

Development of a Risk Scoring System for Predicting Anastomotic Leakage Following Laparoscopic Rectal Cancer Surgery

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Purpose: To develop a risk scoring system that can predict the incidence of anastomotic leakage after laparoscopic rectal cancer surgery.

Patients and Methods: The clinical data of 387 patients with rectal cancer who underwent laparoscopic low anterior resection were retrospectively collected. Univariable and multivariable logistic regression analyses were used to evaluate independent risk factors for postoperative anastomotic leakage. A simplified points system was then developed based on the corresponding regression coefficient β of each risk factor. Receiver operating characteristic (ROC) analysis was used to evaluate the performance and the optimal cut-off value in predicting anastomotic leakage. The performance of the points system was then externally validated in an independent cohort of 192 patients based in another institution.

Results: Anastomotic leakage occurred in 36 of 387 patients with rectal cancer (9.30%). Logistic multivariable regression analysis showed that males, maximum tumor diameter (≥ 5 cm), operation time (≥ 180 min), preoperative chemoradiation, intraoperative blood transfusion and the anastomosis level from the anal verge (≤ 5 cm) were independent risk factors for the incidence of anastomotic leakage. According to the scoring standard, the risk points of each patient were calculated. ROC analysis based on the risk points showed that the area under the curve (AUC) was 0.795 (95% CI: 0.752–0.834) and the optimal cut-off value was 6, yielding a sensitivity of 88.89% and a specificity of 62.96%. Using this risk points system, the AUC of another cohort of 192 patients from another institution who underwent laparoscopic low anterior resection for rectal cancer was 0.853 (95% CI: 0.794–0.900, $p < 0.001$) and patients with risk points ≥ 6 had a 21.05% chance of developing anastomotic leakage.

Conclusion: This risk points system for predicting anastomotic leakage following laparoscopic rectal cancer surgery may be useful for surgeons in their decisions to perform intraoperative diversion stoma, which can reduce the incidence of postoperative anastomotic leakage.

Keywords: anastomotic leakage, rectal cancer, laparoscopic surgery, risk score

Introduction

Rectal cancer is one of the most common malignant tumors of the digestive tract. Current evidence suggests that laparoscopic radical resection of rectal cancer has similar long-term oncological outcomes compared with conventional open surgery and is the most widely recommended surgical strategy for the management of rectal cancer.^{1–3} Anastomotic leakage after low anterior resection is a common and severe complication during the management of rectal cancer.⁴ It leads to increased

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hospitalization costs and delays in postoperative adjuvant chemotherapy, which may affect the treatment efficacy and subsequently lead to a decline in long-term survival.^{5–7} For patients with a high risk of anastomotic leakage, intraoperative diversion stoma can reduce the incidence of postoperative anastomotic leakage.^{8,9} Therefore, the need to accurately predict the risk of anastomotic leakage and minimize the creation of unnecessary diversion stomas is of great clinical significance.

Several studies have been published on risk factors for anastomotic leakage following rectal cancer surgery, but the results are inconsistent.^{10–13} Frequently reported risk factors include low rectal anastomosis, preoperative radiotherapy and male gender.^{14,15} Other risk factors reported to be related to anastomotic leakage are body mass index (BMI), American Society of Anesthesiologists (ASA) score, tumor size, longer operative time, intra-operative blood transfusions/loss, number of stapler firings and tumor stage, among others.^{14,15} A possible explanation for the lack of consensus on potential risk factors for anastomotic leakage among studies might be the heterogeneous nature of several factors related to the studies. These could include study designs, population, methods and analysis. To assess potential preoperative risk factors, observational cohort designs are the best choice instead of randomized controlled trials (RCTs). In a meta-analysis, Pommergaard and colleagues demonstrated that anastomotic leakage had a multifactorial origin.¹⁴ We hypothesize that all the risk factors mentioned above influence the risk of anastomotic leakage, but the degrees of impact may vary. Using these potential risk factors for anastomotic leakage to guide the decision-making in whether to create a diversion stoma or not during surgery represents a challenging practical problem.¹⁶ In 2009, Dulk designed and proposed a standardized postoperative leakage scoring system (Dutch leakage score) for the early diagnosis of anastomotic leakage.¹⁷ The variables included in the Dutch Leakage score can easily be obtained during history taking and physical examination. An assessment of the score showed a significant difference in leakage-score between patients with and without anastomotic leakage. The Dutch leakage scoring system was the driver for developing a risk scoring system for predicting anastomotic leakage.

