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Review Article

Diagnostic Accuracy of Intestinal Ultrasound in the Detection of Intra-Abdominal Complications in Crohn's Disease: A Systematic Review and Meta-Analysis

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Abstract

Background: Crohn's disease [CD] is frequently associated with the development of strictures and penetrating complications. Intestinal ultrasound [IUS] is a non-invasive imaging modality ideal for point-of-care assessment. In this systematic review and meta-analysis we provide a current overview on the diagnostic accuracy of IUS and its advanced modalities in the detection of intra-abdominal complications in CD compared to endoscopy, cross-sectional imaging, surgery, and pathology.

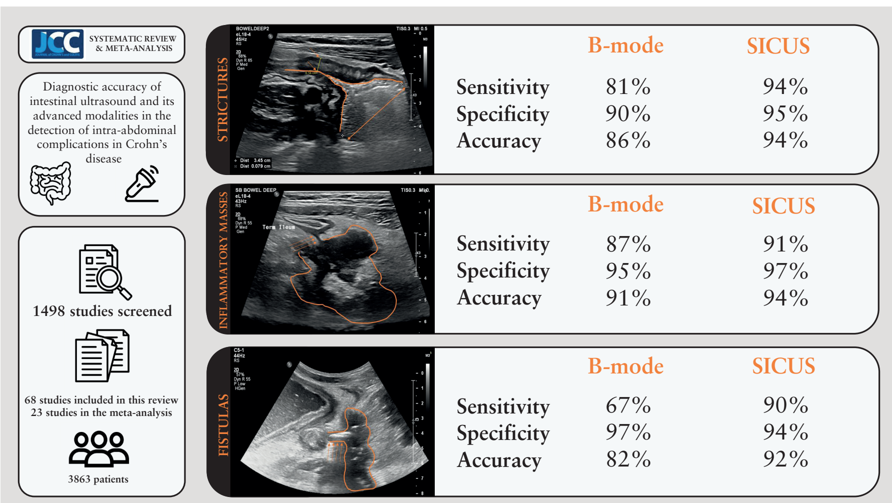
Method: We conducted a literature search for studies describing the diagnostic accuracy of IUS in adult patients with CD-related intra-abdominal complications. Quality of the included studies was assessed with the QUADAS-2 tool. Meta-analysis was performed for both conventional IUS [B-mode] and oral contrast IUS [SICUS].

Results: Of the 1498 studies we identified, 68 were included in this review and 23 studies [3863 patients] were used for the meta-analysis. Pooled sensitivities and specificities for strictures, inflammatory masses, and fistulas by B-mode IUS were 0.81 and 0.90, 0.87 [sensitivities] and 0.95, and 0.67 and 0.97 [specificities], respectively. Pooled overall log diagnostic odds ratios were 3.56, 3.97 and 3.84, respectively. Pooled sensitivity and specificity of SICUS were 0.94 and 0.95, 0.91 and 0.97 [sensitivities], and 0.90 and 0.94 [specificities], respectively. The pooled overall log diagnostic odds ratios of SICUS were 4.51, 5.46, and 4.80, respectively.

Conclusion: IUS is accurate for the diagnosis of intra-abdominal complications in CD. As a non-invasive, point-of-care modality, IUS is recommended as the first-line imaging tool if there is a suspicion of CD-related intra-abdominal complications.

Key Words: Intestinal ultrasound; IUS; Crohn's disease; CEUS; SICUS; elastography; Doppler; abscess; fistula; stricture

Graphical Abstract



1. Introduction

Crohn's disease [CD] is associated with the development of complications including strictures and penetrating lesions such as fistulas and inflammatory masses [i.e. phlegmons and abscesses]. At the time of diagnosis, penetrating lesions and strictures are already seen in 15% and 30% of patients, respectively, and up to 50% of patients develop complications during their disease course.[1,2]

For the diagnosis of complications, cross-sectional imaging allows transmural and extramural assessment and in the case of impassable or proximal small bowel strictures, is complementary to endoscopy.[2,3] In contrast to computed tomography [CT] and magnetic resonance imaging [MRI], intestinal ultrasound [IUS] is available in the point-of-care setting, is inexpensive and non-invasive, and is well tolerated by patients without imparting exposure to radiation.[4] Previous studies suggested that IUS is accurate not only to evaluate disease activity, but also to detect CD-related complications when surgery was used as the reference standard. The sensitivity and specificity of IUS to detect strictures and abscesses was comparable with CT and MRI.[3,5–7]

However, no up-to-date systematic review with meta-analysis is currently available on CD-related complications. In addition, previous publications have not assessed IUS when complemented by colour Doppler signal [CDS], oral or intravenous contrast enhancement [SICUS or CEUS], or elastography.

Therefore, the purpose of this systematic review and meta-analysis is to provide a comprehensive assessment of the diagnostic accuracy of trans-abdominal IUS, including its advanced modalities, in the detection of intra-abdominal complications in CD compared to endoscopy, cross-sectional imaging, surgery, and histopathology.

2. Methods

2.1. Search strategy

This systematic review was conducted according to PRISMA guidelines. The literature search was performed in the MEDLINE [Ovid] and EMBASE [Ovid] databases with the assistance of a scientific librarian of the Amsterdam University Medical Center. Databases were searched from January 1970 up to and including October 17, 2022. Search criteria were 'Crohn's disease' AND ['Ultrasonography' OR 'Elastography' OR 'Doppler' OR 'small intestine contrast ultrasound, SICUS' OR 'contrast enhanced ultrasound, CEUS'] OR ['Pathologic constriction' OR 'Stricture' OR 'Stenosis'] OR ['Phlegmon' OR 'Abdominal abscess'] OR 'intestinal fistula'.

Inclusion criteria were observational studies with adult CD patients diagnosed with intra-abdominal complications [i.e. fistulas, abscesses, phlegmons, stenosis/strictures] assessed by trans-abdominal ultrasonography [i.e. B-mode, contrast-enhanced ultrasound; CEUS, SICUS, elastography, and/or Doppler]. We excluded studies using endo-anal or endoscopic ultrasonography, studies including <15 patients, case-reports and case-series, *in vitro*, *ex vivo*, and animal studies, and conference abstracts published before January 2018.

B-mode [i.e. brightness mode] ultrasound refers to conventional ultrasound utilizing a two-dimensional greyscale image in which organs appear as areas of variable brightness.[8] Contrast-enhanced ultrasound [CEUS] is an additional ultrasound technique where gas-filled microbubbles are injected intravenously. Dedicated contrast agent-specific software in the IUS machine enables visualization of the microbubble signals, allowing better visualization of tissue vascularization and blood vessels in real time.[9] Oral contrast ultrasound [small intestine contrast ultrasonography; SICUS] refers to a technique in which patients are examined after ingestion of an oral macrogol contrast solution dissolved in water which distends the intestinal lumen, enhancing bowel wall characterization.[10]

Two reviewers [M.P. and F.dV.] independently screened each study's title and abstract and, if eligible, the full-text. Discrepancies on the eligibility of studies were resolved by consensus.

2.2. Methodological quality

Quality and risk of bias were assessed by one reviewer [M.P.] using an adaptation of the Quality Assessment of Diagnostic Accuracy Studies [QUADAS-2] tool. The QUADAS-2 tool is used to determine the quality of each individual study in systematic reviews comparing an index test and a reference test.[11]

2.3. Data analysis

Studies that were suitable for data extraction were included for data analysis. A bivariate random-effects model in Meta-DiSc was used to calculate pooled sensitivity and specificity.[12] Pooled accuracy was based on these pooled sensitivities and specificities. A univariate random-effects model was used to calculate the diagnostic test accuracy variables, including the log diagnostic odds ratio and area under the pooled receiver operating characteristic curve [AUC for SROC]. All data were calculated with 95% confidence intervals [CIs]. The chi-squared [χ^2] test was used to assess study heterogeneity with $p < 0.05$ indicating significant heterogeneity.[13] Funnel plots were created to assess publication bias. The meta-analysis was performed using the R-package Meta-Analysis of Diagnostic Accuracy [mada].[14]

3. Results

3.1. Included studies

A total of 1498 records were identified through the database search after removing duplicates [Supplementary Table S1 and Figure 1]. After screening the titles and abstracts we excluded 1368 records and checked 130 full articles. Reasons for exclusion were small sample size [i.e. inclusion of fewer than 15 patients, $n = 15$]; full text unavailability [$n = 10$]; use of a different outcome [$n = 8$]; inclusion of a different population [$n = 9$]; use of the wrong intervention [$n = 6$]; no description of complications at IUS [$n = 9$]; use of a different study design [$n = 3$]; and duplicates [$n = 2$]. A total of 68 studies were finally included in this systematic review and 23 studies were included in the meta-analysis.

