International Journal of Colorectal Disease (2025) 40:92
https://doi.org/10.1007/s00384-025-04875-0

RESEARCH

# Development of clinical inflammatory models to predict the efficacy of neoadjuvant chemoradiotherapy and survival in patients with locally advanced rectal cancer: a retrospective study

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Accepted: 25 March 2025


## Abstract

**Aim** To assess the ability of clinical inflammatory models to predict tumor regression grade (TRG) in response to neoadjuvant chemoradiotherapy (NCRT) and survival in patients with locally advanced rectal cancer (LARC).

**Methods** We retrospectively analyzed 161 patients with LARC who underwent NCRT followed by total mesorectal excision at Beijing Hospital between May 2007 and March 2022. By using logistic and Cox regression analyses, we developed prediction models for TRG in response to NCRT and overall survival (OS), respectively.

**Results** Multivariable logistic regression analysis indicated that variations in neutrophil, lymphocyte, and monocyte counts and pre-NCRT (preneoadjuvant chemoradiotherapy) CA19 - 9 levels independently predicted TRG in response to NCRT (all $P < 0.05$). Multivariate Cox regression analysis revealed that clinical tumor (cT) stage, pre-NCRT platelet count, CA19 - 9 level, number of lymph node metastases, and TRG could independently predict OS (all $P < 0.05$). On the basis of these results, we developed models to predict TRG and OS, respectively. The final predictive model for predicting the response to NCRT had areas under the curve (AUCs) of 0.783 and 0.809 in the training and testing cohorts, respectively; for predicting the 5-year OS rate, the AUC rates were 0.842 and 0.930 in the training and test sets, respectively. The calibration and decision curves showed favorable performance in our prediction models.

**Conclusion** We combined inflammatory markers with tumor characteristics and successfully developed clinical prediction models for TRG in response to NCRT and OS in patients with LARC. Our findings offer insights for optimizing treatment in patients with LARC.

**Keywords** Inflammatory biomarkers · Locally advanced rectal cancer · Neoadjuvant chemoradiotherapy · Prediction model · Tumor regression response · Survival

**Synopsis:** Clinical inflammatory models predict tumor regression grade in response to neoadjuvant chemoradiotherapy and survival in patients with locally advanced rectal cancer, aiding in the identification of patients who are more likely to achieve favorable treatment responses and improved survival outcomes.

## Abbreviations

| | |
|---|---|
| LARC | Locally advanced rectal cancer |
| LNM | Lymph node metastasis |
| NCRT | Neoadjvant chemoradiotherapy |
| PLT | Platelets |
| TR | Tumor regression |

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Published online: 14 April 2025

## Introduction

Rectal cancer is among the most common malignancies, ranking third in incidence and second in cancer-related mortality worldwide [1]. According to the National Comprehensive Cancer Network guidelines, patients with locally advanced rectal cancer (LARC) are routinely treated with neoadjuvant chemoradiotherapy (NCRT) followed by total mesorectal excision (TME) [2]. NCRT is an indispensable part of radical treatment, increasing the possibility of tumor downsizing, reducing the tumor stage, and achieving a pathological complete response (pCR) in a subset of patients. It also increases the possibility of achieving circumferential margin-free resections, tumor resection and sphincter retention, and disease-free survival (DFS) [3, 4]. Despite NCRT's ability to improve LARC prognosis, patients' response to NCRT varies widely, from complete nonresponse [5] to approximately 15–30% of patients achieving pCR [6]. Studies have reported a 5-year recurrence rate of 6–17% and a 5-year overall survival (OS) rate of 87–92.9% in patients achieving pCR [7, 8]. Patients who do not achieve pCR are likely to experience local or distant recurrence and have a poor prognosis [9]. Considering the patient's quality of life and the possibility of avoiding surgical complications, a "wait and see" strategy can be adopted for patients who achieve a complete response after NCRT [10, 11]. For patients who do not reach pCR, especially those with yp stage (Postneoadjuvant therapy pathologic stage) III and "high-risk" yp stage II rectal cancer, the guidelines of the European Society for Medical Oncology emphasize that postoperative adjuvant chemotherapy can be considered [12].

Clinically, for patients with rectal cancer undergoing NCRT, preoperative evaluation of treatment response is typically conducted via morphological magnetic resonance imaging (MRI), endorectal ultrasound, or colonoscopy at the conclusion of NCRT [13–16]. However, fibrosis and inflammatory responses induced by NCRT can hinder the accurate assessment of residual cancer, leading to potential misinterpretation of the treatment response [17]. These methods, when used alone, have inherent limitations in detecting changes in rectal tissue post-NCRT. Definitive confirmation of tumor regression (TR) requires histopathological examination of surgical samples, and the preoperative identification of pCR remains a significant challenge [18]. Therefore, identifying effective biomarkers to predict the TRG and complement existing assessment modalities is urgently needed. Such advancements would enhance the evaluation of treatment response and guide surgical decisions and subsequent management for patients with LARC [17].

Systemic inflammation plays a crucial role in the occurrence, progression, response to treatment, and prognosis of malignancies, including colorectal [19], lung [20], and gastric [21] cancers. It can affect the immune response, thereby promoting tumor proliferation, angiogenesis, and metastasis [22]. Circulating biomarkers, including carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA19 -9); inflammatory biomarkers, including C-reactive protein, albumin, and lymphocytes; and blood biomarkers, including hemoglobin and platelets, have been investigated for their predictive abilities [23]. Systemic inflammatory indicators can predict short-term pathological response and long-term DFS and OS in patients with LARC following NCRT [24]. Additionally, serological infection-based indicators, including the systemic immune-inflammation index, neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet–lymphocyte ratio (PLR), have shown promise in this regard [25, 26].

However, data on the prognostic value of these biomarkers in response to NCRT in patients with LARC are limited. It remains unclear whether combinations of these inflammatory markers can provide additional predictive and prognostic benefits. This study aimed to evaluate the predictive ability of clinical inflammatory models for TRG in response to NCRT and survival in patients with LARC.

## Materials and methods

### Patients

Data from 161 patients with LARC who underwent NCRT and radical surgery at Beijing Hospital between May 2007 and March 2022 were retrospectively analyzed. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Beijing Hospital Ethics Review Committee (approval number: 2024BJYYEC-KY041 -01). Written informed consent was not required owing to the retrospective nature of the study. The inclusion criteria were as follows: (1) age > 18 years, (2) complete acceptance of NCRT before radical surgery, (3) rectal adenocarcinoma confirmed through pathological examination, (4) the tumor, pathologically confirmed by colonoscopic biopsy, was located < 12 cm from the anal verge, (5) clinical stages T3–T4 or N +, and (6) accessibility of baseline hematologic indicators 4 weeks before and 2 weeks after initializing NCRT. The exclusion criteria were as follows: (1) incomplete clinical data or failure to follow up, (2) distant metastases (assessed via computed tomography [CT] or MRI), and (3) a combination of hematologic illnesses with acute or chronic infections.

### Neoadjuvant therapy

All patients received NCRT (including radiotherapy) with 45–50 Gy radiation delivered in 25 fractions and 2 regimens

of chemotherapy (oral capecitabine only and oral capecitabine plus oxaliplatin injection). Each regimen was administered in 2 courses before surgery and 4 courses after surgery, with one course lasting 21 days. Oxaliplatin (130 mg/m$^2$) was administered on day 1 of each course. Capecitabine 1000 mg/m$^2$ was administered from days 1 to 14. All patients underwent surgery following the TME guidelines 6 to 8 weeks after NCRT. The TME guidelines for abdominoperineal resection (Miles) and low anterior resection (Dixon) were followed.

## Evaluation of treatment response

The American Joint Committee on Cancer (AJCC) Staging Manual and Association of American Pathologists Guidelines recommend TRG for assessing the treatment response for rectal cancer patients [27]. Therefore, we chose the TRG as an outcome indicator for a tumor's response to NCRT, which was evaluated according to the 8th edition of the AJCC-TRG classification criteria [28]. TRG was assessed microscopically, and the following scores were provided: TRG0 (complete regression), no tumor cells; TRG1 (near-complete regression), only a single or small foci of tumor cells; TRG2 (partial regression), residual tumor showing significant regression but with an accumulation of single or small foci of tumor cells; and TRG3 (poor or no regression), extensive residual tumor without significant regression. TRG scores of zero to one indicate a good response to NCRT, and patients with these scores were categorized into the TR group. TRG scores of two to three indicate a poor response to NCRT, and patients with these scores are categorized into the non-TR group [29, 30]. The TRG was independently assessed by two experienced pathologists, both of whom were blinded to the patient outcomes. Any discrepancies in the initial TRG evaluation were resolved through consensus, and a dual-pathologist review was conducted to ensure the accuracy and reproducibility of the TRG data.

