

# Platelet Mass Index and Other Platelet Parameters in the Assessment of Inflammatory Bowel Diseases Activity

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**ABSTRACT:** Different qualitative and quantitative changes in platelets are involved in the pathophysiological processes in inflammatory bowel diseases (IBD): ulcerative colitis (UC) and Crohn's disease (CD). The aim of the study was to determine the diagnostic accuracy of Platelet mass Index (PMI) and other platelet parameters in assessment disease activity in patients with UC and CD. A cross-sectional, observational study consisted of 60 IBD patients (30 UC and 30 CD) and 30 healthy subjects (Control group). Patients were grouped according to disease activity into active and inactive (remission). Platelet count (PLC), Plateletcrit (PCT), Mean Platelet Volume (MPV), Platelet Distribution Width (PDW) and PMI were determined for all study participants. Receiver operating characteristic (ROC) curve and their corresponding areas under the curve (AUC) were used to determine diagnostic accuracy. Although PLC had the highest AUC (0.756) compared to PCT (AUC: 0.731), PDW (AUC: 0.722) and PMI (AUC: 0.724), they all had fair diagnostic accuracy in distinguishing active and inactive UC patients. Discriminatory accuracy of PLC was excellent (AUC: 0.909), PCT and PMI good to excellent (AUC: 0.809 and AUC: 0.893, respectively) and PDW fair (AUC: 0.789) in classifying CD patients as active and inactive. Platelet parameters are simple, routinely available biomarkers more useful for assessing disease activity for patients with CD than for patients with UC. Our results indicate, for the first time, that PMI may serve as a novel and simple marker in identifying whether IBD patients are in the active or inactive phase of the disease.

**KEYWORDS:** Inflammatory bowel disease, Platelet mass index, Platelet parameters.

## Introduction

Inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's disease (CD), is a disorder that mainly affects the gastrointestinal tract.

IBD is induced and followed by developing local signs of inflammation and activation of counterregulatory mechanisms that damage intestinal epithelial cells [1,2].

There is a growing body of scientific evidence that other cells, whose role is not primarily in the immune system's function, are involved in the pathogenesis of IBD.

These findings aim to clarify the relationship between the two phenomena in IBD development, namely the occurrence of chronic inflammation and the procoagulant state [3].

In this sense, it is thought that platelet activation could be the missing link between inflammation and coagulation.

The role of activated platelets in the pathogenesis of IBD becomes even more important when it is known that patients with IBD are prone to develop arterial

thromboembolic events and venous thromboembolism [4,5].

Platelets are small blood components, formed by the fragmentation of megakaryocytes.

It has been confirmed that in addition to the traditional role in hemostasis, platelets have other roles, such as involvement in inflammation, immunity, wound healing, and malignancy [6].

The platelet granules, upon platelet activation, release numerous inflammatory mediators, proving their active role in the development of the inflammatory process [7].

Morphological changes in platelet shape and size can be seen by analysis of the platelet count (PLC) and other platelet parameters, such as plateletcrit (PCT), mean platelet volume (MPV) and platelet distribution width (PDW) [8,9].

Platelet mass index (PMI) is considered a novel platelet parameter that provides more useful information about inflammatory status than MPV and PLC alone, since the overall platelet function more depends on platelet mass than on platelet count.

According to recent studies, larger platelets are enzymatically more active than smaller platelets [10].

Researchers' interest in analyzing changes in platelet parameters to determine the degree of activity of the inflammatory process has increased because available serological markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), usually shows low accuracy and sensitivity in predicting IBD activity status [11].

It has been shown that the use of non-invasive markers, such as platelet parameters, can monitor the activity of the inflammatory process, the prognosis of the disease, as well as the response to therapy [12].

Therefore, the aim of the present study was to determine the diagnostic accuracy of PMI and other platelet parameters in assessment disease activity in patients with UC and CD.

## Materials and Methods

A total of 60 IBD patients of both genders were enrolled in this cross-sectional, observational study, 30 of which were diagnosed as having UC and 30 with CD.

The patients' diagnosis of UC and CD was determined by a clinical gastroenterologist based on anamnesis, clinical symptoms, serological tests, histopathology, and imaging techniques.

