

Evaluation of the Relationship Between Prognostic Nutritional Index and Survival in Operated Stage II and III Colorectal Cancer Patients Receiving Adjuvant Chemotherapy

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Abstract

Objectives: The prognostic nutritional index (PNI) is an important parameter that reflects nutritional and immunological status and serves as a prognostic marker for many types of gastrointestinal cancer. In this study, we aimed to evaluate the relationship between PNI and survival outcomes among patients with colorectal cancer (CRC) who underwent surgery and received adjuvant chemotherapy.

Methods: Demographic, clinical, and pathological data; treatments received; inflammatory and nutritional prognostic markers, including PNI, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR); and survival outcomes of 314 patients diagnosed with stage II and III CRC were examined retrospectively. Pre- and post-chemotherapy values of PNI, NLR, and PLR, and their associations with 5-year overall survival (OS) and disease-free survival (DFS), were analyzed. Patients were divided into two groups based on median values of each biomarker.

Results: The median pre-chemotherapy PNI, NLR, and PLR were 38.01, 3.85, and 197.15, respectively; the post-chemotherapy medians were 41.31, 2.47, and 143.80. In stage II CRC, pre-chemotherapy PNI ≤ 38.01 significantly decreased OS ($p=0.022$) and DFS ($p=0.033$) compared to PNI >38.01 . In stage III CRC, PNI did not significantly affect OS ($p=0.746$) or DFS ($p=0.438$). In multivariate Cox regression analysis for 5-year DFS, pre-chemotherapy NLR, pre-chemotherapy PNI, post-chemotherapy PNI, and body mass index were independent prognostic factors ($p=0.010$, $p=0.018$, $p=0.008$, and $p=0.005$, respectively).

Conclusion: Pre-chemotherapy PNI was significantly associated with OS in univariate analysis of stage II CRC; however, it was not retained as an independent predictor in the multivariate OS model. Both pre- and post-chemotherapy PNI values were independent predictors of 5-year DFS. These findings suggest that PNI may serve as a valuable and easily accessible prognostic marker, particularly for disease recurrence in early-stage CRC.

Keywords: Colorectal cancer, prognostic nutritional index, overall survival, disease-free survival, prognostic factors, platelet-to-lymphocyte ratio

Introduction

Cancer is a major global public health problem. In the United States, lung, prostate, and colorectal cancer (CRC) in men and lung, breast, and CRC in women are the leading causes of cancer-related death (1). CRC is the second leading cause of death when both sexes are combined (2). It is estimated that

there were a total of 151.030 new CRC cases in the United States in 2022 (1).

Survival outcomes of CRC patients are mainly predicted by tumor-related factors such as tumor, node, metastasis (TNM) staging, tumor grade, and tumor location. However, studies have demonstrated that prognosis is also related to host factors (3,4).



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The preoperative nutritional status of the host and the systemic inflammatory response play a crucial role in the progression and metastasis of many cancer types. Accordingly, the importance of prognostic markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and the prognostic nutritional index (PNI) has been investigated in various malignancies (5-8). PNI is a prognostic marker that reflects both immunological and nutritional status and is calculated from the serum albumin level and peripheral lymphocyte count.

In the literature, a study of stage II and III patients undergoing curative resection investigated whether nutritional scores [PNI and controlling nutritional status (CONUT) score] and inflammatory scores were independent prognostic factors for overall survival (OS) and found that nutritional scores were superior (9). Another study examining preoperative and postoperative PNI values in operated stage II and III patients found that the combination of preoperative and postoperative PNI was an independent predictor of poor OS (10).

In this study, we aimed to determine the prognostic significance of PNI and its relationship with clinicopathological and other prognostic factors in surgically treated CRC patients receiving adjuvant chemotherapy.

Material and Methods

A total of 314 patients diagnosed with early-stage CRC who were admitted to the Medical Oncology Department of Necmettin Erbakan University between January 2010 and December 2021 were included in this study. The cohort included patients with both colon and rectal cancer. Patients with rectal cancer who received radiotherapy (n=62, 19.7%) were treated in accordance with contemporary National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology Guideline recommendations. Pelvic radiotherapy is indicated for stage II (T3-T4, N0) and stage III (any T, N1-2) rectal cancer because of the elevated risk of local recurrence after surgery alone. Radiation was administered either as neoadjuvant chemoradiotherapy prior to total mesorectal excision or as adjuvant postoperative chemoradiotherapy at the discretion of the multidisciplinary tumor board. Patient data were retrospectively analyzed. Patients with missing pathology results, those who did not receive or could not complete adjuvant chemotherapy, or those who had incomplete laboratory data were excluded from the study. Patient data were obtained retrospectively from the hospital's electronic databases, the prescription system, and the national health system network. Ethical approval was obtained from the Ethics Committee of

Necmettin Erbakan University for Non-Pharmaceutical and Non-Medical Device Research (approval no: 2021/3430, date: 01.10.2021). The research was conducted in accordance with the principles of the Declaration of Helsinki.

