ROLE OF MEAN PLATELET VOLUME AS A MARKER OF DISEASE ACTIVITY IN PATIENTS WITH ULCERATIVE COLITIS

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ABSTRACT

Objective: *Treatment of ulcerative colitis (UC) is based on disease activity. There isn't widely accepted single indicator or group of parameters with high precision to determine the level of disease activity. The aim of this study is to determine the mean platelet volume (MPV) in the disease activity of ulcerative colitis.*

Materials and methods: *83 patients with UC were enrolled in this study, and double samples were taken from each patient both in activation and remission phase. In order to evaluate the disease activity, MPV, Neutrophil (Neu), platelet count (Plt) in activation and remission phase of each patient were compared.*

Results: *83 patients (30 females, 53 males, mean age was 43.23±12.63 years) with UC were enrolled in this study, double samples from each patient (166 samples) were compared. MPV value was significantly decreased in patients with active UC compared to inactive UC and healthy donors (p=0.001). Additionally MPV value was significantly increased in controls compared to patients with inactive UC (p=0.016). However, receiver operating characteristic (ROC) analysis of MPV wasn't provided a statistically discriminative value in differentiating active from inactive UC.*

Conclusion: *This is the first study to analyze mean platelet volume (MPV) in active-inactive phases of the disease course in ulcerative colitis, which is comparing blood samples taken during remission and activation periods in the same patient. Although there was significant difference in measurements of our patient population, we did not find consistent cut-off levels for MPV value to reliably use as distinct activity indicator.*

Keywords: *Mean platelet volume, Neutrophil, ulcerative colitis, inflammatory markers.*

DOI: 10.19193/0393-6384_2019_6_528

Received *November 30, 2018;* ***Accepted*** *February 20, 2019*

Introduction

Ulcerative colitis (UC) is systemic inflammatory bowel disease (IBD) characterized by alternate periods of remission and activation. Early detection is of paramount importance in these patients, some studies have shown that early diagnosis in patients with severe IBD significantly reduces mortality rates[1,2]. Non-invasive tests such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cells (WBC) and fecal calprotectin have been considered as sensitive and important markers in patients with UC for diagnosis and disease activity interpretation[3-5]. Several studies have reported that CRP, ESR, platelets and mean platelet volume (MPV) may be potential markers of clinical disease activity and additionally MPV levels has been shown to be associated with CRP and ESR levels[5-8]. Although some studies reported that MPV decreased in active rheumatological diseases, in other studies MPV found to be increased in myocardial infarction and cerebrovascular disease[9-11].

In some previous studies were found, MPV levels of patients with active UC decreased, while some studies reported an increase in active UC, and also, overall accuracy, sensitivity and specificity of MPV in determining disease activity were found to be moderately reliable[5,8,12].

To date there are studies conducted with MPV, ESR, CRP and other parameters in patients with UC with diverse results which, one of the major limitations of these studies, patients within the activation period had been compared with a different group of patients in remission. In our study, parameters of patients in activation were compared with those of the same patients in remission.

The aim of this study was to determine the mean platelet volume (MPV) could be used as indicators of disease activity.

Materials and methods

Study design

This was a retrospective, single center, controlled study. All patients selected from the outpatient clinics of Gastroenterology Department of Dışkapı Yıldırım Beyazıt Education and Research Hospital. This study was reviewed and approved by the local ethical committee of Dişkapi Yildirim Beyazit Education and Research Hospital.

Patients and control groups

From August 2007 to January 2015, 407 patients at our center diagnosed with UC. Eighty three patients with UC were enrolled in this study, which have had available information for activation and remission periods. 324 patients were excluded due to absence of all the data in activation and remission periods. Clinical and laboratory findings were recorded individually in all patients at of their remission and activation periods. 20 healty volunteers in our center working, were enrolled in this study as control group.

The diagnosis of active and remission phase of UC was based on determined criteria of clinical, endoscopic, histological and radiological findings. The patients were divided into two groups which were definedremission and activation phases. The disease activity was classified according to Rachmilewitz endoscopic activity index (RAI) and Trulove and Witts' criteria for UC. Three anatomical localization is defined for UC; proctitis (limited to rectum), left side colitis (from anal verge of rectum to splenic flexura) and extensive colitis (involvement extends proximal to the splenic flexure, including pancolitis).

