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Preoperative Albumin to Alkaline Phosphatase Ratio and Inflammatory Burden Index for Rectal Cancer Prognostic Nomogram-Construction: Based on Multiple Machine Learning

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Purpose: Preoperative albumin to alkaline phosphatase ratio (AAPR) and inflammatory burden index (IBI) are prognostic indicators for a multitude of cancers, and our study focuses on evaluating the prognostic significance of the AAPR and the IBI on rectal cancer (RC) patients to provide a more accurate guideline for patient prognosis.

Patients and Methods: This study enrolled patients who underwent laparoscopic rectal cancer surgery from January 2016 to January 2021. We utilized three machine learning approaches to select variables most relevant to prognosis in the training cohort. Finally, based on the screened variables, a nomogram was established to predict RC patients' overall survival (OS). The improvement in predictive ability and clinical benefit was assessed through the concordance index (C-index), receiver operating characteristic (ROC), calibration curve, and decision curve analysis (DCA).

Results: A total of 356 patients were enrolled and they were randomly divided into a training cohort (60%, n=214) and a validation cohort (40%, n=143). Overall survival (OS) was worse for patients in either the low AAPR or the high AAPR group, whereas patients in the low AAPR with both high IBI group had the lowest OS (P<0.001). Finally, five variables were obtained after screening the best variables by three machine learning, and the nomogram was constructed. In both the development and validation cohorts, the C-index values exceeded 0.85, indicating that the predictive model has a strong predictive performance in terms of overall survival. The calibration curves and the decision curve analysis (DCA) showed that the nomogram demonstrated a superior benefit.

Conclusion: Preoperative AAPR and IBI can serve as effective indicators for predicting the OS of RC patients. We have developed a nomogram for predicting the OS of patients who underwent laparoscopic rectal cancer surgery.

Keywords: albumin to alkaline phosphatase ratio, inflammatory burden index, rectal cancer, overall survival, prediction nomogram

Introduction

According to statistics, colorectal cancer (CRC) ranks third in incidence but second in mortality worldwide,[1] and rectal cancer (RC) accounts for about 30% of all newly diagnosed CRCs,[2] and the incidence is the highest in East Asia. Although there are various diagnostic and therapeutic means such as positron emission tomography (PET) scanning, electron fiberscopes, surgery, and radiotherapies, and the overall survival rate has been increasing, the 5-year survival rate is only 67%.[1,2] Furthermore, it is currently challenging to accurately predict the prognosis of patients undergoing laparoscopic rectal cancer surgery and thus develop individualized treatment strategies. Therefore, finding more simple, useful, and reliable indicators that can help predict the survival of rectal cancer patients is one of the urgent issues to be overcome.

Currently, the prognosis prediction and treatment decisions of RC patients depend on the traditional tumor-node-metastasis (TNM) staging,[3] But its accuracy and reliability are still unsatisfactory,[4–6] therefore, more indicators are needed to further improve its application. As a simple, accurate, and easily available sample, preoperative blood composition has been reported to

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be a significant factor in the pathogenesis, progression, and response to treatment of cancer. They are indispensable factors affecting the clinical outcomes of cancer patients.[7–9] In the progression of many types of cancer, a low level of albumin (ALB) or a high level of alkaline phosphatase (ALP) usually predicts a low OS.[10,11] Currently, a new blood indicator, AAPR, has been proven to play a significant predictive role in multiple studies.[12,13] Previous studies have suggested that various inflammatory indicators have important predictive roles in cancer.[14,15] The IBI is a novel inflammatory indicator that has recently been developed to predict the prognosis of cancer patients, and its validity and accuracy have been preliminarily recognized,[16,17] which is defined as C-reactive protein × neutrophils/lymphocytes.

Machine learning (ML), a new type of artificial intelligence (AI), is beginning to be widely used in medical data analysis[18,19] and also plays a significant role in constructing nomograms, which have demonstrated predictive efficacy superior to that of traditional COX regression,[20] and the reliability of the included model was further increased in our study by screening variables through ML.

Most studies have focused on the prognostic value of AAPR or IBI alone for various types of cancers.[12,13,16,17] Due to the existence of multiple factors influencing the survival of oncology patients, it is unreliable to use a single indicator to predict the prognosis of patients with RC, and the prognostic value and scope of application of both for the prognostic assessment of patients who underwent laparoscopic surgery for RC are still unknown. Therefore the prognostic study of AAPR combined with IBI for RC patients is essential. The purpose of this study was to establish a prognostic model by screening variables through ML to assess the prognostic value of preoperative AAPR or IBI in patients with RC.

Material and Methods

Patients and Ethical Approval

We enrolled patients diagnosed with RC and underwent laparoscopic rectal cancer surgery from January 2016 to January 2021, collected through the electronic medical record system of the Second Affiliated Hospital of Soochow University (Figure 1).

The inclusion criteria were: (1) preoperative and postoperative histopathological confirmation of primary RC; (2) patients underwent laparoscopic radical surgery; (3) complete and reliable clinical and pathological data of patients; (4) no distant metastatic lesions were seen in preoperative auxiliary examinations.

The exclusion criteria were: (1) patients with large tumors that cannot be surgically removed or require open surgery; (2) patients who underwent emergency surgery due to intestinal obstruction caused by the tumor; (3) patients who received radiotherapy or chemotherapy before surgery; and (4) patients had non-primary RC.

Data Collection

For the enrolled patients, the following indicators were retrospectively collected in our electronic medical record system:

(1) Basic patient characteristics: age, gender, American Society of Anaesthesiologists score (ASA), comorbidities (hypertension and diabetes).

(2) Laboratory data: ALB, ALP, C-reactive protein, neutrophil count, lymphocyte count, carcinoembryonic antigen (CEA) within two weeks before surgery.

(3) Intraoperative and postoperative data: surgery time, pathological results, postoperative hospital stay, and whether radiotherapy was administered after surgery.

(4) Calculation of variables: AAPR = serum albumin/alkaline phosphatase; IBI = C-reactive protein × neutrophil count (10^9/L)/lymphocyte count (10^9/L).

Follow-Up Visits

This study adopted a combined approach of outpatient follow-up and telephone interviews for the follow-up process. The first follow-up was conducted 1-month after the surgery, followed by follow-ups every 1–3 months in the first year after surgery, every 6-months in the second year, and annually from the third year onward. The follow-up ended in December 2023 or upon the patient's death. The primary outcome indicator was the overall survival period after surgery, which was calculated from the date of surgery to the final follow-up endpoint or the time of death.