## Baseline hematological variables

We performed routine blood tests for CEA (carcinoembryonic antigen) and CA19 - 9 and blood biochemistry 1 week before and after NCRT. To enhance comparability between the TR and non-TR groups, we introduced the concept of "variation" in inflammatory indicators by dividing the post-NCRT value by the pre-NCRT value of each indicator. The "variations" in white blood cell, monocyte (vMonocyte), neutrophil (vNeutrophil), lymphocyte (vLymphocyte), and platelet (vPlatelet) counts were assessed. Moreover, we combined five inflammatory biomarkers: the NLR, the PLR, the LMR, the neutrophil × monocyte count (NXM), and the neutrophil–albumin ratio (NAR). We determined the cutoff values for the NLR, PLR, LMR, NXM, and NAR to attain the highest possible discrimination power between the TR and non-TR groups.

## Clinicopathological data collection

We retrieved data on age, sex, body mass index, distance of the tumor from the anal verge (distance), and clinical tumor, node, and metastasis stage (cTNM) from electronic medical records. We reviewed pathology reports for the histological type, tumor stage post-NCRT, lymph node metastasis (LNM), and TRG. DFS was defined as the period from the start of radical surgery for rectal cancer to tumor recurrence, metastasis, or death due to any cause. The time from surgery to patient death or last follow-up was defined as the OS. The last follow-up for all patients was in February 2024, with a minimum follow-up duration of 33 months and a median follow-up of 51 months. Follow-up visits were scheduled every 3 months during the first 2 years after surgery and every 6 months thereafter.

## Statistical analysis

We used IBM SPSS Statistics software (version: IBM SPSS Statistics 26, https://www.ibm.com/support/pages/downloading-ibm-spss-statistics-26) and R software (version: R4.4.0, https://www.R-project.org/, Vienna, Austria) for data analysis and plotting. The cutoff values for the NLR, PLR, LMR, NXM, and NAR were predicted via receiver operating characteristic (ROC) curves and Youden index. Variables with a normal distribution are expressed as the mean ± standard deviation and were analyzed via Student's *t* test. Nonnormally distributed variables are expressed as medians (interquartile ranges) and were analyzed via the Kruskal–Wallis or Mann–Whitney *U* test. The chi-square test or Fisher's exact test was used for categorical variables. Univariate and multivariate analyses were performed via logistic regression. Multivariate logistic analysis included variables with values of $P < 0.10$ identified in the univariate logistic analysis. Survival outcomes were analyzed via the Kaplan–Meier (KM) method, and differences were assessed via the logarithmic rank test. Univariate Cox analysis was performed, and variables with $P < 0.10$ were selected for multivariate Cox analysis. A nomogram was established to predict pCR and OS via multivariate analysis. The internal verification method and area under the curve (AUC) were used to evaluate the performance of the nomogram. Calibration was graphically evaluated via a calibration curve. Decision curve analysis (DCA) was performed to assess the clinical practicability of the nomogram. Statistical significance was set at $P < 0.05$ (two sided).

## Results

### Basic patient characteristics and correlations between inflammatory biomarkers and TR in response to NCRT

Among the 244 patients who were initially included, those with incomplete laboratory records ($n = 22$), distant metastases ($n = 19$), missing follow-up data ($n = 31$), or combined hematological illnesses and acute infections ($n = 11$) were excluded. Finally, 161 patients (47 females and 114 males) with a median age of 65 years were included in the study (Fig. 1). Among them, 52 and 109 (32.3% and 67.7%) were included in the TR and non-TR groups, respectively. According to whether TR was achieved as the outcome, the cutoff values for the baseline characteristics were determined via ROC curves. Baseline characteristics and comparisons between the TR and non-TR groups are shown in Table 1. The following parameters were lower in the TR group than in the non-TR group: distance; NXM; NAR; pre-NCRT white blood cell, monocyte, and neutrophil counts; CA19-9 level; and vMonocyte and vLymphocyte counts (all $P < 0.05$). No statistically significant differences were observed between the groups in terms of cTNM stage, age, sex, albumin, hemoglobin, CEA, LNM, or type of surgery (all $P > 0.05$). KM curve analysis revealed that the OS rates were significantly greater in the TR group than in the non-TR group ($P = 0.005$, Fig. 2A); however, the difference in the DFS rate between the two groups was not statistically significant ($P = 0.49$, Fig. 2B).

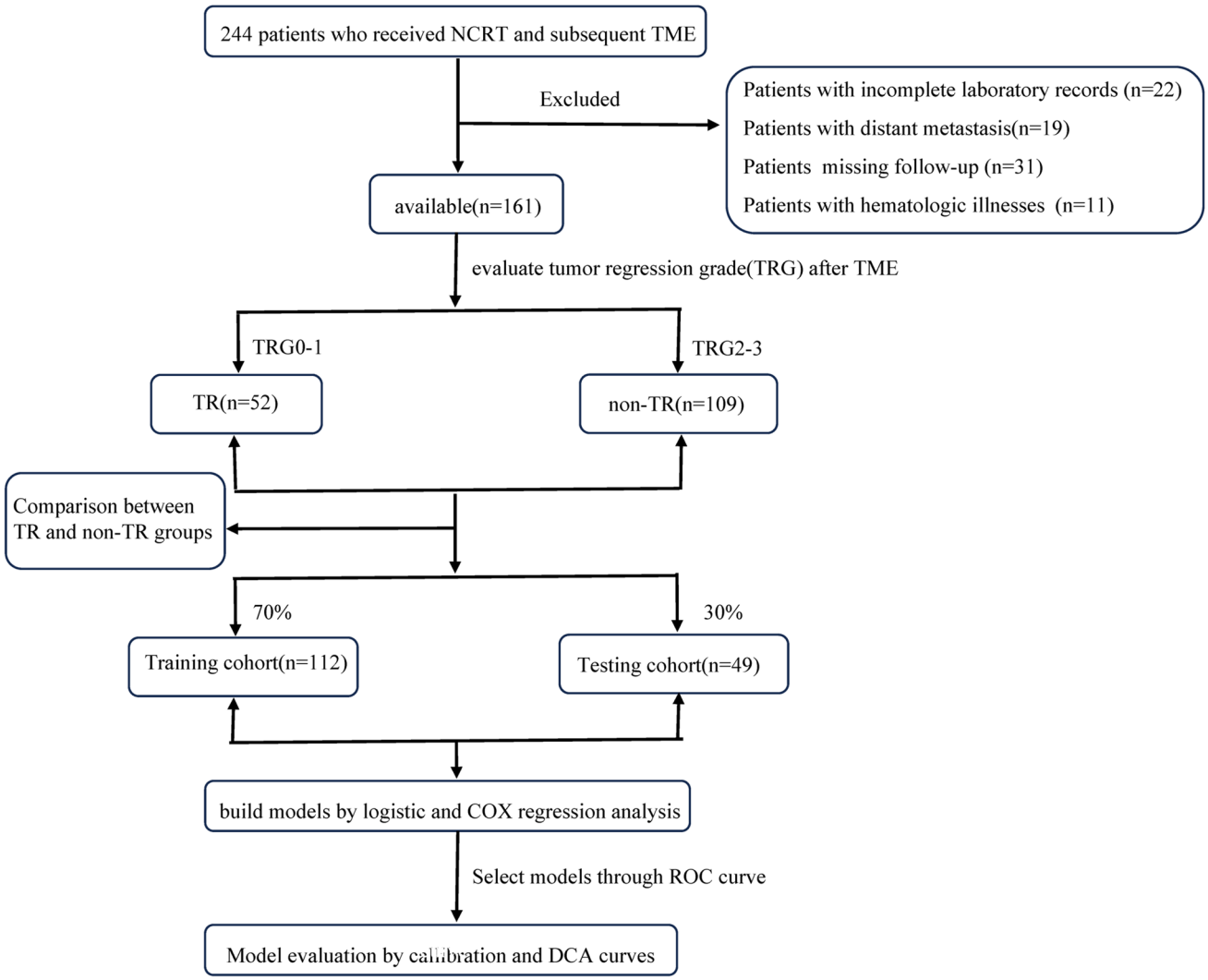



**Fig. 1** Filtering process of patient data from the initial inclusion of patient

**Table 1** The baseline characteristics and difference between the TR and non-TR groups. Values in bold indicate statistical significance ($P < 0.05$)

