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ORIGINAL ARTICLE

Intestinal Conventional Ultrasonography, Contrast-Enhanced Ultrasonography and Magnetic Resonance Enterography in Assessment of Crohn's Disease Activity: A Comparison with Surgical Histopathology Analysis

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Abstract

Background and Aims Contrast-enhanced ultrasonography (CEUS) is a potential interesting method for assessing accurately Crohn's disease (CD) activity. We compared the value of intestinal ultrasonography (US) coupled with contrast agent injection with that of magnetic resonance enterography (MRE) in the assessment of small bowel CD activity using surgical histopathology analysis as reference.

Methods Seventeen clinically active CD patients (14 women, mean age 33 years) requiring an ileal or ileocolonic resection were prospectively enrolled. All performed a MRE and a US coupled with contrast agent injection (CEUS) less than 8 weeks prior to surgery. Various imaging qualitative and quantitative parameters were recorded and their respective performance to detect disease activity, disease extension and presence of complications was compared to surgical histopathological analysis.

Results The median wall thickness measured by US differed significantly between patients with non-severely active CD ($n=5$) and those with severely active CD ($n=12$) [7.0 mm, IQR (6.5–9.5) vs 10.0 mm, IQR (8.0–12.0), respectively; $p=0.03$]. A non-significant trend was found with MRE with a median wall thickness in severe active CD of 10.0 mm, IQR (8.0–13.7) compared with 8.0 mm, IQR (7.5–10.5) in non-severely active CD ($p=0.07$). The area under the ROC curve (AUROC) of the wall thickness assessed by US and MRE to identify patients with or without severely active CD on surgical specimens were 0.85, 95% CI (0.64–1.04), $p=0.03$ and 0.80, 95% CI (0.56–1.01), $p=0.07$, respectively. Among the parameters derived from the time-intensity curve during CEUS, time to peak and rise time were the two most accurate markers [AUROC = 0.88, 95% CI (0.70–1.04), $p=0.02$ and 0.86, 95% CI (0.68–1.04), $p=0.03$] to detect patients with severely active CD assessed on surgical specimens.

Conclusion The accuracy of intestinal CEUS is close to that of conventional US to detect disease activity. A thickened bowel and shortened time to peak and rise time were the most accurate to identify CD patients with severe histological disease activity.

Keywords Crohn's disease · MRE · CEUS · Preoperative assessment · Inflammation · Complication · Pathology

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Abbreviations

CEUS	Contrast-enhanced ultrasonography
MRE	Magnetic resonance enterography
CD	Crohn's disease
CRP	C-reactive protein
AUROC	Area under the receiver operating characteristic curve
ROC	Receiver operating characteristic
SB	Small bowel
CT	Computed tomography
US	Ultrasonography
HBI	Harvey-Bradshaw Index
SD	Standard deviation
Min	Minutes
Sec	Seconds
A.U.	Arbitrary unit
I.V.	Intravenous
ROI	Region of interest
Sen	Sensitivity
IQR	Interquartile range
Spe	Specificity

Background

Crohn's disease (CD) is a chronic inflammatory bowel disorder, characterized by repeating relapses, which lead to progressive intestinal damages and subsequent complications such as strictures, fistulae and abscesses. Surgery is ultimately required for most of the CD patients presenting major complications and/or medical treatment failure [1]. Appraisal of CD activity, evaluation of disease extent, and detection of potential complications remain challenging. Ileocolonoscopy allows visual and histopathological assessments of mucosal surface of colon and distal ileum. However, the vast majority of the small bowel (SB) cannot be investigated by this tool. Enteroscopy can be an alternative to better explore SB but it is a long and cumbersome tool that requires specific endoscopes and as colonoscopy, a general anesthesia. Videocapsule endoscopy is of interest in this setting, but its indication is limited to CD patients in whom intestinal strictures have been previously ruled out by imaging or calibration capsule. In addition, although endoscopic procedures are highly sensitive to investigate mucosal lesions and to detect luminal narrowing, they cannot accurately assess transmural intestinal and surrounding perienteric tissue damages that characterize CD.

Cross-sectional imaging, magnetic resonance enterography (MRE), computed tomography (CT) as well as high-resolution bowel ultrasonography (US) provide important information on the SB mucosal lesions, the intestinal wall, gut environment, and complications [2–7]. CT, due to radiation safety, should not usually be used for monitoring disease activity if MRE or US is available [4]. MRE suffers from limitations, including a traditional lack of widespread availability, a relatively high cost, a low spatial resolution and a variable patient acceptance, as reported in a French nationwide patient-based cohort survey [8].

High-resolution bowel US represents a non-invasive, low cost, non-ionizing, easily available and repeatable imaging tool and, in contrast to endoscopy and MRE, offers excellent patient acceptance [4, 8]. The sensitivity and specificity of US can be enhanced by using contrast agents administered orally (small intestine contrast ultrasound, SICUS) or intravenously (contrast-enhanced US, CEUS). CEUS is a relatively new technique that allows with real-time examination a precise depiction of both the bowel wall microvasculature and the adjacent perienteric tissues. Therefore, CEUS may have an added value in comparison with conventional high-resolution US by improving the detection, characterization and quantification of CD activity [9–16]. In addition, some mathematical parameters may be defined with CEUS and monitored over time allowing a quantitative assessment of outcomes and treatment efficacy.

