ORIGINAL ARTICLE

THE ASSOCIATION BETWEEN PREOPERATIVE PROGNOSTIC NUTRITIONAL INDEX AND TUMOR RESPONSE TO TOTAL NEOADJUVANT THERAPY IN RECTAL CANCER

Rektum Kanserinde Preoperatif Prognostik Beslenme İndeksi ile Total Neoadjuvan Tedaviye Tümör Yanıtı Arasındaki İlişki

Efe Cem ERDAT[1], Merih YALCINER[1], Gungor UTKAN[1]

[1]Ankara Üniversitesi,
Tıp Fakültesi,
Tıbbi Onkoloji Bilim Dalı

ABSTRACT

Objective: The Prognostic Nutritional Index (PNI) reflects patients' nutritional and immunological status, calculated using serum albumin levels and lymphocyte counts. While PNI has been studied for prognostic evaluation and mortality prediction in various cancers, its role in predicting tumor response to total neoadjuvant therapy (TNT) in rectal cancer remains unclear.

Material and Methods: This single-center retrospective study included rectal cancer patients aged ≥18 years who received TNT and underwent surgery at Ankara University Hospitals between January 2018 and June 2023. PNI was calculated using the formula: PNI = (10 × serum albumin [g/dL]) + (0.005 × total lymphocyte count [per mm^3]). The cut-off value for PNI was determined using ROC curve analysis. Statistical analyses assessed the association between PNI and tumor response.

Results: A total of 51 patients were enrolled, with a median age of 64 years; 62.7% were male. Complete response was observed in 25.5% of patients, partial response in 72.6%, and no response in 1.9%. The mean PNI was higher in patients with complete response compared to those with partial or no response (48.80 vs. 45.51; p = 0.056). Using a PNI cut-off value of 50.65, patients with higher PNI had a significantly higher rate of complete response (38.5% vs. 10.5%; p = 0.023). The odds ratio for achieving complete response in patients with PNI > 50.65 was 5.31.

Conclusion: Higher preoperative PNI values are associated with better tumor response to TNT in rectal cancer patients. PNI may serve as a useful predictor of treatment response and survival outcomes in this population.

Keywords: *Prognostic Nutritional Index; Rectal Cancer; Total Neoadjuvant Therapy; Tumor Response; Nutritional Status*

Efe Cem ERDAT, Uzm. Dr.
(0000-0002-1250-1297)
Merih YALÇINER, Uzm. Dr.
(0000-0003-3337-2188)
Güngör UTKAN, Prof. Dr.
(0000-0001-8445-6993)

ÖZET

Amaç: Rektum kanseri hastalarında total neoadjuvan tedavi (TNT) alanlarda, preoperatif Prognostik Beslenme İndeksi (PBI) değerleri ile tümör yanıtı arasındaki ilişkiyi incelemek.

Gereç ve Yöntemler: Ocak 2018 ve Haziran 2023 tarihleri arasında Ankara Üniversitesi Hastaneleri'nde TNT alan ve cerrahi uygulanan rektum kanseri hastaları retrospektif olarak incelendi. PBI, serum albümin düzeyleri ve lenfosit sayıları kullanılarak hesaplandı: PBI = (10 × serum albümin [g/dL]) + (0,005 × toplam lenfosit sayısı [mm^3 başına]). PBI için eşik değeri ROC eğrisi analizi ile belirlendi. İstatistiksel analizler PBI ile tümör yanıtı arasındaki ilişkiyi değerlendirdi.

Bulgular: Toplam 51 hasta dahil edildi; medyan yaş 64 ve %62,7'si erkekti. Hastaların %25,5'inde tam yanıt, %72,6'sında kısmi yanıt ve %1,9'unda yanıt yoktu. Tam yanıtı olan hastalarda ortalama PBI, kısmi veya yanıt olmayan hastalara göre daha yüksekti (48,80 vs. 45,51; p = 0,056). PBI için 50,65 eşik değeri kullanıldığında, daha yüksek PBI değerine sahip hastalarda tam yanıt oranı anlamlı olarak daha yüksekti (%38,5 vs. %10,5; p = 0,023). PBI > 50,65 olan hastalarda tam yanıt elde etme olasılık oranı 5,31 idi.

