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Original Article

Prognostic value of albumin-to-alkaline phosphatase ratio and CONUT score in rectal cancer patients undergoing XELOX-based chemotherapy: development of a nomogram-based predictive model

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Abstract: Objective: To evaluate the prognostic significance of the albumin-to-alkaline phosphatase ratio (AAPR) and the Controlling Nutritional Status (CONUT) score in rectal cancer (RC) patients receiving XELOX-based chemotherapy, and to develop a nomogram for predicting recurrence risk. Methods: This retrospective study included 389 RC patients treated at the First Affiliated Hospital of Chongqing Medical University, along with an independent validation cohort of 120 patients. Clinical variables, including AAPR and CONUT were analyzed using Cox regression and cumulative incidence function curves. A nomogram was constructed and validated using calibration plots and time-dependent receiver operating characteristic (ROC) curves. Results: Both AAPR (HR = 0.073, P<0.001) and CONUT score (HR = 1.497, P<0.001) were identified as independent predictors of recurrence. Additional factors significantly associated with increased recurrence risk included TNM stage III, tumor size ≥5 cm, vascular invasion, and carcinoembryonic antigen (CEA) level ≥5 ng/ml. The nomogram demonstrated strong predictive performance with a C-index of 0.860 in the training cohort, and 0.835 in the validation cohort. Calibration plots showed excellent agreement between predicted and observed recurrence probabilities. Conclusions: AAPR and CONUT score are independent prognostic indicators for recurrence in RC patients treated with XELOX-based chemotherapy. The proposed nomogram, incorporating these variables, provides a reliable tool for individualized risk prediction and may support personalized treatment decision-making.

Keywords: Albumin-to-alkaline phosphatase ratio, CONUT score, rectal cancer, XELOX-based chemotherapy, prognostic model, nomogram

Introduction

Rectal cancer (RC) is a significant malignancy with a steadily increasing global incidence and mortality in recent years [1]. According to the American Cancer Society, RC ranks third in incidence among men and second among women worldwide, and it holds the second-highest cancer-related mortality rate overall [2]. In China, RC accounted for 10.13% of all malignancies in men and 9.25% in women in 2018, reflecting a notable rise [3]. This increase is largely attributed to lifestyle changes, particularly the Westernization of dietary habits, making RC one of the leading causes of cancer-related deaths in the country [4].

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Despite ongoing advancements in treatment strategies, surgery remains the cornerstone of RC management. However, chemotherapy, radiotherapy, targeted therapy, and immunotherapy have become increasingly integrated into treatment regimens, promoting a shift toward more personalized therapeutic approaches [5, 6]. Among these, neoadjuvant chemotherapy (NACT) has emerged as a key component, as it reduces tumor burden, increases the likelihood of complete surgical resection, improves local disease control, and delays recurrence - particularly in patients with advanced or locally advanced RC [7, 8].

Nonetheless, recurrence and metastasis continue to present major challenges in RC treatment, especially in patients undergoing chemotherapy. Some patients exhibit limited response or even develop resistance to chemotherapeutic agents [9]. Conventional prognostic tools, such as the tumor-node-metastasis (TNM) stage and carcinoembryonic antigen (CEA) levels, offer some predictive value. However, under certain conditions, these indicators are insufficient for accurately assessing recurrence risk and long-term survival [10]. Therefore, identifying more accurate and accessible prognostic biomarkers has become a focus of recent research.

In this context, the albumin-to-alkaline phosphatase ratio (AAPR) and the Controlling Nutritional Status (CONUT) score have gained attention for their potential to predict cancer prognosis [11, 12]. AAPR reflects both nutritional and hepatic function, integrating serum albumin (ALB), a marker of nutritional reserves and systemic health, and alkaline phosphatase (ALP), an enzyme associated with liver and bone metabolism. A lower AAPR may indicate impaired liver function or poor nutritional status, both of which can negatively impact treatment response and prognosis, especially during chemotherapy [13].

The CONUT score, which incorporates serum ALB, total cholesterol, and lymphocyte count, provides a comprehensive assessment of nutritional and immune status. It has demonstrated prognostic value across several malignancies, including colorectal, gastric, and lung cancers, by predicting both chemotherapy response and overall survival [14]. In RC, both AAPR and the CONUT score offer meaningful insights into a patient's systemic condition and immune competence, allowing for improved prediction of treatment outcomes and recurrence risks. Moreover, they are cost-effective and non-invasive, making them ideal for routine clinical assessment.

The present study aims to investigate the associations of AAPR and CONUT score with treatment outcomes in RC patients undergoing XELOX-based chemotherapy and to evaluate their predictive value for recurrence and survival. By integrating these biomarkers into a prognostic model and validating its performance through multivariate Cox regression analysis, this study seeks to establish a robust tool for recurrence risk stratification. This model can support personalized treatment strategies based on patients' nutritional and metabolic profiles, thereby improving clinical decision-making, prolonging survival, and enhancing the overall management of RC.

Materials and methods

Sample size determination

Based on the parameters provided in the article by Xie et al [15] (risk ratio HR = 0.56, significance level α = 0.05, and statistical efficacy 80%), the process of estimating the sample size by Schoenfeld's formula was as follows:

$$D = \frac{(Z_{\alpha/2} + Z_{\beta})^2}{p_1 p_2 (ln(HR))^2}$$

assuming an equal proportional distribution of the two groups (1:1 number of people in the high ACR group and the low ACR group), the total number of events demanded was approximately 94 cases. Based on the event rates of the two groups (33% in the high ACR group and 62.8% in the low ACR group), the average event rate was calculated to be 47.9%, and the final theoretical sample size was approximately 196 cases. If non-equal allocation in the actual cohort is considered (73% in the high ACR group and 27% in the low ACR group), the total event number requirement increases to 119 cases, corresponding to a sample size of approximately 290 cases (**Figure 1**).

Sample source

This retrospective study included 389 RC patients treated at the First Affiliated Hospital

