Original Article

Prognostic significance of systemic inflammatory markers in rectal cancer

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Abstract

Aim: The neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR), which is indicators of systemic inflammatory response, have been demonstrated to be prognostic factors in many types of cancer. The aim of this study was to investigate importance of NLR and PLR in rectal cancer.

Materials and Methods: The data of 114 patients who underwent curative resection after neoadjuvant chemoradiotherapy (NACRT) for rectal cancer (RC) between January 2012 to June 2017 and 113 healthy subjects were retrospectively analyzed. Blood samples obtained prior to NACRT were examined. The NLR and PLR in RC patients were compared with the results of healthy individuals.

Results: The distribution of NLR and PLR results was significantly different between the RC patients and the control group (p<0.001 for both). According to the ROC curve, the cut-off value for NLR was 2.70 and for PLR it was 151.18 in estimating the survival of the patients. NLR and PLR only correlated significantly with tumor wall involvement (T stage). The Kaplan-Meier method of predicting survival revealed no significant difference between groups with increased or decreased NLR and PLR in terms of overall survival (OS) and disease-free survival (DFS).

Conclusion: The NLR and PLR of the study group treated with NACRT and those of the control group were significantly different. However, elevated NLR and PLR before NACRT were not found to be significant prognostic biomarkers for OS and DFS in surgically treated RC patients.

Keywords: Neutrophil-lymphocyte ratio; platelet-lymphocyte ratio; rectal cancer; systemic inflammatory indicators

INTRODUCTION

According to the GLOBOCAN 2018 data colorectal cancers (CRC) are still the third leading cause of mortality and fourth most commonly diagnosed cancer in the world despite significant advances in early diagnosis, surgical techniques, and adjuvant treatments (1). Curative resection of rectal cancer (RC) is the mainstay of treatment and patients with nonresectable RC have a relatively shorter life expectancy (2).

The conventional prognostic factors, such as TNM staging, tumor type, tumor grade, presence of perineural and lymphovascular invasions, and Dukes classification, are used to predict the survival of patients with RC (3). However, these parameters are are not always reliable, even if the patients are at the same disease stage (4). Hence, there is a search for new methods to estimate the prognosis more accurately.

Studies have shown that cancer progression is associated with both the tumor itself and the systemic inflammatory response (5). The systemic inflammatory response occurs by an increase in neutrophil level and a decrease in lymphocyte levels in the peripheral blood. It has been reported that a higher neutrophil concentration accelerates tumor progression and suppresses the antitumor effect of lymphocytes (6).

Blood neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) values, which are indicators of systemic inflammatory response, were shown to be correlated with survival in many cancers, such as renal, gastrointestinal, lung and ovarian cancer (7-10). Several studies on CRC have showed that increased NLR and/ or PLR values are independent factors that indicate an adverse prognosis (11,12).

The purpose of the study was to contribute to the clarification of this ambiguity.

MATERIALS and METHODS

Two groups were formed of patients from the period between January 2012 and June 2017. Patients operated for rectal adenocarcinoma (Group 1) and healthy individuals (Group 2). The medical records of the individuals were examined retrospectively. Patients with metastatic disease, synchronous tumors, clinically manifest infection, hematological disease, chronic renal failure, heart disease, and patients without complete blood test results from before the initiation of neoadjuvant chemoradiotherapy (NACRT) were excluded from the study. Patients without a histological confirmation of disease were also excluded. Ethics committee of Kartal Training and Research Hospital approved this study (IRB number: 2018/514/134/4).

Information concerning the patients' age; gender; tumor size; pathology; total and positive number of lymph nodes; tumor TNM stage; blood count of neutrophils, lymphocytes and platelets before NCRT; and pathology data were retrieved from the hospital automation system and patient files. Blood values from all of the patients were based on the results of blood samples obtained within 2 weeks before the start of NCRT, since chemoradiotherapy (CRT) can affect blood levels.

At 3-month intervals, all the patients in this study were treated with a total of 45 grays (Gy) of radiation delivered as daily doses of 1,8 Gy for 5 weeks and with 5-fluorouracil-based CRT as a continuous infusion during radiotherapy for 5 weeks, and standardized total mesorectal excision was performed 6 to 8 weeks after CRT (14). Histopathological staging was performed according to the American Joint Committee on Cancer Staging Guidelines (15). Complete pathological response was evaluated as complete disappearance of the primary tumor. Adjuvant chemotherapy was routinely performed in pathologically positive patients, while node-negative patients were treated according to the discretion of the surgeons and the oncologists.

