

# Nomogram for Predicting Anastomotic Leakage after Rectal Cancer Surgery in Elderly Patients with Dysfunctional Stomata

This article was published in the following Dove Press journal:  
*Cancer Management and Research*

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**Purpose:** Anastomotic leakage after rectal cancer surgery in elderly patients is a critical challenge. Many risk factors have been found and many interventions tried, but anastomotic leakage in elderly patients remains difficult to deal with. This study aimed to create a nomogram for predicting anastomotic leakage after rectal surgery in elderly rectal cancer patients with dysfunctional stomata.

**Methods:** We collected data from 326 consecutive elderly patients with dysfunctional stomata after rectal cancer surgery at the Sixth Affiliated Hospital, Sun Yat-Sen University from January 2014 to December 2019. Risk factors of anastomotic leakage were identified with multivariate logistic regression and used to create a nomogram. Predictive performance was evaluated by the area under the receiver-operating characteristic (ROC) curve.

**Results:** American Society of Anesthesiologists score  $\geq 3$ , male sex, and neoadjuvant radiotherapy were identified as significantly associated factors that could be combined for accurate prediction of anastomotic leakage on multivariate logistic regression and development of a nomogram. The area under the ROC curve for this model was 0.645. The C-index value for this model was 0.645, indicating moderate predictive ability of the risk of anastomotic leakage.

**Conclusion:** The nomogram showed good ability to predict anastomotic leakage in elderly patients with rectal cancer after surgery, and might be helpful in providing a reference point for selection of surgical procedures and perioperative treatment.

**Keywords:** nomogram, rectal cancer, anastomotic leakage, elderly patients

## Introduction

Colorectal cancer (CRC) is one of the most common cancers.<sup>1</sup> Many treatments have been reported for CRC, but surgery is the principal means of achieving a radical effect.<sup>2</sup> However, there are many surgical complications, especially for elderly patients. Anastomotic leakage (AL) is regarded as the leading cause of morbidity and mortality in colorectal cancer surgery, with a rate of 3%–21%.<sup>3</sup>

AL not only causes serious perioperative consequences, such as pelvic abscesses, peritonitis, septic shock, and even death, but is also the main risk factor of long-term complications, such as postoperative anastomotic stenosis and bowel dysfunction.<sup>4,5</sup> Although surgical techniques and technologies and perioperative care have greatly evolved over the last several decades, AL is still the main challenge, especially for elderly patients. Compared with open surgery, laparoscopic surgery can significantly reduce the incidence of AL; however, there is no

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difference in the AL incidence between the techniques.<sup>6</sup> Factors that may impact the risk of AL after surgery are the experience of the surgeon performing the procedure and hospital volume, not the nuances of rectal cancer surgery.<sup>7</sup> It has been reported that the AL death rate is 0.8%–27% after CRC surgery.<sup>8</sup> There is a high frequency of selective stoma to prevent potential severe consequences of AL after CRC surgery in elderly patients, reflecting poor predictive ability of surgeons to identify AL risk in elderly patients.<sup>9,10</sup> We focused on patients aged >70 years. According to 2018 recommendations of experts on rectal cancer in the elderly<sup>11</sup> and guidelines for perioperative management of elderly CRC patients in China in 2020,<sup>12</sup> the average detection age of rectal cancer has reached 70 years and 50% of newly added patients with rectal cancer are aged >70 years.

Therefore, the development of a prediction model for AL in elderly patients after rectal surgery and determination of the risk-reduction factors in controllable strategies are very important. Risk factors of AL have been extensively studied, and common ones mentioned are male sex, age, high American Society of Anesthesiologists (ASA) score, comorbidities, emergency operation, and preoperative radiotherapy.<sup>13–15</sup> Many authors have tried to compose models to predict AL that made sense in terms of treatment decisions and risk assessment.<sup>16–18</sup> However, there have been few studies on predicting the rate of AL in elderly patients after CRC surgery. This study thus aimed to construct a nomogram for predicting the incidence of postoperative AL after CRC surgery in elderly patients. Eventually, the nomogram could be applied by clinician to achieve the goal of individualized management and precise treatment for elderly patients with rectal cancer and improve prognosis and quality of life while improving their survival rate. We present the protocol in accordance with TREND (Transparent Reporting of Evaluations with Nonrandomized Designs) checklist.

