Intestinal ultrasound for intestinal Behçet disease reflects endoscopic activity and histopathological findings

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**Background/Aims:** Intestinal Behçet disease is typically associated with ileocecal punched-out ulcers and significant morbidity and mortality. Intestinal ultrasound is a noninvasive imaging technique for disease monitoring. However, no previous reports have compared intestinal ultrasound with endoscopic ulcer activity or histopathological findings for intestinal Behçet disease. We evaluated the usefulness of intestinal ultrasound for assessing the activity of ileocecal ulcers in intestinal Behçet disease.

**Methods:** We retrospectively compared intestinal ultrasound findings with 73 corresponding endoscopic images and 6 resected specimens. The intestinal ultrasound findings were assessed for 7 parameters (bowel wall thickness, vascularity evaluated using the modified Limberg score with color Doppler, bowel wall stratification, white-plaque sign [strong hyperechogenic lines or spots], mesenteric lymphadenopathy, extramural phlegmons, and fistulas), and endoscopic ulcer activity was classified into active, healing, and scar stages. Histopathological findings were evaluated by consensus among experienced pathologists.

**Results:** Bowl wall thickness ($P < 0.001$), vascularity ($P < 0.001$), loss of bowel wall stratification ($P = 0.015$), and white-plaque sign ($P = 0.013$) were significantly exacerbated in the endoscopic active ulcer stage. Receiver operating characteristic curve analysis revealed that a bowel wall thickness of $> 5.5$ mm (sensitivity 89.7%, specificity 83.3%) was potentially useful for detecting active lesions. When compared with histopathological findings, an increase in bowel wall thickness reflected the ulcer marginal ridge, and the white-plaque sign reflected the ulcer bottom.

**Conclusions:** Intestinal ultrasound is useful for monitoring intestinal ulcer activity in intestinal Behçet disease. (Intest Res, Published online)

**Key Words:** Behçet disease; Intestinal diseases; Ultrasonography; Ulcer; Endoscopy

**INTRODUCTION**

Behçet disease (BD) is a chronic relapsing–remitting inflammatory immune disorder characterized by orogenital aphthae and ocular, vascular, mucocutaneous, central nervous system, and gastrointestinal involvement. The prevalence of BD varies depending on the geographical region, and it is common in the area along the ancient Silk Road.

Intestinal BD is a subtype that accounts for 10% to 35% of cases of BD. Ileocecal solitary punched-out ulcers are typical lesions. Active ulcers in intestinal BD are very fragile and can easily lead to severe complications, such as massive bleeding and ulcer perforation, occasionally culminating in mortality. Colonoscopy is considered to be the reference stan-
standard procedure for monitoring the activity of intestinal lesions in BD. However, it is difficult to repeat colonoscopy frequently as a routine monitoring because of potential patient discomfort, and inherent risk of intestinal bleeding or perforation associated with pretreatment laxatives or air insufflation during the examination, especially in active intestinal BD. Therefore, more simple, noninvasive, and repeatable follow-up examination methods are required to assess disease activity and optimize treatment.

Cross-sectional imaging, such as computed tomography, magnetic resonance imaging, and intestinal ultrasound (IUS), have demonstrated their utility in evaluating intestinal lesions of inflammatory bowel disease (IBD). IUS has high diagnostic accuracy for detecting active intestinal inflammation and is a minimally invasive and cost-effectiveness diagnostic technique with good repeatability and favorable patient tolerance. Although the usefulness of IUS for the evaluation of intestinal lesions in IBD has been well-established, few reports have examined the utility of cross-sectional imaging for intestinal BD. Three studies of computed tomography and magnetic resonance imaging showed that intestinal BD lesions were depicted as thickening of the intestinal wall with mural enhancement and could be distinguished from Crohn’s disease by imaging features. There is only 1 report on IUS, in which Ma et al. compared the IUS images from 22 patients with intestinal BD with those of patients with Crohn’s disease, revealing that focal lesions and larger ulcers could be the defining characteristics of intestinal BD.

None of these reports compared the imaging findings with endoscopic or histopathologic findings, and the relationship between ultrasonographic findings of intestinal lesions in BD, endoscopic activity, and specific pathologic changes remains unknown. Therefore, we conducted the present study to investigate whether IUS findings reflect the ulcer activity of intestinal lesions in patients with BD, using colonoscopy and histopathological findings as a reference for ulcer activity. The purpose of this study was to evaluate the ability and usefulness of IUS to assess intestinal ulcer activity in intestinal BD.

