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SYSTEMATIC REVIEWS

Role of intestinal ultrasound in ulcerative colitis: A systematic review

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Abstract

BACKGROUND

Intestinal ultrasound (IUS) is an emerging, non-invasive, and highly sensitive diagnostic tool in inflammatory bowel disease (IBD), including ulcerative colitis (UC). Despite its potential, its adoption in clinical practice is limited due to a lack of standardization and awareness.

AIM

To perform a comprehensive scoping review based on a systematic literature review on IUS in UC to inform current practice.

METHODS

Ninety-nine original articles about ultrasonography in UC were identified among 7608 citations searching PubMed and EMBASE databases for systematic review.

RESULTS

IUS can be useful as an initial diagnostic strategy in patients with suspected IBD/UC. In UC, IUS can predict endoscopic response, histologic healing, and steroid responsiveness in acute severe cases. IUS can predict response to biologics/small molecules (as early as 2 wk). IUS correlates well with ileo-colonoscopy, but IUS could miss rectal, jejunal, and upper GI lesions in suspected IBD and colon polyps or extra-intestinal manifestations in known IBD. IUS is useful in special situations (children, pregnancy, and postoperative Crohn's disease). Inter-observer agreement is acceptable and trained physicians have comparable diagnostic accuracy. Point-of-care ultrasound impacted management in 40%-60% of cases. Hand-held IUS has excellent agreement with conventional IUS.

CONCLUSION
IUS is a non-invasive, highly sensitive tool in the diagnosis and monitoring of UC, offering excellent patient satisfaction. Point-of-care ultrasound by IBD physicians can significantly impact clinical decision-making.

Key Words: Ulcerative colitis; Intestinal ultrasound; Inflammatory bowel disease; Diagnosis; Monitoring

Core Tip: Intestinal ultrasound (IUS) is an emerging non-invasive diagnostic tool for ulcerative colitis (UC) with high sensitivity. This scoping review demonstrates IUS's effectiveness in predicting endoscopic response, histologic healing, and steroid responsiveness in UC, as well as its role in early prediction of biologic response. While IUS may not detect all lesions, it shows excellent agreement with ileo-colonoscopy and is valuable in special situations like pregnancy and pediatric cases. Hand-held IUS matches conventional IUS in accuracy. Point-of-care IUS by inflammatory bowel disease physicians can significantly influence clinical decisions, underscoring its potential for broader clinical adoption.

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INTRODUCTION

Intestinal ultrasound (IUS) is emerging as a non-invasive, sensitive monitoring tool to assess inflammatory bowel disease (IBD) activity. Although IUS was first described more than two decades ago, it was not widely adopted, possibly due to a lack of proper training and concerns about accuracy compared to standard cross-sectional imaging or endoscopy. Current diagnostic methods, such as ileo-colonoscopy and magnetic resonance enterography (MRE), are effective but have limitations. Ileo-colonoscopy, while considered the gold standard for assessing mucosal inflammation, is invasive, costly, and not always well-tolerated by patients. MRE, though non-invasive and highly accurate, is expensive, time-consuming, and not universally accessible. These limitations underscore the need for a complementary diagnostic tool that is accurate, non-invasive, cost-effective, and widely accessible[1].

Recently, there has been renewed interest in gastroenterologist-led IUS. Patient satisfaction is excellent due to its non-invasive nature and point-of-care ultrasound (POCUS) with minimal waiting time. Over the last five years, there has been a surge in the literature investigating various aspects of IUS, ranging from validation of accuracy with endoscopy/cross-sectional imaging to its impact on managing IBD[2].

Current indications include suspected IBD, assessment of disease activity and complications (intestinal and extra-intestinal), monitoring therapeutic response, and prediction of clinical outcomes[2-4]. However, there is a need for more studies on several aspects of the evidence-based application of this tool, such as its use in a treat-to-target strategy. There is also a lack of validated scores for response or outcome prediction and a lack of age-specific cutoffs for the pediatric population. Despite current limitations and knowledge gaps, IUS can significantly impact clinical decision-making in IBD.

We aimed to present a comprehensive and updated review of IUS in ulcerative colitis (UC) by systematically analyzing the existing evidence, which is expanding like never before. The objective is to highlight the evidence behind IUS in UC to inform clinical decision-making.

MATERIALS AND METHODS

Search strategy

For the review, we searched PubMed and EMBASE with the following search criteria: ('intestinal ultrasound' OR 'bowel ultrasound' OR 'transabdominal ultrasound' OR 'ultrasonography') AND ('ibd' OR 'inflammatory bowel' OR 'colitis ulcerosa'/exp OR 'colitis ulcerosa' OR 'ulcerative colitis'/exp OR 'ulcerative colitis'). After excluding duplicates, we found 7608 records between 1986 and April 2024 (PP and KP performed the search individually). We screened all the titles and abstracts as well as the full text of selected articles. Finally, 99 original research articles on IUS were included for this scoping review excluding review articles/letters to the editor/editorials/pictorial surveys/case reports/ narrative reviews/systematic reviews/consensus/articles in a language other than English/translational research/articles not focused on the topic (Figure 1). We summarized the evidence under each subheading based on the review of the existing literature. In the areas where the literature was substantial, we represented it in a tabular form.

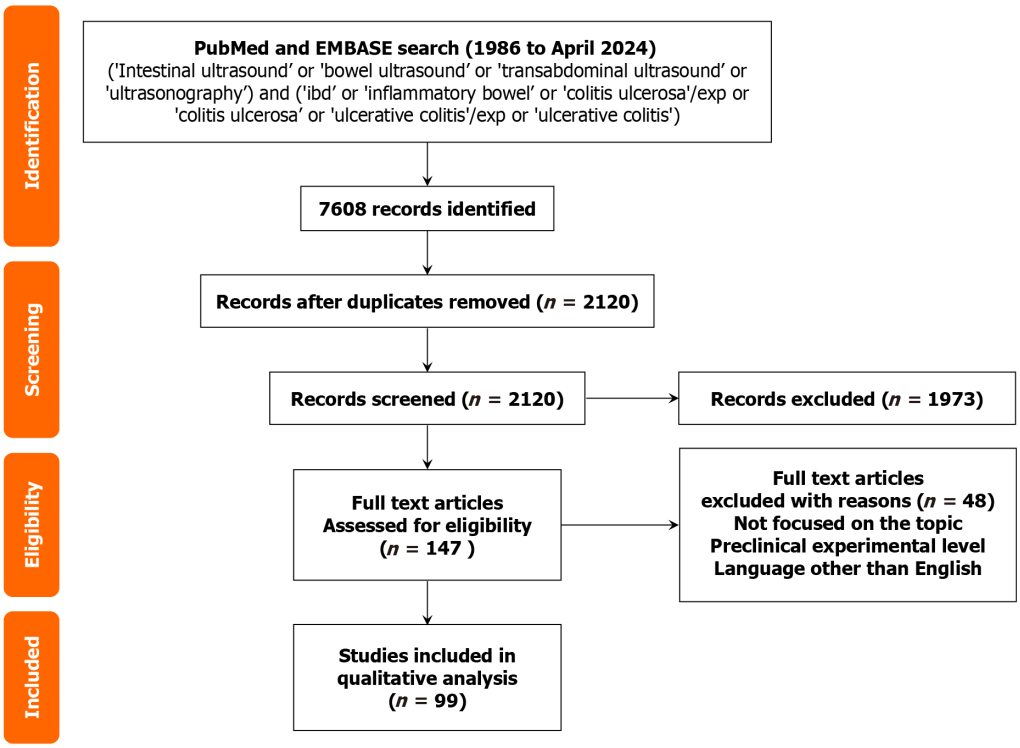

Figure 1 PRISMA diagram for systematic review.

