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Usefulness of Serum Leucine-Rich Alpha-2 Glycoprotein as a Surrogate Marker of Small Bowel Mucosal Injury in Crohn's Disease

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Keywords
Leucine-rich alpha-2 glycoprotein · Crohn's Disease Activity in Capsule Endoscopy · Capsule Endoscopy Crohn's Disease Activity Index · Capsule endoscopy

Abstract
Introduction: Although the importance of mucosal healing has been suggested in Crohn's disease, it is difficult to repeat endoscopy, especially for the entire small bowel. Recently, serum leucine-rich alpha-2 glycoprotein (LRG) has been used as a surrogate marker of endoscopy. However, few studies have investigated a correlation between LRG and mucosal injury of the entire small bowel. ***Methods:*** We retrospectively analyzed the clinical data of 30 patients with Crohn's disease from June 2020 to August 2022 at Yamaguchi Red Cross Hospital. All the patients were surveyed through the gastrointestinal tract by esophagogastroduodenoscopy, total colonoscopy, and capsule endoscopy (CE). Subjects with mucosal injury only in the small bowel were selected. Then, we assessed the relationship between serum biomarkers (LRG, C-reactive protein [CRP], hemoglobin, albumin) and small bowel mucosal injury scores (Lewis score [LS], Capsule Endoscopy Crohn's Disease Activity Index [CECDAI], and Crohn's Disease Activity in Capsule Endoscopy [CDACE]) calculated by CE. ***Results:*** LRG and CRP were significantly correlated with small bowel mucosal injury scores (LS, CECDAI, CDACE) ($p < 0.05$, Spearman's rank correlation coefficient). The degree of correlation was greater for LRG than for CRP. ***Conclusions:*** LRG is a useful surrogate marker that closely reflects small bowel mucosal injury in the entire small bowel.

Introduction

Recently, treat-to-target has been considered for the treatment of inflammatory bowel disease. The STRIDE-II study suggested that an improvement in clinical symptoms, decline in inflammatory responses, and endoscopic mucosal healing are treat-to-target strategy [1]. When achieving endoscopic mucosal healing, patients undergo long-term clinical remission and mucosal healing [2], and the risk of intestinal resection is reduced [3]. Therefore, it is important to evaluate endoscopic mucosal healing properly.

Approximately 70–80% of Crohn's disease (CD) patients have small bowel lesions [4, 5], which should be observed and evaluated. When using an ordinary colonoscopy scope,

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only the terminal ileum can be observed, and thus, the entire small bowel cannot be reached. Although CD lesions frequently appear in the terminal ileum, CD lesions have been detected in the upper part of the small bowel [6], and jejunal lesions are a risk factor for the recurrence of CD [7]. Therefore, endoscopic evaluation of the entire small bowel is required.

Small bowel capsule endoscopy (CE) has the advantage of the easy observation of the entire small bowel with minimal invasion if intestinal stenosis associated with CE retention is excluded. Assessing the Lewis score (LS), Capsule Endoscopy Crohn's Disease Activity Index (CECDAI), and Crohn's Disease Activity in Capsule Endoscopy (CDACE) can quantify the degree of small bowel mucosal injury [8–10].

Although it is reasonable to perform CE for all CD patients, the burden on patients and medical staff makes it difficult to achieve. Therefore, various biomarkers, mainly from the blood and feces, have been investigated as surrogate markers to predict endoscopic activity. Recently, serum leucine-rich alpha-2 glycoprotein (LRG) was reported to correlate significantly with simple endoscopic score for Crohn's disease (SES-CD) [11]. Several studies have reported the efficiency of LRG, but few studies have investigated a relationship between LRG and mucosal injury of the entire small bowel. Therefore, we retrospectively analyzed the correlation between serum biomarkers including LRG and entire small bowel mucosal injury evaluated by CE.

Materials and Methods

Patients and Data Collection

Among patients who underwent CE at Yamaguchi Red Cross Hospital between June 2020 and August 2022 to search for small bowel lesions, the patients with ileitis type (L1) or ileocolitis type (L3) CD were selected retrospectively. All patients were analyzed through the gastrointestinal tract by esophagogastroduodenoscopy, total colonoscopy, and CE. Among the patients with ileocolitis type CD, patients with at least one mucosal break in the colon were excluded from the study. Mucosal break includes not only ulcer but also erosion.

