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Title	Crohn's Disease Activity Evaluation by Transabdominal Ultrasonography Correlation with Double-Balloon Endoscopy
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Citation	Journal of ultrasound in medicine, 40(12), 2595-2605 <a href="https://doi.org/10.1002/jum.15645">https://doi.org/10.1002/jum.15645</a>
Issue Date	2021-12
Doc URL	<a href="https://hdl.handle.net/2115/87382">https://hdl.handle.net/2115/87382</a>
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Type	journal article
File Information	J Ultrasound Med 15645.pdf



1 **Original Research**

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3 **Crohn's disease activity evaluation by transabdominal ultrasonography:**  
4 **correlation with double-balloon endoscopy**

5 Short running title: Crohn's disease activity and transabdominal ultrasonography

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30 **Abstract**

31 **Objectives:** Transabdominal ultrasonography (US) has been reported as a useful tool  
32 for evaluating Crohn's disease (CD) activity. Endoscopic findings and Crohn's  
33 disease activity index (CDAI) are currently considered the gold standard for  
34 assessing CD activity. We assessed the correlation between US and double-balloon  
35 endoscopy (DBE), and CDAI for evaluating CD activity.

36 **Methods:** We analyzed patients with CD undergoing US and DBE within 10-days  
37 between the procedures. The intestine was divided into four segments and analyzed  
38 by the US scoring system (US-CD) and the simple endoscopic score for Crohn's  
39 disease (SES-CD). Crohn's disease activity index (CDAI) was compared with US-CD  
40 and SES-CD. Spearman's rank correlation coefficient was used for statistical analysis.

41 **Results:** Twenty-five patients with CD (11 women, 14 men; mean age  $35.4 \pm 14.9$  years,  
42 range 16–65 years) were enrolled. Twenty-four patients received anti-tumor necrosis  
43 factor inhibitor therapy. CDAI was 128.1 (range 36–227). A significant moderate  
44 correlation was found between the US-CD and SES-CD in all segments ( $\rho=0.64$ ,  
45  $p<0.01$ ). The US-CD showed a strong correlation with CDAI ( $\rho=0.78$ ,  $p<0.01$ ),  
46 whereas the SES-CD showed a moderate correlation ( $\rho=0.55$ ,  $p<0.05$ ).

47 **Conclusions:** US-CD and SES-CD showed a moderate correlation for assessing CD  
48 activity. US-CD showed a stronger correlation with CDAI than SES-CD, suggesting  
49 that US could more accurately evaluate the disease activity.

50

51 **Key Words:** Transabdominal ultrasonography; Double-balloon endoscopy; Crohn's  
52 disease; Disease activity; Small intestine

53

## 54 INTRODUCTION

55 Crohn's disease (CD) is a chronic inflammatory disease that can cause  
56 tissue erosion and ulcers in every part of the digestive tract, from the oral cavity to  
57 the anus<sup>1</sup>. Characteristic abdominal symptoms are abdominal pain, diarrhea, and  
58 bloody stool, and as the disease progresses, it causes stenosis, fistula formation, and  
59 intestinal perforation<sup>2</sup>. Approximately half of all patients with CD undergo surgery  
60 within 10 years of disease diagnosis<sup>2</sup>. Conversely, mucosal healing can be considered  
61 a sign of relapse-free remission. The appropriate evaluation is vital to the  
62 improvement of patient prognosis<sup>3</sup>. Ileocolonoscopy (ICS) is a standard tool to  
63 evaluate intestinal diseases. Although ICS is useful for evaluating the large intestine  
64 and distal ileum, evaluation of the entire small intestine is needed, as small bowel  
65 inflammation occurs in >60% of patients with CD<sup>1</sup>, and the procedure is very  
66 invasive for patients<sup>4</sup>. The small bowel series is capable in imaging lesions in the  
67 small intestine; however, it is less capable of detecting tissue erosion and aphthous  
68 ulcers, and exposes the patient to X-ray radiation. Recent modalities; computed  
69 tomography (CT) enterography, magnetic resonance enterography (MRE), and  
70 transabdominal ultrasonography (US) are reported to be useful<sup>5</sup>. CT enterography  
71 with an intravenous contrast agent, intestinal wall thickness and perfusion can be  
72 evaluated in detail<sup>6-7</sup>. However, frequent use of CT enterography to evaluate the  
73 disease activity can increase the carcinogenic risk in young patients with CD due to  
74 the accumulated radiation dosage<sup>8</sup>. MRE, in contrast, presents no radiation exposure  
75 and is often used to monitor the disease activity in inflammatory bowel disease<sup>1</sup>.  
76 However, only a limited number of institutions have the equipment, procedural  
77 throughput is low, expensive, and the methodology has yet to be standardized<sup>9</sup>.

78 Also, allergies and contrast induced nephropathy in patients with an impaired renal  
79 function are the risks of contrast media administration in CT and magnetic resonance  
80 imaging (MRI). Contrast administration in MRI is restricted in patients with renal  
81 insufficiency due to the risk of nephrogenic systemic fibrosis<sup>10</sup> .

82 In comparison, US has the following advantages: it is non-invasive, radiation-  
83 free, highly cost-effective, and can provide real-time images. US is a useful tool in  
84 the evaluation of CD activity<sup>11-13</sup>, studies compared it with contrast imaging, CT,  
85 MRI<sup>14</sup>, ICS<sup>2</sup> and Crohn's disease activity index (CDAI) scores were reported<sup>15-18</sup>.

86 In recent years, the double-balloon endoscopy (DBE) enabling the accurate  
87 observation of small bowel lesions in CD<sup>19</sup>, and the simple endoscopic score for  
88 Crohn's disease (SES-CD) which is derived from DBE has been used as assessing CD  
89 activity. There have been no studies comparing DBE and US.<sup>16,20-21</sup>. Validated  
90 comprehensive scoring system of US findings have yet been reported at the time of  
91 starting our study<sup>22</sup>.

92 The main indication or strength of double balloon DBE is that it can assess  
93 active lesions and stenosis exclusively in the small intestine. The differences of DBE  
94 from US are that it can perform biopsy and balloon dilatation for small intestinal  
95 strictures.

96 Therefore, we aimed to evaluate the correlation between our newly developed  
97 ultrasonographical scoring system for Crohn's disease (US-CD) and SES-CD<sup>23-24</sup>, and  
98 CDAI in evaluating CD activity.

