Nomogram for Prediction of Prolonged Postoperative Ileus after Colorectal Resection

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Research Article

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Abstract

Background: Prolonged postoperative ileus (PPOI) is a major complication in patients undergoing colorectal resection. The aim of this study was to analyze the risk factors contributing to PPOI, and to develop an effective nomogram to determine the risks of this population.

Methods: A total of 1,233 patients with colorectal cancer who underwent radical colorectal resection at Fujian Cancer Hospital from March 2016 to August 2021 were enrolled as a training cohort in this study. Univariate analysis and multivariate logistic regressions were performed to determine the correlation between PPOI and clinicopathological characteristics. A nomogram predicting the incidence of PPOI was constructed. The cohort of 151 patients from Fujian Provincial Hospital were enrolled as a validation cohort. Internal and external validations were used to evaluate the prediction ability by area under the receiver operating characteristic curve (AUC) and a calibration plot.

Results: In the training cohort, 125 patients (10.1%) had PPOI after colorectal resection. The independent predictive factors of PPOI were identified, and included gender, age, surgical approach, perioperative fluid overload and postoperative use of opioid analgesics. The AUC of nomogram were 0.788 (95% CI: 0.747-0.829) and 0.812(95% CI: 0.697-0.928) in the training and validation cohort, respectively. The two cohorts of calibration plots showed a good consistency between nomogram prediction and actual observation.

Conclusions: A highly accurate nomogram was developed and validated in this study, which can be used to provide individual prediction of PPOI in patients after colorectal resection, and this predictive power can potentially assist surgeons to make the optimal treatment decisions.

Introduction

Postoperative ileus (POI) refers to a temporary impairment of gastrointestinal transit due to nonmechanical causes following surgery. As POI occurs in almost all patients following intra-abdominal surgery, especially major abdominal surgery, it may be considered as a normal physiologic response [[i],[ii]]. Usually, it is resolved within 3 days, but may persist or reoccur, in which case it is termed prolonged postoperative ileus (PPOI)[[iii]]. The point at which POI becomes PPOI has not been clearly established. Manifestations of PPOI are characterized as a variable mixture of nausea and vomiting, intolerance of oral diet, abdominal distension and delayed passage of flatus and stool. PPOI is one of the most common complications after colorectal surgery, with an incidence of 3-32% [[iv],[v]]. The variability of reported incidences can be explained by absence of accurate classification criteria and heterogeneous definition of PPOI [[vi]]. PPOI could result in a range of significant consequences, including nutritional deficiencies and the need for parenteral nutrition, increased length of stay, a significant fiscal burden and a negative impact on quality of life which is higher than with other postoperative morbidities [[vii],[viii]].

The Enhanced Recovery after Surgery (ERAS) program is an effective and safe protocol, and has been widely implemented in colorectal cancer surgery [[ix]]. Early return of bowel function and prevention of PPOI are important items of clinical practice guidelines for ERAS in Elective Colorectal Surgery [[x]]. There

is currently still a lack of effective treatment options for PPOI, and therefore, it is important to identify high-risk patients of PPOI, and allow early intervention with preventive strategies [[xi]].

Nomogram is a popular and simple tool used to predict the probability of an individual's particular outcome, and has been frequently implemented in clinical practice [[xii],[xiii]]. The aim of this study was to develop an effective nomogram for prediction of the occurrence of PPOI after colorectal resection.

Materials And Methods

Patients

A total of 1,233 patients hospitalized with colorectal cancer at Fujian Cancer Hospital from March 2016 to August 2021 were enrolled as a training cohort in this study. The inclusion criteria were as follows: (1) Pathologic diagnosis of adenocarcinoma of the colorectum; (2) Elective radical operation; (3) age ≥18 years. The exclusion criteria were as follows: (1) Preoperative intestinal obstruction; (2) Unassessable on account of dementia or postoperative delirium; (3) Some complications considered to be the cause of PPOI, including postoperative anastomotic leakage, intraabdominal abscess and peritonitis; (4) Conversion to an open approach.

151 patients hospitalized at Fujian Provincial Hospital from June 2018 to September 2020 were enrolled as a validation cohort. The inclusion and exclusion criteria were the same as those for training cohort. The entire flowchart of the selection of patients was depicted in Fig. 1.

