Cancer Management and Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Analysis of Risk Factors for Anastomotic Leakage After Laparoscopic Anterior Resection of Rectal Cancer and Construction of a Nomogram Prediction Model

Keli Wang[1], Meijiao Li[1], Rui Liu[1], Yang Ji[2], Jin Yan[1,3]

[1]Department of Clinical Medicine, Southwest Medical University, Luzhou, People's Republic of China; [2]Department of Clinical Medicine, University of Electronic Science and Technology of China, Chengdu, People's Republic of China; [3]Department of Gastrointestinal Surgery, Sichuan Cancer Hospital & Institute, Affiliated Cancer Hospital, School of Medicine, University of Electronic Science and Technology, Chengdu, People's Republic of China

Correspondence: Jin Yan, Email yanjin_1111@163.com

Objective: To explore the risk factors of anastomotic leakage (AL) after laparoscopic anterior resection (AR) of rectal cancer and establish a nomogram prediction model.

Methods: Clinical and surgical data of patients who underwent AR of rectal cancer at Sichuan Cancer Hospital from January 2017 to December 2020 were retrospectively collected. Univariate and multivariate logistic regression analyses were used to screen the independent risk factors of AL after AR. A nomogram risk prediction model was established based on the selected independent risk factors and the predictive performance of nomogram was evaluated.

Results: A 1013 patients undergoing laparoscopic AR were included, of which 67 had AL, with an incidence of 6.6%. Univariate and multivariate logistic regression analyses showed that male gender, tumors distance from the anus verge of ≤ 5cm, tumors distance from the anus verge of 5–10cm, circumferential tumor growth, operation time ≥ 240min, and no diverting stoma were independent risk factors for AL after AR. A nomogram prediction model was established based on these results. The calibration curve showed that the predicted occurrence probability of the nomogram model was in good agreement with the actual occurrence probability. The area under the receiver operating characteristic (ROC) curve was 0.749.

Conclusion: The nomogram prediction model based on the independent risk factors of patients undergoing AL after AR can effectively predict the probability of AL.

Keywords: rectal cancer, laparoscopic anterior resection, anastomotic leakage, risk factor, nomogram prediction model

Induction

Colorectal cancer is the second leading cause of cancer death and the third most diagnosed cancer globally. The incidence rate of colorectal cancer is increasing annually.[1] At present, rectal cancer treatment involves a combination of multiple therapies with surgery as the mainstay.[2] Laparoscopic surgery is currently the primary surgical technique. Compared with laparotomy, laparoscopic surgery shows promising efficacy and multiple benefits.[3] However anastomotic leakage (AL) has remains a devastating problem.

Anastomotic Leakage (AL) is one of the most severe laparoscopic rectal cancer operation complications related to perioperative mortality.[4] Multiple studies have pointed out that AL can increase the probability of local tumor recurrence and reduce the overall survival (OS) rate of patients.[5,6] The incidence of AL is between 1.6% and 20%的,[3,4,7,8] and its etiology is believed to be related to various factors, including patient, tumor, and surgical related factors. Patient-related factors include gender, age, albumin, preoperative neoadjuvant therapy, body mass index (BMI), and American Society of Anesthesiologists (ASA) score.[9–12] Tumor-related factors include tumor size and tumor distance from the anus

Received: 24 April 2022
Accepted: 18 July 2022
Published: 28 July 2022

verge.[10,13] Operation-related factors include operation time, and intraoperative blood loss.[10,13,14] However, AL cannot be accurately predicted at present because it is complex and multi-factor, including several global and local variables.

A nomogram is a graphical model that combines various risk factors for accurate predictions and assessments. Several nomograms predict AL after rectal operation.[8,9,12] The present study evaluated and identified risk factors of patients before and during the operation and established a nomogram based on the identified risk factors to predict the probability of the occurrence of AL to prevent the occurrence of AL and improve the prognosis of patients.

Methods

Patients

A total of 1261 patients who underwent laparoscopic rectal cancer surgery at the Gastrointestinal Surgery Department of Sichuan Cancer Hospital from January 2017 to December 2020 were recruited. Among these, 65 patients who underwent laparoscopic Hartmann surgery and 183 who underwent laparoscopic Miles surgery were excluded. A total of 1013 patients who underwent laparoscopic anterior resection (AR) were included in the final analysis. All patients underwent endoscopy before surgery and were confirmed to have rectal adenocarcinoma by pathological examination. Tumor distance from the anal verge was assessed by magnetic resonance imaging (MRI). All patients underwent total mesorectal excision (TME).