A total of 54 studies had a prospective design [79.4%]. Sample size ranged between 15 and 796 with a mean age ranging between 27.5 and 56.8 years; 45% of the population was female. A total of 60, 42, and 46 studies reported information on IUS in diagnosing strictures, inflammatory masses, and fistulas, respectively. In addition, 11 studies described the added value of SICUS[10,15–24] and 15 of CEUS in the detection of CD-related complications.[25–39] Eight studies described the role of elastography as an advanced modality of IUS in strictures [Supplementary Table S3].

3.2. Quality of studies and risk of bias

Overall, the studies had moderate to high risk of bias, but low concerns regarding applicability [Supplementary Table S2 and Figure 2]. In eight studies a low risk of bias was scored for all domains of the QUADAS-2. The highest risk of bias in studies was related to the reference standard, flow, and timing. Common examples of high risk of bias were reference standards that were not blinded to index test results, inappropriate interval between index and reference standard [i.e. >3 months or not mentioned in article], and not all patients receiving the same reference standard. Regarding applicability, a high risk of bias was detected in studies in which patients underwent surgery.

3.3. CD-related strictures

3.3.1. Definition of CD-related strictures on IUS

Forty-four studies reported a definition for stricture. In the included studies the three main items for stricture definition were: increased bowel wall thickness [BWT; ≥3 or ≥4 mm], narrowed lumen [not further specified or <10 mm], and

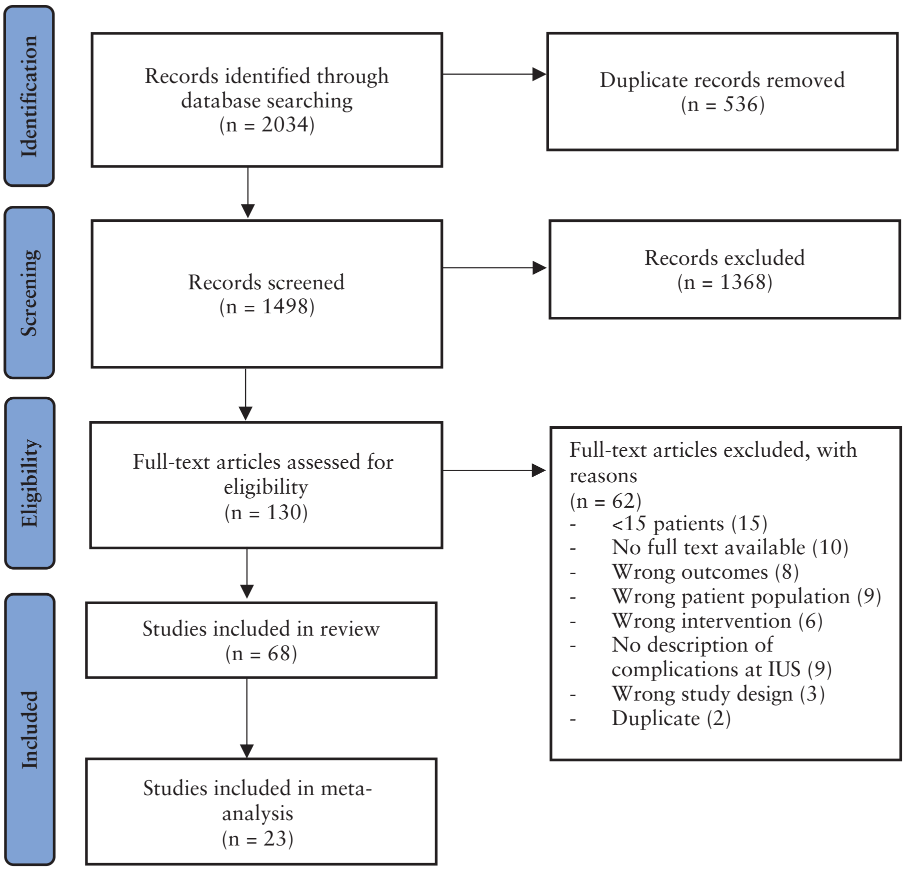


Figure 1. PRISMA [Preferred Reporting Items for Systematic Reviews and Meta -Analyses] flowchart.

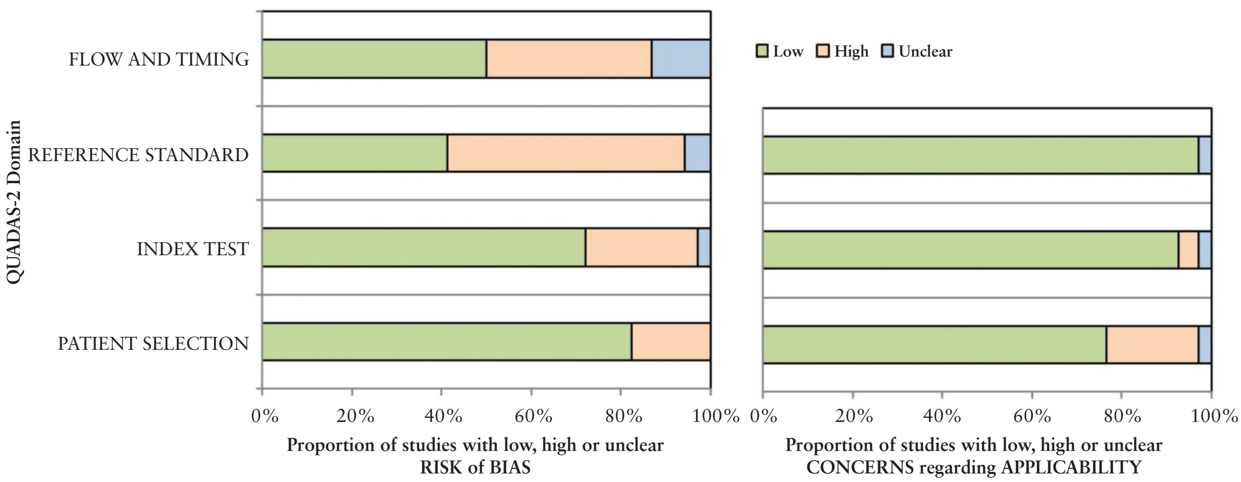


Figure 2. Results of QUADAS-2 assessment of the included studies.

pre-stenotic or proximal dilation [≥25 or ≥30 mm], mentioned in 82%, 93%, and 95% of the studies, respectively [Supplementary Table S4a].

Cooper et al. compared fibro-stenotic strictures defined on CT or magnetic resonance enterography [MRE] to IUS in histological confirmed strictures and reported that 40% [8/20] of the strictures diagnosed on IUS, met the CONSTRICT criteria [increased BWT > 3 mm or increase in wall thickness of 25%, narrowed luminal apposition, and pre-stenotic dilation of >3 cm, defined by MR/CT expert consensus]. All patients had bowel wall thickening and luminal narrowing, but 60% did not meet the pre-defined pre-stenotic dilation criteria on IUS.[40]

Takeuchi et al. focused on three IUS findings in strictures: narrowing of the intestinal lumen, pre-stenotic dilation on the proximal side of the stricture, and poor liquid flow in the expanded intestine [to and fro movement]. BWT was not included in their study. When lesions met all three stricture criteria on IUS a sensitivity of 36.7% was found compared to double balloon enteroscopy [DBE] as a reference standard. If, instead, lesions met two or more parameters, sensitivity increased to 70% and specificity remained 98.2%.[41]

3.3.2. Diagnostic accuracy of B-mode IUS for CD-related strictures

Sixteen studies reported data on the accuracy of B-mode IUS in diagnosing strictures in a total of 2002 patients [Table 1].[10,15,40–53] Eight of these studies had surgery or pathology as their reference standards[40,44,45,47,50–53] and four studies had a retrospective study design.[40,41,51,52]

Pooled sensitivity and specificity were 0.81 [95% CI, 0.78–0.84] and 0.90 [95% CI, 0.89–0.92], respectively [Table 2]. Heterogeneity of studies was significant for both sensitivity [$I^2 = 75.3\%$, $\chi^2 = 68.74$; $p < 0.0001$] and specificity [$I^2 = 82.9\%$, $\chi^2 = 99.56$; $p < 0.0001$].

