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The Relationship of Clinical Activation and Mean Platelet Volume (MPV) in Inflammatory Bowel Disease

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Abstract

Introduction: Inflammatory bowel disease (IBD) is a chronic disease that can involve various regions and layers of the gastrointestinal tract from the mouth to the anus, with exacerbations-remissions, genetic predisposition and extra intestinal symptoms. Although many activity indices have been used to show the activation of the disease, there is still no consensus on the determination of disease activation. The aim of this study was to investigate the utility of mean platelet volume (MPV), an inexpensive, easily accessible test, as a marker for clinical activation in IBD.

Materials and Methods: 94 clinically active ulcerative colitis, 45 Crohn's patients and 140 healthy individuals over 18 years of age, colonoscopically and histopathologically confirmed in our clinic, were included in the study. Demographic and clinical characteristics of the patients, laboratory results, colonoscopy and pathology reports were evaluated retrospectively.

Results: While 87 (62.6%) of the patients included in the study were male, 85 (60.7%) of the control group were male. The mean ages of the patient and control groups were 45.7±16.5 years and 42.9±14.2 years, respectively. Infection in both active and remission periods of the IBD group, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and leukocyte values were statistically higher in IBD compared to the control group. MPV was found to be lower in IBD compared to the control group. In addition, MPV values were also lower in the active disease period compared to the remission period.

Conclusion: Inflammatory parameters are used in the diagnosis and activation of IBD. We suggest that MPV can also be used as an inflammation marker to show the activation of IBD.

Keywords: Crohn's disease; inflammatory bowel disease; mean platelet volume; ulcerative colitis.

Introduction

Inflammatory bowel disease (IBD) is a chronic disease with two forms, ulcerative colitis (UC) and Crohn's disease (CD), which may involve various regions and layers of the gastrointestinal system from the mouth to the anus, progress with exacerbations-remissions, show genetic predisposition and extra intestinal symptoms (1,2). In epidemiological studies conducted in different geographical regions of the world, differences have been observed in the incidence and prevalence of UC and CD. IBD is observed more frequently in groups with high socio-economic status and in those living in inurban areas. The disease is more common in people of Jewish ethnic origin. The incidence and prevalence of both diseases have the highest rates in Europe, England and North America (3-5). In an epidemiological study conducted in our country based on hospital data, 74% of the cases were UC and 25% were CD and their incidences were reported as 4.1/100.000 and 2.6/100.000, respectively (6). Although their etiology is not known exactly, it is thought that they occur as a result of a complex interaction with genetic, environmental, microbial factors and especially immunity (7,8). However, the contribution of platelets to the pathogenesis of the disease has been shown in studies. Increased platelet count has been found to be related with disease activity (9,10). There are activity indices defined by various authors and groups to demonstrate the activity of UC. Almost all of the activity indices have been developed for objective evaluation and measurement of disease activity in clinical studies. Indices such as "Crohn's Disease Activity Index" and "Harvey-Bradshaw Index" are used to determine the degree of activation in CD. Laboratory findings in IBD are important in evaluating the activity of the disease and guiding

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the diagnosis. Leukocytosis, thrombocytosis, C-reactive protein (CRP), increase in erythrocyte sedimentation rate (ESR), increase in acute phase reactants including fibrinogen and ferritin are important markers used to demonstrate the degree of disease activity (11,12). Platelet size and volume may vary depending on the production conditions in the bone marrow. Platelet volume has been shown to be related with platelet production and activation (13,14). There is an inverse relationship between platelet count and MPV. MPV increases in conditions where platelet count decreases and platelet production increases (15,16). It has been suggested that overproduction of proinflammatory cytokines and acute phase reactants in infection, inflammation and malignancy may affect the megakaryopoiesis process and lead to release of small volume platelets from the bone marrow and thus decrease in platelet size (17). In a study performed in patients with acute infectious disease in the active inflammatory period, it was shown that MPV levels were low in the acute phase of the disease before treatment and these levels increased statistically significantly after treatment (18,19).

