La radiologia medica (2022) 127:1068–1078
https://doi.org/10.1007/s11547-022-01535-z

ABDOMINAL RADIOLOGY

Contrast-enhanced ultrasound in the assessment of Crohn's disease activity: comparison with computed tomography enterography

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Received: 11 June 2022 / Accepted: 25 July 2022 / Published online: 9 August 2022

Abstract

Background and objective Continuous assessment of disease activity remains a huge challenge during the follow-ups of patients with Crohn's disease (CD). In this paper, we aimed to evaluate the performance of contrast-enhanced ultrasound (CEUS) by comparing with computed tomography enterography (CTE) in the assessment of disease activity in CD.

Materials and methods Fifty-two patients diagnosed with CD were included in this study, using the CEUS and CTE as imaging methods for comparison. The selected parameters included the location and thickness of the thickest part of the intestinal wall, mesenteric fat proliferation, mesenteric vessels change, enhancement pattern and the presence of complications. Patients were clinically assessed using the Crohn's disease activity index (CDAI), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Simple endoscopic score for Crohn's disease (SES-CD) was regarded as the reference standard.

Results The location of the thickest part of the intestinal wall ($\kappa = 0.653$), bowel wall thickness (ICC = 0.795), mesenteric vessels change ($\kappa = 0.692$) and complications ($\kappa = 0.796$) displayed substantial agreement (0.61–0.80) between CEUS and CTE, while the detection of mesenteric fat proliferation ($\kappa = 0.395$) and enhancement pattern ($\kappa = 0.288$) showed fair consistency (0.21–0.40) for comparison. In CEUS, bowel wall thickness, mesenteric fat proliferation, enhancement pattern and mesenteric vessels change were statistically significant in assessing CD activity, while bowel wall thickness, mesenteric fat proliferation and mesenteric vessels change in CTE. Bowel wall thickness showed the best diagnostic performance in the assessment of CD activity at CEUS and CTE.

Conclusion CEUS provides a radiation-free and effective way to assess the CD activity in comparison with CTE, which also avoids frequent colonoscopy examinations, improves tolerance of patients, and reduces the cost of medical care, thereby serving as a useful tool for CD follow-up.

Keywords Crohn's disease · Contrast-enhanced ultrasound · Computed tomography enterography

Abbreviations

CD	Crohn's disease
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
CDAI	Crohn's disease activity index
SES-CD	Simple endoscopic score for Crohn's disease
CEUS	Contrast-enhanced ultrasound

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CTE	Computed tomography enterography
ICC	Intra-group correlation coefficient
PPV	Positive predict value
NPV	Negative predict value
AUROC	Area under the receiver operating characteristic

Introduction

Crohn's disease (CD) is a chronic nonspecific inflammatory bowel disease characterized by alternating periods of relapse and remission, which can affect the entire gastrointestinal tract, and commonly occurs in the ileocolonic segments [1, 2]. Although the clinical manifestations of the disease vary greatly, the most common symptoms are recurrent abdominal pain and diarrhea which result in impaired quality of daily life [3, 4]. The adjustment of the clinical management for CD patients is usually carried out according to changes in clinical manifestations, laboratory examinations, endoscopy and imaging methods [5].

Currently, ileocolonoscopy is regarded to be the primary evaluation modality for the diagnosis of CD [1]. Furthermore, researchers have attempted to quantify the severity of inflammation severity and have developed a variety of endoscopic scoring systems, including the Crohn's disease endoscopic index of severity (CDEIS) and simple endoscopic score for Crohn's disease (SES-CD) [6]. SES-CD is the easiest system for use and has been applied to many endoscopic reporting systems [7]. However, the drawbacks of ileocolonoscopy are as follows: invasive, failure to reach the proximal small intestine, only the mucosal layer was assessed and susceptible to secondary edema [8]. To thoroughly assess the activity of CD, more comprehensive exploration methods besides ileocolonoscopy are imperative [9].

However, due to the prolonged course of CD, imaging monitoring needs to be integrated into the management of the whole disease course in order to delay the progression of the disease and improve the quality of life. Different contrast-enhanced cross-sectional imaging techniques, represented by computed tomography enterography (CTE), magnetic resonance enterography (MRE) and contrast-enhanced ultrasound (CEUS), have proved superior ability to assess CD activity [10, 11]. Among them, CEUS appears to be a convenient, radiation-free method for continuous tracking of disease activity. At present, most studies focused on the assessment of terminal ileitis and extra-enteric complications, few studies assessed the correlation between each typical imaging feature with disease activity in the comparisons of MRE with conventional US or CTE, and there were no studies using ileocolonoscopy as a standard to compare CEUS to CTE [12–14].

The purpose of this study was to investigate the consistency of imaging features between CTE and CEUS and compare the diagnostic performance of imaging parameters in the evaluation of CD activity between these two imaging modalities.

Materials and methods

The study protocol was approved by the hospital ethics committee. All patients were informed and agreed to use their data for this study.

