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# A Clinical Parameters-Based Model Predicts Anastomotic Leakage After a Laparoscopic Total Mesorectal Excision

## *A Large Study With Data From China*

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**Abstract:** Anastomotic leakage after colorectal surgery is a major and life-threatening complication that occurs more frequently than expected. Intraoperative judgment in predicting potential leakage has shown extremely low sensitivity and specificity. The lack of a model for predicting anastomotic leakage might explain this insufficient judgment. We aimed to propose a clinical parameters-based model to predict anastomotic leakage after laparoscopic total mesorectal excision (TME).

This study was a retrospective analysis of a prospectively designed colorectal cancer dataset. In total, 1968 patients with a laparoscopic TME were enrolled from November 1, 2010, to March 20, 2014. The independent risk factors for anastomotic leakage were identified, from which the parameters-based model for leakage was developed.

Anastomotic leakage was noted in 63 patients (3.2%). Male sex, a low level of anastomosis, intraoperative blood loss, diabetes, the duration time of the surgery, and low temperature were significantly associated by the bivariate analysis and the Cochran–Mantel–Haenszel test with an increased risk. From these factors, the logistic regression model identified the following 4 independent predictors: male sex (risk ratio [RR] = 1.85, 95% confidence interval [CI]: 1.13–4.87), diabetes (RR = 2.08, 95% CI: 1.19–5.8), a lower anastomosis level (RR = 3.41, 95% CI: 1.17–6.71), and a high volume of blood loss (RR = 1.03, 95% CI: 1.01–1.05). The locally weighted scatterplot smoothing regression showed an anastomosis within 5 cm from the anus and intraoperative blood loss of >100 mL as the cutoff values for a significantly increased risk of leakage. Based on these independent factors, a parameters-based model was established by the regression coefficients. The high and low-risk groups were classified according to scores of 3–5 and 0–2, with leakage rates of 8.57% and 1.66%, respectively ( $P < 0.001$ ).

This parameters-based model could predict the risk of anastomotic leakage following laparoscopic rectal cancer. After further validation, this model might facilitate the intraoperative recognition of high-risk patients to perform defunctional stomas.

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**Abbreviations:** CI = confidence interval, RR = risk ratio, TME = total mesorectal excision.

## INTRODUCTION

Laparoscopic colorectal surgery is associated with improved perioperative outcomes including better magnified visualization during the procedure, less pain, a shorter hospital stay, and an increased rate of sphincter preserving and leads to similar long-term oncological outcomes.<sup>1,2</sup> Laparoscopic surgery is now considered to be the first choice for the surgical treatment of malignant colorectal diseases, whereas anastomotic leak rates remain unchanged.<sup>3</sup> It has been hypothesized that the surgical technique might not be the primary cause of anastomotic leakage. As anastomotic leakage, which is associated with increased local recurrence and reduced overall survival, leads to significant morbidity and mortality<sup>4,5</sup> and intraoperative judgment in predicting potential leakage has extremely low sensitivity and specificity, we may not be able to recognize a poorly created anastomosis intraoperatively. Thus, a system that reveals patient subgroups with a high risk for leakage is required so that defunctional stoma could be selected. Although the clinical and tumor-specific characteristics associated with anastomotic leakage after open surgery have been delineated, few data are available on the risk factors contributing to leakage after a laparoscopic total mesorectal excision (TME). A parameters-based model has not been created to predict anastomotic leakage after laparoscopic TME. This study aimed to propose a feasible parameters-based model to predict anastomotic leakage after laparoscopic TME for rectal cancer.