METHODS

1. IRB/IACUC Approval
We conducted this study in compliance with the principles of the Declaration of Helsinki. The study’s protocol was reviewed and approved by the Ethics Committee of Yokohama City University (B190200027, B230300028). Informed consent was obtained in the form of opt-out on the website because all data were handled and analyzed after anonymization.

2. Description of Participants
We performed a retrospective, case-control, single-center study. All patients had a confirmed diagnosis of intestinal BD on the basis of published diagnostic criteria. The types of BD were classified according to a published algorithm.

Patients who had typical intestinal BD ulcers in ileocecal lesions and underwent comparable colonoscopy and IUS within 2 weeks between 2007 and 2019 were included. Given the practical nature of the study, cases falling within the 4-week timeframe were acceptable if the patient had maintained endoscopic remission. If both IUS and colonoscopy were performed several times on a single patient, only examinations that were performed at least 6 months after the previous examination were included, and no more than 2 examinations were included for a single patient to avoid case bias. Ileo-cecal lesions within 10 cm proximal or distal to the ileocecal valve were included for accurate comparison with the IUS findings. We excluded postoperative Anastomotic lesions, multiple lesions in close proximity and intestinal lesions not delineated or IUS images of lesions not stored. The IUS findings of 10 healthy subjects were compared as controls.

For histologic evaluation, patients who required ileal resection within 4 weeks of preoperative IUS were included. Additionally, 2 patients whose IUS could not be performed within the 4-week timeframe due to severe abdominal pain or obstructive symptoms and whose medical condition and treatment remained consistent between IUS and surgery were also included. In one patient, the resected bowel specimen contained 2 ulcers located > 5 cm apart, and they were analyzed as separate lesions.

3. Endoscopy and IUS Procedures
The colonoscopy examinations were performed by endoscopists specializing in IBD (Yoshinori Nakamori and M.M.). A detailed report was obtained describing the distribution, morphology, and activity of the ulcers. Endoscopic images were stored under the patient’s identification record.

The IUS examinations were performed by experienced sonographers with more than 5 years of experience in IUS (K.H., M.I., Y.F., M.T., and M.O.), without special patient preparation, such as prior fasting or parenteral contrast reagents, using APLIO XG SSA-790A, APLIO 300, and APLIO α/Veriřa (Canon Medical Systems, Tochigi, Japan). A general scan was per-
formed using a 3.5–6-MHz convex probe (PVT-375BT, PVT-674BT; Canon Medical Systems), and a more localized and detailed scan of the affected area was conducted using a 7.5-MHz linear probe (PLT-704SBT; Canon Medical Systems). Color Doppler was performed in the area of interest to evaluate vascularity. The range of blood flow velocity was adjusted to 4–5 cm/sec, and color gain was reduced from the maximum value and evaluated at a maximum gain that eliminated noise. Both static images and dynamic videos were saved throughout the examination for every patient.

4. Evaluation of Endoscopic and Ultrasound Images
The colonoscopy and IUS images of the patients were meticulously compared and paired by one physician (R.K.) with more than 15 years of experience in IUS and colonoscopy for intestinal BD. After careful review of the images and videos, only lesions that completely corresponded were selected according to the distance from the ileocecal valve. The documents for assessment were prepared and blindly evaluated by investigators specializing in IUS (Sho Sato and K.N.) and in colonoscopy (M.N. and T.O.).

