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Abdominal ultrasonography with color Doppler analysis in the assessment of ileal Crohn's disease: comparison with magnetic resonance enterography

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Background/Aims: Consistently defining disease activity remains a critical challenge in the follow-up of patients with Crohn's disease (CD). We investigated the potential applicability of abdominal ultrasonography with color Doppler (USCD) analysis for the detection of morphological alterations and inflammatory activity in CD. **Methods:** Forty-three patients with CD ileitis/ileocolitis were evaluated using USCD analysis with measurements obtained on the terminal ileum and right colon. Sonographic parameters included wall thickening, stricture, hyperemia, presence of intra-abdominal mass, and fistulas. Patients were evaluated for the clinical activity (Harvey-Bradshaw Index [HBI]), fecal calprotectin (FC) and C-reactive protein (CRP). The USCD performance was assessed using magnetic resonance enterography (MRE) as a criterion standard. **Results:** Most measurements obtained with USCD matched the data generated with MRE; however, the agreement improved in clinically active patients where sensitivity, positive predictive value, and accuracy were >80%, considering wall thickening and hyperemia. Complications such as intestinal wall thickening, stricture formation, and hyperemia, were detected in the USCD analysis with moderate agreement with MRE. The best agreement with the USCD analysis was obtained in regard to FC, where the sensitivity, positive predictive value, and accuracy were >70%. The overall performance of USCD was superior to that of HBI, FC and CRP levels, particularly when considering thickening, stricture, and hyperemia parameters. **Conclusions:** USCD represents a practical noninvasive and low-cost tool for evaluating patients with ileal or ileocolonic disease, particularly in clinically active CD. Therefore, USCD might become a useful asset in the follow-up of patients with CD. **(Intest Res 2019;17:227-236)**

Key Words: Crohn disease; Ileitis; Color Doppler ultrasonography; Magnetic resonance imaging; Calprotectin

INTRODUCTION

Crohn's disease (CD) represents one of the major forms of IBD and is characterized by chronic and relapsing inflammation of the gut, with the potential to determine highly heterogeneous outcomes and different complications.[1,2] The routine diagnosis and follow-up of patients with CD relies on a combination of clinical manifestations and the results of complementary examinations including laboratory tests, endoscopy and imaging techniques.[3-5] Although colonoscopy remains the gold standard for the evaluation of IBD, the technique is carried out basically to assess mucosal inflammation or healing, hence encompassing important limitations.[6] In addition to invasiveness and costs of repeated examinations, colonoscopy

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may not provide access to proximal ileal lesions in CD, and does not reach the small bowel.[7-9] Moreover, the transmural pathological involvement of CD renders cross-sectional imaging techniques as critically necessary in the follow-up of patients.[10]

While the unbiased estimation of disease activity and response to treatment in CD have been increasingly emphasized, with clear implications in the outcome of patients,[11,12] determining the inflammatory activity continues to be rather challenging. Currently, imaging techniques have a compelling role in the diagnosis and management of IBD and have continuously evolved with increasing improvements in quality. In this context, magnetic resonance enterography (MRE) has risen as a convenient radiation-free substitute to CT, with equivalent diagnostic performance.[13,14] However, general availability and costs still constitute a limitation for its widespread use. Nevertheless, ultrasound has been investigated as an interesting approach, being less expensive, and without any risk for the patients. In addition to the assessment of wall thickness, the search for abscess, tumor, and fistulas, sonography has also been used for evaluating blood flow and vascular abnormalities, using the Doppler technique for this purpose.[15,16]

In particular, in CD evaluation, most Doppler sonography studies, specially the ones regarding superior mesenteric artery (SMA) flow analysis, have attempted to identify a potential relationship between data of the splanchnic hemodynamics and disease activity, nevertheless yielding contradictory results.[17-20] In contrast, considering the analysis of hyperemia in the intestinal wall there is evidence indicating a positive correlation with endoscopic inflammatory activity and/or surgical specimens.[10]

The aim of this prospective study was to examine the usefulness of transabdominal ultrasonography with color Doppler (USCD) analysis for the evaluation of disease activity and complications in patients with ileal CD, in comparison with MRE.

METHODS

1. Study Population

The study population was illustrative of a cohort of patients submitted to regular follow-up in the outpatients unit of the division of gastroenterology. Forty-three consecutive patients with CD involving the ileum and/or the right colon were enlisted in this study. Diagnosis of CD was confirmed by the combination of imaging, endoscopic and histological criteria. Patients with CD consisted of 27 women and 16 men, with a median age of 46 years (range, 18–82 years). Demographic and clinical information were collected using a standard questionnaire, including elements of the Montreal classification.[21] Disease location and predominant behavior were determined based on the patient's latest endoscopic and/or imaging method assessment, within the last 12 months of follow-up. Exclusion criteria were defined by disease localization in the colon and/or in the upper GI tract, a history of multiple intestinal resections, age under 18 years, chronic conditions with potential significant hemodynamic effect, including late-stage renal disease, vascular disease, cardiac failure and pulmonary hypertension, inability to undergo MR imaging without sedation or because of the presence of incompatible metallic hardware within the patient's body. None of the patients enrolled in the study were using any cardiovascular medications such as α- or β-blocking agents, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, calcium-channel blockers hydralazine, nitrates, or α-2 agonists.