Patients

This was a retrospective study that included patients in a tertiary hospital from January 2014 to December 2016. Fifty-two patients were finally enlisted in the study. The patient inclusion criteria were as follows: Patients with an established diagnosis of CD who were over the age of 18, had undergone CEUS, CTE and ileocolonoscopy and in line with conventional clinical practice. The exclusion criteria were patients with incomplete data, patients who refused to participate in the study, the interval between CEUS and CTE was greater than 1 weeks and previous history of bowel segments resection (Fig. 1).

Examination protocol

CEUS examination

A series of standard CEUS assessments for all patients were completed by an experienced operator, who had more than 10 years of ultrasound examination experience and was major in intestinal ultrasound, using Siemens S2000 ultrasound device (Siemens Medical Solutions, Mountain View, CA). The operator was blind to clinical and laboratory results. Patients fasted for 8 h before the examination and were kept fluid diet 1 day before examination. Firstly, the ileocecal section, ascending colon, transverse colon, descending colon and sigmoid colon were observed with a convex array probe (C1-6, with a frequency of 1–6 MHz), and then, the remaining intestinal segment was scanned around the umbilicus.

Afterward, a linear array probe (L4-9, with a frequency of 4–9 MHz) was used to focus on the thickest intestinal segment. The longitudinal section of the thickest intestinal segment was selected as the scanning section. Next, 2.4 mL of ultrasound contrast agent of SonoVue (Bracco, Milan, Italy) was dissolved in 5.0 mL of 0.9% sodium chloride and mixed with shaking for the solution preparation and then injected through peripheral venous with a bolus fashion for examination. The US machine was adjusted according to the depth of the lesion and the body size of the patient. Image collection

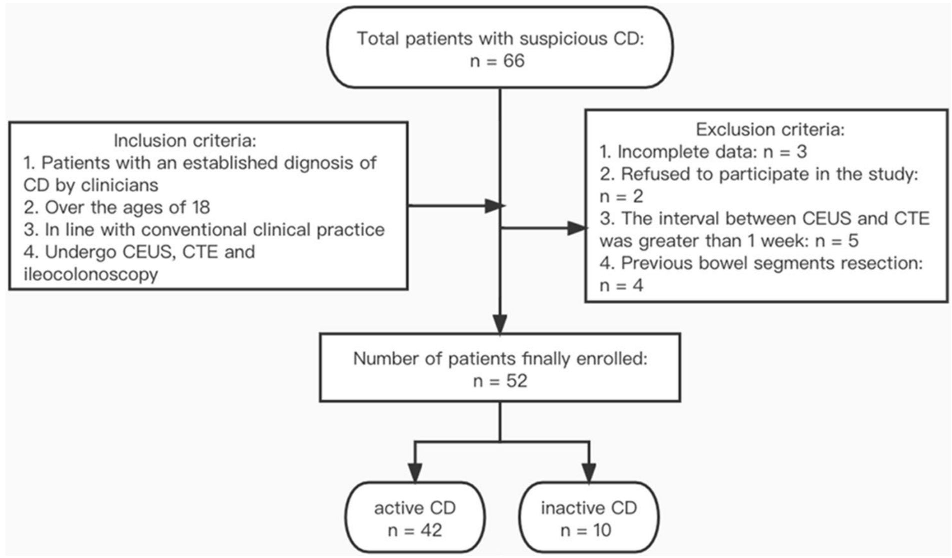

Fig. 1 Patients enrollment methods adopted in this study

was started at the same time of contrast agent injection to record the intestinal wall perfusion within 180 s of contrast agent injection, and the above cine clips and static images were stored. Two senior radiologists evaluated the affected intestinal wall. When disagreements existed, they reached an agreement after discussion.

CTE examination

After the exclusion of contraindications of acute intestinal obstruction and anisodamine, CTE examination was scheduled. The patients were fasted for 8 h before the examination, and fluid diet was taken 1 day before the examination. In the meantime, bowel cleaning preparation work also took place within 12 h before the examination, by taking orally 1500 mL of liquid prepared by polyethylene glycol electrolyte powder. One hour before the examination, 500 mL of 2.5% isotonic mannitol solution was taken orally every 15 min for a total of four times (2000 mL). The 64-slice multidetector CT scanner (SOMATOM Definition, Siemens, Germany) was used as the examination device. Firstly, the plain scan of the abdomen was performed, and an enhanced scan of the abdomen was performed after the injection of iohexol contrast agent. The image was reconstructed in the coronal and sagittal plane at the post-processing workstation. All images were assessed by two senior radiologists independently, and their opinions were negotiated to a consensus when they disagreed.

