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Prediction model for anastomotic leakage after laparoscopic rectal cancer resection

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Abstract

Objective: This study was performed to identify risk factors for anastomotic leakage (AL) and combine these factors to create a prediction model for the risk of AL after laparoscopic rectal cancer resection.

Methods: This retrospective study involved 185 patients with rectal cancer who underwent laparoscopic resection from March 2012 to February 2017. Five risk factors were analyzed by multivariate analysis. A prediction model was established by combining the risk factors from the multivariate analysis, and the accuracy of the model was evaluated by a receiver operating characteristic curve.

Results: The overall AL rate was 17.84%. The multivariate analysis identified the following independent risk factors for AL: high body mass index (odds ratio [OR], 3.009; 95% confidence interval [CI], 1.127–7.125), preoperative radiochemotherapy (OR, 3.778; 95% CI, 1.168–12.219), larger tumor size (OR, 2.710; 95% CI, 1.119–6.562), and longer surgical time (OR, 2.476; 95% CI, 1.033–5.932). We established a prediction model that can evaluate the risk of AL by determining the predictive probability. The area under the curve for the model's predictive performance was 0.70 (95% CI, 0.598–0.795).

Conclusion: A prediction model was created to predict the risk of AL after laparoscopic rectal cancer resection.

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Keywords
Anastomotic leakage, laparoscopic surgery, prediction model, rectal cancer, receiver operating characteristic curve, risk factors

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Introduction

With the growing incidence of rectal cancer, laparoscopic surgery has become a safe and major treatment approach. Laparoscopic surgery for rectal cancer has been shown to have good outcomes and many benefits, and its safety and feasibility are well known. However, anastomotic leakage (AL) has become a serious problem for surgeons.

AL adversely affects patients' health condition and is associated with high morbidity and mortality rates, negatively impacting patient's oncological, clinical, and functional outcomes.[1–5] It is associated with a perioperative mortality rate ranging from 6.12% to 10.00%.[5] AL leads to immediate clinical consequences such as intra-abdominal or pelvic abscesses, peritonitis, sepsis, increased in-hospital morbidity and mortality, a prolonged hospital stay, the need for systemic antibiotics, the need for reintervention, and increased overall costs. It also has long-term adverse effects including impaired pelvic organ or anorectal function, increased local cancer recurrence and cancer-specific mortality rates, decreased long-term survival, and a poor prognosis.[6]

The etiology of AL is multifactorial and includes patient-, tumor-, and surgery-related factors. Patient-related factors include older age,[7] a high body mass index (BMI),[7] male sex,[4,7,8] smoking,[1,8] a high American Society of Anesthesiologists (ASA) score,[9] preoperative anemia,[10] preoperative radiochemotherapy (pRCT)[10,11] and an advanced tumor stage.[11] Tumor-related factors include a larger tumor size[12,13] and lower tumor location.[9,12] Finally, surgery-related factors include a longer surgical time,[3,9,14,15] higher intraoperative blood loss,[8,9,11] the need for blood transfusion,[9] and a lower anastomosis site from the anal verge.[3,4,7,11] However, these risk factors have not been combined to create a prediction model for the risk of AL after laparoscopic rectal cancer resection (LRCR).

The present study was therefore performed to identify the risk factors for AL and combine them to establish a prediction model for the risk of AL after LRCR.

Methods

Study population

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of Beijing Friendship Hospital (IRB: 2017-P2-122-01). Written informed consent was obtained from all patients. The study was performed from March 2012 to February 2017. Patients who had been diagnosed with rectal cancer and underwent laparoscopic resection at Beijing Friendship Hospital were included. Patients with rectosigmoid cancer were excluded. Rectal cancer was diagnosed based on clinical signs and symptoms, colonoscopy, biopsy, and computed tomography (CT). The patients were divided into two groups: those with and without AL.