2. Ethical Considerations

The Ethical Committee of the University Hospital of the Federal University of Rio de Janeiro approved the study protocol (CAAE: 34165014.9.0000.5257), which was implemented in consonance with the ethical standards described in the 1964 Declaration of Helsinki. All subjects provided their informed consent prior to inclusion in the study.

3. Study Protocol

This cross-sectional study was carried out at the University Hospital of the Federal University of Rio de Janeiro (a tertiary care setting) between July 2015 and December 2016. All patients were evaluated according to the well-established Harvey-Bradshaw Index (HBI),[22] and were submitted to fecal calprotectin and plasma CRP measurements, in addition to MRE and abdominal USCD analysis (interval of less than 2 weeks for all parameters). The same investigators (G.M. and A.A.), with more than 20 years of experience and with no previous knowledge on the medical status of the patients, analyzed all imaging examinations.

4. Abdominal Ultrasonography and Doppler Analysis

All patients underwent transabdominal USCD analysis for the assessment of morphological abnormalities, and disease location, activity, and potential complications. Exams were performed with a Philips iU22 ultrasound system (Amsterdam, the Netherland), using a linear (10–12 MHz) and convex (5–

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10 MHz) transducer. In order to avoid the potential effects of physical activity, body position, and meals, on hemodynamic status, all the assessments began after at least 15 minutes of rest, always in the supine position, and following 6 hours fasting. After a basic standardized inspection of the whole abdomen, the most relevant ileal segment was selected for further analysis, as described previously.[23]

The following parameters were considered: maximum bowel wall thickness (<4 mm, normal; ≥4 mm, abnormal), intestinal complications such as strictures, fistulas, and mass or abscesses (present or absent), as described previously.[24] The range of blood flow velocities was adjusted to 4 cm/sec on color Doppler ultrasonography, and semi-quantitatively graded based on previously published parameters.[25] Briefly, according to the Limberg score, a normal intestinal wall without a color Doppler signal characterized grade 0. A hypoechoic intestinal wall without increased vascularity determined grade 1. Grades 2 and 3 were exemplified as intestinal wall thickness with short or long stretches of vascularity, respectively, while grade 4 as longer stretches of vascularity extending into the neighboring mesentery.[25] Bowel wall hyperemia was then defined as increased color signals (grades 2, 3, or 4), compared to normal loops (grades 0 or 1), assessed at the SMA territory using a high-resolution microconvex probe, with the patient's breath held in expiration.[26]

5. Magnetic Resonance Enterography

Exams were performed on a GE 1.5 Tesla scanner Signa Excite HD, with EchoSpeed SR120 type 8916 HFD gradient of 8-Channel MR imaging (General Electric Co., Boston, MA, USA). Briefly, after 6 hours fasting, 1,200 mL of a hyperosmotic mannitol solution was orally administered in 200 mL aliquots, every 10 minutes. Patients were then placed supine on the MRI scanner table and 3 plane images were acquired for general evaluation and quality check. Sequences comprised both coronal and axial single-shot fast spin echo T2 images, coronal fast steady state free precession, and axial fast recovery T2 with fat suppression. Following the intravenous administration of an antispasmodic agent, T1-weighted sequence was performed before and 30 seconds, as well as 1 and 3 minutes after an intravenous injection of gadolinium.

The following parameters were analyzed: presence of complications such as fistulas, strictures, mass or abscess; wall thickening of terminal ileum and/or right colon (>10 mm); stratified bowel wall contrast enhancement and vascular engorgement of vasa recta (comb sign). Bowel wall enhancement and/or comb sign were the MRE parameters used for comparison with USCD hyperemia.

6. Statistical Analysis

All statistical analyses were carried out using the statistical software SPSS for Windows version 20 (IBM Corp., Armonk, NY, USA). Simple descriptive statistics was used to characterize the distribution of the individual features. Sensitivity, specificity, both positive and negative predictive values, and overall accuracy related to CD activity were calculated for selected sonographic parameters. Differences among the distributions of the selected variables were assessed by the chi-square McNemar test for categorical data. Cohen's weighted κ statistic was used to assess agreement between the tests. All tests applied were two-tailed, and statistical significance was considered when *P*-value was less than 0.05.