All stage II patients in this cohort were classified as high-risk and received adjuvant chemotherapy accordingly. High-risk stage II disease was defined based on the presence of one or more of the following clinicopathological features, in accordance with NCCN Clinical Practice Guidelines (version 2.2025, colon cancer): T4 disease, poorly differentiated or undifferentiated histology [exclusive of microsatellite instability-high (MSI-H) tumors], lymphovascular invasion, perineural invasion, fewer than 12 lymph nodes examined, tumor presentation with bowel obstruction or localized perforation, and close, indeterminate, or positive surgical margins. The decision to administer adjuvant chemotherapy for stage II patients was made by the treating oncologist based on the individual risk profile of each patient.

Patient demographics [age, sex, height, weight, body mass index (BMI)], comorbidities, date of diagnosis, date of operation, history of emergency surgery, primary tumor location, history of radiotherapy and chemotherapy, tumor histopathology (histological type, stage, grade, lymphovascular invasion, T4 disease), MSI (evaluated by immunohistochemistry for MLH1, MSH2, MSH6, and PMS2), genetic mutation analysis (K-RAS, N-RAS, BRAF), carcinoembryonic antigen (CEA) level, and laboratory values measured preoperatively and after adjuvant chemotherapy [neutrophil count, lymphocyte count, platelet count, albumin, NLR, PLR, C-reactive protein (CRP), and PNI] were recorded.

NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. PLR was calculated as the absolute platelet count divided by the absolute lymphocyte count. PNI was calculated using the formula: $PNI = 10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total lymphocyte count (/mm}^3\text{)}$, as originally described by Onodera et al. (11). Since no consensus cut-off values for NLR, PLR, and PNI have been established in the literature, median values were used as cut-off points to divide patients into two groups. This approach has been widely adopted in comparable exploratory retrospective studies (9,10,12). However, using population-specific median values may limit reproducibility across populations; receiver operating characteristic (ROC)-based or externally validated thresholds should therefore be explored in future studies.

Post-chemotherapy laboratory values (PNI, NLR, and PLR) were obtained from blood samples collected during the first scheduled follow-up visit, approximately one month after completion of adjuvant chemotherapy.

Patients were divided into two groups based on the median PNI value before and after chemotherapy. The effects of PNI on 5-year OS and disease-free survival (DFS) were evaluated.

Statistical Analysis

Data were analyzed using SPSS 18.0. Descriptive analyses included frequency (n, %), mean $\pm$ standard deviation, median (interquartile range), relative risk, and 95% confidence interval (CI). Categorical data were compared using chi-square and Fisher's exact tests. Normality was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Independent samples t-test and Mann-Whitney U test were used as appropriate. Kaplan-Meier survival analysis was performed, and univariate and multivariate Cox regression analyses were conducted to identify independent prognostic factors. For multivariate Cox regression, all clinically relevant prognostic variables were entered into the model using the forced entry method, regardless of their significance in univariate analysis, to account for potential confounding effects. Results were evaluated at the 95% confidence level, and significance was set at $p < 0.05$.

Results

Patients were divided into two groups based on the pre-chemotherapy PNI median value: ≤ 38.01 and > 38.01 . The mean age of the patients in the low PNI group was higher than that in the high PNI group ($p < 0.001$). No significant differences were found between the two groups with respect to other sociodemographic characteristics (BMI, sex, comorbidity, Eastern Cooperative Oncology Group). There were no significant differences between the two groups tumor location, lymph node count, T4 disease, lymphovascular invasion, MSI, and mutations (Table 1).

As adjuvant chemotherapy, 134 patients (42.7%) received 5-fluorouracil, leucovorin, oxaliplatin, 67 (21.3%) received 5-fluorouracil/leucovorin, 60 (19.1%) received capecitabine, and 53 (16.9%) received capecitabine, oxaliplatin. No significant difference in survival was observed between chemotherapy groups.

Among the patients, 66 (21.0%) were MSI-H/deficient mismatch repair (dMMR) and 61 (19.4%) were microsatellite stable (MSS)/pMMR.

Among pre-chemotherapy laboratory values, the mean albumin was lower in the low PNI group than in the high PNI group ($p < 0.001$). CRP, neutrophil count, and NLR were higher in the low PNI group than in the high PNI group ($p < 0.001$, $p = 0.002$, and $p = 0.002$, respectively). No significant differences were observed between the two groups with

respect to pre-chemotherapy platelet counts, lymphocyte counts, and PLR values. Post-chemotherapy PNI was also lower in the group with low pre-chemotherapy PNI ($p < 0.001$). Post-chemotherapy albumin levels were lower in the low PNI group than in the high PNI group ($p < 0.001$). No significant differences were observed between the two groups in post-chemotherapy CRP, neutrophil, platelet, and lymphocyte counts, NLR, and PLR (Table 2).

The effects of pre-chemotherapy PNI, NLR, and PLR values on OS in patients with stage II and stage III CRC were analyzed by grouping patients according to median values. In patients with stage II CRC, the mean OS was 97.29 months (CI: 81.05-112.78) in the group with pre-chemotherapy PNI ≤ 38.01 , and 117.31 months (CI: 108.34-126.27) in the group with PNI > 38.01 . In patients with stage II CRC, a PNI level of ≤ 38.01 at initial diagnosis significantly decreased OS compared to PNI > 38.01 ($p = 0.022$) (Figure 1).

The effect of pre-chemotherapy PNI on OS in patients with stage III CRC was not statistically significant ($p = 0.746$). In patients with stage II and III CRC, the effects of pre-chemotherapy NLR and PLR levels on survival were not statistically significant (NLR: $p = 0.106$ for stage II and $p = 0.845$ for stage III; PLR: $p = 0.522$ for stage II and $p = 0.706$ for stage III).