Individuals with acute or chronic infections, cardiovascular and autoimmune diseases, hematologic disorders, pregnancy, and history of surgery in the last 3 months were excluded from the study.

Additionally, individuals recently treated with blood transfusion, anticoagulant agent, hormone replacement therapy, oral contraception were excluded.

According to the modified Truelove-Witts Severity Index (MTWSI) [13], and Harvey Bradshaw Simple Index for CD [14], all patients were classified as having an active disease and inactive (remission) disease status.

Apparently healthy age-and gender-matched 30 participants from the general community, without any clinical and biochemical features of IBD or illness that can affect the observed parameters served as the control group.

All patients gave their informed consent to participate in the study.

The study was conducted with the approval of the Ethics Committee of the Faculty of Medicine, University of Sarajevo (protocol number 02-3-SA-1258) according to the recommendations contained in the Declaration

of Helsinki on Biomedical Research Involving Human Subjects as revised in 2013.

Blood specimens for laboratory analyses were carefully obtained from all individuals' antecubital vein after overnight fasting and under all aseptic precautions.

The following platelet morphology parameters were calculated and provided by an automatic blood cell counter in all blood samples: PLC, PCT, MPV, PDW.

Standard reference values were used for the interpretation of all parameters. The range of normal values for PCT was 0.15-0.32%. The reference values for MPV ranged between 6.0-10.0fL. The range of normal values for PDW was 10.0-16.0fL.

The PMI for each participant was calculated manually by multiplying the platelet count (PLC) and the mean platelet volume (MPV) [15].

SPSS (Statistical Package for Social Science Inc., Chicago, IL, USA) version 13.0 for Windows was used for statistical analysis.

Normality of continuous data was determined by the Shapiro-Wilk normality test. Data are presented as mean±standard deviation (SD) for normally distributed variables and as number of cases (n) and as frequencies (%) for categorical variables.

Categorical data were compared between the two groups using the Chi-square test.

The One-Way ANOVA followed by post hoc using Tukey test is used to analyze the difference of means between more than two groups.

Statistical difference between the two groups was tested using an independent Student's t-test.

To determine the accuracy and respective best cut-off values of the platelet parameters for differentiation between active and inactive patients, the Receiver Operating Characteristic (ROC) curves and their corresponding areas under the curve (AUC) were used.

The test with AUC between 0.9-1.0 has excellent discrimination ability; 0.8-0.9 good; 0.7-0.8 fair; 0.6-0.7 poor, and 0.5-0.6 fail discrimination ability [16].

A p-value <0.05 was considered statistically significant for all comparisons.

## Results

The total sample comprised 90 participants (40 (44.4%) subjects of male gender and 50 (55.6%) subjects of female gender).

In the total sample of participants, the mean age was 38.4±12.7 years.

The baseline characteristics of all subjects enrolled in the study are presented in Table 1.

There were no statistically significant intergroup differences in age and gender

between the study groups and between active and inactive patients with UC and CD.

**Table 1. Demographic features of the patients and control group of subjects.**

Variable	UC (n=30)		CD (n=30)		Ctr (n=30)	Sig.
Age (years)	34.7±9.8		40.7±15.2		39.8±12.1	0.136
Gender/Female (n (%))	16 (53.3)		17 (56.7)		17 (56.7)	0.956
Variable	Active UC (n=15)	Inactive UC (n=15)	Sig.	Active CD (n=15)	Inactive CD (n=15)	Sig.
Age (years)	34.7±11.4	34.6±8.3	0.971	41.3±15.7	40.2±15.1	0.851
Gender/Female (n (%))	8 (53.3)	8 (53.3)	1.0	6 (40.0)	11 (73.3)	0.07

Note: Data are presented as mean±standard deviation (SD) and as number of cases (n) and percentages (%); Sig.-probability; UC-Ulcerative Colitis; CD-Crohn’s Disease; Ctr-Control group

A statistically significant difference in PLC, PCT, MPV, PDW, and PMI was found between the three groups, that is, the UC group, CD group, and healthy controls (p=0.002; p=0.05; p=0.01; p<0.001; p=0.004, respectively).

By comparing the two groups, patients in the UC group had significantly higher PLC (p=0.011) and significantly lower MPV

(p=0.012) compared to the control group of subjects.

