Biomolecules and Biomedicine
ISSN: 2831-0896 (Print) | ISSN: 2831-090X (Online)
Journal Impact Factor® (2024): 2.2
CiteScore® (2024): 5.2
www.biomolbiomed.com | blog.bjbms.org

RESEARCH ARTICLE

Wang et al: Pretreatment CNI predicts survival in LARC

Pretreatment comprehensive nutritional index predicts survival in locally advanced rectal cancer after neoadjuvant chemoradiotherapy and surgery

Zhexue Wang[#], Liming Zhao[#], Pu Cheng[#], Mandula Bao, Fei Huang, Ruoxi Tian, Jiyun Li, Hengchang Liu[*], Zhaoxu Zheng[*]

Department of Colorectal Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

[#]These authors contributed equally to this work: Zhexue Wang, Liming Zhao, and Pu Cheng.

*Correspondence to Zhaoxu Zheng: zzx_20003@126.com and Hengchang Liu: drhengchang_liu@163.com

DOI: https://doi.org/10.17305/bb.2026.13609

ABSTRACT

Nutritional status significantly influences treatment tolerance and long-term outcomes in patients with locally advanced rectal cancer (LARC); however, individual nutritional markers may not fully capture overall nutritional reserves. This study aimed to evaluate the prognostic value of a comprehensive nutritional index (CNI), derived from principal component analysis, in patients with LARC undergoing neoadjuvant chemoradiotherapy (NCRT) followed by surgical intervention. We conducted a retrospective analysis of 336 patients with LARC who received NCRT followed by surgery between 2014 and 2019. The CNI was constructed using body mass index, usual body weight percentage, total lymphocyte count, serum albumin, and hemoglobin levels. Patients were categorized into low- and high-CNI groups based on an outcome-oriented cut point, and survival outcomes were assessed through Kaplan–Meier analysis and Cox regression. Patients with lower CNI scores exhibited significantly poorer overall survival and disease-free survival compared to those with higher CNI scores. Furthermore, CNI remained independently associated with both endpoints after adjusting for established pathological factors, including tumor regression grade and ypN stage. A nomogram that integrates CNI, tumor regression grade, and ypN stage demonstrated favorable discrimination and calibration during internal validation. These findings support the use of pretreatment CNI as a practical nutritional composite associated with prognosis in LARC patients treated with NCRT, and the proposed nomogram may enhance individualized risk estimation.

Keywords: Comprehensive nutritional index, nutritional status, neoadjuvant chemoradiotherapy, prognosis, locally advanced rectal cancer.

INTRODUCTION

Colorectal cancer (CRC) remains one of the most common malignancies worldwide and continues to impose a substantial disease burden despite advances in screening and treatment(1). Locally advanced rectal cancer (LARC) constitutes a major subset of CRC and is associated with high risks of recurrence and metastasis, making the optimization of prognostic evaluation and treatment strategies a key clinical challenge(2).

In recent years, LARC treatment paradigms have shifted from surgery alone to multidisciplinary integrated therapy. For LARC patients, neoadjuvant chemoradiotherapy (NCRT) followed by total mesorectal resection has become the classical therapeutic approach, offering improved resectability and better local control(3,4). Nonetheless, tumor responses to NCRT are highly heterogeneous, and LARC patients still face severe complications and poor prognosis(5,6). Therefore, it is necessary to utilize preoperative clinical parameters for more precise prognosis prediction.

Malnutrition is common in rectal cancer due to tumor burden, treatment toxicity, and metabolic alterations, and is closely associated with increased complications, reduced treatment tolerance, and poorer survival(7). Conventional nutritional markers, such as body mass index (BMI) and serum albumin (ALB) and prognostic nutritional index (PNI), only partially reflect a patient's systemic condition(8–10). The Comprehensive Nutritional Index (CNI), derived from five nutrition-related indicators including BMI, usual body weight percentage (UBWP), total lymphocyte count (TLC), albumin (ALB), and hemoglobin (HB), integrates anthropometric and laboratory parameters into a composite score. Recent studies have demonstrated the prognostic relevance of CNI in several malignancies, including patients with LARC treated with NCRT, suggesting that CNI may serve as a robust indicator of systemic nutritional and immune status(11–15).

However, further independent validation of CNI in larger, well-characterized cohorts and exploration of its integration with established pathological prognostic factors remain warranted. Therefore, the present study aimed to independently validate the prognostic value of CNI in patients with LARC treated at a high-volume cancer center and to further develop a CNI-based prognostic model by integrating pathological

response and nodal status, with the goal of improving postoperative risk stratification and clinical applicability.

MATERIALS AND METHODS

Patients

A total of 336 patients with LARC treated at our institute between September 2014 and July 2019 were retrospectively analyzed. All patients had histologically confirmed rectal adenocarcinoma and received standardized long-course NCRT, followed by total mesorectal excision. During the study period, 978 patients with LARC were initially screened. Patients were excluded if they did not receive neoadjuvant therapy, had non-adenocarcinoma histology, received neoadjuvant chemotherapy or radiotherapy alone, had a history of other malignancies, were managed with a watch-and-wait strategy after neoadjuvant treatment, underwent surgery at outside institutions, or had incomplete key clinicopathological data or were lost to follow-up. After the stepwise application of these predefined criteria, 336 patients who completed standard NCRT followed by radical surgery and had complete data were included in the final analytical cohort. This study was a retrospective cohort analysis based on routinely collected clinical data. All patient information was anonymized prior to analysis, and no additional interventions or patient contact were involved. According to institutional policy and national regulations, this type of retrospective analysis using de-identified data was exempt from formal ethics committee approval, and the requirement for informed consent was waived.

Patient selection

From 2014 to 2019, 978 patients with rectal cancer were screened. After excluding patients without neoadjuvant chemoradiotherapy (n = 596), non-adenocarcinoma histology (n = 3), non-standard neoadjuvant treatment (n = 23), a history of other malignancies (n = 9), and missing key clinical data or follow-up (n = 11), 336 patients were ultimately included in the study.

Clinicopathological data

The clinicopathological data were collected, including age, gender, smoking history, drinking history, hypertension, diabetes, BMI, serum carcinoembryonic antigen (CEA)

and cancer antigen (CA) 19-9 levels, T-stages and N-stages evaluated by MRI, vessel invasion, perineural invasion, ypT and ypN stages evaluated by histopathology. Tumor regression grade (TRG) was evaluated on postoperative surgical specimens using the Dworak grading system(16), which classifies tumor response to NCRT into five levels based on the proportion of residual tumor cells and the extent of fibrosis. In this system, TRG 0 indicates no evidence of regression, TRG 1 reflects minimal tumor response, TRG 2 denotes moderate regression with a mixture of fibrosis and residual tumor, TRG 3 represents marked regression with only small clusters of viable cells, and TRG 4 corresponds to complete tumor regression with an absence of residual carcinoma. For analytical purposes, patients were further categorized into two groups according to their pathological response. Those with TRG 3–4 were defined as having a good response, whereas those with TRG 0–2 were classified as having a poor response. This dichotomization allowed for clearer comparison of treatment outcomes within the study cohort.

NCRT

All patients received long-course NCRT according to a standardized institutional protocol. Pelvic radiotherapy was delivered with a total dose of 45–50.4 Gy in 25–28 fractions. Concurrent chemotherapy consisted of fluoropyrimidine-based regimens, including continuous-infusion 5-fluorouracil or oral capecitabine, administered during radiotherapy.