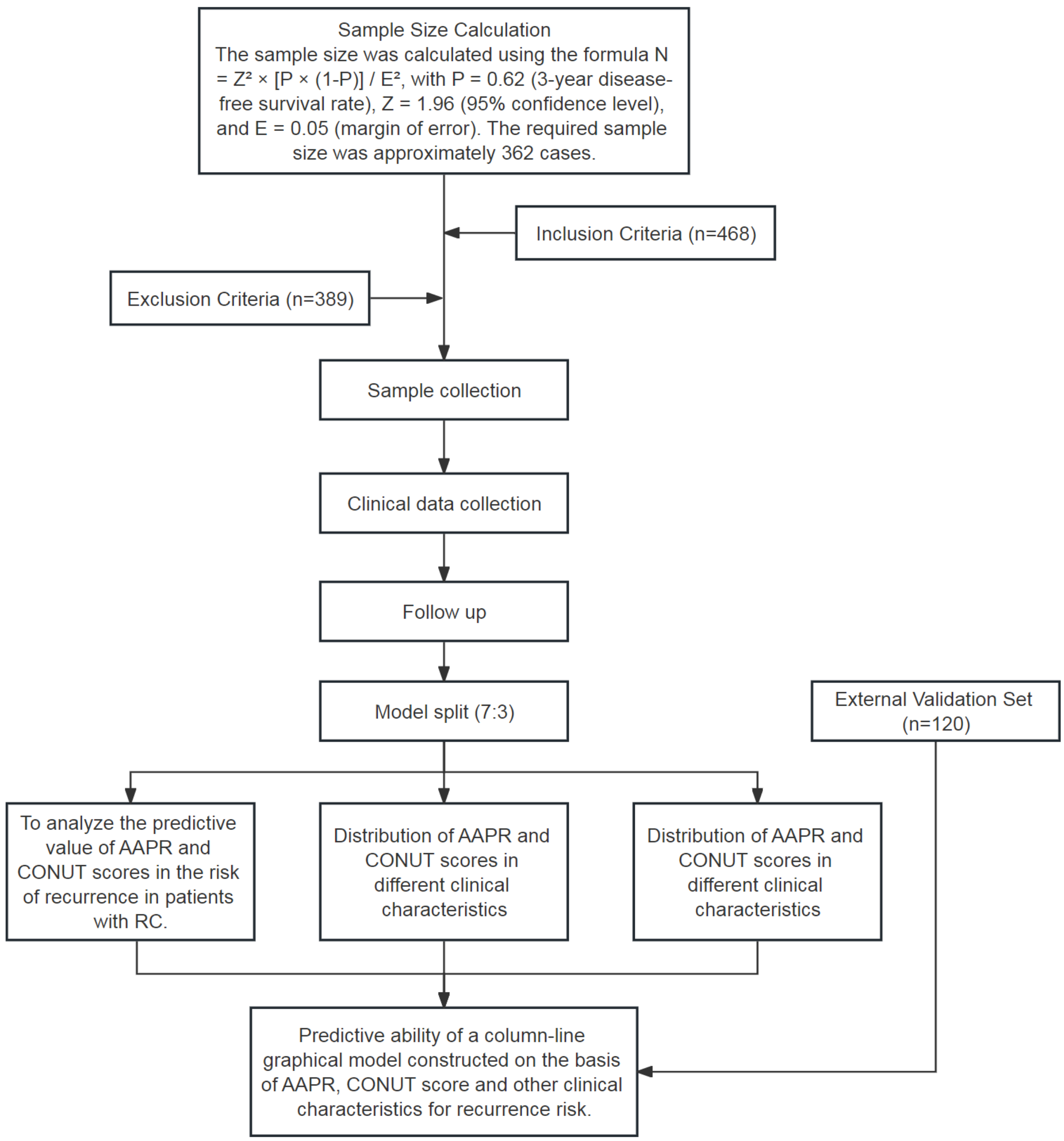

Figure 1. Study flow chart.

of Chongqing Medical University between March 2018 and February 2021. Ethical approval was obtained from the hospital's Ethics Committee. Additionally, an independent validation cohort comprising 120 RC patients treated between January 2016 and January 2018 was included. These patients met the same inclusion and exclusion criteria as the primary cohort, ensuring comparability of baseline characteristics and enabling objective validation of the prognostic model.

Inclusion and exclusion criteria

Inclusion criteria: 1. Histologically confirmed diagnosis of RC; patients must have undergone curative surgery and received adjuvant XELOX-based chemotherapy according to standard treatment guidelines [16]. 2. Age between 40 and 80 years. 3. Absence of severe comorbidities, such as advanced cardiovascular, hepatic, or renal diseases. 4. Normal hepatic and renal function, complete blood count, and comprehensive clinical records at the time of initial hospital admission.

Exclusion criteria: 1. Prior treatment with non-XELOX chemotherapy regimens. 2. Concurrent diagnosis of other malignancies or major systemic diseases. 3. Failure to initiate postoperative adjuvant chemotherapy within the required time frame. 4. Pregnant or breastfeeding women. 5. Presence of chronic liver or kidney disease, or other serious conditions (e.g., diabetes, cardiovascular diseases). 6. Long-term use of medications that may affect nutritional or immune status (e.g., immunosuppressants, corticosteroids). 7. Use of antibiotics or other medications within three months before surgery. 8. Patients with obesity (body mass index (BMI) ≥30) or extremely low levels of physical activity.

Incomplete clinical data or inability to complete follow-up.

Clinical data collection

Clinical and laboratory data for RC patients were obtained from the hospital's electronic medical records and follow-up documentation to evaluate the prognostic impact of AAPR and CONUT score in patients undergoing XELOX-based chemotherapy. The data encompassed several domains as follows.

Patient demographics: Age, gender, and medical history.

Tumor characteristics: TNM stage, tumor size, histological subtype, vascular invasion, and perineural infiltration.

Chemotherapy-related data: XELOX regimen administration, treatment efficacy assessment, and adverse events, including myelosuppression, gastrointestinal symptoms, and hand-foot syndrome.

Laboratory parameters: ALB, ALP, complete blood count indices, CONUT score, and carcinoembryonic antigen (CEA).

Follow-up data: Occurrence and timing of recurrence.

All data collection adhered to strict ethical standards. Patient information was anonymized to protect privacy, in compliance with ethical and legal regulations.

Therapeutic regimen

The XELOX regimen administered to colorectal cancer patients consisted of Capecitabine (Xeloda), manufactured by Shanghai Roche Pharmaceutical Co., Ltd., in 0.15 g tablets. The dosage was 1000 mg/m^2 per day, divided into two oral doses (500 mg/m^2 each in the morning and evening), administered for 14 consecutive days followed by a 7-day rest period, forming a 21-day treatment cycle. Capecitabine is approved under National Medicine License No. H20073023.

Oxaliplatin was administered as an intravenous infusion at a dose of 130 mg/m^2 over 2 hours, concurrently with Capecitabine, once every 21 days. It was produced by Jiangsu Hengrui Medicine Co., Ltd., in 20 mL: 100 mg vials (National Medicine License No. H20213313). The full course of treatment generally consisted of 6 to 8 cycles.

Laboratory assays

The CONUT score is a validated index that reflects both nutritional and immune function, calculated from three laboratory parameters: 1. ALB: 0-6 points; lower levels indicate worse nutritional status. 2. Lymphocyte count: 0-3 points; lower values suggest impaired immune function. 3. Total cholesterol: 0-3 points; lower levels reflect poorer nutritional reserves.

The total CONUT score ranges from 0 to 12, with higher scores indicating greater nutritional and immunological impairment and correlating with poorer outcomes in various cancers.

Laboratory Parameters and Instruments Used: 1. CEA: Measured using the Cobas e411 electrochemiluminescence immunoassay analyzer (Roche, Germany). 2. Serum ALB and ALP: Measured with the ADVIA 2400 automated biochemical analyzer (Siemens, Germany). 3. Lymphocyte count and total cholesterol: Measured using the XN-9000 automated hematology analyzer (Sysmex, Japan).

The AAPR was calculated as serum ALB (g/dL) divided by alkaline phosphatase (IU/L). A higher AAPR indicates better nutritional and hepatic status and is associated with improved prognosis.

All laboratory assessments were performed by trained technicians following standard operating procedures specific to each device. All measurements were taken within one week prior to surgery.

Follow-up

Patients were followed up via telephone calls, emails, or outpatient visits. The follow-up period spanned three years, with assessments conducted every three months. The follow-up content included documentation of recurrence status and chemotherapy-related adverse effects.

Outcome measurements

The primary outcome of this study was to assess the association between the AAPR and CONUT score with the prognosis of RC patients, particularly their predictive value for recurrence risk.

Secondary outcomes included: The distribution of AAPR and CONUT score across patients with different clinical characteristics.

The relationship between chemotherapy efficacy and adverse reactions.

The correlation between laboratory parameters (e.g., CEA levels) and recurrence.

The predictive performance of a nomogram model incorporating AAPR, CONUT score, and other clinical variables for recurrence risk estimation.

Statistical methods

All statistical analyses were performed using SPSS version 26.0 and R version 4.3.3. Quantitative data were expressed as mean ± standard deviation (Mean ± SD). The Kolmogorov-Smirnov (K-S) test was used to evaluate the normality of distributions. For normally distributed data, independent-sample t-tests were applied for group comparisons. Non-normally distributed data were described using medians and interquartile ranges and compared using the non-parametric Z-test. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. Cox regression analysis was conducted to identify recurrence-associated risk factors. The cumulative incidence function (CIF) was used for dynamic risk assessment of recurrence.

A nomogram was developed for visual recurrence risk prediction. Model performance was evaluated using calibration curves and time-dependent receiver operating characteristic (ROC) curves. A P value <0.05 was considered statistically significant.

Results

AAPR and CONUT scores in patients with different therapeutic effects

Among the 389 patients, all achieved either partial response (PR) or stable disease (SD) after chemotherapy: 155 had PR and 234 had SD. Comparison of AAPR and CONUT scores between the two groups showed no statistically significant differences in AAPR (t = 0.145, P = 0.889) or CONUT score (Z = 1.315, P = 0.180) (**Figure 2**).

AAPR and CONUT scores in patients with diverse adverse reactions

This study further analyzed the distribution of AAPR and CONUT scores among patients with various chemotherapy-related adverse effects, including bone marrow suppression, gastrointestinal reactions, and hand-foot syndrome.

For bone marrow suppression, patients in the affected group had significantly lower AAPR values compared to those without (t = 2.532, P = 0.009), while CONUT scores did not differ significantly (Z = 0.417, P = 0.671) (**Figure 3A**).

In patients with gastrointestinal reactions, neither AAPR (t = 0.501, P = 0.821) nor CONUT score (Z = -1.413, P = 0.150) showed significant differences compared to those without such reactions (**Figure 3B**).

For patients with hand-foot syndrome, no significant differences were observed in AAPR (t = -0.639, P = 0.481) or CONUT score (Z = 0.537, P = 0.585) (**Figure 3C**).