## Methods

### Patients

From January 2014 to December 2019, we collected data from 326 consecutive elderly patients after rectal cancer surgery at the Sixth Affiliated Hospital, Sun Yat-Sen University. We defined elderly patients as being aged  $\geq 70$  years. Inclusion criteria were age  $\geq 70$  years, tumors less than 15 cm from the anus and pathologically confirmed as rectal adenocarcinoma, and had undergone rectal

cancer surgery. Exclusion criteria were abdominal metastases and those who had undergone Hartmann's surgery or abdominoperineal resection (Miles). Finally, 326 patients were included. The patients were divided into two groups: those with AL and those without.

All surgeries were performed by a clinical colorectal surgeon. Tumor staging was determined by The American Joint Committee on Cancer staging system (eighth edition).<sup>19</sup> All patients received a complete preoperative assessment, including physical and laboratory examinations, colonoscopy with biopsy, thoracic and abdominal computed-tomography scan, and pelvic magnetic resonance imaging. The guidelines of the National Comprehensive Cancer Network were used for perioperative management. This retrospective study was approved by the ethics committee of the Sixth Affiliated Hospital, Sun Yat-Sen University.

### Definition of AL and Follow-Up

In this study, AL was defined as damage to the integrity of the intestinal wall of the anastomotic site due to necrosis or abscess formation, resulting in intraperitoneal and extracellular communication, which was diagnosed according to the 2010 protocol of the International Study Group of Rectal Cancer. AL was classified into three grades: A, only radiological evidence of AL, without any required treatment; B, AL with clinical symptoms requiring either antibiotics or drainage; and C, symptomatic AL requiring a return to hospital and a second operation. AL was diagnosed by meeting the criteria for grades A, B or C in the present study.<sup>20</sup>

### Variables

Variables analyzed as risk factors were AL were sex, age, BMI, comorbidity, ASA score, preoperative Hb, preoperative albumin, neoadjuvant chemotherapy, neoadjuvant radiotherapy, surgical method, operation time, pathological T stage, pathological N stage, metastasis, distance from anal margin, and anastomosis method.

### Statistical Analysis

IBM SPSS 25.0 was used for data analysis. Data are expressed as means  $\pm$  SD or medians (range). Mann-Whitney rank-sum tests or *t*-tests were used to compare data between groups. Logistic regressions were used to analyze univariate and multivariate factors. Variables with  $P < 0.1$  on univariate analysis were included in the

**Table I** Patient characteristics

	AL, n (%)	No AL, n (%)	P
Patients, n	63 (19.33%)	263 (80.67%)	—
Age (years)			0.667
<75	39 (61.90%)	155 (58.94%)	
≥75	24 (38.10%)	108 (41.06%)	
Sex			0.003
Male	53 (84.13%)	177 (67.30%)	
Female	10 (15.87%)	86 (32.70%)	
BMI (kg/m <sup>2</sup> )	22.40±3.11	22.20±3.17	0.661
Comorbidity	31 (49.21%)	90 (34.22%)	0.035
ASA score			0.010
I or 2	49 (77.78%)	243 (92.40%)	
≥3	14 (22.22%)	20 (7.60%)	
Preoperative Hb (g/dL)	118.70±17.39	120.93±16.84	0.323
Preoperative albumin (g/L)	39.73±4.26	39.29±4.06	0.319
Neoadjuvant chemotherapy	21 (33.33%)	68 (25.86%)	0.258
Neoadjuvant radiotherapy	10 (15.87%)	23 (8.75%)	0.154
Surgical approach			0.198
Laparoscopy	55 (87.30%)	245 (93.16%)	
Open	8 (12.70%)	18 (6.84%)	
Surgical method			0.539
Dixon	40 (63.49%)	179 (68.06%)	
Parks and Nose	23 (36.51%)	84 (31.94%)	
Operation time	291.92±90.22	268.15±88.59	0.083
Pathological T stage			0.034
T1–T2	15 (23.81%)	99 (37.64%)	
T3–T4	48 (76.19%)	164 (62.36%)	
Pathological N stage			0.018
N0	34 (53.97%)	190 (72.24%)	
N1	20 (31.75%)	56 (21.29%)	
N2	9 (14.28%)	17 (6.46%)	
Metastasis			0.147
Yes	7 (11.11%)	13 (4.94%)	
No	56 (88.89%)	250 (95.06%)	
Distance from anal verge (cm)			0.327
>5	32 (50.79%)	151 (57.41%)	
≤5	31 (49.21%)	112 (42.59%)	
Anastomosis method			0.480
Stapled	51 (80.95%)	202 (76.81%)	
Hand-sewn	12 (19.05%)	61 (23.19%)	