Sonuç: Yüksek preoperatif PBI değerleri, rektum kanseri hastalarında TNT'ye daha iyi tümör yanıtı ile ilişkilidir. PBI, bu popülasyonda tedavi yanıtı ve sağkalım sonuçlarını tahmin etmede yararlı bir gösterge olabilir.

Anahtar Kelimeler: *Prognostik Beslenme İndeksi; Rektum Kanseri; Total Neoadjuvan Tedavi; Tümör Yanıtı; Beslenme Durumu*

İletişim:
Uzm. Dr. Efe Cem ERDAT
Ankara Üniversitesi Tıbbi Onkoloji Bilim Dalı, Mamak/Ankara

Geliş tarihi/Received: 07.11.2024
Kabul tarihi/Accepted: 27.01.2025
DOI: 10.16919/bozoktip.1580916

Bozok Tıp Derg 2025;15(1):37-42
Bozok Med J 2025;15(1):37-42

INTRODUCTION

Colorectal cancer is the third most common malignancy and ranks third in cancer-related deaths among both genders worldwide (1). Recent advancements in treatment have significantly improved the survival rates of colorectal cancer patients over the years (2). The introduction of neoadjuvant therapy, particularly total neoadjuvant therapy (TNT) combining chemoradiotherapy (CRT) with chemotherapy, has substantially contributed to decreased mortality rates in rectal cancer by enhancing tumor response (3,4). Several prognostic markers, such as albumin levels, derived neutrophil-to-lymphocyte ratio, Prognostic Nutritional Index (PNI), and inflammatory markers, have been studied for assessing the response to neoadjuvant treatment in rectal cancer (5-7).

PNI is a novel marker used to assess the nutritional and immunological status of patients, typically calculated using serum albumin levels and lymphocyte counts (8). Initially developed to evaluate perioperative nutritional status, PNI has been examined in various cancer types for prognostic evaluation and mortality prediction (9-11). The systemic immune-inflammatory index and PNI have been shown to predict pathological response in gastric cancer patients receiving sintilimab and capecitabine and oxaliplatin (CAPOX) chemotherapy (12). In a retrospective study by Zhang et al., pretreatment inflammation-nutrition scores predicted the response to neoadjuvant treatment in rectal cancer, albeit with some limitations (7). Additionally, preoperative PNI was suggested to be a predictor of overall response in rectal cancer patients in another retrospective study (13).

However, studies assessing the utility of PNI in rectal cancer are mostly limited to survival and complication prediction. Given the lack of information regarding tumor response to TNT in rectal cancer patients, we designed this study to examine the association between preoperative PNI values and tumor response in rectal cancer patients receiving TNT.

MATERIAL AND METHODS

This single-center retrospective study included rectal cancer patients who received TNT. Patients admitted to the Department of Medical Oncology outpatient clinics at Ankara University between January 2018 and June 2023 were screened for eligibility. Inclusion criteria were rectal cancer patients aged ≥18 years without second malignancies, who received TNT as perioperative treatment and underwent surgery at Ankara University Hospitals. Exclusion criteria included lack of tumor response data in pathology reports, incomplete TNT, and missing data on serum albumin levels or lymphocyte counts required for PNI calculation.

Collected data included age at diagnosis, gender, comorbidities, histopathological diagnosis, distance from the anal verge, clinical stage, TNT protocol administered, surgical methods, final pathological staging, tumor response to treatment (complete response/partial response/no response) according to institutional standards, preoperative albumin levels and lymphocyte counts, adjuvant treatments, and survival data. The PNI was calculated using the standard formula: PNI = (10 × serum albumin [g/dL]) + (0.005 × total lymphocyte count [per mm^3]).