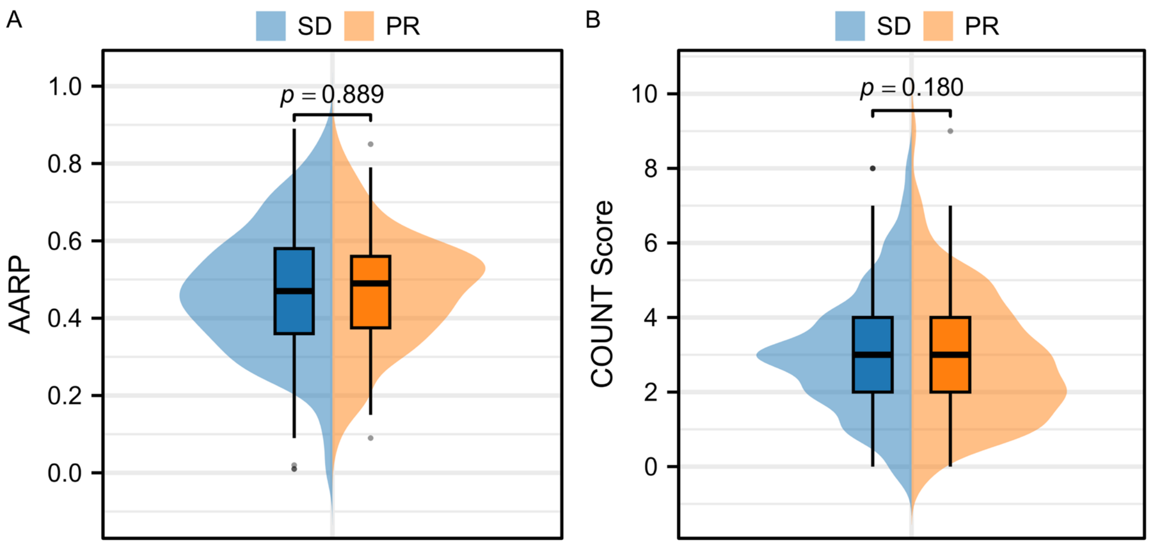

Figure 2. Comparison of AAPR and CONUT scores between patients with PR and SD after chemotherapy. A. Distribution of AAPR in PR and SD patients. B. Distribution of CONUT scores in PR and SD patients. Note: AAPR, albumin-to-alkaline phosphatase ratio; CONUT, Controlling Nutritional Status; PR, partial response; SD, stable disease.

Association of AAPR and CONUT score with clinical parameters

This study investigated the distribution patterns of the AAPR and CONUT across various clinical parameters. Results showed that AAPR was significantly associated with TNM stage (P = 0.028) and tumor size (P<0.001). Specifically, a greater proportion of patients with lower AAPR values were observed in TNM stage II and among those with tumors <5 cm. No significant associations were found between AAPR and other clinical variables, including age (P = 0.342), gender (P = 0.648), BMI (P = 0.635), vascular invasion (P = 0.495), perineural infiltration (P = 0.767), histological subtype (P = 0.339), and CEA level (P = 0.505) (**Table 1**). Variable categorizations followed the criteria outlined by Chen et al. [17].

For the CONUT score, a significant difference was observed in TNM stage, with stage II patients showing significantly lower scores (P = 0.005). Other clinical parameters - including age (P = 0.056), gender (P = 0.874), BMI (P = 0.409), tumor size (P = 0.477), vascular invasion (P = 0.141), perineural infiltration (P = 0.469), histological subtype (P = 0.896), and CEA level (P = 0.634) - did not exhibit statistically significant associations with the CONUT score (**Table 2**).

Analysis of baseline characteristics in recurrent and non-recurrent patients

This study compared baseline characteristics between patients who experienced recurrence and those who did not. Multiple variables showed significant associations with recurrence. Patients with recurrence were more likely to be: Aged 60 years or older (P = 0.011); diagnosed with tumors ≥5 cm (P = 0.017); exhibiting vascular invasion (P = 0.003); exhibiting perineural infiltration (P = 0.003); diagnosed with poorly differentiated tumors (P = 0.013); presenting CEA levels ≥5 ng/mL (P = 0.008); exhibiting lower AAPR values (P<0.001); exhibiting higher CONUT scores (P<0.001).

In contrast, no significant differences were found with respect to gender (P = 0.427), BMI (P = 0.444), or TNM stage (P = 0.178) between recurrent and non-recurrent groups (**Table 3**).

Prognostic factors and CIF curves for RC recurrence

Univariate Cox regression analysis identified several factors significantly associated with recurrence risk in rectal cancer: Age <60 years (P = 0.015, hazard ratio (HR) = 0.675); TNM stage III (P = 0.048, HR = 1.422); tumor size <5 cm (P = 0.021, HR = 0.696; absence of vascular invasion (P = 0.001, HR = 0.611); absen-

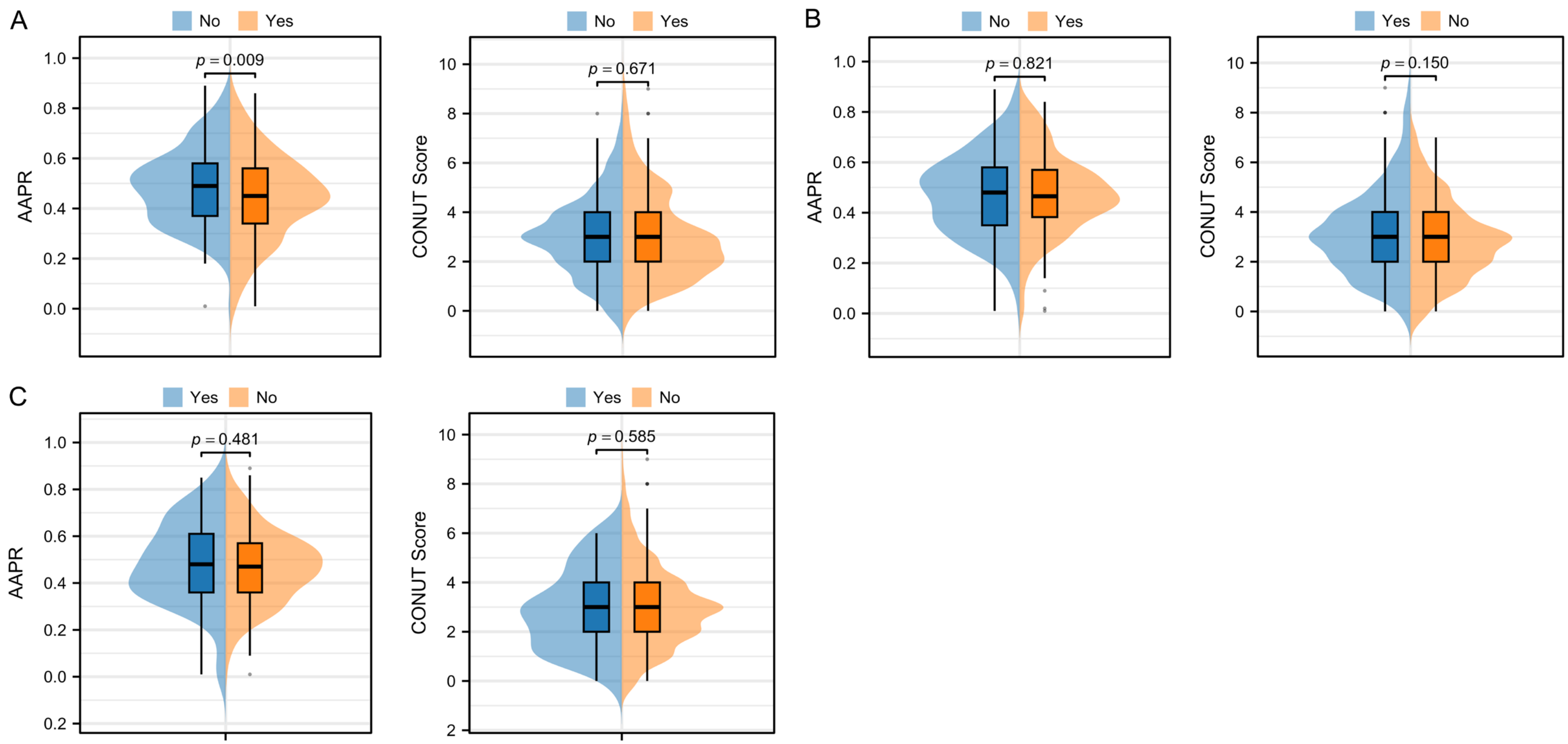

Figure 3. AAPR and CONUT scores in patients with or without adverse reactions. A. Comparison of AAPR and CONUT scores between patients with and without bone marrow suppression. AAPR was lower in patients with bone marrow suppression, while CONUT scores showed no difference. B. Comparison of AAPR and CONUT scores between patients with and without gastrointestinal reactions. No differences were observed in either AAPR or CONUT scores. C. Comparison of AAPR and CONUT scores between patients with and without hand-foot syndrome. Both AAPR and CONUT scores showed no notable differences. Note: AAPR, albumin-to-alkaline phosphatase ratio; CONUT, Controlling Nutritional Status.

