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Leucine-rich alpha-2 glycoprotein is useful in predicting clinical relapse in patients with Crohn's disease during biological remission

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Background/Aims: Serum leucine-rich alpha-2 glycoprotein (LRG) is a potential biomarker of Crohn's disease (CD). This study aimed to evaluate the usefulness of LRG in predicting clinical relapse in patients in remission with CD. **Methods:** This retrospective observational study assessed the relationships among patient-reported outcome (PRO2), LRG, and other blood markers. The influence of LRG on clinical relapse was assessed in patients in remission with CD. **Results:** Data of 94 patients tested for LRG between January 2021 and May 2023 were collected. LRG level did not correlate with PRO2 score ($\rho = 0.06$); however, it strongly correlated with C-reactive protein (CRP) level ($r = 0.79$) and serum albumin level ($r = -0.70$). Among 69 patients in clinical remission, relapse occurred in 22 patients (31.9%). In the context of predicting relapse, LRG showed the highest area under the curve, followed by CRP level, platelet count, and albumin level. Multivariate analysis revealed that only LRG ($P = 0.02$) was an independent factor for predicting clinical remission. The cumulative non-relapse rate was significantly higher in patients with LRG < 13.8 μg/mL than in patients in remission with LRG ≥ 13.8 μg/mL and normal CRP level ($P = 0.002$) or normal albumin level ($P = 0.001$). Cumulative non-relapse rate was also higher in patients with LRG < 13.8 μg/mL compared to those with LRG ≥ 13.8 μg/mL in patients with L3 or B2+B3 of Montreal calcification. **Conclusions:** LRG is useful in predicting clinical relapse in patients with CD during biological remission. LRG is a useful biomarker for predicting prognosis, even in patients with intestinal stenosis, or previous/present fistulas. **(Intest Res 2025;23:170-181)**

Key Words: Crohn disease; Leucine-rich alpha-2 glycoprotein; Biomarkers

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract, the incidence of which has increased considerably in East Asian countries,[1-3] including Japan. CD is characterized by periods of remission and relapse, which can lead to complications such as strictures and fistulas, resulting in significant reduction in the quality of life of patients. Although clinical improvement is one of the most critical treatment goal, endoscopic remission is also attracting attention because it has been associated with better outcomes in patients with CD.[4,5] A treat-to-target strategy has been proposed for treating patients with inflammatory bowel disease.[6] More recently, the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) statement indicated that therapy modification should be considered if endoscopic remission is not achieved.[7] Achieving clinical and mucosal remission is important to avoid surgical interventions.[8]

Although endoscopy is useful for assessing the severity of

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mucosal damage, it is relatively invasive and burdensome for patients. Therefore, other diagnostic devices have been used for this purpose, such as capsule endoscopy,[9] magnetic resonance enterography,[10-12] and intestinal ultrasound.[13,14] Moreover, several noninvasive biomarkers have also been recently identified to assess the severity of mucosal damage. Fecal calprotectin (FCP), which leaks from the intestinal mucosa into the lumen, has been identified as a noninvasive biomarker.[15] FCP has been reported to correlate with endoscopy severity,[16-19] clinical course of patients with CD,[20] and predictive markers for clinical relapse.[21-24] Although FCP has been identified as a useful noninvasive marker, some patients find it difficult to collect stool samples. However, the usefulness of FCP in assessing the severity of disease in small bowel is limited because the diagnostic accuracy of FCP for small-intestinal lesions is reportedly lower than that for colonic lesions.[25]

More recently, serum leucine-rich alpha-2 glycoprotein (LRG) was identified as a potential biomarker of inflammation in patients with rheumatoid arthritis.[26] LRG has been reported to correlate with endoscopy activity in patients with CD.[27] LRG has also been reported to be a sensitive biomarker for predicting intestinal ulcers in patients with CD using balloon-assisted enteroscopy.[28] In addition, LRG reportedly aids in small-bowel ulcer detection[29] and mucosal healing using capsule endoscopy.[30] Furthermore, LRG has been reported to act as a predictor of endoscopic remission treated with biologic agent in patients with CD.[31] In recent years, it has been indicated that simultaneous measurement of 2 biomarkers (FCP and fecal immunochemical test) in patients with ulcerative colitis makes it easier to identify individuals that are prone to relapse.[32] Similar to ulcerative colitis,[32] a recent study indicated that the combination of LRG and FCP is a useful predictor of hospitalization, surgery, and relapse in patients with CD.[33]

Collecting stool samples for testing is labor-intensive, and simultaneous measurement of both LRG and FCP is not allowed due to the regulations of the Japanese health insurance system. Therefore, markers that can be used adequately in clinical practice are required.

In addition, although numerous studies have reported an association between LRG and endoscopy severity, only a few have evaluated the relationship between LRG and long-term prognosis in patients in remission with CD. Thus, this study aimed to evaluate the usefulness of LRG compared to other biomarkers in predicting clinical relapse in patients in remission with CD.

