Development and validation of a prognostic nomogram incorporating preoperative NLR, CEA and CA19-9 for overall survival in colorectal cancer

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Abstract. Reliable evaluation methods serve an important role in improving the prognosis of patients with colorectal cancer (CRC), guiding the development of treatment plans and prolonging patient survival. In the present study, several preoperative inflammatory indicators and tumor markers were evaluated for their ability to predict CRC prognosis. A total of 224 eligible patients with CRC were enrolled and divided into the training (n=150) and validation (n=74) groups. The training group underwent both Least Absolute Shrinkage and Selection Operator (LASSO) regression and Cox regression analyses to discern pivotal prognostic factors, to formulate a nomogram for overall survival prediction. The results showed that LASSO regression, along with univariate and multivariate Cox regression analyses, identified neutrophil-lymphocyte ratio (NLR), carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) as effective risk factors for CRC. The concordance index of the nomogram was 0.716 in the training group and 0.700 in the validation group. The areas under the curve for predicting 3-year survival were 0.748 and 0.776 in the training and validation groups, respectively, and for 5-year survival were 0.749 and 0.731, respectively. In conclusion, NLR, CA19-9 and CEA may serve as effective additions to traditional clinical assessment methods and a nomogram incorporating these three preoperative indicators could be used efficiently to predict the prognosis of patients with CRC.

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Introduction

Colorectal cancer (CRC), a prevalent gastrointestinal malignant neoplasm, remains the second leading cause of cancer-related mortality worldwide, with an estimated 1.93 million new cases and approximately 904,000 deaths reported globally in 2022, accounting for 9.6% of all cancer incidence and 9.3% of cancer-related deaths (1). The integration of curative resection and adjuvant cancer chemotherapy has emerged as a paradigmatic treatment modality, yielding notable overall improvement in the prognosis of patients with CRC (2). However, a cascade of alterations in epigenetic and metabolic processes can lead to a strong transfer and invasive capacity in CRC cells, ultimately resulting in a poor 5-year overall survival (OS) rate of ~12% in patients with metastatic CRC (3). Over decades, the American Joint Commission on Cancer/International Union against Cancer tumor (T)-lymph node (N)-metastasis (M) staging system has stood as the benchmark for predicting CRC outcomes (4). Nonetheless, the considerable variability in clinical prognoses among patients classified under the same stage implies inherent limitations in the predictive efficacy of the TNM staging system for CRC prognosis (5). Accordingly, an integrated approach that amalgamates the TNM staging system with other salient prognostic parameters needs to be urgently adopted to direct the clinical decision-making process and uncover individualized therapeutic strategies.

Cancer-associated inflammation can occur throughout the course of the disease and inflammatory cells serve a major role in the tumor microenvironment. Inflammatory cells are mediators of tumorigenesis and progression, provide cytokines to cancer cells, and enhance cell survival and proliferation (6). The neutrophil-lymphocyte ratio (NLR), a measure of the number of neutrophils per gram of body weight, is increased in patients with higher disease stage and more aggressive disease, indicated by an increased number of metastatic sites, constituting a particularly high risk patient population (7). Consequently, a blood-value assay may be useful to estimate prognosis in patients with cancer.

A nomogram is a statistical prediction model presented as a simple graphical display, which integrates prognostic factors to produce an individualized numeric probability of a clinical event (8). Compared with conventional TNM staging, a nomogram has more advantages for treating numerous types of cancer, thus it has been presented as a replacement or even a new standard (9,10). Prognostic biomarkers, which can predict clinicopathological features and survival in patients with CRC, are useful in the screening, diagnosis, classification and treatment of CRC (11).

In the present study, a prognostic model was formulated that was rooted in clinical parameters intricately associated with clinical prognosis in CRC. The primary objective was to predict the prognosis of individuals diagnosed with CRC, thereby providing valuable insights to guide clinicians in therapeutic strategies for patients with CRC.

Materials and methods

Study population. A total of 224 cases of surgically resected CRC treated between June 2012 and June 2018 at The First Affiliated Hospital of Soochow University (Suzhou, China) were included in the retrospective cohort (Fig. 1). The inclusion criteria for the selection of these patients were as follows: i) Pathologically confirmed primary CRC; ii) underwent primary surgical resection at The First Affiliated Hospital of Soochow University within the specified timeframe; and iii) complete preoperative laboratory data, clinicopathological parameters and follow-up data were available. Among the 224 eligible patients, there were 119 men and 105 women. The median age of the cohort was 63 years (age range, 49-90 years). All patients underwent surgical resection and followed the standard treatment guidelines outlined during this period. The exclusion were as follows: i) Patients with a prior medical history of other malignancies, including those related to the cervix, uterus or bladder; ii) recent chemotherapy or radiotherapy; iii) postoperative severe complications of the heart, lungs and kidneys; iv) addiction or mental disorder; and v) patients who did not attend follow up.

Prior to data collection, written informed consent was obtained from all participants. The present study received approval from the Committee for the Ethical Review of Research at the First Affiliated Hospital of Soochow University (approval no. 125) and was conducted with adherence to institutional guidelines and the principles outlined in the Declaration of Helsinki. Prior to formal ethics approval, only a preliminary feasibility assessment was conducted using limited registry data to evaluate the available case pool. Patient hospital records were first formally accessed for research purposes in April 2023, after ethics approval had been obtained. Full data extraction, confirmation of eligibility, cohort assignment and statistical analyses were performed only after ethics approval.

Data collection. The collected clinical data were randomly divided into the validation (n=74) and training (n=150) sets. The following clinical data were collected and grouped separately: Sex, blood type, age, hypertension status, diabetes, prognostic nutritional index (PNI), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), body mass index (BMI), levels of carbohydrate antigen (CA)19-9, CA72-4, CA125, carcinoembryonic antigen (CEA), lymphocytes, thrombocytes, hemoglobin, neutrophils, monocytes, alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP), albumin and fibrinogen, tumor site, tumor size, T stage, N stage, M stage, survival time, survival status, systemic immune-inflammation index (SII), postoperative adjuvant therapy, NLR and pathological type. The PNI score was derived from the serum albumin level and lymphocyte count, with the following formula: PNI=[albumin (g/l) + 5]x lymphocytes (10^9/l).

Treatment. In the Department of General Surgery of the First Affiliated Hospital of Soochow University, patients with CRC underwent surgical resection and the resected tissues were examined pathologically in frozen sections to confirm the diagnosis and negative surgical margin. According to the postoperative pathological results, adjuvant chemotherapy was initiated within 3 months after the surgery, which included oxaliplatin plus capecitabine or oxaliplatin plus capecitabine plus bevacizumab. Specifically, patients received 130 mg/m^2 oxaliplatin intravenously on day 1 and 1,000 mg/m^2 oral capecitabine twice daily on days 1-14, repeated every 3 weeks. For patients receiving the bevacizumab-containing regimen, 7.5 mg/kg bevacizumab was administered intravenously on day 1 of each cycle. A maximum of 8 cycles was planned per patient.

Follow-up. OS was defined as the time from surgery to death in any case. Follow-up evaluation was performed every 3 months for 5 years and OS data were collected until December 2022. Survival was determined by reviewing the medical records, which included laboratory data, computed tomography scans, colonoscopy results and telephone follow-up results.

