Survival prediction in stage II/III rectal cancer: Role of immune-inflammatory biomarkers post neoadjuvant chemoradiotherapy

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Abstract. The precise prediction of survival outcomes in rectal cancer is essential for the development of personalized treatment strategies, particularly due to the heterogeneity in patient prognosis and response to therapy. The present study examined the prognostic significance of immune-inflammatory markers, in predicting outcomes of patients with stage II and III rectal cancer undergoing neoadjuvant chemoradiotherapy (NCRT). The present retrospective cohort analysis included 651 patients diagnosed with stage II/III rectal cancer, all of whom underwent NCRT as part of their treatment regimen. Data relative to clinical and pathological variables, including carcinoembryonic antigen (CEA), neutrophil count, lymphocyte count, eosinophil count and the neutrophil-to-lymphocyte ratio (NLR) were collected and examined. These variables were subjected to multivariate Cox regression analysis to independently predict overall survival (OS) and disease-free survival (DFS). Furthermore, prognostic nomograms were constructed and validated to enhance the prediction of patient outcomes. CEA, neutrophil count, lymphocyte count, eosinophil count and the NLR were determined to be independent predictors of OS and DFS in Cox regression analyses. A nomogram was constructed to incorporate these five prognostic biomarkers, which demonstrated good calibration and accurately predicted outcomes, with close agreement between the predicted and observed results. Notably, elevated post-NCRT NLR was significantly associated with poorer survival. In conclusion, the present study constructed and validated a prognostic model to predict OS and DFS in patients with stage II/III rectal cancer receiving NCRT, based on readily accessible clinical biomarkers. This model may have potential clinical utility for prognosis.

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Key words: risk stratification, immune-inflammatory biomarkers, neoadjuvant chemoradiotherapy, rectal cancer, overall survival, disease-free survival

Introduction

In the United States, neoadjuvant chemoradiotherapy (NCRT) combined with total mesorectal excision (TME) remains the standard of care for patients with resectable stage II/III rectal cancer (1,2). Although NCRT is able to effectively reduce local recurrence rates, its impact on overall survival (OS) remains uncertain (3,4). Total neoadjuvant therapy (TNT), a novel approach that combines chemotherapy and chemoradiotherapy prior to TME, has demonstrated improved survival outcomes in patients with locally advanced rectal cancer. Additionally, TNT can increase the number of patients eligible for organ-sparing therapies without increasing treatment toxicity or negatively impacting patient compliance (5-9). Although the benefits of TNT in improving OS remain limited, there is a need for more targeted and personalized treatment strategies. Identifying prognostic factors in clinical stage II/III rectal cancer is crucial, as this would enable clinicians to make informed decisions about whether to initiate intensified chemotherapy regimens. Such an approach would facilitate the development of personalized treatment plans tailored to individual risk profiles and thereby improve survival outcomes while minimizing treatment-related toxicities.

For predicting the prognosis of rectal cancer, clinical factors, tumor staging and histopathological features are crucial; however, their utility is often limited by the reliance on surgical procedures (10,11). As a result, research has increasingly focused on identifying reliable biomarkers that can effectively predict the prognosis of rectal cancer. Among these, blood cell-related biomarkers, such as carcinoembryonic antigen (CEA), neutrophil-to-lymphocyte ratio (NLR), as well as white blood cells, lymphocytes, neutrophils and

eosinophils, have garnered notable attention from clinicians due to their ease of measurement and proven ability to predict disease progression and prognosis (12-15).

The objectives of the present study were to develop a prognostic model using readily available clinical biomarkers, such as CEA, CA19-9, post-NCRT NLR, neutrophils, lymphocytes and eosinophils, to predict OS and disease-free survival (DFS) in patients undergoing NCRT. The rationale for this approach is that combining clinical biomarkers with clinical and pathological characteristics will produce a robust model capable of accurately forecasting OS and DFS while providing valuable insights into clinical treatment strategies. To achieve this aim, clinical biomarkers associated with OS and DFS were first identified, which were then integrated with clinical characteristics. The predictive performance of the model was assessed using calibration and discrimination metrics. Based on readily accessible and non-invasive biomarkers, this model serves as a practical tool for risk stratification and outcome prediction in patients treated with NCRT, facilitating personalized treatment and optimizing clinical management.

Materials and methods

Study design and patients. The present retrospective cohort analysis focused on patients with rectal cancer diagnosed at West China Hospital, Sichuan University (Chengdu, China), between January 2017 and December 2022. All included patients underwent NCRT followed by radical surgical resection (TME), with consecutive enrollment. Inclusion criteria were the following: i) Histopathologically confirmed diagnosis of rectal adenocarcinoma; ii) receipt of NCRT prior to surgery; iii) availability of clinicopathological and laboratory data; and iv) complete follow-up information for survival analysis. Patients were excluded if: i) Key laboratory values were missing; ii) they had concomitant malignancies or severe inflammatory/hematological conditions that could notably affect peripheral blood cell counts; or iii) they were lost to follow-up immediately after surgery. The present study was approved by the Ethics Committee of West China Hospital, Sichuan University (Chengdu, China; approval no. 2025-378).

