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ORIGINAL RESEARCH

Significance of Nutritional-Inflammatory Index as Predictors for Total Neoadjuvant Therapy-Induced Tumor Regression in Locally Advanced Rectal Cancer Patients

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Purpose: To evaluate the predictive capacity of the nutritional-inflammatory index and clinicopathological characteristics in patients with locally advanced rectal cancer (LARC) receiving total neoadjuvant therapy (TNT).

Methods: Data from 127 patients with LARC receiving TNT from January 2017 to January 2021 were retrospectively analyzed. Clinicopathological characteristics with different TNT-induced responses were compared. The Chi-square test and the Mann–Whitney test were used to analyze the association between pre-TNT factors and TNT-induced responses. Multivariable logistic regression analysis was used to construct a predictive model.

Results: In the cohort of 127 patients with LARC who underwent total neoadjuvant therapy (TNT), the mean age was 54.1 ± 11.4 years; 88 (69.3%) were male. Seventy patients (55.1%) exhibited a favorable response to TNT, while 57 patients (44.9%) demonstrated a poor response. Tumor characteristics, including diameter, distance from the anal verge, pre-TNT lymphocyte, pre-TNT hemoglobin, CA199, PLR, and HALP, exhibit correlations with TNT-induced tumor regression. Multivariate logistic regression analysis identified large tumor diameters (> 5.0 cm; $p = 0.005$, HR 2.958; 95% CI 1.382–6.335) and low HALP (≤ 40; $p = 0.002$, HR 0.261; 95% CI 0.111–0.612) as predictors of TNT-induced poor responses. Additionally, low levels of HALP were associated with an increased risk of recurrence in patients with LARC with TNT, but this was not statistically significant ($p = 0.087$, HR 2.008, 95% CI 0.906–4.447).

Conclusion: A large tumor diameter and low HALP predict poor tumor regression induced by the CAPOX-based TNT regimen in patients with LARC.

Plain Language Summary: Recent studies have shown that total neoadjuvant therapy (TNT) is becoming a key treatment for some people with advanced rectal cancer. However, there's still a lot we do not know about what affects how well patients respond to this treatment. The aim of this study was to see if certain nutritional and inflammatory measures, along with other clinic characteristics, can predict how well patients with advanced rectal cancer will respond to TNT. We looked back at medical records from 127 patients who received TNT between 2017 and 2021. We examined how certain pre-treatment factors were linked to patients' responses to the therapy. Certain tumor characteristics and blood test results were connected to how well the tumors responded to treatment. Specifically, patients with larger tumors (over 5 cm in diameter) and lower levels of a specific blood marker called HALP were more likely to have a poor response to treatment. Although low HALP was also linked to a higher chance of the cancer coming back, this result was not strong enough to be certain about.

Keywords: Rectal cancer, Total neoadjuvant therapy, HALP, Tumor regression

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Introduction

Colorectal cancer is the fourth most common cancer and the second leading cause of cancer death in the world.[1] Rectal cancer accounts for approximately 30% of colorectal cancers, and locally advanced rectal cancer (LARC) accounts for 70% of rectal cancers.[1,2] Locally advanced rectal cancer, defined here as T3–4 or N-positive disease, generally requires multimodal therapy that includes total mesorectal excision (TME), radiation therapy, and chemotherapy. The previous standard of care for patients with LARC includes neoadjuvant chemoradiotherapy (nCRT) followed by TME.[3] With the release of data from randomized controlled trials (RAPIDO, PRODIGE-23, STELLAR), total neoadjuvant therapy (TNT) has moved to the forefront of LARC treatment and is considered a standard option in selected patients.[4–7] TNT is a comprehensive approach to cancer treatment that involves the administration of chemotherapy and nCRT prior to surgical resection of the primary tumor. TNT consists of two main Methods: induction chemotherapy, which involves chemotherapy followed by concurrent chemoradiation, and consolidation chemotherapy, which entails systemic chemotherapy following concurrent chemoradiation. This integrated approach aims to reduce tumor size, minimize the risk of metastasis, and optimize the potential for successful surgical removal, ultimately improving patient outcomes.[8] Additionally, TNT also promises improved control of systemic diseases, better adherence to treatment, and less time with an ostomy.[9]

Despite the common occurrence of tumor regression after TNT treatment, approximately 20% of patients demonstrate resistance, presenting with minimal or no tumor regression.[5] These individuals do not benefit from additional preoperative chemotherapy cycles during TNT or extended intervals between radiotherapy and surgery. Notably, one study revealed that patients with incomplete tumor regression faced a poorer prognosis than those with complete tumor regression.[10] Therefore, early identification of patients who are unlikely to benefit from TNT and adjustment of treatment are imperative to improve prognosis. However, there is a current research gap on the possible risk factors associated with TNT-induced tumor regression in patients with LARC. According to Chapman et al, predictive factors for the complete TNT-induced response in patients with LARC include tumor diameter, p53 and SMAD4 mutations, and cN stage.[10] Additionally, Zhang et al identified cN stage, tumor diameter, and CEA level as predictive factors for the TNT-induced response.[8]

Mounting evidence suggests a link between systemic inflammatory response, malnutrition, and treatment sensitivity, as well as prognosis of various gastrointestinal tumors, such as gastric cancer,[11,12] colorectal cancer,[8,13] liver cancer,[14] pancreatic cancer,[15] and gastrointestinal stromal tumor.[16] Therefore, surveillance of the correlation between nutritional-inflammatory index and TNT-induced tumor regression can aid in the early identification of patients who are unlikely to derive benefits from TNT. Our study aimed to collect the clinicopathological characteristics of patients with LARC who underwent TNT to explore the potential nutritional inflammatory indices associated with TNT-induced tumor regression.