RESULTS

IUS as a diagnostic strategy in suspected IBD/UC

IUS aids in IBD/UC diagnosis in those with low-risk GI symptoms by excluding irritable bowel syndrome. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of IUS in suspected IBD based on three prospective studies ranged between 55%-85%, 95%-100%, 92%-98%, and 58%-92%, respectively. However, there were wide variations in criteria for abnormal IUS findings [including cut-off for abnormal bowel wall thickness (BWT)], reference standard to the diagnosed IBD, age group studied, and frequency of ultrasound probes used to diagnose IBD (Table 1)[1,3,5,6]. Sensitivity was higher for the diagnosis of Crohn's disease (CD) (84%) than UC (38%-66%) [1,5]. Location-wise, sensitivity was higher for inflammatory ileal (92%-96%) and left colonic lesions (81%-87%) whereas it was low for duodenal/jejunal (29%-33%) and rectal lesions (14%-15%) (Table 1)[3,5]. Reduction in the BWT cut-off from ≥ 7 mm to ≥ 5 mm increases the sensitivity marginally with a reduction in specificity and PPV[1]. Among various IUS parameters, loss of stratification had the highest sensitivity (78.3%), whereas any of the three parameters (BWT, loss of stratification, and inflammatory fat) had an 82.6% sensitivity in a retrospective study of suspected pediatric IBD. The presence of all the three parameters had a 100% specificity and 100% PPV[7]. The presence of any of the three parameters had a 95.1% NPV (Table 1). A small study (n = 28) in suspected pediatric IBD showed that the sensitivity of IUS (55%) can be improved by magnetic resonance imaging (MRI) (sensitivity: 83%-87%)[8].

Utilization of IUS in those with low-risk GI symptoms from general practitioner referrals was shown to reduce colonoscopies and gastroenterology consults in a prospective study from Australia (Table 1)[9].

Role of IUS in differentiating UC from its mimics: It is not known whether IUS can help differentiate UC from its mimics. One of the initial retrospective studies concluded that high vascularity alone, without spectral waveform analysis, cannot differentiate between various inflammatory and neoplastic pathologies. Color Doppler sonography can only help to differentiate inflammatory lesions from small bowel ischemia. Vascularity was more pronounced in CD and cytomegalovirus colitis whereas a mild increase was noted in UC and diverticulitis[10]. However, contrast-enhanced ultrasound (CEUS) findings can help differentiate IBD from colon cancer: Disordered enhancement (94.7% cancer, 9.1% IBD), heterogeneous enhancement (78.9% cancer, 0% IBD), delayed enhancement (wash in time 14.7 ± 3.2 s cancer, 9.9 ± 3 s IBD), longer time to peak intensity (8.7 ± 2.9 cancer, 5.4 ± 2 IBD) (P < 0.001), and slow washout (in cancer)[11].

A small retrospective study from India (n = 76) used a two-step protocol to differentiate causes of chronic diarrhea with abdominal pain. Initially, lesions on IUS were divided based on shear wave elastography (SWE) and dispersion (SWD) to differentiate fibrotic (high SWE, normal SWD), inflammatory (normal SWE, high SWD), and mixed strictures (high SWE and SWD). Then CD (fat, fistula, vascularity), UC (inflammatory, thickened submucosa, preserved stratification, high SWD in submucosa), neoplastic etiology (BWT > 9 mm, SWE > 90 kPa), tuberculosis (nodes, fluid), infective ileocolitis (inflammatory or mixed), and diverticulitis could be differentiated based on involved bowel length, thickness, stratification, vascularity, fat, fluid, fistula, and lymph nodes[12].

IUS in UC

Assessing disease activity: Several IUS parameters have been used to assess disease activity[13,14]. Among them, the interclass correlation was perfect, substantial, moderate, and fair for BWT, Color Doppler signal (CDS) intensity, lymph node and mesenteric fat/loss of haustrations/bowel wall stratification as shown in an inter-observer agreement (IOA) study of six expert sonographers. Hence, it was concluded that BWT and CDS are reliable and can be incorporated in future UC scoring indexes[15]. Although there are several scoring systems available for assessing disease severity, we included those that are validated in original studies.

Milan criteria: In the developmental phase of Milan criteria (earlier Humanitus ultrasound criteria), BWT and CDS independently predicted colonoscopic activity on multivariate analysis (Table 2). Milan ultrasound criteria (MUC) [1.4 × BWT (mm) + 2 × CDS (CDS = 1 if present, 0 if absent)] was highly predictive of endoscopic activity [Mayo endoscopic score (MES) ≥ 2] (sensitivity: 71%, specificity: 100%, area under the curve (AUC): 0.891) with high IOA (kappa 0.86). The additional fecal calprotectin (FCP) increased sensitivity to 100%[16]. In an external validation study (n = 43), MUC > 6.2 had a 95% sensitivity and 94% specificity[17]. At more than 1 year follow-up, MUC > 6.2 could predict adverse disease outcomes (treatment escalation, steroid use, hospitalization, colectomy)[18]. MUC ≤ 6.2 at 12 wk (for UC patients on biologics) independently predicted endoscopic activity (MES ≤ 1) at 1 year (odds ratio [OR]: 5.8). A ≥ 2 reduction in MUC predicted MES = 0 (AUC: 0.816) (100% sensitivity, 62% specificity). MUC ≤ 4.3 was the most accurate for predicting MES = 0 (sensitivity 100%, specificity: 76%)[19].

In those with clinical remission, MUC > 6.2 predicted clinical relapse in a small retrospective study[20]. One step ahead, a small (n = 29), paired, cross-sectional study has shown that MUC > 6.2 along with elevated FCP ≥ 100 μg/g can accurately predict histologic activity in 88% of cases[4]. A higher cut-off of MUC > 7.7 was better in predicting colectomy (AUC: 0.83) risk than MES (AUC: 0.71)[21]. MUC calculated *via* a hand-held IUS machine has excellent agreement (kappa 0.86) and comparable accuracy (0.84) as compared to MUC calculated by conventional IUS (0.87)[22].

