




ORIGINAL ARTICLE

# Lymphocyte-to-monocyte ratio is a short-term predictive marker of ulcerative colitis after induction of advanced therapy

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## Abstract

Advanced therapies for patients with mild-to-severe ulcerative colitis (UC) may result in treatment failure. We examined whether the lymphocyte-to-monocyte ratio (L/M ratio) could predict the failure of advanced therapies. This retrospective, observational, cohort study included 73 patients who were treated with advanced therapies at the Hamamatsu University School of Medicine (Shizuoka, Japan) between February 2011 and November 2020. The patients were divided into the non-failure and failure groups, and their leukocyte counts and ratios before induction were examined. Univariate and multivariate analyses were performed to identify the prognostic factors. Advanced therapies failed within 3 months in 15 (20.5%) patients. Only the L/M ratio was significantly lower in the failure group than in the non-failure group ( $P = 0.004$ ). Receiver-operating characteristic (ROC) curve analysis revealed that an L/M ratio of  $\leq 3.417$  was predictive of treatment failure; the area under the curve (AUC) was 0.747 (95% CI, 0.620–0.874). Kaplan–Meier analysis revealed that the failure-free rate was significantly lower in the group with an L/M ratio of  $\leq 3.417$  than in the group with an L/M ratio of  $> 3.417$  (log-rank test  $P = 0.002$ ). Cox proportional hazard regression analysis identified an L/M ratio of  $\leq 3.417$  as an independent risk factor for failure within 3 months after the induction of advanced therapies. Furthermore, ROC analysis of patients who did not receive immunomodulators also revealed that the cut-off L/M ratio was 3.417 and the AUC was 0.796 (95% CI, 0.666–0.925). In patients receiving advanced therapies for active UC, the L/M ratio can predict treatment failure within 3 months. L/M ratios could facilitate the transition from advanced therapies to subsequent treatments.

**Key words:** advanced therapy; failure; lymphocyte-to-monocyte ratio; ulcerative colitis

Submitted: 14 October 2021; Revised: 4 May 2022; Accepted: 4 May 2022

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## Introduction

The incidence of ulcerative colitis (UC), an inflammatory bowel disease, is increasing worldwide [1]. In the past, corticosteroids comprised the first-line treatment for patients with mild-to-severe UC; however, due to steroid dependence or steroid resistance, 50% of the patients developed refractory UC 1 year after steroid treatment [2]. Therefore, advanced biopharmaceutical therapies have emerged as alternatives to steroids, and infliximab (IFX; an antitumor necrosis factor [TNF]- $\alpha$  antibody) can achieve both clinical and endoscopic remission in patients with UC [3]. Additionally, the anti-TNF- $\alpha$  antibodies adalimumab (ADA) and golimumab (GLM) have proven effective for UC and have been used in clinical practice to treat many patients [4, 5]. Moreover, advanced therapies targeting various molecules involved in the pathophysiology of UC have also been identified. For example, studies have reported the usefulness of vedolizumab (VDZ; an anti-integrin antibody), tofacitinib (TOF; an oral small Janus kinase inhibitor), and ustekinumab (UST; an antagonist of the p40 subunit of interleukin-12 and interleukin-23) [6–8]. Accordingly, advanced therapies for UC comprise treatment with IFX, ADA, GLM, VDZ, TOF, and UST.

Despite the availability of various advanced drug therapies for UC, each drug is associated with cases of treatment resistance. Accordingly, a switch to other advanced therapies or to oral tacrolimus may be required in these cases; however, if there is no improvement with these treatments, colectomy may be required. Therefore, to maintain the patient's quality of life and to ensure a timely transition to the next treatment without worsening the general condition, accurate and prompt evaluation of the need to switch to other treatments of UC are essential.

The responses to advanced therapies for UC have been evaluated in several studies. Many studies have focused on the relationship between the drug trough levels, anti-drug antibody levels, and prognosis. These studies have found that high trough and low anti-drug antibody levels indicated a therapeutic effect of the advanced therapies and predicted a good clinical course [9–12]. Advanced therapies have also shown good therapeutic effects in naive cases [13]. Studies that predicted the prognosis of patients with UC who were treated with anti-TNF- $\alpha$  antibodies investigated the data on baseline blood biomarker concentrations and the short-term changes in these markers between before and after treatment induction [14–18].

