Monocyte/High-Density Lipoprotein Ratio Is an Indicator of Activity in Patients with Ulcerative Colitis

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Cite this article as: Yalçın MS, Yalaki S, Ölmez Ş, Taş A. Monocyte/high-density lipoprotein ratio is an indicator of activity in patients with ulcerative colitis. *Turk J Gastroenterol.* 2022;33(4):329-335.

ABSTRACT

Background: *In patients with ulcerative colitis, endoscopic and clinical indices are used to assess the disease activity. In addition, studies have been carried out for easier and cheaper markers in recent years. For this purpose, we evaluated the monocyte/high-density lipoprotein ratio of the disease activity.*

Methods: *According to clinical activity and partial Mayo scores, a total of 114 patients, 53 in the active ulcerative colitis group and 61 in the ulcerative colitis remission group were included in the study. Monocyte/high-density lipoprotein ratio, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, C-reactive protein, and erythrocyte sedimentation rate measurements of these 2 groups were recorded. Ulcerative colitis remission group and active ulcerative colitis group were compared in terms of activity.*

Results: *The monocyte/high-density lipoprotein ratio value in the active ulcerative colitis group was significantly higher than that of the ulcerative colitis remission group (10.68 ± 3.39, 6.68 ± 1.39, $P < .001$, respectively). The monocyte/high-density lipoprotein ratio value for active ulcerative colitis at a cut-off value of 7.4 had 83% sensitivity and 81% specificity. In the active ulcerative colitis group, neutrophil/lymphocyte ratio, C-reactive protein, and erythrocyte sedimentation rate values were significantly higher than the ulcerative colitis remission group ($P < .001$, $P < .001$, $P < .001$, respectively).*

Conclusion: *Monocyte/high-density lipoprotein ratio is an inexpensive and effective marker that can be used to determine the activity of ulcerative colitis.*

Keywords: *C-reactive protein, monocyte/HDL ratio, neutrophil/lymphocyte ratio, ulcerative colitis*

INTRODUCTION

Ulcerative colitis (UC) is a chronic and repetitive disease characterized by inflammation of the colon mucosa. The most important problem in UC is the evaluation of the healing of mucosal inflammation.[1] Despite the success in practice, endoscopic and histopathological examinations are invasive, costly, and include some complications.[2] Ulcerative colitis is a disease associated with industrialization. Epidemiological studies revealed that UC is seen in 8.8-23.14 people in every 100 000 in North America, in 0.97-57.9 people in every 100 000 in Europe, in 0.19-6.76 people in every 100 000 in South America, and in 0.15-6.5 in every 100 000 in Asia.[3] In UC, the treatment plan is determined according to the site on the colon and the disease activity. There are many methods for measuring disease activity for UC. They are generally nonspecific. Therefore, patients with bowel disorders other than UC can obtain high scores.[4] Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), CRP/albumin ratio (CAR), calprotectin and lactoferrin value in feces, serum neutrophils, monocytes and lymphocytes, Truelove–Witt's criteria were used in previous studies to measure the disease activity.[5-9]

Monocytes, which are an important part of the hereditary immune system, constitute 3%-8% of circulating leukocytes. During the inflammatory response, monocytes secrete pro-inflammatory and pro-oxidant cytokines.[10] Conversely, high-density lipoprotein (HDL) cholesterol neutralizes the pro-inflammatory and pro-oxidant effects of monocytes.[11] Based on this, it is thought that the monocyte/HDL (M/HDL) ratio may be a new inflammatory marker.[12] When we reviewed the literature, we found that monocytes/HDL ratio (MHR) was not studied to detect UC activity. In this

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Received: ***May 6, 2021*** *Accepted:* ***June 15, 2021*** *Available Online Date:* ***April 11, 2022***

DOI: ***10.5152/tjg.2022.21401***

study, we aimed to determine the relationship between the UC activity and MHR.