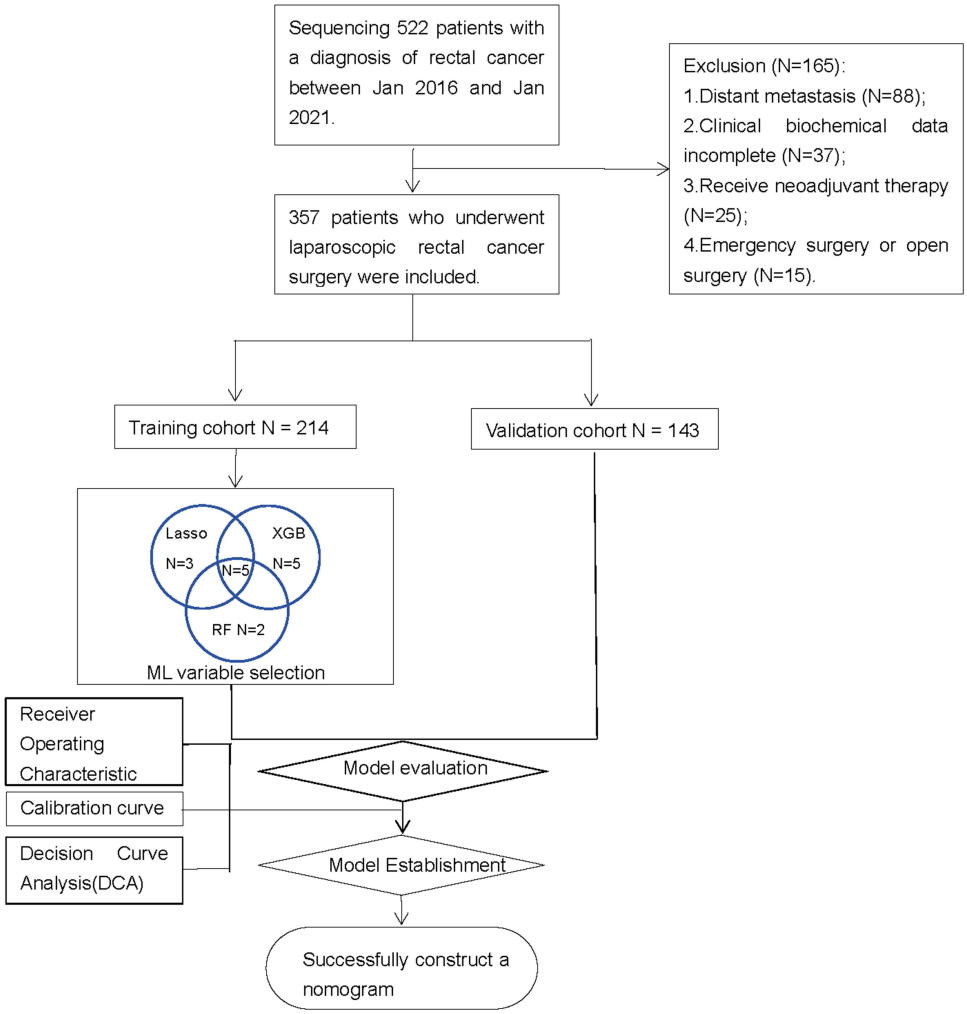

Figure 1 Flow chart of study design.
Abbreviation: XGB, XGBoost; RF, random forest.

Statistical Analysis

Statistical analysis was performed using R programming language (v4.4.0). The primary R packages employed in this study were ggplot2 (version 3.5.1), glmnet (version 4.1.8), xgboost (version 1.7.7.1), randomForestSRC (version 3.3.0), ggvenn (version 0.1.10), and rms (version 6.8.1), among others. The maximum choice log-rank statistic was used to determine the optimal cut-off value for AAPR versus IBI. The Mann–Whitney *U*-test was applied to analyze continuous variables, while the chi-square test was used for continuous variables. Continuous variables were presented as inter-quartile ranges and categorical variables were represented by absolute numbers or percentages. Differences between the two groups were compared using chi-square or *t*-tests. Predicted risks were expressed using hazard ratios (HR) and 95% confidence intervals (CI). Based on the independent prognostic factors screened by ML, we utilized R software to construct a nomogram prediction model for patients undergoing laparoscopic rectal cancer surgery. Internal validation of the model was performed using the 1000-time bootstrap resampling method. The receiver operating characteristic (ROC) curve and calibration curve were used to evaluate the discriminative ability and predictive effect of the nomogram. The discriminative ability and predictive effect of the nomogram were evaluated using the receiver operating characteristic curve and calibration curve. A two-sided p-value < 0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 357 patients were enrolled, and no significant correlation was observed among the included variables (Supplementary Figure S1). There were no notable differences in baseline comparisons between the training cohort and the validation cohort, and no significant differences were also observed in the Kaplan-Meier survival curves between the two cohorts (P>0.05) (Supplementary Figure S2). The median age of the enrolled patients was 65 years, comprising 218 males (61.06%) and 139 females (38.94%), with a male predominance. Among the patients, 125 had hypertension, and 43 had diabetes. The moderately differentiated histological type accounted for the highest proportion (81.51%), followed by poorly differentiated (13.45%) and well-differentiated (5.04%). One hundred and twenty-nine patients (36.13%) had CEA levels above the normal range. Approximately half of the patients (54.06%) received chemotherapy, and around one-fifth (19.61%) received radiotherapy (Table 1).

Table 1 Clinical Characteristics in the Training Cohort and Validation Cohort

Variables	Total (n = 357)	Training cohort (n = 214)	Validation cohort (n = 143)	P
Age, median (IQR)	65.00 (57.00, 73.00)	64.50 (57.00, 72.75)	66.00 (57.00, 73.50)	0.396
Sex, n (%)				0.553
Male	139 (38.94)	86 (40.19)	53 (37.06)	
Female	218 (61.06)	128 (59.81)	90 (62.94)	
Hypertension, n (%)				0.251
No	232 (64.99)	134 (62.62)	98 (68.53)	
Yes	125 (35.01)	80 (37.38)	45 (31.47)	
Diabetes, n (%)				0.797
No	314 (87.96)	189 (88.32)	125 (87.41)	
Yes	43 (12.04)	25 (11.68)	18 (12.59)	
ASA, n (%)				0.884
I	80 (22.41)	49 (22.90)	31 (21.68)	
2	194 (54.34)	114 (53.27)	80 (55.94)	
3	83 (23.25)	51 (23.83)	32 (22.38)	
pT stage, n (%)				0.416
I	210 (58.82)	120 (56.07)	90 (62.94)	
2	81 (22.69)	49 (22.90)	32 (22.38)	
3	50 (14.01)	35 (16.36)	15 (10.49)	
4	16 (4.48)	10 (4.67)	6 (4.20)	
pN stage, n (%)				0.917
0	230 (64.43)	138 (64.49)	92 (64.34)	
I	87 (24.37)	51 (23.83)	36 (25.17)	
2	40 (11.20)	25 (11.68)	15 (10.49)	
TNM stage, n (%)				0.543
I	187 (52.38)	78 (54.55)	109 (50.93)	
II	43 (12.04)	14 (9.79)	29 (13.55)	
III	127 (35.57)	51 (35.66)	76 (35.51)	
Differentiation type, n (%)				0.021
High	18 (5.04)	11 (5.14)	7 (4.90)	
Middle	291 (81.51)	183 (85.51)	108 (75.52)	
Low	48 (13.45)	20 (9.35)	28 (19.58)	
Nerve invasion, n (%)				0.5
No	281 (78.71)	171 (79.91)	110 (76.92)	
Yes	76 (21.29)	43 (20.09)	33 (23.08)	

