Nomogram for Benign Anastomotic Stricture After Surgery for Colorectal Cancer

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Research

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Abstract

Background

Benign anastomotic stricture remains among the most prevalent complications following surgery for colorectal cancer, albeit its incidence is very low.

Objective

This study is aimed at identifying risk factors of anastomotic stricture as well as generating an effective nomogram for the stricture.

Design:

This is a retrospective study.

Setting:

This study was conducted from January, 2015 to December, 2019 in a single tertiary center with colorectal cancer.

Patients:

A total of 117 colorectal patients after surgery without recurrence including 39 with anastomotic stricture (the distance between anastomotic site and anal margin < = 20 cm) and 78 without the stricture were enrolled in this study.

Main outcome measures:

Their clinical and pathological data were collected. Multiple logistic regression analysis was conducted for identifying risk factors for anastomotic stricture, and the nomogram prediction model was generated.

Results

Multivariate analysis of the primary cohort led to identification of LCA (left colon artery) preservation (OR, 0.074; P = 0.0015), protective stoma (OR, 5.353; P = 0.012), anastomotic leakage (OR, 12.027; P = 0.005), and anastomotic distance (OR, 7.578; P = 0.012) as independent risk factors for anastomotic stricture. The following predictive model was derived: Logit (anastomotic stricture) = 0.074* LCA + 5.353*

Protective stoma + 12.027* Anastomotic leakage + 7.578* Anastomotic distance. Assessment of the predictive model revealed that the area under curve (AUC) was 0.871, while the cutoff value was 15.444, with a sensitivity of 64.1% and a specificity of 94.8%.

Limitations:

A retrospective and case-controlled design with a small sample size from one single center is the main Limitation.

Conclusions

LCA preservation, protective stoma, anastomotic leakage, and anastomotic distance may affect the occurrence of anastomotic stricture following surgery for colorectal cancer. The nomogram model generated in the present study can be valuable in prediction of anastomotic stricture. Registered at Chinese Clinical Trial Registry (http://www.chictr.org.cn, ChiCTR 2100043775).

Introduction

Colorectal cancer remains the most prevalent gastrointestinal malignancy in China and the second most common cancer in the world, leading to over 600000 deaths annually worldwide[1]. The long-term survival of patients is mainly dependent on surgical removal of the tumor. Intestinal anastomosis is an indispensable part of colorectal cancer surgery, and anastomotic complications are common complications after intestinal anastomosis.[2, 3]. Although surgical technique has been improved in recent years, anastomotic complications including strictures, leaks and bleeding remain associated with a marked morbidity as well as occasional mortality.

Benign anastomotic stricture is among the most prevalent complications of colorectal cancer surgery, with a rate of up to 8.7–13%[4, 5]. Anastomotic stenosis is a complication that cannot be ignored. It has been reported that anastomotic stricture may cause intestinal dysfunction, including frequent bowel movements, bowel obstruction and incontinence[6]. Although the pathophysiology of anastomotic stricture is not clear, multiple techniques have been used for treatment of anastomotic stricture. In this case, endoscopic treatments such as endoscopic electrocautery, balloon dilatation and self-expandable metal stent placement showed feasible outcomes for the stricture within the peritoneal cavity[6, 7]. However, endoscopic treatments still have some shortcomings. Studies have shown that in most cases, while anastomotic stricture is amenable to balloon dilatation, it has a high recurrence rate and requires repeated dilatation[8]. Moreover, Soo Young Lee et al reported that endoscopic management has a limited role in very low-lying cancer surgery due to complex anatomical features[9]. Therefore, identification of risk factors for anastomotic stricture after surgery for colorectal cancer is of practical significance to improve understanding of the stricture and the outcomes. Currently, studies on the risk factors are still lacking.

Here, we are aimed at identifying the risk factors, investigating management of patients with anastomotic stricture following colorectal cancer surgery, as well as establishing an effective nomogram model.

Materials And Methods

Patients and Ethics

This study is a retrospective chart review from January 2015 to December 2019 at a single center. The clinicopathologic data of patients with colorectal cancer were retrospectively reviewed. The following cases were excluded from this study: (1) patients who underwent Hartmann's procedure or Miles procedure; (2) those who underwent emergency surgery due to perforation, obstruction, etc; (3) those who had multiple primary tumors simultaneously; (4) the occurrence of extensive implant metastatic nodules in the abdominal cavity detected during the operation; (5) Tumor involving the surrounding organs; (6) The distance between anastomotic site and anal margin > 20 centimeter(cm); (7) Patients who recurrence after examination. A total of 2300 patients were enrolled in our department, including 39 with anastomotic stricture. Matched 78 patients without anastomotic stricture on a one-to-two ratio according to length of stay. All patients in this study are anastomosed with a stapler. The flow chart illustrated the detailed process of case enrollment (Fig. 1). The professors in our department undertook the surgical operations.