UC-IUS index: This index was developed based on a prospective study in which IUS and colonoscopy were done within 3 wk (60 patients, 207 colonic segments). UC-IUS index (scores 0-7) is based on BWT (scores 1, 2, and 3 for > 2 mm, > 3 mm, and > 4 mm, respectively), CDS intensity (present: Score 1, stretches: Score 2), lack of haustrations (score 1, predicting active disease), and fat wrapping (score 1, predicting severe disease). This scoring is based on the fact that BWT > 2.1 mm, > 3.2 mm, and > 3.9 mm can effectively differentiate between Mayo 0 and Mayo 1-3, Mayo 0-1 and Mayo 2-3, and Mayo 3 and others, respectively, with excellent accuracy (AUC > 0.9 for all) and sensitivity/specificity (all > 80%). The UC-IUS score showed a strong correlation with endoscopic scores, specifically the Mayo and UC Endoscopic Index of Severity (UCEIS) (Table 2) with substantial inter- and intra-rater agreement[23]. In the same study, a BWT > 2 mm and FCP > 200 μg/g resulted in a sensitivity of 76.9% and specificity of 93.3% for detecting endoscopically active disease[23].

Kyorin ultrasound criteria/submucosal index: Kyorin ultrasound criteria (KUC) can predict endoscopic activity without color Doppler. KUC is defined as BWT < 3.8 mm with submucosal index (SMI) (thickness of submucosa/entire bowel wall) < 50%. The PPV (95%) was higher than that of conventional criteria (BWT > 3 mm) to predict endoscopic improvement[24].

Monitoring therapeutic response and disease course in UC

The short-term, intermediate, and long-term goals of the management of UC are clinical response followed by normalization of biomarkers and finally mucosal healing with optional histologic healing. We found 13 studies (2 retrospectives, 1 *post-hoc* analysis of randomized trial, and 10 prospective studies) evaluating response to treatment in UC. Study designs vary from cross-sectional to follow-up periods of up to 1 year (Table 3).

One very early, small (n = 9 UC), retrospective study by Dubbins *et al*[25] did not show any significant changes in BWT for UC treated with conventional therapy at 2-4 mo as opposed to a significant reduction in CD (n = 19). However, Maconi *et al*[13] demonstrated that active UC treated with steroids resulted in a significant reduction in BWT in clinical responders, showing excellent correlation between IUS parameters and clinical, biochemical, and endoscopic measures. Further studies showed that early IUS response at 2-3 wk (2.5 mm reduction in BWT) for UC on conventional therapy and cytapheresis could predict treatment response (91% *vs* 40%) at 1 year with a lower probability of relapse (9% *vs* 47%)[26]. A small study (n = 7 UC) demonstrated significant changes in CEUS parameters, such as peak enhancement, and amplitude-dependent parameters with vedolizumab therapy at 14 wk, while no significant changes were observed in time-dependent parameters, such as time to peak[27].

A large, multi-center, German, prospective study (TRUST UC) has shown that 89% of patients with the clinical flare of UC had increased BWT in the descending/sigmoid colon which decreased significantly as early as 2 wk preceding clinical and biomarker response. Normalization of BWT at 12 wk had an excellent correlation with clinical response. This study supports the role of IUS as a noninvasive monitoring tool in IBD[28]. Subsequently, another prospective study including UC (n = 28) and CD (n = 89) from Romania showed that IUS parameters [BWT, CDS, and bowel wall stratification (BWS)] could predict immediate and subsequent treatment escalation over the next 6 mo[29].

A small (n = 31, 8 UC), retrospective study showed that a 16% improvement in BWT at 6 wk and 10% improvement at 14 wk predicted long-term treatment response at 46 wk in patients on biologics[30].

A more recent, prospective cross-sectional study showed that for UC patients on maintenance infliximab, lower trough levels were associated with IUS activity (higher CDS)[31]. A *post-hoc* analysis of prospective studies has shown that after 12 wk of treatment intensification, transmural healing (TH) was achieved in 45%-61% of UC cases and transmural response [(TR): ≥ 25% reduction or normalization of BWT)] in 76%[32].

Table 1 Summary of studies evaluating intestinal ultrasound for diagnosis of inflammatory bowel disease/ulcerative colitis and differentiating inflammatory bowel disease mimics

Ref.	Study type	Number of patients	Equipment	Criteria for abnormal findings	Reference	Sensitivity	Specificity	PPV	NPV
Hollerbach *et al*[5]	Prospective	227 suspected IBD patients	5 MHz curved array probe	BWT > 4 mm, target sign, lumen < 4 mm, ascites, abscess, reduced compressibility, conglomerate tumor (any 2 of the above)	Colonoscopy, entero-clysis, enema, CT scan, surgery	76% (84% CD, 66% UC) (10%-20% in jejunum, duodenum, rectum)	95%	98%	58%
Astegiano *et al*[1]	Prospective	313 (abdominal pain and altered bowel habits ≥ 3 mo)	7.5-10 MHz linear probe and 3.5 MHz convex probe	BWT ≥ 7 mm, BWT between 5-6 needs follow-up	Radiology and endoscopy	74% (84% CD, 38% UC)	98%	92%	92%
Chavannes *et al*[72]	Cross-sectional, single centre	33 children with suspected IBD (11 UC)	3-12 MHz linear probe and 3-10 MHz convex probe	BWT > 1.9 mm cut-off for inflamed bowel	Colonoscopy	64%	76%	-	-
Rossaint *et al*[3]	Prospective	487 suspected IBD patients	7.5 MHz linear, 3.5 MHz convex	BWT > 4 mm	Endoscopy, small bowel enteroclysis, CT	85% Rectum: 14% Duodenum/jejunum: 29%	95%	98%	75%
Dell'Era *et al*[7]	Retrospective	113 suspected pediatric IBD patients	3.5-5 MHz curvilinear probe, 4-8 MHz microconvex probe	BWT, BWS, lymph nodes, i-fat	Ileo-colonoscopy	BWS: 78.3% i-fat: 65.2%; BWT > 3: 69.6%. All 3: 56.5%. Any of 3: 82.6%	BWS: 93.3. i-fat: 92.2%; BWT > 3: 96.7%. All 3: 100%; Any of 3: 86.7%	BWS: 75% i-fat: 68.2%; BWT > 3: 84.2%; All 3: 100%. Any of 3: 61.3%	BWS: 94.4% i-fat: 91.2%; BWT > 3: 92.6%; All 3: 90%. Any of 3: 95.1%
Ziech *et al* [8]	Prospective	28 children with suspected IBD	Linear probe 5-12 MHz	BWT, BWS, lymph nodes, Doppler of mesenteric arteries	Ileo-colonoscopy and endoscopy	55% (improved with combination of MRI 83%-87%)	100%	-	-
White *et al* [9]	Prospective	37 patients with low-risk GI symptoms, FCP < 150 μg/g, CRP < 10 g/d	5-8 MHz curvilinear probe, 18 MHz linear probe	BWT > 3 mm, increased CDS, loss of BWS, inflammatory fat, lymph nodes	NA	-	-	-	-
Jeffrey *et al* [10]	Retrospective	32 patients with focal GI lesions, 20 controls	5 MHz linear array transducer	≥ 4 blood vessels measuring 3 mm or more over 5 cm segment/extending into mesentery	Surgery, biopsy, endoscopy	-	-	-	-
Zhang *et al* [11]	Retrospective	13 IBD, 38 colon cancer	Curvilinear probe 2-5 MHZ (for CEUS, MI 0.07-0.10, dynamic range 50 dB), linear probe 3-9 MHz, SonoVue contrast	Increased BWT, loss of BWS, "comb-teeth like" vessels on color Doppler, disordered enhancement, hetero-geneous enhancement	Histology for colon cancer, clinical/pathologic and endoscopic exams for IBD	Colon cancer BWS: 97.4%; Disordered enhancement: 94.7%. Heterogeneous enhancement: 78.9%	Colon cancer BWS: 69.2%; Disordered enhancement: 92.3%. Heterogeneous enhancement: 100%	-	-
Kapoor *et al* [12]	Retrospective, single centre	76 patients with chronic diarrhoea and abdominal	Convex probe: 3.5-8 MHz, linear probe: 8-14 MHz	Abnormal bowel wall stiffness (> 12 kPa) and abnormal inflammation (> 14 m/s/kHz); wall thickening (> 3	Contrast enhanced CT, endoscopic and surgical biopsy	100%	99%	-	-