(*Continued*)

Table 1 (Continued).

Variables	Total (n = 357)	Training cohort (n = 214)	Validation cohort (n = 143)	P
Vascular invasion, n (%)				0.691
No	298 (83.47)	180 (84.11)	118 (82.52)	
Yes	59 (16.53)	34 (15.89)	25 (17.48)	
Tumour size, n (%)				0.092
≤3cm	149 (41.74)	97 (45.33)	52 (36.36)	
>3cm	208 (58.26)	117 (54.67)	91 (63.64)	
AAPR, n (%)				0.184
≤0.44	101 (28.29)	55 (25.70)	46 (32.17)	
>0.44	256 (71.71)	159 (74.30)	97 (67.83)	
IBI, n (%)				0.968
≤21.82	275 (77.03)	165 (77.10)	110 (76.92)	
>21.82	82 (22.97)	49 (22.90)	33 (23.08)	
CEA, n (%)				0.409
≤5 μg/L	228 (63.87)	133 (62.15)	95 (66.43)	
>5 μg/L	129 (36.13)	81 (37.85)	48 (33.57)	
Surgical time, n (%)				0.557
≤240 min	268 (75.07)	163 (76.17)	105 (73.43)	
>240 min	89 (24.93)	51 (23.83)	38 (26.57)	
Postoperative hospital stay, n (%)				0.06
≤10 days	169 (47.34)	110 (51.40)	59 (41.26)	
>10 days	188 (52.66)	104 (48.60)	84 (58.74)	
Chemotherapy, n (%)				0.172
No	164 (45.94)	92 (42.99)	72 (50.35)	
Yes	193 (54.06)	122 (57.01)	71 (49.65)	
Radiotherapy, n (%)				0.579
No	287 (80.39)	170 (79.44)	117 (81.82)	
Yes	70 (19.61)	44 (20.56)	26 (18.18)	

Abbreviations: ASA, American Society of Anesthesiologists; AAPR, Albumin to alkaline phosphatase ratio; IBI, Inflammatory burden index; TNM stage, The 8th edition of the American Joint Committee on Cancer (AJCC) staging system; CEA, carcinoembryonic antigen; IQR, interquartile range.

Determination of Optimal Critical Values for AAPR and IBI

In the training cohort, we used the maximally selected log-rank statistic to determine the optimal cut-off values for AAPR and IBI (Supplementary Figure S3). Significant differences were observed in the Kaplan-Meier curves when AAPR=0.44 and IBI=21.82 (P<0.001) (Figure 2A and B). A total of 101 RC patients (28.29%) were classified as having low AAPR, and 82 RC patients (22.97%) were classified as having high IBI. Patients with low AAPR were closely correlated with older age, later N stage, poorer pathologic differentiation, nerve invasion, high CEA levels, and longer surgery time. Patients with high IBI were closely associated with poorer pathologic differentiation, high CEA levels, and postoperative chemotherapy (Table 2). To further investigate the predictive value of AAPR combined with IBI for the prognosis of RC, we divided the patients into four groups based on their AAPR and IBI values: high AAPR-high IBI, high AAPR-low IBI, low AAPR-high IBI, and low AAPR-low IBI. The median OS of patients in the low AAPR-high IBI group was 19 months, which was lower than that of the high AAPR-high IBI group (median OS 42 months), high AAPR-low IBI group (median OS 52 months), and low AAPR-low IBI group (median OS 26 months). The difference in OS between the groups was statistically significant (p<0.001) (Figure 2C).

Variable Selection

We employed three ML methods to screen variables from the training cohort. Subsequently, we took the intersection of the variables selected by each method and presented them in a venn diagram. The Lasso regression model encompassed

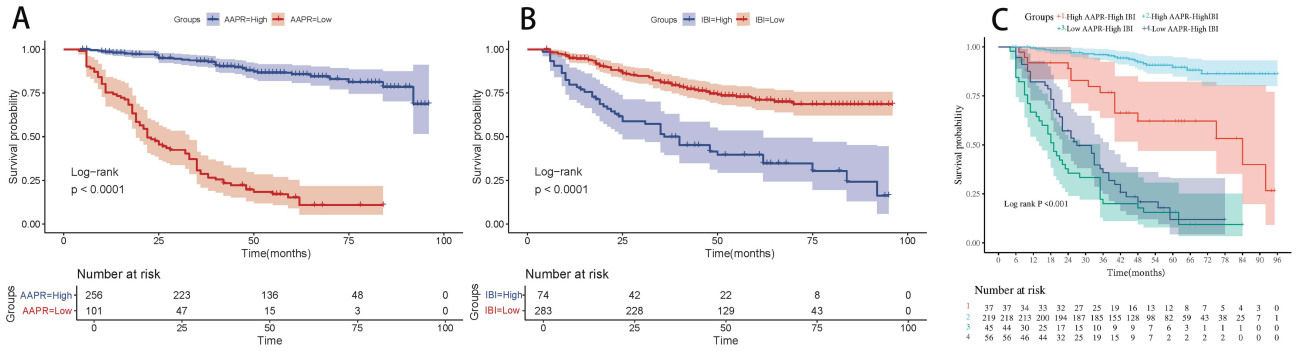

Figure 2 (**A**) Kaplan-Meier survival curves for overall survival (OS) of rectal cancer patients classified according to AAPR cut-off values (P < 0.001). (**B**) Kaplan-Meier survival curves for OS of rectal cancer patients classified according to IBI cut-off values (P < 0.001). (**C**) Kaplan-Meier survival curves for OS of rectal cancer patients comparing different groups (P < 0.001).