Enhanced recovery program

The ERAS program has been applied in the department of Gastrointestinal Surgery Oncology since November 2014, and has achieved remarkable results. Briefly, our ERAS protocol contains the following: (1) Preoperative period: Preadmission patient education and instruction; Nutritional evaluation and optimization; No routine use of mechanical bowel preparation carbohydrate loading beverage 12 h and 2 h prior to general anesthesia. (2) Intraoperation period: Minimally invasive surgery is preferred; Intraoperative fluid restriction and avoidance of hypothermia; Nasogastric tubes and drains should be avoided when possible. (3) Postoperative period: Multimodal analgesia; Antiemetic prophylaxis; Early feeding and mobilization.

Definition

PPOI was defined in accordance with the systematic review and global survey by Vather et al. [[i]]. Specifically, PPOI was diagnosed if patients met ≥2 of the following five criteria on POD 4 (postoperative day 4) or later: (1) Nausea or vomiting over the preceding 12 hours; (2) Inability to tolerate an oral diet over the prior 24 h; (3) Absence of flatus over the preceding 24 h; (4) Abdominal distention; (5) Radiologic confirmation.

Total intravenous (IV) volume administration on the day of surgery was used to calculate IV fluids at POD 0. Perioperative fluid overload was defined as POD 0 IV fluids of ≥3L and/or POD 2 weight gain of ≥2.5kg. These cutoffs were independent risk factors for postoperative ileus, and have been identified as critical thresholds for complications in colorectal surgery [[ii], [iii]].

Statistical analysis

Continuous variables with normal distributions are presented as the mean ± SD, and were compared using Student's t test; Continuous variables with non-normally distributed variables were expressed as medians and interquartile ranges (IQR), and were assessed with Mann-Whitney U tests. Categorical variables were shown as numbers and percentages. Univariate analysis was performed with a Chi-square test to compare categorical variables. Parameters with significance ($p<0.05$ in univariate analysis) were selected into multiple logistic regression analysis. R software (version 4.1.1) was used to construct a nomogram based on multiple analysis. The nomogram was evaluated internally for the training cohort and externally for the validation cohort. Internal and external validations were adopted to assess regarding prediction ability by area under the receiver operating characteristic (ROC) curve (AUC) and calibration plot. The Hosmer-Lemeshow test was used to assess the goodness-of-fit of the model. Statistical analyses were performed through SPSS 26.0 software. A two-tailed P value <0.05 was considered statistically significant.

Results

Patient characteristics and outcomes

125 patients (10.1%) and 14 patients (9.3%) in the training and validation cohort, respectively had PPOI after colorectal resection. No statistically significant differences in the baseline demographic and the clinicopathological characteristics of the patients were found between the two cohorts ($P > 0.05$), with the exception of hypertension ($P = 0.027$, Table 1).

Table 1. Characteristics of patients in the training and validation cohort

	Training cohort (n=1233)	validation cohort (n=151)	P value
Gender			0.344
Male	847	98	
Female	386	53	
Age (years)			0.362
≤65	613	81	
65	620	70	
BMI(kg/m^2)			0.241
≤24	591	80	
24	642	71	
Smoking habit			0.340
Yes	307	43	
No	926	108	
Alcohol use			0.674
Yes	525	67	
No	708	84	
Diabetes Mellitus			0.712
Yes	286	33	
No	947	118	
Hypertension			0.027
Yes	350	56	
No	883	95	
Hyperlipidemia			0.511
Yes	400	53	
No	833	98	
Respiratory comorbidity			0.232
Yes	243	36	
No	990	115	

Cardiac comorbidity			0.486
Yes	240	33	
No	993	118	
Peripheral vascular disease			0.713
Yes	190	25	
No	1043	126	
Previous abdominal surgery			0.387
Yes	172	25	
No	1061	126	
Preoperative anemia			0.817
Yes	413	52	
No	820	99	
Preoperative hypoalbuminemia			0.286
Yes	195	29	
No	1038	122	
Preoperative WBC count, mean±SD, *10^3/μL	6.8±1.7	6.9±1.6	0.332
Neoadjuvant treatment			0.456
Yes	238	33	
No	995	118	
ASA-classification			0.328
ASA I	763	84	
ASA II	333	47	
ASA III	137	20	
Surgical approach			0.512
Minimally invasive surgery	1097	137	
Open surgery	136	14	
Surgical procedure			0.180
Right colectomy	323	33	