Ethical approval for this study was obtained from the Ethical Committee of the Fourth Hospital of Hebei Medical University (Ethical approval number: 2020kt417). Informed consent was not required for this retrospective study, while all personal information of patients will not be disclosed. This study was a retrospective study design, registered in China clinical trial center (http://www.chictr.org.cn, registration number: ChiCTR 2100043775).

The Diagnosis Of Anastomotic Stricture

The diagnosis of anastomotic stenosis was made when at least one of the following criteria was met: (1) the 12-mm colonoscope could not pass the anastomosis[10]; (2) The digital rectal examination revealed that the index finger could not pass the anastomosis or there was an obvious palpable stenosis ring; (3) The gastrointestinal fluoroscopy showed anastomotic stenosis (< 10mm).

The Clinical Variables

We chose the following clinical variables that may be associated with anastomotic stricture: sex, age, family history, BMI, diabetes, RCT (neoadjuvant radiotherapy and chemotherapy), preoperative SAB (serum albumin), preoperative HB (hemoglobin), anastomotic distance, surgical methods (open or Laparoscopy), protective stoma, anastomotic leakage, LCA (left colon artery) preservation, operative time, tumor size, Stapler size, Stapler origin, and TNM stage.

Statistical analysis

R software version 3.5.3 (www.R-project.org) and IBM SPSS 23.0 software were used to conduct the statistical analysis. While quantitative variables were expressed as the mean ± SD, qualitative ones were described by absolute frequencies and percentages. The descriptive statistics (mean ± SD) and the method of describing frequencies and percentages were adopted to analyze the measurement and counting data, respectively. Kruskal-Wallis rank sum test, Chi square test and the Fisher exact probability test were performed respectively for continuous variables and counting ones with theoretical number less than 10. Multiple logistic regression analysis was used to identify the risk factors ($P < 0.05$).

Decision Curve Analysis

Decision curve analysis (DCA) was applied to evaluate the clinical utility of the models in decision making and to plot the net benefit across a range of clinically reasonable risk thresholds. In this study, DCA analysis was performed by using R package “decision Curve”.

Nomogram Generation

R software and Empower Stats (X&Y Solutions, Boston, MA, USA) were used to generate the nomogram.

Establishment Of Logit Model (Anastomotic Stricture)

Logit (anastomotic stricture) construction involved clinical variables that were identified as risk factors of anastomotic stricture in multiple logistic regression analysis. The OR value of each risk factor in multiple logistic regression analysis was used as the coefficient and multiplied with the value of the corresponding risk factor. The final equation for Logit (anastomotic stricture) was derived by adding the multiplication products of each risk factor: 0.074* LCA + 5.353* Protective stoma + 12.027* Anastomotic leakage + 7.578* Anastomotic distance. ROC analysis was performed based on the total score in Logit (anastomotic stricture) to assess the reliability of the Logit.

Results

Relationships between clinical variables and anastomotic stricture

In this study, the rate of benign anastomotic stricture was 1.7% (39/2300). We undertook Kruskal-Wallis rank sum test and Fisher exact probability test to determine the relationships between clinical variables and benign anastomotic stricture. As shown in Table 1, a number of the variables, including anastomotic distance ($P < 0.01$), protective stoma ($P < 0.01$), anastomotic leakage ($P = 0.019$), and LCA preservation ($P = 0.008$), were significantly associated with benign anastomotic stricture.

