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New trends associated with disease activity in patients with ulcerative colitis

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Ethics Committee Approval
The study was approved by the Clinical Ethics Committee of Celal Bayar University Medical Faculty (April 18, 2018 -E.no.10-008CC). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The severity and extent of ulcerative colitis (UC) guide us in determining the treatment method for each case. It has been suggested in the literature that high neutrophil-lymphocyte and platelet-lymphocyte ratios can serve as markers of active ulcerative colitis. This study retrospectively analyzes the relationship between neutrophil-lymphocyte ratio and platelet-lymphocyte ratio with clinical activity indices and endoscopic activity indices in predicting disease severity in patients with ulcerative colitis. There are few studies in the literature regarding the relationship between platelet-lymphocyte ratio (PLR) and disease activation in ulcerative colitis. This study contributes to the follow-up and outcomes of these patients, as there is a lack of sufficient retrospective studies on the platelet/lymphocyte ratio in patients diagnosed with UC in our country and worldwide.

Methods: This study is a population-based, single-center, case-controlled study. It was conducted by retrospectively analyzing the hospital information system for data recorded during the routine diagnosis and treatment of ulcerative colitis patients followed and treated at Celal Bayar University Medical Faculty Gastroenterology Division between January 2014 and December 2021. A total of 135 patients with ulcerative colitis were included in the study. The patients were divided into 2 groups, active disease and disease in remission, based on clinical activity indices and endoscopic activity indices. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin (Hb), white blood cell (WBC), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) levels were checked during routine follow-up of patients with ulcerative colitis. These values were recorded at the first presentation to the hospital and 3 months after treatment.

Results: Laboratory values at presentation were compared with those at the third month of treatment in a group of 113 patients with UC in remission: NLR (5.529 (3.485) and 4.374 (2.335), [P<0.001]), erythrocyte sedimentation rate (26.81 (20.42) and 21.78 (19.32), [P=0.015]), C-reactive protein (4.087 (6.729) and 1.696 (3.525), [P<0.001]), and white blood cell count (9,864 (3,514) and 8,067 (1,927), [P<0.001]) were found to be lower than the baseline values. As expected, decreases in inflammatory markers were observed in patients in remission. In a group of 22 patients with active disease, values at presentation were compared with those at the third month of treatment: neutrophil count (8,508 (2,908) and 9,646 (3,265), [P=0.037]) and platelet count (289,591 (95,123) and 323,364 (127,647), [P=0.010]) were found to be high. Similarly, ESR (19.63 (15.43) and 27.89 (21.11), [P=0.036]) was found to be high. These values were higher in active disease compared to the time of admission.

Conclusion: In our study, neutrophil-lymphocyte ratios and platelet-lymphocyte ratios were significantly higher in patients with active ulcerative colitis. The level of inflammatory markers in ulcerative colitis patients at the time of diagnosis and in the early stages of the disease is helpful in predicting the course of the disease, and this was shown to be related to clinical, endoscopic, and laboratory indices. These inflammatory markers can predict disease activity alone or in combination. However, a threshold value could not be calculated due to the insufficient number of patients, and thus, more comprehensive prospective studies are needed.

Keywords: ulcerative colitis, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, C-reactive protein, erythrocyte sedimentation rate

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that develops due to diffuse inflammation of the colonic mucosa. It is characterized by periods of activation and remission and by ulcers in the colonic mucosa. The disease typically has an insidious course. The proposed hypothesis for the etiopathogenesis of UC is the development of an immunologic disorder in genetically susceptible individuals, influenced by environmental and microbial factors [1].

The course of UC is related to disease activity, the risk of inflammation progression, the number of relapses, the need for surgery, and mortality. Parameters such as increased neutrophil count, increased neutrophil-lymphocyte ratio (NLR), increased platelet-lymphocyte ratio (PLR), increased C-reactive protein (CRP), increased erythrocyte sedimentation rate (ESR), along with decreased hemoglobin (Hb) and decreased albumin, indicate disease flare. Additionally, mucosal inflammation is frequently used to monitor the disease and evaluate treatment response [2-4].