Materials and Methods

Patient Population

This retrospective study analyzed the data of 157 consecutive patients newly diagnosed with LARC, who received TNT at the Gastrointestinal Cancer Center of Chongqing University Cancer Hospital from 1 January 2017 to 30 December 2020.

Patients were included in the study based on the following criteria: 1) diagnosis: confirmed rectal adenocarcinoma diagnosis through preoperative colonoscopy and histology; 2) cancer stage: no distant metastases, with tumors classified as T3, T4 or N+; 3) treatment protocol: receiving the CAPOX-based TNT regimen-; 4) age range: age between 18–75 years; 5) performance status: ECOG PS score of 0–1; 6) previous treatment: no prior tumor-related treatment (except colostomy); 7) laboratory values: white blood cell count (4000 to 10,000 cells/μL), neutrophil percentage (40–60% of total white blood cells), aspartate aminotransferase and alanine aminotransferase levels not exceeding three times the upper limit of normal, and creatinine levels not exceeding 1.5 times the upper limit of normal, all measured within one week before diagnosis; 8) systemic health: absence of serious systemic diseases; 9) treatment tolerance: capability to tolerate radiotherapy and chemotherapy, as assessed in the preoperative evaluation; 10) informed consent: willingness to undergo TNT treatment after understanding the principles and procedures of the treatment.

Exclusion criteria were as follows: 1) highly suspected lateral lymph node metastasis; 2) previous or concurrent malignant tumors, pregnancy, or lactation; 3) severe cardiovascular and cerebrovascular diseases, poor blood sugar

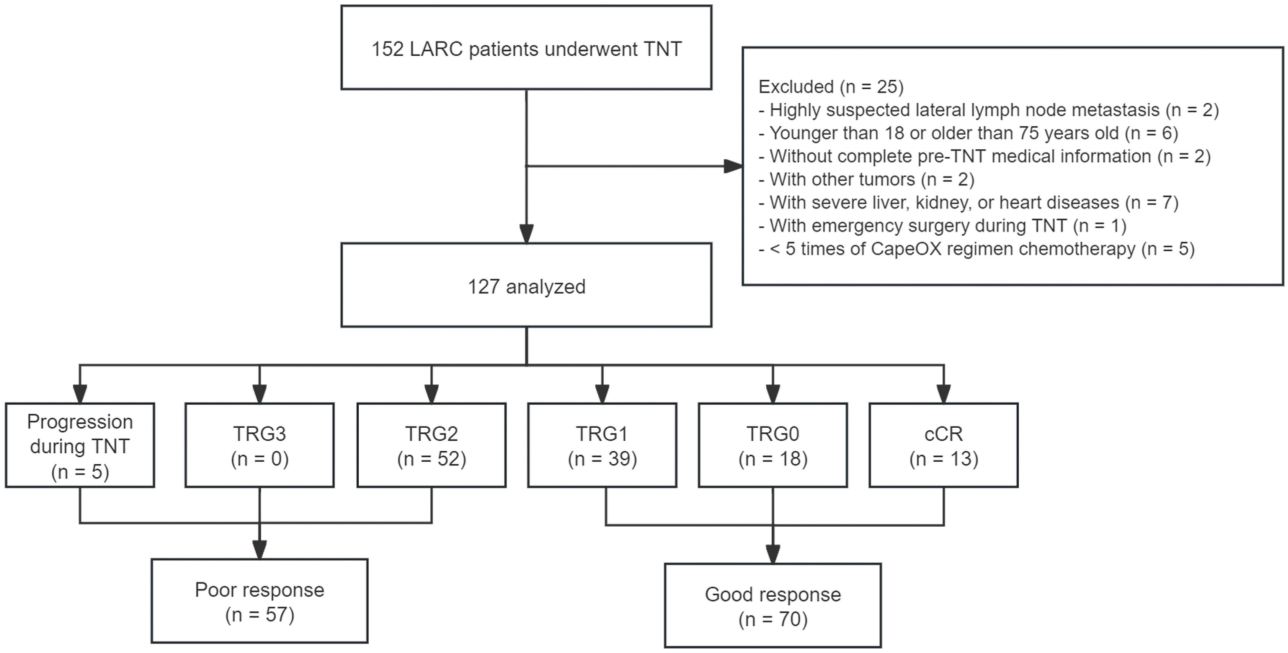

Figure 1 Study flow chart.
Abbreviations: TNT, total neoadjuvant treatment;TRG, tumor regression grade.

control; 4) allergy to fluorouracil or platinum preparations, severe infections; and 5) not having received ≥5 concurrent CapeOX regimen chemotherapy.

After exclusions, the study included 127 patients. A flow diagram depicting the patient selection process is presented in Figure 1. The study adhered to the Declaration of Helsinki and obtained approval from the Ethics Committee of Chongqing University Cancer Hospital (reference number 2023(011)). All patients provided their informed consent in writing before TNT treatment, surgery, or before a watch-and-wait strategies (W&W) strategy.