Follow-up

Postoperative surveillance was conducted for all patients at regular intervals, with follow-up visits scheduled every three months during the first postoperative year and every six months thereafter for a minimum of three years. The primary survival endpoints were overall survival (OS) and disease-free survival (DFS). OS was defined as the interval from the date of surgery to death attributable to rectal cancer or to the most recent follow-up for patients who were still alive. DFS was defined as the time from surgical resection to the occurrence of tumor recurrence. Follow-up assessments were carried out through outpatient clinic visits or telephone interviews.

Calculation of nutritional status

Based on previous research, CNI was calculated from five single nutritional indicators, including HB, TLC, BMI, ALB, and UBWP, using principal component analysis

(PCA). In the PCA framework, the coefficients (loadings) represent the contribution of each standardized variable to the derived components rather than independent prognostic effects. Therefore, the direction of an individual loading (positive or negative) should be interpreted in the context of the overall multivariate nutritional pattern captured by the CNI, rather than as a direct inverse clinical association. All nutritional parameters, including BMI, UBWP, TLC, serum albumin, and hemoglobin, were assessed uniformly within one week prior to the initiation of NCRT. The BMI was defined as weight (kg)/height (m) square. UBWP was defined as the ratio of current body weight (CBW) to a reference body weight, expressed as a percentage. In the present study, CBW referred to the body weight recorded prior to the initiation of NCRT. The reference body weight, formerly referred to as usual body weight (UBW), was estimated using the height-based Lorentz formula: for women, [height (cm) − 100] − [height (cm) − 150]/2.5; and for men, [height (cm) − 100] − [height (cm) − 150]/4. This calculated value represents a theoretical reference weight rather than a historically measured body weight. The nutrition risk index (NRI) was calculated according to the following equation: 1.519 × ALB (g/L) + 41.7 × (CBW / ideal body weight). Ideal body weight (IBW) was estimated as 22 × height² (m^2). The PNI was calculated using the formula: ALB (g/L) + 0.005 × TLC (μL). Correlations among nutritional indicators were assessed using Pearson correlation analysis and visualized using a heatmap.

Statistical analysis

The CNI was constructed using PCA based on five nutritional indicators. Components were retained to achieve a cumulative explained variance exceeding 80%. The suitability of data for PCA was assessed using the Kaiser–Meyer–Olkin (KMO) measure and Bartlett's test of sphericity, with a KMO value > 0.60 and a significant Bartlett's test considered acceptable. The optimal CNI cut-off was determined using an outcome-oriented approach based on overall survival, aiming to maximize separation of survival curves rather than applying a distribution-based threshold. Based on this cut-off, patients were categorized into low- and high-CNI groups, and this categorized CNI variable was used in subsequent Cox regression analyses and nomogram development. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were assessed for normality using the Shapiro–Wilk test; normally distributed variables were analyzed

using Student's t-test, while non-normally distributed variables were analyzed using non-parametric methods. Cox proportional hazards regression analyses were performed to identify prognostic factors for OS and DFS. The proportional hazards assumption was evaluated using Schoenfeld residuals, with no major violations observed. CNI was first analyzed as a continuous variable for exploratory purposes, and restricted cubic spline analyses were used to explore potential non-linear associations with survival outcomes. In addition to CNI, other nutritional indices, including the PNI and NRI, were calculated and evaluated in univariate Cox analyses for contextual comparison; CNI was predefined as the primary nutritional index, whereas analyses of other indices were considered exploratory. Multivariable Cox models included a limited number of covariates selected a priori based on clinical relevance and univariate significance. A prognostic nomogram was developed using variables independently associated with outcomes. Internal validation was performed using 400 bootstrap resamples with replacement. Model discrimination was primarily assessed using concordance index (C-index) and time-dependent receiver operating characteristic (ROC) analyses at prespecified time points. Calibration curves and decision curve analysis (DCA) were used to evaluate model calibration and clinical utility. All analyses were performed using R software (version 4.3.4), and a two-sided P value < 0.05 was considered statistically significant.

After determining the optimal cut-off value, CNI was treated as a categorical variable (low vs high) and used in subsequent Cox regression analyses and nomogram development.

RESULTS

Patient Characteristics

A total of 336 patients with LARC were included in the study. The mean age was 56.40 ± 10.82 years, and 66.7% of the patients were male. The average BMI was 24.07 ± 3.22 kg/m². A history of smoking and drinking was reported in 39.0% and 34.5% of patients, respectively. Hypertension was present in 28.6%, while 14.9% had diabetes. Regarding clinical staging, 15.5% of patients were classified as cTNM stage II and 84.5% as stage III. Postoperative pathological staging showed 18.5% with ypTNM stage I, 48.5% with stage II, and 33.0% with stage III. Complete tumor regression (TRG 4, pathological complete response) was observed in 53 patients, who

were included in the good-response group (TRG 3–4). The median follow-up duration was 49 months (range, 8 – 90 months). The baseline characteristics of the cohort are summarized in Table 1.

Construction of CNI

The KMO measure indicated adequate sampling adequacy, and Bartlett's test of sphericity was statistically significant ($P < 0.001$), supporting the use of PCA. PCA was applied to five nutritional indicators, including TLC, BMI, ALB, HB, and UBWP. The first three principal components (PCs) were retained based on the criterion that the cumulative explained variance exceeded 80%. The first three PCs were retained based on the criterion that the cumulative explained variance exceeded 80%. The first three PCs were derived as linear combinations of the standardized nutritional variables. Specifically, PC1 was defined as $0.693 \times Y1 + 0.663 \times Y2 + 0.039 \times Y3 + 0.098 \times Y4 + 0.165 \times Y5$; PC2 as $-0.134 \times Y1 - 0.139 \times Y2 + 0.356 \times Y3 + 0.615 \times Y4 + 0.678 \times Y5$; and PC3 as $-0.011 \times Y1 - 0.015 \times Y2 - 0.875 \times Y3 + 0.484 \times Y4 + 0.016 \times Y5$. The CNI was subsequently computed by combining these three components according to their respective variance contributions, using the formula: $CNI = 0.406 \times PC1 + 0.265 \times PC2 + 0.198 \times PC3$. By substituting the component loadings into this expression, the CNI could be equivalently represented as a weighted sum of the original standardized variables: $CNI = 0.244 \times Y1 + 0.229 \times Y2 - 0.063 \times Y3 + 0.299 \times Y4 + 0.250 \times Y5$, where Y1-Y5 represent normalized TLC, BMI, ALB, HB, and UBWP, respectively. Specifically, BMI was measured in kg/m^2, UBWP was expressed as a percentage (%), TLC as cells per microliter (cells/μL), serum albumin as g/L, and hemoglobin as g/L prior to normalization.

Association between continuous CNI and survival outcomes

When modeled as a continuous variable, higher CNI values were significantly associated with improved OS in Cox regression analysis. Restricted cubic spline analysis demonstrated an approximately linear inverse relationship between CNI and the risk of death, with no clear evidence of a non-linear association. These results support the robustness of CNI as a continuous prognostic indicator (Figure S1).