## METHODS

### Study Population

The research has been conducted in accordance with the Declaration of Helsinki (2008) of the World Medical Association and approved by the Ethics Committee on Human Research at the First Affiliated Hospital of Chongqing Medical University, Chongqing, China. The participants provided written informed consent to participate in this study. The prospective colorectal cancer dataset used in the study was obtained from the First Affiliated Hospital of Chongqing Medical University, a nonprofit leader in medical care, research, and education in southwestern China. Between November 1, 2010, and March 20, 2014, 2331 consecutive primary rectal cancer patients, comprising patients from the outpatient department of our center as well as transfers from other hospitals, were included for laparoscopic surgery at the First Affiliated Hospital of Chongqing Medical University. Of this cohort, 1968 TME patients were enrolled in the study. The eligibility criteria

included histologically proven rectal cancer carcinoma and laparoscopic surgery with intracorporeal colorectal anastomosis. The patients who had undergone Hartmann procedure, palliative resection, and procedures converted to open surgery were excluded. The following variables were recorded prospectively in the analysis: the sex, age, body mass index, American Society of Anesthesiologists classification, preoperative chemoradiation, operation duration time, type of anastomosis, maximum tumor diameter, histopathology details, and the month in which the operation was performed. The data were analyzed retrospectively.

## Surgical Technique

All the procedures were performed by 4 senior surgeons specialized in colorectal surgery. Mechanical bowel preparation was performed within 24 hours before surgery. The surgical technique utilized by each surgeon was standardized in terms of the laparoscopic approach and has been described previously.<sup>6,7</sup> Briefly, the tumor resections were performed en bloc after ligation of the inferior mesentery vessels, followed by lymph node dissection. Standard resections were defined as tumor resections including standard lymph node dissections restricted to the tumor-bearing bowel section. Multivisceral resections were defined as “organs or structures adherent to the tumor with a need for en bloc removal to ensure sufficient safe margin and to obtain a curative situation.” The radical treatment for rectal cancer followed the TME principle. In all the cases, a no-touch technique of the tumor was applied. A small abdominal incision of <5 cm was performed to remove the specimen. Fluorouracil implants (0.6 g) were applied in the peritoneal cavity.

## Definition of Anastomotic Leakage

Anastomotic leakage was defined preoperatively<sup>8</sup> by either of the following: radiological—demonstration on abdominal computed tomography scans; peritonitis—the presence of fecal fluid at the relaparotomy; local sepsis—the presence of a localized abscess in the vicinity of the anastomosis; and fecal discharge from the drain/wound.

## Statistical Analysis

The continuous variables were expressed as the mean  $\pm$  standard deviation. The variables and their association with anastomotic leakage were investigated in univariate analyses using the  $\chi^2$  test and the Cochran–Mantel–Haenszel test. Multivariate logistic regression analysis was used to identify the independent risk factors for anastomotic leakage. A 2-tailed  $P$  value of <0.05 was considered to be statistically significant. The statistical analysis was conducted using the SPSS 17 statistical package. For the continuous risk factors, an additional LOWESS regression analysis with an estimation of a pointwise 95% confidence interval (CI) was applied in STATA. The clinical parameters-based model was proposed in line with the regression coefficient for each significant risk factor, calculated according to Sullivan et al.<sup>9</sup>

## RESULTS

Over the 3-year study period, 1968 patients underwent laparoscopic TME and met the inclusion criteria for the study. The mean age was 61 years (ranging from 27 to 83 years). Preventive defunctioning of stoma is not a routine procedure in China and in our hospital, except for ultralow sphincter-preserving procedures and in patients with a high-risk for cancer

recurrence; the procedure was performed in 32 patients (approximately 1.63%) among all the patients included in the study. The level of anastomosis is classified into an anastomosis with a distance of  $\leq 5$  cm ( $n = 1010$ ) and an anastomosis with a distance of  $>5$  cm ( $n = 958$ ) from the anal verge. The median intraoperative blood loss was 100 mL (ranging from 10 to 1000 mL). The patient demographic information for the entire study group is summarized in Table 1.

Sixty-three patients developed clinical anastomotic leakage in the postoperative period, and the overall anastomotic leak rate of 3.2% (63 of 1968). Only 1 patient was readmitted after discharge because of delayed anastomotic dehiscence (1.6%). The diagnosis of anastomotic leakage was made between postoperative days 3 and 15, at a median of 5 days postoperatively. Of these patients, 17 patients were cured with conservative treatment, whereas the remaining 45 patients received diverting stoma therapy.

