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MEAN PLATELET VOLUME (MPV) FOR PREDICTING PROGNOSIS OF RECTUM CANCER AFTER NEOADJUVANT TREATMENT

Rektum Kanserinin Prognozunu Öngermede Ortalama Trombosit Hacmi (MPV)'nin Rolü

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Abstract

Aim: Rectum cancer is a subtype of colorectal cancer. Its etiology and etiopathogenesis is similar to colon cancer. However, it is differentiated from colon tumors because of its anatomic location and treatment approach. In the literature, Mean Platelet Volume (MPV) has been shown to correlate with inflammation in gastrointestinal cancer patients. Based on this fact, we aimed to evaluate the MPV value for predicting prognosis of rectum cancer patients who are treated with neoadjuvant chemoradiotherapy.

Materials and Methods: We retrospectively collected the data of 80 operated rectum adenocarcinoma patients who were treated neoadjuvant chemoradiotherapy between 2011 and 2018. MPV value was investigated as prognostic factors for disease free survival.

Results: Fifty-five patients were male (69%). Median age was 56 (range 22 to 83 years). The most common histopathologic was adenocarcinoma (94%). The ideal cut-off value of pretreatment MPV that predicted disease-free survival was 7.65 in the ROC analysis [AUC:0.74 (0.63-0.85); p<0.002] with a sensitivity of 81%, and specificity of 69 %. Median DFS was 43 months in patients with MPV <7.65 (95%CI: 35.5-54.6). In multivariate analysis, MPV was found to be an independent prognostic factor for disease free survival (p = 0.02).

Conclusion: According to our study, we suggest that high levels of MPV at the time of diagnosis can be used as a predictive biomarker for early relapse in rectum cancer patients.

Keywords: Rectum cancer, Mean platelet volume, Disease free survival, Predictive marker.

Öz

Amaç: Rektum kanseri kolorektal kanserlerin alt tipidir. Etyopatogenezi kolon kanserlerine benzemekle birlikte, tedavi yaklaşımında farklılıklar vardır. Literatürde ortalama trombosit volümü (MPV) ile gastrointestinal kanser hastalarındaki inflamasyonla ilişki gösterilmiştir. Bu nedenle çalışmamızda neoadjuvan tedavi alan rezeke rektum kanseri hastalarının prognozunu belirlemede MPV değerinin rolünü değerlendirmeyi amaçladık.

Materyal ve Metot: 2011-2018 yılları arasında neoadjuvan kemoradyoterapi almış opere 80 rektum adenokarsinom tanılı hastanın verileri retrospektif olarak değerlendirildi. MPV 'nin hastalıksız sağ kalım için prognostik önemi araştırıldı.

Bulgular: Hastaların 55'i (%69) erkekti. Medyan yaş 56 (minimum 22-maksimum 83) idi. En sık görülen histopatolojik tip adenokarsinomdu(94%). MPV için ideal kestirim değeri 7,65 saptandı [AUC:0.74 (0.63-0.85) / p<0.002 duyarlılık %81 ve özgüllük %69]. MPV <7,65 olan hasta grubunda medyan hastalıksız sağ-kalım 43 ay'dı (95%CI: 35.5-54.6). Çok değişkenli analizde MPV hastalıksız sağkalım için bağımsız prognostik faktör bulundu (p 0.02).

Sonuç: Çalışmamıza göre, neodjuvan kemoradyoterapi sonrası opere edilen rektum kanseri hastalarında tanı sırasındaki yüksek MPV seviyelerinin erken nüks ile ilişkili olduğu gösterilmiştir.

Anahtar Kelimeler: Rektum kanseri, Ortalama trombosit hacmi, Hastalıksız sağkalım, Prediktif belirteç.

INTRODUCTION

Colorectal cancers (CRC) are the third most common cancer among all cancers in developed countries[1].CRC is the second most common cancer in men and the fourth most common cancer in women in our country[2]. Neoadjuvant chemoradiotherapy is a standard therapeutic approach in patients with non-metastatic rectum cancer[3,4]. Twenty-five percent of patients with early-stage CRC develop distant metastases[5]. Several prognostic factors have been investigated as potential prognostic biomarkers for colorectal cancer. But in current times, there is no ideal biomarker for predicting disease-free survival in these patient populations[6,7].