Post-chemotherapy PNI, NLR, and PLR values were grouped based on their median levels and their effects on OS were analyzed. In patients with stage II CRC, the mean OS was 98.69 months (CI: 86.89-110.50) in the group with post-chemotherapy PNI ≤ 42.00 , and 125.64 months (CI: 118.51-132.77) in the group with PNI > 42.00 . A post-chemotherapy PNI level of ≤ 42.00 significantly decreased survival compared to PNI > 42.00 ($p = 0.002$) (Figure 2).

The effect of post-chemotherapy PNI on survival in patients with stage III CRC was not statistically significant ($p = 0.462$). The effect of post-chemotherapy NLR on survival in patients with stage II and III CRC was not statistically significant ($p = 0.054$ and $p = 0.706$, respectively). In patients with stage II CRC, the mean OS was 126.32 months (CI: 118.80-133.85) in the group with post-chemotherapy PLR ≤ 111.36 , and 101.44 months (CI: 90.51-112.37) in the group with PLR > 111.36 . A post-chemotherapy PLR ≤ 111.36 significantly increased OS compared to PLR > 111.36 ($p = 0.007$) (Figure 3). In patients with stage III CRC, the effect of post-chemotherapy PLR on survival was not statistically significant ($p = 0.804$).

Univariate analysis examined the effects of independent prognostic factors on 5-year OS. Among these, the effects of pre-chemotherapy NLR and PNI, and of post-chemotherapy NLR and BMI, on 5-year OS were statistically significant ($p = 0.017$, $p = 0.042$, $p = 0.009$, and $p = 0.015$, respectively). In

Table 1. General characteristics of patients

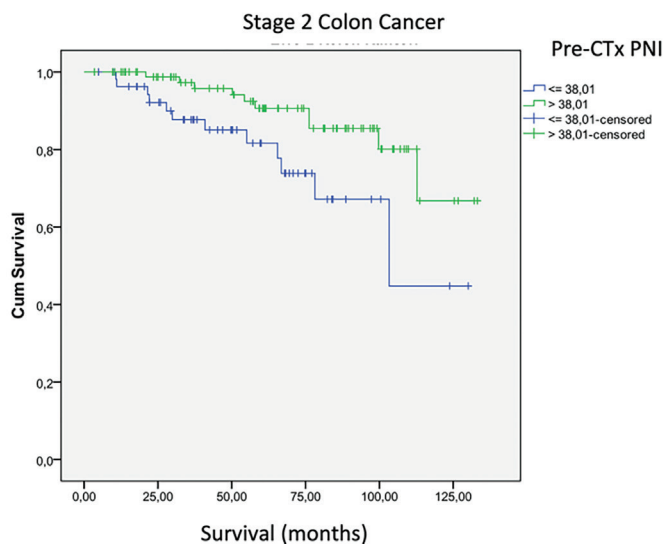
	Pre-chemotherapy PNI		
	≤38.01 (n=127)	>38.01 (n=187)	p-value
Age (years)	70.00 (63.00-75.00)	65.00 (56.00-72.00)	<0.001*
BMI (kg/m²)	26.36 (22.85-29.38)	26.66 (23.83-30.09)	0.208*
Gender			
Female	48 (37.80)	80 (42.80)	0.378**
Male	79 (62.20)	107 (57.20)	
Comorbidity			
Yes	60 (47.20)	103 (55.10)	0.173**
None	67 (52.80)	84 (44.90)	
ECOG PS			
ECOG 0	19 (15.00)	41 (21.90)	0.052**
ECOG 1	94 (74.00)	137 (73.30)	
ECOG 2	14 (11.00)	9 (4.80)	
Tumor location			
Left colon	92 (72.40)	130 (70.70)	0.732*
Right colon	35 (27.60)	54 (29.30)	
Number of lymph nodes removed			
≥12	95 (74.80)	140 (74.90)	0.990*
<12	32 (25.20)	47 (25.10)	
Histological type			
Adenocarcinoma	115 (92.00)	157 (84.00)	0.037*
Mucinous adenocarcinoma	10 (8.00)	30 (16.00)	
Lymphovascular invasion			
Yes	60 (47.20)	72 (38.50)	0.124*
None	67 (52.80)	115 (61.50)	
MSI			
MSI high (dMMR) (n=66)	30 (56.60)	36 (48.60)	0.376*
MSS (n=61)	23 (43.40)	38 (51.40)	
K-RAS mutation			
Yes (n=33)	17 (45.90)	16 (38.10)	0.480*
None (n=46)	20 (54.10)	26 (61.90)	
N-RAS mutation			
Yes (n=3)	1 (3.10)	2 (5.10)	1.000**
None (n=68)	31 (96.90)	37 (94.90)	
BRAF mutation			
Yes (n=1)	0 (0.00)	1 (2.70)	1.000**
None (n=67)	31 (100.00)	36 (97.30)	
Radiotherapy			
Yes	29 (22.80)	33 (17.60)	0.257**
None	98 (77.20)	154 (82.40)	
Adjuvant CTx protocol			
FOLFOX	58 (45.70)	76 (40.60)	0.516**
5-FU/LV	22 (17.30)	45 (24.10)	
Capecitabine	26 (20.50)	34 (18.20)	
XELOX	21 (16.50)	32 (17.10)	
Progression			
Yes	31 (24.40)	40 (21.40)	0.530*
None	96 (75.60)	147 (78.60)	
Latest status			
Alive-disease-free	87 (68.50)	140 (74.90)	0.326*
Alive-diseased	8 (6.30)	13 (7.00)	
Deceased	32 (25.20)	34 (18.20)	