Parameters in different imaging techniques: CEUS versus CTE

The imaging parameters were selected for comparing as follows: (1) the site of the largest thickening of the intestinal wall (1, ileocecal/terminal ileum; 2, right hemicolon; 3, transverse colon; 4, left hemicolon); (2) the thickness (in mm) of the largest thickening of the intestinal wall; (3) mesenteric fat proliferation (0, absent; 1, present). Mesenteric fat proliferation is defined when the ultrasound image shows hyperechoic mass surrounding the bowel; or the CTE image is characterized by striped thickening of density shadows around the intestinal segments [15, 16]; (4) mesenteric vessels change (0, Limberg type 0, I, II on power Doppler ultrasound or the absence of comb sign on CTE; 1, Limberg type III, IV on power Doppler ultrasound or the presence of comb sign on CTE). The power Doppler ultrasound signal was graded according to Limberg B [17], which was subcategorized into Limberg type 0-IV: Grade 0, normal intestinal wall, Grade I, thickened intestinal wall with no blood flow signal is detected; Grade II, thickened intestinal wall with spotty or short striped blood flow signal; Grade III, thickened intestinal wall thickening with long strip of blood flow signal; Grade IV, thickened intestinal wall with long strip of blood flow signal connected to the mesentery. The comb sign on CTE is defined when the mesenteric vessels are increased and arranged in a comb along the wall of the intestine; (5) the presence of complications, including stenosis, abscess, or fistula (0, absent; 1, present); (6) CEUS and CTE enhancement pattern (0, pattern III or IV on CEUS or absence of target sign on CTE; 1, pattern I or II on CEUS or the presence of target sign on CTE). The CEUS enhancement pattern was classified according to Serra et al. [18], pattern I, enhancement of the entire intestinal wall from mucous to serous layer; pattern II, enhancement of the inner lining of the intestinal wall (mucosa, muscularis and submucosa); pattern III, enhancement of submucosal; pattern IV, no enhancement in the entire bowel segment. The target sign on CTE is defined when the affected thickened bowel wall shows the stratified enhancement as concentric rings of varying attenuation [19].

Diagnostic performance of selected parameters in different imaging techniques: CEUS versus CTE

Selected imaging signs were used to identify active or inactive CD: the thickness of the largest thickening of the intestinal wall, mesenteric fat proliferation, mesenteric vessels change, the presence of complications and the enhancement pattern. The diagnostics performance of these signs was compared between CEUS and CTE.

Endoscopic evaluation

After standard bowel cleaning preparation, all ileocolonoscopies were performed by several endoscopists with more than 10 years of experience in the assessment of inflammatory bowel disease (IBD), who were anonymous to the imaging results. The SES-CD scoring system was used to evaluate the CD activity. And the intestinal tract was divided into 5 segments under endoscopy, which were terminal ileum, right half colon (including ileocecal valve and ileocecal junction), transverse colon, left half colon and rectum, and was scored, respectively. The ulcer size, area of the ulcer, area of the affected intestinal tract, and luminal stenosis were assessed, and then, the total score was calculated (value of each 0 to 3). When the SES-CD score was 0–2, it was considered to be endoscopic remission, and the score ≥ 3 was considered endoscopic activity [7].

Statistical analysis

Statistical analyses were performed using SPSS v20.0 for Mac (IBM, Armonk, NY, USA). Simple descriptive statistics were used to describe the distribution of individual characteristics. Consistency between the two imaging features (unordered categorical variable) was carried out using Cohen's kappa coefficient (κ) statistical analysis, when κ index between 0–0.20 indicating poor consistency, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good and 0.81–1.00 excellent consistency. In addition to continuous variable like BWT, intra-group correlation coefficient (ICC) was adopted, when ICC value less than 0.40 was considered poor consistency, while ICC value greater than 0.75 was considered good consistency. The sensitivity, specificity, positive predict value (PPV), negative predict value (NPV) and area under the receiver operating characteristic (AUROC) of the selected parameters of CEUS, CTE and clinical indicators for active evaluation were calculated according to SES-CD. All $p < 0.05$ was considered statistically significant.

Results

Patients' characteristics

In the study, a total population of 52 patients (31 males, 21females, a median age of 38.5 years, range 8–51) was retrospectively included. The characteristics of these patients are shown in Table 1.

Ileocolonoscopy results

In ileocolonoscopy, ten cases were in remission and 42 cases were in activity when SES-CD was regarded as the reference standard for evaluation.

CEUS versus CTE based on selected parameters

In the parameter comparison, six radiological parameters of CEUS and CTE associated with CD were selected for comparison. Table 2 depicts the Kappa level and ICC value of intermodality agreement values (CEUS versus CTE). According to the commonly cited scale of interpretation of Kappa and ICC, the Kappa values (κ) varied between substantial agreement (0.61–0.80) for the thickest affected segment ($\kappa = 0.653$), and mesenteric vessels change ($\kappa = 0.692$) and complications ($\kappa = 0.796$), the ICC value showed good consistency (> 0.75) for BWT (ICC = 0.795), and Kappa values (κ) were fair (0.21–0.40) for detection of mesenteric fat proliferation ($\kappa = 0.395$) and enhancement pattern ($\kappa = 0.288$) (Figs. 2, 3, 4, 5, 6, 7).