	pain	and > 4 for small and large bowel), stratification, node, fluid, fat, and fistula

IBD: Inflammatory bowel disease; BWT: Bowel wall thickness; CD: Crohn's disease; UC: Ulcerative colitis; CT: Computed tomography; IBS: Irritable bowel syndrome; PPV: Positive predictive value; NPV: Negative predictive value.

Table 2 Studies evaluating scoring systems to assess disease activity in ulcerative colitis based on intestinal ultrasound

Ref.	Study type	Follow-up duration	IUS activity	Comparator	Number of patients	Results
Allocca *et al*[16]	Prospective	6 mo	BWT, CDS, BWS, lymph nodes	Colonoscopy	53 UC patients	BWT and CDS were independent predictors of colonoscopic activity; Humanitus ultrasound criteria: (1) BWT > 3 mm with CDS; and (2) BWT > 4.43 and absence of CDS. MUC > 6.2: Sensitivity 71%, specificity: 100%, AUC: 0.891. Addition of FCP increased sensitivity to 100%
Allocca *et al*[17]	Prospective	6 mo	BWT, CDS	Colonoscopy	43 UC patients	MUC score > 6.2 discriminated active UC (sensitivity 85%, specificity 94%, AUC 0.902); external validation study
Allocca *et al*[18]	Prospective	1.6 years (median)	MUC	-	98 UC patients	Milan ultrasound criteria > 6.2 at baseline was statistically significantly associated with adverse disease outcomes (treatment escalation, steroid use, hospitalization, and colectomy) (HR: 3.87)
Allocca *et al*[19]	Prospective	1 year	MUC	Colonoscopy	49 UC patients	MUC ≤ 6.2 at wk 12 is independent predictor of MES ≤ 1 at 1 year (OR: 5.8)
Maeda *et al*[20]	Retrospective	1 year	Milan criteria	Endoscopic Mayo score, fecal calprotectin	58 UC patients	MUC > 6.2 predicted 1 year relapse (HR: 3.22)
Goodsall *et al*[4]	Prospective cohort	8 wk	Milan criteria, BWT	NHI, colonoscopy (UCEIS score)	29 UC patients	IUS + FC accurately predicted histological activity in 88% of cases (sensitivity 88%, specificity 80%, positive predictive valve 95%, and negative predictive valve 57%)
Piazza *et al*[21]	Prospective, multi centre	11.5-31.9 mo	MUC, BWT	MES, FCP, CRP	141 UC patients	MUC > 7.7 was better in predicting colectomy (AUC: 0.83) risk than MES
Rispo *et al*[22]	Prospective	Cross-sectional	MUC	Colonoscopy (MES)	86 UC patients	Conventional and hand-held ultrasound had excellent agreement for MUC (kappa = 0.86). No difference in diagnostic accuracy (0.87 IUS *vs* 0.84 hand-held IUS)
Bots *et al*[23]	Prospective	3 wk	BWT, vascularity, haustrations, fat wrapping	Colonoscopy	60 UCpatients	UC-IUS score was developed which has strong correlation with endoscopic disease activity (ρ = 0.83 for Mayo score, ρ = 0.76 for UCEIS score)
Komatsu *et al*[24]	Retrospective validation	-	BWT, submucosal index	Colonoscopy	44 UC patients	High PPV (95%) and NPV (80%) to predict endoscopic improvement

CD: Crohn's disease; IUS: Intestinal ultrasound; FC: Faecal calprotectin; UC: Ulcerative colitis; MUC: Milan ultrasound criteria; CI: Confidence interval; HUS: Humanitas ultrasound criteria; CWF: Colon wall flow; CWT: Colon wall thickness; SUS-CD: Simple ultrasound score-Crohn's disease; IBUS-SAS: International bowel ultrasound-segmental activity score; BWT: Bowel wall thickness; CDAI: Crohn's disease activity index; DBE: Double balloon enteroscopy; US-CD: US scoring system for Crohn's disease; UC-IUS: Ulcerative colitis intestinal ultrasound; ρ: Spearman's rho; UCEIS: Ulcerative colitis endoscopic index of severity; PPV: Positive predictive value; NPV: Negative predictive value.

Table 3 Role of intestinal ultrasound in predicting response to therapy in ulcerative colitis