## Univariate Analysis

In the univariate analysis with simple logistic regression, 14 factors possibly associated with anastomotic leakage were studied (Table 2). The results showed that male sex ( $P = 0.012$ ), diabetes ( $P = 0.01$ ), and months with low climatic temperature from October to March ( $P = 0.026$ ) were associated with an increased leakage rate. The intraoperative blood loss, operation time, and low anastomosis were significantly related (each with  $P < 0.01$ ).

## Cochran–Mantel–Haenszel Test

Table 3 reflects the tests for the independent risk factors in anastomotic leakage following rectal surgery. With the other compound factors under control, the analyses revealed that male sex (risk ratio [RR] = 2.032, 95% CI: 1.156–3.57), diabetes (RR = 3.387, 95% CI: 1.719–6.67), low climatic temperatures from October to March (RR = 1.86, 95% CI: 1.07–3.24), a high volume of intraoperative blood loss (RR = 8.18, 95% CI: 4.41–15.18), the operation time (RR = 5.01, 95% CI: 2.92–8.95), and a low level of anastomosis from the anal verge (RR = 2.641, 95% CI: 1.5–4.64) remained as the significant risk factors for anastomotic leakage.

## Multivariate Analysis

The results of the multivariate logistic regression analysis are shown in Table 4. Among all the significantly concerning factors in the univariate analysis, we identified that male sex, diabetes, high-volume intraoperative blood loss, and a shorter distance to the anal verge were the independent risk factors. Anastomotic leakage could be observed in 4.77% of the patients with an anastomosis located within 5 cm from the anal verge compared to 1.18% patients with an anastomosis  $>5$  cm ( $P = 0.001$ ), and male patients had a leakage rate of 4.23% whereas the females showed a rate of 2.07% ( $P = 0.003$ ). Additionally, high-volume blood loss and concomitant diabetes increased the anastomotic leakage rate.

## LOWESS Regression

The analysis of the association between the continuous factors, which in this case were the intraoperative blood loss volume and anastomosis level, and the leakage rate using LOWESS regression is demonstrated in Figure 1. Increasing intraoperative blood loss was shown to correlate with an elevated risk of anastomotic leakage if the blood loss were

**TABLE 1.** Patient Characteristics of Possible Factors Associated With Anastomotic Leakage in Patients Undergoing TME in Laparoscopy

	No Leakage (n = 1905)	Leakage (n = 63)	P Value
Age, y	61.69 ± 12.50	62.41 ± 11.00	0.65
Sex			
Male (%)	1088 (57.11)	46 (73.02)	0.01
BMI	21.71 ± 2.43	22.38 ± 3.96	>0.05
Diabetes (%)	112 (5.89)	11 (17.46)	0.01
Preoperative radiochemotherapy (%)	38 (1.99)	1 (1.58)	0.57
ASA score	2.4 ± 0.74	2.5 ± 0.7	0.29
Tumor size (cm)	4.21 ± 2.00	3.99 ± 1.37	0.38
Level of anastomosis (%)			<0.01
≤5 cm	964 (50.60)	46 (73.02)	
>5 cm	941 (49.40)	17 (26.98)	
Blood loss (%)			<0.01
≥100 mL	609 (31.97)	50 (79.36)	
<100 mL	1296 (68.03)	13 (20.64)	
Anastomosis technique			0.99
Only stapled	1784	59	
Plus hand sewn	121	4	
Operating time, h			<0.01
≥4	572	43	
<4	1333	20	
Concomitant resection (%)	49 (2.57)	2 (3.17)	1
TNM stage			0.08
I–II	1235	34	
III–IV	670	29	
Months			0.03
Low temperature months (October–March)	1092 (57.34)	45 (71.43)	

ASA = American Society of Anesthesiologists, BMI = body mass index, TME = total mesorectal excision, TNM = tumor node metastasis.

over the threshold of 100 mL (see Figure 1A). For the patients with an anastomosis level of <5 cm from the anal verge, the significance to an increased risk for leakage was observed (Figure 1B).