Initial Assessment

The patients underwent a comprehensive evaluation that included medical history, physical examination, digital rectal examination, colonoscopy with biopsy, optional endorectal ultrasound, pelvic magnetic resonance imaging (MRI), computed tomography (CT), and biochemical evaluation. Pelvic MRI served to determine the clinical T stage, identify metastatic lymph nodes, assess circumferential resection margin (CRM) involvement, and evaluate extramural vascular invasion (EMVI). CRM involvement is defined as tumor invasion within 1 mm of the mesorectal surgical margin. EMVI involvement was characterized by intermediate signal intensity within vessels, noticeable irregular vessel contours, or nodular expansion of vessels due to tumor growth. CT scans of the brain, chest, abdomen, and pelvis were performed for the detection of metastatic lesion. All patients were staged according to the UICC TNM classification (8th edition) classification.[17]

TNT Protocol

We performed consolidation chemotherapy TNT based on the CapeOX regimen. The TNT protocol in this study consisted of 1–2 cycles of CapeOX regimen-based chemotherapy, 2–3 cycles of concurrent chemoradiotherapy (IMRT/VMAT (50–50.4Gy/25-28f. 1.8–2.0Gy/d, 5f/w plus CapeOX regimen), and 3–4 cycles of consolidation chemotherapy (CapeOX regimen) at 7–14 days after completion of radiotherapy. In this study, patients who received ≧5 CapeOX chemotherapy regimens after the start of radiotherapy were identified as TNT mode.[18,19] If there was intestinal obstruction before treatment, colostomy was performed first.

Reassessment and Surgical Intervention

Following preoperative therapy, patients underwent reassessment via digital rectal examination, pelvic MRI, colonoscopy, endorectal ultrasound (optional), chest CT, and liver MRI/CT. After TNT, patients willing to and eligible for surgery underwent radical surgery, performed at least three weeks after completion of consolidation chemotherapy. Surgical approaches included TME, with options of Dixon's procedure, Miles' procedure, or Hartmann's procedure, based on tumor distal extension from the anal verge and intraoperative conditions. The protocol allowed for the W&W strategy in cases of clinical complete response (cCR), patient preference for organ preservation, or refusal of radical surgery (nonoperative management).

Follow-Up

Follow-up investigations were scheduled every 3 months during the first 2 years, then every 6 months for the next 3 years, and annually thereafter. Evaluation consisted of physical examination, blood tests, serum carcinoembryonic antigen (CEA) level, chest and abdomen CT, and pelvic MRI. Patients employing a W&W approach were no longer subjected to chemotherapy; instead, a rigorous follow-up observation protocol was advocated. In instances of suspected metastases or recurrent lesions, diagnostic modalities such as PET/CT or needle biopsy were used as deemed suitable Systemic therapy was prescribed according to the guidelines for patients with confirmed metastasis or recurrence. All follow-up data were meticulously documented and patient confidentiality was maintained throughout the process. The follow-up period ended on 30 September 2023.

Safety and Efficacy Analysis

To determine feasibility and toxicity, all patients were clinically and hematologically evaluated weekly to identify adverse events (AEs) before each chemoradiotherapy or chemotherapy cycle throughout the course of TNT. Postoperative complications were defined as those that occurred within the first 30 days after surgery. Adverse events during TNT were reported based on CTCAE version 5.0 criteria.[20]

Efficacy was assessed using the post-treatment clinical TNM (ycTNM), post-treatment pathological TNM (ypTNM), TRG system, and by progression-free survival (PFS). The tumor stage was determined according to the pathological tumor-node-metastasis (pTNM) classification of the Union for International Cancer Control (UICC), 8th edition.[17] TRG system used was recommended by the American Pathologists Tumor Regression Grading System.[21] cCR criteria were defined by Maas et al.[22] A pathological complete response (pCR) was defined as no residual cancer cells observed in the resection specimen, which was also regarded as TRG0 (ypT0N0M0).[23] PFS was defined as the time from the end of TNT to disease progression or death (whichever occurs first).

Data Collection

In this retrospective study, data were collected from patient medical records, which included a comprehensive array of demographic information, laboratory variables, and clinical outcomes. Demographic data included age, sex, and BMI. Laboratory data included serum albumin, white blood cell count, neutrophil count, lymphocyte count, platelet count, hemoglobin level, CEA, CA19-9. Immunological profiles detailing CD4+ T cells, CD8+ T cells, and natural killer (NK) cell counts were also collected. Clinical assessments, including pre- and post-TNT TNM staging, MRI-predicted CRM status, EMVI status, tumor diameter, and tumor distance from anal verge were retrospectively reviewed and collected. For surgical patients, the operative surgical method, operation time, blood loss, stage of pTNM, surgical margin status, tumor regression grade, differentiation grade, perineural invasion, and vascular invasion were documented.

Definition

The hemoglobin and albumin levels and lymphocyte and platelet index (HALP), prognostic nutritional index (PNI), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and geriatric nutritional risk index (GNRI) were calculated using the following formulas: The HALP = hemoglobin level (g/L) × albumin level (g/L) × lymphocyte count (/L) / platelet count (/L);[24] PNI = albumin level (g/L) + 5 × lymphocyte count (n/mm^3);[25] NLR = neutrophil count

(n/mm^3) / lymphocyte count (n/mm^3);[26] PLR = platelet count (n/mm^3) / lymphocyte count (n/mm^3);[27] GNRI = 14.89 × serum albumin level (g/dL) + 41.7 × current body weight (kg)/ideal body weight (kg).[28] A good response to TNT is characterized by TRG 0/1 or cCR, while a negative response is indicated by TRG 2/3 or progression during TNT.

Statistical Analysis

Statistical analysis utilized SPSS 25.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA). Data presented as numbers (n) and percentages (%) were analyzed with chi-square or Fisher's exact tests, while means and standard deviations were compared using *t*-tests or Mann–Whitney *U*-test. PFS was assessed using the Kaplan-Meier method, and analysis involved the Log rank test and Cox regression model. Statistical significance, for two-tailed tests, was established at $p < 0.05$. Variables with a significant association ($p < 0.05$) in univariate analysis were included in a logistic multivariable model. The area under the curve (AUC) summarized the receiver operating characteristics (ROC) curve for discrimination ability.

