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Significance of Serum Leucine-rich Alpha-2 Glycoprotein as a Diagnostic Marker in Pediatric Inflammatory Bowel Disease

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Serum leucine-rich alpha-2 glycoprotein (LRG) has been utilized for adult inflammatory bowel disease (IBD); however, its efficacy in pediatric IBD remains unknown. The aim of this study was to compare the diagnostic accuracy of serum LRG for pediatric IBD with that of current inflammatory markers, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). This retrospective case-control study included pediatric patients, aged <16 years, who underwent colonoscopy and/or esophagogastroduodenoscopy between April 2017 and March 2022. All eligible patients were divided into two groups: patients with IBD, diagnosed with ulcerative colitis and Crohn's disease, and non-IBD controls. The optimal cut-off value of serum LRG for IBD diagnosis was determined from receiver operating characteristic analysis, and diagnostic accuracy of serum LRG was compared to serum ESR and CRP. A total of 53 patients (24 with IBD and 29 non-IBD controls) met the inclusion criteria. The cut-off value of serum LRG for IBD diagnosis was determined to be 19.5 μg/ml. At this cut-off value, serum LRG had a positive predictive value (PPV) of 0.80 and negative predictive value (NPV) of 0.88. In contrast, PPV and NPV were 0.78 and 0.70 for serum ESR and 0.82 and 0.72 for serum CRP, respectively. Serum LRG can be a potential diagnostic marker for pediatric IBD, with higher diagnostic accuracy than that of the conventional serum markers ESR and CRP.

Inflammatory bowel disease (IBD) is a chronic gastrointestinal inflammatory disorder primarily classified into ulcerative colitis (UC) and Crohn's disease (CD). Approximately 25% of patients are diagnosed with IBD during childhood and adolescence, and pediatric IBD incidence has been rising over the last few decades (1). To make a definitive diagnosis for children with IBD-related symptoms, endoscopy is required; however, adequate diagnostic markers are still lacking for the indication.

Serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are currently primary screening markers for suspected IBD in children (2). However, approximately one-third of children with IBD have been reported to show normal ESR and CRP levels at diagnosis (2, 3); their diagnostic accuracy is insufficient to provide an indication for endoscopy. Thus, an easily measurable new biomarker is necessary for diagnosing pediatric IBD.

Leucine-rich alpha-2 glycoprotein (LRG) is an approximately 50 kDa glycoprotein, containing a leucine-rich motif, that was first purified from human serum in 1977 (4, 5). LRG was identified as a novel serum marker for monitoring disease activity of rheumatoid arthritis in 2010 (6). Subsequent studies revealed that serum LRG has been a useful marker for monitoring disease activity in adult patients with UC (7, 8). Furthermore, in recent years, several reports indicated that serum LRG can be used to assess disease activity in adult patients with CD (9–11). On the other hand, in the pediatric field, serum LRG has been reported to be effective in diagnosis of appendicitis (12, 13), Kawasaki disease (14) and sepsis (15), and as a disease activity marker in juvenile idiopathic arthritis (16). However, the efficacy of serum LRG in pediatric patients with IBD is still limited with only one report (17).

The aim of this study was to investigate the diagnostic accuracy of serum LRG for pediatric patients with IBD, compared to current serum inflammatory markers ESR and CRP.

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MATERIALS AND METHODS

Patient selection

Pediatric patients, who were less than 16 years old and received a colonoscopy and/or esophagogastroduodenoscopy between April 2017 and March 2022 at our institution, were included in this study. According to their final diagnosis, these patients were divided into two groups: patients with IBD and non-IBD controls. The IBD group included patients with a definite diagnosis of UC or CD based on endoscopy.

Data collection

Demographic information and patient history, including sex, age, height, body weight, symptoms, diagnosis, and blood sample data, were retrospectively collected from medical records for analysis. Blood sample data, including hemoglobin, albumin, cholinesterase, LRG and CRP levels, and ESR, were recorded from within 1 month before and after endoscopy and before starting treatment.

Receiver operating characteristic (ROC) curve and area under the curve (AUC)

ROC curves were generated for each parameter; LRG, ESR, CRP, and AUC were calculated. LRG cut-off for pediatric IBD diagnosis was determined using the ROC curve for LRG.

Diagnostic accuracy of serum LRG, ESR, and CRP

To compare diagnostic accuracy for each parameter, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR−) were calculated. Standard cut-off limits were obtained from institutional protocols (LRG < 16.0 μg/ml, ESR < 10 mm/h, and CRP < 0.15 mg/dl), and this cut-off limit for LRG was compared to the value calculated from the ROC curve.

