Determining the Accuracy of Intestinal Ultrasound Scores as a Prescreening Tool in Crohn's Disease Clinical Trials

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INTRODUCTION: **High rates of screen failure for the minimum Simple Endoscopic Score for Crohn's Disease (SES-CD) plague Crohn's disease (CD) clinical trials. We aimed to determine the accuracy of segmental intestinal ultrasound (IUS) parameters and scores to detect segmental SES-CD activity.**

METHODS: **A single-center, blinded, cross-sectional cohort study of children and young adult patients with CD undergoing IUS and ileocolonoscopy, comparing segmental IUS bowel wall thickness (BWT), hyperemia (modified Limberg score [MLS]), and scores to detect segmental SES-CD activity: (i) SES-CD ≤2, (ii) SES-CD ≥6, and (iii) SES-CD ≥4 in the terminal ileum (TI) only. Primary outcome was accuracy of BWT, MLS, and IUS scores to detect SES-CD ≤2 and SES-CD ≥6. Secondary outcomes were accuracy of TI BWT, MLS, and IUS scores to detect SES-CD ≥4 and correlation with the SES-CD.**

RESULTS: **Eighty-two patients (median [interquartile range] age 16.5 [12.9–20.0] years) underwent IUS and ileocolonoscopy of 323 bowel segments. Segmental BWT ≤3.1 mm had a similar high accuracy to detect SES-CD ≤2 as IUS scores (area under the receiver operating curve [AUROC] 0.833 [95% confidence interval 0.76–0.91], 94% sensitivity, and 73% specificity). Segmental BWT ≥3.6 mm and ≥4.3 mm had similar high accuracy to detect SES-CD ≥6 (AUROC 0.950 [95% confidence interval 0.92–0.98], 89% sensitivity, 93% specificity) in the colon and an SES-CD ≥4 in the TI (AUROC 0.874 [0.79–0.96], 80% sensitivity, and 91% specificity) as IUS scores. Segmental IUS scores strongly correlated with the SES-CD.**

DISCUSSION: **Segmental IUS BWT is highly accurate to detect moderate-to-severe endoscopic inflammation. IUS may be the ideal prescreening tool to reduce unnecessary trial screen failures.**

KEYWORDS: intestinal ultrasound; Crohn's disease; clinical trials; endoscopy; screening

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D148, http://links.lww.com/AJG/D149, http://links.lww.com/AJG/D150, http://links.lww.com/AJG/D151, and http://links.lww.com/AJG/D152.

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INTRODUCTION

Crohn's disease (CD) is an inflammatory bowel disease (IBD) with a relapsing and remitting course that results in progressive bowel damage over time (1). Inflammation in patients with CD often occurs silently, in the absence of clinical symptoms. Thus, tight control monitoring of CD activity requires accurate, noninvasive, objective biomarkers that accurately reflect endoscopic disease activity (2,3). Intestinal ultrasound (IUS) is a noninvasive, patient-centric, cross-sectional imaging tool, which provides real-time information regarding transmural disease activity, lacks ionizing radiation, and does not require sedation, bowel preparation, fasting, or oral contrast, yielding several advantages over both magnetic resonance enterography (MRE) and computed tomography enterography (4–8). As IUS utilization for monitoring CD activity by adult and pediatric gastroenterologists grows, and incorporation of IUS into CD clinical trials emerges, it is vital to understand the accuracy of IUS to the gold standard of endoscopy. Endoscopy screen failures for minimum endoscopic activity based on the Simple Endoscopic Score for Crohn's Disease (SES-CD) (9) plague up to 70% of patients recruited for CD

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clinical trials, of whom an unnecessary invasive colonoscopy could have been avoided with an accurate noninvasive prescreening tool (10).

