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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Effect of Prognostic Nutritional Index and Inflammatory Markers on Survival in Elderly Patients with Locally Advanced Rectal Cancer

Yaşlı Lokal İleri Evre Rektum Kanserli Hastalarda Prognostik Nutrisyonel İndeks ve İnflamatuvar Markerların Sağkalıma Etkisi

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ABSTRACT

Aim: This study aimed to evaluate the prognostic value and survival effects of the prognostic nutritional index (PNI), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and lymphocyte-monocyte (LMR) ratio in the pretreatment peripheral blood count of elderly (age≥70) patients with locally advanced rectal cancer (ELARC).

Material and Method: From 2010 to 2020, 86 ELARC who received pre-operative or post-operative chemoradiotherapy (CRT) were included, and their medical records were analyzed retrospectively. Before treatments, complete blood counts and blood biochemistry counts were obtained within one week. Hematological parameters which included PNI, NLR, LMR and PLR were analyzed in relation to long-term toxicity, tumor downstaging, pCR (pathologic complete response), OS (overall survival), and DFS (disease-free survival).

Results: In univariate analysis, low NLR, low PLR and high PNI values were associated with increased OS, and high LMR, low PLR and high PNI values were associated with increased DFS. In multivariate analysis, low PLR, high PNI values, male gender and younger age were independent prognostic factors for predicting increased OS, and high LMR values and absence of lymph node involvement remained the only independent prognostic factors for increased DFS. The level of pathological tumor response increased as the PLR value decreased.

Conclusion: PNI and PLR were found to be a significant independent prognostic factor for OS in ELARC. LMR was found to be a significant independent prognostic factor for DFS. PLR was also found to be a significant independent prognostic factor for OS and downstaging.

Keywords: Radiotherapy, prognostic nutritional index, rectal cancer, Inflammatory markers

ÖZ

Amaç: Bu çalışmada, lokal ileri rektum kanseri (ELARC) olan yaşlı (yaş ≥70) hastalarda tedavi öncesi periferik kanda prognostik nutrisyonel indeks (PNI), nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR) ve lenfosit-monosit (LMR) oranının prognostik değerini ve sağkalım etkilerini değerlendirme amaçlandı.

Gereç ve Yöntem: 2010'dan 2020'ye kadar ameliyat öncesi veya ameliyat sonrası kemoradyoterapi (KRT) alan 86 ELARC dahil edildi ve tıbbi kayıtları retrospektif olarak analiz edildi. Tedavi öncesi bir hafta içinde tam kan sayımı ve kan biyokimya sayımları yapıldı. PNI, NLR, LMR ve PLR'yi içeren hematolojik parametreler, uzun vadeli toksisite, tümör evresinin düşürülmesi, pCR (patolojik tam yanıt), OS (genel sağkalım) ve DFS (hastalıksız sağkalım) ile ilişkili olarak analiz edildi.

Bulgular: Tek değişkenli analizde, düşük NLR, düşük PLR ve yüksek PNI değerleri artmış OS ile; yüksek LMR, düşük PLR ve yüksek PNI değerleri ise artmış DFS ile ilişkilendirildi. Çok değişkenli analizde, düşük PLR, yüksek PNI değerleri, erkek cinsiyet ve daha genç yaş, artmış OS'yi öngörmek için bağımsız prognostik faktörlerdi ve yüksek LMR değerleri ve lenf nodu tutulumunun olmaması, artmış DFS için tek bağımsız prognostik faktörler olarak kaldı. PLR değeri düştükçe patolojik tümör yanıtının seviyesi arttığı saptandı.

Sonuç: PNI ve PLR, ELARC'de OS için önemli bir bağımsız prognostik faktör olarak bulundu. LMR'nin DFS için önemli bir bağımsız prognostik faktör olduğu bulundu. PLR'nin OS ve evre küçültme için önemli bir bağımsız prognostik faktör olduğu da bulundu.