99

## 100 **MATERIALS AND METHODS**

### 101 *Study protocol*

102           The institutional review board approved the study protocol (study number  
103 2017-0500). Informed consent was obtained from all patients according to the  
104 Declaration of Helsinki. All patients underwent both US and DBE within 10-days  
105 between the procedures. This study was performed under realistic conditions as seen  
106 in daily practice. At our hospital, the number of patients with CD who underwent  
107 DBE and US within 10 days was about 10 patients per year at the time to start this  
108 study. So that based on the fact, we set sample number of patients as thirty during  
109 study period. The indication for DBE was Crohn's diseases patients who were  
110 suspected to have lesions in small intestine. We used colonic cleaning when US and  
111 DBE were performed on the same day. Otherwise, only 8 h of fasting was required for  
112 the US examination. Because of Endoscopic findings and CDAI are thought to be  
113 current gold standards for assessing CD activity<sup>25</sup>. Clinical activity was assessed at the  
114 time of DBE or US according to the CDAI. CDAI was determined before DBE. CDAI  
115 was categorized as follows: <150 = inactive disease; 150-220 = mild disease; 220-450  
116 = moderate disease; and >450 = severe disease<sup>17</sup> (Table 1). Disease was classified as  
117 clinically active if CDAI >150, a value that has been previously validated<sup>17</sup>. Laboratory  
118 values of C-reactive protein, hemoglobin, and serum albumin were measured in all  
119 patients.

120           We also evaluated whether the US-CD and SES-CD scoring systems could  
121 predict the necessity for treatment escalation. We focused on patients who required  
122 strengthening of treatment during the observation period and checked their pre-  
123 strengthening US-CD and SED-CD values. DBE findings and CDAI were used to  
124 make decision to change treatment. The observation period was defined within 8  
125 weeks after DBE. Treatment escalation was defined as the requirement of another

126 course of anti-tumor necrosis factor (TNF) therapy, different administration method  
127 (i.e., double-dose or shortened administration), prednisolone administration, or  
128 surgical treatment. When "treatment escalation" is needed, it has the same meaning as  
129 "predict the need for correction or supplemental treatment".

130

131

### 132 *Transabdominal US*

133 US was performed by two gastroenterologists (KY and KK) and four  
134 sonographers (MN, SO, MS, and KY) using several US devices (Aplio 500, Aplio i800,  
135 Cannon Medical Systems Corp., Otawara, Japan). For the conventional ultrasound,  
136 probe center frequency (range); 3.75-MHz (4.0-6MHz) convex, 6-MHz (4-9.5MHz)  
137 convex, and 7.5-MHz (6.0-9.0MHz) linear probes were used. The operator's median  
138 duration of experience with transabdominal US was 8 years (range 1-32 years).

139 We followed a systematic scanning protocol for evaluation of entire colon  
140 which was published previously<sup>26</sup>. After scanning the colon, the terminal ileum was  
141 then identified by the ileocecal valve, after which the ileum was followed as far as  
142 possible in the oral direction.

143 We divided the intestine into four segments (ileum, right-sided colon,  
144 transverse colon, left-sided colon), and the images of each part were stored. The  
145 rectum was excluded from this study, because this region was difficult to evaluate by  
146 US<sup>7-8,15,26</sup>.

147 Considering the possibility that the lesion may be affected through the use of  
148 an endoscope, all patients underwent US prior to DBE. A color Doppler study was  
149 performed using a 7.5-MHz linear probe, with color gain adjusted until the

150 disappearance of noise for maximization of the sensitivity. The color Doppler  
151 frequency was set from 3.3 to 4.5 MHz, with a pulse repetition frequency from 4.7 to  
152 10.1 cm/sec, which was adjusted according to the depth of the lesion. The wall filter  
153 was set between 3 and 4. The blood flow signal was semi-quantitatively classified as  
154 Grades 0 to 3 (Figure 1). US-CD was calculated by taking the sum of the above US  
155 findings.

156 We scored the US severity as 0-52, calculating the following US parameters:  
157 bowel wall thickness (BWT) (0-3), loss of stratification (0-2), degree of blood flow  
158 signaling by a color Doppler study (0-3), presence of increasing echogenicity  
159 mesentery (0-2), and intestinal stenosis (0-3) (Table 2). The US-CD score of  $\geq 11$  was  
160 also defined as moderately active, because SES-CD  $\geq 11$  indicates a moderately active  
161 disease<sup>7,27</sup>.

162 Moreover, all still images and movie clips were analyzed and interpreted in a  
163 consensus manner by two registered sonographers at Hokkaido University Hospital  
164 (MN and SO) who had 32 and 10 years, respectively, of experience with US. They were  
165 aware of the CD diagnosis but were blinded to the other patient's clinical information  
166 and identity.

167

168 *DBE*

169 DBE was performed by seven gastroenterologists (TK, RO, KK, KN, SO, KS,  
170 and KY) who each had >4 years of endoscopic examination experience. They were  
171 aware of the CD diagnosis but blinded to the patient's clinical records and US findings.  
172 The one who performed US did not perform DBE, and vice versa. DBE was performed  
173 with a standard endoscope (Fujifilm, EN-580T, Tokyo, Japan). To allow comparison

174 with US, the same area as the US evaluation was performed by DBE. Disease activity  
175 was assessed according to the SES-CD (Table 3). SES-CD was calculated by sum of  
176 DBE findings.

177 The SES-CD was defined as follows: inactive 0–3, mild 4–10, moderate activity  
178 11–19, and high activity  $\geq 20$ <sup>27</sup>. A SES-CD score of  $\geq 11$  was defined as endoscopically  
179 active. All endoscopic findings were evaluated by two experienced  
180 gastroenterologists (TK and RO), each with >6 years of experience. They were blinded  
181 to the patient’s clinical records and US findings.

182

### 183 *Statistical analysis*

184 GraphPad Prism 8 for Windows (version 8.20, 2018; GraphPad Software Inc.,  
185 La Jolla, CA) was used for all analyses. A value of  $p < 0.05$  was considered to indicate  
186 statistical significance. Spearman’s rank correlation coefficient was used to verify the  
187 correlation between US-CD and SES-CD, the CDAI and US-CD, and the CDAI and  
188 SES-CD. As an evaluation of treatment escalation, the risk ratio (RR) at a 95%  
189 confidence interval (CI) was analyzed.

190

191 **RESULTS**

192 Thirty-seven patients with an established diagnosis of CD were enrolled  
193 between December 2015 and July 2019. Patients were excluded if they had severe  
194 intestinal stenosis (n=3), unevaluated jejunal lesions (n=2), DBE from the oral cavity  
195 (n=4), or overly complicated bowel surgery (n=3). Seven patients underwent  
196 enterectomy [ileocecal resections (n=3), partial resection of the small intestine (n=2),  
197 both (n=2)]. Finally, 25 patients (11 women, 14 men; mean age 35.4±14.9 years, range  
198 16–65 years) underwent both US and DBE.

