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The prognostic role of inflammation-based hematologic markers in stage I–III colorectal cancer: a retrospective analysis

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Abstract

Background Colorectal cancer (CRC) is a major global health burden with significant prognostic heterogeneity among patients with stage I-III disease. Conventional clinicopathological parameters insufficiently predict individual outcomes, highlighting the need for novel, cost-effective biomarkers. The neutrophil percentage to albumin ratio (NPAR), reflecting systemic inflammation and nutritional status, has emerged as a promising prognostic indicator, but its role in early-stage CRC remains unclear.

Methods We conducted a retrospective multicenter study involving 691 patients with stage I-III CRC from two independent centers, divided into training ($N=484$) and validation ($N=207$) cohorts. Clinicopathological features and blood-based biomarkers, including albumin-to-globulin ratio (AGR) and NPAR, were evaluated. Independent prognostic factors were identified using least absolute shrinkage and selection operator (LASSO) and multivariate Cox regression analyses. A nomogram incorporating these factors was constructed to predict overall survival (OS). Model performance was assessed by concordance index (C-index), area under the receiver operating characteristic curve (AUC), calibration plots, and decision curve analysis (DCA).

Results Nerve invasion, AGR, and NPAR were independently associated with OS (all $p<0.001$). The nomogram demonstrated strong predictive accuracy with a C-index of 0.79 (95% CI, 0.73–0.84) in the training cohort. The AUCs for 1-, 3-, and 5-year OS were 0.80, 0.84, and 0.84, respectively, and were similarly validated in the external cohort (AUCs: 0.81, 0.82, 0.80). Calibration curves showed excellent concordance between predicted and observed survival. DCA confirmed the nomogram's clinical benefit in individualized prognostication.

Conclusions This multicenter study establishes nerve invasion, AGR, and NPAR as potential independent prognostic biomarkers in stage I-III CRC. The developed nomogram provides a practical tool for personalized survival prediction, which may assist in risk stratification and treatment decision-making.

Keywords Colorectal cancer, NPAR, AGR, Nomogram model, Prognosis

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Introduction

Colorectal cancer (CRC) is among the most prevalent malignancies worldwide, accounting for approximately 10% of all cancer cases and ranking as the third leading cause of cancer-related mortality globally [1]. Despite significant advances in screening techniques and therapeutic strategies, considerable heterogeneity in prognosis persists among patients with stage I-III CRC [2–4]. The 5-year overall survival (OS) rate declines markedly from over 80% in stage I to around 50% in stage III [5]. This variability underscores the urgent need for reliable and accessible prognostic biomarkers to refine risk stratification and inform individualized treatment strategies [6, 7].

Conventional clinicopathological parameters—such as tumor-node-metastasis (TNM) staging, lymph node involvement, and tumor differentiation—have long served as the cornerstone of prognostic assessment [8]. However, these factors alone often fail to capture the complex biological behavior of individual tumors [9–11]. Accordingly, there is a growing emphasis on identifying novel, cost-effective, and readily available biomarkers, particularly those derived from routine laboratory tests, to enhance prognostic accuracy and practical clinical utility.

Systemic inflammatory responses and nutritional status have recently emerged as key determinants of cancer progression and survival [12–15]. The albumin-to-globulin ratio (AGR) [16–18], a simple yet informative indicator that reflects both nutritional reserve and systemic inflammation, has demonstrated prognostic significance in several malignancies, including CRC. Likewise, the neutrophil percentage to albumin ratio (NPAR) has been associated with poor outcomes in various solid tumors [19]. These laboratory-based biomarkers are attractive for clinical use due to their low cost, wide availability, and high reproducibility [20]. However, their prognostic relevance in early-stage CRC remains inadequately defined, and their value as independent prognostic factors beyond traditional factors has yet to be systematically validated.

Despite growing interest in inflammation- and nutrition-based indices, several important gaps persist in current literature. First, most existing CRC prognostic models focus either on clinicopathological factors or on isolated laboratory biomarkers, with limited investigation into their combined predictive value [21, 22]. Second, the utility of emerging indices such as NPAR in early-stage CRC has not been thoroughly evaluated [23, 24]. Third, to date, few validated prognostic tools have integrated both traditional and novel markers into a unified model—such as a nomogram—specifically tailored for patients with stage I-III CRC.

In this retrospective study, we aim to address these gaps by integrating clinicopathological features with easily accessible blood-based biomarkers to develop and validate a comprehensive prognostic model for patients with stage I-III CRC. Through multivariate Cox regression analysis and nomogram construction, we seek to provide a practical and individualized tool to aid clinicians in risk assessment and therapeutic decision-making. Ultimately, this approach has the potential to improve prognostic accuracy, guide tailored treatment strategies, and enhance clinical outcomes in CRC management.

Methods

Study population

This study was approved by the Ethics Committee of Nanfang Hospital, Southern Medical University, and written informed consent was obtained from all participants (approval number:2025-KY-150-12). Clinical data of CRC patients admitted to Nanfang Hospital, Southern Medical University, between January 2018 and December 2019 were retrospectively collected.

This retrospective study enrolled patients diagnosed with stage I-III CRC who underwent curative surgical resection between January 2018 and December 2019. Inclusion criteria were as follows: (1) availability of complete clinicopathological data, including tumor staging based on the AJCC TNM classification, histopathological subtype, and lymph node status; (2) availability of preoperative laboratory blood biomarkers, specifically serum albumin, globulin, neutrophil count, and platelet count; (3) absence of distant metastases at diagnosis; and (4) availability of follow-up data for OS analysis. Patients were excluded if they met any of the following criteria: (1) receipt of neoadjuvant therapy prior to surgery; (2) incomplete clinical or laboratory data; (3) history of other malignancies; (4) death within 30 days after surgery due to postoperative complications. Additionally, patients with missing or lost follow-up data were excluded from the final analysis to ensure data integrity (Fig. 1).

