Accepted Manuscript

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PII: S1743-9191(18)30502-8

DOI: 10.1016/j.ijsu.2018.01.024

Reference: IJSU 4401

To appear in: *International Journal of Surgery*

Received Date: 16 October 2017

Revised Date: 26 December 2017

Accepted Date: 3 January 2018

Name of Journal: International Journal of Surgery

Manuscript Type: RETROSPECTIVE COHORT STUDY

Unique Identifying Number (UIN) from the Research Registry: 3420

Title: **Conversion Is a Risk Factor for Postoperative Anastomotic Leak in Rectal Cancer Patients - A Retrospective Cohort Study**

Running Title: Conversion and Anastomotic Leak

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Conversion Is a Risk Factor for Postoperative Anastomotic Leak in Rectal Cancer Patients - A Retrospective Cohort Study

ABSTRACT

AIM: The impact of conversion from laparoscopic surgery to laparotomy on the development of anastomotic leak (AL) in rectal cancer patients following laparoscopic low anterior resection (LAR) with total mesorectal excision (TME) has not been evaluated. The aim of this study was to evaluate the impact of conversion on the risk of AL and develop a prediction nomogram for postoperative AL.

METHODS: All rectal cancer patients following laparoscopic LAR with TME from January 2010 to October 2014 were enrolled in the primary cohort. Comparisons of the postoperative anastomotic leak incidence rate between converted patients and non-converted patients were performed using both univariate and multivariate logistic regression analyses. The result of multivariable analysis was used to develop the predicting model and the performance of nomogram was assessed with respect to its calibration, discrimination, and clinical usefulness. An independent validation cohort containing 200 patients from November 2014 to October 2015 was assessed.

RESULTS: Of all patients enrolled (*n=646*), 592(91.6%) patients underwent totally laparoscopic surgery, and 54(8.4%) were converted from laparoscopic surgery to laparotomy. Converted group patients were more likely to have a higher body mass index (BMI), prolonged length of stay (LOS), increased overall postoperative complication rates and advanced clinical T stage (T3 or T4), pathological N stage (N1 or N2) and pathological TNM stage (III or IV). The percentage of patients who had preoperative radiotherapy for rectal cancer was higher in non-converted patients. Patients who underwent conversion to laparotomy (*n=10, 18.5%*) were more likely to suffer from postoperative AL than those undergoing totally laparoscopic surgery (*n=38, 6.4%*) (*P=0.004*). Multivariate logistic regression analyses confirmed the association between conversion and postoperative AL (*Odds ratio [OR], 95% confidence interval [CI]: 2.71 [1.31-5.63], P=0.007*). Conversion, gender, and clinical N stage incorporated in the individualized prediction nomogram showed good discrimination, with a C-index of 0.697 (*C-index, 0.621 and 0.772 through internal validation*), and good calibration. In the validation cohort, the main results were consistent with the findings of the primary cohort, with a C-index of 0.670 (C-index, 0.562 and 0.777 through internal validation). Decision curve analysis demonstrated that the prediction nomogram was clinically useful.

CONCLUSION: Conversion during laparoscopic LAR was found to be associated with an increased risk for the postoperative AL in RC patients. A nomogram model incorporating conversion, gender and patient's clinical N stage seems to offers a useful tool for predicting postoperative AL in these patients.

Key words: Rectal Cancer; Anastomotic Leak; Primary Anastomosis; Risk Factor; Laparoscopic surgery; Conversion to Laparotomy; Prediction Nomogram

INTRODUCTION

Anastomotic leak, one of the most severe postoperative complications, was found to be associated with a higher frequency of mortality and a poorer quality of life (QOL) in rectal cancer (RC) patients after laparoscopic low anterior resection (LAR) with total mesorectal exision (TME) [1, 2]. Furthermore, it may be associated with the risk for local recurrence, thus affecting patients' overall survival [3, 4]. Therefore, it is vital for the surgeons to identify the patients who are at a high risk of postoperative AL. Previous studies showed that the incidence of postoperative AL was about 3% to 21% [1, 5-12]. A great number of risk factors associated with postoperative AL have been reported, such as gender, location of anastomosis, malnutrition, and blood transfusions [13-16]. However, whether conversion from laparoscopic surgery to open procedure is a risk factor for postoperative AL remains unknown. Therefore, we designed this study to systematically evaluate the impact of conversion on postoperative AL and develop a prediction model with a large cohort of 646 patients.

MATERIALS AND METHODS

Patients

646 rectal cancer patients who underwent laparoscopic low anterior resection with total mesorectal excision in our hospital (Guangzhou, China) from January 2010 to October 2014 were included in the primary cohort. Another 200 rectal cancer patients using the same criteria as that for the primary cohort from November 2014 to October 2015 were assessed as a validation cohort for the nomogram model. Demographics, clinicopathological variables, and outcomes were all prospectively maintained in the Colorectal Cancer (CRC) Database. Both paper charts and electronic medical records were carefully reviewed when necessary. This study was approved by the Institutional Review Board (IRB) of our hospital and stayed in line with STROCSS criteria [17].

Inclusion and Exclusion Criteria

In order to be included in the study, patients needed to meet all the following inclusion criteria: (1) RC patients; (2) patients undergoing laparoscopic LAR with TME. The exclusion criteria included: (1) patients with colon cancer; (2) patients who initially underwent palliative surgery or laparotomic surgery; (3) patients with familiar adenomatous polyposis (FAP).

Patient Groups

In this study, patients were divided into two groups based on patients' surgical procedure: laparoscopic (non-conversion) group and conversion group.

Definition and Variables

According to the International Study Group of Rectal Cancer definition and grading system proposed by Rahbari et al [18] and Kulu et al [19], anastomotic leak was deemed to have occurred within 3 months after TME surgery in terms of the following indications: clinical indicators, biochemical or observation abnormalities, radiological evidence and/or operative evidence. Conversion to an open operation was defined by the need for an abdominal incision to complete mobilization of rectum.