199 The demographic, clinical, and biological parameters of the 25 CD patients are  
200 shown in Table 3. The median number of days between the examinations of US-CD  
201 and SES-CD was 2.5 (range 0–10). None of the patients received additional treatment  
202 between US-CD and SES-CD. In this study, 24 patients received anti-TNF inhibitor  
203 therapy. The median CDAI was 128.1 (range 36–227). A significant moderate  
204 correlation was found between US-CD and SES-CD ( $\rho=0.64$ ,  $p<0.01$ ; Figure 2).

205 The comparative analysis between US-CD and SES-CD for each intestinal  
206 segment showed a moderate correlation (Table 5). The correlation between US-CD  
207 and SES-CD in the ileum, right-sided colon, transverse colon, and left-sided colon was  
208 0.53, 0.44, 0.42, and 0.49, respectively.

209 When comparing the US-CD and SES-CD between the small intestine area  
210 (ileum) and large intestine area (right-sided colon, transverse colon, and left-sided  
211 colon), the small intestine area showed more correlation than the large intestine area  
212 (small intestine;  $\rho=0.53$ ,  $p<0.01$ , large intestine;  $\rho=0.39$ ,  $p<0.01$ ).

213 A strong correlation was found between US-CD and CDAI ( $\rho=0.78$ ,  $p<0.01$ ;  
214 Figure 3A), whereas a moderate correlation was observed between SES-CD and CDAI

215 ( $\rho=0.55$ ,  $p<0.05$ ; Figure 3B) (Spearman's rank correlation coefficient).

216 Although no significant correlation was found between the maximum BWT  
217 and CDAI ( $\rho=0.28$ ,  $p=0.19$ ; Figure 4A), maximum color Doppler signals and CDAI  
218 showed a strong correlation ( $\rho=0.73$ ,  $p<0.01$ ; Figure 4B). Other US parameters  
219 (presence of stenosis, increase mesenteric fat echogenicity, and loss of stratification)  
220 did not show any statistical correlation (Table 4).

221 Moreover, 9 (36%) of 25 patients were confirmed to require strengthening of  
222 treatment during the observation period (median 17.5 days). No patient had surgical  
223 treatment. Among the 9 patients, US-CD score  $\geq 11$  was found in 6 patients, SES-CD  
224 score of  $\geq 11$  was observed in 4 patients, and both were observed in 4 patients. The  
225 percentage of the strengthening treatment for each score is shown in Table 6. The  
226 number of patients requiring strengthening of treatment was larger in patients with  
227 US-CD score  $\geq 11$  and/or SES-CD. Patients with US-CD score  $\geq 11$  had a RR for the  
228 need for strengthening treatment (RR, 5.14; 95% CI, risk difference 0.067-0.53;  $p=0.001$ ),  
229 but no significant difference was found in those with SES-CD score  $\geq 11$  (RR, 2.53; 95%  
230 CI, risk difference 0.16-1.09;  $p=0.073$ ).

231

## 232 DISCUSSION

233 Although some studies have used US to evaluate CD, all of them compared  
234 it with ICS, which can only examine as far as the terminal ileum. To the best of our  
235 knowledge, this study was the first to conduct a comparative analysis between US  
236 and DBE and to show a significant correlation between SES-CD and US-CD. Thus,  
237 the US-CD could reflect the presence of endoscopically active lesions. Particularly,  
238 among the US-CD parameters, BWT and increased blood flow signals correlated

239 significantly with the SES-CD. Previous reports similarly indicated that BWT and  
240 increased blood flow signals correlated with the CDAI <sup>28-30</sup>.

241 In this study, we observed a significant correlation between the CDAI and  
242 increased blood flow signals. However, we did not find a significant correlation  
243 between BWT and CDAI. Fibrotic stenosis can also be observed as BWT with no  
244 blood flow signals<sup>31-32</sup>. In this case, decorrelation occurs. The blood flow signals  
245 would be a more accurate evaluator of active inflammation<sup>3</sup> and useful in  
246 distinguishing fibrotic stenosis from inflammatory stenosis. When assessing CD  
247 lesions, combining B-mode and color Doppler imaging is necessary. The US-CD was  
248 more correlated with the CDAI than the SES-CD. This indicates that the US-CD is  
249 likely to predict the treatment escalation, regardless of the patient's clinical  
250 symptoms. Furthermore, the US-CD can be easily conducted daily for patients with  
251 low CDAI and mild clinical symptoms.

252 A typical case with CDAI  $\geq 150$  (indicating the presence of clinical activity)  
253 showing a correlation between US-CD and SES-CD is presented in Figure 5. This  
254 case had a period of clinical activity with CDAI of 220. The patient's SES-CD and US-  
255 CD were 22 and 23, respectively. Moreover, endoscopic findings revealed extensive  
256 ulcers, and US revealed increased BWT and blood flow signals, and loss of  
257 stratification at the same site. We also experienced cases with divergent SES-CD and  
258 US-CD. A patient in a period of clinical activity with a CDAI of 198 and divergent  
259 US-CD and SES-CD is shown in Figure 6. In this case, US detected BWT, increased  
260 blood flow signals, loss of stratification, and increased blood flow signals in the  
261 ileum and right-sided colon, where endoscopy failed to detect any inflammatory  
262 lesions. Only an aphthae was shown in the ileum. Thus, the SES-CD for this patient

263 was 2, whereas the US-CD showed a quiet divergence at 13. Usually, US is  
264 understood to have difficulty in identifying small shallow lesions, such as aphthae,  
265 where inflammation is only limited to the mucosal surface. In this case, increased  
266 BWT and blood flow signals, and loss of stratification are not detected.

267 We also focused on cases with US-CD and SES-CD scores  $\geq 11$  and monitored  
268 their treatment progress. Over the course of their observation periods (range 1-61  
269 days, median 17.5 days), 4 of 6 patients (67%) had an SES-CD score  $\geq 11$ , and 6 of 7  
270 patients had a US-CD score  $\geq 11$  (85%); treatment strengthening was therefore  
271 necessary. In particular, an increase in the RR that treatment strengthening would  
272 become necessary was demonstrated for cases with US-CD score of  $\geq 11$ .