All 16 studies were suitable for meta-analysis [Table 4, Figure 3 and Supplementary Figure S1]. The pooled overall log diagnostic odds ratio for strictures by B-mode IUS was 3.56 [2.90–4.21] and the AUC for SROC was 0.926 [0.949–0.904]. Heterogeneity was significant among these studies [$\chi^2 = 28.846$; $p = 0.025$].

Vigano et al. conducted a prospective study involving 65 CD patients who were scheduled for an ileal and/or colonic resection. Prior to the surgery, all patients underwent B-mode IUS and MRE examinations, and the findings were compared to the final pathology results. They reported similar performance for IUS and MRE in identifying intestinal strictures [sensitivity, specificity, and accuracy of 86.8%, 50%, and 83.8% for both, respectively].[53]

3.3.3. Diagnostic accuracy of SICUS for CD-related strictures

Four studies reported data on the accuracy of SICUS for the detection of strictures in a total of 202 patients [Table 1].[10,15,20,22] Two studies had surgery as their reference standard,[20,22] while the other two used small bowel enemas [SBE] and barium enteroclysis.[10,15] One study had a retrospective study design.[20]

Pooled sensitivity and specificity were 0.94 [95% CI, 0.87–0.98] and 0.95 [95% CI, 0.88–0.98], respectively [Table 2]. There was no significant heterogeneity of studies for either sensitivity [$I^2 = 0.0\%$, $\chi^2 = 2.42$; $p = 0.490$] or specificity [$I^2 = 55.2\%$, $\chi^2 = 6.70$; $p = 0.082$].

All four studies were suitable for a meta-analysis[10,15,20,22] [Table 4, Figure 3 and Supplementary Figure S1]. The pooled overall log diagnostic odds ratio for strictures by SICUS was 4.51 [95% CI, 3.28–5.73] the AUC for SROC was 0.955 [−0.19 to 0.14]. No significant heterogeneity was seen among these studies [$\chi^2 = 0.02$; $p = 0.992$].

Calabrese et al. evaluated the diagnostic value of SICUS compared to B-mode IUS with SBE as the reference standard. Sensitivity of B-mode IUS and SICUS in the detection of at least one stricture was 76% and 94% respectively. For the detection of pre-stenotic dilation, SICUS had a sensitivity and specificity of 100% and 90%, respectively, compared to 50% and 100%, respectively, with B-mode.[15] In post-operative patients the same authors assessed the accuracy of SICUS in detection of disease recurrence and strictures compared to endoscopy. SICUS detected strictures in 31 patients [sensitivity, specificity, and accuracy of 92.5%, 20.0%, and 87.5% respectively], of which 16 were associated with proximal bowel dilation with a median lumen diameter of 28 mm [range 25–32 mm].[16] Retrospectively, Calabrese et al. evaluated the detection of ileal stenosis by SICUS compared to CT enteroclysis in 59 patients. SICUS detected ileal stenosis with 95.5% sensitivity, 80% specificity, and 91.5% diagnostic accuracy, and pre-stenotic dilation with 87% sensitivity, 67% specificity, and 75% diagnostic accuracy.[17]

Pallotta et al. described a sensitivity and specificity of 97.5% and 100% for detecting at least one stricture using SICUS, and two or more strictures with 75% and 100% sensitivity and specificity, respectively, when compared to surgery. The accuracy of SICUS was higher than that of B-mode IUS [sensitivity 97.5% vs 80%, specificity 100% vs 75%]. Parente et al. assessed SICUS and B-mode IUS compared to SBE and ileocolonoscopy in detecting strictures and found a sensitivity of 75% for B-mode IUS and 89% for SICUS.

Kumar et al. described that the sensitivity of SICUS in detecting strictures was 87.5% and 100% for pre-stenotic dilation when compared to surgery.[20]

3.3.4. Characterizing CD-related strictures with B-mode, CEUS, and elastography

Characterization of strictures by B-mode IUS was assessed by Maconi et al. and compared to surgery. Strictures with bowel wall thickening and preserved bowel wall stratification on IUS [stratified echo pattern] showed significantly higher degrees of fibrosis, while strictures characterized by a bowel wall with loss of stratification [hypoechoic echo pattern] showed a higher degree of inflammation as defined by histopathology from resection specimens. High degrees of both fibrosis and inflammation were shown in mixed echo stratification patterns.[47] Furthermore, Maconi et al. assessed differences in the sensitivity of stricture detection based on location: sensitivity was 84.6% in ileal and 58.8% in colonic strictures.[46]

Several studies described the use of CEUS in the characterization of strictures. Lu et al. report a negative correlation with CEUS peak enhancement [PE] and fibrosis defined by histopathological grading [$r = -0.59$, $p = 0.02$]. PE had a fair correlation with chronic inflammation scores [$r = 0.6$, $p = 0.03$] and no correlation with active inflammation scores [$p > 0.05$].[27] Ripolles et al. compared CEUS to surgical resection specimens and found a significant association between the pathological inflammatory score and transmural complications, CDS, and percentage increase in contrast enhancement [$p = 0.018$, $p = 0.036$, and $p = 0.005$, respectively].[37]

Table 1. Overview of currently available studies assessing the sensitivity, specificity, and accuracy of intestinal ultrasound for the detection of Crohn's disease-associated intra-abdominal complications.