Surgery

All patients underwent laparoscopic AR. Patients who received neoadjuvant therapy underwent surgery 8 weeks after the end of radiotherapy. Preoperative bowel preparation was performed one day before surgery, and prophylactic antibiotics were given 0.5–1h before the operation. TME was a standard technique. After the pneumoperitoneum was established, laparoscopic exploration was performed conventionally. The inferior mesenteric vein and artery were dissected, and the inferior mesenteric artery (IMA) was routinely ligated at a high position to complete the lymph node dissection. Based on the intraoperative situation, the splenic flexure was loosened to reduce the tension if necessary.

Along with the pelvic viscera and parietal fascia, the visceral fascia inside the left and right hypogastric nerves, the malignant tumor, and the perirectal mesangium were completely freed until the level of the levator ani muscle. The rectum was cut using linear staples (Echelon 45 or Echelon 60), then the tumor was removed through a minor incision. The anvil head of a circular staple was placed in the proximal colon, the circular staple was inserted into the rectum, and the intracorporeal anastomosis was competed. The integrity of the anastomosis was tested by blowing air through the anus and immersing the anastomosis in saline. The surgeon decides to construct a diverting stoma (DS) for a patient who meets two or more of the following criteria: 1. The operation time is more than 240min; 2. The distance between the tumor and the anus is less than 5cm; 3. The tumor grows around the circumference; 4. The maximum diameter of the tumor is greater than 5cm. Pelvic drainage was placed in the presacral space.

Anastomotic Leakage Definition

The International Rectal Cancer Research Group defines AL as the lack of integrity of the intestinal wall at the anastomosis between the colon and the rectum or the colon and the anus, which results in the communication between the inner and outer chambers of the lumen. AL Includes pelvic abscess; fecal peritonitis; discharge of gas, stool, or pus from the pelvic drainage tube; and discharge of pus from the anus.[15]

Statistical Analysis

SPSS 26.0 was used for data analysis. Measurement data were expressed as $\bar{x}\pm s$. Normally distributed data were analyzed using the Student's *t*-test and non-normally distributed data were analyzed using the Mann–Whitney *U*-test. Comparisons between groups were analyzed by the chi-square test or Fisher's exact test. The receiver operating characteristic (ROC) curve was used to determine the cut-off values of neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and prognostic nutritional index (PNI), and they were divided into high and low groups. Univariate analysis was performed on all variables, and then multivariate logistic regression analysis was performed on variables with $P<0.1$ in univariate analysis to identify independent risk factors ($P<0.05$ was considered statistically significant) to determine the valuable combination of factors that can most accurately predict AL. A nomogram prediction model was established based on the selected independent risk factors using R software, the calibration curve was obtained by the bootstrap method, the c-index was calculated, the ROC curve of independent risk factors was drawn, the area under the curve (AUC) was calculated to verify the nomogram.

Result

Patient Characteristic

A total of 1013 patients who underwent AR from 2017 to 2020 were retrospectively analyzed, including 597 males (58.9%) and 416 females (41.1%). The average age was 61 years (range 25–87 years). AL occurred in 67 patients, with an incidence rate of 6.6%. Among them, 36 patients improved after conservative treatment, 31 patients underwent stoma diversion, and 1 patient died of severe abdominal infection.

Univariate Analysis of Patient Characteristics

Patient characteristics were compared, and the results showed that only gender (P = 0.007) was the risk factor for postoperative AL (Table 1).

Univariate Analysis of Tumor Characteristics

Tumor characteristics between the two groups were compared, and the results showed that the maximum tumor size (P = 0.004) and tumor growth mode (P<0.001) were risk factors for postoperative AL. And tumors distance from the anus verge (P=0.094) can be included in multivariate logistic regression (Table 2).

Univariate Analysis of Hematological Indexes

Hematological indexes were compared, and the results showed that only neutrophils (P = 0.034) was the risk factor for postoperative AL (Table 3).

Univariate Analysis of Surgery

Surgical conditions between the two groups were analyzed, and the results showed that DS (P = 0.026) and operative time (P=0.003) were the risk factor for postoperative AL (Table 4).