In the recent literature, parameters such as neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR), obtained from full blood count parameters, have been investigated as markers of inflammatory disease [5,6]. The ratio of these two subgroups is used as an inflammation marker because the physiological response of leukocytes to stress leads to an increase in neutrophil count and a decrease in lymphocyte count [7,8]. Thrombocytosis occurs as a result of stimulation of megakaryocytes by proinflammatory cytokines [9]. The association of thrombocytosis with clinical prognosis, as demonstrated in relevant studies, can be explained by the high platelet count being an indicator of the severity of inflammation.

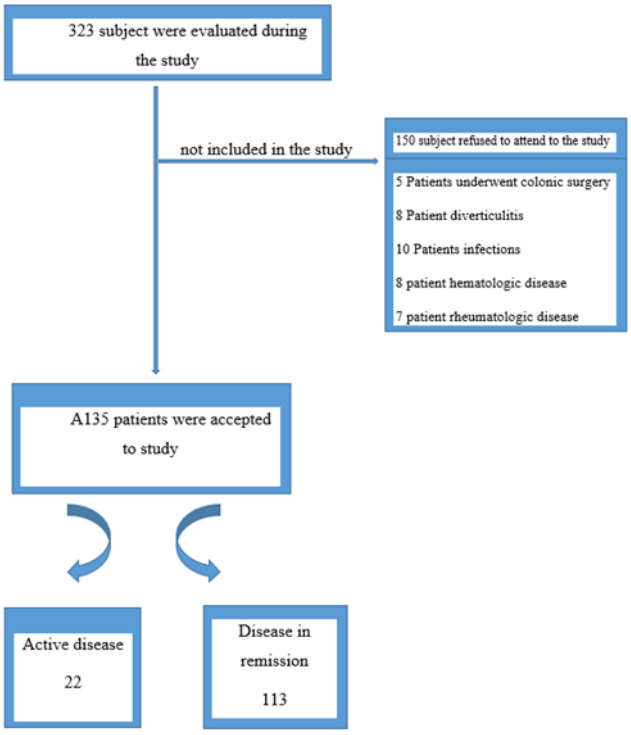
While the previous ideal treatment of ulcerative colitis focused on improving disease symptoms, achieving remission, and maintaining that remission period, the current ideal treatment aims to induce disease remission, prevent exacerbations, reduce the need for hospital admission, and provide long-term symptomatic and deep mucosal improvements without corticosteroids and with minimal need for surgery [10].

In this study, we retrospectively analyzed the relationship between neutrophil-lymphocyte ratio and platelet-lymphocyte ratio with clinical activity indices and endoscopic activity indices in predicting disease severity in patients with ulcerative colitis. There are few studies in the literature that consider the relationship between platelet-lymphocyte ratio (PLR) and disease activation in ulcerative colitis. This study contributes to the follow-up of these patients and the outcomes obtained, as there is a lack of sufficient retrospective studies on the platelet/lymphocyte ratio in patients diagnosed with UC in our country and worldwide.

Materials and methods

Our study is a population-based, single-center case-control study. We conducted this study by retrospectively analyzing the hospital information system for information recorded during the routine diagnosis and treatment of patients with ulcerative colitis. These patients were followed and treated at the Gastroenterology Division of Celal Bayar University Medical Faculty and presented to our hospital between January 2014 and December 2021. A total of 135 patients with ulcerative colitis were included in the study. The patients were divided into two groups, active disease and disease in remission, based on clinical activity indices and endoscopic activity indices (Figure 1). Cases with concomitant diseases such as infection, hematologic disease, rheumatologic disease, or malignancy that would cause an increase in serum neutrophil, leukocyte, and platelet values were excluded from the study.

Figure 1: Flow diagram of the study



Consent for the study was obtained from the Celal Bayar University Medical Faculty Ethics Committee (April 18, 2018-E. no.10-008CC).

During routine follow-up of ulcerative colitis patients, we evaluated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin (Hb), white blood cell (WBC) count, platelet count, lymphocyte count, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR). We evaluated these parameters separately for each patient at their initial presentation to the hospital and at the 3-month follow-up after starting appropriate treatment. Based on their clinical condition and endoscopic findings, we divided the patients into two groups: the patient group in remission and the active patient group unresponsive to treatment.