In this study, we aimed to develop a quantitative risk points system for predicting anastomotic leakage by using preoperative and intraoperative data of patients as potential risk factors. These risk factors were the significant risk

factors influencing anastomotic leakage and included the clinical and inherent tumor characteristics of the patient before and during the operation.¹⁸ Based on these risk factors, surgeons would be able to decide on whether to perform a diversion stoma during the surgery. This risk points scoring system was developed to predict the risk of anastomotic leakage and provide a reference comparison for decision-making during the operation. Furthermore, this system could assist in avoiding the use of anastomosis in patients at very high risk of leakage, thus minimizing the use of aids for fecal incontinence and defecation frequency.¹⁹

Patients and Methods

Patients

The clinical data of 387 patients with rectal cancer who underwent laparoscopic low anterior rectal resection in the Department of Gastrointestinal Surgery of Zibo Central Hospital, Shandong University, from January 2015 to December 2019 were retrospectively analyzed. The inclusion criteria were as follows: preoperatively diagnosed as rectal cancer by colonoscopy and biopsy pathology; newly diagnosed patients with rectal cancer; the lower edge of the tumor was 3–12 cm from the anal verge; no operative contraindications were confirmed by preoperative multidisciplinary consultation and discussion and laparoscopic low anterior rectal resection was successfully performed without conversion to laparotomy. Patient exclusion criteria were: (i) those with local organ invasion and distant metastasis by MRI and enhanced CT before operation; (ii) patients with multiple colon tumors; (iii) patients who underwent Miles or Hartmann surgery and (iv) patients with intraoperative diversion stoma. Using the same inclusion/exclusion criteria, the clinical data of another cohort of 192 patients who underwent laparoscopic low anterior resection for rectal cancer in Jiangyin people's Hospital, School of Medicine, Southeast University, from January 2015 to December 2019 were also collected. The Ethics Committee of Zibo Central Hospital, Shandong University and Jiangyin People's Hospital, School of Medicine, Southeast University approved the study. Written informed consent was obtained from all patients.

Surgical Procedures

Conventional five ports laparoscopic surgery for rectal cancer was performed according to the technique described previously.²⁰ The surgical procedures strictly followed the TME and standard oncologic practices:

adequate distal margin, ligation at the origin of the arterial supply for the involved rectal segment and mesorectal excision. To ensure a tension-free anastomosis, vascular ligation occurred either at the takeoff of the inferior mesenteric artery from the aorta or just distal to the takeoff of the left colic artery. Then, end-to-end colorectal anastomosis was performed with a circular stapler and the air leak test was confirmed to be negative. The same group of surgeons performed all surgical operations.

Diagnosis of Anastomotic Leakage

The definition of anastomotic leakage after anterior resection for rectal cancer is in line with the International Study Group of Rectal Cancer: ie, a communication between the intra- and extraluminal compartments owing to a defect of the integrity of the intestinal wall at the anastomosis between the colon and rectum/anus.²¹ Anastomotic leakage was diagnosed when any of the following conditions occurred: sudden increase in the pelvic drainage tube, combined with turbid or fecal/purulent content; persistent fever with signs of peritonitis or pelvic abscess; radiographic contrast enema or CT with transrectal instillation of contrast revealing leakage of the contrast agent and palpable anastomotic defect on digital rectal examination.

