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Research Article

Predictive Values of Preoperative Inflammatory Based Indices in Prognosis of Patients with Resected Rectal Cancer

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Abstract

Objectives: Rectum cancer is a type of colorectal cancer. Its etiology and etiopathogenesis are similar to other colon diseases. However, it is differentiated from other colon tumors because of its different anatomy and treatment. We aimed to evaluate the inflammatory based indices value for predicting prognosis of rectum cancer patients who treated with neoadjuvant chemoradiotherapy.

Methods: We retrospectively collected the data of 80 operated rectum adenocarcinoma patients who were treated neoadjuvant chemoradiotherapy between 2013 and 2018 in Umraniye Research and Training Hospital and Acıbadem University Medical Oncology Outpatient Clinic. Peripheral venous blood samples were collected for analysis of lymphocyte (Lym), neutrophile (Neu) and platelet (Plt) numbers, and, hemoglobin levels at the time of diagnosis. NLR, PLR, and SII were investigated as prognostic factors for disease free survival.

Results: This study included 80 rectum cancer patients and 55 were male (68.8%). Median age was 56 (range 22 to 83 years). According to clinical parameters, histopathological types were adenocarcinoma in 75 (93.8%) patients and mucinous adenocarcinoma in 5 (6.2%) patients). In multivariate analysis, PLR were found to be independent prognostic factors for disease free survival (p=0.02).

Conclusion: According to our study, we suggest that high levels of PLR at the time of diagnosis can be used as a predictive biomarker for rectum patients who may show relapse predisposition.

Keywords: Rectum cancer, prognosis, Inflammatory based Indices

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Colorectal cancer (CRC) is one of the most common cancer worldwide. It is the third most frequently diagnosed cancer in men, and second in women.[1] Although CRC mortality has been rapidly declining since 1990, nowadays its rate of approximately 1.7 to 1.9 % per year.[2] Neoadjuvant chemoradiotherapy is the standard therapeutic approach in rectal cancer.[3, 4] There is no ideal marker for predicting prognosis after chemoradiotherapy. Recent studies have reported that primary tumor SUVmax in PET-CT can be used to predict prognosis in patients receiving neoadjuvant chemoradiotherapy.[5, 6] Unfortunately, approximately sixty percent of early or local advanced stage patients develop metastasis in the follow-up period.[7] Currently, the combination of cytotoxic chemotherapeutic drugs with

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molecularly-targeted agents provide long-term survival in metastatic CRC patients. However, most patients can not be curable.[8, 9] The prognosis of CRC is influenced by some factors such as individual (age, sex, family history), clinical, biochemical, pathologic prognostic factors, stage at the time of diagnosis and treatment modality.[10, 11]

Systemic or local inflammation has known for promoting cancer development and progression. Researchers have shown that the relationship between inflammation and cancer development or progression in several trials.[12-14] Combinations of systemic inflammation parameters such as neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) have been reported as prognostic factors in some malignant solid tumors in literature. The systemic immune- inflammation index (SII) which is based on neutrophil, lymphocyte, and platelet counts was firstly described in patients after curative resection for hepatocellular carcinoma by Hu et al.[15-17] Chen et al. reported to the advantage of the prognostic value of SII than NLR and PLR in patients with CRC after radical surgery. Another study also confirmed the prognostic value of SII. However, SII has not shown any advantage than PLR and NLR.[18, 19] Thus, the independent contribution of SII to disease-free survival in the context of established prognostic factors remain to be investigated in CRC with patients who underwent curative surgery.

We aimed to investigate the prognostic value of PLR, NLR, and SII in patients with rectum cancer who underwent radical curative surgery after neoadjuvant chemoradiotherapy in our study.

Methods

Patients

We retrospectively evaluated the data of 80 operated rectum adenocarcinoma patients who were treated neoadjuvant chemoradiotherapy between 2013 and 2018 in Umraniye Research and Training Hospital and Acıbadem University Medical Oncology Outpatient Clinic. Inclusion criteria were the histological diagnosis of non-metastatic rectal adenocarcinoma, treated with neoadjuvant chemoradiotherapy and having complete medical records. All patients were older than eighteen years old. Patients who had confounding factors affecting neutrophile, platelet, and lymphocyte counts such as smoking, hyperlipidemia, the presence of active infection disease, and hepatosplenomegaly were excluded from the study.