Anahtar Kelimeler: Radyoterapi, prognostik beslenme indeksi, rektal kanser, enflamatuar belirteçler

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer diagnosed in both sexes in the Western World. There were approximately 44,180 new cases of rectal cancer diagnosed in the United States in 2019. The high prevalence of rectal cancer causes an important health issue in the World (1). Rectal cancer is predominantly a disease of older patients, as the median age at diagnosis is 69 years (2). With the aging population, the number of older rectal cancer patients is expected to increase further. Older patients often have more comorbidities, an increased complication rate, and a poorer prognosis (3).

Studies on the prognostic value of nutritional and inflammatory parameters in cancer patients have been going on for years (4-5). The mostly used among these parameters include lymphocyte, neutrophil, platelet, and C-reactive protein levels and their combined use with certain formulas. Roughly, albumin level reflects nutritional status, whereas lymphocyte counts reflect immunity status. One prognostic index that uses a combination of these parameters is Onodera's prognostic nutritional index (PNI). PNI is an useful parameter for showing the nutritional and immunological status. PNI can be calculated using serum albumin level and peripheral blood lymphocyte count (6). This index is usually used for perioperative risk assessment purposes in patients. Despite there is a limited data on prognostic effect of PNI in elderly patients with locally advanced rectal cancer, PNI was shown to be of prognostic value in several other cancer types (7-12). Inflammation is a critical component of tumor progression, and the causal relationship between inflammation and cancer is widely accepted (13). Systemic inflammatory markers have recently been reported to be correlated with survival and prognosis among patients with various types of cancer (14-22).

Cancer treatments have more or less toxic side effects. Elderly patients are more fragile. There is no definite consensus or guideline regarding the way to be followed for cancer treatments in elderly patients. Therefore, it can be very difficult and confusing to make a treatment decision for this group. Studies conducted to predict survival, treatment results, and complications are in a great interest for researchers.

This study aimed to evaluate the prognostic value and survival effects of the prognostic nutritional index (PNI), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio in the pretreatment peripheral blood count of elderly (age≥70) patients with locally advanced rectal cancer (ELARC) who treated for curative intent. As far as we know, this is the first study of this population.

MATERIAL AND METHOD

A retrospective study was conducted at the XX University Hospital (in Turkey). The institutional review board approved the study, which was conducted in accordance with the Helsinki Declaration, and the study was approved by the Selcuk University Faculty of Medicine Ethics Committee (Date: 11.08.2021, Decision No: 2021/406). Informed consent stating that patient's medical data would be used to conduct retrospective studies was systematically obtained before radiation initiation.

Patient population

The medical records of 86 patients with non-metastatic, stage 2-3, elderly (age ≥70), diagnosed with rectal adenocarcinoma who received postoperative or preoperative radiotherapy between January 2010 and January 2020 were retrospectively reviewed. Patient characteristics (age, sex), tumor histology and staging, lymph node involvement, downstaging, pathological complete respons (pCR), late toxicities were also reviewed.

Lymph node status and staging: In the preoperative group, it was performed according to the abdo-pelvic magnetic resonance (MR) imaging results taken before the treatments; In the postoperative group, it was performed according to the pathology specimen obtained from operation. Staging was performed according to the American Joint Committee on Cancer (AJCC) 8th edition 2017.

Defination of downstaging: When the MR obtained before the preoperative treatment and the MR obtained before the surgery were compared, the regression in the T and/or N stages, which showed a decrease in staging, was accepted as 'Downstaging'.

Pathological complete response (pCR): The absence of any malignant cells as a result of the pathological examination of the surgical specimen was accepted as a pathological complete response.

Prognostic nutritional index (PNI) calculation: The pre-treatment PNI was calculated (10× serum albumin concentration (g/dL) + 0.005 × lymphocyte count (per mm3)), and blood samples were obtained and tested within 2 weeks before treatments.

Statistical analysis

All statistical analyses were performed using R version 3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org). Shapiro-Wilk's normality test and Q-Q plots were used to assess the normality of the data, and also Levene's test was used to check the homogeneity of the variances. Numerical variables were presented as mean±standard deviation (range: minimum-maximum) or median (interquartile range (IQR): 1st quartile-3rd quartile), as appropriate.