Statistical Analysis

Continuous data (age, BMI, preoperative albumin, ASA score, NRS score, maximum tumor diameter, operation time, intraoperative hemorrhage and anastomosis level from the anal verge) were expressed as mean \pm SD and compared between groups using two-tailed Student's *t*-test. Categorical data (gender, smoking status, preoperative clinical AJCC stage, preoperative chemoradiation and intraoperative blood transfusion) were analyzed using a chi-square test or Fisher's exact probability test. Only the risk factors with a *p*-value less than 0.20 in the univariable logistic regression analysis were selected for input into the multivariable model. Based on the method proposed by Sullivan, each statistically significant factor in the multivariable logistic regression analysis was assigned point according to the corresponding regression coefficient β .²² Specifically, $0 < \beta < 1$, assigned 1 point; $\beta > 1$, assigned 2 points; $\beta > 2$, assigned 3 points; and $\beta > 3$, assigned 4 points. The risk score of each patient was calculated as the sum of the risk factor points. A ROC analysis was conducted according to the risk score points of each patient. The area under the curve (AUC) and optimal cut-off value were calculated. In ROC analysis, AUC values of 0.7–0.8 were considered acceptable, 0.8–0.9 as excellent, and those above 0.9 as

outstanding.²³ Using anastomotic leakage as the classification variable, the optimal cut-off value for risk score points was obtained by applying Youden's index (sensitivity + specificity – 1), choosing AUC values where the index was maximal. Using this risk points system, the ROC analysis of an external validation cohort of 192 patients who underwent laparoscopic low anterior resection for rectal cancer was conducted and the AUC value was calculated. SPSS26.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. MedCalc® Statistical Software version 19.5.6 (MedCalc software Ltd, Ostend, Belgium) was used for ROC analysis. *P* < 0.05 was considered to be statistically significant.

Results

Univariate and Multivariate Logistic Regression Analysis for Anastomotic Leakage After Laparoscopic Rectal Cancer Surgery

The preoperative and intraoperative clinical data of 387 patients with rectal cancer are summarized in Table 1. The number of patients who developed anastomotic leakage was 36/387 (9.3%). Of the 36, 29 cases were successfully managed by continuous negative pressure irrigation and drainage by a modified double-lumen irrigation-suction tube;²⁴ 7 cases were successfully managed with temporary diversion loop stoma (transverse colostomy or terminal ileostomy) combined with continuous negative pressure irrigation and drainage. Following univariable logistic regression, potential risk factors were selected for the multivariable analysis (Table 1). Multivariable logistic regression confirmed that male gender, preoperative chemoradiation, maximum tumor diameter, operation time, intraoperative blood transfusion and anastomosis level from the anal verge to be independent risk factors for anastomotic leakage after laparoscopic rectal cancer surgery (Table 1). The regression coefficient (β) of each statistically significant risk factor is reported in Table 1.

Establishment of a Simple Risk Scoring System and ROC Analysis Based on Patients' Risk Scores

Based on the regression coefficient (β) of each statistically significant risk factor in the multivariable logistic regression analysis, the risk score points of each patient were calculated. The risk score of each patient ranged from 0–13 points. ROC analysis based on the risk score points showed that the AUC was 0.795 (95% CI:0.752–0.834)

Table 1 The Clinical Data of 387 Patients with Rectal Cancer Who Underwent Laparoscopic Low Anterior Resection for Rectal Cancer

Parameters		No. of AL/Total	Univariate Analysis		Multivariate Analysis			
			HR	p	HR	β	95% CI	p
Gender	Male Female	29/243 (11.9%) 7/144 (4.9%)	2.652	0.025	20.682	3.029	3.938–108.621	<0.001
Age	<70 ≥70	24/273 (8.8%) 12/114 (10.5%)	1.059	0.879				0.810
BMI	<25 ≥25	28/33 (8.5%) 8/56 (14.29%)	1.761	0.188				
Smoke	Yes No	21/208 (10.1%) 15/179 (8.4%)	1.228	0.563				
Preoperative albumin (g/dL)	<3.5 ≥3.5	8/105 (7.6%) 28/282 (9.9%)	1.036	0.927				
ASA Score	1–2 3	32/352 (9.1%) 4/35 (11.4%)	1.290	0.651				
NRS Score	<3 ≥3	29/324 (8.9%) 7/63 (11.1%)	1.272	0.590				
Preoperative clinical AJCC stage	I+II III	14/228 (6.1%) 22/159 (13.8%)	2.445	0.012				0.288
Preoperative chemoradiation	Yes No	13/64 (20.3%) 23/323 (7.1%)	3.325	0.002	8.629	2.155	2.205–33.769	0.002
Maximum tumor diameter	>5cm ≤5cm	20/133 (15.0%) 16/254 (6.3%)	2.633	0.006	2.211	0.793	1.001–4.834	0.047
Operation time	<180min ≥180min	16/241 (6.6%) 20/146 (13.7%)	2.178	0.028	2.612	0.960	1.194–5.716	0.016
Intraoperative hemorrhage	<150mL ≥150mL	25/314 (7.9%) 11/73 (15.1%)	2.051	0.064	3.984	1.382	1.009–15.732	0.049
Intraoperative blood transfusion	Yes No	12/77 (15.6%) 24/310 (7.7%)	2.200	0.038				
Anastomosis level from anal verge	≤5cm >5cm	26/153 (17%) 10/234 (4.3%)	3.960	<0.001	3.393	1.222	1.517–7.586	0.003