Transverse colectomy	78	16	
Left colectomy	325	37	
Rectal resectiona	507	65	
Diverting ileostomy			0.447
Yes	175	18	
No	1058	133	
Operation duration(min)			0.559
≤180	557	72	
180	676	79	
Intraoperative Blood loss (mL), median (IQR)	180(90-200)	160(80-200)	0.172
Bowel resection length (cm), median (IQR)	20(18-21)	20(17,22)	0.112
Anastomosis technique			0.797
Side-to-end	314	37	
End-to-end	919	114	
Perioperative fluid overload			0.352
Yes	694	91	
No	539	60	
Perioperative transfusion			0.502
Yes	110	11	
No	1123	140	
Postoperative opioid analgesic			0.670
Yes	322	37	
No	911	114	
Differentiation			0.350
Well	64	4	
Moderate	1034	132	
Poor	135	15	
TNM stage			0.512

I	208	31
II	627	75
III	398	45

Univariate and multivariate analysis of PPOI in the training cohort

Clinical characteristics, including gender, age, surgical approach, operation duration, perioperative fluid overload, postoperative opioid analgesic were significantly associated with PPOI after univariate analysis ($p<0.05$, Table 2). Multivariate analysis showed that gender, age, surgical approach, perioperative fluid overload, postoperative opioid analgesic were independent predictive factors of PPOI ($p<0.05$, Table 2).

Table 2. Univariable analysis and multivariable logistic regression of clinicopathological variables associated with PPOI

	PPOI, No.		P value	Multivariate Analysis	
	Absence (n =125)	Presence (n = 1108)		OR(95% CI)	P value
Gender			0.004	1.826(1.150-2.899)	0.011
Male	100	747			
Female	25	361			
Age(years)			0.001	1.781(1.206-2.630)	0.004
≤65	45	568			
65	80	540			
BMI(kg/m^2)			0.092		
≤24	51	540			
24	74	568			
Smoking habit			0.200		
Yes	37	270			
No	88	838			
Alcohol use			0.362		
Yes	58	467			
No	67	641			
Diabetes Mellitus			0.117		
Yes	36	250			
No	89	858			
Hypertension			0.344		
Yes	40	310			
No	85	798			
Hyperlipidemia			0.487		
Yes	44	356			
No	81	752			
Respiratory comorbidity			0.425		

Yes	28	215			
No	97	893			
Cardiac comorbidity			0.266		
Yes	29	211			
No	96	897			
Peripheral vascular disease			0.329		
Yes	23	167			
No	102	941			
Previous abdominal surgery			0.130		
Yes	23	149			
No	102	959			
Preoperative anemia			0.220		
Yes	48	365			
No	77	743			
Preoperative hypoalbuminemia			0.274		
Yes	24	171			
No	101	937			
Preoperative WBC count, mean±SD,*10^3/μL	7.0±1.5	6.8±1.7	0.269		
Neoadjuvant treatment			0.160		
Yes	30	208			
No	95	900			
ASA-classification			0.261		
ASA I	69	694			
ASA II	39	294			
ASA III	17	120			
Surgical approach			0.000	2.575(1.600-4.143)	0.000
Minimally invasive surgery	97	1000			
Open	28	108			

Surgical procedure			0.129		
Right colectomy	36	287			
Transverse colectomy	8	70			
Left colectomy	22	303			
Rectal resectiona	59	448			
Diverting ileostomy			0.378		
Yes	21	154			
No	104	954			
Operation duration(min)			0.047	0.680(0.459-1.005)	0.053
≤180	46	511			
180	79	597			
Intraoperative Blood loss (mL), median (IQR)	200(100,250)	180(90,230)	0.063		
Bowel resection length (cm), median (IQR)	20(18,22)	19(17,21)	0.366		
Anastomosis technique			0.406		
Side-to-end	28	286			
End-to-end	97	822			
Perioperative fluid overload			0.011	1.618(1.108-2.362)	0.013
Yes	57	637			
No	68	471			
Perioperative transfusion			0.346		
Yes	14	96			
No	111	1012			
Postoperative opioid analgesic			0.008	1.636(1.098-2.436)	0.015
Yes	45	277			
No	80	831			
Differentiation			0.865		
Well	7	57			