Categorical variables were described as counts (n) and percentages (%). The primary aim of the study was to determine the effects of NLR, LMR, PLR and PNI on overall survival (OS) and disease-free survival (DFS). The secondary aim of the study was to investigate the association between these values, which is determined to have statistically significant effects on OS and DFS, and clinicopathological characteristics of the patients. OS was defined as the time from the date of diagnosis to the date of death of any cause. DFS was defined as the time from the date of the patient's diagnosis to the date of disease recurrence. Survival curves of NLR, LMR, PLR and PNI were estimated using the Kaplan-Meier method and Log-rank tests were used to compared difference. Univariate Cox proportional hazard regression models were applied to identify the risk of NLR, LMR, PLR and PNI on death and recurrence in patients with rectal cancer. Hazard ratios (HRs) were calculated with 95% confidence intervals (CIs). Next, we examined NLR, LMR, PLR and PNI as independent predictors of survival in multiple adjusted Cox HR models, which were adjusted for age, gender, treatment, stage, lymph node, downstaging, late grade 3-4 toxicity and pCR. Significant variables at p <.10 were entered into multiple models and stepwise elimination was performed. Finally, we carried out Fisher's exact and Cochrane-Armitage trend test to investigate the association between PLR level and downstaging, late grade 3-4 toxicity, and pCR. A two-tailed p values less than .05 was considered statistically significant.

RESULTS

Treatment details

Radiotherapy (RT) delivered a total dose of 5040 cGy (6-MV photons) in 28 fractions of 180 cGy/daily, five days per week, to the pelvis the use of four-field box or intensity modulated RT technique. Concurrent chemotherapy could not be prescribed to 10 (11,6%) patients due to having comorbidities and the fear of possible toxicity. Seventy-six (88,4%) patients were able to received concurrent chemotherapy treatments. While 14% of patients received fluorouracil IV bolus at a dose of 400 mg/m2 and leucovorin 20 mg/m2 IV bolus for 4 days during week 1 and 5 of chemoradiotherapy (CRT), 86% received capasitabine 825 mg/m2 perioral twice daily 5 days/week for 5 weeks along with CRT. RT was generally well tolerated. While all patients could complete the RT course, 4 of them couldn't achieve to complete concurrent chemotherapy due to side effects such as, diarrhea, nausea, vomiting, cytopenia. Adjuvant chemotherapy consisted of 6 cycles of capecitabine (2500 mg/m2/day for 14 days, followed by a 1-week break) or 6 cycles of bolus 5-FU/leucovorin (375 mg 5-FU/m2/day and 20 mg leucovorin/m2/day for 5 days every 4 weeks). Adjuvant chemotherapy was planned for 74 of 86 (86,04%) patients, but 12 of 74 (16,2%) failed to complete treatment due to chemotherapy intolerance and serious adverse events. All patients underwent a curative surgery. Curative surgery was performed in preoperative group 4 to 8 weeks after the end of RT and in postoperative group 4 to 8 weeks before the start of RT. Total mesorectal excision (TME) was performed as the standard surgical procedure.

Of the 86 rectal cancer patients, 26 (30.23%) developed tumor recurrence and 18 (20.93%) died within the follow-up period. The median follow-up period was 40 months (range: 9-120 months).