Demographic and clinic-pathological variables were defined and analyzed as follows: general information, age at the time of surgery, smoking (active smoking—consumption of more than 7 cigarettes per week for at least 6 months prior to the data entry; ex-smoking—cessation of smoking 6 months prior to data entry), alcohol (cessation of drinking for at least 6 months prior to data entry), concurrent comorbidity (other diseases which are not relative with RC, such as hypertension, diabetes and so on), history of abdominal surgery, body mass index (BMI), preoperative albumin (<35g/L vs ≥35g/L), elevated CEA (>5ng/ml), preoperative bowel obstruction, distance of tumor from anal verge, tumor diameter, clinical T stage, clinical N stage, preoperative radiotherapy, preoperative chemotherapy, the need for a temporary stoma, pathological T stage, pathological N stage, pathological M stage, pathological TNM stage, 90-day mortality, length of stay

(LOS), overall postoperative complication rates, readmission. The HARM score (HospitAl stay, Readmission, and Mortality rates) was calculated using the following formula : LOS category (0–5) + readmission (0/1) + mortality (0/1) × 5 [20].

Statistical Analysis

Statistical analysis was conducted with the statistical package for social sciences (SPSS version 22.0.0, IBM SPSS statistics, IBM Corporation, Armonk, NY) and R software (version 3.0.1; http://www.Rproject.org). Descriptive statistics were computed for all variables. These included means and standard deviations (SD) or medians and interquartile ranges (IQR) for continuous factors, and frequencies for categorical factors. Comparisons of the distribution of clinic-pathological characteristics between the converted-patients and non-converted patients were made by using the 2-tail t test (or Wilcoxon rank sum test as appropriate) for continuous variables and chi-square test (or the Fisher exact test as appropriate) for categorical variables. Both univariate and multivariate analyses of risk factors associated with the outcome of postoperative anastomotic leak were constructed using the logistic regression analysis. Candidate predictors incorporated in the prediction nomogram was based on multivariate logistic regression analysis. Decision curve analysis was conducted to determine the clinical usefulness of the nomogram by quantifying the net benefits at different threshold probabilities. P value less than 0.05 was considered statistically significant.

RESULTS

Patient Demographics

A total of 646 eligible patients were enrolled, including 592 (91.6%) patients underwent totally laparoscopic surgery and 54 (8.4%) patients who were converted to laparotomy. The mean body mass index (BMI) was 22.6±3.3 kg/m^2 for non-converted group patients, and 23.5±3.0 kg/m^2 for converted group patients (P=0.047). The percentage of patients who had preoperative radiotherapy before radical dissection surgery were higher in non-converted group patients (12.1% vs. 1.9%, P=0.023). On the other hand, the percentage of patients who had advanced clinical T stage (T3 or T4) were higher in the converted group patients (91.1% vs. 75.5%, P=0.018). Similar results were also found on the patient's pathological N stage (N1 or N2) (50.0% vs. 25.1%, P=0.03) and pathological TNM stage (III or IV) (53.7% vs. 38.5%, P=0.029). **(Table 1)** Of all the patients enrolled, converted group patients had an increased postoperative complication rates (37.0% vs. 20.8%, P=0.006) and prolonged LOS (12 vs. 11 days, P=0.001) compared to non-converted group patients. 48 patients (7.4%) developed postoperative AL, with 10 (18.5%) being in the conversion group and 38 (6.4%) being in the non-conversion group (P=0.004). (**Table 1**) There was no significant difference in other clinicopathological characteristics.

Risk Factors Associated with Conversion from Laparoscopy to Laparotomy

Body mass index, patient's clinical T stage (cT3-4 vs. cT1-2) and preoperative radiotherapy were identified as risk factors for conversion from laparoscopy to laparotomy. The association between patient's clinical T stage and the risk for conversion during laparoscopic surgery was then confirmed in the multivariate logistic regression analysis [odds ratio (OR): 3.38; 95%CI: 1.18-9.66, P=0.023], while preoperative radiotherapy was shown to have a tendency to reduce the risk of conversion from laparoscopic surgery to open [OR: 0.54; 95%CI: 0.02-1.03, P=0.054]. **(Table 2)**

Conversion Is Associated with an Increased Risk for Postoperative AL

The indications for conversion from laparoscopy included difficult surgery (n=28, 51.9%), iatrogenic injuries in (n=10, 18.5%), bleeding (n=5, 9.3%) and others (n=11, 20.4%). Subgroups analysis of patients with conversion showed that there was no significant difference in postoperative AL rate between the difficult surgery group and non-difficult surgery group (13.0% vs. 5.6%, P=0.298).

Univariate logistic regression analysis revealed that conversion during laparoscopic surgery was significantly associated with a higher risk for the development of postoperative AL, with an OR of 3.31 [95% confidence interval (CI): 1.55-7.09, P=0.002]. **(Table 3)** Of the clinicopathological variables, other potential risk factors for postoperative AL identified by the univariate analysis included gender (P=0.002), smoking (P=0.049), preoperative hemoglobin (P=0.017), elevated CEA (P=0.044), patient's clinical N stage (P=0.004), pathological N stage (P=0.021) and pathological TNM stage (P=0.037). **(Table 3)** The association between conversion and the risk for postoperative AL was further confirmed by the multivariate logistic regression analysis after adjusting for gender and patient's clinical N stage [OR: 3.28, 95%CI: 1.41-7.61, P=0.006]. (**Table 4**)

A Prediction Nomogram for Postoperative AL

A prediction model incorporating conversion, gender and patient's clinical N stage, which were identified in the multivariate logistic regression analysis of primary cohort was developed and presented. **(Fig 1)** The calibration curve of the nomogram for the probability of postoperative AL demonstrated good agreement between prediction and observation in both primary and validation cohorts. **(Fig 2A and B)** The C-index for the prediction nomogram was 0. 696 (95% CI, 0.621 to 0.772) in the primary cohort and 0. 670 (95% CI, 0.562 to 0.777) in the validation cohort. Decision curve analysis for the nomogram showed that if the threshold probability of a patient or doctor is between 0 to 31%, using the nomogram to predict postoperative AL adds more benefit than either the treat-all-patients scheme or the treat-none scheme.**(Fig 3)**