PNI: Prognostic nutritional index, BMI: Body mass index, ECOG-PS: Eastern cooperative oncology group- performance status, MSI: Microsatellite instability, dMMR: Deficient mismatch repair, MSS: Microsatellite stable, CTx: Chemotherapy, FOLFOX: 5-fluorouracil, leucovorin, oxaliplatin, 5-FU/LV: 5-fluorouracil/leucovorin, XELOX: Capecitabine, oxaliplatin

Table 2. Comparison of laboratory parameters of pre-chemotherapy PNI groups

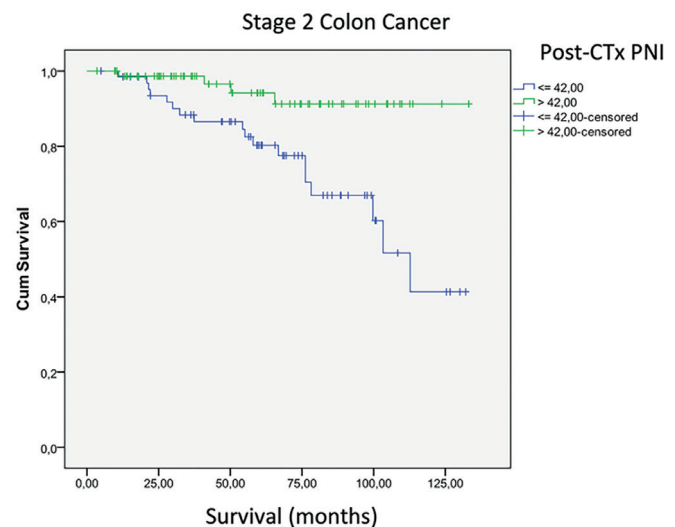
	Pre-chemotherapy PNI		p-value
	≤38.01 (n=127)	>38.01 (n=187)	
CEA	1.92 (1.20-3.80)	2.20 (1.37-3.97)	0.312*
Before chemotherapy			
Albumin	3.40 (3.10-3.60)	4.10 (4.00-4.30)	<0.001*
CRP	23.50 (3.10-104.00)	5.20 (2.00-25.00)	<0.001*
Neutrophil	6.00 (4.30-8.40)	5.10 (3.90-6.84)	0.002*
Platelets	324.00 (261.00-410.00)	307.00 (253.50-378.75)	0.188*
Lymphocyte	1.80 (1.40-2.40)	1.90 (1.40-2.60)	0.282*
NLR	3.30 (2.16-5.50)	2.61 (1.72-4.55)	0.002*
PLR	180.19 (133.75-248.75)	169.05 (120.21-227.47)	0.059*
After chemotherapy			
PNI	41.00 (38.00-43.00)	42.00 (40.01-44.01)	<0.001*
Albumin	4.10 (3.80-4.30)	4.20 (4.00-4.40)	<0.001*
CRP	2.70 (2.00-7.30)	2.30 (1.70-6.70)	0.275*
Neutrophil	3.30 (2.50-4.60)	3.40 (2.42-4.40)	0.323*
Platelets	240.00 (180.00-300.00)	252.00 (180.00-320.00)	0.370*
Lymphocyte	1.86±0.83	1.95±0.90	0.363**
NLR	1.94 (1.30-3.00)	1.92 (1.36-2.88)	0.245*
PLR	111.30 (80.00-187.33)	116.54 (87.06-177.86)	0.900*

*, Mann Whitney U-Test, **: Independent samples t-test, PNI: Prognostic nutritional index, CEA: Carcinoembryonic antigen, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

**Figure 1.** The effect of pre-chemotherapy PNI levels on overall survival in patients with stage 2 colon cancer

PNI: Prognostic nutritional index, CTx: Chemotherapy

the multivariate Cox regression analysis for 5-year OS, the effects of pre-chemotherapy NLR and PLR values, and of post-chemotherapy NLR and BMI values, were statistically significant ($p=0.010$, $p=0.006$, $p=0.010$, and $p=0.010$, respectively) (Table 3).

**Figure 2.** The effect of post-chemotherapy PNI levels on overall survival in patients with stage 2 colon cancer

PNI: Prognostic nutritional index, CTx: Chemotherapy

Univariate analysis was performed to assess the effects of independent prognostic factors on 5-year DFS. The effects of pre-chemotherapy NLR and PNI and of post-chemotherapy NLR, PLR, PNI, and BMI on 5-year DFS were statistically significant ($p=0.004$, $p=0.002$, $p=0.003$, $p=0.048$, $p=0.016$, and $p=0.008$, respectively). In the multivariate Cox regression

analysis for 5-year DFS, the effects of pre-chemotherapy NLR and PNI, and of post-chemotherapy PNI and BMI, were statistically significant ($p=0.010$, $p=0.018$, $p=0.008$, and $p=0.005$, respectively) (Table 4).

