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THE ROLE OF PLATELET TO LYMPHOCYTE RATIO AND NEUTROPHIL TO LYMPHOCYTE RATIO AS NON-INVASIVE MARKERS OF MUCOSAL ACTIVITY IN ULCERATIVE COLITIS AT A TERITIARY CARE HOSPITAL IN TAMIL NADU

Arshiya Mubin S.P

Department of medical gastroenterology,Coimbatore medical college and hospital,coimbatore,Tamil Nadu

ABSTRACT

Background: Economical and readily available biomarkers for assessing Ulcerative colitis are need of the hour,for this purpose we evaluated platelet to lymphocyte ratio and neutrophil to lymphocyte ratio in patients with ulcerative colitis. **Methods:** We analyzed 48 patients with UC who underwent measurement of fecal calprotectin (FC) and endoscopy and 96 matched healthy controls. NLR and PLR were compared between the patients and healthy controls. The endoscopic activity was divided into 2 groups: group 1 (mild to moderate inflammation) and group 2 (severe inflammation) according to the Mayo endoscopic score in UC **Results:** To diagnose UC,the optimal cutoff of NLR and PLR was 2.26(sensitivity 54.2%; specificity 90.6%)and 179.8(sensitivity 35.4%; specificity 90.6%) respectively. The optimal cut off to differentiate group 1 and group 2 was 3.44, 175.9, and 453 µg/g for NLR,PLR, and FC,respectively (sensitivity, 63.6% vs. 90.9% vs. 81.8%; specificity, 81.1% vs. 78.4% vs. 73.0%; positive likelihood ratio,3.364 vs. 4.205 vs. 3.027; AUC, 0.714 vs. 0.897 vs. 0.813). PLR had the highest AUC and positive likelihood ratio. **Conclusion:** NLR and PLR are useful in patients with UC from healthy controls. NLR, PLR, and FC may reflect intestinal mucosal conditions.

KEY WORDS : ulcerative colitis,platelet to lymphocyte ratio,neutrophil to lymphocyte ratio

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) that diffusely involves various parts of the colon (1, 2). The disease may be limited to the rectum, or it may involve the entire colon. The main complaints of the patients are bloody diarrhea and abdominal pain (3). Mucosal examination via colonoscopy is the basic method in diagnosis; it monitors the activity of the disease and is used in the follow-up of patients (4).The exacerbations of UC may appear in varying frequency and severity. Bleeding, abdominal pain,and fever are frequent during exacerbations (5).Exacerbation is mild in most patients, and 15% of the patients need hospitalization (6). Colonoscopy is performed after excluding infectious causes, and determining the disease severity is beneficial and guides the clinician for treatment and prognosis of the disease. Ulcers, exudates, fragile mucosa, and bleeding are frequent in cases of active disease (7). Early diagnosis and appropriate treatment of disease exacerbation is important in the course of the disease. Some indirect methods have been recently used to determine the disease activity, and their sensitivity has been studied. The neutrophil-to-lymphocyte ratio (NLR) is one of them (8).Inflammatory markers, including leukocyte count,erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) have been well known to increase in case of active diseases. However, the data on the sensitivity of some inflammation markers, including NLR and platelet-to-lymphocyte ratio (PLR) on identifying endoscopic active disease, and their correlation with mucosal injury are scarce. In this study, we investigated the sensitivity of new inflammation markers, NLR and PLR,as well as conventional inflammation markers to determine endoscopically active disease, and their correlation with mucosal injury. In addition, we investigated the sensitivity of NLR and PLR combination to predict disease severity according to mucosal disease.

METHODS

1. Study Design and Subjects

48 patients with UC were analyzed against 96 healthy controls who took colonoscopy and laboratory tests between January 2022 and January 2023 at the coimbatore medical college and hospital ,coimbatore ,Tamil Nadu.

The healthy controls included people who had undergone checkup at our hospital and had normal colonoscopy findings. Patients were matched based on age and sex to the healthy controls in a 1:2 ratio during the study period. Patients with UC were classified according to the Montreal classification (9).The exclusion criteria included previous bowel resection, indeterminate colitis, infection, neoplastic disorders, hematologic disease, heart or pulmonary disease, autoimmune disease, hepatosplenic disease, and renal insufficiency. The patient's age, sex, disease duration, medical and operation history, disease and endoscopic activity score, classification, laboratory findings, and disease treatment were recorded. This study was approved by the Institutional ethical and research Board of our hospital. The informed consent was obtained.