The demographical and pathological characteristics and laboratory findings of ELARC were given in **Table 1**. A total of 86 rectal cancer patients (ECOG performance status 0-1), 40 (46.5%) were male, and 46 (53.5%) were female, and the mean age was 73.7±3.63 years (range, 70-84 years). Of the 86 patients, 42 (48.8%) had received postoperative therapy, and 44 (51.2%) had received preoperative therapy. There were 18 (20.9%), and 68 (79.1%) patients in stage II and III, respectively. Thirty-four (39.5%), 32 of 44 (preoperatively treated) (72.7%), 8 of 44 (preoperatively treated) (18.2%) and 10 (11.6%) patients had lymph node involvement, downstaging, pCR and late grade 3-4 toxicity, respectively. Of this 10 late grade 3-4 toxicity, 5 were related with genitourinary, 5 were related with gastrointestinal region. The median value of NLR was 3.32 (iqr, 2.48-5), LMR was 2.79 (iqr, 1.76-3.90), PLR was 177.5 (iqr, 134-290.47), and the mean value of PNI was 48.56±5.82 (range, 35-65.5). NLR values were divided into two groups as low (<3.75) and high (≥3.75). There were 36 (41.9%) patients in NLR-high group. LMR values were divided into two groups as high (>1.76) and low (≤1.76). There were 22 (25.6%) patients in LMR-low group. The PLR values were divided into two groups, and a PLR value <285 was defined as PLR-low and ≥285 as PLR-high. There were 26 (30.2%) patients in PLR-high group. And also, PNI values were divided into two groups, and a PNI value >48.6 was defined as PNI-high and ≤48.6 as PNI-low. There were 39 (45.3%) patients in PNI-low group.

In univariate analysis (**Figure 1**), low NLR values were significantly associated with increased OS (Log-rank $\chi2$=5.027, p=.025, HR=2.87 (95% CI, 1.07-7.67), p=.035, **Figure 1A**), but not with DFS (Log-rank $\chi2$=3.522, p=.061, HR=2.12 (95% CI, 0.94-4.77), p=.071, **Figure 1B**). High LMR values were significantly associated with increased DFS (Log-rank $\chi2$=9.919, p=.002, HR=3.53 (95% CI, 1.52-8.21), p=.003, **Figure 1D**), but not with OS (Log-rank $\chi2$=3.278, p=.070, HR=2.46 (95% CI, 0.89-6.81), p=.083, **Figure 1C**). Low PLR values were significantly associated with increased OS (Log-rank $\chi2$=4.653, p=.031, HR=2.79 (95% CI, 1.05-7.45), p=.041, **Figure 1E**) and DFS (Log-rank $\chi2$=4.213, p=.040, HR=2.33 (95% CI, 1.01-5.41), p=.048, **Figure 1F**). High PNI values were significantly associated with increased OS (Log-rank $\chi2$=8.848, p=.003, HR=4.63 (95% CI, 1.51-14.27), p=.007, **Figure 1G**) and DFS (Log-rank $\chi2$=7.295, p=.007, HR=2.93 (95% CI, 1.26-6.81),

Table 1. The demographical and pathological characteristics, and laboratory findings of ELARC

	Patients (n=86)
Demographical characteristics	
Age (years), mean±SD (min-max)	73.7±3.63 (70-84)
Gender (male/female), n (%)	40 (46.5)/46 (53.5)
Pathological characteristics	
Treatment (postoperative/ preoperative), n (%)	42 (48.8)/44 (51.2)
T Stage (T2/T3/T4), n (%)	6 (7)/64 (74.4)/16 (18.6)
N Stage (N0/N1/N2), n (%)	18 (20.9)/46 (53.5)/22 (25.6)
Stage (Stage 2/Stage 3), n (%)	18 (20.9)/68 (79.1)
Lymph node involvement, n (%)	34 (39.5)
Downstaging, n (%)	32 (72.7)
Late grade 3-4 toxicity, n (%)	10 (11.6)
pCR (No response/partial response/ complete response), n (%)	12 (27.3)/24 (54.5)/8 (18.2)
Laboratory findings	
NLR, median (interquartile range)	3.32 (2.48-5)
NLR (<3.75/≥3.75), n (%)	50 (58.1)/36 (41.9)
LMR, median (interquartile range)	2.79 (1.76-3.90)
LMR (>1.76/≤1.76), n (%)	64 (74.4)/22 (25.6)
PLR, median (interquartile range)	177.5 (134-290.47)
PLR (<285/≥285), n (%)	60 (69.8)/26 (30.2)
PNI, mean±SD (min-max)	48.56±5.82 (35-65.5)
PNI (>48.6/≤48.6), n (%)	47 (54.7)/39 (45.3)
PNI (>40.8/≤40.8), n (%)	78 (90.7)/8 (9.3)

Abbreviations: SD-standard deviation, pCR-pathological complete response, NLR-neutrophile to lymphocyte ratio, LMR-lymphocyte to monocyte ratio, PLR-platelets to lymphocyte ratio, PNI-prognostic nutritional index

p=.012, **Figure 1H**).

