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Lymphocyte-to-Monocyte Ratio as a Marker for Endoscopic Activity in Ulcerative Colitis

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Abstract: Leukocyte subtypes can be used to evaluate the severity of ulcerative colitis (UC). In this study, we examined the relationship between the lymphocyte-to-monocyte ratio (LMR) and the Mayo endoscopic score (MES) in assessing endoscopic activity in UC. Eighty-nine samples of leukocyte subtypes and biomarkers, including fecal calprotectin (FC), the fecal immunochemical occult blood test (FIT), and C-reactive protein (CRP), from 71 patients with UC were retrospectively investigated, along with the MES. The MES was significantly correlated with the LMR, FC, the FIT, and CRP. There were significant differences in the LMR, FC, the FIT, and CRP between groups with an MES < 1 and >2 ($p = 0.001$, $p = 0.003$, $p < 0.001$, and $p < 0.001$, respectively). In the receiver operating characteristic (ROC) analysis for predicting mucosal healing (MES 0 or 1), the areas under the curve (AUCs) for the LMR, FC, the FIT, and CRP, were 0.712, 0.860, 0.908, and 0.796, respectively. In the analysis of patients without immunomodulators, the correlation of the MES with the LMR and CRP was significant. The LMR can be used to assess endoscopic activity in UC, particularly in patients without immunomodulators.

Keywords: ulcerative colitis; lymphocyte-to-monocyte ratio; Mayo endoscopic subscore; C-reactive protein; fecal calprotectin; fecal immunochemical occult blood test

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1. Introduction

Ulcerative colitis (UC) is a chronic idiopathic inflammatory disease characterized by diarrhea, bloody stool, and abdominal pain [1]. The goal of treatment is to achieve clinical remission. However, some patients with UC are in clinical remission but still have endoscopic activity. Endoscopic evaluation to observe the mucosal state is very important in UC treatment. The goal of the current treatment of UC is to achieve mucosal healing, which contributes to the maintenance of remission, reduction in hospital stays, and avoidance of colectomy in patients with UC [2]. To determine the achievement of mucosal healing, an endoscopic evaluation is necessary. However, frequent colonoscopy should be avoided, because of the physical and psychological burden on the patient, the risk of complications, and the high cost of examination.

Biomarker measurement is an alternative to the endoscopic examination of UC. Furthermore, the usefulness of biomarkers, such as the fecal immunochemical occult blood test

(FIT) and fecal calprotectin (FC), has been reported [3–7]. These biomarkers significantly correlated with endoscopic scores, including the Mayo endoscopic subscore (MES). Moreover, there were significant differences in marker values between groups that achieved mucosal healing and those that did not. An optimal cut-off value, which predicts the achievement of mucosal healing, has also been analyzed and is one of the therapeutic goals in the treatment of UC. Urinary prostaglandin E-major urinary metabolite (PGE-MUM), which is covered by insurance for UC in Japan, is useful as a biomarker in UC. The relationship between PGE-MUM and endoscopic scores was previously reported [8,9]. Recently, leucine-rich 2 glycoprotein (LRG) using blood samples has also been reported to be a useful biomarker in UC, and is now being used in clinical practice [10,11]. Although various biomarkers for UC have emerged, the identification of simple markers that are inexpensive and can be measured at any institution would be of great help in the objective evaluation of UC in clinical practice.

The lymphocyte-to-monocyte ratio (LMR), using the ratio of leukocyte subtypes, has been reported to have a prognostic impact on malignancy [12]. Cherfane et al. were the first to report the LMR as a valid marker associated with UC severity [13]. Thereafter, an association between UC severity and the LMR has been demonstrated, and patients with active UC have been reported to have low LMRs [14,15]. In some of these reports, an association with endoscopic severity has also been shown; however, most of these reports reported mainly on the association between clinical activity and the LMR. Thus, few studies on the LMR and UC have focused on only endoscopic scores and evaluated the LMR in comparison with other markers. The LMR is related to the immune system of the intestine, as a leukocyte subtype ratio, and is familiar in general practice. In this study, we investigated whether the LMR reflects endoscopic scores better than other markers.

2. Materials and Methods

2.1. Patients

Eighty-nine samples and colonoscopies from 71 patients with UC treated at Hamamatsu University School of Medicine between February 2019 and May 2021 were enrolled in this study. Data from these patients were retrospectively analyzed. The diagnosis of UC in enrolled patients was made according to recent guidelines, based on typical history, clinical features, and endoscopic and histological evaluation [16]. Patients with inflammatory bowel disease (IBD) and undiagnosed UC were excluded from the study.