Table 1
The association between clinical and pathological characteristics and anastomotic Stricture

Clinical variables	**No stricture** **n = 78**	**Stricture** **n = 39**	**t(χ2) value**	**P value**
Sex				
Male	52	23	0.669	0.414
Female	26	16		
Age (years)	60.63 ± 13.01	58.77 ± 12.80	0.733	0.465
Family history				
Yes	10	6	0.145	0.778
No	68	33		
BMI (kg/m^2)	24.75 ± 3.67	24.75 ± 3.23	0.999	0.320
Diabetes				
Yes	5	6	2.458	0.176
No	73	33		
RCT				
Yes	7	5	0.418	0.531
No	71	34		
Preoperative SAB(g/L)	42.37 ± 2.76	41.94 ± 3.48	0.733	0.465
Preoperative HB(g/L)	136.46 ± 17.84	130.27 ± 17.84	1.691	0.093
Anastomotic distance (cm)	9.192 ± 2.83	4.98 ± 3.70	6.828	< 0.01
Surgical methods				
Open	15	9	0.204	0.411
Laparoscopy	62	30		
Protective stoma				
Yes	22	30	24.99	< 0.01
No	56	9		

Note: BMI body mass index, RCT neoadjuvant radiotherapy and chemotherapy, SAB serum albumin, HB hemoglobin, LCA left colon artery, PCT pathological complete response. The data was presented with Mean + SD/N (%). For continuous variables, the rank sum test of Kruskal Wallis was used. For counting variables with theoretical number < 10, the Fisher exact probability test was used. *P-value ≤ 0.05

Clinical variables	No stricture n = 78	Stricture n = 39	t(χ2) value	P value
Anastomotic leakage				
Yes	4	8	6.686	0.019
No	74	31		
Preserve LCA				
Yes	37	8	7.963	0.008
No	41	31		
Operative time (h)				
≥ 3	30	50	1.976	0.207
< 3	9	28		
Tumor size (cm)	3.71 ± 1.381	3.46 ± 1.14	0.967	0.336
Stapler size (mm)				
≥ 31	24	11	0.082	0.883
< 31	54	28		
Stapler Origin				
China	22	35	8.212	0.004
Oother	56	4		
TNM stage				
0(T0N0M0, PCR)	1	0	0.166	0.684
[illegible]	8	22		
[illegible]	20	31		
[illegible]	10	23		
[illegible]	0	2		

Note: BMI body mass index, RCT neoadjuvant radiotherapy and chemotherapy, SAB serum albumin, HB hemoglobin, LCA left colon artery, PCT pathological complete response. The data was presented with Mean + SD/N (%). For continuous variables, the rank sum test of Kruskal Wallis was used. For counting variables with theoretical number < 10, the Fisher exact probability test was used. *P-value ≤ 0.05

Identification Of Independent Risk Factors For Benign Anastomotic Stricture

To improve the credibility of this study and effectively control for the effects of confounding variables, we chose to undertake a multivariate logistic regression analysis. The risk factors with statistical significance in univariate logistic regression analysis were subjected simultaneously to the multivariate analysis. As illustrated in Table 2, a number of independent risk factors for benign anastomotic stricture were identified, including LCA preservation (OR, 0.074; P = 0.0015), protective stoma (OR, 5.353; P = 0.012), anastomotic leakage (OR,12.027; P = 0.005), and anastomotic distance (OR,7.578; P = 0.012).

Table 2
Correlative effect on anastomotic Stricture based on multiple logistic regression analysis

Characteristics	SSI		
	OR	95% CI	P
Preserve LCA	0.074	0.235–0.751	0.015
Protective stoma	5.353	1.454–19.708	0.012
Anastomotic leakage	12.027	2.126–68.048	0.005
Anastomotic distance	7.578	2.248–25.547	0.001

OR, odds ratio; 95% CI, 95% confidence interval. *P < 0.05

The Nomogram And Predictive Model

Figure 2 showed the nomogram that integrated all independent risk factors for the anastomotic stricture in the primary cohort. We generated a model for risk estimation of anastomotic stricture based on the regression coefficients in the multivariate regression analysis. And the formula was used as follows: Logit (anastomotic stricture) = 0.074* LCA + 5.353* Protective stoma + 12.027* Anastomotic leakage + 7.578* Anastomotic distance. As shown in Fig. 2, a DCA analysis for the Logit (anastomotic stricture) was carried out, and the model using only the independent risk factors was constructed. Moreover, we calculated and determined the high-risk threshold, standardized net benefit, and benefit ratio of the model (Fig. 3). The DCA curves revealed that if the threshold probability of a particular patient is > 0, prediction of the anastomotic stricture using the Logit provides more benefit than the treat-none- or treat-all-patients scheme. Meanwhile, Logit (anastomotic stricture) displayed greater benefits as compared to the model using only the independent risk factors.

Validation Of The Predictive Model

We further conducted receiver operating characteristic curve analysis to evaluate the predictive power of the model. As depicted in Fig. 4, the area under curve (AUC) was 0.871, while the cutoff value was 15.444, with a specificity of 94.8% and a sensitivity of 64.1%.