Statistical analyses

JMP® 15 (SAS Institute Inc.; Cary, NC, USA) was used for statistical analysis. Nominal variables were compared using the Fisher's exact test. Continuous variables were presented as mean ± standard deviation and compared using the student's t-test. The Youden method was used to determine the LRG cut-off for pediatric IBD diagnosis from the ROC curve for LRG. Statistical significance was set at $p < 0.05$.

Ethical approval

This study was approved by the local Institutional Review Board (B220051).

RESULTS

Patient selection and diagnosis

Fifty-three patients were included in this study; 24 were considered to have IBD, and the remaining 29 were classified in the non-IBD control group (Figure 1). For patients diagnosed with IBD, disease locations of the 15 patients with UC indicated pancolitis ($n = 7$), left-sided colitis ($n = 5$), proctitis ($n = 2$), and right-sided colitis ($n = 1$), whereas those of the 9 patients with CD had ileocolitis ($n = 8$) and colitis ($n = 1$). Contrastingly, in the 29 non-IBD controls, 8 patients were not diagnosed using pathological identification, and the other patients were diagnosed of irritable bowel syndrome ($n = 5$), chronic anal fistula without IBD ($n = 5$), juvenile polyps ($n = 4$), eosinophilic gastroenteritis ($n = 3$), and miscellaneous ($n = 4$).

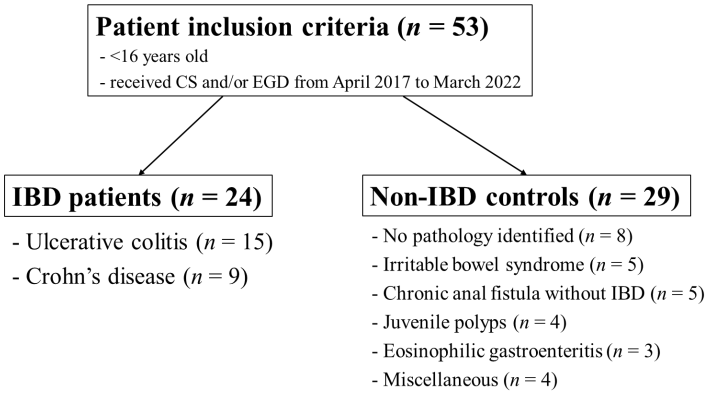

Figure 1.
Patient selection flowchart and diagnosis of patients with IBD ($n = 24$) and non-IBD controls ($n = 29$).
CS, colonoscopy; EGD, esophagogastroduodenoscopy; IBD, inflammatory bowel disease.

Patient demographics

The patient demographics of both IBD and non-IBD control groups are presented in Table I. The most common symptoms for endoscopy indication were hematochezia and abdominal pain, with hematochezia being more prevalent in patients with IBD (66.7% vs. 34.5%, $p = 0.028$). In addition, diarrhea was predominantly present in patients with IBD (54.2% vs. 17.2%, $p = 0.008$), and none of the non-IBD controls showed fever or weight loss. Esophagogastroduodenoscopy and colonoscopy were required to make a definite diagnosis in approximately 60% of patients in both groups (62.5% vs. 62.1%, $p = 1.000$).

IBD patients were characterized by fewer boys and an older age than non-IBD controls (41.7% vs. 72.4%, $p = 0.029$ and 10.4 ± 3.5 years vs. 8.1 ± 4.3 years, $p = 0.043$). Serum LRG, ESR, and CRP in patients with IBD were all significantly higher than those in non-IBD controls (32.5 ± 16.4 μg/ml vs. 14.8 ± 6.1 μg/ml, $p < 0.001$; 29.5 ± 10.2 mm/h vs. 10.5 ± 9.2 mm/h, $p = 0.004$; and 1.29 ± 1.84 mg/dl vs. 0.11 ± 0.27 mg/dl, $p = 0.001$, respectively, Figure 2).