Leukocytes include neutrophil, basophil, eosinophil, lymphocyte, and monocyte fractions. Churfane et al. [19] reported that the lymphocyte-to-monocyte ratio (L/M ratio) is a useful biomarker of UC activity. Moreover, biomarkers such as fecal calprotectin (FC) and the fecal immunochemical test (FIT) not only indicate a relationship with clinical or endoscopic activity, but also predict clinical relapse [20–25]. In addition, some studies on patients with UC treated with anti-TNF- $\alpha$  preparations have identified FC as a useful marker for prognosis [26–28]. However, no previous study has attempted to predict the clinical prognosis on the basis of the L/M ratio. Therefore, in this study, we have retrospectively examined the relationship between the L/M ratio and treatment failure during induction with advanced therapies.

## Materials and methods

### Study design and patients

This retrospective cohort study included patients with UC who were treated with advanced therapies at the Hamamatsu University School of Medicine (Shizuoka, Japan) between

February 2011 and November 2020. The diagnosis of UC in these patients was based on typical medical history and clinical features, as well as on the endoscopic and histological evaluations performed in accordance with recent guidelines [29]. The inclusion criteria were as follows: (i) advanced treatment-naive patients (to avoid the influence of previous advanced therapies) and (ii) patients diagnosed with mild-to-severe UC based on the clinical activity index (CAI) and biological data. Patients with UC who underwent intestinal resection were excluded. Patients who discontinued treatment due to adverse events or who were lost to follow-up were also excluded. Similarly to our previous study [30], the primary endpoint in this study was the association between the L/M ratio and treatment failure, which was defined by the need to switch to other advanced therapies or colectomy within 3 months from induction with advanced therapies. The secondary endpoints were the recurrence-free periods divided into two groups based on the cut-off L/M ratio.

### Disease assessment

The CAI (Rachmilewitz index) was used to evaluate the included patients [31]. In this study, a CAI of <4 was defined as remission and a CAI of  $\geq 4$  was defined as active UC (mild-to-severe). The white blood cell count and the neutrophil, lymphocyte, and monocyte counts at the start of the treatment were evaluated; all included patients underwent colonoscopy before induction. The Mayo endoscopic subscore (MES) was used for the assessment of the UC mucosal status based on the following criteria: 0, normal or inactive disease; 1, mild disease (erythema, decreased vascular pattern, and mild friability); 2, moderate disease (marked erythema, absent vascular patterns, friability, and erosions); and 3, severe disease (spontaneous bleeding and ulceration) [32]. Complete mucosal healing was defined by an MES of 0.

### Advanced therapies and follow-up

Each advanced therapy was administered with eligible doses and dosages (Supplementary Table 1). The included patients were followed up for >3 months as inpatients or outpatients. Failure of advanced therapies was defined as the requirement of colectomy or of switching to other advanced therapies or calcineurin inhibitors within 3 months from the previous induction with advanced therapies. Patients were divided into the failure and non-failure groups accordingly.

### Statistical analysis

Statistical analyses of the data were performed using SPSS version 24 (IBM, Armonk, NY, USA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). P-values of <0.05 were considered statistically significant. Differences in the values between the non-failure and failure groups were compared using the Mann-Whitney U test and the Student's t-test. Receiver-operating characteristic (ROC) analysis was conducted to determine the optimal cut-off value of the L/M ratio for predicting failure within 3 months of the therapy. The accuracy of this cut-off ratio was evaluated using the area under the ROC curve (AUC). The cumulative remission rate was analysed using Cox proportional hazard regression and Kaplan–Meier analyses; intergroup comparisons were performed using the log-rank test.

### Ethics statement

The protocol for this retrospective study was reviewed and approved by the Ethics Committee of Hamamatsu University

School of Medicine (No. 21–029). This study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from all participants of the study.