Up to now, few studies have investigated the relationships between qualitative and quantitative imaging parameters from MRE or CEUS findings and histopathological analyses from surgical specimens in the assessment of CD activity and fibrosis [12, 16–20]. Our objective was to compare the performance of US coupled with contrast agent injection to that of MRE for investigating the ileum of CD patients. For this purpose, the two methods were compared to the findings of pathological analysis of the surgical ileal or ileocolonic specimens taken as the reference method in patients with planned surgical resection.

Patients and Methods

From October 2016 to April 2018, 17 consecutive CD patients were prospectively enrolled. Eligibility criteria were the following: patients at least 18 years of age; diagnosis of CD according to the usual endoscopic, histological, and imaging criteria; SB ileal disease location identified by endoscopy and/or cross-sectional imaging techniques (L1, ileal disease or L3, ileocolonic disease according to the Montreal classification); active disease based on clinical disease activity estimated by the Harvey-Bradshaw index (HBI) > 4 and failure to respond to medical therapy requiring elective ileal or ileocolonic resection. The patients had to have a stable medical treatment within the 3 months prior to surgery. Patients with non-resolutive SB obstruction requiring change in medical therapy or emergency surgery were excluded as well as those who needed modification of the CD-related therapy (including corticosteroids, azathioprine,

6-mercaptopurine, methotrexate and biologics) during the previous 3 months before surgery.

Included patients performed a preoperative SB CEUS followed the same day by a MRE within 8 weeks prior to surgery. Demographic data, as gender, age, duration of disease, previous medical and surgical treatments were prospectively collected, and inflammatory laboratory parameters including serum C-reactive protein (CRP) and fecal calprotectin were measured within 8 weeks before surgery. The Human Research Ethics Committee and the Institutional Review Board (IRB 001612 UCB) of Lyon University approved the study and all patients provided a written informed consent.

Conventional Ultrasonography (US) and Contrast Enhancement US (CEUS) Techniques

In each patient, who had been fasting for at least 8 h, a conventional US (before contrast agent injection) followed by a CEUS was performed before MRE with a Toshiba Aplio 500 (Toshiba Medical System Europe, Zoetermeer, The Netherlands) using linear (14 MHz) and convex (6.0 MHz) probes (ref PVT-674BT) in harmonic mode, without specific bowel preparation. All unenhanced US and CEUS were performed and reviewed by two experienced senior radiologists who were blinded to the clinical, biologic, MRI and histopathological results. All technical parameters were kept constant between the different patients. The following parameters were recorded from the visible SB before contrast agent injection (1) from the bowel wall analysis: length of the involved SB and length and location of the most diseased SB segments, maximum wall thickness, bowel wall differentiation (graded from dedifferentiated wall to well differentiated wall); and (2) from the extramural findings: presence or absence of fatty proliferation, comb sign (i.e., segmental dilatation or engorgement of the vasa recta), lymph nodes enlargement, deep ulceration or fistula and presence of abscess. After contrast agent injection, the following parameters were also recorded from the most severe diseased segment: degree of wall enhancement (graded as mild, moderate and severe), pattern of contrast enhancement (graded as weak, intense and very intense), time to enhancement arrival and time to enhancement delayed.

The most severe diseased segment of the terminal ileal loop characterized by unenhanced gray-scale US was scanned prior and after intravenous (i.v.) injection of sulfur hexafluoride-filled microbubbles used as contrast agent (Sonovue®, Bracco, Milan, Italy). Briefly, the prepared solution of Sonovue® was injected through a 20-gauge catheter into an antecubital vein as a bolus of 2.4 mL secondary followed by 10 mL of normal saline solution (0.9% NaCl). From 5 s after contrast agent injection, the first-pass dynamic enhancement of the SB wall was monitored in real-time during breath-holding to minimize breathing-related movements. The record started as soon as the end of the contrast agent i.v. injection and was extended during 30 s to 1 min after. The contrast uptake was measured over a period of 40 s and the quantitative analysis of the brightness in the intestinal wall was recorded.

In each image, a manually defined polygonal region of interest (ROI) was drawn and was analyzed by the Vuebox™ 4.2 software (Bracco) to generate a brightness-time curve. From the time-intensity curves that were fitted, various individual quantitative kinetic parameters were calculated, including the peak enhancement, wash-in area under the curve (AUC), rise time, time to peak, mean transit time and mean transit time local, wash-in rate, wash-in perfusion index, wash-out AUC, fall time, wash-out rate. AUC were expressed in arbitrary unit (a.u.) and times in sec. Supplementary Fig. 1 provides a schematic overview of a time-intensity curve with quantitative parameters. To minimize the impact of variability related to individual physiologic parameters, including the cardiac output, the time-intensity curve was calculated from the time of contrast agent visualization in the scanning plane. Representative images of conventional US and CEUS in inactive and active CD patients are shown in Supplementary Fig. 2.

