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Could platelet indices be new biomarkers for inflammatory bowel diseases?

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Abstract. – BACKGROUND AND AIM: Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory diseases. Many serum biomarkers have been studied for diagnosis and monitoring of disease activity in inflammatory bowel diseases (IBD). Platelets play an important role in inflammation. The aim of the present study is to determine whether platelet indices; mean platelet volume (MPV), platelet distribution width (PDW) and platelet-crit (PCT) would be useful, cheap, non-invasive biomarkers for following up and determining severity of IBD.

MATERIALS AND METHODS: The study group consisted of 175 patients with IBD (UC n: 103 and CD n: 72) and the control group included 40 healthy subjects. Disease activity was evaluated both by endoscope and clinically. Platelet indices and inflammatory parameters were measured for all study participants. Patients were checked in both active and remission phase of the diseases.

RESULTS: In patients with active UC and CD, there was a statistically significant decrease in MPV, PDW levels and increase in PCT levels when compared to healthy controls. In remission phase of IBD while MPV levels were lower, PDW and PCT levels were higher than control group. Both PDW (r: –0.271 *p*: 0.032) and PCT (r: 0.295 *p*: 0.027) had a significant correlation with UC disease activity. There was statistically significant change in all platelet indices during diseases follow-up.

CONCLUSIONS: The present report revealed that changes of platelet indices in IBD are noteworthy. They can be added to other inflammatory markers especially to monitor disease from active phase to remission phase.

Key Words:
Blood platelet count, Crohn's disease, Inflammation, Ulcerative colitis.

Abbreviations

AUC: area under curve
CBC: complete blood count
CD: Crohn's disease
CRP: C-reactive protein
EDTA: ethylenediaminetetraacetic acid
ESR: erythrocyte sedimentation rate
IBD: inflammatory bowel diseases
IL-1: interleukin-1
MPV: mean platelet volume
NPV: negative predictive value
PDW: platelet distribution width
PCT: platelet crit
PLT: platelet
PPV: positive predictive value
REI: Rachmilewitz endoscopic activity index
ROC: receiver operating characteristics
UC: Ulcerative colitis
WBC: white blood cells

Introduction

The pathogenesis of inflammatory bowel diseases (IBD) likely involves genetic, environmental and immunological factors[1]. The assessment of IBD is based on a combination of symptoms, clinical examination, laboratory indices, radiology and endoscopy with histology. There is no single gold standard test or examination. The search for a non-invasive biomarker that determines the type, disease activity, prognosis and response to therapy of IBD has been a focus in IBD research[2-4]. The main biomarkers in IBD are C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cells (WBC), acid glycoprotein, platelet count, albumin with faecal

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and serologic markers[5-7]. But they have little accuracy in predicting IBD activity. Therefore new, cheap and non-invasive additional serum biomarkers are needed for diagnosis and determination of disease activity. It has been shown decreased mean platelet volume (MPV) may be an indicator for increased disease activity in patients with ulcerative colitis (UC)[7,8]. Recent studies also revealed the association of platelet indices (platelet crit (PCT), platelet distribution width (PDW) and MPV) with WBC count and CRP which underline the wide relation between platelets and inflammation[9]. But the relation between these platelet indices and IBD has not been investigated before. The primary objective of this study was to determine whether PDW, PCT and MPV could be used for assessment of disease activity and as follow up markers in patients with IBD.

Materials and Methods

One hundred and three patients with UC and 72 patients with Crohn's disease (CD) were enrolled into the study. The diagnosis of active and remission phase of UC and CD was based on established criteria of clinical, radiological, endoscope and histological findings. Forty age and sex-matched healthy volunteers formed the control group.