Materials and Methods

Between January 2010 and December 2015, 94 clinically active patients with ulcerative colitis, 45 patients with Crohn's disease and 140 healthy patients whose clinical, endoscopic, radiological and histopathological diagnoses were confirmed in gastroenterology services and polyclinics and internal medicine polyclinics were included as control group. Patients with malignancy, heart failure, any active infection, chronic haematological disease and pregnant women were excluded. Demographic and clinical characteristics, active endoscopic activity index, active and remission clinical activity index, type and duration of disease, site and extent of intestinal involvement, smoking, biochemical parameters (LDH, CRP, ESR, Albumin) and haematological parameters (Leukocyte, Neutrophil, Haemoglobin, Haematocrit, Platelet, MPW, RDW, PDW) were evaluated retrospectively. Rachmilewitz Clinical and Endoscopic Activity Indexes were used for UC activation. Crohn's Disease Activity Index (CDAI) was used for CD activation. Patients with Rachmilewitz Clinical Activity Index ≤ 4 were considered in remission, while patients with >4 were considered clinically active. If the score obtained in the Rachmilewitz Endoscopic Activity Index was between 0-4, the disease was considered to be in remission, while a score of >4 was considered active disease. In the CDAI used for CD activation, a score of <150 was considered as disease in remission, 150-220 as mild-moderate disease, 220-450 as moderate-severe disease, and >450 as severe-fulminant disease. Approval for this study was obtained from Necmettin Erbakan University Non-interventional Clinical Research Ethics Committee with decision number 665 dated 30.09.2016.

Statistical analysis: SPSS (Statistical Package for Social Sciences) 16.0 programme was used for statistical analyses. Descriptive measures of all variables were calculated and categorical variables were given as frequency and percentage and numerical variables were given as mean±ss. Chi-square test was used to compare categorical data. Continuous numerical variables were analysed by Kolmogorov-Smirnov test and histogram method. Group comparisons were made with parametric methods for variables that fit the normal distribution. Paired-Samples T test was used for comparison of two dependent groups; ANOVA analysis of variance and post-hoc (tukey) were used for multiple group comparisons. Receiver Operating Characteristic (ROC) analysis was performed to determine the sensitivity of the inflammatory parameters investigated in the study. A value of $p<0.05$ was considered statistically significant in our study.

Results

Of the 279 cases included in the study, 50.5% (n=141) were female and 62.6% (n=87) of the patient group were male. UC was present in 67.6% (n=94) and CD was present in 32.4% (n=45) of the patients. 63.8% (n=60) of UC patients, 60% (n=27) of CD patients and 60.7% (n=85) of the control group were male. The mean age of 139 patients in our study was 45.7±16.5 years, while the mean age of 140 control group was 42.9±14.2 years. The mean age of 94 UC patients in the patient group was 46.6±16.9 years, while the mean age of 45 CD patients was 43.9±15.5 years. Distal type was found in 22.3% (n=21), left type in 39.4% (n=37) and pancolonic involvement in 12.9% (n=36) of our UC patients. Colonic involvement was present in 24.4% (n=11), ileo-colonic in 24.4% (n=11), and ileal in 51.1% (n=23) of CD patients. The mean disease duration of UC patients was 41.9 months and the mean disease duration of CD patients was 22.2 months. Sixteen per cent (n=15) of UC patients, 40% (n=18) of CD patients and 53.6% (n=75) of the control group were smokers. CRP, ESR and leucocyte values, which are among the infection