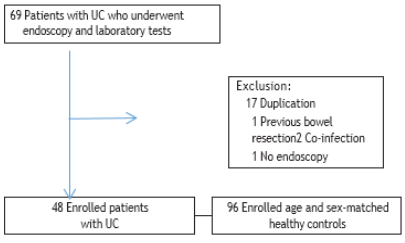

Fig. 1. Flowchart of the study subjects. UC, ulcerative colitis.

2. Laboratory Values

NLR and PLR were calculated by dividing the absolute neutrophil count by the absolute lymphocyte count and dividing the absolute platelet count by the absolute lymphocyte count, respectively. In healthy controls, the findings of the blood test on
the day of the endoscopy were used. In patients with UC, blood and FC tests performed within 1 month and of the endoscopy within 3 months were used. The time between the laboratory tests and endoscopy was 2 days and the interval between FC measurement and endoscopy was 4.5 days.

3. Assessment of Clinical and Endoscopic Activities

The UC disease activity was evaluated using the Mayo score. The endoscopic activity was assessed using the Mayo endoscopic subscore. Mayo endoscopic subscore grades were as follows–
grade 0: normal or inactive,
grade 1: mild,
grade 2: moderate,
grade 3: severe (10).

In pan-colitis or left-sided colitis, endoscopic activity was scored

***Corresponding Author Arshiya Mubin S.P**

Department of medical gastroenterology,Coimbatore medical college and hospital,coimbatore,Tamil Nadu

based on the most inflamed segment of the colon. The patients were divided into 2 groups based on the severity of the degree of inflammation (group 1: no, mild, and moderate inflammation vs. group 2: severe inflammation) to evaluate the usefulness of NLR, PLR, and FC as biomarkers of disease activity in UC. The primary endpoint was the ability of NLR, PLR, and FC to serve as biomarkers of mucosal severity in UC.

4. Statistical Analysis

Student t-test was used to compare continuous data between patients with UC and healthy controls. The Mann-Whitney U test was used to analyze the continuous variables. The receiver operating characteristic (ROC) curve analysis was performed to assess the performance of each biomarker for differentiating mucosal severity in UC. The sensitivity, specificity, and cutoff values were assessed using the ROC curve. A P-value < 0.05 was considered to be statistically significant. The De-Long test was performed to compare the measures and the P-value was adjusted by Bonferroni correction. All statistical analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) and R version 3.6.1 ('pRoc' and 'OptimalCutpoints' packages; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

1. Study Population

144 subjects including 48 patients with UC and 96 healthy controls were reviewed during the study period. The mean age of the patients with UC was 38.9 ± 14.8 years. The male: female ratio was 1.18 (males 26, females 22). The mean Mayo score was 6.8 ± 2.3. The clinical characteristics of the 48 patients with UC are summarized in Table 1.

Table 1. Demographic and Clinical Characteristics of the Study Population

Variable	UC (n = 48)
Age at UC diagnosis (yr)	38.9 ± 14.8
Male sex	26 (54.2)
Previous operation history	5 (10.4)
Appendectomy	1 (20.0)
Perianal operation	2 (40.0)
Othersa	2 (40.0)
Disease extension at diagnosis at diagnosis	
E1 (proctitis)	18 (37.5)
E2 (left-sided colitis)	10 (20.8)
E3 (pan-colitis)	20 (41.7)
Disease activity at diagnosis	
Clinical remission (Mayo score 0-2)	1 (2.1)
Mild activity (Mayo score 3-5)	17 (35.4)
Moderate activity (Mayo score 6-10)	28 (58.3)
Severe activity (Mayo score 11-12)	2 (4.2)
Disease activity at NLR, PLR and FC measurement	
Clinical remission (Mayo score 0-2)	9 (18.8)
Mild activity (Mayo score 3-5)	19 (39.6)
Moderate activity (Mayo score 6-10)	15 (31.2)
Severe activity (Mayo score 11-12)	5 (10.4)
Medication use at NLR, PLR and FC measurement	
5-ASA	33 (68.7)
5-ASA+AZA	5 (10.4)
5-ASA+steroid	4 (8.3)
5-ASA+steroid+AZA	2 (4.2)
5-ASA+AZA+anti-TNF	2 (4.2)
5-ASA+anti-TNF	2 (4.2)

Values are presented as mean ± standard deviation or number (%).
aOthers: hysterectomy, transurethral resection of bladder.

