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Importance of preoperative hematological parameters in patients undergoing surgical resection for colorectal cancer

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ABSTRACT

Objective. Colorectal cancer has a high prevalence worldwide, and new predictive and prognostic factors are needed for its early diagnosis, treatment, and follow-up. In this study, we have investigated the relationship between colorectal cancer and neutrophil to lymphocyte ratio (NLR), mean platelet volume (MPV), and platelet to lymphocyte ratio (PLR) values. ***Methods.*** Data from 71 patients admitted to our hospital between May 2013 and May 2015, who underwent surgical resection for colorectal cancer, and met the criteria of the study, was evaluated retrospectively. NLR, MPV and PLR data detected in the preoperative period was noted. Demographic data, the presence of comorbidity, colonic localization of the tumor, colonoscopic findings, and surgical resection type and method were compared with the data of morbidity and mortality, lymphovascular and perineural invasion, lymph node and distant metastasis and stage of the disease. ***Results.*** No statistical significance was detected between preoperative NLR, MPV, and PLR, demographical data, the presence of comorbidity, colonic localization of the tumor, colonoscopic findings, surgical resection type and method and morbidity, lymph node and distant metastasis, lymphovascular invasion, or stage of the disease. However, a statistically significant relationship was detected between mortality development and NLR and PLR values (p=0.030; p=0.043; respectively). There was also a statistically significant relationship between the presence of perineural invasion and PLR (p=0.031). ***Conclusion.*** Hematological parameters (NLR, MPV, and PLR) evaluated in preoperative period in patients who have been applied surgical resection for colorectal cancer may help clinical and pathological staging.

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Keywords: Colorectal cancer, surgery, mean platelet volume, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio

Introduction

Colorectal cancer is common worldwide and an important cause of cancer-related deaths [1]. Despite recent advances in treatmentsavailable for patients with colorectal cancer, such as curative resections, chemotherapy, and radiotherapy, 5-year survival rates rangebetween 44% and 93%, decreasing to 12% in patients with advanced stages of the disease [2]. Despite similarclinical phases and pathological

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features, diversity in the biology of the tumor results in different oncologicaloutcomes for colorectal cancer patients.

Alternative treatments and prognostic evaluation may improve as weknow that angiogenesis and the stromal microenvironment, including inflammation in the body,play an important role in tumor progression and metastasis development [3]. Commonly used biomarkers such as fecal occult blood test(used in diagnosis in the preoperative and postoperative follow-up periods); carcinoembryonic antigen (CEA); and carbohydrate antigen (CA-19.9) have low sensitivity for colorectal cancer and are not specific to the organ [4]. Subsequently, there is a real need formore efficient biomarkers,useful for both early diagnosis and predictingtreatment effectiveness. We have focused on biomarkers that are low-cost, highly efficient, sensitive in the preoperative period, beneficial in clinical usage, and with both prognostic and predictive features. Prognostic biomarkers such as neutrophil to lymphocyte ratio (NLR), mean platelet volume (MPV), and platelet to lymphocyte ratio (PLR) may have strong predictive and prognostic features which can be used in addition to classical pathological staging [5, 6].

In our study, we have retrospectively evaluated the data of colorectal cancer patients who underwenta resection operation; investigating the relationship between systemic inflammatory and hematological parameters detected in the preoperative period (NLR, MPV, and PLR), and patient characteristics and tumor histopathological features.

Methods

Study design and patients

The data of 84 colorectal cancer patients who were admitted to Bursa Yuksek Ihtisas Training and Research Hospital between May 2013 and May 2015 was evaluated retrospectively. Thirteen patients were excluded from the study: these were patients with systemic inflammatory or hematologic disease; patients using anticoagulant drugs; those undergoing emergency operations; those with missing data; and patients operated on for recurrent tumors. Data from the remaining 71 patients who had undergone elective surgical resection and who met the study criteria was evaluated. The following data was taken into consideration: NRL, MPV, and PLR values of the patients detected in the preoperative period; demographic data; presence of comorbidities; colonic localization of tumor; colonoscopic findings; type of surgical resection and method applied; morbidity and mortality; lymph node and distant metastasis; lymphovascular and perineural invasion; and the stage of disease.

A complete blood count was measured on the day previous to the operation, and NLR, MPV, and PLR values were noted. The NLR value was calculated by dividing the neutrophil count by the lymphocyte count. The PLR value was found by dividing the platelet value by the lymphocyte value. The MPV was measured automatically in the complete blood count. All colorectal cancer patients were given oral, enteral supplements and a liquid diet in the preoperative period. Neoadjuvant chemotherapy and radiotherapy were used primarily in patients with a locally advanced stage rectal tumor. No extra preoperative evaluation or postoperative care was employed and mechanical bowel preparations were not used.