multivariate model. Forest plots were constructed with GraphPad Prism 7.

The nomogram was validated internally through 1,000-bootstrap resampling to calculate the estimated Harrell concordance index (*C* index), thus indicating the performance of the model. In addition, we used a calibration curve to represent the relationship between observed frequency and predicted probability. Predictive performance was evaluated by the area under the receiver-operating characteristic (ROC) curve (AUC). Differences were considered statistically significant at  $P < 0.05$ .

## Results

### Patients

Characteristics of patients are shown in Table 1. A total of 326 elderly patients who had undergone rectal cancer surgery were included. Of these, 63 (19.33%) developed AL and 53 (84.13%) were men, the latter being significantly higher than in those without AL ( $P = 0.003$ ).

Compared to patients without AL, those with AL had poor ASA scores ( $\geq 3$ ), more at T3 and T4 stages (76.19%), higher prevalence of N1 and N2 (46.03%).

### Univariate and Multivariate Analysis

Univariate and multivariate logistic regression analyses are presented in Table 2. On univariate analysis, sex, comorbidity, ASA score, operation time, pathological T stage, and pathological N stage were associated with AL. Multivariate analysis showed that sex (HR 0.339, 95% CI 0.144–0.802;  $P = 0.014$ ), ASA score  $\geq 3$  (HR 3.250, 95% CI 1.310–8.064;  $P = 0.011$ ), and neoadjuvant radiotherapy (HR 2.876, 95% CI 1.030–8.032;  $P = 0.044$ ) were independent risk factors of AL. On the basis of these results, we developed a forest plot (Figure 1).

### Nomogram for AL

The nomogram was developed to predict the risk of AL after rectal cancer surgery based on the three independent factors on multivariate logistic regression analysis, and

**Table 2** Univariate and multivariate logistic regression model for risk factors of AL

		Univariate	Multivariate	
		<i>P</i>	HR (95% CI)	<i>P</i>
Sex	Male vs female	0.010	0.339 (0.144–0.802)	0.014
Age (years)	$\geq 75$ vs $< 75$	0.666		
BMI (kg/m <sup>2</sup> )		0.660		
Comorbidity	Absent vs present	0.028	1.806 (0.886–3.670)	0.102
ASA score	1 or 2 vs $\geq 3$	0.001	3.250 (1.310–8.064)	0.011
Preoperative Hb (g/dL)		0.347		
Preoperative albumin (g/L)		0.448		
Neoadjuvant chemotherapy	Absent vs present	0.233		
Neoadjuvant radiotherapy	Absent vs present	0.097	2.876 (1.030–8.032)	0.044
Surgical approach	Laparoscopy vs open	0.129		
Surgical method	Dixon vs Parks or Nose	0.319		
Anastomosis method	Stapled vs hand-sewn	0.479		
Operation time		0.016	4.314 (0.972–19.157)	0.055
Pathological T stage	T1 and T2 vs T3 and T4	0.048	1.063 (0.722–1.567)	0.755
Pathological N stage	N0 vs N1 vs N2	0.009	1.420 (0.876–2.300)	0.155
Metastasis	Absent vs present	0.074	1.552 (0.460–5.231)	0.479
Distance from anal verge (cm)	$> 5$ vs $\leq 5$	0.327		