Feature selection and survival analysis. Before starting the analysis, non-hierarchical categorical variables were converted into dummy variables and ordinal factor variables were transformed into numerical variables. In addition, CA19-9 and CEA were dichotomized at the upper limits of their clinically established reference ranges (CA19-9, 37 U/ml; CEA, 5 ng/ml) for the analyses presented in Fig. 2C and D. NLR was analyzed as a continuous variable in the Cox regression analyses, and no cut-off value was applied. Least Absolute Shrinkage and Selection Operator (LASSO) analysis was employed to identify prognostic factors using the glmnet package (version 4.1-1; https://CRAN.R-project.org/package=glmnet) in R. The estimation of the optimal penalty parameter was accomplished through a 10-fold cross-validation procedure performed on

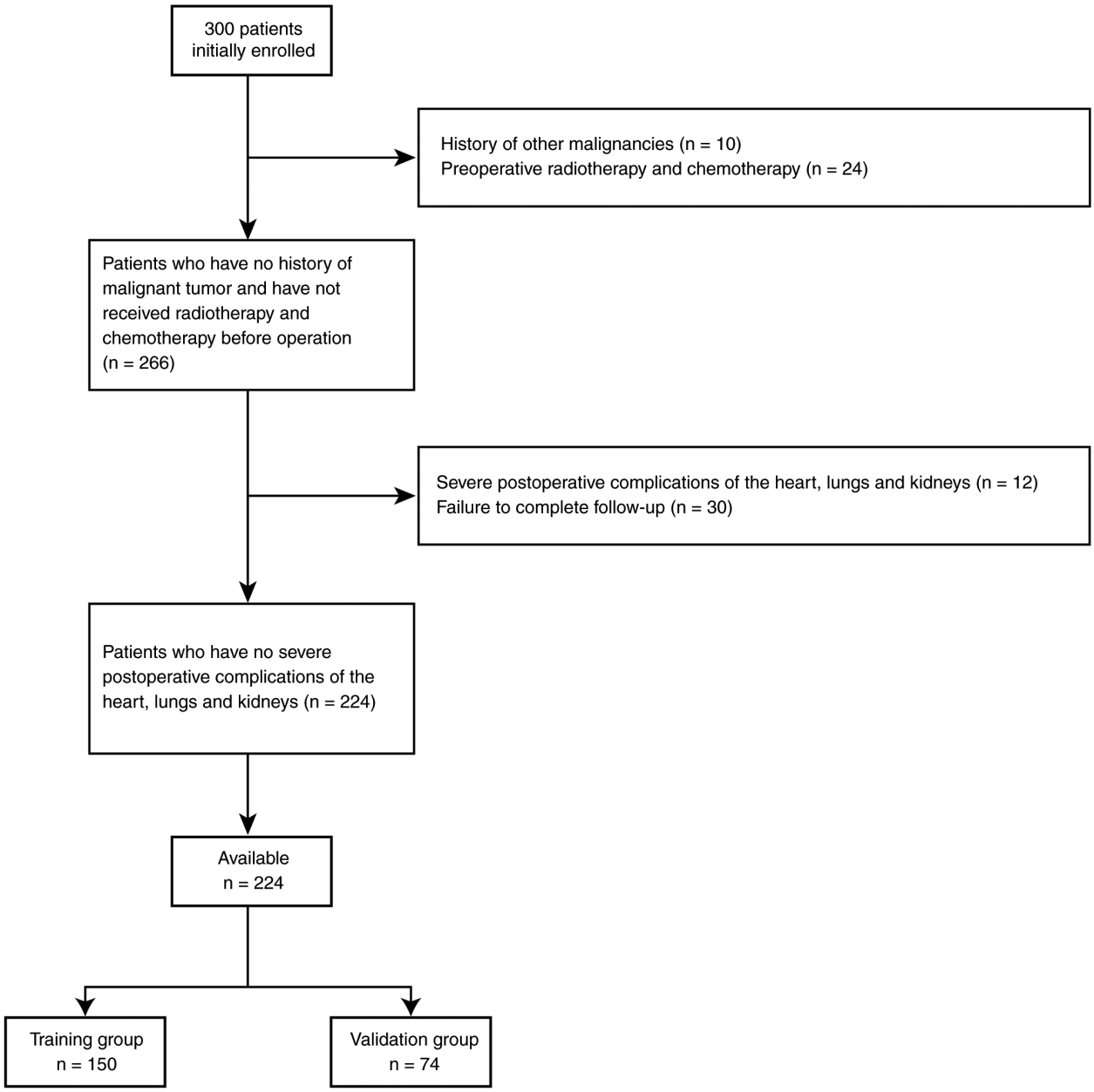

Figure 1. Filtering process for patient inclusion.

the training dataset. To ascertain the statistical significance of the aforementioned prognostic factors, univariate Cox proportional hazards regression analysis was conducted. This approach allowed for the assessment of the impact of each factor on survival time and the calculation of the corresponding hazard ratio (HR), 95% confidence interval (CI) and two-sided P-value. Factors with P<0.05 were included in the construction of the prognostic clinical signature using the multivariate Cox proportional hazards model. Subsequently, individual risk scores were computed for each patient using the following formula: Risk score=[β_1 (variable1) x value of variable1] + [β_2 (variable2) x value of variable2] + ... + [β_n (variablen) x value of variablen], where β represents the regression coefficient obtained from the multivariate Cox proportional hazards regression model. The univariate and multivariate Cox proportional hazards regression analyses were conducted using the 'survival' (version 3.2-7; https://CRAN.R-project.org/package=survival) and 'survminer' (version 0.4.8; https://CRAN.R-project.org/package=survminer) R packages, respectively. The median risk score was used as the cut-off to stratify patients into high- and low-risk subgroups. For the Kaplan-Meier analyses, the optimal cut-off value was determined by the minimum P-value approach.

Nomogram construction and evaluation. The discerned factors from the training group were utilized to construct a nomogram employing the 'rms' (version 6.1-1; https://CRAN.R-project.org/package=rms) R package. To evaluate its discriminatory capability, the nomogram underwent bootstrapping validation (1,000 bootstrap resamples) to compute a relatively corrected concordance index (C-index). Kaplan-Meier (KM) survival curves with the log-rank test were employed to assess differences in OS between the high- or low-risk groups. Additionally, time-dependent receiver operating characteristic (ROC)