Moderate	106	928	
Poor	12	123	
TNM stage			0.435
I	16	192	
II	66	561	
III	43	355	

Construction of a nomogram for prediction of PPOI

The five variables that were finally determined to be significant in the multivariate logistic regression analysis were used to establish the intuitive nomogram model (Fig. 2). A total score is calculated by summing the scores for each variable, and the final predicted risk of PPOI is the corresponding probability of the total points of individual patients.

Validation of the nomogram

Internal validation was first performed in the training cohort. The AUC of the training cohort was 0.788 (95% CI: 0.747-0.829) (Fig. 3). A bootstrap resampling procedure was applied and a calibration curve was plotted (Fig. 4). There was good agreement between the predicted and observed probabilities. The Hosmer-Lemeshow test showed an excellent fit (χ^2=7.314, p=0.503).

External validation was further performed in the validation cohort. The AUC was still as high as 0.812 (95%CI: 0.697-0.928) (Fig. 5). The nomogram calibration curve showed acceptable agreement between prediction and actual observation (Fig. 6).

Discussion

In the present study, there was a 10.1% and 9.3% rate of PPOI in the training and validation cohort, respectively. This incidence was different from previous reports. Wolthuis et al. [3,4] found the rate of PPOI was 15.9% after colorectal resection [3] and Vather et al. [14] reported that PPOI occurred in 88 of 327 patients (26.9%) undergoing elective colorectal surgery [[i]]. Liang et al. demonstrated that the overall PPOI rate was 21.5% in 311 patients diagnosed with gastric or colorectal cancer [[ii]]. The difference of incidence was possibly due to ERAS programs have been widely implemented in our study.

Statistically significant differences were found in hypertension between the training and validation cohorts, but hypertension itself was not found to be associated with PPOI. In general, baseline data were essentially balanced in the two cohorts. The AUC of the nomogram was 0.788 in the training. The calibration plots showed a good agreement between nomogram prediction and actual observation, indicating that the model had a good diagnostic performance and an excellent calibration. In addition, the

external validation of the nomogram showed a satisfactory outcome, which indicated that our nomogram could be used in various populations and clinical scenarios.

An age older than 65 years was identified as an independent risk factor for PPOI. This may be due to the fact that older individuals generally have more medical comorbidity and clinical frailty, and poorer nutritional and functional status compared with their younger counterparts [[iii]]. Our result emphasizes that postoperative surveillance should be especially carefully achieved in such patients who have an increased risk of morbidity and mortality after colorectal cancer surgery [[iv]].

The fact of male sex has also been shown to affect PPOI following colorectal resection. Consistent with the present study, some studies confirmed that the male sex was associated with increased risk of PPOI in elective colorectal surgery [[v]-[[vi]] [vii]]. This difference is explained by the narrower male pelvis which may make the surgery more difficult and challenging, and potentially secondary to the effects of estrogen and progesterone receptors throughout the gastrointestinal tract and differences in enteric nervous system signaling [17,[viii]].

Minimally invasive approaches include laparoscopic and robotic surgery. The advantages of robotic surgical systems such as superior instrumentatione and field of vision enable precise dissection in confined spaces such as the pelvis, allowing it to have rapidly gained acceptance in colorectal surgery [[ix]]. The robotic surgical systems for the treatment of colorectal cancer were introduced into this hospital in 2020, but only a minority of patients have been treated with robotic surgery because of its high cost. Previous studies have shown that there are no significant differences between laparoscopic and robotic approaches to PPOI and perioperative mortality [[x], [xi]]. Therefore, we combined laparoscopic and robotic surgery into one group in this study. The surgical approach was the strongest predictor of PPOI in our study. There is high-quality evidence supporting the routine use of a minimally invasive approach to patients with colorectal cancer. Compared with open surgery, minimally invasive surgery has shown better outcomes, including less postoperative pain, shorter time to flatus/bowel motion and oral nutrition, improved cosmesis, less intraoperative blood loss, reduced length of stay, improved cosmesis and similar long-term survival [[xii]-]-[[xiii]][xiv]].

