

Prognostic Value of Preoperative Neutrophil-lymphocyte/Platelet-lymphocyte Ratio in Patients with Stage II-III Rectal Cancer Who Underwent Curative Resection

Küratif Rezeksiyon Uygulanan Evre II-III Rektum Kanserli Hastalarda Preoperatif Nötrofil-lenfosit/Trombosit-lenfosit Oranının Prognostik Değeri

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ABSTRACT

Introduction: This study aimed to evaluate the prognostic value and survival effects of the neutrophil-lymphocyte/platelet-lymphocyte ratio (NLR/PLR) in the preoperative peripheral blood count of patients who underwent curative resection due to stage II-III rectal cancer.

Methods: Between 2011 and 2017, a total of 156 patients with stage II-III rectal cancer who underwent curative resection were evaluated. Before the curative resection, complete blood counts were obtained within 3 days. The last follow-up was in December 2018. NLR and PLR were calculated by dividing the absolute neutrophil or platelet count by the absolute lymphocyte count, respectively.

Results: Postoperatively, adenocarcinoma histology ($p=0.025$), R1 resection ($p<0.001$), T4 stage ($p=0.001$), N stage positivity ($p=0.003$), tumor-node-metastasis (TNM) stage III disease ($p=0.002$), presence of lenfovasküler invasion ($p<0.001$), presence of perineural invasion ($p<0.001$), preoperative NLR ≥ 3.6 ($p<0.001$) and PLR ≥ 192 ($p<0.001$) were identified in the rectal cancer patients as factors that influence survival in univariate analysis. In our study, R1 resection [hazard ratio (HR): 0.341; 95% confidence interval (CI): 0.157-0.740; $p=0.007$]; T4 stage (HR: 0.261; 95% CI: 0.129-0.527; $p<0.001$), N0 stage vs N1 positivity (HR: 0.071; 95% CI: 0.010-0.525; $p=0.010$), N0 stage vs N2 positivity (HR: 0.068; 95% CI: 0.008-0.565; $p=0.013$), presence of metastases (HR: 0.130; 95% CI: 0.054-0.309, $p<0.001$), TNM stage III (HR: 0.261; 95% CI: 0.129-0.527, $p<0.001$) and preoperative NLR ≥ 3.6 (HR: 0.378; 95% CI: 0.154-0.930, $p=0.034$) were identified as independent factors affecting survival in multivariate analysis.

ÖZ

Amaç: Bu çalışmada evre II-III rektum kanseri ile küratif rezeksiyon uygulanan hastalarda preoperatif periferik kan sayımlarında nötrofil-lenfosit/trombosit-lenfosit oranının (NLO/PLO) prognostik değeri ve sağkalım etkilerinin değerlendirilmesi amaçlanmıştır.

Yöntemler: 2011-2017 yılları arasında küratif rezeksiyon uygulanan evre II-III rektum kanserli 156 hasta değerlendirildi. Küratif rezeksiyondan önce, tam kan sayımı 3 gün içinde elde edildi. Son takip Aralık 2018 oldu. NLO ve PLO, mutlak nötrofil veya trombosit sayısının mutlak lenfosit sayısına bölünmesiyle hesaplandı.

Bulgular: Postoperatif olarak, rektum kanseri hastalarında adenokarsinom histolojisi ($p=0,025$), R1 rezeksiyonu ($p<0,001$), T4 evre ($p=0,001$), N evre pozitifliği ($p=0,003$), tümör-nod-metastaz (TNM) evre 3 hastalığı ($p=0,002$), lenfovasküler istila varlığı ($p<0,001$), perinöral invazyon varlığı ($p<0,001$), preoperatif NLO $\geq 3,6$ ($p<0,001$) ve PLO ≥ 192 ($p<0,001$) univariate analizde sağkalımı etkileyen faktörler olarak tanımlanmıştır. Çalışmamızda R1 rezeksiyonu [tehlile oranı (HR): 0,341; %95 güven aralığı (GA): 0,157-0,740; $p=0,007$]; T4 evresi (HR: 0,261; %95 GA: 0,129-0,527; $p<0,001$), N0'a karşı N1 pozitifliği (HR: 0,071; %95 GA: 0,010-0,525; $p=0,010$), N0'a karşı N2 pozitifliği (HR: 0,068; %95 CI: 0,008-0,565; $p=0,013$), metastaz varlığı (HR: 0,130; %95 GA: 0,054-0,309, $p<0,001$), TNM evre III (HR: 0,261; %95 GA: 0,129-0,527, $p<0,001$) ve preoperatif NLR $\geq 3,6$ (HR: 0,378; %95 GA: 0,154-0,930, $p=0,034$) multivariate analizde sağkalımı etkileyen bağımsız faktörler olarak tanımlandı.