Discussion

This study identified the independent risk factors for benign anastomotic stricture following colorectal cancer surgery. Here, we analyzed clinicopathologic characteristics of 117 colorectal cancer patients undergoing the surgery from January 2015 to December 2019. These patients were classified as either the group with anastomotic stricture or that without the stricture. The statistical analysis revealed associations between anastomotic stricture and clinical variables including the anastomotic distance, protective stoma, anastomotic leakage, and LCA preservation. Moreover, multivariate logistic regression analysis identified anastomotic distance, protective stoma, anastomotic leakage, and LCA preservation as independent risk factors for benign anastomotic stricture. The predictive model used in the study was as follows: Logit (anastomotic stricture) = 0.074* LCA + 5.353* Protective stoma + 12.027* Anastomotic leakage + 7.578* Anastomotic distance. We showed that accurate assessment of anastomotic stricture risk could be made by using this predictive model.

It has been shown that the rate of benign anastomotic stricture, one of the most prevalent complications following surgery in colorectal cancer patients, is 8.7–13%[11−13]. Contrary to the previous reports, this study observed a rate of anastomotic stricture of 1.7%. In this case, it is difficult to compare the incidence of anastomotic stricture among different studies because of the different definition and diverse inclusion criteria of anastomotic stricture. So far, the definition of anastomotic stenosis remains inconsistent. In the present study, the diagnosis of anastomotic stenosis was made based on the following criteria: the 12-mm colonoscope could not pass the anastomosis[10]; the digital rectal examination revealed that the index finger could not pass the anastomosis or there was an obvious palpable stenosis ring; the gastrointestinal angiography showed anastomotic stenosis (< 10mm). Further studies are required for standardization and categorization of anastomotic stricture.

Here, we identified anastomotic distance, protective stoma, anastomotic leakage, and LCA preservation as independent risk factors for benign anastomotic stricture. Consistently, Ashok Kumar et al demonstrated that decreased distance between the tumor and the anal verge serves as a risk factor for benign anastomotic stricture[14]. L Polese et al looked at the rate of anastomotic stricture in 211 patients and identified anastomosis located between 8 and 12 cm away from the anal as verge risk factors based on the univariate analysis [11]. It has been reported that pelvic floor surgery for low anterior rectal resection may produce enlarged wound area and decrease local anti-infection ability, resulting in compromised healing ability of the local tissue of the anastomosis [15, 16]. Moreover, low position of the anastomosis can affect its healing due to colonic ischemia following surgery [17, 18]. All these observations may explain why the rate of anastomotic stricture remains high.

The protective stoma has also been shown to affect the rate of the stricture following surgery for colorectal cancer. Consistent with the present study, multiple studies identified the presence of a stoma as an independent risk factor for anastomotic stricture[19, 20]. B P Waxman et al reported that dilatation due to fecal stream may be involved in prevention of anastomotic stricture[21]. Thus, protective stoma could prevent the patients from benefiting from fecal dilatation. It has been demonstrated that protective stoma can cause a decrease in bowel movements[22], which may induce anastomotic stricture frequently. We, therefore, reason that early reacceptance and preventive finger expansion may effectively reduce the occurrence of anastomotic stricture.

Anastomotic leakage was another independent risk factor for benign anastomotic stricture. Multiple studies have shown that anastomotic leakage predisposes patients to develop anastomotic stricture [14, 23, 24]. Anastomotic leakage is a common and feared complication, while it could cause intense inflammation[23, 24], which may contribute to a high rate of the stricture. Moreover, formation of scars caused by the infected surrounding tissues and fibroblast collagen during the healing process of anastomotic leakage may frequently induce anastomotic stricture[14]. Thus, prevention of anastomotic leakage could effectively decrease the occurrence of anastomotic stenosis, thereby promoting the safety and long-term prognosis of patients after surgery.

LCA preservation could reduce the rate of anastomotic stricture following colorectal cancer surgery. When conducting laparoscopic lymph node dissection around the inferior mesenteric artery with LCA preservation, the surgeon often ligates the mesenteric artery at the root to ensure the effectiveness of the operation. Niels Komen et al measured the colonic perfusion of patients undergoing rectal resection for malignancy, and found a significant increase in the blood flow ratio in the low tie group as compared to high tie group [25]. Once both the inferior mesenteric artery and LCA are cut off during surgery for colorectal cancer, the blood supply for the anastomosis may become obstructed. Therefore, preserving LCA may effectively reduce the occurrence of anastomotic stricture through maintaining the blood supply for the proximal sigmoid colon [26]. Further research is needed to evaluate its applicability and safety.