Previous studies have demonstrated that IUS has a high degree of accuracy to detect endoscopic CD activity (11–14). Segmental bowel wall thickness (BWT) on IUS has previously been shown to be accurate to detect segmental endoscopic disease activity in children and adults with CD (11,15–19). In attempt to achieve greater accuracy to detect endoscopic activity with IUS, several segmental IUS scores have been developed, but they are heterogeneous and without consistent and sufficient external validation (20,21). Furthermore, there is no total IUS score equivalent to the total SES-CD for the entire visualized bowel, which limits the utility and correlation between these 2 measures. Most recently, 3 segmental IUS scores have been developed and internally validated with the segmental SES-CD in adults, the Simple Ultrasound Activity Index for Crohn's Disease (SUAS-CD) (22), the Simple Ultrasound Score for Crohn's Disease (SUS-CD) (23), and the Bowel Ultrasound Score (BUSS) (24), but they lack sufficient external validation with the SES-CD (25). In addition, another recent segmental IUS score, the International Bowel Ultrasound Segment Activity Score (IBUS-SAS) (26), was the first to be developed based on international expert consensus of inflammatory activity parameters by centrally read blinded agreement and offers promise but has not been sufficiently validated with the SES-CD. Last, the Simple Pediatric Activity Ultrasound Score (SPAUSS) (27), developed specifically for children with CD, has been internally validated with subjective assessments of endoscopic activity and lacks objective validation with the segmental SES-CD and external validation in both children or adults.

Given the high CD clinical trial screen failure rate because of unnecessary ileocolonoscopy that do not meet the minimum endoscopic activity based on the SES-CD, we hypothesized that IUS may be an accurate noninvasive prescreening tool to potentially reduce screen failures. Therefore, we aimed to determine the accuracy of segmental IUS parameters of BWT and bowel wall hyperemia (BWH) classified by the modified Limberg score (MLS) (26) and segmental IUS scores to detect segmental endoscopic activity based on the SES-CD in a cohort of children and young adults and determine whether IUS scores add any utility to BWT or MLS on their own.

METHODS

This is a single-center, blinded, cross-sectional cohort study conducted between September 2021 and March 2023 of patients with CD comparing the accuracy of segmental IUS BWT, BWH, and scores to detect different thresholds of segmental endoscopic CD activity based on the SES-CD: (i) endoscopic remission (SES-CD $\leq$2), (ii) moderate-to-severe endoscopic inflammation (SES-CD $\geq$6), and (iii) SES-CD $\geq$4 in the terminal ileum (TI) only.

Pediatric and young adult patients with CD in the Mount Sinai PRospective IUS Database who underwent IUS examination during a routine pediatric IBD clinic visit and a planned ileocolonoscopy within 6 weeks, without subsequent treatment changes between the 2 examinations, were enrolled. Exclusion criteria included a diagnosis of UC/IBD-U, age less than or equal to 6 years (for the exclusion of children with very-early onset IBD that may be classified as CD), previous IBD surgery such as an ileocolic resection, a history of stricturing or internal penetrating complications, ileocolonoscopy in which the SES-CD was not recorded, or the TI was not intubated. Baseline demographics collected included age at the time of IUS, age at diagnosis, disease duration, sex, CD location and behavior (Montreal Classification (28)), medications, and treatment history.