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Conclusion: In our study, due to the low cost, it extensive use, and association with overall survival, NLR was found to be a better prognostic marker. Besides, R1 resection, T4 stage, lymph node positivity, presence of metastases, TNM stage III were found to be prognostic factors that negatively affect overall survival. NLR is a biomarker that is thought to be an indicator of the systemic inflammatory response and can be easily obtained as a prognostic biomarker candidate.

Keywords: Stage II, III rectum cancer, neutrophil-lymphocyte, platelet-lymphocyte ratio, prognosis

Sonuç: Çalışmamızda, düşük maliyetli, yaygın olarak kullanılan, genel sağkalım ile ilişkili, NLO'nun daha iyi bir prognostik belirteç olduğu bulunmuştur. Ayrıca R1 rezeksiyon, T4 evresi, lenf nodu pozitifliği, metastaz varlığı, TNM evre III genel sağkalımı olumsuz etkileyen prognostik faktörler olarak bulundu. NLO sistemik enflamatuvar yanıtın bir göstergesi olduğu düşünülen ve prognostik biyobelirteç adayı olarak kolayca elde edilebilen bir biyobelirteçtir.

Anahtar Kelimeler: Evre II, III rektum kanseri, nötrofil-lenfosit, trombosit-lenfosit oranı, prognoza

Introduction

Colorectal cancers is the third most common cancer in the world. Surgery is chosen for the treatment of non-metastatic diseases and postoperative treatment is usually managed according to the tumor-node-metastasis (TNM) staging system (1). Cancer-related inflammation, tumour and host-derived cytokines, immune cells and small inflammatory protein agents cover leukocytes, neutrophils, lymphocytes and platelets and is determined by the levels of acute-phase proteins (2,3). Lymphocytes play a crucial role in cytotoxic cell death and cytokine production, which prevents proliferation and metastasis of malignant cells (4). Elevated neutrophil count increases tumour growth and metastasis by remodelling the extracellular matrix, thereby releasing reactive oxygen species and suppressing lymphocyte activity (5). Also, the presence of tumour cells affects platelets and causes cancer-related thrombosis (6). Platelets excrete growth factors that support tumour growth, angiogenesis and metastasis (7). Increased NLR seems to be related with a poor prognosis in different cancers (8-11). We know that patients at an equal stage can have separate clinical features and outcomes. In clinical practice, simple methods such as NLR added to TNM staging can help with this situation to create an individualised treatment strategy.

We aimed to evaluate the prognostic value and survival effects of the neutrophil-lymphocyte ratio (NLR)/platelet-lymphocyte ratio (PLR) in the preoperative peripheral blood counts of patients who underwent curative resection with stage II-III rectal cancer.

Methods

A total of 156 patients with stage II-III rectal cancer who underwent curative resection between 2011 and 2017 were evaluated. The last follow-up was in December 2018. Before the curative resection, complete blood count were obtained within 3 days. Complete blood count was performed with XN-900 Haematology analyser (Symex, Japan). The normal reference range for lymphocytes was $1.18-3.57 \times 10^9/L$, for neutrophils $1.56-6.13 \times 10^9/L$ and platelets for $142-424 \times 10^9/L$. We determined the cut-off with the receiver operating characteristic curve for NLR 3.6 [area under the curve (AUC): 0.791; 95% confidence interval (CI): 0.711-0.872; $p < 0.001$] and PLR 192 (AUC: 0.784; 95% CI: 0.704-0.864; $p < 0.001$). Colonoscopy and biopsy were performed to diagnose all the patients preoperatively. For staging, a computed tomography (CT) scan of the thorax and abdomen or an 18-fluorodeoxyglucose positron emission tomography CT was performed. Pelvic magnetic resonance imaging for local disease staging was performed. R0 resection has no

postoperative residual tumour and R1 resection has been accepted as the presence of the microscopic residual tumour. In 25-28 fraction, daily dose of 180-200 cGy, 5,000-5,040 cGy, 5-6 weeks, radiotherapy (RT) was applied. From the first day of RT, continuous bolus infusion 5-FU (225 mg/m^2) or 5-FU (425 mg/m^2) + calcium leucovorin (20 mg/m^2) was given throughout RT. T-test or Mann-Whitney U test were used for non-categorical variables; chi-square and Fisher's exact tests were used for categorical variables. Categorical variables were presented as absolute numbers and percentage values for the NLR and PLR. Prognostic values of each variable were evaluated with univariate and multivariate Cox proportional regression analyses. Overall survival (OS) was calculated and compared using the Kaplan-Meier method and Log-rank test. Inclusion criteria of patients: (1) primary rectal cancer diagnosed in the postoperative stage II,III; (2) patients undergoing radical surgery without neoadjuvant therapy; (3) those with complete blood count and follow-up data. Exclusion criteria were as follows: (1) the presence of infection or haematological disease; (2) to apply neoadjuvant radiochemotherapy first; (3) to have emergency surgery due to bowel obstruction; (4) synchronous/metacron other than cancers; (5) use of anti-inflammatory or immunosuppressive drugs; (6) except neuroendocrine tumours.