Our finding describes an increased risk for PPOI in those who had opioid analgesic treatment. A multimodal, opioid-sparing, pain management plan should be employed throughout the ERAS [[xv]]. Patient controlled analgesia (PCA) of intravenous opioids was used when the pain control was poor. In addition to their intended central effect on pain receptors, opioids have an undesired influence peripherally in the GI tract, including decreased gastric motility and emptying and inhibiting bowel propulsion [[xvi]]. Opioid related dysmotility plays a central role in postoperative gut dysfunction [[xvii]]. More recently, peripheral μ-opioid receptor antagonists in patients have been developed for treatment or prevention of PPOI after surgery [[xviii]].

Previous studies believed that adherence to judicious intra-operative fluid management protocols was protective against development of PPOI [[xix],[xx]]. Similarly, this study showed that perioperative fluid overload was significantly associated with PPOI. This may be because hypervolemic management may

result in electrolyte disturbances and splanchnic edema and increased abdominal pressure with decreased mesenteric blood flow, which in turn elicits disruptive tissue oxygenation and ultimately leads to prolongation of the recovery of bowel function [16].

Conclusions

PPOI is a common complication after colorectal surgery. Our results have shown that gender, age, surgical approach, perioperative fluid overload, postoperative opioid analgesic are significantly related to the risk of PPOI. The nomogram with these five factors can accurately predict the probability of PPOI and enable oncologists to guide clinical individualized activities.

Abbreviations

PPOI: Prolonged postoperative ileus; POI: Postoperative ileus; ERAS: Enhanced recovery after surgery; AUC: Area under the receiver operating characteristic curve; IV: Total intravenous; POD: Postoperative day; IQR: Interquartile ranges; ROC: Receiver operating characteristic; PCA: Patient controlled analgesia

Declarations

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Not applicable.

Authors' contributions

ZL and YL contributed to analysis data, secured funding and write the manuscript. Data collection was performed by JW. HZ review the manuscript. CY contributed to the conception, design. All authors read and proved the final manuscript.

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Availability of data and materials

The datasets generated and analyzed in this paper can be made available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was performed in accordance with the principles of the Declaration of Helsinki. The study was reviewed and approved by the Institutional Ethics Committee of Fujian Cancer Hospital (NO. SQ2020-007-

02) . As this study was strictly retrospective and collecting the existing data, the informed consent was waived by the Institutional Review Board of Fujian Cancer Hospital.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interest.