Surgical Technique

Low anterior resection (LAR), right or left hemicolectomy, or abdominoperineal resection (APR) were the three types of resection used. In some cases, laparoscopic surgery could not be performed for technical reasons, or in patients with a previous intraabdominal operation history. Laparoscopic surgery, open surgery and a third group of conversion surgery that included patients with a transition from laparoscopic operation to open surgery were defined as our three resection methods. Hybrid attempts were not used in laparoscopic methods. An ostomy was opened in patients with a history of radiotherapy in the rectal area or with anastomosis localized in the lower rectum.

In this study, AJCC (American Joint Committee on Cancer) and TNM (T tumor, N node, and M metastasis) classifications were used for postoperative histopathologic and clinical evaluations for staging.

Statistical Analysis

In our statistical analysis, data was analyzed with SPSS for Mac version SPSS 20.0 (Inc., Chicago, IL) Software Package. Mann-Whitney U test, Kruskal-Wallis H test, and Spearman Correlation Coefficient methods were used to determine the significant difference. The variables of gender, comorbidity, preoperative metastasis, colonoscopic findings, morbidity, mortality, lymph node metastasis, lymphovascular invasion and perineural invasion were analyzed using Mann-Whitney U test as there was not a normal distribution. Kruskal-Wallis H Test was used

Table 1. Patient demographic and clinic characteristics

	n	%	*p* NLR	*p* MPV	*p* PLR
Age (years)					
n, mean(range)	71	63.6 (35-83)	0.545*	0.957*	0.392*
Sex	F :25	35.2%			
	M :46	64.8%	0.380	0.077	0.962**
Tumor localization					
Right colon	16	22.5%			
Left colon	26	36.6%			
Rectum	29	40.8%	0.270	0.388	0.253***
Comorbidity					
(+)	44	62%			
(-)	27	38%	0.281**	0.995**	0.962**
Preoperative metastasis (+)	5	7%	0.608**	0.623**	0.350**
Permeation in colonoscopy					
Narrowing	39	54.9%			
Normal	32	45.1%	0.799**	0.917**	0.908**

F=female, M=male, NLR=neutrophil lymphocyte ratio, MPV=mean platelet volume, PLR=platelet lymphocyte ratio
* Spearman Correlation Coefficient, ** Mann-Whitney U, ***Kruskal-Wallis H methods

for the analysisof variables comprising tumor localization, operation type, and technique, tumor differentiation and stage, which were not normally distributed, and the Spearman Correlation Coefficient test was used forage and tumor diameter variables, also not normally distributed. In the case of non – normal distribution, Mann-Whitney U test replaced the t-test, Kruskal-Wallis H Test replaced Analysis of Variance (ANOVA), and Spearman Correlation Coefficient was used instead of Pearson Correlation Coefficient. *p* values less than 0.05 were considered as statistically significant.

Results

The data of 71 colorectal cancer patients undergoing resection was evaluated. In the study, the NLR median was 2.92 (min: 1.27, max: 54.54); the MPV median was 8.9 (min: 7.30, max: 12.10); and the PLR median came out as 178.57 (min: 6.91, max: 302.27).

Patient characteristics, tumor localization, the presence of comorbidities, preoperative metastasis, and colonoscopic findings were compared with NLR, MPV, and PLR median values;with the statistical results shown in Table 1. Operation type and method, morbidity and mortality values were also compared with NLR, MPV, and PLR median values, and these statistical results are given in Table 2. The most common operation was lower anterior resection (59.1%), and a statistically significant relationship was detected between PLR and this type of operation (*p*=0.040). During the postoperative period, morbidity

Table 2. Operation type and method, morbidity and mortality values; statistical relationship of the data with NLR, MPV, and PLR

	n	%	*p* NLR	*p* MPV	*p* PLR
Operation type					
LAR	42	59.15%			
APR	6	8.45%	0.245**	0.477**	**0.040****
Right Hemicolectomy	16	22.53%			
Left Hemicolectomy	7	9.85%			
Operation technique					
Laparoscopy	32	45.1%			
Open	28	39.4%	0.991**	0.597**	0.667**
Conversion	11	15.5%			
Morbidity (+)	24	33.8%	0.504*	0.733*	0.884*
Mortality (+)	3	4.2%	**0.030***	0.777*	**0.043***

NLR=neutrophillLymphocyte ratio, MPV=mean platelet volume, PLR=platelet lymphocyte ratio, LAR=low anterior resection, APR=abdominoperineal resection *Mann-Whitney U, **Kruskal-Wallis H methods.

