Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios as Noninvasive Predictors of the Therapeutic Outcomes of Systemic Corticosteroid Therapy in Ulcerative Colitis

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Keywords

Ulcerative colitis · Corticosteroid · Neutrophil/lymphocyte ratio · Platelet/lymphocyte ratio

Abstract

Introduction: Predictive biomarkers for the therapeutic outcome of induction therapy with systemic corticosteroid for active ulcerative colitis (UC) have not been established. This study aimed to investigate whether neutrophil-to-lymphocyte ratio (NLR) and/or platelet-to-lymphocyte ratio (PLR) can be predictive biomarkers for the therapeutic outcomes of systemic corticosteroid therapy in UC. **Methods:** This was a single-center retrospective cohort study. In total, 48 patients with UC who received induction therapy with systemic corticosteroid were enrolled. Based on the achievement of clinical remission after 8 weeks of treatment, the patients were divided into the remission group ($n = 28$) and the non-remission group ($n = 20$). Clinical characteristics, NLR, and PLR at baseline between the remission and nonremission groups were compared via a univariate analysis. The independent risk factors of nonremission were identified via a multivariate analysis. **Results:** The baseline Mayo score, platelet count, lymphocyte count, C-reactive protein (CRP)

levels, NLR, and PLR between the 2 groups significantly differed. The nonremission group had higher NLR and PLR than the remission group (4.70 [3.04–11.3] vs. 3.10 [1.36–16.42]; $p < 0.05$, and 353.6 [220.3–499.8] vs. 207.2 [174.4–243.6]; $p < 0.001$, respectively). A multivariate analysis revealed that a Mayo score of ≥ 9 , CRP level of ≥ 1.26 mg/dL, and PLR of ≥ 262 (hazard ratio: 23.1, 95% confidence interval: 1.29–413.7, $p = 0.033$) were considered independent risk factors for non-remission. **Conclusion:** This report first identified the efficacy of NLR and PLR as candidate biomarkers for predicting the therapeutic outcomes of systemic corticosteroid therapy in UC.

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Introduction

Ulcerative colitis (UC) is a chronic idiopathic inflammatory bowel disease that affects the colonic and rectal mucosa. The initial treatment for active mild or moderate UC is topical and/or systemic administration of 5-aminosalicylic acid. Systemic corticosteroids can be used in patients with moderate to severe disease activity. Prednisolone (PSL) is a common systemic corticosteroid therapy,

and its starting doses are 40 mg/day for active moderate UC and 60 mg/day for active severe UC [1]. The recommended tapering strategy for PSL is reducing the daily dose by 5 mg per week, resulting in a treatment course of 8 weeks [2]. More than 80% of patients respond to systemic corticosteroid therapy, and about 55% of patients can achieve complete remission within 30 days. Meanwhile, about 45% present with partial or no response to treatment [3]. However, response to systemic corticosteroids is challenging to predict before treatment. Moreover, predictive biomarkers for the therapeutic outcome of systemic steroids have not been established. Hence, further studies should be conducted.

Previous studies have focused on the efficacy of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as noninvasive biomarkers for assessing the disease activity of UC [4–9]. NLR and/or PLR are significantly correlated with both clinical and endoscopic disease activity in patients with UC. Recently, several studies have shown that NLR and/or PLR can be simple biomarkers for predicting the therapeutic outcomes of UC treatment. Nishida et al. [10, 11] have shown that NLR can be a possible predictor of nonresponse to infliximab and for clinical relapse after tacrolimus induction in patients with UC. Bertani et al. [12] have revealed that NLR and PLR can predict mucosal healing in patients with UC treated with anti-TNF antibodies. However, only few studies have examined the relationship between pretreatment NLR and PLR and the therapeutic outcomes of induction therapy with systemic corticosteroid in UC. Therefore, the current study aimed to determine whether NLR and PLR can be predictive biomarkers for the therapeutic outcomes of systemic corticosteroid therapy in UC.