Data collection and variables. Clinicopathological characteristics were extracted from the electronic medical records, including age, sex, pathological T stage (T0-2 vs. T3-4), pathological N stage (N- vs. N+), pathological TNM stage and the presence of vascular, lymphatic and perineural invasion. Pre-treatment laboratory biomarkers were obtained from routine blood tests conducted before NCRT, including CEA (ng/ml), CA 19-9 (U/ml), white blood cell count ($x10^9$/l), neutrophil count ($x10^9$/l), lymphocyte count ($x10^9$/l), eosinophil count ($x10^9$/l), albumin (ALB, g/l) and globulin (g/l). The post-NCRT inflammatory status was assessed using the post-NCRT NLR, calculated by dividing the neutrophil count by the lymphocyte count. Patients were then categorized into low-NLR and high-NLR groups based on the median NLR value of the study population.

Study endpoints and follow-up. The primary endpoints of the present study were OS and DFS. OS was defined as the time interval from the date of surgery to the time the patient succumbed to illness from any cause or the date of the last follow-up. DFS was defined as the time interval from the date of surgery to the first occurrence of tumor recurrence, distant metastasis, patient death or the date of the last follow-up. For patients who did not experience any of these events, their data were censored at the time of the last follow-up.

Statistical analysis. Continuous variables are presented as median and interquartile range (IQR), whereas categorical variables are expressed as frequencies and percentages. Initially, univariable Cox proportional hazards regression analysis was performed to identify variables significantly associated with OS and DFS. $P<0.05$ was considered to indicate a statistically significant difference. The significant variables from the univariable analysis were then used as predictors in a multivariable Cox regression analysis to identify independent prognostic factors associated with OS. This stepwise selection approach based on univariable $P<0.05$ is a widely used method in clinical prognostic studies for identifying candidate predictors (16). The results are presented as hazard ratios (HRs) with the corresponding confidence intervals (CI). Before performing the multivariable analysis, multicollinearity among the candidate predictors was assessed using the variance inflation factor (VIF). A VIF value <10 was considered indicative of the absence of significant multicollinearity, ensuring the stability of the regression coefficients.

Using the identified independent prognostic variables, individualized nomograms were constructed based on the multivariable Cox regression models using the 'rms' package (R package version 6.6-2; https://CRAN.R-project.org/package=rms) in R to predict OS and DFS at 3 years. The discrimination ability of the model was assessed using the concordance index, whereas calibration was evaluated using bootstrap-based calibration curves. The Brier score was also calculated to compare the predicted probabilities with the observed results. Internal validation was performed through bootstrap resampling with 1,000 iterations. Statistical analyses were conducted using SPSS software (version 31.0.2.0; IBM, Corp.) and R software (version 4.3.1; RStudio, Inc.), with a significance level set at $\alpha=0.05$.

To evaluate the stability and robustness of the prognostic models over time, sensitivity analyses were performed by stratifying the study population into two treatment periods: 2017-2019 and 2020-2022. The interaction between treatment periods and each prognostic factor was assessed to ensure consistency of the findings.

Results

Characteristics of the patients. The present study included 651 patients who underwent surgical resection following NCRT for rectal cancer (Fig. 1). The median age of the patients was 56.0 years (IQR: 50.0-66.0 years), with 411 (63.1%) males and 240 (36.9%) females. All patients were diagnosed with clinical stage II/III disease at baseline (pre-treatment), which was the primary inclusion criterion. Specifically, 382 (58.7%) patients had clinical stage II disease and 269 (41.3%) had clinical stage III disease prior to NCRT. Following NCRT and