19 variables. The screening criterion was based on lambda. min and the model achieved the best fit when lambda. min was 0.04415 (Supplementary Figure S4). Ultimately, eight candidate variables with non-zero coefficients were selected (Figure 3A). As there is no unanimous consensus on the number of important variables selected by Xgboost, we chose the top ten significant variables (Figure 3B). The Random forest provides a permutation variable importance (VIMP), for the random forest model, we conducted an analysis using the minimum depth variable selection method, ultimately identifying seven variables as significant (Figure 3C). The intersection of important variables selected by the three ML methods included age, AAPR, IBI, CEA, and surgical time (Figure 4). To further validate the reliability of the included

Table 2 Clinicopathological Characteristics of RC Patients Stratified by AAPR and IBI Cut-off Values

Variables	Total (n = 357)	AAPR		P	IBI		P
		Low (n = 101)	High (n = 256)		Low (n = 275)	High (n = 82)	
Age, median (IQR)	65.00 (57.00, 73.00)	69.00 (61.00, 77.00)	63.00 (56.00, 71.00)	<0.001	65.00 (57.00, 73.00)	65.00 (56.50, 76.00)	0.501
Sex, n (%)				0.686			0.126
Male	139 (38.94)	41 (40.59)	98 (38.28)		113 (41.09)	26 (31.71)	
Female	218 (61.06)	60 (59.41)	158 (61.72)		162 (58.91)	56 (68.29)	
Hypertension, n (%)				0.165			0.939
No	232 (64.99)	60 (59.41)	172 (67.19)		179 (65.09)	53 (64.63)	
Yes	125 (35.01)	41 (40.59)	84 (32.81)		96 (34.91)	29 (35.37)	
Diabetes, n (%)				0.674			0.468
No	314 (87.96)	90 (89.11)	224 (87.50)		240 (87.27)	74 (90.24)	
Yes	43 (12.04)	11 (10.89)	32 (12.50)		35 (12.73)	8 (9.76)	
ASA, n (%)				0.352			0.502
1	80 (22.41)	18 (17.82)	62 (24.22)		63 (22.91)	17 (20.73)	
2	194 (54.34)	56 (55.45)	138 (53.91)		152 (55.27)	42 (51.22)	
3	83 (23.25)	27 (26.73)	56 (21.88)		60 (21.82)	23 (28.05)	
pT stage, n (%)				0.514			0.879
1	210 (58.82)	65 (64.36)	145 (56.64)		162 (58.91)	48 (58.54)	
2	81 (22.69)	18 (17.82)	63 (24.61)		63 (22.91)	18 (21.95)	
3	50 (14.01)	14 (13.86)	36 (14.06)		39 (14.18)	11 (13.41)	
4	16 (4.48)	4 (3.96)	12 (4.69)		11 (4.00)	5 (6.10)	
pN stage, n (%)				0.022			0.695
0	230 (64.43)	56 (55.45)	174 (67.97)		180 (65.45)	50 (60.98)	
1	87 (24.37)	27 (26.73)	60 (23.44)		66 (24.00)	21 (25.61)	
2	40 (11.20)	18 (17.82)	22 (8.59)		29 (10.55)	11 (13.41)	
TNM stage, n (%)				0.072			0.733
I	187 (52.38)	47 (46.53)	140 (54.69)		147 (53.45)	40 (48.78)	
II	43 (12.04)	9 (8.91)	34 (13.28)		33 (12.00)	10 (12.20)	
III	127 (35.57)	45 (44.55)	82 (32.03)		95 (34.55)	32 (39.02)	

(*Continued*)

Table 2 (Continued).

Variables	Total (n = 357)	AAPR		P	IBI		P
		Low (n = 101)	High (n = 256)		Low (n = 275)	High (n = 82)	
Differentiation type, n (%)				0.001			0.033
High	18 (5.04)	3 (2.97)	15 (5.86)		15 (5.45)	3 (3.66)	
Middle	291 (81.51)	74 (73.27)	217 (84.77)		230 (83.64)	61 (74.39)	
Low	48 (13.45)	24 (23.76)	24 (9.38)		30 (10.91)	18 (21.95)	
Nerve invasion, n (%)				0.031			0.654
No	281 (78.71)	72 (71.29)	209 (81.64)		215 (78.18)	66 (80.49)	
Yes	76 (21.29)	29 (28.71)	47 (18.36)		60 (21.82)	16 (19.51)	
Vascular invasion, n (%)				0.173			0.065
No	298 (83.47)	80 (79.21)	218 (85.16)		235 (85.45)	63 (76.83)	
Yes	59 (16.53)	21 (20.79)	38 (14.84)		40 (14.55)	19 (23.17)	
Tumour size, n (%)				0.608			0.112
≤3cm	149 (41.74)	40 (39.60)	109 (42.58)		121 (44.00)	28 (34.15)	
>3cm	208 (58.26)	61 (60.40)	147 (57.42)		154 (56.00)	54 (65.85)	
CEA, n (%)				<0.001			0.003
≤5 μg/L	228 (63.87)	44 (43.56)	184 (71.88)		187 (68.00)	41 (50.00)	
>5 μg/L	129 (36.13)	57 (56.44)	72 (28.12)		88 (32.00)	41 (50.00)	
Surgical time, n (%)				<0.001			0.651
≤240 min	268 (75.07)	62 (61.39)	206 (80.47)		208 (75.64)	60 (73.17)	
>240 min	89 (24.93)	39 (38.61)	50 (19.53)		67 (24.36)	22 (26.83)	
Postoperative hospital stay, n (%)				0.508			0.963
≤10 days	169 (47.34)	45 (44.55)	124 (48.44)		130 (47.27)	39 (47.56)	
>10 days	188 (52.66)	56 (55.45)	132 (51.56)		145 (52.73)	43 (52.44)	
Chemotherapy, n (%)				0.3			0.029
No	164 (45.94)	42 (41.58)	122 (47.66)		135 (49.09)	29 (35.37)	
Yes	193 (54.06)	59 (58.42)	134 (52.34)		140 (50.91)	53 (64.63)	
Radiotherapy, n (%)				0.516			0.355
No	287 (80.39)	79 (78.22)	208 (81.25)		224 (81.45)	63 (76.83)	
Yes	70 (19.61)	22 (21.78)	48 (18.75)		51 (18.55)	19 (23.17)	

Abbreviations: ASA, American Society of Anesthesiologists; AAPR, Albumin to alkaline phosphatase ratio; IBI, Inflammatory burden index; TNM stage, The 8th edition of the American Joint Committee on Cancer (AJCC) staging system; CEA, carcinoembryonic antigen; IQR, interquartile range.

variables, we incorporated the selected significant variables into a multivariate COX regression analysis. We found that all five variables were independent prognostic factors for RC (P<0.05). Specifically, low AAPR (HR: 0.14, 95% CI: 0.08–0.26, p <0.001) and high IBI (HR: 2.31, 95% CI: 1.39–3.86, p = 0.001) were independently associated with OS (Supplementary Table S1).