MATERIALS AND METHODS

In our study, patients who were diagnosed with UCs based on endoscopic, clinical, and pathological findings in the Gastroenterology Clinic at Aksaray University Training and Research Hospital were reviewed retrospectively. Ethical principles have been followed for the present study, and ethics committee approval has been obtained from Aksaray University Ethics Committee with the identification number of 2021/01-62. The files of patients who came with an acute UC attack and those who came for routine control between June 2015 and May 2020 were examined. The files of 148 UC patients who were admitted to the hospital during the specified period in the study were examined retrospectively. Thirty-four patients who did not meet the study criteria or had certain files/facts/documents missing in their files were excluded from the study. A total of 114 patients who met the study criteria were included in the study.

As exclusion criteria, patients with a malignant disease, chronic organ failure, history of rheumatological diseases, vasculitis, corticosteroid therapy, coronary heart disease, hypertension (dipper and non-dipper), metabolic syndrome diseases; the patients who use antihyperlipidemic drugs; and those with a history of infection in the last month and had infectious etiology in the stool analysis during an acute attack were not included in the study.

Blood pressure levels reach the highest during the daytime; it decreases slowly during the day and reaches their lowest levels at night for healthy individuals. Blood pressure has been classified into 2 based on this change: The first classification is dipper hypertension patients whose blood pressure levels decrease by 10% or more during the night when compared to daytime values. The second classification is non-dipper hypertension patients who have more than 10% decrease in their blood pressure levels.[13]

Demographic characteristics, disease activity, place of involvement of patients at the time of admission, endoscopic activity and CRP, ESR, leukocytes, neutrophils, lymphocytes, monocytes, HDL and biochemical parameters and the clinical activity were evaluated and recorded.

According to Truelove–Witt's criteria:

1. Patients with acute severe UC were described as patients who had more than 6 bloody stools per day and one or more of the following: body temperature > 37.8°C, pulse rate above 90 per minute, hemoglobin level (Hb) below 10.5 g/dL, or ESR > 30 mm/s.
2. Moderate activity was described as having 4 or more bloody stools per day and having a body temperature ≤37.8°C, pulse ≤ 90 bpm, Hb ≥ 10.5 g/dL, ESR ≤ 30 mm/s.
3. Mild activity was described as having less than 4 bloody stools per day and a body temperature <37.8°C, pulse < 90 pulse/min, Hb > 11.5 g/dL, ESR < 20 mm/s.[5] Remission was described as normal stools 3 times a day and lack of abdominal pain and stool urgency.[4]

Total colonoscopy with intubation of terminal ileum was performed, and multiple biopsies were taken. The disease was divided according to the site and extent of the colonic involvement as follows according to the Montreal classification: ulcerative proctitis, proctosigmoiditis, left side colitis, extensive colitis (>splenic flexure), and pancolitis. The endoscopic activity was assessed according to the Mayo endoscopic activity index; normal endoscopic mucosal appearance was defined as Mayo 0. The presence of mucosal erythema, decreased vascular pattern, and mild friability were defined as Mayo 1. The presence of marked erythema, the absence of vascular pattern, friability, and erosions were defined as Mayo 2. The presence of spontaneous bleeding and ulceration were defined as Mayo 3.[14]

Patients were divided into 2 groups according to the clinical activity criteria. Sixty-one patients were identified as UC remission group and 53 patients as active UC group. Distribution and endoscopic activity indices of 107 patients with total colonoscopy reports were calculated in terms of colon involvement.

Statistical Analysis

Results are presented as mean ± standard deviation for normally distributed data, median (min-max) for abnormally distributed data and percentage (%). To investigate the distribution pattern of the data, Kolmogorov–Smirnov normality test was used. The age, white blood cell (WBC), hemoglobin, ESR, albumin, and MHR data were distributed normally and thus were compared using Student's independent samples *t*-test; the CRP, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, NLR, and platelet lymphocyte ratio (PLR) data did not distribute normally and thus were compared using Mann–Whitney *U* test. We performed the