Surgical method

All surgical procedures were performed by highly experienced board-certified laparoscopic colorectal surgeons at our

institution. All patients underwent standard bowel preparation within 24 hours before surgery and antibiotic prophylaxis. The surgical technique used by each surgeon was standardized in terms of the laparoscopic approach. Laparoscopic exploration was performed in the routine manner after the establishment of pneumoperitoneum. High ligation of the inferior mesenteric artery (IMA) was routinely performed, and low ligation of the IMA was performed depending on the condition of the patient's blood vessel followed by lymph node dissection. The splenic flexure was mobilized completely or partially depending on the bowel length. During partial splenic flexure mobilization, we divided the splenocolic and phrenicocolic ligaments; during complete splenic flexure mobilization, we divided the splenocolic and phrenicocolic ligaments following division of the gastrocolic and pancreaticomesocolic attachments. These procedures were technically accomplished through either a lateral-to-medial or medial-to-lateral approach. A sufficient safe margin and curative condition were ensured during tumor resection by using a linear endoscopic stapler with a margin of $\geq$5 cm for patients with upper rectal cancer and $\geq$1 cm for patients with lower rectal cancer. In all cases, a no-touch technique was applied when handling the tumor. After skeletonizing the rectal portion, a single linear stapler cartridge was used to transect the rectum. All reconstructions were completed using the double-stapling technique. A small abdominal incision of 4 to 5 cm was performed on the umbilical or suprapubic area to remove the specimen. A preventive ileostomy was created when deemed necessary according to the surgeon's evaluation. Each procedure was completed with placement of an abdominal drainage tube around the anastomosis along the presacral space. The height of the anastomosis level from the anal margin was measured by digital rectal examination. The operation time was measured from skin incision to skin closure, and the intraoperative blood loss volume was calculated.

Definitions of clinical terms

The rectum is the distal part of the large intestine that begins immediately following the sigmoid colon and ends at the anal canal. Based on its distance from the anal verge, the rectum is divided into three sections: the upper rectum (10.1–15 cm), middle rectum (5–10 cm), and lower rectum ($<$5 cm).

Clinical AL was defined as the presence of signs of leakage (fever or leukocytosis; gaseous, fecal, or purulent discharge from a drainage tube; dehiscence of suture lines; peritonitis; pelvic abscess; or rectovaginal or rectourethral fistula) that were confirmed by one or more of the following methods: CT scan, colon barium enema, rigid or flexible sigmoidoscopy, digital rectal palpation, or laparotomy.

Diabetes mellitus (DM) is a chronic metabolic disease characterized by a high blood glucose concentration. If a patient was diagnosed with DM and treated with at least one prescribed medication for a hypoglycemic agent during admission, then this patient was classified as having DM in the present study. Every patient with DM was asked to undergo measurement of their HbA1c concentration, and their blood glucose concentration was controlled (HbA1c of $<$7%) with at least one hypoglycemic drug.

Risk factors and follow-up

Several independent clinical variables were analyzed. Continuous and categorical variables were patient age ($<$60 or $\geq$60 years), BMI ($<$25 or $\geq$25 kg/m^2), tumor size ($<$5 or $\geq$5 cm), tumor distance (upper or mid/lower rectum), preoperative hemoglobin concentration (anemia; hemoglobin

concentration of <110 g/L), preoperative albumin concentration (hypoalbuminemia; albumin concentration of <35 g/L), surgical time (<180 or ≥180 minutes), intraoperative blood loss (<100 or ≥100 mL), and distance of anastomosis from anal verge (≤5 or >5 cm). Categorical variables were sex, smoking (present or past smoker), alcohol intake (present or past drinker), DM, hypertension, pRCT, ASA score (1–4), blood vessel ligation (high or low tie), blood transfusion, surgical field irrigation, and use of preventive stoma. The tumor location was classified as the lower rectum if the distance was <5 cm from the anal verge, the mid-rectum if the distance was 5 to 10 cm from the anal verge, and the upper rectum if the distance was 10.1 to 15 cm from the anal verge. A high tie was defined as ligation of the IMA at its origin, and a low tie was defined as ligation of the superior rectal artery below the branching of the left colic artery. Patients were routinely followed up until they had been confirmed to have a good prognosis for ≥3 years, until the date of death (worst prognosis), or until the last medical visit. The follow-up data collected were the abdominal and pelvic CT, chest radiography, or CT and colonoscopy findings.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation. The variables and their association with AL were investigated in univariate analyses and multivariate analyses using logistic regression. The cut-off points for all variables were as described above. A two-tailed P value of <0.05 was considered statistically significant. After the multivariate analysis, we established a prediction model using coefficient values. Receiver operating characteristic (ROC) analysis was used to confirm the prediction model for AL. An area under the curve of >0.5 was considered statistically significant for confirmation of the prediction model. The three criteria chosen for the cut-off points were 95% sensitivity, 95% specificity, and the maximum sensitivity and specificity.