Multivariate Analysis

Based on the results of univariate analysis, variables with P<0.1 were included in the multivariate logistic regression, including gender, tumor distance from the anal verge, the maximum diameter of the tumor, tumor growth pattern, operation time, diverting stoma, and neutrophils. Among them, male gender (OR = 2.52, 95% CI: 1.377–4.614), tumor distance from the anal verge of ≤5 cm (OR = 5.392, 95% CI: 2.076–14.004), tumor distance from the anal verge of 5–10 cm (OR = 2.651, 95% CI: 1.133–6.207), circumferential tumor growth (OR = 3.16, 95% CI: 1.77–5.642), operation time ≥240 min (OR = 2.357, 95% CI: 1.373–4.047), and no DS (OR = 4.15, 95% CI: 2.085–8.264) were independent risk factors for AL (Table 5).

Nomogram Model

The independent risk factors screened by multivariate logistic regression were imported into R software to construct a nomogram prediction model (Figure 1). Each risk factor was scored respectively, and the corresponding value of the total score was the predicted probability of AL. The bootstrap self-sampling method and the discrimination of the prediction model were used to verify the model internally. Data were bootstrapped 1000 times to obtain the calibration curve of the model (Figure 2), which showed that the nomogram model had good consistency between the predicted probability and the actual probability of AL. The C-Index was 0.749, suggesting that the nomogram prediction model had good discrimination ability. The ROC curve was drawn (Figure 3), and the results showed that the AUC of the ROC curve for the prediction model was 0.749, which confirmed that the prediction model had a good predictive performance and good discriminative ability.

Table 1 Univariate Analysis of Patient Characteristics

Variables	Leakage (%)	No Leakage (%)	P-value
Gender			0.007
Male	50 (8.4)	547 (91.6)	
Female	17 (4.1)	399 (95.9)	
Age (years)			0.783
>70	15 (6.8)	206 (93.2)	
60~70	20 (5.9)	321 (94.1)	
≤60	32 (7.1)	419 (92.9)	
BMI			0.572
>24	22 (5.6)	370 (94.4)	
18~24	43 (7.3)	545 (92.7)	
<18	2 (6.1)	31 (93.9)	
ASA score			0.147
I	10 (4.1)	231 (95.9)	
II	51 (7.2)	662 (92.8)	
III	6 (10.2)	53 (89.8)	
Intraoperative chemotherapy			0.979
Yes	46 (6.6)	648 (93.4)	
No	21 (6.6)	298 (93.4)	
Hypertension			0.742
Yes	12 (6.1)	185 (93.9)	
No	55 (6.7)	761 (93.3)	
Diabetes			0.406
Yes	5 (4.7)	101 (95.3)	
No	62 (6.8)	845 (93.2)	
Operation history			0.199
Yes	24 (5.5)	415 (94.5)	
No	43 (7.5)	531 (92.5)	
Preoperative chemotherapy			0.799
Yes	9 (7.1)	117 (92.9)	
No	58 (6.5)	829 (93.5)	
Preoperative radiotherapy			0.847
Yes	7 (7.1)	92 (92.9)	
No	60 (6.6)	854 (93.4)	

Discussion

AL is one of the most severe complications after rectal cancer surgery and one of the main causes of postoperative mortality. Patients usually show a triad of increased body temperature, abdominal or perineal pain, and increased serological inflammation parameters.[11] Studies have shown that the leading causes of AL are anastomotic ischemia and increased anastomotic tension.[16] High IMA ligation is usually necessary to achieve tension-free anastomosis in AR,[17] but this decreases blood flow in the anastomosis. Seike et al[18] monitored the colonic blood flow at the proximal end of the anastomosis using a laser Doppler blood flowmeter to assess the impact of high ligation and found that the IMA was clamped and the proximal colonic blood flow was significantly reduced. The reduced blood flow at the anastomosis site may increase the risk of AL.

Multiple studies pointed out that male gender and anastomotic level are risk factors for AL.[14,19,20] A study by Park[20] involving 1734 patients indicated that males were more likely to develop AL than females (HR: 1.943; 95% CI: 1.104–3.420; P = 0.021), which was consistent with our findings (OR = 2.52, 95% CI: 1.377–4.614; P = 0.003). The reason for this may be that compared with open surgery, laparoscopic surgery can provide a cleaner and better surgical field. However, it increases the difficulty of rectal resection and anastomosis. Male pelvises are generally deeper and narrower than female pelvises, making manipulation more difficult.[14,20]