## Results

### Patient characteristics

Figure 1 presents the flow diagram depicting the patient selection process and Table 1 shows the baseline characteristics of the 73 patients with UC included in this study at the time of advanced therapy induction. The mean age and disease duration of the patients were 45.2 and 6.9 years, respectively. The mean CAI was 7.4, and MESs of 1, 2, and 3 were recorded in 6, 47, and 20 patients, respectively; no patients were noted to have an MES of 0. Other medications taken by the patients at the time of the study were oral 5-aminosalicylic acid (5-ASA;  $n=44$ ), suppository steroids ( $n=7$ ), systemic steroids ( $n=27$ ), and immunomodulators ( $n=28$ ). The agents used in advanced therapies were IFX ( $n=30$ ; 41.1%), ADA ( $n=24$ ; 32.9%), GLM ( $n=6$ ; 8.2%), TOF ( $n=8$ ; 11.0%), VDZ ( $n=4$ ; 5.5%), and UST ( $n=1$ ; 1.4%).

### Comparison of the non-failure and failure groups

Of the 73 patients included, 15 (20.5%) experienced treatment failure at the 3-month follow-up after the start of the study (Table 1 and Figure 1). The non-failure and failure groups showed no significant differences in the baseline patient background data. The absolute counts of leukocytes and their subtypes and the subtype ratios were compared between the non-failure and failure groups (Table 2). The absolute counts of the neutrophils, lymphocytes, and monocytes did not differ significantly between the groups; however, the monocyte count tended to be higher in the failure group than in the non-failure group ( $P=0.060$ ). Among the leukocyte subtype ratios, only the L/M ratio was significantly lower in the failure group than in the non-failure group ( $P=0.004$ ).

### Prediction of treatment failure within 3 months of advanced therapy induction using the L/M ratio

As the L/M ratio was suggested to predict treatment failure within 3 months of advanced therapy induction, ROC analyses were performed using this ratio (Figure 2A). The optimal cut-off L/M ratio was 3.417, and its sensitivity and specificity were 0.733

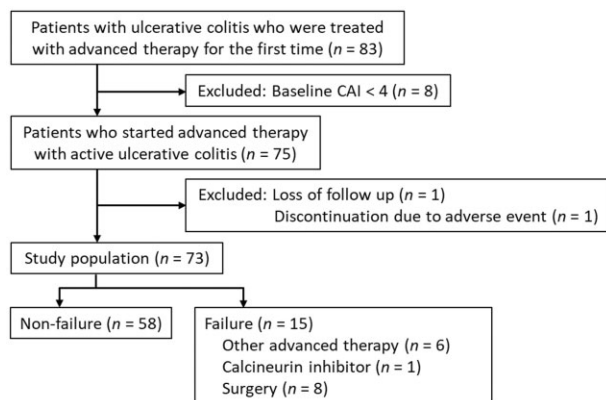


Figure 1. Flow diagram depicting the patient selection process. CAI, clinical activity index.

and 0.707, respectively. ROC analysis revealed an AUC of 0.747 (95% CI, 0.620–0.874). A Kaplan–Meier analysis was then performed for two groups: one with an L/M ratio of  $>3.417$  and the other with an L/M ratio of  $\leq 3.417$  (Figure 2B). The group with an L/M ratio of  $\leq 3.417$  had a significantly lower failure-free ratio in the log-rank test than the group with an L/M ratio of  $>3.417$  ( $P=0.002$ ). Cox proportional hazard regression analysis showed that an L/M ratio of  $\leq 3.417$  could be an independent risk factor for treatment failure within 3 months of the induction of advanced therapies (Table 3).

### Subgroup analysis

To predict the prognosis more accurately using the L/M ratio, a subgroup analysis was performed based on combination therapies (other than the advanced therapies) that were administered at the time of therapy induction (Table 4). Significant differences were observed between the non-failure and failure groups in terms of the patients who received systemic steroids ( $P=0.009$ ) and those who did not receive oral 5-ASA and immunomodulators ( $P=0.020$  and  $P=0.009$ , respectively; Figure 3). ROC analysis of the L/M ratio predictive of treatment failure within 3 months of therapy induction in subgroups with significant differences showed that the cut-off L/M ratio was 3.417 in all subgroups, and the largest AUC was 0.796 (95% CI, 0.666–0.925) for the group of patients who did not receive immunomodulators (Table 5).

