**Original Research**

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

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

Kana Yamanashi, MD, PhD[1], Takehiko Katsurada[1] MD, PhD, Mutsumi Nishida[2] PhD, Reizo Onishi[1] MD, PhD, Satomi Omotehara[2], PhD, Shinsuke Otagiri[1] MD, Kensuke Sakurai[1] MD , Kazunori Nagashima[3] MD, PhD, Kenji Kinoshita[4] MD, PhD, Ryo Takagi[5], PhD, Naoya Sakamoto[1] MD, PhD

[1]Department of Gastroenterology and Hepatology, Hokkaido University Faculty of Medicine and Graduate School of Medicine, Sapporo, Japan

[2]Division of Laboratory and Transfusion Medicine/Diagnostic Center for Sonography, Hokkaido University Hospital, Sapporo, Japan

[3]Department of Gastroenterology, National Hospital Organization Hokkaido Medical Center, Sapporo, Japan

[4]Department of Gastroenterology, Hakodate Municipal Hospital, Hakodate, Japan

[5]Clinical Research and Medical Innovation Center, Hokkaido University Hospital, Sapporo, Japan

**Corresponding author: Takehiko Katsurada, MD, PhD**, Division of Gastroenterology and Hepatology/Inflammatory Bowel Disease Group, Hokkaido

University Hospital, Sapporo 0608648, Hokkaido, Japan.

Email: tkatsu@med.hokudai.ac.jp

Tel.: +81-11-706-7715

Fax: +81-11-706-7867

**Abstract**

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

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

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

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

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

## INTRODUCTION

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

Also, allergies and contrast induced nephropathy in patients with an impaired renal function are the risks of contrast media administration in CT and magnetic resonance imaging (MRI). Contrast administration in MRI is restricted in patients with renal insufficiency due to the risk of nephrogenic systemic fibrosis[10] .

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

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

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

Therefore, we aimed to evaluate the correlation between our newly developed ultrasonographical scoring system for Crohn's disease (US-CD) and SES-CD[23-24], and CDAI in evaluating CD activity.

## MATERIALS AND METHODS

*Study protocol*

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

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

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

*Transabdominal US*

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

We followed a systematic scanning protocol for evaluation of entire colon which was published previously[26]. After scanning the colon, the terminal ileum was then identified by the ileocecal valve, after which the ileum was followed as far as possible in the oral direction.

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

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

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

We scored the US severity as 0–52, calculating the following US parameters: bowel wall thickness (BWT) (0–3), loss of stratification (0–2), degree of blood flow signaling by a color Doppler study (0–3), presence of increasing echogenicity mesentery (0–2), and intestinal stenosis (0–3) (Table 2). The US-CD score of ≥11 was also defined as moderately active, because SES-CD ≥11 indicates a moderately active disease[7,27].

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

*DBE*

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

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

The SES-CD was defined as follows: inactive 0–3, mild 4–10, moderate activity 11–19, and high activity ≥20[27]. A SES-CD score of ≥11 was defined as endoscopically active. All endoscopic findings were evaluated by two experienced gastroenterologists (TK and RO), each with >6 years of experience. They were blinded to the patient's clinical records and US findings.

*Statistical analysis*

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

## RESULTS

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

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

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

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

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

(ρ=0.55, p<0.05; Figure 3B) (Spearman's rank correlation coefficient).

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

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

## DISCUSSION

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

significantly with the SES-CD. Previous reports similarly indicated that BWT and increased blood flow signals correlated with the CDAI [28-30].