**Parameters-Based Model**

To develop ready-to-use bedside applications, the regression coefficients from the multivariate analysis were used to devise a parameters-based model (Table 5). A point was given

for each of the following: male sex, diabetes, a high volume of intraoperative blood loss (>100 mL), and an anastomosis within 5 cm from the anal verge; these factors were combined, resulting in the parameters-based model. Classification into low and high-risk groups was proposed using the  $\chi^2$  test (Table 6). The patients in the low-risk group were scored from 0 to 2, and the patients in the high-risk group had scores from 3 to 5. The leakage rate for the high-risk group was shown to be significantly higher than that for the low-risk group (8.57% vs 1.66%;  $P < 0.05$ ).

**DISCUSSION**

To date, there has been no large-scale evaluation of the risk factors and no parameters-based model predicting anastomotic leakage after laparoscopic TME surgery. To address this need, we performed this comprehensive evaluation of laparoscopic TME to provide surgeons a practical guide with quantitative measurements for reducing the harm from leakage. This study identified that male sex, concomitant diabetes, a high volume of intraoperative blood loss, and a low-lying anastomosis (located 5 cm from the anal verge) were independently associated with anastomotic leakage. To our knowledge, this model is the first to predict anastomotic leakage after laparoscopic TME.

Our results confirmed male sex as a well-known risk factor for leakage. The molecular reason could be the sex differences in the cellular pathways for collagen metabolism and tissue healing. Based on the collagen formation during tissue healing,

**TABLE 2.** Univariate Analysis of Risk Factors for Anastomotic Leakage

	RR	95% CI	P Value
Sex (male)	1.99	1.15–3.45	0.01
Diabetes	3.17	1.7–5.92	0.01
Operating time (>4 h)	4.73	2.8–7.97	<0.01
Level of anastomosis			
≤5 cm	2.57	1.48–4.45	<0.01
Blood loss (≥100 mL)	7.64	4.18–13.96	<0.01
Low temperature months (October–March)	1.83	1.06–3.13	0.03

CI = confidence interval, RR = risk ratio.

**TABLE 3.** CMH Test for Independent Risk Factors in Anastomotic Leakage After TME

	RR	95% CI	CMH P
Sex (male)	2.03	1.16–3.57	0.02
Diabetes	3.39	1.72–6.67	0.01
Operating time (>4h)	5.01	2.92–8.95	<0.01
Level of anastomosis			
≤5 cm	2.64	1.5–4.64	<0.01
Blood loss (≥100 mL)	8.18	4.41–15.18	<0.01
Low temperature months (October–March)	1.86	1.07–3.24	0.02

CI = confidence interval, CMH = Cochran–Mantel–Haenszel, RR = risk ratio, TME = total mesorectal excision.

**TABLE 4.** Multivariate Analysis of Risk Factors for Anastomotic Leakage

	RR	95% CI	P Value
Sex (male)	1.85	1.13–4.87	0.003
Diabetes	2.08	1.19–5.80	0.029
Level of anastomosis			
≤5 cm	3.41	1.17–6.71	0.001
Blood loss (≥100 mL)	1.03	1.01–1.05	<0.01

CI = confidence interval, RR = risk ratio.