Abbreviations: AL, anastomotic leakage; BMI, body mass index; ASA, American Society of Anesthesiologists; NRS, nutrition risk screening; AJCC, American Joint Committee on Cancer.

with an optimal cut-off value of 6, yielding a sensitivity of 88.89% and a specificity of 62.96%, as shown in [Figure 1](#).

Evaluation of the Performance of the Risk Scoring System for Predicting Anastomotic Leakage

Based on the cut-off value of the risk score points in the ROC analysis, 387 patients with rectal cancer were divided into two groups (≥ 6 and < 6). Of 159 patients with a risk score points ≥ 6 , 29 (18.24%) developed postoperative anastomotic leakage.

Only 7 patients (3.07%) of 228 patients with risk score points < 6 developed postoperative anastomotic leakage ([Figure 2](#)). The incidences of anastomotic leakage due to other risk factors are listed in [Table 1](#). We also used ROC analysis to compare the diagnostic performance of a risk score with three continuous variables (maximum tumor diameter, operation time and anastomosis level from the anal verge). As shown in [Figure 3](#), the AUC and the diagnostic accuracy of the risk scoring system were significantly greater than that of the three continuous variables.

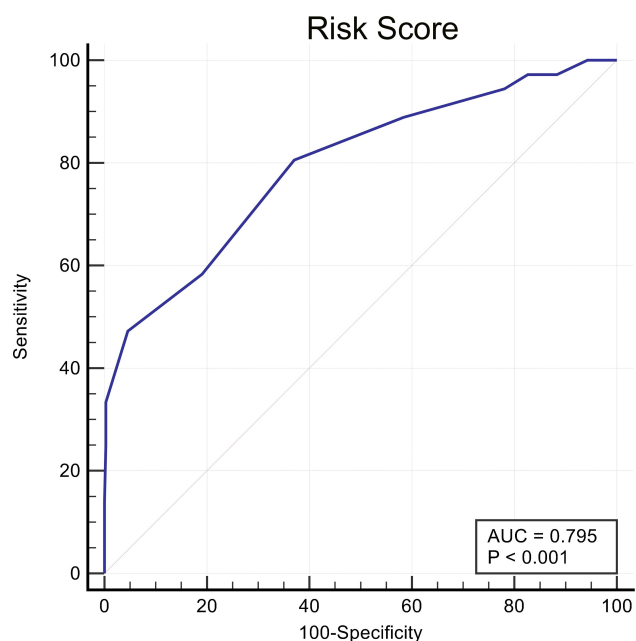


Figure 1 ROC curve based on the risk points. The area under the curve (AUC) was 0.795 (95% CI:0.752–0.834) and the optimal cut-off value was 6.

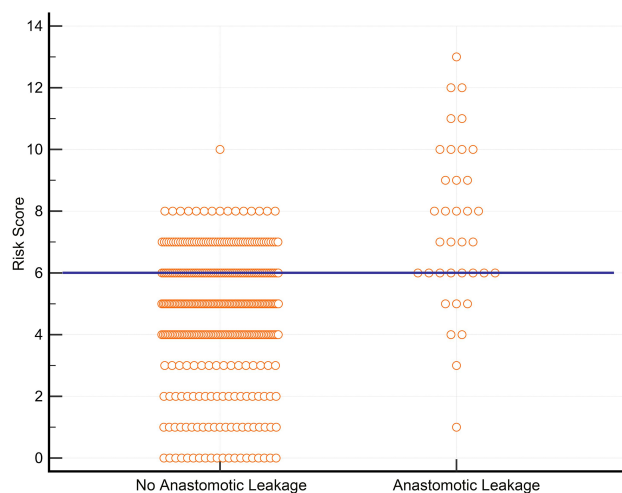


Figure 2 The distribution of patients according to the high or low risk score. 387 patients with rectal cancer were divided into two groups (≥ 6 and < 6).