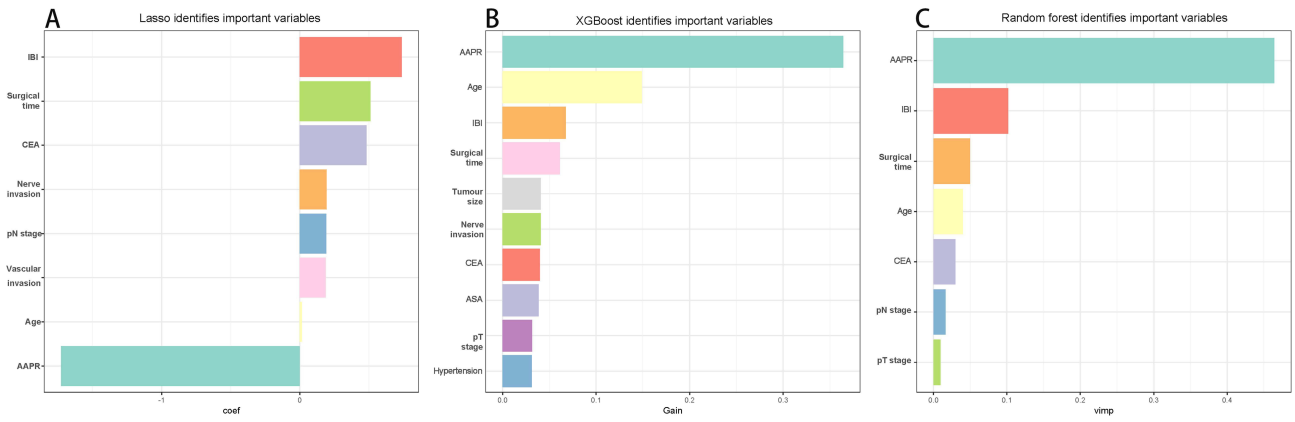

Figure 3 Three important feature selection methods in ML are (**A**) Lasso regression; (**B**) Xgboost; and (**C**) Random Forest.

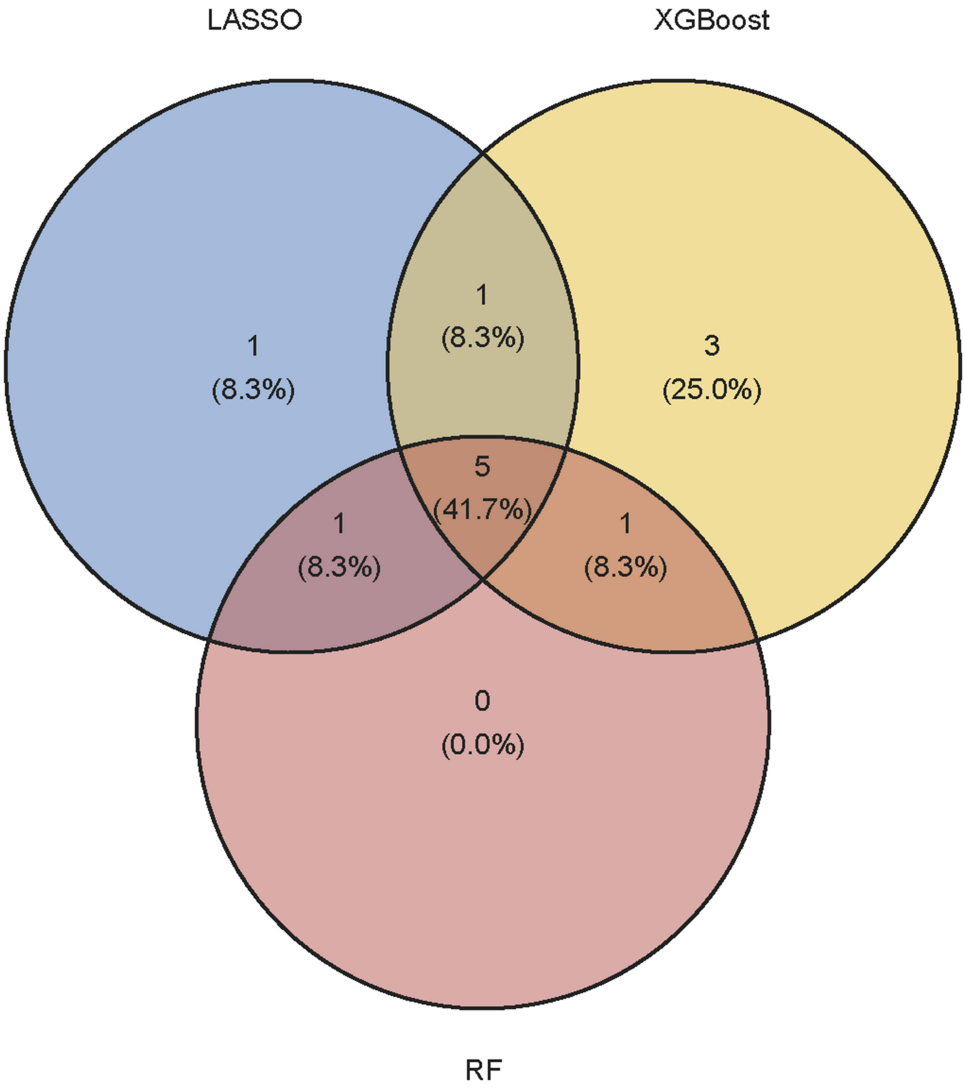

Figure 4 A Venn diagram showing three important feature selection methods in ML, with blue representing Lasso regression, yellow representing Xgboost, and pink representing Random Forest.