| Characteristics | Level | Overall | TR | Non-TR | *P* |
|---|---|---|---|---|---|
| *n* | | 161 | 52 | 109 | |
| Age (years, %) | < 65 | 107 (66.46) | 29 (55.77) | 78 (71.56) | 0.07 |
| | ≥ 65 | 54 (33.54) | 23 (44.23) | 31 (28.44) | |
| Sex (%) | Female | 47 (29.19) | 17 (32.69) | 30 (27.52) | 0.62 |
| | Male | 114 (70.81) | 35 (67.31) | 79 (72.48) | |
| BMI ($kg/m^2$, %) | < 24 | 147 (91.30) | 47 (90.38) | 100 (91.74) | 1.00 |
| | ≥ 24 | 14 (8.70) | 5 (9.62) | 9 (8.26) | |
| Distance (cm, %) | < 7 | 139 (86.34) | 50 (96.15) | 89 (81.65) | **0.02** |
| | ≥ 7 | 22 (13.66) | 2 (3.85) | 20 (18.35) | |
| Clinical T stage (%) | cT3 | 95 (59.01) | 32 (61.54) | 63 (57.80) | 0.78 |
| | cT4 | 66 (40.99) | 20 (38.46) | 46 (42.20) | |
| Clinical N stage (%) | cN0 | 33 (20.50) | 11 (21.15) | 22 (20.18) | 1.00 |
| | cN1 - 3 | 128 (79.50) | 41 (78.85) | 87 (79.82) | |
| Pre-NCRT NLR (%) | < 2.2 | 85 (52.80) | 32 (61.54) | 53 (48.62) | 0.17 |
| | ≥ 2.2 | 76 (47.20) | 20 (38.46) | 56 (51.38) | |
| Pre-NCRT PLR (%) | < 121 | 70 (43.48) | 28 (53.85) | 42 (38.53) | 0.10 |
| | ≥ 121 | 91 (56.52) | 24 (46.15) | 67 (61.47) | |
| Pre-NCRT LMR (%) | < 4.4 | 77 (47.83) | 21 (40.38) | 56 (51.38) | 0.26 |
| | ≥ 4.4 | 84 (52.17) | 31 (59.62) | 53 (48.62) | |
| Pre-NCRT NXM (%) | < 1.8 | 95 (59.01) | 38 (73.08) | 57 (52.29) | **0.02** |
| | ≥ 1.8 | 66 (40.99) | 14 (26.92) | 52 (47.71) | |
| Pre-NCRT NAR (%) | < 0.104 | 93 (57.76) | 38 (73.08) | 55 (50.46) | **0.01** |
| | ≥ 0.104 | 68 (42.24) | 14 (26.92) | 54 (49.54) | |
| Pre-NCRT WBC ($\times 10^9$,%) | < 6.28 | 66 (40.99) | 28 (53.85) | 38 (34.86) | **0.03** |
| | ≥ 6.28 | 95 (59.01) | 24 (46.15) | 71 (65.14) | |
| vWBC ($\times 10^9$, %) | < 0.603 | 57 (35.40) | 13 (25.00) | 44 (40.37) | 0.08 |
| | ≥ 0.603 | 104 (64.60) | 39 (75.00) | 65 (59.63) | |
| Pre-NCRT monocyte ($\times 10^9$, %) | < 0.515 | 119 (73.91) | 45 (86.54) | 74 (67.89) | **0.02** |
| | ≥ 0.515 | 42 (26.09) | 7 (13.46) | 35 (32.11) | |
| vMonocyte ($\times 10^9$, %) | < 0.694 | 20 (12.42) | 11 (21.15) | 9 (8.26) | **0.04** |
| | ≥ 0.694 | 141 (87.58) | 41 (78.85) | 100 (91.74) | |
| Pre-NCRT neutrophil ($\times 10^9$, %) | < 4.27 | 98 (60.87) | 39 (75.00) | 59 (54.13) | **0.02** |
| | ≥ 4.27 | 63 (39.13) | 13 (25.00) | 50 (45.87) | |
| vNeutrophil ($\times 10^9$, %) | < 1.282 | 145 (90.06) | 42 (80.77) | 103 (94.50) | **0.01** |
| | ≥ 1.282 | 16 (9.94) | 10 (19.23) | 6 (5.50) | |
| Pre-NCRT lymphocyte ($\times 10^9$, %) | < 1.805 | 77 (47.83) | 22 (42.31) | 55 (50.46) | 0.42 |
| | ≥ 1.805 | 84 (52.17) | 30 (57.69) | 54 (49.54) | |
| vLymphocyte ($\times 10^9$, %) | < 0.463 | 95 (59.01) | 37 (71.15) | 58 (53.21) | **0.05** |
| | ≥ 0.463 | 66 (40.99) | 15 (28.85) | 51 (46.79) | |
| Pre-NCRT Alb (g/L, %) | < 40 | 74 (45.96) | 18 (34.62) | 56 (51.38) | 0.07 |
| | ≥ 40 | 87 (54.04) | 34 (65.38) | 53 (48.62) | |
| Pre-NCRT Platelets ($\times 10^{12}$, %) | < 250 | 85 (52.80) | 33 (63.46) | 52 (47.71) | 0.09 |
| | ≥ 250 | 76 (47.20) | 19 (36.54) | 57 (52.29) | |
| vPlatelets ($\times 10^{12}$, %) | < 0.791 | 76 (47.20) | 23 (44.23) | 53 (48.62) | 0.72 |
| | ≥ 0.791 | 85 (52.80) | 29 (55.77) | 56 (51.38) | |
| Pre-NCRT Hgb (g/L, %) | < 138 | 108 (67.08) | 39 (75.00) | 69 (63.30) | 0.19 |
| | ≥ 138 | 53 (32.92) | 13 (25.00) | 40 (36.70) | |
| Pre-NCRT Hct (%) | < 34 | 31 (19.25) | 7 (13.46) | 24 (22.02) | 0.28 |
| | ≥ 34 | 130 (80.75) | 45 (86.54) | 85 (77.98) | |
| Pre-NCRT CEA (ng/ml, %) | < 5 | 72 (44.72) | 23 (44.23) | 49 (44.95) | 1.00 |
| | ≥ 5 | 89 (55.28) | 29 (55.77) | 60 (55.05) | |

**Table 1** (continued)

| Characteristics | Level | Overall | TR | Non-TR | *P* |
|---|---|---|---|---|---|
| Pre-NCRT CA19 -9 (U/ml, %) | < 5 | 46 (28.57) | 21 (40.38) | 25 (22.94) | **0.04** |
| | ≥ 5 | 115 (71.43) | 31 (59.62) | 84 (77.06) | |
| Pre-NCRT Glu (mmol/L, %) | < 6.1 | 146 (90.68) | 51 (98.08) | 95 (87.16) | 0.05 |
| | ≥ 6.1 | 15 (9.32) | 1 (1.92) | 14 (12.84) | |
| ypN (%) | ypN0 | 103 (63.98) | 37 (71.15) | 66 (60.55) | 0.26 |
| | ypN1 - 3 | 58 (36.02) | 15 (28.85) | 43 (39.45) | |
| ypT (%) | 0 | 15 (9.32) | 15 (28.85) | 0 (0.00) | < **0.0001** |
| | 1 | 2 (1.24) | 2 (3.85) | 0 (0.00) | |
| | 2 | 40 (24.84) | 12 (23.08) | 28 (25.69) | |
| | 3 | 89 (55.28) | 21 (40.38) | 68 (62.39) | |
| | 4 | 15 (9.32) | 2 (3.85) | 13 (11.93) | |
| LNM (%) | < 7 | 155 (96.27) | 51 (98.08) | 104 (95.41) | 0.40 |
| | ≥ 7 | 6 (3.73) | 1 (1.92) | 5 (4.59) | |
| Type of surgery (%) | Dixon | 120 (74.53) | 38 (73.08) | 82 (75.23) | 0.77 |
| | Miles | 41 (25.47) | 14 (26.92) | 27 (24.77) | |

## Construction of prediction models for TR in response to NCRT

The patients were randomly allocated into a training set (70%, $n = 112$) for model development and a testing set (30%, $n = 49$) for internal validation, using the createDataPartition function from the R caret package, ensuring stratification by critical clinical factors. In the training set, 42 patients achieved TR, whereas 10 patients in the test set achieved TR. Table 2 shows the results of the univariate and multivariate logistic regression analyses in the training cohort. Univariate logistic regression analysis indicated that distance (odds ratio [OR] = 5.00, 95% confidence interval [CI] 1.08–23.1, $P = 0.04$), monocyte count (OR = 3.35, 95% CI = 1.01–11.1, $P = 0.05$), lymphocyte count (OR = 3, 95% CI = 1.28–7.03, $P = 0.01$), pre-NCRT albumin level (OR = 0.38, 95% CI = 0.17–0.87, $P = 0.02$), pre-NCRT hematocrit level (OR = 0.31, 95% CI = 0.1–0.99, $P = 0.05$), pre-NCRT CA19 -9 level (OR = 2.59, 95% CI = 1.12–5.98, $P = 0.03$), and pre-NCRT glucose level (OR = 7.8, 95% CI = 0.97–2.4, $P = 0.01$) were risk factors for TR. We subsequently used variables from the univariate logistic regression analysis with values of $P < 0.1$) to perform a multivariate logistic regression analysis. The analysis results suggested that the vMonocyte count (OR = 0.19, 95% CI = 0.04–0.79, $P = 0.03$), vNeutrophil count (OR = 5.7, 95% CI = 1.32–28.56, $P = 0.02$), vLymphocyte count (OR = 0.35, 95% CI = 0.12–0.98, $P = 0.05$), and pre-NCRT CA19 -9 level (OR = 0.35, 95% CI = 0.12–0.99, $P = 0.05$) were independent risk factors for TR.