All complete blood count (CBC) analysis was performed in haematology laboratory of our Hospital. Two millilitres of blood were taken into standardized tubes containing 0.04 ml of the 7.5% K3 salt of ethylenediaminetetraacetic acid (EDTA) from each subject. MPV increases over time as platelet swell in EDTA; therefore, optimal MPV measurement should be within 2 hours of blood sampling[10]. Our CBC analysis was performed with the same analyzer within 2 hours after collection of blood samples with the use of a Cell-Dyn 3700 SL analyzer (Abbott Diagnostics, Chicago, IL, USA). Haematological parameters which consisted of hemoglobin (HGB) range 14-18 g/dl for men, 12-16 g/dl for women, WBC range 4.5-10.3 × 10^9/L, platelet (PLT) count range 156-373 × 10^9/L, MPV range 7.4-10.4 fL, PDW range 15.6-18.2 fL and PCT range 0.155-0.320% were analyzed by standard methods, with a time-to-result of approximately 5 min. Also blood samples were collected into tubes 3.2% sodium citrate for ESR and 10 ml serum tube for CRP, ESR and CRP were determined using automatic devices. The threshold levels for ESR and CRP were 20 mm/h and 0-46.67 nmol/L, respectively.

The activity of the disease was classified according to Trulove and Witts' criteria for UC into mild, moderate or severe[11]. Patients who have moderate or severe disease were accepted as having active UC, whereas the patients in the mild group were considered to be in the remission period. Rachmilewitz endoscopic activity index (REI) which takes granularity, vascular pattern, and mucosal vulnerability also used to assess disease activity in UC patients[12]. The degree of CD activity was defined by using Crohn's Disease Activity Index (CDAI). Mild disease was presented by score of less than 150, moderately severe disease had a score from 150-450 and severe disease had a score of more than 450.

The patients in this study within the activation period were reassessed after clinical remission. Anatomical localization is defined by using four categories for UC; proctitis: the mucosal involvement limited to rectum, distal colitis: mucosal involvement limited from anal verge of rectum to proximal sigmoid colon, left side colitis: from anal verge of rectum to splenic flexura of the colon, extensive colitis; from anal verge of rectum to hepatic flexure and pancolitis: full mucosal involvement of the colon. Ileitis, colitis and ileocolitis are defined for CD.

Exclusion criteria were atherosclerotic heart disease, heart failure, peripheral vascular disease, malignancy, acute or chronic infection, haematological disorders, chronic obstructive pulmonary disease and renal insufficiency. All patients and controls did not use medication such as aspirin, oral contraceptives, oral anticoagulants and corticosteroids.

The study was approved by the Local Ethics Committee of Gaziantep University, Faculty of Medicine.

Statistical Analysis

SPSS (Statistical Package for Social Sciences Inc., Chicago, IL, USA) for Windows 15.0 programme was used for statistical analysis. All data were entered into a database and were verified by a second independent person. The variables were investigated using visual (histograms, probability plots) and analytical methods to determine whether or not they are normally distributed. Data are presented as mean and ± SD for normally distributed variables (age, HGB, WBC, PLT, MPV, RDW, PDW, PCT) and as median ± IQR

for skew distributed continuous variables (ESR, CRP). Categorical variables are shown as frequencies. Paired samples T test for normally distributed and Wilcoxon test for ESR and CRP variables were used to compare active and remission phase in patients with UC and CD.

One-Way ANOVA was used to compare normally distributed variables. Levene test was used to assess the homogeneity of variances. Post-hoc Tukey or Tamhane's T2 tests were used according to homogeneity of variances. Kruskal-Wallis test was conducted to compare ESR and CRP parameters. The Mann-Whitney U test was performed to test the significance of pair wise differences using Bonferoni correction to adjust for multiple comparisons. An overall % 5 type-1 error level was used to infer statistical significance. Correlation analyses to examine the correlation between MPV, PDW, PCT, ESR and CRP were performed using Pearson and Spearman correlation tests. MPV, PDW, PCT, ESR, CRP and WBC values in predicting inflammation of acute phase of UC and CD were analyzed using Receiver Operating Characteristics (ROC) curve analysis. When a significant cut-off value was observed, the sensitivity, specificity, positive and negative predictive values were presented. While evaluating the area under the curve, a 5% type-1 error level was used to accept a statistically significant predictive value of the test variables. Two-sided values of $p < 0.05$ were considered as statistically significant.