After the surgery, the patients were followed up at 3 months intervals for the first 2 years, then every 6 months. Serum carcinoembryonic antigen values were checked at each visit. Local and distant recurrences were identified using chest and abdominal computed tomography scanning at intervals of six months, and a total colonoscopy was performed first year, and every 2 years. OS was defined as the time from the date of surgery to the date of death, or until June 30, 2017. DFS was defined as the time period from surgery to tumor recurrence, a second cancer, or all-cause death.

Statistical analysis

The frequency, percentage, means, SD, median, and lowest and highest values were used in descriptive statistical methods. In pairwise comparisons between groups, an independent t-test was used for variables with a normal distribution, and the Mann-Whitney U test for variables without a normal distribution. To compare categorical variables chi-square test was used. In addition, receiver operating characteristic (ROC) analysis was conducted to determine cut-off values for NLR and PLR. Length of survival analysis was performed using the Kaplan-Meier method and intergroup comparisons were evaluated using the logrank test. The results were evaluated with a significance level of $p<0.05$.

RESULTS

Clinicopathological characteristics

We retrospectively reviewed the records of a total of 227 patients: 114 patients who underwent curative resection and received NACRT due to RC (male: n=69, 61.06%; female: n=45, 38.94%) and 113 healthy individuals who came for routine check-up. The mean age at diagnosis was 61.7 years (±11.59 years). Eighty-seven (76.3%) patients had tumors <4 cm in diameter, while 27 (23.7%) patients had tumors >4 cm in diameter.

Eight (7.02%) of 114 patients had a recurrence. The median length of time between surgery and recurrence was 195 days (range: 15-969 days). The distribution of NLR and PLR in RC patients was compared with 113 healthy individuals and there was a significant difference ($p<0.001$ for both) (Table 1).

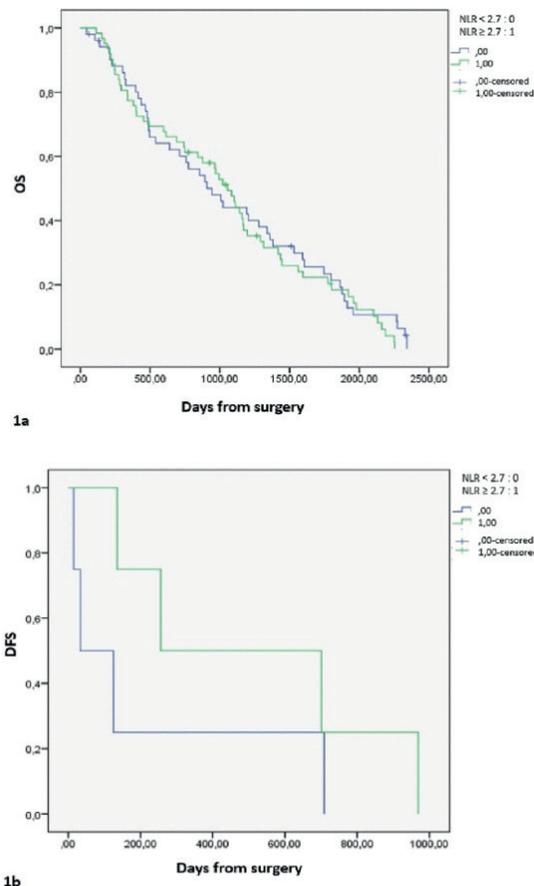| Table 1. Demographic characteristics of the participants			
	Control (n=113)	Rectal Cancer (n=114)	p
Age(years)	62.00±11.77	61.76±11.59	0.878*
Gender			
Male	69 (61.06)	69(61.06)	1.000**
Female	44 (38.94)	45 (38.94)	
NLR	2.76 (0.22-55.15)	1.76 (0.55-5.96)	<0.001***
PLR	181.70 (29.39-2000.00)	109.58 (49.19-366.00)	<0.001***

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio
*Student's t-test; ** Chi-square test; *** Mann-Whitney U test
Data are expressed as mean±SD, n (%), and median values (min-max)

The median length of the follow-up period was 32 months (min-max: 2-78 months). According to the ROC curve, the cut-off values to estimate survival for NLR and PLR were 2.70 and 151.18. The NLR value of patients with RC was lesser than 2.7 in 52 (45.6%) cases and ≥ 2.7 in 62 (54.4 %) cases. The PLR value was < 151.18 in 49 (43%) patients and ≥ 151.18 in 65 (57%) patients. The RC patients were grouped according to some characteristics and the cut-off values in Table 2. The NLR and PLR only correlated significantly with tumor wall involvement (T stage) (p=0.008 and p=0.013, respectively); no significant relationship was found between NLR and PLR and other factors.