DISCUSSION

Of all the patients enrolled in the primary cohort (n=646), 54 (8.4%) RC patients were identified to have a laparoscopic surgery converted to laparotomy in this study, a frequency that was consistent with the reported rates ranging from 0% to 25% [21-24]. Previous studies indicated that locally advanced cancers as well as extent of tumor spread from the muscularis propria were independent predictors for conversion [25, 26]. Consisted with these findings, patient's preoperative advanced clinical T stage (T3 or T4) was identified as an independent predictor for conversion in this study. This may also explained why there was a tendency that preoperative radiotherapy, which can reduce tumor size and cause down staging in patient's T stage [27], may reduce the rate of conversion in our study. Tomoki Makino and colleagues [28, 29] evaluated the impact of BMI on laparoscopic colorectal resection and found that the conversion rate of high BMI patients was comparable with normal BMI patients. This might be explained by the development of surgical technique such as medial-to-lateral approach for the dissection, due to which obesity does not seem to cause any greater technical challenge for laparoscopic surgery. In accordance with these findings, BMI was not shown to be a risk factor associated with conversion in the multivariate analysis.

The overall postoperative AL rate was 7.4% (n=48) in this cohort, which was in line with the reported incidence rate of 10% in CLASICC study [30]. LAR with TME achieved by laparoscopy had a lower incidence rate of anastomotic leak (6.4%) compared to converted patients (18.5%). In multivariate analysis which included the factors which may influence the occurrence of postoperative AL, we showed that conversion from laparoscopic surgery to laparotomy was an independent risk factor for postoperative AL in RC patients undergoing laparoscopic LAR with TME. This was consistent with our observations in the clinical practice at our hospital. One possible reason for this difference is that the bowel, omentum, and peritoneum are less exposed in totally laparoscopic surgery than in conversion, and the inflammatory response after totally laparoscopic surgery is lower compared to the converted procedure [31]. Furthermore, laparoscopic surgery can offer a smaller incision and has less impact on immune function than the open procedure [32]. Considering these benefits, patients underwent totally laparoscopic surgery exhibited a more rapid return of bowel function than those underwent open surgery. Conversion from laparoscopy to laparotomy is similar to open surgery. In another word, it may eliminates the advantages of laparoscopy and tends to produce postoperative AL [33, 34]. Therefore, the risk of postoperative AL may be increased after conversion from laparoscopic surgery to open procedure. Additional attention especially in the intraoperative evaluation of mesenteric tension, anastomosis blood supply and gas leakage should be given to these patients. An adequate pelvic drain and/or construction of a protective stoma should be under consideration when it is necessary. Interestingly, compared to patients in the non-converted group, conversion also seemed to be associated with a higher risk for overall postoperative complication and a longer LOS but had no impact on mortality and the postoperative course evaluated by the HARM score. These findings were similar to the results of previous studies [35, 36].

Other variables such as gender, and patient's clinical N stage were also confirmed to be the independent risk factors for postoperative AL in the multivariate logistic regression analysis in this study. One possible reason for the difference of risks in postoperative AL between the two genders is that a narrower pelvis in males makes the surgical procedure technically more challenging than in females [37, 38]. In the present register which patient's clinical N stage was recorded, our result, which is similar to other studies [39-41], showed that advanced N stage was associated with a higher risk for postoperative AL.

Nomograms have been developed and shown to be more accurate than the conventional systems for predicting prognosis as well as surgical outcomes [42-44]. To the best of our knowledge, this is a novel study to develop a nomogram incorporating conversion and other risk factors to predict the postoperative AL for RC patients underwent laparoscopic LAR with TME. This nomogram in our study performed well in predicting postoperative AL if the threshold probability was between 0 to 31%, and its prediction was supported by a satisfactory C-index (0.696

in the primary cohort and 0.670 in the validation cohort) and good calibration.

The findings of the current study have several clinical implications. Although the predictors for postoperative AL have been previously evaluated [5], this study expanded the list and identified conversion from laparoscopic surgery to open procedure as a new risk factor associated with postoperative AL. This information is valuable to patients as well as colorectal surgeons, as it may help to refine the risk calculation of postoperative complications after surgical treatment in rectal cancer patients. Furthermore, we propose this prediction nomogram to be used in daily clinical practice in order to determine the postoperative AL rate expected for a given patient.

There are limitations to our study, particularly relating to the study design. Firstly, our results of this study should be carefully evaluated due to the shortage of the retrospective study. Secondly, the nomogram was established and validated based on the data from a single institution. To be more objectively, further validation using external data from other medical centers would be ideal and necessary before its application in the clinical practice.

In conclusion, among the rectal cancer patients following laparoscopic LAR with TME, converted patents were found to have an increased risk for the postoperative AL. The nomogram incorporating conversion, gender and patient's clinical N stage in this study seems to offer a useful tool for predicting postoperative AL in patients undergoing laparoscopic LAR with TME. More closely perioperative nursing, including preoperative assessment, intraoperative modified techniques and postoperative care might be required for those patients.

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Table 1. Patient Characteristics.