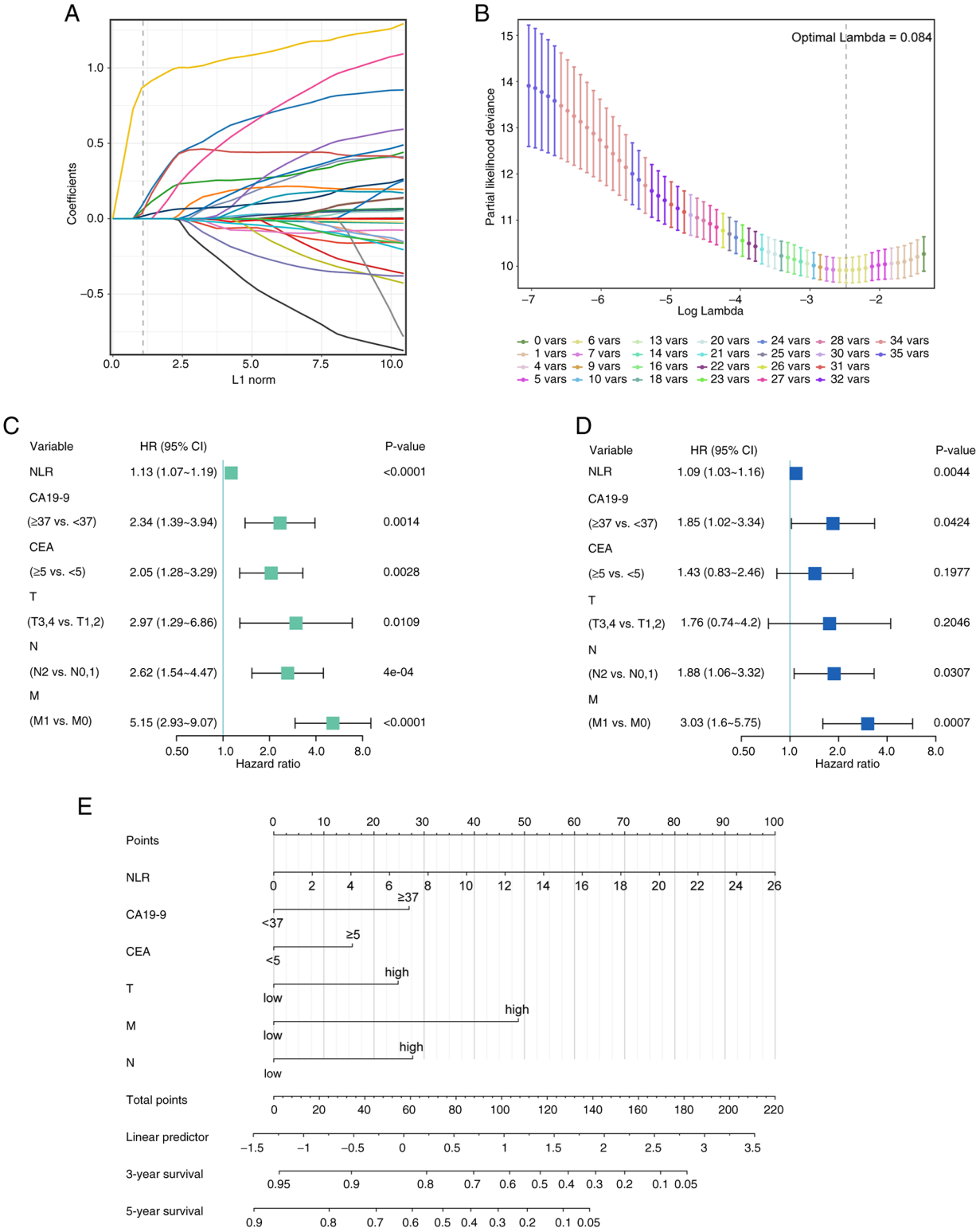

Figure 2. Prognostic factors and nomogram development for CRC. (A) LASSO coefficient profiles of 34 preoperative indicators and clinicopathological factors associated with CRC. (B) 10-fold cross-validation used for tuning parameter selection in the LASSO model. (C) Forest plot displaying the HRs of prognostic factors identified through univariate Cox analysis of the training group. (D) Forest plot illustrating the HRs of prognostic factors identified through multivariate Cox analysis of the training group. (E) Nomogram designed for predicting 3- and 5-year survival rates for patients in the training group. The nomogram was constructed based on the training group data and integrated NLR, CA19-9, CEA and TNM staging information. HR, hazard ratio; NLR, neutrophil-lymphocyte ratio; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; TNM, tumor-lymph node-metastasis; CRC, colorectal cancer; CI, confidence interval; LASSO, Least Absolute Shrinkage and Selection Operator; vars, variables.

(timeROC package; version 0.4; https://CRAN.R-project.org/package=timeROC) and calibration curves were utilized to evaluate the predictive performance of the nomogram within the training group. Furthermore, ROC analysis and decision curve analysis (DCA) (rmda package; version 1.6; https://CRAN.R-project.org/package=rmda) were employed

Table I. Demographic and clinical characteristics of patients in the validation (n=74) and training (n=150) groups.

Variable	Validation group	Training group	P-value
Sex, n (%)			0.570
Female	37 (50.00)	68 (45.33)	
Male	37 (50.00)	82 (54.67)	
Age, n (%)			0.203
≥60 years	34 (45.95)	83 (55.33)	
<60 years	40 (54.05)	67 (44.67)	
Hypertension, n (%)			0.881
No	50 (67.57)	99 (66.00)	
Yes	24 (32.43)	51 (34.00)	
Diabetes, n (%)			0.200
No	68 (91.89)	128 (85.33)	
Yes	6 (8.11)	22 (14.67)	
Blood type, n (%)			0.157
A	15 (20.27)	50 (33.33)	
AB	8 (10.81)	12 (8.00)	
B	22 (29.73)	45 (30.00)	
O	29 (39.19)	43 (28.67)	
Median CA19-9 [IQR], U/ml	9.77 [3.78,16.48]	9.89 [4.32, 29.00]	0.276
Median CA125 [IQR], U/ml	11.40 [7.40, 15.90]	11.55 [8.10, 15.35]	0.885
Median CA72-4 [IQR], U/ml	2.26 [1.16, 3.72]	1.75 [0.97, 3.72]	0.350
Median CEA [IQR], ng/ml	3.45 [1.52, 7.39]	3.46 [1.80, 7.45]	0.652
Median lymphocytes [IQR], $x10^9$/l	1.48 [1.20, 1.92]	1.38 [1.11, 1.78]	0.098
Median thrombocytes [IQR], $x10^9$/l	211.50 [176.25,270.50]	215.50 [177.50, 275.50]	0.988
Median hemoglobin [IQR], g/l	124.00 [107.50,136.25]	128.00 [107.00, 140.00]	0.394
Median neutrophils [IQR], $x10^9$/l	3.62 [2.89, 4.54]	3.78 [2.85, 5.00]	0.217
Median monocytes [IQR], $x10^9$/l	0.39 [0.32, 0.51]	0.38 [0.29, 0.51]	0.283
Median ALT [IQR], U/l	13.85 [11.10, 18.00]	15.00 [11.00, 21.00]	0.324
Median AST [IQR], U/l	18.45 [15.43, 22.00]	18.65 [16.00, 22.00]	0.676
Median CRP [IQR], mg/l	2.71 [1.07, 6.42]	2.57 [0.98, 9.41]	0.745
Median albumin [IQR], g/l	40.20 [37.60, 42.88]	40.00 [37.60, 43.68]	0.812
Median fibrinogen [IQR], g/l	3.12 [2.62, 3.60]	3.21 [2.82, 3.66]	0.309
Tumor site, n (%)			0.088
Left colon	31 (41.89)	42 (28.00)	
Rectal	26 (35.14)	73 (48.67)	
Right colon	17 (22.97)	35 (23.33)	
Median Size [IQR], cm	4.00 [3.00, 5.00]	4.00 [3.00, 5.00]	0.793
Pathological type, n (%)			0.040
High differentiation	1 (1.35)	0 (0.00)	
Low differentiation	6 (8.11)	8 (5.33)	
Moderate differentiation	66 (89.19)	129 (86.00)	
Mucous gland	1 (1.35)	13 (8.67)	
T, n (%)			0.307
1	5 (6.76)	9 (6.00)	
2	7 (9.46)	18 (12.00)	
3	56 (75.68)	119 (79.33)	
4	6 (8.11)	4 (2.67)	
N, n (%)			0.538
0	37 (50.00)	85 (56.67)	
1	24 (32.43)	38 (25.33)	
2	13 (17.57)	27 (18.00)	

Table I. Continued.