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

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

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

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

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

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

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

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

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

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

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

## Conflicts of interest

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

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**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 |

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

**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≦ and <5 | 5≦ and <7 | 7≦ |
| **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 | − |

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

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

| | SES-CD values | | | |
|---|---|---|---|---|
| **Variables** | **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 |

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

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 |

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

Among the US parameters, the maximum BWT and maximum color Doppler flow were also correlated with the US-CD and SES-CD. The maximum BWT and maximum color Doppler flow showed a moderate or higher correlation in all intestinal segments

**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%) |

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

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

490

## Figure legends

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

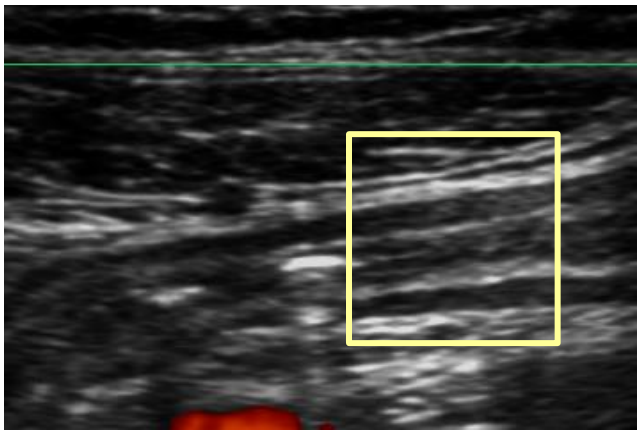
**Figure 6. Crohn's disease in a 22-year-old male patient**

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

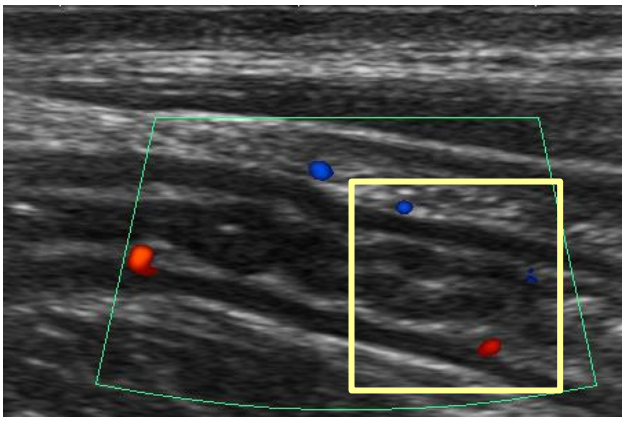
(A) The margin of the intestinal tract is marked by arrows. Thickening of the intestinal

