Machine learning prediction model of prolonged delay to loop ileostomy closure after rectal cancer surgery：A retrospective study

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Abstract

Background: Delayed closure of a temporary ileostomy in patients with rectal cancer may cause psychological, physiological, and socioeconomic burdens to patients.

Objective: This study aimed to develop and validate a machine learning-based model to predict the delayed ileostomy closure after surgery in patients with rectal cancer.

Methods: LASSO regression was used for feature screening, and XGBoost was used for machine learning model construction. Model performance was assessed by receiver operating characteristic (ROC) curve analysis, calibration curve analysis, clinical decision curve analysis, sensitivity, specificity, accuracy, and F1 score. The SHAP method was used to interpretate the results of the machine learning model.

Results: A total of 442 rectal cancer patients who received a loop ileostomy were included in the analysis, included in this study, and 305 experienced delayed closure (69%). The XGBoost model area under the ROC curve (AUC) of the training set was 0.744 (95% confidence interval [CI]: 0.686-0.806) and of the test set was 0.809 (95% CI: 0.728-0.889). The importance of each variable, in descending order was body mass index (BMI), postoperative chemotherapy, distance from tumor to anal margin, depth of tumor infiltration, neoadjuvant chemoradiotherapy, and anastomotic stenosis. The importance of SHAP variables in the model from high to low was: ‘BMI’ ‘postoperative chemotherapy’ ‘distance of the tumor from the anal verge’ ‘depth of tumor infiltration’ ‘neoadjuvant radiotherapy’ ‘anastomotic stenosis’.

Conclusions: The XGBoost machine learning model we constructed showed good performance in predicting delayed closure of loop ileostomy in rectal cancer patients. In addition, the SHAP method can help better understand the results of machine learning models.

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Keywords: Machine learning; rectal cancer; loop ileostomy; delayed closure

Introduction

Rectal cancer (RC) is one of the most common malignant digestive tract tumors, and colorectal cancer (CRC) is the third most common cancer globally, and the second leading cause of cancer-related death [1]. Total mesorectal excision (TME) proposed by Heald et al. in 1982 [2] became the standard for radical resection of rectal cancer. Its basic principle is to completely remove the mesentery surrounding the tumor at the anatomical and embryonic levels. Surgical methods have been improved over the years, and currently laparoscopic transabdominal tumor excision (laTME) has become one of the common methods for treating resectable rectal cancer [3]. After rectal cancer surgery, various complications may occur, among which the most serious is anastomotic leakage which has a significant impact on patient recovery, medical costs, and oncological outcomes [4] [5]. Thus, in patients undergoing rectal surgery for cancer a diverting ileostomy is often performed along with intestinal anastomoses [6].

However, there is debate if a temporary ileostomy can prevent or reduce anastomotic leakage. A considerable number of scholars have affirmed the positive role of a temporary ileostomy in preventing anastomotic leakage [7] [8]. Garg et al. [9] conducted a meta-analysis of 390 patients who underwent temporary ileostomy during surgery, and 378 patients who did not undergo a temporary ileostomy in 5 randomized controlled trials in 2019. The results showed that ileostomy significantly reduced the incidence of anastomotic leakage and reoperation. In recent decades, in order to prevent anastomotic leakage a prophylactic stoma has been widely used in anal sphincter preservation surgery for rectal cancer, especially for low rectal cancer [10]. However, some studies have shown that ileostomy after rectal cancer surgery does not reduce the incidence of anastomotic leakage, but can reduce the risk of abdominal infection[11] [12] [13]. Currently, there is no unified standard for determining which patients should receive a temporary ileostomy. In order to reduce postoperative complications, the use of a temporary preventive ileostomy has increased, leading to unnecessary stoma related complications in patients without anastomotic leakage.

Notably, a temporary ileostomy can have an adverse psychological and mental impact on the patient, and there can be complications associated with stoma. Complications of ileostomy mainly include intestinal obstruction, diarrhea, anastomotic leakage, incision infection, and enterocutaneous fistulae [14]. An international study that included 279 patients with an ileostomy reported an overall complication rate of 83% [15]. As such, a temporary ileostomy should be closed as soon as possible. Delayed closure of an ileostomy for more than 6 months is associated with a 3.7-fold increased risk of severe intestinal dysfunction after restoring intestinal continuity [16]. In addition, the incidence of stoma-related complications increases as the time to ileostomy closure increases [17]. Patients who undergo ileostomy closure more than 3 months after rectal surgery experience a significant decline in their quality of life [18] [19]. There is also an economic cost to delayed closure due to complications [20]. The timing of ileostomy closure can be influenced by a variety of factors, and a model to predict the possibility of delayed closure would have clinical value.

Machine learning (ML) is one of the most commonly used intelligence-driven health technologies, and is often used for patient risk assessment [21]. ML can extract clinical information from large amounts of data to assist in making sound clinical decisions [22] [23]. The SHapley Additive exPlans (SHAP) is an advanced, interpretable ML framework designed to provide in-depth explanations for the predictions of any ML model [24]. ML is currently widely used in the diagnosis, treatment, and prediction of cancer recurrence, and models have practical applications [25] [26] [27].