Variable	Validation group	Training group	P-value
M			0.679
0	63 (85.14)	131 (87.33)	
1	11 (14.86)	19 (12.67)	
Postoperative adjuvant therapy, n (%)			0.458
No	23 (31.08)	55 (36.67)	
Yes	51 (68.92)	95 (63.33)	
Median PNI [IQR]	48.20 [45.23, 52.86]	48.15 [43.99, 51.88]	0.613
Median LMR [IQR]	3.85 [2.46, 5.21]	3.65 [2.58, 5.15]	0.713
Median PLR [IQR]	145.22 [93.74, 206.87]	153.14 [111.41,211.62]	0.197
Median BMI [IQR], kg/m^2	23.01 [20.81, 24.94]	23.02 [20.70, 25.22]	0.651
Median NLR [IQR]	2.24 [1.62, 3.49]	2.54 [2.01, 3.74]	0.029
Median SII [IQR]	495.55 [295.91,819.47]	567.07 [381.88, 946.02]	0.088
Status			0.569
Alive	42 (56.76)	78 (52.00)	
Dead	32 (43.24)	72 (48.00)	
Median Time [IQR], months	65.67 [50.67, 70.57]	64.28 [41.59, 71.07]	0.398

Normal ranges: CA19-9, ≤37.0 U/ml; CA125, ≤35.0 U/ml; CA72-4, ≤6.9 U/ml; CEA, ≤5.0 ng/ml; lymphocytes, 1.1-3.2 x10^9/l; thrombocytes, 100-300 x10^9/l; hemoglobin, 115-175 g/l; neutrophils, 1.8-6.3 x10^9/l; monocytes, 0.1-0.6 x10^9/l; ALT, 9-50 U/l; AST, 15-40 U/l; CRP, ≤10.0 mg/l; albumin, 35.0-50.0 g/l; fibrinogen, 2.0-4.0 g/l; BMI, 18.5-23.9 kg/m^2. CA, carbohydrate antigen; CEA, carcinoembryonic antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; T, tumor; N, node; M, metastasis; PNI, prognostic nutritional index; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index.

to quantitatively assess and compare the clinical utility of the nomogram, PNI score and standard TNM staging system. These comparative analyses were replicated in the validation group.

Statistical analysis. Continuous variables are presented as the median [interquartile range], while categorical variables are presented as the count (proportion). Continuous variables were compared between the two groups using the Mann-Whitney U test, and categorical variables were compared using Fisher's exact test. All statistical analyses were performed using R software (version 4.0.0; R Foundation for Statistical Computing). P<0.05 was considered to indicate a statistically significant difference.

Results

Clinical characteristics. The demographic and clinical profiles of 224 suitable participants who underwent radical resection for CRC are presented in Table I. This includes a cohort of 150 patients in the training group and 74 patients in the validation group. Patients in both groups exhibited no statistically significant differences in terms of sex, blood type, age, hypertension status, diabetes, PNI, LMR, PLR, BMI, levels of CA19-9, CA72-4, CA125, CEA, lymphocytes, thrombocytes, hemoglobin, neutrophils, monocytes, ALT, AST, CRP, albumin and fibrinogen, tumor site, tumor size, T stage, N stage, M stage, survival time, survival status, SII or postoperative adjuvant therapy. However, there were differences in NLR and pathological type between the two groups. The median NLR in the training group was 2.54, while it was 2.24 in the validation group. In the training group, the proportion of patients with moderate differentiation was slightly lower (86.0%) compared with that in the validation group (89.2%). The existence of significant differences in the pathological type may be due to an unbalanced distribution of very few samples of high/low differentiation.

Identification of prognostic factors and development of the nomogram. LASSO was first performed to identify significant factors related to prognosis. Sex, age, BMI, tumor diameter, tumor stage, degree of differentiation, surgical procedure, chemotherapy, and levels of lymphocytes, albumin, CA19-9, hemoglobin, platelets, AST, ALT, prealbumin and CRP in the training group were included in the LASSO regression analysis. With a λ value of 0.084, six pivotal factors were discerned to hold significance in determining the prognosis of patients with CRC, namely, NLR, CA19-9 and CEA, and the T, M and N stages (Fig. 2A and B). The univariate Cox regression analysis further unveiled the prognostic relevance of all these six factors in relation to patient outcomes (Fig. 2C). In the multivariate Cox regression analysis encompassing all variables, a multitude of independent prognostic factors surfaced, prominently featuring NLR (HR=1.09; P=0.0044), CA19-9 (HR=1.85; P=0.042), M stage (HR=1.88; P=0.031) and N stage (HR=3.03; P=0.0007) (Fig. 2D).

With the aim of screening preoperative inflammatory indicators and enhancing the predictive capacity beyond the