METHODS

1. Study Design and Participants

This single-center retrospective observational study analyzed the medical records of patients with CD who underwent laboratory investigations for determining LRG levels at the clinic of the Division of Gastroenterology and Hepatology, Kansai Medical University Hospital (Osaka, Japan), between January 2021 and May 2023. All patients with CD were diagnosed in accordance with the guidelines of the Research Committee on Inflammatory Bowel Disease of Japan. All procedures in this study were carried out in accordance with the relevant guidelines and regulations of Kansai Medical University and the tenets of the Declaration of Helsinki. The study was approved by the Ethics Committee (2022136) as a partial investigation of factors predicting the diagnosis and treatment efficacy of inflammatory bowel disease. Informed consent was obtained from the participants and/or their legal guardians, and the ethics committees approved that patients were also allowed an opt-out approach to refuse study participation via the institutional website, as the study posed no risk to the participants.

2. Study Procedures

Patient demographic data were collected. Additionally, information regarding disease characteristics, including sex, age, disease duration, blood biomarkers (hemoglobin, platelet count, serum albumin, C-reactive protein [CRP] level, and erythrocyte sedimentation rate [ESR]), patient-reported outcome (PRO2) score (abdominal pain and stool frequency), and medications at the time of commencement of the study were also recorded.

3. Definition of Remission and Relapse

Clinical remission was defined as PRO2 score of abdominal pain ≤1 and stool frequency ≤3.[7] Clinical relapse was defined as the requirement for addition or modification of medications for clinical relapse. In our cohort, no alterations or additions of treatments were observed according to only LRG levels.

4. Assessment of LRG and Other Blood Markers

LRG levels were measured using Nanopia LRG® (Sekisui Medical, Tokyo, Japan). The first value of LRG measured during the period was adopted. The limit of detection for LRG, below 5 μg/mL, was defined as 5 μg/mL; for CRP, below 0.008 mg/dL, was defined as 0.008 mg/dL; and for ESR, below 0.2 mm/hr, was defined as 0.2 mm/hr.

5. Outcomes and Statistical Analysis

Categorical variables were presented as absolute numbers and relative frequencies using percentages, while continuous variables were described as medians and ranges. The primary endpoint was the assessment of the association between clinical characteristics, including LRG at baseline and clinical relapse in patients in remission with CD, using the Kaplan-Meier curve, log-rank test, and Cox proportional hazard model. The main secondary endpoints were assessment of the correlations among LRG, PRO2 score, and serum CRP level, ESR, platelet count, and serum albumin level in patients with CD using the Pearson and Spearman correlation test. LRG levels of patients in the remission and active groups were compared using the Mann-Whitney *U* test. To determine the cutoff value of LRG for predicting clinical relapse, receiver operating characteristic (ROC) curves were plotted and the area under the curve (AUC) was calculated to predict the diagnostic ability of LRG, CRP, albumin, and platelet for clinical relapse. Statistical significance was set at $P<0.05$. JMP Pro version 16.2.0 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. As this study aimed to assess the usefulness of biomarkers for predicting long-term outcomes in a real-world clinical setting, we did not collect data regarding endoscopy severity because, in most cases, endoscopic procedures were not conducted simultaneously with assessment of LRG.

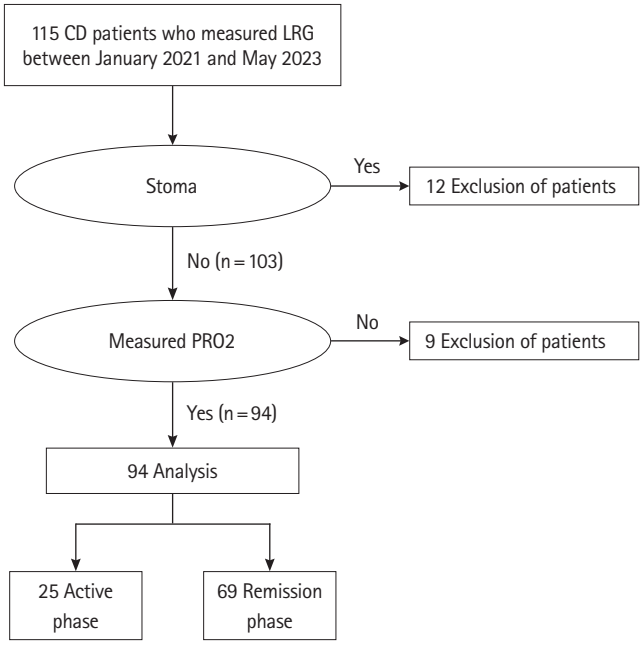

Fig. 1. Flowchart depicting the study design. CD, Crohn's disease; LRG, leucine-rich alpha-2-glycoprotein; PRO2, patient-reported outcome.

RESULTS

1. Characteristics of the Study Participants at the Baseline

The flowchart of this study is shown in Fig. 1. Among patients

Table 1. Characteristics of the Study Participants at Baseline

Characteristics	Value (n = 94)
Sex	
Male	69 (73.4)
Female	25 (26.6)
Age (yr)	35.5 (15–83)
Clinical remission	69 (73.4)
Duration of disease (yr)	8 (0.1–35)
Previous intestinal resection	34 (36.2)
Location	
L1	23 (24.5)
L2	18 (19.1)
L3	53 (56.4)
Behavior	
B1: Inflammatory	13 (13.8)
B2: Stricturing	40 (42.6)
B3: Penetrating	41 (43.6)
Active anal disease	13 (13.8)
Hemoglobin (g/dL)	14.1 (7.3–16.9)
CRP (mg/dL)	0.086 (0.008–6.889)
Albumin (g/dL) (n = 93)	4.3 (2.4–5.2)
Platelet count ($\times 10^4$ μL)	24.5 (11.5–39.9)
ESR (mm/hr) (n = 71)	7.0 (0.2–62.2)
LRG (μg/mL)	12.2 (6.6–41.7)
Concomitant medication	
5-ASA	66 (70.2)
Oral	64 (68.1)
Enema	2 (2.1)
Oral prednisolone	4 (4.3)
Thiopurine	31 (33.0)
AZA	28 (29.8)
Range of daily dose	25–125
6-MP	3 (3.2)
Range of daily dose	15–30
Biologics	73 (77.7)
Anti-TNF agent	52 (55.3)
Ustekinumab	21 (22.3)