Table 2 Univariate Analysis of Tumor Characteristics

Variables	Leakage (%)	No Leakage (%)	P-value
Distance from anus (cm)			0.094
>10	7 (3.3)	202 (96.7)	
5~10	37 (7.2)	478 (92.8)	
≤5	23 (8.0)	266 (92.0)	
Maximum tumor size (cm)			0.004
>5	20 (11.6)	152 (88.4)	
≤5	47 (5.6)	794 (94.4)	
T stage			0.721
1	7 (9.1)	70 (90.9)	
2	16 (7.4)	199 (92.6)	
3	31 (6.0)	485 (94.0)	
4	13 (6.3)	192 (93.7)	
Lymph node metastasis			0.101
No	46 (7.7)	553 (92.3)	
Yes	21 (5.1)	393 (94.9)	
Metastasis			0.813
Yes	4 (5)	76 (95)	
No	63 (6.8)	870 (93.2)	
Growth mode			<0.001
Non circumferential growth	39 (4.9)	761 (95.1)	
Circumferential growth	28 (13.1)	185 (86.9)	

Table 3 Univariate Analysis of Hematological Indexes

Variables	Leakage (%)	No Leakage (%)	P-value
Neutrophils (10^9/L)	4.03±1.43	3.74±1.49	0.034
Lymphocyte (10^9/L)	1.47±0.56	1.45±0.62	0.556
Platelet (10^9/L)	211.73±83	195.6±66.13	0.223
Anemia			
No	51 (6.2)	767 (93.8)	0.32
Yes	16 (8.2)	179 (91.8)	
Albumin (g/L)			0.993
>40	46 (6.6)	650 (93.4)	
≤40	21 (6.6)	296 (93.4)	
NLR			0.18
≥ 2.8208	33 (7.9)	387 (92.1)	
<2.8208	34 (5.7)	559 (94.3)	
PLR			0.221
≥187.1059	21 (8.3)	233 (91.3)	
<187.1059	46 (6.1)	713 (93.9)	
PNI			0.176
≥46.225	54 (7.2)	691 (92.8)	
<46.225	13 (4.9)	255 (95.1)	

Notes: PNI: albumin (g/L)+5×lymphocyte (×10^9 /L). Anemia: male hemoglobin <120g/L, female hemoglobin <110g/L.
Abbreviations: NLR, neutrophils/lymphocyte ratio; PLR, platelet/lymphocyte ratio.

The present study found that tumor distance from the anal verge was related to the occurrence of AL. The lower the tumor location, the greater the possibility of AL. Wang and Liu[19] investigated 496 patients and found that patients with tumors <4 cm from the anal verge were more likely to develop AL (OR = 3.224, 95% CI: 1.124–9.249; P = 0.030). Our study confirmed that patients with median and low rectal cancer had a higher probability of developing AL after surgery

Table 4 Univariate Analysis of Surgery

Variables	Leakage (%)	No Leakage (%)	P value
Operative time (min)			0.003
≥ 240	35 (9.7)	326 (90.3)	
<240	32 (4.9)	620 (95.1)	
Intraoperative blood loss (mL)			0.346
≥ 100	35 (7.4)	438 (92.6)	
<100	32 (5.9)	508 (94.1)	
Diverting stoma			0.026
Yes	14 (4.2)	323 (95.8)	
No	53 (7.8)	623 (92.2)	

Table 5 Multivariate Analysis of Risk Factors Associated with Anastomotic Leakage

Variables	B	SE	Wald	P -value	OR	95% CI
Distance from anus (cm) (>10cm)			12.436	0.002		
Distance from anus (cm) (5–10cm)	0.975	0.434	5.046	0.025	2.650	1.132~6.204
Distance from anus (cm) (≤5cm)	1.685	0.487	11.968	0.001	5.392	2.076~14.006
Maximum tumor size (cm)	0.331	0.320	1.066	0.302	1.392	0.743~2.609
Neutrophils	0.033	0.086	0.147	0.701	1.033	0.874~1.222
Growth mode	1.153	0.295	15.240	<0.001	3.167	1.775~5.648
Diverting stoma	−1.419	0.350	16.479	<0.001	0.242	0.122~0.480
Gender	0.924	0.308	8.968	0.003	2.519	1.376~4.610
Operative time (min)	0.858	0.276	9.662	0.002	2.357	1.373~4.048

compared with those with high rectal cancer (OR = 5.392, 95% CI: 2.076–14.006;P = 0.001; OR = 2.65, 95% CI: 1.132–6.204; P = 0.025). This could be because as the distance from the tumor to the anal verge decreases, the area of rectal dissociation during surgery is more extensive, and the surgery is more complicated and challenging.[19] Meanwhile, anastomosis surgery is relatively complicated, and the tension of the anastomosis is relatively increased, making the blood supply of the rectum relatively poor. This usually affects the anti-infection ability and local healing of the