The exclusion criteria were as follows: chronic liver disease, acute or chronic renal failure, decompensated heart failure, pregnancy, malignancy, acute or chronic infection, hematological disorders, and chronic obstructive pulmonary disease. None of the patients have used any medications other than disease specific drugs including oral anticoagulants and non-steroidal anti-inflammatory drugs.

Laboratory parameters

All complete blood count (CBC) and other test analyses were performed in our hospital laboratory using routine methods. Hematological parameters which consisted of hemoglobin (HGB) range 13.2-17.3 g/dl for men, 11.7-15.5 g/dl for women, WBC range 3.57-11 x 103/μL, Neutrophil (Neu) range 1.69-7.5 x 103/μL platelet (PLT) count range 150-372 x 103/μL, MPV range 7.57-11.58 fL. The normal ranges ESR and CRP were 0-20 mm/h and 0-8 mg/L, respectively.

Statistics

Data were statistically analyzed using SPSS for Microsoft Windows 17.0 (SPSS Inc., an IBM Company, Chicago, IL).Two-related-samples test and paired-samples T test were used for comparison of two dependent activation and remission groups. Chi-square test was used for categorical measures. Pearson correlation analysis was used to analyze the correlation between CBC parameters and other inflammatory markers. The Wilcoxon test was used to compare the changes of in CBC parameters and inflammatory markers between remission and activation phase. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cutoff values for CBC parameters and other inflammatory markers. When a significant cut-off value observed, the sensitivity, specificity, positive and negative predictive values were presented. P values below 0.05 were considered significant in all analyses.

Results

Eighty three patients with UC were enrolled, which have had activation and remission period information and20 healthy volunteers were participated in this study. There were 30 females and 53 males, mean age of patients was 43.23±12.63 and of controls was 38.5±10.65 year. The clinical and the baseline characteristics of patients and control group were presented in Table 1.

		Ulcerative colitis (n=83)	Control group (n=20)	P value
Age (mean/year)		43.23 ± 12.63	38.5 ± 10.65	0.144
Sex (male/female) (n)		53/30	8/12	0.052
Disease location (n, %)	Proctit	26 (31.33%)		
	Left side	30 (36.14%)		
	Extensive	27 (32.53%)		

Table 1: Clinical characteristics of the patients and controls.

Statistically significant differences were found in WBC, Neu, Hb and Plt values between active and

inactive phases; however there were no significant differences between patient and control groups. Statistically significant differences were found in MPV, ESR and CRP values between patient and control groups. Comparison of CBC parameters and other inflammation markers were provided in table 2.

	UC Remission	UCActivation	p[a]	Control patients	p[b]	p[c]
WBC(x10³ µl)	7.68 ± 1.8	8.6 ± 2.55	0.001	7.76 ± 2.06	0.987	0.175
Neu (x10³ µl)	4.81 ± 1.53	5.61 ± 2.24	0.002	5.03 ± 1.56	0.433	0.471
Hb (g/dL)	14.22 ± 1.8	13.47 ± 2.01	0.000	13.6 ± 1.94	0.131	0.940
Hct (%)	42.5 ± 5	40.48 ± 5.25	0.000	41.5 ± 5.34	0.414	0.742
Plt (x10³ µl)	268 ± 88	309.6 ± 115.7	0.000	272.5 ± 72.2	0.623	0.175
MPV (fl)	8.59 ±0.8	8.35 ± 0.89	0.003	9.04 ± 0.74	0.016	0.001
ESR (mm/hour)	21.9 ± 14.1	33.3 ± 20.6	0.000	16.35 ± 9.66	0.175	0.000
CRP (mg/dL)	6 ± 9.3	18.6 ± 27.6	0.000	5.33 ± 6.62	0.611	0.000

Table 2: Comparison of CBC parameters and other inflammation markers in UC patients with active and inactive period and controls.
UC: Ulcerative colitis, WBC: white blood cells, Neu: Neutrophil, Hb: hemoglobin, Hct: hematocrit, Plt: platelet count, MPV: mean platelet volume, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate
ap value between Ulcerative Colitis activation and remission phase.
bp value between Ulcerative Colitis remission phaseand control group.
cp value between Ulcerative Colitis activation phaseand control group.