This observational study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Institutional ethics committee approved the study (Ankara University Faculty of Medicine, Ethics Committee Approval Number:İ10-694-23, Approval date: 16.11.2023).

Statistical Analysis

Descriptive statistics were presented as median and interquartile range (IQR) for continuous variables and counts and percentages for categorical variables. The cut-off value for PNI was determined using receiver operating characteristic (ROC) curve analysis to achieve suitable sensitivity and specificity. Categorical variables were compared using the chi-square test, and continuous variables were compared using the Mann-Whitney U test. Survival estimates were calculated from the date of diagnosis to the date of progression for progression-free survival (PFS), date of death for overall survival (OS), or date of last follow-up if no event had occurred. Statistical analyses were performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria), and graphics were generated using the ggplot2 and ggroc packages.

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RESULTS

After exclusion, 51 patients were enrolled in the study. The median age was 64 years (IQR 51.75–68.5), and 62.7% (32 patients) were male. Adenocarcinoma was the most common histological diagnosis, observed in 88.2% (45 patients). The median distance from the anal verge was 7 cm, and the median tumor vertical length was 6 cm. Thirty-nine patients had complete clinical staging using the TNM system (AJCC 8th edition), with stage III disease in 36 patients and stage II disease in 3 patients.

Approximately half of the patients underwent long-course radiotherapy with concurrent capecitabine chemotherapy (26 patients), while the other half received short-course radiotherapy (25 patients). All patients received fluoropyrimidine combined with oxaliplatin (either FOLFOX or CAPOX) as neoadjuvant chemotherapy. The median duration of neoadjuvant chemotherapy was 2.5 months.

Forty-four patients underwent low anterior resection, and 7 patients underwent abdominoperineal resection as primary surgery. Pathological examination of surgical specimens revealed partial response in 37 patients, complete response in 13 patients, and no response in 1 patient. Postoperative T staging showed ypT3 in 19 patients, ypT2 in 17 patients, ypT0 in 13 patients, ypT1 in 1 patient, and ypT4 in 1 patient. Nodal staging showed ypN0 in 39 patients, ypN1 in 10 patients, and ypN2 in 2 patients.

The mean serum albumin level was 4.11 g/dL, mean lymphocyte count was 1.07×10^9/L, and the mean PNI was 46.49. The demographics and disease-related characteristics of the patients are presented in Table 1.

Using ROC curve analysis, the cut-off value for PNI in predicting complete response versus partial/no response was calculated as 50.65, with an area under the curve (AUC) value of 0.676, sensitivity of 43.8%, and specificity of 91.7%. The ROC curve is presented in Figure 1.

The mean PNI was higher in patients with complete response compared to those with partial or no response (48.80 vs. 45.51; p = 0.056). When stratified by the cut-off value of 50.65, 5 patients (38.5%) with complete response had PNI values higher than the cut-off, while only 4 patients (10.5%) with partial or no response had PNI values above the cut-off. This difference was statistically significant (p = 0.023). The odds ratio for achieving complete response with PNI values higher than 50.65 was 5.31 (95% CI: 1.16–23.38). Details of PNI values and responses are provided in Table 2.

The median follow-up duration was 21 months. During this period, 3 patients experienced disease recurrence, and 3 deaths were observed. The median overall survival and disease-free survival durations were not reached. There was no significant difference in survival between patients with PNI values below or above the cut-off value. All three patients with recurrent disease had PNI values below the cut-off, with a median PNI of 39.75. All deceased patients also had PNI values below the cut-off, with a median PNI of 41.15. Survival curves are presented in Figure 2.

DISCUSSION

The Prognostic Nutritional Index (PNI) is increasingly being studied in oncological practice for its potential role in predicting overall survival and perioperative mortality in colorectal cancer (CRC) patients undergoing surgery. However, limited information exists regarding its utility in assessing treatment response in rectal cancer patients receiving TNT.