Thus, the purpose of this study is to develop an interpretable ML model to predict the risk of delayed closure of an ileostomy after rectal cancer surgery, and to use SHAP to improve the interpretability and transparency of the ML model.

Methods

Study Setting and Patients

An observational prospective cohort study was conducted in a large oncology hospital in China. The data of patients who underwent TME for rectal cancer and received a temporary ileostomy at the Colorectal Surgery Department of Sun Yat-sen University Cancer Center from January 1, 2022 to December 31, 2023 were retrospectively collected and reviewed. This study was approved by the Ethics Review Committee of Sun Yat-sen University Cancer Center. This study has obtained informed consent from the participants and signed the informed consent form.

Inclusion criteria and exclusion criteria

Inclusion criteria were: 1) Diagnosed with rectal cancer by colonoscopy and pathological examination of a biopsy tissue specimen; 2) Received an ileostomy; 3) Regular follow-up at Sun Yat-sen University Cancer Center; 4) No tumor recurrence during follow-up. Exclusion criteria were: 1) Diabetes mellitus or hypertension; 2) Ongoing steroid treatment; 3) Immune or inflammatory diseases such as inflammatory bowel disease and autoimmune diseases; 4) Concomitant small intestine or colon resection during surgery; 5) Repeat or multiple surgeries during the period from rectal cancer surgery to ileostomy closure.

Feature collection and screening

Prior to data collection, we conducted a comprehensive literature review to identify potential factors that may delay ileostomy closure. Patient data were collected from the standardized database of Sun Yat-sen University Cancer Center, and included age, sex, body mass index (BMI), distance between tumor and anal margin, pathological type, depth of tumor infiltration, lymph node metastasis, distant metastases, preoperative neoadjuvant chemoradiotherapy, postoperative chemotherapy, anastomotic leakage, anastomotic stenosis, low anterior resection syndrome (LARS), complications related to ileostomy. Variables were selected by LASSO regression (n-fold = 20) using the “glmnet” package in R.

Model development and validation

The data set was partitioned before building the model: 75% of the patients were assigned to the training set using the "caret" package, and the remaining 25% were assigned to the validation set. The model was built using the "XGBoost" package, and used the train() function to optimize the parameters in the caret package, and output the optimal parameter configuration. The XGBoost model is constructed by setting the learning rate eta to 0.1, the maximum depth (max_depth) to 2, and the number of iteration rounds (i.e., enhancement rounds) to 100. Accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and F1 score, ROC curve, calibration curve, and clinical decision curve analysis (DCA) were used to evaluate the performance of the model in the training and test sets. Predicted outcome probabilities were converted to binary outcomes using a threshold of 0.5.

Visualizing Data

"Shapviz" is an R package for interpreting ML model predictions, which provides visual explanations based on SHAP (SHapley Additive explanations) values. The SHAP value explains how much each feature contributes to the model's predictions, and whether it is positive or negative. The feature importance plot was used to display the features with the greatest impact on model predictions. Feature importance is ranked based on the average absolute value of the SHAP value. Two samples were selected to create a forced plot of SHAP values for predicting and interpreting the one-sample model.

Statistics Analysis

Categorical data were described as frequency and composition ratio. Continuous data that conform to a normal distribution were presented as mean ± standard deviation. Non-normally distributed data were presented as frequency (percentage). The chi-square test was used for comparing categorical data, and the t-test for continuous data. A 2-sided value of $P < 0.05$ was considered statistically significant. R language was used for organizing, analyzing, and visualizing data.

Results

Patient Characteristics

Of the 442 patients included in the analysis, 305 experienced delayed ileostomy closure (69.0%). There were no significant differences between the 2 groups in sex distribution, distant metastasis, tumor pathological type, anastomotic leakage, LARS, and other postoperative complications (all, $P > 0.05$). There were significant differences between the 2 groups in age, BMI, distance between the tumor and the anal verge, lymph node metastasis, depth of tumor infiltration, neoadjuvant chemoradiotherapy, postoperative chemotherapy, and anastomotic stenosis (all, $P < 0.05$) (Table 1).

Table 1 Comparison of basic information between case group and control group.