According to the aforementioned inclusion and exclusion criteria, clinical data from CRC patients who underwent radical surgical resection at the Affiliated Tumor Hospital of Xinjiang Medical University between January 2018 and December 2019 were collected as an external validation cohort for model validation (Approval No.: KY20250304).

The median follow-up time was estimated using the inverse Kaplan-Meier method, which was 72 months for the training cohort and 79 months for the test cohort. The final follow-up was conducted in September 2024. Overall survival (OS) was defined as the duration from surgery to death from any cause or the last follow-up. The total number of deaths was 168 in the training cohort and 17 in the test cohort.

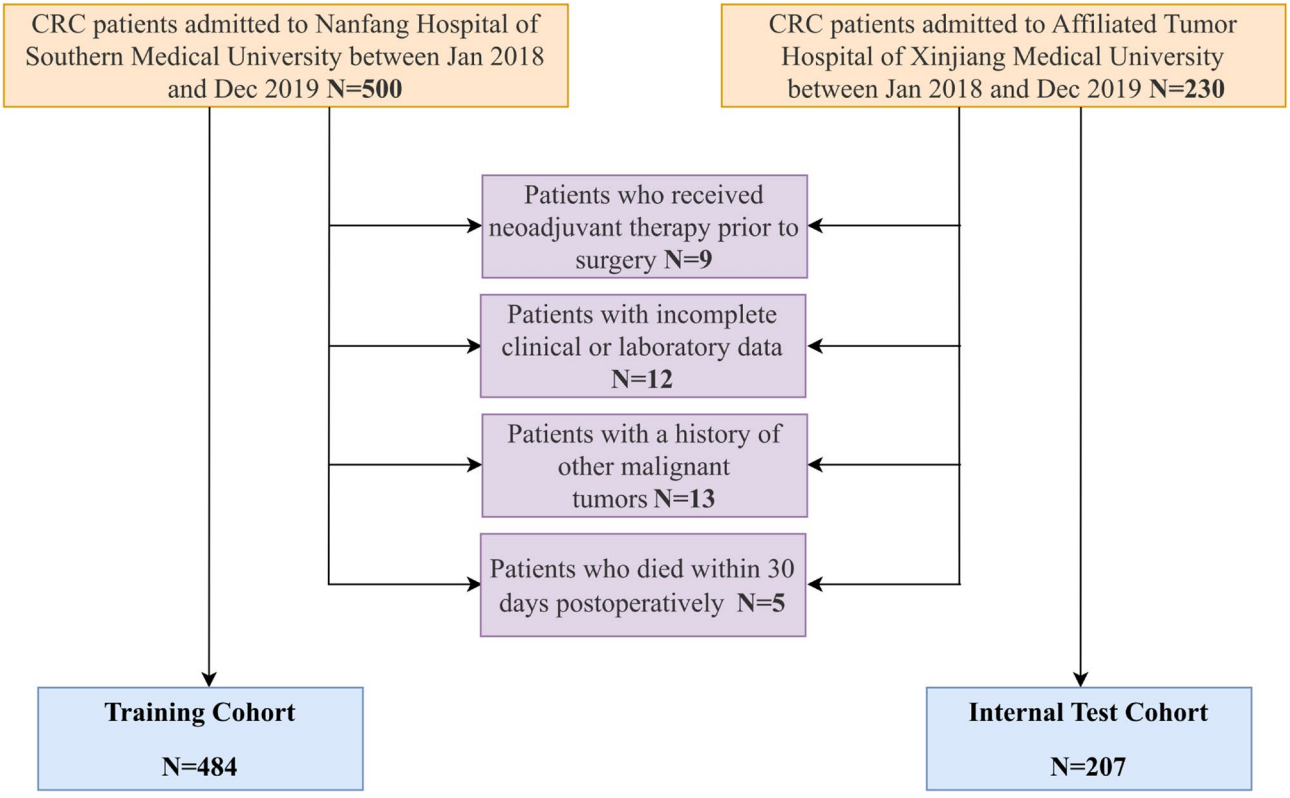

Fig. 1 Flowchart of the process of data collection

Laboratory blood biomarkers

Multiple laboratory blood biomarkers reported to have prognostic value were retrospectively collected and calculated. All biomarker measurements were obtained within one week prior to surgery or other therapeutic interventions. The calculation formula was as follows. Neutrophil lymphocyte ratio(NLR) = neutrophil counts/lymphocyte counts [25]; Monocyte-to-lymphocyte ratios(MLR) = monocyte counts/lymphocyte counts [26]; Platelet lymphocyte ratio(PLR) = platelet counts/lymphocyte counts [27]; Pan-immune-inflammation value(PIV)=[neutrophil counts×platelet counts×monocyte counts]/lymphocyte counts [28]; Systemic immune-inflammation index(SII) = platelet counts×absolute neutrophil counts/absolute lymphocyte counts [29]; Systemic inflammation response index(SIRI) = neutrophil counts ×monocyte counts/lymphocyte counts [30]; PNI = albumin + 5×lymphocyte counts [31]; Geriatric Nutritional Risk Index(GNRI) = 1.489×albumin + 41.7×present body weight/ideal body weight [32]; AGR = albumin/globulin [33]; NPAR = neutrophil percentage (%)×100/albumin [23].