Results

The clinical and the demographic characteristics of patients and control group are demonstrated in Table I. The mean age of UC, CD and control group was 37.69±13.32, 37.74±12.30 and 34.67±10.03 years, respectively. There was no statistically significant difference between the ages of the groups. While pancolitis and extensive are the most common localities in UC, ileitis and ileocolitis account for 90% of CD. Of the UC and CD patients in active phase, 33% and 31.9% had severe disease while 67% and 68.1% were moderate, respectively.

All of the laboratory parameters except PDW were significantly different between groups. When parameters of active and remission phase of UC and CD patients were compared all of these parameters were significantly different. While MPV was decreasing in UC patients with remission, in contrast MPV was increasing with remission in CD. Comparison of laboratory data with active CD-UC versus those in remission and the control group was shown in Table II.

In active UC group, PCT was positively correlated with both of WBC and ESR respectively (r: 0.465 p: < 0.001, r: 0.242 p: 0.043). REI was positively correlated with platelet count, ESR, and PCT. PDW was negatively correlated with CRP (r: –0.303 p: 0.005) and RAS (r: 0.032 p: –0.271). MPV was weakly negative correlated with ESR and CRP in active phase of UC and CD respectively. PCT was also negatively correlated with WBC and ESR in active CD group. The correlation analyse results of laboratory parameters in active and remission phase of UC and CD were demonstrated in Table III.

The severity of disease measured by CDAI was only correlated with ESR and CRP levels in CD group ($p < 0.001$ r: 0.693, p: 0.001 r: 0.432 respectively). However MPV levels were not significantly different in both UC (p: 0.173) and CD (p: 0.404) patients according to location of disease, PCT levels were showing significant difference (p: 0.011, p: 0.033 respectively). Patients have higher PCT levels particularly in pancolitis and ileocolitis (Figures 1, 2). PDW levels were affected from location only in UC patients.

Table I. Demographic and clinical characteristics of patients and controls.

	UC (n: 103)	CD (n: 72)	Control (n: 40)	p
Age (years)	37.69 ± 13.32	37.74 ± 12.30	34.67 ± 10.03	0.362
Gender (male)	54 (52.4%)	43 (59.7%)	23 (57.5%)	0.615
Localization of disease, n (%)	Proctitis, 3 (2.9%) Distal colitis, 22 (21.4%) Left sided, 17 (16.5%) Extensive, 35 (34%) Pancolitis, 26 (25.2%)	Ileitis, 38 (52.8%) Colitis, 7 (9.7%) Ileocolitis, 27 (37.5%)		

UC: Ulcerative Colitis, CD: Crohn's Disease.

Table II. Comparison of laboratory data in patients with active CD-UC versus those in remission and the control group.