Features	Total (n = 442)	No delayed closure (n = 137)	Delayed closure (n = 305)	p
Gender, n (%)				0.498
Male	156 (35)	52 (38)	104 (34)	
Female	286 (65)	85 (62)	201 (66)	
Age, n (%)				0.015
≥18~□40	23 (5)	5 (4)	18 (6)	
≥40~□60	206 (47)	52 (38)	154 (50)	
≥60	213 (48)	80 (58)	133 (44)	
BMI, n (%)				<

				0.001
<24	294 (67)	108 (79)	186 (61)	
≥24	148 (33)	29 (21)	119 (39)	
Tumor distance from the anal verge, n (%)				0.005
≥5cm	377 (85)	127 (93)	250 (82)	
<5cm	65 (15)	10 (7)	55 (18)	
Distant Metastasis, n (%)				0.613
No	370 (84)	117 (85)	253 (83)	
Yes	72 (16)	20 (15)	52 (17)	
Lymph Node, n (%)				0.021
No	328 (74)	112 (82)	216 (71)	
Yes	114 (26)	25 (18)	89 (29)	
Depth of tumor infiltration, n (%)				0.002
Ⅰ-Ⅱ	223 (50)	85 (62)	138 (45)	
Ⅲ-Ⅳ	219 (50)	52 (38)	167 (55)	
Pathological Type, n (%)				0.269
Adenocarcinoma	420 (95)	132 (96)	288 (94)	
Mucinous adenocarcinoma	15 (3)	2 (1)	13 (4)	
Signet ring cell carcinoma	7 (2)	3 (2)	4 (1)	
Neoadjuvant Chemotherapy, n (%)				< 0.001
No	112 (25)	58 (42)	54 (18)	
Yes	330 (75)	79 (58)	251 (82)	
Postoperative Chemotherapy, n (%)				< 0.001
No	138 (31)	65 (47)	73 (24)	
Yes	304 (69)	72 (53)	232 (76)	
Anastomotic Leakage, n (%)				0.058
No	385 (87)	126 (92)	259 (85)	
Yes	57 (13)	11 (8)	46 (15)	
Anastomotic Stenosis, n (%)				0.004

No	401 (91)	133 (97)	268 (88)	
Yes	41 (9)	4 (3)	37 (12)	
LARS, n (%)				0.2
No	299 (68)	99 (72)	200 (66)	
Yes	143 (32)	38 (28)	105 (34)	
Complications, n (%)				1
No	373 (84)	116 (85)	257 (84)	
Yes	69 (16)	21 (15)	48 16)	

Feature Selection

A total of 14 variables were included in the analysis: LASSO regression was used for the selection of variables due to the fact that too many variables may lead to overfitting of the model, as well as covariance problems (Fig. 1). By choosing lambda values that were 1 standard deviation from the minimum lambda value (within 1 standard error of the minimum value), we identified the 7 most predictive variables (Fig. 2). After screening out the 7 variables with LASSO regression, we fitted a stepwise multifactor logistic regression based on the variables to screen them again. Ultimately, age was excluded because it was not an independent risk factor. Finally, 6 independent variables showed the strongest associations with the dependent variables, ensuring model simplicity and mitigating overfitting problems. The 6 variables were BMI, tumor distance from the anal verge, depth of tumor infiltration, neoadjuvant radiotherapy, postoperative chemotherapy, and anastomotic stenosis (Table 2). Using multivariate logistic regression, we determined that all of these variables were independent risk factors for delayed ileostomy closure.