Table 1: Comparison of laboratory values of UC, CD groups and control group

	Ulcerative Colitis (n=94)	Crohn's Disease (n=45)	Control (n=140)	P
Smokers (n,%)#	15 (16)	18 (40)	75 (53,6)	0.001a
LDH-1 (g/dL)*	231.30±74.52	254.02±110.85	184.02±40.64	0.001b
LDH-2 (g/dL) *	212.91±86.53	210.17±89.99	184.02±40.64	0.004c
CRP-1(mg/dL) *	38.39±41.99	47.48±51.68	3.20±4.08	0.001b
CRP-2(mg/dL) *	10.42±19.55	11.90±16.31	3.20±4.08	0.001b
ESR-1(mm/h) *	36.98±30.42	31.62±23.24	11.26±12.42	0.001b
ESR-2(mm/h) *	23.55±24.15	20.84±17.31	11.26±12.42	0.001b
Albumin-1 (g/dL) *	3.56±0.65	3.45±0.43	4.76±3.62	0.001b
Albumin-2 (g/dL) *	3.64±0.65	3.38±0.49	4.76±3.62	0.001d
Leukocyte-1 (mm3) *	8.79±3.16	10.10±4.37	7.05±1.77	0.001b
Leukocyte-2 (mm3) *	8.29±3.05	8.29±2.50	7.05±1.77	0.001b
Hemoglobin-1 (g/dL) *	11.06±2.49	11.63±2.37	14.11±1.80	0.001b
Hemoglobin-2 (g/dL) *	11.75±2.55	11.67±1.95	14.11±1.80	0.001b
Hematocrit-1 (%)*	34.51±6.28	35.97±5.99	42.17±4.84	0.001b
Hematocrit-2 (%)*	36.19±6.55	35.68±5.06	42.17±4.84	0.001b
Trombocyte-1 (mm3) *	365.46±171.07	345.80±137.25	267.87±62.32	0.001b
Trombocyte-2 (mm3) *	326.25±135.03	325.53±106.72	267.87±62.32	0.001b
MPV-1 (fl) *	7.62±1.86	7.85±2.09	10.36±1.13	0.001b
MPV-2 (fl) *	8.28±1.90	8.28±1.91	10.36±1.13	0.001b

LDH: Lactate dehydrogenase (normal value 50-150 U/L), **CRP:** C-reactive protein (normal value 0-0.05 mg/L), **ESR:** Erythrocyte sedimentation rate (normal value < 15 mm/h for male, < 20 mm/h for female), **MPV:** Mean platelet volume (normal value 7-11.5 fl), 1: Data of the groups in active period, 2: Data of the groups in remission period, # Chi-square test, * ANOVA analysis of variance and post-hoc (tukey), a: There is a statistical difference between ulcerative colitis group and control group, There is a statistical difference between ulcerative colitis group and crohn's group, There is no difference between Crohn's group and control group. b: There is no statistical difference between ulcerative colitis and crohn's group, there is statistical difference between ulcerative colitis group and control group, there is statistical difference between crohn's group and control group. c: There is no statistical difference between ulcerative colitis and crohn's group, there is statistical difference between ulcerative colitis group and control group, there is statistical difference between crohn's group and control group. d: There is statistical difference between ulcerative colitis and crohn's group, there is statistical difference between ulcerative colitis group and control group, there is statistical difference between crohn's group and control group.

Table 2: Comparison of laboratory values in active and remission periods of UC

	UC Active (n=94)	UK Remission (n=94)	P
LDH (g/dL) *	231.30±74.52	212.91±86.53	0,134
CRP (mg/dL) *	38.39±41.99	10.42±19.55	0.001
ESR (mm/h) *	36.98±30.42	23.55±24.15	0.001
Albumin(g/dL) *	3.56±0.65	3.64±0.65	0.386
Leukocyte (mm3) *	8.79±3.16	8.29±3.05	0.178
Hemoglobin (g/dL) *	11.06±2.49	11.75±2.55	0.001
Hematocrit (%)*	34.51±6.28	36.19±6.55	0.002
Trombocyte (mm3) *	365.46±171.07	326.25±135.03	0.002
MPV (fl) *	7.62±1.86	8.28±1.90	0.001

LDH: Lactate dehydrogenase (normal value 50-150 U/L), **CRP:** C-reactive protein (normal value 0-0.05 mg/L), **ESR:** Erythrocyte sedimentation rate (normal value < 15 mm/h for male, < 20 mm/h for female), MPV: Mean platelet volume (normal value 7-11.5 fl), * Paired-Samples T test

parameters, were found to be statistically significantly higher in the IBD group in active and remission periods when compared with the control group (P<0.0001). While no significant