Diagnostic performance of selected parameters in the evaluation of CD activity

Finally, the diagnostic performance of the selected parameters of CEUS/CTE for detecting active CD is shown in Tables 3 and 4, including BWT, mesenteric vessels change, mesenteric fat proliferation, enhancement pattern and complications. In CEUS, the following imaging parameters were statistically significant in assessing CD activity, including BWT, mesenteric fat proliferation, enhancement pattern and mesenteric vessels change. In CTE, the following imaging parameters were statistically significant in assessing CD activity, including BWT, mesenteric fat proliferation and mesenteric vessels change. CEUS showed higher sensitivity in comparison with CTE in BWT, mesenteric fat proliferation and mesenteric vessels change in the assessment of CD activity (BWT: 90.5% vs 88.1%; mesenteric fat proliferation: 71.4% vs 54.8%; mesenteric vessels change: 61.9% vs 50%). In particular, BWT showed the best diagnostic performance

Table 1 Clinical characteristics of the patients with CD

Characteristics	Inactive	Active	All
Female sex	1	20	21
Age (year)	35 (18–46)	39.5 (19–73)	38.5 (18–73)
CD duration (month)	36 (2–62)	24 (1–360)	24 (1–360)
Age (year) at diagnosis			
A1 (< 17)	1	1	2
A2 (17–40)	6	22	28
A3 (> 40)	3	19	22
Location			
L1 (terminal ileum)	–	21	21
L2 (colon)	–	10	10
L3 (ileocolon)	–	11	11
Newly diagnosed/relapse			
Newly diagnosed	0	3	3
Relapse	10	39	49
CRP (mg/L)	3.0 (0.5–67.5)	14.5 (3.3–169.9)	13.4 (0.5–169.9)
ESR	4.0 (3.0–39.0)	25.0 (3.0–57.0)	23.0 (3.0–57.0)
CDAI	120.85 (98.0–155.0)	163.5 (80.2–413.0)	152.5 (80.2–413.0)
SES-CD			
0–2	10	0	10
≥ 3	0	42	42

CD Crohn's disease, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *CDAI* Crohn's disease activity index, *SES-CD* simple endoscopic score for Crohn’s disease

Table 2 Agreement between selected common parameters of CEUS analysis and CTE in patients with CD

Parameter	CEUS	Total	CTE				κ-value/ ICC value	*p* value
Location		52	1	2	3	4	0.653	< 0.001
	1	26	20	4	1	1		
	2	12	1	11	0	0		
	3	6	3	0	2	1		
	4	8	0	1	0	7		
	Total	52	24	16	3	9		
Thickening	52						0.795	< 0.001
			Normal		Abnormal			
Mesenteric fat proliferation	Normal	20	16		4		0.395	0.003
	Abnormal	32	12		20			
	total	52	28		24			
Complications	Normal	41	37		4		0.796	< 0.001
	Abnormal	11	0		11			
	Total	52	37		15			
Mesenteric vessels change	Normal	26	20		6		0.692	< 0.001
	Abnormal	26	6		20			
	Total	52	26		26			
Enhancement pattern	Normal	25	7		18		0.288	0.003
	Abnormal	27	0		27			
	Total	52	7		45			

All $p < 0.05$ indicated that the results were statistically significant

CD Crohn's disease, *CEUS* contrast-enhanced ultrasound, *CTE* computed tomography enterography, *ICC* intra-group correlation coefficient

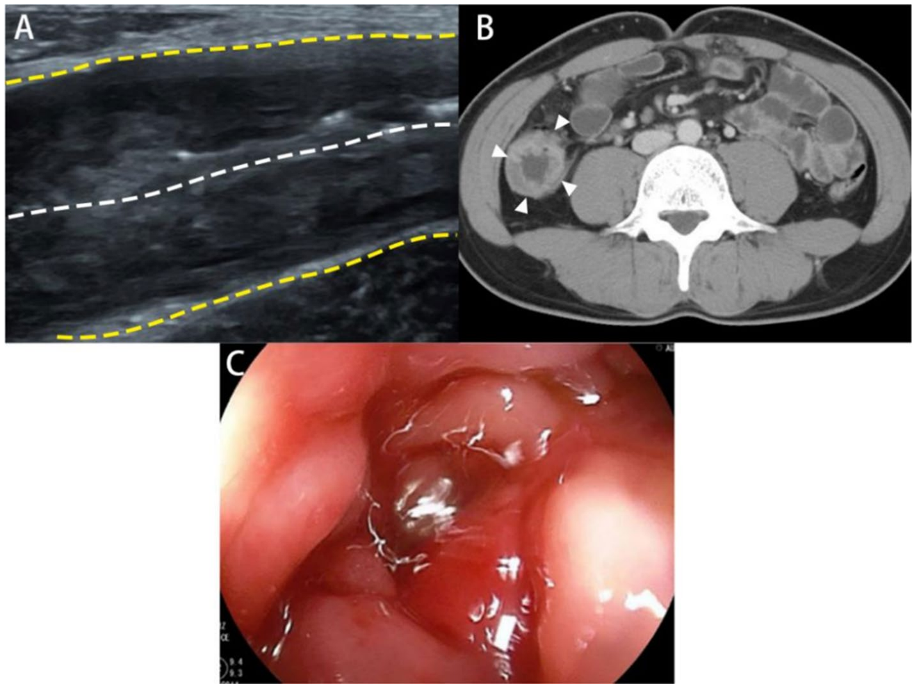

Fig. 2 The thickness of the largest thickening of the intestinal wall in active CD. **A** Longitudinal section of the beginning of the ascending colon at intestinal ultrasound. The BWT is 11.2 mm, and the intestinal wall layer is not clearly stratified (the yellow dotted lines represent the boundary between the serosal layer of the intestinal wall and the surrounding tissue, and the white dotted lines represent the bowel lumen, and the same is applied to the figure legends shown below); **B** At CTE, the intestinal segment indicated by the triangle is obviously thickened and the intestinal wall layer is not clearly stratified, with BWT about 11.0 mm; C. CD patient with bowel wall thickening on endoscopy. The total SES-CD is 14