Development and Validation of a Nomogram for OS

Utilizing independent predictors screened through ML in the training cohort, we have constructed a nomogram model for predicting OS in patients with RC (Figure 5). The ROC analysis of the nomogram revealed AUCs of 0.911 (95% CI: 0.855–0.967), 0.934 (95% CI: 0.899–0.970), and 0.909 (95% CI: 0.855–0.963) for 1-, 3-, and 5-year OS in the training cohort, respectively (Figure 6A). In the validation cohort, the AUCs were 0.874 (95% CI: 0.809–0.939), 0.929 (95% CI: 0.884–0.975), and 0.889 (95% CI: 0.812–0.966) for the same duration (Figure 6B). The validity of the nomogram model in the training cohort was verified using the C-index and calibration curves. Specifically, the C-indices for the training and validation cohorts were 0.877 (95% CI: 0.845–0.909) and 0.862 (95% CI: 0.818–0.906), respectively. The calibration curves of the nomogram exhibited strong consistency between actual observations and predictions (Figure 7). Furthermore, the decision curve analysis (DCA), widely employed in assessing the clinical value of nomograms, demonstrated significant net benefits of the nomogram, indicating its substantial clinical utility in predicting OS for patients undergoing laparoscopic surgery for RC (Figure 8A-F).

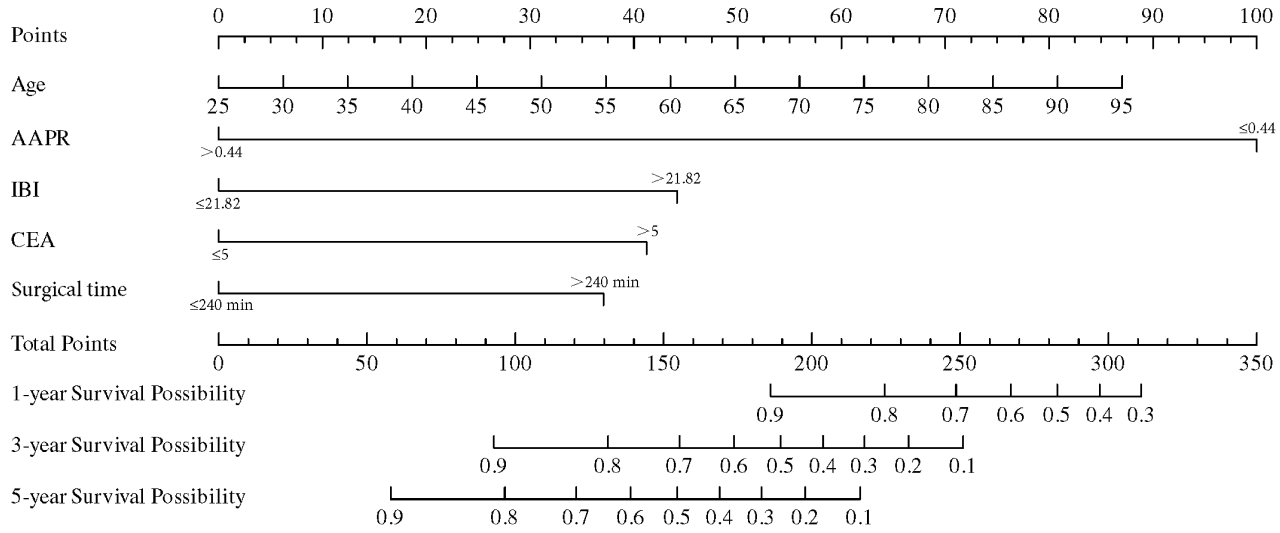

Figure 5 Nomogram model predicting 1-, 3- and 5-year OS in patients with RC.

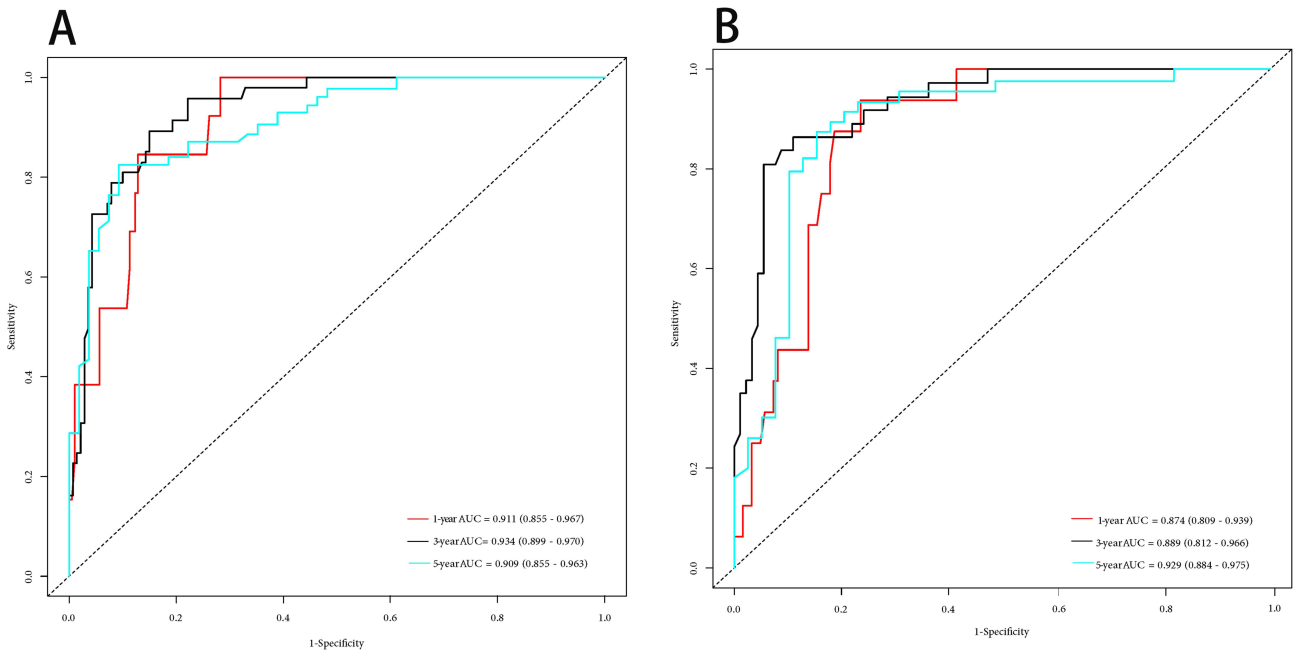

Figure 6 The ROC curves of the nomogram for predicting 1-year, 3-year, and 5-year overall survival (OS) in rectal cancer patients in the training cohort (**A**), and the ROC curves of the nomogram for predicting 1-year, 3-year, and 5-year OS in rectal cancer patients in the validation cohort (**B**).