comparisons of the WBC, ESR, albumin, and MHR values according to endoscopic disease activity using one-way analysis of variance (ANOVA), and we chose the post hoc test according to the result of the Levene homogeneity test (Tukey or Tamhane). We performed the comparisons of the WBC, ESR, albumin, and MHR values according to endoscopic disease activity using Kruskal–Wallis test and performed post hoc analyses using Mann–Whitney *U* test. To assess the predictive value of variables and to calculate the cut-off values, receiver operating characteristics (ROC) curve analysis test was used. If the area under the ROC curve is 0.5, the model does not discriminate; 0.5-0.7, the model has poor to fair discrimination; 0.7-0.8, the model has acceptable discrimination; 0.8-0.9, the model has excellent discrimination; 0.9-1.0, is a very rare outcome. For statistical analysis of all data, we used The Statistical Package for Social Sciences (SPSS) version 23.0 software (IBM Corp.; Armonk, NY, USA). A *P* value under .05 was considered statistically significant. In addition, for non-parametric post hoc comparison tests, we used Bonferroni correction of 4 groups (hexed combination), and a *P* value less than .008 (0.05/6) was considered statistically significant.

RESULTS

One hundred forty-four patients with UC were eligible for the study. The active UC group consisted of 53 patients (39 males and 14 females, mean age: 40.21 ± 15.45 years), and the remission group consisted of 61 patients (30 males and 31 females, median age: 43.67 ± 16.37). The groups were age-matched (*P* = .25). In addition, the rate of the smokers in the active UC group (13 patients, 24.5%) was not different from the remission group (13 patients, 21.3%) (*P* = .683 and χ^2 = 0.167). However, the percentage of male patients were significantly higher in active lesion group, compared to the remission group (73.6% vs 49.2%, *P* = .008 and χ^2 = 7.07). The distribution of involvement type in the whole study population was presented in Table 1. The most common involvement type was left side colitis (41 patients, 35.9%), followed by proctosigmoiditis (27 patients, 23.7%)

The comparison of laboratory blood analysis parameters using Student's *t*-test between the groups was presented in Table 2. According to the Student's *t*-test, the mean WBC, ESR, albumin, and MHR (Figure 1) were significantly higher in the active UC group, compared to the remission group (*P* < .001 and *P* = .026, respectively). However, the mean hemoglobin did not significantly differ between the groups (*P* = .054).

Table 1. Distribution of Involvement, Clinical Activity, and Endoscopy Activity Index (EAI) Among the Study Population

Disease Involvement	Number (%)
Proctitis	6 (5.3)
Proctosigmoiditis	27 (23.7)
Left side colitis	41 (35.9)
Extensive colitis	23 (20.2)
Pancolitis	10 (8.8)
Unknown (missing endoscopy report)	7 (6.1)
Total	114 (100)
EAI (Mayo scores)	
Mayo 0	18 (15.8)
Mayo 1	27 (23.7)
Mayo 2	24 (21.1)
Mayo 3	38 (33.3)
Unknown (missing endoscopy report)	7 (6.1)
Total	114 (100)
Clinical activity	
Remission	61 (53.5)
Mild	11 (9.6)
Moderate	13 (11.4)
Severe	29 (25.4)
Total	114 (100)

The comparison of laboratory blood analysis parameters using Mann–Whitney *U* test between the groups was presented in Table 3. The median CRP and NLR values were significantly higher in the active UC group, compared to the remission group (*P* < .001). However, the median BUN, creatinine, AST, ALT, glucose, and PLR did

Table 2. Comparison of Laboratory Blood Analysis Parameters (Student's *t*-Test)

	Active UC Group	Remission UC Group	*P*
Age (years)	40.21 ± 15.45	43.67 ± 16.37	.25
WBC (/μL)	10750.57 ± 3492.66	8073.61 ± 2272.19	**<.001**
Hemoglobin(g/dL)	11.857 ± 2.29	12.625 ± 1.91	.054
ESR (mm/h)	32.65 ± 18.72	21.21 ± 12.84	**<.001**
Albumin (mg/dL)	4.0967 ± 0.53	4.3200 ± 0.43	**.026**
MHR	10.6800 ± 3.39	6.6809 ± 1.89	**<.001**

WBC, white blood cell; ESR, erythrocyte sedimentation rate; MHR, monocyte/high-density lipoprotein ratio; L ratio; UC, ulcerative colitis. Statistically signifance values are highlighted in bold.