We used ROC curves to assess the model prediction efficiency for TR. On the basis of the results of the multivariate logistic regression analysis, we included the vMonocyte count, vNeutrophil count, vLymphocyte count, and pre-NCRT CA19 -9 level to construct a model for predicting TR; the model yielded an AUC of 0.752. We subsequently added several indicators with values of $P < 0.1$ in the univariate logistic regression, including distance and PLR, to construct four models and compared their AUC values. The results revealed that Model 4 (vMonocyte, vNeutrophil, and vLymphocyte counts; pre-NCRT CA19 -9 level; distance; and PLR) had the highest AUC value (0.783) (Fig. 3A). Therefore, the top-performing model4 in terms of AUC was selected as the final model for predicting TR. Consequently, we constructed a predictive nomogram of Model 4 for TR post-NCRT (Fig. 3B). In the nomogram, the straight line at the bottom represents the chance of achieving TR post-NCRT. The calibration curve revealed that the predicted probability of Model 4 correlated with the actual probability (Fig. 3C). The DCA results revealed that utilizing the optimal Model 4 was associated with benefits relative to the prediction of TR post-NCRT for LARC patients (Fig. 3D). Finally, we performed an internal validation of Model 4 in the testing cohort. The AUC of Model 4 in the testing cohort was 0.809 (Fig. 4A). The calibration curve (Fig. 4B) and DCA (Fig. 4C) showed favorable performance in Model 4, thus indicating that the TR prediction model was successful.

## Construction of prediction models for OS in patients with LARC after NCRT

Table 3 shows the univariate and multivariate Cox regression analyses of OS in patients with LARC in the training cohort. Univariate Cox regression analysis revealed that cT stage (hazard ratio [HR] = 2.17, 95% CI = 1.06–4.43, $P = 0.03$), ypN stage (HR = 0.51, 95% CI = 0.26–0.99, $P =$

0.04), LNM (HR = 0.14, 95% CI = 0.04–0.48, $P = 0.002$), and group (TR and non-TR) (HR = 2.66, 95% CI = 1.1–6.42, $P = 0.02$) were predictors of OS in patients with LARC. We then conducted a multivariate Cox regression analysis including variables with values of $P < 0.1$ in the univariate Cox regression analysis. The results suggested that cT stage (HR = 3.15, 95% CI = 1.5–6.62, $P = 0.002$), pre-NCRT platelet count (HR = 0.47, 95% CI = 0.23–0.96, $P = 0.03$), pre-NCRT CA19 - 9 level (HR = 0.35, 95% CI = 0.13–0.91, $P = 0.03$), LNM (HR = 0.1, 95% CI = 0.02–0.41, $P = 0.001$), and group (TR and non-TR) (HR = 2.6, 95% CI = 1.05–6.45, $P = 0.03$) were independent predictors of OS in patients with LARC.

According to the Cox regression analysis results, we combined the cT stage, pre-NCRT platelet count, CA19 - 9 level, LNM, group (TR and non-TR), and ypN stage to construct four different models for predicting survival in patients with LARC post-NCRT. We compared these four models via ROC curves. The AUCs of Model 4 (including cT stage, pre-NCRT platelet count, CA19 - 9 level, LNM, ypN stage, and group (TR and non-TR)) were 0.842 and 0.803 for the 5- and 3-year survival rates, respectively. The values were higher for Model 4 than for the other models (Fig. 5A and B). Therefore, We selected the final predictive model4 based on its highest AUC value in the training set and created a predictive nomogram for survival (Fig. 5C). The calibration curves of Model 4 for 5- and 3-year survival prediction (Fig. 5D and E) and DCA (Fig. 5F) were constructed for the training cohort. Finally, we performed an internal validation of Model 4 in the testing cohort. This model achieved an AUC for predicting the 5- and 3-year survival rates of 0.930 and 0.836, respectively, in the test cohort (Fig. 6A). Additionally, 5- and 3-year survival calibration curves (Fig. 6B and C) and DCA (Fig. 6D) were constructed to validate the performance of our model for predicting survival.

To assess the absence of overfitting in the two final selected predictive models, we applied a tenfold cross-validation approach. This method involves dividing the data into 10 equal parts: 9 parts are used for training, and the remaining 1 part is used for testing in each iteration. For each of the 10 randomly partitioned test sets, we evaluated model performance via ROC curves and calculated the area under the curve (AUC) for each set (see supplementary figure). The average AUC for TRG prediction Model 4 across the 10 test sets was 0.846, with a standard deviation of 0.033. For Model 4 for the prediction of 3-year overall survival (OS), the AUC was 0.847, with a standard deviation of 0.052. For the prediction of 5-year OS, Model 4 achieved an average AUC of 0.868, with a standard deviation of 0.077 (see supplementary table). These results indicate that both models demonstrate robustness across multiple random test sets, suggesting strong generalizability and no evidence of overfitting.

KM curve analysis revealed that patients in the low pre-NCRT platelet group had higher OS ($P = 0.004$, Fig. 2C) and DFS ($P = 0.026$, Fig. 2D) rates than those in the high pre-NCRT platelet group. Patients in the LNM − group had higher OS ($P = 0.005$, Fig. 2E) and DFS ($P = 0.011$, Fig. 2F) rates than those in the LNM + group did. Conversely, the OS and DFS rates were not significantly different between the upper and lower pre-NCRT CA19 - 9 level groups ($P > 0.05$, Fig. 2G and H).

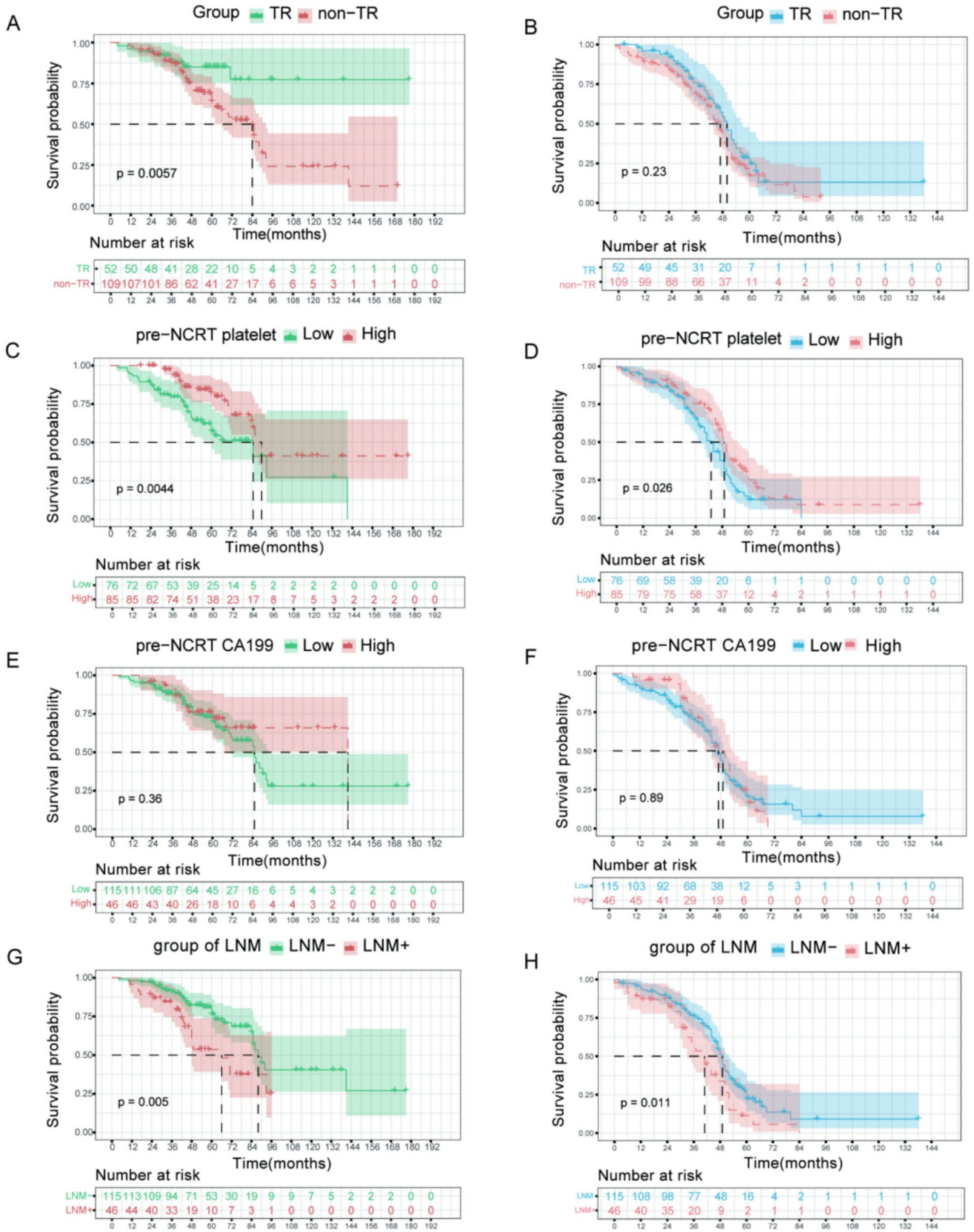
## Discussion

We investigated the relationships between several biomarkers that predict tumor response to NCRT and long-term outcomes, including OS and DFS, in patients with LARC. KM curve analysis revealed that the OS rate of the TR group was better than that of the non-TR group ($P = 0.005$), indicating that our data are reliable and valid for the long-term survival of patients.