Discussion

In this study, we investigated the prognostic significance of PNI in patients with early-stage CRC and whether it was superior to other prognostic markers such as NLR and PLR.

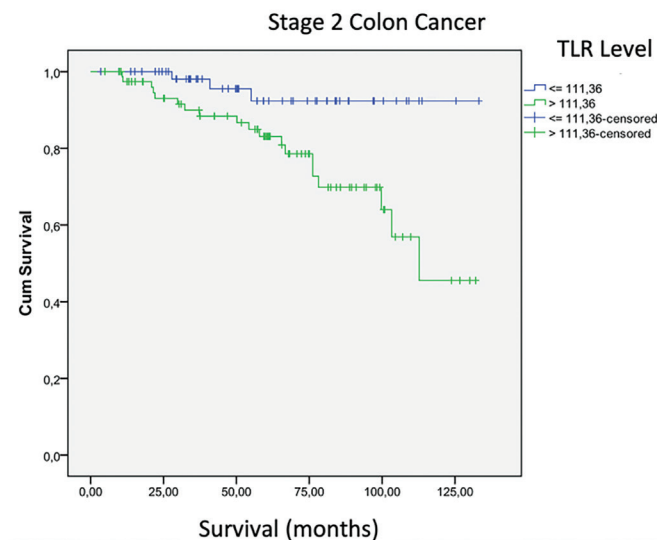


Figure 3. The effect of post-chemotherapy TLR levels on overall survival in patients with stage 2 colon cancer

TLR: Trombosit-lenfosit ratio

Surgical resection is the main treatment for stage I-III CRC. A significant proportion of patients develop recurrence or metastases within 5 years of surgical resection. Disease prognosis can vary greatly even among patients with the same stage. Therefore, new parameters are needed to predict survival and prognosis accurately. Molecular parameters such as MSI and RAS/RAF mutations have been associated with prognosis; however, complex and expensive laboratory techniques are required to measure these parameters.

Survival outcomes of CRC patients are mainly predicted by tumor-related factors, including TNM staging, tumor grade, and tumor location (3,4). Studies have reported that prognosis is related to host and tumor factors.

The preoperative nutritional status of the host and the systemic inflammatory response play a crucial role in triggering progression and metastasis in many types of cancer. The inflammatory response is indicated by the levels of neutrophils, lymphocytes, platelets, and acute phase proteins such as CRP (4). One of the indicators of nutritional status is albumin level. Hypoalbuminemia and malnutrition are common among cancer patients. Based on this, the importance of prognostic markers (such as NLR, PLR, PNI) has been investigated in many oncological malignancies (5-8). However, there is no consensus on which marker is more useful.

While the prognostic significance of PNI in CRC has been reported in several studies, the present study offers several distinct contributions. First, to our knowledge, this is one of the few studies to evaluate both pre- and post-

Table 3. Cox-regression analysis of independent prognostic factors on 5-year overall survival

5-year overall survival				
	Univariate Cox-regression		Multivariate Cox-regression	
	RR (CI)	p-value	RR (CI)	p-value
NLR (pre-chemotherapy)	1.523 (1.079-2.148)	0.017	1.730 (1.199-2.497)	0.010
PLR (pre-chemotherapy)	0.940 (0.670-1.320)	0.721	0.998 (0.997-1.000)	0.006
PNI (pre-chemotherapy)	0.694 (0.488-0.987)	0.042	-	-
NLR (post-chemotherapy)	1.601 (1.126-2.276)	0.009	1.605 (1.121-2.300)	0.010
PLR (post-chemotherapy)	1.293 (0.917-1.823)	0.143	-	-
PNI (post-chemotherapy)	0.711 (0.505-1.000)	0.050	-	-
BMI	0.645 (0.454-0.919)	0.015	0.619 (0.430-0.890)	0.010
Comorbidity	0.945 (0.670-1.333)	0.746	-	-
Lymph node count	0.797 (0.546-1.163)	0.240	-	-
T4 disease	1.202 (0.847-1.705)	0.303	-	-
MSI	0.588 (0.201-1.719)	0.332	-	-
CEA	1.084 (0.772-1.522)	0.641	-	-
K-RAS mutation	1.104 (0.458-2.663)	0.826	-	-

RR: Relative risk, CI: Confidence interval, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, PNI: Prognostic nutritional index, BMI: Body mass index, MSI: Microsatellite instability, CEA: Carcinoembryonic antigen

chemotherapy PNI values in a cohort in which all patients completed adjuvant chemotherapy, thereby allowing a more homogeneous assessment of treatment-related nutritional changes. Second, the combined analysis of PNI, NLR, and PLR at two time points provides a more comprehensive inflammatory-nutritional prognostic profile than those from most existing single-time-point studies. Third, the finding that post-chemotherapy PNI was an independent predictor of DFS highlights the potential clinical utility of serial PNI monitoring during adjuvant treatment, an area that remains underexplored in CRC.

In our study, the mean age of patients in the low PNI group was higher, which is consistent with the results of previous studies (13,14). The findings support the conclusion that malnutrition and immunosuppression have become more prevalent among elderly patients with cancer.