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Mean platelet volume (MPV) is a common marker for platelet function and activation. It is being evaluated as a part of routine complete blood count testing in complete blood count analyzers[8-9]. The normal value is ranged between 4,5 and 8,5 fL (femtoliter) (mean 6,5 fL)[10]. It has higher levels in young adults and children[8]. Platelet parameters are stable in men and women, and parameters of women are thought not to be affected by the menstrual cycle[8,10-11]. Platelet shape and ultrastructure varies according to the ambient temperature, method of analysis and Ethylene Diamine Tetra acetic acid (EDTA), which is used as an anticoagulant[8,12]. The platelets collected with EDTA are globular and the ones collected with citrate are discoid shaped. EDTA causes platelets to swell over time. Increased MPV is associated with an increase in megakaryocytic growth against thrombopoietic stress response[8]. MPV decreases in cases of increased peripheral thrombocytopenia and decreases in defective platelet production[12-13].

The relationship between cancer cells and platelets has long been known. Thrombocyte activation and thromboembolic events occur frequently in cancer patients[14-15]. Thrombocytosis is common in many cancer patients, including lung cancer, and increased platelet counts are associated with poor survival[16-17]. According to the evaluation of MPV and cancer progression in various cancer types, findings showed heterogeneity. In some cancers higher MPV values were associated with disease progression such as colorectal cancers, endometrium cancer while lower MPV values were associated with disease progression in gastric cancer, non-small cell lung cancer[18-22]. Since there are few studies questioning the relationship between MPV values and cancer survival; as a unique value, in this study we aimed to evaluate the association between all clinical parameters including both MPV values and disease free-survival rates of rectum cancer patients retrospectively.

METHOD

Patients

We retrospectively collected the data of 80 operated rectum adenocarcinoma patients who were treated neoadjuvant chemoradiotherapy between 2011 and 2018 in Umraniye Research and Training Hospital and Acıbadem University Medical Oncology Outpatient Clinic.Inclusion criteria were histological diagnosis of non metastatic rectal adenocarcinoma, treated with neoadjuvant chemoradiotherapy and having complete medical records. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee (Ethics/institutional review board approval of research Faculty of Medicine, Acibadem University, Istanbul, Turkey. Number: 2019-12/12 Date:11.07.2019) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants included in the study.

All patients were older than eighteen years old. Patients who had confounding factors affecting MPV, neutrophil and lymphocyte such as hypertension, smoking, hyperlipidemia, the presence of active infection disease, hepatosplenomegaly and some antihypertensive drugs (beta blockers and calcium channel blockers), were excluded from the study.

Blood Analysis

Peripheral venous blood samples were obtained early in the morning 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 MPV, lymphocyte (Lym), neutrophil (Neu) and platelet (Plt) numbers, carcinoembryonic antigen (CEA) and CA19-9 level were obtained for time of diagnosis. All parameters were evaluated relatively with clinical characteristics of each patient.

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 MPV 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 MPV. SPSS 22 program was used for statistical analysis.

RESULTS

This study included 80 rectum cancer patients and 55 (69%) were male,25 (31%) were female. Median age was 56 (range 22 to 83 years). According to clinical parameters, histopathological types were adenocarcinoma in 75 (94%) patients and mucinous adenocarcinoma in 5 (6 %) patients. All patients received neoadjuvant chemoradiotherapy. Radiotherapy was given total 45 Gy / 28 days. Capecitabine 825 mg / m2 / day or 5 fluorouracil 200mg /m2 D1-5 weekly was administered. And then patients were operated on average 8-12 weeks. Demographic and clinicopathologic characteristics of patients for the entire study cohort were shown in Table 1. Pretreatment laboratory parameters are given in Table 2.