Validation of the Risk Scoring System for Predicting Anastomotic Leakage

To independently validate the performance of the risk score in predicting anastomotic leakage, we collected the clinical data of 192 patients with rectal cancer who underwent laparoscopic low anterior resection for rectal cancer in Jiangyin people's Hospital, School of Medicine, Southeast University, as shown in Table 2. There were no differences in the case-mix between the training and

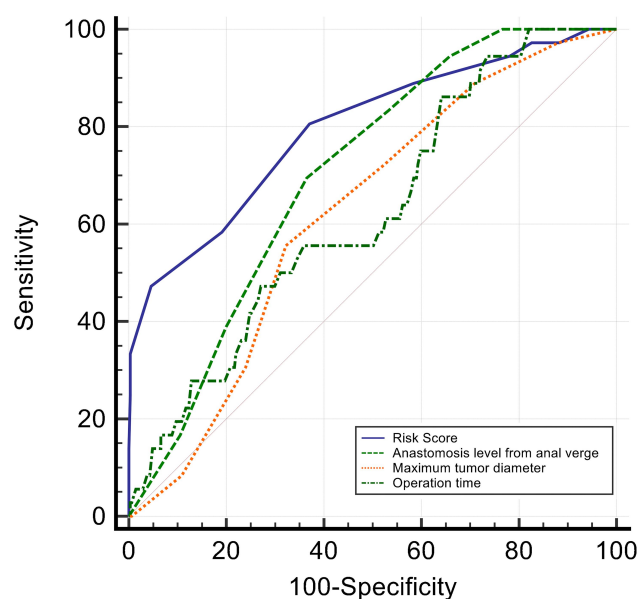


Figure 3 Comparison of the risk score system with the three continuous variables (maximum tumor diameter, operation time and anastomosis level from anal verge). For risk score system, AUC=0.795 (95% CI:0.752–0.834); For maximum tumor diameter, AUC=0.621 (95% CI:0.570–0.669); For operation time, AUC=0.624 (95% CI:0.573–0.672); For anastomosis level from anal verge, AUC=0.703 (95% CI:0.655–0.748).

validation sets (Table S1). The number of patients who developed anastomotic leakage was 23/192 (11.98%). There were 95 patients with risk score points ≥ 6 and 20 (21.05%) of them had developed postoperative anastomotic leakage. Whereas only 3 patients (3.09%) out of 97 patients with risk score points < 6 had developed postoperative anastomotic leakage (Figure 4A). As shown in Figure 4B, the AUC of the risk scoring system for the 192 patients by ROC analysis was 0.853 (95% CI:0.794–0.900, $p < 0.001$). Therefore, the validity of the risk score in predicting anastomotic leakage is reliable and stable.

Discussion

Anastomotic leakage is a serious complication following low anterior resection for rectal cancer. The occurrence of anastomotic leakage not only increases the length of hospital stay and medical costs, but also causes further delays in the adjuvant treatment of patients after surgery, thereby affecting the overall survival rate of patients.^{15,25,26} Anastomotic leakage is a complication that represents a real challenge for rectal cancer surgeons. Although there have been innovations in laparoscopic surgical techniques in recent years, the incidence of anastomotic leakage has been reported to range between 9.3% and 13%.^{9,27,28} The temporary diverting stoma has proved to

Table 2 The Clinical Data of 192 Patients with Rectal Cancer Who Underwent Laparoscopic Low Anterior Resection for Rectal Cancer from Another Center