Ref.	Study type	Number of patients	Treatment agent(s)	IUS predictor(s)	Follow-up duration	Time points of IUS	Therapeutic outcomes
Dubbins [25]	Retrospective	9 UC (19 CD)	Steroid ± immunosuppressive therapy	BWT	2-4 mo	Baseline, 2-4 mo	No significant change in BWT in UC but there was significant response in CD
Maconi *et al*[38]	Prospective	30 active UC	Steroids	BWT	2 mo	Baseline and 2 mo	Significant reduction in BWT in clinical responders; IUS response significantly correlated with clinical biochemical and endoscopic activity
Yoshida *et al*[26]	Prospective	26 UC	Cytaphresis + conventional therapy	BWT	1 year	Baseline and 2-3 wk	Early IUS response (decrease in BWT by 2.5 mm at 2-3 wk) predicted 1 year response (91% *vs* 40%) lower relapse (9% *vs* 47%)
Goertz *et al*[27]	Prospective	7 UC	Vedolizumab	BWT, CDS, CEUS-amplitude and time derived parameters	14 wk	Baseline, 14 wk	Decrease in CDS intensity. Decrease in amplitude dependent CEUS parameters (peak enhancement and wash in rates)
Maaser *et al*[28]	Prospective, multi centre	224 UC	Steroid, anti-TNF, anti-integrin, AZA/6-MP	BWT, BWS, CDS, haustration, lymph nodes, inflammatory fat, ascites	16 wk	Baseline, 2, 6, and 12 wk	Significant improvement in IUS parameters was seen as early as 2 wk. Significant correlation of normalisation of BWT at 12 wk with clinical improvement and biomarkers
Les *et al* [29]	Prospective	28 UC (89 CD)	5-ASA, budesonide, AZA, anti-TNF	BWT, BWS, CDS, i-fat, lymph nodes	6 mo	Baseline	Predictors (overall IBD); immediate treatment escalation (31.7%) Score = 1/[1 + Exp (-XB)] where XB = 0.75 × [BWT (mm)] + 3.5 × (CDS = 1) – 7.31; AUC: 0.94, score > 0.5 100% sensitivity, 83% specificity; subsequent treatment escalation (17.9%), AUC: 0.92; Score = 1/[1 + Exp (-XB)] where XB = 0.8X [bowel wall thickness (mm)] - 1.3X (Presence of wall stratification =1) – 3.82 Score > 0.6 has 90% sensitivity, 86.4% specificity
Smith *et al* [30]	Retrospective	23 CD, 8 UC (22 CD and 7 UC on biologics)	Anti-TNF, ustekinumab, vedolizumab	BWT, CDS	46 wk	2, 6, and 14 wk	16% improvement in BWT at 6 wk and 10% improvement at wk 14 predicted treatment persistence/response at 46 wk
Vaughan *et al*[31]	Prospective	79 UC and 24 CD	Maintenance infliximab	BWT, CDS	Cross-sectional (median disease duration 8 years)	Cross-sectional data	Lower infliximab trough level was associated with higher CDS in both UC and CD
Helwig *et al*[32]	*Post-hoc* analysis of prospective, multi centre studies	131 UC (118 CD)	Standard of care	BWT, CDS, BWS, i-fat, transmural healing, transmural response	52 wk	0, 12, 52 wk	76.6% TR and 45%-61.4% TH at 12 wk after treatment intensification
de Voogd *et al*[33]	Longitudinal, prospective	30 UC on tofacinib	Tofacitinib	BWT	8 wk	Baseline and 8 wk	Most accurate BWT cut-off for endoscopic remission was 2.8 mm; for endoscopic response: 3.9 mm and > 32% decrease in BWT

Ilvemark *et al*[34]	Blinded, prospective multi centre, observational	56 acute severe UC	IV steroid	BWT	48 h and 6 d	Baseline, 48 ± 24 h and 6 ± 1 d	≤ 20% reduction in BWT has 84.2% sensitivity and 78.4% specificity for determining non-response (AUC: 0.85)
Allocca *et al*[19]	Prospective	49 UC	Infliximab, adalimumab, vedolizumab, ustekinumab	Milan ultrasound criteria based on BWT and CDS intensity	1 year	Baseline, week 12, and 1 year	MUC ≤ 6.2 at week 12 independent predictor of MES ≤ 1; A ≥ 2 reduction in MUC predicted MES = 0
de Voogd *et al*[33]	Prospective, single center	51 UC patients	Steroids, 5-ASA, thiopurines, biologics, tofacitinib, cyclosporin	BWT, CDS, haustrations, BWS, fat wrapping, lymph nodes	26 wk	Baseline, week 2, week 6, weeks 8-26	BWT and CDS at weeks 2 and 6 predicted endoscopic remission and response at 8-26 wk

CD: Crohn's disease; TNF: Tumor necrosis factor; TH: Transmural healing; BWT: Bowel wall thickness; CDS: Color doppler signal; IUS: Intestinal ultrasound; CEUS: Contrast enhanced ultrasound; TI: Terminal ileum; RCT: Randomized controlled trial; IFX: Infliximab; SWE: Shear wave elastography; SUS-CD: Simple Ultrasound Activity Score for CD; IBUS-SAS: International Bowel Ultrasound Segmental Activity Score; BUSS: Bowel Ultra-Sound Score; SICUS: Sall Intestine Contrast Ultrasonography.

More recently, IUS was shown to be a good surrogate marker for endoscopic response and remission in moderate to severe UC. In a study, 30 patients started on tofacitinib induction therapy were monitored using IUS, colonoscopy, and Robert's histological index (RHI) at baseline and after 8 wk. BWT cutoffs of 2.8 mm and 3.9 mm had excellent accuracy (AUC > 0.85) for endoscopic remission (MES 0) and improvement (MES ≤ 1), respectively. A decrease in BWT by 32% correlated with the endoscopic response (decrease in MES ≥ 1). Among the wall layers, the submucosa was most responsive to change. BWT correlated with both MES and RHI[2]. Another recent, single-center, prospective observational study showed that MUC < 6.2 at 12 wk can effectively rule out endoscopic activity at 1 year (NPV 96%) in UC on biologic therapy. A 2-point decrease in MUC predicted eMS ≤ 1 with an 89% sensitivity and 71% specificity[19]. A prospective study demonstrated that BWT, CDS, and submucosal thickness (SMT) predicted endoscopic parameters (improvement and remission) by 6 wk. Hence, IUS can be used as a surrogate marker for endoscopy. BWT was reduced significantly at 2 wk in patients on infliximab and tofacitinib whereas it took longer time (6 wk) for vedolizumab. After 8 wk, there was no difference between the different agents regarding changes in BWT[33].

IUS in acute severe UC: Two studies have addressed the role of IUS in hospitalized patients with severe UC requiring intravenous steroids. A prospective, blinded, Danish, multi-center study (n = 56) showed that a > 20% reduction in BWT (mostly in sigmoid) at 48 ± 24 h after IV steroid predicted clinical response (partial Mayo score decrease > 30%) and need for rescue therapy at day 7[34]. Similarly, a single-center, retrospective study in pediatric severe UC (n = 52) showed that colonic BWT > 3.4 mm and loss of colonic wall stratification independently predicted steroid resistance when assessed within day 3 of hospitalization[35]. A recent study has shown that MUC can predict severity (cut-off > 8.54 for severe UC, sensitivity: 64.3%, specificity: 93.3%), corticosteroid failure (MUC > 10.54, sensitivity: 50%, specificity: 90.9%), and colectomy (MUC > 12.5, sensitivity: 55.6%, specificity: 97%) in UC[36].

IUS to detect appendiceal inflammation in UC: Regardless of the extent of UC, IUS findings of transverse appendicular diameter ≥ 6 mm are seen in 43% of patients with active UC (in the absence of clinical appendicitis) (n = 35) compared to 6% and 0% with quiescent (n = 30) and inactive disease (n = 30) as shown in a prospective study. The submucosal wall thickness is also increased in UC (1 mm in active and quiescent disease) compared to 0.7 mm in healthy controls[37]. The finding implies that IUS might help to select patients who would benefit from an appendectomy. However, future

validation is warranted by incorporating histologic findings in appendectomy specimens.