Study identification	Complication	Reference standard[s]	Exam type	Sample size [*n*]	Sens [%]	95% CI	Spec [%]	95% CI	Acc [%]	95% CI
Calabrese 2005	Stricture	SBE	B-mode	25	76.5	50.1–93.2	25.0	3.2–65.1	60.0	38.7–78.9
Carter 2017	Stricture	CTE MRE	B-mode	26	94.4	72.3–99.9	87.5	47.4–99.7	92.3	74.9–99.1
Cooper 2021	Stricture	Surgery	B-mode	30	95.2	76.2–99.9	66.7	29.9–92.5	86.7	69.3–96.2
Da Silva 2019	Stricture	MRE	B-mode	43	55.0	31.5–76.9	78.3	56.3–92.5	67.4	51.5–80.9
Gasche 1999	Stricture	Surgery Pathology	B-mode	33	100.0	84.6–100.0	90.9	58.7–99.8	97.0	84.2–99.9
Kohn 1999	Stricture	Surgery Pathology	B-mode	44	82.1	63.1–93.9	100.0	79.4–100.0	88.6	75.4–96.2
Maconi 1996	Stricture	Endoscopy SB X-ray Contrast enema CT	B-mode	101	74.4	58.8–86.5	93.1	83.3–98.1	85.2	76.7–91.4
Maconi 2003	Stricture	Surgery Pathology	B-mode	43	100.0	83.9–100.0	63.6	40.7–82.8	81.4	66.6–91.6
Nakano 2013	Stricture	DBE	B-mode	796	93.3	86.1–97.5	87.4	84.7–89.8	88.1	85.6–90.2
Neye 2010	Stricture	MRI CT enteroclysis Endoscopy Histology	B-mode	78	85.7	67.3–96.0	90.0	78.2–96.7	88.5	79.2–94.6
Parente 2002	Stricture	Barium X-ray	B-mode	212	78.7	67.7–87.3	97.1	92.7–99.2	90.6	85.8–94.1
Parente 2002	Stricture	Surgery Pathology	B-mode	85	90.0	80.5–95.9	100.0	78.2–100.0	91.8	83.8–96.6
Parente 2004	Stricture	Barium X-ray	B-mode	102	74.1	53.7–88.9	93.3	85.1–97.8	88.2	80.4–93.8
Potthast 2002	Stricture	Endoscopy Enteroclysis Surgery	B-mode	44	58.8	32.9–81.6	100.0	87.2–100.0	84.1	69.9–93.4
Sey 2013	Stricture	CT MRI SBFT Endoscopy Surgery	B-mode	103	14.3	0.4–57.8	100.0	96.2–100.0	94.2	87.8–97.8
Takeuchi 2022	Stricture	DBE	B-mode	86	70.0	50.6–85.3	98.2	90.5–100.0	88.4	79.7–94.3
Takeuchi 2022	Stricture	DBE	B-mode	86	36.7	19.9–56.1	98.2	90.5–100.0	76.7	66.4–85.2
Vigano 2019	Stricture	Surgery Pathology	B-mode	65	86.9	75.8–94.2	50.0	6.7–93.2	84.6	73.5–92.4
Calabrese 2005	Stricture	SBE	SICUS	25	94.1	71.3–99.9	75.0	34.9–96.8	88.0	68.8–97.5
Kumar 2015	Stricture	Surgery Pathology	SICUS	26	88.9	51.8–99.7	88.2	63.6–98.5	88.5	69.9–97.6
Pallotta 2012	Stricture	Surgery Pathology	SICUS	49	97.5	86.8–99.9	100.0	66.4–100.0	98.0	89.2–100.0
Parente 2004	Stricture	Barium X-ray	SICUS	102	88.9	70.8–97.7	97.3	90.7–99.7	95.1	88.9–98.4
Allocca 2018	Inflammatory mass	Endoscopy MRE	B-mode	60	100.0	2.5–100.0	96.6	88.3–99.6	96.7	88.5–99.6
Carter 2017*	Inflammatory mass	CTE MRE	B-mode	8						
Da Silva 2019*	Inflammatory mass	MRE	B-mode	43						
Gasche 1999	Inflammatory mass	Surgery Pathology	B-mode	33	100.0	66.4–100.0	91.7	73.0–99.0	93.9	79.8–99.3
Kamel 2020	Inflammatory mass	Endoscopy MRE	B-mode	48	100.0	63.1–100.0	100.0	91.2–100.0	100.0	92.6–100.0
Kohn 1999	Inflammatory mass	Surgery Pathology	B-mode	25	72.7	39.0–94.0	85.7	57.2–98.2	80.0	59.3–93.2
Maconi 1996	Inflammatory mass	Endoscopy SB X-ray Contrast enema	B-mode	58	83.3	35.9–99.6	94.2	84.1–98.8	93.1	83.3–98.1

Table 1. Continued

Study identification	Complication	Reference standard[s]	Exam type	Sample size [n]	Sens [%]	95% CI	Spec [%]	95% CI	Acc [%]	95% CI
Maconi 2003	Inflammatory mass	Surgery Pathology	B-mode	128	80.8	60.7–93.5	93.1	86.4–97.2	90.6	84.2–95.1
Neye 2010	Inflammatory mass	MRI CT enteroclysis Endoscopy Histology	B-mode	78	90.0	55.5–99.8	98.5	92.1–100.0	97.4	91.0–99.7
Pallotta 2012	Inflammatory mass	Surgery Pathology	B-mode	49	90.0	55.5–99.8	94.9	82.7–99.4	93.9	83.2–98.7
Potthast 2002	Inflammatory mass	Endoscopy Enteroclysis Surgery	B-mode	34	88.9	51.8–99.7	88.0	68.8–97.5	88.2	72.6–96.7
Calabrese 2013	Inflammatory mass	CT-enteroclysis	SICUS	59	77.8	40.0–97.2	100.0	92.9–100.0	96.6	88.3–99.6
Kumar 2015	Inflammatory mass	Surgery Pathology	SICUS	25	100.0	39.8–100.0	95.2	76.2–99.9	96.0	79.7–99.9
Pallotta 2012	Inflammatory mass	Surgery Pathology	SICUS	49	100.0	69.2–100.0	94.9	82.7–99.4	95.9	86.0–99.5
Allocca 2018	Fistula	Endoscopy MRE	B-mode	60	100.0	15.8–100.0	98.3	90.8–100.0	98.3	91.1–100.0
Da Silva 2019	Fistula	MRE	B-mode	43	0.0	0.0–52.2	97.4	86.2–99.9	86.1	72.1–94.7
Gaitini 2011	Fistula	CT	B-mode	52	66.7	22.3–95.7	97.8	88.5–99.9	94.2	84.1–98.8
Gasche 1999	Fistula	Surgery Pathology	B-mode	33	87.0	66.4–97.2	90.0	55.5–99.8	87.9	71.8–96.6
Kamel 2020	Fistula	Endoscopy MRE	B-mode	40	85.7	57.2–98.2	100.0	86.8–100.0	95.0	83.1–99.4
Kohn 1999	Fistula	Surgery Pathology	B-mode	25	66.7	9.4–99.2	95.5	77.2–99.9	92.0	74.0–99.0
Maconi 1996	Fistula	Endoscopy SB x-ray Contrast enema CT	B-mode	98	66.7	34.9–90.1	95.4	88.5–98.7	91.8	84.6–96.4
Maconi 2003	Fistula	Surgery Pathology	B-mode	128	71.4	57.8–82.7	95.8	88.3–99.1	85.2	77.8–90.8
Neye 2010	Fistula	MRI CT enteroclysis Endoscopy Histology	B-mode	78	78.3	56.3–92.5	94.6	84.9–98.9	89.7	80.8–95.5
Pallotta 2012	Fistula	Surgery Pathology	B-mode	49	53.6	33.9–72.5	100.0	83.9–100.0	73.5	58.9–85.1
Potthast 2002	Fistula	Endoscopy Enteroclysis Surgery	B-mode	42	31.3	11.0–58.7	100.0	86.8–100.0	73.8	58.0–86.1
Ripolles 2013*	Fistula	Surgery CT MRI	B-mode	11	90.9	58.7–99.8				
Sey 2013	Fistula	CT MRI SBFT Endoscopy Surgery	B-mode	103	50.0	23.0–77.0	100.0	95.9–100.0	93.2	86.5–97.2
Vigano 2019	Fistula	Surgery Pathology	B-mode	66	75.0	47.6–92.7	98.0	89.4–100.0	92.4	83.2–97.5
Calabrese 2013	Fistula	CT-enteroclysis	SICUS	59	78.6	49.2–95.3	95.6	84.9–99.5	91.5	81.3–97.2
Kumar 2015	Fistula	Surgery Pathology	SICUS	26	87.5	47.4–99.7	94.4	72.7–99.9	92.3	74.9–99.1
Pallotta 2012	Fistula	Surgery Pathology	SICUS	49	96.4	81.7–99.9	90.5	69.6–98.8	93.9	83.1–98.7

B-mode: conventional ultrasound, SICUS: small intestine contrast ultrasound, CT: computed tomography, MRI: magnetic resonance imaging, MRE: magnetic resonance enterography, SB: small bowel, DBE: double balloon enteroscopy, SBFT: small bowel follow through, Sens: sensitivity, Spec: specificity, CI: confidence interval, Acc: accuracy.
*No calculations possible based on the available raw data.

Table 2. Pooled sensitivity, specificity, and accuracy for all reference standards.

Complication	Exam type	Included studies [*n*]	Patients [*n*]	Sens	95% CI	I^2 [%]	χ^2	Spec	95% CI	I^2 [%]	χ^2	Acc
Stricture	B-mode	18†	2002	0.808	0.775–0.838	83.1	100.89*	0.902	0.885–0.917	83.4	102.21*	0.855
Stricture	SICUS	4	202	0.935	0.865–0.976	0.0	2.42	0.945	0.884–0.980	55.2	6.7	0.940
Inflammatory mass	B-mode	9	513	0.867	0.779–0.929	0.0	7.65	0.948	0.922–0.967	31.6	11.69	0.908
Inflammatory mass	SICUS	3	133	0.913	0.720–0.989	50.7	4.06	0.973	0.922–0.994	46.1	3.71	0.943
Fistula	B-mode	13	817	0.665	0.598–0.727	65.6	34.91*	0.973	0.957–0.985	11.0	13.48	0.819
Fistula	SICUS	3	134	0.900	0.782–0.967	39.5	3.3	0.940	0.867–0.980	0.0	0.61	0.920

B-mode: conventional ultrasound, SICUS: small intestine contrast ultrasound, Sens: sensitivity, Spec: specificity, CI: confidence interval, Acc: accuracy.
*$p < 0.05$.
†Within 16 unique studies.