Values are presented as number (%) or median (range).
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LRG, leucine-rich alpha-2-glycoprotein; 5-ASA, 5-aminosalicylic acid; AZA, azathioprine; 6-MP, 6-mercaptopurine; TNF, tumor necrosis factor.

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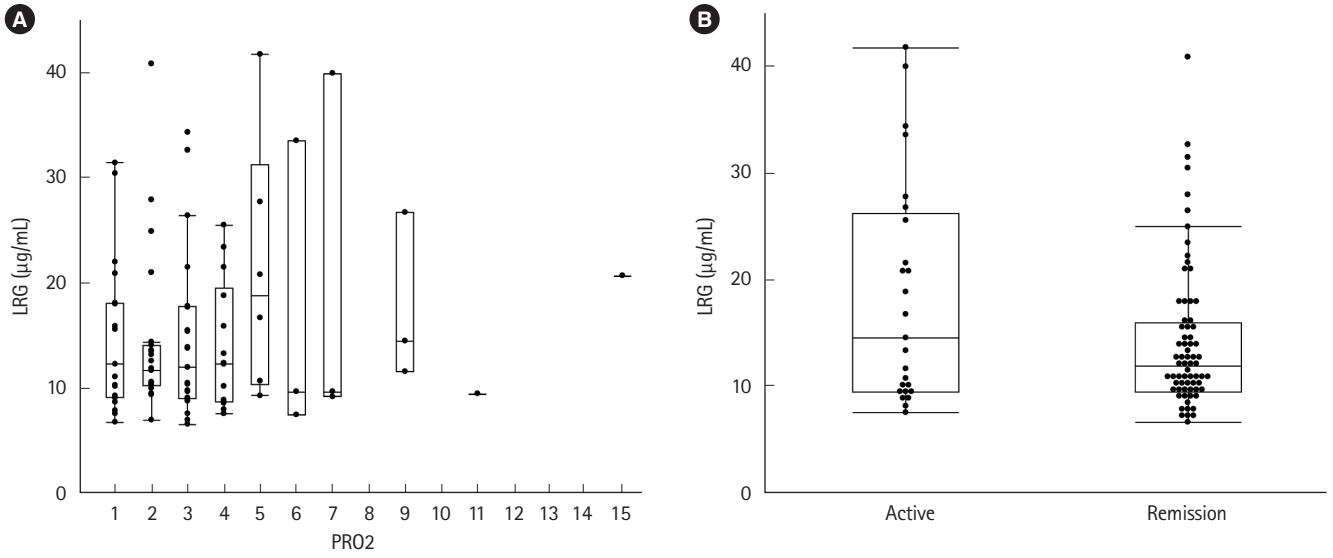

Fig. 2. Analysis of LRG levels. (A) Analysis of LRG levels in patients with different PRO2 scores; PRO2 scores did not correlate with a gradual increase in LRG level (ρ = 0.061, *P* = 0.559, Spearman rank correlation coefficient). (B) Analysis of LRG levels in patients with active and remission phases (*P* = 0.186, Mann-Whitney *U* test). LRG, leucine-rich alpha-2-glycoprotein; PRO, patient-reported outcome.

with CD who underwent LRG measurement during the study period, those with abdominal stomas were excluded from this study. Patients for whom PRO2s were not obtained from the medical charts were also excluded (Fig. 1). The clinical characteristics of the 94 patients with CD are summarized in Table 1. Among them, 69 (73.4%) were in clinical remission at the time of commencement of the study. The median CRP level, hemoglobin level, ESR, and platelet count of the study participants were normal. The median LRG level was 12.15 μg/mL. Upon entry into the study, 68.1% of the patients were treated with oral 5-aminosalicylic acid, 33.0% were administered thiopurines, and most patients (77.7%) received biologics (Table 1).

2. Correlation among LRG, Clinical Severity, and Other Blood Markers

Next, the correlation between clinical severity (PRO2) and blood markers, including LRG, was analyzed. LRG level did not correlate with PRO2 score (ρ = 0.061) (Fig. 2A). In addition, LRG levels in active phase CD (18.3 ± 10.5 μg/mL) tended to be higher than that during clinical remission (14.1 ± 7.0 μg/mL); however, the difference was not statistically significant (*P* = 0.186) (Fig. 2B). LRG strongly correlated with CRP level (*r* = 0.79), ESR (*r* = 0.71) and albumin level (*r* = –0.70), and moderately with, platelet count (*r* = 0.40), and hemoglobin level (*r* = –0.49) (Table 2).