Mesenteric blood flow and UC activity: Earlier studies (4 prospective studies) recognized changes in mesenteric blood flow patterns in active UC[38-41]. The common theme in these studies was an increase in blood flow (both volume and velocity) and low pulsatility/resistance index in the mesenteric vessels, a differential increase in blood flow based on the location of colonic active disease (superior mesenteric artery for right colon and inferior mesenteric artery for left colon) (Table 4)[38-41]. However, the clinical usefulness of such findings is currently questionable.

CEUS: Three studies (2 prospective and 1 retrospective) evaluated CEUS in UC/IBD. The retrospective study was discussed earlier by Zhang *et al*[11] for differentiation of colonic cancer and IBD. CEUS can predict treatment response as discussed earlier for vedolizumab with a significant decrease in amplitude-dependent parameters in responders (Table 5)[27]. Increased vascularity in CEUS correlated histologically with increased vascular density (CD34+)[42].

Correlation of IUS with other modalities

Several clinical indices in UC correlate with IUS. Apart from clinical indices, IUS correlated with biomarkers and even histological activity (Table 6).

Correlation with biomarkers (*e.g.*, FCP/C-reactive protein): A recent retrospective study has shown that FCP and C-reactive protein (CRP) levels significantly correlated with the number of segments with active inflammation/complications and IUS scores (Table 7). The highest accuracy was seen for FCP cut-off 150 μg/g (AUC: 0.756) [concordance with active small bowel (n = 33), large bowel (n = 3), and combined disease (n = 24) were 72.7%, 66.7%, and 70.8%, respectively][43]. FCP also correlated with vascularity on color Doppler[44]. Another retrospective study (n = 213) showed that leucine-rich glycoprotein (> 14.6 μg/mL) was a better marker than CRP to predict active IUS findings for CD in clinical remission[45]. Another recent study showed that a combination of fecal immunochemical testing (FIT) > 100 ng/mL and BWT > 2 mm predicted mucosal inflammation (MES > 0) with good accuracy (AUC: FIT: 0.93, BWT: 0.84-0.97)[46].

Correlation with colonoscopy: The correlation between colonoscopy and IUS has been evaluated in 26 studies (7 retrospective, 19 prospective) in UC (Table 8)[14,20,47-64]. The sensitivity, specificity, accuracy, PPV, and NPV of IUS as compared to colonoscopy as gold standard varied from 50%-100%, 23%-100%, 83%-93.3%, 92%-100%, and 73%-100%, respectively (Table 8)[47,48,53,58,61,63]. Different time intervals between IUS and colonoscopy, study design (retrospective/prospective, including CD), and variable sample size may account for the widespread variation. The sensitivity, specificity, PPV, and NPV decreased from 100% (all with same-day colonoscopy) to 92%, 86%, 92%, and 86% when colonoscopy was done within 30 d[58]. The sensitivity, specificity, PPV, NPV, and agreement with colonoscopy for disease extent in UC were 92%, 80%, 88%, 86%, and 0.7, respectively[58]. There was a significant correlation between IUS (MUC, UC-IUS) and colonoscopic scores (MES, UCEIS)[20,23,51,54,60,62-64]. The correlation between MUC and MES varied between 0.61-0.653 (highest in severely affected areas: 0.88)[20]. The specificity of MUC to predict endoscopic activity increased from 94% (> 6.2) to 100% (> 8.2) with no incremental benefit of FCP[17]. Similarly, the correlation between MUC and UCEIS varied between 0.32-0.648[63]. UC-IUS had a higher correlation with endoscopic scores than MUC (MES: 0.83, UCEIS: 0.76)[23]. In pediatric UC, UC-IUS (sensitivity: 88%-100%, specificity: 84%-87%) was better than Civitelli index (sensitivity: 65%-80%, specificity: 89%-93%) [significantly better in ascending colon (AUC 0.82 *vs* 0.76) and transverse colon (AUC 0.88 and 0.77) but not in sigmoid (AUC both 0.84)][64]. MUC > 6.2 calculated by hand-held IUS (dual probe 5-7.5 MHz) (V san, General Electric Co.) had an 84% accuracy (highest in sigmoid colon and lowest in rectum)[22]. SWE showed a significant negative correlation (-0.404) with UCEIS[62]. IUS scores after 3 mo of high-dose steroids in severe UC also correlated with future risk of endoscopic activity at 15 mo[50,51]. In a recent study, the median FCP was lower in those with inactive IUS (median 50 μg/g) as compared to active IUS (270 μg/g).

Among the IUS parameters, BWT had the most consistent correlation with colonoscopic findings in the majority of studies[20,49,52,55,57,60,61]. BWT cut-offs of 2.1 mm, 3.2 mm, and 3.9 mm could differentiate Mayo 0 *vs* Mayo 1-3 (sensitivity: 82.6%, specificity: 93%, AUC: 0.91), Mayo 0-1 *vs* Mayo 2-3 (sensitivity: 89.1%, specificity: 92.3%, AUC: 0.946), and Mayo 3 *vs* others (sensitivity: 80.6%, specificity: 84.1, AUC: 0.909)[23]. In response to tofacitinib therapy, cut-off values of BWT for endoscopic remission (MES = 0), improvement (MES ≤ 1), and response (MES ≥ 1 decrease) were 2.8 mm (AUC 0.87, sensitivity 73%, specificity 100%), 3.9 mm (AUC 0.92, sensitivity 81%, specificity 100%), and 32% decrease (AUC 0.87, sensitivity 71%, specificity 90%), respectively[2]. In pediatric UC, BWT cut-offs of 2.9 mm in the colon and 2.5 mm in the ileum had excellent accuracy[49]. Change in BWT correlated well with change in endoscopic scores in the sigmoid (MES: 0.50, UCEIS: 0.68) and descending colon (MES: 0.67, UCEIS: 0.50)[2]. Combination of BWT < 3.75 mm and SMI (SMT divided by BWT%) < 49.7 has a sensitivity, specificity, PPV, NPV, and accuracy of 70%, 97.7%, 95.5%, 82.7%, and 86.5%, respectively[61]. Additionally, two studies showed a significant correlation between CDS and IUS activity (OR: 2.49-26.23)[14,59]. The correlation of CDS with MES was 0.98 (*c.f.*, BWT: 0.88, MUC: 0.88) in the worst affected segment[20].

Anteroposterior diameter of ≥ 12 mm and the presence of intra-luminal vascular signals correlated with pseudopolyposis in a small series (n = 12, both UC and CD) with a high sensitivity (75%) and specificity (100%)[65].