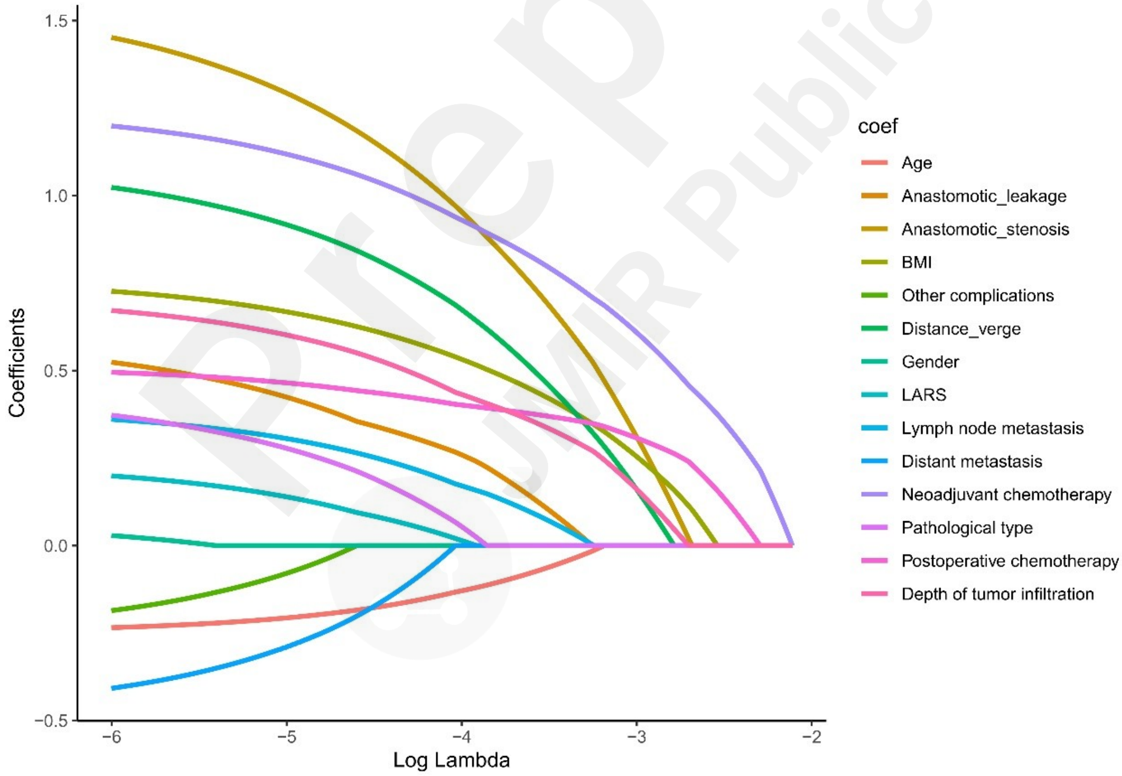

Figure 1. LASSO coefficient path diagram.

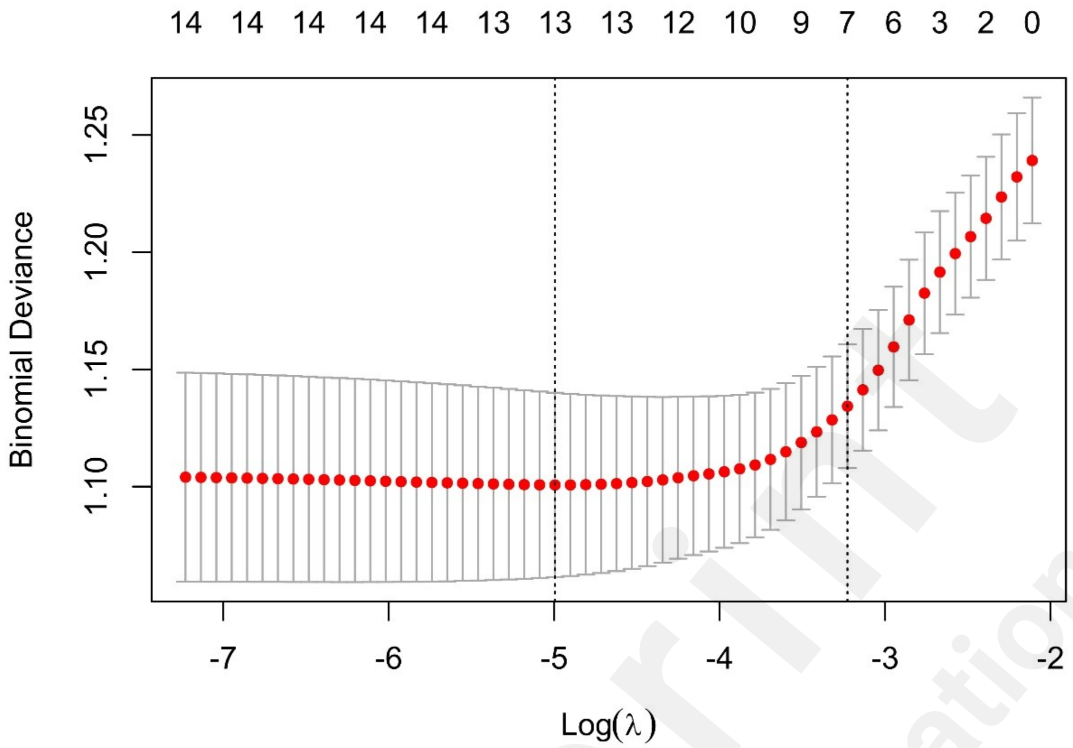

Figure 2. LASSO regularization path diagram, where the model has fewer features. while maintaining predictive performance when the regularization parameter value is set to one standard deviation.

Table 2 Multivariate Logistics Regression of Model Variables.

	B	SE	Wald	OR_with_CI	P
(Intercept)	-0.818	0.313	6.843	0.441(0.236~0.806)	0.009
BMI	0.824	0.303	7.387	2.281(1.276~4.212)	0.007
Tumor distance from the anal verge	1.137	0.482	5.558	3.118(1.291~8.808)	0.018
Depth of tumor infiltration	0.555	0.279	3.956	1.741(1.011~3.024)	0.047
Neoadjuvant Chemotherapy	0.716	0.310	5.341	2.047(1.113~3.765)	0.021
Postoperative Chemotherapy	0.620	0.300	4.273	1.859(1.03~3.348)	0.039
Anastomotic stenosis	1.203	0.584	4.249	3.329(1.165~12.106)	0.039

Model Performance

The performance evaluation metrics of the model are shown in Table 2. The XGBoost model had high area under the ROC curve (AUC) for predicting delayed ileostomy closure in the training set and the validation set: training set AUC = 0.744, 95% confidence interval (CI): 0.686-0.806; test set AUC = 0.809, 95 % CI: 0.728-0.889 (Fig. 3A-B). The model had high sensitivity, but low specificity in the training and validation sets: PPV (training set: 0.753, 95 % CI: 0.701 - 0.805; validation set: 0.782, 95% CI: 0.705 - 0.859), NPV (training set: 0.698, 95% CI: 0.56 - 0.835; validation set: 0.773, 95 % CI: 0.598 - 0.948). The F1 score of the training set was 0.836, and of the validation set was 0.856) (Table 3).