MRE Technique

All MRE were performed 30 min after oral administration of 1500 mL hyperosmotic water solution (1250 mL water + 250 mL mannitol 20%). They were performed on a 1.5 Tesla system (Philips Healthcare Ingenia, Best, The Netherlands). Breath-hold imaging was first performed in the coronal plane using a T2-weighted single shot turbo spin echo sequence with fat suppression, and in the coronal and axial planes using a true Fast Imaging with Balanced Steady-state (true FISP) sequence. After i.v. administration of an antispasmodic agent (GlucaGen, Novo Nordisk, Bagsvaerd, Denmark), an i.v. injection of Gadolinium chelates (Dotarem, Guerbet, France) at a dose of 0.2 mL/kg of body weight was administrated and a T1-weighted sequence was performed before, 90 s (coronal plane) and 8 min (axial and coronal planes) later. Ninety sec were considered to be the parenchymatous time and eight min the delayed time.

All MRE studies were reviewed by senior radiologists with many years of experience with MRE different from those who reviewed US and CEUS. They were also fully blinded of the clinical, biological, ultrasonographic and surgical findings. The following imaging parameters were systematically recorded and concerned the entire visible SB: length of the diseased SB; wall thickness in T2 and T1-weighted images; wall signal intensity on T2-weighted images; degree of wall enhancement on parenchymatous and delayed T1-weighted images compared with enhancement of adjacent normal bowel; pattern of enhancement

(homogeneous or layered) on parenchymatous and delayed T1-weighted images; well-defined or blurred wall enhancement on delayed T1-weighted images; extramural findings, including presence or absence of fatty proliferation, comb sign, lymph nodes, fistula and abscess. The following imaging disease activity score was calculated: MaRIA (Magnetic Resonance Index of Activity) calculated by 1.5 * wall thickness + 0.02 * relative contrast enhancement + 5 * edema + 10 * ulceration [17]. Representative images from MRE are shown in Supplementary Fig. 3.

Histopathological Analysis

Each unfixed ileal ($n = 1$) or ileocolonic ($n = 16$) surgical specimens were transferred immediately to the Department of Pathology and were macroscopically examined by two specialist gastrointestinal pathologists (with 15 years of experience) who were unaware of the clinical, biological, and radiological findings. The length of bowel involvement and different pathological lesions (ulcerations, strictures, fissures, fistulae or abscesses) were recorded. After fixation with 4% formalin, all lesions observed macroscopically were sampled. All hematoxylin-phloxin-saffron (HPS)-stained slides were analyzed by the same pathologist and the most severe microscopic lesions were retained to score inflammation and fibrosis.

We used the CD pathological inflammatory score and the fibrosis score previously described by Zappa et al. [17]. Inflammation was classified in three categories as follows: grade 0 (mildly or non-active CD): minimal neutrophil infiltrate limited to the mucosa; grade 1 (moderately active CD): neutrophil infiltrate limited to the mucosa and submucosa without muscular involvement; grade 2 (severely active CD): transmural neutrophil infiltrate through the *muscularis propria* and/or fistula and/or abscess in the subserosa. Fibrosis was graded as follows: grade 0: minimal fibrosis limited to submucosa; grade 1: massive submucosal fibrosis with preserved layers; grade 2: massive transmural fibrosis with effacement of normal layers (Supplementary Fig. 4).

Because of the small number of patients with grades 0 and 1 in both scores, patients were then dichotomized into two different groups for inflammation and fibrosis: non-severely active CD including inactive or mild to moderate active CD (grades 0 and 1) versus severely active CD (grade 2) for inflammation and non-transmural fibrosis (grades 0 and 1) versus transmural fibrosis (grade 2) for fibrosis. As only three patients presented non-transmural fibrosis, analysis of results according to the fibrosis score was not performed.

Statistical Analysis

Statistical analyses were performed using the Statistical Prism Package GraphPad software Inc. (v6, Graphpad Software Inc., San Diego, CA, USA). Results of quantitative and qualitative data are presented as median and range or interquartile range (IQR) for non-normally distributed variables, mean ± standard deviation (SD) for normally distributed variables, and percentages. The correlations between the US and MRE findings and pathology grading were performed using the Spearman's rank correlation coefficient.

Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut off points for each quantitative CEUS parameters generated from the time-intensity curves and to assess the overall performance of each parameters using the area under the ROC curve (AUROC) for discriminating patients with non-severely active CD from those with severely active CD, according to the histopathological analysis. The performance of various quantitative parameters (including the peak of enhancement, time to peak, rise time, wash-in AUC, wash-out AUC, fall time) to predict non-severely active CD from severely active CD was derived from the time-intensity curves and was also expressed in terms of sensitivity (Sen) and specificity (Spe). For comparison purpose, the non-parametric Mann–Whitney test was used. A $p < 0.05$ was considered as statistically significant. The standard of reference was the histopathological analysis of the ileal resection specimens.