Characteristic	All cases	Non-conversion	Conversion from laparoscopic to open	P value
Number of patients	646	592 (91.6%)	54 (8.4%)	
Age at the time of surgery, yrs	59.7±13.1	59.7±12.9	59.0±14.8	0.703
Male patients, n (%)	398	366 (61.8%)	32 (59.3%)	0.711
Smoking, n (%)				0.58
Non e	599	550 (92.9%)	49 (90.7%)	
Ex or active	47	42 (7.1%)	5(9.3%)	
Alcohol, n (%)				1.00
None	620	568 (95.9%)	52 (96.3%)	
Ex or active	26	24 (4.1%)	2 (3.7%)	
Concurrent comorbidity, n (%)	185	166 (28.0%)	19 (35.2%)	0.266
History of abdominal surgery, n (%)	76	68 (11.5%)	8 (14.8%)	0.467
Body mass index, kg/m^2	22.6±3.2	22.6±3.3	23.5±3.0	0.047
Preoperative albumin<35g/L, n (%)	15	13 (2.2%)	2 (3.8%)	0.354
Elevated CEA (>5ng/ml), n (%)	159	142 (24.4%)	17 (32.1%)	0.217
Bowel obstruction, n (%)	53	49 (8.3%)	4 (7.4%)	1.00
Distance of tumor from anal verge, cm	8.7±3.0	8.7±3.0	9.2±3.2	0.247
Tumor diameter, cm	3.8±2.2	3.8±2.2	4.3±2.0	0.104
Clinical T stage, n (%)				0.018

cT1 or cT2	128	124 (24.5%)	4 (8.9%)	
cT3 or cT4	424	383 (75.5%)	232 (91.1%)	
Clinical N stage, n (%)				0.066
cN0	279	262 (52.1%)	17 (37.8%)	
cN1 or cN2	269	241 (47.9%)	28 (62.2%)	
Preoperative radiotherapy, n (%)	72	71 (12.1%)	1 (1.9%)	0.023
Preoperative chemotherapy, n (%)	178	165 (27.9%)	13 (24.1%)	0.55
The need for a temporary stoma, n (%)	227	209 (35.3%)	18 (33.3%)	0.772
Pathological T stage, n (%)				0.145
pT0 or pT1 or pT2	226	212 (35.8%)	14 (25.9%)	
pT3 or pT4	420	380 (64.2%)	40 (74.1%)	
Pathological N stage, n (%)				0.03
pN0	411	384 (64.9%)	27 (50.0%)	
pN1 or pN2	235	208 (35.1%)	27 (50.0%)	
Pathological M stage, n (%)				0.418
pM0	572	526 (88.9%)	46 (85.2%)	
pM1	74	66 (11.1%)	8 (14.8%)	
Pathological TNM stage, n (%)				0.029
pTNM0 or pTNM1 or pTNM2	389	364 (61.5%)	25 (46.3%)	
pTNM3 or pTNM4	257	228 (38.5%)	29 (53.7%)	
90-day mortality, n (%)	5(0.8%)	4(0.7%)	1(1.9%)	0.355
Length of stay, days	11(9, 14)	11(9, 14)	12(10, 20)	0.001
The HARM score	5.3±0.7	5.3±0.71	5.3±0.59	0.682
Overall postoperative	143(22.1%)	123(20.8%)	20(37%)	0.006

complication rates, n (%)				
Anastomotic leak, n (%)	48(7.4%)	38 (6.4%)	10 (18.5%)	0.004

Table 2. Multivariate Analysis of Risk Factors Associated with Conversion in Rectal Cancer Patients Who Underwent Laparoscopic Low Anterior Resection.

Characteristics	OR (95% CI)	P value
Preoperative radiotherapy (yes vs. no)	0.14 (0.02-1.03)	0.054
Clinical T stage (cT3-4 vs. cT1-2)	3.38 (1.18-9.66)	0.023

Table 3. Univariate Analysis of Risk Factors Associated with Anastomotic Leak in Rectal Cancer Patients Who Underwent Laparoscopic Low Anterior Resection.

Characteristics	OR (95% CI)	P value
Age at the time of surgery, every 1-yr increase	0.99 (0.97-1.01)	0.24
Gender (male vs. female)	3.35 (1.54-7.29)	0.002
Smoking (ever vs. never)	2.38 (1.01-5.65)	0.049
Alcohol (ever vs. never)	0.49 (0.07-3.68)	0.486
Significant comorbidities (yes vs. no)	1.27 (0.68-2.37)	0.455
History of abdominal surgery (yes vs. no)	0.86 (0.33-2.25)	0.763
Body mass index, every 1-kg/m^2 increase	1.02 (0.93-1.12)	0.651
Preoperative Hemoglpbin, every 1-g/L increase	1.02 (1.00-1.03)	0.017
Preoperative albumin<35g/L (yes vs. no)	0.91 (0.12-7.04)	0.924
Elevated CEA (yes vs. no)	1.92 (1.02-3.60)	0.044
Bowel obstruction (yes vs. no)	1.33 (0.51-3.52)	0.563
Distance of tumor from anal verge, every 1-cm increase	0.93 (0.84-1.03)	0.187
Tumor diameter, every 1-cm increase	1.10 (0.99-1.21)	0.077
Clinical T stage (cT3-4 vs. cT1-2)	1.39 (0.63-3.08)	0.414
Clinical N stage (cN1-2 vs. cN0)	2.67 (1.36-5.21)	0.004
Preoperative radiotherapy (yes vs. no)	1.15 (0.47-2.81)	0.757
Preoperative chemotherapy (yes vs. no)	0.87 (0.44-1.71)	0.681
Conversion (yes vs. no)	3.31(1.55-7.09)	0.002
The need for a temporary stoma (yes vs. no)	1.23 (0.67-2.24)	0.503
Pathological T stage (pT3-4 vs. pT0-2)	1.33 (0.70-2.54)	0.381
Pathological N stage (pN1-2 vs. pN0)	2.01 (1.11-3.63)	0.021
Pathological M stage (pM1 vs. pM0)	0.69 (0.24-1.97)	0.483
Pathological TNM stage (pTNM3-4 vs. pTNM0-2)	1.88 (1.04-3.39)	0.037

Table 4. Multivariate Analysis of Risk Factors Associated with Anastomotic Leak in Rectal Cancer Patients Who Underwent Laparoscopic Low Anterior Resection.