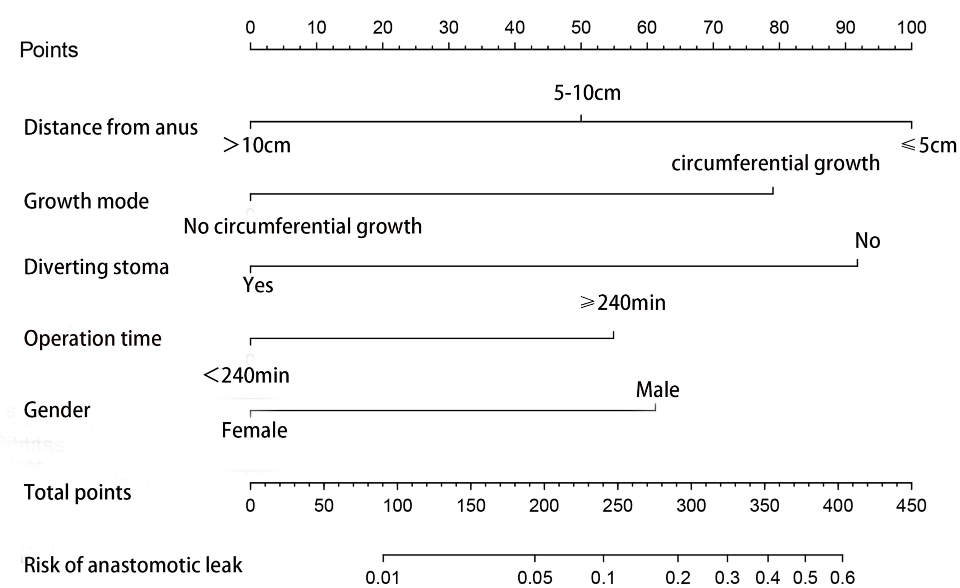

Figure 1 Nomogram for predicting anastomotic leakage.

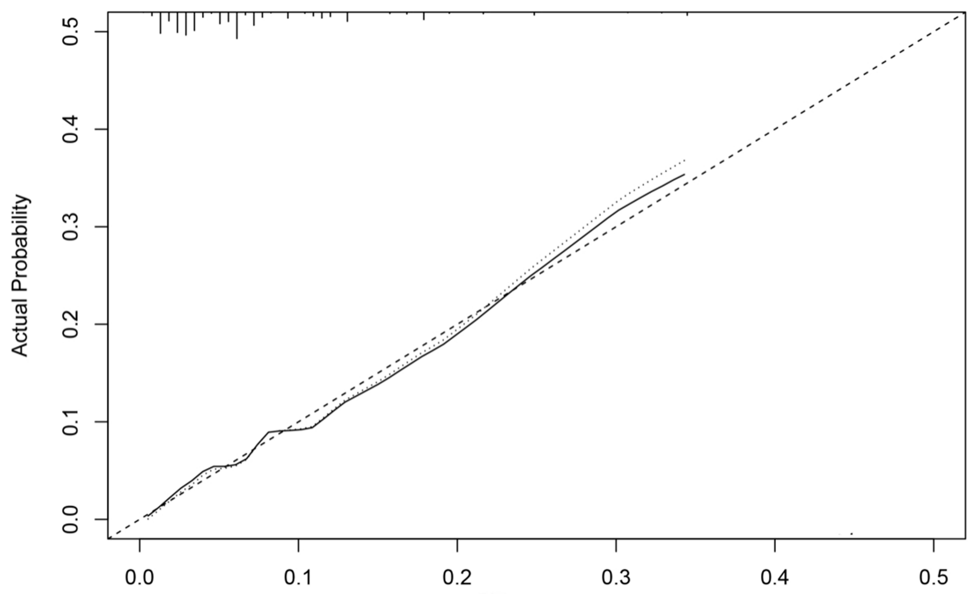

Figure 2 Bootstrap self-sampling method.
Notes: Predicted probability. B = 1000 repetitions, boot mean absolute error = 0.005 n = 1013.