273 CD often develops in relatively young patients, and its progress can often  
274 stretch over long, chronic periods. In patients with CD, medication nonadherence  
275 and mild clinical symptomology are both frequently encountered, and a lack of  
276 periodic testing and treatment can lead to problems. Thus, the prognostic evaluation  
277 of patients with CD is needed.

278 The methodology for the evaluation of the digestive tract using US evolves  
279 with each passing year and is worthy of our attention. Contrast-enhanced US,  
280 elastography, and other new US methodologies continue to emerge<sup>29-30</sup>. However,  
281 the evaluation parameters and methodologies for US in patients with CD have not  
282 been standardized. Despite various reports of evaluation methodologies for blood  
283 flow signals in US, each methodology was performed according to the author's own  
284 indices, with no consistency among studies<sup>4,5</sup>. To turn US-CD into a standardized  
285 evaluation system, a future validation study is necessary.

286           Approximately 60% of all cases of CD involve small bowel lesions <sup>1</sup>.  
287   Comprehensive evaluation of the small bowel is important in the diagnosis and  
288   treatment of CD. At present, endoscopic analysis is indispensable for the close  
289   examination of the mucosal membranes. While DBE (developed in Japan) enables  
290   direct examination of the mucosal membranes of the small bowel, it is invasive and  
291   technically difficult. Thus, it is not yet commonly performed. For this reason, cross-  
292   sectional imaging and multiple imaging modalities such as CT and MRE, and US,  
293   have been used for evaluation of patients with CD <sup>16-17,30</sup>. Cross-sectional imaging is  
294   not merely a replacement for endoscopy. As lesions in patients with CD can develop  
295   anywhere in the digestive tract, these modalities can evaluate deep, small bowel  
296   lesions, extra-digestive lesions, and other lesions that endoscopy cannot detect.

297           Although CT and MRE are commonly used to evaluate extra-digestive  
298   lesions, such as abscesses and fistulae, CT enterography causes radiation exposure,  
299   and MRE is costly. In contrast, US can detect not only BWT but also blood flow  
300   signals and extra-digestive lesions with a high resolution. In addition, it is painless,  
301   radiation-free, low cost, and accessible. Furthermore, if stenosis is present, it can  
302   make endoscopy challenging<sup>33</sup>, whereas US can perform close examination  
303   regardless of the presence of stenosis. Patients with CD tend to be young, and given  
304   the need for frequent testing over the long clinical course of the disease, US –  
305   because it is less risky and repeatable – is arguably a very useful test. Despite these  
306   advantages, US has several limitations. Previous reports indicate that US evaluation  
307   of the rectum showed a poor concordance rate<sup>25,34</sup> because of deep attenuation.  
308   Transvaginal and transrectal ultrasound can solve this limitation. Whereas they are  
309   invasive, and limited use in Japan, which is strictly performed by physicians in

310 obstetrics, gynecology, and urology. Therefore, we only used transabdominal US in  
311 this study. US is sometimes difficult to perform in obese patients. Physicians  
312 consider these points when conducting US evaluations.

313         This study had several limitations. First, it incorporated retrospectively  
314 studied cases. Second, this single-center study examined only a small number of  
315 cases that had been performed by different operators and with different machines.  
316 However, we reported a high concordance rate in evaluating ulcerative colitis  
317 activity in different facilities<sup>35</sup>. Thus, a future multicenter prospective study should  
318 be performed in a large number of patients. In this study, an investigation of US  
319 alongside DBE in CD patients showed a significant correlation between US and DBE.  
320 The US-CD is an easy-to-use, minimally invasive, low-cost method for evaluating  
321 intestinal lesions, including small bowel lesions, in patients with CD.

322         In conclusion, the US-CD proved to be useful in the evaluation of CD  
323 activity, since it accurately reflected both endoscopic and clinical disease activities.  
324 Furthermore, the US-CD could be a prognostic tool for evaluating the treatment  
325 progress. In the future, we will conduct a multicenter prospective study to confirm  
326 the validation of US-CD.

327

328 **Conflicts of interest**

329 No funding was received for this study. All authors declare no conflicts of interest  
330 related to this article.

331

332 **Acknowledgments**

333 We thank the others involved in the study as well as colleagues from the Department  
334 of Ultrasound for their support.

335

336

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458 **Table 1. Crohn's disease activity index (CDAI)**

<b>Clinical or laboratory variable</b>	<b>Weighting factor</b>
Number of liquid or soft stools each day for 7 days	×2
Abdominal pain (grade from 0 to 3 based on severity) each day for 7days	×5
General well-being, subjectively assessed from 0(well) to 4(terrible) each day for 7 days	×7
Complications*	×20
Use of diphenoxylate or opiates for diarrhea	×30
An abdominal mass (0 for none;2 for questionable;5 for definite)	×10
Absolute deviation of hematocrit from 47% in men and 42% in women	×6
Percentage deviation from standard weight	×1

459 \*One point is added for each set of complications: arthralgia or frank arthritis;  
460 inflammation of the iris or uveitis; erythema nodosum, pyoderma gangrenosum, or  
461 aphthous ulcers; anal fissures, or abscesses; other fistulas, and fever (>100°F) during  
462 the previous week.

463

464

465 **Table 2. Ultrasonographical scoring system for Crohn's disease (US-CD)**

<b>US-CD scoring system</b>				
<b>Parameters</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>
<b>Bowel wall thickness (mm)</b>	<3	$3 \leq$ and <5	$5 \leq$ and <7	$7 \leq$
<b>Loss of stratification</b>	Absent	-	Present	-
<b>Presence of stenosis</b>	-	Single, fluid can be passed	Multiple, fluid can be passed	Fluid cannot be passed (to and fro)
<b>Color Doppler signal</b>	No signal	Few spotty vessel signals	Confluent vessel signals in less than half of the area of the bowel wall	Confluent vessel signals in more than half of the area of the bowel wall
<b>Increasing mesenteric fat tissue echogenicity</b>	Absent	-	Present	-

466 For US-CD, the following five US parameters were selected: bowel wall thickness, loss  
 467 of stratification, presence of stenosis, color Doppler signal, and mesenteric fat  
 468 alteration

469

470 **Table 3. Simple endoscopic score for Crohn's disease (SES-CD)**

Variables	SES-CD values			
	0	1	2	3
<b>Size of ulcers</b> <b>(cm)</b>	None	Aphthous ulcers (diameter 0.1-0.5)	Large ulcers (diameter 0.5-2)	Very large ulcers (diameter >2)
<b>Ulcerated surface</b>	None	<10%	10-30%	>30%
<b>Affected surface</b>	Unaffected segment	<50%	50-75%	>75%
<b>Presence of narrowing</b>	None	Single, can be passed	Multiple, can be passed	Cannot be passed