Statistical analysis

Data analysis was performed using SPSS software version 25.0 and R software version 4.2.3. Continuous variables with non-normal distributions were summarized as medians with interquartile ranges (IQR). In univariate analyses, categorical variables were compared using the chi-square test or Fisher's exact test as appropriate, while continuous variables were analyzed using the Student's t-test or the Mann-Whitney U test based on data distribution. For multivariate analysis, the training cohort was subjected to least absolute shrinkage and selection operator (LASSO) logistic regression to identify independent prognostic factors and to construct a survival prediction nomogram. LASSO regression was implemented using the "glmnet" package in R. The optimal penalty parameter (λ) was determined via 10-fold cross-validation, and the λ value corresponding to the minimum mean cross-validation error (λ-min) was selected to screen for prognostic variables. To calibrate the nomogram, internal validation was performed using 1000 bootstrap resamples to assess the agreement between predicted survival probabilities and actual observed outcomes. The proportional hazards assumption of the Cox proportional hazards model was evaluated using Schoenfeld residuals, and no significant violations were detected. The predictive performance of the model was evaluated using receiver operating characteristic (ROC) curves, with the area under the curve (AUC) values ranging from 0.5 (no discrimination) to 1.0 (perfect discrimination). Calibration of the nomogram was assessed by calibration plots comparing predicted versus observed survival probabilities. Additionally, decision curve analysis (DCA) was conducted to evaluate the

clinical utility of the model by quantifying the net benefit across a range of threshold probabilities.

Results

Baseline demographics and clinical characteristics

Baseline demographic and clinical characteristics of the study population were analyzed and compared between the training cohort ($N = 484$) and the validation cohort ($N = 207$), as summarized in Table 1. Both cohorts demonstrated balanced distributions across the majority of variables. No significant differences were observed in sex distribution or age stratification. Lifestyle factors, including smoking and alcohol consumption, were similarly distributed between groups. However, certain clinical parameters exhibited statistically significant differences. The proportion of patients with elevated carcinoembryonic antigen (CEA) levels was significantly lower in the validation cohort compared to the training cohort (30.4% vs. 39.5%, $p = 0.024$). In contrast, the trend toward a lower proportion of elevated carbohydrate antigen 19 – 9 (CA19-9) in the validation cohort did not reach statistical significance (6.3% vs. 10.5%, $p = 0.077$). Continuous inflammatory and nutritional biomarkers showed no significant inter-group differences. Overall, the two cohorts were highly comparable in terms of baseline characteristics, with only modest differences observed in select clinical and tumor-related variables. These findings support the appropriateness of both cohorts for subsequent development and external validation of the prognostic prediction model.

Univariate analysis of prognostic factors

In the univariate Cox proportional hazards regression analysis (Table 2), several demographic, clinical, and laboratory variables were significantly associated with OS in the training cohort. Inflammation- and nutrition-related biomarkers demonstrated significant prognostic value. Notably, NLR was associated with increased mortality risk (HR = 1.34; 95% CI, 1.25–1.45; $p < 0.001$). MLR showed an exceptionally high hazard ratio (HR = 103.28; 95% CI, 45.10–236.53.10.53; $p < 0.001$), indicating strong predictive power. PLR, PIV, SII, and SIRI were also significantly associated with OS (all $p < 0.001$). Conversely, higher PNI and GNRI were protective factors, correlating with improved survival (HR = 0.87; 95% CI, 0.84–0.90; $p < 0.001$ and HR = 0.96; 95% CI, 0.94–0.98; $p < 0.001$, respectively). The AGR was strongly protective, with a notably low hazard ratio (HR = 0.04; 95% CI, 0.02–0.09; $p < 0.001$). Additionally, ALI and NPAR were significantly associated with poorer prognosis (both $p < 0.001$).

Independent prognostic factors for CRC patients

To identify key prognostic factors from multiple variables, the LASSO regression model was employed with 10-fold cross-validation. As illustrated in Fig. 2A, the LASSO model was optimized by minimizing the partial likelihood deviance. The cross-validation curve exhibited a distinct minimum at log(λ)=−3.5. When this optimal λ value was applied, the model retained six non-zero coefficients (Fig. 2B), indicating strong associations between these variables and the study outcomes. The ultimately selected prognostic factors were subsequently incorporated into a multivariate Cox proportional hazards model for further analysis. The final established Cox proportional hazards model included three independent prognostic factors: nerve invasion, AGR and NPAR (Table 3). This multivariate model was adjusted for demographic, clinical, and pathological variables, including age, gender, BMI, smoking, alcohol consumption, CEA, CA19-9, macroscopic appearance, histological type, degree of differentiation, intravascular tumor emboli, T stage, N stage, and TNM stage.

Development and validation of the nomogram model for predicting the overall survival

To evaluate the predictive efficacy of nerve invasion, AGR, and NPAR for overall survival, a nomogram was constructed based on the prognostic factors selected through multivariate regression analysis in the training cohort (Fig. 3). To further visualize the impact of key prognostic factors on survival, K-M survival curves were plotted for significant factors identified in the multivariate Cox regression analysis. As shown in Fig. 4, patients with positive nerve invasion exhibited significantly worse overall survival compared to those with negative nerve invasion (log-rank test, $p < 0.001$) (Fig. 4A). Similarly, the low AGR group and patients with high NPAR showed poorer prognosis ($p < 0.001$) (Fig. 4B and C). The predictive C-index of the training cohort was 0.79 (95% confidence interval: 0.73–0.84), with AUC values of 0.800, 0.844, and 0.842 for 1-, 3-, and 5-year survival, respectively (Fig. 5A). The external validation cohort demonstrated corresponding AUC values of 0.812, 0.817, and 0.804 at the same time points (Fig. 5B), indicating good predictive performance of the model. Calibration curves generated through 1000 bootstrap resampling iterations revealed excellent agreement between the observed and predicted 1-, 3-, and 5-year overall survival rates in both the training and validation cohorts (Fig. 6). Furthermore, DCA further validated the significant clinical efficacy of the training cohort and validation cohort in predicting 1-year, 3-year, and 5-year survival probabilities (Fig. 7A-F).