Intestinal ultrasound

All IUS were performed by 1 of 2 gastroenterologists (M.T.D. or A.K.) who were both trained and certified according to the International Bowel Ultrasound Group criteria (www.IBUS-group.org), having performed greater than 1500 IUS examinations each at the time the study was conducted. Both M.T.D. and A.K. were blinded to the clinical, laboratory, and endoscopy data available at the time IUS was performed for each case. Patients did not undergo any fasting, bowel preparation, or ingestion of oral contrast agents before the IUS examination. The IUS examinations were performed with a Samsung RS85 Prestige (Samsung, South Korea) located in the clinic exam room using a convex probe (3–10 MHz) for global abdominal assessment and a linear probe (2–14 MHz) for detailed bowel segment measurements. IUS technique included a brief survey of the pelvis followed by a complete grayscale and color Doppler evaluation of the colon beginning with the sigmoid colon in the left lower quadrant of the abdomen until the TI was identified in the right lower quadrant of the abdomen, superior to the iliac vessels. Standard assessments were reported for each bowel segment based on international expert consensus (26): (i) BWT (mm), measured and recorded as the average of 4 measurements, 2 in the longitudinal plane, and 2 in the cross-sectional plane, from the lumen-mucosa interface to the muscularis propria-serosal interface; (ii) BWH as measured by the presence or absence of color Doppler signal, with a velocity rate of $\pm$ 5.2 cm/s, and graded according to the semi-quantitative MLS (scored 0–3); (iii) presence or absence of mesenteric inflammatory fat wrapping; (iv) loss of preservation of bowel wall layer stratification; and (v) presence or absence of reactive lymph nodes in the mesentery. The following segmental IUS scores were calculated at the time of IUS examination for the left colon, transverse colon, right colon, and TI: IBUS-SAS, BUSS, SUS-CD, SUAS-CD, and SPAUSS (see Supplementary Table 1, Supplementary Digital Content 1, http://links.lww.com/AJG/D148). Total IUS scores for the IBUS-SAS, BUSS, SUS-CD, SUAS-CD, and SPAUSS were then calculated by the summation of each segmental IUS score (left colon, transverse colon, right colon, and TI).

Endoscopic evaluation

Ileocolonoscopy was performed independently at the discretion of and by the treating gastroenterologist within 6 weeks of IUS examination. The SES-CD (9) was calculated within Provation endoscopic software (Minneapolis, MN) by the proceduralist according to findings at the time of ileocolonoscopy for each bowel segment and the total SES-CD was calculated.

Outcomes

Primary outcome was the accuracy of segmental BWT, MLS, and IUS scores to detect segmental endoscopic remission (SES-CD $\leq$2) and moderate-to-severe segmental endoscopic inflammation (SES-CD $\geq$6). Secondary outcomes included the accuracy of terminal ileal BWT, MLS, and IUS scores to detect SES-CD $\geq$4, the accuracy of total IUS scores to detect clinical trial eligibility (total SES-CD $\geq$6), correlation of segmental BWT, MLS, and IUS scores with the segmental SES-CD, and correlation of total IUS scores with the total SES-CD.

Table 1. Patient characteristics at baseline

Characteristics	Children and young adults (N = 82)	
Female, n (%)	41 (50)	
Age, yr, median (IQR)	16.5 (12.9–20.0)	
Disease duration, yr, median (IQR)	2.25 (0.19–5.31)	
Time between IUS and endoscopy, d, median (IQR)	20.5 (8–37.5)	
Disease location, n (%)		
Ileal	25 (30.5)	
Colonic	7 (8.5)	
Ileocolonic	50 (61)	
Complications, n (%)		
None	82 (100)	
Current therapy, n (%)		
Infliximab	17 (21)	
Adalimumab	18 (22)	
Ustekinumab	29 (35)	
Vedolizumab	5 (6)	
Tofacitinib	2 (2.5)	
Upadacitinib	2 (2.5)	
Other	1 (1)	
No therapy	8 (10)	
Concomitant steroids, n (%)	25 (30.5)	
Total bowel segments	323	
Left colon	82 (25.4)	
Transverse colon	81 (25.1)	
Right colon	80 (24.75)	
Terminal ileum	80 (24.75)	
Bowel segment, n (%)	Colon (N = 243)	Terminal ileum (N = 80)
Endoscopic remission (SES-CD ≤2)	213 (88)	51 (64)
SES-CD ≥4	28 (12)	29 (36)
Moderate-to-severe inflammation (SES-CD ≥6)	22 (9)	22 (27.5)

IQR, interquartile range; IUS, intestinal ultrasound; SES-CD, Simple Endoscopic Score for Crohn's Disease.