We compared the neutrophil count, platelet count, lymphocyte count, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, hemoglobin, sedimentation rate, CRP values, clinical findings, endoscopic findings, and clinical and endoscopic activity indices of the patients at their initial presentation to the hospital (control 1) with the same parameters at the 3-month follow-up after starting treatment (control 2).

Multiple activity indices were used to evaluate disease activity. We used the Truelove-Witts classification, calculated with clinical and laboratory findings, and the Rachmilewitz Endoscopic Activity Index, which includes endoscopic findings, in the study [11,12].

Statistical analysis

We used the SPSS 22.0 program for statistical evaluation. Descriptive statistics included mean, standard deviation, median, minimum, and maximum values for continuous variables and percentage values for discrete variables. We tested the conformity of numerical variables to a normal distribution using the Shapiro-Wilk test. Categorical variables were presented as frequency and percentage, and numerical variables were presented as mean and standard deviation values. We analyzed the relationship between two independent categorical variables using the chi-squared test. We compared the means of repeated measurements using the dependent sample t-test for variables that showed a normal distribution and the Wilcoxon signed rank test for variables that did not show a normal distribution. A *P*-value of <0.05 was considered statistically significant.

Results

A total of 135 UC patients who were followed at the Gastroenterology Division of Celal Bayar University Medical Faculty between January 2014 and December 2021 were included in the study. Of the 135, 76 (56.3%) were male and 59 (43.7%) were female, with a mean age of 45 (5). The demographic characteristics of the patients are shown in Table 1.

Table 1: Demographic characteristics of the patients

	UC patients in remission with treatment		Active UC patients not in remission with treatment	
	n	%	n	%
Gender				
Female	49	43	10	45
Male	64	57	12	55
Age range				
18-28	15	13.5	4	18.2
29-39	34	30	6	27.3
40-50	23	20.3	4	18.2
51-61	24	21.2	3	13.6
62-72	12	10.6	3	13.6
73+	5	4.4	2	9.1
Total	113	100	22	100

In the patient group in remission with treatment, the mean neutrophil count was 9,864 (3,514) at first presentation and 8,067 (1,927) after 3 months of treatment. The mean neutrophil count after treatment was significantly lower than the mean neutrophil count at first presentation (*P*<0.001). The mean platelet count of the same patient group was 318,257 (108,354) at first presentation and 288,310 (90,251) after 3 months of treatment. The mean platelet count after treatment was significantly lower than the mean platelet count at first presentation (*P*=0.001). The mean lymphocyte count of the same patient group was 2,106 (835.4) at first presentation and 2,132 (746.1) after 3 months of treatment. There was no significant difference between the mean lymphocyte counts before and after treatment (*P*=0.340).

In the patient group in remission with treatment, the mean neutrophil-lymphocyte ratio was 5.529 (3.485) at first presentation and 4.374 (2.335) after 3 months of treatment. The mean neutrophil-lymphocyte ratio after treatment was significantly lower than the mean neutrophil-lymphocyte ratio at first presentation (*P*<0.001). The mean platelet-lymphocyte ratio of the same patient group was 174.3 (88.37) at first presentation and 155.6 (81.20) after 3 months of treatment. The mean platelet-lymphocyte ratio after treatment was significantly lower than the mean platelet-lymphocyte ratio at first presentation (*P*=0.027).

In the patient group in remission with treatment, the mean erythrocyte sedimentation rate was 26.81 (20.42) at first presentation and 21.78 (19.32) after 3 months of treatment. The mean erythrocyte sedimentation rate after treatment was significantly lower than the mean erythrocyte sedimentation rate at first presentation (*P*=0.015). The mean CRP of the same patient group was 4.087 (6.729) at first presentation and 1.696 (3.525) after 3 months of treatment. The mean CRP after treatment was significantly lower than the mean CRP at first presentation (*P*<0.001). The mean hemoglobin value of the same patient group was 12.49 (2.129) at first presentation and 12.73 (1.864) after 3 months of treatment. There was no significant difference between the mean hemoglobin values before and after treatment (*P*=0.163). The comparison of laboratory parameters of UC patients in remission with treatment is shown in Table 2.

