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Assessment of inflammatory markers in ulcerative colitis and association with the disease

Ulcerative colitis and inflammatory markers

Ahmed Ramiz Baykan[1], Serkan Cerrah[1], Büşra Karahan[2], Sedat Çiftel[1], Ayetullah Temiz[3], Elmas Kasap[4]
[1] Gastroenterology, Erzurum Regional Training and Research Hospital, Erzurum
[2] Department of Internal Medicine, Erzurum Regional Training and Research Hospital, Erzurum
[3] Department of General surgery, Regional Training and Research Hospital, Erzurum
[4] Department of Gastroenterology, Celal Bayar University, Manisa, Turkey

Abstract
Aim: In daily routine practice, non-invasive tests are needed in addition to symptoms to determine activation in patients with ulcerative colitis (UC). In this study, it was aimed to compare the results of non-invasive tests used frequently at the time of diagnosis of patients diagnosed with UC with endoscopic severity.
Material and Methods: This retrospective cohort study was carried out on 202 patients between 2018 and 2022. The white blood count (WBC), mean platelet volume (MPV), hemoglobin (HB), hematocrit (Hct), C-reactive protein (CRP), albumin, neutrophil-lymphocyte ratio (NLR), CRP-albumin ratio (CAR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR) of the patients were calculated at the time of diagnosis. The severity of UC was assessed via colonoscopy using the Mayo Endoscopic Subscore (Mayo Score). In addition, patients with active UC were re-evaluated during remission to calculate the predictive values of tests in UC activation and severity.
Results: There was a significant correlation between the Mayo Subscore and CRP (r: 0.34, P < 0.01), WBC (r: 0.23, P = 0.01), HB (r: –0.23, P = 0.01), NLR (r: 0.49, P < 0.01), CAR (r: 0.51, P < 0.01), PLR (r: 0.32, P < 0.01), and LMR (r: –0.34, P < 0.01). The sub-assessment, taking colon involvement into consideration, showed a correlation between the Mayo Subscore and NLR and CAR with pancolitis, left colon involvement, and distal colitis. The highest area under the curve (AUC) value, found in the tests, was with the CAR (0.919). When the CAR cut-off value was taken as 0.11, the sensitivity was 80.2%, and the specificity was 94.4%, indicating UC activation.
Discussion: Inflammatory markers in UC have adequate sensitivity in indicating activation, and they also aid in the identification of severity of involvement in patients.

Keywords
Ulcerative Colitis, CRP-Albumin Ratio, Neutrophil-Lymphocyte Ratio

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Corresponding Author: Ahmed Ramiz Baykan, Gastroenterology, Erzurum Regional Training and Research Hospital, Erzurum, Turkey.
E-mail: ahmedbaykan@hotmail.com P: +90 555 506 18 78
Corresponding Author ORCID ID: https://orcid.org/0000-0001-6798-0240

Introduction

Ulcerative colitis (UC) is characterized by mucosal inflammation that can exacerbate and remit over time. A recent important development is that the treatment of UC is based on mucosal inflammation rather than symptoms, as it provides better results [1,2]. Symptoms do not represent the presence or severity of mucosal inflammation consistently. In fact, it was revealed that symptoms did not show endoscopic activity in 30% of patients with UC [3].

Determining the severity of intestinal inflammation in UC is very important for the clinician, and remains a challenging problem at the same time. Although endoscopic methods are the most reliable approach in combination with biopsy, their invasive and expensive nature are the disadvantages of the method. Another significant downside is that endoscopic procedures posed a high risk of transmission during the recent COVID-19 pandemic. As a matter of fact, endoscopic procedures decreased by 95% during this period [4]. Non-invasive tests used at this stage are widely available, and play a key role with their modest accuracy. In this study, it was aimed to determine which marker best predicts intestinal inflammation in patients diagnosed with UC by comparing the results of noninvasive tests at the time of application to our clinic with the results of the subsequent colonoscopic evaluation.

Material and Methods

Study design and patients

The retrospective cohort study was carried out from January 1, 2018 to 2022. Patients over the age of 18 who were diagnosed with UC via colonoscopy, performed after applying to the gastroenterology clinic were included in the study. Patients who had been previously diagnosed with UC and were on medication, those with acute or chronic renal failure, cirrhosis, cancer, or acute or chronic infectious diseases, with a history of immunosuppressive use at the follow-up examination, blood assays and colonoscopy exceeding two weeks were excluded from the study. The control group consisted of patients without comorbidities in a similar age group. Patients included in the study were re-evaluated during clinical remission. Follow-up blood tests were conducted for patients who were in remission and did not use immunosuppressants.