Conclusion

A combined use of anastomotic distance, protective stoma, anastomotic leakage, and LCA preservation could better predict the occurrence of benign anastomotic stricture after surgery for colorectal cancer, while it may contribute to prevention of the stricture.

Declarations

Competing interests

The authors declare that they have no competing interests.

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Ethical approval and consent to participate section

All patients consented to their data being used in this study. All procedures were in accordance with the ethical standards of the Ethical Committee of the Fourth Hospital of Hebei Medical University (Ethical approval number: 2020kt417) and with the 1964 Helsinki declaration and its later amendments. The written informed consent was obtained from the all patients.

Consent for publication

All patients consented to the publication of the results of this study.

Availability of data and materials

Due to the protection of patient privacy, we do not proactively provide data. All data used in the study are available at the request of the editors and reviewers. And you can contact the corresponding author for data.

Authors' contributions

(1). Design of the work: Wang Guiying, Hu Xuhua and Guo Peiyuan.

(2). Acquisition and analysis of data: Hu Xuhua, Guo Peiyuan, Zhang Ning, Guo Ganlin, Li Baokun and Liu Youqiang, Niu Jian and Wang Guiying.

(3). Manuscript writing: Hu Xuhua and Guo Peiyuan.

(4). Final approval of manuscript: Wang Guiying.

(5). Administrative support: Wang Guiying.