Characteristics	OR (95% CI)	P value
Gender (male vs. female)	3.23 (1.39-7.48)	0.006
Conversion (yes vs. no)	3.28 (1.41-7.61)	0.006
Clinical N stage (cN1-2 vs. cN0)	2.22 (1.11 -4.43)	0.023

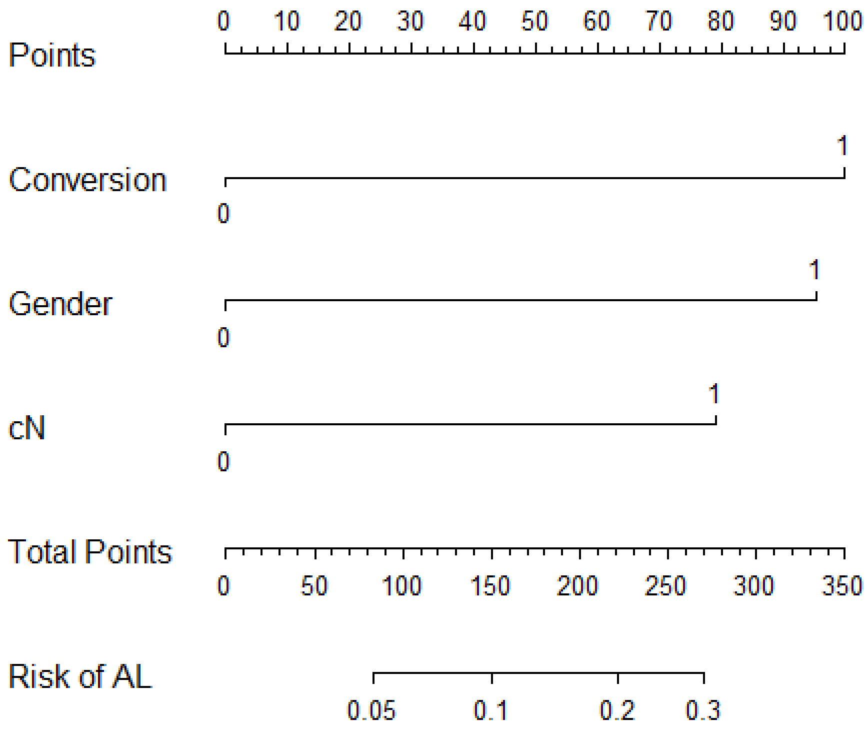

Figure 1: Nomogram for prediction of postoperative AL. To calculate the probability of anastomotic leak, we first obtained the value for each predictor by drawing a vertical line straight upward from that factor to the points' axis, then summed the points achieved for each predictor, and located this sum on the total points' axis of the nomogram, where the probability of AL can be located by drawing a vertical line downward.

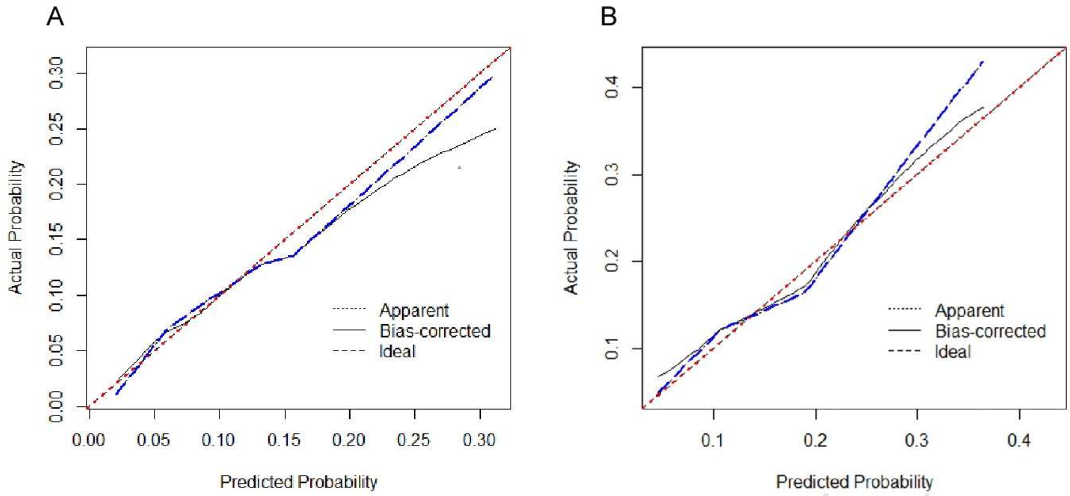

Figure 2: Calibration curves analysis of the predicted nomogram model in the primary cohort (A) and the validation cohort (B). Calibration curves depict the calibration of the model in terms of the agreement between the predicted risks of postoperative AL and observed outcomes of postoperative AL. The Y-axis represents the actual AL rate. The X-axis represents the predicted risk of AL. The diagonal dotted red line represents a perfect prediction by an ideal model. The dotted blue line represents the performance of the nomogram. A closer fit of the dotted blue line to diagonal dotted red line represents a better prediction.

