Gastrointestinal ultrasound can predict endoscopic activity in Crohn's disease

Fredrik Sævik[1,2], Odd Helge Gilja[2,1], Kim Nylund[2,1]

[1]Department of Clinical Medicine, University of Bergen, Bergen, Norway
[2]National Centre for Ultrasound in Gastroenterology, Haukeland University Hospital, Bergen, Norway

Corresponding author: Fredrik Sævik, MD, Department of Clinical Medicine, University of Bergen, Haukeland University Hospital, Jonas Lies vei, 5021 Bergen, Norway. Tel.: +47 40 01 39 10; email: fredrik.savik@gmail.com.

Abstract

Purpose: To explore the ability of gastrointestinal ultrasound (GIUS) to separate patients in endoscopic remission from patients with active disease in a heterogenous hospital cohort with CD.

Material and Methods: 145 CD patients scheduled for ileocolonoscopy were prospectively included. The endoscopic disease activity was quantified using the Simple Endoscopic Score for Crohn's disease (SES-CD), and mucosal healing was strictly defined as SES-CD=0. Ultrasound remission was defined as wall thickness <3 mm (<4 mm in the rectum). Additionally, SES-CD was compared to colour Doppler, Harvey Bradshaw's index (HBI), C-reactive protein (CRP) and calprotectin. 23 patients were examined by two investigators for interobserver assessment.

Results: 102 had active disease and 43 patients were in remission. GIUS yielded a sensitivity of 92.2% and specificity of 86% for wall thickness and sensitivity 66.7% and specificity 97.7% for colour Doppler. For HBI sensitivity was 34.3% and specificity 88.4%, CRP sensitivity 35.7% and specificity 82.9% and calprotectin sensitivity 55.9 % and specificity 82.1%. The interobserver analysis revealed excellent agreement for wall thickness- (k=0.90) and colour Doppler (k=0.91) measurements.

Conclusion: GIUS has a high sensitivity for detecting endoscopic activity. Accordingly, bowel ultrasound has the potential to reduce the number of routine ileocolonoscopies in patients with CD.

Keywords: Crohn's disease, mucosal healing, gastrointestinal ultrasound

Introduction

Crohn's disease (CD) is characterized by alternating periods of remission and disease flare-ups, requiring subsequent adjustments of medical therapy. However, there is a lack of correlation between patients' symptoms and inflammatory activity [1], putting patients at risk of receiving wrong treatment. Persistent inflammation may be present during clinical remission allowing for development of complications, ultimately leading to irreversible bowel damage [2]. Consequently, new treatment goals have emerged from symptomatic control to objective endpoints, where mucosal healing (MH) evaluated by ileocolonoscopy is considered the main therapeutic target. Current evidence suggests that patients achieving MH experiences less hospitalization, relapse rates, surgery and bowel damage, which may alter the natural disease course [3].

Endoscopic remission is usually defined as absence of ulcerations at ileocolonoscopy or as a score of 0-2 using the Simple Endoscopic Score for Crohn's Disease (SES-CD) [4]. However, previous work suggest that patients with complete absence of endoscopic inflammation reflected by a SES-CD score of 0 points have the best prognosis [5]. On the downside, ileocolonoscopy is invasive, resource intensive, and patients are reluctant to undergo frequent examinations. Thus, non-invasive markers for measuring disease status are warranted.

Faecal calprotectin is a well-established biomarker of intestinal inflammation that correlates well with endoscopy and may be useful in discriminating between active and inactive disease [6]. Still, higher accuracies are achieved in ulcerative colitis than CD [7] as well as in colonic versus small bowel CD [8].

Cross-sectional imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound (US) are important tools in CD assessment, enabling detection of location, complications and extent, as well as disease activity evaluation [9]. Due to radiation exposure of CT, it is recommended that MRI and US are used in follow-up examinations [9]. Recent studies demonstrate that MRI is accurate for evaluating ulcer healing and endoscopic remission [10], and may thus gain further importance in the treat-to-target era. Still, it is resource intensive, requires specific preparations and has relatively low availability.