MPV value was significantly decreased in patients with active UC compared to inactive UC and healthy donors (p=0.001, p= 0.001, respectively).

Ulcerative Colitis		p	r
Activation phase	**MPV-Plt**	0.001	-0.373
	MPV-CRP	0.159	-
	MPV-ESR	0.164	-
	Hb-Plt	0.000	-0.538
	Hb-CRP	0.013	-0.271
	Hb-ESR	0.000	-0.49
	Plt-CRP	0.000	+0.508
	Plt-ESR	0.000	+0.59
Remission phase	**MPV-Plt**	0.001	-0.351
	Hb-Plt	0.000	-0.487
	Hb-ESR	0.000	-0.493
	Plt-ESR	0.000	+0.445

Table 3: Comparison of two kinds of scoring systems after 90d to predict the long-term prognosis of patients with cerebral infarction.

Additionally MPV value was significantly increased in controls compared to patients with inactive UC (p=0.016). There was significant negative correlation between MPV and platelet count in patients with active and inactive UC (r = -0.373, r= -0.351, respectively; p = 0.001), but no significant correlations were found between MPV and CRP; MPV and ESR in patients with active and inactive UC. CRP values were significantly increased in patients with active UC group compared to inactive UC and healthy group (p=0.000). There was not found any significant correlation between MPV and CRP or ESR. The correlation analyses were provided in table 3.

The receiver operating characteristic (ROC) analysis was performed to investigate the capacity of all inflammatory markers in differentiating active from inactive UC (Table 4 and Figure 1).

	AUC	Sensitivity (%)	Spesificity (%)	PPV (%)	NPV (%)	Overall accuracy
ESR (Cut off :28.5)	0.679	53	73.5	66.7	61	63.3
CRP (Cut off :5.05)	0.743	74.7	66.3	68.9	72.4	70.5
WBC (Cut off :9.25)	0.598	38.6	80.7	66.7	56.8	59.6
Neu (Cut off :6.24)	0.606	34.9	83.1	67.4	56.1	59
Plt (Cut off :328)	0.628	32.5	83.1	65.9	55.2	57.8
MPV	**0.422**					

Table 4: Accuracy and ROC analyses of inflammatory and other laboratory markers in differentiate patients with ulcerative colitis activation and remission phase.
AUC: Area under curve, PPV: Positive predictive value, NPV: Negative predictive value.

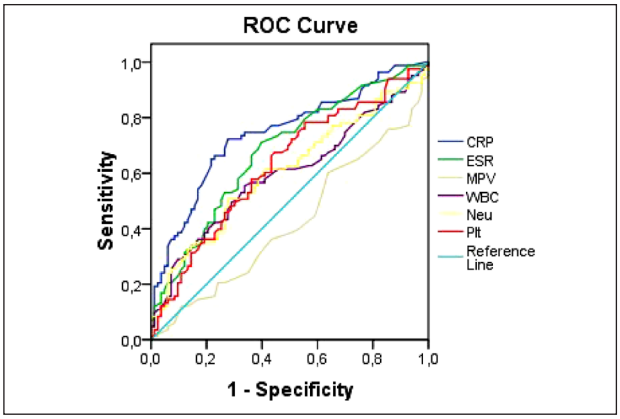

Fig. 1: ROC curves of Mean platelet volume and other inflammatory markers

The optimal cutoff levels for CRP and ESR were 5.05 mg/dl (sensitivity: 74.7%, specificity: 66.3%, AUC: 0.743,) and 28.5 mm/hour (sensitivity: 53%, specificity: 73.5%, AUC: 0.679), and with overall accuracy 70.5% and 63.3%, respectively. However, ROC analysis of MPV was not provided a statistically discriminative value in differentiating active from inactive UC (AUC: 0.422).