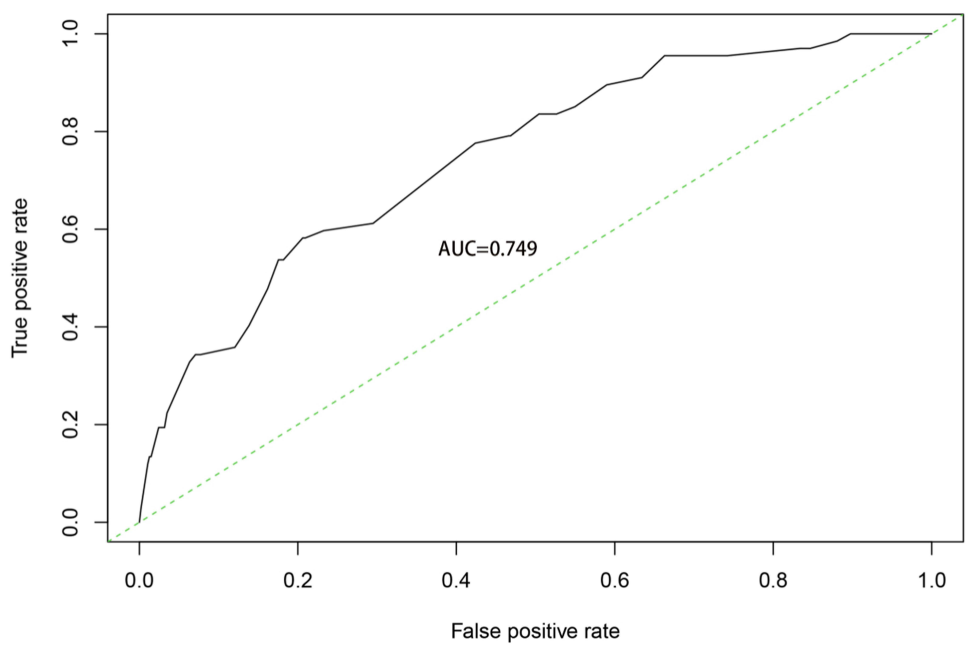

Figure 3 Receiver operating characteristic (ROC) curve.

anastomosis, thereby increasing the possibility of bacterial infection and AL.[7] Low anastomotic levels leading to insufficient blood supply may be another cause of AL. According to TME standards, branch blood vessels from the uterus or bladder need to be cut during the resection of low rectal cancer, which has a more significant impact on the blood supply of the anastomosis, leading to an increased risk of AL.[21]

Few studies have investigated the relationship between tumor growth patterns and AL. The current study found that circumferential growth tumors are more likely to develop AL than non-circumferential growth tumors (13.1% vs 4.9%). The reason may be that circumferential growth of the tumor may cause intestinal stenosis, resulting in intestinal wall edema, tissue embrittlement, poor tissue healing ability, and increased incidence of AL. In addition, intestinal stenosis may lead to intestinal fecal stasis and intestinal bacteria growth, thereby increasing the risk of postoperative intestinal infection.[22]

Several studies have proved that operation time is closely related to the occurrence of AL. The longer the operation time, the higher the possibility of AL occurrence.[10,11] Yang et al[11] pointed out that operation time >180 min was an independent risk factor of AL after rectal cancer surgery (OR = 3.419, 95% CI: 1.047–10.987; P = 0.041). Silva-Velazco et al[28] found an increasing OR of 1.03 for every 30 min of surgical duration. The results of our study showed that the operation time was more than 240 min, and the probability of AL was higher (OR = 2.357, 95% CI: 1.373–4.048; P = 0.002). The prolonged operation may reflect the difficulty of intraoperative surgery. A prolonged operation may increase the risk of tissue damage and bacterial infection, which may cause inflammation and edema and affect the healing of the anastomosis, thereby leading to AL.[3] Moreover, the operation time may lead to increased intraoperative exudation and loss of more protein, which may affect the postoperative recovery of patients.[13] The anesthesia time is correspondingly prolonged with the operation time. Some studies have shown that prolonged anesthesia may cause a decrease in blood perfusion and insufficient blood in the anastomosis, which increases the risk of AL.[8]

Currently, DS is commonly used to prevent AL. Theoretically, the structure of DS is to divert the fecal flow from the anastomotic site, thereby protecting the fragile anastomotic site.[14] Therefore, surgeons usually construct preventive DS when there are risk factors for AL. A previous study confirmed that DS can significantly reduce the incidence of AL (HR 0.334, 95% CI 0.212).[23] However, some studies have pointed out that DS cannot prevent AL.[24] Therefore, whether DS can prevent AL remains controversial. DS can only relieve severe abdominal infection caused by AL and reduce the need for emergency operation.[25–27] Nonetheless, DS increases the cost of surgery and the economic burden on patients and reduces the quality of life of patients. In addition, there may be surgical complications such as AL and abdominal infection during the second operation.[20] Therefore, precisely assessing the risk of AL is essential to selectively build preventive DS in high-risk patients.