difference was observed in the comparison of the same parameters between the active periods of UC and CD (P=0.271, P=0.299, P=0.077, respectively), these parameters were found to be significantly higher in the active period of the diseases when both the active period of UC and CD were compared with the control group (P<0.0001). Albumin, which is used as a negative acute phase reactant, was significantly lower in both active (P<0.0001) and remission periods of the disease (P=0.001) compared with the control group. Platelet count was significantly higher in the active and remission periods of the patients compared with the control group (P<0.0001). In the IBD group, MPV values were significantly lower in both active and remission periods compared with the control group (P<0.0001). No statistically significant difference was observed between the MPV values of UC and CD in both active and remission periods (P=0.526, P=0.990, respectively), and the MPV values of both patient groups in active and remission periods were found to be significantly lower when compared with the control group (P<0.0001). The laboratory values of UC, CD and control groups are shown in Table 1. It was observed that MPV values were significantly lower in the active period compared to the remission period in UC patients (P<0.0001) (Table 2). MPV values in the active period of CD were significantly lower than those in the remission period (P=0.025) (Table 3). When active and remission periods of UC were compared, the area under the curve (AUC)=0.592 (95% CI: 0.508-0.677) for MPV value was analysed and the sensitivity and specificity for MPV cut-off value of 8.25 were found to be 63% and 58.2%, respectively. For CRP value, AUC=0.772 (95% CI: 0.703-0.840) was analysed and sensitivity and specificity for CRP cut-off value of 9.07 were found to be 72.8% and 65.5%, respectively. For ESR value, AUC=0.658 (95% CI: 0.578-0.739) was analysed and sensitivity and specificity were found as 67.4% and 63.2% for ESR cut-off value of 20.50. When the remission period of UC was compared with the control group, AUC=0.748 (95% CI: 0.686-0.810) was analysed for MPV value in differentiating UC in the remission period and sensitivity and specificity for MPV cut-off value were found to be 69% and 63.7%, respectively.

Table 3: Comparison of laboratory values in CD active and remission periods

	Crohn Active (n=45)	Crohn Remission (n=45)	P
LDH (g/dL) *	254.02±110.85	210.17±89.99	0.017
CRP (mg/dL) *	47.48±51.68	11.90±16.31	0.001
ESR (mm/h) *	31.62±23.24	20.84±17.31	0.002
Albumin (g/dL) *	3.45±0.43	3.38±0.49	0.336
Leukocyte (mm3) *	10.10±4.37	8.29±2.50	0.008
Hemoglobin (g/dL) *	11.63±2.37	11.67±1.95	0.893
Hematocrit (%)*	35.97±5.99	35.68±5.06	0.700
Trombocyte (mm3) *	345.80±137.25	325.53±106.72	0.190
MPV (fl) *	7.85±2.09	8.28±1.91	0.025

LDH: Lactate dehydrogenase (normal value 50-150 U/L), **CRP:** C-reactive protein (normal value 0-0.05 mg/L), **ESR:** Erythrocyte sedimentation rate (normal value < 15 mm/h for male, < 20 mm/h for female), MPV: Mean platelet volume (normal value 7-11.5 fl), * Paired-Samples T test.

Table 4: ROC analysis of MPV and other inflammation markers in active and remission periods of UC and CD

	AUC	P	95% CI	Sensitivite	Spesifite	Cutoff
MPV (UC)	0.592	0.017	0.508-0.677	63	58.2	8.25
MPV (CD)	0.558	0.298	0.438-0.679	57.8	48.8	8.54
CRP (UC)	0.772	0.001	0.703-0.840	72.8	65.5	9.07
CRP (CD)	0.809	0.001	0.721-0.897	77.8	65.1	8.78
ESH (UC)	0.658	0.001	0.578-0.739	67.4	63.2	20.50
ESH (CD)	0.643	0.021	0.527-0.760	60	55.8	18.50

CRP: C-reactive protein (normal value 0-0.05 mg/L), **ESR:** Erythrocyte sedimentation rate (normal value < 15 mm/h for men and < 20 mm/h for women), **MPV:** Mean platelet volume (normal value 7-11.5 fl).

For CRP value, AUC=0.653 (95% CI: 0.582-0.723) was analysed and its sensitivity was 73.6% and specificity was 64.4% for the CRP cut-off value of 1.99. For ESR value, AUC=0.632 (95% CI: 0.559-0.705) was analysed and its sensitivity and specificity for ESR cut-off value of 11.50 were found to be 59.8% and 65.1%, respectively.
When the active and remission periods of CD were compared, the area under the curve (AUC)=0.558 (95% CI: 0.438-0.679) for the MPV value was analysed and the sensitivity and specificity for the MPV cut-off value of 8.54 were found to be 57.8% and 48.8%, respectively. For CRP value, AUC=0.809 (95% CI: 0.721-0.897) was analysed and sensitivity and specificity for CRP cut-off value of 8.78 were found to be 77.8% and 65.1%, respectively. For ESR value, AUC=0.643 (95% CI: 0.527-0.760) was analysed and its sensitivity and specificity were found to be 60% and 55.8%, respectively, for ESR cut-off value of 18.50. When the remission period of CD was compared with the control group, AUC= 0.753 (95% CI: 0.653-0.854) was found for MPV value and its sensitivity was 71.1% and specificity was 58.1% for MPV cut-off value of 9.55. For CRP value, AUC=0.809 (95% CI: 0.721-0.897) was analysed and its sensitivity and specificity were found to be 78.2% and 64.4% for the CRP cut-off value of 8.22. For ESR value, AUC=0.643 (95% CI: 0.527-0.760) was analysed and its sensitivity and specificity were found to be 64.4% and 51.2% for the ESR cut-off value of 17.50. ROC analysis of MPV and other inflammation markers in active and remission periods of UC and CD is given in Table 4.