All patients received neoadjuvant chemoradiotherapy. Radiotherapy was given a total of forty-five gray/28 days. Capecitabine 825 mg/m^2/day or 5-fluorouracil total of 1000 mg/m^2/five-days/weekly was administered. All of the patients were operated on average 8-12 weeks.

The tumor grading were categorized into well differentiated (>95% gland formation), moderately differentiated (50%–95% gland formation), and poorly differentiated (<50% gland formation). Patients were grouped into four categories according to the tumor-node-metastasis (TNM) staging, based on the American Joint Cancer Committee (AJCC) cancer staging manual 7th edition. Tumor regression was assessed by the four-tier AJCC/CAP tumor regression grading system. It is categorized as: No viable cancer cells – 0 (Complete response), Single cells or small groups of cancer cells – 1 (Moderate response), Residual cancer outgrown by fibrosis – 2 (Minimal response), and Minimal or no tumor kill; extensive residual cancer – 3 (Poor response).

Peripheral venous blood samples were obtained early in the morning (7 am) from the patients on an empty stomach. Blood specimens were collected in sterile EDTA tubes and hematological parameters were analyzed based on routine procedures. The data of lymphocyte (Lym), neutrophil (Neu), and platelet (Plt) numbers were obtained for the time of diagnosis. The SII, NLR, and PLR were calculated as follows; SII=Neutrophile counts* platelet counts/lymphocyte counts, NLR=Neutrophil count/lymphocyte count, and PLR=Platelet count/lymphocyte count.

We defined the follow-up duration as the time from the start of neoadjuvant chemoradiotherapy treatment until death any reason/the last visit. Disease-free survival was defined as the time from date of surgery until radiological progression or death/the last visit. The data cut-off date was accepted as September 2018.

Statistical Analysis

Disease-free survival (DFS) were calculated using the Kaplan-Meier method from operated date. Prognostic factors were compared using the log-rank test in univariate analysis. Hazard ratios (HR) with 95% confidence intervals (CI) were also calculated. All p values were 2-sided in the tests, and p values of 0.05 were considered statistically significant. Multivariate analysis was carried out using the Cox proportional hazards model to assess the effect of prognostic factors on survival. To evaluate the optimal cut-off value of SII, NLR, and PLR for predicting disease free survival, receiver operating characteristic (ROC) analysis was performed. A ROC curve was used to indicate the variability of sensitivity and specificity for cut-off points of SII, NLR, and PLR. SPSS 22 program was used for statistical analysis.

Results

Fifty -five of eighty patients were male (%68.8) and the median age was 56 (range 22-77 years). According to clinical parameters, histopathological types were adenocarcinoma in 75 (93.8%) patients and mucinous adenocarcinoma in five (6.2%) patients. Twenty patients were poorly differentiated (25%), twelve (15%) patients showed moderately differentiation, and forty-eight (60%) patients were well differentiated. The data for demographic and clinicopathologic findings are given in Table 1. Median Neutrophil, Lymphocyte, and Platelet counts were 3850 µ/L (min 1690-max 14600), 1800 µ/L (min 1800 -max 7800), and 282000 µ/L (min 110000-max 607000) respectively.

Median follow up thirty-five months (min 9 months -max 65 months). During the follow-up 52 % of the patients relapsed. Twenty-four patients had systemic recurrence. Median disease-free survival (DFS) 31months. Twelve-month DFS rate was 87% and twenty-four months DFS rate was 77%. Median disease-free survival could not be reached in patients with complete response. Median DFS was 42 months in pathologic stage 1, 30 months in stage 2 and 28 months in stage 3 ($p<0.05$).

SII calculated as median 545.9 (min 124.2-max 4484.2). The ideal cut-off value of SII, optimal cut-off value predicted disease-free survival was 498 in the ROC analysis [AUC:0.86 (0.78-0.94)/$p<0.00$] with a sensitivity of 79%, and specificity of 74% Median DFS was 42 months in patients with SII <498, 26 months in patients with ≥498 ($p=000$) (Fig. 1 a, b).

