Original Article

Pilot case-control study to explore the value of intestinal ultrasound in the differentiation of two common diseases involving the ileocecal region: intestinal Behçet's disease and Crohn's disease

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Background: Intestinal Behçet's disease (BD) and Crohn's disease (CD) are two diseases that commonly involve the ileocecal region and are difficult to differentiate. We aimed to investigate the value of intestinal ultrasound (IUS) in differentiating between these diseases.

Methods: In this case-control study, patients diagnosed with intestinal BD or CD in the ileocecal region involved were recruited. The IUS characteristics of the two disease groups in terms of disease location, ileocecal region characteristics, and complications were compared. The differences were analyzed using univariate and multivariate analyses.

Results: We consecutively enrolled 22 intestinal BD and 44 age- and sex-matched CD patients. On univariate analysis, focal lesion, ileocecal region involvement only, presence of ulcers on ultrasound (US), large ulcers (>2 cm) on US, and fistulas were significantly more common in intestinal BD than in CD, whereas small intestine involvement was significantly more common in CD. On multivariate analysis, focal lesion [odds ratio (OR) 0.156, 95% confidence interval (CI): 0.043–0.564], and large ulcers (OR 0.056, 95% CI: 0.006–0.550) were independent predictors of intestinal BD over CD. The area under the curve for the receiver-operating characteristic was 0.808 (95% CI: 0.706–0.929), and the sensitivity and specificity with a cutoff value of 0.7 were 75.0% and 77.3%, respectively.

Conclusions: IUS can provide useful information for the differential diagnosis of intestinal BD and CD.

Keywords: Behçet's disease (BD); Crohn's disease; ultrasonography

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Introduction

The ileocecal region is commonly involved in many gastrointestinal diseases, and differential diagnosis can be challenging to gastroenterologists because they share confusing similarities in clinical, colonoscopic, and pathologic features. In particular, intestinal Behçet's disease (BD) and Crohn's disease (CD) constitute one of the pairs that is the most difficult to distinguish (1). BD is a relapsing immunologic disorder characterized by multisystemic lesions, including oral aphthous ulcers, genital ulcerations, ocular disease, and skin lesions (2). Among BD patients, 0–60% have an affected gastrointestinal tract (i.e., intestinal BD) (3-5). CD is a chronic, transmural, and granulomatous inflammatory bowel disease (6). Differentiation between the two diseases is important because they have distinct medication options, surveillance plans, and long-term prognosis (6-8).

Generally, intestinal BD features sporadic ulcerations that can affect any segment of the alimentary tract, but the ileocecal region is predominately involved. CD features skipped lesions separated by normal segments, which also mostly involve the ileocecal region (7). Under colonoscopy, intestinal BD generally features solitary and large ulcers, whereas CD shows longitudinal, deep fissuring ulcers and a cobblestone appearance (9). However, the real clinical situations are always more diverse and complicated (1). Intestinal BD mimics CD in many aspects. Both diseases commonly have a young onset age, a long and relapsing disease course, nonspecific gastrointestinal complications, and similar systemic manifestations such as oral ulcers, arthralgia, and erythema nodosum (10). Although multiple studies have explored various methods for differential diagnosis, to date there are still no ideal tools that can effectively accomplish this difficult task (9-12).

Intestinal ultrasound (IUS) is a mature, routinely used methodology in many European countries, and is recommended by the European Crohn's and Colitis Organization (ECCO) for the assessment and follow-up of CD (13). It has been proven that IUS has similar efficacy for diagnosing small bowel CD as compared with magnetic-resonance enterography (MRE) and computed tomography enterography (CTE), while having the highest accuracy in the differentiation of inflammation and fibrosis (14). Its strengths lie in the evaluation of bowel wall layers and extraintestinal complications, such as stenosis, fistulas, and abscesses (15). It can also assess lesions in the small intestine, which is beyond the capacity of colonoscopy. Increased wall thickness and Doppler flow are the most important ultrasound (US) features of CD (16). Being radiation free and cost-effective further make IUS a convenient modality for clinical use. To our knowledge, no study has yet explored the value of IUS in differentiating intestinal BD from CD. The purpose of our study was thus to identify the differential IUS manifestations between intestinal BD and CD, and to determine the diagnostic value of IUS in discriminating between the two diseases.