As there are no well-established criteria for assessing ulcer activity in intestinal BD, this study adopted the classification system proposed by Sakita and Miwa, which is widely used to assess gastric ulcers. The ulcers of intestinal BD were classified into the 3 stages: active stage, white-plaque adhering to the ulcer bottom and/or exposed blood vessels and clots, with ulcer margins accompanied by edema; healing stage, regenerative epithelium appearing around the ulcer and a shallower ulcer bottom; and scar stage, ulcers with scarring (Fig. 1). The size of the ulcer was evaluated as the maximum diameter with a comparative object (e.g., biopsy forceps) according to a previously reported protocol. IUS images were evaluated according to the following 7 variables: bowel wall thickness, vascularity, bowel wall stratification, white-plaque sign, mesenteric lymphadenopathy, extramural phlegmons, and fistulas (Fig. 2A-D). Bowel wall thickness was noted as the average of 3 measurements in the thickest part of the lesion (Fig. 2A). Vascularity was graded by the modified Limberg scoring system in the following fashion: grade 0, no color flow; grade 1, short stretches of vascularity as spots; grade 2, longer stretches of vascularity; grade 3, longer stretches of vascularity reaching the mesentery (Fig. 2D). Bowel wall stratification was classified as “preserved” or “unclear” depending on whether the 5 layers of the bowel wall could be identified (Fig. 2A-C). The white-plaque sign, which suggested the presence of an active ulcer, was defined as strong hyperechogenic lines or spots > 1.5 mm in diameter indicating immobility of the bowel wall (Fig. 2A-C). The immobility was reliably confirmed by either compressing the intestinal tract from outside the body or observing the lesion at least twice in both the long and short axes during IUS examination. Mesenteric lymphadenopathy was defined as mesenteric lymph nodes with an axis of > 10 mm. Extramural phlegmons were defined as hypoechoic areas in the hypertrophic and hyperechoic adipose tissue around the intestine (Fig. 2A and B). Fistula was defined as a tubular hypoechoic structure passing through and extending out of the intestinal wall.

5. Histopathological Evaluation
The preoperative IUS images and histopathological findings of the corresponding lesions were compared. The images of gross pathology and the histopathological samples after he-
Fig. 2. Typical intestinal ultrasound (IUS) images of intestinal Behçet disease ulcers. (A) Ulcer 1 is a large, shallow ulcer that straddles the ileocecal valve. The images show obscurity of the 5 layers of the bowel wall, hyperechogenic spots in the bowel wall (light blue arrow), and extramural phlegmons (light green arrow). Bowel wall thickness was noted as the average of 3 measurements in the thickest part of the lesion (double-headed arrows). (B) IUS image of ulcer 1 observed from a different angle than that in panel (A). Loss of the 5 layers of the bowel wall, hyperechogenic line in the intestinal lumen (light blue arrows), and extramural phlegmons (light green arrows) are seen. (C) Ulcer 2 is a typical circular punched-out ulcer in the terminal ileum. The intestinal tract is thickened segmentally, and the 5 layers of the bowel wall have disappeared (double-headed arrows). Hyperechogenic spots in the bowel wall can also be seen (light blue arrow). The image shows the preoperative IUS measurements of bowel wall thickness (arrow ①) and distance from the outer muscular layer to the white-plaque sign (arrow ②). (D) Vascularity was evaluated by color Doppler and graded according to the modified Limberg scoring system. Longer stretches of vascularity reaching the mesentery can be seen (grade 3). (E) Gross findings in a formalin-fixed specimen of the resected intestinal tract removed by ileocecal resection. The red dotted lines represent the resection lines. (F) Gross findings of ulcer 1 in a formalin-fixed tissue section. (G) Gross findings of ulcer 2 in a formalin-fixed tissue section. (H) Histopathological sample of ulcer 2 (hematoxylin and eosin staining, × 6.6). (I) Histopathological sample of ulcer 2 (hematoxylin and eosin staining, × 11.2). The muscular layer is the area indicated by the red bent arrow, and the subserosal fibrous layer is the area indicated by the blue bent arrow. Histopathological measurement of the distance from the top of the ulcer marginal ridge to the outside of the muscular layer (arrow ①) and the distance from the ulcer bottom to the outside of the muscular layer (arrow ②). (J) Ultrasound image of ulcer 2 with water-immersion observation after formalin fixation; the muscular layer (red bent arrow) and the subserosal fibrosis layer (blue bent arrow) are observed as distinct layers with different concentrations on ultrasound.
Matoxylin and eosin staining were reviewed and evaluated by consensus between 2 experienced pathologists (E.K. and Y.S.) (Fig. 2E-I). Digital images were generated from all slides using a whole-slide scanner (NanoZoomer S60; Hamamatsu Photonics, Iwata, Japan). To investigate which histopathological findings reflected the IUS findings of wall thickness and the white-plaque sign, we compared the measurement obtained using IUS (maximum bowel wall thickness and distance from the white-plaque sign to the outside of the muscular layer) with the measurement obtained using histopathology (distance from the top of the ulcer marginal ridge and distance from the ulcer bottom to the outside of the muscular layer) (Fig. 2C and I). Histopathological measurement was conducted by one pathologist (E.K.), and the average of 3 measurements was recorded.