471 For SES-CD, the following four endoscopic variables were selected: ulcers, ratio of surface coverage by ulcers, ratio of surface  
 472 coverage with other lesions, and stenosis

473

474 **Table 4. Clinical and demographic characteristics of the 25 patients with Crohn's disease**

Characteristics	N (%)
Median age (range)	35.4 (16–65)
Sex	
Men (%)	14 (56.0)
Disease location	
Ileal-type (%)	12 (48.0)
Ileocolonic-type (%)	1 (4.0)
Colonic-type (%)	12 (48.0)
Median CDAI (range)	128.1 (36–227)
Treatment	
Infliximab (%)	6 (24.0)
Adalimumab (%)	8 (32.0)
PSL (%)	1 (4.0)
Infliximab and azathioprine (%)	7 (28.0)

Adalimumab and azathioprine (%)	3 (12.0)
Previous surgery (%)	7 (28.0)
Median serum Alb. concentration (mg/L) (range)	3.9 (3.0–4.9)
Median serum Hb concentration (mg/L)	12.9 (10.2–16.6)
Median serum CRP concentration (mg/L)	1.19 (0.02–7.76)

475 Alb, albumin; CDAI, Crohn's disease activity index; CRP, C-reactive protein; Hb, hemoglobin; PSL, prednisolone

476

477 **Table 5. Correlation of each intestinal segment with US-CD and SES-CD**

	Correlation with US-CD and SES-CD	
Intestinal segment	$\rho$	p
All segments	0.64	<0.01
Ileum	0.53	<0.01
Right-sided colon	0.44	<0.05
Transverse colon	0.42	<0.05
Left-sided colon	0.49	<0.05
	Correlation with maximum BWT and SES-CD	
Intestinal segment	$\rho$	p
All segments	0.47	<0.05
Ileum	0.41	<0.05

Right-sided colon	0.21	0.32
Transverse colon	0.42	<0.05
Left-sided colon	0.43	<0.05
<b>Correlation with maximum color Doppler signal and SES-CD</b>		
<b>Intestinal segment</b>	<b><math>\rho</math></b>	<b>p</b>
All segments	0.42	<0.05
Ileum	0.24	0.12
Right-sided colon	0.27	0.18
Transverse colon	0.35	0.08
Left-sided colon	0.16	0.44
<b>Correlation with other maximum US parameters and SES-CD</b>		
<b>US parameters</b>	<b><math>\rho</math></b>	<b>p</b>

Presence of stenosis	0.19	0.37
Increasing mesenteric fat tissue echogenicity	0.32	0.12
Loss of stratification	0.13	0.53

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478 **BWT, bowel wall thickness; US-CD, ultrasonographical scoring system for Crohn's disease; SES-CD, simple endoscopic score**  
479 **for Crohn's disease**

480 Among the US parameters, the maximum BWT and maximum color Doppler flow were also correlated with the US-CD and SES-CD.

481 The maximum BWT and maximum color Doppler flow showed a moderate or higher correlation in all intestinal segments

482

483 **Table 6. Percentage of required strengthening treatment during the observation period**

US-CD	Number of patients	Need to strengthen treatment	No need to intensify treatment
$\leq 10$	18	3 (17%)	15 (83%)
$\geq 11$	7	6 (86%)	1 (14%)

SES-CD	Number of patients	Need to strengthen treatment	No need to intensify treatment
$\leq 10$	19	5 (26%)	15 (74%)
$\geq 11$	6	4 (67%)	2 (33%)

484 **US-CD, ultrasonographical scoring system for Crohn's disease; SES-CD, simple endoscopic score for Crohn's disease**

485 The pre-strengthening US-CD and SED-CD values show that the US-CD values were higher than the SES-CD values

486

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489



491 **Figure legends**

492

493 **Figure 1. Grading system of color Doppler signal**

494 The examples of the semi-quantitative grading system of the color Doppler signals in  
495 the intestinal wall. Region of interest is shown as a 1-cm yellow square.

496 (A) Grade 0=no color Doppler signal; (B) Grade 1=few spotty signals; (C) Grade  
497 2=confluent vessel signals in less than half of the area of the bowel wall; (D) Grade  
498 3=confluent vessel signals in more than half of the area of the bowel wall.

499

500 **Figure 2. Correlation between the US-CD and SES-CD**

501 There is a moderate correlation between the US-CD and SES-CD in all patients;  $\rho=0.64$ ,  
502  $p<0.01$  (Spearman's rank correlation coefficient). SES-CD, simple endoscopic scoring  
503 for Crohn's disease; US-CD, ultrasonographical scoring system for Crohn's disease

504

505 **Figure 3. Correlation between the US-CD and CDAI (A) and between the SES-CD  
506 and CDAI (B)**

507 Both showed a positive correlation with the CDAI, although a stronger correlation  
508 was found between US-CD and CDAI. A strong correlation was found with maximum  
509 US-CD and CDAI;  $\rho=0.78$ ,  $p<0.01$  (Spearman's rank correlation coefficient). A  
510 moderate correlation was found between SES-CD and CDAI;  $\rho=0.55$ ,  $p<0.05$   
511 (Spearman's rank correlation coefficient).

512 CDAI, clinical disease activity index; SES-CD, simple endoscopic scoring system for  
513 Crohn's disease; US-CD, ultrasonographical scoring system for Crohn's disease

514

515 **Figure 4. Correlation between BWT and CDAI (A), and between color Doppler**  
516 **grade and CDAI (B)**

517 No significant correlation was identified between maximum BWT and CDAI;  $\rho=0.28$ ,  
518  $p=0.19$  (Spearman's rank correlation coefficient). A strong correlation was found  
519 between maximum color Doppler grade and CDAI;  $\rho=0.73$ ,  $p<0.01$  (Spearman's rank  
520 correlation coefficient).

521 CDAI, Crohn's disease activity index; BWT, bowel wall thickness

522

523 **Figure 5. Crohn's disease in a 20-year-old male patient**

524 This patient had clinically active (CDAI=221) CD, which was characterized by  
525 abdominal pain and diarrhea. In our examinations, the SES-CD and US-CD were 22  
526 and 23 points, respectively.

527 (A) The margin of the transverse colon is marked by arrows. Thickening of the  
528 intestinal wall and significant blood flow in the wall can be observed. (B) Evaluation  
529 of color Doppler signaling: Grade 2. (C) Endoscopic image showing a longitudinal  
530 ulcer (arrow).