Discussion

In this study, we found that whilst WBC, neutrophil, platelet, ESR and CRP were increased, MPV

and hemoglobin levels were decreased in patients UC with activation compared to those with in remission. There was a negative correlation between MPV and platelet count on the contrary MPV was not correlated with CRP and ESR levels. ESR and CRP may be used as an indicator of disease activity but the overall accuracy level of MPV predicting disease activity in UC was not statistically significant. Cut-off value of MPV in this context was indefinite so MPV could not be used as a reliable indicator of disease activity in contrast with the previous studies.

Determining inflammatory activity is an important step for the assessment of disease activity, in order to plan the treatment regimen which depends on disease activity and anatomical involvement. ESR, CRP, WBC and fecal calprotectin are considered as sensitive and reliable markers for detecting activation in patients with UC[3-5]. In addition, these parameters do not robustly predict disease activity due to low sensitivity rates[5,13,14]. Despite widely used in clinical practice CRP has low sensitivity for determining the disease activity in IBD population[14,15].

Reported sensitivity rates of CRP in discriminating disease activity vary between 50-60% in published studies[16-18]. In our study, ROC analysis revealed 5.05 mg/dl and 28.5 mm/hour as optimal points for CRP (overall accuracy 70.5%, sensitivity %74.7, specificity %66.3) and ESR (overall accuracy 63.3%, sensitivity %53, specificity %73.5), respectively. ESR analysis has given an average accuracy but CRP analysis showed a moderate accuracy for differentiating UC activation phase from remission.

Platelet count is of current interest for inflammatory processes such as UC[12]. Molecules releasing from activated thrombocytes lead to a procoagulant state and increase the risk of thromboembolic events in IBD[19-22]. Activated thrombocytes were found in systemic and mesenteric circulation and intestinal mucosa[23-26]. As it is previously reported, thrombocytes were activated due to local inflammatory process in IBD[26,27]. With this in mind it could be suggested that platelet count is a useful activity marker[28].

Consistent with previous studies[12,29,30]we found that, platelet counts were increased in patients with active phase compared, with those of in remission ($p = 0.000$) and Plt count was positively correlated with ESR and CRP levels ($p<0.001$, r:+0.59, r:+0.504, respectively). Decline in the level of platelet number may be an indicator of remission in patients with active phase. Although the clinical use couldn't reach to an optimum due to low sensitivity rates (sensitivity 31.3%, specificity 84.3%) 328 x 10 3 μl may be used as the platelet number cut-off level discriminating active and remission states. These figures suggest the clinical use of platelet count is limited in patients with ulcerative colitis, for distinguishing active and remission phases.

The relevancy between MPV and inflammatory process has been well studied previously[31-33]. In some studies MPV was reported to be correlated with platelet function[9,34] and associated with inflammatory conditions such as acute appendicitis, chronic hepatitis B, rheumatoid arthritis, Crohn's disease and ulcerative colitis[5,8,11,35-37].In some previous reports MPV level of patients with active UC, was decreased[5,12,37,38], on the contrary some studies reported an increase in active UC[8]. In recent studies of Yuksel et al and Öztürk et al, overall accuracy, sensitivity and specificity of MPV in determining disease activity were found at a moderately reliable level[5,8]. Main limitation of these studies was to compare different patient groups with different activity levels instead of performing a multi-measurement procedure in a study population composed of the same patients. In our study, activation parameters were compared with the remission parameters of the same patients.

As MPV values were highest in healthy controls, significantly decreased in remission phase, and also MPV values were lowest in active phase in UC patients. Statistically significant difference found between healthy controls and ulcerative colitis patients with remission suggests MPV level as an important marker to monitor the disease activity ($p=0.016$). Statistically significant difference found between remission phase and activation phase in ulcerative colitis patients for MPV value. However the decrease in MPV values thought to be used as indicator of proceeding to remission state but we were not able to set a cut-off level as it is previously reported in published studies. We found MPV levels were decreased in patients with active UC ($p=0.001$) but any cut-off value could not be determined from ROC analysis (AUC: 0.422), so MPV has no discriminative value to differentiate active from inactive UC.

Conclusion

To the best of our knowledge, this is the first study evaluating MPV intra-individually at different phases of UC in each patient and, in contrast with widely adopted concept, according to our findings, the MPV was not as reliable to determine the activation phase of UC.

There is need for well-designed studies to enlighten the role of platelet and MPV in inflammatory bowel disease activity in the near future.

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