Statistical Analysis

Statistical analysis was performed using SPSS software version 22.0 (SPSS, Chicago, IL, USA). A p-value of less than 0.05 from a two-tailed test was considered statistically significant. This study was approved by University Health Sciences Turkey, İstanbul Training and Research Hospital's Ethics Committee (decision no: 2244/ date: 27.04.2020). Due to the retrospective design of the study, informed consent was not obtained from the patients.

Results

The median age was 61 (range: 22-83). The median tumour diameter was $5.06 \pm 1.85 \text{ cm}$ (range: 2-12.5). Of our patients, 71 (46%) were females and 85 (54%) were males. Male/female ratio was 1.1/.ost of our patients were located in the upper rectum (n 95; 61%). Thirty-one (20% in the middle rectum and 30 (19%) in the lower rectum. One hundred and twenty-six (81%) patients were operated by low anterior resection and 30 (19%) by abdominoperineal resection. One hundred and nineteen (76%) patients were adenocancers, 20 (13%) patients were mucinous cancers, 16 (11%) patients were in mixed type (adenocancer + mucinous) histology. There were 7 (5%) patients who did not apply RT and 4 (3%) patients who did not use chemotherapy. Liver metastasis was detected in 17 (11%)

patients, lung metastasis in 17 (11%) patients, local recurrence in 14 (9%) patients and peritoneal metastasis in 14 (9%) patients. The number of patients with fewer than 12 lymph nodes removed during surgery was 28 (18%). Since carcinoembryonic antigen was not assessed in all the patients (only 94 patients were evaluated), we did not evaluate the survival with tumour markers in our study. The general characteristics of the patients are shown in Table 1.

NLR ≥ 3.6 values were in present 68 (44%) patients and PLR ≥ 192 values

Table 1. General demographics of patients (lenfovacular invasion, perineural invasion, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio)

	Number of patients	%
Age (median \pm SD)	61 \pm 12.29	-
Gender		
Female	71	45
Male	85	55
Histology		
Adenocancer	119	76
Others	37	24
LVI		
Absent	80	51
Present	76	49
PNI		
Absent	95	61
Present	61	39
Surgical resection		
R1	23	15
R0	133	85
T stage		
2	13	8
3	110	71
4	33	21
N stage		
0	66	42
1	57	37
2	33	21
TNM Stages		
II	63	40
III	93	60
Metastases		
Absent	94	60
Present	62	40
NLR		
NLR <3.6	88	56
NLR ≥ 3.6	68	44
PLR		
PLR <192	84	54
PLR ≥ 192	72	46

NLR: Neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, LVI: lenfovacular invasion, PNI: perineural invasion, SD: standard deviation, TNM: tumor-node-metastasis

in 72 (46%) patients. According to NLR <3.6 vs NLR ≥ 3.6 and PLR <192 vs PLR ≥ 192 , lymph node involvement, TNM stage III, lenfovacular invasion (LVI) and perineural invasion (PNI) were statistically significant. The demographic comparisons of the patients according to NLR and PLR values are shown in Table 2.

Postoperatively, adenocarcinoma histology (p=0.025), R1 resection (p<0.001), T4 stage (p=0.001), N stage positivity (p=0.003), TNM stage III disease (p=0.002), presence of LVI (p<0.001), presence of PNI (p<0.001), preoperative NLR ≥ 3.6 (p<0.001) and PLR ≥ 192 (p<0.001) were identified as factors in rectal cancer patients that influence survival in univariate analysis.

In our study, R1 resection [hazard ratio (HR): 0.341; 95% CI: 0.157-0.740; p=0.007]; T4 stage (HR: 0.261; 95% CI: 0.129-0.527; p<0.001), N0 stage vs N1 positivity (HR: 0.071; 95% CI: 0.010-0.525; p=0.010), N0 stage vs N2 positivity (HR: 0.068; 95% CI: 0.008-0.565; p=0.013), presence of metastases (HR: 0.130; 95% CI: 0.05-0.309, p<0.001), TNM stage III (HR: 0.261; 95% CI: 0.129-0.527, p<0.001) and preoperative NLR ≥ 3.6 (HR: 0.378; 95% CI: 0.154-0.930, p=0.034) were identified as independent factors affecting survival in multivariate analysis (Table 3).