Ultrasound is non-invasive, well tolerated by patients and can be performed bedside, making the modality well suited for repeated examinations. As numerous follow-up examinations for monitoring disease status are needed, gastrointestinal ultrasound (GIUS) might be an attractive modality. GIUS has high diagnostic accuracy for detecting CD [11], where increased bowel wall thickness (BWT) is the most important and common ultrasonographic parameter [12]. Previous studies showed that ultrasonographic changes during medical treatment correlates with endoscopic response and may provide measurements of MH [13-15]. These studies evaluate post-therapeutic changes in patients with active CD, thus, the usefulness of ultrasonography in different disease statuses remains unknown. In this study, we aimed to explore the ability of GIUS to separate patients in endoscopic remission from patients with active disease in a heterogeneous hospital cohort with CD.

Material and methods

Patients and design:

145 patients with established CD were prospectively recruited in a single-centre cross-sectional study, from 2015 to 2019. Each patient was scheduled for ileocolonoscopy as part of routine work at the hospital. Included patients underwent clinical scoring, blood and stool sampling as well as ultrasound examination. Exclusion criteria were age <18 years, pregnancy, previous colectomy, isolated disease in the upper GI tract or ongoing gastroenteritis.

Clinical and biochemical tests

Patient history, demographics and phenotype, according to the Montreal classification [16] , were recorded on each study participant. Harvey Bradshaw Index (HBI) [17] was used to evaluate clinical disease activity. The biochemical markers haemoglobin (g/dL), leucocyte- (10^9/L) and platelet (10^9/L) count, C-reactive protein (CRP) (mg/L) and albumin (g/L) were measured from blood samples, while stool samples were analysed for calprotectin (mg/kg). The biochemical tests were sampled within one week prior to or after the ultrasound examination. Clinical remission was considered as HBI <5 points, while calprotectin < 50 mg/kg and CRP <5 mg/L were defined as biochemical remission.

Endoscopy

Ileocolonoscopy was performed as part of standard care by 20 endoscopists with approximately 1-30 years of experience. Disease activity measurements were assessed using the SES-CD. This scoring system evaluates the severity of CD-lesions by creating a numerical value of 0-3 in four parameters (ulcer size, ulcerated surface, affected surface and stenosis), summarized in five bowel segments (rectum, left colon, transverse colon, right colon and the terminal ileum). Then, segmental- and total endoscopic activity can be quantified [18]. Although endoscopic remission is commonly considered as SES-CD 0-2 [4], validated scores of MH are lacking [19]. Furthermore, as long-term prognosis seems to improve when there is no macroscopic inflammation [5], we used a strict definition of endoscopic remission as SES-CD=0. In addition, all patients were scored for the presence or absence of ulcerations.

Ultrasound examination

The ultrasound examinations were performed within two weeks prior to or after the endoscopic procedure, with no treatment alterations between the examinations. Ultrasonography was not performed during bowel preparation or just after ileocolonoscopy as the intestine usually collapses, making standardization more complicated. Patients were examined after an overnight fast with no further bowel preparations. GIUS was performed using a Logiq E9 ultrasound scanner (GE Healthcare, Milwaukee, Wisconsin, USA), equipped with a curvilinear transducer (C1-6, 1-6 MHz) for abdominal overview and a linear probe (9L, 5.5-9 MHz) for detailed examinations of the bowel wall. The GIUS examinations

were performed by two investigators with 2 and 13 years of experience, and interobserver assessments were performed in a subgroup of the included patients.