The following clinical information was retrospectively collected from patients' charts: clinical features, underlying disease, medications, laboratory data, and CE data. Because it is difficult to perform CE and the measurement of serum LRG in the same month because of the insurance coverage in Japan, the maximum intervals between these were 1.5 months. However, clinical symptoms were stable during these periods, and treatments were unchanged.

The Ethics Committee of Yamaguchi Red Cross Hospital approved the research protocol (approval number R4-2), and the study was conducted according to the Declaration of Helsinki. Before collecting the data, written informed consent was obtained from each patient included in this study.

CE Examination

All patients swallowed patency capsules in advance. Confirmation that the patency capsule was excreted via the anus or that it reached the colon by computed tomography (CT) indicated it was not retained in the small bowel. No cases retained the patency capsule, and the cecum delivery rate of the capsule was 100%.

PillCam SB3 (Given Imaging, Yoqneam, Israel) was used to perform CE. After fasting overnight, each patient underwent preparation with simethicone and mosapride citrate hydrate. CE was performed according to the manufacturer's recommendations. Each patient was instructed to position the sensor array and data recorder and swallow the capsule with a small amount of water. CE images were shown in a real-time viewer, and recording was stopped when the capsule reached the colon. Patients could drink water 2 h after swallowing the capsule and eat a snack 4 h after swallowing the capsule. All digital video images were downloaded to an image and data reporting and processing system (RAPID, Given Imaging) and evaluated by two experienced CE observers (A.H., H.S.) belonging to the Japan Gastroenterological Endoscopy Society and the Japanese Association for Capsule Endoscopy. The video images were analyzed at an average rate of 15–20 frames/s and were then subjected to simultaneous manual inspection for precise evaluation on a Multiview system. For each patient, the LS, CECDAI, and CDACE were calculated as small bowel mucosal injury scores.

A small bowel ulcer was defined as a mucosal break larger than 5 mm. As reported by Omori et al. [12], the maximum lumen in the CE image was estimated as 25 mm and a mucosal break larger than one-fifth of that was defined as an ulcer.

Study Endpoints

The endpoint of this study was to assess the relationships between serum biomarkers including LRG and small bowel mucosal injury scores.

Statistical Analysis

All analyses were performed using JMP version 14.0.2 software (SAS Institute Inc., Tokyo, Japan). Categorical variables are presented as the frequency and percentage, and numerical variables are presented as the mean or median. The endpoint was evaluated using Spearman's rank correlation coefficient. A p value <0.05 was considered statistically significant.

Results

Patient Characteristics

Table 1 summarizes the clinical characteristics of the enrolled 30 patients. The patients comprised 21 men and 9 women with ages ranging from 17 to 80 years (median, 51 years). The CD duration ranged from 0 to 43 years (median, 18.5 years). L1 was confirmed in 10 cases, and L3 was confirmed in 20 cases using the Montreal classification. Twenty patients had a history of bowel resection. All eligible patients were confirmed to have no mucosal break in the esophagus, stomach, duodenum, or

Table 1. Clinical characteristics of CD patients in the study

Characteristics	*n* = 30
Sex (male/female), *n*	21/9
Age at diagnosis, median (range), years	28 (9–71)
Age, median (range), years	51 (17–80)
Disease duration, median (range), years	18.5 (0–43)
Montreal classification, *n* (%)	
Ileitis type (L1)	10 (33)
Ileocolitis type (L3)	20 (67)
History of intestinal resection, *n* (%)	20 (67)
Anal lesion, *n* (%)	6 (20)
Body mass index (kg/m^2), median (range)	21.7 (15.8–29.4)
Medication, *n* (%)	
5-ASA	25 (83)
Immunomodulator	1 (3)
Oral steroid	2 (7)
Elemental diet	8 (27)
Biologics	15 (50)
Infliximab (IFX)	12 (40)
Ustekinumab (UST)	2 (7)
Vedolizumab (VDZ)	1 (3)
Clinical symptoms	
CDAI, median (range)	71.7 (22.3–197.5)
Serum biomarkers, median (range)	
CRP, mg/dL	0.085 (0.02–3.06)
LRG, μg/mL	11.65 (5–31.9)
Hb, g/dL	13.55 (7.5–18)
Alb, g/dL	4.1 (2.7–4.9)
Small bowel mucosal injury scores (range)	
LS	225 (135–618)
CECDAI	6 (3–21)
CDACE	320 (210–1,240)

CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; LRG, leucine-rich alpha-2 glycoprotein; Hb, hemoglobin; Alb, albumin; LS, Lewis score; CECDAI, Capsule Endoscopy Crohn's Disease Activity Index; CDACE, Crohn's Disease Activity in Capsule Endoscopy.

colon by esophagogastroduodenoscopy and total colonoscopy. Six patients had anal lesions (anal fistula [*n* = 4] and perianal abscess [*n* = 2]) under control by Seton drainage, when examinations were performed. In addition, CT revealed no other inflammation was present in other organs.

Regarding medications, 5-Aminoisophthalic acid was used in 25 cases (83%), and biologics were used in 15 cases (50%). Regarding clinical symptoms, Crohn's Disease Activity Index (CDAI) ranged from 22.3 to 197.5 (median, 71.7). Regarding laboratory tests, serum C-reactive protein (CRP) levels ranged from 0.02 to 3.06 (median, 0.085 mg/dL), serum LRG ranged from 5 to 31.9 (median, 11.65 μg/mL), hemoglobin (Hb) ranged from 7.5 to 18 (median, 13.55 g/dL), and albumin (Alb) ranged from 2.7 to 4.9 (median, 4.1 g/dL). Regarding the small bowel mucosal injury scores, LS ranged from 135 to 618 (median, 225), CECDAI ranged from 3 to 21 (median, 6), and CDACE ranged from 210 to 1,240 (median, 320).

Correlation between Small Bowel Mucosal Injury Scores and Serum Biomarkers or CDAI

Figures 1–3 show the correlation between various serum biomarkers (LRG, CRP, Hb, Alb), CDAI, and the small bowel mucosal injury scores (LS, CECDAI, CDACE). LRG and CRP were significantly correlated with the small bowel mucosal injury scores ($p < 0.05$, Spearman's rank correlation coefficient). The correlation coefficient of LRG was higher than that of CRP for every small bowel mucosal injury score. No significant correlations were detected between the other serum biomarkers (Hb, Alb), CDAI, and the small bowel mucosal injury scores.