Blood samples of the patients were taken after 8 h of fasting at the time of diagnosis, and at the follow-up examination. The white blood count (WBC), neutrophil, lymphocyte, monocyte, mean platelet volume (MPV), hemoglobin (Hb), hematocrit (Hct), C-reactive protein (CRP), and albumin results were evaluated. The neutrophil-lymphocyte ratio (NLR), CRP-albumin ratio (CAR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR) were calculated using current results. The severity of UC was assessed via colonoscopy, using the Mayo Endoscopic Subscore (Mayo Subscore).

Accordingly, normal mucosa and inactive disease were rated Mayo 0, and severe disease (spontaneous bleeding, large ulcerations) was rated up to Mayo 3. The involvement of the disease was evaluated in 3 groups, as distal colitis, left colon involvement, and pancolitis.

Endoscopic imaging was carried out using a Fujinon ED-450XT5 device (Minato City, Tokyo, Japan) by 3 experienced gastroenterologists. Biochemical parameters were studied with a Siemens Atellica analyzer (Malvern, PA, USA), and the hemogram was studied with Sysmex xn 9000 device (Kobe, Japan).

Ethical approval

This retrospective cohort study was approved by the Ethics Committee of Erzurum Training and Research Hospital in accordance with the Declaration of Helsinki (Ethics Committee approval number: 2021/23-294).

Statistical Analysis

Statistical analysis was performed using SPSS Statistics for Windows 17.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as the mean ± SD or median with range. Categorical parameters were compared using the x2 or Fisher's exact test when appropriate, and continuous variables were compared using the student t-test. $P < 0.05$ was considered statistically significant. The Spearman correlation analysis was used to determine the association of the Mayo Subscore and the inflammation markers. The relationship between the localization of involvement in the colon and the levels of markers was evaluated using ANOVA. The values of the inflammatory markers in predicting activation in patients with inactive UC were evaluated using receiver operating characteristic (ROC) analysis. Optimum cut-off values, sensitivity, specificity, negative predictive values, and positive predictive values were calculated.

Results

The study was carried out on 202 patients, consisting of 114 males and 88 females. The average age was 46.5 ± 13.3 years among male participants, and 42.9 ± 15.8 years among the female participants ($P = 0.09$). There was a significant difference between the patients with active disease and the control group in terms of the WBC, hemoglobin, platelet, CRP, albumin, NLR, CAR, and PLR. The group of patients in remission and the control group were similar, except for hemoglobin values ($P < 0.001$) (Table: 1).

A significant correlation between the Mayo Subscore and CRP (r: 0.34, $P < 0.01$), WBC (r: 0.23, $P = 0.01$), hemoglobin (r: –0.23, $P = 0.01$), NLR (r: 0.49, $P < 0.01$), CAR (r: 0.51, $P < 0.01$), PLR (r: 0.32, $P < 0.01$), LMR (r: –0.34, $P < 0.01$) was found in the Spearman correlation analysis in the patients with UC. As shown in Table 2, the sub-assessment, taking colon involvement into consideration, showed a correlation between the Mayo Subscore and NLR and CAR with pancolitis, left colon involvement, and distal colitis.

When UC involvement localization in the colon and the WBC, CRP, CAR, NLR, PLR levels were compared in the post hoc analysis, the NLR and WBC values were significantly higher in the patients with pancolitis compared to distal colitis involvement ($P = 0.01$ and $P = 0.004$, respectively).

The values of the inflammation markers (WBC, NLR, CAR, LMR, PLR) in predicting activation in the patients with inactive UC were evaluated using ROC analysis. As shown in Table 3, the highest area under the curve (AUC) value was also found in CAR (0.919). When the CAR cut-off value was taken as 0.11, the sensitivity was 80.2%, and the specificity was 94.4%, indicating UC activation (Figure 1).

Table 1. Demographic and laboratory results of patients

	Patient (n: 112)	Control (n: 90)	P value
Active Disease			
WBC (10^9/L)	8.94±3.23	7.03±1.35	<0.01*
Hemoglobin (g/dL)	12.89±2.22	14.75±1.43	<0.01*
Platelets (K/mm3)	333741.07±107116.99	270400.00±58843.49	<0.01*
Albumin (g/dL)	39.06±6.54	45±2.48	<0.01*
CRP (mg/L)	23 (0.1-209.2)	0.9 (0-4.3)	<0.01*
MPV (fl)	10.08±0.92	10.23±0.79	0.16
NLR	2.77±1.77	2.1±1.04	<0.01*
CAR	0.82(0-5.37)	0.01 (0-0.09)	<0.01*
PLR	168921.81±86390.28	137319.92±48319.63	<0.01*
LMR	3.43±1.51	4.46±1.56	0.77
Localization of the disease			
Distal colitis n (%)	49 (43.8)		
Left sided n (%)	26 (23.2)		
Pancolitis n (%)	37 (33)		
Inactive disease			
WBC (10^9/L)	7.35±1.8	7.03±1.35	0.14
Hemoglobin (g/dL)	14.12±1.53	14.75±1.43	<0.01*
Platelets (K/mm3)	285901.79±77172.31	270400.00±58843.49	0.10
Albumin (g/dL)	44.2±3.51	45±2.48	0.06
CRP (mg/L)	1.46±1.31	1.22±1.2	0.16
MPV (fl)	10.14±1.05	10.23±0.79	0.47
NLR	2.15±1.09	2.1±1.04	0.76
CAR	0.03±0.02	0.02±0.01	0.06
PLR	152616.43±79479.38	137319.92±48319.63	0.09
LMR	4.13±1.97	4.46±1.56	0.19