Table 1. Association between AAPR and clinical characteristics

Variable	Total	AAPR≥0.439 (n = 230)	AAPR<0.439 (n = 159)	Statistic	P
Age					
≥60	224 (57.58%)	137 (59.57%)	87 (54.72%)	0.905	0.342
<60	165 (42.42%)	93 (40.43%)	72 (45.28%)		
Sex					
Male	232 (59.64%)	135 (58.7%)	97 (61.01%)	0.209	0.648
Female	157 (40.36%)	95 (41.3%)	62 (38.99%)		
BMI					
≥23	216 (55.53%)	130 (56.52%)	86 (54.09%)	0.225	0.635
<23	173 (44.47%)	100 (43.48%)	73 (45.91%)		
TNM stage					
II	111 (28.53%)	56 (24.35%)	55 (34.59%)	4.837	0.028
III	278 (71.47%)	174 (75.65%)	104 (65.41%)		
Tumor size					
≥5 cm	207 (53.21%)	141 (61.3%)	66 (41.51%)	14.796	<0.001
<5 cm	182 (46.79%)	89 (38.7%)	93 (58.49%)		
Vascular invasion					
With	173 (44.47%)	99 (43.04%)	74 (46.54%)	0.466	0.495
Without	216 (55.53%)	131 (56.96%)	85 (53.46%)		
Perineural infiltration					
With	133 (34.19%)	80 (34.78%)	53 (33.33%)	0.088	0.767
Without	256 (65.81%)	150 (65.22%)	106 (66.67%)		
Histological subtyping					
Poorly differentiated	75 (19.28%)	48 (20.87%)	27 (16.98%)	0.913	0.339
Moderately or well differentiated	314 (80.72%)	182 (79.13%)	132 (83.02%)		
CEA					
≥5 ng/ml	232 (59.64%)	134 (58.26%)	98 (61.64%)	0.445	0.505
<5 ng/ml	157 (40.36%)	96 (41.74%)	61 (38.36%)		

Note: AAPR, albumin-to-alkaline phosphatase ratio; BMI, body mass index; TNM, tumor-node-metastasis; CEA, carcinoembryonic antigen.

Table 2. Association between CONUT scores and clinical characteristics

Variable	Total	CONUT≥3 (n = 236)	CONUT<3 (n = 153)	Statistic	P
Age					
≥60	224 (57.58%)	145 (61.44%)	79 (51.63%)	3.655	0.056
<60	165 (42.42%)	91 (38.56%)	74 (48.37%)		
Sex					
Male	232 (59.64%)	140 (59.32%)	92 (60.13%)	0.025	0.874
Female	157 (40.36%)	96 (40.68%)	61 (39.87%)		
BMI					
≥23	216 (55.53%)	135 (57.2%)	81 (52.94%)	0.683	0.409
<23	173 (44.47%)	101 (42.8%)	72 (47.06%)		
TNM stage					
II	111 (28.53%)	55 (23.31%)	56 (36.6%)	8.047	0.005
III	278 (71.47%)	181 (76.69%)	97 (63.4%)		
Tumor size					
≥5 cm	207 (53.21%)	129 (54.66%)	78 (50.98%)	0.505	0.477
<5 cm	182 (46.79%)	107 (45.34%)	75 (49.02%)		

Vascular invasion					
With	173 (44.47%)	112 (47.46%)	61 (39.87%)	2.164	0.141
Without	216 (55.53%)	124 (52.54%)	92 (60.13%)		
Perineural infiltration					
With	133 (34.19%)	84 (35.59%)	49 (32.03%)	0.525	0.469
Without	256 (65.81%)	152 (64.41%)	104 (67.97%)		
Histological subtyping					
Poorly differentiated	75 (19.28%)	46 (19.49%)	29 (18.95%)	0.017	0.896
Moderately or well differentiated	314 (80.72%)	190 (80.51%)	124 (81.05%)		
CEA					
≥5 ng/ml	232 (59.64%)	143 (60.59%)	89 (58.17%)	0.226	0.634
<5 ng/ml	157 (40.36%)	93 (39.41%)	64 (41.83%)		

Note: CONUT, Controlling Nutritional Status; BMI, body mass index; TNM, tumor-node-metastasis; CEA, carcinoembryonic antigen.

Table 3. Baseline characteristics of patients with and without recurrence

Variable	Total	Recurrence (n = 168)	Non-recurrence (n = 221)	Statistic	P
Age					
≥60	224 (57.58%)	109 (64.88%)	115 (52.04%)	6.447	0.011
<60	165 (42.42%)	59 (35.12%)	106 (47.96%)		
Sex					
Male	232 (59.64%)	104 (61.9%)	128 (57.92%)	0.630	0.427
Female	157 (40.36%)	64 (38.1%)	93 (42.08%)		
BMI					
≥23	216 (55.53%)	97 (57.74%)	119 (53.85%)	0.585	0.444
<23	173 (44.47%)	71 (42.26%)	102 (46.15%)		
TNM stage					
II	111 (28.53%)	42 (25%)	69 (31.22%)	1.812	0.178
III	278 (71.47%)	126 (75%)	152 (68.78%)		
Tumor size					
≥5 cm	207 (53.21%)	101 (60.12%)	106 (47.96%)	5.664	0.017
<5 cm	182 (46.79%)	67 (39.88%)	115 (52.04%)		
Vascular invasion					
With	173 (44.47%)	89 (52.98%)	84 (38.01%)	8.658	0.003
Without	216 (55.53%)	79 (47.02%)	137 (61.99%)		
Perineural infiltration					
With	133 (34.19%)	71 (42.26%)	62 (28.05%)	8.563	0.003
Without	256 (65.81%)	97 (57.74%)	159 (71.95%)		
Histological subtyping					
Poorly differentiated	75 (19.28%)	42 (25%)	33 (14.93%)	6.216	0.013
Moderately or well differentiated	314 (80.72%)	126 (75%)	188 (85.07%)		
CEA					
≥5 ng/ml	232 (59.64%)	113 (67.26%)	119 (53.85%)	7.137	0.008
<5 ng/ml	157 (40.36%)	55 (32.74%)	102 (46.15%)		
AAPR	0.473±0.160	0.415±0.150	0.517±0.155	6.476	<0.001
CONUT score	3.00 [2.00, 4.00]	4.00 [3.00, 5.00]	2.00 [1.00, 3.00]	10.380	<0.001

Note: BMI, body mass index; TNM, tumor-node-metastasis; CEA, carcinoembryonic antigen; AAPR, albumin-to-alkaline phosphatase ratio; CONUT, Controlling Nutritional Status.

Table 4. Univariate COX regression analysis of prognostic factors for recurrence

Variable	Beta	Std Err	P	HR	Lower	Upper
Age						
≥60						
<60	-0.393	0.162	0.015	0.675	0.492	0.927
Sex						
Male						
Female	-0.130	0.159	0.415	0.878	0.643	1.199
BMI						
≥23						
<23	-0.156	0.156	0.318	0.856	0.630	1.162
TNM stage						
II						
III	0.352	0.178	0.048	1.422	1.003	2.017
Tumor size						
≥5 cm						
<5 cm	-0.362	0.158	0.021	0.696	0.511	0.948
Vascular invasion						
With						
Without	-0.493	0.155	0.001	0.611	0.451	0.827
Perineural infiltration						
With						
Without	-0.458	0.156	0.003	0.633	0.466	0.860
Histological subtyping						
Poorly differentiated						
Moderately or well differentiated	-0.539	0.178	0.003	0.584	0.411	0.828
CEA						
≥5 ng/ml						
<5 ng/ml	-0.403	0.165	0.014	0.668	0.484	0.923
AAPR	-2.913	0.476	0.000	0.054	0.021	0.138
CONUT score	0.426	0.039	0.000	1.532	1.418	1.655

Note: HR, hazard ratio; Std Err, Standard Error; BMI, body mass index; TNM, tumor-node-metastasis; CEA, carcinoembryonic antigen; AAPR, albumin-to-alkaline phosphatase ratio; CONUT, Controlling Nutritional Status.

ce of perineural infiltration (P = 0.003, HR = 0.633).

