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# The Role of Prognostic Nutritional Index in Prognosis Prediction in Cases Diagnosed with Stage-IV Colorectal Cancer

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## ABSTRACT

**Objective:** Systemic inflammation and nutrition are closely linked to cancer prognosis. The prognostic nutritional index (PNI) has shown prognostic value in various gastrointestinal cancers. This study evaluates the prognostic value of PNI in Stage-IV colorectal cancer at diagnosis.

**Material and Methods:** We retrospectively analyzed 82 patients diagnosed with Stage-IV colorectal cancer via biopsy at Akdeniz University Faculty of Medicine, Oncology Clinic between 01/01/2014 and 30/08/2022. Receiver operating characteristic (ROC) analysis determined the PNI cut-off for overall survival (OS). Cox regression was used for prognostic factor analysis.

**Results:** A total of 82 patients were included (69.5% male; mean age 59.6 years). The ROC-defined baseline PNI cut-off was 45.25. Median OS was 35.5 months in the high PNI group versus 18.0 months in the low PNI group [hazard ratio (HR)=0.29, 95% confidence interval (CI): 0.18-0.48, p<0.001). Median progression-free survivals were 15.0 months for the treatment group versus 9.0 months for the control group (HR=0.35, 95% CI: 0.21-0.58, p<0.001). Patients with high baseline PNI also had higher complete response rates (29% vs. 2.9%) and lower rates of haematological toxicity. Analysis of PNI change showed that patients with greater increases in PNI had longer OS (36.5 vs. 20.0 months, HR=0.42, 95% CI: 0.26-0.68, p=0.001) and PFS (14.0 vs. 9.0 months, HR=0.49, 95% CI: 0.30-0.79, p=0.004).

**Conclusion:** PNI, a simple calculation, may aid prognosis prediction in metastatic colorectal cancer.

**Keywords:** Stage-IV colorectal cancer; prognostic nutritional index; progression-free survival; overall survival

## INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths worldwide. The epidemiology of CRC varies significantly across different regions of the world, as well as among different ages, sexes, and races. This variability is influenced by numerous factors, including genetic predisposition, exposure to risk factors, demographic differences, genetic mutations, and their effects on prognosis and treatment response.[1]

For cancer classification, prognosis prediction, and treatment decision-making, the tumor, lymph node, metastasis (TNM) staging system and histological differentiation grade are commonly used. Surgical removal of the primary tumor followed by adjuvant chemotherapy is the primary treatment for colon cancer. However, the TNM staging system is insufficient in practical terms for predicting prognosis and determining treatment options for patients with colon cancer. Survival cannot be fully explained by the pathological stage or established prognostic factors. Recent advances in personalized treatment have underscored the prognostic significance of genetic biomarkers. Identifying biomarkers that predict recurrence and mortality, facilitate early diagnosis and treatment, and reduce the global burden of CRC is

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***Our study was presented at the 8th National Immunotherapy and Oncology Congress.**

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crucial.[2] The integration of molecular and clinical biomarkers has become essential for tailoring treatment strategies and improving prognostic assessment in patients with metastatic CRC.[3]

Recently, the importance of factors related to an individual's immune response and the tumor microenvironment has been highlighted.[1,2] The cancer-related immune inflammatory response in the systemic circulation and tumor microenvironment is now recognized as a significant determinant of disease progression and survival in CRC.[1,2] Previous studies support the independent prognostic value of the prognostic nutritional index (PNI), which reflects the nutritional and immunological status of cancer patients.[4,5]

While baseline PNI has been extensively studied, evidence on dynamic changes in PNI during treatment remains limited, highlighting the novelty of our study in addressing this gap. This study aimed to investigate the adequacy of the PNI in predicting prognosis in the follow-up of patients diagnosed with metastatic CRC, considering various factors such as age, genetics, sex, primary tumor, and metastasis location, as well as contributing to the literature.

## MATERIAL AND METHODS

### Selection of Cases

Patients aged 18 years and above who were diagnosed with CRC through tissue biopsy between January 1, 2014, and August 30, 2022, at the Oncology Clinic of Akdeniz University Faculty of Medicine and had Stage-IV disease, at the time of diagnosis according to TNM staging, were included in our study. The follow-up and treatment of these patients was conducted at the Oncology Clinic of Akdeniz University Faculty of Medicine.

A retrospective analysis of patient files was conducted, documenting the age, sex, body mass index (BMI), diagnosis date, progression and death dates, primary tumor location (right colon, left colon, rectum), histological subtype of the tumor, and genetic mutation analysis (K-RAS, N-RAS, BRAF status). In addition, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels, metastasis sites, (lymph node, liver, lung, peritoneum, bone, and other), chemotherapy details, treatment responses (progression, stable disease, partial response, complete response), post-chemotherapy neutrophil, lymphocyte, and platelet counts, hemoglobin, albumin, and PNI values before treatment and after the first-line systemic therapy for all patients were documented.