WBC, White blood cell; MPV, mean platelet volume; CRP, C-reactive protein; CAR, CRP albumin ratio; PLR, platelet lymphocyte ratio; LMR, lymphocyte monocytes ratio
* P <0.05 is considered significant for statistical analyses.

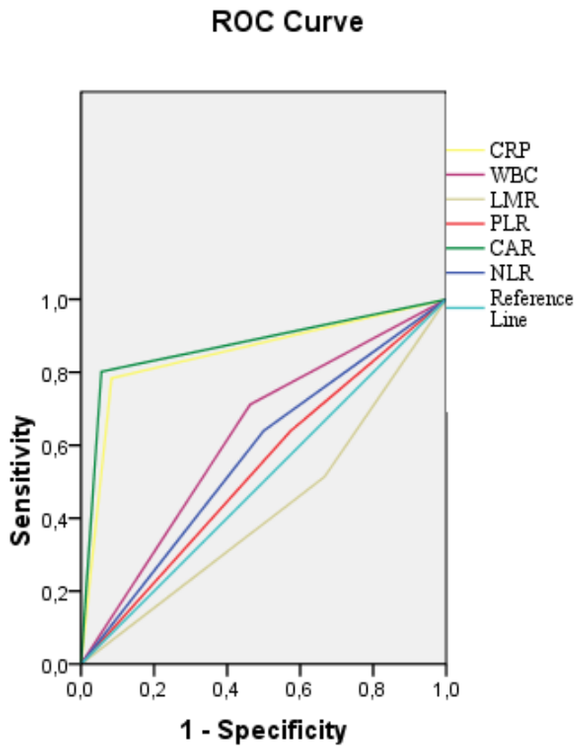

Figure 1. Receiver operating characteristic (ROC) curve of inflammatory markers in predicting active disease

Table 2. Correlation between mayo sub score and inflammatory markers

	Pancolitis		Left-sided colitis		Distal colitis	
	r	p	r	p	r	P
CRP	0.54	<0.01*	0.50	<0.01*	0.08	0.58
WBC	0.44	0.06*	0.13	0.22	0.19	0.18
Platelets	0.12	0.45	0.08	0.67	0.13	0.36
Albumin	-0.34	0.03*	-0.06	0.77	-0.05	0.97
Hemoglobin	0.17	0.25	-0.25	0.20	-0.24	0.08
NLR	0.55	<0.01*	0.51	<0.01*	0.35	0.01*
CAR	0.55	<0.01*	0.51	<0.01*	0.44	0.02*
PLR	0.38	0.01	0.41	<0.03*	0.15	0.27
LMR	-0.48	0.02*	-0.46	<0.01*	-0.03	0.78

WBC, White blood cell; CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio; CAR, CRP to albumin ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocytes ratio * P <0.05 was considered significant for statistical analyses

Table 3. ROC analyses of inflammatory markers to differentiate between active and inactive UC

	Cut-off	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CAR	0.11	0.919	80.2	94.4	93.6	82.2
NLR	1.87	0.598	64	50	55.9	57.7
CRP	3.3	0.897	78.4	91.7	90.7	81.1
PLR	128114.46	0.551	64	42.6	52.9	54.5
LMR	3.10	0.388	51.4	33.3	43.5	40.2
WBC	7.26	0.668	71.2	53.7	60.1	64.8

WBC, White blood cell; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio; CAR, CRP to albumin ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocytes ratio; AUC, the area under the curve; PPV, positive predictive value; NPV, negative predictive value

Discussion

Invasive interventions are often used to detect the activation of the disease in patients with UC. In routine clinical practice, non-invasive and accessible tests are needed to determine activation. There have been numerous studies carried out with various markers that predict the activation of the disease using hemograms and biochemical parameters [5–7]. In this study, it was aimed to assess the effectiveness of commonly used markers in patients diagnosed with UC based on the Mayo Subscore. Consequently, the NLR and CAR were found to be correlated with colon involvement severity in all segments. When the CAR cut-off value was taken as 0.11, the sensitivity was 80.2%, and the specificity was 94.4%, predicting UC activation.