The GIUS examinations were performed on bowel segments available for ileocolonoscopy. The examination of the large bowel was performed by scanning systematically from the terminal ileum and further distally in longitudinal section, as recommended in international guidelines [20]. All BWT measurements were performed perpendicular to the anterior wall in longitudinal section, measured from the start of the hypoechoic proper muscle layer to the end of the hypoechoic mucosal layer [20], and two representative measurements were averaged. Remission was defined as a BWT <3 mm in both colon and terminal ileum (Fig.1) [12], while a cut-off of <4 mm was used in the rectum.

Colour Doppler was performed only on intestinal segments with pathological wall thickness. The velocity scale was adjusted to 5 cm/s for detection of vessels with low blood flow velocities. Gain was increased until flash artefacts occurred and then lowered until the artefacts disappeared. The acquisition was performed during patient breath-hold. Colour Doppler was evaluated by counting the number of Doppler signals per cm^2 using a modified version of [21], where 0-1, 2-5 and >5 signals were scored as 0, 1 and 2, respectively. Remission was defined as a Doppler score of 0, while activity defined as 1-2.

The study investigators were blinded to the results from the corresponding ileocolonoscopy but knew the Montreal classification and HBI.

Statistics

Demographical data were analysed using descriptive statistics and tested for normality by inspecting histograms as well as using the Shapiro-Wilk test. Comparison between patients in endoscopic remission and activity was performed using the Student's T-test or the Mann-Whitney U-test for continuous variables, while Chi-square- and Fischer exact test were used for categorical variables. Diagnostic accuracy of GIUS, CRP, calprotectin and HBI were calculated in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and total accuracy. Further, evaluation of interobserver agreement as well as concordance between endoscopy and clinical-, biochemical- and ultrasonographic parameters were performed using Cohen's kappa. Kappa statistics considers the amount of agreement that may occurred by chance, interpreted as poor if <0, slight if 0-0.2, fair if 0.21-0.4, moderate if 0.41-0.6, substantial if 0.61-0.8, and excellent if >0.8 [22]. The agreement between GIUS and ileocolonoscopy was evaluated per patient. Finally, the BWT and colour Doppler measurements were correlated with SES-CD in the corresponding segments using Spearman Rank. The level of significance was $p<0.05$. All statistical analyses were performed using SPSS software version 25 (IBM Inc., Armonk, NY, USA).

Ethical consideration

The study was approved by the Regional Ethics Committee for Medical and Health Research in Western Norway, and patients gave written informed consent prior to participation.

Results

102 patients had active disease and 43 patients were in endoscopic remission. There were no significant differences in demographics between the activity- and remission groups, except for CRP, calprotectin and HBI (Tab. 1), as well as disease behaviour and previous surgery (Tab. 2). There were significant differences ($p<0.001$) (Student's T test) between the thickest wall section in the activity group (5.3 mm ± 1.7 SD) and each segment in the remission group (ileum: 2.0 mm ± 0.7 SD, right colon: 1.3 mm ± 0.4 SD, transverse colon: 1.3 mm ± 0.5 SD, left colon 1.7 mm ± 0.7 SD, rectum: 2,6 mm ± 0.6 SD). Further patient characteristics are presented in Tab. 1 and 2.

Ultrasonographic measurements of BWT >3mm yielded a sensitivity of 92.2% and a specificity of 86% to detect endoscopic activity. By increasing the threshold to >4mm BWT, a sensitivity of 80.4% and specificity of 90.7% was found. Colour Doppler measurements on pathologically thickened bowel walls provided a sensitivity of 66.7% and specificity of 97.7%. A sub-analysis using presence or absence of ulcerations as endoscopic criterion revealed a sensitivity of 92% and specificity of 56.5% for BWT >3 mm. Further results are presented in Tab. 3.

There were 14 mismatches between GIUS and ileocolonoscopy of which 8 were false negatives (median BWT 2.1 mm, range 1.4 – 2.8 mm). False negative results were due to small aphthous lesions in the terminal ileum in most cases (5/8) each scored as SES-CD=3, one patient had aphthous lesions and oedema in the terminal ileum (1/8) scored as SES-CD=6, while erythema and faded vascular pattern in colon were present in two patients (2/8) scored as SES-CD=1 and 6.