Prognostic stratification using the CNI

The median pretreatment CNI in the entire cohort was −0.0087. Using an outcome-oriented optimal cut-off value of 0.3879 identified by the surv_cutpoint function using

R software, patients were stratified into a low-CNI group (CNI < 0.3879, n = 144) and a high-CNI group (CNI ≥ 0.3879, n = 192). The receiver operating characteristic analysis for OS yielded an area under the curve (AUC) of 0.81, with a statistically significant association between CNI and survival outcome ($P < 0.05$). As shown in Fig. 1A, the baseline nutritional characteristics differed significantly between the two groups. Baseline clinicopathological characteristics stratified by CNI group are summarized in Table S1. Importantly, key tumor-related baseline factors, including clinical TNM stage, pathological TNM stage, vessel invasion, and perineural invasion, were well balanced between the low- and high-CNI groups. Patients in the high-CNI group had markedly superior levels of key nutritional parameters, including BMI, UBWP, ALB, and HB. Kaplan–Meier survival analysis demonstrated significantly poorer OS in the low-CNI group compared with the high-CNI group ($P = 0.0019$; Fig. 1B). Accordingly, CNI was evaluated both as a continuous variable and as a categorical variable in Cox regression analyses, with the categorized CNI used for multivariable modeling and nomogram construction to enhance clinical interpretability. Among the nutritional indices evaluated, CNI, which was predefined as the primary index, showed a significant association with OS. This superior predictive performance was further confirmed by univariate Cox regression analysis in Table 2. Among all the nutritional indices evaluated, the CNI exhibited the most potent protective effect on OS (HR = 0.697, 95% CI: 0.497-0.978, $P = 0.037$). The correlations between the CNI and its constituent nutritional indicators, as visualized in the Fig. 1C.

CNI as an independent prognostic factor for OS and DFS

During the follow-up period, a total of 75 deaths and 120 disease recurrence or death events were observed. To determine the independent prognostic value of the CNI, univariate and multivariate Cox regression analyses were performed for both OS and DFS. CNI was entered into the survival analyses as a categorical variable (low vs high) based on the predefined cut-off value. In the univariate analysis (Fig. 2A, C), a low CNI was significantly associated with worse OS (HR = 2.03, 95% CI: 1.28-3.21, $P = 0.002$) and DFS (HR = 2.10, 95% CI: 1.35-3.26, $P = 0.001$). Other factors significantly associated with outcomes included poor TRG and positive ypN stage. Subsequently, multivariate Cox analyses were conducted, adjusting for these significant clinicopathological factors. The categorized CNI remained an independent

prognostic factor for both OS (HR = 2.13, 95% CI: 1.36-3.35, P = 0.001) and DFS (HR = 1.88, 95% CI: 1.20-2.94, P = 0.001), alongside TRG and ypN stage (Fig. 2B, D).

Development and validation of a prognostic nomogram

To translate the independent prognostic factors (categorized CNI, TRG, and ypN stage) into a practical tool, nomograms were developed to predict OS and DFS, respectively (Fig. 3A, B). Internal validation was performed using bootstrap resampling (n = 400), and good agreement between predicted and observed outcomes was demonstrated by the calibration curves (Fig. 3C, D).

Nomogram discrimination was primarily assessed using C-index. The optimism-corrected C-index of the nomogram for OS was 0.677, indicating acceptable discriminative ability. Calibration plots showed good agreement between predicted and observed survival probabilities, with no major deviation from the ideal line. Time-dependent ROC analyses were used for descriptive evaluation of nomogram performance (Fig. 3E, F). In addition, DCA suggested potential clinical utility of the nomogram across a range of threshold probabilities (Fig. 3G, H).

DISCUSSION

Nutritional status plays a central role in the treatment and prognosis of patients with rectal cancer because inadequate nutrition can reduce treatment tolerance and increase the risk of adverse events(17,18). Identifying patients at nutritional risk may therefore support early intervention and improve long term outcomes. In the present study, we evaluated the CNI, which is derived from BMI, UBWP, TLC, ALB and HB, and examined its value in patients with LARC treated with NCRT. CNI demonstrated favorable prognostic performance compared with traditional nutritional indices in predicting survival outcomes. Although CNI incorporates multiple nutritional and immune-related parameters, the present study was not designed to perform formal head-to-head comparisons with other established nutritional indices. Therefore, while CNI demonstrated independent prognostic value, caution is warranted when interpreting its relative performance compared with other nutritional scores. Patients with low CNI had significantly worse OS and DFS compared with those with higher CNI. CNI also remained an independent prognostic factor after adjustment for TRG and ypN stage. These findings indicate that CNI captures multiple dimensions of host

status and provides more reliable prognostic information than individual nutritional indicators in this setting. It should be noted that the cut-off value used for CNI stratification was derived from the same cohort using an outcome-oriented approach. Based on this cut-off, CNI was operationalized as a dichotomous variable and incorporated into multivariable Cox regression analyses and nomogram construction to facilitate clinical interpretability. However, because the threshold was outcome-derived within the same cohort, the effect estimates from cut-off–based modeling may be subject to optimism.

In recent years, the CNI has gained increasing attention as a prognostic marker across a range of malignant and chronic diseases(19). Prior investigations in nasopharyngeal carcinoma (NPC) have demonstrated that lower CNI values are associated with more advanced disease stages and unfavorable survival outcomes(12,13). These studies further suggested that CNI may provide stronger prognostic information than conventional nutritional indices, such as the NRI and PNI, in this patient population. In addition to survival, low CNI has also been linked to impaired overall nutritional status and reduced quality of life among patients with NPC(13,14). Beyond NPC, evidence from hepatocellular carcinoma cohorts treated with transcatheter arterial chemoembolization has shown that patients with lower CNI are more likely to experience severe treatment-related complications and poorer prognosis(20). A recent investigation reported that a processed CNI derived from multiple nutrition-related parameters serves as a sensitive and reliable predictor of treatment response, postoperative morbidity, and survival outcomes in patients with esophageal squamous cell carcinoma undergoing neoadjuvant immunotherapy combined with chemotherapy(11). In the present study, CNI demonstrated stronger prognostic ability than its individual components and outperformed traditional indices. This suggests that CNI may offer a more reliable method for evaluating nutritional status and treatment tolerance in patients receiving NCRT for LARC.

BMI, UBWP, ALB, TLC and HB are routinely used clinical parameters that capture complementary dimensions of nutritional and physiological condition. BMI reflects overall body composition and nutritional reserve, with lower values commonly associated with malnutrition, sarcopenia, and metabolic imbalance(21,22). Previous studies have shown that a reduced preoperative BMI is linked to unfavorable outcomes in patients with gastrointestinal malignancies(23). UBWP represents recent

changes in body weight and may indicate protein–energy deficiency. ALB is widely regarded as an indicator of protein stores and systemic nutritional status; however, although hypoalbuminemia has been associated with postoperative complications, its prognostic significance and responsiveness to nutritional intervention remain controversial(24–26). TLC reflects immune competence, particularly cell-mediated immunity, which can be compromised by malnutrition. Reduced immune function has been shown to adversely affect cancer prognosis, underscoring the relevance of TLC as a marker of host defense and tumor surveillance(27,28). HB reflects chronic protein status and has been associated with outcomes in several gastrointestinal cancers(29,30). Many clinicians rely on single nutritional parameters, but these isolated markers only capture part of the patient's condition and often yield inconsistent results. Although TLC is generally regarded as a marker of immune and nutritional status, its loading in the PCA-derived CNI was negative in the present study, and no marked difference in TLC was observed between the high- and low-CNI groups. This finding does not imply that higher TLC is associated with adverse outcomes, but rather reflects the correlations among the included nutritional variables within a multivariate PCA framework after standardization. Within this composite model, TLC may therefore contribute limited incremental discriminatory information beyond other nutritional indicators. Importantly, this observation suggests that while the current CNI is prognostically informative, there remains scope for further refinement. Future studies may explore alternative combinations of nutritional and immune-related markers to optimize composite indices and enhance both clinical interpretability and predictive performance.

Composite indices such as PNI or NRI attempt to provide a broader view, but they still rely on limited components and may not fully represent overall nutritional status. Studies in colorectal cancer show mixed conclusions regarding their prognostic value(10,31). For example, lower PNI has been associated with higher rates of postoperative complications and shorter survival(32), although the relationship between PNI and complications remains uncertain in some reports(33,34). These limitations highlight the need for a more comprehensive approach.