Methods

Study Design and Patients

This was a single-center retrospective cohort study, and it was approved by the ethics committee of our institution (Institutional Review Board of the Tohoku Medical and Pharmaceutical University School of Medicine). Approved IRB number is 2021-2-036. We enrolled 48 consecutive patients with active UC who received remission induction therapy via the systemic administration of corticosteroid between January 2017 and December 2020. Systemic administration of corticosteroid was defined as induction therapy with a PSL starting dose of >30 mg/body. The administration route and the dose of PSL were determined based on disease activity and body weight. For the outpatient with moderate disease activity, PSL was administrated orally at a dose of 30–40 mg/body. For the inpatient with moderate to severe disease activity, intravenous PSL was started at a dose of 40 mg–60 mg/body. All patients

were not treated with concomitant immunomodulators, calcineurin inhibitors, biologics, and tofacitinib at baseline. Data about sex, age, disease extension, disease duration, Mayo score, and laboratory findings at baseline were collected from the patients' medical records. NLR at baseline was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. PLR at baseline was calculated by dividing the absolute platelet count by the absolute lymphocyte count.

Comparisons between the Remission and Nonremission Groups after 8 Weeks of Treatment

Information about the achievement of clinical remission 8 weeks after the start of systemic steroid therapy was obtained from the patients' medical records. Clinical remission was defined as a partial Mayo score of 0 (without the endoscopic subscore). The patients were divided into the remission and nonremission groups based on the achievement of clinical remission after 8 weeks of treatment. Patients with a partial Mayo score of 0 after 8 weeks were included in the remission group. Meanwhile, patients with a partial Mayo score of ≥ 1 after 8 weeks of treatment and those who were steroid refractory and who required additional treatment or change of drug regimen within 8 weeks were classified under the nonremission group. Clinical characteristics, NLR, and PLR at baseline between the remission and nonremission groups were compared via a univariate analysis. For continuous variables that were statistically different between the 2 groups, the optimal cutoff values for nonremission were determined via a receiver operating characteristic (ROC) analysis.

Risk Factors for Predicting Nonremission after 8 Weeks of Treatment

To identify the independent risk factors of nonremission after 8 weeks of treatment, we performed a multivariate analysis of possible factors that significantly differed between the remission and nonremission groups in the univariate analysis.

Statistical Analysis

Statistical analyses were performed using JMP Pro 13.2.1 (SAS Institute Inc., Cary, NC, USA). Categorical variables were presented as numbers and percentages and continuous variables as median and interquartile ranges. Data between the 2 groups were compared using the χ^2 test for categorical variables and the Mann-Whitney U test for numerical variables. Correlations between 2 continuous data were analyzed using the Spearman's correlation coefficient. The optimal cutoff values of continuous parameters for diagnosing nonremission after 8 weeks of treatment were determined via an ROC curve analysis. The independent risk factors for nonremission after 8 weeks of treatment were identified via a logistic regression analysis. A *p* value of <0.05 was considered statistically significant.

Results

Baseline Characteristics of the Patients

Table 1 shows the baseline characteristics of the patients. The study included 29 (60.4%) male patients. The median age of the patients was 36.5 years, and the median

Table 1. Baseline characteristics of the patients

Variables	UC (n = 48)
Male sex, n (%)	29 (60.4)
Age, years	36.5 (22.5–43)
Disease duration, years	0.5 (0–3)
Disease extension, n (%)	
Proctitis	0 (0)
Left-sided colitis	5 (10.4)
Pan-colitis	43 (89.6)
Newly diagnosed or relapse, n (%)	
Newly diagnosed	20 (41.7)
Relapse	28 (58.3)
Mayo score	8 (7–9)
WBC count, / μ L	8,350 (6,250–10,075)
Hemoglobin level, g/dL	12.6 (11.1–14.2)
Platelet count, $\times 10^4$ / μ L	34.1 (25.2–44.2)
Neutrophil count, / μ L	5,467 (3,716–8,403)
Lymphocyte count, / μ L	6,270 (988–5,735)
Albumin level, g/dL	3.7 (3.2–3.9)
CRP level, mg/dL	1.19 (0.435–6.35)
NLR	3.55 (2.48–7.04)
PLR	230.2 (176.0–378.6)

Continuous variables were presented as median and interquartile ranges. CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

disease duration was 0.5 years. Five (10.4%) patients had left-sided colitis and 43 (89.6%) had pan-colitis. In total, 20 (41.7%) patients were newly diagnosed and 28 (58.3%) had relapse. Twenty-four cases were treated with oral PSL, and 24 cases were treated with intravenous PSL. The median dose of PSL was 40 mg/body (40–50 mg/body). The median Mayo score at baseline was 8. The median NLR and PLR at baseline was 3.55 (2.48–7.04) and 230.2 (176.0–378.6), respectively.

