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Systematic review: Defining, diagnosing and monitoring small bowel strictures in Crohn's disease on intestinal ultrasound

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Summary

Background: Stricturing Crohn's disease (CD) occurs most commonly in the terminal ileum and poses a clinical problem. Cross-sectional imaging modalities such as intestinal ultrasound (IUS), computed tomography enterography (CTE), and magnetic resonance enterography (MRE) allow for assessment of the entire bowel wall and associated peri-enteric findings. Radiologic definitions of strictures have been developed for CTE and MRE; their reliability and responsiveness are being evaluated in index development programs. A comprehensive assessment strategy for strictures using IUS is needed.

Aims: To provide a detailed summary of definitions, diagnosis and monitoring of strictures on IUS as well as technical aspects of image acquisition.

Methods: We searched four databases up to 6 January 2024. Two-stage screening was done in duplicate. We assessed risk of bias using QUADAS-2.

Results: There were 56 studies eligible for inclusion. Definitions for strictures on IUS are heterogeneous, but the overall accuracy for diagnosis of strictures is high. The capability of IUS for characterising inflammation versus fibrosis in strictures is not accurate enough to be used in clinical practice or trials. We summarise definitions for improvement of strictures on IUS, and discuss parameters for image acquisition and standardisation.

Conclusions: This systematic review is the first step for a structured program to develop a stricture IUS index for CD.

1 | INTRODUCTION

More than 50% of patients with Crohn's disease (CD) develop clinically apparent strictures over their lifetime.[1] The terminal ileum (TI) is the most common stricture location. However, strictures can be multifocal and may occur at any gastrointestinal site.[2] Limitations of endoscopy to diagnose or monitor strictures include its invasive nature, inability to reach all small bowel segments and failure to assess transmural complications.[3] Transmural assessment of CD is clinically relevant for inflammation[4] and is considered critical for the evaluation of strictures.[5] To achieve this, computed tomography enterography (CTE), magnetic resonance enterography (MRE) and intestinal ultrasound (IUS) are invaluable techniques, particularly for stricturing CD.

IUS is a non-invasive, well-tolerated, and repeatable technique for comprehensive clinical assessments in CD.[3,6,7] Consensus recommendations for definitions, diagnosis and treatment targets of CD strictures are available for CTE and MRE.[8] However, such consensus is lacking for IUS, and it is unclear whether CTE and MRE stricture definitions can be applied to IUS. In addition, technical parameters including the approach to image/video acquisition and use of oral/intravenous (IV) contrast or elastography in differentiating inflammatory from fibrotic stricture components are not standardised. These key considerations along with other priority areas of study for IUS are provided in Table 1. Developing a framework for these parameters is of pivotal importance if IUS is to become a standardised assessment tool.

As a first step towards a formal IUS index development program in small bowel stricturing CD, this systematic review aims to comprehensively summarise existing IUS definitions, monitoring strategies and image/video capture techniques, in addition to the role of oral contrast-enhanced ultrasound, IV contrast-enhanced ultrasound, and elastography within this disease area.

TABLE 1 Priority areas of study for intestinal ultrasound of small bowel Crohn's disease strictures.

Priority areas
• Standarising diagnosis and definitions of small bowel strictures, including cut-offs for bowel wall thickness, luminal narrowing and pre-stenotic dilation
• Assessing the accuracy of IUS (colour Doppler intensity, wall stratification, inflammatory fat, and stricture parameters) or adjunct techniques (elastography, contrast enhancement) to distinguish between inflammatory and fibrotic components of small bowel strictures
• Understanding the wall layer composition of strictures on IUS using full-thickness histopathology as the gold standard
• Standardising definitions for therapeutic response parameters of strictures on IUS
• Confirming inter and intra-rater variability of small bowel strictures measures on IUS
• Determining best technical parameters for image and cine-loop acquisition of strictures
• Evaluating if fasting or non-fasting state for IUS of small bowel strictures is most appropriate

2 | METHODS

2.1 | Search strategy, study selection and eligibility criteria

This systematic review was conducted and reported in accordance with Cochrane and PRISMA guidelines, respectively.[9,10] MEDLINE (Ovid), Embase (Ovid), CINAHL (EBSCOhost) and the Cochrane Central Register of Controlled Trials (Ovid) were searched from database inception to 6 January 2024. The protocol was registered at PROSPERO (CRD42023485114).

Studies were eligible for inclusion if (1) the design was interventional (randomised or non-randomised) or observational (prospective, retrospective or case–control); (2) the population consisted of adults (18 years old or greater); (3) participants had been diagnosed with an anastomotic or naïve small bowel CD stricture and (4) full-thickness histopathology was available as a gold standard in papers that graded inflammation and fibrosis. Studies were excluded if (1) strictures were located outside of the small bowel; (2) strictures were related to ileal pouch-anal anastomosis and (3) full-thickness histopathology was not available as a gold standard (when inflammation and fibrosis were graded). Animal studies, narrative reviews, case reports and non-English studies were also excluded. For studies evaluating inflammation and fibrosis on IUS with comparison to CT or MR, and without histopathology as a gold standard, these studies were included for other components such as definitions of strictures.