Following NCRT, achieving pCR is a critical indicator of a favorable prognosis in patients with LARC. Previous studies and treatment guidelines for rectal cancer have shown that patients who achieve PCR have improved survival rates [31, 32]. Patients who achieved pCR had far better oncological outcomes than patients who did not achieve pCR, with higher 5-year OS (88% vs. 76%, respectively) and DFS (83% vs. 66%, respectively) rates [33]. And our data align with these findings. Once pCR is reached, these patients may be selected to adopt a "wait and see" strategy without excessive surgical treatment [34].

Unfortunately, no reliable model for predicting pCR in patients with LARC after NCRT exists [24]. Existing methods, such as MRI, endorectal ultrasound, and colonoscopy, are limited in their ability to judge tumor regression [34]. In addition, the preoperative judgment of the NCRT response grade determines our surgical approach and whether additional adjuvant therapy is needed after surgery [35]. Therefore, effective indicators are needed to help predict the TRG of patients after NCRT before surgery [24].

Scholars have recognized that the occurrence and progression of rectal cancer are determined by tumor characteristics and host-related variables [36]. Neutrophils, lymphocytes, monocytes, and platelets are well-known inflammatory indicators that play prognostic roles in malignancies [37]. Studies investigating inflammation-related indicators, including the NLR, LMR, PLR, NAR, and systemic inflammation response index (SIRI) as predictors of treatment response or patient prognosis, have reported varying results [38]. Lee et al. reported a strong correlation between poor tumor response and increased PLR following preoperative chemoradiotherapy [39]. Chiloiro et al. identified an NLR > 1.2


A
Group TR non−TR
Survival probability
p = 0.0057
Time(months)
Number at risk
TR 52 50 48 41 28 22 10 5 4 3 2 2 1 1 1 0 0
non−TR 109 107 101 86 62 41 27 17 6 6 5 3 1 1 1 0 0
B
Group TR non−TR
Survival probability
p = 0.23
Time(months)
Number at risk
TR 52 49 45 31 20 7 1 1 1 1 1 1 0
non−TR 109 99 88 66 37 11 4 2 0 0 0 0 0
C
pre−NCRT platelet Low High
Survival probability
p = 0.0044
Time(months)
Number at risk
Low 76 72 67 53 39 25 14 5 2 2 2 2 0 0 0 0 0
High 85 85 82 74 51 38 23 17 8 7 5 3 2 2 2 0 0
D
pre−NCRT platelet Low High
Survival probability
p = 0.026
Time(months)
Number at risk
Low 76 69 58 39 20 6 1 1 0 0 0 0 0
High 85 79 75 58 37 12 4 2 1 1 1 1 0
E
pre−NCRT CA199 Low High
Survival probability
p = 0.36
Time(months)
Number at risk
Low 115 111 106 87 64 45 27 16 6 5 4 3 2 2 2 0 0
High 46 46 43 40 26 18 10 6 4 4 3 2 0 0 0 0 0
F
pre−NCRT CA199 Low High
Survival probability
p = 0.89
Time(months)
Number at risk
Low 115 103 92 68 38 12 5 3 1 1 1 1 0
High 46 45 41 29 19 6 0 0 0 0 0 0 0
G
group of LNM LNM− LNM+
Survival probability
p = 0.005
Time(months)
Number at risk
LNM− 115 113 109 94 71 53 30 19 9 9 7 5 2 2 2 0 0
LNM+ 46 44 40 33 19 10 7 3 1 0 0 0 0 0 0 0 0
H
group of LNM LNM− LNM+
Survival probability
p = 0.011
Time(months)
Number at risk
LNM− 115 108 98 77 48 16 4 2 1 1 1 1 0
LNM+ 46 40 35 20 9 2 1 1 0 0 0 0 0

◂**Fig. 2** Survival outcome in patients with LARC after NCRT **A** OS and **B** DFS between TR and non-TR groups in patients with LARC after NCRT. **C** OS and **D** DFS between low and high PLT groups in patients with LARC after NCRT. **E** OS and **F** DFS between low and high CA19 -9 groups in patients with LARC after NCRT. **G** OS and **H** DFS between low and high number of LNM groups in patients with LARC after NCRT Abbreviations: LARC:, locally advanced rectal cancer; LNM:, lymph node metastasis; NCRT:, neoadjvant chemoradiotherapy; PLT:, platelets; TR:, tumor regression.

and an SIRI > 500 as independent risk variables for pCR post-NCRT [40]. William et al. reported that a lower baseline LMR and higher NLR and PLR are associated with shorter OS [38]. However, other scholars reported no predictive value for these markers. Kim et al. confirmed that post-NCRT, NLR, PLR, and LMR could not distinguish between total regression of tumors and residual disease [41]. Michael et al. reported that in patients with LARC who underwent radical surgery post-NCRT, the NLR and PLR neither predicted pCR and TR nor were they identified as risk factors for OS and DFS [42]. An et al. reported that a PLR < 300 and NLR < 2.8 did not correlate with pCR or 5-year OS [43]. This may be because previous studies have focused mostly on simple inflammatory markers and their relationship with the efficacy of NCRT and overlooked patient demographics and tumor characteristics [44].

No single biomarker can reliably predict pCR. Furthermore, the prognostic value of the aforementioned biomarkers' persistence post-NCRT remains unknown because prior research has generally focused on identifying variables linked to long-term survival or treatment response [45]. Therefore, we need to develop models that incorporate multiple parameters, including inflammatory markers, tumor markers, and tumor pathological characteristics, to comprehensively assess their value for the prediction of treatment response and long-term prognosis in patients with LARC. In this study, we investigated the relationships between several biomarkers in response to NCRT and long-term outcomes, especially OS, in patients with LARC.

**Table 2** Univariate and multivariate logistic regression analysis in the training cohort. Values in bold indicate statistical significance ($P < 0.05$)

| Characteristics | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | OR | CI | *P* | OR | CI | *P* |
| Age (years) | 0.7 | 0.32–1.57 | 0.39 | | | |
| Sex | 1.1 | 0.47–2.53 | 0.83 | | | |
| BMI (kg/m$^2$) | 1.29 | 0.37–4.47 | 0.69 | | | |
| Distance (cm) | 5 | 1.08–23.12 | **0.04** | 0.33 | 0.05–1.50 | 0.19 |
| Clinical T stage | 1.34 | 0.61–2.94 | 0.46 | | | |
| Clinical N stage | 0.95 | 0.36–2.48 | 0.92 | | | |
| Pre-NCRT WBC (× 10$^9$) | 1.31 | 0.59–2.88 | 0.51 | | | |
| vWBC (× 10$^9$) | 0.6 | 0.26–1.38 | 0.23 | | | |
| Pre-NCRT monocyte (× 10$^9$) | 2.18 | 0.79–5.98 | 0.13 | | | |
| vMonocyte (× 10$^9$) | 3.35 | 1.01–11.06 | **0.05** | 0.19 | 0.04–0.79 | **0.02** |
| Pre-NCRT neutrophil (× 10$^9$) | 1.87 | 0.82–4.24 | 0.14 | | | |
| vNeutrophil (× 10$^9$) | 0.35 | 0.1–1.19 | 0.09 | 5.74 | 1.32–28.56 | **0.02** |
| Pre-NCRT lymphocyte (× 10$^9$) | 0.5 | 0.23–1.09 | 0.08 | 1.39 | 0.48–4.16 | 0.55 |
| vLymphocyte (× 10$^9$) | 3 | 1.28–7.03 | **0.01** | 0.35 | 0.12–0.98 | **0.05** |
| Pre-NCRT Platelets (× 10$^{12}$) | 1.96 | 0.88–4.36 | 0.10 | | | |
| vPlatelets (× 10$^{12}$) | 0.73 | 0.34–1.59 | 0.43 | | | |
| Pre-NCRT NLR | 1.68 | 0.77–3.67 | 0.2 | | | |
| Pre-NCRT PLR | 2.01 | 0.92–4.39 | 0.08 | 0.85 | 0.28–2.56 | 0.76 |
| Pre-NCRT LMR | 0.63 | 0.29–1.38 | 0.25 | | | |
| Pre-NCRT NXM | 1.66 | 0.74–3.73 | 0.22 | | | |
| Pre-NCRT NAR | 1.96 | 0.88–4.4 | 0.10 | | | |
| Pre-NCRT Alb (g/L) | 0.38 | 0.17–0.87 | **0.02** | 2.08 | 0.78–5.79 | 0.15 |
| Pre-NCRT Hgb (g/L) | 1.17 | 0.51–2.69 | 0.72 | | | |
| Pre-NCRT Hct (%) | 0.31 | 0.1–0.99 | **0.05** | 2.43 | 0.58–12.26 | 0.24 |
| Pre-NCRT CEA (ng/ml) | 0.79 | 0.36–1.73 | 0.55 | | | |
| Pre-NCRT CA19 -9 (U/ml) | 2.59 | 1.12–5.98 | **0.03** | 0.36 | 0.12–0.99 | **0.05** |
| Pre-NCRT Glu (mmol/L) | 7.8 | 0.97–62.4 | **0.05** | 0.19 | 0.01–1.21 | 0.14 |