Results

Characteristics of the Cohort

Within an 18-month period, a total of 17 consecutive patients (14 women, median age 31 years) undergoing an elective ileal or ileocolonic resection after failure to respond to medical therapy were prospectively enrolled in a single center. The main demographic characteristics of the cohort, as well as therapies prior intestinal resection are summarized in Table 1. Indications for surgery were symptomatic strictures in 10 patients, penetrating complications in six patients and drug-refractory inflammatory luminal disease in the remaining patient. The median time interval between both imaging techniques (US-CEUS and MRE) and surgery was 7 days (range 1–56 days). Overall pathologic findings, according to the severity of inflammation and fibrosis on ileal surgical specimens are summarized in Table 2. Regarding inflammation, there were 12 patients with severely active CD (grade 2) versus only five patients with non-severely active CD (grades 0 and 1). Concerning tissue fibrosis, there were 14 patients with transmural severe fibrosis (grade 3) versus only three patients with mildly or moderately

Table 1 Patients' characteristics

Patients' characteristics ($n=17$)		
Age (years)	Median age (range)	31 (24–52)
Gender	M/F	3/14
CD duration (years)	Median (range)	9 (2–23)
CD location	Ileum (L1), *n* (%)	4 (24%)
	Ileocolonic (L3), *n* (%)	13 (76%)
Perianal disease, *n* (%)		4 (24%)
Disease phenotype	Inflammatory (B1), *n* (%)	1 (6%)
	Stenotic (B2), *n* (%)	10 (59%)
	Penetrating (B3), *n* (%)	6 (35%)
Therapy (mono or combined) within the 3 months prior to surgery	Corticosteroids, *n* (%)	3 (18%)
	Immunosuppressants, *n* (%)	8 (47%)
	Anti-TNF	9 (53%)
	Adalimumab, *n* (%)	4 (24%)
	Infliximab, *n* (%)	5 (29%)
	Ustekinumab, *n* (%)	1 (6%)
	Vedolizumab, *n* (%)	4 (24%)
Patient with prior history of ileocolonic resection, *n* (%)		5 (29%)
Harvey-Bradshaw Index	Median (range)	6 (5–10)

CD Crohn's disease, *M/F* male/female

Table 2 Distribution of the 17 surgical specimens of CD patients according to pathological inflammatory and fibrosis scores

Pathological fibrosis score					
	Grade	0	1	2	Total
Pathological inflammatory score	0	0	0	1	1
	1	2	0	2	4
	2	0	1	11	12
	Total	2	1	14	17

non-transmural bowel fibrosis (grades 0 and 1). In addition, there was a coexistence of substantial inflammation and fibrosis in the majority of patients. Indeed, 11 out of 17 patients (65%) had both severely active CD and transmural fibrosis. Only one patient with severely active CD had no transmural fibrosis. Conversely, one patient had transmural fibrosis without inflammation. Finally, two patients had a moderately active CD without transmural fibrosis and the two remaining patients had transmural fibrosis and a moderate inflammation score (Table 2).

Ability of Conventional US and MRE to Estimate Disease Extension and to Detect Complications

When comparing conventional US and MRE, the median difference in the length of diseased SB lesions was 40 mm, IQR (5–75 mm). US underestimated the length of diseased SB measured by MRE in 14 out of 17 patients. The length was similar between US and MRE in only two patients and US overestimated disease extension in one patient. Extension of lesions measured by US failed to correlate significantly with that measured by MRE ($r=0.40$; $p=0.10$). By taking pathological analysis as the reference, US and MRE underestimated the real disease extension in all patients and in 15 out of 17 patients, respectively. The median difference of disease extension estimated by US or by MRE compared with that assessed by pathological analysis was 11 mm, IQR (5–23) and 8 mm, IQR (1–16), respectively ($p=0.27$).

Internal fistulae (including 6 enteroenteric and 3 enterocolonic) and abscesses were detected by pathologists in 9 (53%) and 5 (29%) out of 17 surgical SB specimens, respectively. Among the nine patients in whom fistulae were detected by pathological analysis, fistulae were detected in 8 patients by MRE and in seven patients by US (Table 3). Among the five patients in whom abscesses were diagnosed by pathological analysis, MRE was capable to detect abscess in all cases, whereas US allowed to detect abscess in only one patient.