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

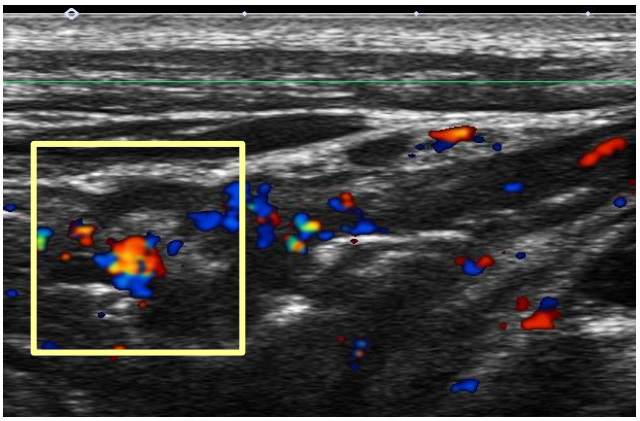
A Grade 0



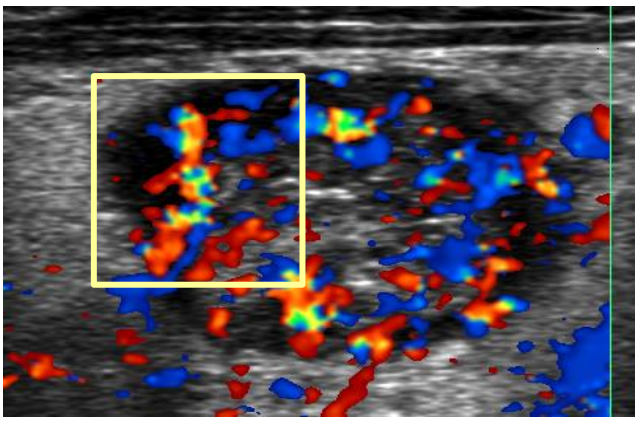
B Grade 1

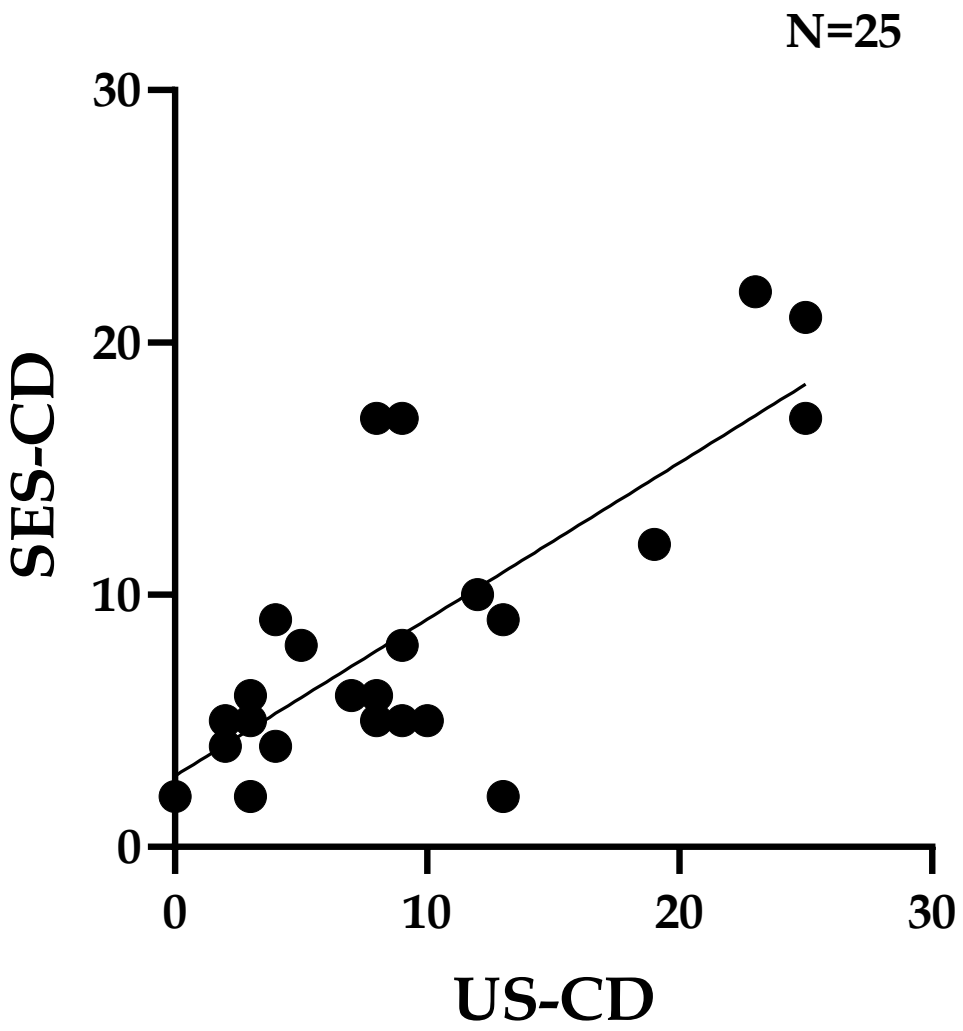


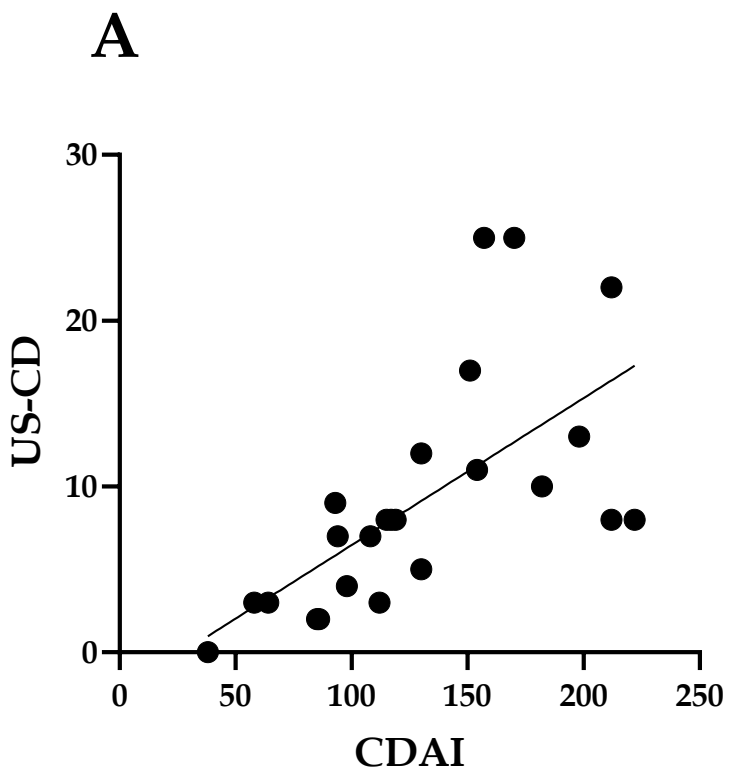