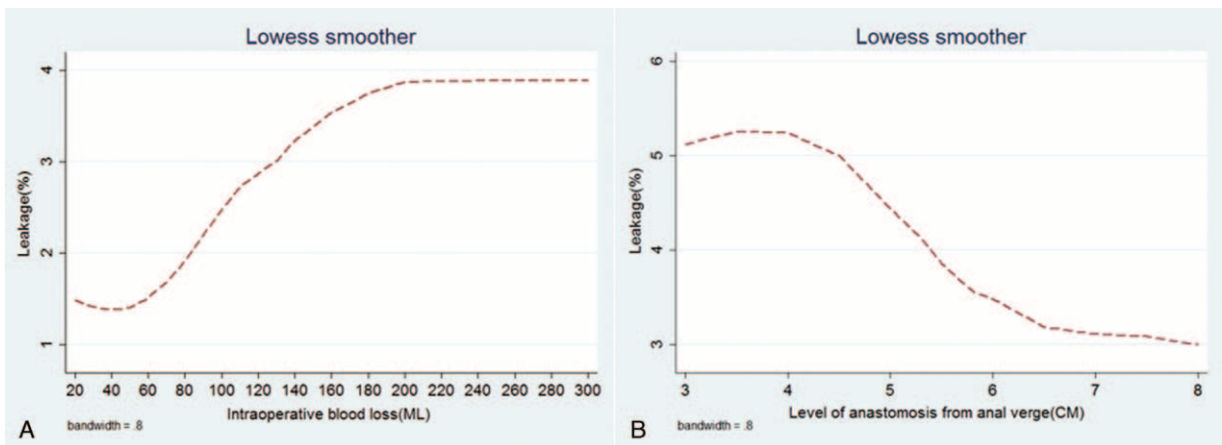
Lenhardt et al<sup>10</sup> reported that males deposited less collagen than age-matched females within the first postoperative week. Jorgensen et al<sup>11</sup> reported that premenopausal women significantly accumulated more collagen than men, indicating higher collagen formation capacity in females. A sex difference with respect to collagen deposition, and presumably anastomotic strength, has been suggested. Hence, the fact that males form less collagen within an anastomosis than that of females

possibly explains the consistent observation that anastomotic leakage is twice as common in males as it is in females.

Diabetes mellitus is one of the causes of delayed wound healing, causing surgery to be very problematic in diabetic patients. Hence, there has been concern that concomitant diabetes affects anastomotic healing. Based on the integrity evaluation of anastomosis by measuring the bursting pressure as well as the maximum and minimal tensile strength, Onodera et al<sup>12</sup> showed that the anastomotic healing of diabetic patients is delayed, presenting significantly weakened anastomotic strength on day 7 postoperatively in diabetics. Concrete messenger RNA expression of collagen types I and III in diabetes had clearly decreased in comparison with that of the control group. In accordance with these statements, our results showed a median odds ratio of 3.387 in patients with diabetes, indicating an increased risk of leaks compared with that of the nondiabetes subjects.

As observed in the previous studies,<sup>13,14</sup> a strong association between the level of anastomosis and anastomotic leakage was presented in this study, which indicates that the anastomosis distance from the anal verge is the most significant factor for the anastomotic leak rate. Among the multiple factors that are typically involved in the healing of gastrointestinal anastomoses, the blood supply plays the main role in developing anastomotic leakage. The effect of ischemia on anastomotic dehiscence is widely accepted. The highest reported leak rates after an ultralow anterior resection reached 11.6%,<sup>15</sup> because these ultralow anastomoses result from the inherently tenuous full mobilization of the blood supply of the rectum or anal tube. Perfusion of the anastomosis frequently depends on a single vascular pedicle delivering only a small fraction of the original blood supply. Subsequently, diminished perfusion and poor anastomotic healing were at high risk in the most distal aspect. Flow reduction in the rectal stump was observed in 6.2% of the patients without anastomotic leakage, whereas it was 16% in the patients who developed anastomosis breakdown.<sup>16</sup> Therefore, near infrared imaging or intraoperative laser Doppler has been used to trans-anally evaluate the anastomotic tissue perfusion following a low anterior resection.<sup>16,17</sup> Because of the specific instrument requirement and complex technological process, intraoperative evaluation has not generally prevailed in practice.

In addition, the months with low climatic temperatures were demonstrated as a risk factor on the univariate analysis.