Table 2. Characteristics of the patients with rectal cancer according to the NLR and PLR cut-off values						
	NLR			PLR		
	<2.70 (n%)	≥2.70 (n%)	p*	<151.18 (n%)	≥151.18 (n%)	p*
Age groups			0.335			0.193
≤ 60 years	23 (44.2)	31 (50.0)		26 (53.1)	28 (43.1)	
>60 years	29 (55.8)	31 (50.0)		23 (46.9)	37 (56.9)	
Gender			0.496			0.475
Male	32 (61.54)	37 (59.7)		29 (59.2)	40 (61.5)	
Female	20 (38.46)	25 (40.3)		20 (40.8)	25 (38.5)	
T stage			**0.008**			**0.013**
T0, T1, T2	32 (61.54)	23 (37.1)		30 (61.2)	25 (38.5)	
T3, T4	20 (38.46)	39 (62.9)		19 (38.8)	40 (61.5)	
N stage			0.323			0.258
N0	43 (82.69)	48 (77.4)		41 (83.7)	50 (76.9)	
N1, N2	9 (17.31)	14(22.6)		8 (16.3)	15 (23.1)	

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio.
*Chi-square test

Survival analysis

Survival curves of Kaplan-Meier were used to investigate whether the NLR and PLR were prognostic factors during the follow-up of nonmetastatic patients who received curative resection after NACRT. Kaplan-Meier curves for OS with high and low NLR/PLR values are shown in figures 1a and 2a. There was no significant difference in OS between the groups with high and low NLR and PLR values (p=0.498 and p=0.765, respectively; logrank test).

The Kaplan-Meier curve that evaluated DFS of 8 (n=8/114: 7.02%) patients with recurrence developed during the follow-up period based on NLR/PLR values is shown in figures 1b and 2b. No significant differences were found between the groups in terms of DFS according to NLR and PLR values (p=0.241 and p=0.553, respectively; logrank test).

2a

2b

OS: Overall survival; DFS: Disease-free survival; PLR: Platelet-lymphocyte ratio

Figure 2. Kaplan−Meier curves depicting OS (a) and DFS (b) according to PLR status
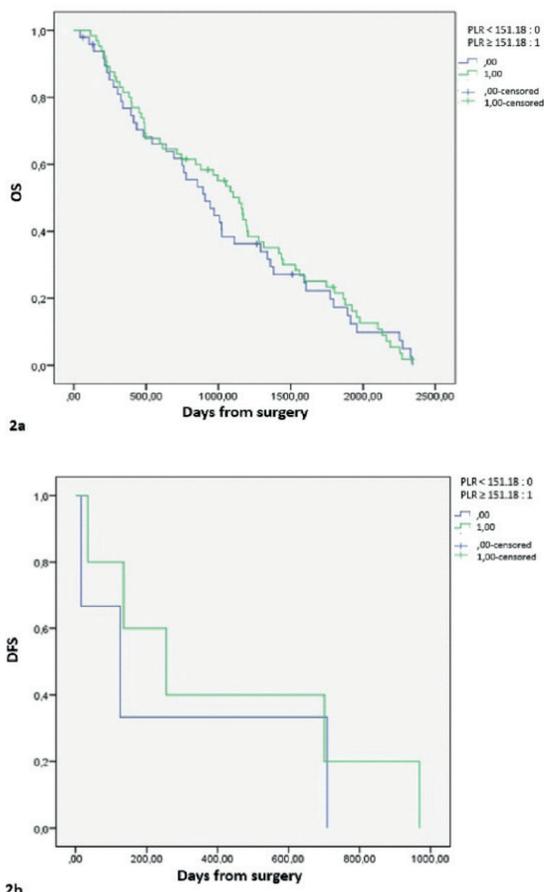

1a

1b

OS: Overall survival; DFS: Disease-free survival; NLR: Neutrophil-lymphocyte ratio

Figure 1. Kaplan−Meier curves depicting OS (a) and DFS (b) according to NLR status

DISCUSSION

Recently, RAS/RAF mutations or proteins involved in cell cycle, angiogenesis and apoptosis have been reported as prognostic factors for RC (16). But, the high cost and difficulty in processing have hampered the practical use of these parameters. There is a growing recognition of the importance of inflammation in determining the progression of many cancers as well as survival (17). The

inflammation will be progress according to progression of tumor due to necrosis of ischemic part, invasion of adjacent mesenchymal tissue, and response of immune system. The inflammatory process would be a findings of progression of disease. The inflammatory response is measured using parameters such as neutrophils, platelets, lymphocytes, and C-reactive protein, which is the acute phase reactant. Evaluating these parameters is both cheaper and easier. Studies have shown that the increase in NLR is significantly related with a poor prognosis in various cancer types (18).