2.2. Disease Assessment

Clinical disease activity was evaluated using the Rachmilewitz clinical activity index (CAI) [17]. Clinical remission and activity were defined as CAIs ≤ 4 and ≥ 5, respectively. In this study, serum C-reactive protein (CRP) levels and leukocyte subtype counts were measured in our facility on the same day as the colonoscopy.

2.3. Endoscopic Assessment

Colonoscopy was performed with normal bowel preparation consisting of a polyethylene glycol–based electrolyte solution or glycerin enema. For UC mucosal status assessment, the MES was used. The MES was defined as follows: 0, normal or inactive disease; 1, mild disease with erythema, decreased vascular pattern, and mild friability; 2, moderate disease with marked erythema, absence of vascular patterns, friability, and erosions; and 3, severe disease with spontaneous bleeding and ulceration [18]. In this study, mucosal healing was defined as an MES of 0 or 1.

2.4. FC Analysis

Enrolled patients prepared fecal samples on or before the day of endoscopic preparation. Samples for FC measurement were collected in tubes and shipped at -20 °C, as recommended by the commercial laboratory used (SRL, Inc., Tokyo, Japan). FC was measured using a fluorescence enzyme immunoassay on a Phadia 250 immunoanalyzer

(HITACHI Ltd., Tokyo, Japan) using the Elia A Calprotectin 2 reagent (Phadia GmbH, Freiburg, Germany).

2.5. FIT Analysis

Fecal samples were prepared on or before the day of endoscopic preparation to prevent bleeding due to endoscopic examination. A collection kit for the FIT (Eiken Chemical Co., Ltd., Tokyo, Japan) was used to collect the stool specimens. The samples were immediately processed and examined using an OC-Sensor io analyzer (Eiken Chemical Co., Ltd., Tokyo, Japan).

2.6. Statistical Analysis

Statistical analyses of the data were performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). The correlation between each biomarker and endoscopic score was analyzed using Spearman's rank correlation. The intergroup differences between the mucosal healing and non-mucosal healing groups were analyzed by the Student's *t* test and Mann–Whitney U test. The accuracy of each value was evaluated using the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. A p-value < 0.05 was considered statistically significant.

2.7. Ethical Statement

The study protocol was reviewed and approved by the Ethics Committee of Hamamatsu University School of Medicine (number 20-178) before the commencement of the study. All enrolled patients agreed to participate in this study after being informed of the purpose and overview of the study, and written informed consent was obtained from them. All investigations were conducted in accordance with the Good Clinical Practice Guidelines for Investigations involving Human Subjects. Further adherence was made to the guidelines of the Declaration of Helsinki at all times.

3. Results

3.1. Patient Characteristics

The baseline characteristics of the patients are shown in Table 1. Blood and fecal specimens (89 specimens each) were collected from the 71 enrolled patients with UC. The mean patient age and disease duration were 47.2 and 11.1 years, respectively (Table 1). Fifty-four (60.7%) patients had extensive colitis, 28 (31.5%) had left colitis, and 7 (7.9%) had proctitis. The mean FC, FIT, and CRP levels were 6294.8 μg/g, 2902.4 ng/mL, and 0.74 mg/dL, respectively.

Table 1. Baseline characteristics.

Characteristic		N = 89
Age (year), mean (range) ± SD		47.2 (17–77) ± 16.6
Sex, n (%)	Male	54 (60.0)
	Female	36 (40.0)
Disease extent, n (%)	Extensive colitis	54 (60.7)
	Left sided colitis	28 (31.5)
	Proctitis	7 (7.9)
Disease duration (year), mean (range) ± SD		11.1 (0.3–72) ± 10.6
CAI (Rachmilewitz index), mean (range) ± SD		2.7 (0–17) ± 3.6
MES, n (%)	0	30 (33.7)
	1	29 (32.6)
	2	24 (27.0)
	3	6 (6.7)

Table 1. *Cont.*

Characteristic		N = 89
FC (μg/g), mean (range) ± SD		6294.8 (8.9–200,000) ± 22,543.1
FIT (ng/mL), mean (range) ± SD		2902.4 (30–45,900) ± 7620.6
CRP (mg/dL), mean (range) ± SD		0.74 (0.02–13.35) ± 2.15
Medication, n (%)	5-ASA (%)	57 (64.0)
	Steroid enema (%)	6 (6.7)
	Systemic steroid (%)	13 (14.6)
	Advanced therapy (%)	31 (34.8)
	Immunomodulators (%)	27 (30.3)

SD, standard deviation; CAI, clinical activity index; MES, Mayo endoscopic subscore; FC, fecal calprotectin; FIT, fecal immunochemical occult blood test; CRP, C-reactive protein; 5-ASA, 5-aminosalicylic acid.