3. Analysis of Serum Markers as Predictive Factors for Relapse of Patients in Remission

In our study cohort, 69 patients were in clinical remission. During the observation period (median duration of observation was 791 days), clinical relapse occurred in 22 patients in remission (31.9%). To investigate the prognostic markers of remission, a Cox proportional hazards regression analysis was performed. Univariate analysis revealed that higher LRG content, CRP level, and platelet count along with lower albumin level were associated with clinical relapse (Table 3).

To assess the diagnostic ability of blood biomarkers in predicting clinical relapse, AUC of ROC curve was analyzed. The AUC for LRG, CRP, platelet, and albumin levels were 0.71, 0.70, 0.68, and 0.65, respectively. The cutoff value for each marker was calculated from the ROC curves. LRG showed a sensitivity of 68% and a specificity of 79% in predicting clinical relapse at a cutoff value of 13.8 μg/mL. We also set the cutoff value for CRP, albumin, and platelet levels as 0.076 mg/dL, 4.2 g/dL, and 30.8×10^4/μL, respectively, using the ROC curves. CRP showed higher sensitivity of 77% and lower specificity at a cutoff value of 0.076 mg/dL. On the other hand, platelet count showed a higher specificity (96%) and lower sensitivity (36%) at a cutoff value of 30.8×10^4/μL (Fig. 3A-D). The cumulative relapse rate was also higher in patients with LRG ≥ 13.8 μg/mL than in those with LRG < 13.8 μg/mL (*P* < 0.001) (Fig. 3E). The cumulative non-relapse rate was higher in patients with CRP < 0.076 mg/dL compared to those with CRP ≥ 0.076 mg/dL (*P* = 0.008)

Table 2. Correlation among Clinical Severity, LRG, and Other Blood Markers

	LRG (n=94)	CRP (n=94)	ESR (n=71)	Albumin (n=93)	Platelet count (n=94)	Hemoglobin (n=94)
LRG		0.79	0.71	−0.70	0.40	−0.49
95% CI		0.69 to 0.85	0.58 to 0.81	−0.79 to −0.57	0.21 to 0.55	−0.63 to −0.32
P-value		<0.001	<0.001	<0.001	<0.001	<0.001
CRP			0.63	−0.50	0.23	−0.30
95% CI			0.47 to 0.75	−0.64 to −0.33	0.033 to 0.42	−0.48 to −0.11
P-value			<0.001	<0.001	0.023	0.003
ESR				−0.61	0.42	−0.54
95% CI				−0.74 to −0.44	0.21 to 0.59	−0.69 to −0.35
P-value				<0.001	<0.001	<0.001
Albumin					−0.30	0.50
95% CI					−0.48 to −0.11	0.33 to 0.64
P-value					0.003	<0.001
Platelet count						−0.24
95% CI						−0.42 to −0.04
P-value						0.022

LRG, leucine-rich alpha-2-glycoprotein; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CI, confidence interval.

Table 3. Univariate and Multivariate Analyses for Predicting Clinical Relapse in Patients in Remission

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Sex		0.383		
Age		0.097		
Duration of disease		0.173		
LRG	1.11 (1.05–1.17)	<0.001	1.16 (1.02–1.31)	0.021
CRP	2.03 (1.18–3.11)	0.003	0.86 (0.36–2.15)	0.730
ESR		0.269		
Albumin	0.32 (0.13–0.81)	0.013	1.80 (0.44–8.60)	0.435
Platelet count	1.11 (1.04–1.18)	0.001	1.06 (0.98–1.13)	0.124
Hemoglobin		0.263		

HR, hazard ratio; CI, confidence interval; LRG, leucine-rich alpha-2-glycoprotein; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

(Fig. 3F). The cumulative non-relapse rate was also higher in patients with platelet count $<30.8\times10^4/\mu L$ compared to those with platelet count $\geq30.8\times10^4/\mu L$ ($P<0.001$) (Fig. 3H). However, there was no significant difference between patients with albumin level ≥4.2 g/dL and in those with albumin level <4.2 g/dL ($P=0.060$) (Fig. 3G). Multivariate analysis revealed that only LRG ($P=0.021$) was an independent factor for predicting clinical remission (Table 3).

4. Usefulness of LRG in Predicting Clinical Relapse in Patients with Biological and Clinical Remission

To investigate whether LRG is useful in predicting clinical relapse in clinical setting, the cumulative non-relapse rate were compared between patients with higher LRG and those with lower LRG whose CRP or albumin level were normal as per our institutional regulations (CRP ≤0.3 mg/dL and albumin ≥3.8 g/dL). Among patients in remission with normal CRP level (≤0.3 mg/dL), the cumulative non-relapse rate was high-