Table 1. Clinical and Demographic Features of the Patients with CD

Characteristics	Value (n=43)
Female sex	27 (62.79)
Age (yr)	46.0 (18–82)
CD duration (yr)	11 (1–30)
Age at diagnosis (yr)	
A1 (<17)	1 (2.32)
A2 (17–40)	29 (67.44)
A3 (>40)	13 (30.23)
Location	
L1 (terminal ileum)	30 (69.76)
L3 (ileocolon)	13 (30.23)
Behavior	
B1 (nonstricturing & nonpenetrating)	12 (27.91)
B2 (stricturing)	19 (44.18)
B3 (penetrating)	12 (27.91)
Surgery for CD	19 (44.18)
Activity index	3.0 (1–17)
CRP (mg/L)	1.67 (0.3–89.0)
Calprotectin (μg/g)	250 (18–1,800)
Immunosuppressive agent	16 (37.21)
Anti-TNF-α and immunosuppressive agent	16 (37.21)
Anti-TNF-α	7 (16.28)
Mesalamine	2 (4.65)
Corticosteroid	2 (4.65)

Values are presented as number (%) or median (range).

RESULTS

1. Clinical Data and Image Acquisition

The clinical and demographic features of the patients enrolled in the investigation are summarized in Table 1.

Appropriate images of transabdominal USCD analysis were acquired from all subjects involved in the investigation (Supplementary Fig. 1). For the purpose of determining USCD parameters for the evaluation of ileal CD activity, measurements obtained for CD patients were analyzed in view of the HBI. Overall, 15 patients were characterized as clinically active, while 28 were in clinical remission by the time of the clinical evaluation.

2. Overall Comparison between USCD and MRE

The comparison between USCD and MRE, regarding predetermined selected parameters, resulted in a general low agreement but without any significant difference (Table 2). The critical analysis of the results, using MRE as a criterion standard, showed a relatively good general performance for USCD, however with a relatively low specificity. Nevertheless, results remarkably improved when considering patients with clinically active disease (Table 3).

3. USCD versus MRE Based on Selected Parameters

Next, we analyzed the selected individual parameters for comparing abdominal USCD analysis with MRE. In regard to common consequences of ileal CD such as intestinal wall thickening (76.2%), the presence of stricture (47.6%), and hyperemia (52.4%), all of them were detected by USCD with a relatively good agreement with MRE. On the other hand, parameters such as mass or abscess, and fistula, present in low rates among the patients (2.4% and 11.9%, respectively), were not detected by USCD (Table 4). Finally, the overall performance of the individual USCD parameters for identifying active ileal CD, including wall thickening, stricture, and hyperemia, were critically analyzed. The sensitivity, specificity, positive and negative predictive values, and accuracy were determined for USCD, using MRE as a criterion standard. The best agreement between USCD and MRE results were obtained among the patients with clinically active disease. In particular, sensitivity, positive predictive value, and accuracy were greater than 80% in patients with clinically active disease, analyzed for wall thicken-

Table 2. Agreement between Abdominal USCD Analysis and MRE in the Context of CD Clinical Activity

Parameter	USCD	Total (%)	MRE (%)		κ-value (95% CI)	*P*-value[a]
			Normal	Abnormal		
Quiescent CD	Normal	6 (21.4)	3	3	0.146 (−0.214 to 0.512)	0.410
	Abnormal	22 (78.6)	7	15		
	Total	28 (100.0)	10 (35.7)	18 (64.3)		
Active CD	Normal	1 (6.7)	0	1	0.000	-
	Abnormal	14 (93.3)	0	14		
	Total	15 (100.0)	0	15 (100.0)		
All CD	Normal	7 (16.3)	3	4	0.200 (−0.134 to 0.527)	0.549
	Abnormal	36 (83.7)	7	29		
	Total	43 (100.0)	10 (23.2)	33 (76.7)		

Abdominal ultrasonography with color Doppler (USCD) analysis and magnetic resonance enterography (MRE) were defined as abnormal whenever one or more parameters (thickening, mass, abscess, stricture, fistula, hyperemia) were present. Clinical activity based on the Harvey-Bradshaw Index.
[a]*P*-value by chi-square McNemar test.

Table 3. Critical Analysis of Abdominal USCD Performance for Detecting Active Ileal CD Regarding the Clinical Activity

USCD	Sensitivity	Specificity	PPV	NPV	ACC
Quiescent CD	83.3 (60.7–94.2)	30.0 (10.8–60.3)	68.2 (47.3–83.6)	50.0 (18.7–81.2)	64.3 (45.8–79.3)
Active CD	93.3 (70.2–98.8)	-	100.0 (78.5–100.0)	0.0 (0.0–79.3)	93.3 (70.2–98.8)
All CD	87.9 (72.7–95.2)	30.0 (10.8–60.3)	80.5 (64.9–90.2)	42.9 (15.8–74.9)	74.4 (59.7–85.1)

Parentheses show lower-upper 95% CI. Magnetic resonance used as a criterion standard. Clinical activity based on the Harvey-Bradshaw Index.
USCD, ultrasonography with color Doppler; PPV, positive predictive value; NPV, negative predictive value; ACC, accuracy.