Table I. Patient demographics

	Patients with IBD ($n = 24$)	**Non-IBD controls** ($n = 29$)	***P* value**
Individual data			
Male (%)	10 (41.7)	21 (72.4)	0.029
Age at endoscopy (years)*	10.4 ± 3.5	8.1 ± 4.3	0.043
Height (cm)*	137.8 ± 23.4	124.3 ± 26.2	0.055
Body weight (kg)*	33.5 ± 12.0	29.0 ± 15.2	0.249
Symptoms			
Hematochezia (%)	16 (66.7)	10 (34.5)	0.028
Abdominal pain (%)	14 (58.3)	12 (41.3)	0.275
Diarrhea (%)	13 (54.2)	5 (17.2)	0.008
Anal pain or mass (%)	4 (16.7)	5 (17.2)	1.000
Fever (%)	4 (16.7)	0 (0)	0.036
Weight loss (%)	4 (16.7)	0 (0)	0.036
Laboratory data			
Hb (g/dl)*	10.9 ± 2.1	13.0 ± 1.3	<0.001
Alb (g/dl)*	3.6 ± 0.7	4.3 ± 0.5	<0.001
ChE (IU/l)*	244 ± 69	370 ± 99	<0.001
LRG (μg/ml)*	32.5 ± 16.4	14.8 ± 6.1	<0.001
ESR (mm/h)*	29.5 ± 10.2	10.5 ± 9.2	0.004
CRP (mg/dl)*	1.29 ± 1.84	0.11 ± 0.27	0.001
Examinations			
EGD + CS (%)	15 (62.5)	18 (62.1)	1.000
CS only (%)	9 (37.5)	11 (37.9)	1.000

*mean ± SD

Alb, albumin; ChE, cholinesterase; CS, colonoscopy; CRP, C-reactive protein; EGD, esophagogastroduodenoscopy; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; IBD, inflammatory bowel disease; LRG, leucine-rich α-2 glycoprotein; SD, standard deviation.

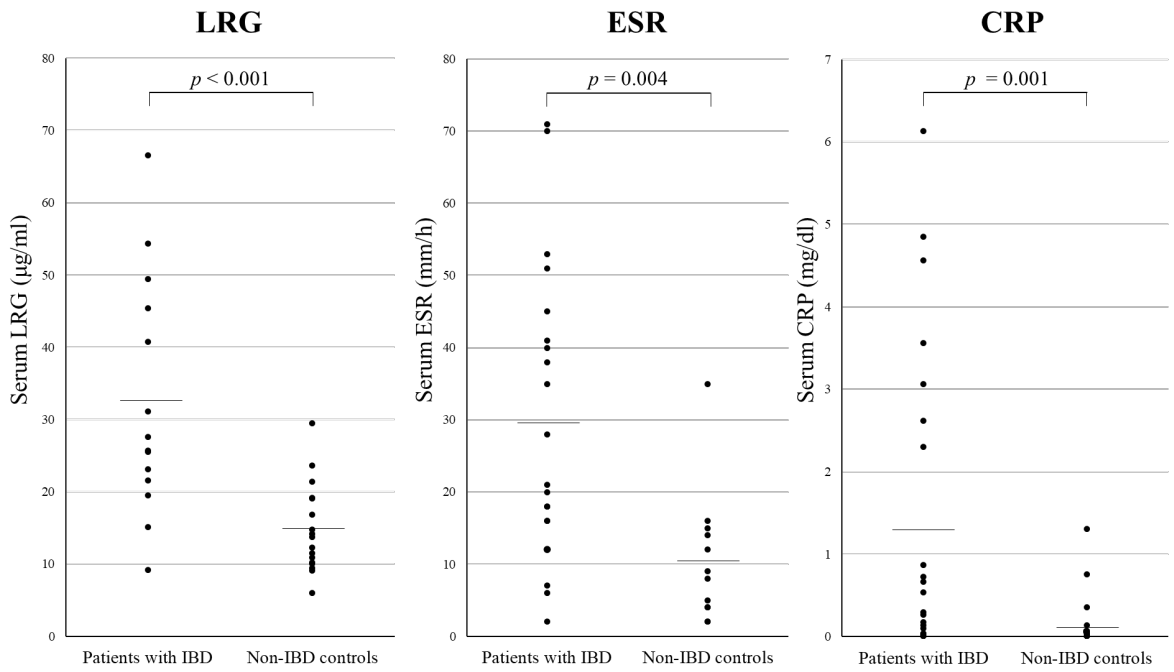

Figure 2. Individual data of serum LRG, ESR, and CRP in patients with IBD and in non-IBD controls.
Individual data of serum LRG, ESR, and CRP are plotted, and the mean is shown as a bar in each group.
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; LRG, leucine-rich α-2 glycoprotein.