Methods

Patients and study design

This was a retrospective case-control study. Any patients who underwent standard diagnostic workup and reached a definite diagnosis of a gastrointestinal disease were registered to the gastrointestinal diseases database of Peking Union Medical College Hospital China. Consecutive newly diagnosed patients with a diagnosis of intestinal BD involving the ileocecal region were collected from the database between September 2015 and July 2019. The inclusion criteria of BD patients were as follows: (I) met the International Study Group's criteria for the diagnosis of BD published in 1990, which requires the presence of oral ulceration plus any 2 of genital ulceration, typically defined eye lesions, typically defined skin lesions, or a positive pathergy test (17); (II) confirmed gastrointestinal involvement on colonoscopy or other cross-sectional modalities, and involvement of the ileocecal region; (III) underwent IUS examination within 2 weeks before or after colonoscopy. The exclusion criteria were as follows: (I) other accompanying bowel diseases, such as malignant intestinal tumors, CD, ulcerative colitis, etc.; (II) normal or resected ileocecal region; (III) absence of IUS examination, or a time interval between US and colonoscopy of >2 weeks.

For the control group, contemporary, newly diagnosed CD patients were randomly selected from the database by sex- and age-matching to the intestinal BD group in a 1:2 ratio, which was determined by the number of patients in the database, and the Pitman efficiency for comparing tests (18). The control patients were selected by the following inclusion criteria: (I) met the diagnostic criteria of CD in the ECCO guidelines in 2011, which requires clinical evaluation and a combination of endoscopic, histologic, radiologic, and/or biochemical investigations. If ileocolonoscopy identifies mucosal cobble-stoning, linear ulceration, discontinuous involvement, and/or anal lesions,

and pathologic findings showed transmural inflammation and/or epithelioid granulomas, plus chronic gastrointestinal symptoms and supporting radiologic features (stricture, fistula, mucosal cobble-stoning, or ulceration), the diagnosis of CD could be established (19); (II) involvement of the ileocecal region confirmed by colonoscopy or other cross-sectional modalities; (III) underwent IUS examination within 2 weeks before or after colonoscopy. The exclusion criteria were the following: (I) ileocecal region not involved or had been resected; (II) other accompanying bowel diseases, such as malignant intestinal tumors, BD, ulcerative colitis, etc.; (III) absence of IUS examination, or a time interval between US and colonoscopy of >2 weeks.

Medical records of the enrolled patients were collected, and general information, including age, sex, clinical course, clinical symptoms, systemic manifestations, past and family history, high-sensitivity C-reactive protein (hsCRP) level, and erythrocyte sedimentation rate (ESR), along with ileocolonoscopic and pathologic results, was documented for both groups.

IUS examination and interpretation

IUS has been included in the standard diagnostic workup at Peking Union Medical College Hospital China since September 2015. The examination was performed using Philips iU22 (Philips, Bothell, WA, USA) with convex (C5-2) and linear (L9-3) transducers. All examinations were completed independently by two experienced radiologists (Q Zhu and W Li, with >5 years of experience and >500 IUS studies), following the European Federation of Societies for Ultrasound in Medicine and Biology guidelines (16). Patients fasted for at least 8 hours before the examination. No other preparations were needed. A standardized, thorough scanning of the intestine was performed. The colon was scanned consecutively from the ileocecal area to the ascending colon, transverse colon, descending colon, and sigmoid colon. The small intestine was examined throughout the abdomen ("mowing the lawn") to look for diseased sections. The convex transducer was used first for an overall perception, followed by the linear transducer for detailed examination and measurements.