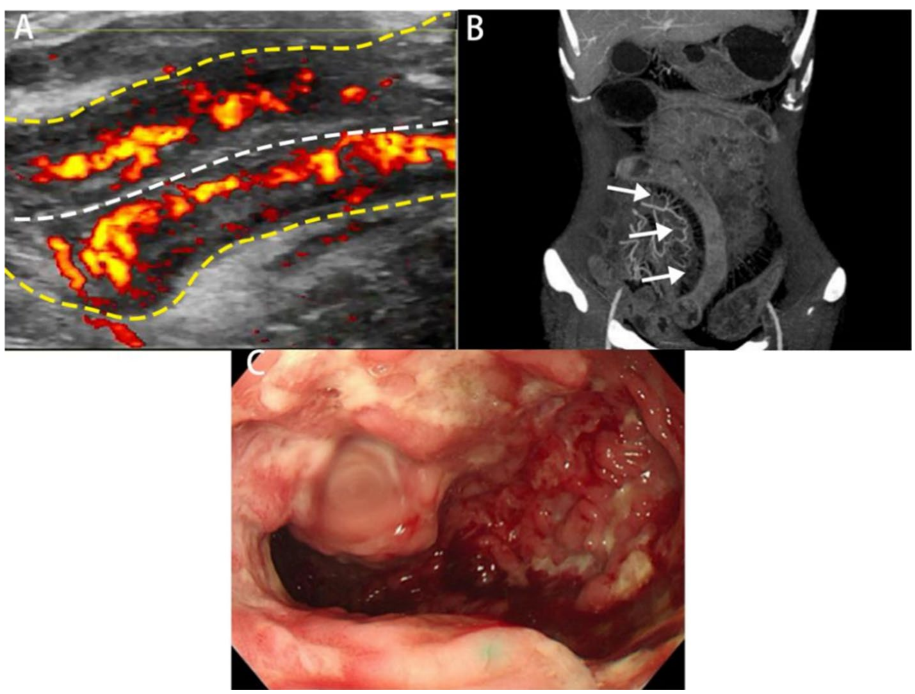

Fig. 3 Mesenteric vessels change in active CD. **A** Longitudinal sections of ascending colon at power Doppler ultrasound. It is classified as Limberg type IV; **B** At CTE, the mesenteric blood vessels are hyperplastic, with 'comb sign' present (white arrow); **C** CD patient with bowel wall thickening and mucosal hyperemia and edema, accompanied by ulceration on endoscopy. The total SES-CD is 11

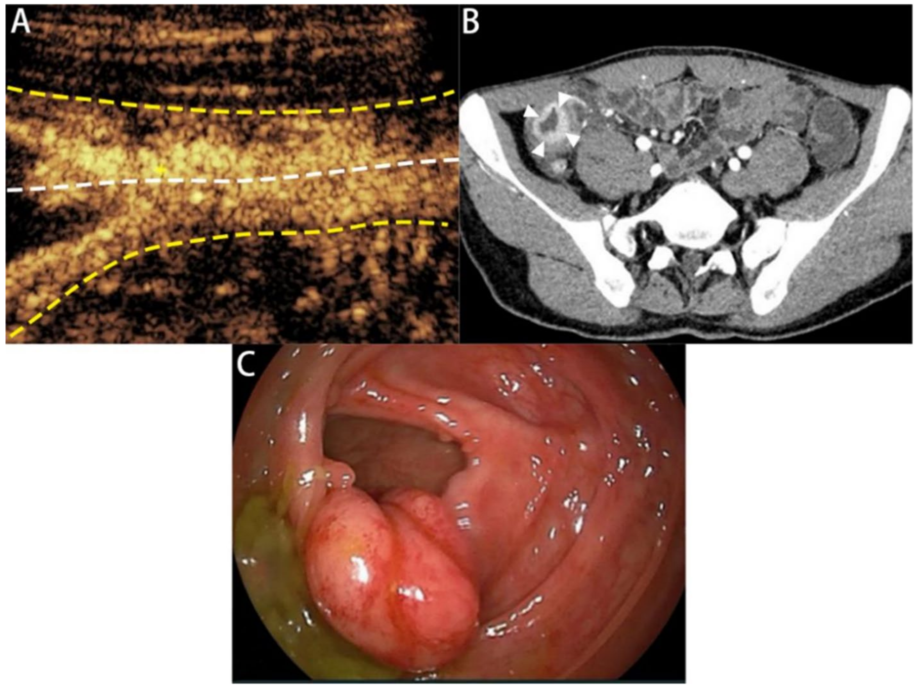

Fig. 4 Enhancement pattern in active CD. **A** Longitudinal section of ascending colon at CEUS shows submucosal hyper-enhancement; **B** At CTE, the affected segment shows stratified enhancement with significant enhancement of the inner intestinal wall, with 'target sign' present (triangle); **C** CD patient with bowel wall thickening, mucosal hyperemia and hyperplasia polyps on endoscopy. The total SES-CD is 20