3.2. Correlation of Endoscopic Score with Leukocyte Subtypes and Biomarkers

The correlation between the MES and leukocyte subtypes and biomarkers was examined (Table 2). Leukocyte subtypes were subdivided into absolute count, rate, and subtype ratio. The following values were significantly correlated with MES: neutrophil count (r = 0.343, $p < 0.001$), monocyte count (r = 0.361, $p < 0.001$), neutrophil rate (r = 0.229, $p = 0.031$), lymphocyte rate (r = −0.308, $p = 0.003$), NLR (r = 0.280, $p = 0.008$), and LMR (r = −0.359, $p < 0.001$). All biomarkers, including FC, FIT, and CRP, were significantly correlated with the MES (r = 0.704, $p < 0.001$; r = 0.735, $p < 0.001$; and r = 0.504, $p < 0.001$, respectively).

Table 2. Correlation between leukocyte subtypes or biomarkers and endoscopic score.

Variable	MES		Variable	MES	
	r	*p*		r	*p*
Neutrophil count	0.343	<0.001	Neutrophil rate	0.229	0.031
Eosinophil count	0.114	0.289	Eosinophil rate	−0.014	0.893
Basophil count	0.020	0.851	Basophil rate	−0.122	0.256
Lymphocyte count	−0.049	0.651	Lymphocyte rate	−0.308	0.003
Monocyte count	0.361	<0.001	Monocyte rate	0.119	0.268
NLR	0.280	0.008	FC	0.704	<0.001
NMR	−0.039	0.717	FIT	0.735	<0.001
LMR	−0.359	<0.001	CRP	0.504	<0.001

r, correlation coefficient; MES, Mayo endoscopic subscore; NLR, neutrophil-to-lymphocyte ratio; NMR, neutrophil-to-monocyte ratio; LMR, lymphocyte-to-monocyte ratio; FC, fecal calprotectin; FIT, fecal immunochemical occult blood test; CRP, C-reactive protein.

3.3. Comparison between Mucosal Healing and Non-Mucosal Healing Groups

There were 59 and 30 patients in the mucosal healing (MES 0 or 1) and non-mucosal healing (MES 2 or 3) groups, respectively (Table 3). Between the mucosal healing and non-mucosal healing groups, there were significant differences in the six values related to leukocyte subtypes and three biomarkers that showed a significant correlation with MES (Table 2). Among the leukocyte subtypes, the LMR had the largest AUC of 0.712 (95% confidence interval [CI] 0.604–0.821), and its optimal cut-off value was 4.35 (Table 4). The AUCs for FC, FIT, and CRP were 0.860, 0.908, and 0.769, respectively.

Table 3. Difference of leukocyte subtypes and biomarkers between Mayo endoscopic subscore (MES) 0, 1 and 2, 3 groups.

Variable	MES 0, 1 n = 59	MES 2, 3 n = 30	*p*
Neutrophil count (/μL), mean ± SD	3595.5 ± 1596.6	5132.2 ± 2980.9	0.002
Eosinophil count (/μL), mean ± SD	182.5 ± 155.9	211.5 ± 191.4	0.446
Basophil count (/μL), mean ± SD	43.8 ± 26.3	42.0 ± 27.7	0.762
Lymphocyte count (/μL), mean ± SD	1647.5 ± 800.6	1419.66 ± 554.6	0.166
Monocyte count (/μL), mean ± SD	355.3 ± 176.7	455.19 ± 227.1	0.025
Neutrophil rate (%), mean ± SD	61.4 ± 8.2	67.0 ± 13.7	0.017
Eosinophil rate (%), mean ± SD	3.1 ± 2.4	3.1 ± 2.3	0.959
Basophil rate (%), mean ± SD	0.8 ± 0.3	0.7 ± 0.4	0.361
Lymphocyte rate (%), mean ± SD	28.5 ± 8.0	22.5 ± 11.2	0.005
Monocyte rate (%), mean ± SD	6.3 ± 2.0	6.6 ± 2.4	0.429
NLR, mean ± SD	2.42 ± 1.09	4.45 ± 3.58	<0.001
NMR, mean ± SD	10.8 ± 4.2	12.9 ± 9.4	0.151
LMR, mean ± SD	5.01 ± 2.09	3.49 ± 1.42	0.001
FC (μg/g), mean ± SD	1368.1 ± 2637.0	15,983.9 ± 37,171.2	0.003
FIT (ng/mL), mean ± SD	738.8 ± 2418.9	7157.7 ± 11,673.2	<0.001
CRP (mg/dL), mean ± SD	0.18 ± 0.35	1.83 ± 3.46	<0.001