The radiologists were aware of the clinical, laboratory, and endoscopic information, but the final diagnosis was made afterward, and thus was unknown to radiologists. After each examination, a detailed report was given describing the distribution of lesions, characteristics of the ileocecal region, and complications. Intestinal lesions were classified as "focal" or "segmental", with focal involvement defined as only 1 focused area with identified bowel lesions, and segmental involvement defined as more than 2 areas with discontinuous lesions. As for ileocecal characteristics, bowel wall thickness (BWT), bowel wall stratification, bowel wall vascularity, and ulcers were examined (15). A BWT ≤3 mm was considered normal; bowel wall stratification was classified as "clear" or "vague" depending on if the 5 layers of the bowel wall could be identified. Vascularity was graded by the Limberg scoring system in the following fashion (20): grade 0, no vascularization; grade 1, dotted or short stretches (≤1 mm) of vascularity; grade 2, longer stretches (>1 mm) but not reaching the serosal layer; grade 3, rich, long stretches of vascularity into the mesentery. Ulcers appeared as hyperechogenic lines or spots that interrupted the wall stratification on IUS (21). The size of ulcers was measured as the largest diameter of the hyperechogenic line or spot. Large ulcers were defined as having a diameter ≥2 cm. Complications included intramural and extramural abscesses, fistulas, strictures, mesenteric lymphadenopathy, and ascites. Mesenteric lymphadenopathy was defined as mesenteric lymph nodes with a short axis >10 mm (22).

Both static images and dynamic videos were saved throughout the examination for every patient. The reports from the two radiologists were compared, and if different opinions emerged, the radiologists would review the images and videos and made a final consensus.

Statistical analysis

Statistical analysis was performed using SPSS statistics software v.23 (IBM Corp.). Descriptive statistics are reported as number (percent) for categorical variables, or mean ± standard deviation (SD) for continuous variables. Categorical data were assessed with the chi-square test, while continuous data were assessed with the *t*-test. A P value <0.05 was considered significant.

The IUS manifestations of intestinal BD and CD are summarized as number (percent) for categorical variables, or mean ± SD for continuous variables. A chi-square test or *t*-test was used for determining the distinguishable findings between the two groups, with the odds ratio (OR) calculated. Multivariate binary logistic regression analysis was used to select independent discriminating factors. Receiver-operating characteristic (ROC) analysis was performed on the predicted probability given by the binary logistic regression analysis. The optimal threshold value of the predicted probability and the sensitivity and specificity

Table 1 Demographic characteristics of intestinal BD and CD patients

Characteristics	Intestinal BD (n=22)	CD (n=44)	P
Age, mean ± SD, years	33.0±16.6	36.0±16.9	0.883
Sex, male:female	9:13	18:26	1.000
Disease duration, median [range], months	12 [1–98]	15 [3–120]	0.674
Perianal involvement, n [%]	5 [23]	11 [25]	0.823
hsCRP, mean ± SD, ng/L	15.9±21.2	15.0±24.7	0.724
ESR, mean ± SD, mm/h	26.5±23.2	21.6±16.7	0.355

BD, Behçet's disease; CD, Crohn's disease; ESR, erythrocyte sedimentation rate; hsCRP, high-sensitivity C-reactive protein; SD, standard deviation.

at that threshold value were assessed. The area under the curve (AUC) with the corresponding 95% confidence interval (CI) was calculated.

Ethics and consent

The Institutional Review Board of Peking Union Medical College Hospital approved the protocol of the study and waived the requirement for written informed consent on the basis that it was a retrospective, observational design.

Results

Study population and demographics

A total of 23 patients who met the inclusion criteria of intestinal BD were identified during the study period. All had undergone IUS examinations but 1 patient was excluded because the time interval between IUS and colonoscopy was 3 weeks. Therefore, 22 patients with intestinal BD were enrolled in this study. A total of 44 age-matched CD patients were enrolled in a 1:2 ratio. The patient characteristics are shown in *Table 1*. There were no significant differences in sex, age, disease duration, perianal involvement, hsCRP, and ESR between the two groups.