In the patient group with active UC not in remission with treatment, the mean neutrophil count was 8,508 (2,908) at first presentation and 9,646 (3,265) after 3 months of treatment. The mean neutrophil count after treatment was significantly higher than the mean neutrophil count at first presentation (*P*=0.037). The mean platelet count of the same patient group was 289,591 (95,123) at first presentation and 323,364 (127,647) after 3 months of treatment. The mean platelet count after treatment was significantly higher than the mean platelet count at first presentation (*P*=0.010). The mean lymphocyte count of the same patient group was 2,162 (979.5) at first presentation and 2,552 (1318) after 3 months of treatment. There was no significant difference between the mean lymphocyte counts before and after treatment (*P*=0.108).

Table 2: Comparison of laboratory parameters of UC patient group in remission with treatment

Patient group in remission with treatment	n	First presentation Mean (SD)	After treatment Mean (SD)	*P*-value
Neutrophil count	113	9,864 (3,514)	80,67 (1,927)	**<0.001**
Platelet count	113	318,257 (108,354)	288,310 (90,251)	**0.001**
Lymphocyte count	113	2,106 (835.4)	2,132 (746.1)	0.340
NLR	113	5.529 (3.485)	4.374 (2.335)	**<0.001**
PLR	113	174.3 (88.37)	155.6 (81.20)	**0.027**
Sedimentation	86	26.81 (20.42)	21.78 (19.32)	**0.015**
CRP	100	4.087 (6.729)	1.696 (3.525)	**<0.001**
Hemoglobin	113	12.49 (2.129)	12.73 (1.864)	0.163

In the patient group with active UC not in remission with treatment, the mean neutrophil-lymphocyte ratio was 4.308 (1.563) at first presentation and 4.386 (2.10944) after 3 months of treatment. There was no significant difference between the mean neutrophil-lymphocyte ratios before and after treatment (*P*=0.689). The mean platelet-lymphocyte ratio of the same patient group was 152.4 (65.59) at first presentation and 153.9 (86.17) after 3 months of treatment. There was no significant difference between the mean platelet-lymphocyte ratios before and after treatment (*P*=0.570).

In the patient group with active UC not in remission with treatment, the mean sedimentation rate was 19.63 (15.43) at first presentation and 27.89 (21.11) after 3 months of treatment. The mean erythrocyte sedimentation rate after treatment was significantly higher than the mean erythrocyte sedimentation rate at first presentation (*P*=0.036). The mean CRP of the same patient group was 2.066 (2.434) at first presentation and 2.451 (3.811) after 3 months of treatment. There was no significant difference between the CRP values before and after treatment

(*P*=0.811). The mean hemoglobin values of the same patient group were 12.88 (1.910) at presentation and 13.03 (1.939) after 3 months of treatment. There was no significant difference between the mean hemoglobin values before and after treatment (*P*=0.585). The comparison of laboratory parameters of active UC patients not in remission with treatment is shown in Table 3.

Table 3: Comparison of laboratory parameters of active UC patient group not in remission with treatment

Active patient group not in remission with treatment	n	First presentation Mean (SD)	After treatment Mean (SD)	*P*-value
Neutrophil count	22	8,508 (2,908)	9,646 (3,265)	**0.037**
Platelet count	22	289,59 (95,123)	323,36 (127,647)	**0.010**
Lymphocyte count	22	2,162 (979.5)	2,55 (1318)	0.108
NLR	22	4.30 (1.563)	4.386 (2.10944)	0.689
PLR	22	152.4 (65.59)	153.9 (86.17)	0.570
Sedimentation	19	19.6 (15.43)	27.8 (21.11)	**0.036**
CRP	19	2.06 (2.434)	2.451 (3.811)	0.811
Hemoglobin	22	12.8 (1.910)	13.0 (1.939)	0.585

Discussion

In our study, we analyzed the clinical and laboratory follow-up, as well as endoscopic findings, of 135 patients with ulcerative colitis. We examined their first presentation at our hospital and their control visit after treatment planning to determine their clinical prognosis. We compared laboratory findings, such as hemoglobin, erythrocyte sedimentation rate, CRP, leukocytes, platelets, and lymphocytes, which are inflammatory markers used to identify flare-ups and determine clinical prognosis. Based on endoscopic and clinical findings, we divided the patients into two groups: the "patient group in remission" and the "active patient group not in remission with treatment." We found that certain parameters, such as neutrophil count, platelet count, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, erythrocyte sedimentation rate, and CRP values, were related to better clinical prognosis in the patient group in remission. In the active patient group, neutrophil count, platelet count, and erythrocyte sedimentation rate were related to worse clinical prognosis.