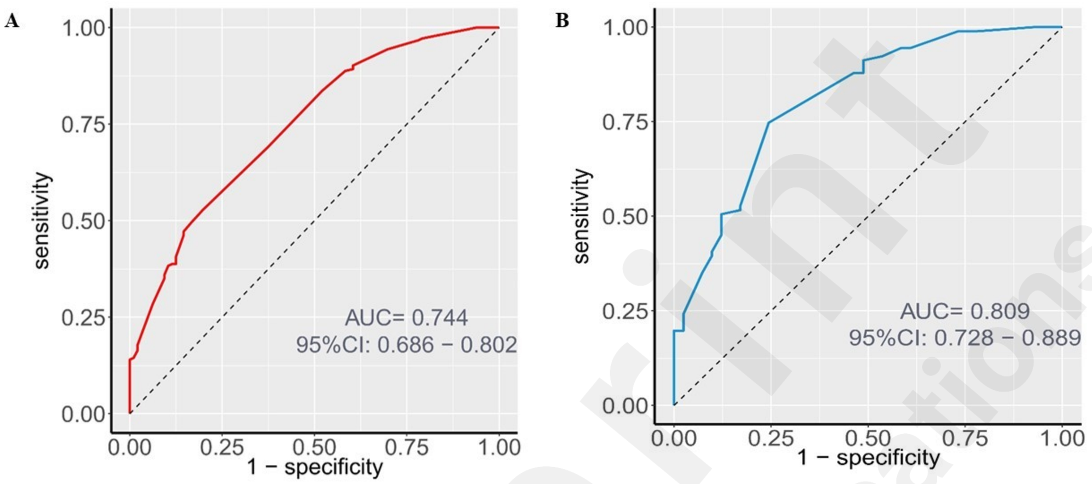

Figure 3. Receiver operating characteristic curve of the model on the training set(A). Receiver operating characteristic curve of the model validation set(B).

Table 3 Evaluation of XGBoost model performance in the training set and testing set.

	Training set	Testing set
AUC	0.744(0.686-0.802)	0.809(0.728-0.889)
Sensitivity	0.939(0.907-0.971)	0.945(0.898 - 0.992)
Specificity	0.312(0.22 - 0.405)	0.415(0.264 - 0.565)
PPV	0.753(0.701 - 0.805)	0.782(0.705 - 0.859)
NPV	0.698(0.56 - 0.835)	0.773(0.598 - 0.948)
F1 score	0.836	0.856

AUC: area under the receiver operating characteristic curve. PPV: Positive predictive value. NPV: Negative predictive value.

We assessed the accuracy of the XGBoost model in predicting the probability of delayed ileostomy closure by analyzing the calibration curves and clinical decision curves of the training and validation sets. The calibration curves for both the training and validation sets showed a good fit, indicating that the model predictions are highly consistent with the actual incidence (Fig. 4A-B). The clinical decision curves of the training and validation sets showed that the model has a good degree of clinical utility (Fig. 5A-B).

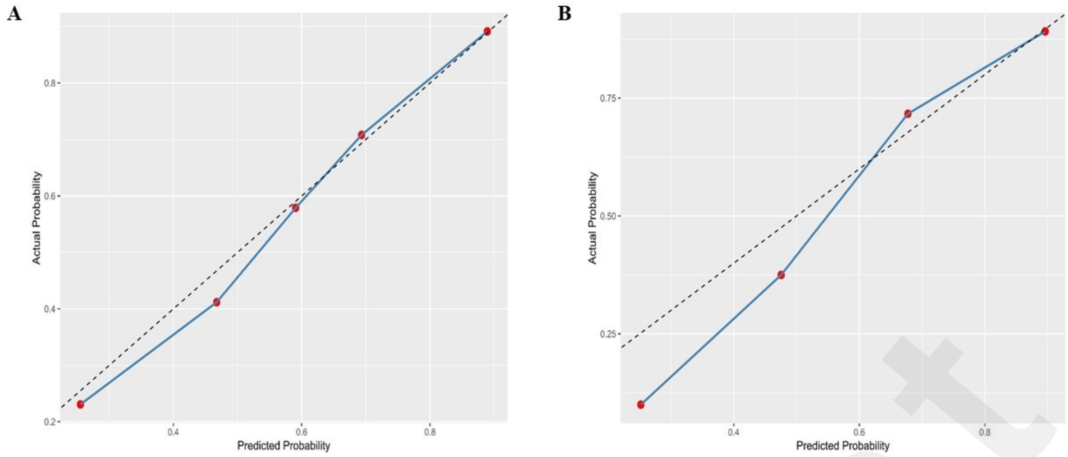

Figure 4. Calibration curve of the model training set(A). Calibration curve of the model validation set (B).