## Discussion

This study investigated the usefulness of the L/M ratio for the prognostication of advanced therapies that are widely used for UC. Many studies have attempted to predict the therapeutic effects of advanced therapies, especially anti-TNF $\alpha$  preparations, on UC. Moreover, high drug trough levels and low levels of anti-drug antibodies after the start of the treatment are reported to be the predictors of treatment response [10, 11, 33]. However, induction with anti-TNF $\alpha$  antibodies and the subsequent tests require time. This can present a major problem in actual clinical practice because many facilities outsource these tests. Biomarkers are alternative prognostic predictors for advanced therapies and FC measurements have been reported to be particularly useful [26–28]. However, for facilities that outsource this evaluation, there is a considerable delay between sample collection and the results even for FC measurements; moreover, frequent tests are expensive. In contrast, the L/M ratio can be determined using conventional blood cell measurement methods; the ability to perform relatively rapid measurements and the low costs are the additional advantages of using the L/M ratio as a prognostic marker. As Cherfane *et al.* [19] reported, the L/M ratio is an evaluation method that indicates the severity of UC. The present study only predicted the short-term prognosis of advanced therapies using this severity-evaluation method; this theory is similar to that of prognosis prediction using biomarkers such as the FC and FIT. We noted that the disadvantage of using the L/M ratio for predicting the prognosis for advanced therapies was the lack of specificity for the therapeutic drug used. However, because of this lack of specificity, we think that the L/M ratio can be an index for predicting the effects of other drugs for UC, such as calcineurin inhibitors. Examining the usefulness of the L/M ratio for predicting the prognosis in other treatments is a subject for our future research.

**Table 1.** Baseline characteristics of the 73 patients with UC included in this study

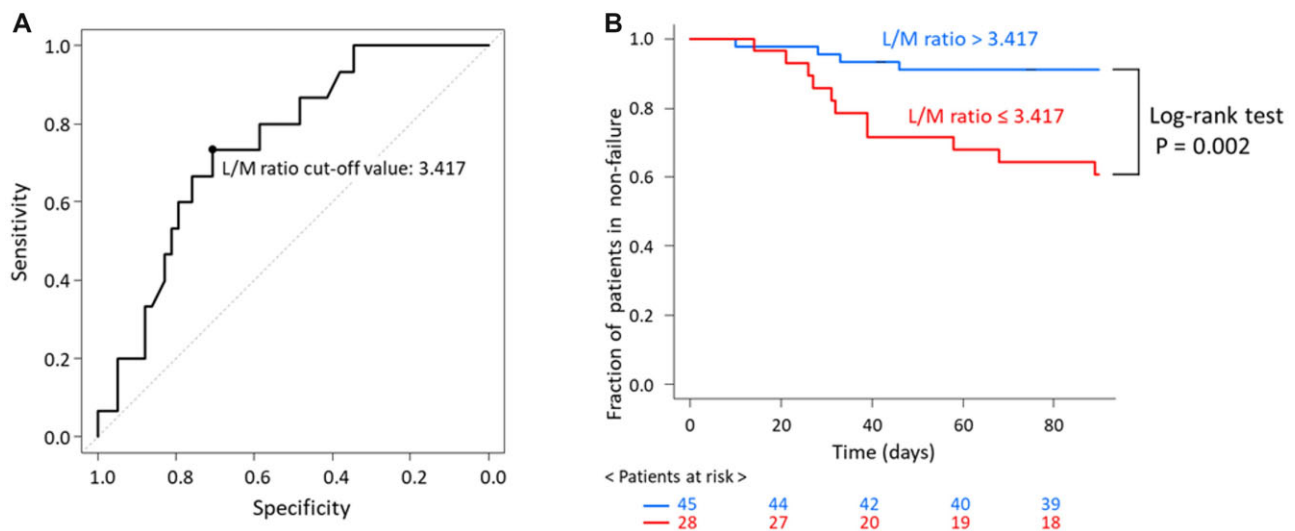
Characteristics	Total (n = 73)	Non-failure group (n = 58)	Failure group (n = 15)	P-value
Age, years, mean $\pm$ SD	45.2 $\pm$ 18.3	45.5 $\pm$ 18.1	44.0 $\pm$ 19.7	0.782
Male, n (%)	44 (60.3)	34 (58.6)	10 (66.7)	0.768
Disease duration, years, mean $\pm$ SD	6.9 $\pm$ 8.4	7.4 $\pm$ 8.6	5.0 $\pm$ 7.7	0.054
Disease extent, n (%)				0.777
Extensive colitis	58 (79.5)	45 (77.6)	13 (86.7)	
Left-sided colitis	14 (19.2)	12 (20.7)	2 (13.3)	
Proctitis	1 (1.4)	1 (1.7)	0 (0.0)	
CAI, mean $\pm$ SD	7.4 $\pm$ 2.9	7.1 $\pm$ 2.7	8.5 $\pm$ 3.4	0.101
MES, n (%)				
MES 1	6 (8.2)	6 (10.3)	0 (0.0)	0.335
MES 2	47 (64.4)	36 (62.1)	11 (73.3)	0.550
MES 3	20 (27.4)	16 (27.6)	4 (26.7)	1
Advanced therapy, n (%)				0.573
Infliximab	30 (41.1)	21 (36.2)	9 (60.0)	
Adalimumab	24 (32.9)	20 (34.5)	4 (26.7)	
Golimumab	6 (8.2)	6 (10.3)	0 (0.0)	
Tofacitinib	8 (11.0)	6 (10.3)	2 (13.3)	
Vedolizumab	4 (5.5)	4 (6.9)	0 (0.0)	
Ustekinumab	1 (1.4)	1 (1.7)	0 (0.0)	
Additional medication, n (%)				
Oral 5-ASA	44 (60.3)	38 (65.5)	6 (40.0)	0.084
Suppository steroids	7 (9.6)	6 (10.3)	1 (6.7)	1
Systemic steroids	27 (37.0)	22 (37.9)	5 (33.3)	1
Immunomodulators	28 (38.4)	21 (36.2)	7 (46.7)	0.555