Overall survival (OS) was calculated as the time from diagnosis to death for patients who died, and from diagnosis to the last follow-up date for those who did not. Progression-free survival (PFS) was calculated as the time from diagnosis to the first detected progression for patients with progression, and to the last follow-up date for those without progression.

### Ethical Committee Approval

Our thesis study was conducted following the 1964 Helsinki Declaration with the ethical approval of the Scientific Research Ethics Committee of Akdeniz University Faculty of Medicine (obtained on: 12.10.2022 with approval number: 70904504/564). Given the retrospective nature of the study, the requirement for informed consent was waived by the ethics committee.

### Type of Study

Our study is a retrospective cohort study.

### Data Collection

Patient data were collected from Medical Oncology archive records, hospital files the MİAMED automation system, and patients'e-Nabız systems. The date of diagnosis was considered the date of the approved pathology report. At the start of the study, 114 patients with Stage-IV disease were included. Twelve patients were excluded due to discontinuation of follow-up during treatment or continuation at another center; six due to receiving diagnosis and initial chemotherapy at external centers; and two due to having a second primary tumor. Eight patients were deemed unsuitable for systemic chemotherapy due to a low performance score, and four patients died before completing their first-line chemotherapy.

PNI values were calculated for patients at diagnosis (before systemic treatment) and after first-line chemotherapy using the following formula: PNI = serum albumin level (g/dL) + 5 × total lymphocyte count (/L). PNI change was defined as the PNI value after first-line chemotherapy.

### Statistical Analysis

In this study, statistical analyses were conducted using IBM SPSS 25.0 and the JAMOVI program based on the R programming language. Data from 82 cases in the dataset were analyzed. Descriptive statistics included the frequency, mean, median, percentage, and mean ± standard deviation (SD). Normal distributions were examined using the Kolmogorov-Smirnov test, and normality was assessed based on whether the Skewness and Kurtosis values fell within the ±1 range. Non-parametric analyses were performed when normal distribution was not observed. Non-parametric receiver operating characteristic (ROC) analyses were used, and optimal cut-off values were determined, based on the Youden index, which maximizes the sum of sensitivity and specificity. The chi-squared test was used to evaluate the relationships between categorical variables. For parametric

tests, Student's t-test was used for comparisons between two groups, and ANOVA was used for three or more groups. When the assumptions for the parametric tests were not met, equivalent non-parametric tests were performed. To identify groups contributing to differences based on the chi-square test results, the Bonferroni-Dunn test was used. Bonferroni corrections were applied to the p-values in the ANOVA. Univariate survival analyses were conducted using the JAMOVI ClinicoPath module, and Cox regression coefficients and Kaplan-Meier survival tables were evaluated. The p-values were derived using log-likelihood estimates. The proportional hazards assumption for the Cox regression models was tested using Schoenfeld residuals, and no violations were detected. Results with p-values less than 0.05 were considered statistically significant.

## RESULTS

### Demographic Findings and Descriptive Statistics

Among the 82 patients included in the study (57 men, 69.5%; 25 women, 30.5%), ages ranged from 29 to 85 years, with a mean age of 59.6 (median =59.5). The average age of the women was 57.4 years, and the average age of the men was 61 years, with no significant age difference between the two groups (p=0.238). No difference in BMI was observed between the men and women (p=0.363); the mean values were 26.1 for men and 25.1 for women, respectively. A total of 69 patients (84.1%) died.

The clinical, pathological, and molecular characteristics of the patient cohort are presented in Table 1.

Hematologic toxicities observed in the study population are detailed in Table 2.

### ROC Analysis of Initial PNI and Change in PNI

In the analysis, ROC cut-off values for classifying PNI values as low or high were determined. ROC analysis for initial PNI values demonstrated significant effectiveness in distinguishing between patients who experienced death (69 patients) and those who were alive (13 patients), with an area under the curve (AUC) of 0.804 [95% confidence interval (CI): 0.703-0.905]. At the initial PNI cut-off value, the sensitivity for distinguishing between patients who experienced death and those who were alive was 100%, and the specificity was 50%. The optimal PNI threshold for sensitivity and specificity, determined by ROC analysis, was 45.25. Patients with a PNI value of 45.25 and above were classified into the high PNI group (Figure 1).