Moderate-to-well differentiation (P = 0.003, HR = 0.584), CEA <5 ng/mL (P = 0.014, HR = 0.668), a higher AAPR (P<0.001, HR = 0.054), and a lower CONUT score (P<0.001, HR = 1.532) (**Table 4**).

The CIF curves illustrated that patients with risk factors such as TNM stage III, tumor size ≥5 cm, vascular invasion, perineural infiltration, poor differentiation, CEA≥5 ng/mL, low AAPR, and high CONUT scores had a significantly higher probability of recurrence within three years, compared to control groups. These findings highlight the utility of these variables as key predictors of RC recurrence (**Figure 4**).

Multivariate COX regression analysis of prognostic factors for RC recurrence

Multivariate Cox regression analysis identified several independent predictors of RC recurrence. Specifically, TNM stage III (P = 0.040, HR = 1.453), vascular invasion (P = 0.010, HR = 0.670), perineural infiltration (P = 0.043, HR = 0.724), poorly differentiated histology (P<0.001, HR = 0.529), lower AAPR (P<0.001, HR = 0.073), and higher CONUT score (P< 0.001, HR = 1.497) were significant prognostic factors.

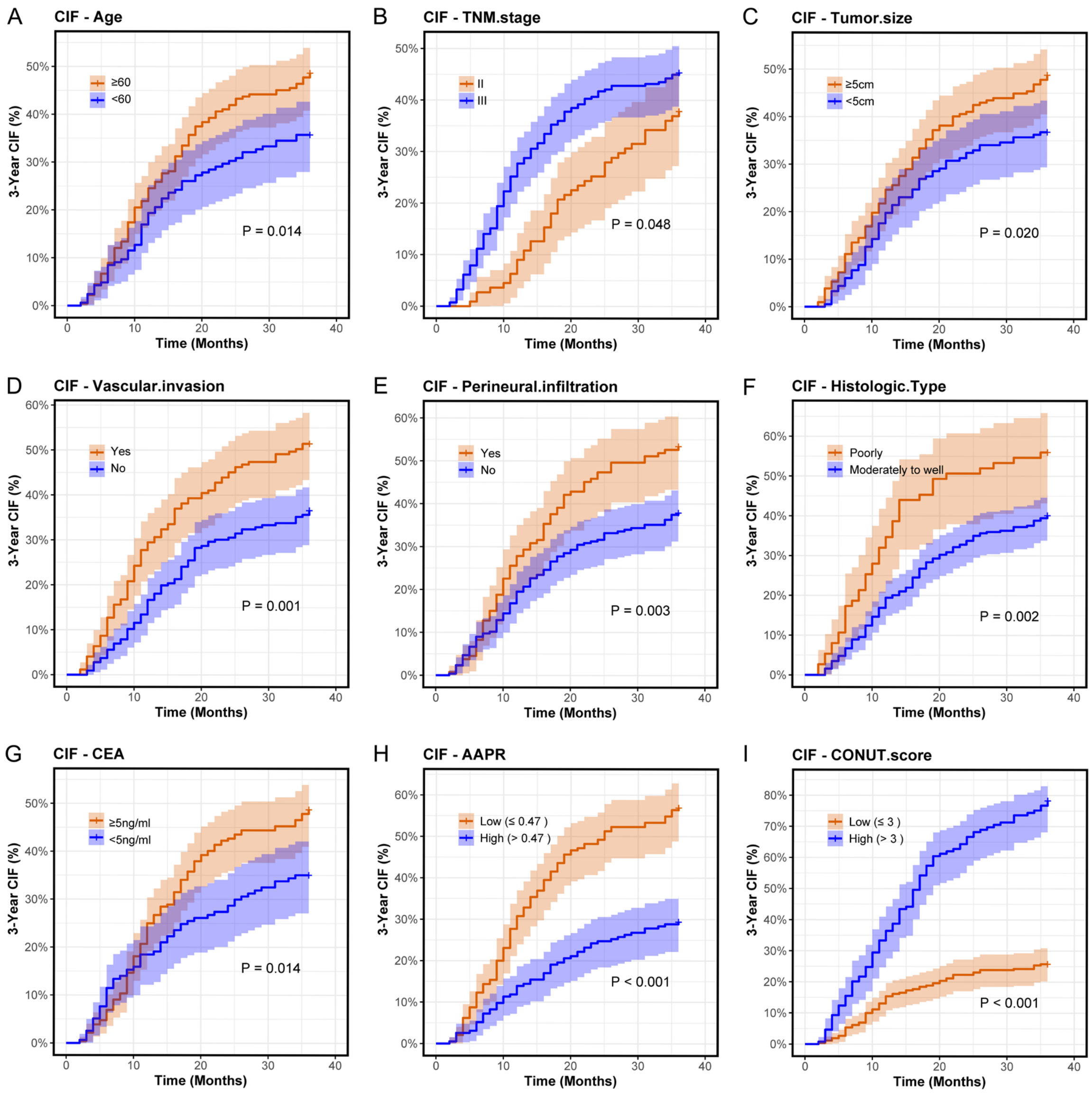

Figure 4. CIF curves for prognostic factors in rectal cancer recurrence. A. The CIF curve for age shows higher 3-year recurrence in patients aged ≥60 years compared to those aged <60 years. B. The CIF curve for TNM stage shows higher 3-year recurrence in stage III patients compared to stage II patients. C. The CIF curve for tumor size indicates higher recurrence in patients with a tumor size ≥5 cm. D. The CIF curve for vascular invasion demonstrates higher recurrence in patients with vascular invasion. E. The CIF curve for perineural infiltration reveals higher recurrence in patients with perineural infiltration. F. The CIF curve for histologic subtyping suggests higher recurrence in poorly differentiated tumors. G. The CIF curve for CEA shows higher recurrence in patients with a CEA level ≥5 ng/ml. H. The CIF curve for AAPR indicates a lower recurrence risk in patients with higher AAPR values. I. The CIF curve for CONUT score determines higher recurrence in patients with higher CONUT scores. Note: CIF, Cumulative Incidence Function; TNM, tumor-node-metastasis; CEA, carcinoembryonic antigen; AAPR, albumin-to-alkaline phosphatase ratio; CONUT, Controlling Nutritional Status.

Notably, patients with TNM stage III disease exhibited a markedly increased risk of recurrence. In contrast, tumor size <5 cm (P = 0.055, HR = 0.727) and CEA <5 ng/mL (P = 0.054, HR = 0.722) were marginally associated with lower recurrence risk (**Table 5**).

Nomogram construction based on prognostic factors

A nomogram model was constructed based on the multivariate Cox regression results. Variables included in the final model were TNM

Table 5. Multivariate COX regression analysis of prognostic factors for rectal cancer recurrence

Variable	Beta	Std Err	P	HR	Lower	Upper
Age						
≥60						
<60	0.003	0.170	0.986	1.003	0.719	1.399
TNM stage						
II						
III	0.374	0.182	0.040	1.453	1.018	2.075
Tumor size						
≥5 cm						
<5 cm	-0.318	0.166	0.055	0.727	0.525	1.007
Vascular invasion						
With						
Without	-0.400	0.156	0.010	0.670	0.494	0.910
Perineural infiltration						
With						
Without	-0.322	0.159	0.043	0.724	0.530	0.990
Histological subtyping						
Poorly differentiated						
Moderately or well differentiated	-0.637	0.180	0.000	0.529	0.371	0.753
CEA						
≥5 ng/ml						
<5 ng/ml	-0.326	0.169	0.054	0.722	0.518	1.006
AAPR	-2.618	0.460	0.000	0.073	0.030	0.180
CONUT score	0.404	0.043	0.000	1.497	1.376	1.629

Note: HR, hazard ratio; Std Err, Standard Error; TNM, tumor-node-metastasis; CEA, carcinoembryonic antigen; AAPR, albumin-to-alkaline phosphatase ratio; CONUT, Controlling Nutritional Status.

stage, vascular invasion, perineural infiltration, histological differentiation, AAPR, and CONUT score. Although tumor size and CEA levels demonstrated borderline significance (both P>0.05), they were excluded due to limited incremental predictive value.