Parameters associated with disease activity in ulcerative colitis, such as white blood cells, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR), have been studied in the literature. Torun et al. compared NLR in active UC, inactive UC, and control groups and found that NLR was higher in the active group than the inactive group. They also showed a correlation between NLR and white blood cell and ESR values [13,14]. Çelikbilek et al. [15] conducted a study on the neutrophil/lymphocyte ratio in ulcerative colitis patients and found that NLR was associated with active disease. Another study in Turkey on 49 UC patients found a correlation between NLR and active UC [4]. A study in Japan analyzed the correlation between NLR and disease activity as well as response to treatment. They found that pre-treatment NLR values were comparatively high in patients with moderate and severe disease activity who were subsequently started on infliximab [16]. Akpinar et al. [17] conducted a study that investigated the use of an NLR-PLR combination for evaluating endoscopic disease activity in UC. They reported that high NLR or PLR levels could predict active endoscopic disease. Demir et al. [18] published a study in 2015 showing that a higher neutrophil-lymphocyte ratio (NLR) was an indicator of active UC.

Consistent with the literature, our study also found a relationship between neutrophil count and worse clinical prognosis. We observed that the mean neutrophil count of patients in remission was high at presentation to the hospital but decreased after 3 months, as expected. On the other hand, the mean neutrophil count of active UC patients not in remission with treatment was low at presentation to the hospital but increased after 3 months, as expected.

When we analyzed the relationship between NLR and disease activation, we found that the mean NLR values of our patients in remission were high at presentation to the hospital but decreased after 3 months, as expected. The mean NLR values of our patients with active UC not in remission with treatment were low at presentation to the hospital but slightly increased after 3 months, as expected.

Regarding the relationship between platelet-lymphocyte ratio (PLR) and disease activation in ulcerative colitis, there are few studies on this in the literature. However, studies analyzing the relationship between PLR and other diseases have been performed. For example, increased platelet/lymphocyte ratio (PLR) has been reported as an independent risk factor for decreased survival in pancreas and colorectal cancers [19,20]. In the study by Akpinar et al. [17], which included 104 patients with active UC, 104 patients in remission, and a control group of 105 healthy individuals, mean NLR and PLR values in the endoscopically active disease group were higher than those in the group with endoscopic remission.

In this study, we also analyzed the relationship among UC, platelet count, and PLR to contribute to the literature and science. This study actively contributes to the follow-up of these patients and the outcomes obtained, as there are insufficient retrospective studies on the platelet/lymphocyte ratio in patients diagnosed with UC in our country and globally. When we considered the relationship between platelet count and clinical prognosis, we found that the mean platelet count of patients in remission was high at presentation to the hospital but lower after 3 months, as expected. The mean platelet count of patients with active UC not in remission with treatment was low at presentation to the hospital but higher after 3 months.

When we considered the relationship between PLR and disease activation, we found that the mean PLR value in patients in remission was high at presentation to the hospital but lower after 3 months. The mean NLR of patients with active disease not responding to treatment was low at presentation to the hospital, but the control value after 3 months was slightly higher. This could be attributed to the small number of patients with progression.

Overall, our study contributes to the understanding of clinical prognosis in ulcerative colitis and highlights the importance of laboratory markers such as neutrophil count, NLR, platelet count, and PLR in predicting disease activity and treatment response.