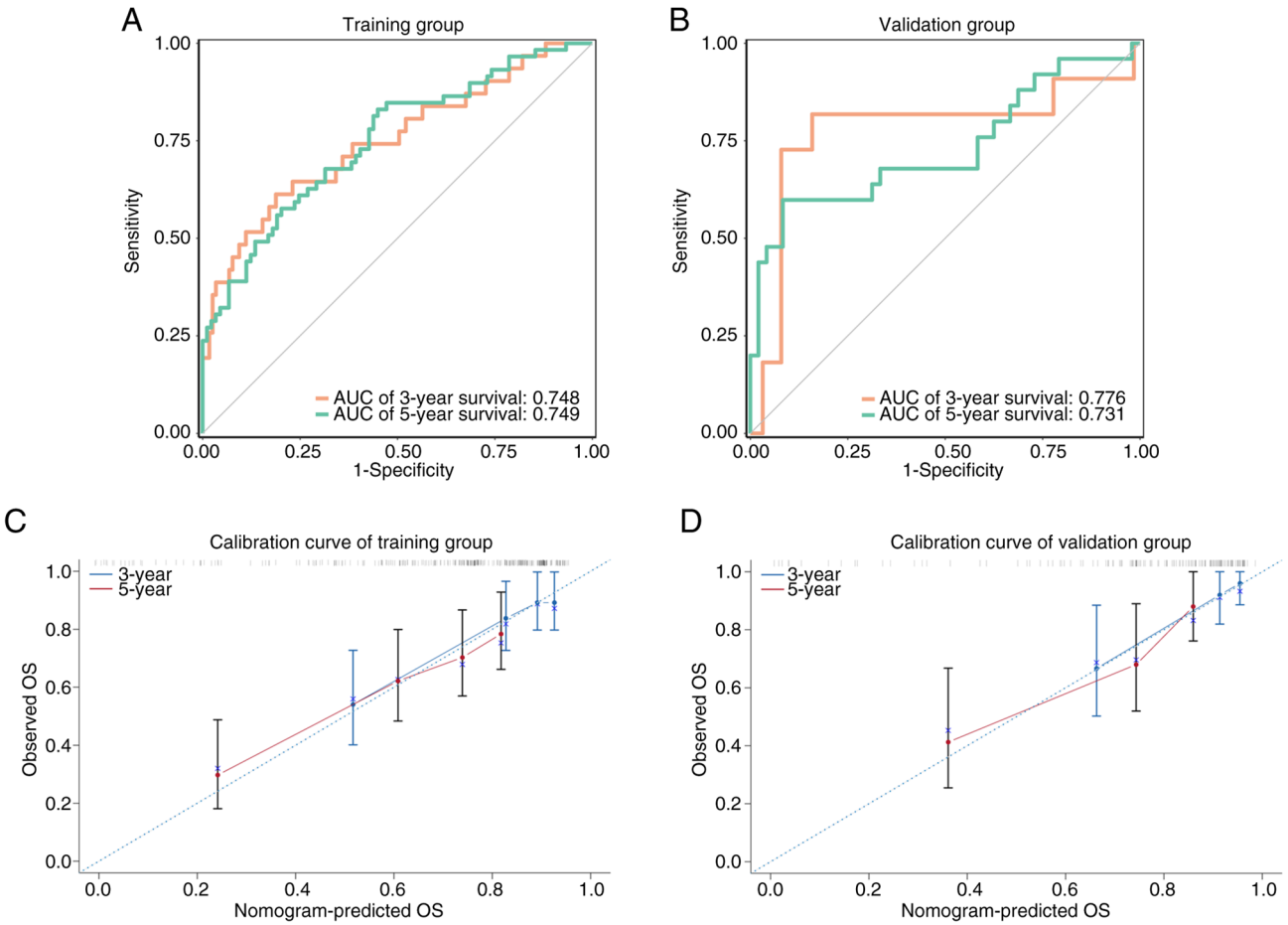

Figure 3. Time-dependent ROC analysis for predicting the 3- and 5-year OS rates of patients with resected colorectal cancer in the training and validation groups, and calibrations of the nomogram for 3- and 5-year OS in the training group. (A) Time-dependent ROC analysis in the training group. (B) Time-dependent ROC analysis in the validation group. (C) Calibration curve of the training group. (D) Calibration curve of the validation group. ROC, receiver operating characteristic; OS, overall survival; AUC, area under the receiver operating characteristic curve.

standard TNM staging system, three accessible preoperative factors (NLR, CEA and CA19-9) were selected and integrated into a nomogram along with the TNM stage. The primary aim was to establish a user-friendly model for predicting the OS of patients who undergo resection for CRC (Fig. 2E).

Assessing performance of the nomogram. To assess the quantitative predictive performance of the nomogram, time-dependent ROC analysis was conducted. For the training group, the areas under the curve (AUCs) were 0.748 at 3 years and 0.749 at 5 years (Fig. 3A). For the validation group, the AUCs were 0.776 at 3 years and 0.731 at 5 years (Fig. 3B). The Harrell's C-index of the nomogram was 0.716 (95% CI, 0.58-0.82) in the training group and 0.700 (95% CI, 0.50-0.84) in the validation group. Moreover, the calibration curve exhibited good concordance between the prognostic predictive model and the ideal reference model (Fig. 3C and D).

To evaluate the effect of this prognostic model, prognostic scores were calculated in both the training and validation groups using the aforementioned risk score formula (Fig. 4A and B). Patients in both the training and validation groups were stratified according to the optimal cut-off value determined by the minimum P-value approach, and Kaplan-Meier curves were then constructed for each group. The findings revealed that the high-risk subgroup exhibited significantly shorter median OS times compared with the low-risk subgroup in both the training (Fig. 4C) and validation (Fig. 4D) groups.

In summary, the nomogram model may be an effective and efficient tool for predicting the OS prognosis of patients with CRC.

Clinical utility. ROC analysis showed that the nomogram could also markedly predict the 5-year OS of patients with CRC (training group: AUC=0.749; validation group: AUC=0.731) and was notably superior to PNI scores (training group: AUC=0.466; validation group: AUC=0.360) and TNM stage (training group: AUC=0.680; validation group: AUC=0.697) (Fig. 5A and B). Subsequently, a DCA was conducted for the nomogram, PNI scores and TNM stage. The DCA of both the training and test groups demonstrated that, when the threshold probability exceeded 0.25, utilizing the developed nomogram for prognostic prediction resulted in greater net benefits compared with PNI scores and the standard TNM staging system. This finding indicates the clinical usefulness of the nomogram (Fig. 5C and D).

In summary, the nomogram model demonstrated improved predictive accuracy and discriminative performance compared with the standard TNM staging system.

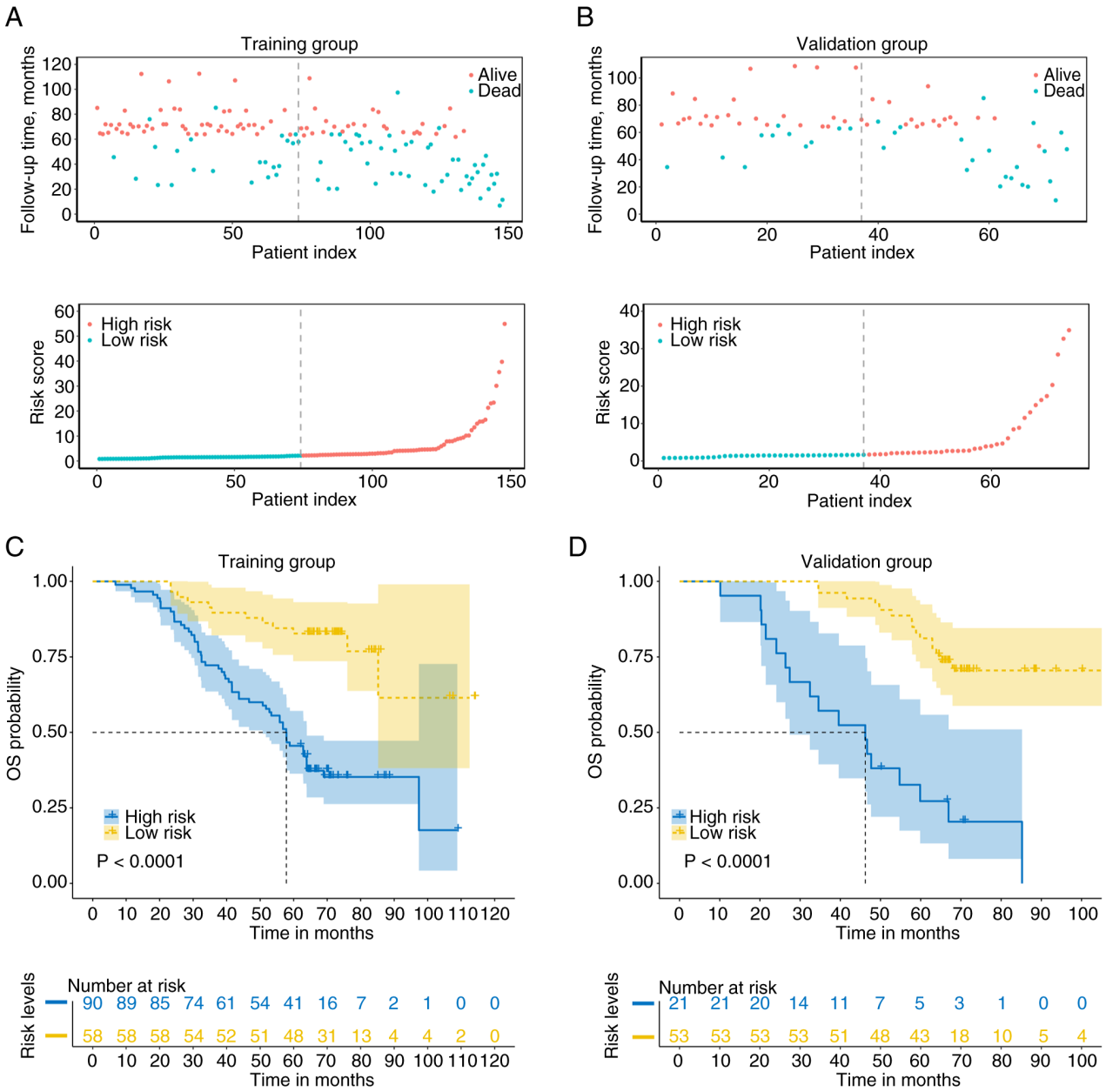

Figure 4. Risk factor correlation diagrams were generated for both the training and validation groups. (A) Correlation visualization of risk factors in the training group. (B) Correlation visualization of risk factors in the validation group. The red dots represent surviving patients with CRC, while blue dots represent deceased patients with CRC. In (A) and (B), the dashed line represents the median risk score, with patients on the left of the line classified into the low-risk subgroup and those on the right into the high-risk subgroup. (C) KM 5-year OS curves for the training group based on nomogram predictions (P<0.0001). (D) KM 5-year OS curves for the validation group based on nomogram predictions (P<0.0001). In (C) and (D), patients were stratified into high- and low-risk subgroups according to the optimal cut-off value determined by the minimum P-value approach. KM, Kaplan-Meier; CRC, colorectal cancer; OS, overall survival.