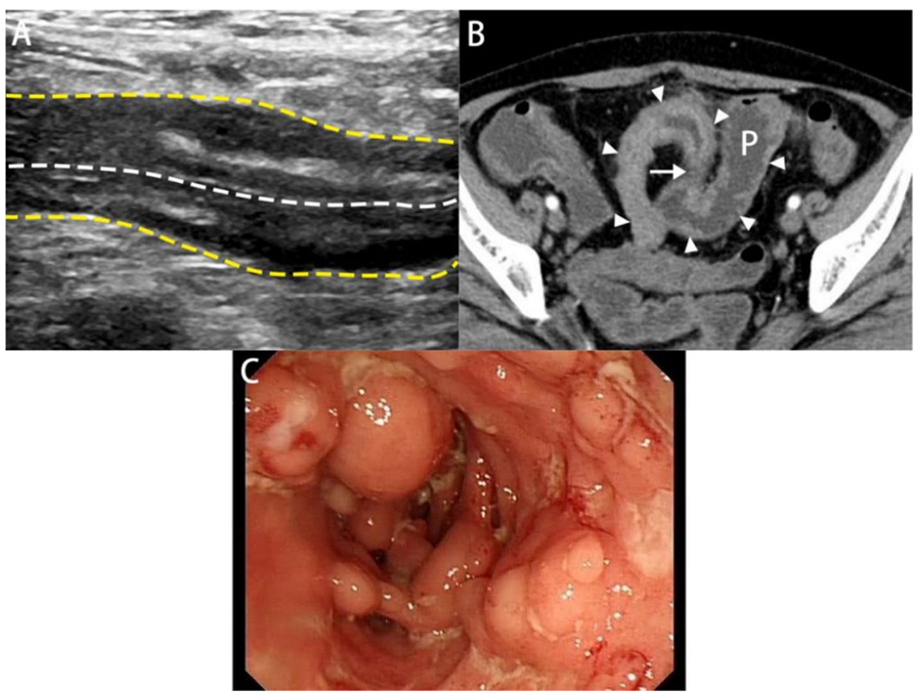

Fig. 5 The presence of complication of strictures in active CD. **A** Longitudinal section of the ileum at ultrasound shows the intestinal wall thickening with lumen stenosis; **B** At CTE, lumen stenosis (white arrow) with distal dilatation of the small intestine is shown (P), as well as strengthening and thickening of the intestinal wall (triangle); **C** CD patient with bowel wall thickening and mucosal hyperemia and multiple polypoid hyperplasia on endoscopy. The total SES-CD is 12

on both CEUS and CTE in the assessment of CD activity (sensitivity, 90.5% vs 88.1%; specificity, 80% vs 90%; PPV, 95% vs 97.3%; NPV 67% vs 64.3%; AUROC, 0.887 vs 0.883).

Discussion

In the present study, we compared the imaging parameters between CEUS and CTE in assessing CD activity. The agreement between CTE and CEUS was evaluated for six