C Grade 2

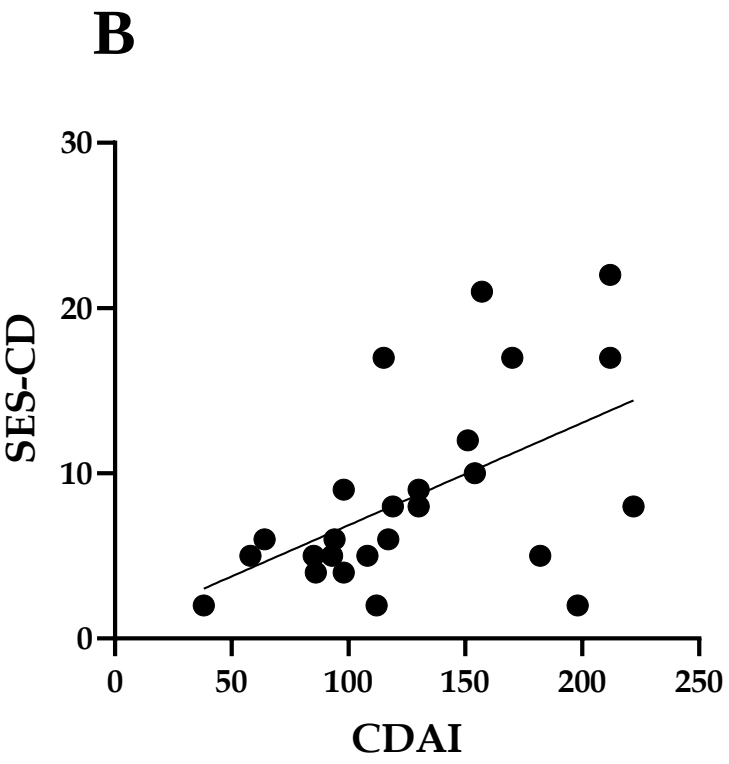


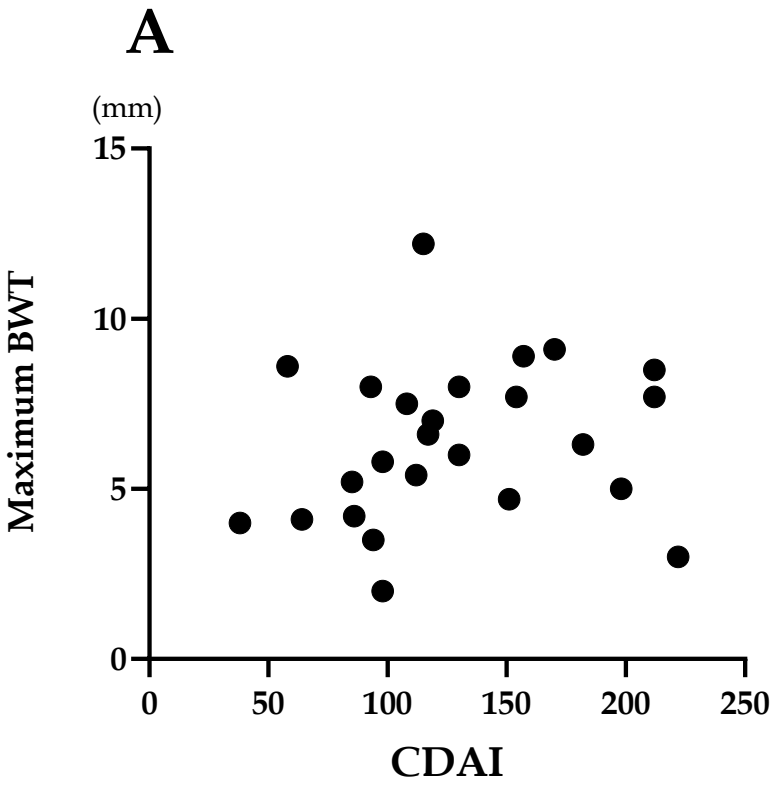
D Grade 3

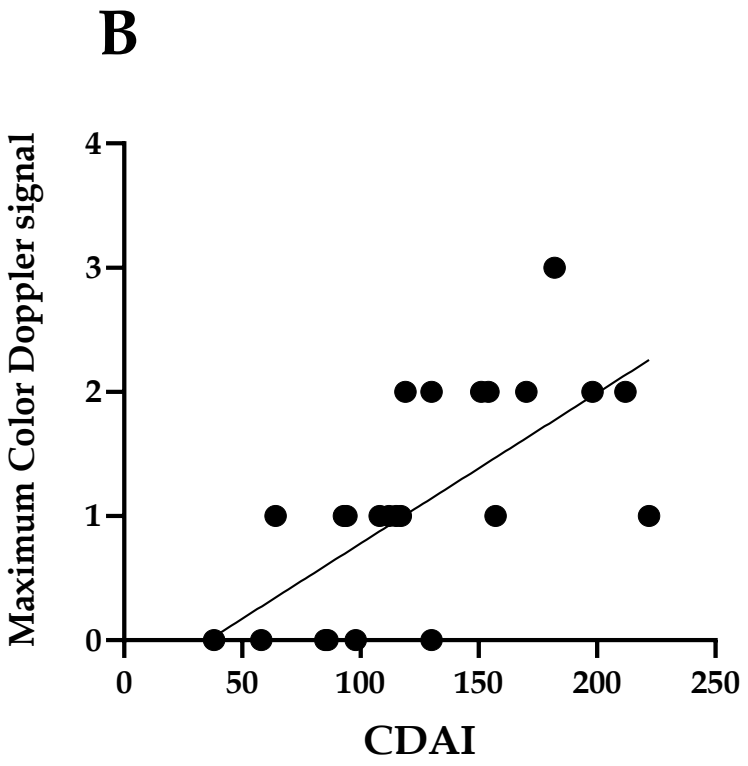



N=25
30
20
10
0
SES-CD
0
10
20
30
US-CD

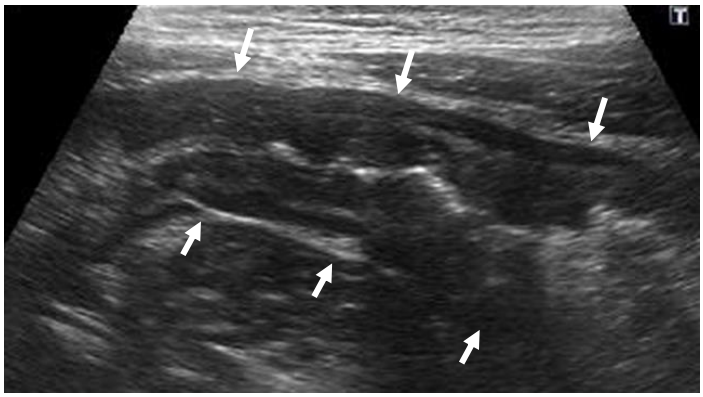