In intestinal ulcers in BD, subserosal fibrosis may be present outside the muscular layer. Therefore, we evaluated whether these 2 layers could be distinguished by the difference in coloration of macroscopic histopathological images. We also evaluated one surgical specimen using the water-immersion ultrasound (US) method and compared the histopathological findings to those of the subserosal fibrosis layer and muscular layer to determine whether the layers could be observed separately (Fig. 2I and J).

6. Statistical Analysis
Statistical analyses were performed using JMP Pro 15 software (SAS Institute Inc., Cary, NC, USA) and R version 4.1.1, RStudio version 1.4.1717. Univariate analysis using the chi-square test and factorial analysis of variance were performed for comparisons between the endoscopic activity classifications. Cutoff values were established using the receiver operating characteristic (ROC) curve analysis. Relationships among the wall thicknesses measured by IUS, endoscopic ulcer size, and histopathological measurement were evaluated using the Spearman correlation coefficient. A significance level of $P < 0.05$ was used to determine statistical significance, and the Bonferroni method was implemented to adjust for statistical significance in multigroup comparisons.

RESULTS

1. Patients’ Clinical Characteristics
Fig. 3 shows the patient flow diagram. Of the 110 patients with intestinal BD treated at our hospital between 2007 and 2019, 259 IUS procedures were performed for 99 patients. There were 87 examinations for 59 patients who had typical ileocecal intestinal BD ulcers, and these patients underwent comparison colonoscopy and IUS within 2 weeks. We excluded 8
examinations of 6 patients who underwent more than 3 examinations, 5 cases of postoperative anastomotic lesions, 2 cases of multiple lesions in close proximity, and 4 cases in which intestinal lesions were not delineated or IUS images of the lesions were not stored. Therefore, data were obtained for 73 examinations of 47 patients for analysis.

The patients’ clinical characteristics are shown in Table 1. Thirty-nine lesions were classified as being in the active stage, 16 in the healing stage, and 18 in the scar stage. Six IUS examinations from 5 patients were comparable to the histopathological findings after surgical resection.

2. Comparison of IUS Findings and Endoscopic Ulcer Activity
The results of the comparison of disease characteristics and IUS findings by endoscopic activity are shown in Table 2. There were no differences in clinical characteristics among the 3 groups. IUS parameters of bowel wall thickness ($P<0.001$), vascularity ($P<0.001$), loss of bowel wall stratification ($P=0.015$), and white-plaque sign ($P=0.013$) were significantly increased in the active stage group. There was no significant difference between the groups regarding the presence of extramural phlegmons, fistulas, and mesenteric lymphadenopathy, but all cases of extramural phlegmons were observed in the active stage.

The IUS findings of bowel wall thickness, vascularity, bowel wall stratification, and white-plaque sign were compared with healthy controls. In terms of bowel wall thickness, there was not only a significant difference between the active stage and the healing stage, scar stage, and healthy controls, but there was also an increase in bowel wall thickness in the healing stage and scar stage compared with healthy controls ($P<0.001$ for each) (Fig. 4A). When performing ROC analysis exclusively for intestinal BD cases, bowel wall thickness > 5.5 mm was indicated for detection of the active stage (sensitivity 89.7%, specificity 85.3%, area under the ROC curve 0.90, 95% confidence interval [CI] 0.83–0.98) (Fig. 4B). Vascularity was significantly different in the active stage compared with all other stages ($P<0.001$ for each), but it was not different in the healing stage or the scar stage when compared with healthy controls (Fig. 4C). Bowel wall stratification ($P=0.008$) and white-plaque sign ($P=0.001$) were significantly different only between the active stage and the healthy controls (Fig. 4D and E). We also examined whether the size of the ulcer affected the wall thickness; bowel wall thickness showed a weak but positive correlation with ulcer size measured by colonoscopy according to Spearman’s correlation coefficient ($r=0.405$, 95% CI [0.103–0.639], $P=0.011$) (Fig. 5).

We measured sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and odds ratios for each of the parameters in intestinal BD patients (Table 3). As for vascularity, although the specificity was high for both the modified Limberg score of ≥ 2 points and = 3 points, considering the comparison of accuracies, a modified Limberg score of ≥ 2 points was considered preferable.