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ing and hyperemia (Table 5).

4. Association between USCD and Common Biomarkers

In regard to other commonly used biomarkers for IBD, CRP values were greater than 3.0 mg/L in 38.2% of patients, while fecal calprotectin was greater than 200 μg/g in 62.2% of the patients. The best agreement with USCD was obtained in regard to fecal calprotectin. In particular, sensitivity, positive predictive value, and accuracy were greater than 70% considering the overall analysis (Table 6). Nevertheless, none of the biomarkers had any significant correspondence with the clinical activity, or the imaging methods, USCD (Supplementary Table 1) and MRE (Supplementary Tables 2, 3). The critical challenges concerning abdominal ultrasonography in CD and the major findings of the present study are summarized in Table 7.

Table 4. Agreement between Selected Parameters of Abdominal USCD Analysis and MRE in Patients with Ileal CD

Parameter	USCD	Total (%)	MRE (%)		κ-value (95% CI)	*P*-value[a]
			Absent	Present		
Thickening	Absent	11 (25.6)	5	6	0.307 (-0.042 to 0.608)	1.000
	Present	32 (74.4)	5	27		
	Total	43 (100.0)	10 (23.3)	33 (76.7)		
Mass (abscess)	Absent	43 (100.0)	42	1	0.000	-
	Present	0	0	0		
	Total	43 (100.0)	42 (97.7)	1 (2.3)		
Stricture	Absent	27 (62.8)	18	9	0.337 (0.057 to 0.581)	0.424
	Present	16 (37.2)	5	11		
	Total	43 (100.0)	23 (53.5)	20 (46.5)		
Fistula	Absent	42 (97.7)	37	5	-0.040 (-0.108 to 0.000)	0.219
	Present	1 (2.3)	1	0		
	Total	43 (100.0)	38 (88.4)	5 (11.6)		
Hyperemia	Absent	25 (58.1)	17	8	0.444 (0.178 to 0.711)	0.388
	Present	18 (41.9)	4	14		
	Total	43 (100.0)	21 (48.8)	22 (51.2)		

[a]*P*-value by chi-square McNemar test.
USCD, ultrasonography with color Doppler; MRE, magnetic resonance enterography.

Table 5. Performance of Selected Parameters of Abdominal USCD Analysis for Detecting Active Ileal CD

USCD parameter	Clinical activity	Sensitivity	Specificity	PPV	NPV	ACC
Thickening	Quiescent	77.8 (54.8-91.0)	50.0 (23.6-76.3)	73.7 (51.2-88.2)	55.6 (26.6-81.1)	67.9 (49.3-82.1)
	Active	86.7 (62.1-96.3)	-	100.0 (77.2-100.0)	0.0 (0.0-65.7)	86.7 (62.1-96.3)
	All patients	81.8 (65.6-91.4)	50.0 (23.6-76.3)	84.4 (68.2-93.1)	45.5 (21.3-72.0)	74.4 (59.7-85.1)
Stricture	Quiescent	50.0 (23.6-76.3)	83.3 (60.8-94.2)	62.5 (30.6-86.3)	75.0 (53.1-88.1)	71.4 (52.9-84.7)
	Active	60.0 (31.3-83.2)	60.0 (23.1-88.2)	75.0 (40.9-92.8)	42.9 (15.8-74.9)	60.0 (35.7-80.2)
	All patients	55.0 (34.2-74.2)	78.3 (58.1-90.3)	68.8 (44.4-85.8)	66.7 (47.8-81.3)	67.4 (52.5-79.5)
Hyperemia	Quiescent	45.5 (21.3-72.0)	76.5 (52.7-90.4)	55.6 (26.6-81.1)	68.4 (46.0-84.4)	64.3 (45.8-79.3)
	Active	81.8 (52.3-94.8)	100.0 (51.0-100.0)	100.0 (70.1-100.0)	66.7 (30.0-90.3)	86.7 (62.1-96.3)
	All patients	63.6 (42.9-80.3)	81.0 (60.0-92.3)	77.8 (54.8-91.0)	68.0 (48.4-82.8)	72.1 (57.3-83.2)

Parentheses show lower-upper 95% CI. Magnetic resonance enterography used as a criterion standard. Clinical activity based on the Harvey-Bradshaw Index.
USCD, ultrasonography with color Doppler; PPV, positive predictive value; NPV, negative predictive value; ACC, accuracy.