UC, ulcerative colitis; SD, standard deviation; CAI, clinical activity index; MES, Mayo endoscopic subscore; 5-ASA, 5-aminosalicylic acid.

**Table 2.** Intergroup comparison of the counts and ratios of the leukocyte subtypes

Variable	Non-failure group (n = 58)	Failure group (n = 15)	P-value
Neutrophil count, / $\mu$ L, mean $\pm$ SD	5,135 $\pm$ 3,162	5,115 $\pm$ 3,350	0.983
Lymphocyte count, / $\mu$ L, mean $\pm$ SD	1,475 $\pm$ 746	1,239 $\pm$ 723	0.275
Monocyte count, / $\mu$ L, mean $\pm$ SD	407 $\pm$ 274	567 $\pm$ 343	0.060
Neutrophil-to-lymphocyte ratio, mean $\pm$ SD	4.72 $\pm$ 4.82	4.64 $\pm$ 2.41	0.952
Neutrophil-to-monocyte ratio, mean $\pm$ SD	17.03 $\pm$ 16.74	12.19 $\pm$ 11.33	0.295
Lymphocyte-to-monocyte ratio, mean $\pm$ SD	4.36 $\pm$ 2.14	2.63 $\pm$ 1.27	<b>0.004</b>

SD, standard deviation



**Figure 2.** Receiver-operating characteristic analysis of the L/M ratio for predicting failure within 3 months (A) and Kaplan-Meier curve of failure-free survival for groups with an L/M ratio of  $>3.417$  and an L/M ratio of  $\leq 3.417$  (B).

**Table 3.** Results of the Cox proportional hazard regression analysis to determine the risk factors for failure within 3 months of the induction of advanced therapy

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Lymphocyte-to-monocyte ratio $\leq 3.417$ (yes vs no)	5.093	1.620–16.01	0.005	7.707	2.170–27.37	0.002
Age (increase by 1 year)	0.996	0.968–1.024	0.775	0.989	0.957–1.022	0.504
Sex (male vs female)	1.283	0.438–3.753	0.650	0.776	0.232–2.600	0.681
Extensive colitis (yes vs no)	1.818	0.410–8.056	0.432	2.276	0.481–10.77	0.300
Disease duration (increase by 1 year)	0.964	0.892–1.043	0.363	0.999	0.909–1.098	0.988
Additional medication (yes vs no)						
Oral 5-ASA	0.439	0.156–1.233	0.118	0.480	0.158–1.460	0.196
Suppository steroids	0.739	0.097–5.618	0.770	0.584	0.065–5.246	0.631
Systemic steroids	0.853	0.292–2.496	0.772	0.622	0.185–2.093	0.443
Immunomodulators	1.522	0.552–4.200	0.417	2.500	0.763–8.186	0.130

HR, hazard ratio; 5-ASA, 5-aminosalicylic acid.