MES, Mayo endoscopic subscore; NLR, neutrophil-to-lymphocyte ratio; NMR, neutrophil-to-monocyte ratio; LMR, lymphocyte-to-monocyte ratio; FC, fecal calprotectin; FIT, fecal immunochemical occult blood test; CRP, C-reactive protein.

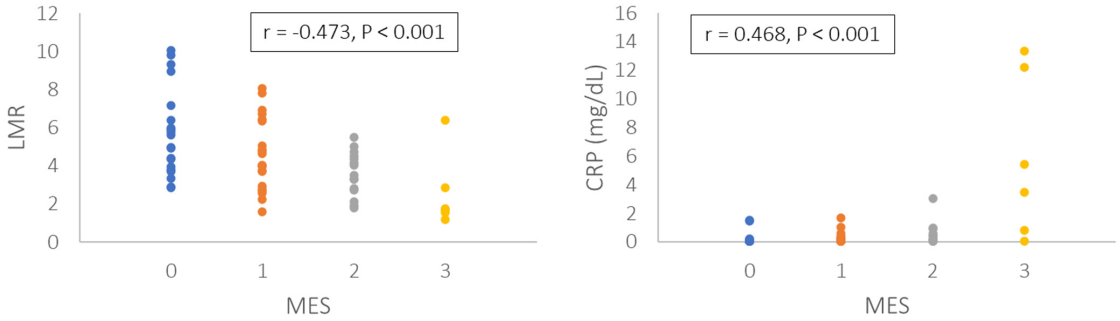
Table 4. Receiver-operating characteristic (ROC) analysis for predicting Mayo endoscopic subscore (MES) 0 or 1.

Variable	Cut-Off Value	AUC [95% CI]	Sensitivity	Specificity
Neutrophil count	4662.0	0.642 [0.510–0.775]	53.3	78.0
Monocyte count	389.6	0.657 [0.537–0.777]	56.7	69.5
Neutrophil rate	68.8	0.630 [0.490–0.770]	50.0	83.1
Lymphocyte rate	23.0	0.677 [0.545–0.809]	56.7	76.3
NLR	3.73	0.659 [0.524–0.795]	43.3	91.5
LMR	4.35	0.712 [0.604–0.821]	76.7	61.0
FC	2510.0	0.860 [0.784–0.937]	76.7	81.4
FIT	261.0	0.908 [0.848–0.968]	93.3	79.7
CRP	0.27	0.769 [0.661–0.876]	56.7	88.1

ROC, receiver operating characteristic; MES, Mayo endoscopic subscore; AUC, area under the curve; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; FC, fecal calprotectin; FIT, fecal immunochemical occult blood test; CRP, C-reactive protein.

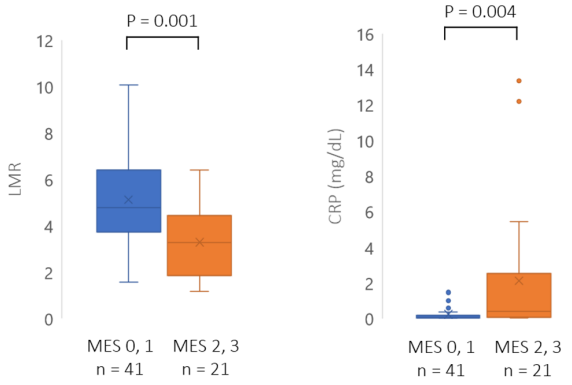
3.4. Comparison of LMR and CRP in the Group of Patients without Immunomodulators