Table 6. Critical Analysis of Clinical and Laboratory Evaluation for Detecting Active CD in the Terminal Ileum Based on Abdominal USCD Findings

Test	Sensitivity	Specificity	PPV	NPV	ACC
Clinical activity	38.9 (24.8–55.1)	14.3 (2.6–51.3)	70.0 (48.1–85.4)	4.3 (0.8–21.0)	34.9 (22.4–49.8)
Calprotectin	70.0 (52.1–83.3)	71.4 (35.9–91.8)	91.3 (73.2–97.6)	35.7 (16.3–61.2)	70.3 (54.2–82.5)
CRP	40.0 (24.6–57.7)	75.0 (30.1–95.4)	92.3 (66.7–98.6)	14.3 (4.9–34.6)	44.1 (28.9–60.5)

Parentheses show lower-upper 95% CI. Abdominal ultrasonography with color Doppler (USCD) used as a criterion standard.
PPV, positive predictive value; NPV, negative predictive value; ACC, accuracy.

Table 7. Study Summary

Challenges	Major findings
Consistently defining disease activity remains a critical challenge in the follow-up of patients with CD.	The sonographic measurements obtained in this study relatively matched the data generated by magnetic resonance, particularly when considering subjects with clinically active disease.
Abdominal ultrasonography has been proposed for the detection of morphological alterations and inflammatory activity in patients with CD.	Characteristic abnormalities of CD including intestinal wall thickening, stricture formation, and hyperemia were detected by abdominal USCD analysis with a moderate agreement with magnetic resonance.
Previous studies focusing on Doppler sonography for evaluating CD activity rendered controversial results.	The results indicate that USCD represents a practical noninvasive and a relative low-cost tool for evaluating patients with ileal or ileocolonic disease, particularly in clinically active CD.

USCD, ultrasonography with color Doppler.

DISCUSSION

In this study, we demonstrated the potential applicability of abdominal USCD analysis in the evaluation of patients with CD involving the ileum. The sonographic parameters investigated demonstrated that most measurements obtained on the wall of the terminal ileum and right colon relatively matched the data generated by MRE, however the agreement remarkably improved when considering subjects with clinically active disease. In terms of individual parameters, common characteristic abnormalities of CD such as intestinal wall thickening, stricture formation, and hyperemia were detected by USCD with a moderate agreement with MRE. Common biomarkers used for IBD, including fecal calprotectin and plasma CRP did not show any significant relationship with the clinical activity, or the findings obtained with the imaging methods, MRE and USCD. The results indicate that USCD represents a practical noninvasive and a relative low-cost tool for evaluating patients with ileal or ileocolonic disease, particularly in clinically active CD.

Currently, consistently defining disease activity remains a critical challenge in the follow-up of patients with CD. As a consequence, optimizing the treatment of patients with CD still largely depends on subjective analysis, with potentially questionable decisions, even for experts in the field of IBD. Although remarkable improvements regarding the detection of abnormalities and complications have been achieved in the field of imaging,[27-30] there are still several concerns involving costs, availability, irradiation, and the need for repeated examinations.[31,32] In this context, techniques involving ultrasonography and Doppler analysis have been investigated in the last decade as potential alternative methods for the assessment of CD activity, primarily based on data acquired in the SMA. Both hyperemia and neovascularization of the gut have been detected by color Doppler and power Doppler,[33,34] and by pulsed Doppler spectral analysis,[35,36] allowing the identification of inflamed areas. In a previous work from our group, we also demonstrated the usefulness of Doppler ultrasound examination for patients with CD by the detection of abnormal patterns of splanchnic hemodynamics, confirming the presence of a hyperdynamic circulation. However, analysis of the SMA parameters could not discriminate disease activity confidently among the individual patients.[37] In another investigation, following a protocol similar to the one presented in this study, investigators demonstrated the effectiveness of combining abdominal ultrasonography and color Doppler for the monitoring of CD, and proposed the method as a strong predictor of mucosal healing.[38]

Previous studies focusing on Doppler sonography for evaluating CD activity rendered controversial results. The investigation of particular SMA measurements indicated that the best parameters for discriminating CD patients, in regard to disease activity, would be the maximum flow volume,[39,40] and the

resistance index.[41,42] On the other hand, a similar investigation with CD patients failed to establish any correspondence between the detected hyperdynamic mesenteric circulation and disease activity based on usual clinical and laboratory evaluation.[15] Results from another study with Doppler sonography suggested that CD activity would be better assessed through the characterization of the SMA segments by grey scale.[43] In contrast, in this study, we propose a novel assessment of ultrasonography with Doppler analysis, ranging from semi-quantitative (wall thickening and hyperemia) to qualitative (stricturing, mass/abscess, and fistula) parameters. In this regard, we demonstrated a relatively low agreement between USCD and MRE concerning the measurements of selected parameters for the evaluation of CD patients, but without any significant difference between the methods. Nevertheless, the critical analysis of the results using MRE as a criterion standard, showed an overall good performance for USCD, but with relatively low specificity. However, the agreement between USCD and MRE improved drastically when analyzing patients with clinically active CD, as opposed to patients in clinical remission. Although there is no obvious explanation for this discrepancy, it is possible that selecting symptomatic CD patients would circumvent a relative low sensitivity of USCD, while increasing the likelihood of finding specific abnormalities in clinically active patients.