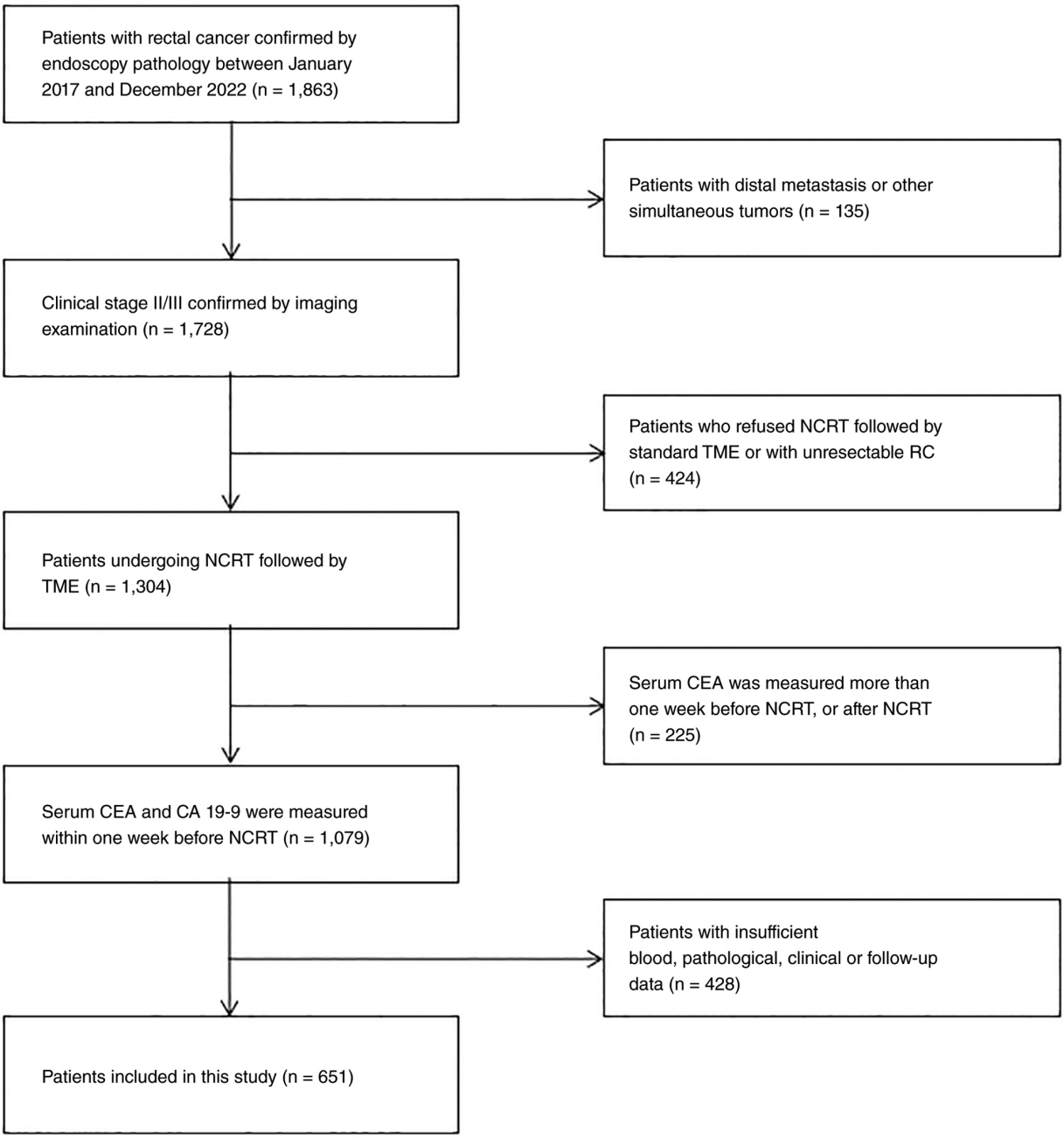

Figure 1. Flow chart of the patient selection process and the study design. NCRT, neoadjuvant chemoradiotherapy; TME, total mesorectal excision; RC, rectal cancer; CEA, carcinoembryonic antigen.

surgery, pathological staging classified 324 (49.8%) tumors as T0-2 and 327 (50.2%) as T3-4. Node-negative (N-) disease was present in 489 (75.1%) patients, whereas 162 (24.9%) had node-positive (N+) disease. Postoperative pathological TNM staging (ypStage 0, n=132, 20.3%; I, n=150, 23.0%; II, n=201, 30.9%; and III n=168, 25.8%) demonstrated a trend towards tumor downstaging from baseline clinical stage II/III. Vascular and lymphatic invasion were each identified in 39 (6.0%) patients, and perineural invasion was observed in 114 (17.5%).

Pre-treatment laboratory parameters indicated median serum levels of CEA and CA 19-9 at 4.21 ng/ml (IQR: 2.20-10.53 ng/ml) and 13.56 U/ml (IQR: 7.77-25.31 U/ml), respectively. The median white blood cell count was 6.14 x10^9/l (IQR: 5.50-7.21 x10^9/l). Specifically, the median counts (x10^9/l) for leukocyte subpopulations were: Neutrophils, 3.73 (IQR: 2.98-4.64); lymphocytes, 1.69 (IQR: 1.30-1.94); monocytes, 0.42 (IQR: 0.33-0.53); and eosinophils, 0.14 (IQR: 0.08-0.23). Additionally, the median concentrations of ALB and globulin were 43.9 g/l (IQR: 41.3-45.7 g/l) and 26.2 g/l (IQR: 23.5-28.3 g/l), respectively.

The median post-NCRT NLR was 2.84 (IQR: 1.98-4.21). During a median follow-up of 37.0 months (IQR: 26-51), 62 deaths (OS events) and 76 recurrences or deaths (DFS events) were observed (Table I). Considering the number of clinical events relative to the predictors included in the multivariable models, the event-per-variable ratio was adequate, indicating a low-risk of statistical overfitting.

Table I. Clinicopathological characteristics.