Discussion

In this multicenter retrospective study, we developed and validated a novel prognostic model for stage I-III CRC by integrating clinicopathological features with accessible

Table 1 Patient demographics and baseline characteristics

Characteristic	Cohort		*P*-value[2]
	Training Cohort *N* = 484[1]	Test Cohort *N* = 207[1]	
Gender			0.529
Male	293 (60.5%)	120 (58.0%)	
Female	191 (39.5%)	87 (42.0%)	
Age			0.409
< 60	208 (43.0%)	96 (46.4%)	
≥ 60	276 (57.0%)	111 (53.6%)	
BMI			0.070
<18.5	8 (1.7%)	8 (3.9%)	
18.5–24	223 (46.1%)	81 (39.1%)	
24–28	198 (40.9%)	85 (41.1%)	
≥ 28	55 (11.4%)	33 (15.9%)	
Smoking			0.972
Yes	156 (32.2%)	67 (32.4%)	
No	328 (67.8%)	140 (67.6%)	
Alcohol consumption			0.891
Yes	91 (18.8%)	38 (18.4%)	
No	393 (81.2%)	169 (81.6%)	
CEA			0.024
Normal	293 (60.5%)	144 (69.6%)	
High	191 (39.5%)	63 (30.4%)	
CA199			0.077
Normal	433 (89.5%)	194 (93.7%)	
High	51 (10.5%)	13 (6.3%)	
Gross appearance			0.049
Bulge	141 (29.1%)	76 (36.7%)	
Infiltration or ulcer	343 (70.9%)	131 (63.3%)	
Histological type			0.340
Adenocarcinoma	446 (92.1%)	195 (94.2%)	
Mucinous adenocarcinoma or signet ring cell cancer	38 (7.9%)	12 (5.8%)	
Differentiated degree			0.235
Well/Moderate	83 (17.1%)	28 (13.5%)	
Poor/Undifferentiated	401 (82.9%)	179 (86.5%)	
Nerve invasion			0.461
Negative	404 (83.5%)	168 (81.2%)	
Positive	80 (16.5%)	39 (18.8%)	
Intravascular tumor emboli			0.253
Negative	389 (80.4%)	174 (84.1%)	
Positive	95 (19.6%)	33 (15.9%)	
T stage			0.816
T1-T2	106 (21.9%)	47 (22.7%)	
T3-T4	378 (78.1%)	160 (77.3%)	
N stage			0.260
N0	282 (58.3%)	130 (62.8%)	
N1	124 (25.6%)	41 (19.8%)	
N2	78 (16.1%)	36 (17.4%)	
TNM stage			0.326
I	95 (19.6%)	43 (20.8%)	
II	187 (38.6%)	90 (43.5%)	
III	202 (41.7%)	74 (35.7%)	
PLR			0.566
Median (Q1, Q3)	130 (102, 171)	132 (107, 176)	

Table 1 (continued)

Characteristic	Cohort		*P*-value[2]
	Training Cohort *N* = 484[1]	Test Cohort *N* = 207[1]	
PIV			0.563
Median (Q1, Q3)	218 (134, 342)	204 (134, 324)	
SII			0.545
Median (Q1, Q3)	480 (333, 705)	475 (321, 678)	
SIRI			0.533
Median (Q1, Q3)	0.86 (0.59, 1.39)	0.84 (0.61, 1.27)	
PNI			0.639
Median (Q1, Q3)	50.2 (46.7, 53.0)	50.2 (47.5, 52.9)	
GNRI			0.395
Median (Q1, Q3)	107 (101, 112)	107 (102, 114)	
AGR			0.485
Median (Q1, Q3)	1.49 (1.33, 1.67)	1.50 (1.32, 1.74)	
ALI			0.341
Median (Q1, Q3)	481 (368, 662)	493 (379, 729)	
NPAR			0.260
Median (Q1, Q3)	14.71 (12.99, 16.43)	14.42 (12.85, 16.08)	

[1]n (%);[2]Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum test

BMI body mass index, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19 – 9

blood-based biomarkers, including the NPAR and AGR. The results demonstrated that nerve invasion, AGR and NPAR were independent prognostic factors for overall survival. The combination of these three factors in a nomogram model provided favorable prognostic stratification capability. To improve clinical applicability, the total score generated by the nomogram was used to categorize patients into distinct risk groups. This risk stratification approach may help identify certain patients with earlier TNM stages but higher comprehensive risk (e.g., some stage II patients), thereby facilitating the formulation of more aggressive adjutant treatment strategies for these individuals. Thus, the model may serve as a valuable supplement to the TNM staging system, enabling individualized survival risk prediction and supporting treatment decision-making.

The significant prognostic value of nerve invasion aligns with previous reports emphasizing its role as a hallmark of aggressive tumor biology and a driver of poor clinical outcomes in CRC [34, 35]. This pathological feature likely reflects tumor invasiveness and interaction with the perineural microenvironment, which may facilitate metastatic dissemination [36].

This study highlights the clinical significance of inflammatory and nutritional biomarkers, particularly NPAR and AGR, which integrate systemic inflammation and nutritional status—both key contributors to cancer progression [37, 38]. The neutrophil percentage reflects systemic inflammatory burden that promotes tumor growth and immune evasion [39], whereas albumin represents nutritional reserves and overall patient condition [40]. Notably, evidence from radiotherapy combined with immunotherapy suggests that systemic inflammatory markers can directly influence treatment responsiveness and immune modulation in malignant tumors [41, 42]. The composite marker NPAR demonstrated significant independent prognostic value, outperforming multiple other inflammatory indicators. Similarly, AGR exhibited a protective effect consistent with its role in reflecting the immune-nutritional balance [43]. Unraveling the role of disulfidptosis-related LncRNAs in colon cancer: a prognostic indicator for immunotherapy response, chemotherapy sensitivity, and insights into cell death [44].