Table 1: Demographic and clinicopathological findings

		n
Gender	**Male**	**55(69%)**
	Female	**25 (31%)**
Tumor localization	Proximal	15(19%)
	Middle	34(42%)
	Distal	31(39%)
Pathology	Adenocarcinoma	75(94%)
	Mucinous adenocarcinoma	5 (6%)
Neodjuvant chemotherapy	5 Fluorouracil	35(44%)
	Capecitabine	45(56%)
Tumor Regression	Complete Response	5 (6%)
	Moderate Response	14(17%)
	Minimal Response	23(29%)
	Poor Response	38 (48%)
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%)
	intermediate	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%)

Table 2. The Results of Hemogram and Biochemistry Parameters

Laboratory parameters	**Median**
Hemoglobin (g/dL)	12,14 (min 7-max 18)
Neutrophile (µ/L)	3850 (min 1690-max 14600)
Lymphocte (µ/L)	1800 (min 1800 -max 7800)
Platelet (µ/L)	282000 (min 110000-max 607000)
Mean Platelet Volume (fL)	8.1 (min 5.9-max 12)
CEA (ng/mL)	5.76 (min 1.04-max 936)
CA19-9 (u/ mL)	44.5 (min 1-max 843

Median follow up 35 months (min 9 months - max 65 months). During the follow-up 52 % of the patients relapsed. 24 patients had the

systemic recurrence. Median disease-free survival (DFS) 31months (95%CI: 27.8-34.1). 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 (95%CI: 24.6-59.3) in stage 1,30 months (95%CI: 19.7-40.2) in stage 2 and 28 months (95%CI: 21.8-34.7) in stage 3 (p =0,01).

The ideal cut-off value of pretreatment MPV that predicted disease-free survival was 7,65 in the ROC analysis [AUC:0.74 (0.63-0.85) / P<0.002] with a sensitivity of 81%, and specificity of 69 % (figure 1,2). MPV 7.65 value had the highest sensitivity and specificity for predicting DFS in ROC curve analysis. Therefore, we accepted the MPV 7.65 value as a cut off value. During the follow up period, disease recurrence occurred in 8 of 34 patients with MPV <7.65, and in 34 of 46 patients with MPV ≥ 7.65. There was a statistical difference between the two groups (p=0.000). Median DFS was 43 months (95%CI: 35.5-54.6) in patients with MPV <7.65, 28 months (95%CI: 24.7-31.2) in patients with ≥ 7.65 (p=0.003).