	UC	Puc	Crohn	Pch	Control	Total *p*
HGB-A (g/dL)	12.27 ± 2.28	0.002	12.66 ± 2.15	0.002	14.65 ± 1.21	< 0.001
HGB-R (g/dL)	12.84 ± 2.07		13.34 ± 1.86			< 0.001
WBC-A (× 10^9/L)	9.54 ± 4.04	0.022	10.56 ± 3.92	< 0.001	7.03 ± 1.42	< 0.001
WBC-R (× 10^9/L)	8.09 ± 2.41		8.36 ± 2.44			0.012
PLT-A (× 10^9/L)	360.69 ± 116.52	0.001	389.80 ± 134.17	< 0.001	259.38 ± 55.60	< 0.001
PLT-R (× 10^9/L)	315.19 ± 116.77		329.47 ± 94.12			0.002
MPV-A (fL)	8.38 ± 1.24	0.028	8.23 ± 1.32	0.600	8.98 ± 0.98	0.006
MPV-R (fL)	8.16 ± 1.20		8.30 ± 1.44			0.001
ESR-A, median, (min-max) (mm/h)	33 (3-99)	< 0.001	31 (8-100)	< 0.001	5.5 (1-22)	< 0.001
ESR-R, median, (min-max) (mm/h)	13 (1-64)		14 (2-54)			< 0.001
CRP-A, median, (min-max) (nmol/L)	131.43 (28.57-1781)	< 0.001	224.77 (28.57-2076.23)	< 0.001	29.33 (27.62-95.24)	< 0.001
CRP-R, median, (min-max) (nmol/L)	29.52 (3.81-161.91)		32.38 (27.62-247.62)			< 0.001
PDW-A (fL)	15.28 ± 2.60	0.001	15.75 ± 2.14	0.014	15.98 ± 1.30	0.476
PDW-R (fL)	16.26 ± 1.77		16.49 ± 1.11			0.213
PCT-A (%)	0.31 ± 0.10	< 0.001	0.30 ± 0.09	0.011	0.23 ± 0.05	< 0.001
PCT-R (%)	0.27 ± 0.07		0.27 ± 0.07			0.044

UC: Ulcerative Colitis; CD: Crohn's Disease; A: Active phase; R: Remission phase; HGB: Hemoglobin; WBC: White Blood Cell; PLT: Platelet; MPV: Mean Platelet Volume; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; PDW: Platelet Distribution Width; PCT: Platelet crit.

The receiver operating characteristic (ROC) curves of platelet indices and other inflammation markers for active phase of UC and CD were shown in Figure 3. CRP and ESR have highest sensitivity and specificity percentage for both of UC and CD and these results are presented in Table IV.

Discussion

This is the first study comparing all of the platelet indices as surrogate marker for disease activity and follow-up in patients with UC and CD. Our study demonstrated both of PDW and

Table III. The correlation analyses results of laboratory parameters in active and remission phase of UC and CD groups.

	Laboratory parameters	*p*	r
UC (Active phase)	MPV-ESR	0.027	-0.244
	PDW-CRP	0.005	-0.303
	PCT-WBC	< 0.001	0.465
	PCT-ESR	0.043	0.242
	REI-Platelet	0.01	0.322
	REI-ESR	0.007	0.339
	REI-PCT	0.027	0.295
	REI-PDW	0.032	-0.271
UC (Remission phase)	MPV-WBC	0.002	-0.336
	MPV-ESR	0.008	-0.292
	PCT-WBC	0.014	0.281
	PCT-ESR	0.007	0.314
CD (Active Phase)	MPV-CRP	0.022	-0.285
	PCT-WBC	0.035	0.296
	PCT-ESR	0.025	0.315
CD (Remission Phase)	PDW-ESR	0.044	0.252

UC: Ulcerative Colitis; CD: Crohn's Disease; WBC: White Blood Cell; PLT: Platelet; MPV: Mean Platelet Volume; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; PDW: Platelet Distribution Width; PCT: Platelet crit; REI: Rachmilewitz endoscopic activity index.