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Figures

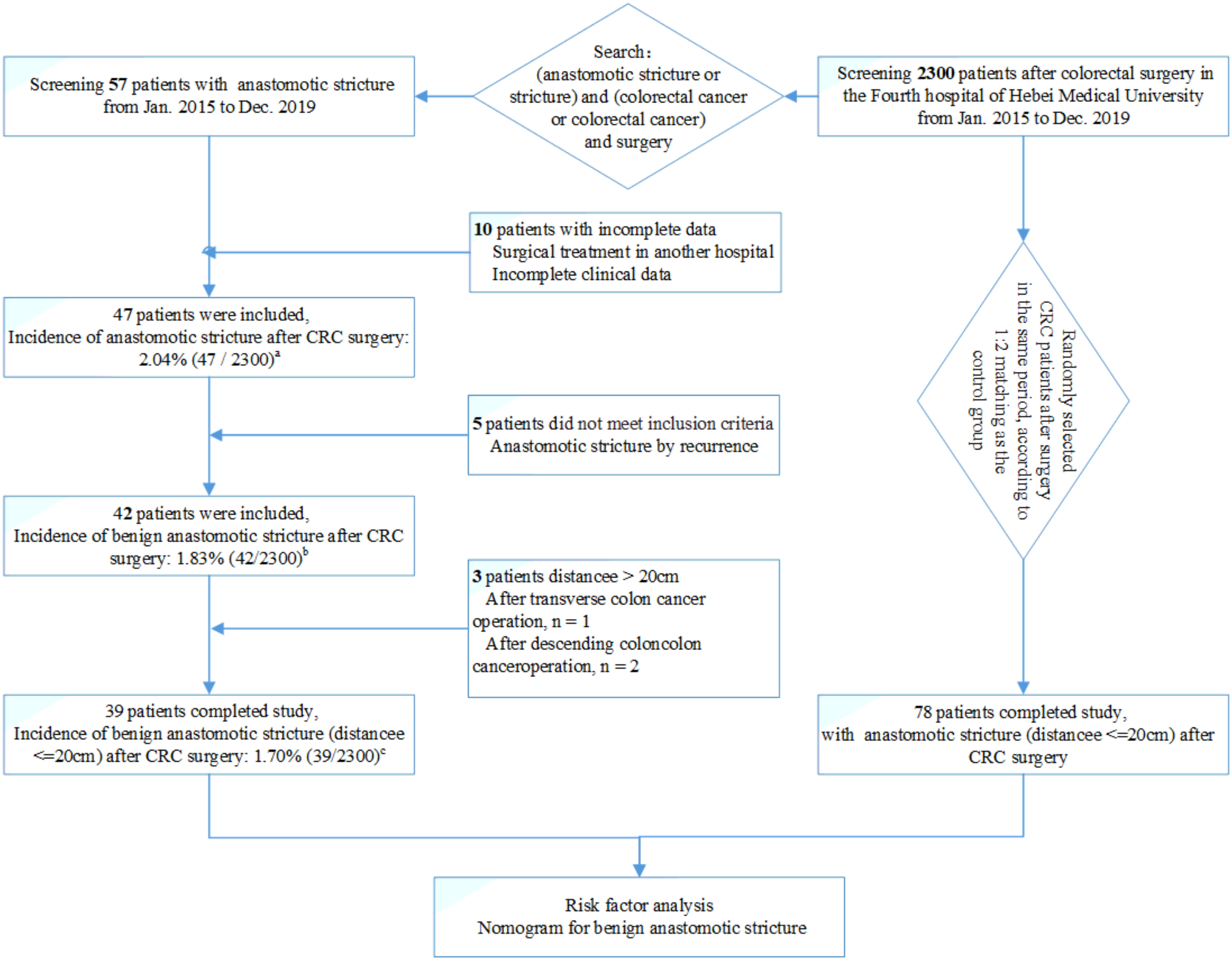

Figure 1

Research flow chart. a is the number of cases with anastomotic stricture diagnosed by medical record retrieval system in the fourth hospital of Hebei Medical University from Jan. 2015 to Dec. 2019. b is the number of cases with anastomotic stricture met the inclusion and exclusion criteria. Abbreviations: CRC for colorectal cancer.