The LMR and CRP, markers that can be easily and commonly used in clinical practice, were analyzed in a subgroup that excluded patients with immunomodulators. The MES was significantly correlated with the LMR and CRP ($r = -0.473$, $p < 0.001$ and $r = 0.468$, $p < 0.001$, respectively; Figure 1). LMRs and CRP levels were significantly different between the mucosal healing and non-mucosal healing groups ($p = 0.001$ and $p = 0.004$, respectively; Figure 2). In addition, ROC analysis was performed to predict mucosal healing in the group of patients without immunomodulators (Figure 3). The cut-off value and AUC were respectively 3.50 and 0.751 (95% CI: 0.626–0.877) for the LMR and 0.34 mg/dL and 0.714 (95% CI: 0.572–0.855) for CRP. Thus, the AUC for the LMR was higher than that for CRP; however, there was no significant difference between these AUCs ($p = 0.570$).



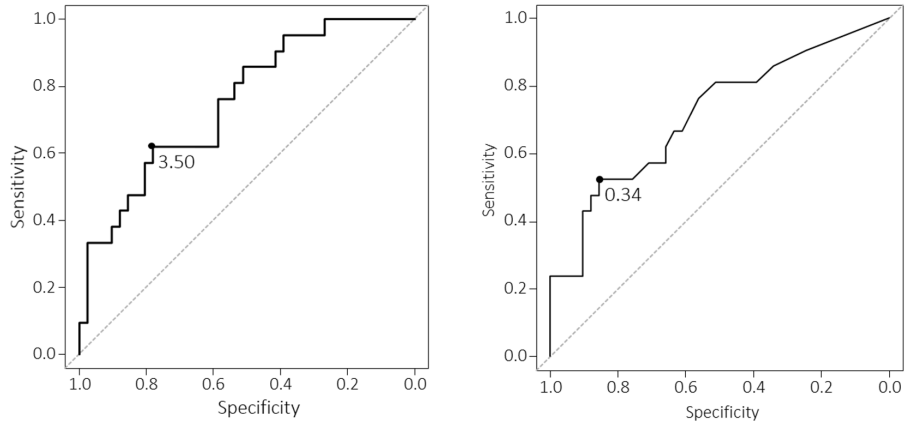
(**a**) (**b**)

Figure 1. Scatter plot diagraph of correlation between Mayo endoscopic subscore (MES) and lymphocyte-to-monocyte ratio (LMR)/C-reactive protein (CRP) in the group of ulcerative colitis patients without immunomodulators. (**a**) There was a significant correlation between the LMR and MES (r = −0.473, $p < 0.001$). (**b**) There was a significant correlation between CRP and the MES (r = 0.468, $p < 0.001$).



(**a**) (**b**)

Figure 2. Comparison of lymphocyte-to-monocyte ratio (LMR) and C-reactive protein (CRP) level between the Mayo endoscopic subscore (MES) 0, 1 and 2, 3 groups in the ulcerative colitis patients without immunomodulators. (**a**) There was a significant difference in the LMR between the two groups ($p = 0.001$). (**b**) There was a significant difference in CRP levels between the two groups ($p = 0.001$).



(**a**) (**b**)

Figure 3. Receiver-operating characteristic (ROC) analysis of lymphocyte-to-monocyte ratio (LMR) and C-reactive protein (CRP) for predicting mucosal healing of ulcerative colitis (UC) patients without immunomodulators. (**a**) ROC curve of the LMR for predicting mucosal healing. (**b**) ROC curve of CRP for predicting mucosal healing.

4. Discussion

Leukocyte subtypes are simple markers that reflect immune mechanisms. The leukocyte subtypes also reflect the disruption of immune mechanisms involved in the inflammatory response in the intestinal tract. Several studies have reported that the LMR, as a marker using the ratios of these leukocyte subtypes, reflects the activity of UC [13–15]. In particular, in these reports, the evaluation was mainly based on clinical activity. Some studies that evaluated endoscopic activity found significant differences between endoscopically quiescent and active groups [13,19], while others did not show statistically significant differences [14]. In this study, we evaluated the association between the LMR and UC, with a focus on endoscopic activity. Among the indicators related to leukocyte subtypes, the LMR best reflected the endoscopic activity of UC. The LMR was negatively correlated with the endoscopic score, indicating that a low LMR is indicative of endoscopic activity.