Results

Baseline Characteristics

From January 2017 to January 2021, 127 patients (88 males, 39 females) aged 30–79 (median: 54 years) were analyzed. The average BMI was 23.5 ± 3.0 kg/m^2. The anal verge distance ranged from 2–9 cm (average: 4.8 ± 1.4 cm), and tumor diameter ranged 2.5–12.0 cm (average: 5.4 ± 1.7 cm). Pelvic MRI and ultrasonic colonoscopy were used for pre-treatment clinical staging. Eighty patients were in cT3 stage, 42 in cT4 stage, and 116 (89.6%) were N+. Pre-TNT CRM+ was observed in 44 patients (34.6%), while Pre-TNT EMVI+ was present in 45 patients (35.4%). The prevalent AEs included neutropenia (13.4%), thrombocytopenia (11.0%), anemia (11.0%), and diarrhea (4.7%). No grade 4 or severe AEs were observed. Post-TNT, 70 patients (55.1%) exhibited favorable tumor regression response. Among them, 13 achieved cCR and entered the W&W protocol, while 57 were histologically confirmed as TRG 0/1 after surgery. The remaining 57 (44.9%) showed a poor response, 5 progressing to inoperable status, 52 having histologically confirmed TRG 2, and none with TRG 3 (Figure 1). Of the 109 (85.8%) patients undergoing surgery, the median interval between surgery and radiotherapy was 13 weeks (range: 9–16 weeks). Surgical approaches included Dixon's procedure with a temporary diverting loop ileostomy in 95 cases, Hartmann's procedure in 4 cases, and Miles' procedure in 10 cases. Histological findings revealed pCR in 18 (16.5%) patients and R0 resection in 107 (98.2%) patients. Overall, 70 (55.1%) patients achieved a favorable response (cCR + TRG 0/1), while 57 (44.9%) patients exhibited a poor response (TRG2 + progression during treatment). The characteristics of the patients are listed in Table 1 and Table S1. The median follow-up period was 17 months (range: 3–61), with 17 months (range: 3–61) in the good response group and 16 months (range: 7–31) in the poor response group.

Comparisons of Inflammatory Parameters Between Groups

Table 2 presents the stratification of patients based on TNT-induced tumor regression. No significant variations were observed in demographic and clinical parameters, including age, sex, BMI, cT stage, cN stage, CRM status, EMVI status, albumin, white blood cell count, neutrophil count, platelet count, CEA levels, CD4+ T cell count, CD8+ T cell count, CD4+/CD8+ ratio, or NK/T cell ratio between the response groups. However, patients in the poor response group exhibited larger pretreatment tumor diameters [(6.0 ± 1.8) cm vs (4.9 ± 1.5) cm, $p = 0.001$], greater distance from the anal verge [(5.2 ± 1.6) cm vs (4.6 ± 1.2) cm, $p = 0.017$], lower lymphocyte count [(1.63 ± 0.56) × 10^9/L vs (1.80 ± 0.54) × 10^9/L, $p = 0.015$], lower hemoglobin levels [(123.2 ± 25.9) g/L vs (133.4 ± 17.9) g/L, $p = 0.027$], higher PLR [(162.3 ± 48.5) vs (155.5 ± 96.5), $p = 0.030$], higher CA19-9 levels [(58.2 ± 97.4) U/mL vs (17.5 ± 16.1) U/mL, $p = 0.024$], higher PLR [(162.3 ± 48.5) vs (155.5 ± 96.5), $p = 0.030$], and lower HALP [(35.2 ± 19.0) cm vs (47.1 ± 25.7) cm, $p = 0.003$].

Notably, the PLR was significantly higher in the poor response group, while the HALP was significantly lower in the poor response group. These findings indicate their possible role in predicting tumor regression. Despite these significant findings, NLR, PNI, and GNRI did not differ significantly between the two groups (Table 2). In summary, these Results underscore the importance of the nutritional-inflammatory index and tumor-related parameters in predicting the efficacy of TNT in patients with LARC.

Table 1 Clinical and Pathological Characteristics of 127 LARC Patients with TNT

Factors	Patients, n (%) or Mean (± SD)
Age (years)	54.1 ± 11.4
Sex	
Male	88 (69.3)
Female	39 (30.7)
BMI	23.5 ± 3.0
Pre-TNT cT stage	
2	5 (3.9)
3	80 (63.0)
4	42 (33.1)
Pre-TNT cN	
0	11 (10.4)
1	49 (41.5)
2	67 (48.1)
Pre-TNT CRM positive	44 (34.6)
Pre-TNT EMVI positive	45 (35.4)
Pre-TNT tumor diameter (cm)	5.4 ± 1.7
Pre-TNT distance from anal verge (cm)	4.8 ± 1.4
Pre-TNT CEA (ng/mL)	9.9 ± 18.7
Pre-TNT CA19-9 (U/mL)	35.8 ± 69.1
Post-TNT tumor diameter (cm)	3.3 ± 1.6
Post-TNT distance from anal verge (cm)	5.3 ± 2.1
Post-TNT cT stage without surgery	
cT0[a]	13 (72.2)
cT3 or cT4[b]	5 (17.8)
Post-TNT pT stage with surgery	
pT0	18 (16.5)
pT1	8 (7.3)
pT2	36 (33.0)
pT3	28 (25.7)
pT4	19 (17.4)
Post-TNT cN stage without surgery	
cN0[a]	13 (72.2)
cN1 or cN2[b]	5 (17.8)
Post-TNT pN stage with surgery	
pN0	73 (67.0)
pN1	33 (30.3)
pN2	3 (2.7)
Grade	
G1	21 (16.5)
G2	58 (45.7)
G3	6 (4.7)
NA[c]	42 (33.1)
Lymphovascular invasion involvement	18 (14.5)
Perineural invasion involvement	16 (12.9)
Resection margin	
R0	107 (84.2)
R1	2 (1.6)
NA[d]	18 (14.2)

(*Continued*)

Table 1 (Continued).