In our study, the cut-off values for pre-chemotherapy PNI, NLR, and PLR were 38.01, 3.85, and 197.15, respectively. In patients with stage II CRC, a PNI level of ≤ 38.01 at initial diagnosis significantly decreased OS and DFS compared to PNI > 38.01 . In patients with stage III CRC, the effect of PNI on OS and DFS was not statistically significant. NLR and PLR levels did not have a significant effect on OS or DFS in either stage II or stage III CRC.

On review of the literature, a study of 197 patients diagnosed with stage IIA colon cancer who underwent curative resection between 2006 and 2016 found that low PNI (< 44.8) was the only independent predictor of DFS. The effects of NLR and

PLR on DFS were not significant. In this study, 37 patients received adjuvant chemotherapy. The results for PNI were similar to our findings (13).

In a study involving 1,035 patients with stage IIA disease who underwent surgery, the prognostic effects of PNI, NLR, PLR, and serum fibrinogen levels on OS and DFS were analyzed. Patients in the poor prognosis group (NLR ≥ 2.4 , PLR ≥ 150.8 , fibrinogen ≥ 339.5 mg/dL, and PNI < 45.5) had higher-grade histology, older age, and lower BMI. While patients with low PNI and high NLR had a worse prognosis, no significant results were obtained for PLR in 5-year survival analysis (15). Unlike these studies, our study made no subgroup distinction among stage II patients. However, all patients received adjuvant chemotherapy and were high-risk stage II patients. The results for PNI in our study were consistent with the literature and demonstrated that PNI is an important prognostic marker in stage II CRC.

In the study by Peng et al. (14) involving 274 patients with stage III colon cancer, a low PNI (≤ 49.22) was significantly related to short OS and DFS in patients with stage IIIC, but not in patients with stage IIIA/IIIB. In our study, the number of stage III patients was 171. The differences between the studies may be due to the unknown number of patients with stage IIIC and the relatively small number of patients (14).

The effect of independent prognostic factors (PNI, NLR, PLR, BMI, comorbidity, number of lymph nodes, T4 disease, MSI, CEA, K-RAS mutation) on 5-year OS was analyzed (Table 3). Among these, the effects of pre-chemotherapy NLR and PNI

Table 4. Cox-regression analysis of independent prognostic factors on 5-year disease-free survival

5 years disease-free survival				
	Univariate Cox-regression		Multivariate Cox-regression	
	RR (CI)	p-value	RR (CI)	p-value
NLR (Pre-chemotherapy)	1.715 (1.182-2.489)	0.004	1.638 (1.125-2.384)	0.010
PLR (Pre-chemotherapy)	0.933 (0.649-1.341)	0.706	-	-
PNI (Pre-chemotherapy)	0.535 (0.362-0.791)	0.002	0.615 (0.412-0.918)	0.018
NLR (Post-chemotherapy)	1.774 (1.214-2.592)	0.003	-	-
PLR (Post-chemotherapy)	1.452 (1.004-2.099)	0.048	-	-
PNI (Post-chemotherapy)	0.637 (0.441-0.920)	0.016	0.588 (0.396-0.873)	0.008
BMI	0.592 (0.403-0.870)	0.008	0.562 (0.374-0.844)	0.005
Comorbidity	0.931 (0.642-1.349)	0.704	-	-
Lymph node count	1.009 (0.673-1.512)	0.966	-	-
T4 Disease	1.241 (0.855-1.801)	0.256	-	-
MSI	0.684 (0.215-2.177)	0.521	-	-
CEA	1.076 (0.746-1.550)	0.696	-	-
K-RAS mutation	2.390 (0.473-12.081)	0.292	-	-

RR: Relative risk, CI: Confidence interval, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, PNI: Prognostic nutritional index, BMI: Body mass index, MSI: Microsatellite instability, CEA: Carcinoembryonic antigen

and of post-chemotherapy NLR and BMI on 5-year OS were statistically significant.

When the effects of independent prognostic factors on 5-year DFS were analyzed, pre-chemotherapy NLR and PNI, and post-chemotherapy NLR, PLR, PNI, and BMI were statistically significant. In the multivariate Cox regression analysis of 5-year DFS, pre-chemotherapy NLR and PNI, and post-chemotherapy PNI and BMI, were significant (Table 4).

In a study of 1.880 patients with stage II and III CRC who underwent curative resection, Ahiko et al. (9) investigated whether two nutritional scores (PNI and CONUT) and four inflammatory scores (modified Glasgow prognostic score, NLR, PLR, and CRP/albumin ratio) are independent prognostic factors for OS. Two nutritional and two inflammatory scores were independent prognostic factors for OS; however, PNI and CONUT were superior to the inflammatory scores. PLR was not a significant independent prognostic factor. This finding is similar to our findings (9). In this study, 715 patients received adjuvant chemotherapy, while all patients in our study did so. Although our study included fewer patients, the results were similar.

In a study evaluating 1.014 CRC patients who underwent surgery in China, PNI was found to be an independent risk factor for 1-5 year OS and DFS and could be used together with TNM staging (16). Similarly, a Japanese study the PNI values of patients with stage II and III CRC. Although the preoperative PNI value was low, the prognosis of patients with increased PNI value after adjuvant treatment was reported to be better (12). Providing adequate energy and protein intake for patients with low PNI values may improve PNI and contribute positively to prognosis and OS.