Differences in Baseline Parameters between the Remission and Nonremission Groups

Of 48 patients, 28 (58.3%) achieved remission after 8 weeks of treatment and 20 (41.7%) did not. Table 2 depicts the baseline parameters between the remission and nonremission groups, as assessed via a univariate analysis. Sex, age, disease duration and extension, and treatment setting did not significantly differ between the 2 groups. The nonremission group had a significantly higher baseline Mayo score than the remission group ($p < 0.05$). Among the baseline laboratory data, significant differences were found in terms of platelet and lymphocyte count, C-reactive protein (CRP) level, NLR, and PLR. The nonremission group had a higher platelet count ($\times 10^4$ /

μ L) than the remission group (39.7 [30.4–48.5] vs. 29.1 [24.3–38.6]; $p < 0.05$). The nonremission group had a lower lymphocyte count (/ μ L) than the remission group (1,143 [862–1,599] vs. 1,375 [1,186–1,923]; $p < 0.05$). The nonremission group had a higher CRP level (mg/dL) than the remission group (4.45 [1.48–9.13] vs. 0.80 [0.10–2.56]; $p < 0.001$). The NLR and PLR of the nonremission group were higher than those of the remission group (4.70 [3.04–11.3] vs. 3.10 [1.36–16.42]; $p < 0.05$, and 353.6 [220.3–499.8] vs. 207.2 [174.4–243.6]; $p < 0.001$, respectively). Based on the ROC curve analysis, the optimal cut-off NLR and PLR for predicting nonremission was 3.6 and 262, respectively (Fig. 1).

Independent Risk Factors for Predicting Nonremission after 8 Weeks of Treatment

A multivariate analysis of pretreatment Mayo score, platelet and lymphocyte count, CRP level, NLR, and PLR, which are candidate predictors for nonremission after 8 weeks of treatment, was performed. The cutoff value of each parameter was determined via an ROC curve analysis. A Mayo score of ≥ 9 (hazard ratio [HR]: 14.83, 95% confidence interval [CI]: 1.88–117.2, $p = 0.016$), CRP level of ≥ 1.26 mg/dL (HR: 17.7, 95% CI: 1.81–173.3, $p = 0.014$), and PLR of ≥ 262 (HR 23.1; 95% CI: 1.29–413.7, $p = 0.033$) were considered independent risk factors for nonremission after 8 weeks of treatment (Table 3).

Discussion

This study showed that both NLR and PLR were correlated with the therapeutic outcomes of systemic corticosteroid therapy for UC. Moreover, PLR was an independent predictor of nonremission after 8 weeks of treatment. To the best of our knowledge, this report first showed the efficacy of NLR and PLR as candidate biomarkers for predicting the therapeutic outcomes of systemic corticosteroid therapy in UC.

Systemic corticosteroid therapy is the standard induction-remission treatment for acute moderate or severe UC. However, about 45% of patients with UC treated with systemic corticosteroid are refractory to treatment [3]. Therefore, predicting the responsiveness to steroid therapy is important in preventing the continuation of ineffective treatment or in preparing for the second-line therapy or colectomy. Previous studies showed possible predictors of responsiveness to systemic corticosteroid. Baseline clinical factors, such as disease extent, stool frequency, temperature, heart rate,

Table 2. Baseline parameters between the remission and nonremission groups

	Remission group (n = 28)	Nonremission group (n = 20)	p value
Male sex, n (%)	16 (57.1)	13 (65.0)	0.7656
Age, years	38 (14–66)	26.5 (15–81)	0.221
Disease duration, years	0.5 (0–29)	0.6 (0–5)	0.4090
Left-sided colitis, n (%)	1 (3.6)	4 (20.0)	0.1457
Newly diagnosed, n (%)	12 (42.9)	8 (40.0)	1.0000
Mayo score	7 (6–8.75)	9 (8.25–10)	<0.05*
WBC count, / μ L	1,900 (5,400–9,925)	9,000 (7,300–11,375)	0.2456
Hemoglobin level, g/dL	12.6 (11.1–14)	12.5 (10.9–14.4)	0.8836
Platelet count, $\times 10^4$ / μ L	29.1 (24.3–38.6)	39.7 (30.4–48.5)	<0.05*
Neutrophil count, / μ L	5,116 (9,285–9,016)	7,474 (5,842–3,800)	0.1295
Lymphocyte count, / μ L	7,375 (6,186–4,923)	7,143 (862–1,599)	<0.05*
Albumin level, g/dL	3.7 (3.35–4.28)	3.4 (2.8–3.8)	0.0957
CRP level, mg/dL	0.80 (0.103–2.56)	4.45 (1.48–9.13)	<0.01*
NLR	3.10 (2.26–4.33)	4.70 (3.04–11.3)	<0.05*
PLR	207.2 (174.4–243.6)	353.6 (220.3–499.8)	<0.01*