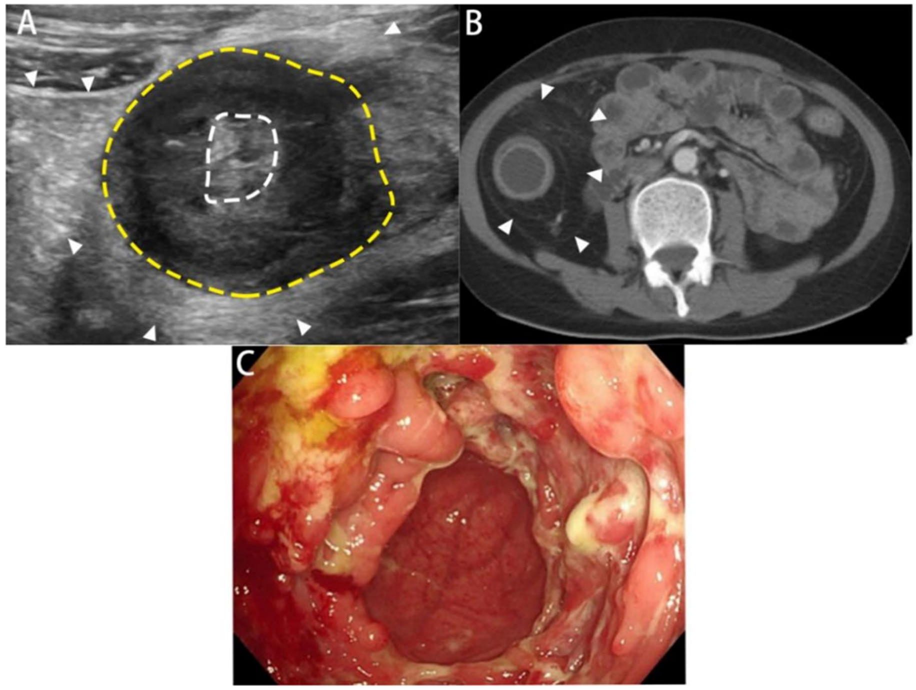

Fig. 6 Mesenteric fat proliferation in active CD. **A** Cross-sectional image of the beginning of the ascending colon at intestinal ultrasound, with hyperechoic mass surrounding the bowel (triangle); **B** at CTE, the mesenteric fat of the affected intestine segment is hyperplasia and is deposited around the intestine; **C** CD patient with mucosal hyperemia and coated with yellowish-white moss on endoscopy. The total SES-CD is 17

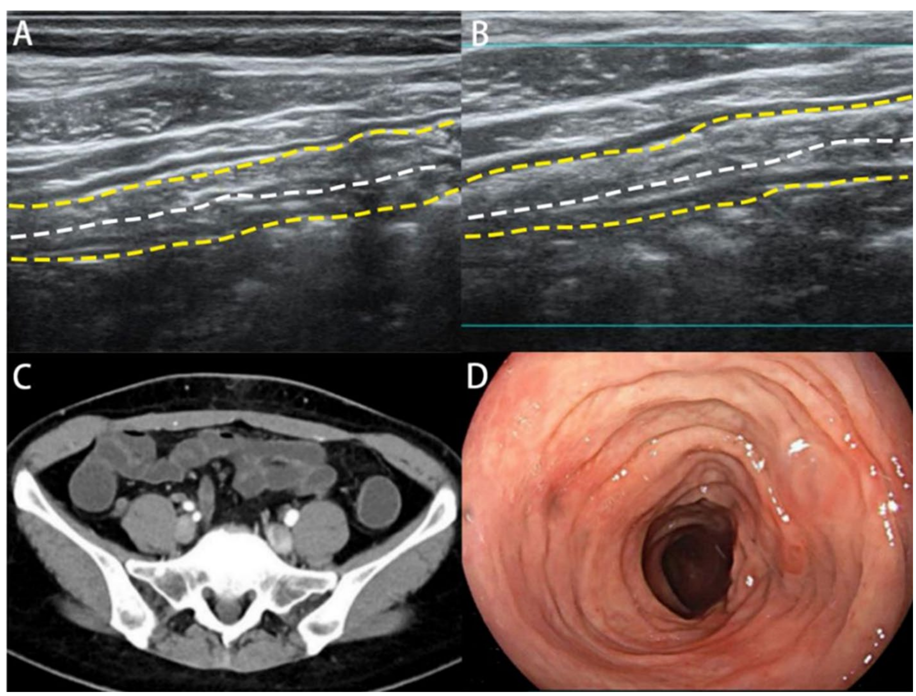

Fig. 7 Characteristics of inactive CD at CEUS, CTE and endoscopy. **A** Longitudinal section of terminal ileum at intestinal ultrasound. No obvious thickening of intestinal wall is observed. The BWT of the thickest segment is 2.9 mm, and the intestinal wall layer is clearly stratified; **B** Longitudinal section of terminal ileum at power Doppler ultrasound. It is classified as Limberg type 0; **C** At CTE, the intestinal wall is not thickened and there are no signs of other abnormalities; **D** Ileocolonoscopy indicates no obvious abnormalities in the intestine, and the total SES-CD is 0

selected imaging signs of CD, four of which were highly consistent, which proved that CEUS is comparable to the CTE with stable consistency.

Most previous studies had compared the imaging parameters of MRE and CTE in assessing CD activity. In the past studies, Amitai et al. compared ten indicators [20], which were different from the parameters we selected, in that they compared each complication as a parameter. It was found that the coherence coefficient of four of the signals exceeded 70%. Another prospective study compared the diagnostic accuracy of bowel US versus MRE in diagnosing CD, using ileocolonoscopy results as the

Table 3 Performance of selected parameters of CEUS for detecting active CD

CEUS parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUROC	*p* value
Thickening	90.5	80	95	67	0.887	< 0.001
Mesenteric fat proliferation	71.4	80	93.8	40	0.757	0.012
Enhancement pattern	97.6	60	91.1	85.7	0.788	0.005
Limberg type	61.9	100	100	38.4	0.810	0.003
Complications	23.8	90	90.9	22.0	0.569	0.501

All $p < 0.05$ indicated that the results were statistically significant

CD Crohn's disease, *CEUS* contrast-enhanced ultrasound, *PPV* positive predict value, *NPV* negative predict value, *AUROC* area under the receiver operating characteristic

Table 4 Performance of selected parameters of CTE for detecting active CD

CTE parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUROC	*p* value
Thickening	88.1	90	97.3	64.3	0.883	< 0.001
Mesenteric fat proliferation	54.8	90	95.8	32.1	0.724	0.029
Enhancement pattern	59.5	80	95.2	80	0.698	0.054
Comb sign	50	61.9	84	22.2	0.810	0.003
Complications	33.3	90	93.3	24.3	0.617	0.255

All $p < 0.05$ indicated that the results were statistically significant

CD Crohn's disease, *CTE* computed tomography enterography, *PPV* positive predict value, *NPV* negative predict value, *AUROC* area under the receiver operating characteristic

reference standard, in which the sensitivity, specificity, and accuracy of intestinal ultrasound for all parameters considered (localization, thickening, disease activity, stenosis, fistula, abscess) were very close to MRE [12].