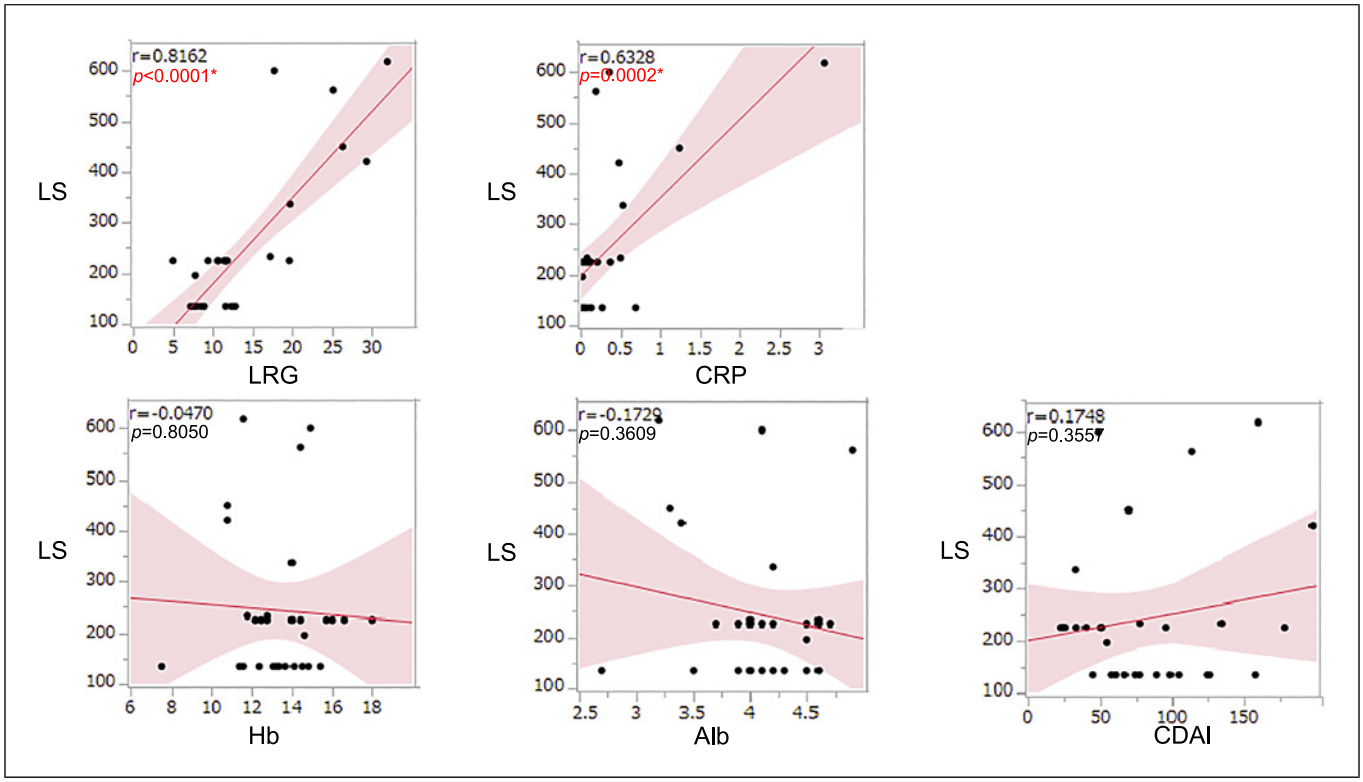

Fig. 1. Correlation curves between serum biomarkers, CDAI, and LS. CDAI, Crohn's Disease Activity Index; LS, Lewis score.

Discussion

The present study showed that LRG had a significant association with the small bowel mucosal injury scores calculated by CE. The correlation of LRG was higher than that of CRP, indicating LRG might reflect the small bowel mucosal injury more precisely.

Previous studies reported that LRG correlated with clinical activity [13] and endoscopic activity [11, 14–16], and it might also be useful for evaluating endoscopic healing [17–19]. Our study is consistent with these reports in terms of identifying a correlation between LRG and endoscopic activity. However, the novel finding of our study is related to the use of the index of only small bowel injury under CE. CRP is widely used as an inflammatory biomarker, but it is produced in the liver; therefore, it does not reflect inflammation derived from cytokines other than IL-6. However, in addition to production in the liver, LRG is also produced by neutrophils, macrophages, and vascular endothelial cells. Therefore, LRG reflects inflammation derived from multiple cytokines including IL-6 [20]. IL-6 and various other cytokines are involved in the formation of CD [21]; thus, LRG might reflect the degree of CD better than CRP. In the present study, LRG correlated with the small bowel mucosal injury scores better than CRP, which is consistent with this idea. A previous report evaluating small bowel injury using a method similar to ours showed that, even in cases with low CRP values, LRG was elevated, suggesting it might be useful for the estimation of small bowel lesions [12]. Thus, LRG might be a precise biomarker for evaluating the activity of CD.

We did not find significant correlations between clinical symptom scores, Hb, Alb, and the small bowel mucosal injury scores. The present study targeted CD patients in the remission phase or mildly active phase; thus, they were less likely to develop significant clinical symptoms, malnutrition, or severe anemia.