Continuous variables were presented as median and interquartile ranges. CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio. * $p < 0.05$ indicates statistical significance.

Table 3. Independent risk factors for nonremission after 8 weeks of treatment based on a logistic regression analysis

	Hazard ratio	95% CI	p value
Mayo score			
<9	Ref		
9 $\leq$	14.83	1.88–117.2	0.0106*
Platelet count			
<34.5	Ref		
34.5 $\leq$	0.88	0.119–6.54	0.9015
Lymphocyte count			
≥ 960	Ref		
<960	2.84	0.123–65.7	0.5143
CRP level			
<1.26	Ref		
1.26 $\leq$	17.7	1.81–173.3	0.0135*
NLR			
<3.6	Ref		
3.6 $\leq$	0.35	0.036–3.325	0.3588
PLR			
<262	Ref		
262 $\leq$	23.1	1.285–413.7	0.0332*

95% CI, 95% confidence interval; ref, reference; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio. * $p < 0.05$ indicates statistical significance.

serum CRP and albumin levels, and radiologic assessment, were found to be the predictors of failed corticosteroid therapy in a previous systematic review [13]. According to the most recent guidelines for the man-

agement of pediatric UC by the international Pediatric Inflammatory Bowel Disease Ahead Program (PIBD-Ahead), the clinical activity score on days 3 and 5 of hospital admission can predict the need for treatment escalation after intravenous corticosteroid therapy [14]. Moreover, the PIBD-Ahead guideline states that higher CRP levels on both days 3 and 5 of treatment can predict response to intravenous steroids [14]. The clinical activity and serum CRP levels are important factors affecting the outcomes of systemic corticosteroid therapy. The current study showed that a Mayo score of ≥ 9 and a CRP level of ≥ 1.26 mg/dL were independent risk factors for nonremission after 8 weeks of treatment. These results are consistent with those of previous systematic review and the PIBD-Ahead guidelines.

We focused on the efficacy of NLR and PLR as candidate noninvasive predictors for the outcomes of systemic corticosteroid therapy in UC. NLR and PLR are simple biomarkers that can predict the disease activity of UC [4–9]. Recent studies have shown that NLR and/or PLR can be reliable markers for predicting the outcomes of tacrolimus and anti-TNF therapy in UC [11, 12]. Therefore, whether NLR and PLR can be candidate markers for predicting response to systemic corticosteroids therapy in UC was evaluated. Results showed that the nonremission group had higher NLR and PLR than the remission group. Moreover, a PLR of ≥ 262 at baseline was an independent risk factor for nonremission after 8 weeks of treatment. Hence, NLR and PLR can be noninvasive biomarkers for

Fig. 1. ROC curve of NLR and PLR for predicting nonremission. **A** Based on the ROC curve analysis, the optimal cutoff NLR for predicting nonremission was 3.6 (sensitivity: 70.0%, specificity: 64.3%, and AUC: 0.702). **B** Based on the ROC curve analysis, the

optimal cutoff PLR for predicting nonremission was 262 (sensitivity: 75.0%, specificity: 85.7%, and AUC: 0.764). ROC, receiver operating characteristic; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; AUC, area under the curve.

predicting the therapeutic outcomes of induction therapy with systemic corticosteroid in moderate or severe UC.