Parameters		AL/Total	P value
Gender	Male	19/122 (15.6%)	0.043
	Female	4/70 (5.7%)	
Age	<70	15/125 (12.0%)	0.990
	≥70	8/67 (11.9%)	
BMI	<25	17/155 (10.9%)	0.377
	≥25	6/37 (16.2%)	
Smoke	Yes	13/108 (12.0%)	0.978
	No	10/84 (11.9%)	
Preoperative albumin (g/dL)	<3.5	8/59 (13.6%)	0.653
	≥3.5	15/133 (11.3%)	
ASA Score	I–II	20/171 (11.7%)	0.722
	3	3/21 (14.3%)	
NRS Score	<3	18/152 (11.8%)	0.909
	≥3	5/40 (12.5%)	
Preoperative clinical AJCC stage	I+II	12/110 (10.9%)	0.597
	III	11/82 (13.4%)	
Preoperative chemoradiation	Yes	10/43 (23.3%)	0.010
	No	13/149 (8.7%)	
Maximum tumor diameter	>5cm	11/68 (16.2%)	0.185
	≤5cm	12/124 (9.7%)	
Operation time	<180min	10/114 (8.8%)	0.098
	≥180min	13/78 (16.7%)	
Intraoperative hemorrhage	<150mL	12/126 (9.5%)	0.148
	≥150mL	11/66 (16.7%)	
Intraoperative blood transfusion	Yes	11/65 (16.9%)	0.131
	No	12/127 (9.4%)	
Anastomosis level from anal verge	≤5cm	16/87 (18.4%)	0.013
	>5cm	7/105 (6.7%)	

Abbreviations: AL, anastomotic leakage; BMI, body mass index; ASA, American Society of Anesthesiologists; NRS, nutrition risk screening; AJCC, American Joint Committee on Cancer.

effectively reduce the incidence of postoperative anastomotic leakage and prevent severe consequences attributed to leakage, such as local recurrence and morbidity.^{25,29}

Although the application of diverting stoma reduces the incidence of anastomotic leakage, the complications related to the stoma are also worthy of attention by surgeons. Holmgren reported that in 24% of patients, the temporary stoma was converted to a permanent stoma and 9% of patients experienced serious complications after stoma reversal.³⁰ The most common reason for a permanent stoma was anastomotic leakage.³² Other risk factors such as tumor stage IV and impaired anorectal

function have also been reported to influence the conversion to permanent stoma.^{30,31} On the other hand, stomas have a negative psychological impact on patients and increase the costs and challenges associated with home care. Therefore, effective creation of stomas in patients with a high risk of anastomotic leakage before the end of the surgical procedure and avoiding unnecessary diversion stomas are of great importance.

In previous studies, there have been inconsistencies on the role of risk factors for anastomotic leakage after rectal cancer surgery.^{10–13} However, these inconsistencies do not suggest that these potential risk factors do not influence the risk of anastomotic leakage following rectal cancer surgery. There is a possibility that the risk of anastomosis attributed to each of these potential risk factors varies. This makes it difficult for surgeons to accurately assess the risk of anastomotic leakage for patients with more than one risk factor and hence unable to decide on whether to perform a diversion stoma or not. This was the main driver for our attempt at developing a risk scoring system to quantify the risk of anastomotic leakage.

Based on the results of previous studies, we included as many potential risk factors as possible in the model. The intent was to create a risk score that would accurately reflect the risk of postoperative anastomotic leakage. From the results of the ROC analysis, the performance of the scoring system was acceptable. The incidence of anastomotic leakage in the low-risk score group was significantly lower than the high-risk score group. To minimize limitations associated with generalizability because of using patients from a single center, we also confirmed the predictive performance of the score in an independent validation cohort from another center. Although we tried to minimize biases as much as possible, there were still some limitations that need to be considered. Our scoring system was based on simple logistic regression. LASSO is a more advanced regression analysis method for variable selection and accurate prediction.³² Another limitation was that the risk scores obtained from the logistic regression were not continuous. This weakened the accuracy of this scoring system to some extent. Since this scoring system was based on the Chinese population, whether it is applicable to Western populations still needs to be evaluated. The present study was based on retrospective data and a relatively small sample size. Hence, whether this risk score system will be essential for decision-making in surgical practice still requires confirmation using multi-center prospective studies with large sample sizes. If this scoring