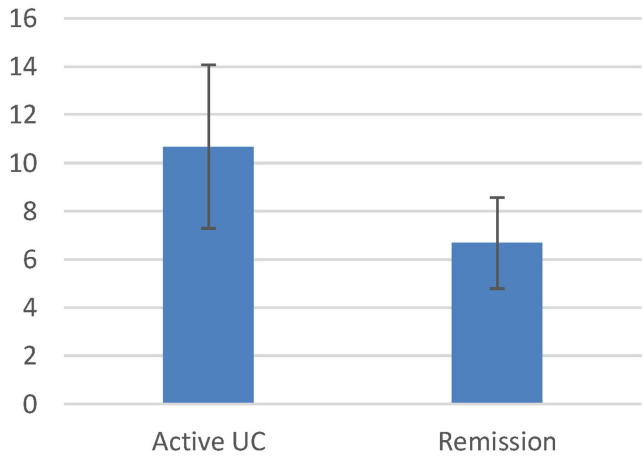

Figure 1. Comparison of the mean MHR of the groups. MHR, monocyte/high-density lipoprotein ratio.

not significantly differ between the groups (P = .322, P = .308, P = .583, P = .624, P = .931, and P = .073, respectively).

The comparison of laboratory blood analysis parameters according to endoscopic disease activity using one-way ANOVA was presented in Table 4. A significant difference was evident among the WBC, ESR, albumin, and MHR values of 4 groups (Mayo 0, Mayo 1, Mayo 2, and Mayo 3) (P < .001, P = .01, and P = .018, P < .001 respectively). According to the post hoc tests, WBC of Mayo 3 group was significantly higher compared to Mayo 3, Mayo 1, and the remission groups (P = .006, P = .001, and P < .001, respectively). However, a significant difference in ESR was evident only between Mayo 3 and Mayo 1 group (P = .005). Additionally, albumin was significantly different between Mayo 3 and Mayo 1 group (P = .01). Moreover, the MHR values of Mayo 3 and Mayo 2 groups were significantly higher compared to the remission group (P < .001). Also, the MHR value of Mayo 3 group was significantly higher compared to both Mayo 2 and Mayo 1 group (P < .001).

Table 3. Comparison of Laboratory Blood Analysis Parameters (Mann–Whitney *U* Test)

	Active UC	Remission UC	*P*
CRP (mg/L)	24.5 (2.8-146)	7.8 (1-34.5)	**<.001**
BUN (mg/dL)	28 (10-53)	24.5 (11-166)	.322
Creatinine (mg/dL)	0.8 (0.3-1.7)	0.7 (0.5-4)	.308
AST (IU/L)	18 (12-68)	18 (9-68)	.583
ALT (IU/L)	18 (5-142)	17 (6-136)	.624
Glucose (mg/dL)	92 (70- 246)	92 (74-167)	.931
NLR	4.73 (0.85 -20)	2.51 (1-11.80)	**<.001**
PLR	195.10 (44.51-769.33)	170.33 (67.32-654.41)	.073

CRP, C-reactive protein; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NLR, neutrophil/lymphocyte ratio; PLR, platelet lymphocyte ratio; UC, ulcerative colitis. Statistically significance values are highlighted in bold.

Table 4. The Comparison of Laboratory Blood Analysis Parameters According to Endoscopic Disease Activity (One-Way ANOVA)

	Endoscopic Disease Activity				
	Mayo 0	Mayo 1	Mayo 2	Mayo 3	*P*
WBC (/μL)	7857 ± 2302	8467 ± 2566	8895 ± 1961	11 395 ± 3647	<.001
ESR (mm/h)	26 ± 12	19 ± 13	28 ± 20	34 ± 17	.01
Albumin (mg/dL)	4.25 ± 0.46	4.45 ± 0.40	4.16 ± 0.39	4.04 ± 0.58	.018
MHR	5.61 ± 1.51	6.98 ± 2.02	8.24 ± 2.00	11.47 ± 3.47	<.001

WBC, white blood cell; ESR, erythrocyte sedimentation rate; MHR, monocyte/high-density lipoprotein ratio.

