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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

6

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29

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 ± 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 anus¹. Characteristic abdominal symptoms are abdominal pain, diarrhea, and
58 bloody stool, and as the disease progresses, it causes stenosis, fistula formation, and
59 intestinal perforation². Approximately half of all patients with CD undergo surgery
60 within 10 years of disease diagnosis². Conversely, mucosal healing can be considered
61 a sign of relapse-free remission. The appropriate evaluation is vital to the
62 improvement of patient prognosis³. 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 CD¹, and the procedure is very
66 invasive for patients⁴. 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 useful⁵. CT enterography
71 with an intravenous contrast agent, intestinal wall thickness and perfusion can be
72 evaluated in detail⁶⁻⁷. 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 dosage⁸. MRE, in contrast, presents no radiation exposure
75 and is often used to monitor the disease activity in inflammatory bowel disease¹.
76 However, only a limited number of institutions have the equipment, procedural
77 throughput is low, expensive, and the methodology has yet to be standardized⁹.

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 fibrosis¹⁰ .

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 activity¹¹⁻¹³, studies compared it with contrast imaging, CT,
85 MRI¹⁴, ICS² and Crohn's disease activity index (CDAI) scores were reported¹⁵⁻¹⁸.

86 In recent years, the double-balloon endoscopy (DBE) enabling the accurate
87 observation of small bowel lesions in CD¹⁹, 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.^{16,20-21}. Validated
90 comprehensive scoring system of US findings have yet been reported at the time of
91 starting our study²².

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-CD²³⁻²⁴, 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 activity²⁵. 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 disease¹⁷ (Table 1). Disease was classified as
117 clinically active if CDAI >150, a value that has been previously validated¹⁷. 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 previously²⁶. 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^{7-8,15,26}.

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 ≥ 11 was
160 also defined as moderately active, because SES-CD ≥ 11 indicates a moderately active
161 disease^{7,27}.

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 ≥ 20 ²⁷. A SES-CD score of ≥ 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 ≥ 11 was found in 6 patients, SES-CD
224 score of ≥ 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 ≥ 11 and/or SES-CD. Patients with US-CD score ≥ 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 ≥ 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 ²⁸⁻³⁰.

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 signals³¹⁻³². In this case, decorrelation occurs. The blood flow signals
245 would be a more accurate evaluator of active inflammation³ 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 ≥ 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 ≥ 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 ≥ 11 , and 6 of 7
270 patients had a US-CD score ≥ 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 ≥ 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 emerge²⁹⁻³⁰. 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^{4,5}. 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 ¹.
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 ^{16-17,30}. 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 challenging³³, 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^{25,34} 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 facilities³⁵. 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

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335

336

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

Clinical or laboratory variable	Weighting factor
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)**

US-CD scoring system				
Parameters	0	1	2	3
Bowel wall thickness (mm)	<3	$3 \leq$ and <5	$5 \leq$ and <7	$7 \leq$
Loss of stratification	Absent	-	Present	-
Presence of stenosis	-	Single, fluid can be passed	Multiple, fluid can be passed	Fluid cannot be passed (to and fro)
Color Doppler signal	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
Increasing mesenteric fat tissue echogenicity	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
Size of ulcers (cm)	None	Aphthous ulcers (diameter 0.1-0.5)	Large ulcers (diameter 0.5-2)	Very large ulcers (diameter >2)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Presence of narrowing	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	ρ	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	ρ	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
Correlation with maximum color Doppler signal and SES-CD		
Intestinal segment	ρ	p
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
Correlation with other maximum US parameters and SES-CD		
US parameters	ρ	p

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

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
≤ 10	18	3 (17%)	15 (83%)
≥ 11	7	6 (86%)	1 (14%)

SES-CD	Number of patients	Need to strengthen treatment	No need to intensify treatment
≤ 10	19	5 (26%)	15 (74%)
≥ 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

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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

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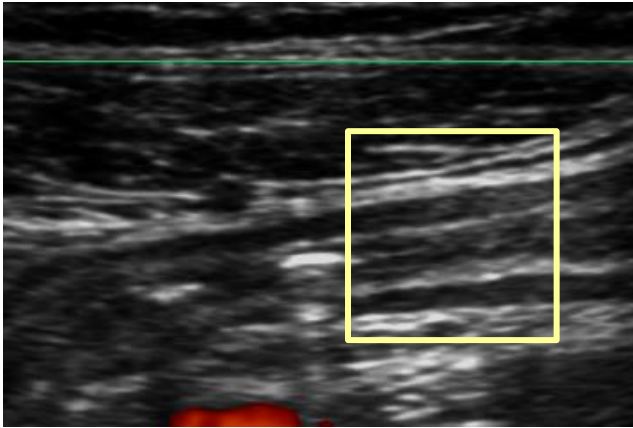
534 **Figure 6. Crohn's disease in a 22-year-old male patient**

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.