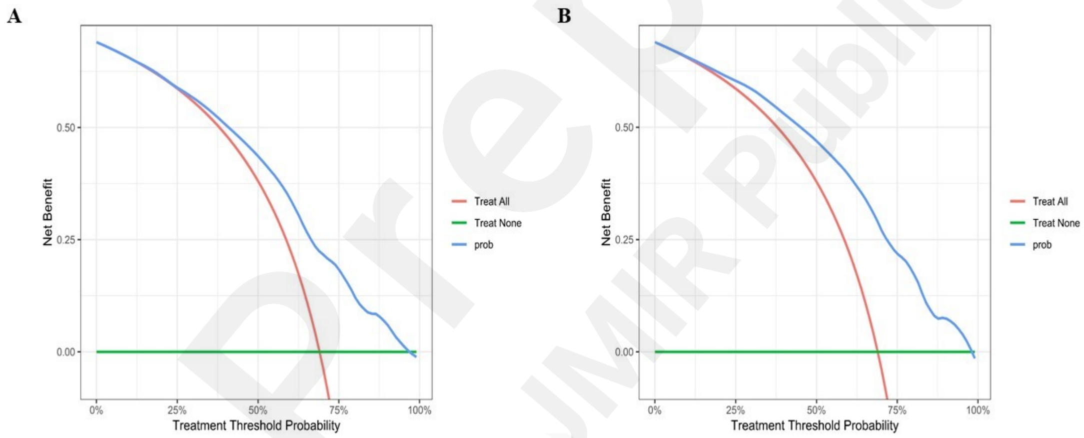

Figure 5. Clinical decision curve of the model on the training set(A). Clinical decision curve of the model validation set(B).

Interpretation of The Model

The SHAP summary plot of the model explains the effect of each variable on the model (Fig. 6). The order of importance of each variable is, in descending order, BMI > postoperative chemotherapy > distance of the tumor from the anal verge > depth of tumor infiltration > neoadjuvant radiotherapy > anastomotic stenosis. SHAP force diagrams are commonly used to explain how an XGBoost model assesses patient individualized variable contributions. We used the SHAP force plot to explain the level of variable contribution for 2 patients in this study. The colors indicate the contribution of each variable, with blue indicating that the feature is a negative predictor variable (arrow to the left, SHAP value decreases), and red indicating that the feature is a positive predictor variable (arrow to the right, SHAP value increases). The length of the color bar indicates the strength of the contribution, and E [f (x)] indicates the SHAP reference value, which is the average of the model predictions. For the "true positive" patient group, the XGBoost model predicted a delayed closure SHAP value of 0.837, exceeding the baseline value and indicating the occurrence of delayed closure (Fig. 7A). For the group of patients classified as “true negative”, the XGBoost model predicted a delayed closure value of 3.12, which did not exceed the reference value thus indicating that no delayed closure occurred (Fig. 7B).