CRP is undoubtedly the most commonly studied inflammatory marker in both Crohn's disease and UC. CRP is a pentameric acute phase protein with a short half-life that is produced by the liver under the influence of interleukin (IL)-6 and other cytokines upon inflammatory stimulation [5]. Lobaton et al.[8] in their study evaluating activation with the Mayo Subscore, also observed that CRP had a moderate correlation with the Mayo Subscore in patients with UC similar to our study (r: 0.307, P < 0.01). Ishida et al. [9] noted that there was a better association between CRP and Mayo Subscore (r: 0.54, P < 0.01). When the localizations of involvement were evaluated in this study, no significant association was observed between

distal involvement and the CRP values. It was believed that there was no significant association since the Mayo Subscores of the patients with distal colitis were lower, and the involvement affected a limited area when compared to other types of involvement. The severity and toxicity of the disease is correlated with the amount of colonic tissue affected by inflammation in UC [10]. Indeed, it was reported in a study carried out in China [5] that a higher CRP value was most likely correlated with the presence of extensive colitis (OR: 9.3, 95% CI: 3.30–26.40). Similarly, Ishida et al. [9] emphasized in their study that high CRP values were associated with disseminated and severe infection.

Chronic inflammation is associated with the higher fractional catabolic speed of albumin, and increases the ejection of albumin from the vascular compartment. Moreover, additional factors such as malnutrition and malabsorption cause reduced albumin levels in patients with UC. Hypoalbuminemia detected at the time of diagnosis is an important parameter indicating the prognosis of UC [6]. The clinical significance of the CAR calculated as CRP divided by albumin has gradually increased after studies showing that it is an independent predictor of mortality in patients with severe sepsis and septic shock. Studies on UC have concluded that it indicated disease activity better when compared to CRP and albumin [11–13]. Furthermore, some studies have shown that the CAR is an important predictor for nonresponse to steroids [14] and colectomy in patients with UC. Liu et al. [15] compared the effectiveness of CRP, the erythrocyte sedimentation rate, and CAR in their study with 231 patients in 2021, and emphasized that the most effective result in demonstrating activation in UC patients was with CAR (cut-off value: 0.06, AUC: 0.918, sensitivity: 82.19%, specificity: 95%). Chen et al. [11] investigated the efficacy of the CAR in 876 patients with inflammatory bowel disease (IBD). They found that the AUC was 0.827, the sensitivity was 67%, and the specificity was 86%, when they took the cut-off value as 0.18 for the CAR in predicting activation in patients with inactive UC. On the other hand, the AUC was 0.919, the sensitivity was 80.2%, and the specificity was 94.4% in this study, where UC activation was assessed using the Mayo Subscore. A study using a different method in predicting activation, but with very similar cut-off values to the current study was carried out by Sayar et al. [12] Patients with UC were categorized as mild, moderate, and severe, and a CAR level of 0.12 was suggested as the cut-off value for severe disease. The AUC, sensitivity, and specificity at this value were reported as 0.877, 97%, and 79% respectively.

In the studies on the NLR among other parameters considered in predicting activation, the sensitivity varied from 54 to 90%, and specificity from 63% to 91%, with varying cut-off values [7,16,17]. Langley et al. [4] carried out a systematical review of 62 studies in 2021 that suggested a significant correlation between NLR and endoscopic activity in UC in most studies, which was similar to that herein, while not in Crohn's disease (no correlation in 4 out of every 5 studies). There are studies that have shown a correlation between the NLR and involvement of the disease [17,18], as well as studies not showing such correlation [19]. In the current study, although not with CRP and the CAR, a significant relationship was observed with endoscopic severity with the NLR, as well as with the size of involvement (P = 0.01, r = 0.298). NLR was also indicated as a predictor [20] in terms of response to anti-tumor necrosis factor drugs [21], the risk of post-ileal pouch-anal anastomosis IBD [22], post-operative hospital stay, and complications. PLR, which is often assessed together for efficacy, has efficacy values similar to the NLR. Although PLR and NLR were found to have similar efficacy in indicating activation, the significant correlation found with the NLR in all of the segments was not found with the PLR when the involvement localization of the endoscopic activity was taken into consideration.

This study had some other limitations in addition to its retrospective nature. Furukowa et al. [13] found the CAR to be associated with moderate and severe involvement in long-standing disease, but they did not observe a significant correlation in patients with short-term involvement in their study carried out on patients with IBD. We consider the fact that the study population herein consisted of newly diagnosed patients, and the fact that the duration of disease was unknown was another limitation of the study. Being a representation of one region due to being monocentric was another limitation of the study.

Conclusion

Inflammatory markers in UC have adequate sensitivity in indicating activation, and they also aid in the identification of the severity of involvement in patients.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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