Another issue addressed in our study was the association of other inflammatory markers (CRP, erythrocyte sedimentation rate, anemia, etc.) with disease activation. Bengi et al. [21] found anemia in more than half (51.6%) of IBD patients; half of those with anemia were receiving treatment for it. The Truelove-Witts scoring system revealed that ESR is the most commonly used parameter for determining clinical activity. A study conducted in Korea aimed to determine which parameter

was most associated with clinical activity in UC patients. The results of a correlation analysis showed that in cases where there was a discrepancy between ESR and CRP, ESR was found to be more useful in evaluating disease activity in UC patients [22]. Many studies have shown a correlation between CRP and UC disease activity, as well as the severity of the activity. In a study by Solem et al. [3] on UC patients, CRP elevation was found to be correlated with disease activity, ESR elevation, hypoalbuminemia, and anemia.

In 2003, Ece et al. [23] studied 35 UC patients (12 active, 23 inactive) and 36 healthy individuals. Full blood count, routine biochemical workup, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels were checked in all individuals. ESR and CRP levels were significantly higher in active cases compared to inactive cases and the control group.

In our study, we analyzed the relationship between CRP and disease activation. We found that while the mean CRP level of patients in remission was high upon presentation to the hospital, the control value 3 months later was low. On the other hand, the mean CRP level of patients with active UC not in remission with treatment was low upon presentation to the hospital, but the control level 3 months later was slightly high. In the patient group in remission, we found a statistical relationship between CRP and disease activation, as reported in many other studies. However, we could not establish this relationship in the active patient group that did not respond to treatment. This absence of a relationship between CRP levels and disease activity in the active UC group may be due to the small sample size of 22 patients.

In a study by Yoon et al., the correlation of ESR and CRP with endoscopic activity was investigated. It was predicted that these markers could be useful in determining activity but would be insufficient in determining remission [25]. In our study, we analyzed the relationship between erythrocyte sedimentation rate (ESR) and disease activation. We found that while the mean ESR value of patients in remission was high upon presentation to the hospital, the control value 3 months later was low. On the other hand, the mean ESR value of patients with active UC not in remission with treatment was low upon presentation to the hospital, but the control value 3 months later was high. In this case, a statistical relationship was shown between ESR and disease activation, as demonstrated in many other studies.

It is believed that hemoglobin value decreases in UC patients due to the frequency of bloody diarrhea, malnutrition, and chronic inflammation. A study by Ibarra-Rodriguez et al. [26] with 45 patients and 15 controls demonstrated a correlation between Hb and hematocrit value and endoscopic disease activity. However, in our study, we could not establish a relationship between mean hemoglobin value and disease activity in either the patient group in remission or the patient group with active UC not in remission with treatment.

Limitations

The limitations of our study include its retrospective nature, the small number of patients, the lack of a healthy control group, and the inability to evaluate disease activity indices together. However, this study contributes to the follow-up of UC patients and the outcomes obtained, as there are insufficient retrospective studies on the platelet/lymphocyte ratio in patients diagnosed with UC in our country and worldwide.

Conclusion

In conclusion, this study investigated the clinical prognostic importance of inflammatory markers and neutrophil/lymphocyte and platelet/lymphocyte ratios in patients with ulcerative colitis. The patients were divided into the patient group in remission and the patient group with active UC not in remission, with treatment based on their clinical and endoscopic findings. The relationship between laboratory parameters and clinical prognosis was investigated in the group in remission, and a relationship between neutrophil count, platelet count, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and better clinical prognosis was determined. In the patient group with active UC not in remission with treatment, a relationship was found between worse clinical prognosis and only neutrophil count and platelet count. The small number of patients with active UC not in remission with treatment was cited as a reason for not establishing a relationship between clinical prognosis and PLR and NLR. Based on the patient group in remission, which had an adequate number of patients, it can be concluded that PLR and NLR are effective clinical prognostic markers in UC patients.

When considering other inflammatory markers, both erythrocyte sedimentation rate and CRP were found to be related to better clinical prognosis in the patient group in remission. However, only erythrocyte sedimentation rate was found to be related to worse clinical prognosis in the patient group with active UC who were not in remission with treatment. Since CRP can sometimes lead to errors in determining the clinical prognosis, it can be concluded that erythrocyte sedimentation rate is superior to CRP in determining clinical prognosis.

Based on this information, it is necessary to conduct comprehensive and prospective studies with a larger number of patients to determine the predictive power of inflammatory markers at the time of diagnosis or in the advanced stages of the disease. This will help to popularize the use of these markers in clinical practice by establishing a threshold value.

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