NLR calculated as median 2.19 (min 0.35-max 10.43) and the ideal cut -off value that predicted disease-free survival was 1.74 in the ROC analysis [AUC:0.83 (0.73-0.91)/$p<0.00$] with a sensitivity of 83%, and specificity of 66 %. Median DFS was 42 months in patients with NLR <1.74, 27 months in patients with ≥1.74 ($p=000$) (Fig. 1 a-c).

PLR calculated as median 157 (min 46-max 640). The ideal cut -off value that predicted disease-free survival was 153 in the ROC analysis [AUC:0.82 (0.72-0.91)/$p<0.00$] with a sensitivity of 78%, and specificity of 74 %. Median DFS was 42 months in patients with PLR <153, 26 months in patients with ≥153 ($p=000$) (Fig. 1 a-d).

Univariate Cox proportional hazards regression analysis showed that pathologic stage, grade, NLR, PLR, and SII had statistically significant associations with disease-free survival. In multivariate analysis demonstrated that PLR was a significant independent prognostic parameter for DFS, whereas NLR and SII were not. The univariate and multivariate analysis results related to disease-free survival were shown in Table 2.

Table 1. Demographic and clinicopathological findings

	n (%)
Gender	
Male	55 (69)
Female	25 (31)
Tumor localization	
Proximal	19 (2)
Middle	34 (42)
Distal	31 (39)
Pathology	
Adenocarcinom	75 (94)
Mucinous adenocarcinoma	5 (7)
Neodjuvant chemotherapy	
5 flouracil	35 (44)
Capesitabine	45 (56)
Pathologic yT Stage	
T 0	5 (7)
T1	14 (17)
T2	25 (31)
T3	36 (45)
Total Lymph Node Excision (Median)	18 (min 5 -max 32)
Pathologic yNode Stage	
N 0	42 (52)
N1	11 (13)
N2	27 (35)
Grade	
Well	48 (60)
Moderately	12 (15)
Poorly	20 (25)
Adjuvan Chemotherapy	
Capesitabine	9 (11)
FUFA	11 (14)
CapeOX	36 (45)
FOLFOX	24 (30)
Relapse	
Yes	42 (52)
No	38 (48)
Relaps Patern	
Local	18 (43)
Visceral	24 (57)

Discussion

Our study is a report describing the prognostic models based on peripheral neutrophil, platelet, and lymphocyte counts. We demonstrated that elevated SII, NLR, and PLR were correlated with poor disease-free survival. But only elevated PLR was found independent prognostic factor compared to NLR and SII by multivariate analysis. Inflammatory-based indices such as NLR and PLR related to poor tumor behavior and disease-free survival outcome in various malignant solid tu-

Table 2. Cox-regression model of Disease-free survival (DFS) in Rectum Cancer

	Median DFS (months)	Univariate Analysis				Multivariate Analysis			
		HR	95% CI		P	HR	95 % CI		P
			Lower	Upper			Lower	Upper	
Gender									
Female (n=25)	28	0.79	0.36	1.37	0.31				
Male (n=55)	31								
Grade									
Poorly (n=20)	16	3.09	1.65	5.79	0.00	3.01	1.6	5.68	0.01
Well-intermediate (n=60)	33								
T stages									
Stage 0-2 (n=44)	38	2.61	1.37	4.97	0.03				
Stage 3 (n=36)	28								
Lymph nodes									
N 0 (n=42)	42	2.54	1.28	4.66	0.06				
N 1-2 (n=38)	28								
Adjuvant treatment									
Capeox/Folfox (n=60)	29	2.1	0.9	4.75	0.06				
FUFA/Capesitabine (n=20)	42								
NLR									
<1.74 (n=32)	42	4.98	2.19	11.3	0.01				
≥1.74 (n=48)	27								
PLR									
<153 (n=37)	42	5.2	2.47	11.07	0.00	5.1	2.44	10.98	0.00
≥153 (n=43)	26								
SII									
<498 (n=37)	42	3.92	1.87	8.2	0.00				
≥498 (n=43)	26								

mors were defined in the literature.[20, 21]