The fluctuation in leukocyte subtypes, including neutrophils, lymphocytes, and monocytes, in active UC is discussed below. Neutrophils are a leukocyte subtype that is mobilized during inflammation, and are one of the most important cells that infiltrate the intestinal mucosa during UC inflammation. During inflammation, neutrophils play a protective role in the injured intestinal epithelium by enhancing the production of protective mucins. They also promote intestinal repair by inducing protein and lipid mediators [20,21]. Similar to our results, other studies also found neutrophil counts to be significantly higher in the active UC group [13,14].

Previous studies of UC and Crohn's disease have shown decreased lymphocyte reactivity in peripheral and mucosal tissues. Thus, it is a reasonable hypothesis that a decrease in lymphocyte count occurs in the presence of inflammation [22–24]. Monocytes play a role in innate immunity by differentiating into macrophages and dendritic cells in tissues during infectious and non-infectious inflammation. Sustained monocyte activation and incomplete innate immune responses are known to be involved in the development of IBD [20]. Therefore, it is also reasonable that monocyte counts are increased in active UC, and previous reports have shown a correlation with disease severity in UC [25]. In several subsequent studies, monocyte counts were significantly higher in patients with active UC [13–15].

Based on the mechanisms of each leukocyte subtype described above, it is reasonable that NLRs and LMRs are higher and lower, respectively, in patients with active UC, as shown in this study. However, the reason for the AUC of the LMR being higher than that of the NLR in the ROC analysis is unclear. Nonetheless, our results suggest that monocytes might reflect the activity of UC itself more than neutrophils do.

Recently, the usefulness of biomarkers, including FC and the FIT, for assessing endoscopic activity has been reported [3–7]. In this study, ROC analysis showed that FC and the FIT were considerably more accurate than the LMR. Fecal biomarkers require the ability to accurately collect fecal samples. In addition, patients' hesitation to bring stool specimens to the hospital and the limited number of facilities where FC measurement and the FIT can be performed are challenges. In contrast, it is advantageous to use CRP and leukocyte subtypes, because they are easily measured, and can be measured by blood collection in normal clinical practice.

The LMR and CRP are both easy markers for use in many institutions. Moreover, the AUC of CRP is relatively close to that of the LMR; therefore, in this study, we investigated these two markers. Although not shown in the results section, the combination of CRP and LMR was evaluated (Supplementary Table S1), and positive results for both CRP and LMR (CRP > 0.27 mg/dL and LMR < 4.35) were better than those for CRP and LMR alone. To evaluate the usefulness of the LMR, patients with immunomodulators were excluded from the analysis. In previous studies using leukocyte subtypes in UC, patients with immunomodulators were excluded from the analysis [24,26]. In this subgroup analysis, the absolute value of the correlation coefficient was higher for the LMR than for CRP. Moreover, the AUC of the LMR was higher than that of CRP in the ROC analysis for predicting MES 0 and 1. The results of this study suggest that the LMR is a less accurate marker than FC

and the FIT. This may be due to the fact that, while the LMR reflects systemic inflammation as well as CRP, FC and the FIT are intestinal-specific markers. Consequently, the LMR does not reflect only UC inflammation, due to the confounding effects of other inflammatory and anti-inflammatory factors. The fact that immunomodulators affected the accuracy of the LMR in this study may also support this theory. Although this is a weakness of the LMR, we believe that it has the advantage that it can be easily measured at any facility, as mentioned above. In addition to immunomodulators, steroids can also affect leukocytes. Because the number of patients using steroids in this study was small, we were not able to examine the effects of steroids on each marker; an analysis that takes steroids into account is a future challenge for us.

This study had several limitations. First, it was a single-center retrospective study with a small number of enrolled patients. Second, there is no comparison with LRG. LRG is a biomarker of UC that can be measured in blood samples as well as in CRP [10,11]. Thus, LRG is a marker that is expected to be widely used in many facilities in the future, because reagents and equipment are easily available, and measurement results can be determined on the same day of consultation. Therefore, comparison of the LMR with LRG is important. Third, a comparison with histological findings was not performed. The achievement of histological healing is considered an important goal in the treatment of UC, which aims to treat the target.

5. Conclusions

Although the LMR is less accurate than FC and the FIT, it may be a marker that reflects the endoscopic score in patients with UC. Furthermore, the LMR may be more useful than CRP in patients without immunomodulators.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/immuno1040024/s1, Table S1: The accuracy of C-reactive protein, lymphocyte to monocyte ratio, and combination of these two markers.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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