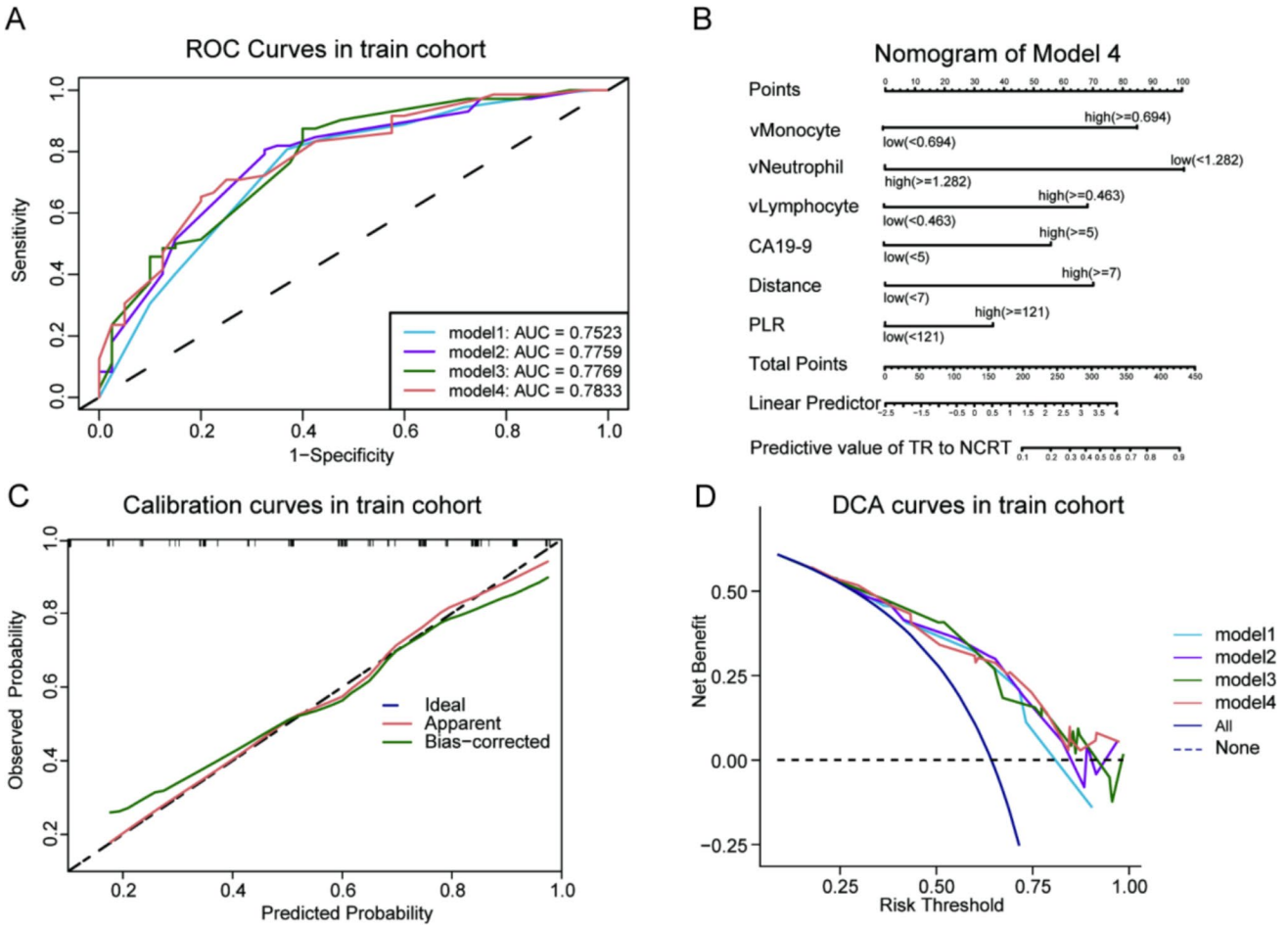



**Fig. 3** Construction of prediction models for TRG in response to NCRT **A** ROC analysis of four models based on multivariate logistic regression analysis results in the training cohort (Model 1: vMonocyte + vNeutrophil + vLymphocyte + pre-NCRT CA19 -9; Model 2: Model 1 + distance; Model 3: Model 2 + pre-NCRT hematocrit; Model 4: Model 2 + PLR). **B** The nomogram of the final selected Model 4, to predict the probability of TR in response to NCRT in patients with LARC. **C** Calibration curve for the nomogram in the training cohort. **D** Decision analysis curves of the nomogram for predicting TRG in response to NCRT in the training cohort. The y-axis represents the net benefit, and the x-axis represents the different threshold probabilities

Currently, no unified cutoff value is available for inflammatory markers, including the NLR, PLR, LMR, NXM, and NAR, to predict TR and prognosis post-NCRT [24]. Colloca et al. suggested that an NLR between 2 and 3 can predict pCR and patient prognosis [46]. In our study, we used ROC curves to predict the ideal cutoff values for the NLR, PLR, LMR, NXM, and NAR, which were 2.2, 121, 4.4, 1.8, and 0.104, respectively. Consistent with previous studies that reported negative results, we infer that the predictive significance of these five inflammatory markers is questionable. Our multivariate analysis revealed that LARC, NLR, PLR, LMR, NXM, and NAR were not associated with TR or survival. These combinations may consider only the ratios of several independent inflammatory markers while ignoring the variation in a certain inflammatory marker before and after NCRT. Therefore, we introduced the concept of "variation," which involves comparing the ratio of each inflammatory indicator within 1 week post-NCRT to that within 1 week pre-NCRT. vMonocyte, vNeutrophil, vLymphocyte, and pre-NCRT CA19 - 9 levels were identified as independent risk factors for TR post-NCRT. We combined the positive results with distance and the PLR to construct a model for predicting TR, which yielded AUCs of 0.783 and 0.809 in the training and test cohorts, respectively.

According to the statistical principles of uni- and multivariate regression analysis, researchers can set the threshold of the included $P$ value between 0.05 and 0.1 on the basis of actual clinical practice. Therefore, we included factors with values of $P < 0.1$ in the univariate regression analysis for the final model. Although distance and the PLR did not

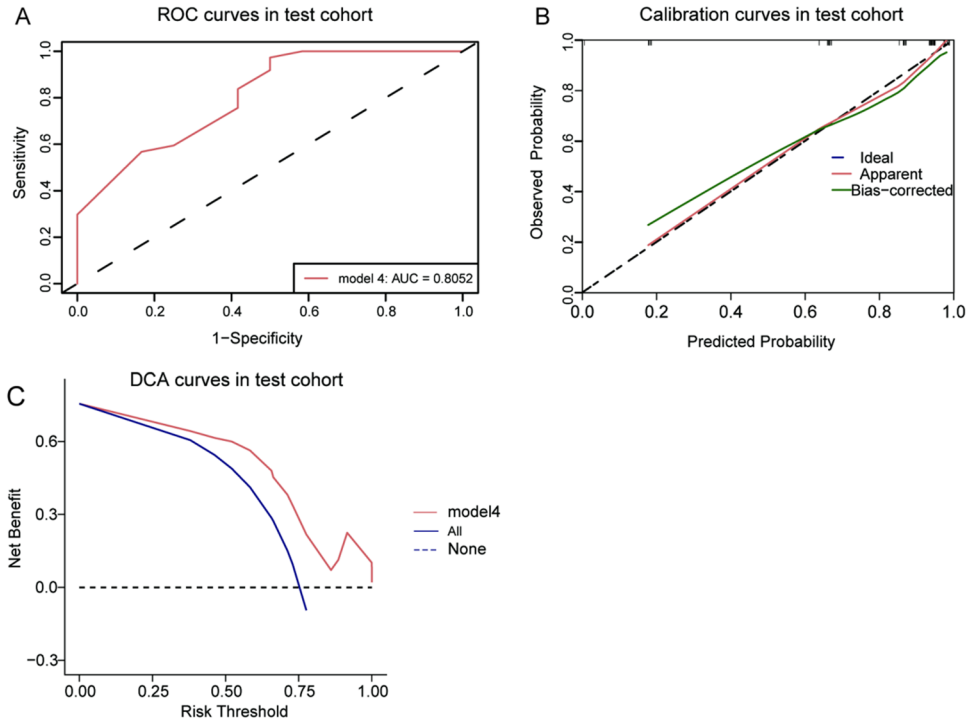



**Fig. 4** Validation of the prediction model4 for TRG in response to NCRT **A** ROC analysis of Model 4 in the testing cohort. **B** Curves with internal validation of the nomogram in the testing cohort. **C** Decision analysis curves of the nomogram for predicting TRG in response to NCRT in the testing cohort

have a value of $P < 0.05$ in the multivariate logistic analysis, they were significantly different in the univariate logistic analysis. Furthermore, a previous study showed that distance is an independent influencing factor in LARC post-NCRT [47]. The role of the PLR has been mentioned in a previous article that there is a strong correlation between increased PLR and poor tumor response following NCRT in patients with LARC [39]. In our study, after incorporating the distance and PLR, the AUC increased, further demonstrating that incorporating these aforementioned indicators is beneficial to the construction of our prediction model. All the validation curves confirmed the successful development of Model 4, which demonstrated high feasibility and practicality for predicting TRG in response to NCRT in patients with LARC.