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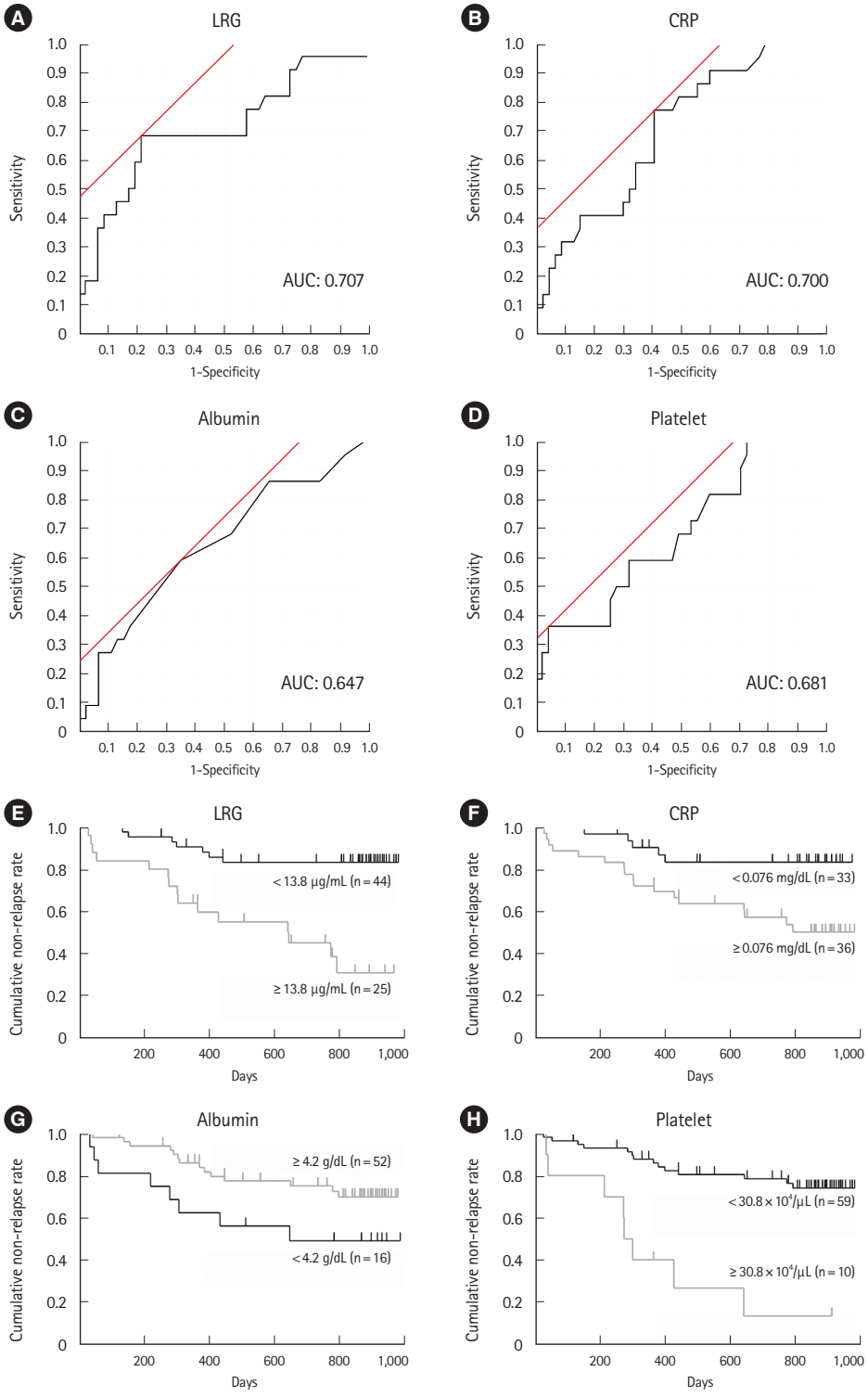

Fig. 3. Analyses of patients in remission (n = 74). ROC curves and AUC for prediction of diagnostic ability of LRG (A), CRP (B), albumin (C), and platelet count (D) in patients in remission. (E) Cumulative non-relapse rate in patients with LRG < 13.8 μg/mL and those with LRG ≥ 13.8 μg/mL (P < 0.001, log-rank test). (F) Cumulative non-relapse rate in patients with CRP < 0.076 mg/dL and those with CRP ≥ 0.076 mg/dL (P = 0.008, log-rank test). (G) Cumulative non-relapse rate in patients with albumin ≥ 4.2 g/dL and those with CRP < 4.2 g/dL (P = 0.060, log-rank test). (H) Cumulative non-relapse rate in patients with platelet count < 30.8 × 10^4/μL and those with platelet count ≥ 30.8 × 10^4/μL (P < 0.001, log-rank test). AUC, area under the curve; LRG, leucine-rich alpha-2-glycoprotein; CRP, C-reactive protein; ROC, receiver operating characteristic.