Statistical analyses

Descriptive statistics summarized the data as frequencies and percentages for categorical variables and median and interquartile range (IQR) for continuous variables. Area under the receiver operating curve (AUROC) was used to determine the accuracy to detect endoscopic activity at the 3 different defined thresholds. Optimal cut-points were calculated based on the Youden index for the SES-CD thresholds. Pearson correlation was performed to determine correlation of segmental IUS parameters and scores with the segmental SES-CD (negligible: 0.00–0.09, weak 0.10–0.39, moderate: 0.40–0.69, strong: 0.70–0.89, and very strong: 0.90–1.00). Statistical analysis was conducted using R studio version 2022.12.0+353.

Ethical considerations

Informed consent was obtained from all patients, and this study was approved by the institutional review board at the Icahn School of Medicine at Mount Sinai (IRB #17-01304).

RESULTS

Study population

A total of 82 children and young adults (41 [50%] female, median [IQR] age 16.5 [12.9–20.0] years) with a disease duration of 2.25 (0.19–5.31) years were enrolled. Of the patients, 53 were ≤18 years of age (median [IQR] age 14 [11.25–16] years, minimum age 9 years) and 29 were ≥18 years of age (median [IQR] age 21 [19.75–23] years, maximum age 26 years). Median time between IUS examination and ileocolonoscopy was 20.5 (8–37.5) days. The majority of patients had either ileocolonic disease (50/82 [61%]) or ileal only (25/82 [31%]) disease, were on biologic therapy (73/82 [90%]), and almost one-third were on concomitant steroids (25/82 [31%]) (Table 1).

Bowel segments examined

A total of 323 bowel segments were examined with both IUS and ileocolonoscopy in 82 patients; 243 (75%) were colonic, and 80 (25%) were the TI. In 2 patients, ileocolonoscopy was aborted before completion because of the presence of severe inflammation, limiting evaluation to the left colon only in 1 patient and the left colon and transverse colon in another. Moderate-to-severe endoscopic inflammation (SES-CD ≥6) was found in 22/243 (9%) colonic segments and 22/80 (27.5%) terminal ileal segments, whereas 213/243 (88%) of colonic segments and 51/80 (64%) ileal segments met criteria for endoscopic remission (SES-CD ≤2).

Accuracy to detect segmental endoscopic remission (SES-CD ≤2)

Segmental BWT, MLS, and IUS scores all demonstrated similarly high accuracy to detect segmental endoscopic remission (Table 2). A segmental BWT alone of ≤3.1 mm had a similar accuracy to detect segmental endoscopic remission as more complex segmental IUS scores with an AUROC of 0.833 (95% confidence interval [CI] 0.76–0.91), 94% sensitivity, 73% specificity, 94% positive predictive value (PPV), and 72% negative predictive value (NPV). A segmental SUS-CD cut-point of 0 had the numerically highest accuracy to detect segmental endoscopic remission with an AUROC of 0.867 (95% CI 0.81–0.92), 90% sensitivity, 80% specificity, 95% PPV, and 64% NPV. Although there was no significant difference between children and young adults in BWT, MLS, and segmental IUS scores to detect segmental endoscopic remission, all measures and scores were numerically higher in children (see Supplementary Table 2, Supplementary Digital Content 2, http://links.lww.com/AJG/D149).