The comparison of laboratory blood analysis parameters according to endoscopic disease activity using Kruskal–Wallis test was presented in Table 5. Both CRP and NLR showed a significant difference among 4 groups (P < .001). According to post hoc analysis, both CRP and NLR values were significantly higher in Mayo 3 group, compared to the remission group (P = .001 and P = .002, respectively), Mayo 1 group (P = .001), and Mayo 2 group (P < .001 and P = .003, respectively) (Figure 2).

Figure 3 shows the ROC curve representing the predictive value of MHR, CRP, NLR, WBC, ESR, and albumin for active UC. The areas under curve were presented in Table 6. The greatest area under curve value was that of MHR (0.906), followed by that of CRP (0.762).

Table 5. The Comparison of Laboratory Blood Analysis Parameters According to Endoscopic Disease Activity Using Kruskal–Wallis Test

Endoscopic Disease Activity	CRP	NLR
Mayo 0	8.25 (1-34.5)	2.43 (1-11.8)
Mayo 1	8.4 (2.1-34)	2.22 (1.42-11.2)
Mayo 2	9.55 (2.8-66)	3.31 (0.85-6.7)
Mayo 3	41.5 (3-146)	6.40 (1.40-20)
P	<.001	<.001

CRP, C-reactive protein; NLR, neutrophil/lymphocyte ratio.

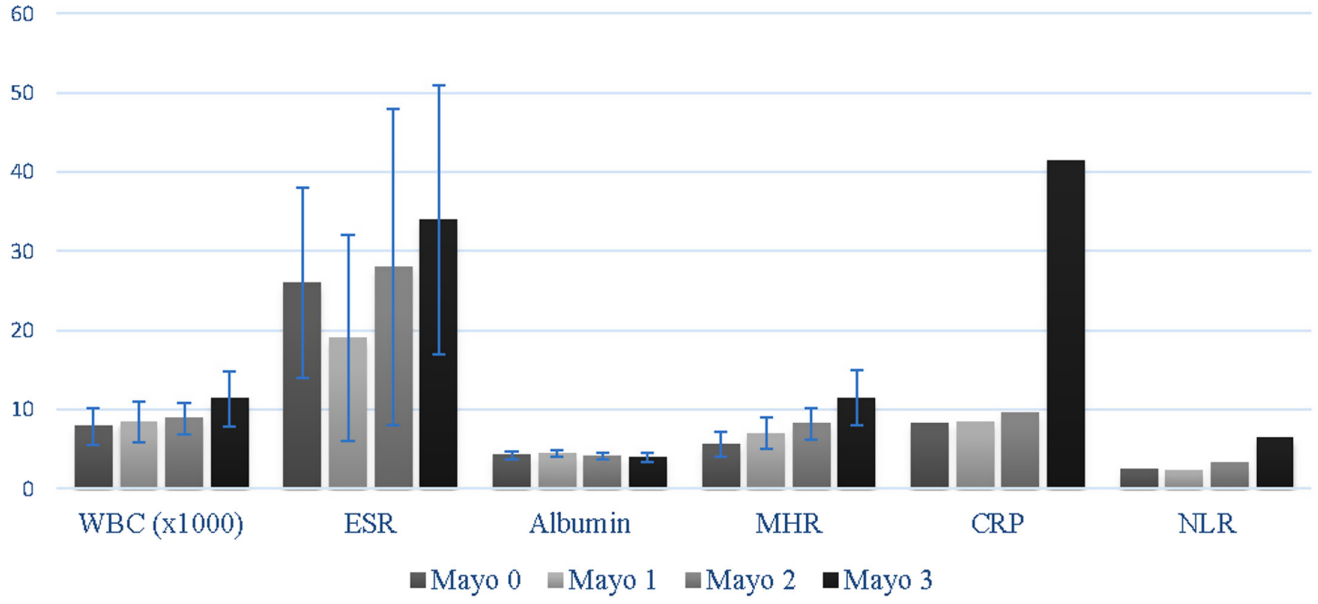

Figure 2. Comparison of parameters according to endoscopic disease activity.