UC, ulcerative colitis; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; FC, fecal calprotectin; 5-ASA, 5-aminosalicylic acid; AZA, azathioprine; TNF, tumor necrosis factor.

2. Comparisons of Serum Biomarkers between Patients with UC and Healthy Controls

WBC, NLR, PLR, ESR, and CRP level was significantly higher in patients with UC versus healthy controls. NLR (3.24 ± 2.78 vs. 1.52 ± 0.61) and PLR (187.01 ± 136.94 vs. 132.88 ± 45.72) were considerably elevated in patients with UC versus healthy controls (Table 2). In patients with UC, ESR (43.45 ± 29.96 mm/hr vs. 18.85 ± 15.81 mm/hr) and CRP (0.79 ± 1.43 mg/dL vs. 0.14 ± 0.31 mg/dL) were higher than the upper limit of the reference range (Table 2).

Table 2. Comparisons of Serum Biomarkers between Patients with UC and Healthy Controls Values are presented as mean ± standard deviation.

Variable	UC group (n = 48)	Control group (n = 96)	P-value	Reference
WBC (/μL)	7,750.00 ± 2,932.21	5,335.42 ± 1,271.46	< 0.001	4,000–10,000
NLR	3.24 ± 2.78	1.52 ± 0.61	< 0.001	-
PLR	187.01 ± 136.94	132.88 ± 45.72	< 0.001	-
ESR (mm/hr)	43.45 ± 29.96	18.85 ± 15.81	< 0.001	0–30
CRP (mg/dL)	0.79 ± 1.43	0.14 ± 0.31	< 0.001	0.0–0.5

UC, ulcerative colitis; WBC, white blood cell; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

3. Comparisons of Serum Biomarkers between Mild to Moderate UC and Severe UC

NLR, PLR, ESR, CRP, and FC were significantly higher in patients with severe UC (group 2) versus mild to moderate UC (group 1). PLR was higher in group 2 versus group 1 (280.04 ± 106.44 vs. 159.35 ± 133.81, P< 0.001). NLR also was higher in group 2 versus group 1 (4.04 ± 2.25 vs. 3.00 ± 2.91, P= 0.034). FC was significantly increased in group 2 versus group 1 (2,476.09 ± 2,572.13 μg/g vs. 575.04 ± 1,181.98 μg/g, P= 0.002) (Table 3).

Table 3. Comparisons of Serum Biomarkers According to Endoscopic Severity in UC Patients

Variable	Group 1 (n = 37) (mild to moderate)	Group 2 (n = 11) (severe)	P-value	Reference
WBC (/μL)	7,635.14 ± 2,917.88	8,136.36 ± 3,089.75	0.508	4,000–10,000
NLR	3.00 ± 2.91	4.04 ± 2.25	0.034	-
PLR	159.35 ± 133.81	280.04 ± 106.44	< 0.001	-
ESR (mm/hr)	37.75 ± 29.06	62.09 ± 25.99	0.007	0–30
CRP (mg/dL)	0.45 ± 0.97	1.90 ± 2.09	< 0.001	0.0–0.5
FC (μg/g)	575.04 ± 1,181.98	2,476.09 ± 2,572.13	0.002	0–100

Values are presented as mean ± standard deviation.
UC, ulcerative colitis; WBC, white blood cell; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; FC, fecal calprotectin.