Discussion

Delayed diagnosis and inadequate treatment in IBD lead to high morbidity, mortality and significant increases in health expenditures. Therefore, these patients should be diagnosed in a timely manner and parameters indicating disease activation should be carefully monitored. Determination of the severity and activity of the disease in patients with IBD is of great importance in approaching the disease, shaping the treatment, monitoring the response to treatment and evaluating the prognosis. For this reason, there is a need for ideal tests to show disease activation in the studies carried out to date. The tests to be used to show activation should be non-invasive, easy to apply, inexpensive, should accurately reflect the activation of the disease, should be specific to the disease and should be able to show the relapse status of the disease in patients. Despite scoring systems in which haematological, biochemical and histopathological findings are added to endoscopic and clinical findings to determine the activity of IBD, an indisputable and gold standard test that can be used to determine the activity of IBD has not yet been defined. It is a fact that the search for the ideal tests to be used in the diagnosis and demonstration of the activity of IBD will continue in the future as it has continued until today. CRP, ESR and complete blood count are the leading routine laboratory tests ordered in the diagnosis of infectious and inflammatory diseases, determination of disease severity and evaluation of response to treatment (11,20). CRP is increased in many inflammatory diseases including IBD (21). CRP response differs between UC and CD. While there is a strong CRP response in CD, there is a more moderate CRP response in UC (22). Fegan et al. (23) showed that CRP and ESR correlated with disease activation, but CRP was shown to be a better marker in this regard. The correlation between laboratory markers and disease activation in UC and CD is stronger in CD than in UC. In the Mayo clinic data, it has been shown that there is a correlation between CRP and endoscopic and histological activity in CD as well as clinical activation, but this correlation is weaker in UC (24). In our study, CRP and ESR results were similar to those in the literature. CRP and ESR were found to be significantly higher in IBD compared to the control group in both active and remission periods of the disease. In our study, MPV was found to be a parameter that can be used to show the activation of the disease, but it was not superior to CRP in showing the severity of the disease. Leukocytes increase as an acute phase reactant in IBD. The leucocytosis that occurs in this condition is not specific to IBD but also increases in other inflammation and stressful conditions. Leucocyte count may also change depending on some drugs used in the treatment of IBD. For example, while leucocyte count increases with glucocorticoid use, leucocyte count decreases with azathioprine and 6-mercaptopurine use. Leukocyte values of the patients in our study were significantly higher when compared with the control group. Platelets contribute to the inflammatory process and microbial host defence (25). Platelets are known to play a role in inflammation in a number of diseases. According to recent studies, there is a correlation between platelet indices and inflammation (10,26). There is an increase in platelet count in IBD and this increase may be an indicator of inflammation. Considering the normal range of platelet count, it has been accepted that this is a less useful

parameter. MPV, which is an indicator of platelet function and activation, can also be evaluated simultaneously with the evaluation of platelets. MPV has been shown to be associated with inflammatory diseases in some studies. Zareifar et al. (19) showed that MPV levels were low in the acute phase of the disease before treatment and increased statistically significantly after treatment in a study conducted with 100 patients with acute infectious disease who were in active inflammatory period. Therefore, it was thought that MPV could be a parameter that could be used to show the activity of the disease and to follow up the treatment response. Recently, it has been the subject of various publications that MPV may be an indicator of disease activity in gastroenterological diseases. In the study conducted by Yüksel et al. (27), it was emphasised that MPV may be a marker of disease activity in patients with UC and it was shown that MPV decreased in IBD especially in the active periods of the disease. In another study, the relationship between low MPV and IBD activation was shown (28). In another study conducted in our country, MPV was found to be lower in the patient group when patients with IBD and the control group were compared (29). In another study, it was shown that platelet count increased and MPV value decreased in patients with CH compared with the healthy population (30). In our study, it was found that MPV similarly decreased especially in the active periods of the disease and there was a significant difference between them when compared with the control groups. It was observed that MPV values were significantly lower in both UC and CH groups compared with the control group. Again, in the comparison of our patient groups between their active and remission periods, it was observed that MPV values in the active periods of both patient groups were significantly lower than those in the remission periods.