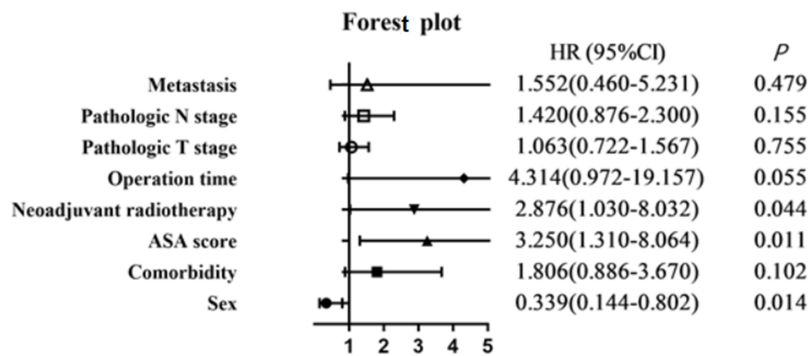


Figure 1 Forest plot.

showed that ASA score, male sex, and neoadjuvant radiotherapy influenced the incidence of AL (Figure 2). We plotted the sum of each variable on the total-point axis and obtained an estimated rate of AL by drawing a vertical line from the drawn total-point axis down to the result axis. ROC analysis showed that the nomogram had considerable predictive potential. The AUC of this model was 0.645 (Figure 3A). The C-index value of this model was 0.645, indicating moderate predictive ability of the risk of AL. The calibration plot showed that the model was close to the ideal state, indicating good calibration (Figure 3B).

### Discussion

We created a nomogram for predicting AL after rectal cancer surgery in elderly patients. Nomography for CRC has the advantage of accurate prediction of risk in patients. Our study retrospectively analyzed risk factors of AL for 326 consecutive elderly patients after rectal cancer and constructed a nomogram for predicting the incidence of AL. Previous reports have described many potential risk factors for AL after low anterior resection in rectal cancer. We found that ASA score  $\geq 3$ , male sex, and neoadjuvant radiotherapy were independent risk factors of AL on

multivariate logistic regression analysis and developed a nomogram based on these three factors. The C-index value of this model showed moderate predictive ability of the risk of AL. These findings may have clinical implications in the careful selection of elderly patients for ileostomy based on our nomogram. Previous reports have described many potential risk factors of AL after low anterior resection in rectal cancer. Hoshino et al<sup>17</sup> reported a nomogram for predicting the risk of AL after anterior resection, which included sex, serum albumin, tumor location and diameter, and simultaneous resection of other organs. That study focused on low anterior resection. Yao et al<sup>21</sup> collected tumor location, operation time, and preservation of the left colic artery, and created a nomogram for predicting the risk of AL after laparoscopic anterior resection. In contrast, our study focused on the rate of AL in elderly rectal cancer patients. To our knowledge, there have been few large-sample clinical studies on elderly rectal cancer patients and helping surgeons select precise surgical strategies.

The overall clinical AL rate was 19.33% in our study, comparable to previous research (3%–21%).<sup>3</sup> The significant difference in AL rates was due not only to the