In our study of 51 patients, we demonstrated that rectal cancer patients with higher preoperative PNI values had a higher rate of complete response to TNT. This may be attributable to better nutritional and immunological status, which could enhance the efficacy of neoadjuvant therapies. Additionally, all mortalities observed occurred in patients with lower PNI values, consistent with findings in the current literature.

Li et al. conducted a large retrospective study showing that higher PNI is associated with improved progression-free and overall survival in CRC patients, with a determined cut-off value of 48.65 (14). Our study calculated a slightly higher cut-off value of 50.65, possibly due to our focus on non-metastatic patients, whereas PNI values may be lower in metastatic cases. Similarly, Zhang et al. suggested that pretreatment inflammation-nutrition scores, including PNI, predict non-responders to neoadjuvant therapy in rectal cancer, with a cut-off value of 50.08, close to our determined value (9).

PNI values can fluctuate due to treatments like

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Table 1. Demographics and disease related properties of the patients

Patient demographics	Total (n = 51)
Age, median (IQR)	64 (51.75-68.5)
Gender, n (%)	
Male gender	32 (62.7 %)
Female gender	19 (38.3 %)
Histological subtype, n (%)	
Adenocarcinoma	45 (88.2 %)
Mucinous carcinoma	6 (11.8%)
Median distance from anal verge, cm (IQR)	7 (4.75-10)
Median tumor vertical length, cm (IQR)	6 (5-8)
TNM stage at diagnosis, n (%) *	
II	3 (7.7 %)
III	36 (92.3 %)
Total neoadjuvant therapy administered, n (%)	
Long-term radiotherapy + FOLFOX/CAPOX	26 (51.0 %)
Short-term radiotherapy + FOLFOX/CAPOX	25 (49.0 %)
Median neoadjuvant chemotherapy duration, months (IQR)	2.5 (1.5-4.0)
Surgery type, n (%)	
Low anterior resection	44 (86.3 %)
Abdominopelvic resection	7 (13.7 %)
Tumor T staging in surgical material, n (%)	
ypT0	13 (25.5 %)
ypT1	1 (1.9 %)
ypT2	17 (33.3 %)
ypT3	19 (37.3%)
ypT4	1 (1.9 %)
Tumor N staging in surgical material, n (%)	
ypN0	39 (76.5 %)
ypN1	10 (19.6 %)
ypN2	2 (3.9 %)
Tumor response to neoadjuvant therapy, n (%)	
Complete response	13 (25.5 %)
Partial response	37 (72.6 %)
No response	1 (1.9 %)
Prognostic nutritional index parameters, mean (± SD)	
Albumin (gr/dL)	4.11 (± 0.46)
Lymphocyte count x 10^9/L	1.070 (± 0.61)
Mean prognostic nutritional index	46.49 (± 6.28)

* Full staging evaluated patient count was 39, Legend: * Full staging evaluated patient count was 39, IQR: interquartile range; SD: standard deviation; n: counts; Legend: * Full staging evaluated patient count was 39 IQR: interquartile range; SD: standard deviation; n: counts, CAPOX: capecitabine and oxaliplatin, FOLFOX: fluorouracil leucovorin and oxaliplatin

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Table 2. PNI values and responses

PNI	Complete response (n = 13)	Partial/no response (n = 38)	p*
Mean, (± SD)	48.80 (± 7.71)	45.51 (± 5.49)	0.056
≤ than cut-off value, n, (%) **	8 (61.5 %)	34 (89.5 %)	0.023
> than cut-off value, n (%)**	5 (38.5 %)	4 (10.5 %)	

Legend: Odds ratio of complete response regarding to higher PNI values is 5.31 (95% CI 1.16 – 23.38), * p values calculated with Student's t test for means and chi-square for percentages, ** cut-off value of PNI calculated as 50.65 PNI: prognostic nutritional index; SD: standard deviation