In this study, mean lymphocyte level was 2.230 /mm3 for healthy individuals (Group 2), 1.814 /mm3 for rectal adenocarcinoma (Group 1) , mean platelet level 240.52/ mm3 for healthy individuals (Group 2), 287.48 /mm3 for rectal adenocarcinoma (Group 1). In addition to this, mean neutrophil level 3.921/mm3 for healthy individuals (Group 2), 4.657 /mm3 for rectal adenocarcinoma (Group 1) and all of these parameters were statistically significant.

Neutrophil-like inflammatory factors are important in tumor proliferation, invasion, induction of angiogenesis, and the production of many ligands leading to tumor cell proliferation (19). Lymphocytes are helpful in tumor suppression (20). A reduction in the lymphocyte count may result in a poor prognosis by destroying the antitumor immunoreactivity of the host (21). Although the importance of the interaction between platelets and tumors is not fully understood, platelet-derived proangiogenic mediators released from endometrial vascular structures may be important in tumor progression (22).

Many of the proinflammatory mediators can stimulate megakaryocyte proliferation, i.e. an increased platelet count may be an additional indicator in the evaluation of inflammatory response (22). Although NLR and PLR are prognostic factors for RC, very limited numbers of studies were conducted on the preoperative prognostic role of NLR and PLR in patients with RC.

These blood parameters are indicators of systemic inflammatory response, and associated with survival in lung, renal, gastrointestinal, and ovarian cancer (7-10). Many studies have shown that increased NLR and PLR may be independent negative prognostic indicators in CRC (11). RC has specific physiological and pathological features when compared with colon cancer.

NLR, which is associated with survival in patients with RC, has been shown to be a better prognostic factor than PLR (14). Another study demonstrated that a high NLR was not associated with DFS, despite being independently associated with a poorer rate of OS (12). Increased NLR values in RC patients treated with surgery after NACRT have been reported to be independently associated with OS, but not with DFS in patients followed up for 31 to 39 months (23,24). Rashtak et al. concluded that increased NLR values were not related to OS or DFS (13).

In our study, we evaluated 114 RC patients who received NACRT. According to the ROC curve, the cut-off value for the estimation of survival of the patients was 2.70 for NLR and 151.18 for PLR. High NLR and PLR values were only significantly correlated with tumor wall involvement (T stage) (p=0.008 and p=0.013, respectively). However, there was no significant relationship between increased NLR and PLR values and OS or DFS. The median follow-up period was 32 months (min-max: 2-78 months). The cut-off values used in other studies that evaluated RC patients who underwent NACRT were 2.8, 3.0, and 5.0 (14).

Carruthers et al. found that a high NLR (≥ 5.0) was independently associated with OS and a shorter DFS in their series of 115 patients (25). In that study, the cut-off value of 5.0 was selected for NLR, but the rate of high and low NLR values in the patients was not documented. According to the ROC curve in our study, 62 (54.4%) patients had an NLR value of ≥ 2.7, and the PLR value of 65 (57%) patients was ≥ 151.18. The difference in this cut-off value may be associated with a different population or using a different hemogram device. Further research is needed to determine an adequate cut-off value with optimal specificity and sensitivity in order to accurately predict the prognosis.

Uncertainty about NLR and PLR use in RC remains, however, due to the limited and contradictory results seen in the literature. RC has specific physiological and pathological features relative to colon cancer. Our results may not be similar to those of other studies as a result of differences in diagnostic research performed to determine the need for neoadjuvant therapy, the adequacy of the total mesorectal excision, the competency of the surgeons performing the resection, or the presence of other factors that may have affected the outcomes. Some authors have concluded that there is no specific relationship between NLR and tumor response to NACRT (25). NACRT contributes to the prevention of local recurrence, which may have an impact on these outcomes. However the reason for this is not yet clear.

Our study has some potential limitations. The number of patients was relatively small as it was a single-center study. The statistically insignificant correlation between NLR/PLR and DFS might be related to the small number of recurrences seen in only 8 (7.02%) of 114 patients. Different cut-off values for NLR/PLR have been determined in various studies. Therefore, larger-scale studies should be performed to determine the optimal value. It should also be noted that the host disease can easily be affected by accompanying diseases during blood sampling, which may lead to errors in the results (26).

CONCLUSION

In conclusion, NLR and PLR values were significantly different in RC patients treated with NACRT than in the control group. However, NLR and PLR that were elevated

before NACRT were not found to be significant prognostic biomarkers for OS and DFS in surgically treated patients.

Due to the small sample size used in our study, the power is limited and it is possible that NLR and PLR do not predict the results for RC patients. Further studies are needed to determine the relationship between NLR and PLR and the prognosis of RC patients who received NACRT.

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