Accuracy to detect moderate-to-severe segmental endoscopic inflammation (SES-CD ≥6)

Segmental BWT, MLS, and IUS scores all demonstrated similarly high accuracy to detect moderate-to-severe segmental endoscopic inflammation (Table 3). BWT alone, with a cut-point of ≥3.6 mm, was as accurate as more complex IUS scores to detect moderate-to-severe endoscopic inflammation with an AUROC of 0.950 (95% CI 0.92–0.98), 89% sensitivity, 93% specificity, 62% PPV, and 99% NPV. A SUAS-CD cut-point ≥4.11 had the numerically highest accuracy to detect moderate-to-severe endoscopic inflammation with an AUROC of 0.959 (95% CI 0.83–0.99), 95% sensitivity, 92%

Table 2. Accuracy of segmental BWT, MLS, and IUS scores to detect segmental endoscopic remission (SES-CD ≤2)

Segmental IUS score or parameter	Cut-point	AUROC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
BWT (mm)	≤3.1	0.833 (0.76–0.91)	94	73	94	72
MLS	≤0	0.836 (0.78–0.90)	91	73	94	65
SUS-CD	≤0	0.867 (0.81–0.92)	90	80	95	64
SUAS-CD	≤2.87	0.851 (0.78–0.92)	90	80	95	64
IBUS-SAS	≤13.6	0.852 (0.78–0.92)	91	80	95	65
SPAUSS	≤1	0.855 (0.80–0.91)	91	76	95	66
BUSS	≤2.55	0.849 (0.78–0.92)	91	80	95	65

AUROC, area under the receiver operating curve; BUSS, Bowel Ultrasound Score; BWT, bowel wall thickness; CI, confidence interval; IBUS-SAS, International Bowel Ultrasound Segment Activity Score; IUS, intestinal ultrasound; MLS, modified Limberg score; NPV, negative predictive value; PPV, positive predictive value; SES-CD, Simple Endoscopic Score for Crohn's Disease; SPAUSS, Simple Pediatric Activity Ultrasound Score; SUS-CD, Simple Ultrasound Score for Crohn's Disease; SUAS-CD, Simple Ultrasound Activity Index for Crohn's Disease.

specificity, 59% PPV, and 99% NPV. All IUS scores and BWT demonstrated similarly high NPVs of 99%. BWT, MLS, and IUS scores had similarly high accuracy to detect moderate-to-severe endoscopic inflammation in children and young adults (see Supplementary Table 3, Supplementary Digital Content 3, http://links.lww.com/AJG/D150).

Accuracy to detect SES-CD ≥4 in the TI

Segmental BWT, MLS, and IUS scores all were found to have similar high accuracy to detect SES-CD ≥4 in the TI (Table 4). The SUAS-CD ≥4.11 demonstrated the numerically highest accuracy to detect an SES-CD ≥4 in the TI with an AUROC of 0.899 (95% CI 0.83–0.97), 92% sensitivity, 79% specificity, 66% PPV, and 96% NPV. A BWT ≥4.3 mm in the TI demonstrated similar accuracy to detect an SES-CD ≥4 with an AUROC of 0.874 (0.79–0.96), 80% sensitivity, 91% specificity, 80% PPV, and 91% NPV. BWT, MLS, and IUS scores had similarly high accuracy to detect an SES-CD ≥4 in children and young adults (see Supplementary Table 4, Supplementary Digital Content 4, http://links.lww.com/AJG/D151).

Analysis of the total SES-CD

All total IUS scores demonstrated similar moderate accuracy to detect clinical trial eligibility based on a total SES-CD ≥6 (Table 5). A total SPAUSS of ≥7 demonstrated the numerically highest accuracy to detect a total SES-CD ≥6 with an AUROC of 0.807 (95% CI 0.70–0.91), 77% sensitivity, 74% specificity, 64% PPV, and 84% NPV. All total IUS scores had a similarly moderate accuracy to detect a total SES-CD ≥6, but all IUS scores were numerically higher in children (see Supplementary Table 5, Supplementary Digital Content 5, http://links.lww.com/AJG/D152). Overall, 39/82 (48%) patients had a total SES-CD ≥6, of whom 33/39 (85%) had a bowel segment with increased BWT >3 mm.