To stay consistent with the terms stricture and fibrostenosis in this manuscript, the term 'stricture' is used to encompass 'stenosis' and 'fibrostenosis'. Additional details pertaining to the search strategy, study selection, data extraction and the risk of bias assessment can be found in Methods S1.

2.2 | Outcomes

Outcomes of interest included IUS-based definitions of small bowel CD strictures; the accuracy of IUS for diagnosing strictures and detecting inflammation or fibrosis; the use of oral contrast-enhanced ultrasound, IV contrast-enhanced ultrasound and elastography for characterising strictures; IUS endpoints for determining therapeutic response to stricture therapy; and technical parameters used for IUS image acquisition.

3 | RESULTS

3.1 | Search results

The literature search identified 3706 records. After the removal of 952 duplicates, 2754 records were screened based on the title and abstract. Full-text review of 206 studies was performed, and after the exclusion of 150 studies, 56 studies met the inclusion criteria (Figure 1).
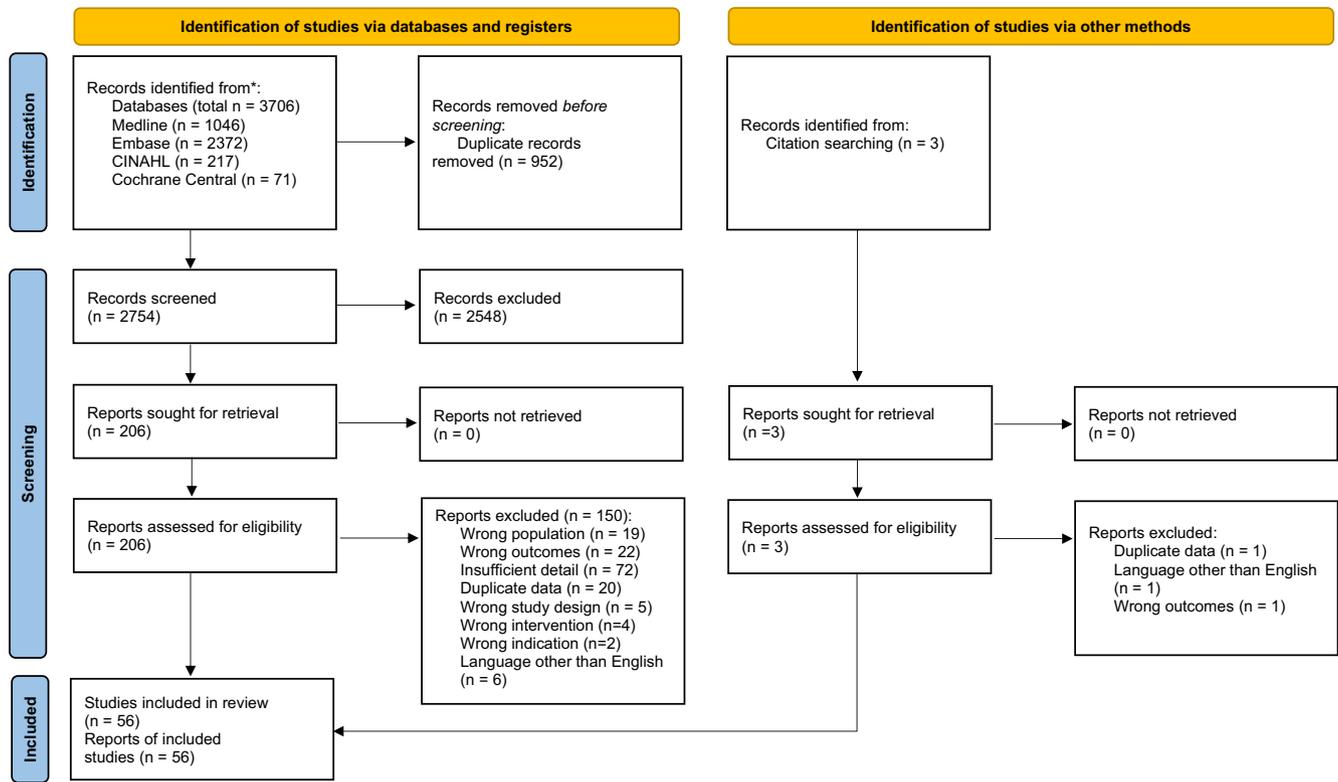
FIGURE 1 PRISMA 2020 flow diagram for systematic review including searches of databases, registers and other sources. From: Page et al.[10] For more information, visit: http://www.prisma-statement.org/.