Factors	Patients, n (%) or Mean (± SD)
Post-TNT treatment	
Dixon's procedure	95 (74.8)
Hartmann's procedure	4 (3.1)
Miles' procedure	10 (7.9)
W&W	13 (10.2)
Systemic therapy	5 (3.9)
Treatment response	
Good response	70 (55.1)
Poor response	57 (44.9)

Notes: [a]Patient entered watch and wait protocol; [b]Patients did not undergo surgery due to tumor progression; [c]The surgical specimen exhibits a TRG0/1 treatment effect, or patients did not undergone surgery; [d]Patient did not undergo surgery due to watch and wait protocol or tumor progression.
Abbreviations: BMI, body mass index; CA19-9, Carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; CRM, circumferential resection margin; cT/N stage, clinical T/N stage; EMVI, extramural venous invasion; NA, not available; TNT, total neoadjuvant therapy; TRG, tumor regression grade; W&W, watch and wait.

Table 2 Association Between Pre-TNT Factors and TNT-Induced Tumor Regression

Factors	Good Response Patients, n (%)	Poor Response Patients, n (%)	Statistics	*p* value
No. of patients	70 (55.1)	57 (44.9)		
Age (Mean ± SD)	53.4 ± 12.4	55.2 ± 10.0	t = −0.883	0.379
≤ 60	50 (71.4)	38 (66.7)		
> 60	20 (28.6)	19 (33.3)		
Sex				
Male	43 (61.4)	41 (71.9)		
Female	27 (38.6)	16 (28.1)	χ^2 = 1.547	0.214
BMI			Z = −1.544	0.123
Pre-TNT cT stage				
2	5 (7.1)	0 (0)		
3	46 (65.7)	34 (59.6)		
4	19 (27.1)	23 (40.4)	χ^2 = 5.912	0.052
Pre-TNT cN				
0	5 (7.1)	6 (10.5)		
1	29 (41.4)	20 (35.1)		
2	36 (51.4)	31 (54.4)	χ^2 = 0.795	0.672
Pre-TNT UICC Stage				
IIA	4 (5.7)	4 (7.0)		
IIIA	3 (4.3)	0 (0)		
IIIB	39 (58.2)	28 (49.1)		
IIIC	24 (34.3)	25 (43.9)	χ^2 = 3.533	0.317
Pre-TNT CRM status				
-	45 (64.3)	38 (66.7)		
+	25 (35.7)	19 (33.3)	χ^2 = 0.079	0.779
Pre-TNT EMVI status				
-	46 (65.7)	36 (63.2)		
+	24 (34.3)	21 (36.8)	χ^2 = 0.090	0.765

(*Continued*)

Table 2 (Continued).

Factors	Good Response Patients, n (%)	Poor Response Patients, n (%)	Statistics	*p* value
Pre-TNT tumor diameter	4.9 ± 1.5	6.0 ± 1.8	Z = 3.419	0.001*
Pre-TNT Distance from anal verge	4.6 ± 1.2	5.2 ± 1.6	Z = 2.379	0.017*
Albumin	42.5 ± 5.1	40.4 ± 6.6	Z = −1.072	0.284
WBC	6.57 ± 1.65	6.73 ± 2.22	Z = 0.005	0.996
Neutrophil	4.13 ± 1.35	4.42 ± 1.86	Z = 0.950	0.342
Lymphocyte	1.80 ± 0.54	1.63 ± 0.56	Z = −2.427	0.015*
Platelet	246.7 ± 80.5	249.3 ± 69.1	Z = 1.004	0.315
Hemoglobin	133.4 ± 17.9	123.2 ± 25.9	Z = −2.207	0.027*
CEA (ng/mL)	8.1 ± 17.3	12.1 ± 20.3	Z = 1.535	0.125
CA19-9 (U/mL)	17.5 ± 16.1	58.2 ± 97.4	Z = 2.260	0.024*
CD4+ T cell	678.8 ± 243.0	604.4 ± 256.8	Z = −1.707	0.088
CD8+ T cell	404.7 ± 188.3	384.1 ± 231.7	Z = −1.406	0.160
CD4+/CD8+ cell ratio	1.88 ± 0.78	1.80 ± 0.73	Z = −0.252	0.801
NK/T cell ratio	16.14 ± 8.42	17.92 ± 9.65	Z = −1.033	0.302
NLR	2.67 ± 2.06	3.01 ± 2.66	Z = 1.818	0.069
PLR	155.5 ± 96.5	162.3 ± 48.5	Z = 2.172	0.030*
HALP	47.1 ± 25.7	35.2 ± 19.0	Z = −2.928	0.003*
PNI	51.5 ± 6.0	48.6 ± 7.3	Z = −1.833	0.067
GNRI	108.8 ± 10.1	103.7 ± 11.7	Z = −1.391	0.164

Note: *$p < 0.05$.

Abbreviations: CRM, circumferential resection margin; EMVI, evaluate extramural vascular invasion; GNRI, geriatric nutritional risk index; HALP, The hemoglobin and albumin levels and lymphocyte and platelet index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; TNT, total neoadjuvant therapy.