Correlation of BWT, hyperemia, and activity scores with the SES-CD

Moderate correlation was found between segmental BWT (0.69) and segmental SES-CD, and strong correlation was found between MLS and IUS scores and segmental SES-CD ranging from 0.73 to 0.77. The segmental IBUS-SAS was found to have the numerically highest correlation with the segmental SES-CD ($r = 0.77$). All total IUS scores demonstrated a strong correlation for the total SES-CD except for the SPAUSS, which demonstrated moderate correlation (Table 6).

DISCUSSION

Our study found that segmental BWT, MLS, and IUS scores were highly accurate to detect moderate-to-severe segmental endoscopic

Table 3. Accuracy of segmental BWT, MLS, and IUS scores to detect moderate-to-severe segmental endoscopic inflammation (SES-CD ≥6)

Segmental IUS score or parameter	Cut-point	AUROC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
BWT (mm)	≥3.6	0.950 (0.92–0.98)	89	93	62	99
MLS	≥1	0.916 (0.86–0.97)	89	88	50	98
SUS-CD	≥2	0.941 (0.90–0.98)	92	90	54	99
SUAS-CD	≥4.11	0.959 (0.93–0.99)	95	92	59	99
IBUS-SAS	≥22.2	0.957 (0.93–0.99)	95	91	58	99
SPAUSS	≥3	0.946 (0.90–0.99)	92	91	58	99
BUSS	≥3.3	0.955 (0.92–0.99)	95	90	54	99

AUROC, area under the receiver operating curve; BUSS, Bowel Ultrasound Score; BWT, bowel wall thickness; CI, confidence interval; IBUS-SAS, International Bowel Ultrasound Segment Activity Score; IUS, intestinal ultrasound; MLS, modified Limberg score; NPV, negative predictive value; PPV, positive predictive value; SES-CD, Simple Endoscopic Score for Crohn's Disease; SPAUSS, Simple Pediatric Activity Ultrasound Score; SUS-CD, Simple Ultrasound Score for Crohn's Disease; SUAS-CD, Simple Ultrasound Activity Index for Crohn's Disease.

Table 4. Accuracy of segmental BWT, MLS, and IUS scores to detect SES-CD ≥4 in the terminal ileum

Segmental IUS score or parameter	Cut-point	AUROC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
BWT (mm)	≥4.3	0.874 (0.79–0.96)	80	91	80	91
MLS	≥1	0.835 (0.74–0.93)	84	73	58	91
SUS-CD	≥2	0.885 (0.80–0.96)	88	77	63	94
SUAS-CD	≥4.11	0.899 (0.83–0.97)	92	79	66	96
IBUS-SAS	≥24.6	0.895 (0.82–0.97)	92	79	66	96
SPAUSS	≥3	0.893 (0.82–0.97)	92	79	66	96
BUSS	≥3.9	0.888 (0.81–0.97)	88	81	67	94

AUROC, area under the receiver operating curve; BUSS, Bowel Ultrasound Score; BWT, bowel wall thickness; CI, confidence interval; IBUS-SAS, International Bowel Ultrasound Segment Activity Score; IUS, intestinal ultrasound; MLS, modified Limberg score; NPV, negative predictive value; PPV, positive predictive value; SES-CD, Simple Endoscopic Score for Crohn's Disease; SPAUSS, Simple Pediatric Activity Ultrasound Score; SUS-CD, Simple Ultrasound Score for Crohn's Disease; SUAS-CD, Simple Ultrasound Activity Index for Crohn's Disease.

inflammation based on the SES-CD. BWT alone demonstrated comparable accuracy to IUS scores to detect segmental endoscopic remission and inflammation at each segmental SES-CD threshold compared with the more complex segmental IUS scores. This is most likely due to the fact that BWT is the most dominantly weighted component in each of the IUS scores. For the SUS-CD, SUAS-CD, and BUSS, the scores only consist of different weighting for BWT and MLS. The SPAUSS adds in the additional component of inflammatory fat, and the IBUS-SAS adds in both inflammatory fat and bowel wall layer stratification components. Thus, in real-world practice, and as a tool for prescreening for clinical trials to detect an SES-CD ≥4 in the ileum or 6 in the colon, BWT greater than or equal to 4.3 mm in the TI and 3.6 mm in the colon is adequate, and the more complex IUS scores are unlikely to add significant value to prescreening for clinical trials. Using BWT on IUS would likely be an extremely effective and important prescreening measure to dramatically reduce the 70% colonoscopy screen failures for clinical trials that do not meet the minimum moderate-to-severe endoscopic activity requirement (10).