By using Cox analysis, we identified cT stage, pre-NCRT platelet count, CA19 - 9 level, LNM, and group (TR and non-TR) as independent predictors of OS in patients with LARC. Additionally, we combined these positive factors with the ypN stage ($P = 0.048$ in univariate Cox regression analysis) to construct a model for predicting OS. This model showed greater accuracy in predicting 5-year survival (AUC = 0.842) than 3-year survival (AUC = 0.803) in the training cohort and testing cohort (AUC of 5-year survival vs. 3-year survival: 0.930 vs. 0.836). Therefore, these indicators should be included to improve the predictive efficiency of survival for LARC patients post-NCRT.

A comprehensive pairwise DeLong test analysis was conducted across all candidate models (Models 1–4) for both TRG and OS endpoints. Although these analyses demonstrated non-significant between-model AUC differences (all $P > 0.05$), Model 4 was selected as the most clinically suitable candidate through a systematic evaluation of: (1) discrimination performance (achieving the numerically highest AUC values), (2) multidimensional clinical validity via integrated routine variables (tumor distance and PLR ratio), and (3) robustness in calibration metrics (detailed in supplementary figure and table). This selection framework aligns with TRIPOD guideline recommendations for balancing statistical performance with clinical utility [48].

Our research included several innovations. Unlike previous studies that focused on single inflammatory markers or tumor characteristics, we combined inflammatory indicators, tumor markers, and tumor pathological characteristics to develop a prediction model for TRG in response to NCRT and long-term survival in patients with LARC. Additionally, we introduced inflammatory marker variation, drawing valuable conclusions. Furthermore, our model achieved high AUC values in both the training and testing cohorts, thus internally validating our data.

While our current model focuses on circulating biomarkers, future prospective studies should integrate quantitative MRI parameters—particularly radiomic features capturing spatial heterogeneity (e.g., gray-level co-occurrence

**Table 3** The results of the univariate and multivariate COX analysis about OS in the training cohort. Values in bold indicate statistical significance ($P < 0.05$)

| Characteristics | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | CI | *P* | HR | CI | *P* |
| Age (years) | 0.71 | 0.35–1.44 | 0.35 | | | |
| Sex | 1.04 | 0.49–2.19 | 0.93 | | | |
| BMI (kg/m$^2$) | 1.93 | 0.46–8.05 | 0.37 | | | |
| Distance (cm) | 0.56 | 0.25–1.25 | 0.16 | | | |
| Clinical T stage | 2.17 | 1.06–4.43 | **0.03** | 3.15 | 1.5–6.62 | **0.002** |
| Clinical N stage | 1.54 | 0.72–3.31 | 0.27 | | | |
| Pre-NCRT WBC ($\times 10^9$) | 0.59 | 0.28–1.23 | 0.16 | | | |
| vWBC ($\times 10^9$) | 0.83 | 0.41–1.68 | 0.61 | | | |
| Pre-NCRT monocyte ($\times 10^9$) | 0.8 | 0.39–1.64 | 0.54 | | | |
| vMonocyte ($\times 10^9$) | 0.32 | 0.08–1.33 | 0.12 | | | |
| Pre-NCRT neutrophil ($\times 10^9$) | 0.97 | 0.49–1.89 | 0.92 | | | |
| vNeutrophil ($\times 10^9$) | 1.64 | 0.39–6.88 | 0.50 | | | |
| Pre-NCRT lymphocyte ($\times 10^9$) | 0.75 | 0.39–1.46 | 0.41 | | | |
| vLymphocyte ($\times 10^9$) | 1.39 | 0.69–2.81 | 0.36 | | | |
| Pre-NCRT Platelets ($\times 10^{12}$) | 0.54 | 0.27–1.05 | 0.07 | 0.47 | 0.23–0.96 | **0.04** |
| vPlatelets ($\times 10^{12}$) | 1.56 | 0.79–3.08 | 0.20 | | | |
| Pre-NCRT NLR | 1.06 | 0.54–2.05 | 0.87 | | | |
| Pre-NCRT PLR | 0.78 | 0.39–1.53 | 0.46 | | | |
| Pre-NCRT LMR | 0.84 | 0.43–1.65 | 0.61 | | | |
| Pre-NCRT NXM | 1.08 | 0.55–2.13 | 0.82 | | | |
| Pre-NCRT NAR | 1.16 | 0.59–2.29 | 0.67 | | | |
| Pre-NCRT Alb (g/L) | 1.19 | 0.61–2.34 | 0.61 | | | |
| Pre-NCRT Hgb (g/L) | 0.78 | 0.39–1.53 | 0.47 | | | |
| Pre-NCRT Hct (%) | 0.99 | 0.43–2.29 | 0.99 | | | |
| Pre-NCRT CEA (ng/ml) | 0.9 | 0.46–1.78 | 0.77 | | | |
| Pre-NCRT CA19 - 9 (U/ml) | 0.44 | 0.18–1.07 | 0.07 | 0.35 | 0.13–0.91 | **0.03** |
| Pre-NCRT Glu (mmol/L) | 1.32 | 0.46–3.79 | 0.61 | | | |
| ypT | 0.5 | 0.15–1.67 | 0.26 | | | |
| ypN | 0.51 | 0.26–0.99 | **0.05** | 0.63 | 0.31–1.32 | 0.22 |
| LNM | 0.14 | 0.04–0.48 | **0.002** | 0.1 | 0.02–0.41 | **0.001** |
| Group (TR/non-TR) | 2.66 | 1.1–6.42 | **0.03** | 2.6 | 1.05–6.45 | **0.04** |

matrix texture) and dynamic contrast-enhanced perfusion metrics—to better characterize TR to NCRT [49]. Furthermore, emerging evidence implicates IL- 6/TNF-α-mediated stromal activation as a bridge between systemic inflammation and radiomic tumor phenotypes [50, 51]. Prospective studies combining serial MRI with spatial transcriptomics could reveal how circulating immune signals (e.g., elevated IL- 8) induce hypoxia-driven treatment resistance through CXCR1/2 signaling [52].

This study has several limitations. First, this was a single-center retrospective study with a small sample size, geographical limitations, and potential follow-up loss bias, and variable control was significantly worse than that in prospective studies. Second, owing to the retrospective nature of this study and the limited comparable datasets available from external institutions, we are unable to conduct formal external validation at this stage, but our model has been internally validated and has received a good response. Third, our analysis of blood biomarkers was nonspecific and subject to various physiological or pathological conditions, and their values changed over time. However, our study was limited in examining the prognostic potential of these biomarkers at two distinct time intervals—before and after NCRT. Therefore, future validation in larger external datasets will be critical to strengthen the validity of our prediction model. We are committed to external validation in the next phase of our study and plan to collaborate with other centers to validate the prediction model we developed in a broader patient population.