Discussion

RC, as a prevalent malignant tumor in the digestive system, poses significant challenges. Our focus is on identifying accurate and comprehensive prognostic factors using the simplest and most accessible indicators, and subsequently developing appropriate personalized treatment plans based on these prognostic factors to improve and extend survival rates. In this context, we evaluated patients from our center to determine the optimal cut-off values for AAPR and IBI. Additionally, we employed three types of ML to identify the variables most relevant to prognosis. Patients with low AAPR or high IBI tend to have poorer OS, while those with both low AAPR and high IBI have the lowest OS. Both AAPR and IBI are independent risk factors for OS in patients undergoing laparoscopic rectal cancer surgery.

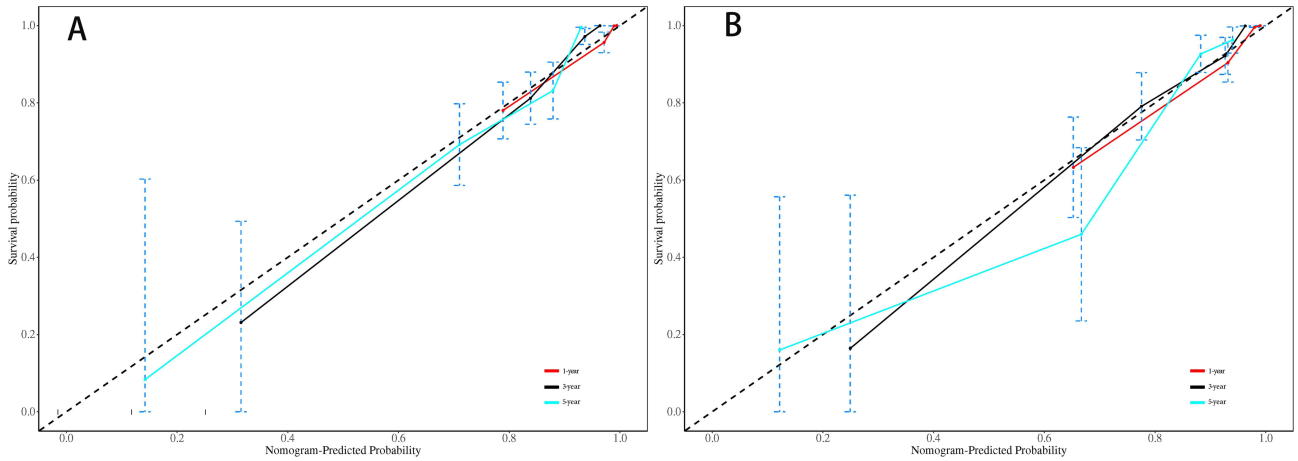

Figure 7 The calibration curves for 1-year, 3-year, and 5-year overall survival (OS) in the training cohort (**A**) and the calibration curves for 1-year, 3-year, and 5-year OS in the validation cohort (**B**). The solid line indicates the performance of the prediction model, and the closer to the diagonal dashed line, the more accurate the prediction.

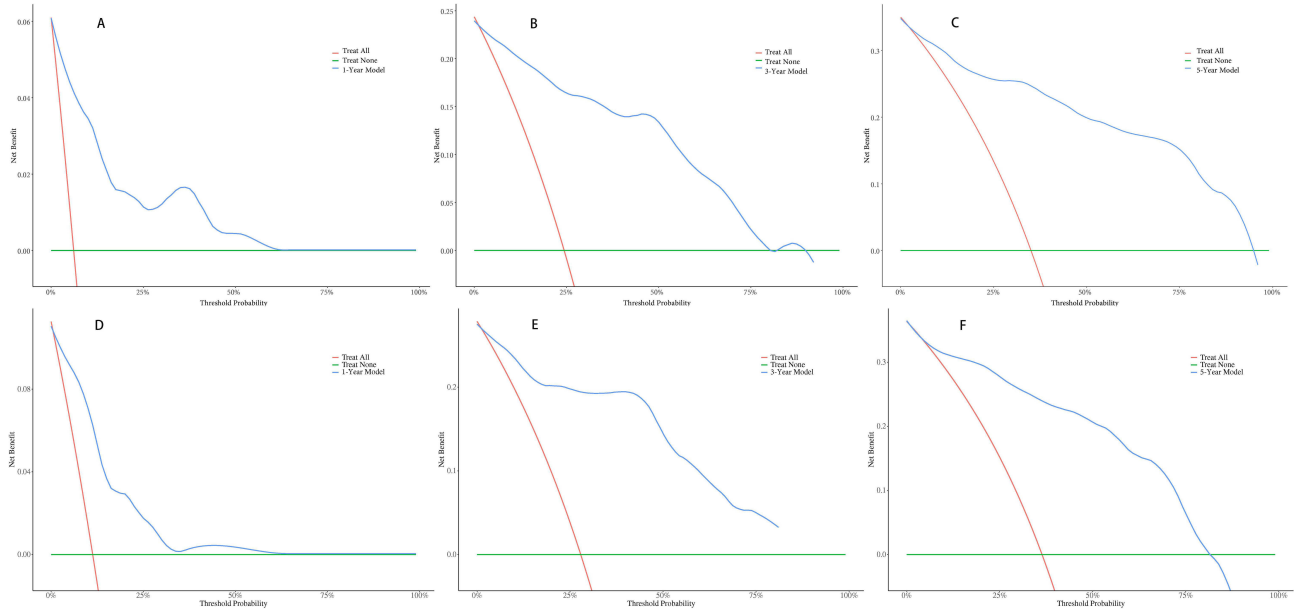

Figure 8 The DCA curves for 1- (**A**), 3- (**B**), and 5-year (**C**) OS in the training cohort, as well as the DCA curves for 1- (**D**), 3 (**E**), and 5-year (**F**) OS in the validation cohort.

Furthermore, we constructed a nomogram for predicting OS in these patients based on the variables identified through ML. Various assessments have demonstrated the broad clinical application potential of this predictive model.