Quaia et al. compared CEUS between inflammatory and fibrotic ileal strictures, defined by deep mucosal biopsies in 28 patients, and reported differences in the percentage of maximal enhancement [45.86 ± 5.32 vs 37.33 ± 16.24%; $p < 0.05$] and area under the enhancement curve [1168.25 ± 437.65 vs 570.47 ± 323.08; $p < 0.05$], whereas the difference in time to PE was not significant [9.25 ± 4.21 vs 12.01 ± 7.34 s; $p > 0.05$].[32] In a second study, the same authors compared CEUS within inflammatory and fibrotic strictures, defined by deep mucosal biopsies, in 65 patients and they reported a significant difference [$p < 0.05$] between the two groups in PE, wash-in rate, wash-in perfusion index, AUC, AUC during wash in [AUCWI], and AUC during wash out [AUCWO].[34]

Eight studies assessed the feasibility and accuracy of elastography in detecting intestinal fibrosis and in differentiating between inflammatory and fibrotic strictures.[19,27,33,39,54–57] Ding et al. evaluated three different methods of elastography, namely strain elastography, acoustic radiation force impulse, and point shear wave elastography [SWE]. Point SWE had the best performance for evaluating and differentiating intestinal stenosis when compared to endoscopy and histology. With an optimal cut-off value of 2.73 m/s, they found a sensitivity of 75% and specificity of 100% with an area under the receiver operating characteristic curve [AUROC] of 0.833 [$p < 0.05$] to differentiate between a predominantly inflammatory and predominantly fibrotic stenosis.[55] Serra et al. aimed to assess whether real-time SE with a mean strain ratio [MSR] can differentiate between an inflammatory and fibrotic stricture compared to histology. They did not find a significant correlation between MSR and a histology fibrosis score [$p = 0.877$].[39] Chen et al. enrolled 35 patients with either ileal or ileocolonic strictures who underwent SWE within 1 week of surgical resection. They reported a significantly higher mean SWE value in the stenotic bowel wall in severe fibrosis compared to mild/moderate and mild fibrosis [23.0 ± 6.3, 17.4 ± 3.8, and 14.4 ± 2.1 kPa respectively, $p = 0.008$] and defined a cut-off value of 22.55 kPa for discriminating between mild/moderate and severe fibrosis with a sensitivity and specificity of 69.9% and 91.7%, respectively [AUC of 0.822, $p = 0.002$]. There was no significant difference between mean SWE values to identify different grades of inflammation.[54]

Two studies combined elastography and CEUS to characterize CD-related strictures. Lu et al. studied the correlation between SWE, CEUS, and histopathological grades of inflammation, fibrosis, and muscle hypertrophy. There was no significant relationship between SWE and fibrosis scores, but a moderate correlation between SWE and muscular hypertrophy [$r = 0.59$, $p = 0.02$] and an inverse relationship between CEUS peak enhancement and SWE velocity measurements [$r = -0.061$, $p = 0.03$] was found.[27] Quaia et al. investigated the feasibility of B-mode, CEUS, and strain elastography in differentiating inflammatory from fibrotic ileal CD-related strictures based on deep mucosal biopsies or surgery. They concluded that combining all three IUS techniques resulted in significantly higher sensitivity, specificity, diagnostic accuracy, and AUROC compared to using the individual techniques alone [$p < 0.05$].[33]

3.3.5. IUS compared to other cross-sectional modalities in detecting or characterizing CD-related strictures

Lenze et al. assessed the best non-invasive imaging method to detect strictures using positron emission tomorgraphy

[PET]-CT, MRE, and IUS vs endoscopy and biopsy histology reports. They found no significant difference in detection rates between PET-CT, MRE, and IUS [81%, 81%, and 67% respectively]. None of these cross-sectional imaging modalities was accurate in differentiating between fibrotic and inflammatory strictures.[58] Vigano et al. reported similar accuracy for MRE and B-mode IUS compared to final pathology, with a sensitivity, specificity, and accuracy of 86.8%, 86.8%, and 100% respectively.[53]

Kumar et al. compared in a retrospective study the diagnostic accuracy of SICUS and MRE with surgical findings. The sensitivity of SICUS and MRE was 87.5% and 100% for strictures, respectively.[20]

3.4. CD-related inflammatory masses

3.4.1. Definition of CD-related inflammatory masses on IUS

CD-related inflammatory masses on IUS are defined as [i] round hypoechoic lesions in 93%, [ii] with irregular walls in 67%, and [iii] containing air and/or hyperechoic debris in 70% of the total 27 studies reporting on definition [Supplementary Table S4b].

3.4.2. Diagnostic accuracy of B-mode IUS in diagnosing CD-related inflammatory masses

Eleven studies reported data on the accuracy of B-mode IUS for the detection of inflammatory masses [Table 1].[22,42–47,49,51,59,60] In five studies surgery was the reference standard[22,44,45,47,51] and one study used a retrospective design.[51]

Across nine studies pooled sensitivity and specificity were 0.87 [95% CI, 0.78–0.93] and 0.95 [95% CI, 0.92–0.97], respectively [Table 2]. There was no significant heterogeneity among studies for both sensitivity [$I^2 = 0.0\%$, $\chi^2 = 7.65$; $p = 0.469$] and specificity [$I^2 = 31.6\%$, $\chi^2 = 11.69$; $p = 0.166$].

All 11 studies were suitable for meta-analysis [Table 4, Figure 3 and Supplementary Figure S1]. The pooled overall log diagnostic odds ratio for inflammatory masses by B-mode IUS was 3.97 [95% CI, 3.30–4.64] and the AUC for SROC was 0.96 [0.93–0.99]. Heterogeneity was not significant among these studies [$\chi^2 = 9.395$; $p = 0.402$].

In a study by Maconi et al., absence of power Doppler signal in the centre of the lesion and increased signalling in the periphery of the lesion were the most significant parameters to detect an abscess.[61] In a second study, Maconi et al. demonstrated that IUS and CT had comparable accuracy to detect abscesses.[62]

IUS also showed very good concordance with MRI in detecting abscesses [$\kappa = 0.88$; $p < 0.01$] in a study by Castiglione et al.[63]

3.4.3. Diagnostic accuracy of SICUS in diagnosing CD-related inflammatory masses

Three studies[17,20,22] reported accuracy of SICUS for diagnosing inflammatory masses [Table 1]. In two studies surgery was the reference standard,[20,22] and all studies used a retrospective design.[17,20,22] Pooled sensitivity and specificity were 0.91 [95% CI, 0.72–0.99] and 0.97 [95% CI, 0.92–0.99], respectively [Table 2]. There was no significant heterogeneity between studies for either sensitivity [$I^2 = 50.7\%$, $\chi^2 = 4.06$; $p = 0.132$] or specificity [$I^2 = 46.1\%$, $\chi^2 = 3.71$; $p = 0.156$].

All three studies were suitable for meta-analysis [Table 4, Figure 3 and Supplementary Figure S1]. The pooled overall log diagnostic odds ratio for inflammatory masses by SICUS was 5.46 [95% CI, 3.61–7.3] and the AUC for SROC was

Table 3. Pooled sensitivity, specificity, and accuracy for surgery [and pathology] as reference standard only.