Table 3 Disease extension and complications assessed by US and MRE

Parameters	US	MRE	*p* value
Length of diseased small bowel lesions. Median, (IQR)	65 mm, (47–80)	110 mm, (60–145)	0.01
Bowel wall thickness. Median, (IQR)			
Overall	8.0 mm, (7.0–11.5)	9.0 mm, (8.0–12.5)	0.25
Non-severely active	7.0 mm, (6.5–9.5)	8.0 mm, (7.5–10.5)	0.28
Severely active	10.0 mm, (8.0–12.0)	10.0 mm, (8.0–13.07)	0.39
Extramural findings, *N*			
Comb sign	11	11	1.0
Fistulae	5	8	0.30
Fatty proliferation	11	14	0.26

Ability of US and MRE to Assess Small Bowel Inflammation

The median SB wall thicknesses, measured by US and by MRE, were 8.0 mm, IQR (7.0–11.5) and 9.0 mm, IQR (8.0–12.5), respectively (Table 3, Fig. 1a). The median SB wall thickness, measured by US differed significantly in patients with non-severely active disease when compared with that in patients with severely active CD (7.0 mm, IQR (6.5–9.5) versus 10.0 mm, IQR (8.0–12.0), respectively; $p=0.03$, Table 4). The same tendency was found with MRE, with a median wall thickness in severe active CD of 10.0, IQR (8.0–13.7) compared with 8.0 mm, IQR (7.5–10.5) in non-severely active CD but the difference failed to reach the level of statistical significance ($p=0.07$, Table 5, Fig. 1a). When examining the relationship between the SB thickness measured by US and by MRE, there was a positive and significant correlation between the two imaging techniques ($r=0.63$; $p<0.005$) (Fig. 1b). When stratifying the patients based on the presence or absence of severe active CD assessed by pathological analysis, the accuracy of US, based on the measurement of the SB wall thickness, was weakly superior to that of MRE to predict severely active versus non-severely active CD [AUROC = 0.85, 95% CI (0.64–1.04), $p=0.03$ vs 0.80, 95% CI (0.56–1.01), $p=0.07$, respectively] without reaching a statistical difference ($p=0.33$) (Fig. 1c). The best cut off points capable of discriminating these two subgroups of patients were 7.5 mm (Sen = 84%; Spe = 75%) for US and 8.5 mm (Sen = 69% and Spe = 75%) for MRE.

Quantitatively, the median global MaRIA disease activity score was 22 points, IQR (16–31 points). It was higher in patients considered by histopathological analysis as severely active CD than in those considered as non-severely active CD [28 points, IQR (18–39) vs 19 points, IQR (13–20); $p=0.20$] (Table 5).

Accuracy of the CEUS Quantitative Parameters to Discriminate Between Inactive or Mildly to Moderately Active Versus Severely Active CD According to the Pathological Inflammatory Score

The time to peak was strongly correlated, and at a lesser degree the rise time, with the SB wall thickness measured by US, whereas the rise time, wash-out AUC, fall time and wash-in AUC were all CEUS-related parameters correlated significantly with the SB wall thickness measured by MRE (Table 6). In addition, among all the parameters from the