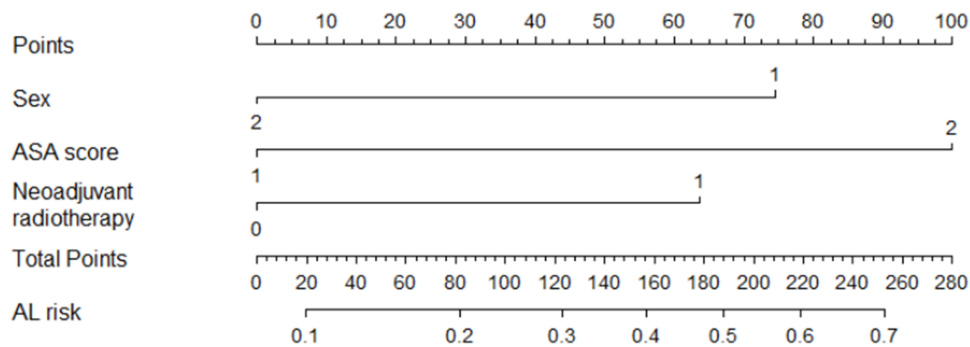
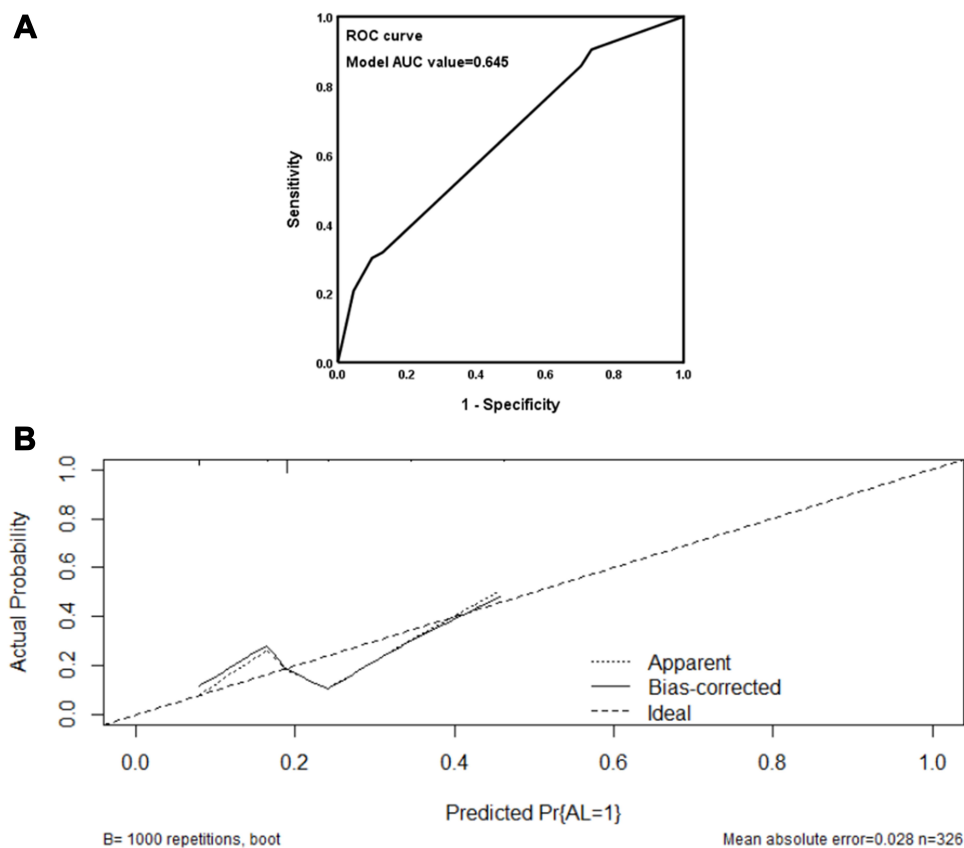


Figure 2 Nomogram for predicting anastomotic leakage (C index 0.645) after rectal cancer surgery. Incidence of anastomotic leakage was estimated by summing scores of sex, ASA score, and neoadjuvant radiotherapy.



**Figure 3 (A)** ROC curve for the nomogram. AUC was 0.645 (95% CI 0.762–0.903). **(B)** Nomogram calibration curve. The y-axis represents the actual probability of anastomotic leakage. The x-axis represents predicted anastomotic leakage probability. The ideal line represents a perfect prediction model. The apparent line represents the performance of the nomogram, and a close fit to the ideal line represents a good prediction.