**FIGURE 1.** LOWESS regression analysis with pointwise confidence envelopes and mean leakage rate.

**TABLE 5.** Weight for Each Factor

Factors	Categories	Regression Coefficient	95% CI	Score
Sex	Female	0.45	0.13–0.82	0
	Male			1
Diabetes	No	0.63	0.27–1.81	0
	Yes			1
Intraoperative blood loss, mL	<100	0.35	0.08–0.79	0
	≥100			1
Level of anastomosis, cm	>5	1.72	1.16–5.34	0
	≤5			2

CI = confidence interval.

Temperature is an important relevant variable in perioperation management, whereas knowledge regarding the effect of temperature on anastomotic healing is rare. Anastomotic healing is a complex process predominantly relying on mucosal epithelization and submucosal bridging. Microcosmically, local inflammation is an essential component of the first phase in anastomotic healing. Hyperthermia experiments<sup>18</sup> have demonstrated increased infiltration of anastomotic tissue with polymorphonuclear cells and macrophages, which have beneficial effects on the bursting pressure and hydroxyproline concentration in rats in wound healing processes.<sup>19</sup> The low-temperature negative effect on anastomoses is logical. Moreover, collagen metabolism regulation is temperature dependent, and temperature-induced accelerated collagen deposition would be a feasible approach to explain enhanced bursting pressure and submucosal bridging. Finally, blood flow tends to be richer at higher temperatures, resulting from temperature-induced dilation of vessels. Metabolic enzymes have been shown to be very plastic in functions that routinely experience fluctuation in demand, which is known as the pattern of enzyme activity and is significantly affected by seasonality. This seasonal decrease in enzyme activity might result from the lower basal metabolic rate observed in low temperature months. Further basic mechanical research is merited in experiments to reveal this phenomenon.

**Strengths and Weaknesses of This Study**

There has been no parameters-based model to predict anastomotic leakage after laparoscopic TME. This study offers a parameters-based model that was proposed based on the regression coefficients of 4 independent risk factors, including the level of anastomosis, sex, history of diabetes, and

intraoperative blood loss. The score uses easy-to-assess clinical parameters those are applicable on a daily basis. This model is simple and, therefore, easier to use at the bedside. This study relied on the collected data from a large nonselected cohort of patients, from whom the daily postoperative data were collected until the patient reached a study endpoint. All the postoperative factors were tested for their association with anastomotic leakage using a univariate logistic regression model. The variables derived with significance ( $P < 0.05$ ) from the univariate analysis were calculated in the multivariate logistic regression model. The proposed system has good distinguishing ability, revealing the patient subgroups at high risk for leakage and requiring a defunctional stoma. The score was proposed and tested only from one dataset, and this model has not been tested for sensitivity, specificity, positive predictive value, and negative predictive value for anastomotic leakage during the primary admission in the same way. Additionally, because of the broad CIs of the RRs, there is insufficient power to draw definitive conclusions regarding this predictive model. Some factors were assumed to produce the broad CIs here. First, a small numbers of events tend to produce wide CIs, as the low overall anastomotic leak rate of 3.2% obtained in this study, might be responsible. Second, the CIs for the standardized rates are much broader when there is a large range of follow-up in an area because the formula commonly used is a simplified version and assumes the same surgical technique all the time. The surgical technique has been modified and improved during the study period. Finally, the inherent flaw of a retrospective analysis is that it recalls significant biases affecting the selection of the controls and the heterogeneity in the results. Although the wide CIs suggest cautious interpretation, the results obtained in this study are consistent in the different methods indicating the true mean. The findings should be confirmed in a different patient cohort before the full clinical application of the model.

The inability to predict anastomotic failure results from the fundamental pathogenesis of leakage being undetermined. We hypothesize that this system will be useful in clinical practice, eventually facilitating the surgeon in selecting a diverting stoma in high-risk patients. Further studies are required to evaluate the sensitivity, specificity, positive predictive value, and negative predictive value for this model.

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**TABLE 6.** Relationship Between the Score and Leakage Rate

Score	Leakage Rate, %
0	0.37
1	0.93
2	2.61
3	4.45
4	6
5	8.57

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