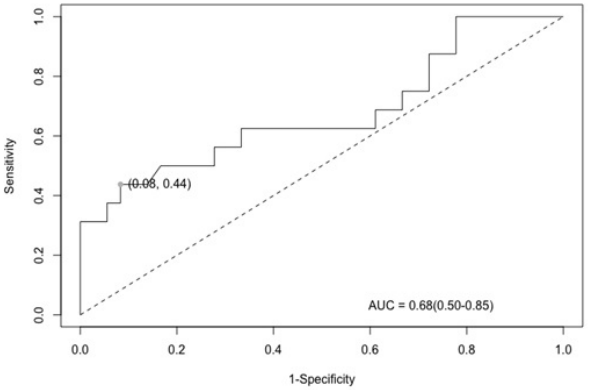

Figure 1. ROC curve of prognostic nutritional index
Legend: ROC: Reciever operating curves;
AUC: Area under curve

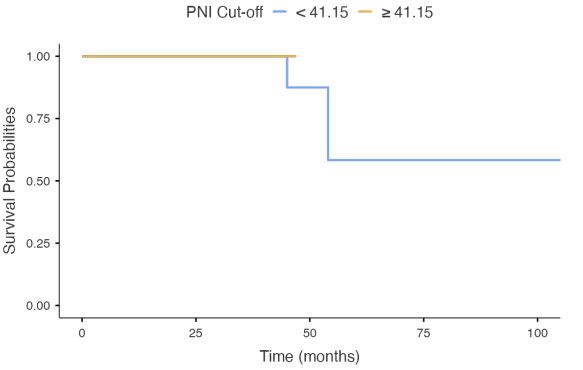

Figure 2. Kaplan-meier survival curves of the patients regarding prognostic nutritional index
Legend: PNI: prognostic nutritional index

radiotherapy and chemotherapy, which can reduce lymphocyte counts, a key component of PNI. Kocak et al. showed that the change in PNI values (delta PNI) before and after treatment is a strong prognostic indicator in CRC patients, with increasing PNI values associated with better prognosis [15]. Moreover, higher preoperative PNI values have been shown to significantly improve overall survival in rectal cancer patients, with a hazard ratio of 0.949 for each one-point increase [16]. large retrospective Mexican cohort also found that increasing PNI values correlate with improved overall survival in CRC patients [17].

Contrarily, Nakamoto et al. reported that PNI values did not predict recurrence in CRC patients who underwent primary resection, though other inflammatory indexes did [18]. This suggests that while PNI is a valuable prognostic marker, its predictive power may vary depending on patient populations and clinical settings. Future prospective and multi-center studies with larger patient cohorts are needed to validate the role of PNI as a predictive marker for tumor response to TNT in rectal cancer. Also, as the survival is not mature yet prospective evaluation of the patients of the study is warranted.

Our study has several limitations. Firstly, its retrospective design limits the level of evidence, and not all patients had complete pretreatment staging. Secondly, the AUC value in our ROC analysis was lower than anticipated, indicating moderate sensitivity and specificity. Despite these limitations, our findings suggest that higher preoperative PNI values are associated with better neoadjuvant treatment response in rectal cancer patients.

CONCLUSION

Higher preoperative Prognostic Nutritional Index values are associated with better tumor response to total neoadjuvant therapy in rectal cancer patients and may predict improved survival outcomes. All observed mortalities occurred in patients with lower PNI values. PNI is a valuable prognostic factor for predicting perioperative mortality in cancer patients. Our study indicates that it can also serve as a predictive marker for response to neoadjuvant treatment in rectal

cancer and may be a significant predictor of mortality. Further prospective studies are warranted to confirm these findings and to explore the integration of PNI into clinical practice for managing rectal cancer patients undergoing TNT.

Acknowledgment

The authors declare that they have no conflict of interest to disclose.

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