3.2 | Definition of small bowel CD stricture on IUS

Fifty-six studies that included definitions of small bowel CD strictures on IUS were identified (Table 2; detailed data extraction in supplement). Considerable heterogeneity was observed across the definitions. Forty-six out of 56 studies provided specific definitions of a stricture, which largely focused on three domains: bowel wall thickness (38 studies), luminal narrowing (35 studies)[6,11-44] and prestenotic dilation (39 studies).[6,11-14,16-34,36-42,45-52] While 26 studies required all three domains, 11 studies required 2 domains for defining a stricture, mainly the combination of bowel wall thickness and prestenotic dilation.[14,35,37-39,41,44,47,49-51] One study required luminal narrowing, prestenotic dilation and 'to and fro' movement.[40] Six studies only utilised one criterion (primarily increased bowel wall thickness). Ten studies included intestinal peristalsis as part of the stricture definition.[12,20,21,26,27,30,40,44,46,49] Six of those 10 studies required the three most common domains (bowel wall thickness, luminal narrowing, prestenotic dilation) in addition to motility criteria to define a stricture.[12,20,21,26,27,30] Thirteen out of 56 studies assessed naïve and anastomotic strictures separately.[11,13,28,31,36,37,39,40,48,49,53-55] In these studies, the definitions of a stricture were the same, regardless of whether the stricture was naïve or anastomotic. Ten studies failed to provide specific information on the stricture definition,[53,54,56-63] although the main objective was CD stricture assessment. A detailed summary of the cut-offs and descriptions used for bowel wall thickness, luminal narrowing, prestenotic dilation, motility abnormalities,

inflammatory fat, hyperemia and lymphadenopathy can be found in Material S1.

In summary, in about half of the evaluated studies, a naive or anastomotic small bowel stricture on IUS were defined by three features: (1) bowel wall thickness >3 mm, (2) luminal narrowing <1 cm and (3) prestenotic dilation was categorised as any increase in diameter greater than the associated luminal narrowing, or an absolute diameter of >2.5 cm.

3.3 | Diagnostic accuracy of IUS for CD small bowel strictures

Forty-five of 56 studies reported on the diagnostic accuracy of IUS in small bowel CD based on a gold standard; 23 studies used histopathology with the majority using resection specimens,[14,15,18,25,26,29,31,36,38,39,44,47,50,53-59,62,63,65] 10 used endoscopy[11,13,25,27,28,33,34,40,50,64] and 17 used CT or MRI.[6,12,20,22,23,27,31,33,35,37,46,50,54,57,59,61,65] Of the studies that utilised endoscopy as a gold standard, the definition was combined with histology in two studies[25,34] and CT in two studies.[27,33] Collectively, the sensitivity estimates for stricture diagnosis in IUS using the various 'gold standards' ranged from 68%[18] to 100%[21] with corresponding specificities from 0%[31] in one study with all other studies reporting a specificity ranging from 86%[6] to 100%.[23,50] Estimates organised by type of gold standard[13,15,31,41,54,56,61,66,67] can be found in Table S2.

TABLE 2 Details of stricture diagnosis of included intestinal ultrasound studies.