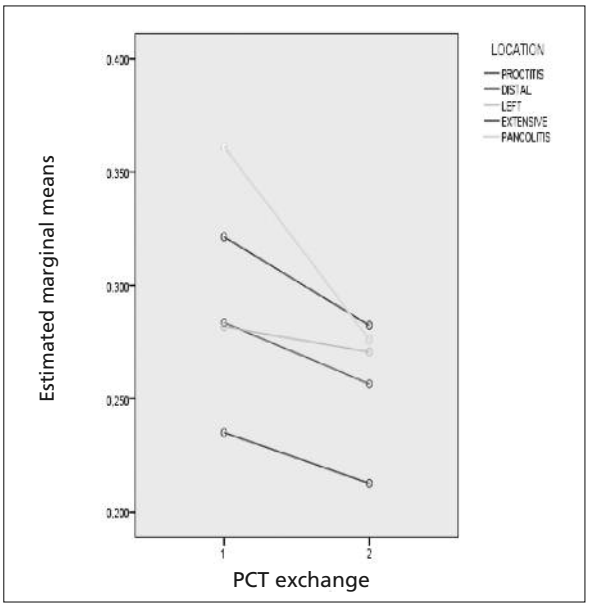

Figure 1. Comparison of platelet crit exchange according to location in ulcerative colitis. PCT: Platelet crit.

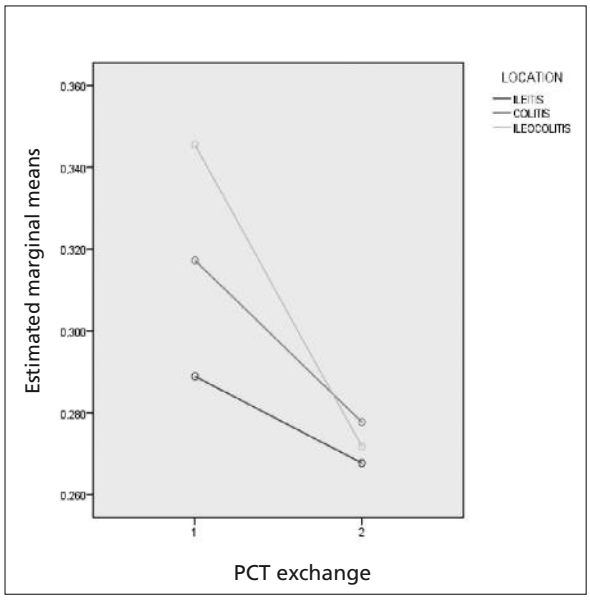

Figure 2. Comparison of platelet crit exchange according to location in Crohn's disease. PCT: Platelet crit.

PCT could be used in IBD to monitor disease progression from active phase to remission phase. Changes in MPV levels were conflicting. While MPV levels were decreasing with remission in UC, in contrast they were increasing with remission in CD. In both of the groups either in acute phase or in remission phase MPV levels was lower than control group. PCT levels were positively and PDW levels were negatively correlated with disease activity in UC patients. But