Multivariate Analysis and ROC Curves for Risk Factors That Affect the TNT Response

We incorporated demographic factors and statistically related factors into the regression analysis. Demographic and statistically relevant factors were included in the regression analysis. The cut-off values for CEA and CA19-9 were based on serum reference values. The tumor diameter and distance from anal verge were determined through clinical experience. Cutoff values for PLR and HALP were established using ROC curve analysis.

A univariate logistic regression model using pre-TNT factors identified large tumor diameter, low hemoglobin, and low HALP as unfavorable predictors of the TNT-induced response (Table 3). In the multivariate analysis, large tumor diameter (>5 cm; HR 2.958; 95% CI 1.382–6.335; $p = 0.005$), and low HALP (≤ 40; HR 0.261; 95% CI 0.111–0.612; $p = 0.002$) were identified as independent unfavorable predictors of TNT-induced response (Table 3).

Table 3 Univariate and Multivariate Analyses of the Clinicopathological Characteristics for Response

Independent Factor	Logistic Univariate Analysis			Logistic Multivariate Analysis		
	HR	95% CI	*p* value	Hazard Ratio	95% CI	*p* value
Age	1.014	0.983–1.046	0.376			NS
Sex (Male vs Female)	0.621	0.293–1.318	0.215			NS
BMI	0.885	0.782–1.001	0.052			NS
cT stage	1.816	0.861–3.831	0.117			NS
cN	1.126	0.559–2.270	0.740			NS
CRM status (+ vs -)	0.900	0.431–1.880	0.779			NS
EMVI status (+ vs -)	1.118	0.539–2.321	0.765			NS
CEA (≤ 5.0 vs > 5.0, ng/mL)	1.284	0.619–2.666	0.502			NI
CA199 (≤ 37.0 vs > 37.0, U/mL)	1.566	0.674–3.638	0.297			NI

(*Continued*)

Table 3 (Continued).

Independent Factor	Logistic Univariate Analysis			Logistic Multivariate Analysis		
	HR	95% CI	*p* value	Hazard Ratio	95% CI	*p* value
Tumor diameter (≤ 5.0 vs > 5.0, cm)	3.251	1.566–6.747	0.002*	2.958	1.382–6.335	0.005*
Distance from anal verge (≤ 5.0 vs > 5.0, cm)	0.654	0.320–1.336	0.244			NI
Lymphocyte	0.574	0.294–1.119	0.103			NI
Hemoglobin	0.979	0.963–0.995	0.012*			NI
PLR (≤ 150 vs > 150)	1.944	0.957–3.950	0.066			NS
HALP (≤ 40 vs > 40)	0.290	0.135–0.624	0.002*	0.261	0.111–0.612	0.002*

Note: *$p < 0.05$.
Abbreviations: CI, confidence interval; CRM, circumferential resection margin; EMVI, evaluate extramural vascular invasion; HALP, The hemoglobin and albumin levels and lymphocyte and platelet index; HR, hazard ratio; NI, not included; NS, not significant; PLR, platelet-to-lymphocyte ratio.

Following multivariate analysis, ROC curves were constructed to evaluate the predictive power of tumor diameter and HALP for TNT response. The ROC curves demonstrated that the tumor diameter and HALP had AUC of 0.678 (95% CI 0.583–0.773) and 0.677 (95% CI 0.583–0.770), respectively. When combined, the AUC for these factors increased to 0.748 (95% CI 0.663–0.833), indicating improved predictive accuracy (Figure 2).

Association of Predictors of the TNT Response with Recurrence

At the end of the follow-up period, 17/57 (29.8%) patients in the poor response group and 10/70 (14.3%) in the good response group developed local recurrence or distant metastases. The PFS rate of the poor response group in the two groups was significantly poor compared to the good response group ($p = 0.006$) (Figure 3A). Next, we investigated the correlation of predictive factors and tumor recurrence. Surprisingly, the tumor diameter did not show a significant association with recurrence ($p = 0.784$) (Figure 3B). Interestingly, low HALP exhibited a nonsignificant trend toward a poor prognosis ($p = 0.086$; HR 2.008, 95% CI 0.906–4.447) (Figure 3C). This trend suggests that lower HALP may be associated with a higher risk of recurrence, indicating its potential as a prognostic marker.

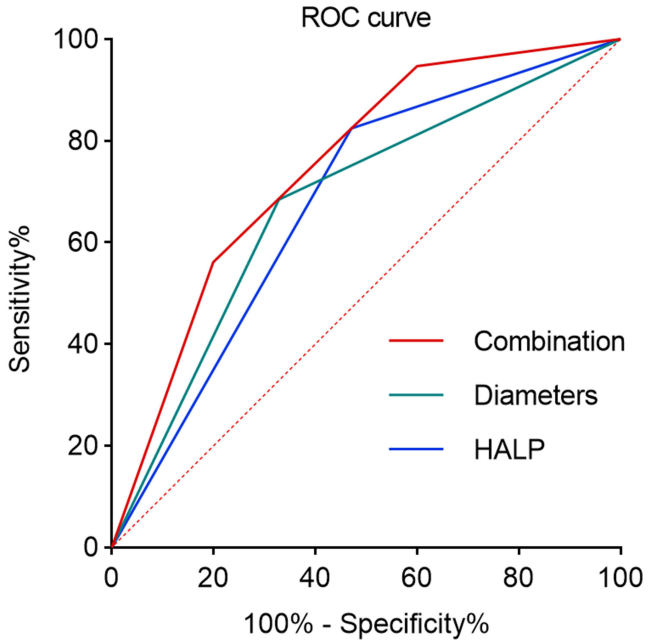

Figure 2 Receiver operating characteristic curve analysis for tumor diameters, HALP, and their combination.
Abbreviation: HALP, combination index of hemoglobin and albumin levels and lymphocyte and platelet.