Study	Study design	Stricture patients (n)	Stricture definition
Allocca, 2018[6]	P	27	BWT >3 mm, wall thickening with narrowed lumen, ±PSD
Allocca 2023[39]	P	17	BWT >3 mm, narrowed lumen, ±PSD. Surgical resection gold standard
Baumgart, 2015[53]	P	10	N/A, elastography
Bezzio, 2013[58]	R	28	N/A
Bhatnagar, 2021[56]	P	7	N/A
Calabrese, 2005[16]	P	17	TUS:BWT ≥4 mm, stiff loop, loss of wall layers, severe lumen narrowing, ±PSD SICUS: BWT >3 mm, luminal diameter <1 cm, ±PSD
Calabrese, 2009[11]	P	34	BWT >3 mm, luminal diameter <1 cm, ±PSD
Calabrese, 2013[45]	R	N/A	BWT >3 mm, ±PSD
Calabrese, 2018[17]	P	N/A	BWT ≥3 mm, loss of wall layers, severe lumen narrowing, ±PSD >25 mm
Carter, 2017[46]	P	18	Absent peristalsis, absent expansion on motility, linear air bubble, PSD
Chatu, 2012[54]	R	10	N/A
Chen, 2018[52]	P	35	±PSD, elastography
De Cristofaro, 2023[41]	P	40	BWT >3 mm, narrowed lumen, ±PSD
Ding, 2019[18]	P	25	Thickened and stiff bowel wall, narrowed lumen with PSD or narrowing not passed on endoscopy
Fraquelli, 2008[42]	P	N/A	BWT ≥4 mm, fixed dilation (>2.5 cm) with reduced lumen, cranial to a thickened bowel wall tract
Fraquelli, 2015[19]	P	12	BWT ≥3 mm, reduced lumen, PSD >2.5 cm. S 3 cm proximal to ICV
Gaitini, 2011[20]	R	19	BWT ≥3 mm, narrowed lumen, PSD, increased peristalsis
Gasche, 1999[21]	P	22	Severe luminal narrowing in areas, BWT ≥3 mm, ±PSD (no size). Destruction of wall layering and loss of peristaltic bowel movement
Horus Talabur Horje, 2015[22]	P	34	BWT >3 mm, narrowing of thickened and rigid bowel lumen, PSD >3 cm
Kakkadasam Ramaswamy, 2020[23]	P	12	Thickened and stiffened bowel wall (>3 mm), lumen narrowing (<10 mm), ±PSD
Kratzer, 2002[24]	P	11	PSD immediately proximal to thickening segment. Intestinal lumen not visualised on sonography in swelling segments
Kumar, 2015[57]	R	8	N/A
Lenze, 2012[25]	P	30	BWT >4 mm, fixed constriction of the intestinal lumen or a prestenotic dilation
Livne, 2020[12]	R	N/A	BWT >3 mm, luminal diameter <1 cm, ±PSD
Lu, 2017[26]	P	95	BWT >4 mm with a fixed narrowed lumen, PSD, ±dysfunctional peristalsis
Ma, 2020[27]	R	20	Thickened bowel wall, luminal diameter <1 cm, ±PSD >2.5 cm
Maconi, 1996[28]	P	40	Narrowed intestinal lumen along with distended fluid or echogenic content-filled loops just above the thickened intestinal tract. BWT >4 mm and stiff intestinal wall
Maconi, 2003[29]	P	43	Luminal narrowing below dilation (>25 mm). BWT >4 mm
Matsumoto, 2023[43]	P	21	BWT >4 mm, luminal diameter <3 mm with or without oral side expansion
Neye, 2010[30]	P	28	Severe luminal narrowing in regions of BWT ≥3 mm, ±PSD, wall layer destruction and loss of peristaltic bowel movement
Nylund, 2013[44]	P	39	Luminal narrowing or closure, BWT >3 mm, stiff appearance, lack of peristaltic movement
Onali, 2012[31]	P	13	BWT >3 mm, luminal diameter <1 cm, ±PSD
Orlova, 2017[55]	R	24	N/A
Pallotta, 2008[13]	P	10	Luminal diameter <1 cm, ±PSD
Pallotta, 2011[63]	P	N/A	N/A
Pallotta, 2012[14]	P	40	Luminal diameter <1 cm
Pallotta, 2014[15]	P	109	Luminal narrowing

TABLE 2 (Continued)

Study	Study design	Stricture patients (*n*)	Stricture definition
Parente, 2002[32]	P	154	Narrowing of the intestinal lumen together with distended fluid. Thickened and stiff bowel wall (≥4 mm). Echogenic content-filled loops just above the thickened bowel segment
Quaia, 2012[64]	P	28	TI BWT >3 mm, transmural or stratified enhancement post-contrast
Quaia, 2017[34]	P	65	TI BWT >3 mm, lumen narrowing with proximal dilation. Inability to pass scope during endoscopy
Quaia, 2018[33]	P	20	TI BWT >3 mm, lumen narrowing with proximal dilation. Inability to pass scope during endoscopy
Ripolles, 2013[47]	P	15	Wall thickening, assessed for PSD. Inflammatory score. Fibrostenotic score
Ripolles, 2016[48]	P	6	±PSD
Schirin-Sokhan, 2011[49]	P	18	PSD, oscillating peristalsis, bowel wall thickening
Schulberg, 2022[37]	P	123	BWT >3 mm, PSD >2.5 cm
Sconfienza, 2016[35]	P	7	Ileum segments with reduced lumen and bowel wall. Appearing iso-intense or hypo-intense compared to muscular tissue visible in the same slice on T2-weighted images. Lack of mesenteric involvement and non-avid enhancement after intravenous contrast material administration
Serra, 2017[36]	P	26	Pathological wall thickness (≥3 mm), narrowed lumen below a significant bowel dilation
Sey, 2013[50]	R	7	Thickened segment (>4 mm) with proximal dilatation
Stidham, 2011[59]	R	7	N/A
Stidham, 2013[60]	P	10	N/A
Stidham, 2016[61]	P	28	N/A
Takeuchi 2023[40]	R	30	Luminal narrowing, PSD, 'to and fro' movement
Wilkens, 2018[65]	R	25	BWT >3 mm
Wilkens, 2022[38]	P	25	BWT >3 mm, narrowed lumen <10 mm, PSD
Yuksel, 2019[51]	P	101	BWT >3 mm, assessed for PSD
Zhang, 2023[62]	R	22	N/A

Abbreviations: BWT, bowel wall thickness; ICV, ileocecal valve; IUS, intestinal ultrasound; MRE, magnetic resonance enterography; N/A, not available; P, prospective; PSD, pre-stenotic dilation; R, retrospective; SE, strain elastography; SICUS, small intestine contrast ultrasonography; TI, terminal ileum; TUS, transabdominal ultrasonography.