In CD group of patients we observed significantly higher PLC (p=0.004), PCT (p=0.003) and PMI (p=0.003), and significantly lower PDW (p<0.001) compared to controls.

There were also significantly lower PDW values (p=0.01) in the CD group compared to patients in the UC group (Table 2).

**Table 2. Comparison of platelet parameters between UC group, CD group and Control group.**

Platelet parameters		UC (n=30)	CD (n=30)	Ctr (n=30)	Sig.
PLC (x10 <sup>9</sup> /L)	Mean±SD	307.6±63.4**	314.1±94.0 <sup>†</sup>	253.2±48.3	0.002
	Min.-Max.	200-441	140-550	168-356	
PCT (%)	Mean±SD	0.26±0.045	0.28±0.72 <sup>†</sup>	0.23±0.05	0.005
	Min.-Max.	0.2-0.3	0.2-0.5	0.1-0.3	
MPV (fL)	Mean±SD	8.4±0.88**	9.0±0.94	9.1±1.1	0.01
	Min.-Max.	6.4-10.7	6.8-11.5	7.2-11.2	
PDW (fL)	Mean±SD	17.1±1.01*	15.5±3.4 <sup>†</sup>	17.8±0.98	<0.001
	Min.-Max.	15.0-19.3	9.6-20.6	16.3-19.9	
PMI (fL/mL)	Mean±SD	2.6±0.5	2.8±0.7 <sup>†</sup>	2.3±0.44	0.004
	Min.-Max.	1.7-3.2	1.6-4.7	1.4-3.4	

Note: Data are presented as mean±standard deviation (SD) and Minimum (Min.) and Maximum (Max.) value; PLC-Platelet count; PCT-Plateletcrit; MPV-Mean Platelet Volume; PDW-Platelet Distribution Width; PMI-Platelet Mass Index; UC-Ulcerative Colitis; CD-Crohn’s Disease; Ctr-Control group; Sig.-probability; <sup>†</sup>-Significant difference between UC and CD group (p<0.05); \*\*-Significant difference between UC and Ctr group (p<0.05); -Significant difference between CD and Ctr group (p<0.05)

The active UC patients had significantly higher PLC and significantly lower PDW compared to inactive UC patients (p=0.003; p=0.046) and control subjects (p=0.017; p=0.002).

The PCT value of active UC patients was significantly higher (p=0.004), while the MPV value was significantly lower (p=0.016) than those of control subjects.

The active UC patients had significantly higher PMI compared with the healthy subjects (p=0.011).

The mean values of the PLC, PCT, and PMI in active CD patients were significantly higher than those with inactive CD patients and healthy control subjects (p<0.001 for all comparisons).

Patients with active CD had a significantly lower PDW values (p<0.001) than the control group (Table 3).

**Table 3. Comparison of platelet parameters between active and inactive patients in UC group and between subjects in the Control group and between active and inactive patients in CD group and between subjects in the Control group.**

Platelet parameters	Active UC (n=15)	Inactive UC (n=15)	Control group (n=30)
PLC (x10 <sup>9</sup> )	336.5±63.3 <sup>#*</sup>	278.7±50.4	253.2±48.3
PCT (%)	0.27±0.05*	0.24±0.04	0.23±0.05
MPV (fL)	8.1±0.88*	8.7±0.81	9.1±1.1
PDW (fL)	16.7±0.96 <sup>#*</sup>	17.6±0.91	17.8±0.98
PMI (fL/mL)	2.7±0.48*	2.4±0.37	2.3±0.44
	Active CD (n=15)	Inactive CD (n=15)	Control group (n=30)
PLC (x10 <sup>9</sup> )	357.3±84.9 <sup>&amp;*</sup>	252.9±55.4	253.2±48.3
PCT (%)	0.33±0.06 <sup>&amp;*</sup>	0.23±0.05	0.23±0.05
MPV (fL)	8.7±0.95	9.3±0.88	9.1±1.1
PDW (fL)	14.4±3.4 <sup>*</sup>	16.5±3.16	17.8±0.98
PMI (fL/mL)	3.2±0.64 <sup>&amp;*</sup>	2.3±0.45	2.3±0.44