Systemic inflammation is widely recognized as a critical driver of tumor initiation, progression, and metastasis [45]. Inflammatory cells and mediators within the tumor microenvironment [46, 47]—such as neutrophils [48], macrophages [49], and pro-inflammatory cytokines including IL-6, TNF-α, and IL-1β [50]—activate diverse signaling pathways that enhance tumor cell proliferation, invasion, and angiogenesis [51]. Notably, neutrophils participate not only in host defense but also in promoting tumor immune escape through the release of reactive oxygen species (ROS), proteases, and immunosuppressive cytokines [52–55]. Moreover, neutrophils facilitate tumor-associated neovascularization, providing nutrients that support tumor growth and dissemination [56]. Therefore, elevated neutrophil percentages often indicate a pronounced pro-tumor inflammatory state [57].

Conversely, nutritional status, as an indicator of the patient's overall health, also plays a vital role in cancer prognosis [58]. Albumin, the predominant plasma protein, reflects not only nutritional intake and metabolism but also indirectly indicates liver function and chronic

Table 2 Results of univariate Cox regression

Characteristic	*N*	Event *N*	HR	95% CI	*P*-value
Gender					
Male	293	89	-	-	
Female	191	47	0.79	0.55, 1.13	0.191
Age					
< 60	208	48	-	-	
≥ 60	276	88	1.43	1.01, 2.03	0.046
BMI					
<18.5	8	4	-	-	
18.5–24	223	55	0.37	0.13, 1.02	0.054
24–28	198	55	0.41	0.15, 1.13	0.086
≥ 28	55	22	0.66	0.23, 1.92	0.449
Smoking					
Yes	156	40	-	-	
No	328	96	1.22	0.85, 1.77	0.284
Alcohol consumption					
Yes	91	26	-	-	
No	393	110	1.05	0.68, 1.61	0.825
CEA					
Normal	293	64	-	-	
High	191	72	1.91	1.36, 2.67	< 0.001
CA199					
Normal	433	110	-	-	
High	51	26	2.52	1.64, 3.87	< 0.001
Gross appearance					
Bulge	141	27	-	-	
Infiltration or ulcer	343	109	1.80	1.18, 2.74	0.006
Histological type					
Adenocarcinoma	446	122	-	-	
Mucinous adenocarcinoma or signet ring cell cancer	38	14	1.46	0.84, 2.53	0.183
Differentiated degree					
Well/Moderate	83	38	-	-	
Poor/Undifferentiated	401	98	0.42	0.29, 0.61	< 0.001
Nerve invasion					
Negative	404	96	-	-	
Positive	80	40	2.69	1.86, 3.89	< 0.001
Intravascular tumor emboli					
Negative	389	104	-	-	
Positive	95	32	1.44	0.97, 2.14	0.072
T stage					
T1-T2	106	9	-	-	
T3-T4	378	127	4.67	2.38, 9.19	< 0.001
N stage					
N0	282	58	-	-	
N1	124	46	1.93	1.31, 2.84	< 0.001
N2	78	32	2.60	1.69, 4.01	< 0.001
TNM stage					
I	95	7	-	-	
II	187	54	4.46	2.03, 9.80	< 0.001
III	202	75	6.14	2.83, 13.33	< 0.001
NLR	484	136	1.34	1.25, 1.45	< 0.001
MLR	484	136	103.28	45.10, 236.53	< 0.001
PLR	484	136	1.01	1.01, 1.01	< 0.001
PIV	484	136	1.00	1.00, 1.00	< 0.001

Table 2 (continued)

Characteristic	*N*	Event *N*	HR	95% CI	*P*-value
SII	484	136	1.00	1.00, 1.00	< 0.001
SIRI	484	136	1.51	1.40, 1.62	< 0.001
PNI	484	136	0.87	0.84, 0.90	< 0.001
GNRI	484	136	0.96	0.94, 0.98	< 0.001
AGR	483	136	0.04	0.02, 0.09	< 0.001
ALI	484	136	1.00	1.00, 1.00	< 0.001
NPAR	484	136	1.33	1.26, 1.40	< 0.001

CI Confidence Interval, *HR* Hazard Ratio

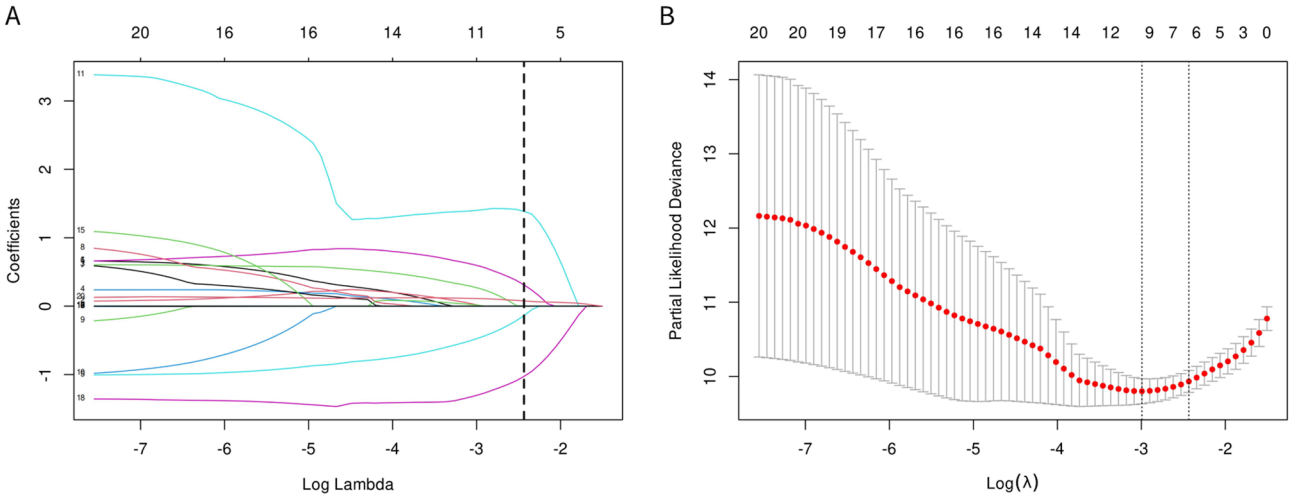

Fig. 2 Feature variable selection based on least absolute shrinkage and selection operator regression. **A** Tenfold cross-validation chart; (**B**) Shrinkage coefficient chart