Discussion

At present, CRC is the third most common malignancy worldwide (1). The TNM staging system is typically used to assess the prognosis of patients with cancer in clinical practice, and although the TNM staging system is considered the gold standard for assessing the clinical outcome of patients, there are notable differences in prognosis even among patients with the same TNM stage (12). The differences in genetic and biological characteristics of patients at the same stage of disease lead to limited predictive accuracy of the TNM staging system (13). In view of this, a more accurate and convenient method for predicting outcome is needed to guide clinicians in the treatment of patients with CRC. Cancer-associated inflammation is considered to be one of the key features in the development of cancer (14). In the present study, preoperative inflammatory indicators and tumor markers were investigated in patients with CRC and combined with TNM staging to create a more accurate and convenient nomogram for predicting OS. The nomogram showed strong calibration and discrimination in both the training and validation groups, and the discrimination, calibration and clinical validity of the nomogram were superior to the TNM staging system prognostic model.

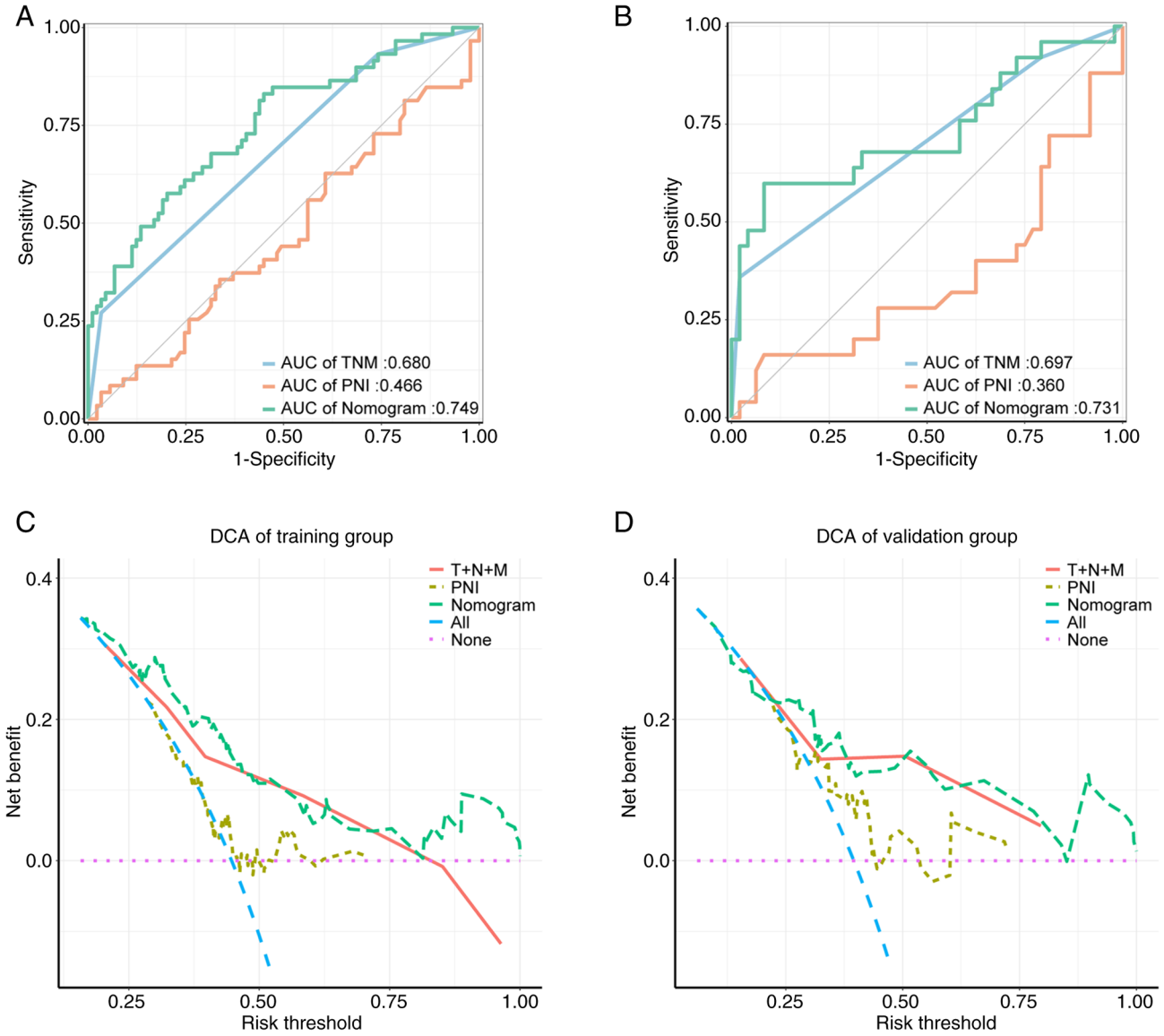

Figure 5. ROC curves of the TNM, PNI and nomogram for predicting the 5-year OS rate of patients with resected CRC in the training and validation groups. (A) ROC curves comparing the nomogram, TNM stage and PNI in the training group. (B) ROC curves comparing the nomogram, TNM stage and PNI in the validation group. (C) DCA comparing the nomogram, TNM stage and PNI in the training group. (D) DCA comparing the nomogram, TNM stage and PNI in the validation group. ROC, receiver operating characteristic; TNM, tumor-lymph node-metastasis; CRC, colorectal cancer; OS, overall survival; DCA, decision curve analysis; PNI, prognostic nutritional index; AUC, area under the receiver operating characteristic curve.

A total of 224 eligible patients with CRC were included in the present study. Patients were divided into training (n=150) and validation (n=74) groups. LASSO regression and Cox regression analyses were performed on the training group to identify meaningful prognostic factors and construct a nomogram to predict OS, which showed NLR, CA19-9 and CEA as valid risk factors. The C-indices of the nomogram were 0.716 and 0.700 in the training and validation groups, respectively. AUCs of the nomogram were 0.748 (training group) and 0.776 (validation group) at 3 years, and 0.749 (training group) and 0.731 (validation group) at 5 years.

Numerous studies have demonstrated the notable involvement of inflammation in tumor initiation and progression. Several recent studies have shown that systemic inflammatory response markers, including CRP, Glasgow prognostic score, PLR and LMR, are associated with CRC and with poor survival in a range of other malignancies, including hepatocellular carcinoma and gastric cancer (15-19). In particular, NLR, which is considered a marker of systemic inflammatory response, is closely related to the prognosis of patients with various types of cancer, including prostate cancer (20) and renal cell carcinoma (21). Initially, neutrophils were considered to have a protective function against tumors, but previous studies have shown that neutrophils in the tumor microenvironment serve a role in promoting the growth, invasion, angiogenesis and metastasis of various cancer types, including colorectal, lung and breast cancers (22-24). Circulating neutrophils migrate to tumor tissues via CXC motif chemokine ligand 2-CXC motif chemokine receptor chemotaxis (25,26) and are termed 'tumor-associated neutrophils' (27). Lymphocytes serve a notable role in cancer-specific immune responses, among which tumor-infiltrating lymphocytes are one of the major cells mediating the local immune response to tumors and are phenotypically characterized by $CD8^+$ and $CD4^+$ status (28).