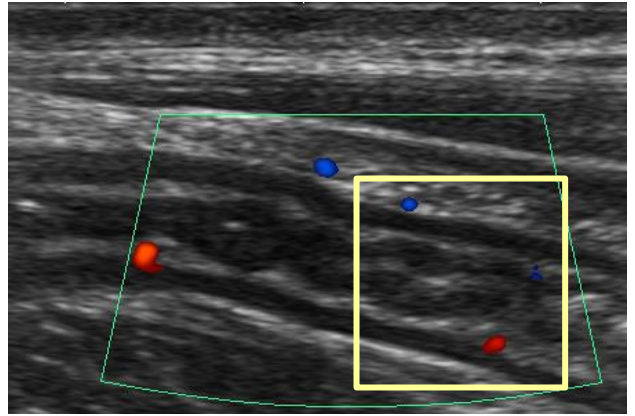
538 (A) The margin of the intestinal tract is marked by arrows. Thickening of the intestinal

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).

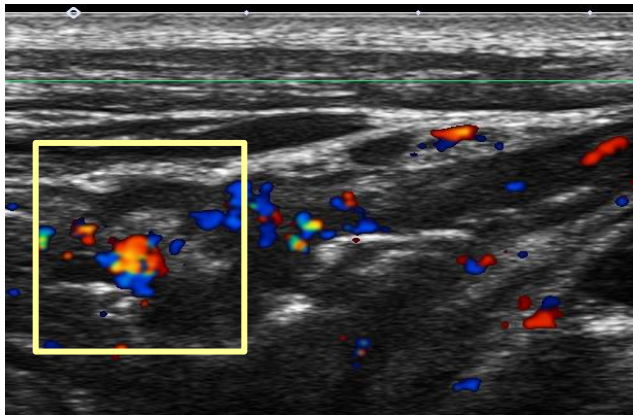
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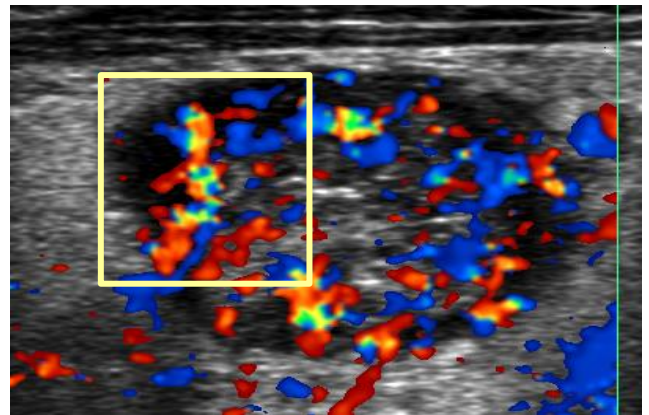
B Grade 1