In a meta-analysis of studies on BMI and survival in CRC, it was found that being underweight (BMI <18.5 kg/m²) or class II/III obese (BMI >35 kg/m²) during CRC surgery may lead to worse long-term survival results, while being slightly overweight (BMI 25-30 kg/m²) may improve survival (17).

We have not found any study in the literature that investigates the prognostic role of post-chemotherapy PNI in CRC or examines its combined analysis with pretreatment PNI. In the study of Küçükarda et al. (18) with 107 patients with non-metastatic nasopharyngeal cancer, PNI values were analyzed both before and after treatment, and PNI was found to be an independent prognostic marker for OS both before and after treatment. In our study, the effect of post-treatment PNI (mean value of 41.31) on 5-year DFS was significant.

Shibutani et al. (10) examined the effect of preoperative and postoperative PNI values on OS. The study included 218 stage II

and III patients, 141 of whom received chemotherapy. The median preoperative PNI was 47.90 and the median postoperative PNI was 48.69. The combination of pre- and postoperative PNI was an independent predictor of poor OS. These results demonstrate the importance of preoperative, postoperative, and post-chemotherapy PNI as prognostic markers.

In most studies, a cut-off value for PNI was determined, and groups were compared. In the study by Luván-Morales et al. (19), patients were divided into four groups according to PNI values (>47.1; 47.0-43.5; 43.4-34.2; and <34.2) and the effect on prognosis was analyzed. Lower PNI values were associated with poorer 5-year survival. Although a different method was used for PNI evaluation, the findings are consistent with ours.

A summary of key studies evaluating PNI as a prognostic factor in CRC is presented in Table 5. Among these studies, cut-off determination methods varied considerably, including ROC curve analysis (13,15), median-based cut-offs (9,10,12), the X-tile program, and quartile-based divisions (19). This heterogeneity highlights the need for consensus-driven or externally validated PNI thresholds. In the present study, median values were used, consistent with several prior reports; however, we acknowledge that this approach may limit external reproducibility.

Regarding molecular subgroup analyses, MSI-H/dMMR status is a well-established favorable prognostic factor in stage II CRC and is known to influence treatment decisions. In our cohort, MSI/MMR data were available for only 127 patients (66 with MSI-H/dMMR and 61 with MSS/pMMR), and MSI status was not a significant predictor in univariate analysis of either OS (p=0.332) or DFS (p=0.521). The potential interaction between MSI-H/dMMR status and PNI is of clinical interest, as both may reflect aspects of the host immune response. However, the limited sample size for this subgroup precluded meaningful interaction analysis. Future studies with larger cohorts should explore whether PNI retains its prognostic value across MSI-defined subgroups.

A potentially important area for future investigation is the dynamic change in PNI values from pre- to post-chemotherapy. Categorizing patients based on the direction of PNI change (e.g., sustained high, sustained low, improving, or declining) may provide additional prognostic information beyond single time-point measurements. Such an approach could help identify patients whose nutritional and immunological status deteriorates during adjuvant treatment, enabling timely nutritional interventions. Prospective studies with larger sample sizes are warranted to further explore this transitional analysis.

Table 5. Summary of studies evaluating PNI as a prognostic factor in colorectal cancer

Author, year	n	Stage	PNI cut-off	Cut-off method	Adj CTx, n (%)	Main PNI findings
Maruyama et al. (13)	197	IIA	44.8	ROC curve	37 (19%)	Low PNI was the only independent predictor of DFS
Park et al. (15)	1.035	IIA	45.5	ROC curve	NR	Low PNI and high NLR predicted worse OS; PLR was not significant
Peng et al. (14)	274	III	49.22	ROC curve	All	Low PNI predicted short OS and DFS in stage IIIC only
Ahiko et al. (9)	1.880	II-III	NR	Median	715 (38%)	PNI and CONUT were superior to inflammatory scores for OS prediction
Xie et al. (16)	1.014	I-IV	Continuous	Per-unit HR	NR	PNI was an independent risk factor for 1-5 year OS and DFS
Tamai et al. (12)	218	II-III	47.90/48.69	Median	141 (65%)	Pre/postoperative PNI combination was an independent predictor of poor OS
Shibutani et al. (10)	218	II-III	47.90	Median	141 (65%)	Combination of pre- and postoperative PNI predicted poor OS independently
Luvián-Morales et al. (19)	NR	I-IV	4 groups*	Quartile-based	NR	Lower PNI groups showed progressively worse 5-year OS
Present study	314	II-III	38.01/42.00†	Median	All (100%)	Pre- and post-chemotherapy PNI independently predicted DFS; pre-CTx PNI significant for OS in stage II

*: PNI groups: >47.1, 47.0-43.5, 43.4-34.2, and <34.2, †: 38.01 (pre-chemotherapy median) and 42.00 (post-chemotherapy median), PNI: Prognostic nutritional index, Adj CTx: Adjuvant chemotherapy, ROC: Receiver operating characteristic, DFS: Disease-free survival, OS: Overall survival, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CONUT: Controlling nutritional status, NR: Not reported, HR: Hazard ratio

Study Limitations

This study has several limitations that should be acknowledged. First, the retrospective single-center design and the relatively limited sample size are inherent limitations.

