation was detected in our multivariate analysis. The explanations for these

differences remain to be elucidated and may provide new insights into the mechanisms involved.

Nomograms are graphical devices or models that use algorithms or mathematical formulae to estimate the probability of an outcome and are optimized for predictive accuracy for each individual patient [34]. To apply the results of our study in clinical practice, we further established a nomogram that incorporated the six predictive factors, and it displayed good accuracy and discrimination in predicting the risk of postoperative intestinal complications, with a corrected AUC of 0.76. The nomogram was validated using bootstrapping methods and the calibration plot showed an excellent agreement between the predicted and observed outcomes. Through this model, clinicians could more precisely estimate the risk of intestinal complications in individual patients after CRC surgery and tailor interventions for patients in need of more intensive care management. To our knowledge, the present study is the first to focus specifically on intestinal complications after CRC surgery. However, our findings should be interpreted in light of several limitations. First, because of the retrospective design of the study, potential selection bias was inevitable. Second, other factors not included in our study such as surgical experience [35] and the methods of anastomosis [36] could not

be examined for confounding effects. Last but not least, the sample size of this study was relatively small, given the incidence of postoperative intestinal complications. Hence, further validation studies with larger samples and incorporation of more well-recognized predictors are encouraged to improve the model performance.

Conclusions

Our study results suggested that intestinal complications were a major cause of morbidity after CRC surgery with an incidence of 8.7%, and were more prevalent in patients with male gender, history of abdominal surgery, preoperative intestinal obstruction/perforation, metastatic cancer, and lower level of hemoglobin and PNI. We constructed a novel nomogram that could provide individual prediction of postoperative intestinal complications with good accuracy and serve as a useful guide in patient management.

Conflicts of interest

None.

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