To the best of our knowledge, this is the largest study designed to externally validate IUS scores with endoscopy and the first to do so in children with CD. The previous external validation study of 4 of 5 IUS segmental scores examined (SUS-CD, SUAS-CD, IBUS-SAS, and BUSS) in 73 adults with CD, 35 of whom were postoperative, found that the segmental scores, specifically the IBUS-SAS (AUROC = 0.96), were all highly accurate to detect any (SES-CD ≥3) and severe (SES-CD ≥9) segmental endoscopic activity. They did not clearly evaluate how accurate IUS scores were to detect meaningful endoscopic activity thresholds for clinical trial enrollment (SES-CD ≥4 in the TI and SES-CD ≥6). We have now shown similar results in children and adults with CD that segmental BWT, MLS, and IUS scores have high accuracy (AUROC 0.822–0.888) to detect moderate-to-severe segmental endoscopic inflammation and SES-CD ≥4 in the TI (AUROC 0.792–0.851).

Although segmental BWT and IUS scores may be highly accurate and ideal as a clinical trial prescreening tool, its place as noninvasive surrogates for endoscopic remission in clinical trials remains less clear. Ongoing multicenter research to develop a more comprehensive total IUS score (the Total SUS-CD), to match the total-SES-CD score, may help to clearly define the role of IUS as a noninvasive surrogate for 50% SES-CD response and endoscopic remission as clinical trial endpoints.

The strength of our study is that this is the largest cohort of patients with CD including both children and young adults prospectively evaluating all segmental IUS scores, BWT, and MLS to date with objective endoscopic scoring with the segmental SES-CD. However, a limitation of our study is the lack of inclusion of older adults, although the accurate cutoff point to detect endoscopic remission was found to be ≤3.1 mm in our study, a value consistent with the international accepted BWT cutoff of ≤3.0 mm in adults. All IUS examinations were performed close to

Table 5. Accuracy of total (combined segmental) IUS scores to detect clinical trial eligibility (total SES-CD ≥6)

Segmental IUS score or parameter	Cut-point	AUROC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
SUS-CD	≥4	0.781 (0.68–0.89)	57	90	77	77
SUAS-CD	≥7.94	0.767 (0.66–0.88)	93	54	55	93
IBUS-SAS	≥79.6	0.797 (0.69–0.90)	53	94	84	77
SPAUSS	≥7	0.807 (0.70–0.91)	77	74	64	84
BUSS	≥6.3	0.757 (0.65–0.87)	90	52	53	90

AUROC, area under the receiver operating curve; BUSS, Bowel Ultrasound Score; CI, confidence interval; IBUS-SAS, International Bowel Ultrasound Segment Activity Score; IUS, intestinal ultrasound; NPV, negative predictive value; PPV, positive predictive value; SES-CD, Simple Endoscopic Score for Crohn's Disease; SPAUSS, Simple Pediatric Activity Ultrasound Score; SUS-CD, Simple Ultrasound Score for Crohn's Disease; SUAS-CD, Simple Ultrasound Activity Index for Crohn's Disease.