3. Comparison of Preoperative IUS Findings and Histopathology of Resected Specimens
We examined whether the muscular layer and subserosal fibrosis layer could be distinguished by the difference in color tone of the macroscopic histopathological images of 6 surgically resected ulcers. There was a sufficient difference in color
density to suggest that these layers could be distinguished (Fig. 2d). In addition, we compared the macroscopic histopathological images and water-immersion US image of one lesion, and found that the muscular and subserosal fibrosis layers were distinguishable on the US images (Fig. 2d and e).

The results of the comparison of wall thickness and white-plaque sign between the preoperative IUS measurement and histopathological measurement are shown in Fig. 6. The maximum bowel wall thickness of the ulcer lesions captured by IUS reflected the distance to the peak of the ulcer margin elevation on histopathological measurement ($r = 0.986$, 95% CI [0.869–0.998], $P < 0.001$; the mean bowel wall thicknesses measured by IUS and histopathology were 10.5 mm and 8.9 mm, respectively), with a strong correlation. In addition, the white-plaque sign reflected the ulcer bottom depending on the distance from the muscular layer ($r = 0.945$, 95% CI [0.547–0.994], $P = 0.004$; the mean values were 3.1 mm and 3.1 mm, respectively). Based on these results, we considered that an increase in bowel wall thickness reflected the ulcer marginal ridge, and the white-plaque sign reflected the ulcer bottom.

### DISCUSSION

In the present study, we show that IUS is useful for the assessment of ulcer activity in patients with intestinal BD. IUS findings of active ulcers demonstrate several distinctive characteristics, including an increased wall thickness, increased vascularity, loss of bowel wall stratification, and presence of the white-plaque sign. The most significant finding was increased bowel wall thickness, with a thickening of > 5.5 mm, which allowed the prediction of active ulcers with high sensitivity and specificity. Compared with the histopathological findings, an increase in bowel wall thickness corresponded with the ulcer marginal ridge, and the white-plaque sign was shown to indicate the ulcer bottom. To the best of our knowledge, this is the first study to show a correlation of endoscopic activity and histopathological findings with IUS findings in patients with intestinal BD.

IUS is widely used for the diagnosis and follow-up of IBD activity, and IUS parameters exhibit a direct correlation with disease severity across various scoring systems. In con-
Fig. 4. Comparison of intestinal ultrasound (IUS) findings and endoscopic ulcer activity. (A) The mean bowel wall thickness for each endoscopic activity of intestinal ulcers in Behçet disease. The mean bowel wall thickness of the control group was 1.9 mm (n = 10), scar group was 4.3 mm (n = 18), healing group was 4.6 mm (n = 16), and active group was 7.9 mm (n = 39). There were significant differences between the active stage and the healing stage, scar stage, and healthy controls, and between the healthy controls and the healing stage and scar stage (P < 0.001 for each). (B) Receiver operating characteristic curve to determine the optimal cutoff value for active lesions. Bowel wall thickness > 5.5 mm was indicated to detect the active stage (sensitivity 89.7%, specificity 85.3%, area under the curve 0.90, 95% confidence interval 0.83–0.98). (C) Assessment of vascularity graded by the modified Limberg scoring system for each endoscopic activity of intestinal ulcers in Behçet disease. Vascularity was significantly different in the active stage compared with the other stages (P < 0.001 for each). (D) Assessment of bowel wall stratification for each endoscopic activity of intestinal ulcers in Behçet disease. There was a significant difference only between the active stage and healthy controls (P = 0.008). (E) Assessment of the white-plaque sign for each endoscopic activity of intestinal ulcers in Behçet disease. The white-plaque sign was significantly different only between the active stage and healthy controls (P = 0.001).
gruence with these trends, our results indicate that these IUS parameters are also useful for the assessment of activity in intestinal BD. Among the variables investigated, bowel wall thickness emerged as the most pivotal indicator. Additionally, it is worth noting that prior reports have underscored the low inter-rater error associated with measuring bowel wall thickness using IUS, contributing to the expected reproducibility and reliability of the examination results.\(^{31}\)