Table 3 Results of multivariate Cox regression for training cohort

Characteristic	*N*	Event *N*	HR	95% CI	*P*-value
Nerve invasion					
Negative	403	96	-	-	
Positive	80	40	2.68	1.85, 3.89	< 0.001
AGR	483	136	0.13	0.06, 0.26	< 0.001
NPAR	483	136	1.25	1.18, 1.32	< 0.001

Multivariate analysis was adjusted for the following variables: gender, age, BMI, smoking, alcohol consumption, CEA, CA199, gross appearance, histological type, differentiated degree, nerve invasion, intravascular tumor emboli, T stage, N stage, and TNM stage

inflammatory status [59, 60]. Hypoalbuminemia frequently signals malnutrition and chronic inflammation [61]. Studies have demonstrated that malnutrition impairs immune competence, diminishes treatment tolerance, and hampers recovery [62]. Nutritional deficiency can also lead to immune cell dysfunction, weakening anti-tumor immune responses and accelerating tumor progression [63].

As a ratio of neutrophil percentage to albumin, NPAR effectively integrates information on pro-inflammatory states and nutritional deficits, offering a more comprehensive assessment of the patient's systemic condition [21]. Its observed prognostic value underscores the intricate interplay between inflammation and nutrition in tumor biology and patient survival. Similarly, the protective effect of AGR may be attributed to its reflection of plasma protein composition, where a low AGR is commonly associated with heightened chronic inflammation and compromised immune function, further supporting the pivotal role of immune-nutritional balance in cancer prognosis [17, 64]. In summary, inflammation and nutritional status jointly influence tumor development and clinical outcomes through complex biological mechanisms. Biomarkers that combine these two dimensions, such as NPAR and AGR, provide a more accurate reflection of the patient's overall pathophysiological state, holding significant potential for clinical application and future research.

Compared to traditional prognostic models relying solely on TNM staging and clinicopathological factors, our integrated model offers improved predictive accuracy, as demonstrated by the high concordance index and consistent validation in an external cohort. The nomogram's strong calibration and decision curve analyses further underscore its potential clinical applicability in individualized risk assessment and therapeutic decision-making.

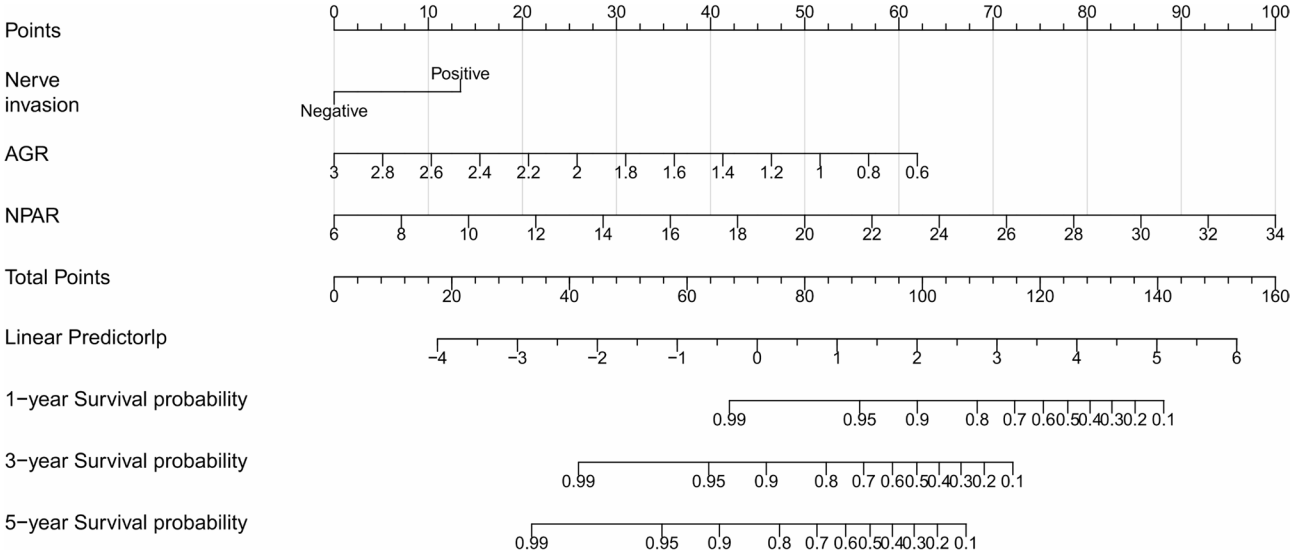

Fig. 3 Nomogram prediction model

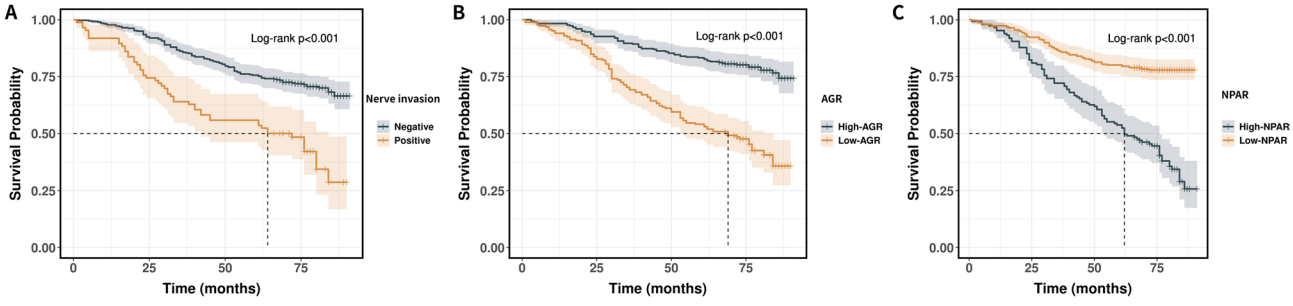

Fig. 4 Kaplan-Meier survival curves for significant prognostic factors. **A** Nerve invasion; (**B**) AGR; (**C**) NPAR