Table 6. Pearson correlation of segmental BWT, MLS, and IUS scores with the segmental SES-CD and total IUS scores with the total SES-CD

IUS measure or score	Segmental correlation (ρ)	Total correlation (ρ)
BWT	0.688	—
MLS	0.748	—
SUS-CD	0.763	0.748
SPAUSS	0.742	0.677
SUAS	0.751	0.739
IBUS-SAS	0.770	0.714
BUSS	0.728	0.711

AUROC, area under the receiver operating curve; BUSS, Bowel Ultrasound Score; BWT, bowel wall thickness; CI, confidence interval; IBUS-SAS, International Bowel Ultrasound Segment Activity Score; IUS, intestinal ultrasound; MLS, modified Limberg score; NPV, negative predictive value; PPV, positive predictive value; SES-CD, Simple Endoscopic Score for Crohn's Disease; SPAUSS, Simple Pediatric Activity Ultrasound Score; SUS-CD, Simple Ultrasound Score for Crohn's Disease; SUAS-CD, Simple Ultrasound Activity Index for Crohn's Disease.

time of ileocolonoscopy, and none of the patients had previously undergone surgery, avoiding any need to assess anastomoses or use alternative endoscopic scoring systems such as the Rutgeerts score. In addition, this was the first study to combine segmental IUS scores into a total IUS score compared with the total SES-CD as previously only individual bowel segments on IUS could be compared with segmental SES-CD scores as no total IUS score yet exists to be studied.

Last, both IUS examiners were trained and certified according to the International Bowel Ultrasound Group (IBUS) training curriculum (www.ibus-group.org) and perform a regular high volume (>50 IUS examinations per week) to maintain proficiency. Although certification to perform IUS can be achieved through the IBUS curriculum, expertise to perform research quality IUS examinations take significantly more time; however, the exact number of examinations or length of training to achieve this level is not yet known and may be different among different operators with varying skillsets. Although previous studies show high inter-rater reliability among experts for measurement of BWT on IUS, future studies are needed to confirm inter-rater reliability for detecting moderate-to-severe CD defined by the SES-CD. To successfully implement IUS as a screening tool for clinical trials, particularly in the United States, there will need to be more gastroenterologists trained and capable of performing research quality IUS examinations. After which, central reading of IUS examinations akin to central reading for colonoscopy, which is already underway, will serve as a tool for IUS examination quality control.

In conclusion, segmental IUS parameters of BWT, MLS, and IUS scores are highly accurate to detect moderate-to-severe segmental endoscopic inflammation based on the SES-CD. Given the high screen failure rate because of inability to meet minimum endoscopic activity requirements for the SES-CD of CD clinical trials, IUS may be the ideal prescreening tool to determine CD clinical trial eligibility, reduce screen failures, and improve the speed for clinical trial execution and completion.

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CONFLICTS OF INTEREST

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Specific author contributions: M.T.D.: conceptualized, planned and conducted the study, collected and interpreted the data, and reviewed and edited the manuscript. I.A.: conducted the study, collected, interpreted, and analyzed the data, and drafted the manuscript. E.S.: conceptualized the study, interpreted data, and reviewed and edited the manuscript. A.K.: collected and interpreted the data and reviewed and edited the manuscript. N.P.: conceptualized the study, interpreted data, and reviewed and edited the manuscript. M.C.D.: conceptualized the study, interpreted the data, and reviewed and edited the manuscript. M.G.: collected and interpreted data and reviewed the manuscript. Each author has approved the final draft of the manuscript submitted.

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Study Highlights

WHAT IS KNOWN

- ✓ Intestinal ultrasound (IUS) is accurate to endoscopy.
- ✓ Most screen failures in Crohn's disease (CD) clinical trials are due to endoscopic eligibility criteria.

WHAT IS NEW HERE

- ✓ Segmental IUS bowel wall thickness and IUS scores are highly accurate to detect moderate-to-severe segmental endoscopic inflammation based on the Simple Endoscopic Score for CD.
- ✓ IUS is highly accurate to detect endoscopic remission based on the Simple Endoscopic Score for CD.
- ✓ IUS may be the ideal prescreening tool to determine CD clinical trial eligibility before screening endoscopy.

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