Variable	Median (IQR)
Age, years	56.0 (50.0-66.0)
Sex	
Male	411
Female	240
Pre-treatment clinical staging	
Clinical stage II	382
Clinical stage III	269
Post-NCRT pathological staging[a]	
ypT0-2	324
ypT3-4	327
ypN-	489
ypN+	162
ypStage 0	132
ypStage I	150
ypStage II	201
ypStage III	168
Post-NCRT NLR	2.84 (1.98-4.21)
Tumor invasion	
Vascular invasion	39
Lymphatic invasion	39
Perineural invasion	114
Pre-treatment laboratory biomarkers[b]	
CEA, ng/ml	4.21 (2.20-10.53)
CA 19-9, U/ml	13.56 (7.77-25.31)
WBC, x10^9/l	6.14 (5.50-7.21)
Neutrophil count, x10^9/l	3.73 (2.98-4.64)
Lymphocyte count, x10^9/l	1.69 (1.30-1.94)
Monocyte count, x10^9/l	0.42 (0.33-0.53)
Eosinophil count, x10^9/l	0.14 (0.08-0.23)
Albumin, g/l	43.9 (41.3-45.7)
Globulin, g/l	26.2 (23.5-28.3)
Survival outcomes	
OS	62
DFS	76

[a]Pathological staging reflects post-NCRT surgical pathology. The proportion of patients with ypStage 0 or I reflects tumor downstaging following effective NCRT. [b]All laboratory biomarkers were measured before NCRT initiation. CEA, carcinoembryonic antigen; NCRT, neoadjuvant chemoradiotherapy; NLR, neutrophil-to-lymphocyte ratio; LYM, lymphocytes; EOS, eosinophil; WBC, white blood cell; OS, overall survival, DFS, disease free survival; IQR, interquartile range.

Independent prognostic factors for OS. Univariable Cox regression analysis identified pre-treatment CEA levels, neutrophil, lymphocyte and eosinophil counts, as well as the post-NCRT NLR group, as significant predictors of OS (P<0.05; Table SI). No significant multicollinearity was observed among the included variables, with all VIF values remaining <10 (Table SII). Multivariable Cox proportional hazards regression identified several pre-treatment variables as independent predictors of OS. Elevated CEA levels (adjusted HR=1.01; 95% CI: 1.01-1.02; P<0.001), higher neutrophil counts (adjusted HR=1.19; 95% CI: 1.07-1.34; P=0.002) and increased eosinophil counts (adjusted HR=1.49; 95% CI: 1.01-2.21, P=0.043) were significantly associated with increased mortality risk. Conversely, a higher lymphocyte count was a protective factor associating with improved OS (adjusted HR=0.62; 95% CI: 0.44-0.88; P=0.008).

Furthermore, post-treatment inflammatory status, as reflected by the post-NCRT NLR, demonstrated a notable prognostic impact. Patients in the high-NLR group exhibited significantly worse OS compared with those in the low-NLR group (adjusted HR=2.73; 95% CI: 1.71-4.36; P<0.001) (Table II).

Independent prognostic factors for DFS. Consistent with the OS results, univariable analysis for DFS indicated that pre-treatment CEA levels, neutrophil, lymphocyte and eosinophil counts, alongside the post-NCRT NLR group, were significant prognostic factors (P<0.05; Table SI). No significant multicollinearity was observed among these variables, with all VIFs remaining <10 (Table SII).

Multivariable Cox regression analysis for DFS similarly revealed that elevated pre-treatment CEA (adjusted HR=1.01; 95% CI: 1.01-1.02; P<0.001), higher neutrophil counts (adjusted HR=1.14; 95% CI: 1.05-1.24; P=0.011) and increased eosinophil counts (adjusted HR=2.47; 95% CI: 1.17-5.22; P=0.018) were independently associated with poorer outcomes. Conversely, a higher lymphocyte count served as a significant protective factor (adjusted HR=0.54; 95% CI: 0.41-0.72; P<0.001). Consistent with the OS findings, the post-NCRT NLR group remained a notable independent predictor of DFS, with the high-NLR cohort demonstrating significantly worse DFS than the low-NLR cohort (adjusted HR=2.27; 95% CI: 1.55-3.34; P<0.001) (Table III).

Sensitivity analysis. The sensitivity analysis stratified by treatment period (2017-2019 vs. 2020-2022) demonstrated that the prognostic impact of all key variables remained consistent over time. For OS, the HRs for pre-treatment CEA, neutrophil and lymphocyte counts and the post-NCRT NLR group showed no significant temporal interaction (all P>0.05 for interaction; Table SIII). Similar consistency was observed with regard to DFS, with the predictive value of all included variables remaining stable across both time cohorts (all P>0.05 for interaction; Table SIV). These findings indicate that the prognostic performance of the model is robust and independent of the treatment era.