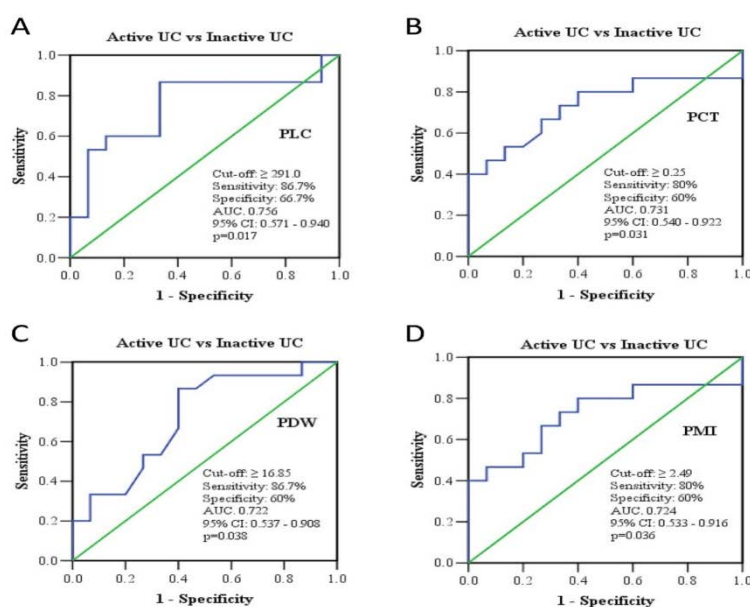
Data are presented as mean±standard deviation (SD); PLC-Platelet count; PCT-Plateletcrit; MPV-Mean Platelet Volume; PDW-Platelet Distribution Width; PMI-Platelet Mass Index; UC-Ulcerative Colitis; <sup>#</sup>-Significant difference between active UC and inactive UC (p<0.05); \*-Significant difference between active UC and Control group (p<0.05); CD-Crohn's Disease; <sup>&</sup>-Significant difference between active CD and inactive CD (p<0.001); <sup>\*</sup>Significant difference between active CD and Control group (p<0.001).

The optimal cut-off value of PLC in differentiating patients in active UC vs. patients in inactive UC was  $\geq 291.0 \times 10^9$ ; AUC was 0.756 with 95% CI of 0.571-0.940 (p=0.017); the maximal sensitivity was 86.7% and maximal specificity 66.7% Figure 1 (A).

The optimal cut-off value of PCT in differentiating patients in active UC vs. patients in inactive UC was  $\geq 0.25\%$ ; AUC was 0.731 with 95% CI of 0.540-0.922 (p=0.031), the maximal sensitivity was 80.0% and maximal specificity 60.0%. (Figure 1 (B)).

Optimal cut-off value of PDW in differentiating patients in active UC vs. patients in inactive UC was  $\geq 16.85\text{fL}$ ; AUC was 0.722 with 95% CI of 0.537-0.908 (p=0.038), the maximal sensitivity was 86.7% and maximal specificity 60.0%. (Figure 1 (C)).

The optimal cut-off value of PMI in differentiating patients in active UC vs. patients in inactive UC was  $\geq 2.49\text{fL/mL}$ ; AUC was 0.724 with 95% CI of 0.533-0.916 (p=0.036), the maximal sensitivity was 80.0% and maximal specificity 60.0% (Figure 1(D)).