IUS manifestations of intestinal BD and CD

IUS findings in the intestinal BD and CD groups are summarized and compared in *Table 2*. The IUS findings included disease location, ileocecal region characteristics, and complications. We compared the ulcers in the ileocecal region detected by IUS with those detected in contemporary colonoscopy and found that the detection rate of IUS on any ulcers was 25/66 (37.9%), and for large ulcers (>2 cm) it was 10/10 (100%). On univariate analysis, 5 parameters, namely focal lesion, ileocecal region involvement only, presence of ulcers on US, large ulcers on US, and fistulas were significantly more common in intestinal BD than in CD, while 1 parameter, small intestine involvement, was significantly more common in CD. The 6 parameters with significant differences between the two groups were entered into the multivariate logistic regression analysis. Focal lesion (OR 0.156, 95% CI: 0.043–0.564), and large ulcers (OR 0.056, 95% CI: 0.006–0.550) were independent predictors of intestinal BD over CD. *Figure 1* shows a representative intestinal BD patient with thickened bowel wall and a large ulcer in the ileocecal region. *Figure 2* shows a representative CD patient with segmental thickened bowel wall in the terminal ileum and the fourth part of the small intestine.

Diagnostic performance of IUS in differentiating intestinal BD from CD

A ROC curve was drawn according to the result of the multivariate analysis (*Figure 3*). The AUC of the ROC was 0.808 (95% CI: 0.706–0.929). The sensitivity and specificity with a cutoff value of 0.7 were 75.0% and 77.3%, respectively.

Discussion

Differential diagnosis between intestinal BD and CD is an important but difficult clinical problem, as these diseases have similar clinical manifestations but distinct treatment strategies (9). In particular, the intestinal and extraintestinal symptoms are nonspecific and infrequent, and laboratory tests such as ESR and hsCRP have unsatisfactory diagnostic

Table 2 Ultrasonographic findings of intestinal BD and CD

Findings	BD (n=22)	CD (n=44)	P	
			Univariate analysis	Multivariate analysis
Disease location				
Ileocecal region only, n (%)	15 [68]	11 [25]	0.000*	1.000
Ileocecal region + colon, n (%)	5 [23]	14 [32]	0.194	
Small intestine, n (%)	1 [5]	16 [36]	0.013*	0.999
Small intestine + colon, n (%)	1 [5]	3 [7]	1.000	
Focal involvement, n (%)	16 [73]	10 [23]	0.000*	0.005*
Ultrasonographic characteristics of the ileocecal region				
Wall thickness, mean [range], mm	6.6 [3–12]	6.1 [4–10]	0.525	–
Clear wall stratification, n (%)	7 [32]	26 [59]	0.294	–
Vascularity, n (%)			0.132	–
0	5 [23]	5 [11]		
1	7 [32]	11 [25]		
2	7 [32]	18 [41]		
3	3 [14]	10 [23]		
Presence of ulcers, n (%)	14 [64]	9 [20]	0.001*	0.458
Large ulcer (>2 cm), n (%)	9 [41]	1 [2]	0.000*	0.013*
Complications				
Fistulas, n (%)	11 [50]	13 [30]	0.068*	0.560
Abscesses, n (%)	1 [5]	5 [11]	0.650	–
Mesenteric lymphadenopathy, n (%)	9 [41]	23 [52]	0.296	–
Ascites, n (%)	3 [14]	2 [5]	0.411	–
Stricture, n (%)	1 [5]	4 [9]	0.869	–

*, In the univariate analysis, P<0.1 was considered significant; in the multivariate analysis, P<0.05 was considered significant. BD, Behçet's disease; CD, Crohn's disease.