Among the selected predictors, TNM stage, vascular invasion, and AAPR had the strongest impact on recurrence risk. CONUT score and perineural infiltration, while less influential, still contributed meaningfully to the model (**Figure 5**).

To assess model robustness, the dataset was divided into a training set, internal validation set, and external validation set. Baseline characteristics - including recurrence status, TNM stage, tumor size, vascular invasion, perineural infiltration, histological subtype, CEA, AAPR, CONUT score, and risk score - did not differ significantly among the three groups (P>0.05) (Table S1).

Performance evaluation using CIF, calibration, and time-dependent ROC curves

The model's predictive performance was comprehensively evaluated using CIF curves, calibration curves, and time-dependent ROC curves.

CIF curves for the overall dataset and individual subgroups (training and validation sets) clearly distinguished patients at higher recurrence risk. In the full cohort, the CIF curve effectively stratified patients by recurrence risk (**Figure 6A**). Similar patterns were observed in the training and validation groups, confirming the model's predictive stability (**Figure 6B**, **6C**).

Calibration curves demonstrated good agreement between predicted and observed recurrence probabilities. The overall model showed strong calibration, with a concordance index (C-index) of 0.860 (95% CI: 0.843-0.877). Likelihood ratio test (P<2e-16), Wald test (P<2e-

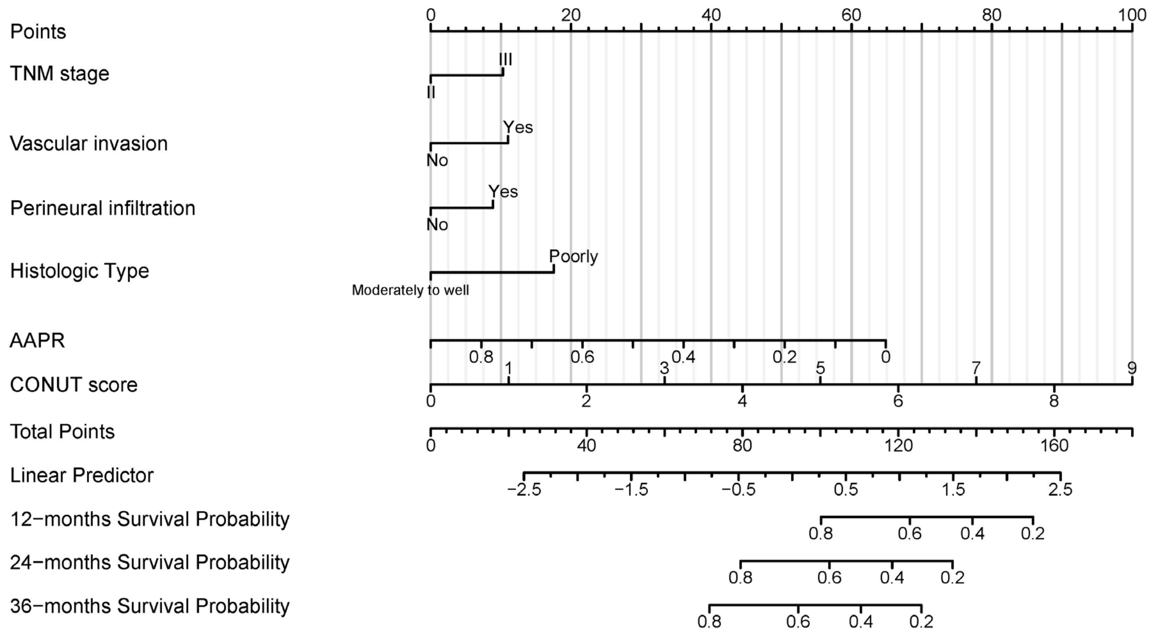

Figure 5. Nomogram for predicting survival probabilities in rectal cancer patients based on Cox Regression. Note: TNM, tumor-node-metastasis; AAPR, albumin-to-alkaline phosphatase ratio; CONUT, Controlling Nutritional Status.

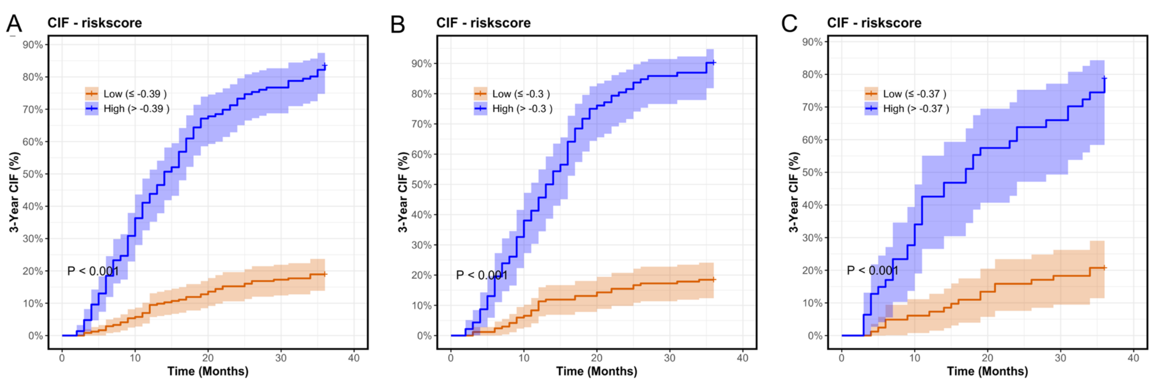

Figure 6. CIF curves for rectal cancer recurrence. A. The overall CIF curve for rectal cancer recurrence, showing the model's predictive performance in the entire dataset. B. The CIF curve for rectal cancer recurrence in the training group, highlighting the model's performance in the training dataset. C. The CIF curve for rectal cancer recurrence in the validation group, assessing the model's predictive accuracy in the validation dataset. Note: CIF, Cumulative Incidence Function.

16), and Score test (P<2e-16) all supported the model's statistical robustness.

The C-indices for the training and validation sets were 0.780 (95% CI: 0.765-0.796) and 0.793 (95% CI: 0.775-0.811), respectively, indicating consistent performance across datasets (**Figure 7A-C**).

Time-dependent ROC curves for 1-, 2-, and 3-year recurrence prediction revealed high sensitivity and specificity. The ROC curves demonstrated strong discriminatory power across all datasets. Notably, the model performed particularly well in both training and validation sets, showing excellent predictive capacity at each time point (**Figure 8A-I**).

External validation of the nomogram model for predicting recurrence in RC patients

To further assess the robustness and generalizability of the prognostic model, external validation was performed using an independent

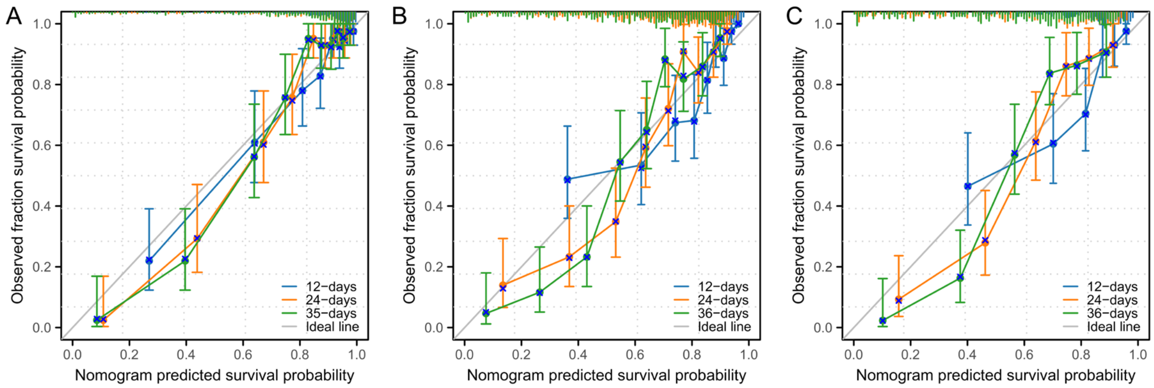

Figure 7. Calibration curves for rectal cancer prognosis. A. The overall calibration curve, showing the agreement between predicted and observed survival probabilities for the entire dataset. B. The calibration curve for rectal cancer recurrence in the training group, displaying the predictive accuracy of the model in the training dataset. C. The calibration curve for rectal cancer recurrence in the validation group, assessing the model's predictive accuracy in the validation dataset.