A
30
20
10
0
US-CD
0
50
100
150
200
250
CDAI


B
30
20
10
0
SES-CD
0
50
100
150
200
250
CDAI

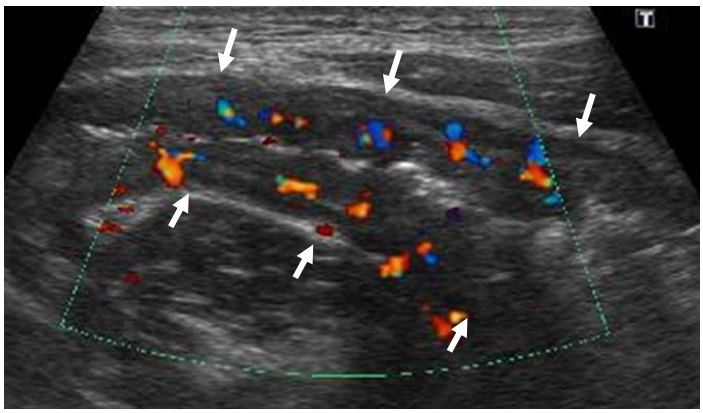

A
(mm)
Maximum BWT
15
10
5
0
0
50
100
150
200
250
CDAI


B
Maximum Color Doppler signal