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Figures

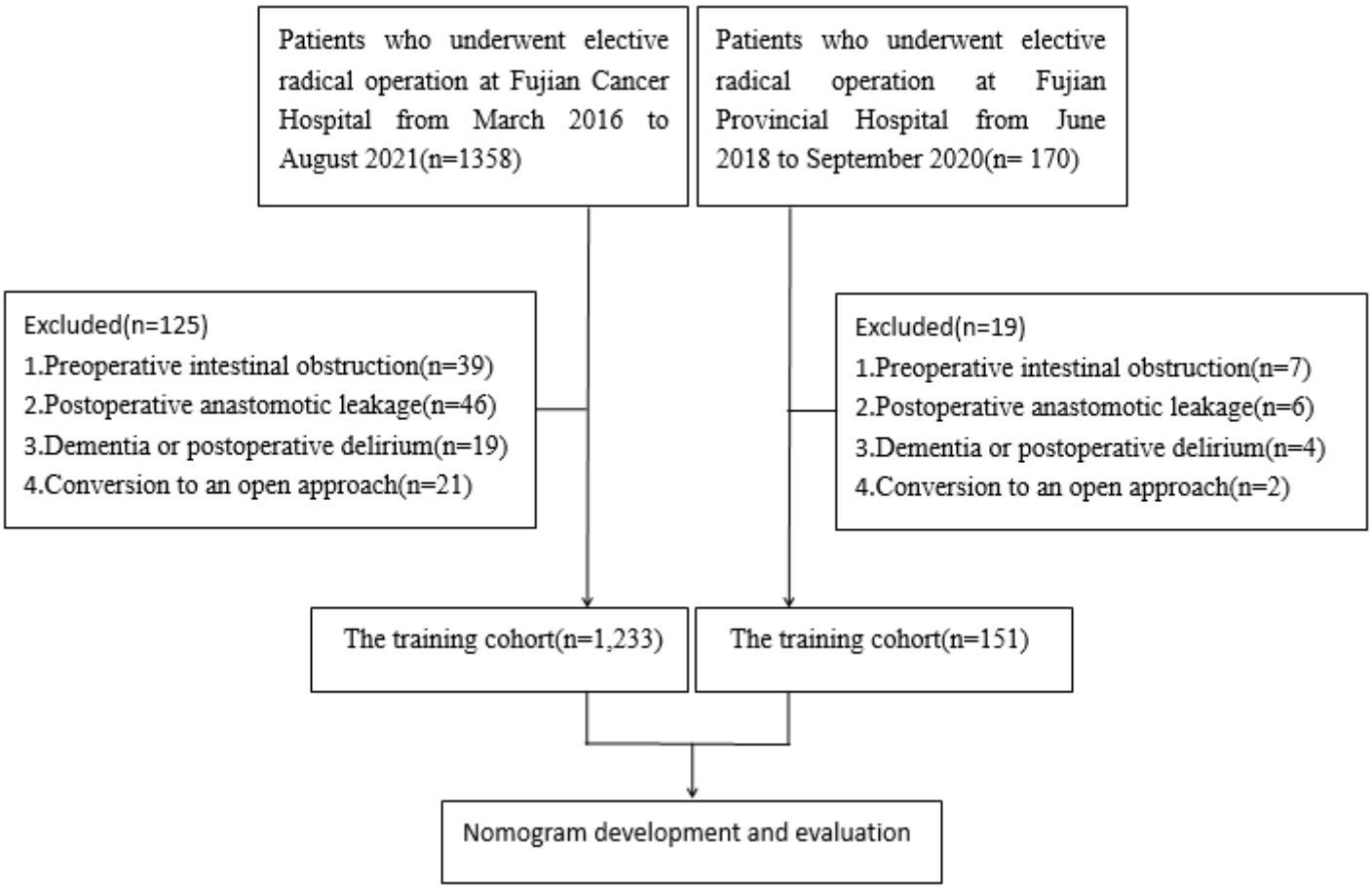

Figure 1

The flowchart of patient selection

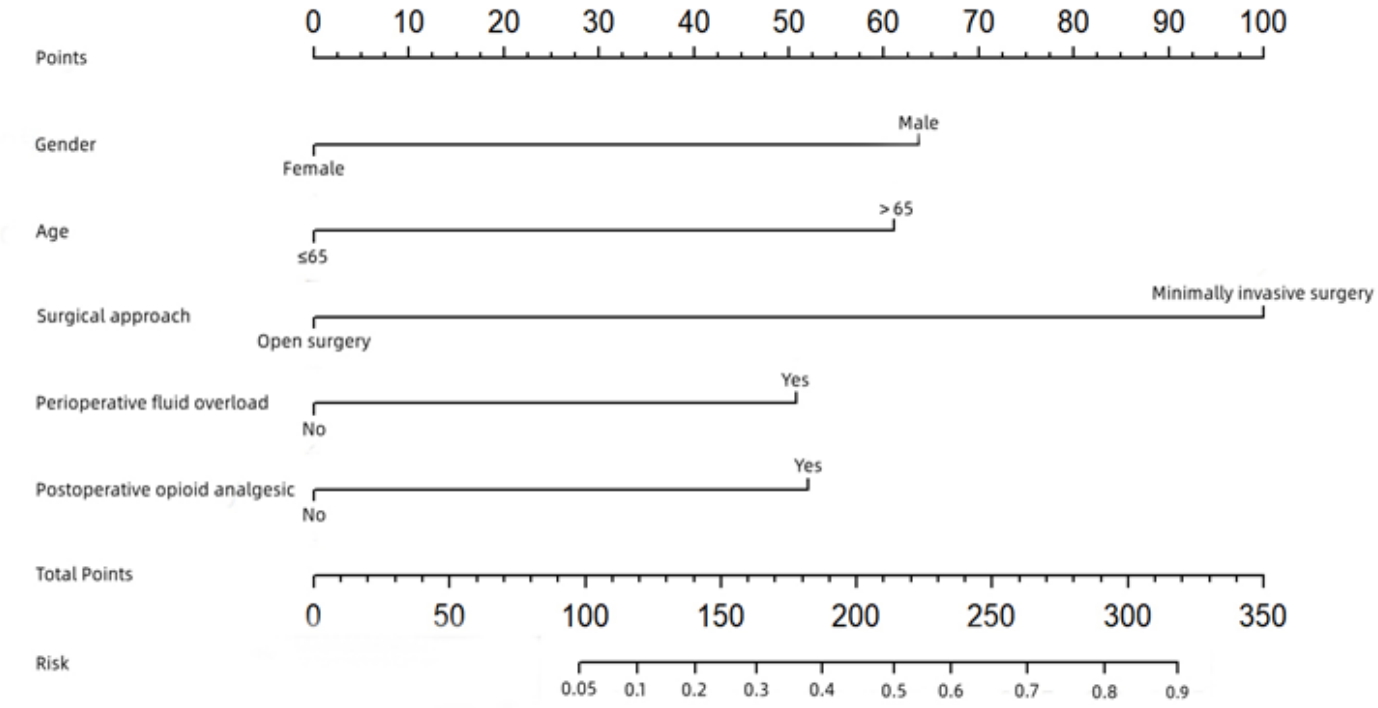

Figure 2

Nomogram to predict the probability of PPOI after colorectal resection