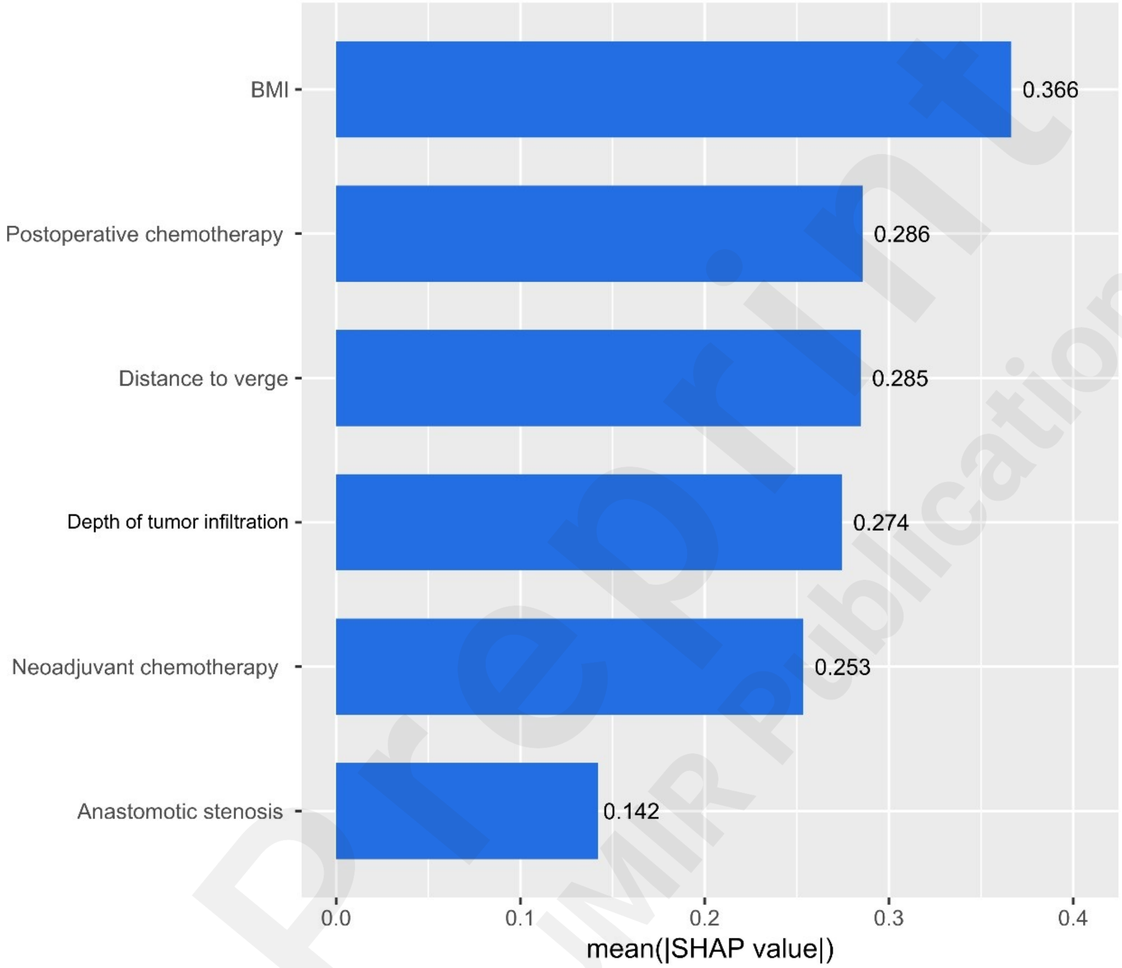

Figure 6. Importance chart for SHAP variables

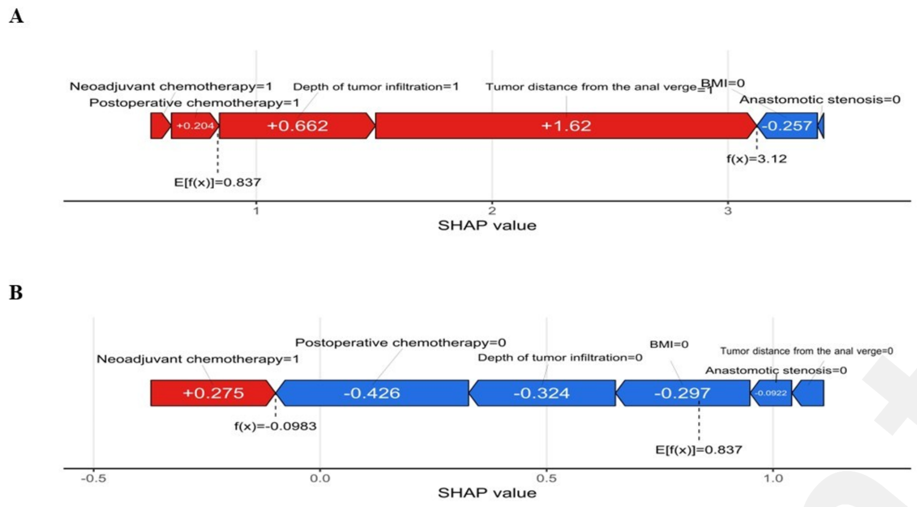

Figure 7.
SHAP force plot for “true positive” (A). SHAP force plot for “true negative” (B).

Discussion

There is currently no consensus on when a temporary loop ileostomy should be closed. Generally, closure is performed at 8-12 weeks after the operation, depending on the situation [28] [17]. In China, patients with a temporary ileostomy usually undergo examinations such as fiber colonoscopy, pelvic magnetic resonance imaging (MRI), defecography, and anorectal pressure measurement to evaluate tumor activity and perianal function before ileostomy closure. The aforementioned examinations take about 1 week. For this study, we defined delayed ileostomy closure as closure ≥ 90 days after the index operation. To our knowledge, this is the first study to develop a SHAP-interpretable XGBoost model to predict the occurrence of temporary ileostomy closure after rectal cancer surgery.

Training and validation sets were used to evaluate the performance of the XGBoost model, and the AUC of the training set for predicting delayed closure was 0.744 (95% CI: 0.686-0.806) and the AUC of the validation set was 0.809 (95% CI: 0.728-0.889). Thus, the model has the potential to assist in the management of patients with a temporary ileostomy by predicting the risk of delayed closure. Additionally, in order to achieve visualization of the data and results, we introduced the SHAP method to attempt to interpretate the model constructed in this study. The order of importance of each variable is, in descending order, BMI > postoperative chemotherapy > distance of the tumor from the anal verge > depth of tumor infiltration > neoadjuvant radiotherapy > anastomotic stenosis.

Previous studies have revealed that temporary ileostomy closure timing is influenced by various factors, and that there are risk factors associated with delayed closure. In this study, SHAP identified BMI as the most important variable, followed by postoperative chemotherapy and distance of the tumor from the anal verge as the second and third most important variables. Obesity has always been a risk factor for many diseases, and studies have shown that obesity (BMI ≥ 30.0 kg/m^2) can cause various stoma related complications, thereby affecting the timely closure of the stoma [29] [30]. Our results showed that a BMI ≥ 24.0 kg/m^2 is a significant risk factor for delayed closure.