Thus, tumor-associated lymphocytes receive different stimuli in different tumor microenvironments, leading to a shift in lymphocyte subtypes that can serve both a tumor growth-promoting and tumor growth-suppressing role. The presence of a severe inflammatory response in the body is indicated by elevated NLR values.

The results of the present study suggest that NLR may be an independent prognostic factor for poor survival in patients with CRC. This finding is consistent with much of the previous literature. For example, a study by Shin *et al* (29) showed that preoperative NLR predicted survival in patients with resectable stage T1-2 N0 CRC. Kubo *et al* (30) also showed that preoperative and postoperative NLR was a good predictor of long-term survival in patients with CRC. These studies and the present study suggest that high NLR values are important for the prognosis of patients with CRC. Therefore, NLR was included in the present prognostic model.

The survival of patients with cancer depends not only on the host systemic inflammatory response but also on the tumor characteristics (31,32). CEA and CA19-9 are tumor-related markers widely used for prognosis prediction in patients with CRC (19,33). Toiyama *et al* (34) proposed that elevated CEA is a predictor of decreased OS after preoperative radiotherapy and chemotherapy in patients with rectal cancer. Thirunavukarasu *et al* (35) demonstrated that serum CEA is an independent prognostic indicator in patients with CRC, with a mean follow-up period of 27 months. Due to the prognostic role of CEA, the American Society of Medical Oncology recommends CEA levels as the gold follow-up standard after CRC treatment (36,37). Therefore, we hypothesized that the inclusion of both tumor markers that reflect tumor characteristics (such as CEA and CA19-9) and NLR might be an improved way to predict patient survival.

In the training group of the present study, univariate and multivariate Cox analyses were performed to identify prognostic variables, including T stage, N stage, M stage, CEA, CA19-9 and NLR, in patients with CRC. Scores were assigned to the patients based on the newly developed model and the patients were subsequently categorized into the low-risk and high-risk subgroups. The results indicated that the high-risk subgroup exhibited a notably shorter survival time compared with the low-risk subgroup, providing valuable suggestions for clinicians to make precise and personalized decisions. While the individual prognostic values of preoperative NLR, CEA and CA19-9 are well-established, the primary clinical utility of the present study lies in integrating these readily available biomarkers with the standard TNM staging system into a unified, quantifiable nomogram. In clinical practice, patients with the identical TNM stage often exhibit highly heterogeneous survival outcomes. The present nomogram translates complex statistical risks into an applicable tool for clinical evaluation. Clinicians can calculate a personalized risk score for each postoperative patient with CRC. If a patient is classified into the high-risk subgroup by the nomogram (even if they present with early-stage disease) clinicians might consider tailoring a more intensive postoperative surveillance strategy and incorporating personalized treatment plans. Furthermore, this integrated model could provide valuable references during multidisciplinary team discussions regarding the administration of adjuvant chemotherapy, particularly for patients with CRC where the benefit of chemotherapy often remains controversial (38).

In the present study, AUC and DCA were evaluated by comparing TNM staging with PNI using column line plots. The results showed that the nomograms had a higher C-index and a clearer calibration curve in predicting OS compared with TNM or PNI.

The present study possesses several limitations. Firstly, the study is retrospective and cannot avoid bias caused by retrospective bias and follow-up compliance. Secondly, only internal validation was used in the present study, which may lead to overfitting of the model. Further external validation is needed to more accurately assess the validity of the model. Thirdly, while the model aims to serve as an intrinsic baseline prognostic tool and includes general adjuvant therapy as a covariate, patients were not further stratified by specific chemotherapy regimens. This decision was made to avoid potential confounding by indication, as the choice and intensity of subsequent treatments in the present retrospective cohort were largely driven by the initial pathological severity of the tumor.