Development of nomograms for individualized survival prediction. Based on independent prognostic factors identified through multivariable Cox regression, two nomograms were developed to estimate the individualized 3-year survival probabilities (Figs. 2 and 3). Both the OS and DFS nomograms incorporated pre-treatment CEA levels, neutrophil, lymphocyte and eosinophil counts, alongside the post-NCRT NLR group. Each variable was assigned a weighted score derived from its regression coefficient, with the cumulative sum corresponding

Table II. Multivariable Cox proportional hazards regression analysis for overall survival in patients with rectal cancer receiving NCRT.

Characteristic	β coefficient	SE	Adjusted HR (95% CI)	P-value
Pre-NCRT variables				
CEA	0.013	0.003	1.01 (1.01-1.02)	<0.001
Neutrophils	0.172	0.055	1.19 (1.07-1.34)	0.002
LYM	-0.471	0.176	0.62 (0.44-0.88)	0.008
EOS	0.401	0.198	1.49 (1.01-2.21)	0.043
Post-NCRT variable				
Low NLR group			1	
High NLR group			2.73 (1.71-4.36)	<0.001

CEA, carcinoembryonic antigen; NCRT, neoadjuvant chemoradiotherapy; LYM, lymphocyte count; EOS, eosinophil count; NLR, neutrophil-to-lymphocyte ratio; HR, hazard ratio; CI, confidence interval.

Table III. Multivariable cox proportional hazards regression analysis for disease-free survival.

Characteristics	β Coefficient	SE	Adjusted HR (95% CI)	P-value
Pre-NCRT variables				
CEA	0.012	0.002	1.01 (1.01-1.02)	<0.001
Neutrophils	0.131	0.041	1.14 (1.05-1.24)	0.011
LYM	-0.621	0.136	0.54 (0.41-0.72)	<0.001
EOS	0.903	0.382	2.47 (1.17-5.21)	0.018
Post-NCRT variable				
Low NLR group			1	
High NLR group			2.27 (1.55-3.34)	<0.001

CEA, carcinoembryonic antigen; NCRT, neoadjuvant chemoradiotherapy; LYM, lymphocyte count; EOS, eosinophil count; NLR, neutrophil-to-lymphocyte ratio; HR, hazard ratio; CI, confidence interval.

to the predicted 3-year probability of OS or DFS. The models achieved a C-index of 0.738 (95% CI: 0.702-0.774) for OS and 0.765 (95% CI: 0.731-0.799) for DFS.

Calibration of the nomograms. The calibration curves for the 3-year OS and DFS nomograms demonstrated notable agreement between predicted probabilities and observed outcomes, indicating satisfactory model calibration (Fig. 4). Furthermore, Brier scores of 0.13 and 0.16 for OS and DFS, respectively, confirmed the predictive accuracy of both nomograms.

Discussion

In the present retrospective cohort study of patients with rectal cancer who underwent NCRT and surgical resection, prognostic nomograms to predict 3-year OS and DFS were developed and internally validated using readily available clinical biomarkers. The principal findings were as follows: i) Pre-treatment CEA was consistently associated with both OS and DFS, confirming its established role as a surrogate marker of tumor burden and aggressive biological behavior (13,17); ii) peripheral immune-inflammatory indicators, particularly neutrophil and lymphocyte counts, independently predicted survival outcomes; iii) post-NCRT NLR stratification demonstrated a notable prognostic effect, with a high-NLR associating with significantly higher risks of mortality and disease recurrence; and iv) calibration curves showed notable agreement between predicted and observed 3-year outcomes, indicating that the proposed models provide clinically meaningful, individualized survival estimates.

CEA is an oncofetal glycoprotein, and in patients with cancer, including rectal malignancies, elevated CEA levels are typically associated with tumor burden and biological aggressiveness. Numerous studies have established CEA as a notable prognostic marker for predicting OS and DFS in rectal, gastric and periampullary cancers (17-19). Specifically, elevated pre-treatment CEA levels in rectal cancer are associated with poor prognosis, higher recurrence rates and reduced survival (20-22). Mechanistically, this effect may be attributed to the role of CEA in mediating tumor cell adhesion, migration and metastasis, thereby facilitating disease progression (23,24). Consistent findings across multiple cohorts highlight CEA as a reliable biomarker for assessing baseline tumor burden and treatment efficacy (25-27). Furthermore, postoperative CEA