different ratios of participants who underwent rectal surgery but also the inconsistent inclusion criteria for AL. AL occurrence is affected by various factors, and the pathogenesis remains unclear. In previous studies, many factors have been found to be related to AL, such as age, sex, ASA score, BMI, preoperative chemoradiotherapy, tumor stage, tumor size, operative time, malnutrition, diabetes, and steroid treatment.<sup>15</sup> However, for elderly patients with rectal cancer, there have been few studies to provide related risk factors for AL in large samples. We found that sex ( $P=0.014$ ), ASA score  $\geq 3$  ( $P=0.011$ ), and neoadjuvant radiotherapy ( $P=0.044$ ) were independent risk factors of AL. The risk of AL in male patients was 5.3-fold that of female patients in this study. The higher risk in men might be associated with a narrower pelvic space than female patients.<sup>22</sup>

As there was a significant difference between ASA scores of 1 or 2 and  $\geq 3$ , we classified ASA scores into these two categories. Our results were consistent with a previous study that reported an ASA score of at least 3 was independently related to a high risk of AL.<sup>15</sup> Some

studies have reported a significant association between neoadjuvant radiotherapy and AL, similar to our results.<sup>3,23</sup> Neoadjuvant radiotherapy can not only kill tumor cells, but can also cause tissue inflammatory edema and fibrotic plaque formation at the radiotherapy site. Among the tumor features, lower tumor location has been reported to be an important risk factor of AL. In a previous study, anal verge distance  $<7$  cm was a risk factor associated with AL occurrence. Vignali et al<sup>24</sup> showed that AL incidence was 8% when the tumor location was within 7 cm of the anal margin and 1% when it was  $>7$  cm. There was no significant difference in tumor location between the two groups in our study, possibly due to different specific locations of upper and lower rectal cancer: we regarded 5 cm from the anal margin as the threshold. Future studies are required to investigate a more feasible number as a cutoff point. Tumor stage has also been reported as significant risk factor of AL after rectal cancer surgery.<sup>6</sup> In our study, pathological T stage and pathological N stage were significantly related to AL occurrence, but not independent risk factors.



We focused on elderly patients following rectal cancer resection, who have been reported to be at high risk of AL. We drew a nomogram based on the results of multivariate logistic regression analysis, including ASA score  $\geq 3$ , sex and neoadjuvant radiotherapy. Our nomogram can offer the surgeons an accurate approximation of AL risk after rectal cancer surgery in elderly patients before surgery, because it is composed of preoperative clinical findings. It is convenient and feasible to help surgeons make better surgical plans before surgery. When patients at higher risk of AL are identified by the nomogram before surgery, Hartmann's procedure or diverting stoma would be an ideal option for these patients. After surgery, delayed resumption of oral intake or removal of the drainage tube might be better. Also, these patients should be monitored carefully and more active interventions taken during the perioperative period.

The strength of our study was that it focused on the problem of AL in elderly patients following rectal cancer surgery, which has been little reported. We investigated multiple factors that may be associated with AL and constructed a nomogram to provide good prediction of AL risk before surgery. However, this study has several limitations. Firstly, it was a retrospective, single-center study with a relatively small sample, which has the limitation of selection bias with regard to different types of procedure. For example, the number of male patients (70.55%) was much higher than female patients (29.35%), which would lead to a higher overall clinical AL rate than the reported data. Secondly, it is still unclear whether the nomogram created in this study can be used by all surgeons, because its performance was not assessed in another cohort. We expect that a prospective large-sample and multi-center study will be conducted in future to improve the reliability and practicability of the prediction model.

## Conclusion

This study screened out the risk factors of AL after rectal cancer surgery in elderly patients through multivariate analysis and constructed a nomogram to predict the possibility of AL. The nomogram showed good ability to predict AL and might be helpful in provide reference points for the selection of surgical procedures and perioperative treatment.

## Ethics Approval and Informed Consent

The study was approved by the institutional ethics board of the Sixth Affiliated Hospital, Sun Yat-Sen University

(2020ZSLYEC-297). 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.

## Acknowledgments

This work was supported by the Science and Technology Program of Guangzhou (201803010074). Chuangkun Li, Weiwen Liang and Lili Chu are co-first authors. Rongkang Huang will handle correspondence, including any queries about methodology and materials.

## Disclosure

The authors have no conflicts of interest to declare.

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