The effectiveness of the PNI change value in distinguishing between patients who experienced death (69 patients) and those who were alive (13 patients) was significant, with an AUC of 0.793 (95% CI: 0.678-0.909). At the PNI change cut-off value, the sensitivity was 85% and specificity was 42%, with the most decisive point for sensitivity and specificity

**TABLE 1: Clinical, pathological, and molecular characteristics of the patient cohort (n=82).**

| Category | Variable | n (%) |
|---|---|---|
| **Histological subtype & localization** | Adenocarcinoma - right colon | 21 (25.6%) |
| | Adenocarcinoma - left colon | 32 (39.0%) |
| | Adenocarcinoma - rectum | 18 (22.0%) |
| | Mucinous - right colon | 7 (8.5%) |
| | Mucinous - left colon | 3 (3.7%) |
| | Mucinous - rectum | 1 (1.2%) |
| **Performance status** | ECOG 0-1 | 70 (85.4%) |
| | ECOG 2 | 12 (14.6%) |
| **Treatment response** | Progressive disease | 10 (12.2%) |
| | Stable disease | 6 (7.3%) |
| | Partial response | 51 (62.2%) |
| | Complete response | 15 (18.3%) |
| **RAS mutation status** | KRAS/NRAS negative | 50 (61.0%) |
| | KRAS/NRAS positive | 28 (34.1%) |
| | KRAS/NRAS unknown | 4 (4.9%) |
| **BRAF mutation status** | Unknown | 53 |
| | BRAF negative | 25 (86.2%)* |
| | BRAF positive | 4 (13.8%)* |
| **Metastasis** | Lymph node positive | 77 (93.9%) |
| | Lymph node negative | 5 (6.1%) |
| | Liver metastasis positive | 70 (85.4%) |
| | Liver metastasis negative | 12 (14.6%) |
| | Lung metastasis positive | 16 (19.5%) |
| | Lung metastasis negative | 66 (80.5%) |
| | Peritoneal metastasis positive | 14 (17.1%) |
| | Peritoneal metastasis negative | 68 (82.9%) |
| | Bone metastasis positive | 7 (8.5%) |
| | Bone metastasis negative | 75 (91.5%) |
| | Other metastasis positive | 11 (13.4%) |
| | Other metastasis negative | 71 (86.6%) |
| **Tumor markers** | CEA normal | 37 (45.1%) |
| | CEA elevated | 45 (54.9%) |
| | CA 19-9 normal | 51 (62.2%) |
| | CA 19-9 elevated | 31 (37.8%) |

* Percentages for BRAF mutation status calculated among tested patients (n=29).

observed at a PNI change value of 50.40. Patients with a PNI change value >50.40 were classified into the high PNI change group. The cut-off values for the ROC curves were determined by considering the skewness and kurtosis of the PNI distributions (Figure 2).

### Overall Survival and Progression-Free Survival

The OS duration for the study cohort (n=82) is 32.5 months (median =26 months) with a SD of 24.1 months. The shortest and longest survival times were 3 and 104 months, respectively.

The second category is PFS, with a median value of 11.0 months. The shortest PFS was 2.00 months, and the longest was 104 months. Tumor localization did not have a significant effect on OS (p=0.596) or PFS (p=0.962). Table 3 presents descriptive survival statistics based on tumor localization in the right colon versus the left colon and rectum.

**TABLE 2: Hematologic toxicities.**

| | | n (%) |
|---|---|---|
| Lymphopenia | No toxicity | 45 (54.9) |
| | Grade 1 | 18 (22) |
| | Grade 2 | 12 (14) |
| | Grade 3 | 6 (7.3) |
| | Grade 4 | 1 (1.2) |
| Anemia | No toxicity | 17 (20.7) |
| | Grade 1 | 41 (50.0) |
| | Grade 2 | 23 (28.0) |
| | Grade 3 | 1 (1.2) |
| Neutropenia | No toxicity | 42 (51.2) |
| | Grade 1 | 26 (31.7) |
| | Grade 2 | 8 (9.8) |
| | Grade 3 | 4 (4.9) |
| | Grade 4 | 2 (2.4) |
| Thrombocytopenia | No toxicity | 76 (92.7) |
| | Grade 1 | 6 (7.3) |