TRG and ypN are well established prognostic markers in LARC(35–37). TRG quantifies tumor response to preoperative therapy and correlates with pathological complete response. Better TRG is generally associated with lower local recurrence

and improved survival. Several TRG systems exist, but all show that patients with marked regression have superior outcomes compared with those with poor regression(38). Posttreatment nodal status is one of the strongest predictors after neoadjuvant therapy. Patients who are ypN positive consistently show early recurrence than those who remain node positive(39). ypN positivity predicts a higher risk of distant metastasis and guides the need for intensified adjuvant therapy. Studies that combine TRG and ypN report improved risk stratification compared with either measure alone(40). In clinical practice, integrating both measures yields more accurate prognostic models and can inform decisions on adjuvant treatment and surveillance intensity.

Patients undergoing NCRT often experience increased metabolic demands and treatment related toxicities. Adequate nutritional reserve is essential for maintaining treatment tolerance, minimizing unplanned interruptions and supporting postoperative recovery(41,42). Early identification of patients with compromised nutritional status may therefore allow clinicians to provide timely support and reduce the likelihood of adverse events. Although the present study was not designed to evaluate the effects of nutritional interventions, identification of patients with low CNI may help to generate hypotheses for targeted nutritional support, intensified monitoring, or tailored supportive care strategies in future prospective studies. In this context, CNI offers a practical tool that captures several dimensions of nutritional and physiological condition. By integrating CNI with TRG and ypN stage, we developed a prognostic nomogram with potential clinical applicability and straightforward interpretability. The nomogram enables individualized survival estimation and may potentially assist clinicians in patient counseling, planning supportive care, and tailoring follow-up strategies. This approach may help refine risk stratification in the setting of multimodality treatment for LARC. Importantly, CNI is derived from routinely available pre-treatment clinical parameters and may therefore serve as an early risk indicator before neoadjuvant therapy. In contrast, the proposed nomogram incorporates postoperative pathological variables, such as tumor regression grade and nodal status, and is primarily intended for postoperative prognostic stratification rather than pre-treatment decision-making.

This study has several limitations. First, its retrospective, single-center design and the inclusion of only patients with complete data introduce potential selection bias and

limit generalizability. External validation was not performed, and the sample size was modest. Second, nutritional status was assessed at a single prespecified time point, and dynamic changes during treatment were not captured. Third, postoperative complications were not systematically analyzed, as the primary focus was on long-term survival outcomes. In addition, several potentially relevant factors were not included in the analysis, such as postoperative adjuvant chemotherapy, inflammatory markers, molecular characteristics, and surgical approach. In particular, emerging evidence suggests that robotic total mesorectal excision may be associated with improved oncological outcomes in selected patients with locally advanced rectal cancer, especially in male patients with mid- to low-rectal tumors(43–45). Therefore, the omission of surgical technique may represent a potential confounder and should be considered when interpreting the results. Taken together, these limitations indicate that while CNI appears to be an independent prognostic indicator in patients with LARC treated with neoadjuvant chemoradiotherapy, further studies incorporating external validation cohorts and direct comparative analyses with other nutritional indices are warranted to clarify its relative performance and clinical utility.

CONCLUSION

In conclusion, pretreatment CNI represents a practical and informative nutritional composite associated with prognosis in patients with locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy. Risk stratification using CNI may assist clinicians in identifying patients with different prognostic profiles and support more individualized therapeutic planning.

Conflicts of interest: Authors declare no conflicts of interest.

Funding: The study was sponsored by Beijing Association of Oncology and Beijing Science And Technology Innovation Medical Development Foundation (KC2024-JX-0819).

Data availability: De-identified data and code used for model training are available upon reasonable request to the corresponding author, in accordance with institutional and national data protection regulations.

Submitted: November 25, 2025

Accepted: January 24, 2026

Published online: January 30, 2026

REFERENCES

1.Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2023. CA Cancer J Clin. 2023;73(3):233–54.
https://doi.org/10.3322/caac.21772

2.Koukourakis IM, Kouloulias V, Tiniakos D, Georgakopoulos I, Zygogianni A. Current status of locally advanced rectal cancer therapy and future prospects. Crit Rev Oncol Hematol. 2023;186:103992.
https://doi.org/10.1016/j.critrevonc.2023.103992

3.Smith HG, Nilsson PJ, Shogan BD, Harji D, Gambacorta MA, Romano A, et al. Neoadjuvant treatment of colorectal cancer: comprehensive review. BJS Open. 2024;8(3):zrae038.
https://doi.org/10.1093/bjsopen/zrae038

4.Scott AJ, Kennedy EB, Berlin J, Brown G, Chalabi M, Cho MT, et al. Management of locally advanced rectal cancer: ASCO guideline. J Clin Oncol. 2024;42(28):3355–75.
https://doi.org/10.1200/JCO.24.01160

5.Gaedcke J, Sahrhage M, Ebeling M, Azizian A, Rühlmann F, Bernhardt M, et al. Prognosis and quality of life in patients with locally advanced rectal cancer after abdominoperineal resection in the CAO/ARO/AIO-04 randomized phase 3 trial. Sci Rep. 2025;15(1):5401.
https://doi.org/10.1038/s41598-024-83105-z

6.Zhao R, Shen W, Zhao W, Peng W, Wan L, Chen S, et al. Integrating radiomics, pathomics, and biopsy-adapted immunoscore for predicting distant metastasis in locally advanced rectal cancer. ESMO Open. 2025;10(3):104102.
https://doi.org/10.1016/j.esmoop.2024.104102

7.Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, et al. Guidelines for perioperative care in elective colorectal surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations: 2018. World J Surg.

2019;43(3):659–95.
https://doi.org/10.1007/s00268-018-4844-y

8.Shao Z, Zou Y, Zou C, Xu Y. Nutritional indicators as predictive and prognostic biomarkers for neoadjuvant chemoradiotherapy outcomes in patients with locally advanced rectal cancer. Support Care Cancer. 2025;33(10):834.
https://doi.org/10.1007/s00520-025-09911-x

9.Christina NM, Tjahyanto T, Lie JG, Santoso TA, Albertus H, Octavianus D, et al. Hypoalbuminemia and colorectal cancer patients: any correlation?: a systematic review and meta-analysis. Medicine (Baltimore). 2023;102(8):e32938.
https://doi.org/10.1097/MD.0000000000032938

10.Shibutani M, Kashiwagi S, Fukuoka T, Iseki Y, Kasashima H, Maeda K. Impact of preoperative nutritional status on long-term survival in patients with stage I–III colorectal cancer. In Vivo. 2023;37(4):1765–74.
https://doi.org/10.21873/invivo.13265

11.Feng J, Wang L, Yang X, Chen Q, Cheng X. Comprehensive nutritional index predicts clinical outcomes for esophageal squamous cell carcinoma receiving neoadjuvant immunotherapy combined with chemotherapy. Int Immunopharmacol. 2023;121:110459.
https://doi.org/10.1016/j.intimp.2023.110459

12.Duan YY, Deng J, Su DF, Li WQ, Han Y, Li ZX, et al. Construction of a comprehensive nutritional index and comparison of its prognostic performance with the PNI and NRI for survival in older patients with nasopharyngeal carcinoma: a retrospective study. Support Care Cancer. 2021;29(9):5371–81.
https://doi.org/10.1007/s00520-021-06128-6

13.Deng J, He Y, Sun XS, Li JM, Xin MZ, Li WQ, et al. Construction of a comprehensive nutritional index and its correlation with quality of life and survival in patients with nasopharyngeal carcinoma undergoing IMRT: a prospective study. Oral Oncol. 2019;98:62–8.
https://doi.org/10.1016/j.oraloncology.2019.09.014