Eleven out of 56 studies[11,13–16,31,41,45,54,57,63] added oral contrast to the IUS examination to diagnose a stricture, most commonly between 250 and 500 mL polyethylene glycol (PEG). The addition of 250 mL PEG 4000 increased the sensitivity from 80% to 98% and specificity from 75% to 100%,[14] and 375 mL PEG 3350 increased sensitivity from 76% to 94%.[16]

3.4 | IUS to characterise the degree of inflammation and fibrosis in CD small bowel strictures

3.4.1 | B-mode IUS

Four studies utilised conventional B-mode IUS.[25,27,29,56] The gold standard in two of these studies was histologic evaluation of the surgical resection specimen.[29,56] In a study by Maconi et al., the echogenicity patterns of the stricture were classified as (1) hypoechoic, (2) stratified or (3) mixed (segments with/without stratification), where the stratified bowel echo pattern was significantly associated with fibrosis in the submucosa and the muscularis mucosa.[29] Fibrosis of both of these layers was semi-quantitatively graded as 0=absent, 1=mild, 2=moderate and 3=severe. A stratified or mixed echo pattern of stenosis detected a moderate to severe or intermediate degree of fibrosis with a sensitivity of 100%, specificity of 63%, positive predictive value of 72% and a negative predictive value of 100%.[29] Hypoechoic pattern (loss of stratification) was associated with inflammation and a stratified pattern with fibrosis. In contrast, a mixed pattern indicated the co-existence of fibrosis and inflammation.[29] However, all three echogenicity patterns did not show a significantly different prevalence compared to transmural inflammation (*p*=0.863).

In the second study evaluating surgical resection CD samples, histologic inflammation and fibrosis were location-matched to small bowel IUS features.[56] Two radiologists evaluated CD strictures for mural, mucosal, submucosal thickness, submucosal/mesenteric echogenicity and clarity, and mural Doppler signal. These parameters were compared to 50 selected bowel cross-sections evaluating acute and chronic inflammation and fibrosis. Submucosal layer

echogenicity ($p=0.03$) and mucosal layer thickness (53.8 [3.19, 908] $p=0.006$) were significantly associated with fibrosis in univariate analyses. In multivariate analyses, only mucosal thickness ($p=0.006$) was significantly associated with fibrosis and acute inflammation ($p=0.02$), while mesenteric fat echogenicity was associated with chronic inflammation ($p=0.009$).[56]

Contrast-Enhanced IUS to Characterise Inflammation and Fibrosis. Fourteen studies used intravenous (IV) contrast IUS.[22,24,26,27,33,34,36,38,44,47–49,64,65] A total of 12 used sulfur hexafluoride-filled microbubble contrast (SonoVue, Bracco, Milan, Italy), one used microparticles consisting of galactose and palmitic acid (Levovist, Schering AG Berling, Germany),[24] and one used octafluropropane microbubble contrast[26] at contrast volume 1.2–4.4 mL followed by a 5–10 mL saline flush. Five studies used full-thickness histopathology from surgical resection specimens as a gold standard. Of these, three[26,44,47] showed a link between contrast enhancement and degree of inflammatory or fibrotic lesions on surgical resection and two studies did not.[36,65] Ripolles et al. observed that a greater degree of contrast enhancement correlated with inflammatory lesions ($r=0.539$, $p=0.003$) and a lesser degree of contrast enhancement correlated with fibrotic lesions ($r=-0.505$, $p=0.006$).[47] Contrast-enhanced ultrasound had a sensitivity of 93%, specificity of 69%, and accuracy of 82% (95% CI: 62–93) for differentiating between predominantly inflammatory and fibrostenotic bowel lesions, as defined by pre-stenotic dilation, colour Doppler grade 0 (absent) or 1 (barely visible vascularity), and contrast enhancement <46%. Consistent with this finding, a higher Doppler score, defined as grade 2 (moderate vascularity) and grade 3 (marked vascularity), was associated with inflammation, while a lower Doppler score was associated with fibrosis ($r=-0.584$, $p=0.001$).[47] When dichotomizing pathology scores into inflammatory versus fibrotic predominant strictures, 82% (23/28) of bowel strictures were correctly classified on IUS ($\kappa=0.63$), with a sensitivity of 100% and specificity of 62%.

Furthermore, Lu et al. described an inverse relationship between peak enhancement and fibrosis ($r=-0.59$, $p=0.02$) in ileal strictures. Strictures were defined as a thickened segment with a fixed narrowed lumen with prestenotic dilation with or without dysfunctional peristalsis. Inflammation on histology was graded as either chronic or active inflammation where there was a negative association between peak enhancement with chronic inflammation histologic scores ($r=-0.49$, $p=0.06$), and no significant relationship with acute active inflammation.[26] Nylund et al. found that percentage of increase in contrast enhancement was significantly associated with pathology inflammatory score ($p=0.005$), while the colour Doppler grade had both an association with the inflammatory score ($p=0.036$) and a significant negative association with fibrostenotic score on pathology.[44] In contrast, Wilkens et al. evaluated both contrast-enhanced ultrasound and dynamic contrast-enhanced MRE, and found that neither modality could distinguish between inflammatory activity (contrast-enhanced ultrasound: $r=0.16$, $p=0.45$) and fibrosis ($r=0.399$, $p=0.048$), nor did they correlate with bowel wall perfusion.[65]