Complication	Exam type	Included studies [n]	Patients [n]	Sens	95% CI	I^2 [%]	χ^2	Spec	95% CI	I^2 [%]	χ^2	Acc
Stricture	B-mode	6	281	0.905	0.857–0.941	62.5	13.34*	0.786	0.671–0.875	64.1	13.92*	0.846
Stricture	SICUS	2	75	0.959	0.860–0.995	7.4	1.08	0.923	0.759–0.991	44.0	1.79	0.941
Inflammatory mass	B-mode	3	107	0.867	0.693–0962	52.0	4.17	0.922	0.838–0.971	0.0	1.12	0.895
Inflammatory mass	SICUS	2	74	1.000	0.768–1.000	0.0	0.0	0.950	0.861–0.990	0.0	0.0	0.975
Fistulas	B-mode	4	173	0.700	0.579–0.804	58.5	7.22	0.971	0.917–0.994	0.0	2.69	0.836
Fistulas	SICUS	2	75	0.944	0.813–0.993	0.0	0.79	0.923	0.719–0.984	0.0	0.22	0.934

B-mode: conventional ultrasound, SICUS: small intestine contrast ultrasound, Sens: sensitivity, Spec: specificity, CI: confidence interval, Acc: accuracy.
*$p < 0.05$.

Table 4. Diagnostic test accuracy variables

Complication	Exam type	Included studies [*n*]	Patients [*n*]	Log diagnostic odds ratio	95% CI	AUC for SROC	95% CI	χ^2
Stricture	B-mode	18†	2002	3.56	2.90–4.21	0.93	0.95–0.90	28.85*
Stricture	SICUS	4	202	4.51	3.28–5.73	0.96	−0.19 to 0.14	0.02
Inflammatory mass	B-mode	11	564	3.97	3.30–4.64	0.96	0.93–0.99	9.40
Inflammatory mass	SICUS	3	133	5.46	3.61–7.30	0.99	0.93–1.05	1.55
Fistula	B-mode	14	828	3.84	3.28–4.41	0.90	0.86–0.94	10.24
Fistula	SICUS	3	134	4.80	3.46–6.14	0.98	0.93–1.05	2.12

B-mode: conventional ultrasound, SICUS: small intestine contrast ultrasound, CI: confidence interval, AUC for SROC: area under the curve of the summary receiver operating characteristics curve.
*$p < 0.05$.
†Within 16 unique studies.

0.99 [0.93–1.05]. Heterogeneity was not significant among these studies [$\chi^2 = 1.552$; $p = 0.21$].

Pallotta et al. compared B-mode IUS and SICUS with surgical findings. They reported a higher sensitivity and identical specificity for SICUS [100% and 95%, respectively] compared to B-mode IUS [89% and 95%, respectively] in diagnosing abscesses.[22]

3.4.4. Differentiation of inflammatory masses by CEUS

Several studies evaluated the potential role of CEUS in detecting inflammatory masses and differentiating between abscesses or phlegmons. Ripolles et al. evaluated this differentiation by CEUS retrospectively in 57 inflammatory masses that were confirmed by either CT, MRI, or surgery. In all abscesses, except one, there was partial or total absence of enhancement of the hypoechoic mass after contrast agent injection whereas all phlegmons showed homogeneous enhancement of the hypoechoic mass after contrast agent injection. The sensitivity, specificity, and accuracy of CEUS for differentiating between abscesses and phlegmons were 97.2%, 100%, and 98.2%, respectively.[35] Estaban et al. combined CEUS with power Doppler IUS in 28 patients with a suspected abdominal inflammatory mass on B-mode IUS and compared it to post-contrast CT scans. In all inflammatory masses signals appeared after contrast injection; in two of the masses, later diagnosed as abscesses on CT scan, this only occurred in the periphery of the lesion. Combined CEUS and power Doppler were able to detect both early and small inflammatory masses [mean size of 18.5 mm] as well as larger lesions [mean size of 35.6 mm].[25] Sallomi et al. also used CEUS combined with power Doppler and found a higher sensitivity and specificity when compared to CT scaning.[38]

3.5. CD-related intra-abdominal fistulas

3.5.1. Definition of CD-related fistulas on IUS

Of the included studies, 29 reported definitions for identifying fistulas. The main items were: hypoechoic tracts with or without hyperechoic content, observed between bowel loops, or between bowel loops and other structures such as the bladder, skin, or mesentery. These items were reported in 97% and 82% of the studies respectively [Supplementary Table S4c].

3.5.2. Diagnostic accuracy of B-mode IUS in diagnosing CD-related intra-abdominal fistulas

Fourteen studies reported data on the accuracy of B-mode IUS in detecting fistulas[22,37,43–47,49,51–53,59,60,64] [Table 1]. Surgery was the reference standard in eight studies[22,37,44,45,47,51–53] and two studies used a retrospective design.[51,52] In 13 out of 14 studies, the pooled sensitivity and specificity were 0.67 [95% CI, 0.60–0.73] and 0.97 [95% CI, 0.96–0.99], respectively [Table 2].[22,43–47,49,51–53,59,60,64] There was significant heterogeneity among studies for sensitivity [$I^2 = 65.6\%$, $\chi^2 = 34.91$; $p < 0.0001$], but not for specificity [$I^2 = 11.0\%$, $\chi^2 = 13.48$; $p = 0.335$].

All 14 studies were suitable for univariate meta-analysis [Table 4, Figure 3 and Supplementary Figure S1]. The pooled overall log diagnostic odds ratio for fistulas by B-mode IUS was 3.84 [95% CI, 3.28–4.41] and the AUC for SROC was 0.90 [0.86–0.94]. Heterogeneity was not significant among these studies [$\chi^2 = 10.24$; $p = 0.59$].

Maconi et al. looked at the prevalence of hypoechoic, stratified, and mixed echo patterns of the bowel wall in stenosis and did not find any significant differences between patients with and without internal fistulas [50%, 64%, and 50% vs 50%, 36%, and 50% of cases, $p = 0.656$].[47] In a second study also by Maconi et al., adding power Doppler to B-mode IUS enhanced fistula detection.[61] In one prospective study IUS was superior to both CT and contrast barium enteroclysis when visualizing intra- and perimural abscesses and sinus tracts [i.e. entero-mesenteric tracts].[65]

Moreno et al. described different types of fistulas on B-mode IUS in 46 patients, including entero-mesenteric tracts as the most common type [69.6%].[31] Garcia et al. reported that entero-enteric fistulas [$p = 0.04$] and entero-mesenteric tracts [$p = 0.003$], detected by IUS, were significantly associated with the need for surgery in the short term.[66]

3.5.3. Diagnostic accuracy of SICUS in diagnosing CD-related intra-abdominal fistulas

Three studies reported data on the accuracy of detecting fistulas using SICUS [Table 1].[17,20,22] Surgery was the reference standard in two studies[20,22] and one study had a retrospective design.[20] Pooled sensitivity and specificity were 0.90 [95% CI, 0.78–0.97] and 0.94 [95% CI, 0.87–0.98], respectively [Table 2]. There was no significant heterogeneity between studies for either sensitivity [$I^2 = 39.5\%$, $\chi^2 = 3.30$; $p = 0.192$] or specificity [$I^2 = 0.0\%$, $\chi^2 = 0.61$; $p = 0.736$].

All studies were suitable for meta-analysis [Table 4, Figure 3 and Supplementary Figure S1]. The pooled overall log diagnostic odds ratio for fistulas by SICUS was 4.80 [95% CI, 3.46–6.14] and the AUC for SROC was 0.98 [0.93–1.05]. Heterogeneity was not significant among these studies [$\chi^2 = 2.12$; $p = 0.15$].