In conclusion, the present study screened various valuable blood biomarkers and clinicopathological characteristics of patients and constructed and validated a nomogram utilizing these factors to evaluate the inflammatory status and predict OS in patients with CRC. The nomogram demonstrates potential enhancements in predictive power, sensitivity and accuracy compared with the conventional TNM staging system. As a more convenient and efficient tool, the nomogram holds promise in assisting clinical practitioners with informed decision-making.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SH, BS, HG and JC conceived and designed the project. ZP, QT, SW and XS collected the data. GC, BS and SH analyzed and interpreted the data. BS and JC drafted the manuscript. All authors read and approved the final version of the manuscript. BS and SH confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of The First Affiliated Hospital of Soochow University (Suzhou, China; approval no. 125). Written informed consent was obtained from all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
2. Riesco-Martinez MC, Modrego A, Espinosa-Olarte P, La Salvia A and Garcia-Carbonero R: Perioperative chemotherapy for liver metastasis of colorectal cancer: Lessons learned and future perspectives. Curr Treat Options Oncol 23: 1320-1337, 2022.
3. Panahi MH, Panahi H, Mahdavi Hezaveh A, Mansournia MA and Bidhendi Yarandi R: Survival rate of colon and rectum cancer in Iran: A systematic review and meta-analysis. Neoplasma 66: 988-994, 2019.
4. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC (eds), *et al*: AJCC Cancer Staging Manual, 8th edition. Springer, New York, NY, 2017.
5. Liu X, Qin J, Nie J, Sun H, Pan Y and Wang S: Reclassifying TNM stage I/II colorectal cancer into two subgroups with different overall survival, tumor microenvironment, and response to immune checkpoint blockade treatment. Front Genet 13: 948920, 2022.
6. Geng Y, Zhu D, Wu C, Wu J, Wang Q, Li R, Jiang J and Wu C: A novel systemic inflammation response index (SIRI) for predicting postoperative survival of patients with esophageal squamous cell carcinoma. Int Immunopharmacol 65: 503-510, 2018.
7. Kang Y, Zhu X, Lin Z, Zeng M, Shi P, Cao Y and Chen F: Compare the diagnostic and prognostic value of MLR, NLR and PLR in CRC patients. Clin Lab: Sep 1, 2021 (Epub ahead of print). doi: 10.7754/Clin.Lab.2021.201130.
8. Chen Y, Jiang W, Xi D, Chen J, Xu G, Yin W, Chen J and Gu W: Development and validation of nomogram based on SIRI for predicting the clinical outcome in patients with nasopharyngeal carcinomas. J Investig Med 67: 691-698, 2019.
9. Liu H, Li Z, Zhang Q, Li Q, Zhong H, Wang Y, Yang H, Li H, Wang X, Li K, *et al*: Multi-institutional development and validation of a nomogram to predict prognosis of early-onset gastric cancer patients. Front Immunol 13: 1007176, 2022.
10. Li Y, Chen D, Xuan H, Dragomir MP, Calin GA, Meng X, Chen M and Jin H: Construction and validation of prognostic nomogram for metaplastic breast cancer. Bosn J Basic Med Sci 22: 131-139, 2022.
11. Ogunwobi OO, Mahmood F and Akingboye A: Biomarkers in colorectal cancer: Current research and future prospects. Int J Mol Sci 21: 5311, 2020.
12. Sugimoto A, Fukuoka T, Shibutani M, Kasashima H, Kitayama K, Ohira M and Maeda K: Prognostic significance of the Naples prognostic score in colorectal cancer patients undergoing curative resection: A propensity score matching analysis. BMC Gastroenterol 23: 88, 2023.
13. Xie T, Wang X, Li M, Tong T, Yu X and Zhou Z: Pancreatic ductal adenocarcinoma: A radiomics nomogram outperforms clinical model and TNM staging for survival estimation after curative resection. Eur Radiol 30: 2513-2524, 2020.
14. Hanahan D: Hallmarks of cancer: New dimensions. Cancer Discov 12: 31-46, 2022.
15. Kubo H, Murayama Y, Arita T, Kuriu Y, Nakanishi M and Otsuji E: The prognostic value of preoperative Neutrophil-to-Lymphocyte ratio in colorectal cancer. World J Surg 40: 2796-2802, 2016.
16. Zhang Y, Zhou GQ, Liu X, Chen L, Li WF, Tang LL, Liu Q, Sun Y and Ma J: Exploration and validation of C-Reactive Protein/Albumin ratio as a novel Inflammation-based prognostic marker in nasopharyngeal carcinoma. J Cancer 7: 1406-1412, 2016.
17. Misiewicz A and Dymicka-Piekarska V: Fashionable, but What is their real clinical usefulness? NLR, LMR, and PLR as a promising indicator in colorectal cancer prognosis: A systematic review. J Inflamm Res 16: 69-81, 2023.
18. Gawiński C, Michalski W, Mróz A and Wyrwicz L: Correlation between Lymphocyte-to-monocyte ratio (LMR), Neutrophil-to-Lymphocyte ratio (NLR), Platelet-to-Lymphocyte ratio (PLR) and Tumor-Infiltrating lymphocytes (TILs) in Left-sided colorectal cancer patients. Biology (Basel) 11: 385, 2022.
19. Mahsuni Sevinc M, Riza Gunduz U, Kinaci E, Armagan Aydin A, Bayrak S, Umar Gursu R and Gunduz S: Preoperative neutrophil-to-lymphocyte ratio and plateletto-lymphocyte ratio as new prognostic factors for patients with colorectal cancer. J BUON 21: 1153-1157, 2016.
20. Maeda Y, Kawahara T, Koizumi M, Ito H, Kumano Y, Ohtaka M, Kondo T, Mochizuki T, Hattori Y, Teranishi J, *et al*: Lack of an association between Neutrophil-to-Lymphocyte ratio and PSA failure of prostate cancer patients who underwent radical prostatectomy. Biomed Res Int 2016: 6197353, 2016.
21. Byun SS, Hwang EC, Kang SH, Hong SH, Chung J, Kwon TG, Kim HH, Kwak C, Kim YJ and Lee WK: Prognostic significance of preoperative Neutrophil-to-Lymphocyte ratio in nonmetastatic renal cell carcinoma: A large, multicenter cohort analysis. Biomed Res Int 2016: 5634148, 2016.
22. Coffelt SB, Wellenstein MD and de Visser KE: Neutrophils in cancer: Neutral no more. Nat Rev Cancer 16: 431-446, 2016.
23. Zheng Z, Xu Y, Shi Y and Shao CL: Neutrophils in the tumor microenvironment and their functional modulation by mesenchymal stromal cells. Cell Immunol 379: 104576, 2022.
24. Chandra R, Karalis JD, Liu C, Murimwa GZ, Voth Park J, Heid CA, Reznik SI, Huang E, Minna JD and Brekken RA: The colorectal cancer tumor microenvironment and its impact on liver and lung metastasis. Cancers (Basel) 13: 6206, 2021.
25. Gijsbers K, Gouwy M, Struyf S, Wuyts A, Proost P, Opdenakker G, Penninckx F, Ectors N, Geboes K and Van Damme J: GCP-2/CXCL6 synergizes with other endothelial cell-derived chemokines in neutrophil mobilization and is associated with angiogenesis in gastrointestinal tumors. Exp Cell Res 303: 331-342, 2005.
26. Eck M, Schmausser B, Scheller K, Brändlein S and Müller-Hermelink HK: Pleiotropic effects of CXC chemokines in gastric carcinoma: Differences in CXCL8 and CXCL1 expression between diffuse and intestinal types of gastric carcinoma. Clin Exp Immunol 134: 508-515, 2003.
27. Que H, Fu Q, Lan T, Tian X and Wei X: Tumor-associated neutrophils and neutrophil-targeted cancer therapies. Biochim Biophys Acta Rev Cancer 877: 188762, 2022.
28. Bai Z, Zhou Y, Ye Z, Xiong J, Lan H and Wang F: Tumor-infiltrating lymphocytes in colorectal cancer: The fundamental indication and application on immunotherapy. Front Immunol 12: 808964, 2021.
29. Shin JS, Suh KW and Oh SY. Preoperative neutrophil to lymphocyte ratio predicts survival in patients with T1-2N0 colorectal cancer. J Surg Oncol 112: 654-657, 2015.
30. Kubo T, Ono S, Ueno H, Shinto E, Yamamoto J and Hase K: Impact of the perioperative neutrophil-to-lymphocyte ratio on the long-term survival following an elective resection of colorectal carcinoma. Int J Colorectal Dis 29: 1091-1099, 2014.
31. Friman TK, Jäämaa-Holmberg S, Åberg F, Helanterä I, Halme M, Pentikäinen MO, Nordin A, Lemström KB, Jahnukainen T, Räty R and Salmela B: Cancer risk and mortality after solid organ transplantation: A population-based 30-year cohort study in Finland. Int J Cancer 150: 1779-1791, 2022.

32. Slagter AE, Vollebergh MA, Caspers IA, van Sandick JW, Sikorska K, Lind P, Nordsmark M, Putter H, Braak J, Meershoe k-Klein Kranenbarg E, *et al*: Prognostic value of tumor markers and ctDNA in patients with resectable gastric cancer receiving perioperative treatment: Results from the CRITICS trial. Gastric Cancer 25: 401-410, 2022.
33. Tsai PL, Su WJ, Leung WH, Lai CT and Liu CK. Neutrophil-lymphocyte ratio and CEA level as prognostic and predictive factors in colorectal cancer: A systematic review and meta-analysis. J Cancer Res Ther 12: 582-589, 2016.
34. Toiyama Y, Inoue Y, Saigusa S, Kawamura M, Kawamoto A, Okugawa Y, Hiro J, Tanaka K, Mohri Y and Kusunoki M: C-reactive protein as predictor of recurrence in patients with rectal cancer undergoing chemoradiotherapy followed by surgery. Anticancer Res 33: 5065-5074, 2013.
35. Thirunavukarasu P, Sukumar S, Sathaiah M, Mahan M, Pragatheeshwar KD, Pingpank JF, Zeh H III, Bartels CJ, Lee KK and Bartlett DL: C-stage in colon cancer: Implications of carcinoembryonic antigen biomarker in staging, prognosis, and management. J Natl Cancer Inst 103: 689-697, 2011.
36. Lakemeyer L, Sander S, Wittau M, Henne-Bruns D, Kornmann M and Lemke J: Diagnostic and prognostic value of CEA and CA19-9 in colorectal cancer. Diseases 9: 21, 2021.
37. Rao H, Wu H, Huang Q, Yu Z and Zhong Z: Clinical value of serum CEA, CA24-2 and CA19-9 in patients with colorectal cancer. Clin Lab: Apr 1, 2021 (Epub ahead of print).
38. Baxter NN, Kennedy EB, Bergsland E, Berlin J, George TJ, Gill S, Gold PJ, Hantel A, Jones L, Lieu C, *et al*: Adjuvant therapy for stage II colon cancer: ASCO guideline update. J Clin Oncol 40: 892-910, 2022.