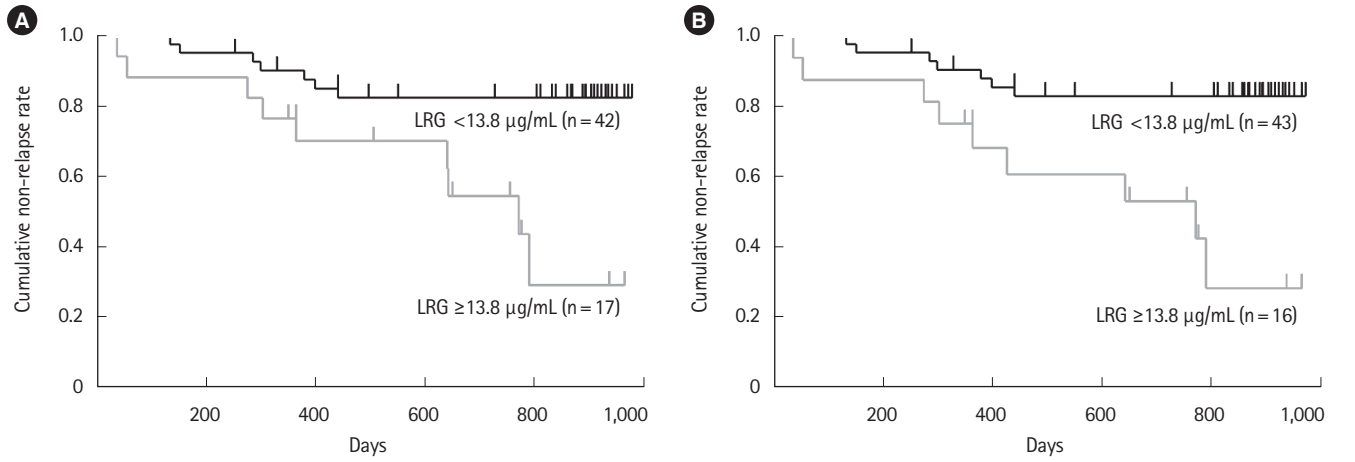

Fig. 4. Analysis of patients in remission with normal level of CRP and albumin. (A) Cumulative non-relapse rate in patients with normal level of CRP (≤0.3 mg/dL). Cumulative non-relapse rate of patients with LRG <13.8 μg/mL was higher compared to those with LRG ≥13.8 μg/mL (P=0.002, log-rank test). (B) Cumulative non-relapse rate in patients with normal level of albumin (≥3.8 g/dL). Cumulative non-relapse rate of patients with LRG <13.8 μg/mL was higher compared to those with LRG ≥13.8 μg/mL (P=0.001, log-rank test). LRG, leucine-rich alpha-2-glycoprotein; CRP, C-reactive protein.

er in patients with LRG <13.8 μg/mL compared to those with LRG ≥13.8 μg/mL (P=0.002) (Fig. 4A). Similarly, among patients in remission with normal albumin level (≥3.8 g/dL), the cumulative non-relapse rate was higher in patients with LRG <13.8 μg/mL compared to those with LRG ≥13.8 μg/mL (P=0.001) (Fig. 4B).

Next, we examined the usefulness of LRG in separately predicting relapse in small bowel and colonic lesions. Among patients in remission with L1, cumulative non-relapse rate tended to be higher in patients with LRG <13.8 μg/mL than those with LRG ≥13.8 μg/mL; however, the difference was not statistically significant (P=0.053) (Fig. 5A). Although among patients in remission with L2, the cumulative non-relapse rate was not significantly higher in patients with LRG <13.8 μg/mL compared to those with LRG ≥13.8 μg/mL (P=0.131) (Fig. 5B) but was significantly higher in those with L3 (P=0.005) (Fig. 5C). Furthermore, we examined the usefulness of LRG in predicting relapse for disease behavior. Among patients in remission with B2 and B3, the cumulative non-relapse rate was higher in patients with LRG <13.8 μg/mL compared to those with LRG ≥13.8 μg/mL (P=0.001) (Fig. 5D). Finally, we examined the usefulness of LRG for future harder outcomes such as hospitalization and surgical rates. The cumulative non-hospitalization and non-surgical rate was higher in patients with LRG <13.8 μg/mL compared to those with LRG ≥13.8 μg/mL (P=0.003, P=0.008) (Fig. 6). Detailed data regarding medication at the time of relapse are shown in Table 4.

Table 4. Medical Treatment at Clinical Relapse in Patients in Remission

Additional or modification of medications	No.
5-ASA increase dose	3
Steroids	5
Antibiotics	3
Biologics	8
Anti-TNF agent, start	1
Anti-TNF agent, increased dose	2
Vedolizumab	1
Ustekinumab	4
Endoscopic dilation	3
Seton, drainage	4

5-ASA, 5-aminosalicylic acid; TNF, tumor necrosis factor.

DISCUSSION

Clinical remission should be considered a mandatory intermediate target during devising treatment strategies for patients with CD.[7] However, not surprisingly, previous studies have indicated that two-thirds of patients with CD had endoscopic lesions even they were in remission,[4] and that a factor of simple endoscopic score of ≤2 for CD was associated with sustained remission.[5] Therefore, the treatment of the target of endoscopic healing should be associated with improved long-term outcomes.[34] Although endoscopic assessment is impor-