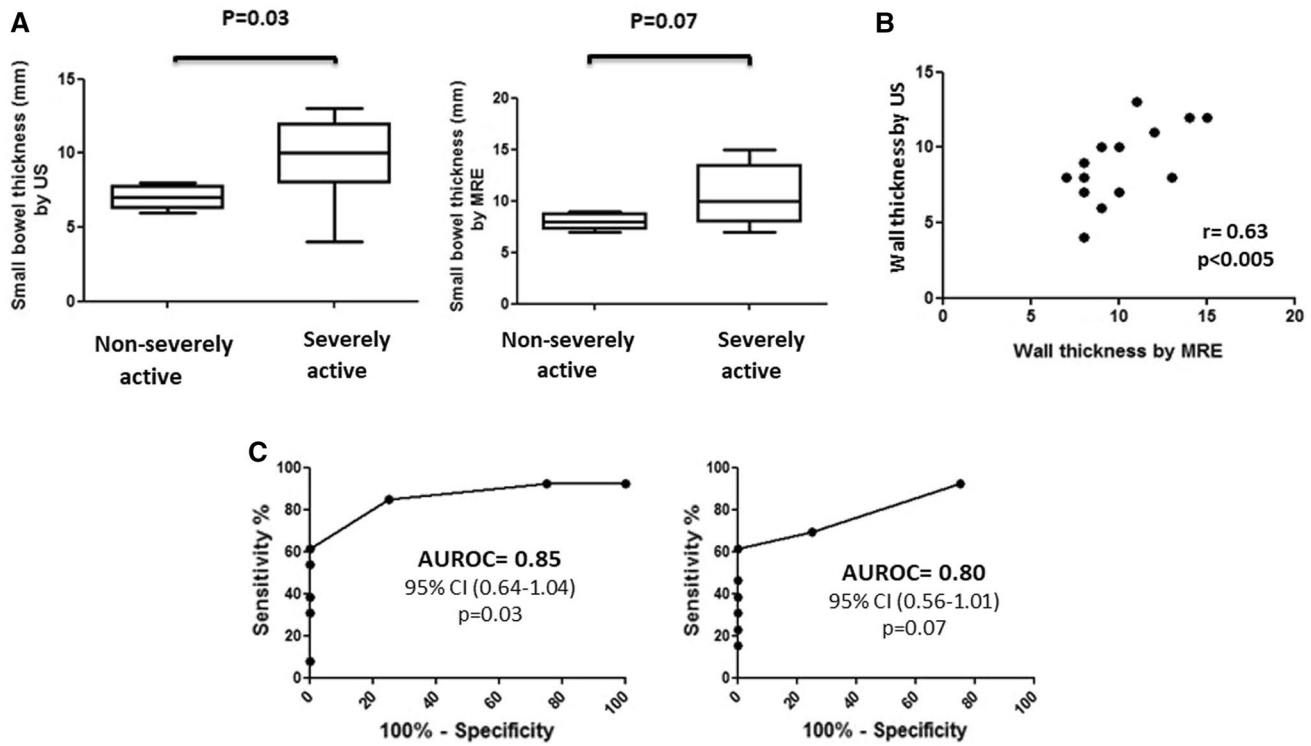

Fig. 1 **a** Maximum small bowel thickness assessed by US (left) and by MRE (right) in patients with histologically non-severely active and severely active CD. The box plots show median, upper and lower quartiles and the whiskers indicate the 95% confidence interval of the values. **b** Relationships between the maximum small bowel wall thicknesses measured by US and by MRE. **c** Accuracies of maximum small bowel thickness assessed by US (left) and by MRE (right) to identify patients with histologically non-severely active CD from patients with severely active CD assessed by the area under the receiver operating characteristic curve (AUROC)

Table 4 US and CEUS findings according to pathological inflammatory score

	CD pathological inflammatory score		
	Grades 0–1[a] ($n=5$)	Grade 2[a] ($n=12$)	*p*
US parameters			
Median (IQR) wall thickness (mm)	7.0 (6.5–9.5)	10.0 (8.0–12.0)	0.03
Bowel wall differentiation			
Dedifferentiated	1 (25%)	5 (39%)	0.62
Intensity of contrast enhancement			
Marked	2 (50%)	9 (69%)	0.48
Extramural findings			
Comb sign	1 (25%)	10 (77%)	0.05
Lymph nodes	0 (0%)	0 (0%)	
Fistulae	2 (50%)	5 (38%)	0.68
Abscess	0 (0%)	1 (7%)	0.56
Fatty proliferation	2 (50%)	9 (69%)	0.48
Median (IQR) quantitative parameters			
Peak enhancement (a.u.)	2369 (908–5068)	5118 (3464–10,357)	0.10
Rise time (s)	4.3 (3.8–4.4)	5.2 (4.9–5.8)	0.03
Time to peak (s)	6.2 (5.7–6.6)	7.5 (6.7–8.5)	0.02
Fall time (s)	8.6 (7.7–9.3)	12.2 (10.0–15.5)	0.06
Wash-in AUC (a.u.)	7544 (2197–14,529)	22,632 (11,176–36,658)	0.04
Wash-out AUC (a.u.)	14,899 (4242–29,308)	49,665 (21,213–87,530)	0.04

a.u. arbitrary unit, *AUC* area under curve

[a]Grade 0–1: inactive, mildly or moderately active CD; Grade 2: severely active CD

Table 5 MRE findings according to pathological inflammatory score

	CD pathological inflammatory score		
	Grades 0–1[a] ($n=5$)	Grade 2[a] ($n=12$)	*p*
MRI parameters			
Median (IQR) wall thickness (mm)	8.0 (7.5–10.5)	10.0 (8.0–13.7)	0.07
Degree of contrast enhancement			
Parenchymatous phase (T1)			
Marked	0 (0%)	5 (39%)	0.13
Delayed phase (T1)			
Marked	0 (0%)	6 (56%)	0.09
Pattern of enhancement			
Parenchymatous phase (T1)			
Layered	3 (75%)	10 (77%)	0.93
Homogeneous	1 (25%)	3 (33%)	0.93
T2 wall hypersignal	0 (0%)	11 (84%)	0.001
Extramural findings			
Comb sign	1 (25%)	10 (77%)	0.05
Lymph nodes	1 (25%)	3 (33%)	0.93
Fistulae	0 (0%)	8 (61%)	0.03
Abscess	0 (0%)	5 (38%)	0.13
Fatty proliferation	2 (50%)	12 (92%)	0.05
Median (IQR) global MaRIA score	19 (13–20)	28 (18–39)	0.20

[a]Grade 0–1: inactive, mildly or moderately active CD; Grade 2: severely active CD

Table 6 Spearman rank correlation coefficient between variables from the time-intensity curves and the bowel wall thickness (BWT) assessed by US and MRE

Quantitative CEUS parameters	BWT by US	*p*	BWT by MRE	*p*
Time to peak	$r=0.75$	0.0005	$r=0.34$	0.17
Rise time	$r=0.57$	0.01	$r=0.55$	0.02
Wash-out AUC	$r=0.43$	0.07	$r=0.55$	0.02
Fall time	$r=0.39$	0.10	$r=0.53$	0.02
Peak enhancement	$r=0.35$	0.15	$r=0.38$	0.12
Wash-in AUC	$r=0.35$	0.14	$r=0.48$	0.04

time-intensity curves tested, only fall time and rise time were significantly correlated with the quantitative index of CD activity (MaRIA score) with a correlation coefficient of $r=0.64$ ($p=0.005$) and $r=0.53$ ($p=0.02$), respectively.