14.He Y, Chen L, Chen L, Hu W, Wang C, Tang L, et al. Relationship between the comprehensive nutritional index and the EORTC QLQ-H&N35 in nasopharyngeal carcinoma patients treated with intensity-modulated radiation therapy. Nutr Cancer. 2017;69(3):436–43.
https://doi.org/10.1080/01635581.2017.1283422

15.Xu Y, Shen P, Zhu J, Qian D, Gu K, Mao Y, et al. Comprehensive malnutritional index for predicting clinical outcomes in locally advanced rectal cancer receiving neoadjuvant chemoradiotherapy. Biomol Biomed. 2025;25(5):1079–91.
https://doi.org/10.17305/bb.2024.11188

16.Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Colorectal Dis. 1997;12(1):19–23.
https://doi.org/10.1007/s003840050072

17.Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017;36(1):11–48.
https://doi.org/10.1016/j.clnu.2016.07.015

18.Barao K, Abe Vicente Cavagnari M, Silva Fucuta P, Manoukian Forones N. Association between nutrition status and survival in elderly patients with colorectal cancer. Nutr Clin Pract. 2017;32(5):658–63.
https://doi.org/10.1177/0884533617706894

19.Antasouras G, Papadopoulou SK, Tolia M, Pandi AL, Spanoudaki M, Tsoukalas N, et al. May nutritional status positively affect disease progression and prognosis in patients with esophageal and pharyngeal cancers? A scoping review of the current clinical studies. Med Sci (Basel). 2023;11(4):64.
https://doi.org/10.3390/medsci11040064

20.Deng J, He JJ, Xie LP, Zheng QW, Wu SL, Shao HY. Comprehensive nutritional index for predicting overall survival in hepatocellular carcinoma patients after multiple transarterial chemoembolization. Asia Pac J Clin Nutr. 2021;30(1):7–14.
https://doi.org/10.6133/apjcn.202103_30(1).0002

21.Kaluźniak-Szymanowska A, Krzymińska-Siemaszko R, Deskur-Śmielecka E, Lewandowicz M, Kaczmarek B, Wieczorowska-Tobis K. Malnutrition, sarcopenia, and malnutrition-sarcopenia syndrome in older adults with COPD. Nutrients. 2022;14(1):44.
https://doi.org/10.3390/nu14010044

22.Xu Y, Zhao Y, Wang J, Gao S, Sun Q, Ali M, et al. Association of preoperative nutritional status with sarcopenia in patients with gastrointestinal malignancies assessed by Global Leadership Initiative in Malnutrition criteria: a prospective cohort study. Ann Nutr Metab. 2025;81(2):68–79.
https://doi.org/10.1159/000542698

23.Kim CH, Park SM, Kim JJ. The impact of preoperative low body mass index on postoperative complications and long-term survival outcomes in gastric cancer patients. J Gastric Cancer. 2018;18(3):274–86.
https://doi.org/10.5230/jgc.2018.18.e30

24.Goh SL, De Silva RP, Dhital K, Gett RM. Is low serum albumin associated with postoperative complications in patients undergoing oesophagectomy for oesophageal malignancies? Interact Cardiovasc Thorac Surg. 2015;20(1):107–13.
https://doi.org/10.1093/icvts/ivu324

25.Onji M, Kakizoe S, Naito K, Date K, Nakai A, Shimizu K, et al. Preoperative frailty as a predictive factor for postoperative complications in patients with pancreatic cancer. Nagoya J Med Sci. 2023;85(3):518–27.
https://doi.org/10.18999/nagjms.85.3.518

26.Ma XB, Lv YL, Qian L, Huang ST, Pu XX, Liu YM. Ratio of red blood cell distribution width to albumin level and risk of mortality in sarcopenic obesity. Sci Rep. 2024;14:27886.
https://doi.org/10.1038/s41598-024-79055-1

27.Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. Lancet Oncol. 2014;15(11):e493–503.
https://doi.org/10.1016/S1470-2045(14)70263-3

28.Sim JH, Bang JY, Kim SH, Kang SJ, Song JG. Association of preoperative prognostic nutritional index and postoperative acute kidney injury in patients with colorectal cancer surgery. Nutrients. 2021;13(5):1604.
https://doi.org/10.3390/nu13051604

29.Li K, Yan J, Zhang H. Correlation between peripheral blood hemoglobin/erythrocyte distribution width ratio and prognosis of patients with primary colorectal cancer. Medicine (Baltimore). 2023;102(23):e34031.
https://doi.org/10.1097/MD.0000000000034031

30.Dagmura H, Daldal E, Okan I. The efficacy of hemoglobin, albumin, lymphocytes, and platelets as a prognostic marker for survival in octogenarians and nonagenarians undergoing colorectal cancer surgery. Cancer Biother Radiopharm. 2022;37(10):955–62.
https://doi.org/10.1089/cbr.2020.4725

31.Han Y, Zhou P, Wang L, Tang Y, Ding Y, Yang Y, et al. Linear inverse association between prognostic nutritional index and colorectal cancer risk based on NHANES data. Sci Rep. 2025;15(1):25647.
https://doi.org/10.1038/s41598-025-10574-1

32.Sun G, Li Y, Peng Y, Lu D, Zhang F, Cui X, et al. Impact of the preoperative prognostic nutritional index on postoperative and survival outcomes in colorectal cancer patients who underwent primary tumor resection: a systematic review and meta-analysis. Int J Colorectal Dis. 2019;34(4):681–9.
https://doi.org/10.1007/s00384-019-03241-1

33.Yuan J, Hu Y, Wang J, Chang L, Guan T, Fu X, et al. A model based on preoperative nutrition-inflammation score for predicting mucocutaneous separation after enterostomy in colorectal cancer patients. Sci Rep. 2025;15(1):31095.
https://doi.org/10.1038/s41598-025-16430-6

34.Xu R, Gong LF. Development and evaluation of a nomogram model for predicting malnutrition in patients with colorectal cancer. Front Med. 2025;12:1637579.
https://doi.org/10.3389/fmed.2025.1637579

35.Yin H, Yao Q, Xie Y, Niu D, Jiang W, Cao H, et al. Tumor regression grade combined with post-therapy lymph node status: a novel independent prognostic factor for patients treated with neoadjuvant therapy followed by surgery in locally advanced gastroesophageal junction and gastric carcinoma. Cancer Med. 2023;12(19):19633–43. https://doi.org/10.1002/cam4.6597

36.Mendoza-Moreno F, Díez-Alonso M, Matías-García B, Ovejero-Merino E, Vera-Mansilla C, Quiroga-Valcárcel A, et al. Effect of tumor regression grade on survival and disease-free interval in patients operated on for locally advanced rectal cancer. Cancers (Basel). 2024;16(10):1797. https://doi.org/10.3390/cancers16101797

37.Wiesmueller F, Schuetz R, Langheinrich M, Brunner M, Weber GF, Grützmann R, et al. Defining early recurrence in patients with resected primary colorectal carcinoma and its respective risk factors. Int J Colorectal Dis. 2021;36(6):1181–91. https://doi.org/10.1007/s00384-021-03844-7

38.Mills MN, Naz A, Sanchez J, Dessureault S, Imanirad I, Lauwers G, et al. Rectal tumor fragmentation as a response pattern following chemoradiation. J Gastrointest Oncol. 2022;13(6):2951–62. https://doi.org/10.21037/jgo-22-477

39.Kim HG, Kim HS, Yang SY, Han YD, Cho MS, Hur H, et al. Early recurrence after neoadjuvant chemoradiation therapy for locally advanced rectal cancer: characteristics and risk factors. Asian J Surg. 2021;44(1):298–302. https://doi.org/10.1016/j.asjsur.2020.07.014