Further, six false positive results were found (median BWT 4.4 mm, range 3.3 – 5.5 mm), of which four located in the terminal ileum (4/6) and two in the colon (2/6). In the terminal ileum, two were considered as mild active lesions, while the remaining two were interpreted as chronic changes after surgical resection in the physicians' report although BWT exceeded 3 mm. The false positive results of the colon (2/6) where considered as mild active lesions. However, all patients with isolated thickening of the colonic wall (n=18) were correctly classified by faecal calprotectin.

The agreement between ileocolonoscopy and ultrasound wall thickness was substantial with a kappa value of 0.772. Corresponding values between endoscopy and colour Doppler, HBI, CRP and calprotectin were 0.53, 0.16, 0.13 and 0.30, respectively (Tab. 3).

The correlation analysis revealed good correlation coefficients between the SES-CD and BWT ($r=0.69$, $p<0.001$), as well as between SES-CD and colour Doppler ($r=0.64$, $p<0.001$).

23 patients were independently examined by two investigators, and the interobserver analysis revealed excellent agreement with kappa values of 0.90 and 0.91 for BWT and colour Doppler, respectively.

Discussion

Our principal finding suggests that wall thickness measured with GIUS is an accurate surrogate marker of endoscopic activity (Fig. 2). The usefulness in daily life is further demonstrated, as real-world data with patients at different disease stages were included.

These results are in concordance with previous reports [11,13,23,24], even if there are some differences in design, ultrasound thresholds and reference standard. To our knowledge, this is the first study comparing the accuracy of BWT measured by GIUS with strictly defined endoscopic remission as SES-CD=0. A recent study by Allocca et al. [24] demonstrated that GIUS achieved high sensitivity (92%) and specificity (100%) in evaluating disease activity defined as the presence of ulcerations >5 mm. Although revealing similar results, the studies are not directly comparable as various reference standards were used. Moreover, the patient populations may differ as their study participants were recruited from a tertiary reference centre. Furthermore, Ripolles et al. [23] demonstrated high positive predictive values for BWT (88.4%) and colour Doppler (97%) to detect endoscopic activity. Although similarities exist, the studies only partly correspond as they used different bowel wall cut-off, endoscopic reference standard (presence and absence of ulcerations) and analysed the diagnostic accuracy per segment. Thus, our results may add to the existing body of evidence as we demonstrate that GIUS is highly accurate to separate remission from minimal endoscopic inflammation.

We found a lower specificity of GIUS than previously reported in the latest meta-analysis [11], which could be due to different definitions of endoscopic activity and patient populations. By increasing the threshold for sonographic activity to 4 mm, a higher specificity was found at the expense of decreased sensitivity and overall accuracy. Although reducing over-diagnosing, patients are then at risk of being undertreated. Therefore, a threshold of 3 mm seems to be an appropriate compromise with high sensitivity as well as acceptable specificity. Furthermore, we found high positive predictive values for all included tests with BWT (3 mm) and colour Doppler being the highest. However, neither ultrasonography nor clinical nor biochemical tests achieved sufficient negative predictive values.

Regular follow-up examinations of patients in remission are recommended for early detection of relapse, requiring escalation of treatment [25]. At outpatient clinics, decision-making is usually limited to clinical assessment accompanied by biochemical samples. Clinical symptoms do not sufficiently measure underlying inflammation [1] while CRP is limited by poor sensitivity [7] and increases in other inflammatory conditions as well. Faecal calprotectin is useful for initial diagnosis and follow-up of CD, and may provide better guidance for treatment decisions compared to symptom-based management [25]. Still, faecal calprotectin is limited by reduced specificity when using common cut-off values [7], and in the small intestine, it may not sufficiently reflect the true severity of the inflammation. Thus, it should be interpreted with caution [7]. In our study, the majority of patients had only terminal ileitis, which could explain why we found a surprisingly low sensitivity for calprotectin. However, higher accuracies were obtained in a subgroup-analysis on patients with colonic affection, confirming that it is more suitable in distal disease. Its optimal use seems to be in monitoring of disease activity, where repeated samples from the same patient are evaluated. However, patient reluctance for providing repeated stool samples limits its utility. This problem was