The time to peak and the rise time were the most accurate CEUS-related quantitative parameters capable to discriminate the patients with or without severe inflammation on surgical specimens (AUROC = 0.88, 95% CI (0.70–1.04), $p=0.02$ and 0.86, 95% CI (0.68–1.04), $p=0.03$, respectively) and at a lesser degree the wash-in, wash-out and wash-in and wash-out parameters (AUROC = 0.84, 95% CI (0.59–1.06), $p=0.04$ for all the 3), the fall time (AUROC = 0.82, 95% CI (0.65–1.04), $p=0.05$) and peak enhancement (AUROC = 0.78; 95% CI (0.50–1.03), $p=0.08$) (Fig. 2). The best cut off points of the time to peak and the rise time to predict severe inflammation from inactive or mildly to moderately inflammation on the surgical pathological specimen was 6.5 s and 4.3 s, respectively with Sen = 84% and Spe = 75% for both. The corresponding best cut off points for wash-in AUC and wash-out AUC were 7277 a.u. and 23,743 a.u. with Sen = 92% and 86% and Spe = 75% and 71%, respectively, and the optimal threshold for the fall time was 9.9 s with Sen = 77% and Spe = 100%.

Discussion

Among the various imaging methods available, US have some unique strengths, including widespread availability, excellent patient acceptance and also noninvasiveness. US can be associated with the administration of a contrast agent to allow a quantitative assessment of the bowel wall flow. To the best of our knowledge, we report for the first time a comparative study investigating the relationships between two non-ionizing imaging patterns (CEUS and MRE) with pathological findings on CD surgical specimens. We confirm

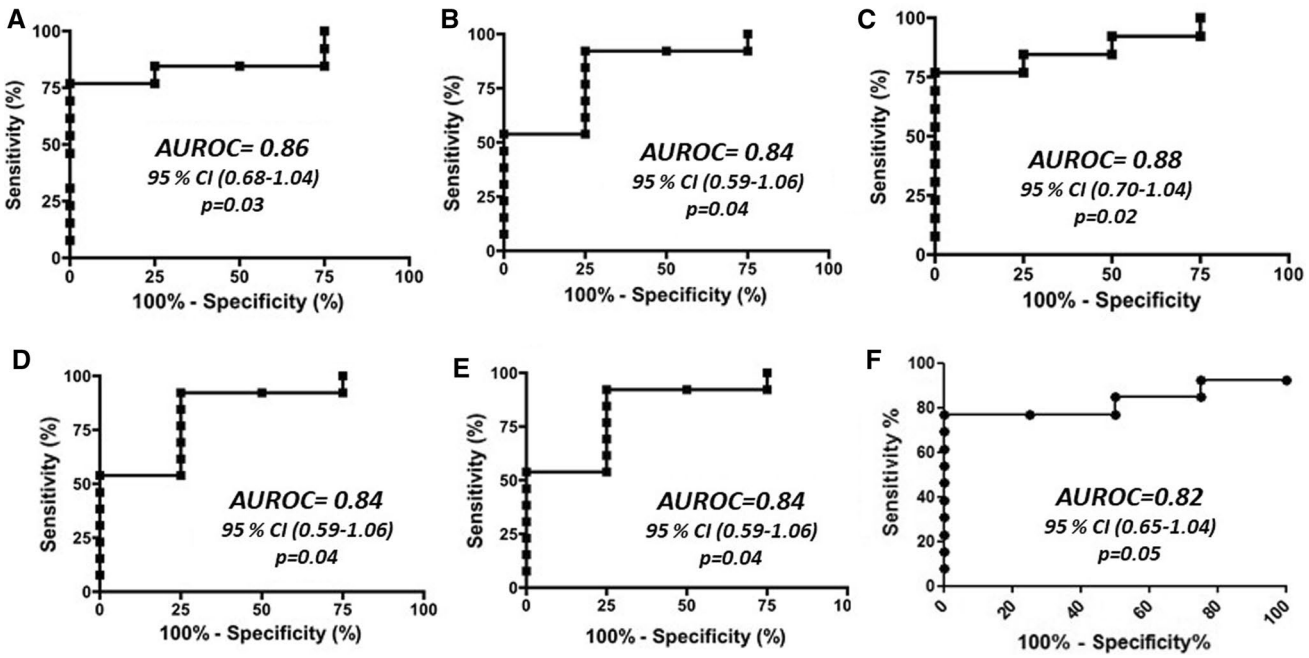

Fig. 2 Accuracies of various quantitative parameters, including rise time (**a**), wash-in (**b**), time to peak (**c**), wash-out (**d**), wash-in and wash-out (**e**), and fall time (**f**) generated from the CEUS-based time-intensity curve analysis to identify CD patients with non-severely active versus severely active CD. *AUROC* area under the receiver operating characteristic curve

previous findings that fibrosis and inflammation often coexist on surgical CD intestinal resection specimens [17] supporting the assumption that inflammation and fibrosis are inseparable.