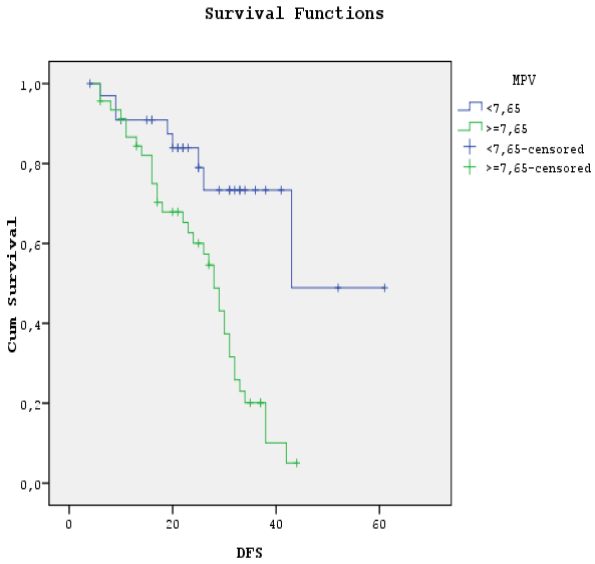

Figure 1. Disease Free Survival Graphic According to MPV by Kaplan Meier

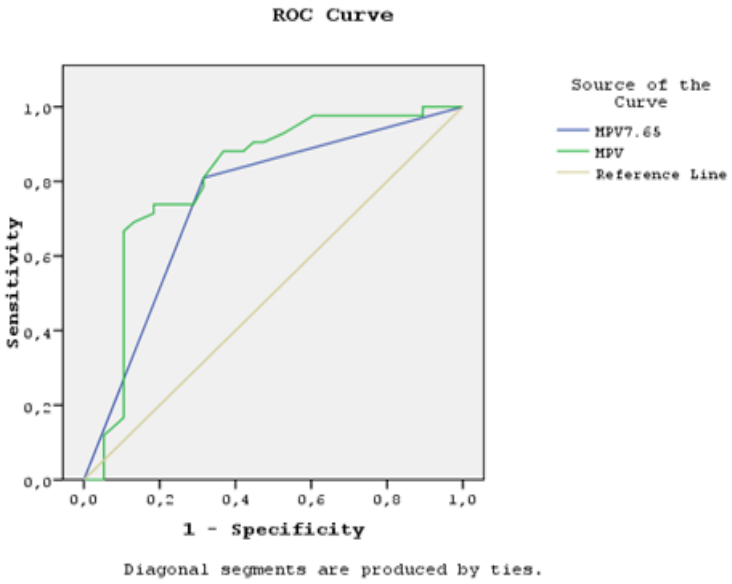

Figure 2. Ideal cut-off value ROC curve for MPV

The univariate and multivariate analysis results related to disease-free survival were shown in Table 2. Grade (poorly vs well-intermediate), ypT stage (T1-2 vs T3), CEA level (<5 ng/mL vs ≥ 5 ng/mL), and MPV (<7.65 vs ≥ 7.65) had a significant statistical association with DFS in univariate analysis. In multivariate analysis, grade and MPV level were found to be independent prognostic factors for DFS (p = 0.01, 0.02 respectively).

Table 2. Cox-regression model of disease-free survival (DFS) in rectum cancer

			Univariate Analysis				Multivariate Analysis			
	N	Median DFS (months)	HR	95% CI Lower	Upper	P	HR	95 % CI Lower	Upper	P
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	**0.003**	2.10	1.06	4.15	**0.03**
	Well-intermediate (n=60)	33								
ypT stage	T1-2 (n=39)	38	2.54	1.31	4.90	**0.006**				
	T3 (n=36)	28								
ypN stage	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								
CEA (n=76)	<5 ng/mL (n=31)	42	2.8	1.3	5.6	**0.002**				
	≥ 5 ng/mL (n=45)	28								
MPV	< 7.65 (n=34)	43	3.62	1.66	7.86	**0.01**	3.00	1.33	6.78	**0.008**
	≥ 7.65 (n=46)	28								

DISCUSSION

According to the previous studies, it is known that lower levels of MPV is associated with inflammatory diseases such as ulcerative colitis, inflammatory bowel disease, rheumatoid arthritis and nasal polyp[23-27]. In a meta-analysis of MPV in critically ill patients defined as patients with physiologic instability, subsequent MPV levels after the third day was found to be associated with lower mortality rate in 3724 critically ill patients[28]. However, there was high heterogeneity between the studies.

Pedersen et al. investigated 1115 pulmonary cancer patients for thrombocytosis and found the prevalence of thrombocytosis in these patients as 32% 16. Although increase of platelet numbers is a common fact in cancers, the situation of MPV is quite different. In a study comparing 221 colorectal cancer patients with 110 healthy controls, it was found that the MPV values of the cancerous group were much alike while the platelet count was high[17]. Kandemir et al. have investigated whether thrombocytosis is a prognostic factor in patients with stage 2 colon cancer. They found thrombocytosis in 24 of the 198 patients they included in the study and showed that thrombocytosis correlated with tumor depth and lymphatic invasion. Patients with thrombocytosis had lower event-free and overall survival[18]. In another study involving 50 patients with gastric cancer, an increase in

platelet count and MPV levels were detected. These increases were associated to the release of young and active platelets from bone marrow. When the patients were grouped as early stage, local advanced stage and metastatic disease, the increase in platelet counts and MPV values became evident as the disease progressed. Aksoy et al. evaluated the significance of MPV in patients diagnosed with bone marrow metastasis and found that MPV was lower in those with metastasis[19]. In a study of preoperative patients with gastric cancer, MPV values in patients with large tumor size were found to be higher than patients with small tumor size[20]. A study comparing MPV values in patients with thyroid cancer and healthy donors showed that MPV in patients with thyroid cancer was higher than in healthy donors[21]. In another study of cancer and MPV association, it was found that MPV levels in 14 endometrium cancer patients were higher than healthy donor group. In addition, MPV levels in patients with advanced stage endometrium cancer were found to be higher than in all groups[22].