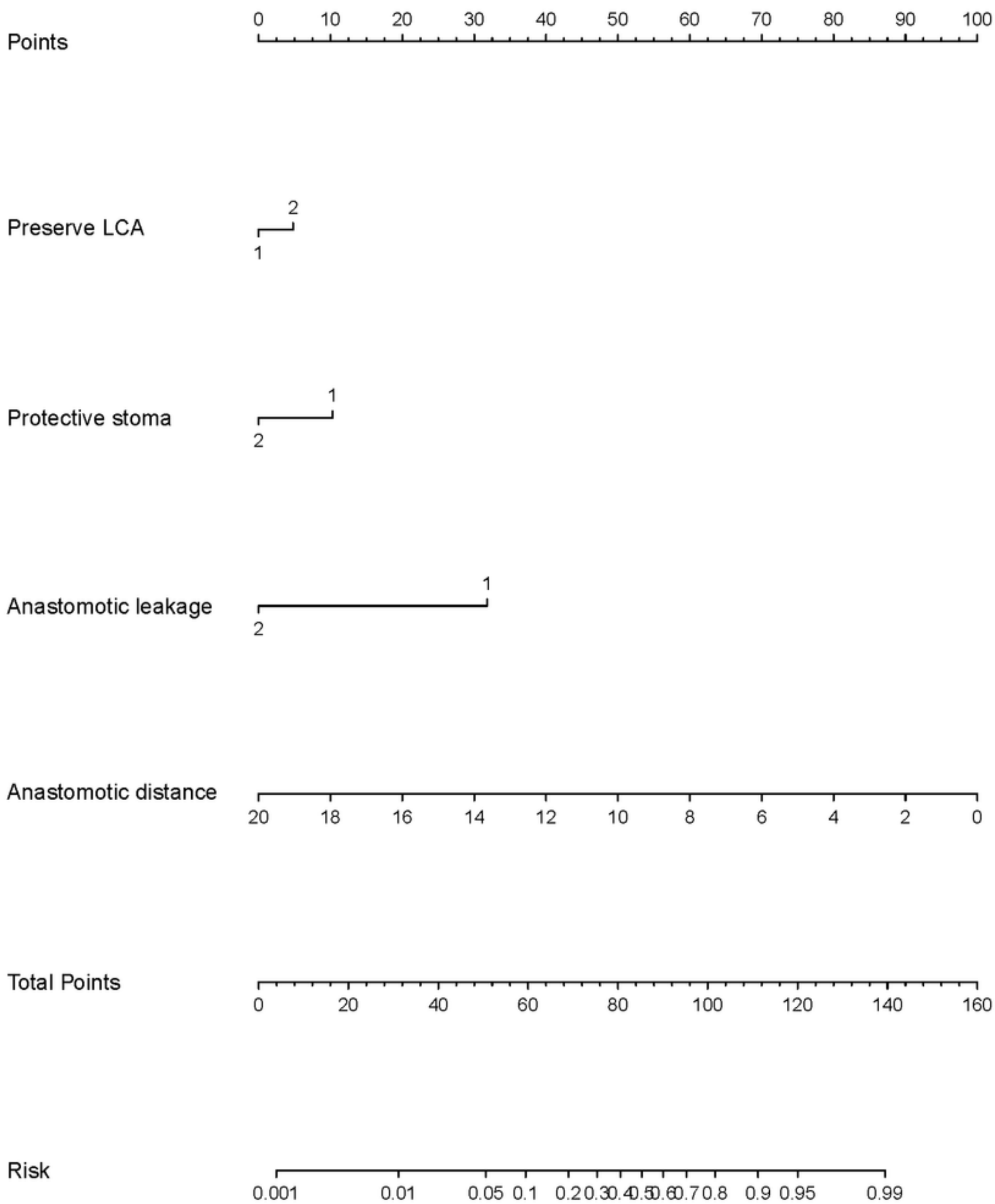

Figure 2

Nomogram for estimating the risk of benign anastomotic stricture in patients

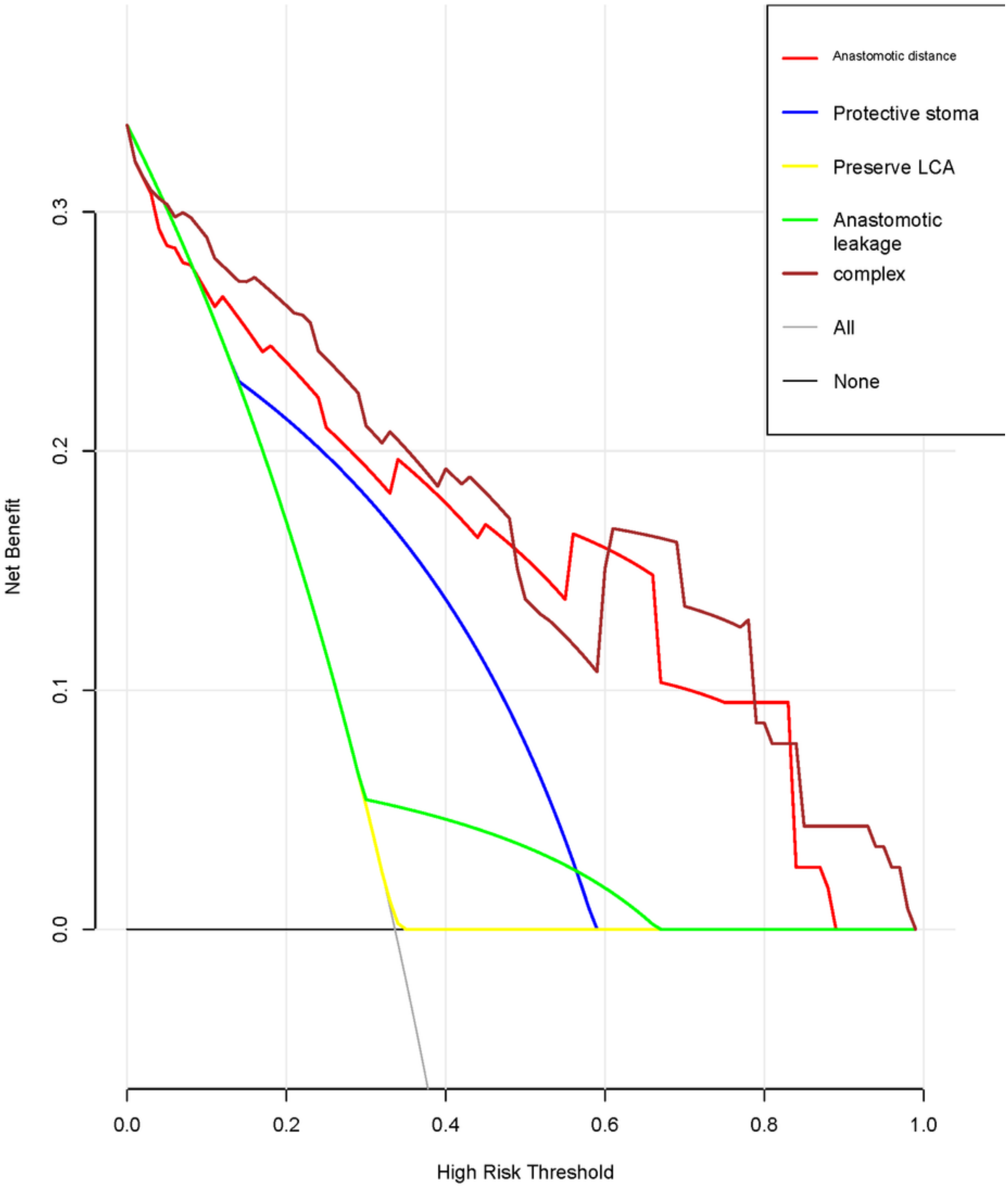

Figure 3

The results of the decision curve analysis for the Logit (anastomotic stricture) and the model using only the independent risk factors. The standardized net benefit, high risk threshold, and benefit ratio of model was shown in Fig.2.