Although CD lesions occur frequently in the terminal ileum, CD lesions were also detected in the upper and middle parts of the small bowel [22], and a mucosal break in the oval or longitudinal alignment in the upper part of the small bowel can help diagnose CD [6]. Another study reported the concept of "transition of the small bowel lesion," which suggested small bowel lesions develop from erosion and that small ulcers become longitudinal ulcers as they proceed from the upper part of the small bowel to the lower part [23]. Therefore, it is reasonable to evaluate the entire small bowel, including minor lesions,

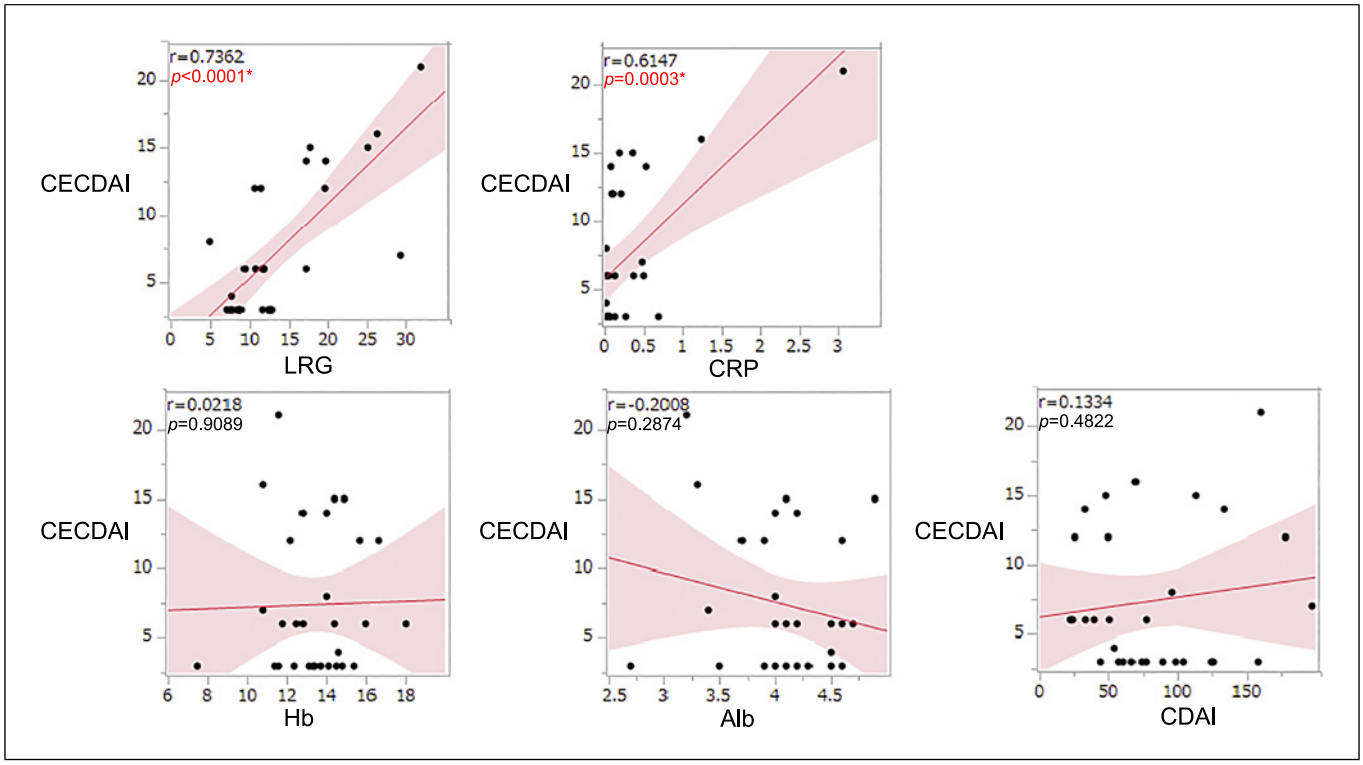

Fig. 2. Correlation curves between serum biomarkers, CDAI, and CECDAI. CDAI, Crohn's Disease Activity Index; CECDAI, Capsule Endoscopy Crohn's Disease Activity Index.

endoscopically and by CE, which is a promising examination modality. Although small bowel X-ray contrast test, CT enterography (CTE), MR enterography (MRE), and intestinal sonography are used for evaluating the small bowel lesions of CD, CE has a higher sensitivity for the detection of minor lesions, lesions limited to the surface of the mucosa, and proximal small bowel lesions [24–27]. Therefore, CE is a useful method for small bowel examination. However, CE cannot be performed for cases with severe stenosis where a capsule cannot pass through or those with a risk of retention. In these cases, CTE [28] and MRE [29] should be selected as they are safer than CE in terms of the risk of retention.