4
3
2
1
0
0
50
100
150
200
250
CDAI

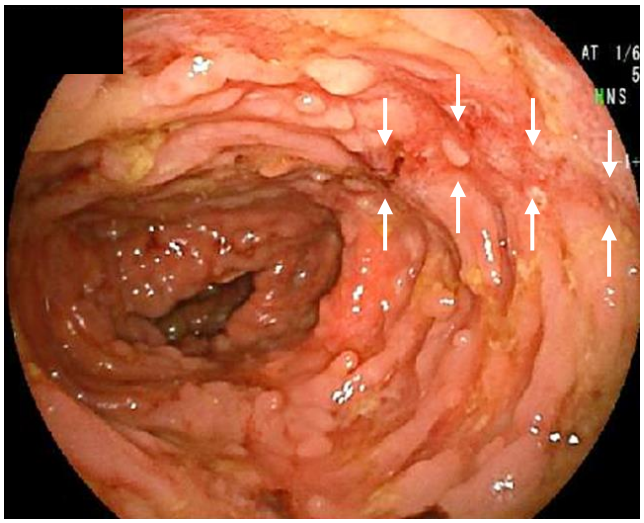
A



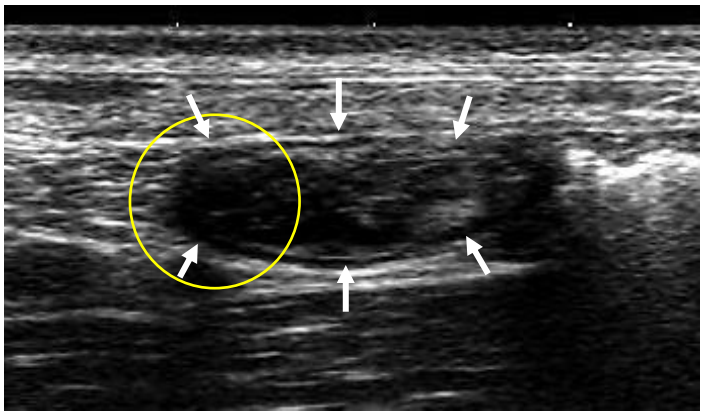
B



C



A



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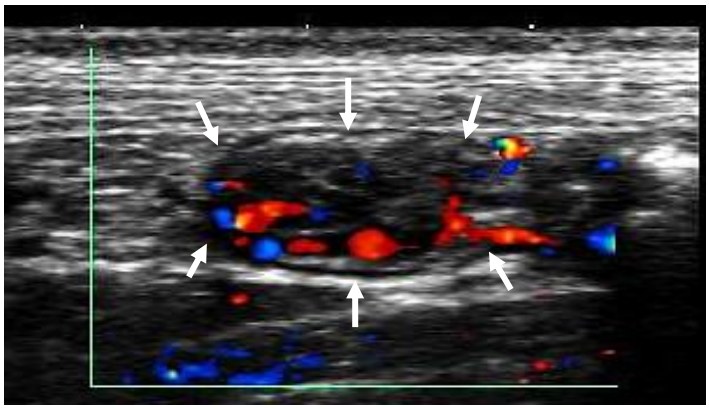

C