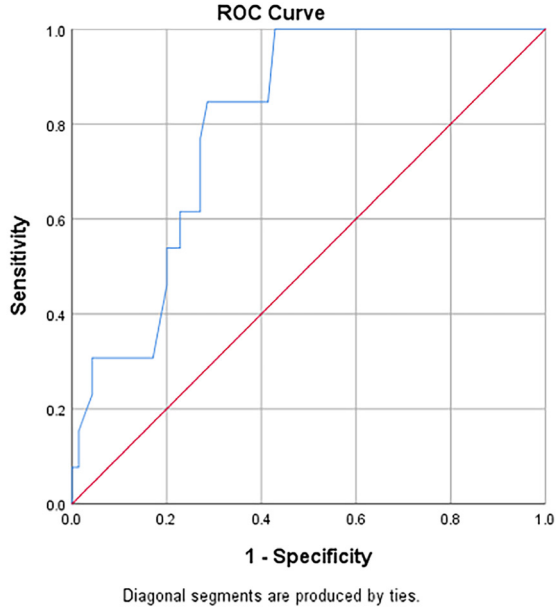


**FIGURE 1:** ROC curve for initial PNI.

*ROC: Receiver operating characteristic; PNI: Prognostic nutritional index*

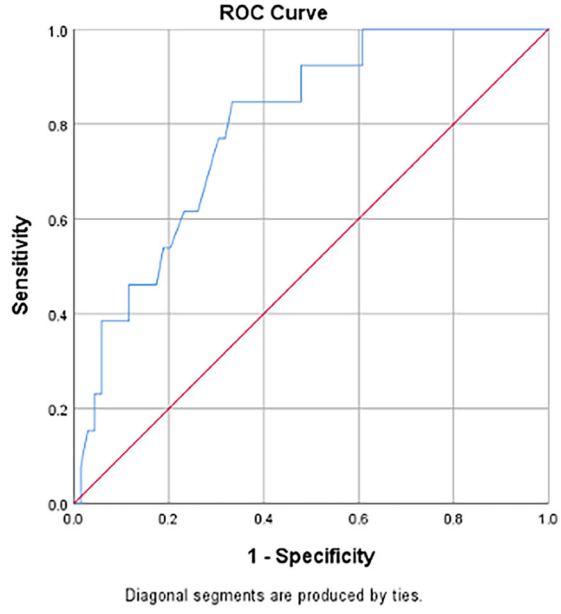


**FIGURE 2:** PNI change ROC curve.

*ROC: Receiver operating characteristic; PNI: Prognostic nutritional index*

**TABLE 3: Survival descriptive statistics.**

| | Tumor localization | n | Mean | Median | Standard deviation | Minimum | Maximum |
|---|---|---|---|---|---|---|---|
| Overall survival | Right | 28 | 30.1 | 21 | 26.1 | 4 | 104 |
| | Left and rectum | 54 | 33.7 | 29.5 | 23.1 | 3 | 103 |
| Progression-free survival | Right | 28 | 16.3 | 8 | 22.9 | 2 | 104 |
| | Left and rectum | 54 | 16.4 | 12 | 14.3 | 3 | 66 |

### Overall Survival and Progression-Free Survival According to Initial PNI Value

In the OS category, the average values (mean =19.7, median =18.0, SD =2.53) for the low initial PNI group were calculated over 34 months. For the high PNI group, the mean value for survival months was 48.5 with a SD of 5.00 over 48 months, while another parameter had a mean of 35.5, showing a significant difference in survival months between the two groups (p<0.001). Patients with a low initial PNI had earlier exits.

In the PFS category, the median survival time was 9 months (range, 6-10, 95% CI) when the initial PNI was low. When the initial PNI was high, the median survival time was 15 months, with a significant difference in survival between the low and high PNI groups (p<0.001). It was observed that the PFS was higher in the high initial PNI group.

In the Cox regression analysis of the initial PNI group, individuals with high initial PNI levels showed a statistically significant increase in survival time [hazard ratio (HR)=0.29, 95% CI: 0.18-0.48, p<0.001]. A high initial PNI was observed to increase OS by 29% (Figure 3).

Another Cox regression analysis was conducted to examine PFS in individuals with different initial PNI levels. In the high PNI group, the HR was measured at 0.35, with a 95% CI ranging from 0.21 to 0.58, and a p-value <0.001. These results indicate that initial PNI values show statistically significant differences in PFS, suggesting that patients with high initial PNI have a 35% greater chance of experiencing higher PFS (Figure 4).

### Overall Survival and Progression-Free Survival Based on Changing PNI Values

In the analysis conducted for PNI Change levels, an event (death) was recorded in 40 of 42 patients with Low PNI Change, with an OS time of 25.2 months for this group. For the 40 patients with a high PNI change, an event was recorded in 29 patients, and the OS time was 48.4 months. Based on the survival analysis results, we evaluated the effects of PNI change on OS. The median survival time for patients with Low PNI Change was 20 months [95% CI: (18-27) range], while the median survival time for those with a High PNI Change was 36.5 months [95% CI: (27-50) range]. According to the Cox Regression Analysis results for PNI Change levels, patients with High PNI Change were found to be at a 42% lower risk than those with Low PNI Change [HR: 0.42, 95% CI: (0.26-0.68), p=0.001].

The same analysis was repeated for the PFS. Among the 42 patients with a low PNI Change, an event (death) was recorded in 40 patients, with a median PFS time of 9 months for this group. For the 40 patients with high PNI changes, an event was recorded in 29 patients, with a median PFS time of 14 months for this group.