clearly demonstrated in this study, as patient compliance on delivering faecal samples was poor. In contrast, focused ultrasound examination of the bowel is feasible in the out-patient clinic, and may add important contributions to the overall assessment and clinical decision making [26].

Previous work suggest that colour Doppler sonography or contrast-enhanced ultrasound (CEUS) is useful for detection and evaluations of disease activity [23,27,28]. Even though CEUS is found to be reliable for disease activity classification [23], the technique holds several limitations leading to reduced reproducibility [29], making comparison between different US vendors difficult [30]. Colour Doppler sonography is well suited for activity evaluation and classification [12], with high positive predictive value. However, absence of Doppler signals is found to have low negative predictive value [23,28], which may be due to insensitivity of equipment as well as reduced sensitivity in patients with increased body mass index or when measuring at increased depths [20]. Similar results regarding PPV and NPV of Doppler sonography were found in the present study. Finally, both colour Doppler and CEUS measurements are usually performed on pathologically thickened bowel walls, increasing the pre-test probability for activity. Thus, these methods seem more useful for disease activity quantification, while BWT measurements seems better suited for determining whether patients are in remission or not. False negative results were due to small aphthous lesions (Fig. 3) in quite a few cases (5/8). Bowel wall oedema is a prerequisite for detecting inflammatory activity on ultrasonography and explains why these changes were not detected. The clinical and prognostic significance of aphthous ulcers without oedema is not clear but may indicate a milder form of disease.

Measurements of BWT in collapsed colon segments could lead to overestimation and false positive results and should be interpreted with caution [20]. Still, all patients with increased BWT limited to the colonic wall were correctly classified by faecal calprotectin. Thus, we suggest that for patients with suspected affection of the colon on GIUS, a secondary test of calprotectin may be appropriate as specificity seems to improve. The false positive results located in the terminal ileum were interpreted as mild active lesions and chronic changes after surgery. Biopsies were only performed in three patients, of which all had normal histology.

A key question regarding biologics is when to discontinue treatment [25]. The best patient outcome is achieved when there is no macroscopic evidence of inflammatory activity (SES-CD or Crohn Disease Endoscopic Index of Severity (CDEIS) = 0) [5,31]. GIUS appears accurate for separating active and inactive disease but does not alone provide the clinician with the confidence to make the decision to discontinue treatment. Our data suggests that patients with active disease on GIUS do not need an ileocolonoscopy as there are few false positives. By including calprotectin in patients with colitis on GIUS, the amount of false positive results is further reduced. Patients with ileocolonic disease and normal findings on ultrasound should, however, be examined with ileocolonoscopy to exclude false negatives. Nevertheless, as the present data are based on a heterogenous CD population, future studies are needed to compare the value of ultrasound with ileocolonoscopy in a subgroup of CD patients eligible for treatment discontinuation.

In another scenario, the physician's objective is to evaluate the disease activity for continuation or escalation of treatment. As we here found a high sensitivity for detecting endoscopic activity, we suggest that increased BWT on GIUS may be sufficient. By adding colour Doppler in pathologically thickened sections as well as faecal calprotectin in sonography-detected colitis, the diagnostic accuracy may be further improved. Consequently, implementation of GIUS in follow-up examinations could potentially reduce the need for ileocolonoscopic examinations, enabling better allocation of endoscopic resources.