The present study not only provides insights into the characteristics of IUS in the assessment of intestinal BD ulcer activity, but it also offers insights into the distinctive characteristics of BD compared with other types of IBD. A bowel wall thickness of \(\geq 3\) mm is considered an indicator of wall thickening, suggesting the presence of active lesions in IBD.\(^{13,32}\) In the present study on intestinal BD, the mean bowel wall thickness of active stage lesions was \(7.6\) mm in the entire cohort, which is extremely high. The histopathological comparison revealed that bowel wall thickness on IUS indicated the thicker part of the raised ulcer marginal ridge, which may reflect the ulcer marginal ridge of active ulcers, described as "volcanic," which is characteristic of intestinal BD.\(^{9,10,33}\) The mean bowel wall thickness on IUS of 22 cases of intestinal BD reported by Ma et al.\(^{20}\) was also high (\(6.6\) mm), suggesting that marked wall thickening might be one of the characteristics of intestinal BD, similar to our results. Interestingly, even during the scar phase, wall thickness increased compared with healthy controls. As some intestinal BD ulcers exhibited irregular lesions, such as inflammatory polyps, even after healing (Fig. 1C), the possibility that wall thickness was overestimated in these small lesions could not be ruled out. However, histologically, the ulcer margins in the healing process showed thickening with not only edema but also a high degree of fibrosis (data not shown). These findings suggest that the scar healing process of intestinal BD ulcers may represent the characteristic of increased bowel wall thickness with marked fibrosis, which differs from the findings in ulcerative colitis and Crohn's disease, and IUS findings may capture this difference.

Abundant flow on color Doppler in the bowel wall, loss of bowel wall stratification, and extramural phlegmons were also highly specific findings for active ulcers. However, it should be noted that some lesions with endoscopic active ulcers in intestinal BD did not show these parameters, which is different from IBD. Increased vascularity and focal loss of bowel wall stratification are associated with severe inflammation in IBD,\(^{34}\) but the present results give a somewhat different impression in intestinal BD. The ileocecal region is physiologically characterized by the prominent presence of lymph nodes, possibly contributing to the lack of a correlation with lymphadenopathy.

![Fig. 5. Comparison of endoscopic ulcer size (maximum diameter) and bowel wall thickness by intestinal ultrasound (IUS). Spearman correlation coefficient revealed that bowel wall thickness showed a weak but positive correlation with ulcer size measured by colono-](image-url)

**Table 3. Sensitivity and Specificity of Intestinal Ultrasound Findings to Predict Active Ulcers in Intestinal Behçet Disease**

<table>
<thead>
<tr>
<th>Ultrasonographic lesion characteristics</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel wall thickness &gt; 5.5 mm</td>
<td>89.7</td>
<td>85.3</td>
<td>85.4</td>
<td>87.5</td>
<td>86.3</td>
<td>40.8</td>
</tr>
<tr>
<td>Vascularity: modified Limberg score (\geq 2)</td>
<td>46.2</td>
<td>97.1</td>
<td>94.7</td>
<td>60.4</td>
<td>68.5</td>
<td>28.3</td>
</tr>
<tr>
<td>Vascularity: modified Limberg score = 3</td>
<td>20.5</td>
<td>100</td>
<td>100</td>
<td>52.3</td>
<td>56.2</td>
<td>-</td>
</tr>
<tr>
<td>Loss of bowel wall stratification</td>
<td>33.3</td>
<td>94.1</td>
<td>86.7</td>
<td>55.2</td>
<td>61.6</td>
<td>8.0</td>
</tr>
<tr>
<td>Presence of white-plaque sign</td>
<td>38.4</td>
<td>91.2</td>
<td>83.3</td>
<td>56.4</td>
<td>63.0</td>
<td>6.5</td>
</tr>
<tr>
<td>Mesenteric lymphadenopathy (\geq 10) mm</td>
<td>12.8</td>
<td>88.2</td>
<td>55.6</td>
<td>46.9</td>
<td>47.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Extramural phlegmons</td>
<td>15.4</td>
<td>100</td>
<td>100</td>
<td>50.7</td>
<td>54.8</td>
<td>-</td>
</tr>
<tr>
<td>Fistulas</td>
<td>5.1</td>
<td>94.1</td>
<td>50.0</td>
<td>46.4</td>
<td>46.6</td>
<td>0.9</td>
</tr>
</tbody>
</table>