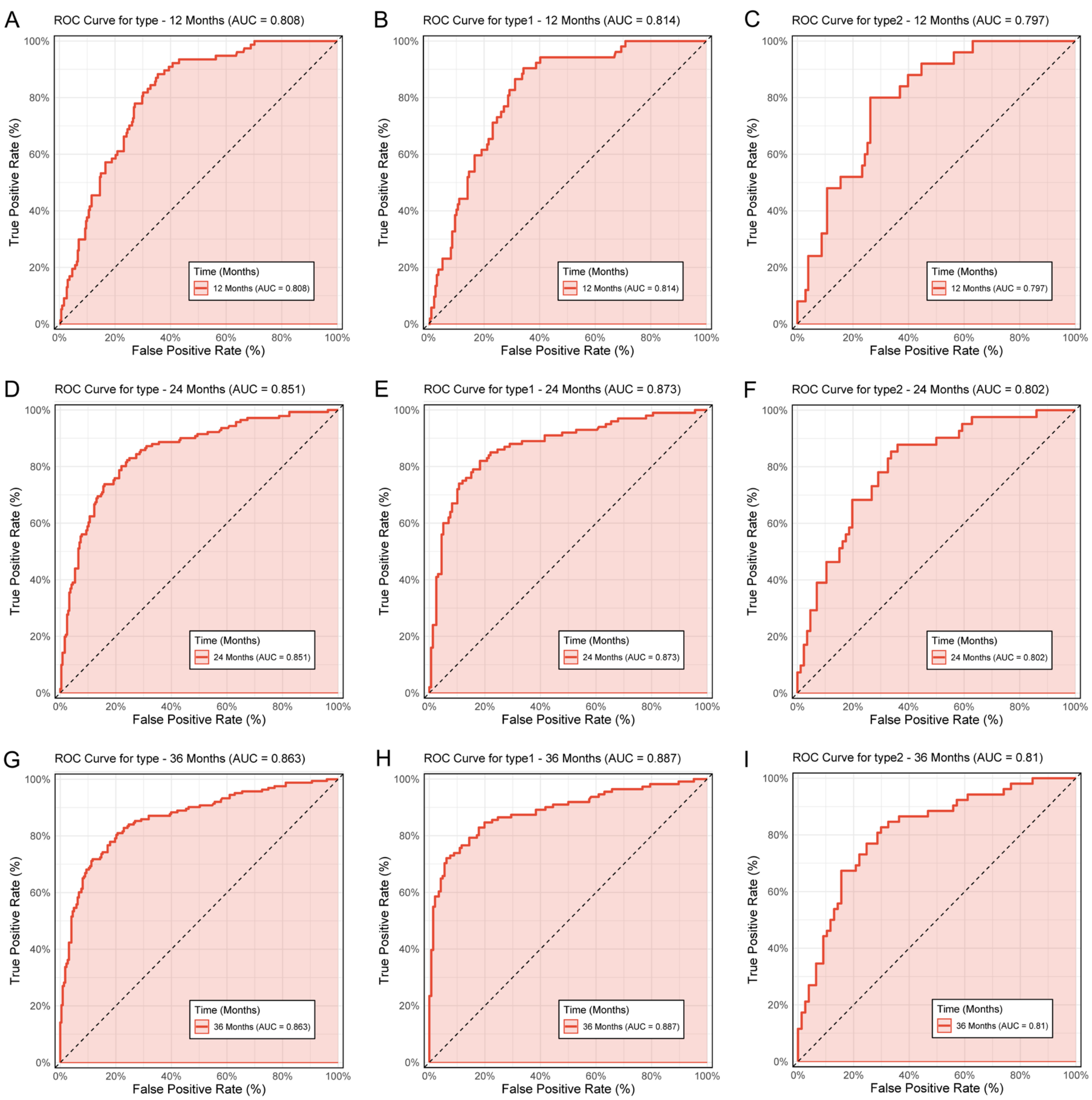

Figure 8. Time-dependent ROC curves for rectal cancer prognosis. A-C. ROC curves for the 1-year survival probability for the overall, training, and validation groups. D-F. ROC curves for the 2-year survival probability for the overall, training, and validation groups. G-I. ROC curves for the 3-year survival probability for the overall, training, and validation groups. Note: ROC, receiver operating characteristic.

cohort. The CIF curves (Figure S1A) demonstrated a significantly higher recurrence probability in the high-risk group (risk score ≥-0.73) compared to the low-risk group (P<0.001), consistent with the findings in the training cohort.

Calibration curves (Figure S1B) demonstrated strong agreement between the predicted and observed 1-, 2-, and 3-year survival probabilities, confirming the model's predictive accuracy.

Time-dependent ROC curves (Figure S2A-C) further verified the model's discriminatory power in the external validation cohort, with area under the curve values of 0.735, 0.709, and 0.709 at 1, 2, and 3 years, respectively.

The C-index for the external dataset was 0.835 (95% CI: 0.810-0.860), confirming the model's reliability in predicting recurrence risk among RC patients receiving XELOX-based chemotherapy.

Discussion

RC is one of the most prevalent malignancies globally, characterized by rising incidence and mortality rates, which severely affect patients' quality of life and long-term outcomes [18]. Although improvements in early screening and therapeutic approaches have enhanced detection rates, recurrence remains frequent, and treatment efficacy following recurrence is often limited. Previous studies [19, 20] have identified tumor biology, clinical features, and treatment responses as key contributors to RC recurrence.

In this study, we investigated two integrated indicators - the AAPR and the CONUT score - to evaluate their potential in predicting recurrence and chemotherapy-related adverse events, particularly bone marrow suppression. A nomogram model incorporating these metrics was constructed to provide an accurate and practical prognostic tool.

The AAPR, calculated from serumALB and ALP levels, serves as a surrogate marker for immunonutritional and hepatic function [21]. Previous studies have shown that lower AAPR values are associated with malnutrition, systemic inflammation, and impaired immune response, all of which may contribute to increased tumor recurrence risk. Sönmez et al. [22] reported that a lower AAPR was an independent predictor of RC recurrence, and was also significantly associated with chemotherapy-induced bone marrow suppression. Similarly, Li et al. [23] and Dalmiglio et al. [24] demonstrated that low AAPR was linked to higher recurrence rates and shorter overall survival. These findings suggest that decreased AAPR reflects compromised nutritional and immune status, potentially impairing bone marrow function and increasing susceptibility to chemotherapy toxicity.

The CONUT score, which integrates serum ALB, total cholesterol, and lymphocyte count, provides a comprehensive evaluation of a patient's nutritional and immune status [25]. A high CONUT score reflects malnutrition or immunosuppression, both of which are associated with poor treatment outcomes. Liu et al. [26] reported a significant correlation between high CONUT scores and increased RC recurrence risk. Although the association with bone marrow suppression was not statistically significant in our study, this may imply an indirect relationship between nutritional status and treatment-related adverse effects. Jiang et al. [27] also demonstrated that high CONUT scores predicted poor survival and reduced therapeutic efficacy in non-small cell lung cancer patients receiving PD-1 inhibitors, further supporting its value as a prognostic marker.

In summary, both AAPR and CONUT score are practical, non-invasive, and cost-effective biomarkers that offer valuable prognostic information. Their integration into a nomogram provides a personalized tool for assessing recurrence risk and guiding treatment strategies in RC patients undergoing XELOX-based chemotherapy.

Our findings demonstrate that a low AAPR and a high CONUT score are independent predictors of RC recurrence, highlighting the critical role of nutritional and immune status in disease progression. Patients with low AAPR values were also at significantly increased risk of developing bone marrow suppression during XELOX-based chemotherapy. This may be attributed to impaired immune function and disrupted hematopoiesis associated with malnutrition and liver dysfunction.

Consistent with Zhang et al. [28], our study found that patients with an AAPR below 0.68 had significantly reduced survival, likely due to increased chemotherapy toxicity resulting from weakened immunity. In addition to AAPR and CONUT score, other established clinical predictors of recurrence - such as TNM stage, tumor size, vascular invasion, perineural infiltration, histological subtype, and CEA level - were confirmed in our analysis, aligning with previous literature. Notably, Chen et al. [29] reported that higher CONUT scores are associated with worse survival outcomes in multiple cancers, especially in gastric cancer, where elevated CONUT scores correlated with higher recurrence rates and poorer prognosis. These findings support the notion that the CONUT score not only reflects recurrence risk but may also indirectly influence chemotherapy-related adverse events by modulating immune and nutritional status.