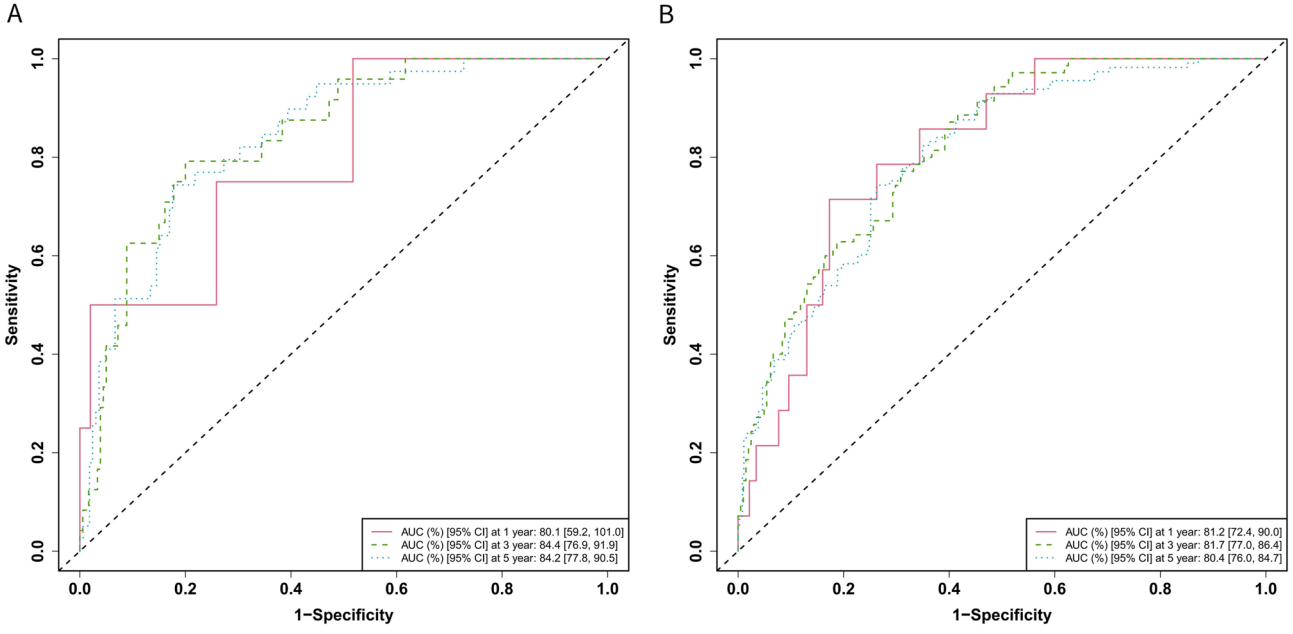

Fig. 5 ROC curves of the nomogram prediction model in the training cohort (**A**) and validation cohort (**B**). The red solid line represents 1-year survival, the green dashed line represents 3-year survival, and the blue dotted line represents 5-year survival