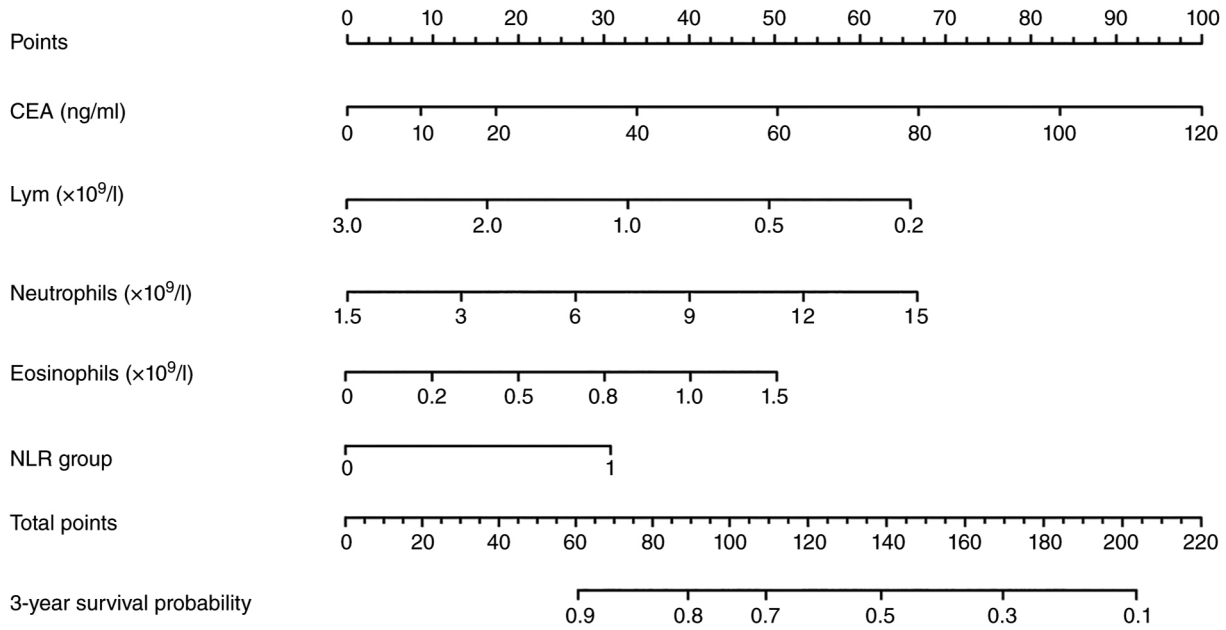

Figure 2. Nomogram for predicting 3-year overall survival based on CEA, neutrophils, lymphocytes, eosinophils, and post-NCRT NLR parameters. CEA, carcinoembryonic antigen; NCRT, neoadjuvant chemoradiotherapy; NLR, neutrophil-to-lymphocyte ratio; LYM, lymphocytes; EOS, eosinophil.

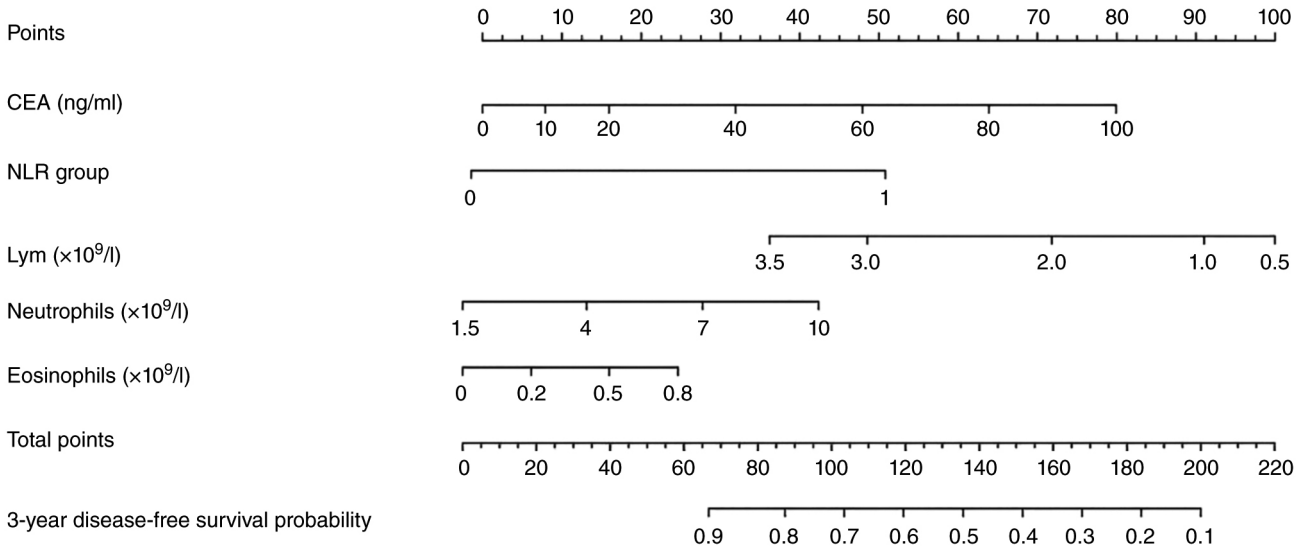

Figure 3. Nomogram for predicting 3-year disease-free survival based on CEA, neutrophils, lymphocytes, eosinophils, and post-NCRT NLR parameters. CEA, carcinoembryonic antigen; NCRT, neoadjuvant chemoradiotherapy; NLR, neutrophil-to-lymphocyte ratio; LYM, lymphocytes; EOS, eosinophil.

elevation serves as an early indicator of disease recurrence, enabling timely clinical intervention (4,28,29). Therefore, CEA remains invaluable not only for cancer diagnosis but also for prognostication, facilitating risk stratification and guiding tailored therapeutic strategies. Integrating CEA with other parameters, such as immune-inflammatory biomarkers, can further enhance its prognostic accuracy.