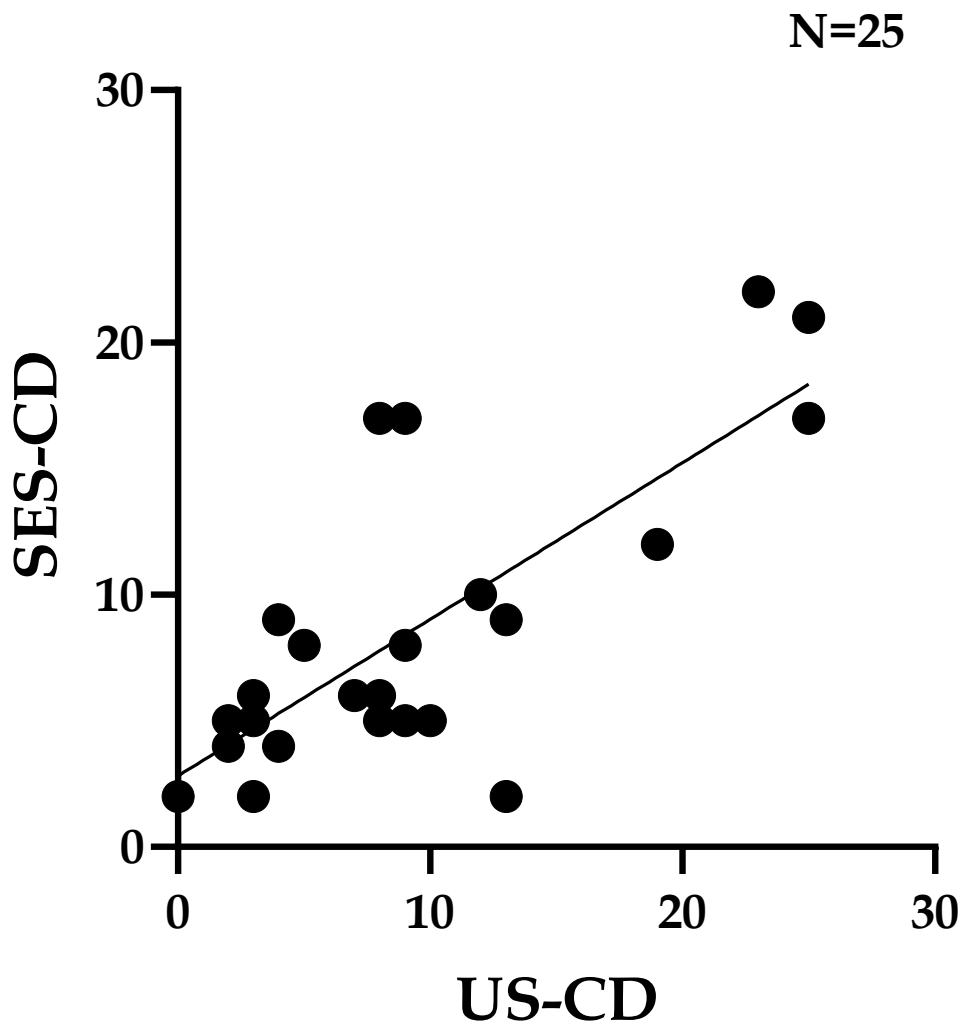


C Grade 2

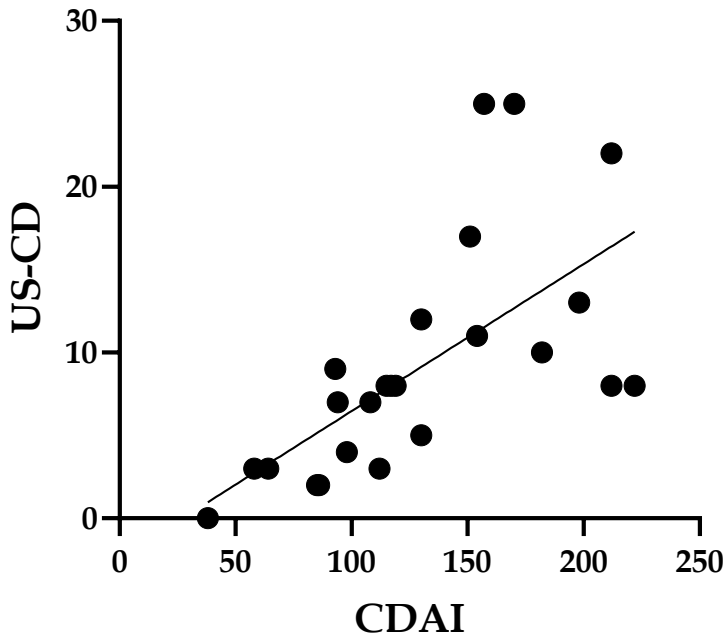


D Grade 3