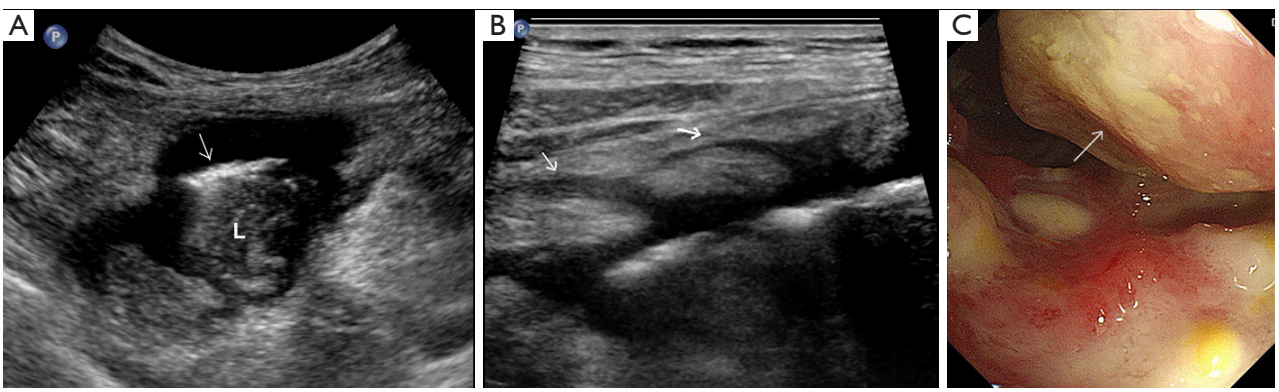

Figure 1 Representative intestinal ultrasound (IUS) images of intestinal Behçet's disease (BD). (A) Transverse view of the ileocecal region shows a large ulcer as a hyperechogenic line within the bowel wall with disappearance of the layered structure (arrow). (B) Longitudinal view of the same location showing the length of the ulcer and short fistulas (arrows). (C) Contemporaneous ileocolonoscopy also revealed a large ulcer in the same region (arrow). L, lumen.

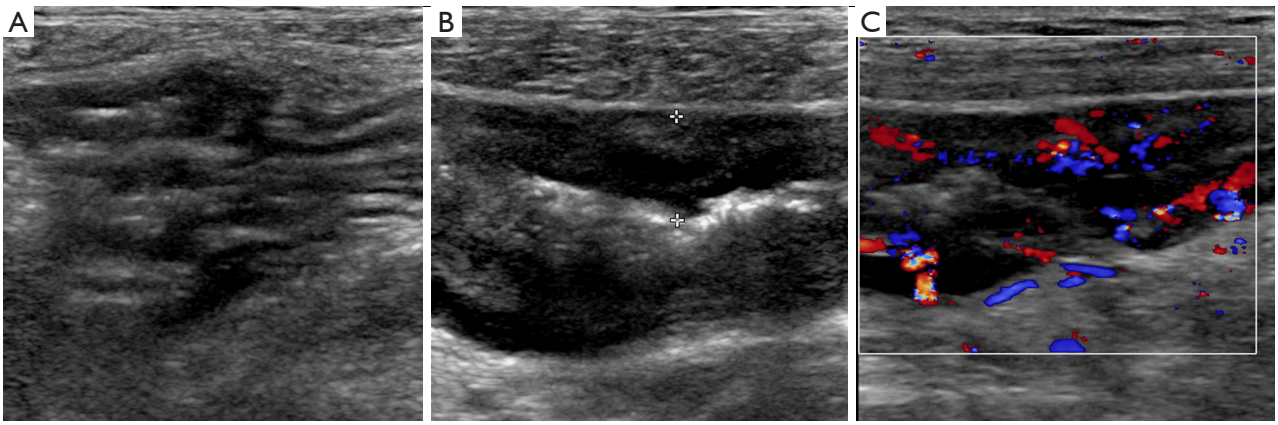

Figure 2 Representative intestinal ultrasound (IUS) images of Crohn's disease (CD). (A) Transverse view showing the thickened ileocecal valve and terminal ileum. (B) Longitudinal view of the fourth part of the small intestine showing the thickened bowel wall (between crosses). (C) Colored Doppler US image shows the long, rich stretches of vascularity into the mesentery.