In the present study, the cut-off values of BWT for identifying active and inactive CD in CEUS and CTE were 6.5 mm and 5.4 mm, respectively. However, the BWT cut-off values for evaluating CD inflammatory activity had not been unified and varied from 3 to 7 mm in the previous studies [21]. Novak et al. found that when the BWT cut-off value was 7 mm, the area under the curve was as high as 0.937 [22]. Liu et al. found that when the cut-off value was 6 mm, the area under the curve was 0.977 [23]. Therefore, the results have yet to be verified by a multi-center study.

The present study also evaluated the consistency of CD activity by comparing the enhancement patterns of CEUS and CTE, and the results showed that the consistency was not stable in the qualitative methods. In the current study, the diagnostic performance of the target sign on CTE was not statistically significant, but it was a significant sign in most of other studies [24, 25]. At the same time, the enhancement patterns of CEUS showed superior advantage. Complementary, there were quantitative methods to assess CD activity in other studies, for instance, the enhanced peak of CEUS [26], and the slope of the Hounsfield unit (HU) curve in CTE [27]. It is imperative for the future studies to compare the quantitative parameters on CEUS.

As for the evaluation of mesenteric vessels changes, although the consistency is acceptable, its sensitivity is still low (CEUS vs CTE, 61.9% vs 50%). Emerging ultrasound technologies such as superb microvascular imaging (SMI) can be added to future studies to achieve a more sensitive evaluation effect. In addition, when evaluating the presence of mesenteric fat proliferation, the consistency between the two imaging methods was poor. CEUS evaluation for mesenteric fat proliferation seemed to be a more sensitive method resulting from the intuitive display of mesenteric changes. Significantly, the present of mesenteric fat proliferation is also one of the important predictors of intestinal wall fibrosis and the accurate evaluation of it is bound to provide important information for the clinical management of CD [28].

In regard to the diagnostic performance of each selected parameter for different modalities, the thickness of the intestinal wall had the highest accuracy in both imaging methods. It was consistent with intestinal wall thickness as the most reliable sign for the diagnosis of CD [29]. Moreover, our study compared the parameters in two different imaging methods more comprehensively. Not only relatively intuitive imaging features (BWT, mesenteric fat proliferation, complications), but also related imaging parameters with the same generation mechanism (mesenteric vessels change, enhancement patterns) were compared to evaluate the consistency in assessing CD activity.

There were still several limitations to the study. Firstly, the sample size was relatively small, and thus, the consistency of complications was not evaluated in detail for the types. And it did not set the weight of each parameter to obtain a scoring system. Second, the study design was retrospective, and thus, some bias might be present.

In general, the clinical manifestations of CD may lag behind the changes in intestinal mucosal changes, so it is crucial to assessing the activity of CD with biomarkers, cross-sectional imaging, and endoscopy [30]. Through this comparative study of various parameters, the assessment ability of CEUS was comparable to CTE. From the perspective of long-term follow-up of patients, CEUS may be an effective non-invasive method that can be used combined with inflammation biomarkers to avoid frequent CTE or colonoscopy examinations, which can improve tolerance of patients and reduce the cost of medical care.

Acknowledgements This work was supported in part from the National Natural Science Foundation of China (Grant 82102048); Shanghai Municipal Health Commission (Grants 2019LJ21 and SHSLCZDZK03502), and the Science and Technology Commission of Shanghai Municipality (Grants 19DZ2251100, and 19441903200), and the Talent Project of Shanghai Tenth People's Hospital (Grant 2021SYPDRC067).

Author contributions DSS, LC and XHX were involved in study design; LC, DSS and XXR contributed to patient recruitment, data collection, statistical analysis and data interpretation; DSS was involved in writing of the first draft of the paper; LC and XHX contributed to revision of the manuscript for important intellectual content; ZYF, SLP, LH, XLH, RWW, ZH, FY, SXM and ZK were involved in providing administrative, technical and material support; XHX and XXR contributed to supervising the study.

Funding This work was supported in part from the National Natural Science Foundation of China (Grant 82102048); Shanghai Municipal Health Commission (Grants 2019LJ21 and SHSLCZDZK03502), and the Science and Technology Commission of Shanghai Municipality (Grants 19DZ2251100, and 19441903200), and the Talent Project of Shanghai Tenth People's Hospital (Grant 2021SYPDRC067).

Declarations

Conflict of interest The authors disclose no conflicts of interest.

Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

Inform consent Not applicable.

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