CA 19-9 is a well-established tumor marker for gastrointestinal malignancies, particularly pancreatic and biliary cancers, and has been explored in colorectal cancer, although its prognostic value in rectal cancer remains less well established (19,30). However, it did not demonstrate a statistically significant association with survival outcomes in the univariable Cox regression analysis performed in the present study and was therefore not retained in the multivariable model. This aligns with previous studies highlighting that CEA offers superior sensitivity and specificity over CA 19-9 to predict recurrence and survival in rectal cancer (30,31). The lack of prognostic significance of CA 19-9 in the present study may be due to its elevation being more frequently associated with advanced disease stages or specific biological subtypes (30). Conversely, CEA serves as a more robust and universal indicator of tumor burden and therapeutic response in stage II/III rectal cancer (30,31).

Immune-inflammatory markers, particularly neutrophil and lymphocyte counts, exhibit notable independent associations with OS and DFS in various malignancies, such as lung, breast and cervical cancers (32-35). Systemic inflammation typically

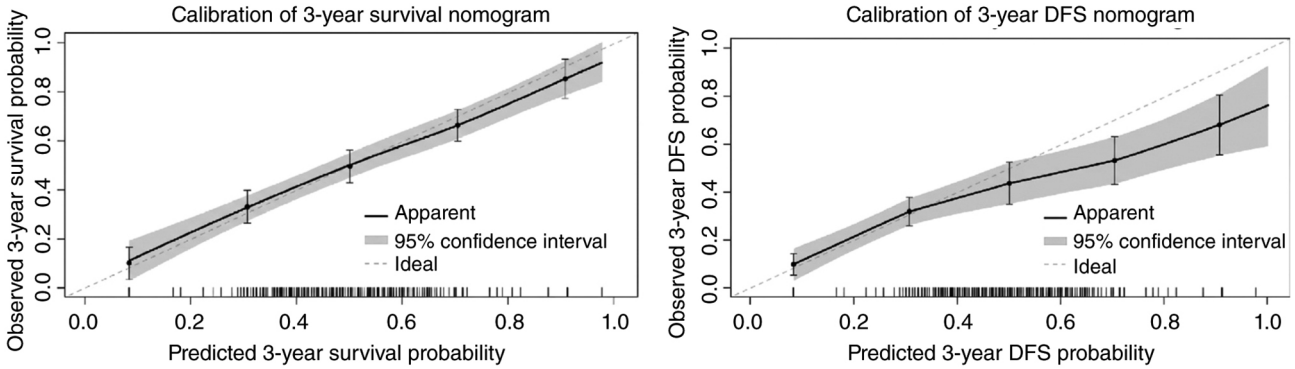

Figure 4. Calibration curves for the nomograms of overall survival and DFS. DFS, disease-free survival.

elevates circulating peripheral neutrophils, which promote tumor progression by secreting pro-inflammatory cytokines, proteases and other pro-tumorigenic factors that facilitate angiogenesis, immunosuppression and metastasis (36-38). By contrast, lymphocytes, such as cytotoxic T lymphocytes, are the primary effectors of antitumor immunity (39). Consequently, peripheral lymphopenia is consistently associated with a poorer prognosis and reduced survival in multiple types of cancer, including breast cancer and cervical cancer (34,35).

A notable finding of the present study is the independent association between elevated eosinophil counts and worse DFS. Although traditionally linked to allergic reactions and parasitic infections, research has revealed a complex role for eosinophils in cancer biology (40). Eosinophils can secrete epidermal growth factor and transforming growth factor-β1, which promote tumor proliferation and epithelial-mesenchymal transition (40). By contrast, eosinophil-derived cationic proteins, neurotoxins and granzymes can induce tumor apoptosis, whereas their production of interferon-γ, CXCL9 and CXCL10 enhances $CD8^+$ T cell-mediated cytotoxicity (40). Despite these antitumor mechanisms, the present study observed that peripheral eosinophilia was associated with inferior DFS, which suggests that eosinophil-driven inflammation may represent an adverse immune signature within the tumor microenvironment. However, the precise underlying pathways remain to be fully elucidated; thus, this preliminary finding warrants cautious interpretation.