To assess the potential of NLR, LMR, PLR and PNI as a predictive marker of death and recurrence, multivariate Cox proportional hazard analysis was conducted. Multivariate Cox regression analysis showed that increased PLR (HR=3.63 (95% CI, 1.29-10.14, p=.014), decreased PNI (HR=5.90 (95% CI, 1.80-19.32, p=.003), increased age (HR=1.22 (95% CI, 1.06-1.40, p=.007) and female gender (HR=4.92 (95% CI, 1.49-16.19, p=.009) were independent unfavorable prognostic factors for OS in ELARC. Moreover, the decreased LMR (HR=3.45 (95% CI, 1.48-8.02, p=.004) and the presence of pathological lymph node involvement (HR=3.32 (95% CI, 1.43-7.69, p=.005) were identified as significant predictors of DFS in these patients group (**Table 2**).

Forty-four patients received their treatments as preoperatively. In this preoperatively treated cohort, downstaging proportion reduced in high PLR values compared to low PLR values (n=10 (55.6%) vs. n=22 (84.6%), p=.045). It was observed that the level of

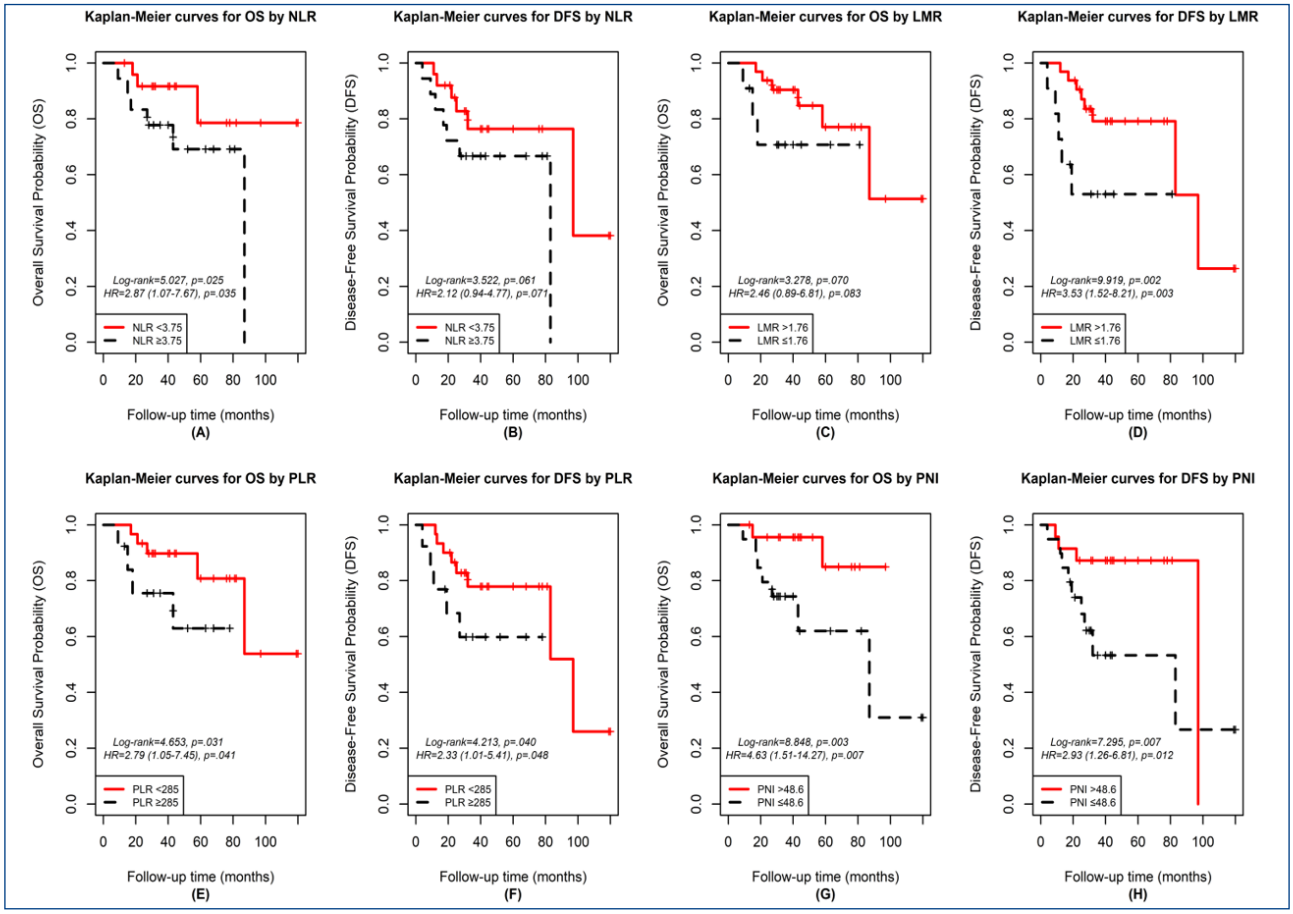

Figure 1. Kaplan-Meier survival curves of NLR, LMR, PLR and PNI for overall survival (OS, A-C-E-G, respectively) and disease-free survival (DFS, B-D-F-H, respectively) in ELARC. Univariate Cox proportional hazard ratios of NLR, LMR, PLR and PNI on death (OS, A-C-E-G, respectively) and recurrence (DFS, B-D-F-H, respectively) in ELARC.

pathological tumor response increased as the PLR value decreased (p=.045).

Table 2. Multivariate analyses for predicting the overall and disease-free survival in ELARC

	HR (95% CI)	p-value
Overall survival (OS)		
Age (years)	1.22 (1.06-1.40)	.007
Gender (Female vs. male)	4.92 (1.49-16.19)	.009
PLR (≥285 vs. <285)	3.63 (1.29-10.14)	.014
PNI (≤48.6 vs. >48.6)	5.90 (1.80-19.32)	.003
Disease-free survival (DFS)		
LMR (≤1.76 vs. >1.76)	3.45 (1.48-8.02)	.004