Correlation with cross-sectional imaging: The correlation between IUS and MRE findings has been studied mainly in CD. However, two prospective studies (one in IBD and another in suspected pediatric IBD) compared IUS and MRI (Table 9). The accuracy of IUS in the large bowel was 70% with MRI as the gold standard with a 100% correlation for active disease[56]. In suspected pediatric IBD, the sensitivity of IUS and magnetic resonance (MR) colonography was

Table 4 Summary of studies on superior mesenteric artery/inferior mesenteric artery artery flow in evaluating inflammatory bowel disease activity

Ref.	Study type	Number of patients	Parameters studied
Ahmed *et al*[41]	Prospective	84 UC (16 CD, 50 normal)	SMA and IMA PSV and EDV significantly higher in UC compared to controls; pulsatility index significantly higher in control group than UC
Maconi *et al*[38]	Prospective	24 UC (31 CD, 10 IBS)	Higher portal and mesenteric blood flow with lower RI of SMA was noted in active UC as compared to quiescent UC
Mirk *et al* [39]	Prospective	22 UC, 24 CD	IBD with active disease in left colon presented increases in flow velocity and flow volume with decrease in pulsatility index
Sığirci *et al*[40]	Prospective	44 (25 active, 19 inactive, 22 healthy)	IMA blood flow volume, mean PSV, ESV, mean velocity, and vessel diameter were higher and pulsatility index lower in active disease compared to quiescent disease; active disease in left colon had high higher mean PSV and velocity in IMA; mean EDV higher with lower mean PI and RI in SMA for those with pancolonic involvement

SMA: Superior mesenteric artery; CD: Crohn's disease; IMA: Inferior mesenteric artery; PSV: Peak systolic velocity; EDV: End diastolic velocity; UC: Ulcerative colitis; ESV: End systolic velocity; RI: Resistive index; PI: Pulsatility index; IBS: Irritable bowel syndrome; IBD: Inflammatory bowel disease.

Table 5 Summary of studies on contrast enhanced ultrasound in ulcerative colitis

Ref.	Study type	Number of patients	Parameters studied
Romanini *et al*[42]	Prospective	18 UC, 15 CD	High vascular density (CD34+; > 265 vessels per high power field, 40 ×) correlated with CEUS (higher and early peak, higher blood flow and volume)
Goertz *et al* [27]	Prospective	7 UC, 11 CD	Decrease in amplitude dependent CEUS parameters (peak enhancement and wash in rates). Time dependent parameters (*e.g.*, time to peak) remained stable
Zhang *et al* [11]	Retrospective	13 IBD, 38 colon cancer	Disordered and heterogeneous enhancement in colon cancer (95% and 79%) compared to IBD (9% and 0%). Colon cancer: Later enhancement, slower washout with lower speed to peak intensity

CD: Crohn's disease; IBD: Inflammatory bowel disease.

similar (55% IUS, 57% MR) whereas IUS was more specific (100% IUS *vs* 75% MR). Differentiation between UC and CD was not possible with either method except in cases where the terminal ileum was involved[8].

Correlation with histology: An earlier single-center, cross-sectional study showed that dynamic tissue perfusion in the inflamed intestine positively correlated with crypt abscess, neutrophils, and lymphocytic invasion, whereas it negatively correlated with wall edema[66]. Similarly, another prospective study showed that vascular density on histology was associated with CEUS parameters (higher and earlier peak, higher blood flow and volume)[42]. More recently, IUS grade based on BWT, CDS, BWS, and wall echogenicity correlated with Matt's histological grade (r = 0.35)[54]. MUC positively correlated with Nancy histological index (NHI) (r = 0.11). MUC > 6.3 and/or FCP ≥ 100 μg/g had a sensitivity of 88% and specificity of 90% for predicting NHI > 1 (Table 10)[4]. Rectal BWT > 4 mm on trans-perineal ultrasonography (USG) had a higher sensitivity (95.5% *vs* 59.1%) but lower specificity (41.6% *vs* 76.2%) than Limberg's score > 2 to predict NHI > 1 [57].

IUS and TH

TH is a therapeutic target in the "treat to target strategy" of CD; however, it can be evaluated in UC as well by IUS[32]. Sonographic assessment of TH has the potential to replace cross-sectional imaging for documentation of TH and make it part of routine practice. TH has been shown to predict relapse/steroid/treatment escalation-free survival[67]. A *post-hoc* analysis of prospective studies has used three definitions of TH and found that TR (≥ 25% reduction or normalization of BWT) was achieved in 76% of UC cases while TH was achieved in 45%-61%[32].

IUS in special populations

IUS in pediatric population: There is growing literature on the role of IUS in children (Table 11)[7,8,47-49,64,68,69]. IUS is preferable in pediatric IBD/UC over colonoscopy and MRI given high patient and caregiver satisfaction as shown in a recent study[69]. A noninvasive monitoring strategy using IUS, FCP, and colon capsule endoscopy has good tolerability with high accuracy as compared to colonoscopic monitoring[70]. We have found 12 studies evaluating the role of IUS in pediatric UC/IBD. Among them, seven evaluated the accuracy of IUS in comparison to ileo-colonoscopy with or without MR colonography (Table 11)[8,47-49,71]. IUS was highly accurate in assessing the location and endoscopic (77% sensitivity, 83% specificity) and histologic severity (75% sensitivity and 82% specificity) of the disease[47]. The cut-off for

Table 6 Summary of studies correlating clinical activity with intestinal ultrasound

Ref.	Study type	Number of patients	IUS predictors	Clinical score	Parameters studied
Goodsall *et al*[4]	Prospective	19 UC (29 paired data)	MUC	SCCAI, Mayo score	Mayo score: $r = 0.307$; 95%CI, 0.020-0.595; $P = 0.036$; SCCAI score: $r = 0.04$; 95%CI, −0.21 to 0.28; $P = 0.768$
Kinoshita *et al*[54]	Prospective, multi-centre	156 UC	Ultrasound severity score based on BWT, BWS, hypoechoic/hyperechoic changes in submucosa/mucosa	Rachmilewitz clinical activity index	$r = 0.40$, $P < 0.001$
Lim *et al* [63]	Prospective cross-sectional	29 UC, 22 CD	BWT, CDS, BWS, i-fat	Partial Mayo score	$r = 0.192$, $P = 0.317$
Maaser *et al*[28]	Prospective, multi-center	224 UC	BWT	SCCAI	Sigmoid colon: Baseline: $r = 0.187$; 12 wk: $r = 0.547$; descending colon: Baseline: $r = 0.262$; 12 wk: $r = 0.5$
Saleh *et al* [89]	Retrospective	39 UC, 108 DC	BWT, CDS, i-fat, BWS, lymph node, free fluid, haustartion, motility	Mayo score, UCAI	$r = 0.016$ Mayo score ($P = 0.002$); UCAI ($P = 0.014$)
de Voogd *et al*[2]	Prospective, single centre	16 UC, 22 CD	BWT, CDS, haustrations, BWS, fatty wrapping	SCCAI, Lichtiger index	SCCAI and BWT in the SC ($r = 0.65$, $P < 0.0001$) and DC ($r = 0.59$, $P < 0.002$). Lichtiger score and BWT SC ($r = 0.65$, $P = 0.001$) and DC ($r = 0.63$, $P = 0.001$)
Yamada *et al*[62]	Prospective	26	SWE, SWD	UCEIS	Negative correlation with SWE ($r = -0.505$, $P = 0.008$); no correlation with ($r = 0.001$, $P = 0.998$)

CD: Crohn's disease; UC: Ulcerative Colitis; SWE: Shear wave elastography; UCEIS: Ulcerative colitis endoscopic activity index; CDAI: Crohn's disease activity index; BWT: Bowel wall thickness; UCAI: Ulcerative colitis activity index; MUC: Mayo ultrasound score.