531 CDAI, clinical disease activity index; SES-CD, simple endoscopic score for Crohn's  
532 disease; US-CD, Ultrasonographical scoring system for Crohn's disease

533

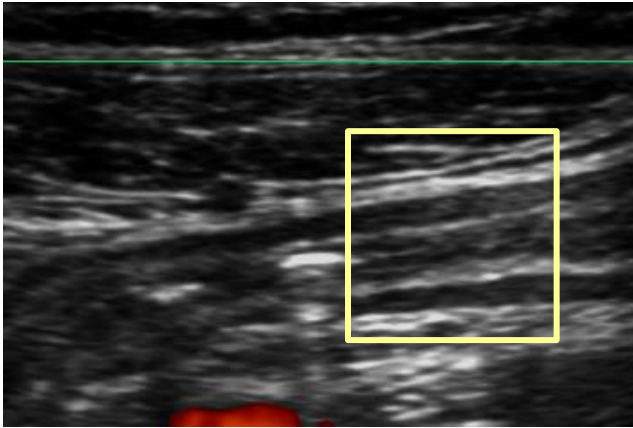
534 **Figure 6. Crohn's disease in a 22-year-old male patient**

535 The patient had clinically active (CDAI=198) CD, which was characterized by  
536 abdominal pain, diarrhea, and joint pain. In our examinations, SES-CD and US-CD  
537 were 2 and 13 points, respectively. US showed CD activity.

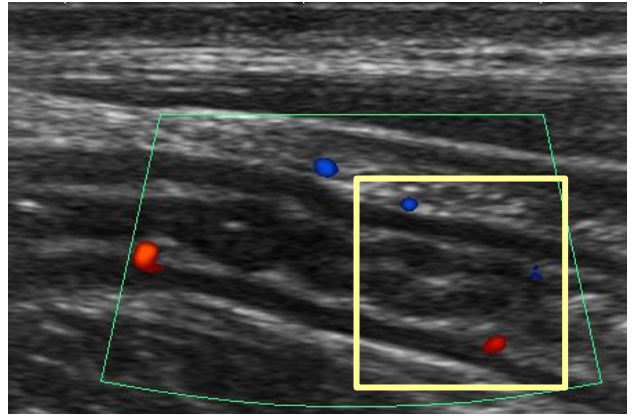
538 (A) The margin of the intestinal tract is marked by arrows. Thickening of the intestinal

539 wall can be observed. The focal disappearance (FD) sign indicates an entire wall layer  
540 of inflammation (yellow circle). (B) Evaluation of color Doppler signaling: Grade 2.  
541 (C) Endoscopic image showing only aphthae (arrow).