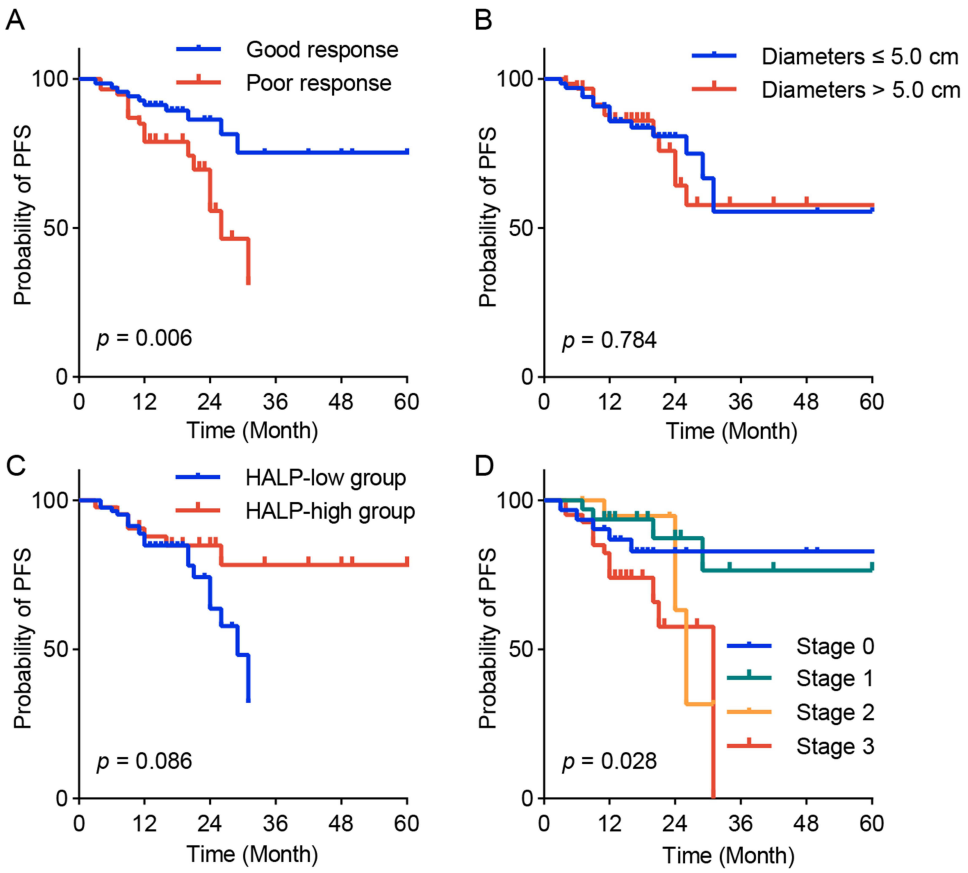

Figure 3 Progression-free survival after TNT in patients with LARC. (**A**) Progression-free survival stratified by TNT-induced tumor regression after TNT. (**B**) Progression-free survival stratified by pre-TNT diameters after TNT. (**C**) Progression-free survival stratified by HALP after TNT. (**D**) Progression-free survival stratified by post-TNT TNM stage after TNT.
Abbreviations: HALP, combinational index of hemoglobin and albumin levels and lymphocyte and platelet; TNT, total neoadjuvant treatment.

Finally, we explored the relationship between post-TNT tumor stage and recurrence. As expected, a higher post-TNT TNM stage was significantly associated with a poorer prognosis ($p = 0.028$) (Figure 3D). This finding reinforces the importance of TNM staging in predicting patient outcomes post-TNT.

Discussion

TNT has been employed as an alternative therapy for patients with LARC, although variable tumor regression responses have been observed.[7] This approach has been shown to increase pCR rates and to potentially reduce the risk of distant metastasis by addressing micrometastatic disease earlier in the treatment course.[4–6] Despite the advantages of TNT, it is important to acknowledge that the total rate of pCR and sustained cCR in TNT was only 21.8% to 28.0%. Therefore, early identification of unfit patients who may benefit from TNT, coupled with adaptive treatment strategies, shows promise in improving the prognosis. This single-center retrospective study examined the clinical and pathological characteristics of patients with LARC undergoing TNT, exploring their potential as factors that predict tumor regression.

In this study, the total rate of pCR/TRG0 and sustained cCR in TNT was 24.4%, which is consistent with previous findings.[4–6] Specifically, 18 patients (16.5%) in our surgical cohort achieved pCR/TRG0, deviating from the rates reported in previous studies.[4–6] This discrepancy may be attributed to 10.2% (13/127) of the patients who achieved cCR in our study without undergoing surgery.

The most prevalent grade 3 of hematologic AEs included neutropenia (17/127, 13.4%), thrombocytopenia (14/127, 11.0%), and anemia (14/127, 11.0%). In particular, no grade 4 or severe AEs were documented. In previous studies, the occurrence rates of grade 3–4 of neutropenia, thrombocytopenia, and anemia were 0.7%-16.8%, 1.0%-11.1%, and 0.7%–

1.0%, respectively.[5,6] The reason for this difference may be the difference in TNT regimens and the frequency of laboratory tests. Consequently, TNT treatment at our center is deemed safe and effective.

In our study, large tumor diameters correlated with a poor TNT-induced response, with logistic multivariate analysis revealing tumor diameter (≥5.0 cm) as an independent risk factor (Table 3). These findings align with the retrospective study conducted by Chapman et al[8,10,29] This outcome aligned with our expectations. Larger tumor diameters are inherently more challenging to reduce. Consequently, for patients with larger tumors, transitioning to more intensive chemotherapy regimens, such as FOLFIRINOX, or extending the duration of chemotherapy cycles may enhance tumor regression.