Second, the exclusion of patients who did not initiate or complete adjuvant chemotherapy may have introduced selection bias, as these patients may represent a frailer subgroup with an inherently worse prognosis. This limits the generalizability of our findings to the broader population of patients with stage II and III CRC who underwent surgery.

Third, median-based cut-off values for PNI, NLR, and PLR were used rather than ROC-derived thresholds. Although the sample size (n=314) would have been suitable for ROC analysis, median values were chosen for consistency with comparable studies in the literature. Future studies should employ ROC-derived or externally validated cut-off values.

Fourth, low PNI values may partly reflect underlying confounding factors such as advanced age, frailty, chronic inflammation, comorbidities, or poor treatment tolerance, rather than representing an independent biological mechanism driving worse survival outcomes. Although we adjusted for age, comorbidity, and BMI in our analyses, residual confounding cannot be entirely excluded.

Fifth, the multivariate Cox regression model was constructed using forced entry of clinically relevant variables; however, major clinicopathological confounders such as age, stage, T stage, MSI status, and performance status were not uniformly pre-specified as mandatory covariates. The unexpected significance of pre-chemotherapy PLR in the multivariate OS model, despite non-significance in univariate analysis, may reflect a suppressor effect and should be interpreted cautiously, given the minimal effect size (hazard ratio: 0.998).

Sixth, potential collinearity among nutritionally and immunologically related variables warrants consideration. PNI is derived from serum albumin and the lymphocyte count, thereby creating an inherent mathematical relationship with these components. Similarly, NLR and PLR share lymphocyte count as a common denominator, and BMI may correlate with albumin levels as a reflection of nutritional status. Formal collinearity diagnostics (e.g., variance inflation factor analysis) were not performed, which may have influenced the multivariate regression estimates.

Seventh, MSI/MMR and molecular mutation data were not available for all patients, which limited subgroup analyses. Future studies with comprehensive molecular profiling are warranted.

Nevertheless, results consistent with the literature were obtained in the majority of analyses.

Conclusion

Pre-chemotherapy PNI was significantly associated with OS on univariate analysis, particularly in stage II CRC patients; however, it was not retained as an independent predictor in the multivariate model for OS. In contrast, both pre- and post-chemotherapy PNI were independent predictors of 5-year DFS in multivariate analysis. These findings suggest that PNI, which can be easily calculated from routine laboratory parameters (serum albumin and lymphocyte count), may serve as a valuable and accessible prognostic marker for disease recurrence in early-stage CRC. Prospective studies with larger sample sizes, ROC-derived cut-off values, and comprehensive molecular profiling are needed to validate these findings and establish standardized PNI thresholds for clinical use.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of Necmettin Erbakan University for Non-Pharmaceutical and Non-Medical Device Research (approval no: 2021/3430, date: 01.10.2021).

Informed Consent: Patient data were obtained retrospectively from the hospital's electronic databases, the prescription system, and the national health system network.

Footnotes

Authorship Contributions

Surgical and Medical Practises: M.U., M.Z.K., M.K.E., M.A., Me.A., Concept: S.Ç., Ş.B.A., M.Z.K., M.K.E., M.A., Design: S.Ç., M.U., Me.A., Data Collection or Processing: M.U., Ş.B.A., M.Z.K., M.K.E., M.A., Me.A., Analysis or Interpretation: S.Ç., M.U., M.Z.K., Me.A., Literature Search: S.Ç., M.U., M.Z.K., Me.A., Writing: S.Ç., M.U., M.Z.K., Me.A.

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Reader Questions

Based on the manuscript: “Evaluation of the Relationship Between Prognostic Nutritional Index and Survival in Operated Stage II and III Colorectal Cancer Patients Receiving Adjuvant Chemotherapy”

1. What formula is used to calculate the prognostic nutritional index (PNI)?

- A. Albumin $\times$ neutrophil count
- B. $10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total lymphocyte count (/mm}^3\text{)}$
- C. Platelet count $\div$ lymphocyte count
- D. CRP $\times$ BMI

Correct Answer: B. $10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total lymphocyte count (/mm}^3\text{)}$

2. Which survival outcome remained independently associated with both pre- and post-chemotherapy PNI in multivariate analysis?

- A. Overall survival (OS)
- B. Progression-free survival (PFS)
- C. Disease-free survival (DFS)
- D. Cancer-specific survival (CSS)

Correct Answer: C. Disease-free survival (DFS)

3. In which patient subgroup did pre-chemotherapy PNI significantly predict overall survival in univariate analysis?

- A. Stage I colorectal cancer
- B. Stage II colorectal cancer
- C. Stage III colorectal cancer
- D. Metastatic colorectal cancer

Correct Answer: B. Stage II colorectal cancer

4. Which inflammatory biomarker is calculated by dividing the absolute neutrophil count by the absolute lymphocyte count?

- A. PNI
- B. PLR
- C. NLR
- D. CONUT

Correct Answer: C. NLR

5. What was the principal conclusion of this study?

- A. PNI replaced TNM staging for prognosis.
- B. PNI may serve as a simple and accessible prognostic marker, particularly for disease recurrence in early-stage colorectal cancer.
- C. PLR was superior to all other biomarkers.
- D. BMI was the strongest predictor of overall survival.

Correct Answer: B. PNI may serve as a simple and accessible prognostic marker, particularly for disease recurrence in early-stage colorectal cancer.