40.Damanakis AI, Gebauer F, Stapper A, Schlößer HA, Ghadimi M, Schmidt T, et al. Combined regression score predicts outcome after neoadjuvant treatment of oesophageal cancer. Br J Cancer. 2023;128(11):2025–35. https://doi.org/10.1038/s41416-023-02232-y

41.Yamano T, Yoshimura M, Kobayashi M, Beppu N, Hamanaka M, Babaya A, et al. Malnutrition in rectal cancer patients receiving preoperative chemoradiotherapy is common and associated with treatment tolerability and anastomotic leakage. Int J

Colorectal Dis. 2016;31(4):877–84.
https://doi.org/10.1007/s00384-016-2507-8

42.Ide S, Okugawa Y, Omura Y, Yamamoto A, Ichikawa T, Kitajima T, et al. Geriatric nutritional risk index predicts cancer prognosis in patients with local advanced rectal cancer undergoing chemoradiotherapy followed by curative surgery. World J Surg Oncol. 2021;19:34.
https://doi.org/10.1186/s12957-021-02139-z

43.Aliyev V, Goksel S, Bakir B, Guven K, Asoglu O. Sphincter-saving robotic total mesorectal excision provides better mesorectal specimen and good oncological local control compared with laparoscopic total mesorectal excision in male patients with mid–low rectal cancer. Surg Technol Int. 2021;38:160–6.
https://doi.org/10.52198/21.STI.38.CR1391

44.Aliyev V, Piozzi GN, Huseynov E, Mustafayev TZ, Kayku V, Goksel S, et al. Robotic male and laparoscopic female sphincter-preserving total mesorectal excision of mid–low rectal cancer share similar specimen quality, complication rates and long-term oncological outcomes. J Robot Surg. 2023;17(4):1637–44.
https://doi.org/10.1007/s11701-023-01558-2

45.Aliyev V, Piozzi GN, Shadmanov N, Guven K, Bakır B, Goksel S, et al. Robotic and laparoscopic sphincter-saving resections have similar peri-operative, oncological and functional outcomes in female patients with rectal cancer. Updat Surg. 2023;75(8):2201–9.
https://doi.org/10.1007/s13304-023-01686-2

TABLES AND FIGURES WITH LEGENDS

Table 1. Baseline characteristics of patients

Characteristics	*n (%)/mean ± SD*
Age (years)	56.40±10.82
Gender (female/male)	112 (33.3)/224 (66.7)
BMI	24.07±3.22
Smoking history (yes/no)	131 (39.0)/205 (61.0)
Drinking history (yes/no)	116 (34.5)/220 (65.5)
Hypertension (yes/no)	96 (28.6)/240 (71.4)
Diabetes (yes/no)	50 (14.9)/286 (85.1)
cTNM (II/III)	52 (15.5)/283 (84.5)
ypTNM (I/II/III)	62 (18.5)/163 (48.5)/111 (33.0)
Vessel invasion (yes/no)	32 (9.5)/304 (90.5)
Perineural invasion (yes/no)	52 (15.5)/284 (84.5)

Note: Due to the absence of clinical T stage data for one patient, the total count for the cTNM stage does not equal 336. Abbreviations: BMI: Body mass index; cTNM: Clinical tumor–node–metastasis stage; ypTNM: Postoperative pathological tumor–node–metastasis stage.

Table 2. Univariate Cox regression results for nutritional indices

Variable	HR (95% CI)	*p* value
BMI	0.906 (0.843–0.973)	0.007
UBWP	0.978 (0.963–0.994)	0.007
TLC	0.782 (0.535–1.141)	0.202
ALB	0.956 (0.891–1.027)	0.218
HB	0.992 (0.981–1.003)	0.165
CNI	0.697 (0.497–0.978)	0.037
NRI	0.960 (0.933–0.988)	0.005
PNI	0.955 (0.907–1.006)	0.082

Abbreviations: HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index; UBWP: Usual body weight percentage; TLC: Total lymphocyte count; ALB: Albumin; HB: Hemoglobin; CNI: Comprehensive nutritional index; NRI: Nutritional risk index; PNI: Prognostic nutritional index.

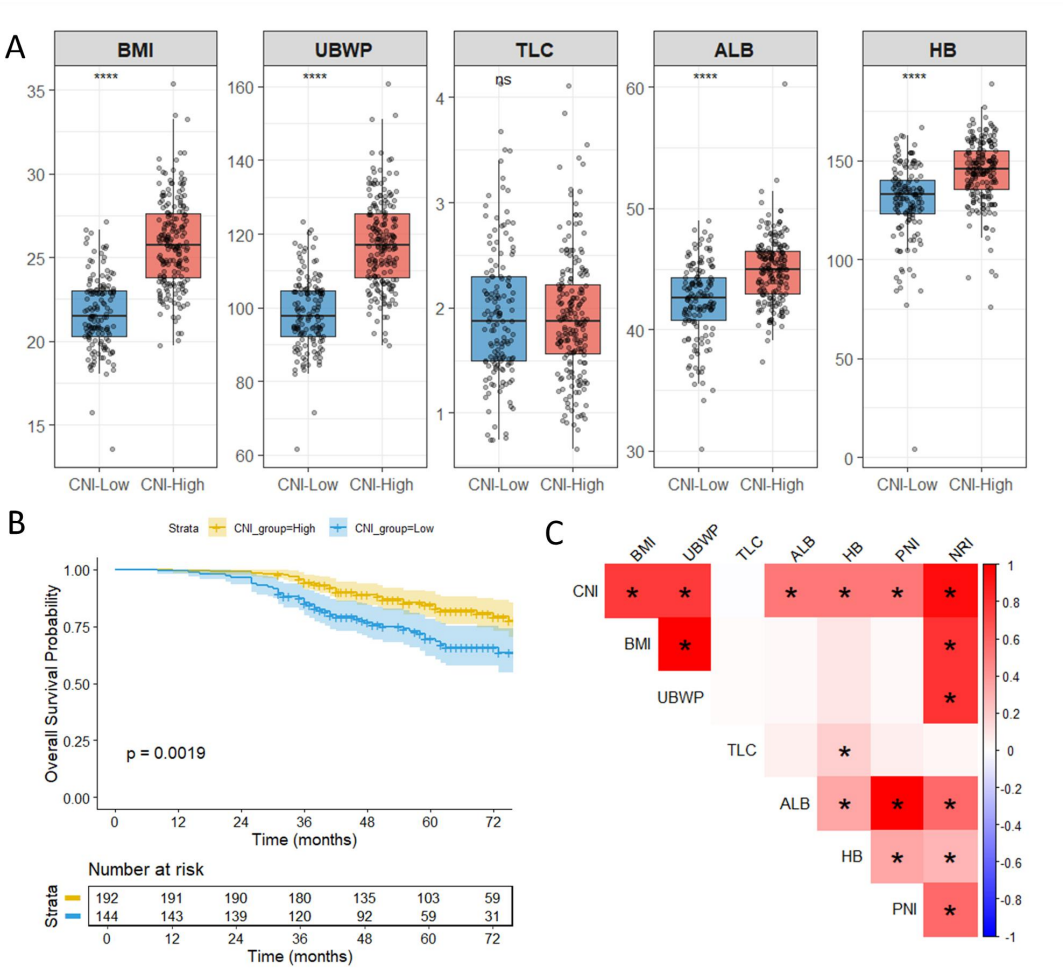

Figure 1. Nutritional characteristics, OS, and correlations stratified by CNI. (A) Pretreatment levels of BMI, UBWP, TLC, ALB, and HB by CNI group (box-and-whisker plots with individual datapoints). **(B)** Kaplan–Meier OS curves by CNI group; shaded bands indicate 95% CIs and numbers at risk are shown below (log-rank p = 0.0019). **(C)** Pearson correlation heatmap showing associations between CNI and nutritional indicators/indices (BMI, UBWP, TLC, ALB, HB, PNI, and NRI); the color scale represents Pearson correlation coefficients (r), and asterisks denote statistically significant correlations ($p < 0.05$). CNI groups were defined using an outcome-oriented cut point of 0.3879: low CNI (CNI < 0.3879, n = 144) and high CNI (CNI ≥ 0.3879, n = 192). In panel A, significance labels indicate between-group differences (****$p < 0.0001$; ns, not significant). **Abbreviations**: CNI: Comprehensive nutritional index; BMI: Body mass index; UBWP: Usual body weight percentage; TLC: Total lymphocyte count; ALB: Albumin; HB: Hemoglobin; OS: Overall survival; CI: Confidence interval; PNI: Prognostic nutritional index; NRI: Nutritional risk index.