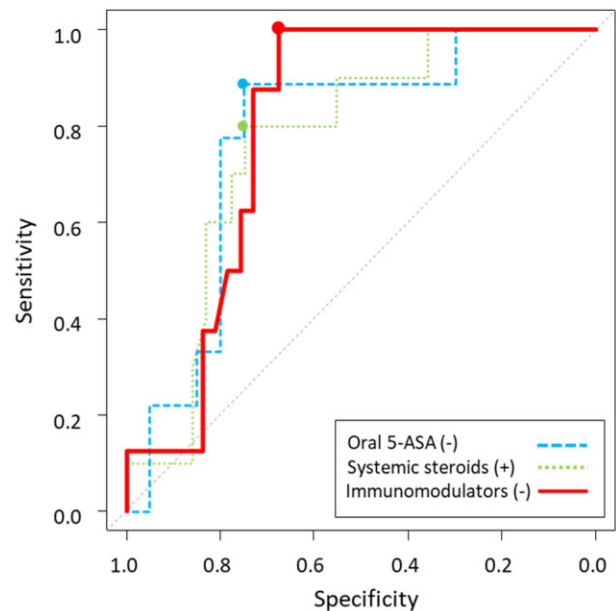
**Table 4.** L/M ratio-based subgroup analysis on additional treatment

Variable	Non-failure group	Failure group	P-value
Oral 5-ASA (+; n = 44), mean $\pm$ SD	4.24 $\pm$ 2.01	2.80 $\pm$ 1.57	0.103
Oral 5-ASA (-; n = 29), mean $\pm$ SD	4.60 $\pm$ 2.41	2.51 $\pm$ 1.11	<b>0.020</b>
Systemic steroids (+; n = 27), mean $\pm$ SD	4.62 $\pm$ 2.27	2.57 $\pm$ 1.24	<b>0.009</b>
Systemic steroids (-; n = 46), mean $\pm$ SD	3.95 $\pm$ 1.88	2.74 $\pm$ 1.46	0.191
Immunomodulators (+; n = 28), mean $\pm$ SD	5.02 $\pm$ 2.56	3.11 $\pm$ 1.53	0.075
Immunomodulators (-; n = 45), mean $\pm$ SD	3.99 $\pm$ 1.79	2.21 $\pm$ 0.89	<b>0.009</b>

5-ASA, 5-aminosalicylic acid; SD, standard deviation.

Several studies have been conducted to evaluate the activity of UC using the leukocyte fraction and many of these have evaluated the UC activity using the neutrophil-to-lymphocyte (N/L ratio) and the L/M ratio [19, 34, 35]. Cherfane *et al.* [19] reported that the L/M ratio was significantly higher in the UC remission group than in the active UC group ( $P < 0.0001$ ); however, the N/L ratio did not show a significant difference between the two groups. Furthermore, these studies also demonstrated significant differences in the L/M and N/L ratios between the active and quiescent colonoscopy groups. Okba *et al.* [34] reported that both the N/L ratio and the L/M ratio showed significant differences between clinically inactive and active UC patients. However, the N/L ratio (but not the L/M ratio) showed a significant correlation with the endoscopic activity ( $P < 0.001$ ), indicating that the N/L ratio reflected the UC activity more accurately than the L/M ratio did. In contrast, Xu *et al.* [35] reported that the L/M ratio, instead of the N/L ratio, showed a significant difference between the inactive UC and the active UC groups ( $P = 0.011$ ). Although the CAI and endoscopic scores of the patients differed among these studies, the studies themselves demonstrated a consistently significant relationship between the clinical activity of UC and the L/M ratio.