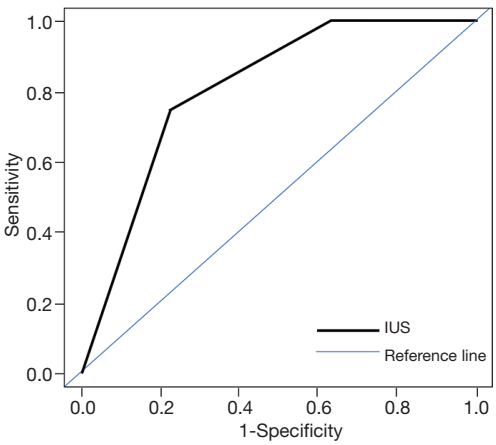

Figure 3 Receiver-operating characteristic (ROC) curve of intestinal ultrasound (IUS) in differentiation of intestinal Behçet's disease (BD) and Crohn's disease (CD). The ROC analysis was based on the predicted probability given by the binary logistic regression analysis of the ultrasonographic findings. The area under the curve was 0.808.

efficiency; there are several reported distinctive endoscopic features that can make a differential diagnosis, but these features are not always present (9,11,12). Therefore, new tools are needed for the differentiation between the two diseases (10).

The advantages of IUS include its noninvasiveness, lack of radiation, and cost-effectiveness, making it a perfect tool for preliminary clinical diagnosis. As addressed by the ECCO guidelines, intestinal IUS is widely used for the diagnosis and follow-up of inflammatory bowel disease (23). However, the sonographic findings of intestinal BD have only been reported in individual cases (24). In our study, the IUS manifestations of intestinal BD and CD were compared, and significant sonographic features for differential diagnosis were identified. To the best of our knowledge, this is the first study to illustrate the usefulness of IUS in differentiating intestinal BD from CD.

Moderately high sensitivity and specificity were found for IUS in differentiating intestinal BD from CD. Several studies used other modalities, including demographic data, clinical manifestations, laboratory tests, cross-sectional imaging, and colonoscopic findings to differentiate the two diseases (9,11,12,25-27). As for clinical manifestations, no gastrointestinal symptoms show a significant difference between BD and CD (7). Even though some extraintestinal symptoms are more predominant in one disease over the other, they have not been found to be very useful in clinical practice because of their low prevalence rates (7). Serological tests also appear to be unhelpful in differentiating intestinal BD from CD (28). Liu *et al.* compared the hsCRP and ESR levels between active CD and BD and found no significant difference (12). A CD-specific marker, anti-saccharomyces cerevisiae antibody, had similar positive rates in CD and BD (26). In 2018, Peker *et al.* conducted a preliminary case-control study to compare the MRE manifestations between the two diseases and showed that positive findings of both polypoid and homogeneous patterns gave an AUC value of 0.833, which is similar to our result (27). Under colonoscopy, ≤5, round, focal, non-aphthous and non-

cobblestone lesions were suggestive of intestinal BD, whereas longitudinal and multiple ulcers were suggestive of CD. The AUC of colonoscopy was 0.874–0.955 according to the literature (11,25). As colonoscopy can only detect lesions on the mucosal surface of the large intestine and terminal ileum, some characteristics of deep lesions and small intestine manifestations remain unveiled.