Study limitations: The biggest limitation of our study is that it is a retrospective study. Our small number of patients is another limitation. We think that new prospective studies with a larger number of patients will contribute more to this issue.

Conclusion

In conclusion, inflammatory parameters can be used in the diagnosis and activation of inflammatory bowel diseases whose main mechanism of occurrence is intestinal inflammation. Although various laboratory parameters have been investigated for this purpose, none of the available diagnostic tools has been shown to be superior to each other. To date, the mechanism of action of mean platelet volume, which has been the subject of research in many diseases, in inflammatory bowel diseases has not been fully understood. Nevertheless, MPV is a parameter that can be easily evaluated during complete blood count, which we frequently use in our daily practice, and does not require any additional cost. As a result of our study, we think that MPV is a parameter that can be used to show activation in inflammatory bowel diseases. In future studies, more specific markers may be investigated to show the activation of IBD.

Ethical approval: Ethics Committee approval was obtained from Necmettin Erbakan University Clinical Research Ethics Committee with decision number 665 dated 30.09.2016.

Conflict of interest: The authors have no conflict of interest related to this study.

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References

1. Daniel CB, Simon RC. Inflammatory bowel disease: cause and immunobiology. Lancet 2007; 369: 1627–1640.
2. Mannaz F. Inflammatory bowel disease. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;108(5): e1-10.
3. GBD 2017 Inflammatory Bowel Disease Collaborators. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2020; 5:17.
4. Manasi A, Heidi SC, Martin B, Jean-Frederic C, Tine J, Kristine HA. The Rising Burden of Inflammatory Bowel Disease in Denmark Over Two Decades: A Nationwide Cohort Study. Gastroenterology 2022; 163:1547.
5. Siew CN, Hai YS, Nima H, Fox EU, Whitney T, Eric IB et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 2017; 390:2769.
6. Ülkü D. Epidemiology and genetics of inflammatory bowel disease in Turkey. Falk Symposium 159. IBD 2007- Achievements