The analysis of selected individual parameters obtained by USCD provided distinct results according to the predominant phenotype or abnormalities associated with CD, but with an overall satisfactory correspondence with MRE data. Again, the best agreement of USCD with MRE occurred when analyzing patients with clinically active CD. In fact, analysis of USCD performance resulted in high levels of sensitivity, positive predictive value, and accuracy, greater than 80%, considering wall thickening and hyperemia, in patients with clinically active CD. Similar to our results, Doppler ultrasound was previously shown to be sensitive to localize affected intestinal segments and to detect transmural complications in patients with CD. In particular, wall thickness and color Doppler flow were related to clinical or biologic activity.[44] Moreover, the moderate association with calprotectin found in the current study appears to reinforce the ability of USCD to detect inflammatory activity. Hence, we hypothesize that if USCD is particularly sensitive and accurate for detecting disease activity, it could be applied, not only in the long-term follow-up of maintenance therapies, but also in the evaluation of inductive therapies. In another study designed to investigate the accuracy of color-coded duplex sonography for the diagnosis of CD relapse and complications, authors concluded that the method is reliable for characterizing wall thickness, and the diagnosis of luminal stricturing showed a good sensitivity but moderate specificity, similar to our results. Because no contrast enhancement has been used in USCD, it is likely that the technique may not be able to detect low-grade stenosis. However, in contrast to our findings, abscesses and fistulas were also consistently detected by the color-coded duplex sonography method.[26] In fact, different study designs, and results from relatively small series of patients, with distinct severity, extension, and possibly different genetic backgrounds and therapeutic regimens, may render subgroup analysis difficult to interpret.

Although Doppler sonography does not constitute a routine first-line tool for the initial diagnosis of CD, it has been proposed as a potential adjunct method for the follow-up of patients.[45] Nevertheless, in this study, results from imaging methods, MRE and USCD, showed no significant agreement with the clinical CD activity, and with the currently used biomarkers, serum CRP and fecal calprotectin. It is possible that, the consecutive recruitment of patients has inadvertently selected individuals with a relatively low clinical disease activity. Hence, it is important to notice that the narrow spectrum of CD activity may not help to distinguish sharply inflammatory or anatomical changes through the imaging techniques. Another critical point in this investigation refers to the question whether the data acquired by Doppler sonography of small size vessels, for the assessment of CD activity is actually reliable.[16,41] In fact, in accordance with this, we previously demonstrated that the results from aorta were more consistent than the ones obtained with SMA measurements, which was attributed to the diameter of the vessels analyzed.[37] On the other hand, the alternative assessment of Doppler sonography proposed in this study relied more on semi-quantitative, and less on quantitative data, such as measurements of diameters and flow values. An additional potential limitation of our study could result from possible anatomical changes secondary to abdominal surgeries, reported in almost half of the patients. However, in contrast to a previous study warning for the likely technical difficulties,[46] in this study, the general imaging quality was apparently not compromised by abdominal surgical scars.

In conclusion, USCD showed an overall relatively good performance for identifying inflammatory activity in the ileum of patients with CD, particularly among patients with the inflammatory and penetrating phenotypes presenting clinically active disease. Additional investigations with a larger number of

patients will be fundamental to confirm the results and to consolidate the selected parameters and the applicability of USCD as an adjunctive noninvasive and low-cost follow-up tool for patients with CD.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTION

Study conception, in the acquisition, analysis, and interpretation of data, and also in the drafting of the manuscript: Moraes AC. Acquisition, analysis, and interpretation of the data, and participated in the drafting of parts of the manuscript: Moraes G, Araújo AL, Elia C. Conception and design of the study, analyzed and interpreted data, and critically revised the manuscript for important intellectual content: Luiz RR, Carneiro AJ, de Souza HS. All authors gave final approval of the submitted version of the manuscript.