Generally, intestinal BD is characterized by deep, round, or oval-shaped ulcers on the mucosal surface of the gastrointestinal tract (29). CD is characterized by segmental transmural inflammation of the bowel wall (6). The distribution of lesions in intestinal BD detected by IUS was found to be similar to that previously reported (9,11,25). In our study, 73% of intestinal BD patients had focal lesions, whereas CD patients predominantly showed segmental lesions (77%). This disparity was in accordance with several previous studies of colonoscopy and MRE (11,25,27). Nevertheless, although in only a small number of cases of both diseases was the small intestine (terminal ileum excluded) involved, intestinal BD had fewer of these cases than did CD [only 2 patients (10%) in our study]. Limited studies have reported the rates of small intestine (terminal ileum excluded) involvement in intestinal BD because it is unreachable by colonoscopy and gastroscopy. The reported rates vary from 8% by MRE to 91–100% by capsule endoscopy (27,30,31). The reason for the large difference between cross-sectional imaging (MRE and IUS) and capsule endoscopy might be that some subtle lesions on the mucosa are hard to detect with cross-sectional imaging techniques. Based on MRE, there is a significant difference in small intestine involvement between intestinal BD and CD, suggesting that it is a valid indicator to discriminate between the two diseases (27).

Evaluation of the ileocecal region is a key point of the IUS examination, as it is the most affected location in both diseases. IUS characteristics, including BWT, stratification, vascularity, and ulcers, were carefully evaluated. Our study showed no significant difference in bowel wall manifestations between intestinal BD and CD. As intestinal BD is a form of vasculitis that causes intestinal ischemia, it is understandable that intestinal BD also manifested as nonspecific bowel wall inflammation (32).

IUS can also detect ulcers on the mural surface of the intestine. Ulcers appear as hyperechoic lines or dots inside the bowel wall on IUS. Ulcers are caused by the disturbance of the gas and contents in the bowel lumen, and the sensitivity of ulcer identification on IUS was not as good as that of colonoscopy (21). However, IUS has a high detection rate in terms of large ulcers (in our study 100%); furthermore, it can give objective measurements of the ulcer's diameter, which is not feasible with colonoscopy. In our study, the prevalence of ulcers on IUS in intestinal BD and CD was 63% and 20%, respectively. Among patients with identified ulcers on IUS, intestinal BD had larger ulcers than did CD, which is consistent with previous findings from colonoscopy (11,25).

Intestinal complications were also identified, and similar occurrences were seen in terms of fistulas, abscesses, strictures, and ascites. Only fistulas showed differences in the univariate analysis. We understand that these complications are a reflection of the severity, but are not characteristic in intestinal BD and CD. As both diseases can affect the deep transmural bowel wall, it is not hard to explain the similarities in complications in both diseases.

It is also worth noting that, although we found that focal lesions and large ulcerations on IUS are more frequent in intestinal BD than in CD, in the real world, the number of intestinal BD patients is far greater than that of CD patients, and the latter might present a wide spectrum of ultrasonographic manifestations. Therefore, we suggest that clinicians should carefully consider the value of including IUS in their current diagnostic workup for differential diagnosis.

Study limitations

First, as a pilot study, our study was performed in a single center and had a relatively small sample size, leaving the possibility of selection bias. Future large-sampled, multicenter research is required to validate our results. Second, we did not compare the IUS manifestations with those from other cross-sectional imaging techniques, such as CTE or MRE to validate the findings of IUS. Third, the AUC of IUS in our study was good but not perfect; therefore, in clinical use, other clinical and imaging features must be considered simultaneously to make an accurate diagnosis. Also, the value of a combined evaluation (i.e., clinical manifestations plus colonoscopy and IUS) is worth further exploring.

Conclusions

Based on our study, focal involvement and large ulcers are the two independent predictors for distinguishing intestinal BD from CD by IUS. IUS can provide important information for the differential diagnosis of the two diseases

although further prospective and large-sample studies are needed to validate our results.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/qims-20-1334). The authors have no conflicts of interest to declare.

Ethical Statement: Patient anonymity was preserved. Photographs were cropped sufficiently to prevent human subjects from being recognized and the eyes and eyebrows (at a minimum) were masked using Coarse Pixilation to make the individual unrecognizable. The study was approved by the Institutional Review Board of Peking Union Medical College Hospital of S-K917. Written informed consent was waived on the basis that it was a retrospective, observational design.

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