The cut-off value of MHR was found as 7.4 (sensitivity: 83% and specificity: 81%), and the cut-off value of CRP was found as 15 (sensitivity: 72% and specificity: 67%) for active UC.

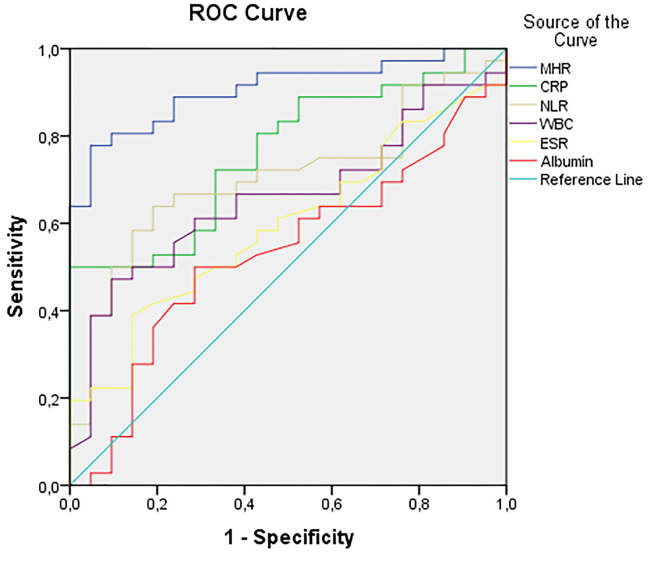

Figure 3. ROC curve representing the predictive value of MHR, CRP, NLR, WBC, ESR, and albumin for active ulcerative colitis. ROC, receiver operating characteristics; MHR, monocyte/high-density lipoprotein ratio; CRP, C-reactive protein; NLR, neutrophil/lymphocyte ratio; WBC, white blood cell; ESR, erythrocyte sedimentation rate.

DISCUSSION

Our study is the first known study where MHR was studied in comparison of activity in patients with UC. In this study, we found that MHR is a better token than parameters such as CRP, ESR, and NLR in active UC. MHR value correlated with endoscopic activity index. It was determined that as the Mayo score increased, the MHR value also increased. We also think that as it is an inexpensive and computable parameter in every hospital, it can be adapted to replace other costly hard-to-reach parameters (e.g., fecal calprotectin).

Ulcerative colitis is a chronic disease characterized by periods of attacks and remission. The best indicator for assessing the disease activity is endoscopic

Table 6. Area Under Curve (AUC) Values of Laboratory Blood Analysis Parameters

	AUC	*P*	Asymptotic 95% CI
MHR	0.906	<.000	0.83-0.982
CRP (mg/L)	0.762	.001	0.639-0.885
NLR	0.706	.010	0.569-0.842
WBC (/μL)	0.660	.045	0.518-0.802
ESR (mm/h)	0.595	.237	0.448-0.742
Albumin (mg/dL)	0.533	.679	0.379-0.687

MHR, monocyte/high-density lipoprotein ratio; CRP, C-reactive protein; NLR, neutrophil/lymphocyte ratio; WBC, white blood cell; ESR, erythrocyte sedimentation rate.

assessment.[7] However, in terms of possible complications and accessibility during the period of an acute attack, endoscopic procedures may not be performed. Therefore, noninvasive and inexpensive biomarker studies have become important to assess the activity of UC.[15] For this purpose, CRP and fecal calprotectin levels are the most useful markers in the estimation of activity of UC. C-reactive protein is synthesized in the liver in response to various inflammatory cytokines. CRP is a better indicator of sedimentation and procalcitonin in showing disease activity. It is therefore a nonspecific inflammatory marker used in many diseases, but its correlation with endoscopic activity is weak. In different studies on UC activity, ESR and CRP, the specificity and sensitivity were between 50% and 60%.[6] A recent study revealed that high CAR was associated with high inflammatory load, poor prognosis, and mortality.[7]