The study has potential limitations. The endoscopists have various clinical experience which could lead to different assessments of endoscopic activity, and no formal consensus on SES-CD calculation were performed. Still, this may be of less importance as endoscopic remission and activity was strictly defined. The interobserver analyses were performed on a limited number of patients due to practical reasons. Future studies should also investigate whether implementation of GIUS in outpatient clinic could provide additional decision-making effects compared to standard follow-up examinations. Finally, as our study was performed on a hospital cohort, the findings may not be applicable in a primary care setting.

In conclusion, GIUS is an accurate surrogate marker of endoscopic activity in Crohn's disease. Accordingly, bowel ultrasound has the potential to reduce the number of routine ileocolonoscopies.

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Figures:

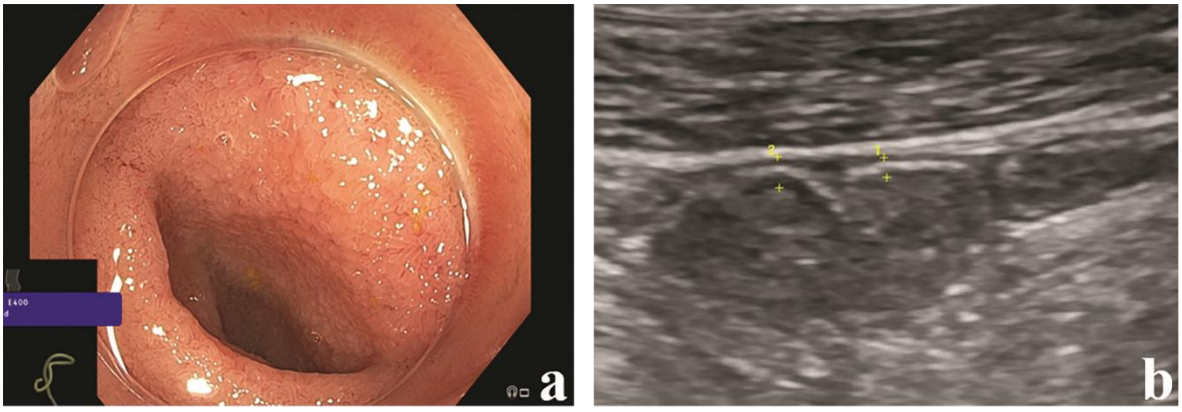

Figure 1: Terminal ileum in endoscopic (a) and sonographic (b) remission. Bowel wall thickness is measured between the yellow calipers in the anterior wall in longitudinal section.

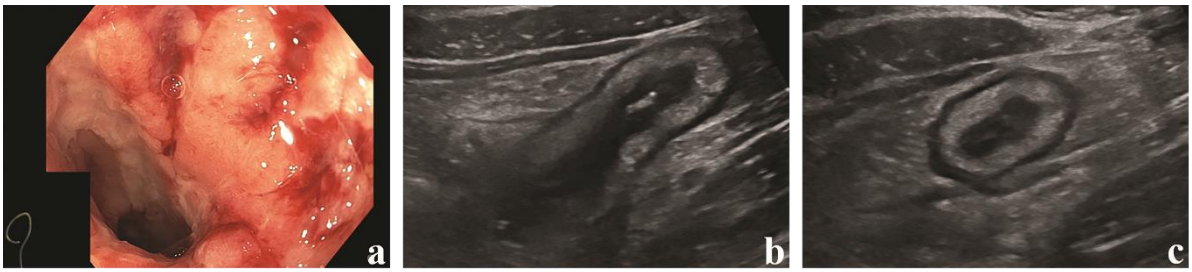

Figure 2: Terminal ileitis with oedema and large ulcerations at ileocolonoscopy (a), identified as increased bowel wall thickness at GIUS in longitudinal (b) and transverse (c) sections**.**