Comparison of the Diagnostic Accuracy for Predicting UC Using NLR and PLR

ROC analysis was performed to determine the cutoff of NLR and PLR to predict UC. To differentiate patients with UC from healthy

controls, WBC had the highest area under the curve (AUC) among NLR, PLR, ESR, and CRP. However, it had the

lowest positive likelihood ratio as compared with the other parameters (sensitivity 72.9%; specificity 74.0%; positive likelihood ratio 2.800, 95% confidence interval [CI], 1.917–4.089; AUC 0.793, 95% CI 0.713–0.874). ROC analysis revealed a sensitivity of 54.2% and specificity of 90.6% when an NLR cutoff of 2.26 was used (positive likelihood ratio 5.778, 95% CI 2.944–11.339; AUC 0.774, 95% CI 0.690–0.859). For identifying UC, the optimal cutoff of 179.8 for PLR had a sensitivity of 35.4% and a specificity of 90.6% (positive likelihood ratio 3.778, 95% CI 1.821–7.838; AUC 0.654, 95% CI 0.556–0.753) (Table 4, Fig. 2A). NLR had a significantly higher AUC versus PLR (P= 0.006) before Bonferroni correction, but the difference was no longer statistically significant after correction (Tables 4, 5).

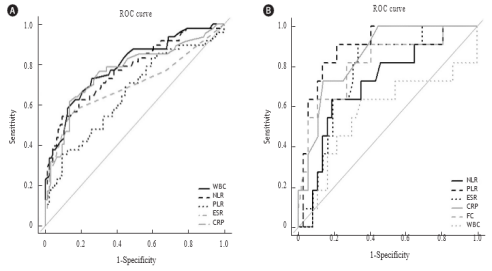

Fig. 2. ROC curve showing the diagnostic performance of NLR, PLR, and FC. (A) In the ROC curve, the optimal cutoff value for NLR and PLR for detecting UC was 2.26 (sensitivity 54.2%; specificity 90.6%; AUC 0.774, 95% CI 0.690–0.859) and 179.8 (sensitivity 35.4%; specificity 90.6%, AUC 0.654, 95% CI 0.556–0.753). (B) The optimal cutoff value for NLR, PLR, and FC for differentiating UC severity were 3.44 (sensitivity 63.6%; specificity 81.1%; AUC 0.714, 95% CI 0.539–0.888), 175.9 (sensitivity 90.9%; specificity 78.4%; AUC 0.897, 95% CI, 0.802–0.992), and 453 µg/g (sensitivity 81.8%; specificity 73.0%; AUC 0.813, 95% CI, 0.655–0.972), respectively. ROC, receiver operator characteristic; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; FC, fecal calprotectin; UC, ulcerative colitis; AUC, area under the curve; CI, confidence interval; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

4.Comparison of the Diagnostic Accuracy for Severe Endoscopic UC Using NLR, PLR, and FC

The optimal cutoff for differentiating group 1 and 2 patients with UC was 3.44 (sensitivity 63.6%; specificity 81.1%; positive likelihood ratio 3.364, 95% CI 1.507–7.507; AUC 0.714, 95% CI 0.539–0.888) for NLR, 175.9 (sensitivity 90.9%; specificity 78.4%; positive likelihood ratio 4.205, 95% CI 2.214–7.894; AUC 0.897, 95% CI 0.802–0.992) for PLR, and 453 µg/g (sensitivity 81.8%; specificity 73.0%; positive likelihood ratio 3.027, 95% CI 1.664–5.507; AUC 0.813, 95% CI 0.655–0.972) for FC (Table 4, Fig. 2B). PLR had the highest AUC among NLR, PLR, ESR, CRP, and FC and it had a higher positive likelihood ratio than NLR and FC. The AUC for PLR was significantly higher than NLR (P= 0.017) before Bonferroni correction but the difference was no longer statistically significant after the correction (Tables 4, 5).

Table 4. Comparison of the Diagnostic Accuracy for Detecting UC and for Severe Endoscopic UC Using Biomarkers