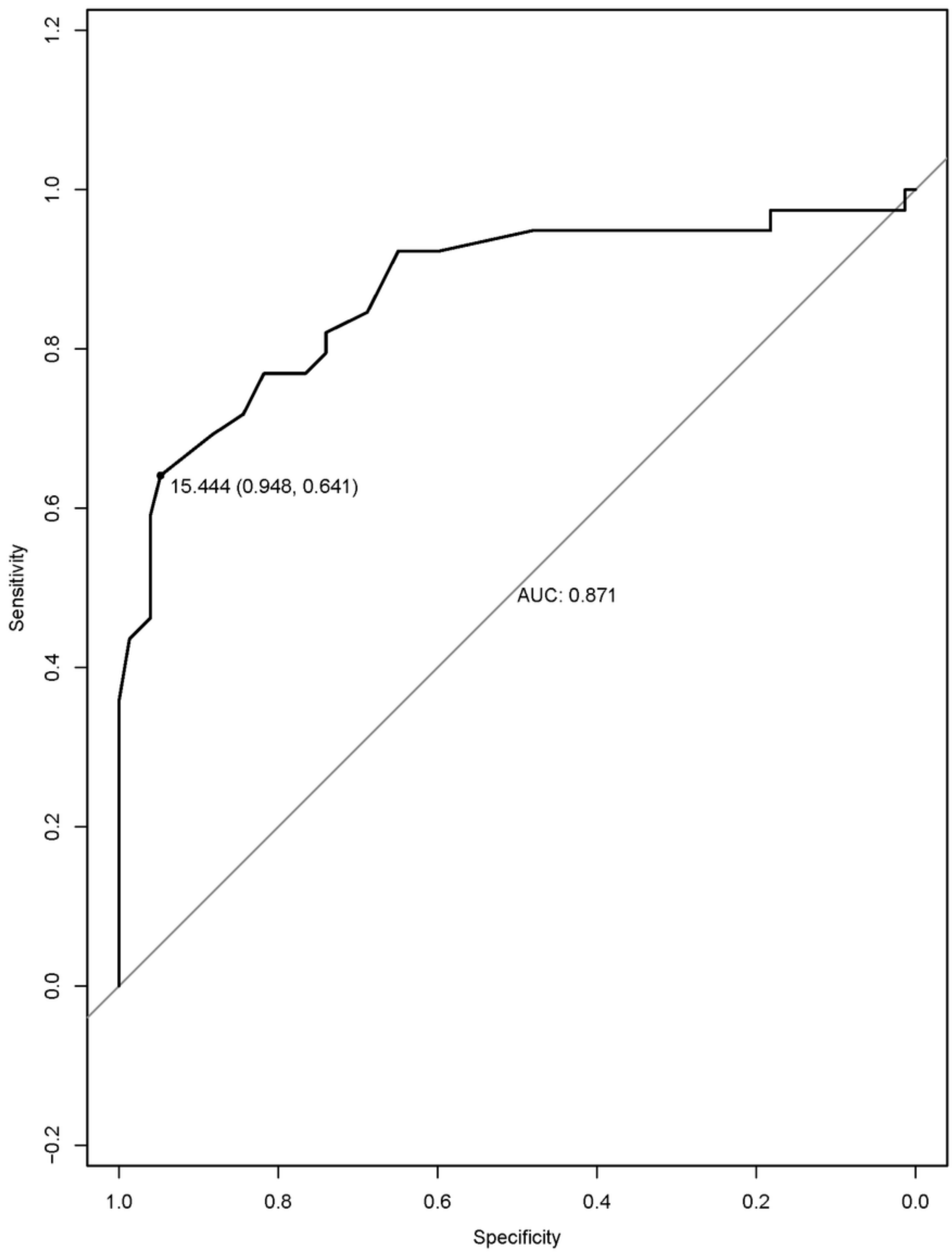

Figure 4

The ROC of the predictive model, the area under curve (AUC) was 0.871. And the cutoff value was 15.444, with a specificity of 94.8% and a sensitivity of 64.1%.