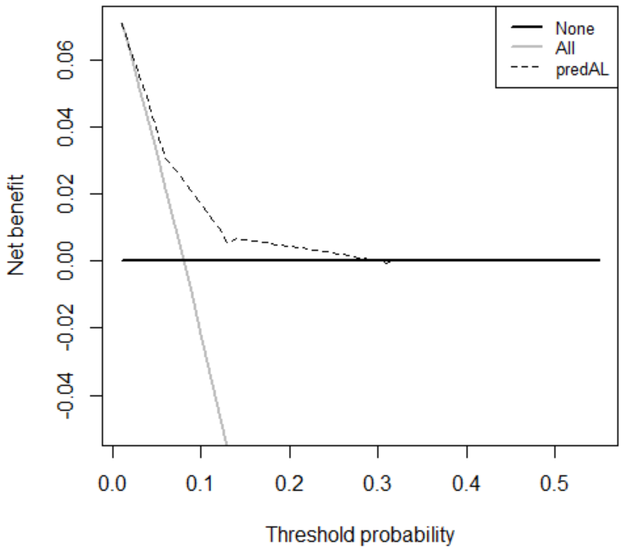

Figure 3： Decision curve analysis of the predicted nomogram model. The Y-axis measures the net benefit. The dotted line represents the predicted nomogram model. The gray line represents the assumption that all RC patients suffer postoperative AL. The black line represents the assumption that no patients suffer postoperative AL. The net benefit was calculated by subtracting the proportion of all patients who are false positive from the proportion who are true positive, weighting by the relative harm of forgoing treatment compared with the negative consequences of an unnecessary treatment. The decision curve showed that if the threshold probability of a patient or doctor is between 0 to 31%, using the nomogram to predict postoperative AL adds more benefit than either the treat-all-patients scheme or the treat-none scheme.

Supplemental Table 1. Univariate Analysis of Risk Factors Associated with Anastomotic Leak in Rectal Cancer Patients Who Underwent Laparoscopic Low Anterior Resection in validation cohort.

Characteristics	OR (95% CI)	P value
Age at the time of surgery, every 1-yr increase	1.00 (0.97-1.03)	0.918
Gender (male vs. female)	3.65 (1.21-10.98)	0.021
Smoking (ever vs. never)	1.25 (0.26-6.01)	0.784
Significant comorbidities (yes vs. no)	0.87 (0.33-2.23)	0.781
History of abdominal surgery (yes vs. no)	1.02 (0.22-4.82)	0.981
Body mass index, every 1-kg/m2 increase	0.98(0.86-1.11)	0.762
Preoperative Hemoglpbin, every 1-g/L increase	0.99 (0.97-1.01)	0.194
Preoperative albumin<35g/L (yes vs. no)	0.30 (0.07-1.28)	0.104
Elevated CEA (yes vs. no)	0.82 (0.31-2.15)	0.684
Bowel obstruction (yes vs. no)	0.86 (0.24-3.11)	0.822
Distance of tumor from anal verge, every 1-cm increase	0.99 (0.88-1.11)	0.867
Tumor diameter, every 1-cm increase	1.37 (1.10-1.71)	0.004
Clinical T stage (cT3-4 vs. cT1-2)	2.14 (0.71-6.51)	0.179
Clinical N stage (cN1-2 vs. cN0)	1.87 (0.79-4.27)	0.160
Preoperative radiotherapy (yes vs. no)	3.25 (1.20-8.82)	0.021
Preoperative chemotherapy (yes vs. no)	1.03 (0.43-2.50)	0.942
Conversion (yes vs. no)	2.85(1.07-7.64)	0.037
The need for a temporary stoma (yes vs. no)	1.42 (0.64-3.17)	0.388
Pathological T stage (pT3-4 vs. pT0-2)	1.29 (1.01-1.65)	0.046
Pathological N stage (pN1-2 vs. pN0)	0.87 (0.72-1.05)	0.145
Pathological M stage (pM1 vs. pM0)	1.10 (0.70-1.70)	0.701
Pathological TNM stage (pTNM3-4 vs.	0.86 (0.71-1.03)	0.107

pTNM0-2)

Supplemental Table 2. Multivariate Analysis of Risk Factors Associated with Anastomotic Leak in Rectal Cancer Patients Who Underwent Laparoscopic Low Anterior Resection in validation cohort.

Characteristics	OR (95% CI)	P value
Gender (male vs. female)	3.52 (1.13-10.97)	0.030
Tumor diameter, every 1-cm increase	1.49 (1.16-1.90)	0.002
Preoperative radiotherapy (yes vs. no)	6.03 (1.95-18.68)	0.002
Conversion (yes vs. no)	3.13 (1.04-9.45)	0.043

Table 1. Patient Characteristics.

Characteristic	All cases	Non-conversion	Conversion from laparoscopic to open	P value
Number of patients	646	592 (91.6%)	54 (8.4%)	
Age at the time of surgery, yrs	59.7±13.1	59.7±12.9	59.0±14.8	0.703
Male patients, n (%)	398	366 (61.8%)	32 (59.3%)	0.711
Smoking, n (%)				0.58
Non e	599	550 (92.9%)	49 (90.7%)	
Ex or active	47	42 (7.1%)	5(9.3%)	
Alcohol, n (%)				1.00
None	620	568 (95.9%)	52 (96.3%)	
Ex or active	26	24 (4.1%)	2 (3.7%)	
Concurrent comorbidity, n (%)	185	166 (28.0%)	19 (35.2%)	0.266
History of abdominal surgery, n (%)	76	68 (11.5%)	8 (14.8%)	0.467
Body mass index, kg/m^2	22.6±3.2	22.6±3.3	23.5±3.0	0.047
Preoperative albumin<35g/L, n (%)	15	13 (2.2%)	2 (3.8%)	0.354
Elevated CEA (>5ng/ml), n (%)	159	142 (24.4%)	17 (32.1%)	0.217
Bowel obstruction, n (%)	53	49 (8.3%)	4 (7.4%)	1.00
Distance of tumor from anal verge, cm	8.7±3.0	8.7±3.0	9.2±3.2	0.247
Tumor diameter, cm	3.8±2.2	3.8±2.2	4.3±2.0	0.104
Clinical T stage, n (%)				0.018
cT1 or cT2	128	124 (24.5%)	4 (8.9%)	
cT3 or cT4	424	383 (75.5%)	232 (91.1%)	
Clinical N stage, n (%)				0.066
cN0	279	262 (52.1%)	17 (37.8%)	
cN1 or cN2	269	241 (47.9%)	28 (62.2%)	
Preoperative radiotherapy, n (%)	72	71 (12.1%)	1 (1.9%)	0.023
Preoperative chemotherapy, n (%)	178	165 (27.9%)	13 (24.1%)	0.55
The need for a temporary stoma, n (%)	227	209 (35.3%)	18 (33.3%)	0.772
Pathological T stage, n (%)				0.145