An important discussion point is the mechanism underlying the significant correlation between NLR and PLR as well as the therapeutic outcomes of systemic corticosteroid therapy in UC. Fundamentally, neutrophils induce systemic inflammation and play a significant role in the development of mucosal inflammatory conditions, such as cryptitis and crypt abscess formation, in UC. Moreover, a high platelet count and presence of activated platelets can exacerbate mucosal inflammation by increasing vascular permeability and by enhancing leukocyte migration ability in UC. In contrast, low lymphocyte counts are found in active UC, which may be associated with complex factors such as mucosal lymphocyte infiltration, apoptosis caused by autoimmune disorder, malnutrition, and leakage due to colonic bleeding. Thus, high neutrophil and platelet counts and a low lymphocyte count can reflect the immunological inflammatory intensity of UC. Therefore, NLR and PLR, which are obtained by dividing the neutrophil and platelet count by the lymphocyte count, are more sensitive in identifying the im-

munological inflammatory intensity of UC than their respective values. Hence, NLR and PLR are excellent in predicting responsiveness to steroid treatment in UC.

Another discussion point is the difference between NLR, PLR, Mayo score, and CRP for predicting the corticosteroid therapeutic efficacy. Fundamentally, we consider NLR, PLR, Mayo score, and CRP to be markers for evaluating the disease activity of UC, each of which has an independent value. These markers can assess the disease intensity from different points of view. Mayo score consists of 4 subscores (stool frequency, rectal bleeding, findings on sigmoidoscopy, and physician's global assessment), which reflects mainly the clinical severity. CRP is an acute-phase protein that increases following interleukin-6 secretion by macrophages and T cells, which reflects the intensity of systemic serological inflammation. NLR and PLR, which are obtained by dividing the neutrophil and platelet count by the lymphocyte count, can reflect the immunological inflammatory intensity of UC. Therefore, each marker has independent significance for assessing the disease activity and can predict the therapeutic outcome of corticosteroid therapy in UC from a

different point of view. Thus, we argue that it is meaningful to predict treatment outcomes using NLR and PLR in addition to commonly used Mayo score and CRP. As for the difference between NLR and PLR, it has not been clarified even in terms of its ability to assess disease activity in UC. The previous study has reported that both NLR and PLR can predict mucosal healing in patients with UC treated with anti-TNF antibodies [12]. Of the NLR and PLR, only PLR was identified as significant for predicting therapeutic outcomes of corticosteroid therapy in the multivariate analysis in our study. In the present study, the case number is too small to analyze the difference between NLR and PLR. Further investigation is needed to clarify this issue.

The current study had several limitations. That is, it was retrospective in nature, and only a single-center cohort was included. Moreover, endoscopic remissions were not evaluated in this study. Endoscopic activities were evaluated before the systemic corticosteroid therapy in all cases enrolled in this study. However, only a few cases were evaluated endoscopically after 8 weeks of the treatment. Ideally, a prospective study should be conducted to investigate the correlation between pretreatment NLR and PLR and endoscopic improvement after systemic corticosteroid therapy. The most important limitation is the inclusion of a small number of patients. Thus, further studies with a large cohort should be performed to validate the predictive value of NLR and PLR for the efficacy of systemic corticosteroid in UC.

In conclusion, pretreatment NLR and PLR were significantly associated with clinical remission after 8 weeks of induction therapy with systemic corticosteroid in patients with UC. Besides a high Mayo score and high CRP level, high PLR was identified as an independent risk factor for nonremission after 8 weeks of systemic corticosteroid therapy. These results indicate that NLR and PLR can be noninvasive biomarkers for predicting the therapeutic outcomes of induction therapy with systemic corticosteroid in UC.

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Statement of Ethics

All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study design was observational. The study was approved by the ethics committee of our institution (Institutional Review Board of the Tohoku Medical and Pharmaceutical University School of Medicine). Approved IRB number is 2021-2-036. The study was performed in accordance with the ethics guidelines in Japan and was allowed implementation without obtaining individual written informed consent. This study was announced by posters in the outpatient ward or on the homepage of the participating institutions. Patients who expressed unwillingness to participate in this study were excluded.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Funding Sources

The authors received no financial support for the research.

Author Contributions

Katsuya Endo established the study design, and he was involved in designing the original study protocol, collecting data, and writing the manuscript. Tomonori Satoh, Yuki Yoshino, Shiho Kondo, Yoko Kawakami, and Tomofumi Katayama participated in data collection. Yoshiteru Sasaki, Atsuko Takasu, Takayuki Kogure, Morihisa Hirota, Takayoshi Meguro, and Kennichi Satoh contributed in discussing and critically reviewing the manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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