3.4.2 | Elastography

Eighteen studies utilised elastography to assess stricture stiffness as a surrogate metric for intestinal fibrosis.[18,19,26,27,33,35,36,38,39,43,52,53,55,58–62] Eleven studies[18,19,33,35,36,39,43,53,55,58,59] used strain or real-time elastography (relative elastography), six studies used shear wave elastography with acoustic radiation forced impulse technology,[18,26,38,60–62] and one study utilised both.[18]

Twelve of 18 studies used full-thickness histopathology as a gold standard.[18,19,26,36,38,39,52,53,55,58,61,62] Of these 12 studies, only three reported sensitivity and specificity for the detection of fibrosis using point shear wave elastography, which ranged from 70%[52] to 95%[18] and 89.5%[62] to 100%,[18] respectively. Ding et al. assessed small bowel strictures with strain elastography and point shear wave elastography. They found equal sensitivities of 75% for detecting fibrosis in a stricture, while specificity was 100% for point shear wave elastography compared to 75% for strain elastography.[18]

All 11 studies reported higher strain ratios for predominantly inflammatory compared to predominantly fibrotic strictures. Three studies combined contrast-enhanced ultrasound and strain or shear wave elastography.[26,27,36] In 26 consecutive patients with symptomatic stricturing CD, there was no correlation between mean strain elastography ratios and fibrosis scores ($r=0.03$, $p=0.87$).[36] In another study of 15 patients with ileal strictures, no relationship between point shear wave elastography and fibrosis scores ($p>0.05$) was detected, however, a moderate correlation between point shear wave elastography and muscular hypertrophy was observed ($r=0.59$, $p=0.02$).[26] Muscular hypertrophy occurred in the mucosa, submucosa, and muscularis propria, with the muscularis propria layer having significantly greater expansion compared to the other layers.[26]

3.5 | Response to therapy of small bowel CD strictures

Four studies evaluated the treatment response of strictures on IUS,[13,37,43,48] following tumour necrosis factor (TNF) antagonist therapy. There was a high degree of heterogeneity across stricture definitions as well as response parameters. In a study by Pallotta et al., 15 patients with obstructive symptoms and endoscopically confirmed stricture underwent IUS with oral contrast or MRI prior to infliximab initiation.[13] Imaging stricture definitions were increased bowel wall thickness >3 mm, luminal diameter <1 cm (measured at the level of maximally distended loop independent of pre-stenotic dilation presence) and pre-stenotic dilation >2.5 cm. Stricture length was defined as the length of the segment with a luminal diameter of <1 cm. To accurately measure luminal diameter independent of intestinal contraction, multiple and prolonged (>15 min) observations were conducted. Strictures located in the neo-TI or TI in reach of colonoscopy were confirmed if an 11 mm diameter colonoscope was unable to pass the narrowing. In contrast, more proximal strictures outside of the reach of colonoscopy were confirmed on at least

two consecutive IUS examinations and MRI. Five of the 15 patients stopped treatment after induction. Of the remaining 10 patients, eight had complete regression of stenoses after 6–22 infliximab infusions defined as normalisation of luminal diameter (>1 cm).

Secondly, the response of transmural lesions to TNF antagonists (33 infliximab, 18 adalimumab) was assessed in 51 patients at 12 weeks and 1 year after treatment initiation.[48] Six patients in this study had strictures at baseline, defined as thickened bowel and stenosis with or without dilation. Sonographic improvement was defined as a decrease in bowel wall thickness by >2 mm, a reduction in one grade of colour Doppler flow, a decline of >20% of mural enhancement using IV contrast and/or the disappearance of stenosis (without providing further parameters). Improvement in all IUS variables after 12 weeks of treatment was noted in 51%[48] of patients except for stenosis, which remained present in 100% of patients. Stricturing behaviour at baseline predicted a lack of response to TNF antagonist therapy. At 52 weeks, only two of the six stricture patients had sonographic improvement. Three of the six cases required early resection, two for obstructive symptoms and one for symptomatic penetrating complications.

More recently, one study has evaluated treatment response of strictures to ustekinumab measured as stricture stiffness using shear wave elastography. Shear wave speed decreased in patients treated with ustekinumab, but not infliximab nor those who switched from infliximab to ustekinumab.[43] However, this study did not have a histologic reference standard to quantify fibrosis in strictures.