We found that SB wall thickness, estimated by unenhanced US, is relatively accurate to detect severe CD activity, assessed on histopathological analysis. US and MRE were both as accurate in detecting internal fistulae but US was inferior when compared with MRE to detect abscess. These results agree with another study showing that MRE is more accurate than US in defining CD extent and enteroenteric fistulae [21]. Our findings confirmed the high concordance between US and MRE in assessing the length of diseased SB, as previously published [14]. In addition, the difference of disease extension estimated by US or by MRE compared with that assessed by pathological analysis was not clinically relevant.

Many previous studies demonstrated that acute or chronic inflammation of the SB wall was accompanied by enhanced perfusion of the mesentery, which can be displayed quantitatively using CEUS analyzing time-intensity curves [22–24]. CEUS subsequently may help to accurately grade CD activity by improving the evaluation of bowel wall mural microvascularity and by providing various quantitative parameters generated from the degree of wall flow during a period of time (time-intensity curves). Few studies have already evaluated the value of quantitative parameters measured by CEUS in assessment of CD histological activity, and they do not agree on which time-intensity curve parameters are important [11, 15, 16]. In our study, the most accurate sonographic quantitative markers capable to discriminate accurately between severely active versus non-severely active CD lesions were the time to peak and the rise time. However, although the performance (based on the AUROC) of the time to peak was the highest (AUROC = 0.88), it was very close to that found with US bowel wall thickness measurement (0.85) to detect reliably patients with histopathological severe disease activity. Two previous studies investigated the effectiveness of CEUS to characterize intestinal inflammation in CD patients with a surgical reference [12, 18]. Ripollés et al. [12] dichotomized surgical specimens from 25 CD patients into inflammatory and fibrostenotic and found that the percentage of increase in contrast enhanced was significantly associated with the pathological inflammatory score, whereas the time to peak was negatively correlated with the pathological fibrostenotic score. This suggests that the time taken to reach the peak is lengthened as the fibrosis increases. This negative correlation between the time to peak and the histopathogical score of surgical specimens was also evidenced by Girlich et al. [18] in 20 CD patients planned for elective bowel surgery. In contrast, Romanini et al. [16] compared quantitative analysis of bowel wall enhancement by CEUS with histological activity in 33 IBD patients (15 CD) undergoing colonoscopy and biopsy. They found that the time to peak was strongly and positively related to inflammatory activity. We have no clear explanation for these contradictory results. They may be related at least in part to differences in the magnitude of inflammatory or fibrostenotic components among included patients and/or to the scoring system used to assess this magnitude.

Ultrasonography is better accepted and cheaper when compared with MRE. Patient acceptance is a critical issue when monitoring chronic disorders such as CD since these investigations need to be repeated in follow-up on a regular basis. A recent nationwide multicenter study has specifically investigated the patient's point of view regarding acceptability and usefulness of IBD monitoring tools. It was clearly reported that US was better accepted compared to MRE according to the CD patient's points of view [8]. In addition, since gadolinium-based contrast agents should not be administered to patients with chronic renal impairment given the potential risk of induced-nephrogenic systemic fibrosis [25], CEUS could be an elegant alternative in this setting to replace MRE for the assessment of disease activity. However, CEUS requires an experienced radiologist or gastroenterologist and US is by definition a dynamic investigation in real-time mode that is overall time-consuming and that is subject to lack of reproducibility compared with other cross-sectional imaging.

The main strengths of our study are its prospective design, a relatively short interval time between both imaging techniques that were performed the same day and surgical bowel resection. In addition, we simultaneously recorded qualitative and quantitative parameters that were subsequently carefully analyzed according to the histopathological surgical specimen assessment. However, our study has some limitations, including a small cohort sample that was subsequently dichotomized into non-severely active (including mild and moderate disease activity) and severely active CD. This precludes any comparisons among patients with different degrees of fibrosis and may result in a lack of power when comparing patients with different degrees of inflammation. In addition, we do not have included diffusion-weighted MRE that has been advocated for assessing CD activity [26]. One more limit of the CEUS is the potential lack of reproducibility in most of the different steps of CEUS despite careful standardization [27]. The greatest challenge for measurement by CEUS of quantitative parameters derived from time-intensity curves comes from the small size of the region of interest (ROI). Indeed, the measurement of such a small structure is subject to inter- and intra-observer variabilities, which remains the main limitation of these parameters for a regular monitoring of CD patients in daily practice.

In conclusion, the accuracy of intestinal CEUS is close to that of conventional US to detect disease activity. CEUS

provides some quantitative perfusion parameters able to analyze accurately the severity of inflammatory micro-vascularization of the SB wall. These parameters, in addition with wall thickness, may help clinicians to better grade inflammation in CD. Further studies are warranted to investigate the usefulness of monitoring the time to peak and/or rise time for assessing disease activity in CD patients in the non-preoperative setting and during medical therapy.

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Declarations

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