Results

Demographic characteristics

In total, 185 patients who underwent LRCR during the 5-year study period were retrospectively analyzed. The patients' median age was 62 years (range, 33–91 years). The median intraoperative blood loss was 50 mL (range, 10–1000 mL). The demographic information for the entire study group is summarized in Table 1.

Thirty-three patients were diagnosed with AL after laparoscopic surgery (incidence rate of 17.84%). Of these patients, 24 were men and 9 were women. The mean age of the patients with AL was 66.515 ± 9.874 years (range, 51–89 years). The mean BMI, tumor size, preoperative albumin concentration, preoperative hemoglobin concentration, intraoperative blood loss, surgical time, and distance of anastomotic site from anal verge among patients with AL were 24.08 ± 2.37 kg/m^2, 4.20 ± 2.03 cm, 37.94 ± 4.20 g/L, 129.94 ± 20.47 g/L, 114.85 ± 187.05 mL, 176.36 ± 96.52 minutes, and 5.00 ± 1.39 cm, respectively. Two patients with AL died during hospitalization. The median time until diagnosis of AL was 3 postoperative days (range, 2–20 postoperative days).

Univariate analysis

In the univariate analysis, 20 variables possibly associated with AL were studied (Table 2). The results showed that the following were associated with a significantly increased risk of AL: a high BMI [odds ratio (OR), 2.290; 95% CI (CI), 1.046–5.013; $P = 0.038$], increasing ASA score

Table 1. Patients' demographic characteristics.

Variables	Category	No anastomotic leakage (n = 152)	Anastomotic leakage (n = 33)
Age, years		63.32 ± 10.82	66.52 ± 9.87
Sex			
	Female	60	9
	Male	92	24
BMI, kg/m^2		22.96 ± 3.29	24.08 ± 2.37
Tumor size, cm		4.02 ± 1.93	4.20 ± 2.03
Preoperative albumin, g/L		39.0 3 ±3.79	37.94 ± 4.20
Preoperative hemoglobin, g//L		126.36 ± 17.53	129.94 ± 20.47
Intraoperative blood loss, mL		58.36 ± 36.18	114.85 ± 187.05
Surgical time, minutes		136.33 ± 52.68	176.36 ± 96.52
Distance of anastomotic site from anal verge, cm		5.11 ± 1.70	5.00 ± 1.39

Data are presented as number of patients or mean ± standard deviation.
BMI, body mass index.

Table 2. Univariate and multivariate analyses for different variables related to anastomotic leakage.

		No. of anastomotic leakages/Total	Univariate analysis			Multivariate analysis		
Variables	Categories	patients (%)	OR	95% CI	*P* value	OR	95% CI	*P* value
Age, years			1.080	0.494–2.358	0.847			–
	<60	12/70 (17.14)						
	≥60	21/115 (18.26)						
Sex			1.739	0.757–3.997	0.193			–
	Female	9/69 (8.69)						
	Male	24/116 (20.69)						
BMI, kg/m^2			2.290	1.046–5.013	0.038	3.009	1.271–7.125	0.012
	<25	19/134 (14.18)						
	≥25	14/51 (27.45)						
Smoking			0.857	0.387–1.899	0.704			–
	No	11//67 (16.42)						
	Yes	22/118 (18.64)						
Alcohol intake			1.611	0.713–3.639	0.251			–
	No	22/138 (15.94)						
	Yes	11/47 (23.40)						
Diabetes mellitus			0.591	0.166–2.104	0.417	0.342	0.086–1.364	0.128
	No	30/160 (18.75)						
	Yes	3/25 (12.00)						
Hypertension			1.452	0.667–3.163	0.348			–
	No	20/125 (16.00)						
	Yes	13/60 (21.67)						
Tumor size, cm			1.758	0.822–3.759	0.146	2.710	1.119–6.562	0.027
	<5	17/116 (14.65)						
	≥5	16/69 (23.19)						
Tumor location			1.115	0.523–2.377	0.777			–
	Upper rectum	18/105 (17.14)						
		15/80 (18.75)						