There are three small bowel mucosal injury scoring systems for CD calculated by CE findings: LS, CECDAI, and CDACE. Because LS is scored using an image and data reporting and processing system (RAPID, Given Imaging), it is easy to calculate [8]. However, LS is not specialized for CD because it was produced for the evaluation of nonsteroidal anti-inflammatory drug-induced ulcers. For example, even if there is no severe inflammation, stenosis leads to high LS, which does not reflect its real activity. Because LS is scored using the highest part of the small bowel divided into three, it is insufficient to evaluate the entire small bowel. CECDAI and CDACE were created as CD-specific indexes. CECDAI is calculated by dividing the small bowel into two parts, scoring inflammation and stenosis separately, and then summing the scores; thus, it reflects the activity of the entire small bowel [9]. This system requires a manual calculation, and there can be difficulty in recognizing the presence of stenosis. CDACE is a recently developed scoring system by Omori et al. [12], which places weight on inflammation rather than stenosis. The entire small bowel is divided into four parts, and each part is evaluated and summed; therefore, CDACE reflects the activity of the entire small bowel. The first digit of the CDACE score indicates whether stenosis is present and the degree of stenosis can be determined instantly. It was reported that CDACE correlated significantly with the reported scores using LS and CECDAI. This system also requires manual calculation [10]. In this study, LS, CECDAI, and CDACE were significantly correlated with LRG, and no difference between small bowel mucosal injury scores was evident. However, the small sample size might have affected our results, and further accumulation