Based on the survival analysis results, we assessed the impact of PNI Change levels on patients' survival time. The median survival time for patients with low PNI Change was 9 months [within a range of (7-14, 95% CI)], whereas the median survival time for patients with high PNI Change was 14 months [within a range of (10-24, 95% CI)]. According to the results of the Cox Regression Analysis for PNI Change levels, it was determined that patients with high PNI Change had a 49% lower risk than those with low PNI Change [HR: 0.49, 95% CI: (0.30-0.79), p=0.004.

### Baseline PNI Value and Patient Response

According to the chi-squared test, a significant relationship was observed between the initial PNI value and patient response. The findings indicated that patients with low initial PNI values were more likely to experience disease progression,

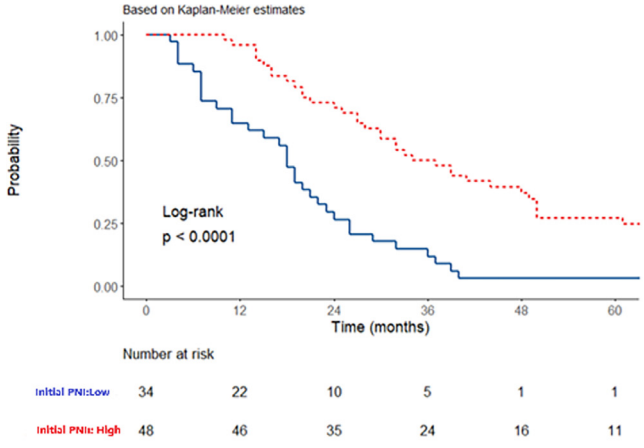


**FIGURE 3:** Overall survival analysis by initial PNI groups.

*PNI: Prognostic nutritional index*

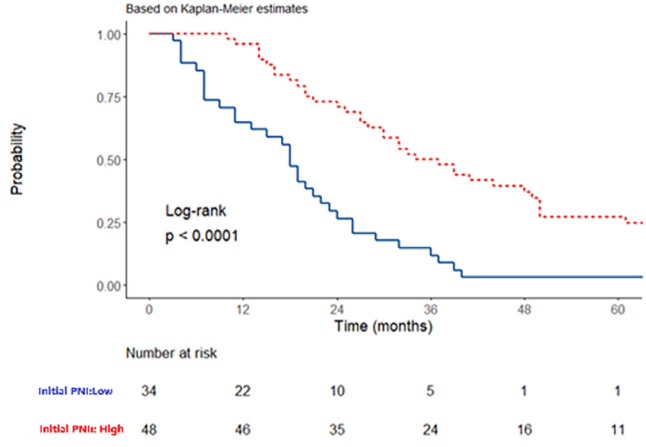


**FIGURE 4:** Effect of initial PNI group on progression-free survival.

*PNI: Prognostic nutritional index*

whereas patients with high initial PNI values were more likely to achieve a complete response (Table 4).

### PNI Change and Patient Response

According to the chi-square test, a significant relationship was found between low and high PNI changes and patient responses (p=0.02). The findings indicated that the likelihood of a progressive disease response was higher in the low PNI change group, whereas the likelihood of a complete response was higher in the high PNI change group (Table 5).

### PNI Baseline and Toxicity

There was a statistically significant difference in toxicity conditions between patients with low and high baseline PNI levels based on lymphocyte, hemoglobin, neutrophil, and platelet values (all p<0.05). However, the small sample size in some categories necessitates a cautious interpretation of these findings, as shown in Table 6.

According to our findings, the likelihood of not experiencing toxicity was higher in the high baseline PNI group than in the low baseline PNI group. When examining albumin levels, it was observed that the low baseline PNI group had lower values (mean =31.9, SD =6.48) than the high baseline PNI group (mean =38.7, SD =5.88) (p<0.001).

### Patients Who Changed Groups During the PNI Initial and PNI Change Process

Among patients with a low initial PNI, 31.7% (26 patients) continued to have a low PNI, while 9.8% (8 patients) transitioned to a high PNI. Among the patients with a high initial PNI, 19.5% (16 patients) transitioned to a low PNI, whereas 39% (32 patients) continued to have a high PNI. No significant findings were observed in toxicity values among patients who changed PNI groups, although attention should be paid to the small sample size.

OS and PFS durations were assessed in patients in the PNI group. The OS time was 29 months for the 24 patients included in the analysis. The median value was 25.5 months, with a SD of 15.1 months. The shortest and longest survival times were 9 and 79 months, respectively. In the analysis of PFS in the 24 patients, the time was 13.67 months. The median PFS time was 9.5 months, with a SD of 9.71 months. The shortest PFS time was 2 months, and the longest was 44 months (Table 7).

Among the patients who changed PNI groups, 3 (12.5%) had progressive disease, 2 (8.3%) had stable disease, 17 (70.8%) had a partial response, and 2 (8.3%) had a complete response, respectively. Because of the small sample size of patients who changed groups, relationships between OS, PFS, and response to treatment could not be analyzed for those who moved from low to high PNI or from high to low PNI.