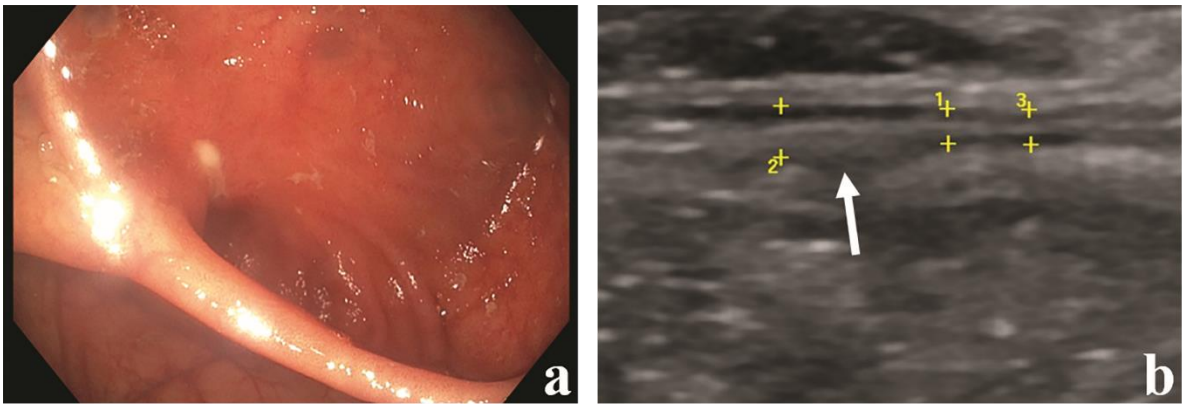

Figure 3: Neoterminal ileum with a solitary aphthous lesion at endoscopy (a). There were normal findings at ultrasonography (b). The arrow shows the neoterminal ileum on GIUS.

Tables:

Clinical or biochemical marker	Activity group Median (Range)	Remission group Median (Range)	P-value
Age, year	42 (18-78)	38 (18-83)	0.554 [a]
Years of sickness	10 (0-44)	8 (1-40)	0.108 [a]
Height, metre	1.7 (0.09)	1.7 (0.1)	0.368
Weight, kg	72 (43.5-112)	71 (47-120)	0.441
Body mass index (BMI)	24.2 (17.8-34.6)	24.2 (17.9-35.8)	0.932 [a]
Haemoglobin, g/dL	13.8 (9.1-16.8)	14.0 (11.1-17.5))	0.261
Leucocyte count, 10^9/L	6.4 (2.5-15.1)	5.2 (2.2-11.1)	0.061 [a]
Platelet count, 10^9/L	284.5 (156-513)	272.5 (118-439)	0.277
C-reactive protein (CRP)	2 (0-96)	1 (0-16)	0.039[a] *
Albumin, mg/L	45 (32-54)	46 (40-53)	0.067
Calprotectin, mg/kg	78 (7.5-2178)	18 (7.5-135.5)	<0.001[a] *
Harvey Bradshaw Index (HBI)	3.0 (0-20)	1.8 (0-9)	0.011[a] *

*Significant differences between the groups

[a] Mann-Whitney U test

Table 1: Demographical, biochemical and clinical data of included CD patients (continuous parameters). The patients are designated to the activity- or remission groups according to endoscopic activity (SES-CD >0 or SES-CD = 0, respectively). There were no significant differences (Student's t test/ Mann-Whitney U test) between the groups except for C-reactive protein, calprotectin and Harvey Bradshaw index.