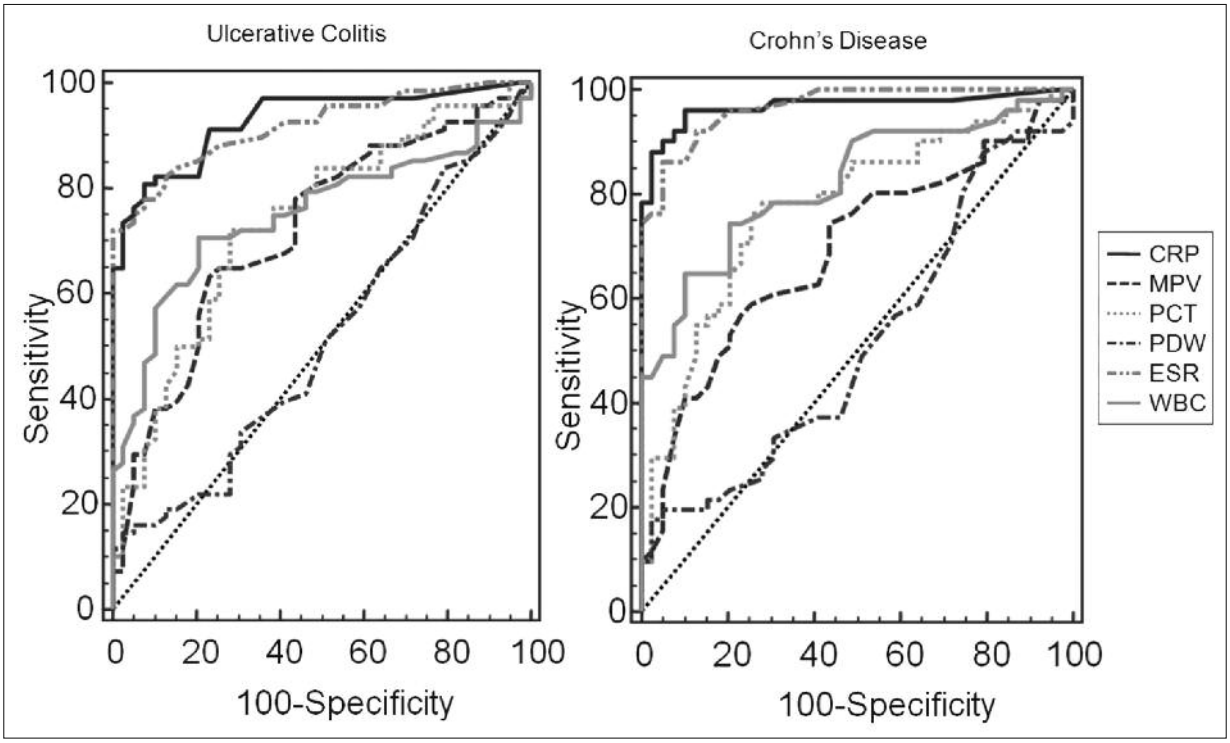

Figure 3. Comparison of platelet crit exchange according to location in Crohn's disease. PCT: Platelet crit.

Table IV. ROC analyses of markers to differentiate active phase of UC and CD from control group.

	Parameters	AUC	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
UC	MPV (Cut off: 8.2 fL)	0.718	60.0	77.5	47.7	85.0
	PDW(Cut off: 16.6 fL)	0.512	52.38	72.50	42.0	80.0
	PCT (Cut off: 0.245%)	0.735	72.6	71.79	82.8	58.3
	ESR (Cut off: 15 mm/h)	0.917	77.38	92.50	66.1	95.6
	CRP (Cut off: 36.19 nmol/L)	0.928	81.61	92.50	50.8	87.7
	WBC (Cut off: 7.9 × 10^9/L)	0.749	64.77	80.0	50.8	95.9
CD	MPV (Cut off: 8.2 fL)	0.691	56.25	77.5	52.5	80.0
	PDW(Cut off: 12 fL)	0.513	85.71	2.50	10	58.1
	PCT (Cut off: 0.253%)	0.774	76.47	74.36	70.7	79.6
	ESR (Cut off: 12 mm/h)	0.967	92.31	87.50	87.5	92.3
	CRP (Cut off: 52.38 nmol/L)	0.969	89.06	95.0	84.4	96.6
	WBC (Cut off: 8.6 × 10^9/L)	0.821	65.62	90.0	62.1	91.3

UC: Ulcerative Colitis; CD: Crohn's Disease; WBC: White Blood Cell; PLT: Platelet; MPV: Mean Platelet Volume; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; PDW: Platelet Distribution Width; PCT: Platelet crit.

none of the platelet indices was showing disease activity in CD group. Platelet indices were also inferior to CRP and ESR in diagnosis of acute UC and CD.

UC and CD are two main disorders consisting IBD. As the name suggests UC is limited to the colon, whereas CD can involve any segment of the gastrointestinal tract from the oral cavity to the anus. The clinical course of diseases is characterized by remission and relapse which may develop spontaneously or in response to medical treatment. Early determination of active disease is important for reducing mortality in severe diseases with development of effective treatment. Since the established serum biomarkers are only modestly useful in reflecting disease activity of IBD, cheap, easy applicable and non-invasive markers are required. In the light of this purpose, the study was made to show the role of platelet indices in predicting UC and CD activation with comparing other disease activity indexes and serologic markers.