pT0 or pT1 or pT2	226	212 (35.8%)	14 (25.9%)	
pT3 or pT4	420	380 (64.2%)	40 (74.1%)	
Pathological N stage, n (%)				0.03
pN0	411	384 (64.9%)	27 (50.0%)	
pN1 or pN2	235	208 (35.1%)	27 (50.0%)	
Pathological M stage, n (%)				0.418
pM0	572	526 (88.9%)	46 (85.2%)	
pM1	74	66 (11.1%)	8 (14.8%)	
Pathological TNM stage, n (%)				0.029
pTNM0 or pTNM1 or pTNM2	389	364 (61.5%)	25 (46.3%)	
pTNM3 or pTNM4	257	228 (38.5%)	29 (53.7%)	
90-day mortality, n (%)	5(0.8%)	4(0.7%)	1(1.9%)	0.355
Length of stay, days	11(9, 14)	11(9, 14)	12(10, 20)	0.001
The HARM score	5.3±0.7	5.3±0.71	5.3±0.59	0.682
Overall postoperative complication rates, n (%)	143(22.1%)	123(20.8%)	20(37%)	0.006
Anastomotic leak, n (%)	48(7.4%)	38 (6.4%)	10 (18.5%)	0.004

Table 2. Multivariate Analysis of Risk Factors Associated with Conversion in Rectal Cancer Patients Who Underwent Laparoscopic Low Anterior Resection.

Characteristics	OR (95% CI)	P value
Preoperative radiotherapy (yes vs. no)	0.14 (0.02-1.03)	0.054
Clinical T stage (cT3-4 vs. cT1-2)	3.38 (1.18-9.66)	0.023

Table 3. Univariate Analysis of Risk Factors Associated with Anastomotic Leak in Rectal Cancer Patients Who Underwent Laparoscopic Low Anterior Resection.

Characteristics	OR (95% CI)	P value
Age at the time of surgery, every 1-yr increase	0.99 (0.97-1.01)	0.24
Gender (male vs. female)	3.35 (1.54-7.29)	0.002
Smoking (ever vs. never)	2.38 (1.01-5.65)	0.049
Alcohol (ever vs. never)	0.49 (0.07-3.68)	0.486
Significant comorbidities (yes vs. no)	1.27 (0.68-2.37)	0.455
History of abdominal surgery (yes vs. no)	0.86 (0.33-2.25)	0.763
Body mass index, every 1-kg/m^2 increase	1.02 (0.93-1.12)	0.651
Preoperative Hemoglpbin, every 1-g/L increase	1.02 (1.00-1.03)	0.017
Preoperative albumin<35g/L (yes vs. no)	0.91 (0.12-7.04)	0.924
Elevated CEA (yes vs. no)	1.92 (1.02-3.60)	0.044
Bowel obstruction (yes vs. no)	1.33 (0.51-3.52)	0.563
Distance of tumor from anal verge, every 1-cm increase	0.93 (0.84-1.03)	0.187
Tumor diameter, every 1-cm increase	1.10 (0.99-1.21)	0.077
Clinical T stage (cT3-4 vs. cT1-2)	1.39 (0.63-3.08)	0.414
Clinical N stage (cN1-2 vs. cN0)	2.67 (1.36-5.21)	0.004
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Pathological M stage (pM1 vs. pM0)	0.69 (0.24-1.97)	0.483
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Table 4. Multivariate Analysis of Risk Factors Associated with Anastomotic Leak in Rectal Cancer Patients Who Underwent Laparoscopic Low Anterior Resection.

Characteristics	OR (95% CI)	P value
Gender (male vs. female)	3.23 (1.39-7.48)	0.006
Conversion (yes vs. no)	3.28 (1.41-7.61)	0.006
Clinical N stage (cN1-2 vs. cN0)	2.22 (1.11 -4.43)	0.023

Supplemental Table 1. Univariate Analysis of Risk Factors Associated with Anastomotic Leak in Rectal Cancer Patients Who Underwent Laparoscopic Low Anterior Resection in validation cohort.

Characteristics	OR (95% CI)	P value
Age at the time of surgery, every 1-yr increase	1.00 (0.97-1.03)	0.918
Gender (male vs. female)	3.65 (1.21-10.98)	0.021
Smoking (ever vs. never)	1.25 (0.26-6.01)	0.784
Significant comorbidities (yes vs. no)	0.87 (0.33-2.23)	0.781
History of abdominal surgery (yes vs. no)	1.02 (0.22-4.82)	0.981
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Characteristics	OR (95% CI)	P value
Gender (male vs. female)	3.52 (1.13-10.97)	0.030
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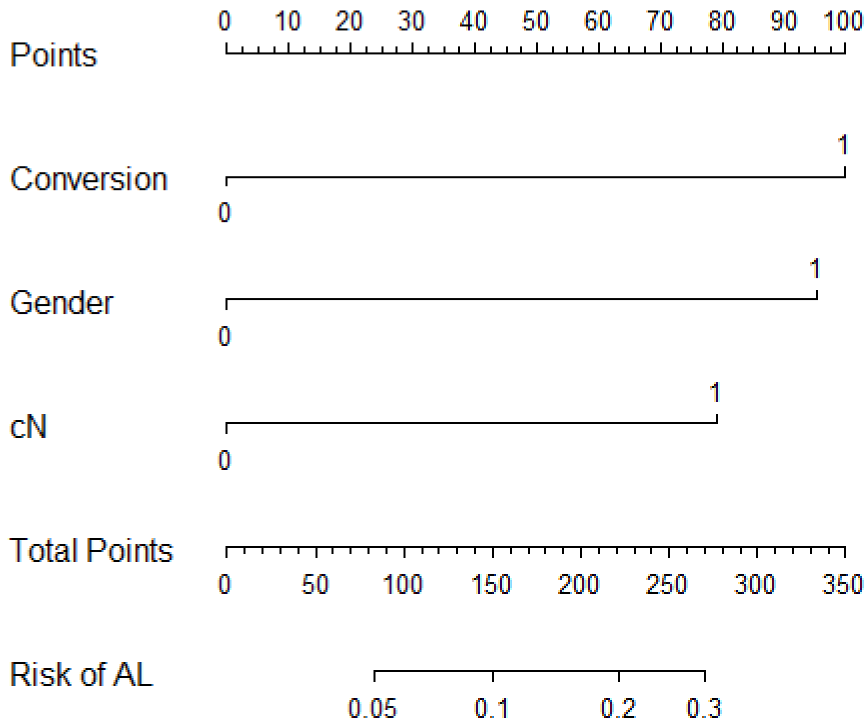