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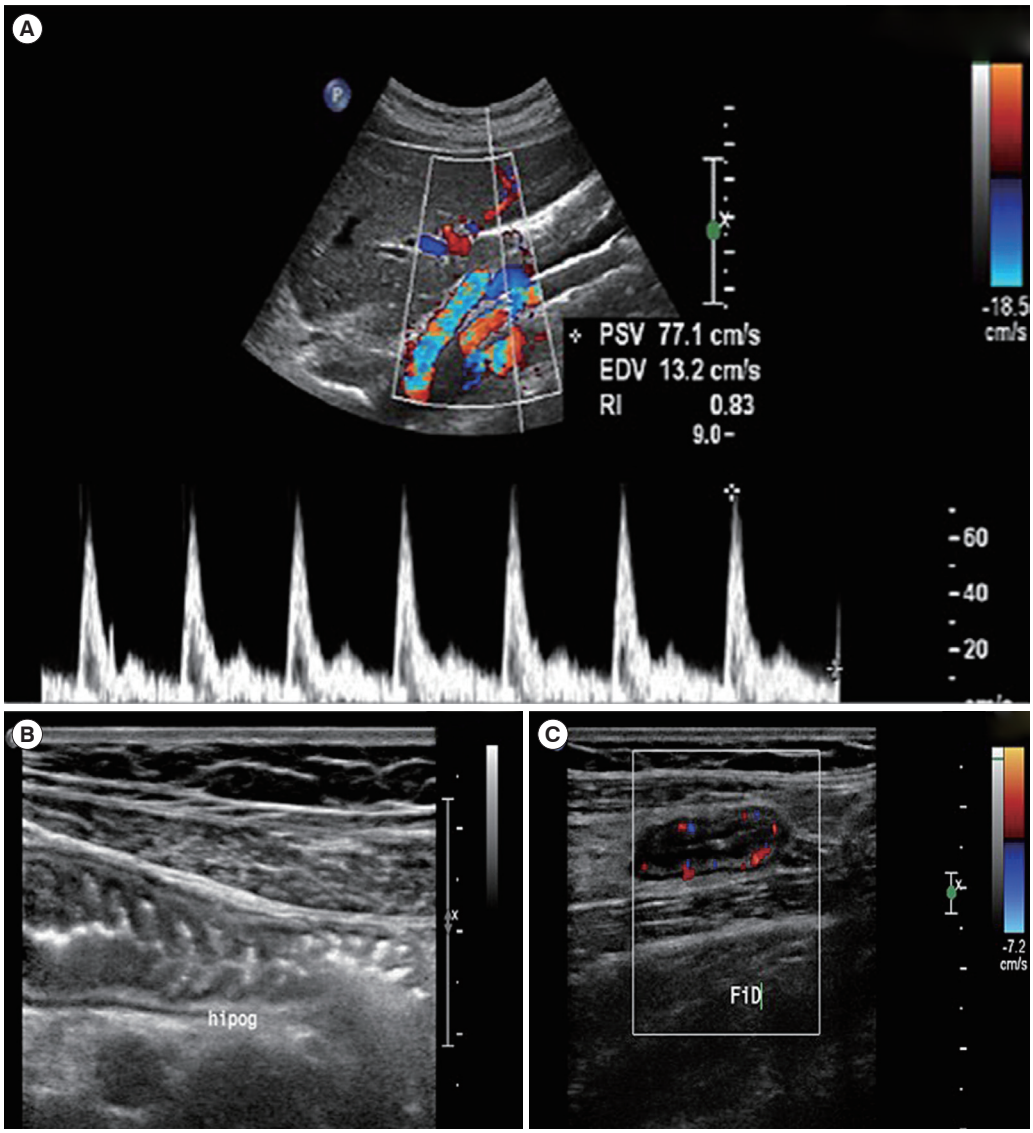
See "Abdominal ultrasonography with color Doppler analysis in the assessment of ileal Crohn's disease: comparison with magnetic resonance enterography" on page 227-236.



Supplementary Fig. 1. Example of color Doppler image acquisition and analysis. Screen capture during examination of the ileum, displaying automated calculation of resistive index (RI) (A); normal ileal loop (B); and ileal hyperemia detected by color Doppler (C). PSV, peak-systolic velocity; EDV, end-diastolic velocity.

Supplementary Table 1. Performance of Clinical and Laboratory Evaluation for Detecting Active CD in the Terminal Ileum, Based on Selected Abdominal USCD Parameters