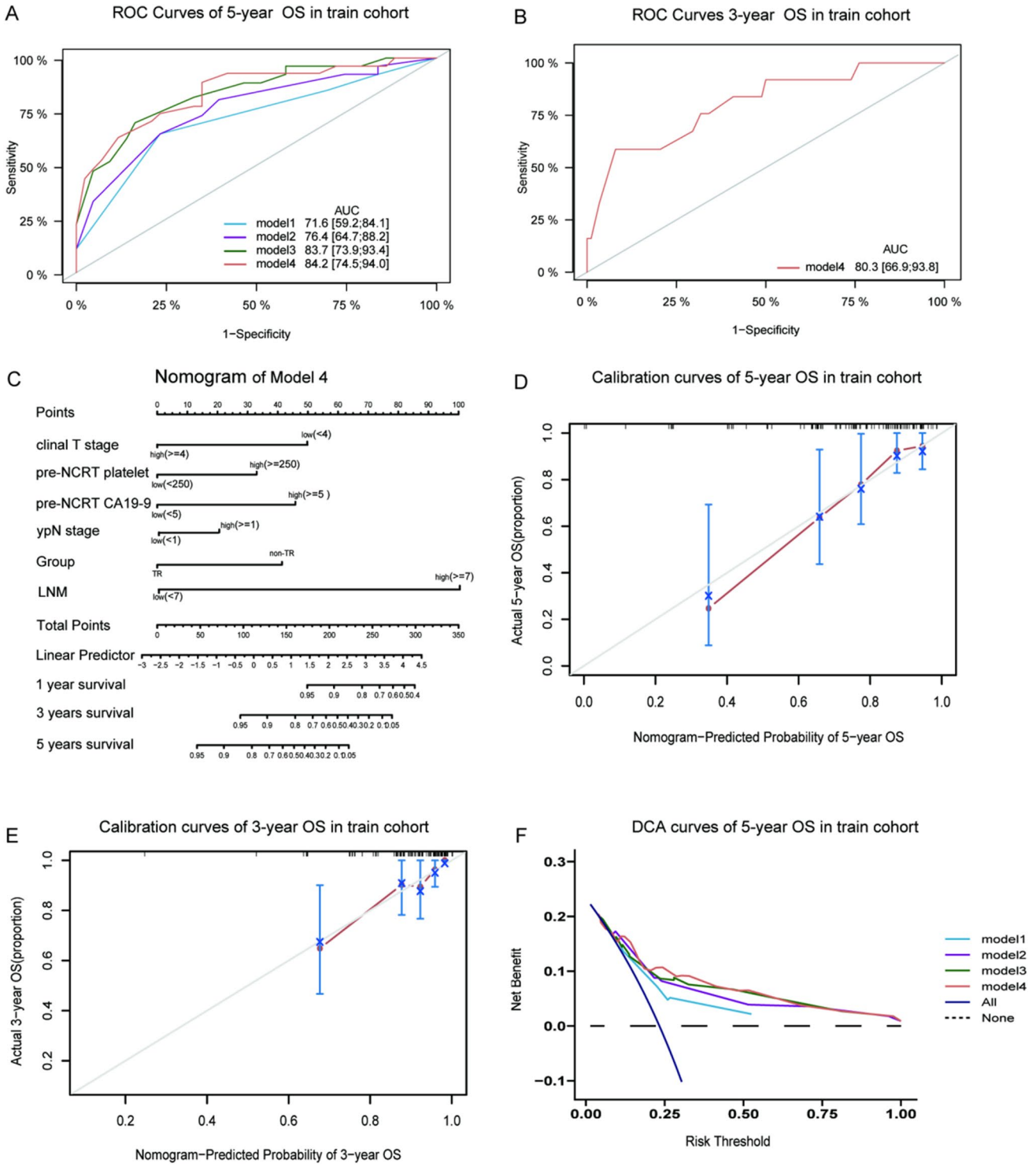



**Fig. 5** Construction of prediction models for OS in patients with LARC after NCRT **A**, **B** ROC analysis of four models in predicting the probability of 5- and 3-year OS rates in the training cohort (Model 1: Pre-NCRT platelets + pre-NCRT + CA19 -9 + cT stage; Model 2: Model 1 + LNM; Model 3: Model 2 + group [TR and non-TR groups]; Model 4: Model 3 + ypN stage). **C** The nomogram of the final selected Model 4, for predicting OS in patients with LARC after NCRT. **D**, **E** Calibration curves for 3- and 5-year OS rates in patients with LARC with internal validation in the training cohort. **F** Decision analysis curves of the nomogram for predicting OS in the training cohort

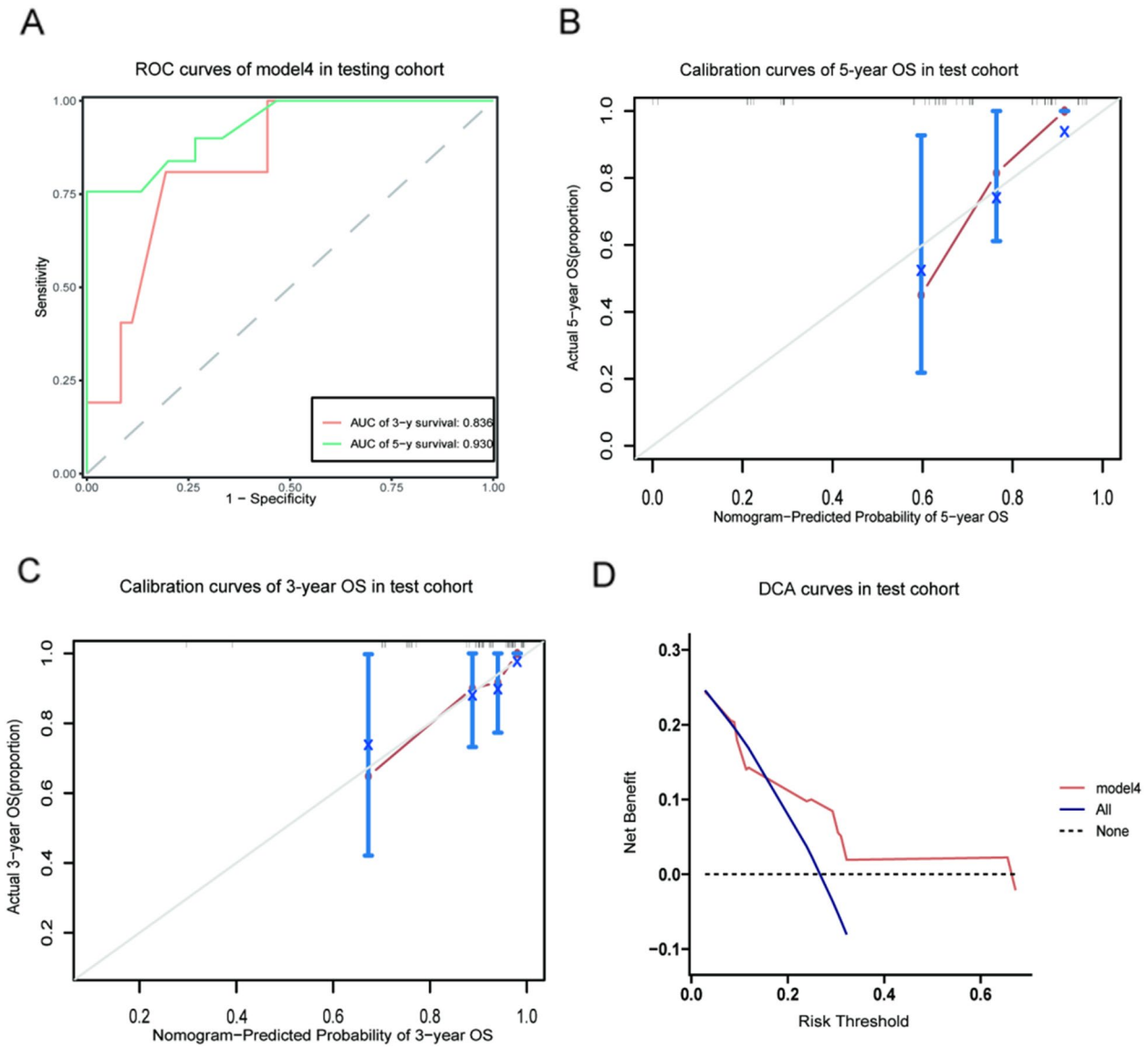



**Fig. 6** Validation of the prediction model4 for OS in patients with LARC after NCRT **A** ROC analysis of Model 4 for predicting 5- and 3-year survival rates in the testing cohort. **B**, **C** Calibration curves for 5- and 3-year OS rates in patients with LARC with internal validation in the testing cohort. **D** Decision analysis curves of the nomogram for predicting OS in the testing cohort

## Conclusion

We successfully combined inflammatory markers with tumor characteristics to develop clinical prediction models for TRG in response to NCRT and OS in patients with LACR. Although further validation in prospective trials is needed, our findings offer valuable insights for optimizing personalized care for patients with LARC.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00384-025-04875-0.

**Author contributions** Min Yang: data acquisition and analysis, statistical evaluation of the results, and drafting of the manuscript; Ruoyu Zhang: data analysis, statistical evaluation; Tao Yu: study design and guidance, critical revision of the manuscript, and study supervision conceptualization, review and critical revision; Yao Li, Fuhai Ma and Wenzhuo Jia: critical revision of the manuscript. All authors reviewed the manuscript.

**Funding** This work was supported by the National High Level Clinical Research Funding (BJ- 2022–170).

**Data availability** No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval** This study was approved by the Beijing Hospital Ethics Review Committee, National Center of Gerontology (approval number: 2024BJYYEC-KY041 - 01). All research was conducted in accordance with the Declaration of Helsinki and Istanbul.

**Consent to participate** Informed consent was obtained from all individual participants included in the study.

**Competing interests** The authors declare no competing interests.



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