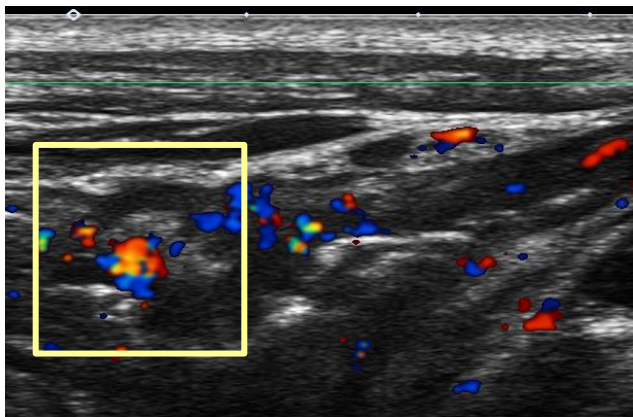
**A** Grade 0



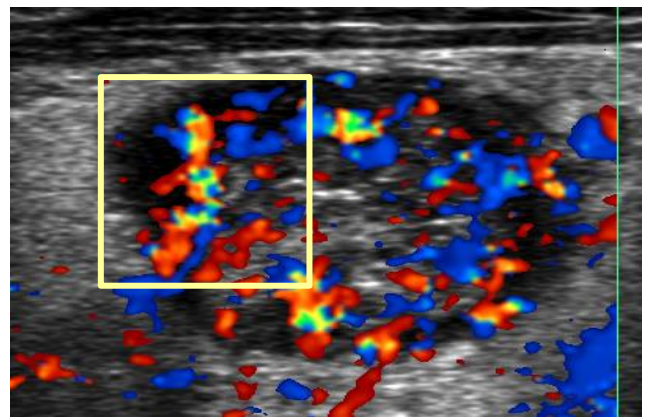
**B** Grade 1

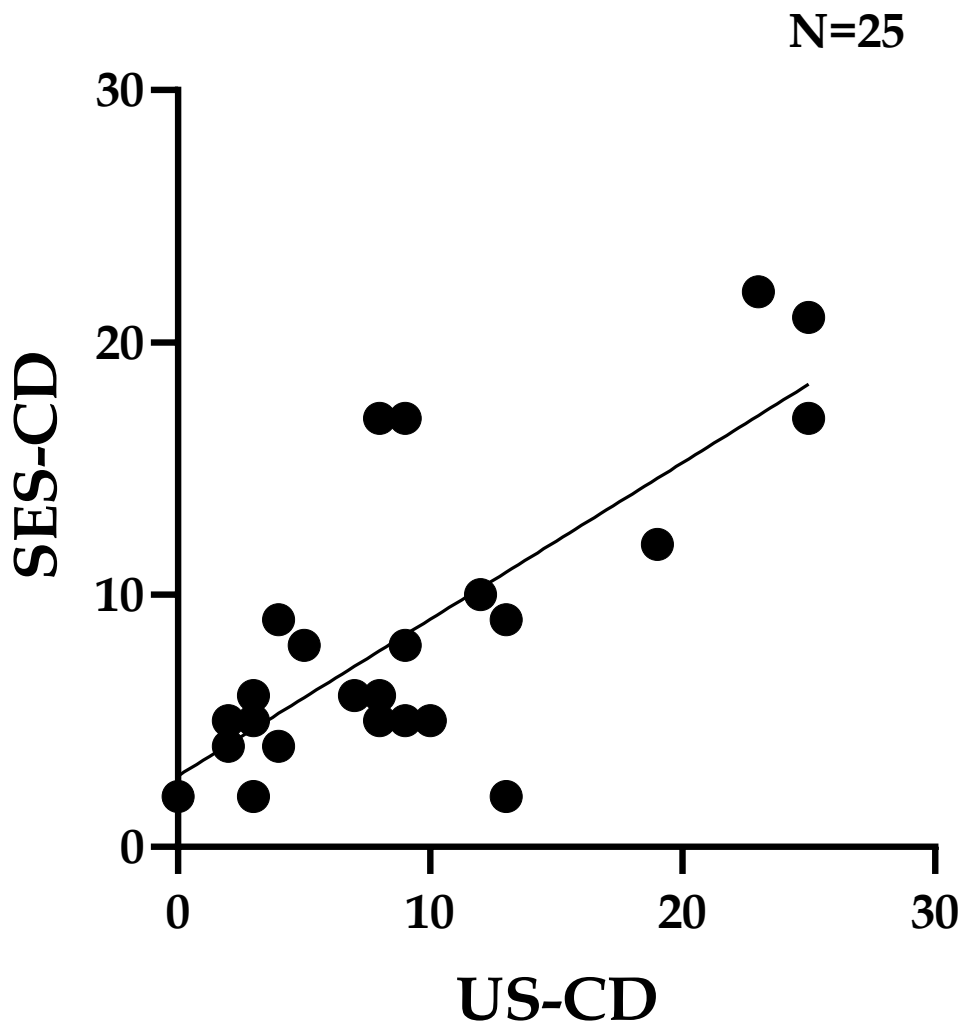


**C** Grade 2

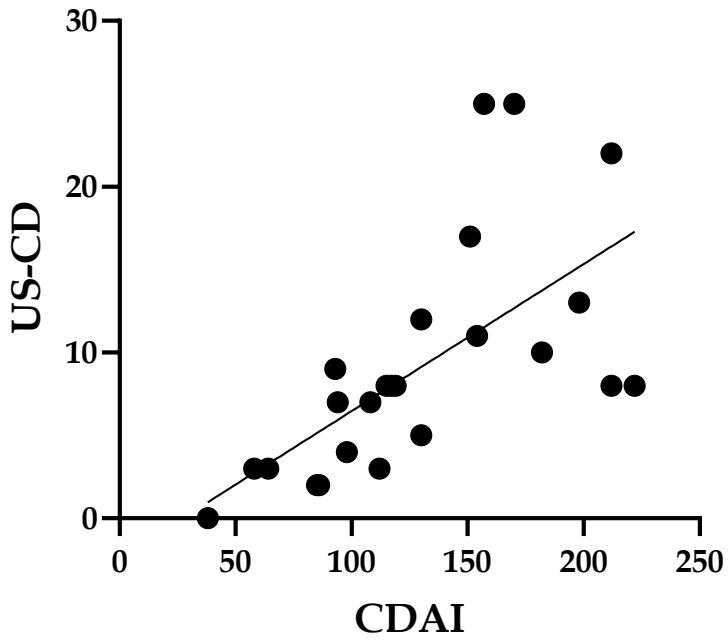


**D** Grade 3

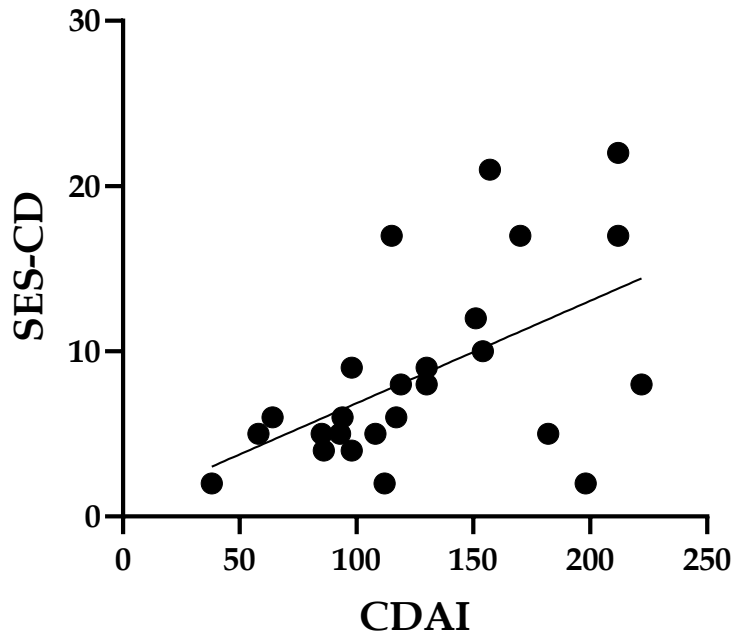


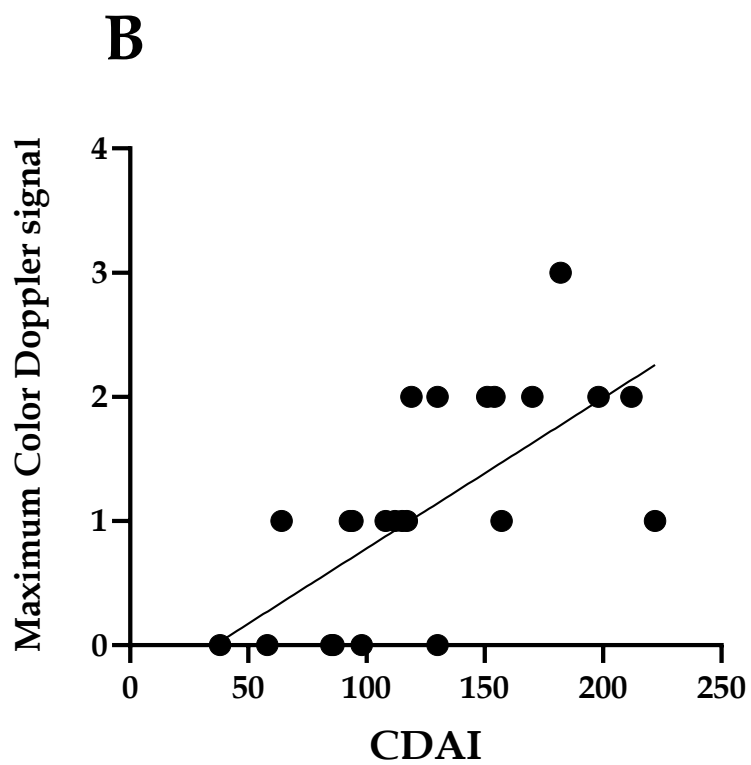
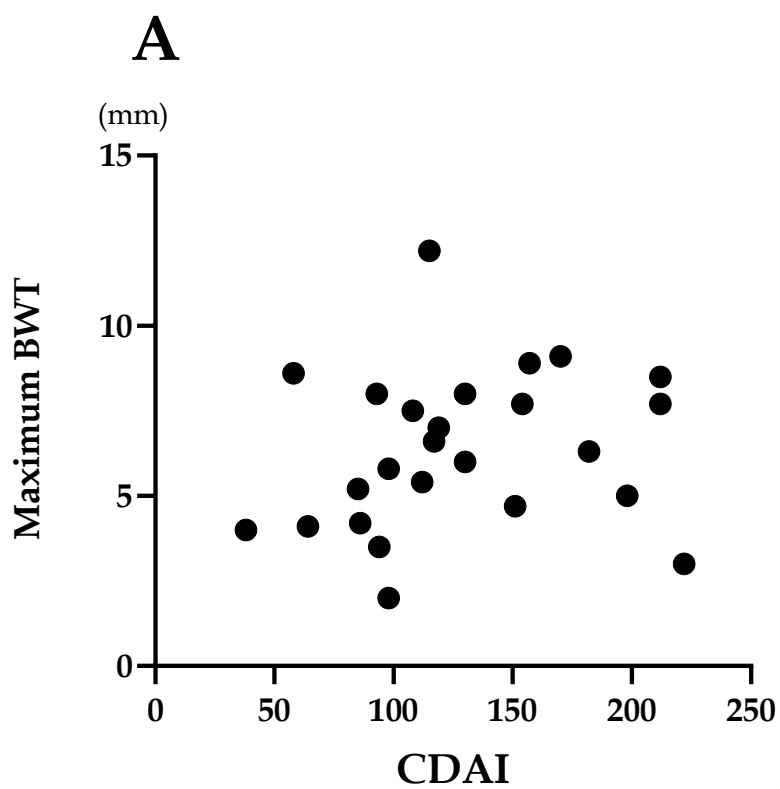