The 5-year OS was 70 % for stage II and 46% for stage III (Figure 1).

Discussion

There are many factors that impact the prognosis of colorectal cancer, due to its tumour heterogeneity(12). Colorectal cancer (CRC) risk increases with age (13). In this study, the median age was found as 61 years. Like in our study, the distribution of gender was nearly equal as in other studies. There was a mild male dominance (14,15). Adenocarcinoma is the most familiar histological subtype of CRC, while the mucinous and signet ring cell subtypes are more common in younger patients (16).

In rectal cancer, R1 resection is an independent risk factor that negatively affects the OS. Neoadjuvant RT decreases R1 resection and we have to avoid R1 resection (17,18). We also found that R1 resection was an independent risk factor that shortens the OS.

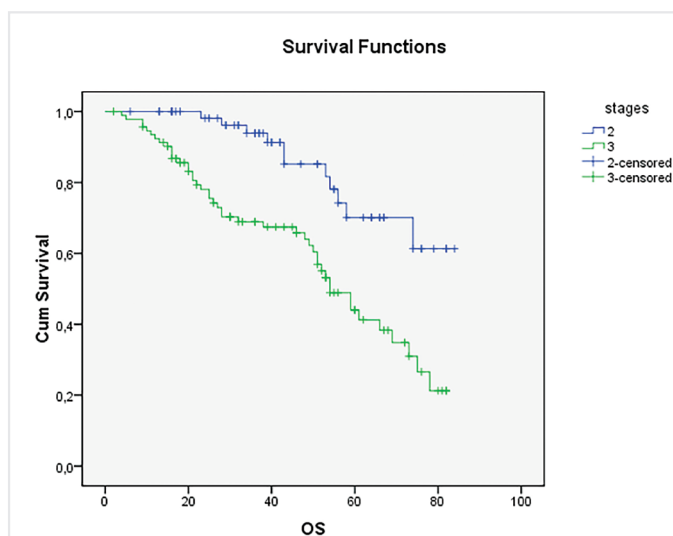


Figure 1. OS, according to stage II and stage III (Log-rank p<0.001)

OS: Overall survival

Table 2. General characteristics of the patients according to neutrophil-lymphocyte ratio and platelet-lymphocyte ratio

	NLR <3.6	NLR ≥3.6	p	PLR ≥192	PLR ≥192	p
Age						
<65	52	41	0.879	47	46	0.314
≥65	36	27	-	37	26	-
Gender						
Female	42	29	0.527	37	34	0.691
Male	46	39	-	47	38	-
Histology						
Adenocancer	71	48	0.142	68	51	0.139
Others	17	20	-	16	21	-
LVI						
Absent	56	24	<0.001	53	27	0.001
Present	32	44	-	31	45	-
PNI						
Absent	64	31	0.001	63	32	<0.001
Present	24	37	-	21	40	-
Surgical resection						
R1	7	16	0.007	9	14	0.125
R0	81	52	-	75	58	-
T stage						
2-3	73	50	0.153	70	53	0.138
4	15	18	-	14	19	-
N stage						
0	47	19	-	48	18	-
1-2	41	49	0.001	36	54	<0.001
TNM stages						
II	45	18	0.002	46	17	<0.001
III	43	50	-	38	55	-
Metastases						
Absent	72	22	<0.001	68	26	<0.001
Present	16	46	-	16	46	-

NLR: Neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, LVI: linfovascular invasion, PNI: perineural invasion, TNM: tumor-node-metastasis

In the analysis of 1,437 patients who underwent curative surgery and were diagnosed with stage II-III colorectal cancer, LVI and PNI were found to be independent prognostic factors affecting OS (19). In a recent study investigating the importance of perineural and lymphovascular invasion in locally advanced rectal cancer, PNI was determined as the independent prognostic factor that presented the OS compared to LVI (20). In the univariate analysis in this study, LVI and PNI were found to be statistically significant, but were not prognostic.

In a study with 508 patients undergoing radical surgery, degree of differentiation, age, T stage, nodal involvement, PNI were identified as independent prognostic factors affecting OS (21). Nodal involvement and advanced T stage were independent prognostic factors negatively affecting the OS, as in our study.