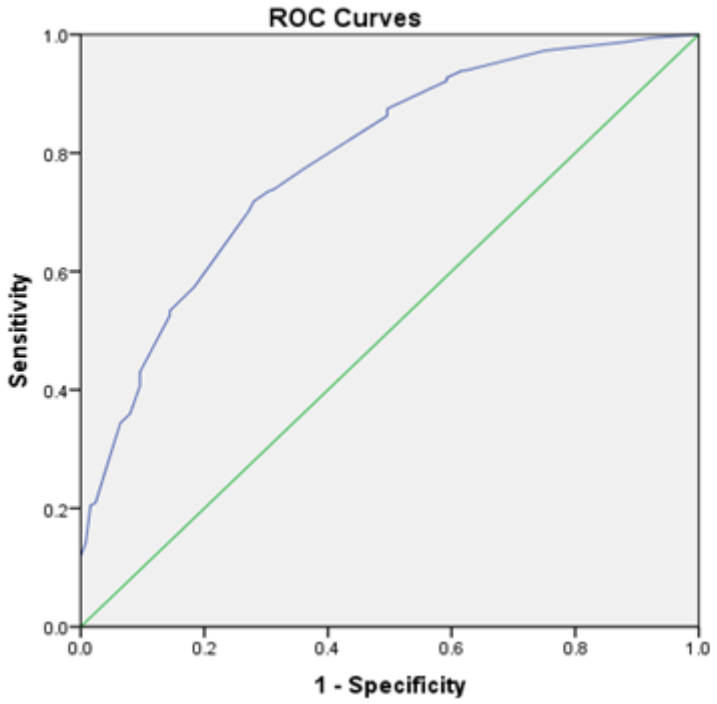

Figure 3

The ROC curve (blue) of nomograms for PPOI in the training cohort

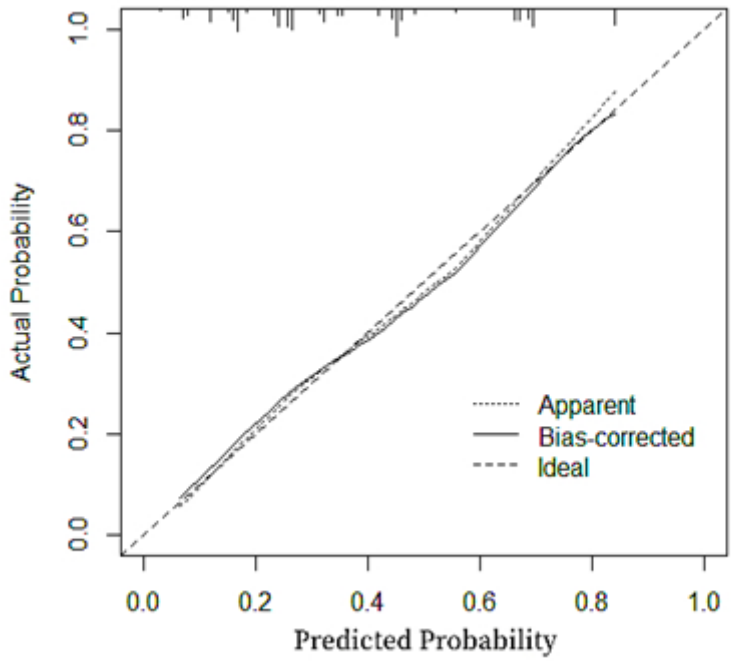

Figure 4

Calibration plots of the nomogram in the training cohort