Hu et al.[17] defined that systemic inflammation index related to prognosis in patients with hepatocellular carcinoma. In later studies, SII has been reported to be a predictive index for survival in patients with esophageal cancer, metastatic renal cell carcinoma, and small cell lung cancer.[22-24] Chen JH et al. showed the prognostic value of NLR, PLR, and SII in patients with colorectal cancer. The optimal cut-off point for SII, NLR, and PLR was calculated as 340, 2.7, and 210 respectively. The overall survival (OS) and disease-free survival (DFS) were worse in patients with elevated NLR, PLR, and SII. But only SII was found an independent predictor of OS and DFS by multivariate analysis. In this study, researchers concluded that SII was a more powerful index for predicting survival outcome in patients with colorectal cancer.[18] In a study published in October 2018, The prognostic significance of the systemic immune-inflammation index was evaluated in patients with metastatic colorectal cancer and the relationship between the tumor-infiltrating lymphocytes (TILs) and SI index. Researchers founded that a high SII was independently related to poor overall survival and also, it was significantly correlated with the tumor-infiltrating lymphocytes value at the tumor's center. As a result, it was reported that patients with low TIL and high SII value had a poor prognosis in this study.[25] Another trial, Yang et al. evaluated systemic inflammation index as a predictor factor for survival in patients with colorectal cancer who received neoadjuvant chemoradiotherapy. The optimal cut-off point for SII, NLR, and PLR was calculated as 437.72, 2.22, and 114.15 respectively. Conversely, SII has been not shown an independent predictor index for survival. In this study, researchers reported that NLR as an independent predictor index for survival.[19] In our trial, we did not find SII as an independent predictive index for disease-free survival. Unlike the other two studies, we found PLR to be an independent prognostic factor for DFS.

There are several meta-analyses or review which have reported the prognostic value of PLR on survival for various tumors including colorectal cancer. In a meta-analysis, Zhou et al.[26] showed that PLR was a negative predictive