Of note, Zhang reported pre-TNT lymph node-positive tumors as indicative of poor TNT-induced regression.[8] In contrast, our study did not observe this phenomenon (Table 2). Discrepancies may have arisen from variations in treatment response Definitions and the limited sample size in our study.

Several studies have investigated the role of nutritional inflammatory factors in predicting the response of tumor regression to nCRT. For example, Novin et al observed that pre-nCRT NLR was unable to predict treatment response in patients with LARC.[30] Similarly, our study did not find an association between NLR and TNT-induced tumor regression ($p = 0.069$) (Table 2). However, we identified a significant association between a low HALP index (≤40) and a lower GNRI index (≤50) with poor TNT-induced regression in patients with LARC (Table 3).

This study also investigated the association between recurrence-free survival and tumor regression effects and their predictors. Patients in the poor response group exhibited worse PFS than those in the good response group (Figure 3A). Similar findings in other studies suggest that TRG 0/pCR is associated with better survival outcomes, indicating that a relatively poor response to TNT is related to worse survival outcomes.[31] Furthermore, we revealed that low HALP emerged as adverse prognostic indicators for recurrence in patients with LARC undergoing TNT (Figure 3C). HALP has been reported as predictive factors for tumor prognosis in various studies. Yalav et al demonstrated the independent prognostic significance of HALP in patients undergoing curative resection for colorectal cancer.[32] In particular, Zhang and Amano et al highlighted the importance of post-nCRT GNRI in predicting overall survival and PFS for patients with LARC over 60 years of age.[33,34] However, our study, with only 39 (30.7%) patients over 60 years of age, did not observe a similar correlation (Table 2).

Although the precise mechanisms underlying systemic inflammation in tumorigenesis, progression, and metastasis remain unclear, some theories propose its role in stimulating angiogenesis, immunosuppression, and the formation of a supportive microenvironment. First, multiple studies have shown that low hemoglobin levels contribute to tumor hypoxia, increasing the risk of local failure and distant metastasis.[16,35] Furthermore, a hypoxic tumor environment can inhibit drug accumulation and efficacy.[36] Second, serum albumin levels have independently emerged as prognostic factors in various cancers.[24] Low albumin levels can increase the concentration of free drugs, increasing the risk of toxic reactions and affecting the patient's tolerance to chemotherapy, requiring adjustment of treatment doses. Low albumin is often associated with a chronic inflammatory state, which can suppress the immune system and reduce the body's ability to defend against tumors.[37] Third, lymphocytes play a pivotal role in suppressing tumor growth, with higher lymphocyte signatures correlated with improved prognosis in various tumors.[38] Finally, platelets can infiltrate the tumor microenvironment and interact with cancer cells, helping circulating tumor cells adhere to endothelial cells and establishing a premetastatic niche.[39] Therefore, it is surprising that HALP, which reflects both systemic inflammation and nutritional status, is associated with TNT-induced tumor regression. Consequently, nutritional support can improve the overall condition of patients and their response to treatment.

This study presents several limitations. First, its retrospective nature and single-center design, with a relatively small cohort of patients, did not allow a comprehensive exploration of risk factors or the construction of a regression prediction model for the TNT-induced response. The potential bias in the data collection process was another concern. Second, the exclusive utilization of Capox-based consolidation of TNT in our center raises uncertainty about the generalizability of our findings to other TNT regimens. Third, the absence of genetic test results, such as MSI status, which can affect the biological behavior of tumor cells, is a notable gap in our study. Fourth, due to the limited duration of follow-up, we did not investigate the relationship of TNT-induced tumor regression and its predictors with overall survival of patients. Fifth, we did not collect data on extended treatment intervals or dose reductions resulting from adverse reactions during TNT treatment. Consequently, we were unable to assess the association between HALP and adverse effects. Lastly, our conclusions require further validation through larger prospective studies.

Conclusion

A large tumor diameter (>5 cm) and low HALP (<40) predict poor tumor regression induced by the CAPOX-based TNT regimen in patients with LARC. Large-scale prospective studies are essential to validate and refine our understanding. Whether this subset of patients requires additional in chemotherapy, such as FOLFIRINOX, remains to be verified in a prospective cohort.

Abbreviations

AE, Adverse events; CEA, Carcinoembryonic antigen; CRM, Circumferential resection margin; CT, Computed tomography; EMVI, Extramural vascular invasion; GNRI, geriatric nutritional risk index; HALP, The hemoglobin and albumin levels and lymphocyte and platelet index; LARC, Locally advanced rectal cancer; MRI, Magnetic resonance imaging; NLR, Neutrophil-to-lymphocyte ratio; NK, Natural killer; PFS, Progression-free survival; PLR, Platelet-to-lymphocyte ratio; PNI, Prognostic nutritional index; TME, Total mesorectal excision; TNT, Total neoadjuvant therapy; W&W, Watch-and-wait.

Data Sharing Statement

Data from this study are available from the corresponding author upon request.

Ethics Approval and Informed Consent

The study adhered to the Declaration of Helsinki and obtained approval from the Ethics Committee of Chongqing University Cancer Hospital (reference number 2023(011)). All patients provided their informed consent in writing before TNT treatment, surgery, or before a watch-and-wait strategies (W&W) strategy.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; and all authors took part in drafting, revising or critically reviewing the article, gave final approval of the version to be published, agreed on the journal to which the article has been submitted and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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