Postoperative radiotherapy and chemotherapy are considered a risk factors for delayed ileostomy closure [30] [31] [32]. Compared to postoperative adjuvant chemotherapy, little study has been done to examine the impact of neoadjuvant chemoradiotherapy on the delay of ileostomy closure. den Dulk et al[31] concluded that neoadjuvant radiochemotherapy significantly delays ileostomy closure, probably because preoperative radiochemotherapy increases the risk of postoperative anastomotic complications in rectal cancer patients, which delays the closure of the ileostomy. In this study, the proportion of patients who underwent neoadjuvant therapy and postoperative adjuvant chemotherapy was significantly higher in the delayed closure group, and the LASSO regression analysis showed that postoperative adjuvant chemotherapy and neoadjuvant radiotherapy were risk factors for delayed ileostomy closure. Ileostomy closure is considered by most patients, families, and physicians to be an elective, non-essential procedure, and therefore is often considered unimportant. As such, during postoperative adjuvant chemotherapy, most patients and treating physicians will agree to delay the timing of ileostomy closure for the sake of continuity of chemotherapy. In addition, postoperative chemotherapy can cause patients to become weak, making it difficult for them to undergo surgery in a short period of time and delaying the return of the stoma.

According to reports, 36% of rectal anastomotic leaks can lead to the formation of anastomotic leakage channels, delaying the reintroduction of prophylactic stomas and even causing them to evolve into permanent stomas [33] [34]. However, in our study there was no difference in the occurrence of anastomotic leakage between the 2 groups, which may be due to an insufficient number of patients. However, a factor related to anastomotic leakage, the distance between the tumor and the anal margin, was shown to be an independent factor for delayed closure. Research has shown that large tumors near the anus are predictive for irreversible or delayed reversal of a shunt stoma [35]. This may be due to the tumor being closer to the anal margin, which may result in greater tension at the anastomotic site and poor local healing, leading to decisions to delay closure. It may also be due to the fact that with the improvement of surgical techniques and treatment, anastomotic leaks are easy to recognize early and thus controlled without related complications. It is noteworthy that anastomotic stenosis was found to be an independent risk factor in this study, a finding different than in some prior studies. Rectal anastomotic stenosis is the second most serious complication related to anastomosis after rectal cancer resection, and a recent meta-analysis reported that the incidence of anastomotic stenosis after rectal cancer surgery is 17% (95% CI: 13%-21%) [36]. Anastomotic stenosis can also delay ileostomy closure and increase the risk of stoma-related complications [13].

Many prior studies have examined risk factors for delayed ileostomy closure after surgery for rectal cancer, but almost all have been limited by using multiple linear regression for model construction[30] [37] [38]. Machine learning is a technique that uses computer algorithms to improve model accuracy and precision, enabling better handling of nonlinear relations between multiple variables [24]. Unlike previous studies, we first used LASSSO regression for variable screening. This feature selection method has good interpretability, and can automatically select important features related to the target variable to avoid overfitting of the model [39]. Then, XGBoost ML was used to construct the model, which can improve the accuracy and generalization ability of models, and handle high-dimensional data and complex classification problems [40]. The SHAP method was used to interpret the model, and visualize the results. Multi-center clinical trial data is needed to further evaluate and clarify the accuracy and precision of this predictive model.

Limitations

This study has various limitations to consider. First, we did not use systematic retrieval to include as many risk variables as possible. The study focused on the limited parameters we are familiar with, without considering more potential influencing factors and subgroups, such as diabetes and hypertension. Second, our XGBoost model was trained and validated using data from a single center, so its generalizability is unknown. In addition, the sample size used is relatively small. Although model performance was evaluated through training and validation sets, sample size may limit the generalization ability of the results. Finally, although the use of SHAP improves the interpretability of the model, comprehension of ML models remains a challenge for persons not experienced with ML.

Conclusion

The XGBoost ML model we built helps predict delayed closure of a temporary ileostomy after rectal cancer surgery. In addition, the SHAP method is able to explain the results generated by the ML model, improving the interpretability of the model and helping to provide explanations for the source of the predicted results for each patient. This model may help to avoid delayed ileostomy closure after rectal cancer surgery, and help practitioners better manage a temporary ileostomy.

Acknowledgments

We would like to thank the patients, doctors, and nurses who participated in this study.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that might influence the work reported in this paper.

Data availability

Data supporting the results of this study are available from the corresponding author upon reasonable request (Baojia Luo, luobj@sysucc.org.cn).

Ethical approval

This study was approved by the Ethics Review Committee of Sun Yat-sen University Cancer Center (SL-B2024-578-01).

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Supplementary Files

Multimedia Appendixes

Research abstract flowchart.
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