Inflammation and oxidative stress are well-known mechanisms during the development and progression of atherosclerosis. In this case, monocytes play an important role. Active monocytes interact with or are damaged by activated endothelial cells. This results in overexpression of pro-inflammatory cytokines/adhesion molecules (monocyte chemotactic protein 1 ligand, vascular cell adhesion molecule 1, and intercellular adhesion molecule 1). Later, monocytes differentiate into the macrophages that ingest oxidized LDL cholesterol and form the dangerous foamy cells.[16] High-density lipoprotein molecules resist the migration of macrophages. Recent studies indicate that HDL has an essential role in controlling the activation, adhesiveness, and inflammation of monocytes and the increase of progenitor cells enabling the proliferation of monocytes.[17] High-density lipoprotein molecules enhance vasorelaxation and increase endothelial nitric oxide synthase expression.[18] Due to these properties of monocytes, they have pro-inflammatory and pro-oxidant effect, while HDL-C has just an opposite function. Therefore, the increase in MHR ratio is a good indicator of inflammation.

In some previous studies, high monocyte count and low HDL cholesterol levels were shown to be associated with inflammation and oxidative stress, while MHR is associated with hypertension and other cardiovascular diseases.[8,9] In a study conducted by Kaplan et al[19] 143 hypertensive patients were included. In this study, end-organ damage was compared in dipper and non-dipper hypertensive patients. In the study by Kaplan et al[19] MHR was found to be successful in distinguishing end-organ damage in hypertensive patients as well as in dipper and non-dipper patients.[19] Cakmak et al[20] used MHR to detect metabolic syndrome in patients with polycystic ovarian syndrome. In this study, MHR was found to be statistically significantly higher in patients with metabolic syndrome compared to patients without metabolic syndrome (10.47 ± 2.81 vs 8.77 ± 2.61, $P = .01$).[20] Kanbay et al[21] investigated the relationship between glomerular filtration rate and cardiovascular events with MHR in 340 patients with chronic kidney disease. In this study, glomerular filtration rate decreased as MHR increased and cardiovascular events increased.[21] In our study, we found that the MHR level that was studied for the first time in terms of activity in UC patients is the most significant indicator of activity. In ROC analysis, we found that the MHR level is a better marker in terms of specificity and specificity than well-known traditional biomarkers such as CRP and ESR. In fact, at a cut-off value of 7.4, MHR was found to have 83% sensitivity and 81% specificity. These rates were determined as 72% and 67% for CRP at a cut-off value of 15. For MHR, along with these important findings, the fact that the cost is low, and it is measurable in all hospitals by studying lipid profile only in hemogram and biochemistry laboratory makes it a more accessible marker. In addition, calprotectin is a marker that can be studied in a limited number of centers and has a higher cost.

As a result, the MHR level can be used as a highly specific, inexpensive, and easily accessible parameter for determining clinical activity of the disease in patients with UC.

Ethics Committee Approval: This study was approved by medical ethics committee of Aksaray University Ethics Committee with the identification number of 2021/01-62. This study was approved by medical ethics committee of Aksaray University Ethics Committee with the identification number of 2021/01-62.

Informed Consent: N/A.

Peer Review: Externally peer-reviewed.

Author Contributions: Consept – M.S.Y., A.T.; Design – M.S.Y., A.T.; Supervision – S.Y., Ş.Ö., M.S.Y.; Resources – A.T., SY.; Materials – Ş.Ö., M.S.Y.; Data Collection and/or Processing – M.S.Y., Ş.Ö., S.Y.; Analysis and/or Interpretation – A.T., S.Y.; Literature Search – M.S.Y., A.T.; Writing Manuscript – M.S.Y., S.Y.; Critical Review – M.S.Y., A.T.

Declaration of Interest: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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