Regarding PNI change and Toxicity, a significant difference in lymphocyte levels was observed between the patients with low and high PNI changes (p<0.05). However, no statistically significant differences were found in toxicity levels based on hemoglobin, neutrophil, and platelet values (p>0.05). Consistent with the PNI baseline observations, albumin levels were lower in the low PNI change group (mean =33, SD =6.64) than in the high PNI change group (mean =39, SD =5.96) (p<0.001). It should be noted that in some groups, the proportion of patients was below 5%. In the high PNI change group, the likelihood of lymphocyte toxicity was lower.

**TABLE 4: Relationships between prognostic nutritional index baseline and treatment response.**

| | n | Low (≤45.25) (n=34) | High (>45.25) (n=48) | Test |
|---|---|---|---|---|
| Treatment response | 82 | | | |
| Progressive disease | | 7 (21%) | 3 (6.2%) | |
| Stable disease | | 2 (5.9%) | 4 (8.3%) | $X^2$=11.66, p=0.01* |
| Partial response | | 24 (71%) | 27 (56%) | |
| Complete response | | 1 (2.9%) | 14 (29%) | |

**TABLE 5: Relationships between prognostic nutritional index change and treatment response.**

| | n | Low (≤50.40) (n=42) | High (>50.40) (n=40) | Test |
|---|---|---|---|---|
| Treatment response | 82 | | | |
| Progressive disease | | 8 (19%) | 2 (5.0%) | |
| Stable disease | | 4 (9.5%) | 2 (5.0%) | $X^2$=9.80, p=0.02* |
| Partial response | | 27 (64%) | 24 (60%) | |
| Complete response | | 3 (7.1%) | 12 (30%) | |

| TABLE 6: Relationship between prognostic nutritional index baseline and toxicity. | | | | |
|---|---|---|---|---|
| (n=34) | | Low (≤45.25) (n=48) | High (>45.25) | Test |
| Lymphopenia | | | | |
| | No toxicity | 7 (21%) | 38 (79%) | $X^2$=29.72, p=0.0012 |
| | Grade 1 | 11 (32%) | 7 (15%) | |
| | Grade 2 | 10 (29%) | 2 (4.2%) | |
| | Grade 3 | 5 (15%) | 1 (2.1%) | |
| | Grade 4 | 1 (2.9%) | 0 (0%) | |
| Anemia | | | | |
| | No toxicity | 3 (8.8%) | 14 (29%) | $X^2$=11.13, p=0.012 |
| | Grade 1 | 15 (44%) | 26 (54%) | |
| | Grade 2 | 15 (44%) | 8 (17%) | |
| | Grade 3 | 1 (2.9%) | 0 (0%) | |
| Neutropenia | | | | |
| | No toxicity | 15 (44%) | 27 (56%) | $X^2$=9.94, p=0.042 |
| | Grade 1 | 11 (32%) | 15 (31%) | |
| | Grade 2 | 2 (5.9%) | 6 (12%) | |
| | Grade 3 | 4 (12%) | 0 (0%) | |
| | Grade 4 | 2 (5.9%) | 0 (0%) | |
| Trombocytopenia | | | | |
| | No toxicity | 30 (88%) | 46 (96%) | $X^2$=1.69, p=0.0192 |
| | Grade 1 | 4 (12%) | 2 (4.2%) | |
| [2]Pearson. | | | | |

| TABLE 7: Overall survival and progression-free survival in prognostic nutritional index (PNI) group changes. | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | PNI group change | Initial PNI | PNI change | n | Mean | Median | Standard deviation | Minimum | Maximum |
| Overall survival | Low-low | Low | Low | 26 | 18.8 | 17.5 | 16.23 | 3 | 79 |
| | Changing groups | Low | High | 8 | 22.8 | 22.5 | 10.28 | 9 | 37 |
| | | High | Low | 16 | 32.2 | 28.5 | 16.43 | 11 | 79 |
| | High-high | High | High | 32 | 46.2 | 42.5 | 27.75 | 10 | 104 |
| Progression-free survival | Low-low | Low | Low | 26 | 8.77 | 8 | 5.23 | 2 | 20 |
| | Changing groups | Low | High | 8 | 10.75 | 9 | 7.05 | 4 | 25 |
| | | High | Low | 16 | 15.13 | 13.5 | 10.71 | 2 | 44 |
| | High-high | High | High | 32 | 24.59 | 15 | 24.23 | 3 | 104 |
| High PNI: >50.40; Low PNI: ≤50.40). | | | | | | | | | |

## DISCUSSION

CRC is the second leading cause of cancer-related death worldwide and poses a significant global socioeconomic burden. Approximately 20% of patients develop metastases at the time of diagnosis, and approximately 50% develop metastases during follow-up. The survival rates vary considerably among patients with the same disease stage. Therefore, there is a need for practical and accessible parameters that can accurately predict survival and prognosis.[3]