As reported, regular intake of non-steroidal anti-inflammatory drugs (NSAID) in subjects can significantly reduce the incidence of colorectal malignancies,[21] which indirectly reflects the non-negligible role of inflammation in the occurrence and progression of RC. Therefore, inflammatory biomarkers are potential prognostic factors for RC patients. Various serum indicators have been developed for the prognostic prediction of cancer.[22,23] Yamamoto T et al summarized and classified inflammatory markers into five categories: neutrophil-related markers, albumin-related markers, monocyte-related markers, CRP-related markers, and platelet-related markers.[24] Several indicators, such as the albumin-to-globulin ratio (AGR), neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-C-reactive protein ratio (LCR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), have been developed for predicting the prognosis of CRC, all showing promising predictive effects.[24–26]

Machine learning plays a pivotal role in dimensionality reduction of model variables. Numerous studies have employed one or more machine learning techniques for variable selection and ultimately constructed nomograms, all demonstrating excellent predictive performance.[27–29] In our study, the intersection of the top 10 variables selected by three machine learning methods included: age, CEA, surgical time, AAPR, and IBI. Notably, advanced age often predicts poorer overall survival (OS), not only due to the declined physical function and higher postoperative complications in elderly patients but also their reduced tolerance to adjuvant therapies such as postoperative radiotherapy and chemotherapy, leading to a worse prognosis. Therefore, early implementation of more aggressive therapeutic interventions, such as nutritional support, is crucial to prolong the life expectancy and improve the quality of life for elderly patients.[30,31] Serum tumor markers play a significant role in the prognosis of patients with colorectal cancer (CRC).[32] CEA is routinely recommended for postoperative follow-up of recurrence and metastasis in CRC patients and is also used for prognostic assessment due to its superiority over other independent prognostic biomarkers. However, the accuracy of CEA alone as a prognostic factor is limited. Models combining multiple markers or incorporating other clinical features have demonstrated impressive predictive performance.[32,33] Similarly, our study included features such as CEA, which further enhanced the stability of our model. In our study, surgical time was also identified as an important feature. Longer surgical time indicates increased surgical difficulty, which has been associated with the prognosis of CRC patients in a previous study,[34] consistent with our findings.

AAPR and IBI are recently highlighted inflammatory indicators.[13,16] AAPR was initially used to predict the prognosis of patients with hepatocellular carcinoma,[13,35,36] as albumin (ALB) and alkaline phosphatase (ALP) are mostly produced by liver tissue and play a crucial role in the occurrence and progression of hepatocellular carcinoma.[37,38] ALB is considered not only an objective indicator of nutritional status but also reflects the protein status and visceral function in the blood. A decrease in albumin levels indicates an increased inflammatory response and poor nutritional status of patients, thus predicting a low survival rate of cancer.[35] Albumin plays a significant role not only in the diagnosis of cancer but also in anti-tumor therapy.[39] Albumin helps enhance tumor specificity, reduces drug-induced cytotoxicity, and serves as an excellent carrier for nanodrug delivery.[39] ALP is a metalloenzyme ubiquitous in various biological species in nature, contributing to various important biological processes.[35] ALP levels have been reported to be closely related to various diseases, including CRC.[40,41] Therefore, it is essential to study AAPR in tumor progression, which has a better predictive effect than ALB or ALP alone. C-reactive protein (CRP) is one of the representative biomarkers of systemic inflammation and is widely used and easily accessible in clinical practice.[42] High CRP levels often predict high mortality and short survival after CRC surgery.[43] Neutrophils and lymphocytes are important components of blood inflammatory cells. Neutrophils are not only the main component of white blood cells but also induce various cancer-promoting factors, including neutrophil elastase, matrix metalloproteinase 9 (MMP9), and vascular endothelial growth factor (VEGF).[44] Under the stimulation of inflammatory factors, neutrophils are activated and play a role in chemotaxis, phagocytosis, intracellular killing, and adaptive immune regulation. Meanwhile, lymphocytes play a vital role in tumor immune surveillance by inducing cytotoxic cell death and inhibiting the proliferation and growth of tumor cells, thus being considered the first line of defense against cancer.[45] In multiple studies, neutrophil/lymphocyte biomarkers have been widely reported to be associated with adverse outcomes in cancer.[24,46] Combining CRP, neutrophils, and lymphocytes, IBI integrates the advantages of these parameters, comprehensively reflecting the inflammatory and immune status of the human body. This may help physicians initially assess patients' clinical status through IBI, pay more attention to potential complications and prognosis during preoperative and hospitalization periods, and intervene promptly to achieve a longer survival period. It is worth mentioning that IBI not only has a significant impact on cancer prognosis but also has a good predictive effect on short-term outcomes such as 90-day outcomes, hospital stay, and hospitalization costs.

In this study, we investigated the impact of patients' inflammatory, immune, and nutritional status on the prognosis of RC. A preoperative state of low AAPR and high IBI in RC patients indicates a poorer prognosis. This trend is not only observed in RC but also in lung cancer[17] and gastric cancer.[47] However, previous research has primarily focused on exploring the clinical significance of AAPR and IBI separately in specific cancer types. Our study is the first to integrate these two promising predictive indicators and develop a nomogram, which presents broad clinical application prospects.

Certainly, this study has several limitations. Firstly, it was a retrospective study conducted at a single center with a relatively small number of recruited patients, thus potentially introducing selection bias. Although utilizing various

machine learning techniques for variable selection can enhance the stability of model variables, it is undeniable that excessive screening through machine learning methods may result in the exclusion of some crucial variables. Further validation of the optimal cut-off values for AAPR and IBI requires a larger sample size from multiple centers. Some of the patients enrolled had a follow-up period of less than 5 years, so the prediction of the 5-year survival rate of patients in the nomogram needs to be further verified in the future. Secondly, the study only included patients with stages I–III, and no subgroup analysis was performed for patients with distant metastases or postoperative adjuvant therapy. Therefore, further exploration is needed to assess the prognostic significance of AAPR and IBI in patients with distant metastases. Finally, as there is significant individual variation in the survival of RC patients, we only selected a subset of clinical and biochemical markers, and unaccounted factors may contribute to residual confounding effects.

Conclusion

Through our research, we have determined the optimal cutoff values for AAPR and IBI, establishing preoperative AAPR and IBI as effective indicators for assessing the prognosis of patients undergoing laparoscopic rectal cancer surgery. These results suggest that preoperative AAPR and IBI can aid in evaluating the inflammatory burden of rectal cancer patients and potentially provide support for anti-inflammatory treatment. Furthermore, we have utilized ML to develop and validate a nomogram for predicting the overall survival of patients undergoing laparoscopic rectal cancer surgery, demonstrating excellent predictive performance.

Data Sharing Statement

The data sets analyzed during the current study are not publicly available for patient privacy purposes but are available from the corresponding author (Wu) upon reasonable request.

Ethical Recognition

The Ethics Committee of the Second Affiliated Hospital of Soochow University approved our retrospective study (JD-HG-2024-051). It conforms to the 1964 helsinki Declaration of the World Medical Association and its subsequent revisions, and the Ethics Committee of the Second Affiliated Hospital of Soochow University waived the need for patient approval or informed consent. Given that this study is retrospective, the ethics committee granted a waiver for the requirement of written informed consent. The data utilized in this study are de-identified, preventing the recognition of individual participants. We are committed to upholding the confidentiality of all patient information.

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Disclosure

The authors report no conflicts of interest in this work.

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