Clinical parameters	Activity group (%)	Remission group (%)	P-value
Female sex,	57 (55.9)	30 (69.8)	0.170
Age at diagnosis			
<16	14 (13.7)	7 (16.3)	0.888
17-40	69 (67.6)	27 (62.8)	0.710
>40	19 (18.6)	9 (20.9)	0.928
Disease location			
Ileal (L1)	50 (49.0)	19 (44.2)	0.726
Colonic (L2)	12 (11.8)	10 (23.3)	0.131
Ileocolonic (L3)	40 (39.2)	14 (32.6)	0.569
Upper disease (L4)	8 (7.8)	2 (4.8)	0.386 [a]
Disease behaviour			
non-stricturing, non-penetrating (B1)	30 (29.4)	29 (67.4)	<0.001*
Stricturing (B2)	57 (55.9)	8 (18.6)	<0.001*
Penetrating (B3)	15 (14.7)	6 (14)	1.000
Perianal involvement	14 (13.7)	5 (11.6)	0.942
Previous surgery	54 (52.9)	11 (25.6)	0.004*
Concomitant treatment			
Aminosalicylate	11 (10.8)	5 (11.6)	0.544 [a]
Azathioprine	32 (31.4)	16 (37.2)	0.625
Methotrexate	7 (6.9)	2 (4.7)	0.468 [a]
Prednisolone	7 (6.9)	0 (0.0)	0.080 [a]
Budesonid	11 (10.8)	2 (4.7)	0.198 [a]
Infliximab	26 (25.5)	16 (37.2)	0.222
Adalimumab	13 (12.7)	2 (4.7)	0.119 [a]
Certolizumab	1 (1.0)	0 (0.0)	0.703 [a]
Vedolisumab	12 (11.8)	2 (4.7)	0.154 [a]

*Significant differences between the groups

[a] Fisher exact test

Table 2: Demographical and clinical data of included CD patients (categorical parameters). The patients are designated to the activity- or remission groups according to endoscopic activity (SES-CD >0 or SES-CD = 0, respectively). There were no significant differences (Chi-square- and Fischer exact test) between the groups except for disease behaviour (B1 and B2) and previous surgery.

Variables	Included patients	Missing data (%)	Sensitivity*	Specificity*	Positive predictive value*	Negative predictive value*	Accuracy*	Agreement (Kappa)⁑
BWT 3mm [a]	145	0 (0)	92.2 (94/102)	86.0 (37/43)	94.0 (94/100)	82.2 (37/45)	90.3 (131/145)	0.772
BWT 4mm [b]	145	0 (0)	80.4 (82/102)	90.7 (39/43)	95.3 (82/86)	66.1 (39/59)	83.5 (121/145)	0.642
Colour Doppler [c]	145	0 (0)	66.7 (68/102)	97.7 (42/43)	98.6 (68/69)	55.3 (42/76)	75.8 (110/145)	0.527
HBI [d]	145	0 (0)	34.3 (35/102)	88.4 (38/43)	87.5 (35/40)	36.2 (38/105)	50.4 (73/145)	0.160
CRP [e]	139	6 (4.1)	35.7 (35/98)	82.9 (34/41)	83.3 (35/42)	35.1 (34/97)	49.6 (69/139)	0.133
Calprotectin [f]	96	49 (33.8)	55.9 (38/68)	82.1 (23/28)	88.4 (38/43)	43.4 (23/53)	63.5 (61/96)	0.301
Calpro colon [g]	42	19 (31.1)	85.7 (12/14)	82.1 (23/28)	70.6 (12/17)	92.0 (23/25)	83.3 (35/42)	0.644
BWT or calpro [h]	145	0 (0)	94.1 (96/102)	76.7 (33/43)	90.6 (96/106)	84.6 (33/39)	88.9 (129/145)	0.728

* Data presented as percentages, with the number of cases used for calculation in parentheses.

⁑ Agreement between ileocolonoscopy and the included parameters using Cohen's Kappa

[a] Bowel wall thickness >3 mm

[b] Bowel wall thickness >4 mm

[c] Colour Doppler score of 1 or 2 (added on bowel segments with BWT >3 mm)

[d] Harvey Bradshaw Index >4 points

[e] C-reactive protein >4 mg/L

[f] Calprotectin >50 mg/kg

[g] Calprotectin after exclusion of terminal ileitis

[h] BWT >3mm or Calprotectin >50 mg/kg

Table 3: The ability of ultrasonography, clinical- and biochemical tests to differentiate between patients in endoscopic remission and activity