Previous studies on UC and Crohn's disease have demonstrated reduced lymphocyte reactivity at the peripheral and mucosal levels, and we believe that it is reasonable for the lymphocyte reactivity to decrease in the presence of inflammation [36–38]. Neutrophils are the first cells to infiltrate and proliferate at the site of infection or inflammation, and some studies have shown that the absolute neutrophil count is significantly higher in patients with active UC than in patients under remission [19, 34, 39]. In contrast, monocytes develop in the bone marrow and circulate in the blood before penetrating the tissues, where they

**Figure 3.** Receiver-operating characteristics curve of the L/M ratio for predicting treatment failure within 3 months of therapy induction in groups of patients receiving systemic steroids with systemic steroids or without oral 5-aminosalicylic acid (5-ASA) or immunomodulators

then differentiate into either macrophages or dendritic cells and participate in inflammation. Therefore, monocytes are considered the precursor cells for the development of inflammation [40]. Based on the mechanisms of neutrophils, lymphocytes, and monocytes in inflammatory responses, we considered that

**Table 5.** Receiver-operating characteristic analysis of the L/M ratio based on additional treatment

Variable	Cut-off value	AUC	95% CI	Sensitivity	Specificity
Oral 5-ASA (–; n = 29)	3.417	0.778	0.593–0.963	0.889	0.750
Systemic steroids (+; n = 27)	3.417	0.768	0.617–0.919	0.800	0.750
Immunomodulators (–; n = 45)	3.417	0.796	0.666–0.925	1.000	0.676

AUC, area under the curve; CI, confidence interval; 5-ASA, 5-aminosalicylic.

the N/L ratio (in which the neutrophils represent an ongoing inflammation) would indicate the current activity of UC. Conversely, the L/M ratio (in which the monocytes are involved in inflammation through differentiation) reflects the activity in the near future. Therefore, only the L/M ratio, and not the N/L ratio, could predict the short-term prognosis in this study.

In addition, a subgroup analysis was performed for concomitant drugs (other than those used for advanced therapy) because immunomodulators are known to cause leukocyte reduction [41]. The M/L ratio enabled a more accurate short-term prognosis prediction only when analysed in patients who did not use immunomodulators. Patients using immunomodulators were also intentionally excluded from previous studies that evaluated the N/L ratio [38, 42]. Thus, in this study, the inclusion of <40% of patients consuming immunomodulators at the beginning of the advanced therapies may have resulted in an inadequate prognosis prediction accuracy; therefore, future studies must accumulate and examine more such cases. Moreover, the high L/M ratio observed in the systemic steroid-treated group of one study may be due to steroid administration increasing the neutrophil count and decreasing the lymphocyte count, thereby changing the L/M ratio [43]. However, the reason for the significantly lower L/M ratio in the oral 5-ASA non-administered group is unclear from this analysis and a follow-up survey to evaluate this finding will be conducted in the future.

This study had several limitations. First, the primary limitations included the single-center and retrospective nature of the study and the small sample size. Second, the consideration of each treatment may have been a potential confounding factor, especially in the analysis of the presence or absence of individual treatments. In order to obtain a correct interpretation, it may be desirable to perform a subgroup analysis for each treatment depending on whether or not the drug alone is used specifically. However, in such a subgroup, the number of subjects is reduced; therefore, more effective analyses cannot be performed. Third, the findings were not compared with those for other biomarkers. FC and FIT are also useful biomarkers for prognosis prediction, and comparing the L/M ratio with them may provide more insights into the advantages and disadvantages of L/M-based predictions; this could serve as the basis for a future study.

In conclusion, the L/M ratio can predict treatment failure within 3 months of advanced therapy induction in patients with active UC. The study findings showed that the L/M ratio might improve the accuracy of prognosis prediction, especially in patients who are not on immunomodulators.

## Supplementary data

Supplementary data is available at *Gastroenterology Report* online.

## Authors' Contributions

N.I. and K.S. designed the study. K.S., Y.A., T.M, S. Tamura, and S. Tani collected the data. M.Y., M.I., and Y.H. analysed the data. N.I. and K.S. wrote the manuscript. S.O. and T.F. provided critical insights into manuscript preparation. All authors read and approved the final manuscript.

## Funding

This work was not supported by any agencies in the commercial, private, or not-for-profit sectors.

## Conflict of Interest

None declared.

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