The intensive drug therapy versus standard drug therapy for symptomatic intestinal CD strictures in an open-label, single-centre, randomised controlled trial (STRIDENT) evaluated standard versus intensive adalimumab therapy.[37] Improvement in the obstructive symptoms score (OSS) at 12 months served as the primary endpoint. Overall, there was no significant difference in the OSS between the intensive adalimumab arm and those in standard dosing, 79% (41/52) versus 64%,[37] respectively. CD strictures were not explicitly defined on IUS, but rather on MRI (≥80% reduction in lumen diameter compared to adjacent proximal loop and bowel wall thickness >3 mm). IUS stricture response was defined as a decrease in bowel wall thickness by 25% or greater, normalisation of prestenotic dilation (<2.5 cm, if present at baseline) and reduction in stricture hyperemia (Limberg score ≤1). Less than 40% of patients had prestenotic dilation >3.0 cm on baseline MRI. At 12 weeks, the intensive adalimumab therapy versus the standard therapy had numerical improvement with ≥25% reduction in bowel wall thickness in 51% (22/43) and 33% (7/21), and normalisation of vascularization (Limberg score ≤1) of 73% (32/44) and 82% (18/22), respectively.

3.6 | Technical aspects of IUS image acquisition

Conventions for image and video capture of CD strictures on IUS have not been uniformly defined, and no consensus exists on how to best procure this type of data. Accordingly, the technical aspects of image or video acquisition, such as the length of a cine-loop of bowel

for a stricture and its associated motility, and the utilisation of the same ultrasound machine or model of machine, were not well described in the 56 included studies. One study described the number of images to be captured in cross-sectional and longitudinal view, where bowel wall thickness was measured on three images in transverse and three in long section.[6] In 20 of the 56 studies, patients were required to fast at varying increments (between 4 h or overnight). Techniques for performing contrast-enhanced ultrasound and elastography have been described by 28 studies, but approaches are highly heterogenous (Table S3).

3.7 | IUS indices for small bowel CD-associated strictures

Only two IUS indices were identified for evaluation of fibrostenosing CD: the US-based Lemann Index and the Maconi Score.[29,66] The Ultrasound Lemann Index includes bowel wall thickness, mural stratification, prestenotic dilation and lumen size,[66] while the Maconi score focuses on the extent of inflammation and fibrosis based on stricture echogenicity.[29] Neither of these instruments were developed according to established methodological criteria,[68] and their reliability and responsiveness have not been established (Table 3). A detailed description of these indices can be found in Materials S1.

4 | DISCUSSION

Cross-sectional imaging modalities play a critical role in clinical practice for diagnosing and monitoring CD strictures. Recently, standardised CTE and MRE definitions have been developed for use in stricturing small bowel CD,[8] however, corresponding IUS definitions are lacking.

The European Crohn's and Colitis Organization (ECCO) and European Society of Gastroenterology and Abdominal Radiology (ESGAR) define an unequivocal stricture as 'upstream bowel dilation ≥3 cm with luminal narrowing' and a probable stricture as 'fixed luminal narrowing alone without upstream dilation'.[69] These definitions are comparable to the CONSTRICT criteria for CT and MR, which recommends using a bowel wall thickness cut-off of >3 mm, a luminal diameter reduction of >50% relative to a normal adjacent bowel loop and a prestenotic dilation of >3 cm.[8]

Our systematic review revealed marked heterogeneity in the definitions used to diagnose a small bowel CD stricture. Various combinations of bowel wall thickness, luminal narrowing and prestenotic dilation have been utilised, with most studies incorporating all three parameters. The most commonly used cut-off for bowel wall thickness was >3 mm for strictures, which is consistent with consensus recommendations from the International Bowel Ultrasound (IBUS) group and recent ECCO/ESGAR recommendations for cross-sectional imaging in IBD.[69,70]

The majority of included studies did not describe prestenotic dilation thresholds or provide a rationale for an absent cut-off of

TABLE 3 Published intestinal ultrasound indices for small bowel strictures in the literature.

Name of index	Parameters scored	Grading scale
Ultrasound Lemann Index[66]	Bowel wall thickness, stratification, pre-stenotic dilation	Grade 1: BWT >3.0 mm or segmental enhancement without pre-stenotic dilation Grade 2: BWT >4.0 mm or mural stratification without pre-stenotic dilation Grade 3: BWT >4.0 mm with narrowed lumen and fluid distended or echogenic content-filled loops proximal to thickened tract
Maconi Score[29]	Bowel wall thickness, stratification	Hypoechoic pattern: higher degree of inflammation Stratified pattern: higher degree of fibrosis Mixed pattern: Co-existence high degrees of both inflammation and fibrosis

Abbreviation: BWT, bowel wall thickness.

prestenotic dilation size. If prestenotic dilation was addressed, it was defined as >2.5 cm[12,19,29] to >3.0 cm.[22] Of note, prestenotic dilation was not required for diagnosis of stricturing CD in 20 studies. The degree of prestenotic dilation for stricturing CD on IUS has been extensively discussed. Due to lack of oral contrast and hence less prominent prestenotic dilation, prestenotic dilation size on IUS may be distinct from CTE or MRE. Thus, a prestenotic dilation cut-off of >2.5 cm may be acceptable. Luminal narrowing was described in 35 studies as a domain for a stricture definition where nine studies utilised a threshold of <1 cm, and the remaining described its presence as important without a size cut-off.[11,16,23,31,38] This indicates a clear need to standardise definitions to allow for comparison across studies.