Lymph node (positive vs. negative)	3.32 (1.43-7.69)	.005

OS-overall survival, DFS-disease free survival, PLR-platelets to lymphocyte ratio, PNI-prognostic nutritional index, LMR-lymphocyte to monocyte ratio, HR-hazard ratio, CI-confidence interval

In all cohort, when we evaluated the relationship of inflammatory markers and PNI values with toxicity, neither inflammatory markers nor PNI values were found to have a statistically significant relationship with late grade 3-4 toxicity. However, there was a statistically significantly close correlation between PLR value and late grade 3-4 toxicity. (p=.060) (**Table 3**).

Table 3. The association between PLR level and downstaging, late grade 3-4 toxicity, and pCR.

	PLR			
	<285 (low-PLR) (n=26)	≥285 (high-PLR) (n=18)	Total	p-value
Downstaging				.045[1]
Absence	4 (15.4)	8 (44.4)	12 (27.3)	
Presence	22 (84.6)	10 (55.6)	32 (72.7)	
Late grade 3-4 toxicity				.060[1]
Absence	56 (93.3)	20 (76.9)	76 (88.4)	
Presence	4 (6.7)	6 (23.1)	10 (11.6)	
pCR				.045[2]
No response	4 (15.4)	8 (44.4)	12 (27.3)	
Partial response	16 (61.5)	8 (44.4)	24 (54.5)	
Complete response	6 (23.1)	2 (11.1)	8 (18.2)	

Data were described as count (n) and percentage (%). [1]Fisher exact test, [2]Cochrane-Armitage trend test

DISCUSSION

To the best of our knowledge, this is the first study to determine the prognostic value of PNI and inflammatory blood markers (NLR, PLR, LMR) in ELARC. In the present study, univariate analysis revealed that low NLR, low PLR, and high PNI values were associated with increased OS, and high LMR, low PLR, and high PNI values were associated with increased DFS. In the multivariate analysis, low PLR, high PNI values, male gender, and younger age were associated with increased OS, and high LMR values and the absence of lymph node involvement remained the only independent prognostic factors for increased DFS.

In the present study, we found PNI to be an independent prognostic factor for OS in ELARC. As a prognostic indicator, pretreatment PNI calculation has easy availability, as serum albumin and total lymphocyte count are standard parameters commonly assessed in the clinic. However, the definitive cut-off point for PNI has not been determined in the literature yet. In a variety of malignancies, the cut-off points were suggested to have a wide range of 40-51 (6-12). In the recent study, PNI values were divided into two groups, and a PNI value >48.6 was defined as PNI-high and ≤48.6 as PNI-low. And the PNI-high group had a median OS of 44 months, whereas the PNI-low group had a median OS of 31 months, which was statistically significant (P < .003). There are a huge number of studies showing that PNI is a predictor of survival in cancer patients. A meta-analysis, published in 2014, aimed to determine the predictive significance of PNI in cancer. They evaluated 14 studies with a total of 3,414 participants. They found that low PNI was associated with poor OS (pooled OR 1.80, 95 % confidence interval (CI) 1.59-2.04) and the presence of post-operative complications (pooled OR 2.45, 95 % CI 1.31-4.58) in cancer patients, but not with cancer-specific survival (CSS) (pooled HR 1.81, 95 % CI 0.94-3.49). In the conclusion part of this meta-analysis, the authors concluded that PNI was an effective predictor of prognosis in cancer patients, particularly in gastrointestinal cancers (9). In the article published by Tominaga et al., a total of 84 patients ≥ 85 years old who underwent resection for primary colon adenocarcinoma were evaluated, and a low preoperative PNI was found to be significantly associated with a poor prognosis in the oldest-old CRC patients (23).

In a large participant-retrospective study, a total of 3569 patients who underwent curative resection for CRC were enrolled, and their medical records were analyzed. Patients with a lower PNI showed a worse survival outcome, and the rate of complication occurrence according to the preoperative PNI was significantly decreased in the higher PNI group (p= 0.011). Furthermore, the duration of postoperative hospital stay was significantly shortened in higher PNI group (p=0.011). The duration of hospital stay gradually decreased from 13.7 (±10.6) days in patients with PNI < 40 to 10.3 (±14.5) days in patients with PNI > 60. To identify the association between PNI and postoperative outcomes, the authors categorized patients into four groups according to the PNI level: <40, 40-50, 50-60, and >60. This categorization was based on the grade of malnutrition defined with PNI, in which >50 is considered the normal range and <40 is defined as malnutrition (24). Further studies regarding the PNI cut-off point are still needed.

Another laboratory component evaluated in this study is blood inflammatory markers calculated from routine

complete blood counts. Inflammation is a critical component of tumor progression, and the causal relationship between inflammation and cancer is widely accepted (13). Systemic inflammatory markers have recently been reported to be correlated with survival and prognosis among patients with various types of cancer (14-22). More specifically, platelets release angiogenic and putative tumor growth factors such as platelet factor 4 (PF4), transforming growth factor beta (TGF-β), and platelet-derived growth factor (PDGF), all of which promote cancer progression and endotelial cell growth (25-27). Moreover, tumor-associated macrophages (TAMs), which are derived from circulating monocyte populations, have been reported to be a key player in the tumor microenvironment, encouraging metastasis and tumor progression. Additionally, infiltration of the neutrophils around the tumor is associated with poor survival of patients (28). The systemic inflammatory response from cancer cells promotes the infiltration of neutrophils, which may cause a favorable tumor environment for cancer progression by secreting interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor α (TNF-α), and vascular endothelia growth factor (VEGF) (29-30). VEGF, as a known pro-angiogenic factor, especially promotes angiogenesis and contributes to cancer development. However, increased TNF-α, and IL-10 levels lead to a decrease in the lymphocyte count as well as lymphocyte dysfunction (31-32). It is well known that lymphocytes are important in the immune defense against cancer cells (33).

Although many studies have reported that inflammatory markers such as NLR, PLR, and LMR predict the prognosis of patients with CRC (34-35), to our knowledge, no one has reported a different prognostic value of these parameters in ELARC. Corrado et al. (34) analyzed 603 R0-resected CRC patients and found that patients with high NLR, high PLR, and a high platelet count showed to be independent predictors of 5-year OS but not cancer-related survival. Joseph et al. (35) concluded that LMR is a superior prognostic predictor of OS in patients with CRC undergoing curative resection. In our cohort, it was determined that NLR, PLR, and LMR values seemed to have prognostic importance in terms of OS and DFS in ELARC.

In recent years, preoperative CRT has been widely accepted as the first treatment option in rectal cancers, and the absence of tumor cells in the pathology specimen evaluated after surgery is considered a desired therapeutic success and is positively associated with both local control and OS (36). In light of this knowledge, a non-surgical treatment method called 'wait-and-see' approach can be considered in some patients with a biopsy-proven and/or clinically complete response, especially in elderly patients with comorbidities. Predicting the treatment-response is one of the main purposes of oncological treatments. Predicting a good treatment-response may provide less-intense treatment to patients, which means less toxicity, and predicting a poor treatment-response may provide more intense treatment to those patients, which may mean a better oncological outcome. All these mean that more individualized treatments, which are a desired goal by clinicians, will be much more talked about and discussed in the near future. In the recent study, 44 (51.2%) patients received their treatments preoperatively. In this preoperatively treated cohort, downstaging proportion was reduced in high PLR values compared to low PLR values (n=10 (55.6%) vs. n=22 (84.6%), p=.045). It was observed that the level of pathological tumor response increased as the PLR value decreased. In the literature, reports on this topic are confusing. While some studies indicated that PLR was an effective predictor in tumor regression, and the others reported the opposite. In the study published by Lee et al., which included 291 consecutive patients with locally advanced rectal cancer who were treated with preoperative CRT followed by curative surgery were retrospectively analyzed. A PLR ≥235 was defined as high. They found that initially high NLR and PLR were significantly associated with poor clinical outcomes. They also reported that the patients who maintained a high platelet count after CRT also had an advanced pathological stage (p=0.028), low pathological complete response rate (p=0.048), and high relapse rate (p=0.021). Moreover, they found that, for patients with an initially low PLR, the multiple logistic regression analysis revealed that a high PLR change (odds ratio (OR)=2.301, 95% confidence interval (CI)=1.269-4.174; p=0.006) and clinical stage II compared to stage III (OR=1.878, 95% CI=1.231-2.865; p=0.003) were significant independent markers predictive of a good response to CRT (37), Oppositely, Hodek et al. found no significant association between PLR value and tumor regression (38). These differing results are due to differences in studys' methodologies, sample size and patient and tumor characteristics. More comprehensive randomized studies are needed in this regard.

CONCLUSION

Present results revealed that many factors may affect prognosis and oncological outcomes. PNI and PLR were found to be a significant independent prognostic factor for OS in ELARC. LMR was found to be a significant independent prognostic factor for DFS. PLR was also found to be a significant independent prognostic factor for OS and downstaging. Administering treatment to elderly cancer patients poses challenges for clinicians when making decisions. Confirming the reliability of these laboratory markers may contribute to stratifying elderly patients into risk groups and implementing individualized treatment options by increasing or

decreasing the dose of radiotherapy and/or increasing or decreasing the intensity of systemic therapy or managing these patients non-operatively.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Selcuk University Faculty of Medicine Ethics Committee (Date: 11.08.2021, Decision No: 2021/406).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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