The established model in this study can help surgeons assess the risk of AL after AR. Compared with a single risk factor analysis, our model combines several risk factors with high statistical significance, scores each risk factor, and evaluates the possibility of AL in patients through a combination of different risk factors. The model was validated by ROC analysis. This model can be used to assess the possibility of AL after AR and identify patients with a high risk of AL. Then for high-risk patients, the surgeon can take preventive interventions to reduce the possibility of AL occurrence. More active and close monitoring can be carried out to detect AL as soon as possible, which can better improve the prognosis of patients.

This study has several limitations. This is a single-center retrospective study, and therefore, there is no external verification of data from other centers. Moreover, this study mainly focused on the analysis of preoperative- and intraoperative-related factors. It did not focus on the related factors of postoperative recoveries, such as postoperative albumin, postoperative defecation, and other factors. In contrast, studies showed that postoperative hypoproteinemia and defecation time are associated with the occurrence of AL.[7]

Conclusion

In summary, our nomogram can help surgeons assess the risk of AL after anterior rectal resection and improve the prognosis of patients with anterior rectal resection.

Abbreviations

AR, anterior resection; TME, total mesorectal excision; IMA, inferior mesenteric artery; ROC, receiver operating characteristic; DS, diverting stoma.

Data Sharing Statement

The datasets used and analysed during the current study are available from the Yanjin on reasonable request.

Ethics Approval

This study was conducted with permission by Ethics Review Committees of Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China. We confirm that we have obtained ethical approval to conduct the study and publish the data set. Data obtained contained no patient identifiers. Patient data was retrieved from our hospital database and there was no intervention, so patient consent was not required. This study complied with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020, GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Benson AB, Venook AP, Al-Hawary MM, et al. NCCN guidelines insights, rectal cancer, version 6. 2020. *J Natl Compr Canc Netw*. 2020;18 (7):806–815. doi:10.6004/jnccn.2020.0032
3. Shiwakoti E, Song J, Li J, et al. Prediction model for anastomotic leakage after laparoscopic rectal cancer resection. *J Int Med Res*. 2020;48 (9):300060520957547. doi:10.1177/0300060520957547
4. Jamal S, Pai VD, Demenezes J, et al. Analysis of risk factors and management of anastomotic leakage after rectal cancer surgery, an Indian series. *Indian J Surg Oncol*. 2016;7(1):37–43. doi:10.1007/s13193-015-0457-1
5. Ma L, Pang X, Ji G, et al. The impact of anastomotic leakage on oncology after curative anterior resection for rectal cancer, A systematic review and meta-analysis. *Medicine*. 2020;99(37):e22139. doi:10.1097/MD.0000000000022139
6. Yang J, Chen Q, Jindou L, et al. The influence of anastomotic leakage for rectal cancer oncologic outcome, A systematic review and meta-analysis. *J Surg Oncol*. 2020;121(8):1283–1297. doi:10.1002/jso.25921
7. Sciuto A, Merola G, De Palma GD, et al. Predictive factors for anastomotic leakage after laparoscopic colorectal surgery. *World J Gastroenterol*. 2018;24(21):2247–2260. doi:10.3748/wjg.v24.i21.2247
8. Zheng H, Wu Z, Wu Y, et al. Laparoscopic surgery may decrease the risk of clinical anastomotic leakage and a nomogram to predict anastomotic leakage after anterior resection for rectal cancer. *Int J Colorectal Dis*. 2019;34(2):319–328. doi:10.1007/s00384-018-3199-z
9. Kim CH, Lee SY, Kim HR, et al. Nomogram prediction of anastomotic leakage and determination of an effective surgical strategy for reducing anastomotic leakage after laparoscopic rectal cancer surgery. *Gastroenterol Res Pract*. 2017;2017:4510561. doi:10.1155/2017/4510561
10. Huh JW, Kim HR, Kim YJ. Anastomotic leakage after laparoscopic resection of rectal cancer, the impact of fibrin glue. *Am J Surg*. 2010;199 (4):435–441. doi:10.1016/j.amjsurg.2009.01.018
11. Yang Q, Tang C, Qi X, et al. Mitigating the consequences of anastomotic leakage after laparoscopic rectal cancer resection, is it achievable by a simple method? *Surg Innov*. 2015;22(4):348–354. doi:10.1177/1553350614537561
12. Frasson M, Flor-Lorente B, Rodríguez JL, et al. Risk factors for anastomotic leak after colon resection for cancer, multivariateanalysis and nomogram from a multicentric, prospective, national study with 3193 patients. *Ann Surg*. 2015;262(2):321–330. doi:10.1097/SLA.0000000000000973
13. Fukada M, Matsuhashi N, Takahashi T, et al. Risk and early predictive factors of anastomotic leakage in laparoscopic low anterior resection for rectal cancer. *World J Surg Oncol*. 2019;17(1):178. doi:10.1186/s12957-019-1716-3
14. Liu Y, Wan X, Wang G, et al. A scoring system to predict the risk of anastomotic leakage after anterior resection for rectal cancer. *J Surg Oncol*. 2014;109(2):122–125. doi:10.1002/jso.23467
15. Rahbari NN, Weitz J, Hohenberger W, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum, a proposal by the International Study Group of Rectal Cancer. *Surgery*. 2010;147(3):339–351. doi:10.1016/j.surg.2009.10.012
16. Nano M, Dal Corso H, Ferronato M, et al. Ligation of the inferior mesenteric artery in the surgery of rectal cancer, anatomical considerations. *Dig Surg*. 2004;21(2):123–126. doi:10.1159/000077347
17. Zeng J, Su G. High ligation of the inferior mesenteric artery during sigmoid colon and rectal cancer surgery increases the risk of anastomotic leakage, a meta-analysis. *World J Surg Oncol*. 2018;16(1):157. doi:10.1186/s12957-018-1458-7
18. Seike K, Koda K, Saito N, et al. Laser Doppler assessment of the influence of division at the root of the inferior mesenteric artery on anastomotic blood flow in rectosigmoid cancer surgery. *Int J Colorectal Dis*. 2007;22(6):689–697. doi:10.1007/s00384-006-0221-7
19. Wang ZJ, Liu Q, Retrospective A. Study of risk factors for symptomatic anastomotic leakage after laparoscopic anterior resection of the rectal cancer without a diverting stoma. *Gastroenterol Res Pract*. 2020;2020:4863542. doi:10.1155/2020/4863542
20. Park JS, Choi GS, Kim SH, et al. Multicenter analysis of risk factors for anastomotic leakage after laparoscopic rectal cancer excision, the Korean laparoscopic colorectal surgery study group. *Ann Surg*. 2013;257(4):665–671. doi:10.1097/SLA.0b013e31827b8ed9
21. Knol J, Keller DS. Total mesorectal excision technique-past, present, and future. *Clin Colon Rectal Surg*. 2020;33(3):134–143. doi:10.1055/s-0039-3402776
22. Ruggiem R, Sparavigna L, Docimo G, et al. Post-operative peritonitis due to anastomotic dehiscence after colonic resection. Multicentric experience, retrospective analysis of risk factors and review of the literature. *Ann Ital Chir*. 2011;82(5):369–375.