USCD parameter	Test	Sensitivity	Specificity	PPV	NPV	ACC
Thickening	Clinical activity	40.6 (25.5–57.7)	81.8 (52.3–94.8)	86.7 (62.1–96.3)	32.1 (17.9–50.7)	51.2 (36.7–65.4)
	Calprotectin	66.7 (47.8–81.4)	50.0 (23.7–76.3)	78.3 (58.1–90.3)	35.7 (16.3–61.2)	62.2 (46.1–75.9)
	CRP	42.3 (25.5–61.1)	75.0 (40.9–92.8)	84.6 (57.7–95.7)	28.6 (13.8–49.9)	50.0 (34.1–65.9)
Stricture	Clinical activity	50.0 (28.0–72.0)	74.1 (55.3–86.8)	53.3 (30.1–75.2)	71.4 (52.9–84.7)	65.1 (50.2–77.6)
	Calprotectin	71.4 (45.3–88.3)	43.5 (25.6–63.2)	43.5 (25.6–63.2)	71.4 (45.3–88.3)	54.1 (38.4–68.9)
	CRP	42.3 (25.5–61.1)	75.0 (40.9–92.8)	84.6 (57.8–95.7)	28.6 (13.8–49.9)	50.0 (34.1–65.9)
Hyperemia	Clinical activity	50.0 (29.0–70.9)	76.0 (56.6–88.5)	60.0 (35.7–80.2)	67.9 (49.3–82.1)	65.1 (50.2–77.6)
	Calprotectin	55.8 (36.0–78.4)	35.0 (18.1–56.7)	43.5 (25.6–63.2)	50.0 (26.8–73.2)	45.9 (31.0–61.6)
	CRP	87.5 (52.9–97.8)	70.0 (48.1–85.4)	53.8 (29.1–76.8)	93.3 (70.2–98.8)	75.0 (56.6–87.3)

Parentheses show lower-upper 95% CI. Abdominal ultrasonography with color Doppler (USCD) used as a criterion standard.
PPV, positive predictive value; NPV, negative predictive value; ACC, accuracy.

Supplementary Table 2. Critical Analysis of Clinical and Laboratory Evaluation for Detecting Active CD in the Terminal Ileum Based on Magnetic Resonance Enterography Findings

Test	Sensitivity	Specificity	PPV	NPV	ACC
Clinical activity	45.5 (29.8–62.0)	100.0 (72.2–100.0)	100.0 (79.6–100.0)	35.7 (20.7–54.2)	58.1 (43.3–71.6)
Calprotectin	65.5 (47.3–80.1)	50.0 (21.5–78.5)	82.6 (62.8–93.0)	28.6 (11.7–54.6)	62.2 (46.1–75.9)
CRP	34.6 (19.4–53.8)	50.0 (21.5–78.5)	69.2 (42.4–87.3)	19.0 (7.7–40.0)	38.2 (23.9–54.9)

Parentheses show lower-upper 95% CI. Magnetic resonance enterography used as a criterion standard.
PPV, positive predictive value; NPV, negative predictive value; ACC, accuracy.

Supplementary Table 3. Performance of Clinical and Laboratory Evaluation for Detecting Active CD in the Terminal Ileum, Based on Selected Enterography by Magnetic Resonance Parameters

MRE parameter	Test	Sensitivity	Specificity	PPV	NPV	ACC
Thickening	Clinical activity	45.5 (29.8–62.0)	100.0 (72.2–100.0)	100.0 (79.6–100.0)	35.7 (20.7–54.2)	58.1 (43.3–71.6)
	Calprotectin	65.5 (47.3–80.1)	50.0 (21.5–78.5)	82.6 (62.9–93.0)	28.6 (11.7–54.6)	62.2 (46.1–75.9)
	CRP	34.6 (19.4–53.8)	50.0 (21.5–78.5)	69.2 (42.4–87.3)	19.1 (7.7–40.0)	38.2 (23.9–55.0)
Stricture	Clinical activity	50.0 (29.9–70.1)	78.3 (58.1–90.3)	66.7 (41.7–84.8)	64.3 (45.8–79.3)	65.1 (50.2–77.6)
	Calprotectin	66.7 (43.7–83.7)	42.1 (23.1–63.7)	52.2 (33.0–70.8)	57.1 (32.6–78.6)	54.1 (38.4–69.0)
	CRP	43.8 (23.1–66.8)	66.7 (43.7–83.7)	53.8 (29.1–76.8)	57.1 (36.5–75.5)	55.9 (39.4–71.1)
Hyperemia	Clinical activity	50.0 (30.7–69.3)	81.0 (60.0–92.3)	73.3 (48.0–89.1)	60.7 (42.4–76.4)	65.1 (50.2–77.6)
	Calprotectin	65.0 (43.3–81.9)	41.2 (21.6–64.0)	56.5 (36.8–74.4)	50.0 (26.8–73.2)	54.1 (38.4–69.0)
	CRP	50.0 (29.0–71.0)	75.0 (50.5–89.8)	69.2 (42.4–87.3)	57.1 (36.5–75.5)	61.8 (45.0–76.1)

Parentheses show lower-upper 95% CI. Magnetic resonance enterography (MRE) used as a criterion standard.
PPV, positive predictive value; NPV, negative predictive value; ACC, accuracy.