Recent studies have focused on the impact of an individual's immune response and factors related to the tumor microenvironment on survival. The cancer-related immune inflammatory response in the systemic circulation and tumor microenvironment is now considered a significant determinant of disease progression and survival in colorectal

cancer. Research in the literature supports the PNI, which reflects the nutritional and immunological status of cancer patients, has independent prognostic value.[4-6]

In this study, we aimed to evaluate the adequacy of the initial PNI value and changes in PNI for predicting the prognosis of patients with Stage-IV CRC, while taking into account various factors such as age, genetics, sex, primary tumor site, and metastasis location.

CRC is 33% more common in men than women.[7] In our cohort of 82 metastatic CRC patients (57 men, 69.5%; 25 women, 30.5%), the mean age was 59.6 years (range: 29-85), which is consistent with previous findings by Ucar et al.[8] (mean: 57.5 years), who reported a male predominance of 62% among 308 patients. Tumor locations in our study were the left colon (42%), right colon (34.1%), and rectum (23.2%), with histological subtypes of adenocarcinoma (86.6%) and mucinous carcinoma (13.4%), aligning with Ucar et al.'s[8] findings (adenocarcinoma 88%, mucinous 12%). The liver was the most common site of metastasis (85.4%), similar to Zhao et al.'s[9] report of 70.8% liver involvement at diagnosis. At presentation, 54.9% of patients had elevated CEA and 37.8% had elevated CA19-9 levels, that were comparable to Ucar et al.[8] (69% and 48.4%, respectively) and Mohri et al.[4] (40% and 17.3%, respectively).

ROC cut-off values were determined to classify PNI values as either low or high. According to the analyses, the most decisive point was an initial PNI value of 45.25. Patients with an initial PNI value of 45.25 or higher were categorized into the high PNI group. In the overall population (n=82), the median OS was 26 months, with the high PNI (>45.25) group having a median OS of 35.5 months and the low PNI (<45.25) group having a median OS of 18 months. A significant difference in survival was observed between the two groups ($p<0.001$), with a notable reduction in OS in the low PNI group. Furthermore, the median PFS for the overall population was 11 months; a high PNI (>45.25) group had a median PFS of 15 months, and a low PNI (<45.25) group had a median PFS of 9 months. A significant difference in PFS was observed between the low and high PNI groups ($p<0.001$). These results indicate a statistically significant difference in PFS based on initial PNI values, with patients in the high PNI group being 35% more likely to have improved PFS. Ucar et al.[8] reported a median OS of 24 months for all patients, with high and low PNI groups having median OS durations of 28.4 months and 19.1 months, respectively. Zhao et al.[9] found that in a study of 243 patients with metastatic CRC who underwent curative liver resection, the OS was 48.5 months for the low PNI group and 95.7 months for the high PNI group. Because this study included patients who underwent R0 resection for both primary tumors and liver metastases, the average and PFS times were longer than those reported in the other studies. Our results are consistent with those of these studies and the literature.

Considering the changes in PNI, the most decisive point in our study was found to be 50.40. Patients with a PNI Change value >50.40 were included in the high PNI change group. ROC curves were constructed by considering the skewness and kurtosis values of the PNI distributions. The median survival time for patients with a low PNI Change was 20 months, while, for those with a high PNI Change, it was 36.5 months. The same analysis was repeated for the PFS. The median PFS time was 9 months for patients with a low PNI Change and 14 months for those with a high PNI Change. According to these analyses, patients with high PNI change had significantly increased OS and PFS.

In our study, regarding the relationship between the initial PNI value and treatment response patients with a low initial PNI showed a progression rate of 21%, while those with a high initial PNI showed a progression rate of 6.2%. The complete response rate was 2.9% in the low PNI group and 29% in the high PNI group. These findings indicate that patients with a low initial PNI are more likely to progress, while those with a high initial PNI are more likely to achieve a complete response compared to those with the low PNI. Johannet et al.[10] conducted a study with 629 patients (268 melanoma, 128 lung cancer, 233 others) and found that lower pre-treatment BMI and low PNI values were associated with worse (best overall response rate, objective response rate, and disease control rate. In our study, similar analyses were applied to PNI changes, and a significant relationship between low and high PNI changes and patient response was found using the chi-squared test ($p=0.02$). These findings suggest that the likelihood of disease progression was higher in the low PNI group, whereas the likelihood of a complete response was higher in the high PNI group. A study on patients with locally advanced cervical cancer found that high initial PNI values were significantly associated with clinical complete response to chemoradiotherapy, whereas low baseline PNI might reduce the probability of complete response after chemoradiotherapy.[11] Additionally, Yang et al.[12] conducted a study involving 107 patients with metastatic gallbladder cancer and reported that a high pre-treatment PNI was an independent prognostic marker for predicting objective complete response (OCR), PFS, and OS. High PNI patients had a higher OCR rate (OCR: 36.8% vs. 9.4%, $p=0.017$). Literature reviews show that high initial PNI values are associated with better treatment responses and prognosis, which is consistent with the results of our study.