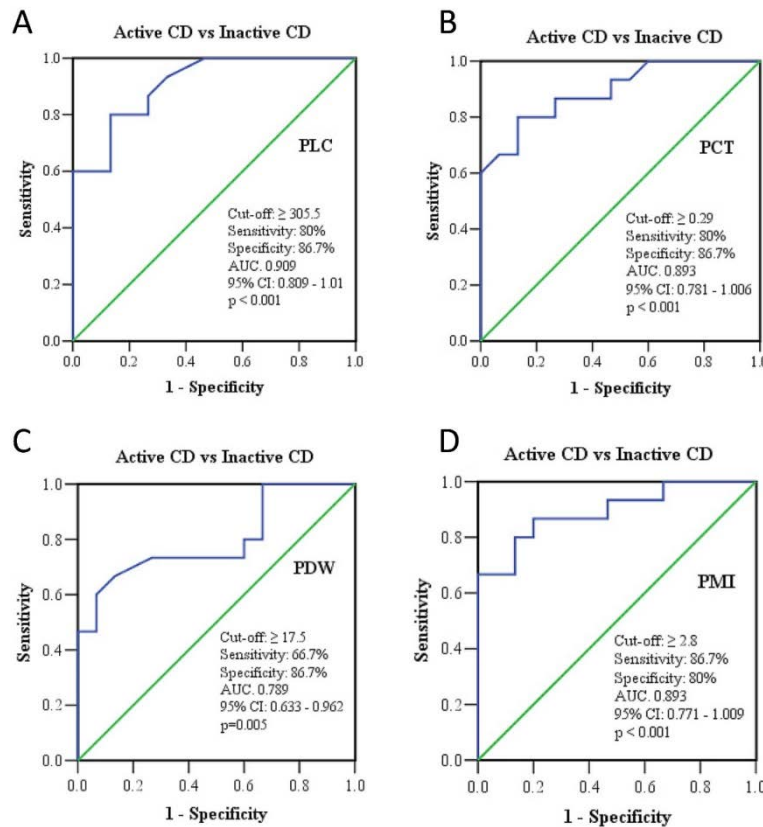
**Figure 1. (A) Receiver operating characteristic (ROC) curve of PLC for differentiation between active and inactive UC patients (B) Receiver operating characteristic (ROC) curve of PCT for differentiation between active and inactive UC patients (C) Receiver operating characteristic (ROC) curve of PDW for differentiation between active and inactive UC patients (D) Receiver operating characteristic (ROC) curve of PMI for differentiation between active and inactive UC patients.**

The optimal cut-off value of PLC in differentiating patients in active CD vs. patients in inactive CD was  $\geq 305.5 \times 10^9$ ; AUC was 0.909 with 95% CI of 0.809-1.01 ( $p < 0.001$ ), the maximal sensitivity was 80.0% and maximal specificity 86.7% (Figure 2 (A)).

The optimal cut-off value of PCT in differentiating patients in active CD vs. patients in inactive CD was  $\geq 0.29\%$ ; AUC was 0.893 with 95% CI of 0.781-1.006 ( $p < 0.001$ ), the maximal sensitivity was 80.0%, and maximal specificity 86.7%. (Figure 2 (B)).

The optimal cut-off value of PDW in differentiating patients in active CD vs. patients in inactive CD was  $\geq 17.15\text{fL}$ ; AUC was 0.798 with 95% CI of 0.633-0.962 ( $p = 0.005$ ), the maximal sensitivity was 66.7%, and maximal specificity 86.7%. (Figure 2 (C)).

The optimal cut-off value of PMI in differentiating patients in active CD vs. patients in inactive CD was  $\geq 2.8\text{fL/mL}$ ; AUC was 0.893 with 95% CI of 0.771-1.009 ( $p < 0.001$ ), the maximal sensitivity was 86.7%, and maximal specificity 80.0% (Figure 2 (D)).



**Figure 2. (A) Receiver operating characteristic (ROC) curve of PLC for differentiation between active and inactive CD patients (B) Receiver operating characteristic (ROC) curve of PCT for differentiation between active and inactive CD patients (C) Receiver operating characteristic (ROC) curve of PDW for differentiation between active and inactive CD patients (D) Receiver operating characteristic (ROC) curve of PMI for differentiation between active and inactive CD patients.**

## Discussion

Undoubtedly, platelets are significantly involved in the chronic intestinal inflammation in IBD.

Alterations of platelet count and platelet parameters, PCT, MPV and PDW are response to the platelet activation induced by proinflammatory cytokines and other agonists in UC and CD [17].

The present study results have demonstrated that although females were more predominant

than males, there were no significant differences in the gender and age between the three study groups and that all three groups were correctly matched and comparable.

Our results are consistent with those of Loftus [18], who stated that there are small gender differences in IBD incidence, with slight female predominance in CD, especially among women in late adolescence and early adulthood.

Hence, this author concluded that hormonal factors might have an important role in disease manifestation. On the other hand, our findings

are inconsistent with some other UC incidence studies, which suggest that, although overall incidence has stabilized, it continues to rise in males, with an analogous decrease in females [19].