PPV, positive predictive value; NPV, negative predictive value.
The white-plaque sign was also a finding suggestive of active ulcers. Similar findings within the bowel wall have also been reported in severe cases of ulcerative colitis, so the white-plaque sign was considered to indicate the presence of an ulcer. It is difficult to differentiate the white-plaque sign from the intestinal residue finding on imaging. White-plaque signs are generally considered present in the bowel wall and intestinal residues on the luminal side. However, in the presence of ulcers with loss of stratification, the distinction between the lumen and the bowel wall may become unclear, which makes it difficult to distinguish the residue from the white-plaque sign. Differentiating by immobility is important in such cases and should be assessed in detail; e.g., by compression with an echo probe from outside the body. After reviewing the IUS findings of all intestinal BD cases with endoscopic ulceration including not in the ileocecal region assessed at our institution, the minimum size of the white-plaque sign was 1.5 mm in diameter (data not shown). In light of these considerations, our study’s strengths lie in its comparison with histological findings, which allowed for a scientifically grounded validation of the significance of the white-plaque sign. Although this hyperechogenic finding could reflect intestinal contents or air entering the ulcer, we propose to call this hyperechogenic finding the “white-plaque sign.” Importantly, previous reports have not established a comparison between the IUS findings of intestinal BD and the pathology of resected specimens, nor have any other IBD cases demonstrated whether the IUS hyperechogenic echoes reflect the ulcer bottoms. In the present study, a strong correlation was observed between preoperative IUS measurement and histopathological measurement for the distance between the outer muscular layer and the ulcer bottom, leading us to speculate that the white-plaque echo sign is reflective of the ulcer bottom.

This study has several limitations. First, this is a retrospective study of a small number of cases. The rarity of intestinal BD as a condition inherently restricted the availability of cases for this single-center study. Second, during the extended study duration, improvements in IUS equipment and technological advancement of IUS sonographers were noted, leading to some variation in the quality of the images. Furthermore, we did not compare the IUS findings with objective parameters, such as clinical disease activities or laboratory data. We also did not make a detailed comparison of the preoperative IUS findings with the micropathological findings of the resected specimens, although these findings will be reported in forthcoming analyses. Despite these limitations, we believe that our study contributes valuable insights and holds significance in the context of assessing ulcer activity in intestinal BD.

Fig. 6. Comparison of wall thickness and the white-plaque sign by preoperative intestinal ultrasound (IUS) and histopathological measurement. Spearman correlation coefficient revealed that the bowel wall thickness captured by IUS reflected the distance to the peak of the ulcer margin elevation (the mean bowel wall thicknesses measured by IUS and histopathology were 10.5 mm and 8.9 mm, respectively), with a strong correlation. Additionally, the white-plaque sign reflected the ulcer bottom depending on the distance from the muscular layer (the mean values were 3.1 mm and 3.1 mm, respectively), also with a strong correlation. CI, confidence interval.
In conclusion, this is the first report to demonstrate that IUS is valuable for assessing the endoscopic activity of intestinal BD. IUS is a minimally invasive and highly repeatable modality for evaluating intestinal ulcer activity in patients with BD, and it may be useful to follow-up and monitor patients with a confirmed diagnosis of intestinal lesions. The widespread adoption of IUS has the potential to benefit both patients and medical practitioners by facilitating safe and well-informed monitoring of bowel ulcer activity. Further studies with larger sample sizes are required to confirm this conclusion.

**ADDITIONAL INFORMATION**

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**Conflict of Interest**
Yaguchi K received lecture fees from AbbVie, EA Pharma., Janssen Pharmaceutical, Mitsubishi Tanabe Pharma, and Zeria Pharmaceutical. Kunisaki R received research grants and speaker’s and/or consultancy fees from AbbVie, EA Pharma., Eli Lilly, Kissel Pharmaceutical, Kyorin Pharmaceutical, Nippon Kayaku, Mitsubishi Tanabe Pharma, Takeda Pharmaceutical Company Limited, Zeria Pharmaceutical, the Janssen Pharmaceutical, and Pfizer, outside of the submitted work. Kimura H received research grants and speaker’s and/or consultancy fees from AbbVie, Astellas, EA Pharma, Janssen Pharmaceutical, Kissui, Kyorin, Kyowa Hakko Kirin, Mitsubishi Tanabe Pharma, Takeda Pharmaceutical Company Limited, Zeria Pharmaceutical, and Mochida Pharmaceutical outside of the submitted work. The other authors have no competing interests to declare.

**Data Availability Statement**
The data underlying this article will be shared on reasonable request to the corresponding author.

**Author Contributions**

**Additional Contributions**
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**REFERENCES**

ant observational study from a dedicated multidisciplinary center. Medicine (Baltimore) 2016;95:e3348.