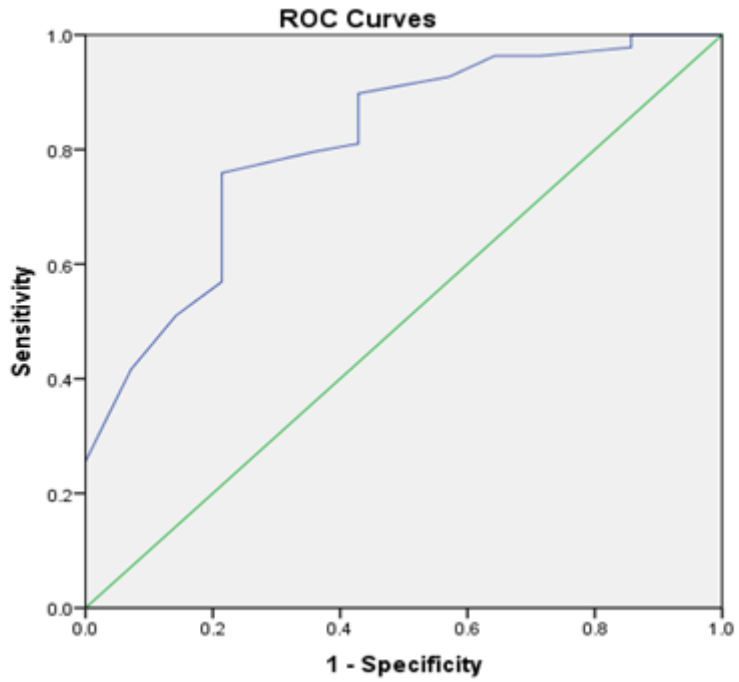

Figure 5

The ROC curve (blue) of nomograms for PPOI in the validation cohort

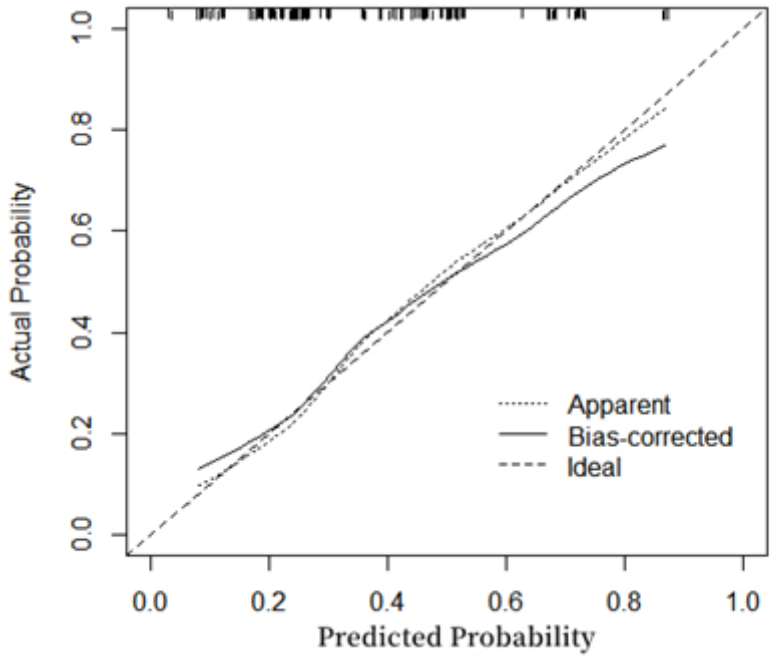

Figure 6

Calibration plots of the nomogram in the validation cohort