When evaluating hemoglobin, lymphocyte, neutrophil, and platelet toxicities based on the initial PNI groups, a statistically

significant difference was found in the toxicity levels among patients with respect to these values (all $p<0.05$). According to our findings, the likelihood of not experiencing any toxicity was higher in the high initial PNI group than in the low initial PNI group. However, the reliability might be questionable because some categories had sample sizes below 5%. In a study by Liu et al.[13] involving 191 patients with gastric cancer, hematological side effects of grade 3 or higher in adjuvant chemotherapy were observed in 20.8% of the high PNI group and 46.7% of the low PNI group. Chang et al.[14] reported higher rates of feeding tube placement, grade 3-4 hematological toxicity, and sepsis during chemoradiotherapy in patients with hypopharyngeal cancer and a low PNI. A study of patients with gastric cancer receiving neoadjuvant chemotherapy showed a significant association between pre-chemotherapy low PNI and post-chemotherapy anemia and lymphopenia.[15] The literature indicates that patients with a low PNI have a higher likelihood of hematological side effects, which is consistent with the findings of our study.

In our study, although a significant difference was observed in lymphocyte values between the low and high PNI change categories ($p<0.05$), no statistically significant difference was detected in toxicity levels based on hemoglobin, neutrophil, and platelet values ($p>0.05$). The likelihood of lymphocyte toxicity was lower in the high PNI change group. It should be noted that some groups had patient numbers below 5%, which may have affected reliability and necessitated further studies, preferably with higher patient numbers.

The absence of BRAF mutation data in a significant portion of the study population may introduce bias in our findings. Since BRAF mutations are known to be associated with worse prognosis and distinct treatment responses in CRC, the inability to stratify patients based on BRAF status limits the generalizability of our results. Moreover, BRAF-mutant CRC cases often present with aggressive tumor biology, which could have influenced OS and PFS outcomes in our cohort. Future studies with complete BRAF mutation data are necessary to assess the independent prognostic significance of PNI in patients with different genetic backgrounds.

### Study Limitations

Our study was limited by its retrospective, single-centre design, relatively small sample size, especially in the PNI Change analysis, and its focus was solely on patients with metastatic cancer at diagnosis. Changes in OS and PFS based on the baseline PNI were consistent with those reported in the literature. Given the single-centre design and relatively small sample size, the generalisability of our findings to broader populations and diverse treatment settings is limited. However, there is a lack of studies on PNI change categories, toxicity, and treatment response. Another limitation is that we were unable to perform multivariate Cox regression analysis adjusting for established prognostic variables such as age, sex, ECOG PS, primary tumour site, metastatic sites, RAS/BRAF status, and treatment regimen. Therefore, our findings regarding the prognostic value of PNI should be interpreted with caution. Further clinical research is needed in this area, and additional analyses from our study are expected to contribute to the literature.

## CONCLUSION

Our study found that patients with a high baseline PNI demonstrated significantly longer OS and PFS, as well as a lower incidence of hematological toxicity, compared to those with low baseline PNI. Moreover, the high baseline PNI group had a greater likelihood of achieving a complete response to first-line therapy, while disease progression was more common in those with lower PNI values. In the context of dynamic changes, patients who exhibited a significant increase in PNI over the course of treatment also experienced improved OS and PFS, along with higher complete response rates. Although hematological toxicity could not be fully evaluated in certain subgroups due to limited sample size, the trend remained consistent. These findings underscore not only the prognostic relevance of baseline PNI but also highlight that changes in PNI during treatment are equally critical indicators, of treatment response and survival in patients with metastatic CRC.

### Ethics

**Ethics Committee Approval:** The study was conducted following the 1964 Helsinki Declaration with the ethical approval of the Scientific Research Ethics Committee of Akdeniz University Faculty of Medicine (obtained on 12.10.2022 with approval number 70904504/564).

**Informed Consent:** Given the retrospective nature of the study, the requirement for informed consent was waived by the ethics committee.

### Footnotes

#### Authorship Contributions

Concept: E.Y.Ö., S.S.G., A.M.T., Design: E.Y.Ö., M.K., A.M.T., Data Collection or Processing: E.Y.Ö., A.Ö., A.M.T., Analysis or Interpretation: E.Y.Ö., S.S.G., A.M.T., Literature Search: E.Y.Ö., A.Ö., A.M.T., Writing: E.Y.Ö., A.Ö., A.M.T.

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