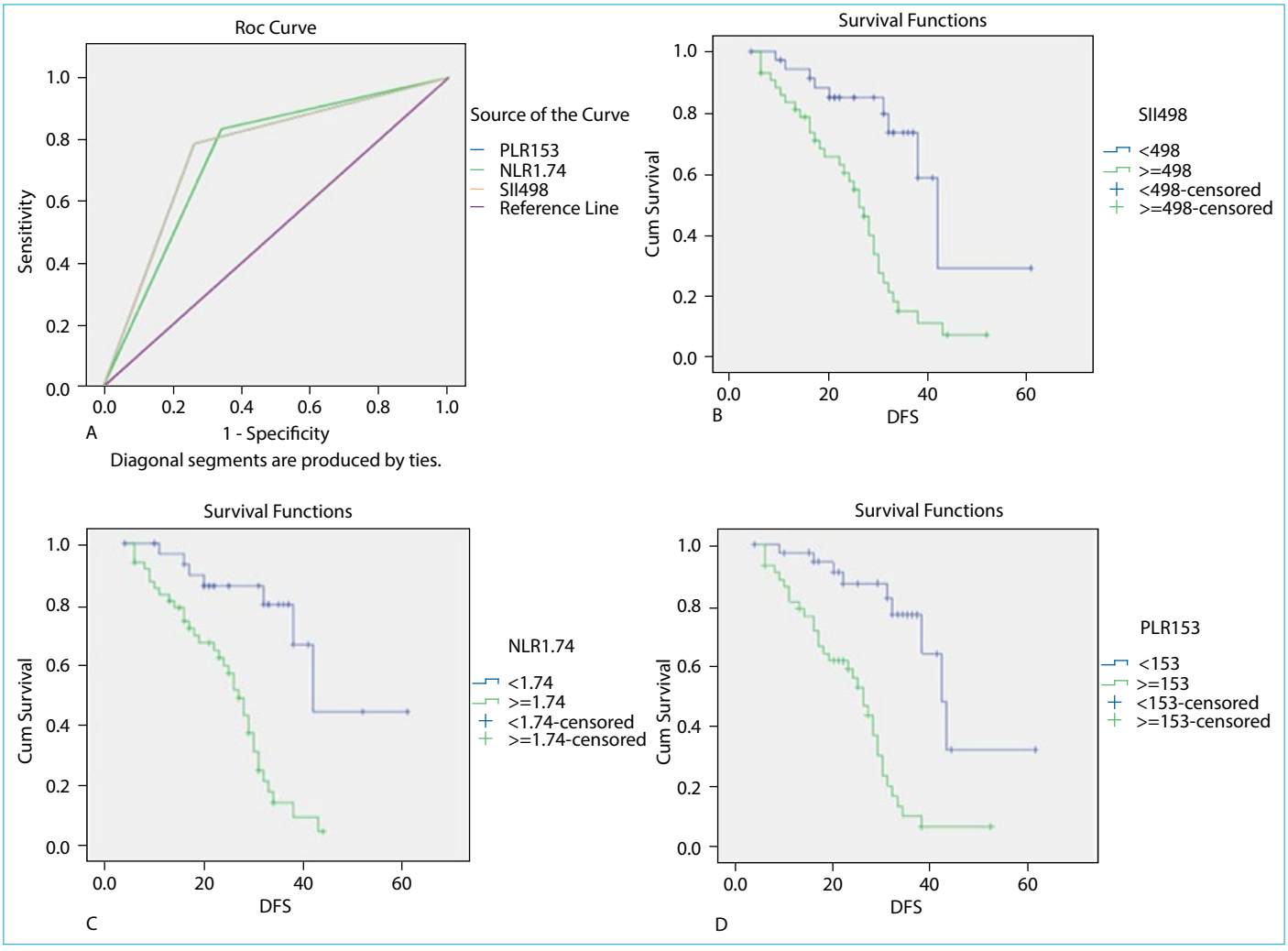

Figure 1. (a) Ideal cut-off values ROC curve analysis; **(b)** Disease Free Survival Graphic According to SII 498 by Kaplan Meier; **(c)** Disease Free Survival Graphic According to NLR 1.74 by Kaplan Meier; **(d)** Disease Free Survival Graphic According to PLR 153 by Kaplan Meier.

factor for overall survival in gastrointestinal cancer, ovarian cancer, and non-small cell lung cancer. In another two meta-analyses by Gue et al.[27] and Huang et al.[28] reported that the prognostic value of PLR to overall survival and disease-free survival in patients with colorectal cancer. Cuadrado et al. in a study with colorectal patients who underwent curative surgery, showed that a high PLR was associated with a poor prognosis in term of overall survival and relapse-free survival.[29] It has also been reported that PLR can predict the response to treatment in head and neck cancer.[30] In contrast, in a recently published study, no prognostic significance of PLR was found in early-stage resected small cell lung cancer patients.[31] In the current study, similar to the literature, we found that elevated PLR was related to poor prognosis for the term of DFS in resected rectal cancer after neoadjuvant treatment.

There were some limitations to this study. First, the relatively low number of patients may be cause selection bias. Second, we did not report the relationship between the inflammatory index and overall survival. This situation may be a negative feature of our study compared to other studies. As a positive point, we included patients with rectal cancer who underwent curative surgery after neoadjuvant therapy. Also, we excluded patients who had confounding factors such as smoking, hyperlipidemia, the presence of active infection disease, and hepatosplenomegaly from the study. And therefore, in our study, we showed that the prognostic value of inflammatory-based indices in the more specific patient's population.

Conclusion

In conclusion, to our knowledge, this is the first retrospective study in patients with resected rectal cancer after neoadjuvant treatment which reports that PLR (<153) may be a prognostic indicator for longer DFS. On the other hand, we could not show that the prognostic value of SII and NLR

in these patients. Our results are limited due to the small number of patients in our study. Therefore, further investigations with had large scale are required to validate these results.

Disclosures

Ethics Committee Approval: Ethics/institutional review board approval of research Faculty of Medicine, Acibadem University, Istanbul, Turkey (Number: 2019-18/10 Date: 21.11.2019).

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