(continued)

Table 2. Continued.

Variables	Categories	No. of anastomotic leakages/Total patients (%)	Univariate analysis			Multivariate analysis		
			OR	95% CI	*P* value	OR	95% CI	*P* value
	Mid/lower rectum							
Preoperative radiochemotherapy			2.004	0.761–5.281	0.160	3.778	1.168–12.219	0.026
	No	26/160 (16.25)						
	Yes	7/25 (28.00)						
Preoperative anemia			1.027	0.323–3.260	0.964			–
	No	29/163 (17.79)						
	Yes	4/22 (18.18)						
Preoperative hypoalbuminemia			1.777	0.682–4.631	0.240			–
	No	7/27 (25.93)						
	Yes	26/158 (16.45)						
ASA score			2.731	1.330–5.608	0.006			–
	1	0/3 (0.00)						
	2	20/137 (14.60)						
	3	11/43 (25.58)						
	4	2/2 (100)						
Surgical time, minutes			2.324	1.030–5.245	0.042	2.476	1.033–5.932	0.042
	<180	21/143 (14.68)						
	≥180	12/42 (28.57)						
Intraoperative blood loss, mL			2.925	1.345–6.360	0.007			–
	<100	17/132 (12.89)						
	≥100	16/53 (30.19)						
Blood vessel ligation			2.496	0.311–20.038	0.389			–
	Low tie	1/12 (8.33)						
	High tie	32/173 (18.49)						
Blood transfusion			4.967	0.956–25.801	0.057			–
	No	30/179 (16.76)						
	Yes	3/6 (50.00)						
Surgical field irrigation			1.050	0.369–2.991	0.927			–
	Yes	28/156 (17.95)						
	No	5/29 (17.24)						
Preventive stoma			1.959	0.575–6.677	0.283			–
	Yes	4/14 (28.57)						
	No	29/171 (16.96)						
Anastomosis level from anal verge, cm			1.060	0.491–2.288	0.882			–
	>5	13/75 (17.33)						
	≤5	20/110 (18.18)						

ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; OR, odds ratio.

(OR, 2.731; 95% CI, 1.330–5.608; $P = 0.006$), longer surgical time (OR, 2.324; 95% CI, 1.030–5.245; $P = 0.042$), and greater intraoperative blood loss (OR, 2.925; 95% CI, 1.345–6.360; $P = 0.007$).

Multivariate analysis

In the multivariate analysis, the following variables were independent risk factors for AL: a high BMI (OR, 3.009; 95% CI,

1.1271–7.125; $P = 0.012$), pRCT (OR, 3.778; 95% CI, 1.168–12.219; $P = 0.026$), larger tumor size (OR, 2.710; 95% CI, 1.119–6.562; $P = 0.027$), and longer surgical time (OR, 2.476; 95% CI, 1.033–5.932; $P = 0.042$) (Table 2).

Prediction model

Using the five clinically significant risk factors identified in the multivariate analysis, we established a prediction model for the risk of AL after LRCR. The prediction model is as follows:

$$P = \frac{e^{(-2.66)+(1.10)(BMI)+(1.33)(pRCT)+(1)(Tumor\,size)+(0.91)(Surgical\,time)+(-1.07)(DM)}}{1+e^{(-2.66)+(1.10)(BMI)+(1.33)(pRCT)+(1)(Tumor\,size)+(0.91)(Surgical\,time)+(-1.07)(DM)}}$$

where P is the probability of the development of AL after LRCR and e is an exponential constant with a value of 2.718. The value of each AL risk factor (BMI, pRCT, tumor size, surgical time, and DM) in the prediction model is shown in Table 3.