We also employed CIF curves to dynamically assess the predictive value of AAPR and CONUT scores for recurrence. The results confirmed their strong predictive performance, supporting their clinical applicability. This is consistent with findings from Zhang et al. [30] and Li et al. [31], who emphasized the prognostic relevance of these markers in predicting both survival and chemotherapy response. As practical and non-invasive biomarkers, AAPR and CONUT score can assist clinicians in evaluating patient condition and tailoring individualized treatment strategies. Overall, both indicators offer significant value in predicting RC recurrence and optimizing treatment plans.

Bone marrow suppression, a common complication of chemotherapy, is characterized by reduced levels of leukocytes, erythrocytes, and platelets, leading to increased risk of infection, anemia, and bleeding. Our data indicate that a low AAPR significantly elevates the risk of bone marrow suppression, reflecting impaired immunonutritional status. Malnutrition and liver dysfunction - conditions commonly associated with low AAPR - may hinder bone marrow hematopoiesis and exacerbate toxicity during chemotherapy.

Wei et al. [32] found that poor nutritional status is associated with early-onset bone marrow suppression in gastric cancer patients undergoing chemotherapy, reducing treatment tolerability and completion rates. Lyu et al. [33] suggested that hepatic dysfunction may impair drug metabolism, leading to chemotherapeutic accumulation and increased toxicity. Similarly, Bian et al. [34] demonstrated that a low prognostic nutritional index correlates with lower chemotherapy tolerance and a higher risk of bone marrow suppression. Together, these studies underscore the predictive value of AAPR in identifying patients at risk of adverse chemotherapy effects, especially bone marrow suppression, due to underlying immunonutritional deficiencies.

While this study provides important clinical insights, several limitations should be acknowledged. First, the retrospective design may introduce selection and information bias. Second, as a single-center study, the generalizability of findings may be limited. Further validation in large-scale, multi-center prospective studies is warranted. Additionally, molecular markers and genetic mutations were not included in the current analysis. Future research should explore the integration of these molecular factors into prognostic models. Investigating AAPR and CONUT scores in other tumor types and their associations with additional chemotherapy-related side effects - such as gastrointestinal toxicity or hand-foot syndrome - may further expand their clinical utility. Longitudinal monitoring of these scores, along with their potential relationship to the tumor microenvironment or metabolic pathways, may offer novel insights into therapeutic targeting and precision medicine strategies for RC.

In conclusion, the AAPR and CONUT score are independent prognostic markers for RC recurrence following XELOX-based chemotherapy. A low AAPR not only correlates with increased recurrence risk but also significantly raises the likelihood of bone marrow suppression. The nomogram model incorporating AAPR and CONUT score provides an effective and individualized tool for recurrence prediction, contributing to improved clinical decision-making and long-term management of RC patients.

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Disclosure of conflict of interest

None.

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Table S1. Baseline characteristics of patients in the training and validation groups

Variable	Total	External validation group (n = 120)	Training group (n = 260)	Validation group (n = 129)	Statistic	P
Recurrence						
With	295	74	146	75	1.026	0.599
Without	214	46	114	54		
TNM stage						
II	144	33	72	39	0.323	0.851
III	365	87	188	90		
Tumor size						
≥5 cm	265	58	139	68	0.894	0.639
<5 cm	244	62	121	61		
Vascular invasion						
With	221	48	118	55	1.012	0.603
Without	288	72	142	74		
Perineural infiltration						
With	170	37	91	42	0.696	0.706
Without	339	83	169	87		
Histological subtyping						
Poorly differentiated	96	21	50	25	0.191	0.909
Moderately or well differentiated	413	99	210	104		
CEA						
≥5 ng/ml	307	75	154	78	0.368	0.832
<5 ng/ml	202	45	106	51		
AAPR	0.48±0.16	0.49±0.17	0.47±0.16	0.48±0.16	0.661	0.517
CONUT score	3.00 [2.00, 4.00]	3.00 [2.00, 4.00]	3.00 [2.00, 4.00]	3.00 [2.00, 4.00]	0.032	0.975
Risk score	-0.73 [-1.24, -0.03]	-0.72 [-1.15, -0.03]	-0.73 [-1.31, 0.03]	-0.76 [-1.36, -0.13]	0.589	0.556

Note: TNM, tumor-node-metastasis; CEA, carcinoembryonic antigen; AAPR, albumin-to-alkaline phosphatase ratio; CONUT, Controlling Nutritional Status.

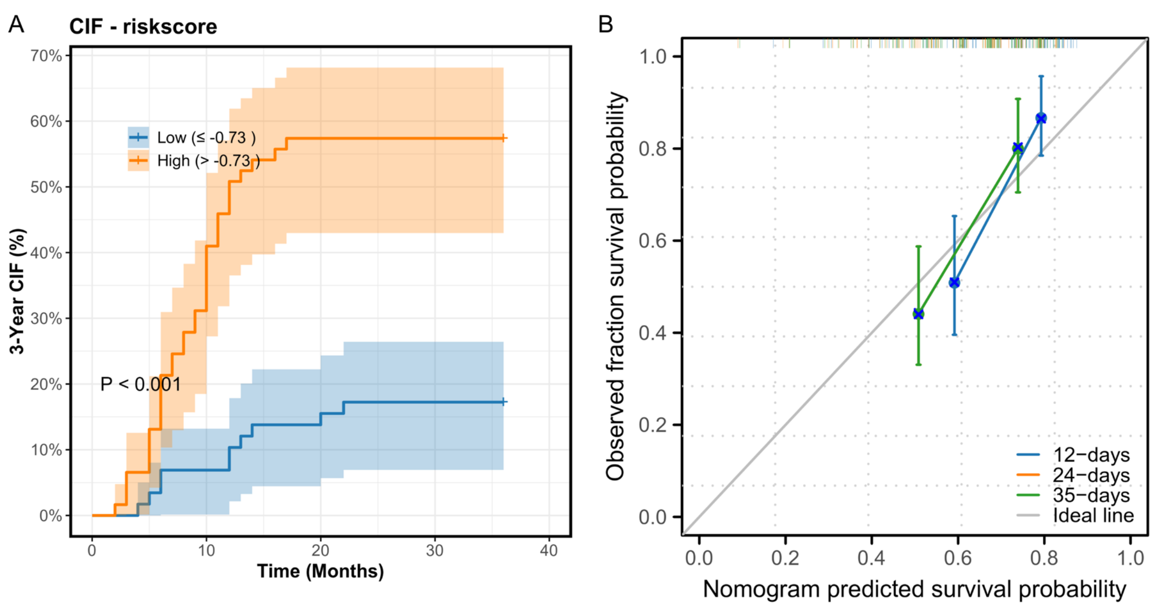

Figure S1. 3-year CIF curve and calibration curve of external validation set. A. 3-year CIF curve of external validation set. B. Calibration curve of external validation set.

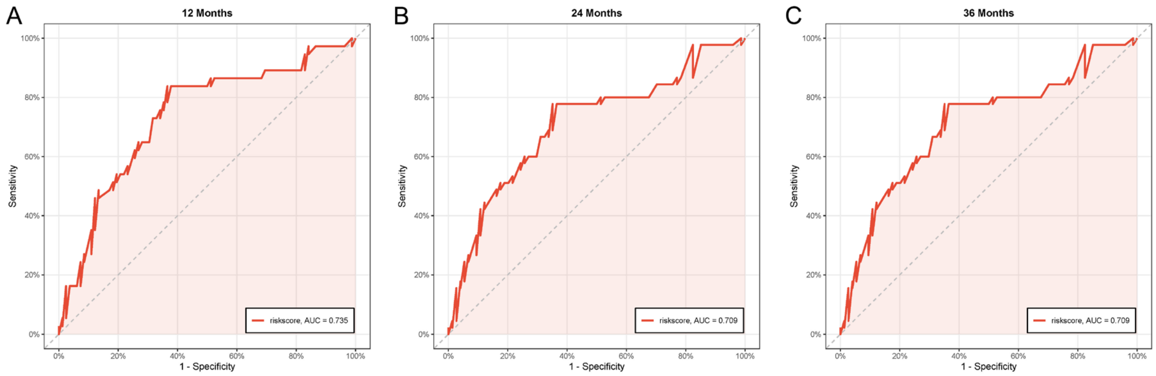

Figure S2. A 3-year time-dependent ROC curve for the external validation group. A. ROC curves for the 1-year survival probability for the overall, training, and validation groups. B. ROC curves for the 2-year survival probability for the overall, training, and validation groups. C. ROC curves for the 3-year survival probability for the overall, training, and validation groups. Note: ROC, receiver operating characteristic.