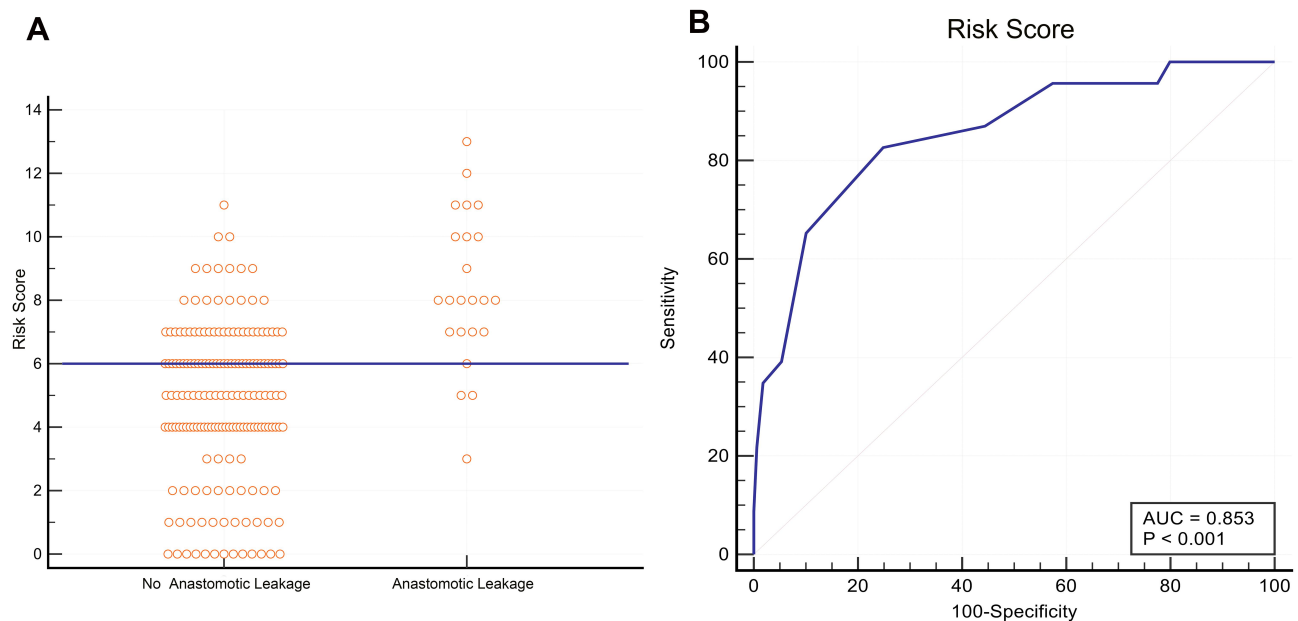


Figure 4 Validation of the risk scoring system for predicting anastomotic leakage. 192 patients with rectal cancer who underwent laparoscopic low anterior resection for rectal cancer from another center were divided into two groups according to the high or low risk score (≥ 6 and < 6). **(A)** The distribution of patients according to the high or low risk score. **(B)** The ROC curve of the risk scoring system for the 192 patients, AUC=0.853 (95% CI:0.794–0.900, $p<0.001$).

system is used in subsequent prospective studies, it is anticipated that the overall incidence of anastomotic leakage and the rates of non-essential stomas will be reduced. If future prospective studies yield promising results, definitive RCTs that randomly allocate patients will be needed.

Conclusion

In conclusion, our study confirmed that the application of a risk scoring system in predicting the risk of anastomotic leakage was significantly better than the use of a single risk factor. Our findings can provide rectal cancer surgeons with a practical quantitative scoring system to evaluate the risk of anastomotic leakage before the end of the surgical procedure and provide a reference comparison for surgical decision-making.

Data Sharing Statement

The data that support the results of this study are available from the corresponding author on reasonable request.

Ethics Statement

This study complied with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Zibo Central Hospital, Shandong University and Jiangyin people's Hospital, School of Medicine, Southeast

University. Written informed consent was obtained from all patients.

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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. All authors approved the final version of the article and its submission.

Disclosure

The authors declare that there are no conflicts of interest.

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