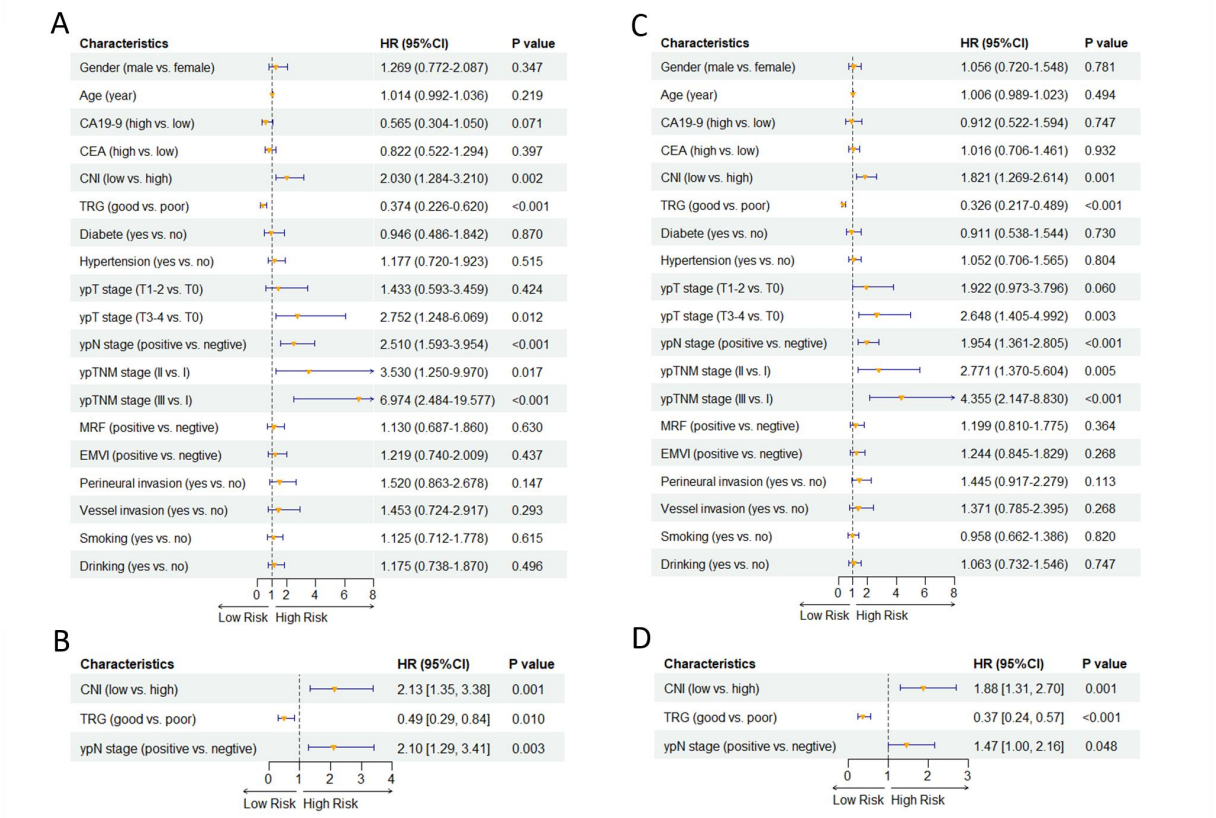

Figure 2. Cox regression analyses for OS and DFS. (A) Univariate Cox proportional hazards analysis for OS. **(B)** Multivariate Cox analysis for OS including CNI, TRG, and ypN stage. **(C)** Univariate Cox proportional hazards analysis for DFS. **(D)** Multivariate Cox analysis for DFS including CNI, TRG, and ypN stage. CNI was analyzed as a categorical variable using the predefined cut point (low vs high; CNI < 0.3879 vs CNI ≥ 0.3879). In univariate analyses, low CNI was associated with worse OS (HR = 2.03, 95% CI: 1.28–3.21; p = 0.002) and DFS (HR = 2.10, 95% CI: 1.35–3.26; p = 0.001). After adjustment for TRG and ypN stage, low CNI remained independently associated with worse OS (HR = 2.13, 95% CI: 1.36–3.35; p = 0.001) and DFS (HR = 1.88, 95% CI: 1.20–2.94; p = 0.001). Points indicate HRs and horizontal bars indicate 95% CIs; the dashed vertical line denotes HR = 1. **Abbreviations**: OS: Overall survival; DFS: Disease-free survival; HR: Hazard ratio; CI: Confidence interval; CNI: Comprehensive nutritional index; TRG: Tumor regression grade; ypN: Post-therapy pathologic regional lymph node stage; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; MRF: Mesorectal fascia; EMVI: Extramural vascular invasion; ypT: Post-therapy pathologic primary tumor stage; ypTNM: Postoperative pathological tumor–node–metastasis stage.