**A**

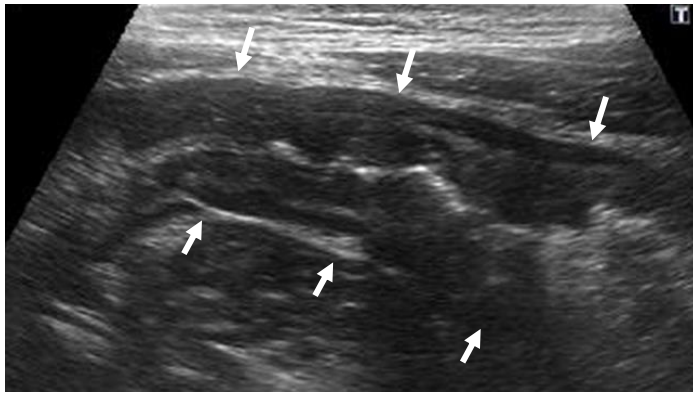


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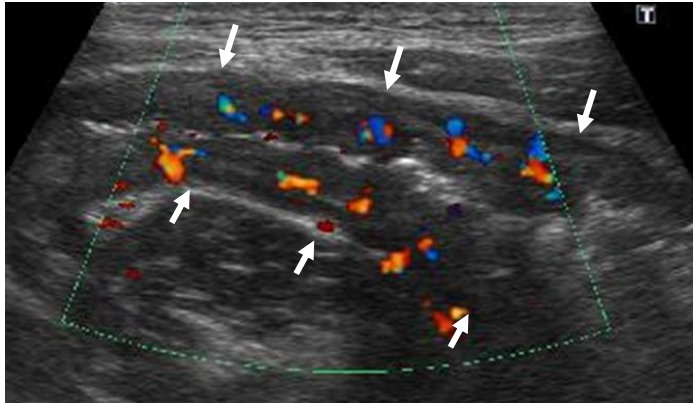




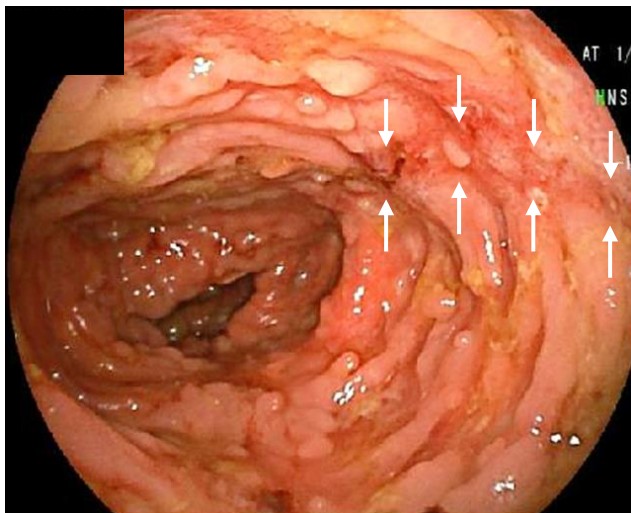
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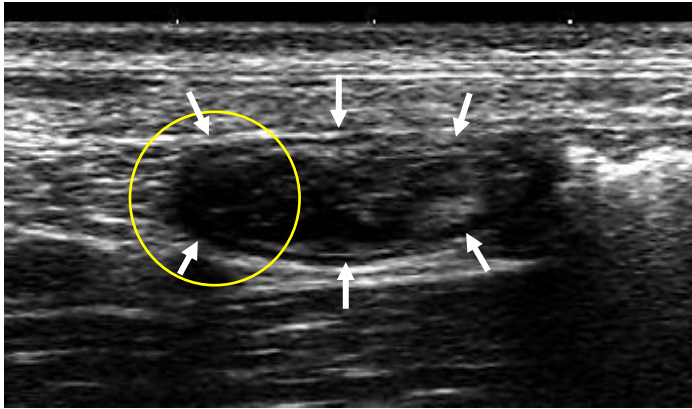
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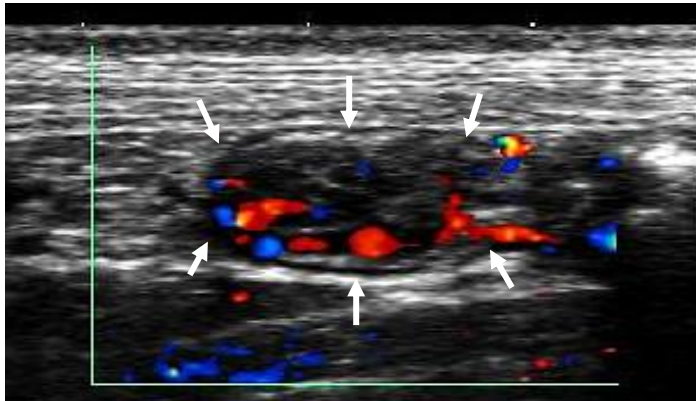
**C**



**A**



**B**



**C**