The major advantage of IUS over other imaging modalities is the ability to assess dynamic properties in real time, translating into either reduced peristalsis at the stricture site or increased motility in the prestenotic segment.[3] Accordingly, multiple IUS definitions identified in the current systematic review incorporate motility assessment on IUS. However, standardised definitions need to be developed and the reliability of these definitions should be evaluated in future studies. Furthermore, the value of this item relative to established morphologic criteria should be investigated.

The distinction between anastomotic and naïve strictures may be relevant for diagnosis and prognosis; at present it is unclear whether they share a common or distinct pathogenesis. Definitions of strictures on CTE or MRE are identical for naïve and anastomotic phenotypes.[8] Approximately one-quarter (23%) of IUS studies that we identified commented on whether the stricture was anastomotic or naïve, and strikingly, no studies proposed definitions specific to surgical status.

Substantial methodological heterogeneity was noted among studies with respect to both the choice of a reference gold standard, and technical aspects of IUS performance (e.g. oral/IV contrast, fasting). As a result, a statistical summary of the findings across studies was infeasible and no conclusive definition can be derived from the available data regarding the validity of the definitions and outcomes identified. Nevertheless, based on the existing literature, combined with expert opinion, the authors recommend defining a stricture on IUS as 'definitive' or 'probable'.[71] In the setting of clinical trials of anti-fibrotic agents, it may be most important to have a maximally specific IUS definition to avoid false-positive findings. In this circumstance, including all three features (bowel wall thickening >3 mm, luminal narrowing <1 cm and prestenotic dilation >2.5 or 3.0 cm) into the stricture definition is likely ideal. However, in clinical practice, two of the three features described by the Society of Abdominal Radiology and several IUS studies[6,67,71] may be sufficient.

Despite considerable variability in definitions and methodology, the accuracy for stricture diagnosis was high regardless of the gold standard definition used.[6,40] These findings are consistent with observations made on CTE or MRE.[72] To date, no studies have evaluated the diagnostic accuracy of IUS for the evaluation of proximal small bowel strictures; the largest body of evidence exists for strictures situated in the TI.

Both contrast-enhanced ultrasound and elastography have been evaluated for differentiating fibrosis from inflammation.[26] Contrast-enhanced ultrasound quantifies blood flow as a measure of inflammation, while elastography measures tissue stiffness as a potential surrogate of fibrosis.[43] Limitations of contrast-enhanced ultrasound include significant time commitment, the need for expertly trained personnel and substantial costs. Elastography may be hampered by technical differences (strain ratio vs shear wave), variable degrees of compression, lack of standardisation for the region of interest and limited reliability.[73] Both techniques could not detect the degree of fibrosis with high enough accuracy to be used in clinical practice or trials. This is consistent with conclusions drawn by a recent systematic review and meta-analysis evaluating IUS for deciphering inflammatory from fibrotic stenoses.[74]

Only four studies, all of which were investigating TNF antagonist therapy with one study additionally including ustekinumab, evaluated the responsiveness of strictures to treatment.[13,37,43,48] These trials used heterogenous inclusion and response criteria, which prevented between-study comparisons. In an effort to facilitate drug development in this area, the CONSTRICT group has proposed criteria for defining stricture improvement on CT and MR.[8] According to this criteria, successful stricture treatment involves (1) prestenotic dilation <2.5 cm or reduction of prestenotic dilation by 50%, (2) bowel wall thickness decreased by 50%, (3) luminal narrowing decrease by 50% and (4) stricture length decrease by 50%. However, the responsiveness of these criteria has not been evaluated, as this requires identification of an anti-fibrotic treatment of known efficacy.

Although IUS is well established in Europe, its use in North America has been limited for multiple reasons, including concerns regarding operator dependence. An initial study has shown excellent inter-rater reliability for stenosis (0.81–1.00) among six

sonographers.[75] These findings require confirmation, and further standardisation will likely improve inter-observer reliability.

The development of a validated IUS index for small bowel CD strictures is essential for accurate diagnosis and assessment. Unlike MRE, CTE and endoscopy, IUS is easily performed, which enables frequent assessments. The next step towards a rigorously developed, validated IUS stricture index is the completion of an international consensus process in which the results of the current study will determine how to optimally standardise CD stricture definitions, inclusion criteria, endpoints and response criteria for use in clinical practice and drug development.

In summary, the current systematic review summarises definitions and data on diagnostic accuracy, therapeutic response, image capture and technical aspects pertaining to IUS evaluation of small bowel CD strictures. This work provides the basis for future index development, which remains a critical barrier to the development of anti-stricture therapies in CD.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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