Immunological disorders like imbalance between pro and anti-inflammatory cytokines have main role in the pathogenesis of IBD. T lymphocytes, B lymphocytes and macrophages located in the mucous membrane are increased in active IBD. Production of immunoglobulin, activation of granulocytes and secretion of cytokines (interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor-) can be seen in this process[13]. The typical laboratory findings of IBD are; elevated CRP, ESR, increased number of blood platelets and leukocytes[7,8]. Since they have low sensitivity and specificity for intestinal inflammation they cannot adequately reflect disease activity[14]. A recent study, determining the disease activity in UC, demonstrated that the sensitivity of WBC and ESR were 70.8% and 54.2% respectively[15]. Similarly Henriksen et al[16] showed that CRP levels were normal in 71% UC patients and 25% with CD patients.

In addition to their primary haemostatic function, platelets are involved in the pathogenesis of chronic inflammations such as IBD[17]. Thrombocyte activation seen in the active period of disease not only regulates coagulation also enhances mucosal inflammation. Platelets initiate and support inflammatory processes by secretion of numerous biologically active substances like platelet activation factor, platelet-derived growth factor, platelets factor 4, IL-1, beta-tromboglobulin[18,19].

MPV is a machine-calculated measurement of the average size of platelets. MPV correlates with platelet function and activation[20,21]. It can be influenced by the inflammation. Larger platelets which are metabolically and enzymatically more active used in inflammatory process[22]. Recently, some studies have investigated a possible association between MPV and some inflammatory conditions such as myocardial infarction, stroke, diabetes mellitus, ulcerative colitis, acute appendicitis, chronic hepatitis B, celiac disease, CD, rheumatoid arthritis[7,23-26]. Previous studies have reported MPV levels in active UC were lower than normal population and inactive UC[7,13,27-29]. According to our results, MPV levels were lowest in remission and highest in control group. Despite Yuksel et al[7] demonstrated a correlation between disease activity and MPV level, we did not found a significant relation. In literature a few

studies evaluated MPV in CD and these studies showed MPV levels were lower than control group[27,29-31]. The results of our CD group were concordant with previous studies as demonstrating highest levels in controls and lowest levels in active disease. We also did not find any correlation between MPV levels and CD activity as similarly to UC. MPV decrease in subjects with UC and CD can be associated with thrombopoiesis disturbance often observed in the early stages of systemic inflammatory processes[32]. Chronic inflammation in IBD increases number of platelets and changes their morphology.

While PCT is a measurement derived from the platelet count and the mean platelet volume; PDW is a direct flow cytometric measurement of platelet cell volume. PDW and PCT are often forgotten platelet indices and clinicians pay less attention than platelet count and MPV. During last decade PDW and PCT were evaluated in various studies including different disorders; e.g. coronary artery disease, diabetes mellitus, pulmonary tuberculosis, obstructive sleep apnoea and inflammation[9,33-35]. In the present study PDW was significantly lower in active phase of UC and CD groups than remission phase. PCT percent was lowest in control group and highest in active phase of UC and CD patients. The differences were shown to be statistically significant. PDW was positively and PCT was negatively correlated with disease activity in UC. PCT percent was also markedly correlated with ESR and WBC levels.

Our study has some superiority to previous reports. Firstly it is including the largest evaluated UC and CD series. Secondly in previous articles there was no data about changes in follow-up period including active and remission phase. Thirdly it is the first study comparing all platelet indices with inflammatory markers.

Conclusions

Chronic inflammatory process in patients with IBD results in increasing in the number of blood platelets and changing in their activation and morphological parameters. Our data suggests that platelet indices PDW, PCT are non-invasive, cost-effective biomarkers for follow-up in comparison with other modalities in IBD. It should not be considered a stand-alone test for this use owing to non-specificity with other diseases. However further studies are needed to establish between platelet functions and IBD.

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