Confirmation of prediction model

The predictive performance of the model was assessed by ROC analysis according to binary outcomes as shown in Figure 1. From the ROC analysis, the area under the curve was 0.70 (95% CI, 0.60–0.80; $P < 0.001$). Three criteria obtained for their sensitivity and specificity by ROC analysis had three different cut-off points as shown in Table 4. When the cut-off point was 0.178, maximum sensitivity and specificity were obtained (0.52 and 0.75, respectively).

Discussion

AL is the most serious complication after LRCR. It is associated with high morbidity and mortality rates and an increased risk of permanent stoma formation. The reported incidence rate of AL after surgery for rectal cancer ranges from 2.5% to 25.0%.[2,3,6,7] The AL rate after LRCR was 17.84% in this study, which falls within the range of previously published series.

According to the present study, AL after laparoscopic surgery was significantly associated with a higher BMI, larger tumor size, pRCT, and longer surgical time. The incidence of AL after LRCR was seemingly unrelated to age, sex, smoking, alcohol intake, DM, hypertension, tumor location, preoperative anemia, preoperative hypoalbuminemia, ASA score, intraoperative blood loss, blood vessel ligation, preventive stoma, blood transfusion, surgical field irrigation, and distance of the anastomosis site from the anal verge.

A high BMI and pRCT are patient-related risk factors for the development of AL after laparoscopic surgery. A BMI of 18.5 to 24.9 kg/m^2 indicates a normal weight, 25.0 to 29.9 kg/m^2 indicates overweight, and $\geq$30 kg/m^2 indicates obesity. A high BMI is defined as a BMI exceeding

Table 3. Values for different categories related to different variables.

Variables	Categories	Values for formula
Body mass index, kg/m^2	<25	0
	≥25	1
Diabetes mellitus	No	0
	Yes	1
Preoperative radiochemotherapy	No	0
	Yes	1
Tumor size, cm	<5	0
	≥5	1
Surgical time, minutes	<180	0
	≥180	1

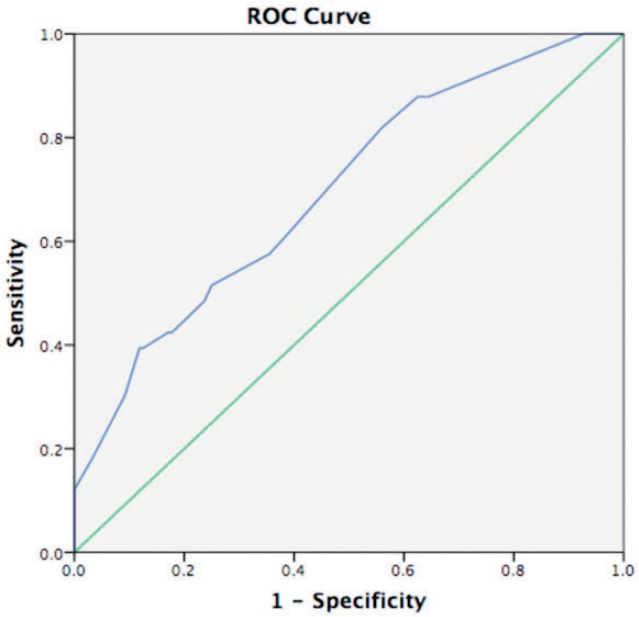

Figure 1. Receiver operating characteristic curve for prediction model related to development of anastomotic leakage.

Table 4. Cut-off points with sensitivity and specificity under certain criteria.