Table 3. AJCC (American Joint Committee on Cancer) TNM staging during and following histopathologic evaluation

	n	%	*p*		
			NLR	MPV	PLR
Tumor differentiation					
Good	53	74.6%			
Bad	14	19.7%	0.989***	0.485***	0.400***
High Grade Dysplasia	4	5.6%			
Tumor diameter (mm)					
n, mean (range)	71	52.14 (10-150)	0.136*	0.417*	0.232*
Lymph metastasis (+)	40	56.3%	0.945**	0.245**	0.954**
Lympho-vascular invasion (+)	14	19.7%	0.885**	0.602**	0.840**
Perineural invasion (+)	11	15.5%	0.253**	0.799**	0.031**
Stage					
1	16	22.53%			
2	16	22.53%	0.927***	0.675***	0.981***
3	34	47.88%			
4	5	7.06%			

NLR=neutrophil lymphocyte ratio, MPV=mean platelet volume, PLR=platelet lymphocyte ratio
*Spearman Correlation Coefficient, **Mann-Whitney U, ***Kruskal-Wallis H methods

developed in 24 (33.8%) patients with the most common causes being wound infection in 9 (12.6%)patients; subileus in 4 (5.6%)patients; and anastomosis leakage in one (1.4%) patient. Mortality was seen in three (4.2%) patients, with statistically significant relationships between mortality and NLR, PLR (p=0.03; p=0.043 respectively). Mortality developed in one (1.4%) patient due to fulminant liver metastasis, one (1.4%) due to necrotizing fasciitis and one (1.4%) due to myocardial infarction during the postoperative period. While the NLR median was found to be 2.90 (min: 1.27, max: 54.5) and the PLR median to be 175.44 (min: 6.91, max: 302.7) in patients without mortality, the NLR median climbed to 7.29 (min: 4, max: 7.35) and the PLR median to 332.43 (min: 214, max: 361.53) in patients with mortality.

Histopathologic evaluation with NLR, MPV and PLR is statistical relationship given in Table 3. Perineural invasion was detected in 11 (15.5%) patients, and a statistically significant relationship was found between this invasion and the PLR value (p=0.031).

Discussion

The main factors determining the progression of the disease and survival in cancer patients are the tumor's characteristics and the host's immune response [7]. Chronic inflammation increases the risk of colon cancer development by affecting carcinogenesis at different stages [8]. It has been shown that host or immune response can be evaluated as an important prognostic indicator in addition to TNM staging [9].

Lymphocytes and neutrophils play important roles in systemic inflammatory response. As the NLR is found by dividing the number of neutrophils by lymphocyte values, an increase in the NLR may be linked to an increase in the number of neutrophils or a decrease in the lymphocyte number. High NLR levels have been shown to be not only an indicator of inflammation in different cancer types but also an independent prognostic factor for short survival, with various threshold values reported [7, 10]. In colorectal cancer, it is reported that NLR>5 [10]. Another study describes NLR>3 as a negative independent prognostic factor for disease-free survival in colorectal cancer patients [11]. A significant relationship between high NLR values, and advanced age and high T-stage has also been mentioned. It has been reported that a NLR>2.5 value in colorectal cancer patients aggravates cancer-specific survival; NLR>4 negatively affects disease-free survival as an independent factor, and it may be used to distinguish patients for adjuvant chemotherapy in stage IIA [12]. In a study involving 243 patients, it was shown that preoperative NLR and PLR values statistically and significantly decrease general survival [13]. In colorectal cancer patients, although NLR has a prognostic value, a standard cut-off value has clearly not yet been determined [14]. In our study, the NLR value was found to be statistically related only to mortality (p=0.030).

MPV is measured automatically with either

electrical impedance or optic fluorescence methods [15]. MPV activated platelet index is used in evaluating disease activity and the effectiveness of anti-inflammatory treatment [16]. Moreover, it is indicated as a diagnostic marker in hepatocellular carcinoma and pancreas cancers [17, 18]. The role of MPV in the diagnosis and treatment of colorectal cancer could not be completely revealed. In our study, the median MPV value was 8.90 (min: 7.30, max: 12.10). Any relationship with patient and tumor characteristics in the preoperative period, postoperative surgical period or histopathologic examination could not be determined.

Platelets have important duties in hemostasis, inflammation and tissue repair [19]. Activated platelets play an important role in cancer metastasis with the cytokines they secrete, chemokinesis and adhesion receptors [20]. Moreover, activated platelets cause thrombosis development and then mortality as they cause coagulation [21]. Also, the usage of antiplatelet drugs has been seen to inhibit the invasion of tumor cells [22]. PLR values vary between 150 and 300 in colorectal cancer patients [23]. In our study, we found the median PLR value to be 178.57. This high PLR is shown as an independent predictor factor regarding T stage (tumor invasion depth) in colorectal cancer patients [24]. It is reported that high PLR values are an independent factor in decreasing general survival in colorectal cancers, and can shorten the recurrence time [25, 26]. In a study involving 200 patients, preoperative high PLR values were an independent factor for decreased general survival, and had a significant relationship with metastatic positive lymph nodes [26]. In our study, a statistical relationship was detected regarding our PLR values and both mortality and perineural invasion positivity (p=0.043, p=0.031, respectively).

The Limitations of the Study

There are certain limitations to our study. Evaluation of the data of a small group of 71 patients, absence of randomization, retrospective assessment of the data and non-evaluation of survival may be listed as examples of these limitations.

Conclusions

NLR, MPV, and PLR values are parameters that can be easily detected during routine preoperative evaluation. With more prospective randomized studies with extensive patient involvement, these biomarkers can be added to the classical staging system and contribute as prognostic and predictive factors in colorectal cancer patients.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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