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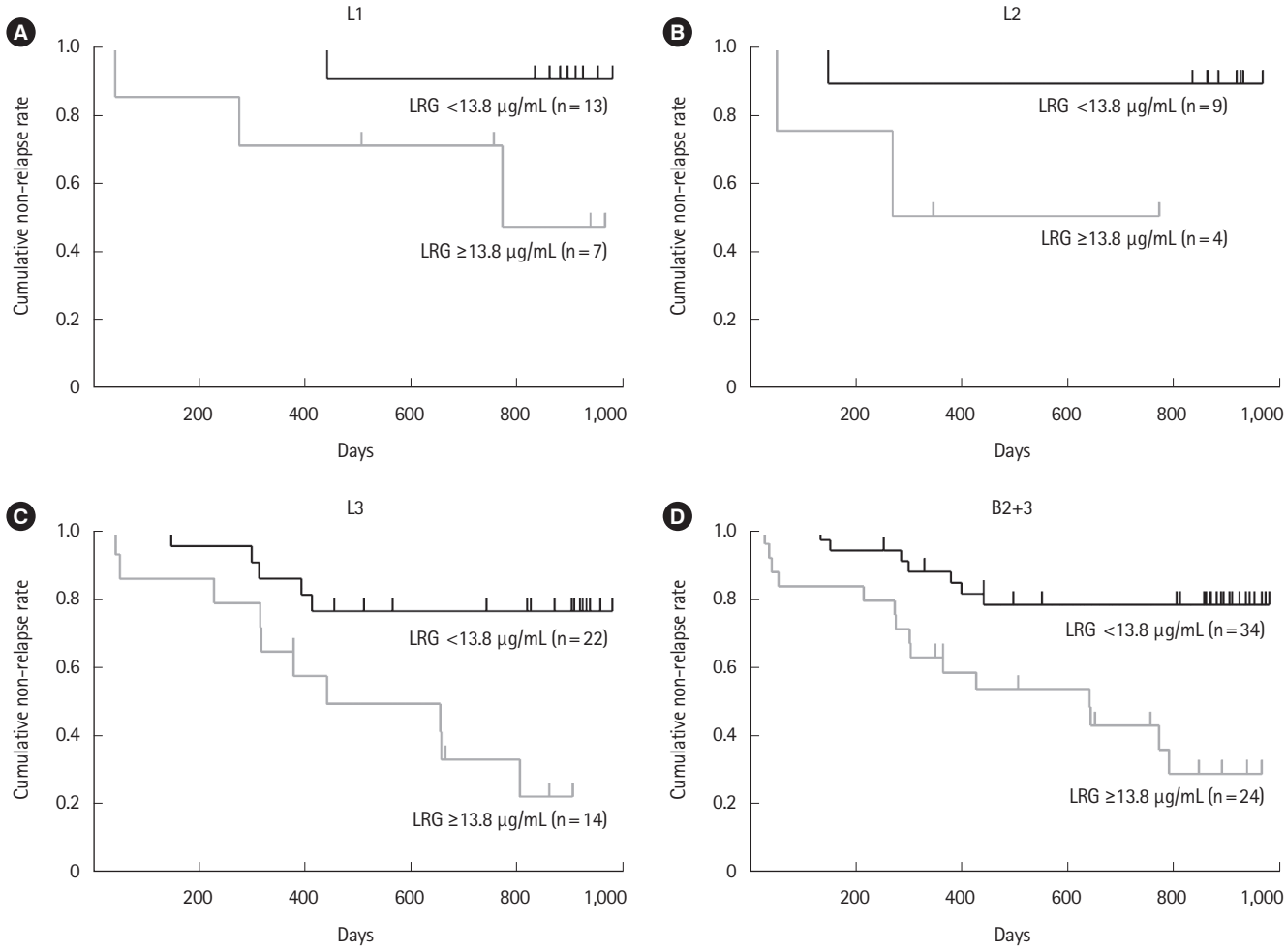

Fig. 5. Analysis of patients in remission with L1, L2, L3, and non-inflammatory type (B2/B3). (A) Cumulative non-relapse rate in patients with L1. Cumulative non-relapse rate of patients with LRG <13.8 μg/mL was not higher compared to those with LRG ≥13.8 μg/mL (P=0.053, log-rank test). (B) Cumulative non-relapse rate in patients with L2. Cumulative non-relapse rate of patients with LRG <13.8 μg/mL was not higher compared to those with LRG ≥13.8 μg/mL (P=0.131, log-rank test). (C) Cumulative non-relapse rate in patients with L3. Cumulative non-relapse rate of patients with LRG <13.8 μg/mL was higher compared to those with LRG ≥13.8 μg/mL (P=0.005, log-rank test). (D) Cumulative non-relapse rate in patients with B2 and B3. Cumulative non-relapse rate of patients with LRG <13.8 μg/mL was higher compared to those with LRG ≥13.8 μg/mL (P=0.001, log-rank test). LRG, leucine-rich alpha-2-glycoprotein.

tant in managing patients with CD, blood and fecal markers are also widely used in clinical practice. While a recent study indicated that FCP generally outperforms other blood markers,[7] LRG has been developed as a novel noninvasive marker to predict the severity of endoscopy findings. Several recent studies have reported that LRG is a useful biomarker for assessing the severity of endoscopy findings,[27-29,35] mucosal healing,[30,31] and disease activity in patients with CD receiving adalimumab.[36] However, only a few studies have investigated the usefulness of LRG as a biomarker to predict clinical relapse in patients in remission with CD. Furthermore, although several studies have assessed the correlation between LRG levels and endoscopic severity, the association between clinical severity and LRG remains unclear.