ROC curve and calculated AUC

For IBD diagnosis, AUC (95% confidence interval) was calculated from ROC curves for each parameter: 0.870 (0.728–1) for serum LRG, 0.831 (0.689–0.973) for serum ESR, and 0.757 (0.621–0.893) for serum CRP (Figure 3). Using the Youden method, the optimal cut-off value of serum LRG was determined to be 19.5 μg/ml.

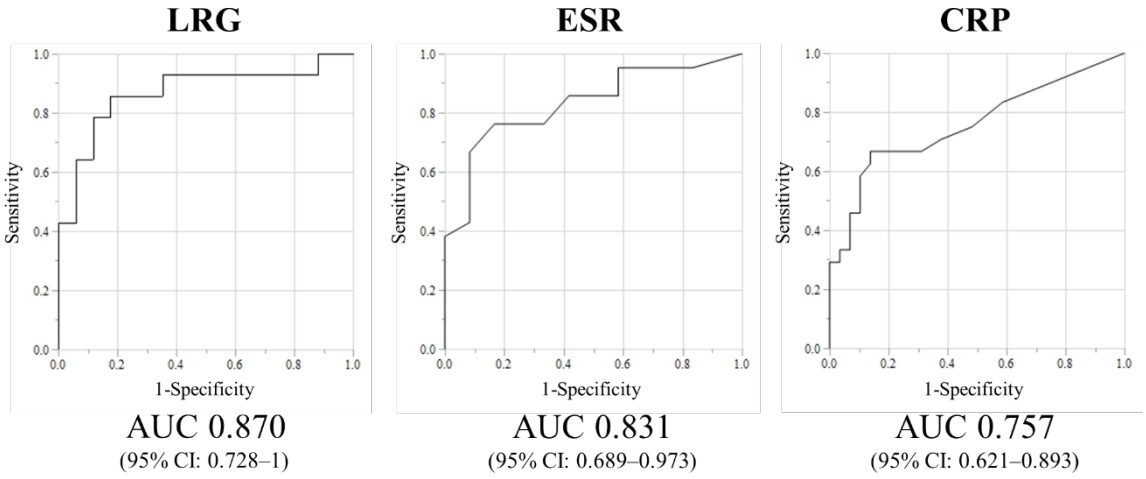

Figure 3. ROC curve and calculated AUC
ROC curve and calculated AUC for pediatric IBD diagnosis based on serum LRG (n = 31), ESR (n = 33), and CRP (n = 53).
AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; LRG, leucine-rich α-2 glycoprotein; ROC, receiver operating characteristic.

Diagnostic accuracy for pediatric IBD

Serum LRG with a cut-off value of 19.5 μg/ml had a sensitivity, specificity, PPV, NPV, LR+, and LR− of 0.86, 0.82, 0.80, 0.88, 4.9, and 0.17, respectively; these values were superior in every respect to those of a cut-off value of 16.0 μg/ml (Table II). Serum ESR was characterized by a high sensitivity (0.86) and a low specificity (0.58),

and both PPV and NPV were lower than those of serum LRG (0.78 and 0.70). Serum CRP had a high specificity at 0.90 but a low sensitivity at 0.58, and PPV at 0.82 was slightly higher, but NPV at 0.72 was lower, than those of serum LRG.

Table II. Diagnostic accuracy of each serum inflammatory parameter for pediatric IBD

Parameters	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR− (95% CI)
LRG						
Cut-off <16.0 μg/ml	0.86 (0.57–0.98)	0.64 (0.38–0.85)	0.67 (0.41–0.87)	0.85 (0.55–0.98)	2.4 (1.2–4.7)	0.22 (0.06–0.84)
Cut-off <19.5 μg/ml	0.86 (0.57–0.98)	0.82 (0.57–0.96)	0.80 (0.52–0.96)	0.88 (0.62–0.98)	4.9 (1.7–13.9)	0.17 (0.05–0.64)
ESR						
Cut-off <10 mm/h	0.86 (0.64–0.97)	0.58 (0.28–0.85)	0.78 (0.56–0.93)	0.70 (0.35–0.93)	2.1 (1.0–4.1)	0.25 (0.08–0.78)
CRP						
Cut-off <0.15 mg/dl	0.58 (0.37–0.78)	0.90 (0.73–0.98)	0.82 (0.57–0.96)	0.72 (0.55–0.86)	5.6 (1.8–17.3)	0.47 (0.29–0.76)

CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; LRG, leucine-rich α-2 glycoprotein; LR+, positive likelihood ratio; LR−, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