The TNM staging system directs us the clinicians to choose the appropriate treatment for the patient and is standard. According to the

American Joint Committee of Cancer-7 rectal cancer staging system, a minimum of 12 lymph nodes are required for the suitable tumour stage and is involved with a good OS in patients treated with surgery (22). In our study, less than 12 lymph nodes were removed in 18% of the patients, which did not affect the OS. In another study, NLR and PLR both demonstrated their potential significance for the TNM stage assessment in CRC patients (23). The increase in NLR was also related to the TNM stages in our study.

A study evaluating 205 surgical CRC patients concluded that preoperative high NLR is an independent prognostic marker for OS and cancer-specific survival (24). In a retrospective evaluation of 300 patients and in another study with 200 patients who underwent curative resection for CRC, NLR and PLR were found as independent prognostic factors that negatively impacted the OS (25,26). In our study, only NLR was an independent prognostic factor.

Table 3. Univariate and multivariate analysis for overall survival

	Univariate			Multivariate		
	HR	%95 CI	p	HR	%95 CI	p
Age						
<65	-	1	-	-	-	-
≥65	0.924	0.537-1.591	0.776	-	-	NI
Gender						
Female	-	1	-	-	-	-
Male	0.846	0.488-1.468	0.533	-	-	NI
Histology						
Adenocancer	-	1	-	-	1	-
Others	0.514	0.288-0.919	0.025	0.546	0.279-1.068	0.077
LVI						
Absent	-	1	-	-	1	-
Present	0.355	0.202-0.624	<0.001	0.917	0.422-1.991	0.826
PNI						
Absent	-	1	-	-	1	-
Present	0.243	0.137-0.430	<0.001	0.721	0.356-1.458	0.362
Surgical resection						
R0	-	1	-	-	1	-
R1	0.264	0.141-0.495	<0.001	0.341	0.157-0.740	0.007
T stage						
T2-3	-	1	-	-	1	-
T4	0.370	0.206-0.663	0.001	0.261	0.129-0.527	<0.001
N stage						
0	-	1	-	-	1	-
1	2.539	1.249-5.163	0.010	0.071	0.010-0.525	0.010
2	5.496	2.625-11.50	<0.001	0.068	0.008-0.565	0.013
TNM stages						
II	-	1	-	-	1	-
III	0.367	0.193-0.699	0.002	0.098	0.013-0.710	0.022
Metastases						
Absent	-	1	-	-	1	-
Present	0.089	0.044-0.183	<0.001	0.130	0.054-0.309	<0.001
NLR						
NLR <3.6	-	1	-	-	1	-
NLR ≥3.6	0.180	0.096-0.338	<0.001	0.378	0.154-0.930	0.034
PLR						
PLR <192	-	1	-	-	1	-
PLR ≥192	0.183	0.096-0.349	<0.001	0.509	0.218-1.188	0.118

NLR: Neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, LVI: lenfovascular invasion, PNI: perineural invasion, CI: confidence interval, TNM: tumor-node-metastasis, NI: not included, HR: hazard ratio

In many studies, inflammatory responses have been evaluated with haematological markers. In colorectal cancer, lymphocytes play a significant role in the immune response. Cellular immunity decreases in the presence of systemic inflammation. This promotes a decrease in CD4 lymphocytes and an increase in CD8 suppressor T lymphocytes. Lymphocytes commonly play a considerable role in the growth and

progression of cancer via regulation of cell-mediated immunity. Myeloid growth factors are produced by tumours, which may increase the number of neutrophilic granulocytes at the site of the tumour (26). Platelets are taken into the tumour microenvironment and release platelet-induced growth factor and transformative growth factor to enable tumour growth. It regulates angiogenesis and protects tumour

cells from host immune surveillance and direct cellular contact with natural killer cells by forming a network with fibrin surrounding tumour cells during haematogenous propagation (27). Tumour cells can manipulate platelet activity to optimise tumour growth, proliferation, survival and metastasis.

The retrospective character of our study, the frequent use of neoadjuvant chemo RT in patients with rectal cancer nowadays and the small number of patients constitutes our limitations.

Conclusion

In our study, due to its low cost, extensive use and association with OS, NLR was found to be a better prognostic marker. Besides, R1 resection, T4 stage, lymph node positivity, presence of metastases, TNM stage III were found to be prognostic factors that negatively affect OS. NLR is a biomarker that is thought to be an indicator of the systemic inflammatory response and can be easily obtained as a prognostic biomarker candidate.

Ethics

Ethics Committee Approval: This study was approved by University Health Sciences Turkey, İstanbul Training and Research Hospital's Ethics Committee (decision no: 2244/ date: 27.04.2020).

Informed Consent: Due to the retrospective design of the study, informed consent was not obtained from the patients.

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