Koksal et al had evaluated MPV in relation with stage of the disease and venous thromboembolism in non-small cell lung cancer patients (NSCLC). The study had included 160 patients with NSCLC and 20 healthy donors as control group. They found that thrombocyte numbers were higher in NSCLC patient while MPV was lower. However, there was no significant correlation between disease stage and MPV[29]. Yun Z et al analyzed the association between MPV and clinicopathological characteristics of patients with renal cell carcinoma. As a result of the study reduced MPV was found to be predictive factor of poor prognosis among 306 patients with renal cell carcinoma[30]. Shen et al assessed the application value of MPV in 168 patients with resectable gastric cancer. According to Kaplan-Meier test, they found that higher preoperative MPV was associated with decreased overall survival and disease-free survival. Thus, MPV measurement was suggested to be applied for providing significant information for diagnosis and prognosis of resectable gastric cancer[31]. Tuncel et al had studied the prognostic value of MPV pretreatment in metastatic and non-metastatic colorectal cancer. In addition, they evaluated pretreatment of MPV in association with the progression of colorectal cancer patient who underwent bevacizumab combined treatment. The study included 53 metastatic and 95 nonmetastatic colorectal patients. MPV was found to be higher in patients with metastatic disease when compared with patients with non-metastatic disease. As a result, MPV was suggested as a prognostic factor for metastatic colorectal cancer patients who were treated with bevacizumab combined chemotherapy[32]. When Li et al compared MPV between 128 healthy controls and 128 patients with colorectal, MPV was found to be higher in patients which suggested MPV as a novel diagnostic factor in colon cancer[33]. With a similar approach to our study, Ferroni et al, had investigated the effect of various anti-cancer drugs on MPV to evaluate its predictive value for thromboembolic episode of patients during treatment. They claimed that variations in MPVs during chemotherapy could supply additional information on thromboembolic risk of patients after anti-cancer treatment drugs[34]. In the study by Wlodarczyk et al., MPV was evaluated as a possible tumor progression biomarker in operated rectum cancer patients without neoadjuvant treatment. One hundred and three rectal cancer patients with surgical resection were included. Pre-operative MPV

was found to be significantly lower. Thus, MPV level was suggested as a candidate predictive biomarker for tumor progression[35]. As a different point, the cohort of our study consisted of patients who received neoadjuvant treatment. To the best of our knowledge, the prognostic value of MPV in rectum cancer patients who were treated with the neoadjuvant approach has been not reported in the literature.

Our study had some limitations. Our cohort consisted of a relatively small patient population compared to other studies literature. This situation may have caused selection bias. We acknowledge that this trial is a retrospectively conducted study, and therefore more clinical trials are needed to identify the association between MPV and tumor progression in rectum cancer patients who are treated with the neoadjuvant approach. On the other hand, many confounding factors can affect MPV such as obesity, hypertension, smoking, hyperlipidemia and some antihypertensive drugs (beta blockers and calcium channel blockers). Therefore, these factors should be considered when evaluating the relationship between MPV and tumor progression in retrospective studies[36-38].

CONCLUSION

We observed that patients with a high level of MPV have a worse prognosis than patients with a low level of MPV. Our result is consistent with that of previous studies evaluating the association between MPV and cancer progression. MPV is calculated automatically during routine analysis of hematological parameters without necessitating extra cost or laboratory work. Therefore, MPV may become a widely used, simple, inexpensive, and useful prognostic biomarker for rectal cancer patients who are undergoing neoadjuvant treatment.

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