in research and clinical practice. Edited by Tözün N, Dağlı Ü, Mantzaris G, Schölmerich J 2007;3-12.
7. Oriana D, Danny JA, Ana P, Lissette G, Maria Alejandra QC et al. Inflammatory bowel disease is presenting sooner after immigration in more recent US immigrants from Cuba. Aliment Pharmacol Ther 2017; 46:303.
8. Manasi A, Giulia C, Sarita S, Nete MN, Morten F, Jean-Frederic C et al. Inflammatory bowel diseases among first-generation and second-generation immigrants in Denmark: a population-based cohort study. Gut 2021; 70:1037.
9. Aleksandra K, Olga Martyna KL, Joanna K, Halina K and Violetta DP. Mean Platelet Volume (MPV): New Perspectives for an Old Marker in the Course and Prognosis of Inflammatory Conditions. Mediators Inflamm 2019; 2019: 9213074.
10. Jonathan M, Martina C, Maria S, Alexey M, Carsten D. Beyond Hemostasis: Platelet Innate Immune Interactions and Thromboinflammation. Int J Mol Sci 2022 Mar 31;23(7):3868.
11. James DL. The utility of biomarkers in the diagnosis and therapy of inflammatory bowel disease. Gastroenterology 2011. May 1;140(6):1817-26.
12. Mahmoud HM, Guangyong Z, Sushil KG, Sean GF, John KM, Nilesh C et al. C-reactive protein, fecal calprotectin, and stool lactoferrin for detection of endoscopic activity in symptomatic inflammatory bowel disease patients: a systematic review and meta-analysis. American Journal of Gastroenterology 2015;110(6):802-819.
13. Bartosz H, Ilona KS, Janusz S, Radosław L, Andrzej L, Barbara ZS et al. Association between multimorbidity and mean platelet volume in diabetic patients with acute myocardial infarction. Acta Diabetol 2018 Feb;55(2):175-183.
14. Al-Amir BM, Hassan ME, Hazem KA, Hesham MH and Ashraf K. The mean platelet volume and plateletcrit as predictors of short-term outcome of acute ischemic stroke Egypt J Neurol Psychiatr Neurosurg 2019;55(1):4.
15. Avi L, David P and Michael L. Are platelet volume indices of clinical use? A multidisciplinary review. Ann Med (2012) 44(8):805-16.
16. Schmoeller D, Picarelli MM, Paz Munhoz T, Poli de Figueiredo CE, Staub HL. Mean platelet volume and immature platelet fraction in autoimmune disorders. Frontiers in Medicine 2017;4:146.
17. Deepa R.J. A and Mike L. Can Mean Platelet Volume Be Used as a Predictor of Vascular Disease? Problems and Pitfalls. Semin Thromb Hemost 2017; 43(06): 599-608.
18. Hamidzade Ş, Majid F and Shiva S. Evaluation of platelet count, erythrocyte sedimentation rate and C-reactive protein levels in paediatric patients with inflammatory and infectious disease. New Microbes New Infect 2020 Sep; 37: 100725.
19. Zareifar S, Farahmand Far MR, Golfeshan F, Cohan N. Changes in platelet count and mean platelet volume during infectious and inflammatory disease and their correlation with ESR and CRP. J Clin Lab Anal 2014 May;28(3):245-8.
20. Mengque X, Mengsha C, Xiaoli C, Haotian C, Xing L, Qian C. Correlation between Serological Biomarkers and Disease Activity in Patients with Inflammatory Bowel Disease. Biomed Res Int 2019 Dec 25:2019:6517549.
21. Paraskevi D, George IP, Marina M, Periklis M, Ifigenia P, Spyros P et al. Relation of Mean Platelet Volume (MPV) with Cancer: A Systematic Review with a Focus on Disease Outcome on Twelve Types of Cancer. Curr Oncol 2023 Mar 14;30(3):3391-3420.
22. Severine V, Gert Van A and Paul R. Laboratory markers in IBD: useful, magic, or unnecessary toys? Gut 2006 Mar; 55(3): 426–431.
23. Elizabeth A. F, Roland F. D, Paul N. M, Humphrey JF. H, Vinton S. C, Aviva. P et al. Serum levels of C-reactive protein in Crohn's disease and ulcerative colitis. European journal of clinical investigation 1982;12(4): 351-359.
24. Craig A. S, Edvard. V. L, William J. T, William S. H, Alan R. Z and William J. S. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. Inflammatory bowel diseases 2005;11(8): 707-712
25. Domenico C and Claudio R. Biological therapy in pediatric inflammatory bowel

disease. Journal of clinical gastroenterology 2017;51(2):100–10.
26. Fabrice C, Sandrine L, Patricia C, Sophie A and Olivier G. Lipopolysaccharide induces sCD40L release through human platelets TLR4, but not TLR2 and TLR9. Intensive Care Med 2007;33(2):382-4.
27. Osman Y, Kaan H, Ömer B, Seyfettin K, Sedat C, Nafiye H, et al. An overlooked indicator of disease activity in ulcerative colitis: mean platelet volume. Platelets 2009; 277-281.
28. Andreas N. K, Michael I. K, Aekaterini S, Spiros P. P, M. I. Koukourakis, A. Sfiridaki, S. P. Potamianos, Maria G. K, Ioannies E. K et al. Mean platelet volume: a useful marker of inflammatory bowel disease activity. The American journal of gastroenterology 2001;96(3): 776-781.
29. Ömer B, İbrahim E and Mehmet İ. The Relationship betwen Mean Platelet Volume Measurement and Disease Activity in İnflammatory Bowel Disease. J New Medical 2000:46-9.
30. Herman R, Sladek M, Pieczarkowski S, Dumnicka P, Fyderek K. Is mean platelet volume a good predictor of sustained response to one year infliximab therapy in pediatric patients with Crohn's disease? Folia Medica Cracoviensia 2017;2:63-71