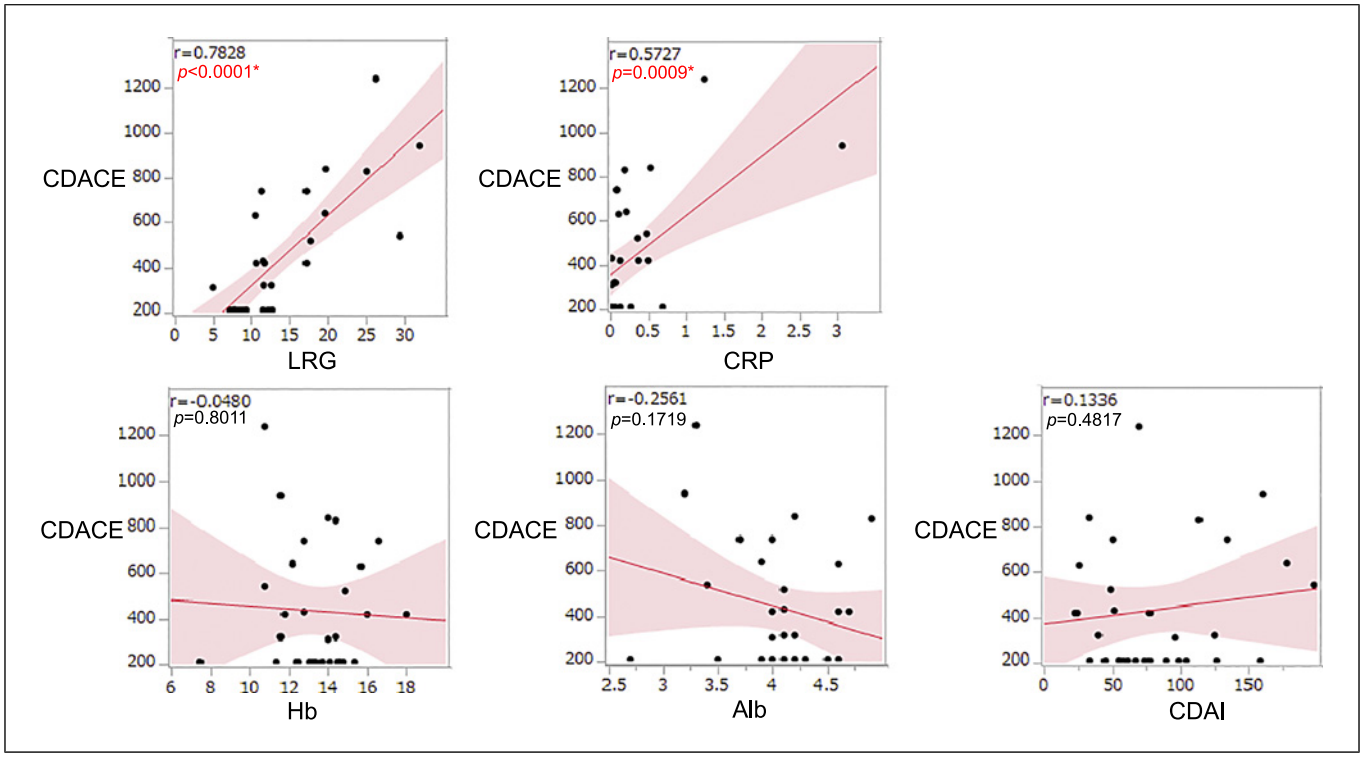

Fig. 3. Correlation curves between serum biomarkers, CDAI, and CDACE. CDAI, Crohn's Disease Activity Index; CDACE, Crohn's Disease Activity in Capsule Endoscopy.

of findings is required. Our study findings suggest that CE is the best examination method for evaluating small bowel lesions of CD. However, in daily clinical practice, it is not reasonable to perform CE frequently because of time and financial constraints. Therefore, as a follow-up during the short and medium term, biomarkers are useful tools. We suggest that LRG is considered the first candidate serum biomarker for CD.

Although there is little evidence to suggest the efficacy of 5-ASA for CD patients, especially for the maintenance of remission [30, 31], in this study, >80% of patients were treated with 5-ASA. Recent study reported that cumulative proportion of CD patients prescribed 5-ASA was approximately 70% in Japan [32, 33] with a regionary bias. Also, the efficacy of 5-ASA for CD patients in remission to mild activity is reported [34]. Approximately half of patients were in mild CD activity, and most patients were treated with step-up approach. These factors may affect the high frequency of 5-ASA use.

Our study had several limitations. First, it was a small, single-center, retrospective study, so a large, multi-center, prospective study is needed. Second, unlike ulcerative colitis, inflammation of CD is not restricted to the mucosal layer but to all layers of the entire intestinal wall. Therefore, the importance of transmural healing has been proposed. Because CE evaluates only the mucosal layer and cannot evaluate the degree of inflammation in layers deeper than the mucosal layer, CE may be insufficient for the assessment of disease activity. Therefore, CTE, MRE, and intestinal sonography should be used to evaluate transmural healing. Recently, it was reported that the MRE score correlated with serum LRG [35]. Further study evaluating the mucosal layer and other biomarkers or indexes is needed. Third, because images of CE were analyzed manually, minor lesions may have been overlooked. Currently, artificial intelligence is being utilized in various industries, including endoscopy. Thus, high-quality analyses of CE images are expected. Finally, because biopsies cannot be performed by CE, histological healing could not be evaluated.

In conclusion, we showed that LRG correlated with small bowel minor mucosal injury. Because CD is a chronic progressive disease, it is ideal to perform therapeutic interventions within a certain period, before irreversible intestinal damage such as stenosis or fistula occurs [36–38]. Therefore, regardless of the clinical symptoms, when LRG is high, early gastrointestinal examination and therapeutic intervention might lead to improvement in the long-term prognosis of patients with CD.

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Statement of Ethics

This study protocol was reviewed and approved by the Ethical and Research Committee of Yamaguchi Red Cross Hospital, approval number R4-2. Before collecting the data, written informed consent was obtained from each patient included in this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

T.S., T.T., and A.H. conceptualized and designed the study. T.S., A.H., Y.K., Y.T., S.M., and H.S. collected the data. T.S. and A.H. performed the statistical analysis. T.S. drafted the manuscript. T.T., A.H., J.U., and H.S. critically revised the manuscript for important intellectual content. T.K. approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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