DISCUSSION

Our study demonstrates the efficacy of serum LRG as a potential diagnostic marker for pediatric IBD patients with a higher diagnostic accuracy exceeding 0.80 in both PPV and NPV, compared to conventional serum ESR and CRP. Recently, serum LRG has been widely used as a marker for monitoring disease activity and diagnosing mucosal healing in adult UC and CD patients; however, few studies have demonstrated its use as a screening marker for IBD diagnosis (18). Therefore, this is the first study to focus on serum LRG as a screening marker for pediatric IBD diagnosis. The high diagnostic accuracy of serum LRG for pediatric IBD provides greater confidence for endoscopy indication, which is advantageous for pediatric patients, who typically have high barriers to invasive procedures, such as endoscopy, sedation, and general anaesthesia.

The currently used cut-off value of 16.0 μg/ml for serum LRG was established to endoscopically identify active and remission stages in adult patients with UC (7). Although several clinical studies have identified cut-off values for mucosal healing in adult UC and CD (19, 20), few studies have been conducted on the appropriate cut-off values for IBD diagnosis. Therefore, its suitability as a criterion for pediatric IBD diagnosis remained to be elucidated, and in this study, 19.5 μg/ml was determined as the optimal cut-off value based on ROC analysis.

Several studies have demonstrated the usefulness of serum LRG in adult patients with IBD (7–11), but there have been few reports regarding serum LRG in pediatric patients with IBD. Recently, Yasuda et al. has first published the efficacy of serum LRG for disease activity and clinical remission in pediatric IBD patients as shown in adult IBD patients (17). This report shows that the AUC of serum LRG in discriminating active from remission IBD in pediatric patients were superior to those of serum ESR and CRP (17). Although our study on serum LRG as a diagnostic marker is different from the study by Yasuda et al. which focused on serum LRG as a marker of disease activity or clinical remission, their findings are consistent with our results that the AUC to determine whether the patients have IBD in serum LRG was 0.870 superior to 0.810 in serum ESR and 0.757 in serum CRP.

Current serum inflammatory markers such as ESR and CRP are unreliable in the diagnosis of pediatric IBD, as approximately one-third of children with IBD have been reported to show normal ESR and CRP levels at diagnosis (2, 3, 21). Furthermore, Henderson et al. pointed out that PPV for both serum ESR and CRP was high (0.86), but NPV was relatively low (0.74 for ESR and 0.67 for CRP) for pediatric IBD diagnosis (22). Our results for serum ESR and CRP are similar to this research, with a high PPV (0.78 and 0.82) but a relatively low NPV (0.70 and 0.72). Compared to these inflammatory markers, serum LRG, with a cut-off of 19.5 μg/ml, was a highly accurate diagnostic marker with PPV 0.80 and NPV 0.88, especially with low false-negative results.

It has been reported that LRG expression in the inflamed colonic mucosa of patients with active UC leads to an increase in serum LRG, and is induced by various inflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, IL-1β and IL-22 (7, 23). The underlying mechanism is different from the one that underpins serum CRP, which is dependent on IL-6 secretion from the liver (7), and from the one that underpins

serum ESR, which is increased by erythrocyte aggregation resulting from nonspecific inflammation such as infection, autoimmune diseases, and cancer (24). Thus, mild mucosal inflammation due to IBD, especially UC, is not thought to increase serum CRP and ESR, but rather serum LRG, which may result in serum LRG being associated with a lower false negative rate compared to serum ESR and CRP.

This study has several limitations. First, this was a single-center retrospective study with a limited number of cases, and selection bias was present, as only patients with indications for endoscopy were included. Second, the non-IBD control group included gastrointestinal inflammatory diseases, such as eosinophilic gastroenteritis, in which serum LRG levels could be elevated. The number of such cases was limited in this study and therefore could not be evaluated as a confounding factor. However, the possibility cannot be discounted; therefore, further investigations on serum LRG levels in eosinophilic gastroenteritis and infectious enterocolitis are needed. Lastly, this study did not examine external validity. It is necessary to design large prospective multicenter studies to verify whether comparable results can be obtained in other populations. By pioneering this study, we hope to demonstrate the need for further research on the usefulness of serum LRG as a marker for disease activity and treatment efficacy in pediatric patients with IBD.

In conclusion, serum LRG can be a potential diagnostic serum marker for pediatric IBD with higher diagnostic accuracy through PPV and NPV than conventional serum markers, ESR and CRP.

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CONFLICTS OF INTEREST

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