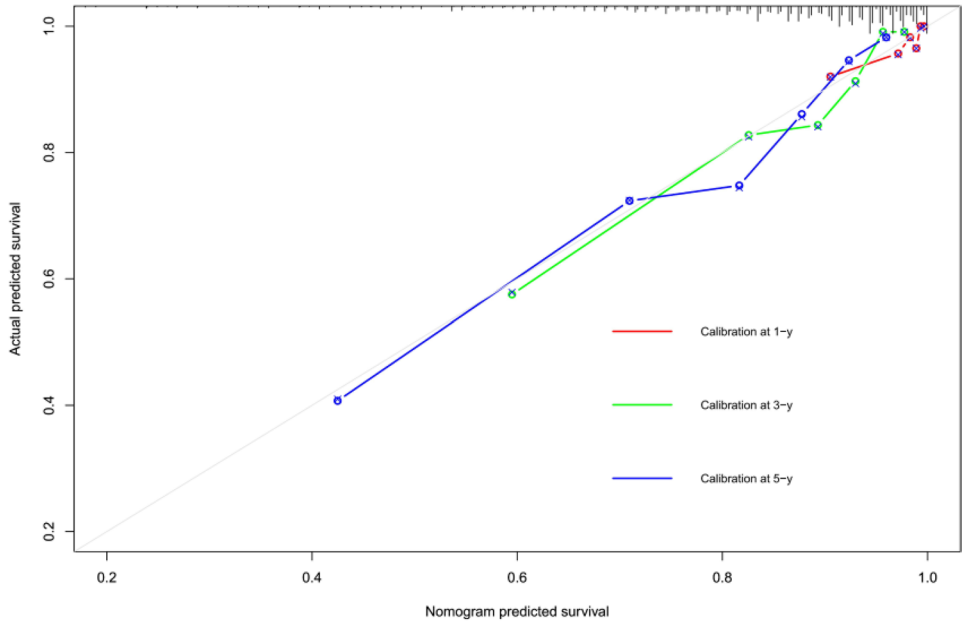

Fig. 6 Calibration curves of the nomogram to predict OS at 1-, 3-, and 5-year

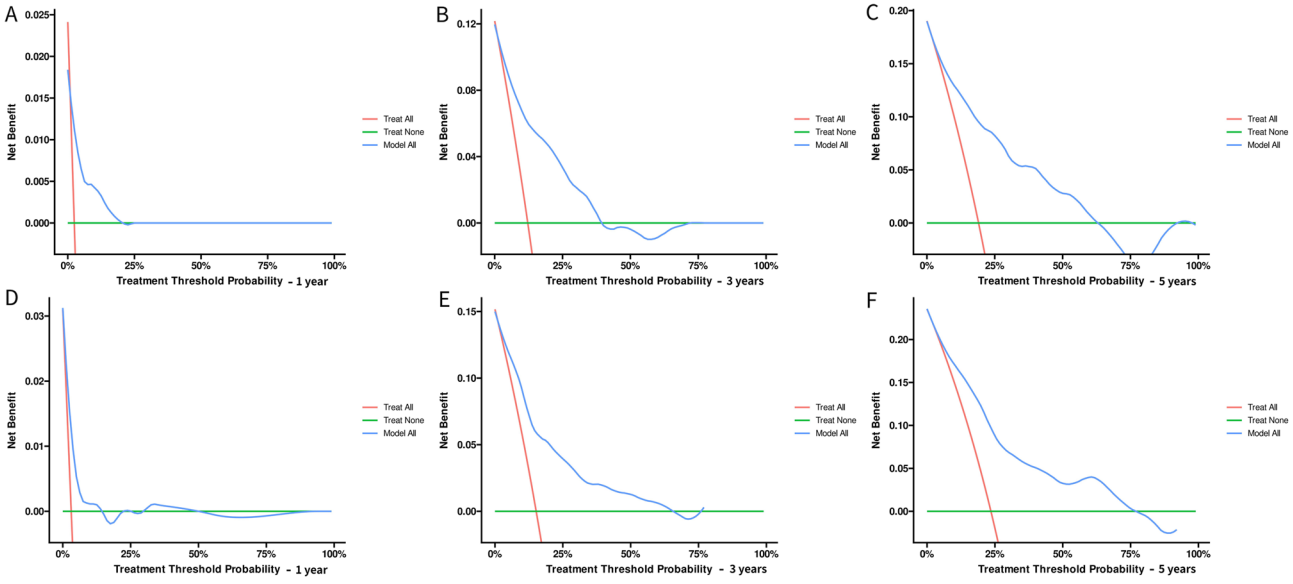

Fig. 7 Decision curve analysis of the nomogram for predicting 1-, 3-, and 5-year survival in the training and validation cohorts. Decision curve analysis for 1-year(**A**), 3-years(**B**), and 5-years(**C**) survival in the training cohort; Decision curve analysis for 1-year(**D**), 3-years(**E**), and 5-years(**F**) survival in the validation cohort

Despite these strengths, some limitations warrant consideration. First, its retrospective and single-center design introduces the risk of selection bias, as the included patients may not be representative of the general population. As a retrospective study, the analysis is inherently subject to bias, and the inclusion of only patients with complete data may have further contributed to selection bias. Second, missing data in some clinical variables could have influenced the accuracy and reliability of the multivariate analyses. Although rigorous statistical methods were applied, missing values may still have affected the stability of the multivariate models and introduced residual confounding. Rigorous data cleaning and statistical methods were applied, however, the possibility of residual bias cannot be excluded. Some baseline characteristics, including CEA levels and gross tumor appearance, showed significant differences between the training and validation cohorts. Furthermore, we noted that the number of death events in the test cohort was relatively low (17 deaths among 207 patients), which may

reduce the statistical power of the external validation. Although the training cohort (484 patients) included a greater number of death events (168 deaths), the limited number of events in the test cohort may constrain the generalizability of the results. These variations may reflect heterogeneity in patient populations or clinical practices across different time periods or subgroups, which could influence the external validity of the model. These discrepancies may further reduce the generalizability of the nomogram to broader patient populations and clinical settings. Therefore, external validation in independent, multi-center cohorts with more diverse characteristics will be essential to confirm the robustness and applicability of the model. Although our nomogram demonstrated good discriminatory ability in the validation cohort, these inconsistencies may still limit the generalizability of its application to other populations. Therefore, the findings should be interpreted with caution and validated in prospective, multi-center studies. A key limitation of our study is the exclusion of patients who underwent neoadjuvant therapy. Neoadjuvant treatments can significantly alter tumor biology and pathological staging, which are key variables in our model. Consequently, the predictive accuracy of our nomogram may be diminished when applied to this patient population, and it should be used with caution for patients who have received prior treatment. Future external validation studies are essential to assess the nomogram's performance in a cohort that includes patients receiving neoadjuvant therapy to broaden its clinical utility. Additionally, patients with a history of other malignancies were excluded to minimize potential confounding effects. However, we acknowledge that this strict exclusion criterion may reduce the generalizability of our findings, as certain non-relevant malignancies (e.g., adequately treated basal cell carcinoma) are unlikely to affect colorectal cancer outcomes. Future studies should refine these criteria to better distinguish clinically relevant from non-relevant prior malignancies.

Conclusion

In conclusion, this study establishes nerve invasion, AGR, and NPAR as key prognostic biomarkers in early-stage CRC and presents a validated nomogram that may facilitate personalized prognosis and management. Future research should explore the integration of these biomarkers with molecular and genetic tumor characteristics to further refine risk stratification and guide precision oncology strategies.

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Not applicable.

Authors' contributions
SD.M and Y.C designed and guidance the research. KJ.L was involved in data collection, analysis and interpretation, and manuscript writing. R.Z, JN.Z and ZL.Z took part in data collection and analysis. ZY.Z, W.K and YQ.L participated in manuscript modification. All authors approved the manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the Nanfang Hospital, Southern Medical University, and written informed consent was obtained from all participants (approval number:2025-KY-150-12) and the Ethics Committee of the Affiliated Tumor Hospital of Xinjiang Medical University (Approval number: KY20250304) in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants or their legal guardians.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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