The NLR integrates two interconnected biological processes: Systemic inflammatory activation and the suppression of anti-tumor immune surveillance, thereby reflecting the balance between pro-tumorigenic inflammation and host immunity (32). As a composite metric, the NLR is less vulnerable to physiological fluctuations in individual leukocyte counts, offering a stable representation of the systemic immune-inflammatory state. The post-NCRT NLR likely captures both baseline host immunity and dynamic biological responses to neoadjuvant therapy, which may explain its robust prognostic value relative to single-cell markers. Mechanistically, systemic inflammation is increasingly recognized as a key driver of colorectal cancer progression. Neutrophils facilitate this through multiple pathways, including the secretion of pro-tumorigenic cytokines, stimulation of angiogenesis and promotion of metastasis (36-38). Conversely, circulating lymphocytes serve as a primary index of host cytotoxic capacity, with lymphopenia denoting compromised immune surveillance and diminished anti-tumor efficacy.

In the present study, elevated neutrophil and reduced lymphocyte counts were significantly associated with inferior OS and DFS, reflecting the delicate balance between pro-tumorigenic inflammation and anti-tumor immunity. Notably, the post-NCRT NLR demonstrated a marked prognostic impact on both survival metrics. By integrating markers of systemic inflammation and immune capacity, the NLR provides an intuitive and clinically applicable surrogate for host immune status. This concurrent reflection of different biological phenomena produces a comprehensive immune-inflammatory profile, likely explaining the superior predictive value of NLR compared with individual cell counts (41). Although baseline leukocyte counts indicate pre-treatment status, the post-NCRT NLR captures treatment-induced inflammatory remodeling and dynamic biological shifts following neoadjuvant therapy (28). Consequently, the association between a high post-NCRT NLR and poor outcomes may indicate persistent inflammatory activation or incomplete immune restoration, reflecting more aggressive tumor biology and an inadequate immune response.

Due to the routine accessibility of these laboratory markers, the nomograms developed in the present study offer a practical tool for individualized risk estimation. By incorporating an established tumor marker (CEA) alongside dynamic immune parameters (neutrophil, lymphocyte and eosinophil counts, as well as post-NCRT NLR), these models facilitate the identification of high-risk patients who may benefit from intensified adjuvant therapy or closer long-term surveillance. Ultimately, this approach enhances clinical risk stratification, addressing the prognostic heterogeneity often observed among patients with identical conventional tumor characteristics. Future studies should explore alternative modeling strategies, such as evaluating the NLR as a continuous variable or employing spline-based techniques, to better elucidate potential non-linear associations.

Further research is required to rigorously validate the proposed prognostic model. External validation in diverse clinical settings and large patient cohorts is essential to confirm its robustness. Additionally, integrating novel biomarkers will be crucial for refining the predictive accuracy of the model. Ultimately, the application of advanced analytical technologies can further improve early risk stratification and personalized prognostication for patients with rectal cancer.

Several limitations of the present study should be acknowledged. First, due to the retrospective single-center study design, the present study was inherently susceptible to selection and information bias. Second, the models underwent only internal bootstrap validation; therefore, external validation in prospective, multicenter cohorts is required to confirm their generalizability. At present, we are unable to perform external validation using publicly available independent cohorts, as existing datasets lack the specific post-NCRT immune-inflammatory biomarkers required by the present model. Third, the proposed nomograms were not directly compared with established prognostic frameworks, such as TNM staging or microsatellite instability (MSI) status. TNM staging remains the cornerstone of prognostic stratification in colorectal cancer, and MSI status has emerged as a notable biomarker predicting treatment response and survival (42,43). Future studies should evaluate the incremental prognostic value of these biomarker-based models relative to standard clinical tools. Finally, relying primarily on univariable significance for multivariable candidate selection may introduce bias and model instability. Subsequent studies should employ more robust variable selection methods, such as penalized regression (such as LASSO), to mitigate these risks.

In conclusion, the present study developed prognostic nomograms to predict OS and DFS in patients with stage II/III rectal cancer undergoing NCRT and surgical resection. The post-NCRT NLR emerged as a notable prognostic determinant, underscoring the role of host immune-inflammatory responses in shaping long-term clinical outcomes. Although the proposed models demonstrated robust predictive accuracy and were successfully internally validated, external multicenter prospective validation are warranted to confirm their generalizability and clinical utility.

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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

The present study was conceptualized and designed by BL and YL. The methodology and implementation were performed by BL, YW, TH, SX, XW and YY. Data were curated (extraction and organization of clinical records, as well as verification of data accuracy and completeness) and validated by TH, SX, XW and YY. Statistical analysis using SPSS and R software was conducted by BL. Data interpretation and manuscript drafting were performed by BL and YW. Critical revision of the manuscript for important intellectual content was performed by YW and XW. TH was responsible for project coordination and management. All authors have read and approved the final version of the manuscript. BL and TH confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The protocol for the present study has been approved by the Ethics Committee of West China Hospital, Sichuan University (approval no. 2025-378) and was conducted in strict accordance with the principles outlined in The Declaration of Helsinki. After review and evaluation by the ethics committee, the study was deemed to meet the criteria for exemption from informed consent, and therefore, no additional informed consent was required from the patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this manuscript, the authors used ChatGPT for language editing. All AI-generated content was reviewed and revised by the authors, who take full responsibility for the content of the present publication.

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