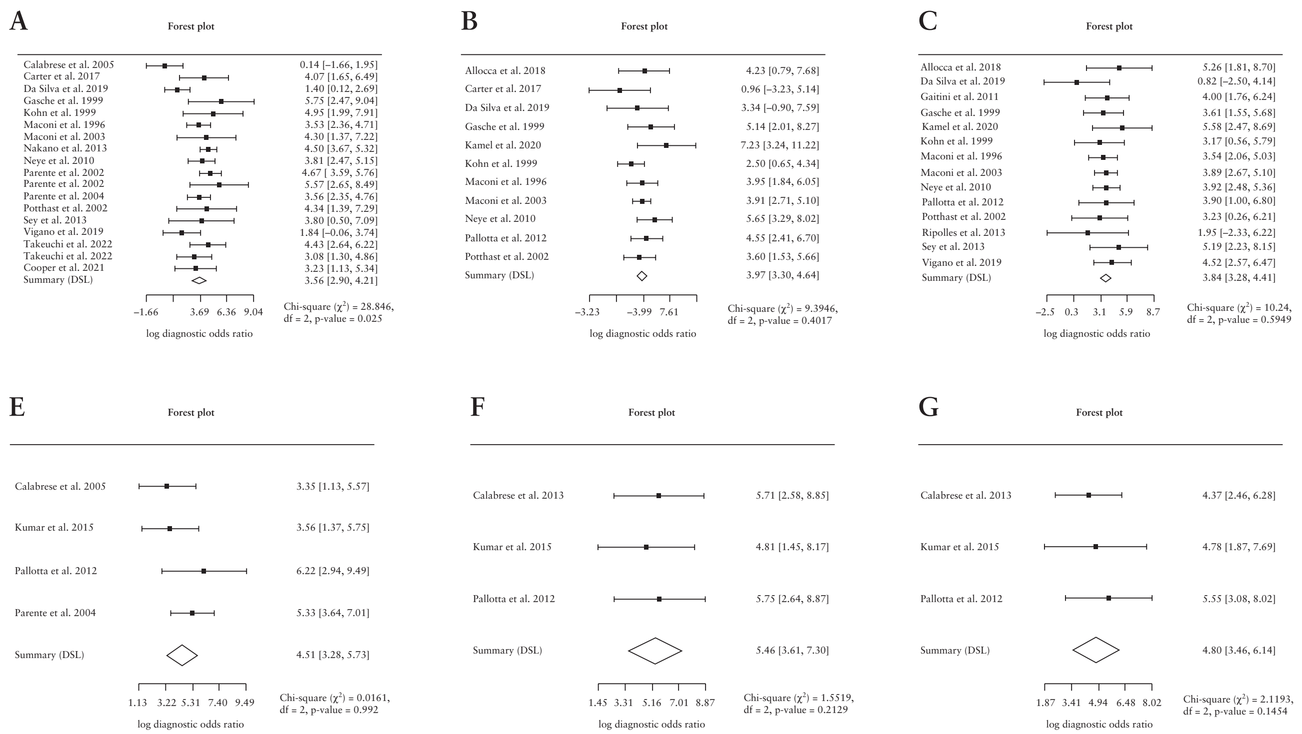


Figure 3. Forest plots for a univariate random effects meta-analysis using the diagnostic odds ratio for diagnosing [a and e] strictures, [b and f] inflammatory masses, and [c and g] fistulas by conventional IUS [B-mode; a–c] and oral contrast IUS [SICUS; e–g], respectively.

Calabrese et al. reported better detection of entero-enteric and entero-cutaneous fistulas with SICUS compared to B-mode IUS, with SBE as a reference standard.[15] SICUS detected a gastro-enteric fistula, not visualized by SBFT, in a study by Chatu et al. in 2012.[18]

Both B-mode IUS and SICUS were more accurate in the detection of internal fistulas and entero-mesenteric tracts compared to SBE using intraoperative findings as the gold standard in a prospective study by Parente et al. B-mode IUS, SICUS, and SBE detected 80%, 86%, and 67% of all fistulas and entero-mesenteric tracts, respectively.[10] Kumar et al. compared intraoperative findings with SICUS and MRE, reporting a sensitivity of 87.7% and 66.7% for fistulas, respectively. Correlated to surgery, there was a high level of agreement in localizing fistulas on SICUS and MRE [κ = 0.82, 0.79]. Concordance between SICUS and MRE was substantial or almost complete in identifying fistulas [κ = 0.65].[20]

3.5.4. Diagnostic accuracy of CEUS in diagnosing CD-related intra-abdominal fistulas

Two studies reported data on the accuracy of CEUS in diagnosing fistulas. Mao et al. performed intra-cavitary CEUS in CD patients diagnosed with an abscess. After ultrasound guided aspiration of the abscess, a diluted contrast agent was injected in the abscess cavity. This ultrasound technique had a sensitivity of 86.7% and a specificity of 100% for demonstrating the presence of fistulous tracts, using surgery and pathology as the reference standard.[29] Maconi et al. assessed hydrogen peroxide-enhanced IUS fistulography for enterocutaneous fistulas; this technique visualized the extent and configuration of fistulas in all 13 cases confirmed by surgery. In contrast, conventional X-ray fistulography missed correct definition of the fistulous branches or communication with intestinal loops in 50% [4/8] and 36% [4/11] of patients respectively; barium radiography showed fistulas in two cases only.[28]

In a study by Ripolles et al. 10 out of 11 fistulas were visualized by CEUS in 14 intestinal segments found in the surgical or pathological specimen reports.[37]

3.5.5. Correlation of IUS techniques and reference standards in CD-related intra-abdominal complications

Kumar et al. found that the agreement between SICUS and MRE was substantial to almost perfect for the presence of CD-related strictures [κ = 0.84], and stricture number and location [κ = 0.85]. They found a high level of agreement in localizing strictures between surgery and SICUS [κ = 0.75].[20]

For the detection of abscesses, the agreement between surgery and B-mode IUS and SICUS were 0.78 and 0.89, respectively.[22] Another study by Kumar et al. showed a higher level of agreement for SICUS in localizing abscesses compared to MRE when correlated to surgery [κ = 0.87, 0.77], with both techniques having a sensitivity of 100%.[20]

The kappa coefficient between CEUS and other techniques in the diagnosis of phlegmons or abscesses was excellent [κ = 0.972]. Statistically significant differences were found between the size of the abscesses before and after contrast agent injection. The inter-observer agreement for the diagnosis of phlegmons or abscesses was excellent [κ = 0.953].[35]

One study assessed reproducibility of fistulas by IUS in 20 CD patients, describing both a fair [κ = 0.31–0.48] and very good [κ = 0.87–1] agreement among six different operators divided in two rooms for the presence of fistulas.[67] Another study showed that IUS had fair concordance for entero-enteric fistulas compared to MRI [κ=0.67].[63]

4. Discussion

In this systematic review and meta-analysis, we have provided a comprehensive assessment of the diagnostic accuracy of trans-abdominal IUS and its advanced modalities in the detection of intra-abdominal complications in CD. The accuracy of IUS for diagnosing strictures, abscesses, and fistulas associated with CD is good to excellent when compared with other cross-sectional imaging modalities, surgery, or pathology.

The accuracy of IUS for the diagnosis of CD-related strictures is high [Tables 2–4], despite heterogeneous diagnostic criteria. Nearly all studies describe the three core imaging features for strictures. However, some studies applied stricture definitions based on fewer features, or mention no definition at all. Interestingly, both Cooper et al. and Takeuchi et al. suggest that strictures do not need to fulfil all three parameters on IUS. Pre-stenotic dilation, for example, was absent in the majority of histologically confirmed strictures.[40,41] However, increased IUS stricture detection rates are described after adding oral contrast.[15,22] Accordingly, studies show SICUS is highly accurate in diagnosing pre-stenotic dilation, even with higher sensitivity than MRE.[17,20] Oral contrast provides more marked dilation of the pre-stenotic segment resulting in better visualization of the narrowed tract. This can also be beneficial in identifying distal strictures in patients with multiple strictures. Therefore, while pre-stenotic dilation probably confirms a stricture when using oral contrast, its absence in B-mode examinations should not exclude stricture presence.