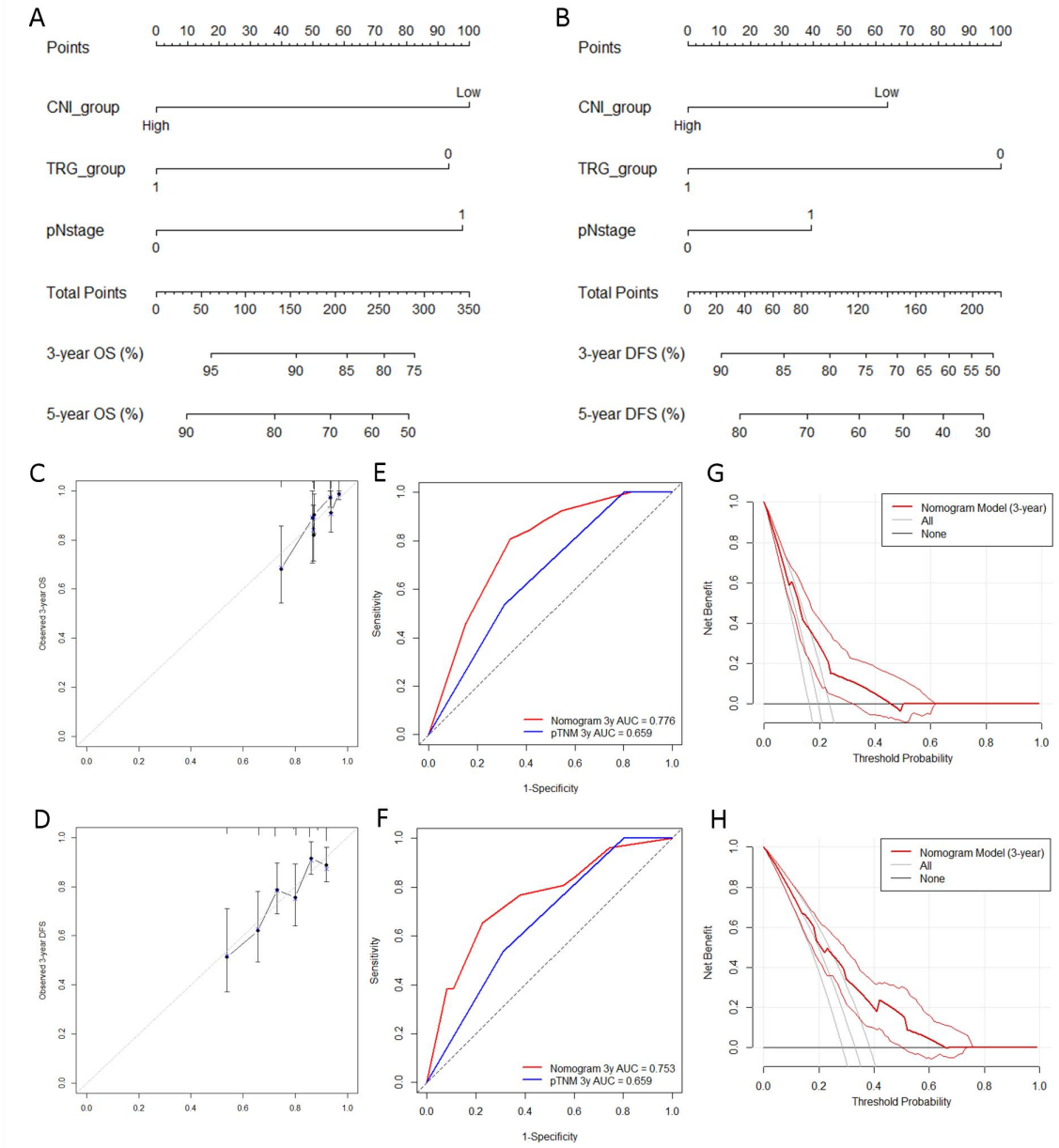

Figure 3. Development and internal validation of CNI-based nomograms for OS and DFS. (A) Nomogram incorporating categorized CNI, TRG, and ypN stage to estimate 3-year and 5-year OS. **(B)** Nomogram incorporating categorized CNI, TRG, and ypN stage to estimate 3-year and 5-year DFS. **(C)** Calibration plots for 3-year and 5-year OS showing agreement between predicted probabilities and observed outcomes following internal validation with bootstrap resampling (n = 400); the diagonal line represents ideal calibration. **(D)** Calibration plots for 3-year and 5-year DFS following bootstrap internal validation (n = 400). **(E)** Time-dependent ROC curves at 3 years comparing discrimination of the nomogram versus ypTNM stage alone for OS. **(F)** Time-dependent ROC curves at 3 years comparing discrimination of the nomogram

versus ypTNM stage alone for DFS. **(G)** DCA at 3 years for OS demonstrating net clinical benefit of the nomogram across a range of threshold probabilities compared with treat-all and treat-none strategies. **(H)** DCA at 3 years for DFS demonstrating net clinical benefit of the nomogram across a range of threshold probabilities. **Abbreviations**: CNI: Comprehensive nutritional index; TRG: Tumor regression grade; ypN: Post-therapy pathologic regional lymph node stage; OS: Overall survival; DFS: Disease-free survival; ROC: Receiver operating characteristic; DCA: Decision curve analysis; ypTNM: Postoperative pathological tumor–node–metastasis stage.

SUPPLEMENTAL DATA

Table S1. Baseline clinicopathological characteristics categorized by CNI group

Characteristics	High-CNI (*n* = 192)	Low-CNI (*n* = 144)	*p* value
Age (years)	58.51 (9.84)	53.60 (11.45)	<0.001
Gender (female/male)	64 (33.3)/128 (66.7)	48 (33.3)/96 (66.7)	1.000
BMI	26.08 (2.47)	21.39 (1.86)	<0.001
Smoking history (yes/no)	118 (61.5)/ 74 (38.5)	87 (60.4)/ 57 (39.6)	0.846
Drinking history (yes/no)	125 (65.1)/ 67 (34.9)	95 (66.0)/ 49 (34.0)	0.868
Hypertension (yes/no)	123 (64.1)/ 69 (35.9)	117 (81.2)/ 27 (18.8)	<0.001
Diabetes (yes/no)	150 (78.1)/ 42 (21.9)	136 (94.4)/ 8 (5.6)	<0.001
cTNM (II/III)	26 (13.6)/165 (86.4)	26 (18.1)/118 (81.9)	0.266
ypTNM (I/II/III)	35 (18.2)/93 (48.4)/64 (33.3)	27 (18.8)/70 (48.6)/47 (32.6)	0.988
Vessel invasion (yes/no)	178 (92.7)/ 14 (7.3)	126 (87.5)/ 18 (12.5)	0.108
Perineural invasion (yes/no)	167 (87.0)/ 25 (13.0)	117 (81.2)/ 27 (18.8)	0.151

Data are presented as means (standard deviations) for continuous variables and as counts (percentages) for categorical variables. Student's t-test was used to calculate p values for continuous variables, whereas the chi-square test or Fisher's exact test was applied to categorical variables, as appropriate. It is important to note that due to missing data, the totals for some variables may not sum to the overall cohort size. Abbreviations: CNI: Comprehensive nutritional index; BMI: Body mass index; cTNM: Clinical tumor–node–metastasis stage; ypTNM: Postoperative pathological tumor–node–metastasis stage.

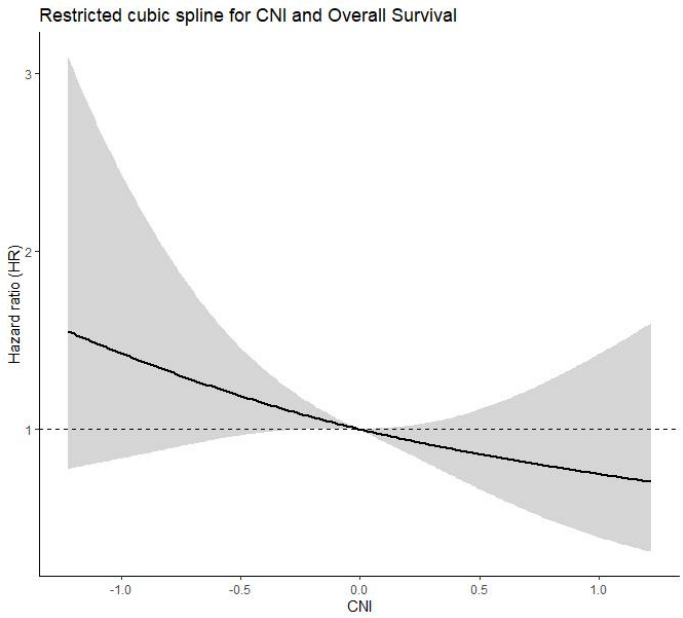

Figure S1. Association between continuous CNI and OS using restricted cubic spline analysis. Restricted cubic spline plot from an adjusted Cox proportional hazards model illustrating the relationship between continuous CNI and OS. The solid curve shows the adjusted HR across CNI values, and the shaded band denotes the 95% CI. The dashed horizontal line indicates the reference HR of 1.0, anchored at the median CNI value. The curve demonstrates an approximately linear inverse association between CNI and the risk of death, with no clear evidence of non-linearity. **Abbreviations**: CNI: Comprehensive nutritional index; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval.