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Predictive Value of Preoperative NLR and PLR in Short-term Survival in Rectal Cancer

Rektum Kanserinde Preoperatif NLR ve PLR'nin Kısa Dönem Sağkalımda Prediktif Değeri

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ABSTRACT

Objective: It was aimed to investigate the use of NLR and PLR values both in diagnosis and as prognostic markers for 2- and 3-year short-term survival in rectal cancer cases.

Method: The study included 121 patients who were operated for rectal and followed up in the General Surgery clinic of our hospital, and 120 healthy individuals who applied to our clinic for various purposes.

Results: The mean age was 61.7±11.5 (min.-max.: 35-86) years. The 2- and 3-year survival rates were 63.2% and 54.9%, respectively. The mean NLR and PLR were 3.6±5.2 (min.-max.: 0.2-55) and 171.8±169.7 (min.-max.: 29.4-2000), respectively. The mean 2- and 3-year survival times were 19.6±8.3 and 26.2±13.9 months, respectively.

In the patient group, the median neutrophil count, platelet count, NLR and PLR were significantly higher than the control group, while the median lymphocyte count was significantly lower ($p<0.001$ for each). No significant difference was found in terms of median laboratory values between patients who survived and those who died according to overall, 2-year and 3-year survival. There was no significant correlation between laboratory values and recurrence, overall survival, 2-year survival and 3-year survival ($p>0.05$ for each).

Conclusion: The findings obtained in the present study show that NLR and PLR values can be used as markers in the detection of rectal cancer, however that they do not provide significant information about 2- and 3-year survival.

Keywords: rectal cancer, neutrophil lymphocyte ratio, NLR, thrombocyte lymphocyte ratio, PLR.

ÖZ

Giriş: Bu çalışmada NLR ve PLR değerlerinin rektal kanser olgularında hem tanıda hem de 2 ve 3 yıllık kısa dönem sağkalım hakkında prognostik belirteç olarak kullanılabilirliğinin araştırılması amaçlanmıştır.

Yöntem: Çalışmaya Ocak 2015 ile Aralık 2019 arasında rektum kanseri nedeniyle opere olan ve hastanemiz Genel Cerrahi kliniğinde takip edilen 121 hasta ve çeşitli amaçlarla kliniğimize başvuran 120 sağlıklı birey dahil edilmiştir.

Bulgular: Ortalama yaş 61,7±11,5 (aralık: 35-86) yıl idi. 2 ve 3 yıllık sağkalım oranları sırasıyla %63,2 ve %54,9 idi. Ortalama NLR ve PLR sırasıyla 3,6±5,2 (aralık 0,2-55) ve 171,8±169,7 (aralık 29,4-2000) idi. Ortalama 2 ve 3 yıllık sağkalım süreleri 19,6±8,3 ay ve 26,2±13,9 ay idi.

Hasta grubunda medyan nötrofil sayısı, trombosit sayısı, NLR ve PLR kontrol grubuna göre anlamlı yüksekti, medyan lenfosit sayısı ise anlamlı düşüktü (her biri için $p<0,001$). Hem genel, hem 2 yıllık hem de 3 yıllık sağkalım durumuna göre hayatta kalan hastalar ile ölenler arasında ortanca laboratuvar değerleri açısından anlamlı fark saptanmadı. Laboratuvar değerleri ile nüks, genel sağkalım, 2 yıllık sağkalım ve 3 yıllık sağkalım arasında anlamlı korelasyon saptanmadı (her biri için $p>0,05$).

Sonuç: Çalışmamızda elde edilen bulgular rektum kanseri hastalarında NLR ve PLR değerlerinin rektum kanserinin saptanmasında belirteç olarak kullanılabileceğini ancak 2 ve 3 yıllık sağkalım konusunda anlamlı bilgi vermediğini işaret etmektedir.

Anahtar Kelimeler: rektal kanser, nötrofil lenfosit oranı, NLR, trombosit lenfosit oranı, PLR.

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INTRODUCTION

Rectal cancers are a type of cancer with an annual incidence of more than one million in the world. Rectal cancers account for nearly one-third of all colorectal cancers. Prognosis is generally poor in rectal cancers. In these cancer cases, the 1-year survival rate is 80%, and the 5-year survival rate is 60%. It has been reported that the five-year recurrence rate is around 30% (1-3).

Clinical, radiological, histopathological, inflammatory and hematological findings are used to determine prognosis in rectal cancers. In addition to the classical staging method, it continues to be investigated whether some hematological parameters, which are easy to apply and obtained from complete blood count, provide reliable data in terms of both diagnosis and prognosis. Among these, it has been reported that neutrophil lymphocyte ratio (NLR) and thrombocyte lymphocyte ratio (PLR) values obtained from neutrophil, lymphocyte and platelet counts can provide information in the diagnosis of rectal cancer and prediction of prognosis (4-6).

It has been suggested that the increase in NLR and PLR values in cancer cases due to the increase in neutrophil and thrombocyte count and a decrease in lymphocyte count indicates a worse prognosis in rectal cancer cases in the long term. However, the amount of data on whether these values provide reliable information about the 2- and 3-year short-term prognosis is not yet sufficient. Accordingly, there are discussions about the prognostic value of these values (4-8). Therefore, in this study, it was aimed to investigate the use of NLR and PLR values both in diagnosis and as prognostic markers for 2- and 3-year short-term survival in rectal cancer cases.

MATERIALS AND METHODS

Patients and Tests

A total of 121 patients who were operated for rectal cancer between January 2015 and December 2019 and followed up in the General Surgery clinic of our hospital, and 120 healthy individuals who applied to our clinic for various purposes were included in the study. Demographic information, histopathological and radiological findings of all patients were obtained from the hospital automation system. Patients with tumors up to 12 cm from the anal outlet and those diagnosed with rectal adenocarcinoma as a result of histopathological examination were included in the study. Those who had additional pathology other than rectal cancer, those with tumors in other parts of the colon, those with metastases, additional tumors or previous cancer history were excluded from the study. This study was approved by the local ethics committee (Date: 29.03.2021 / No: 2021/514/198/11).

Statistical analysis

All statistical analyzes in the study were done using SPSS 25.0 software (IBM SPSS, Chicago, IL, USA). Descriptive data are given as numbers and percentages. In terms of categorical variables, comparisons between groups were made with Pearson's Chi Square test and Fisher's Exact Test. Whether continuous variables are suitable for normal distribution was confirmed by the Kolmogorov-Smirnov Test. The differences between the groups in terms of continuous variables were analyzed using Student's t Test, and the comparison of mean values between multiple groups by variance analysis. The relationship between continuous variables was tested usingPearson's correlation analysis. The ability of NLR and PLR rates to predict the presence of rectal cancer and short-term survival in patients was analyzed using receiver operating characteristic (ROC) curve analysis. The results were evaluated within the 95% confidence interval, and $p<0.05$ values were considered significant. Bonferroni correction was made where appropriate.

RESULTS

A total of 60.6% of the patients were male. Recurrence was detected in eight (6.6%) of the patients during follow-up. During follow-up, the overall survival rate was 73.6%, the 2-year survival rate was 63.2%, and the 3-year survival rate was 54.9%. All patients in the present study received neoadjuvant chemotherapy.

The mean age was 61.7±11.5 (min.-max.: 35-86) years. The mean tumor diameter was found

as 2.6±2.1 (min.-max.: 0-13) cm, the mean NLR as 3.6±5.2 (range 0.2-55), and the mean PLR as 171.8±169.7 (range 29, 4-2000). The mean overall survival was 27.7±22 months, the mean 2-year survival time was 19.6±8.3 months, and the mean 3-year survival time was 26.2±13.9 months.

In the rectal cancer patient group, the median neutrophil count, platelet count, NLR and PLR were significantly higher than the control group, while the median lymphocyte count was significantly lower ($p<0.001$ for each) (Table 1).

No significant difference was found between the patients who survived and those who died in terms of overall, 2-year and 3-year survival in terms of median laboratory values ($p>0.05$ for each) (Table 2).

In correlation analyzes, no significant correlation was found between laboratory values and recurrence, overall survival, 2-year survival and 3-year survival ($p>0.05$ for each) (Table 3).

In the ROC analysis; the sensitivity of the threshold value of 2.15 for NLR in the diagnosis of rectal cancer was 71.4%, and the specificity was found to be 71.7% (AUC: 0.749; $p<0.001$; LB: 0.686; UB: 0.812; CI 95%). The sensitivity of the threshold value of 145.35 for PLR in the diagnosis of rectal cancer was 63.9%, and the specificity was found to be 83.3% (AUC: 0.744; $p<0.001$; LB: 0.680; UB: 0.808; CI 95%) (Figure 1). No significant threshold value could be determined for predicting 2- and 3-year survival of NLR and PLR values ($p>0.05$ for each).

Table 1: The Mean and the Median Laboratory Values in the Patient and the Control Groups

	Patients		Controls		P*
	Mean	**SS**	**Mean**	**SS**	
Age (years)	61.7	11.5	61.9	11.8	0.895
Neutrophils (10^9/L)	4.7	1.9	3.9	1.1	<0.001
Lymphocytes (10^9/L)	1.8	1.0	2.2	0.8	<0.001
Platelets (10^3/L)	287.5	95.9	241.0	67.5	<0.001
NLR	3.6	5.2	2.0	0.9	<0.001
PLR	224.5	222.5	118.6	50.2	<0.001
	Median	**IQR**	**Median**	**IQR**	**P****
Age (years)	62	17	62	16	0.938
Neutrophils (10^9/L)	4.5	2.3	3.9	1.5	0.001
Lymphocytes (10^9/L)	1.8	1.3	2.1	1.1	<0.001
Platelets (10^3/L)	259	122	239.5	100	<0.001
NLR	2.8	1.7	1.8	0.9	<0.001
PLR	185	135.8	110.2	54.1	<0.001

*Independent Samples' t test was used. **Mann-Whitney U test was used. SS: Standard deviation, NLR: Neutrophil-to-lymphocyte ratio, PLR: Plathelet-to-lymphocyte ratio, QR: Inter-quartile range.

Table 2: Comparisons between Groups in terms of Median Values by Overall, 2-Year, and 3-Year Survival, and Recurrence (in the Patients Group)

		Alive		Deceased		p
		Median	IQR	Median	IQR	
In terms of overall survival	Neutrophils (10^9/L)	3.9	2.4	4.8	2.0	0.072
	Lymphocytes (10^9/L)	1.7	1.3	1.9	1.3	0.226
	Platelets (10^3/L)	258	128	280.5	124	0.812
	NLR	2.9	1.7	2.5	2.4	0.72
	PLR	190	148.4	149.7	135.1	0.189
In terms of 2-year survival	Neutrophils (10^9/L)	3.9	2.4	4.8	2.0	0.129
	Lymphocytes (10^9/L)	1.6	1.4	1.9	1.3	0.218
	Platelets (10^3/L)	248	119	280.5	124	0.625
	NLR	2.9	1.7	2.5	2.4	0.679
	PLR	190	131.8	149.7	135.1	0.243
In terms of 3-year survival	Neutrophils (10^9/L)	3.9	2.4	4.8	2.0	0.023
	Lymphocytes (10^9/L)	1.6	1.2	1.9	1.3	0.173
	Platelets (10^3/L)	248	124	280.5	124	0.409
	NLR	2.7	2.0	2.5	2.4	0.963
	PLR	189.9	120.8	149.7	135.1	0.337
		Recurrence occured		Recurrence not occured		p
In terms of recurrence	Neutrophils (10^9/L)	4.3	2.6	4.5	2.3	0.925
	Lymphocytes (10^9/L)	1.8	1.4	1.8	1.3	0.925
	Platelets (10^3/L)	246.5	162	260	121	0.802
	NLR	2.8	1.7	2.8	1.8	0.892
	PLR	187.3	183	178.5	134.5	0.909

Mann-Whitney UTest was used. NLR: Neutrophil-to-lymphocyte ratio, PLR: Plathelet-to-lymphocyte ratio, QR: Inter-quartile range.

Table 3 : Correlation Analyzes

		Neutrophils	Lymphocytes	Platelets	NLR	PLR
Age	r	-.223	-.152	-.217	-.043	-.014
	p	.014	.095	.017	.642	.879
Tumor volume	r	.131	.017	.161	.021	.015
	p	.153	.854	.078	.816	.874
Tumor size	r	.109	-.120	.148	.157	.163
	p	.235	.190	.106	.085	.075
T	r	.048	-.243	.093	.154	.227
	p	.599	.007	.310	.091	.012
N	r	-.052	-.011	.034	-.003	.040
	p	.574	.909	.711	.977	.665
Stage	r	.042	-.139	.150	.108	.181
	p	.647	.128	.101	.240	.047
DFS (recurrence)	r	.015	.011	-.013	-.074	-.074
	p	.874	.902	.891	.422	.423
OS	r	-.098	-.039	-.070	-.077	-.028
	p	.286	.674	.448	.402	.759
2-year OS	r	-.040	-.078	-.003	.063	.113
	p	.715	.471	.980	.559	.299
3-year OS	r	-.113	-.073	-.022	.008	.110
	p	.347	.545	.858	.946	.361

Pearson's correlation analysis was used. NLR: Neutrophil-to-lymphocyte ratio, PLR: Plathelet-to-lymphocyte ratio, DFS: disease-free survival, OS: Overall survival.

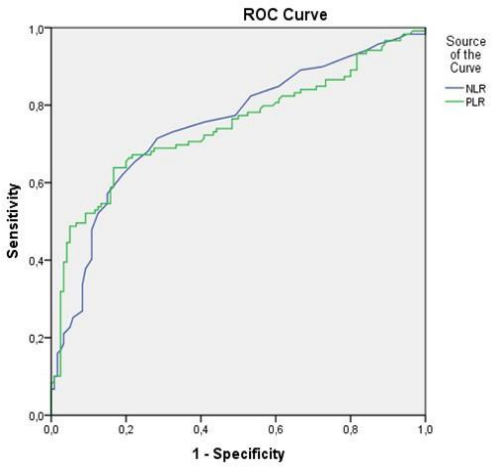


Figure 1. In the ROC Analysis

DISCUSSION

Some of systematic inflammatory biomarkers such as NLR and PLR are reported to give some valuable information about the prognosis in gastrointestinal tract cancer cases (9,10). Predicting the prognosis in rectal cancer cases is important in terms of patient management. Apart from the classical staging methods used for this purpose, there are studies on the ratios and indices obtained from some hematological values. Although there are studies reporting that NLR and PLR can be used in the diagnosis of rectal cancer and predicting long-term prognosis, there are conflicting reports about the short-term prognosis (4-7). In this study, it was observed that NLR and PLR values could be used in diagnosis, but did not provide reliable data aboutshort-term prognosis.

It has been shown that there is a link between high NLR value and tumor associated macrophages derived from splenic monocytes and T cells producing interleukin-17 (IL-17). It has been suggested that this linkage is related to the significant role of IL-17 in neutrophil chemotaxis through the release of CCL2 and CXC chemokines. In addition, it has been shown that the production of various cytokines increases in those with low NLR values and this can suppress the immune response against the tumor. In addition, it has been reported that with the effect of neutrophils increasing cytokines, lymphocytes suppress cellular immunity by decreasing T4 cells and increasing T8 cells, and this balance affects tumor immunology. In addition to all these, it has been stated that there is a relationship between intestinal flora and NLR, and this may have an effective role in the immune response developing against the tumor (4). In the present study, the median neutrophil count and NLR value were found to be significantly higher in rectal cancer patients compared to the control group, and the median lymphocyte count was found to be significantly lower. In addition, in the ROC analysis; the sensitivity and thespecificity of the threshold value of 2.15 for NLR in the diagnosis of rectal cancer were found as 71% and 71.7%, respectively. All these findings show that the number of neutrophils increases significantly in rectal cancer cases, that the number of lymphocytes decreases significantly, and that the NLR value can be used as a marker in determining rectal cancer patients.

Many studies have reported that the NLR rate in rectal cancer patients is associated with long-term survival, that patients with high NLR values have a shorter survival time, and that patients with high NLR values show worse long-term prognosis (7,8,11-17). Nevertheless, it has been stated that the NLR value provides conflicting information about the pathological response after chemotherapy and this issue is controversial (11). For example, no relationship was found between NLR and prognosis in two studies (6,18). In the study of Ke *et al*. (12), in the graph showing survival with high and low NLR values, it is seen that the differentiation is not very pronounced in the short-term and becomes more evident as the period progresses. Ke *et al*.(12) also emphasized that NLR value is not related with prognosis in early stage cases. In another study, it was reported that the NLR value increased with the stage, but this increase was not statistically significant (19). In another study, it was shown that the NLR value was associated with 3-year survival in early-stage rectal cancer cases, but it was not an independent risk factor for 3-year survival (20). In the present study, no significant difference was found in terms of median NLR values between patients who survived

and those who died in terms of overall, 2-year and 3-year survival. In addition, in correlation analysis, no significant correlation was found between NLR value and recurrence, overall survival, 2-year survival and 3-year survival. In addition, in the ROC analysis, a reliable threshold value could not be determined for predicting 2- and 3-year survival for NLR value. All these findings show that the NLR value is not informative in terms of short-term survival in rectal cancer patients.

It has been reported that platelet aggregation and the release of platelet-derived proangiogenic mediator molecules by degranulation into the vascularization in the micro-periphery of the tumor affect tumor growth (4). Accordingly, it has been shown that PLR value can be used in the diagnosis of patients with rectal cancer (21-23). Mo *et al* (21). reported that the threshold value of

135.11 for PLR in the diagnosis of rectal cancer has a sensitivity of 45% and a specificity of 75%. In the present study, the median platelet count and PLR value in rectal cancer patients were found to be significantly higher than the control group. In addition, in the ROC analysis; the sensitivity and the specificity of the threshold value of 145.35 for PLR in the diagnosis of rectal cancer were 63.9% and 83.3%, respectively. All these findings show that platelet counts increase significantly in rectal cancer cases, and that PLR value can be used as a marker in determining rectal cancer patients.

Long-term prognosis has been reported to be worse in rectal cancer patients with high PLR values (11,12,24,25). Nevertheless, it has been stated that the PLR value provides conflicting information about the pathological response after chemotherapy and this issue is controversial (11). In the study of Ke *et al*.(12), in the graph showing survival with high and low PLR values, it is seen that the differentiation is not very pronounced in the short-term and becomes more evident as the period progresses. Ke *et al*. (12) also stated that NLR value is not related with prognosis in early stage cases. Portale *et al*. (6) also reported that there is no relationship between PLR and prognosis. In the present study, no significant difference was found in terms of median PLR values between patients who survived and those who died in terms of overall, 2-year and 3-year survival. In correlation analysis, no significant correlation was found between PLR value and recurrence, overall survival, 2-year survival and 3-year survival. In addition, in the ROC analysis, no significant threshold value was determined for the PLR value in predicting 2- and 3-year survival. In addition, no significant correlation was found between PLR value and recurrence, overall survival, 2-year survival and 3-year survival in correlation analysis. All these findings show that the PLR value is not informative in terms of short-term survival in rectal cancer patients.

Limitations of the Study

There were some limitations in the present study. In the present study, it was planned to focus on short-term survival by keeping the follow-up periods short, so the usability of NLR and PLR values in terms of long-term survival was not analyzed. In addition, since all patients received neoadjuvant chemotherapy, the prognosis results of this treatment could not be compared in the study.

Conclusion

In conclusion, the findings obtained in the present study show that NLR and PLR values can be used as markers in the detection of rectal cancer due to a marked increase in neutrophil and thrombocyte counts and a significant decrease in lymphocyte count in rectal cancer patients compared to healthy individuals. However, the findings of the present study indicate that NLR and PLR values, which have been shown to be associated with long-term prognosis, do not provide significant information about 2- and 3-year survival.

Conflict of Interest

There is no conflict of interest.

Funding

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Ethics Committee Approval

This study was approved by the local ethics committee, and was planned retrospectively (Date: 29.03.2021 / No: 2021/514/198/11).

Authors Contributions

All authors have contributed significantly to the work

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