23. Lee BC, Lim SB, Lee JL, et al. Defunctioning protective stoma can reduce the rate of anastomotic leakage after low anterior resection in rectal cancer patients. *Ann Coloproctol*. 2020;36(3):192–197. doi:10.3393/ac.2019.11.19.1
24. Sparreboom CL, Komen N, Rizopoulos D, et al. A multicentre cohort study of serum and peritoneal biomarkers to predict anastomotic leakage after rectal cancer resection. *Colorectal Dis*. 2020;22(1):36–45. doi:10.1111/codi.14789
25. Cong ZJ, Hu LH, Zhong M, et al. Diverting stoma with anterior resection for rectal cancer, does it reduce overall anastomotic leakage and leaks requiring laparotomy? *Int J Clin Exp Med*. 2015;8(8):13045–13055.
26. Shiomi A, Ito M, Saito N, et al. Diverting stoma in rectal cancer surgery. A retrospective study of 329 patients from Japanese cancer centers. *Int J Colorectal Dis*. 2011;26(1):79–87. doi:10.1007/s00384-010-1036-0
27. Pekka K, Everhov ÅH, Heinius G. Long-term results after anastomotic leakage following rectal cancer surgery, a comparison of treatment with endo-sponge and transanal irrigation. *Dig Surg*. 2020;37(6):456–462. doi:10.1159/000508935
28. Silva-Velazco J, Stocchi L, Costedio M, et al. Is there anything we can modify among factors associated with morbidity following elective laparoscopic sigmoidectomy for diverticulitis? *Surg Endosc*. 2016;30(8):3541–3551. doi:10.1007/s00464-015-4651-6