In the present study, we confirmed that clinical severity indicator, such as PRO2, was not associated with LRG levels in patients with CD. LRG is also a useful prognostic marker of relapse in patients in remission with CD. Univariate analysis of the Cox proportional hazard model revealed that LRG, CRP, albumin, and platelet levels were predictive markers of relapse, and thereafter the cutoff values for LRG, CRP, and platelet levels were set. Significant differences were observed in terms of cumulative non-relapse rate using the Kaplan-Meier curve and log-rank test. Furthermore, in multivariate analysis

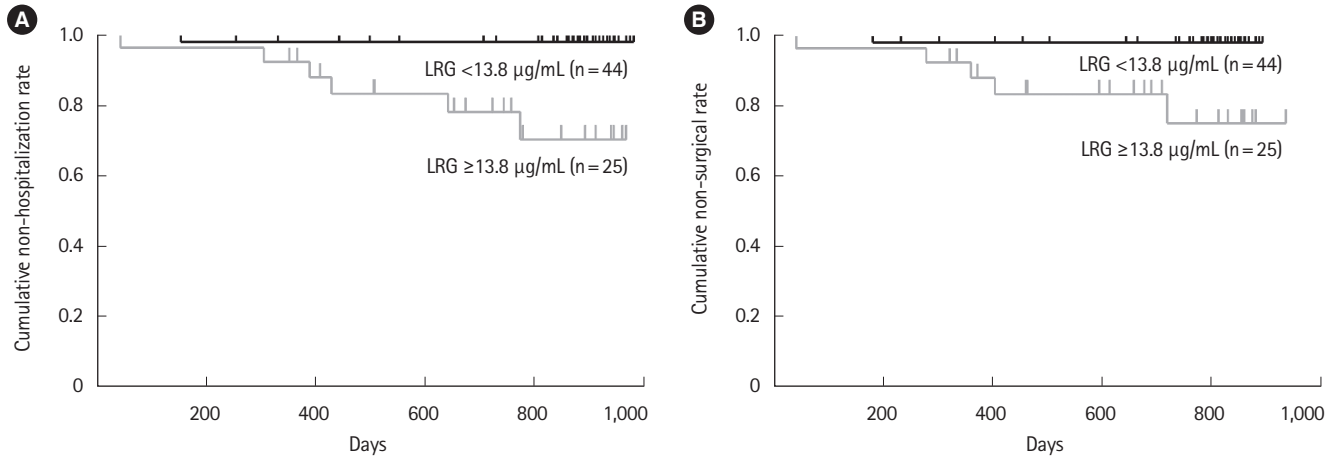

Fig. 6. Analysis of hospitalization and surgical rates in patients in remission. (A) Cumulative non-hospitalization rate in patients. Cumulative non-hospitalization rate of patients with LRG <13.8 μg/mL was higher compared to those with LRG ≥13.8 μg/mL (P=0.003, log-rank test). (B) Cumulative non-surgical rate in patients. Cumulative non-surgical rate of patients with LRG <13.8 μg/mL was higher compared to those with LRG ≥13.8 μg/mL (P=0.008, log-rank test). LRG, leucine-rich alpha-2-glycoprotein.

of the Cox proportional hazard model, LRG was found to be the only predictive marker for relapse. The results of our study are consistent with those of other recent studies, indicating that high LRG levels are strongly associated with CD-related hospitalization, surgery, and clinical relapse compared with low LRG levels.[37] At present, there is little evidence to provide patients with optimized medical treatments based only on LRG values. Recently, the CALM study showed that timely escalation of medical treatments based on a combination of CRP and FCP levels in patients with CD resulted in better endoscopy outcomes.[38] Like FCP, LRG may be incorporated as a candidate in treat-to-target strategy in the future.

In this study, LRG was found to be a useful prognostic marker for relapse, even in patients with normal CRP and albumin levels. Furthermore, LRG independently predicted clinical relapse regardless of disease behavior (Fig. 5). These results indicate that LRG is a useful biomarker for predicting prognosis, even in patients with intestinal stenosis, or previous/present fistulas. Since it may be difficult to occasionally perform endoscopy in patients with B2 and B3 types, measuring LRG makes it possible to identify cases that are likely to experience clinical relapse. For patients with higher LRG, physicians can plan to use other diagnostic devices, such as computed tomography/magnetic resonance enterography or intestinal ultrasound, to assess the severity and extent of inflammation for complicated diseases.

This study had a few limitations that need consideration. First, sample sizes were not calculated to assess the predictors of relapse. Second, data regarding endoscopy severity were not collected. Third, high LRG levels are observed in patients with clinical remission in this study. LRG level is also elevated by infections and other inflammation. In this study, we confirmed that there were no major infections at the time of LRG measurement. Patients in clinical remission with high LRG values might have severe intestinal inflammation. However, this was not confirmed because endoscopy was not performed in all cases. Fourth, institutional bias might have existed because our hospital is a specialized institution for inflammatory bowel disease. This is one of the reasons why the proportion of patients with B3 seems to be high compared to the general population. Finally, we did not investigate the usefulness of FCP levels in predicting relapse. Although FCP is a useful biomarker for patients with CD, some patients may find it difficult to collect stool samples. Patients treated with thiopurines or biologics often have periodic blood samples collected to check for side effects. Therefore, it may be more efficient to measure LRG using regular blood tests.

In conclusion, LRG is a useful marker for predicting clinical outcomes in clinical patients in remission with normal CRP or albumin levels. LRG is also a useful biomarker for predicting prognosis, even in patients with complicated diseases who have difficulty performing conventional colonoscopy. If a high LRG level is confirmed, physicians should assess the severity and extent of inflammation, abscesses, and fistulas, and might consider the possibility of treatment escalation.

ADDITIONAL INFORMATION

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Data Availability Statement
All authors shared raw data for this study. The datasets generated and/or analyzed during the current study are not publicly available because we did not receive permission to make the data currently accessible to researchers from outside the organization. However, it will be available from the corresponding author upon reasonable request after permission is obtained from the Ethics Committee of Kansai Medical University.

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