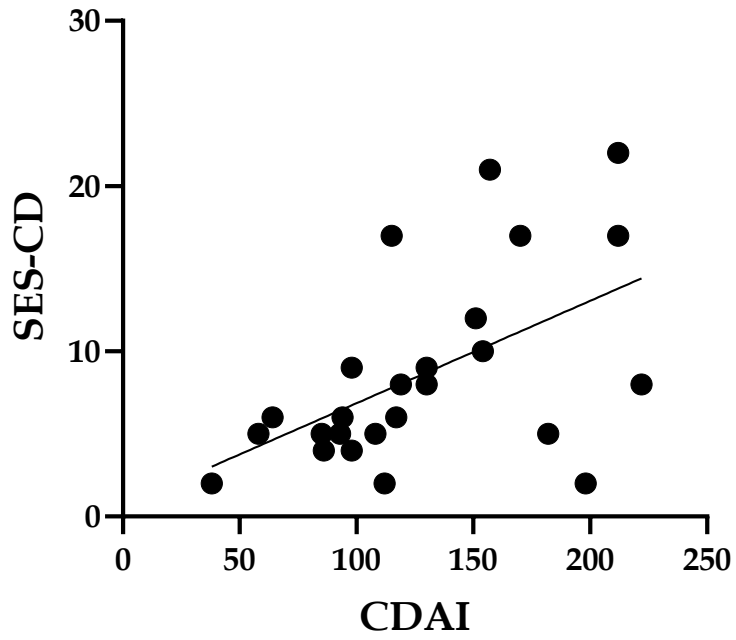


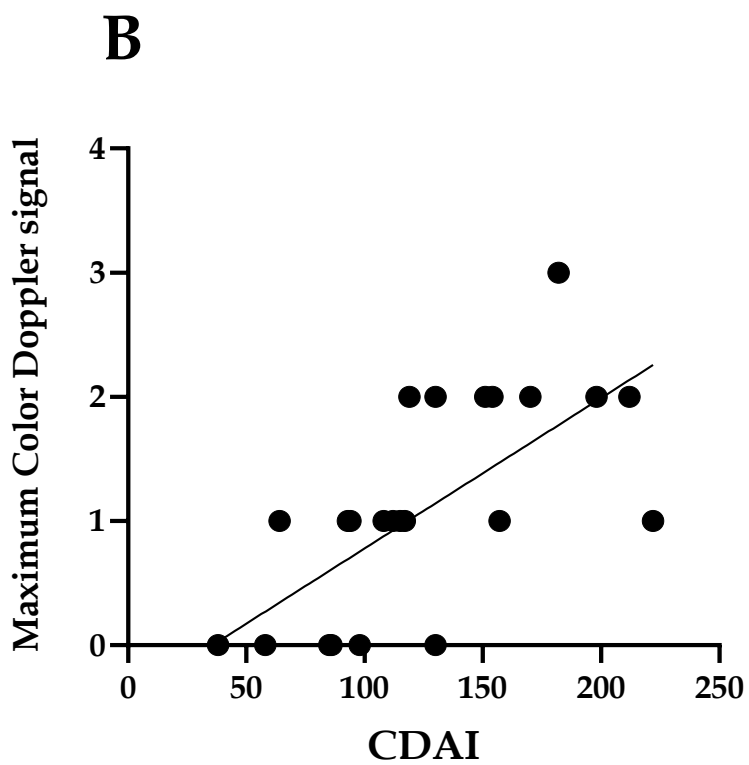
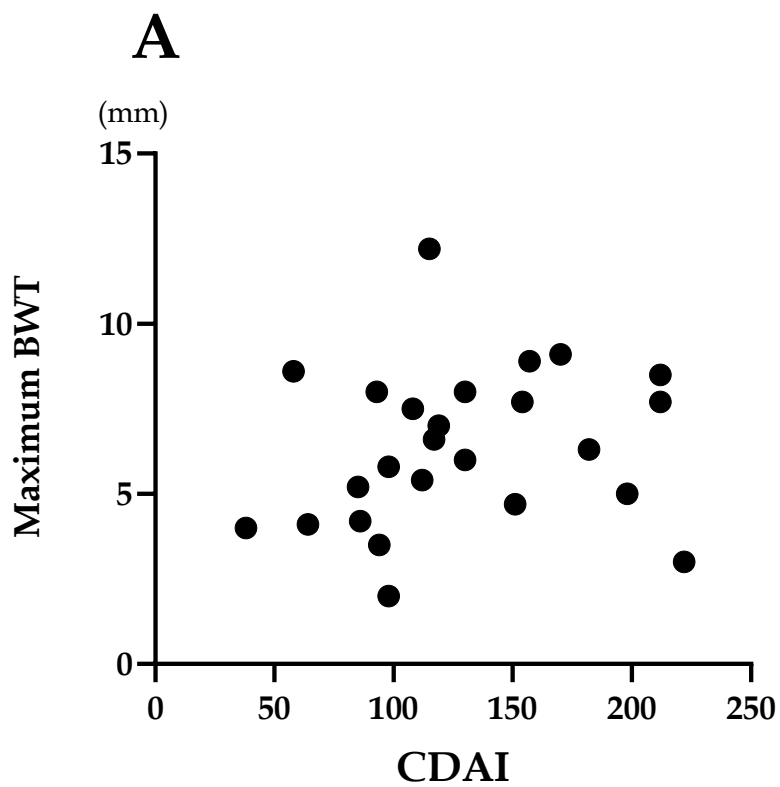