Parameter	WBC (/µL) Esti- Lower Upper mate	NLR Esti- Lower Upper mate	PLR Esti- Lower Upper mate	ESR (mm/hr) Esti- Lower Upper mate	CRP (mg/dL) Esti- Lower Upper mate	FC (µg/g) Esti- Lower Upper mate
Control vs.						- -
Cutoff	6,000		2.26		34	0.2
Sensitivity	0.729	0.582	0.847	0.542	0.392	0.686	0.354	0.222	0.505	0.617	0.464	0.755	0.574	0.422	0.717
Specificity	0.740	0.640	0.824	0.906	0.829	0.956	0.906	0.829	0.956	0.865	0.780	0.926	0.833	0.744	0.902
Positiv	0.583	0.467	0.743	0.743	0.592	0.842	0.654	0.487	0.779	0.690	0.553	0.810	0.628	0.495	0.760
Negative predictive value	0.845	0.738	0.900	0.798	0.683	0.899	0.737	0.593	0.864	0.822	0.712	0.900	0.800	0.684	0.880
Positiv	2.800	1.917	4.089	5.778	2.944	11.339	3.778	1.821	7.838	4.556	2.620	7.924	3.447	2.069	5.743
Negative likelihood ratio	0.366	0.227	0.591	0.506	0.369	0.692	0.713	0.572	0.887	0.443	0.306	0.642	0.511	0.362	0.720
AUC	0.793	0.713	0.874	0.774	0.690	0.859	0.654	0.556	0.753	0.767	0.677	0.856	0.796	0.696	0.896
Mild to moderate vs. severe															
Cutoff	7,300		3.44					41			0.8				
Sensitivity	0.636	0.308	0.81	0.636	0.308	0.891	0.909	0.587	0.909	0.909	0.587	0.909	0.727	0.390	0.940
Specificity	0.649	0.475	0.798	0.811	0.648	0.920	0.784	0.618	0.902	0.676	0.490	0.814	0.861	0.705	0.953
Positiv	0.350	0.209	0.751	0.500	0.301	0.823	0.556	0.358	0.782	0.455	0.286	0.673	0.615	0.381	0.904
Negative predictive value	0.857	0.604	0.928	0.882	0.656	0.953	0.967	0.805	0.987	0.960	0.773	0.981	0.912	0.713	0.971
Positiv	1.811	0.969	3.385	3.364	1.507	7.507	4.205	2.214	7.984	2.727	1.657	4.889	5.236	2.150	12.754
Negative likelihood ratio	0.561	0.248	1.269	0.448	0.202	0.995	0.116	0.018	0.757	0.136	0.021	0.896	0.317	0.120	0.839
AUC	0.566	0.339	0.794	0.714	0.539	0.888	0.897	0.802	0.992	0.769	0.623	0.915	0.854	0.741	0.966

UC, ulcerative colitis; WBC, white blood cell; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; FC, fecal calprotectin; AUC, area under the curve.

Table 5. Comparisons between Biomarkers on Healthy Control versus UC and Mild to Moderate versus Severe UC

Parameter			Control vs. UC		Mild to moderate vs. severe	
			P-valuea[3]	Adjusted P-valueb	P-valuea[3]	Adjusted P-valueb
WBC	PLR	0.690		1.000	0.037	0.560
	NLR	0.036		0.363	0.005	0.071
	ESR	0.712		1.000	0.143	1.000
	CRP	0.131		1.000	0.046	0.693
	FC	-		-	0.122	1.000
PLR	NLR	0.006		0.059	0.017	0.165
	ESR	0.962		1.000	0.680	1.000
	CRP	0.190		1.000	0.214	1.000
	FC	-		-	0.457	1.000
NLR	ESR	0.061		0.612	0.045	0.449
	CRP	0.511		1.000	0.490	1.000
	FC	-		-	0.374	1.000
ESR	CRP	0.181		1.000	0.260	1.000
	FC	-		-	0.714	1.000
CRP	FC	-		-	0.674	1.000

aP-value by DeLong test.

bP-value adjusted by Bonferroni correction.
UC, ulcerative colitis; WBC, white blood cell; PLR, platelet to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; FC, fecal calprotectin.

DISCUSSION

In this study, the we studied the use of NLR, PLR, and FC to diagnose UC and their ability to indicate the disease activity. The results suggest that increased NLR and PLR helped to categorise patients with UC from healthy controls.Also NLR, PLR, and FC indicated endoscopic activity. To the best of our knowledge, though previous studies have compared NLR and PLR with clinical indices, no study has fully investigated the connection between NLR, PLR, and FC with endoscopic activity in UC.