Figure 1： Nomogram for prediction of postoperative AL. To calculate the probability of anastomotic leak, we first obtained the value for each predictor by drawing a vertical line straight upward from that factor to the points' axis, then summed the points achieved for each predictor, and located this sum on the total points' axis of the nomogram, where the probability of AL can be located by drawing a vertical line downward.

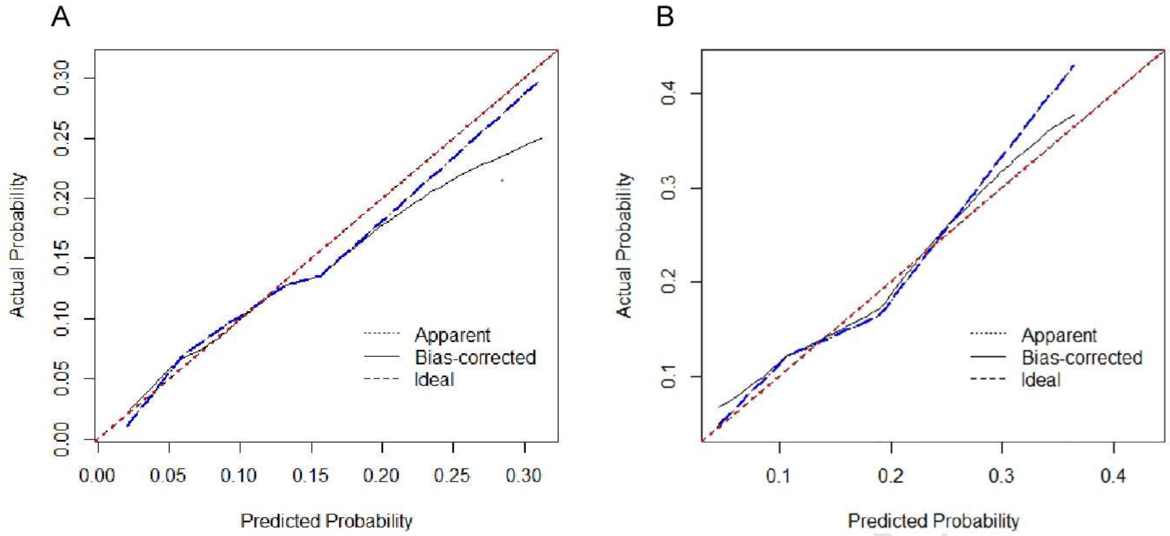

Figure 2: Calibration curves analysis of the predicted nomogram model in the primary cohort (A) and the validation cohort (B). Calibration curves depict the calibration of the model in terms of the agreement between the predicted risks of postoperative AL and observed outcomes of postoperative AL. The Y-axis represents the actual AL rate. The X-axis represents the predicted risk of AL. The diagonal dotted red line represents a perfect prediction by an ideal model. The dotted blue line represents the performance of the nomogram. A closer fit of the dotted blue line to diagonal dotted red line represents a better prediction.

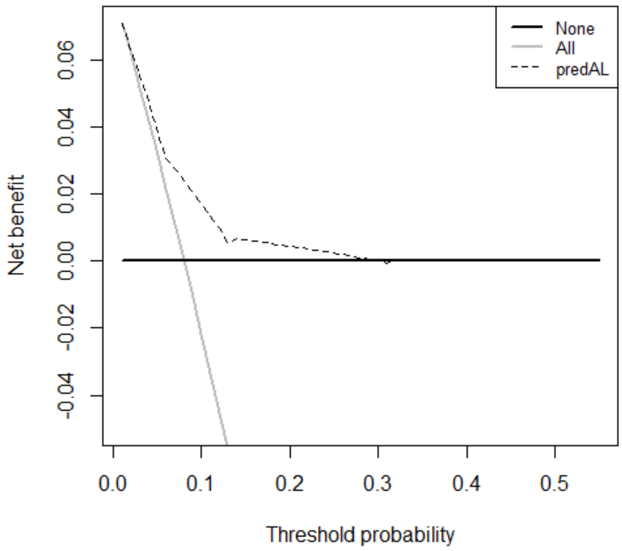

Figure 3： Decision curve analysis of the predicted nomogram model. The Y-axis measures the net benefit. The dotted line represents the predicted nomogram model. The gray line represents the assumption that all RC patients suffer postoperative AL. The black line represents the assumption that no patients suffer postoperative AL. The net benefit was calculated by subtracting the proportion of all patients who are false positive from the proportion who are true positive, weighting by the relative harm of forgoing treatment compared with the negative consequences of an unnecessary treatment. The decision curve showed that if the threshold probability of a patient or doctor is between 0 to 31%, using the nomogram to predict postoperative AL adds more benefit than either the treat-all-patients scheme or the treat-none scheme.

1、Conversion during laparoscopic LAR was found to be associated with an increased risk for the postoperative AL.

2、Conversion is a predictor for postoperative AL in RC patients underwent laparoscopic surgery.

3、Nomogram incorporating conversion, gender and clinical N stage form our study offer a useful tool for predicting postoperative AL in those patients.