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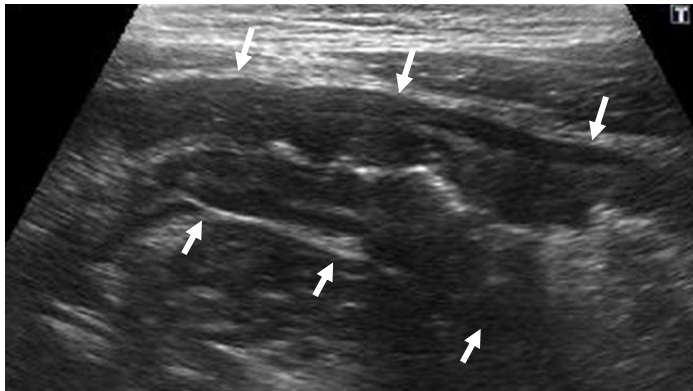


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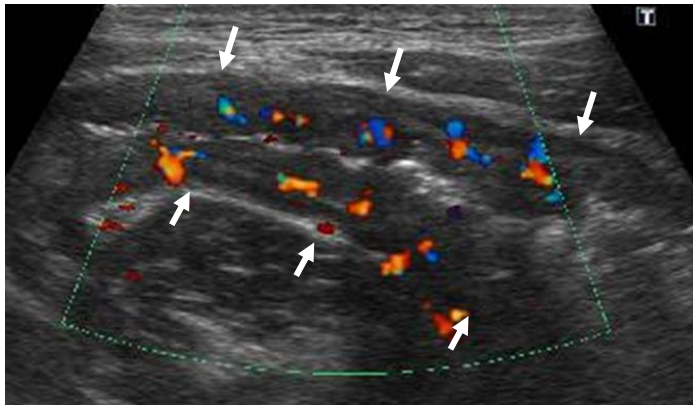




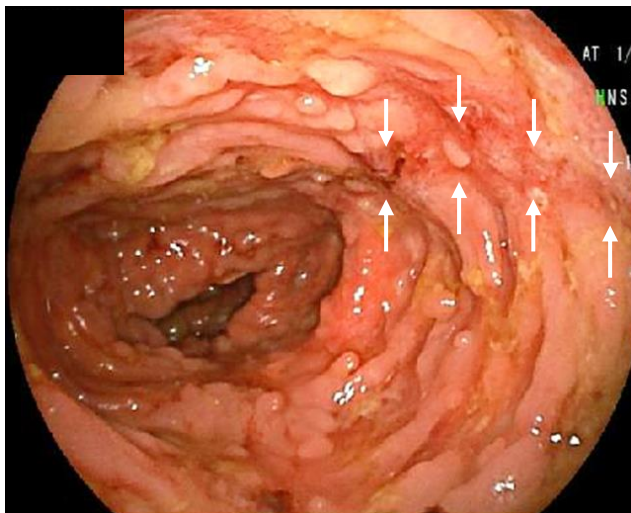
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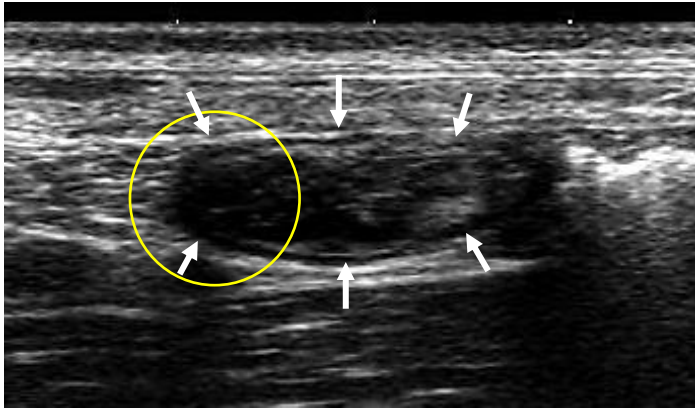
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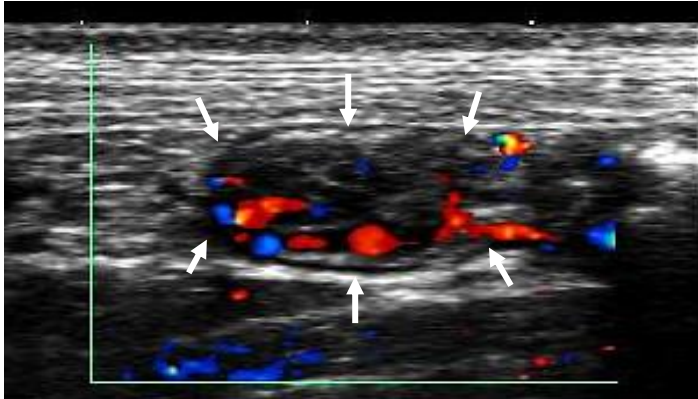
C



A



B



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