Mucosal healing, indicated by the absence of ulcerations and erosions, is assessed by endoscopy and is the treatment aim in UC as it may prevent relapse and complications and to minimize the need for hospitalization or surgery(11-13). Although endoscopy is a irreplacable tool to identify mucosal inflammation, it is invasive, inconvenient, and may be inappropriate in severe cases as it can cause major complications such as perforation(14).Therefore, noninvasive biomarkers such as WBC, CRP, ESR have been used to identify intestinal inflammation in patients with IBD, albeit with insufficient sensitivity(15,16) .NLR and PLR can diagnose and predict the severity of IBD(17-20). Our study suggests that elevated NLR and PLR help segregate patients with UC from healthy controls. WBC, including neutrophils (that reflect systemic inflammation), contribute to the innate and adaptive immunity and these cells migrate to the inflamed tissues by releasing proinflammatory cytokines and chemokine (21).

An elevated platelet count can contribute to the pathogenesis of mucosal inflammation by its pro-inflammatory properties such as the release and recruitment of inflammatory mediators and modulation of other inflammatory cells(22-24). In contrast, a reduced lymphocyte count in UC may result from mucosal infiltration(25). This results in an elevation of NLR and PLR, which was considerably elevated in patients with UC versus healthy controls in our study. A cutoff of 2.26 for NLR and 179.8 for PLR suggested UC. NLR was more significant than PLR for diagnosing UC. In previous studies, the optimal cutoff for NLR and PLR was 2.13–3.10 and ~139, respectively which is similar to our results (2.26 for NLR and 179.8 for PLR)(17,19,20) .The cutoff for PLR was slightly higher than previously reported. The difference in PLR cutoff between our study and the previous study may influence the number of enrolled patients and the use of drugs such as azathioprine, steroids, anti-tumor necrosis factor (anti-TNF) and disease activity.

Our results demonstrated that NLR, PLR, and FC reflect intestinal mucosal conditions in UC. Recently, stool tests such as FC have been suggested as novel biomarkers. FC is a calcium- and zinc-binding protein that comprises 60% of the neutrophil-cytosolic protein(26). A high level of FC in IBD can be due to an increased neutrophil migration into the intestinal mucosa and an increased leukocyte turnover(27). However, FC requires stool sampling(19,28,29)and is relatively expensive as compared with NLR and PLR. In this study, PLR had the highest AUC among NLR, PLR, ESR, CRP, and FC. Although there were no significant differences, these results suggest that a high PLR was more meaningful to measure the severity of mucosal inflammation than FC. Interestingly, NLR is a more significant biomarker than PLR to differentiate patients with UC from healthy controls, but PLR was more significant in distinguishing severe UC from mild to moderate UC. This difference could be due to a comparison between different groups. Therefore, our study suggests that NLR and PLR should be considered together when evaluating and treating patients with UC.

This study has several limitations.
1. It was a single-center study with a relatively small sample size.

2.There may be a selection bias as only patients with UC who underwent both endoscopy and FC testing were enrolled. This limits the strength of our conclusions.

3. FC data were not available for controls because this test is not routinely performed . However, NLR and PLR, which were calculated from CBC, can be used routinely as a noninvasive and low-cost biomarker for identifying UC as per our results.

4. Although CBC (especially absolute neutrophil counts) is affected by drugs such as azathioprine, steroids, and anti-TNF, we did not exclude all patients who took these drugs. However, the difference in neutrophil, lymphocyte, platelet, NLR, and PLR was not statistically significant between the patients on these drugs versus the patients on only 5-aminosalicylic acid. This may be because we included a relatively small number of patients on these medications, and those with an abnormal CBC had previously adjusted the drug dose or changed the medication. Finally, we could not use blood and FC tests performed on the same day as the endoscopy for patients with UC. For more precise comparisons between FC or other biomarkers and endoscopic activity, patients must provide stool and blood samples on the day of endoscopy. However, in clinical practice, these tests are not usually performed on the same day. Therefore, the interval between FC and endoscopy may have contributed to the relatively low correlation between them as compared with previous studies. The results of our study should be interpreted in light of these limitations. To overcome these limitations, prospective studies, including larger cohorts are needed. Despite these limitations, our results suggest that an elevated PLR and NLR instead of FC could be used to indicate endoscopic activity and differentiate patients with UC from healthy controls in real practice.

In conclusion, both NLR and PLR can serve as biomarkers to separate patients with UC from healthy controls. These ratios may also reflect the state of the intestinal mucosa, especially in patients with UC where colonoscopy is not possible.

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