Previous studies reported that both a prothrombotic state and a hypercoagulable state are recognized IBD features [20,21].

Clinical evidence indicates that inflammation is a potent prothrombotic stimulus that activates markers of coagulation, inhibits endogenous anticoagulant pathway, and reduces fibrinolytic system [22].

Thrombocytosis in IBD is considered a non-specific bone marrow response to inflammation.

Gavronska et al. [23] demonstrated that the PLC was significantly higher in patients with UC than the values obtained in the control group, which indirectly indicates that the chronic inflammatory process stimulates thrombocytopoiesis.

Our results showed statistically significantly higher PLC values in both groups of patients, UC and CD, compared to the controls.

Additionally, we observed lower MPV values in UC and CD groups than in the control group, but the difference was statistically significant only for the patients in the UC group.

MPV provides more comprehensive information about the platelet size and activity.

It is suggested that MPV can be influenced by the inflammatory processes and used as a prognostic factor in a number of inflammatory diseases [24].

Gavronska et al. [23] found significantly lower MPV values in patients with UC than the control group and concluded that MPV determination might be used to assess inflammation exacerbation of colonic mucosa in patients with UC.

Yüksel et al. [25] found significantly reduced MPV values in patients with UC and suggested that decreased MPV may be an indicator for increased disease activity in those patients.

Similarly, Polińska et al. [26] stated that patients with UC had significantly lower MPV values compared to the control group.

Possible explanation for low MPV in active UC may be that overproduction of proinflammatory cytokines and acute-phase reactants may suppress bone marrow activity and induce the production and the release of immature and smaller platelets resulting in a decrease in MPV [27].

Studies have already confirmed that PDW directly represents the heterogeneity in the

platelet size and may occur as a result of the change in the shape of platelets from discoid to spherical or because of changes with platelet activation [28].

Increased PDW values may reflect that the patient still has platelet activation, and that a new thrombus is forming [29].

However, only a few studies have evaluated the role of PDW in IBD. In a recent study, Öztürk et al. [12] reported that PDW positively correlated, while PCT negatively correlated with disease activity in UC patients.

These authors also reported that PCT percentage markedly correlated with ESR and WBC count.

In our study, patients with UC showed significantly higher PDW when compared to CD patients.

On the other side, the increase in PCT and PMI and a decrease in PDW were significant in patients with CD than the controls.

To the best of our knowledge, PMI has not been evaluated in IBD before. PMI is based on the observations that larger platelets are generally younger, more active, and functionally more effective in platelet plug formation and hemostasis than smaller ones.

During the last period, the value of PMI was analyzed in just a few studies in the neonatal and adult age groups.

Gerday et al. [30] first reported that PMI is closely related to the platelet function and suggests that PMI measurement may be used as a better indicator of the need for platelet transfusion than platelet count alone, especially in prophylactic transfusions.

In patients with psoriasis, plasma PMI was found to be higher than those in the control group, but PMI correlation with PASI score or disease duration was not confirmed [31].

According to the results published by Öztürk et al. [12], PDW was significantly lower in an active phase of UC and CD patients compared with patients in the remission phase.

Their results are very similar to Tang et al. [32] who stated that PDW level in active CD patients was lower than those in healthy controls and patients in remission.

In our cohort, PDW was significantly lower in active UC patients compared to inactive UC patients.

Even though the PDW value was decreased in patients with active CD, this was not significant compared to inactive CD patients, but it was significant compared to healthy subjects.

The areas under the ROC curve in discriminating active UC from inactive UC patients by PDW had fair diagnostic accuracy (AUC: 0.722).

The AUC for CD patients also yielded a fair discriminatory value (AUC: 0.798), which was increased only marginally comparing with the AUC of the UC patients.

The present study has also shown that PLC was significantly higher in active UC and CD patients compared to the inactive UC and CD patients and control group, which indirectly suggests that the increase in the level of platelet number can be used as a potential complementary indicator of disease exacerbation in IBD patients.

Our results shown that PLC has a fair diagnostic accuracy in distinguishing patients with active from inactive UC, with AUC of 0.756.

Obtained results are in accordance with that of Coşkun [33], who stated that the clinical use of PLC is limited in patients with UC for distinguishing active and remission phases.