Some studies reported strikingly low sensitivities for IUS compared to the pooled data [Table 2]. For example, Da Silva et al. included a cohort consisting of patients without obstructive symptoms or indication for surgery, resulting in reduced risk of selection, and referral bias.[43] Additionally, some studies use a per-segment-based evaluation instead of a per-patient evaluation, which is known to have a lower sensitivity.[68]

Data are contradictory on the capability of IUS to distinguish between fibrosis and inflammation. Maconi et al. suggest that bowel wall stratification is useful in distinguishing inflammatory and fibrotic strictures. In cases of fibrotic stenosis there was a noticeable increase in echogenicity and thickening of the bowel wall, predominantly observed in the submucosa.[47] This could be attributed to the deposition of collagen in the submucosal layer, leading to an overall increase in both volume and density. By contrast, Nylund et al. showed in an *in vitro* study that fibrosis in the submucosa actually resulted in a decrease in echogenicity. They suggest that this is due to reduction of fatty tissue in the submucosa.[69] According to other studies, smooth muscle hyperplasia and hypertrophy were the main contributors to BWT.[70,71] Interestingly, elastography was reported to detect muscle hypertrophy.[27]

In general, the two main types of elastography (SWE and strain elastography [SE]) are distinguished by [i] the need for external compression, which is a subjective component for SE, and [ii] while SE is qualitative [provides information in relation to the surrounding tissue], SWE provides quantitative information. SWE has the best reproducibility of elastography techniques for assessing bowel wall stiffness.[72,73] Indeed, higher SWE values have been reported in severe compared to mild and moderate fibrosis.[54]

Intravenous contrast may also improve stricture differentiation: CEUS parameters showed good correlation with inflammatory activity and a negative correlation was described both between time to peak and peak enhancement, and histopathological fibrosis.[27,32–34,37,74,75] Furthermore, the combination of elastography and CEUS improved the accuracy. However, current studies show high heterogeneity in results and only a few use histopathology as the reference standard, where, as yet, no validated scoring system exists. An ongoing study is further investigating the role of SWE and CEUS combined with B-mode IUS in defining predominant stricture composition and is trying to mitigate some of the previously mentioned pitfalls [Netherlands Trial Register: NL9105].

Most studies report the three main features of inflammatory masses on IUS. If studies describe fewer features, they all describe an inflammatory mass at least as a round hypoechoic lesion. Consequently, this might be the most important feature of an inflammatory mass. However, further standardization of the definition, including more than one feature, would irrefutably improve reducibility.

Studies report higher detection rates of superficial abscesses compared to deep intra- and retroperitoneal abscesses. This can be explained by common difficulties associated with transabdominal US, such as overlying bowel gas that may obscure structures located deep in the pelvis or lying in between intestinal loops. In combination with poorly compressible abdomens, this may result in more false-negative results in detecting deep intra- and retroperitoneal abscesses.[62,64]

Compared to B-mode IUS, Pallotta et al. show increased sensitivity and level of agreement for SICUS in detecting intra-abdominal masses. Distending the intestinal lumen of the entire small bowel with oral contrast can result in better differentiation between an abscess and a bowel loop.[22]

Studies focusing on the differentiation between phlegmons and abscesses by IUS mainly report differences in the vascularization of the mass. Abscesses are characterized by increased peripheral and absent central vascularization whereas phlegmons show increased vascularization in the lesion. Therefore, both Doppler and CEUS increase accuracy and help differentiation.[35] This might indicate that during CEUS examinations, vascularization pattern should be added as a feature of inflammatory mass definition. Although a quantitative analysis with CEUS is more reliable than semi-quantitative measurements of the number of vessels, colour Doppler emerges as a more practical choice in a point-of-care setting.[9]

A lack of consensus on fistula definition is frequently observed in the reported studies. Consequently, Fraquelli et al. report on low reproducibility among six different operators for entero-enteric fistulas, which they relate to this lack of standardized definition of fistulas.[67] For example, Maconi et al. define a fistula as a connection between two structures, whose lumen contains either fluid or gas, while Gasche et al. do not mention visualization of fluid or gas at all.[44,76] Tarjan et al. assume that the presence of gas bubbles can be considered as indicating an active fistula.[65] Gasche et al. describe difficulties in discriminating between abscesses and fistulas. A diameter of 2 cm has been proposed to distinguish between fistulas and abscesses.[44]

Our data demonstrate moderate to good detection rates of CD-related fistulas using IUS, with a relatively low presence of heterogeneity in our meta-analysis. Observed lower pooled sensitivity of fistulas by B-mode IUS compared to MRE could be explained by two things. First, some studies assessed all types and locations of fistulas. MRE will find more deep pelvic, retroperitoneal and peri-anal fistulas compared to transabdominal IUS, resulting in lower reported fistula detection rates for IUS.[77] Second, Neye et al. point out that scar development seen in abscesses and fistulas is better detected by MRE by evaluating defects in perfusion, resulting in lower detection using B-mode IUS.[49]

Our meta-analysis reveals increased detection of fistulas with SICUS compared to B-mode IUS. One study even reports better detection of fistulas by SICUS when compared to MRE.[20] This can be explained by the fact that oral contrast expands the bowel and therefore increases the visualization of extra-luminal complications.[17]

One proposed mechanism of fistula formation suggests that fissures may evolve into sinus tracts, which penetrate through the muscular layer into the mesentery, ultimately resulting in fistulas.[78] On B-mode IUS, Gasche et al. describe a demarcation between a hypoechoic inflammatory lesion and the surrounding hyperechoic masses, which corresponds to the fibrofatty proliferation or fatty wrapping of the mesentery. Fissures may appear as fatty wrapping on IUS and can be considered as early, pre-complication inflammatory reactions. Therefore, these studies advocate for careful sonographic examination to detect potential fistulas in hyperechoic regions.[44] Additionally, Moreno et al. report a higher prevalence of entero-mesenteric tracts in IUS studies; if entero-mesenteric tracts can be seen as a preliminary stage of penetrating disease they may be detected earlier using IUS.[31]

Fistulas are histologically characterized by a rich microvasculature, which may explain the fistula vascularity revealed by power Doppler US in a study by Maconi et al.[61] Moreover, Estaban et al. report that CEUS and power Doppler can be used to detect early and small inflammatory lesions [mean size of 18.5 mm], before developing a fistula.[25] In clinical practice power Doppler and CEUS could be used to strengthen the diagnostic accuracy of IUS in detecting fistulas.

All of these findings support the use of IUS, including CEUS and Doppler, for detecting fistulas even when they are in a preliminary stage. Earlier detection may result in a greater chance of success with medical treatment, avoiding the need for subsequent drainage or surgery.[79]

In general, interpretation of our meta-analysis data for all CD-related complications should be done with caution. The estimates for diagnostic accuracy are influenced by a lack of uniform definitions for CD complications on IUS, a high degree of heterogeneity within reference standards, and a high risk of referral bias. According to the ECCO guidelines, the gold standard for monitoring CD-associated extramural complications is cross-sectional imaging modalities such as MRE or IUS or both, in combination with clinical and laboratory parameters.[2] In the studies included, not only were MRE and surgery, but also X-ray studies such as SBE, CT, and endoscopy used as reference standards. The referral bias is explained by a majority of the studies assessing complications in patients already planned for surgery; patients in these studies have more severe CD-related complications making them easier to detect which and may lead to increased estimates of sensitivity. The funnel plots [Supplementary Figure S1] may indicate evidence of publication bias in studies reporting data on diagnosing strictures with B-mode IUS only.

This systematic review and meta-analysis has some limitations. First, despite selecting studies with sample sizes of >15 patients they often reported lower numbers of complications, especially for abscesses and fistulas. Low sample sizes may have resulted in an overestimation of the specificity in our analysis. Second, despite the high degree of heterogeneity of reference standards within studies we decided to perform a meta-analysis of all studies and not only those in which surgery was the reference standard as it would not reflect clinical practice. Finally, we found an overall moderate to high risk of bias in our included studies.

Despite these limitations, our study offers a comprehensive assessment of the diagnostic accuracy of IUS in detecting CD-related complications based on the currently available literature.

5. Conclusion

IUS [B-mode and Doppler] is an accurate tool for the diagnosis of intra-abdominal complications related to CD. As a non-invasive, point-of-care modality, IUS is recommended as the first-line imaging tool if there is suspicion of a CD-related intra-abdominal complication. Of the additional IUS modalities, SICUS can increase the detection of strictures and fistulas and CEUS helps differentiating between abscesses and phlegmons. These extra modalities, however, require preparation and are more time-consuming. Future studies should focus on consensus among experts on IUS definitions for CD-related complications, which is likely to further increase reproducibility.

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Conflict of Interest

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Author Contributions

MP, FV, and KG were involved in the study concept and design. MP, NM, and FE were involved in data acquisition. MP and NM performed all statistical analyses. MP and NM were involved in data analysis and interpretation of data. MP, FV, and KG drafted the initial manuscript. Critical revision of the final manuscript for important intellectual content was performed by all authors.

Data Availability

The data underlying this article are available in the article and in its online supplementary material.

Supplementary Data

Supplementary data are available online at *ECCO-JCC* online.

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