Cut-off point	Criteria	Sensitivity	Specificity
0.066	95% sensitivity	0.95	0.36
0.379	95% specificity	0.18	0.95
0.178	Maximum sensitivity and specificity	0.52	0.75

the BMI that is considered to indicate a normal weight for a given height and includes both overweight and obese (BMI of $\geq$25 kg/m^2). A high BMI causes poor exposure of the surgical field because of increased intra-abdominal pressure and can result in accidental injury, ischemia of the resection margin, and AL.[7] The construction of an anastomosis may be more demanding in patients with a high BMI because of the thick mesenteries and epiploic appendices.[16] In the present study, AL was found in 27.45% of patients with a BMI of $\geq$25 kg/m^2 compared with 14.18% of patients with a BMI of <25 kg/m^2. Komen et al.[16] and Yang et al.[7] showed that AL is associated with a high BMI, consistent with our results.

Possible explanations for the increased rates of AL after pRCT may be impairment of the immune system with respect to anti-infectious and anti-tumor immunity.[17] Mucosal hyperemia and acute tissue edema are early findings following radiotherapy. In the later stage, obliterating endarteritis and fibrosis impair the rectal compliance and tissue oxygenation.[18] All of these alterations affect anastomotic healing and may give rise to AL. Hayden et al.[10] and Park et al.[11] reported that patients who had received

pRCT tended to have a higher risk of AL than patients who underwent surgery alone, which is similar to the findings of our study.

Tumor size is a tumor-related factor associated with the development of AL. The pelvic space is limited in patients with larger tumors, which can adversely affect the ease of rectal transection and anastomosis. This can result in more difficult mobilization of large tumors with increased tissue tension and compromised microcirculation, especially in patients with comorbidities. Kawada et al.[13] and Eberl et al.[12] also found that a larger tumor size was a risk factor for AL. In the present study, a larger tumor size of $\geq$5 cm (23.40%) was associated with a higher risk of AL than was a smaller tumor size of $<$5 cm (14.65%).

The surgical time is a surgery-related factor that impacts the prognosis of wound healing at the anastomotic site. Highly experienced surgeons play a vital role in the success of surgery because they can achieve a shorter surgical time and lower postoperative complication rate. Moreover, surgery can be delayed in patients with severe obesity, male patients with a narrow pelvis, patients with large tumors, and in cases of adverse intraoperative events. A longer surgical time might increase the risk of bacterial exposure and tissue damage, which may cause inflammation and thus give rise to AL.[3] Consistent with previous studies,[3,14,15] we found that a longer surgical time played a significant role in the development of AL after LRCR.

We have successfully established a prediction model that can assist surgeons in calculating the risk of AL after LRCR with the specific risk predictors shown in Table 3. This model includes both clinical and surgical factors that can be directly used to evaluate the risk of AL as early surgery is completed. The model uses a combination of several risk factors with high statistical significance in contrast to a single risk factor analysis. The performance of this model was validated by the ROC analysis in this study.

With the help of this model, we can predict the probability of AL after LRCR. If the predictive probability is higher than the cut-off values, then the patient will have a higher risk of AL. The patient can then be closely monitored during the postoperative period. Hence, it is possible to identify patients at high risk of postoperative AL and conduct more active surveillance to detect AL as soon as possible. Moreover, this provides an opportunity to schedule a follow-up program. The main aim of clinical follow-up is to improve the patient's health after surgery and maintaining a low risk of AL. This can be made possible by early and efficient management of complications and specification of outcomes after evaluating the patient's risk based on follow-up care. In addition, this model is very simple and easy to use during daily clinical practice.

The main limitation of our study is the retrospective patient selection, which may have caused recall bias in terms of the details of each patient's medical history. Another potential weakness of this study is its small sample size, which may have prevented us from detecting the statistical significance of some important factors such as male sex, smoking, larger intraoperative blood loss, lower tumor location, increasing ASA score, and anastomosis site nearer to the anal verge.

In conclusion, we have created a prediction model for AL after LRCR. We found that a high BMI, pRCT, larger tumor size, and longer surgical time were independent risk factors for AL after LRCR.

Authors' contributions

ES, JL, and JS performed data collection. ES and ZZ were responsible for manuscript concept and design. ES was responsible for manuscript preparation and drafting. SW and ES conducted statistical analysis. All authors performed

critical review of subsequent drafts and all authors were involved in the submission decision.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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