Our data have also shown that PLC had the highest diagnostic accuracy for CD patients.

The AUC for PLC in CD patients achieved an excellent diagnostic accuracy (AUC: 0.909) in distinguishing active from inactive CD patients.

Güçlü and colleagues [34] reported that the PLC of active UC patients was higher, while the MPV was significantly lower than that of the UC patients in remission.

The authors concluded that due to the low values in the active UC patients and association with clinical, pathological, and colonoscopic indexes, the MPV could reflect UC disease activity.

Similar to findings reported in the literature, our results showed a reduction in MPV values in the active UC patients compared to inactive UC patients, but the difference was not significant.

We also found that MPV values decreased in the active UC group and inactive UC group compared to the controls, but only the decrease in MPV in the active UC group was significant.

Our study showed that although the MPV value was lowest in patients with active CD, this was not significant compared with the inactive CD patients and age and gender-matched healthy subjects.

Concerning MPV, our results agree with Öztürk et al. [12] whose results showed the highest MPV in controls and lowest in patients with active disease.

Saler et al. also did not find any significant association between MPV and disease activity in CD patients [35].

The present study results emphasized that serum level of PCT was significantly higher in patients with active UC compared to controls.

However, there was an insignificant difference between the active and inactive UC patients in terms of the PCT.

Besides, we also found raised PCT values in active CD patients compared to inactive CD patients and healthy subjects in the control group.

These results are in accordance with the results of Öztürk et al. [12] who reported that PCT percent was lowest in the control group and highest in patients with active phase of UC and CD.

The reported differences between groups were significant.

The present study has also shown a fair diagnostic accuracy of PCT in differentiating active from inactive UC patients, with an AUC of 0.731.

In addition, in CD patients, the diagnostic accuracy of PCT was good-to-excellent, with an AUC of 0.893.

Obtained results are in accordance with the recent studies that reported that PCT might be used as a specific and sensitive biomarker for determining active CD patients, especially in patients with a hs-CRP level lower than 10.0mg/L [32].

However, we did not measure ESR and hs-CRP values in our study population, so further research is still needed to confirm the relationship between inflammatory markers and platelet parameters.

Our study results showed that PMI was higher in patients with active UC compared with inactive UC patients and the healthy controls; however, only the difference regarding controls was significant.

Additionally, PMI value was significantly increased in patients with active CD compared to patients with inactive CD and controls.

Theoretically, elevated PMI may result from both, increase in MPV and/or PLC. Bearing in mind that MPV values in active UC and CD patients were lower than that in the inactive UC and CD patients and the control group, we concluded that PMI is probably a more useful parameter than MPV alone in explaining the mechanism of IBD.

However, several different factors, such as the age of disease onset, disease duration, family

history, smoking and diet pattern, blood sampling time, individual technologies for platelet measurement, can impact PMI and other platelet parameters.

All these factors should be considered when interpreting and translating results into everyday clinical practice.

To our knowledge, there is no study examining the discriminative capacity of PMI in the assessment of the disease activity in IBD using ROC curve analysis.

Since this study is the first to evaluate the diagnostic accuracy of PMI in determining whether the UC and CD patients in the active phase or not, a direct comparison of our results with results of other studies was unfeasible.

The AUC of the PMI was 0.724, which was lower than that of CD patients (AUC:0.893).

## Conclusions

For the first time, these results highlight the diagnostic value of PMI and suggest that PMI, as a novel biomarker, could be used as a possible indicator of disease activity in CD.

Having in mind that PMI is calculated by multiplying MPV and platelet count, it can be considered that PMI reflect the pathophysiology of diseases predisposed to inflammation more accurately than MPV and platelet count separately.

Both, the increase of platelet count and a low platelet volume are established features of IBD.

The data we obtained from our study revealed that increased PMI levels may due to severe chronic inflammation and raised platelet activity and aggregability, and that the number of platelet is at least as important as its volumetric size.

However, the main limitations of the current study were the small number of patients and a single-center design and, therefore, the results cannot be generalized over the whole population.

Multicenter prospective studies based on the larger sample size are needed in the future to provide additional information on this topic.

## Acknowledgements

The authors would like to acknowledge Dr. Milovan Regodic for critical reading of the manuscript.

## Conflict of interests

None to declare.

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