BWT was lower than for adults. The accuracy of the 1.9 mm cut-off was 0.743 (AUC) (sensitivity: 64%, specificity: 76%) which needs further validation[72]. IUS has a good correlation with MRE and colonoscopy on the location and severity of disease[8,72]. Various IUS scores for pediatric UC and CD have been described which need external validation. For UC, The UC-IUS score was better than the Civitelli index[64]. The sum of adjusted BWT was shown to be better than FCP in predicting moderate colonic inflammation (Mayo 2) in children with UC[73]. A study evaluated the role of IUS in predicting steroid responsiveness in pediatric acute severe UC as discussed earlier[35]. A combination of grayscale, color Doppler, and shear wave ultrasound was shown to increase diagnostic accuracy (92%) with a 100% sensitivity in an observational study[74]. In a study in pediatric UC ($n = 12$), dynamic tissue perfusion measurement (calculated from color Doppler videos using software to calculate perfusion velocity and perfused area) positively correlated with histologic findings of inflammatory cell infiltration and inversely correlated with wall edema (Table 11)[66].

IUS in pregnancy: IUS can be valuable in IBD disease monitoring for pregnant women, being non-invasive and radiation-free. In a prospective cohort study (16 UC, 22 CD), it was shown that the feasibility of IUS decreases significantly in the third trimester due to the gravid uterus especially in the sigmoid colon (96% to 69%) and terminal ileum (91% to 22%). IUS had a good correlation with clinical activity ($r = 0.60$) and FCP ($r = 0.73$). IUS identified active disease with an 84% sensitivity and 98% specificity. Treatment response was detected with an 80% sensitivity and 92% specificity[75]. A case series ($n = 5$, UC post-ileal-pouch anal anastomosis [IPAA]) has shown that FCP and IUS can help detect inflammatory pouch complications in pregnancy after ileal-pouch anal anastomosis, avoiding pouchoscopy[76].

IUS in IBD management during coronavirus disease 2019 pandemic: Bedside, IUS could lead to a change in clinical management in up to 80% of IBD patients with acute symptoms or suspected IBD as shown in a prospective, observational study during the coronavirus disease 2019 (COVID-19) pandemic when access to endoscopic services was limited [77]. Another prospective, multi-center study showed that point-of-care IUS in urgent care pathway showed active disease in 65% of cases, resulting in acute change in management in 57% and avoiding/delaying colonoscopy in 85%[72]. This highlighted the potential of IUS to improve care delivery without exhausting acute care services.

Trans-perineal and transvaginal USG: Trans-perineal ultrasound (TPUS) with microconvex or linear probes has shown that rectal wall thickness ≤ 4 mm predicted endoscopic (AUC = 0.90) and histological (AUC = 0.87-0.89) healing with high accuracy and was better than FCP[57]. Moreover, a decrease in rectal wall thickness within 1 wk assessed by TPUS predicted clinical remission at 8 wk (Table 12)[78].

The usefulness of transvaginal sonography (TVS) has been described for evaluating rectal involvement in UC and evaluation of rectal/perianal CD in select parous females in a small series ($n = 20$, UC-8) with matched controls (TVS done for gynecological indications). Rectal wall thickness (> 5 mm) and modified Limberg score ≥ 1 predicted endoscopic activity with high accuracy (AUC: 0.968 and 1, respectively)[79].

Table 7 Summary of studies correlating blood (C-reactive protein/erythrocyte sedimentation rate) or fecal biomarkers (fecal calprotectin) with intestinal ultrasound in ulcerative colitis

Ref.	Study type	Number of patients	IUS comparator	Biomarker(s)	Time between IUS and biomarker testing	Conclusion
Bots *et al*[23]	Retrospective, single centre	65 UC (280 CD)	BWT, CDS, BWS, i-fat, haustrations, lymph nodes, motility	FCP, CRP	Within 1 wk	Higher FCP and CRP in IUS active disease Median FCP Active disease: 1720 μg/g; Inactive disease: 75 μg/g ($P < 0.001$); Median CRP Active disease: 3.6 mg/L; Inactive disease: 1.8 mg/L ($P < 0.076$)
Goodsall *et al*[4]	Prospective	19 severe UC (29 paired data)	BWT, CDI, BWS	FCP	Baseline	Log converted FCP had significant correlation with NHI ($r = 0.027$, 0 = 0.044), but not with MUC ($r = 0.01$, $P = 0.064$); Composite of MUC and FCP has 88% sensitivity, 80% specificity, 95% PPV, and 57% NPV ($P = 0.007$)
Ilvemark *et al*[34]	Blinded, prospective multi centre, observational	56 acute severe UC	BWT	CRP	Baseline	FCP is not a predictor of IV steroid response; BWT has significant association with CRP at 48 ± 24 h, $r = 0.47$, $P < 0.005$
Les *et al*[29]	Prospective	28 UC, 89 CD	BWT, loss of stratification, CD, mesenteric hypertrophy, lymph nodes	CRP, FCP	Baseline	FCP predicted immediate (AUC 0.86) and subsequent treatment intensification (AUC 0.81); CRP predicted immediate (AUC 0.81) and subsequent treatment intensification (AUC 0.55)
Lim *et al*[63]	Prospective cross-sectional	29 UC, 22 CD	BWT, BWS, vascularity, mesenteric fat, complications	FCP, CRP	Baseline	IUS parameters have good correlation with FCP ($r = 0.489$, $P < 0.01$) and CRP ($r = 0.604$, $P < 0.01$) significant
Maaser *et al*[28]	Prospective, multicentre	224 UC	BWT	FCP	Baseline, 2, 6, 12 wk	At 12 wk, 16% with increased BWT had FCP < 250 μg/g and 44.4% with normal BWT had FCP ≥ 250 μg/g
Sagami *et al*[57]	Single centre, prospective, cross-sectional	53 UC	BWT, CDS (rectum)	FCP	Baseline	BWT better than FCP (> 50 μg/g) for predicting histologic and endoscopic activity (MES > 1) in rectum by trans-perineal ultrasound; CDS not better than FCP
Sagami *et al*[78]	Prospective, single centre	100 UC	BWT, CDS (rectum)	FCP, CRP	Baseline 1, 8 wk	FCP and CRP were not independent predictors of remission at 8 wk; BWT and CDS were independent predictors of remission at 8 wk
Saleh *et al*[89]	Retrospective	39UC, 108 CD	BWT, BWS, CDS, mesenteric fat, complications	FCP, CRP	Baseline	54% of those with combined clinical and biochemical remission (ESR ≤ 40 mm/h and CRP ≤ 10 mg/L and FCP ≤ 50 μg/mg and fecal lactoferrin ≤ 30 μg/mL) had active IUS findings; 67% without combined remission had active IUS findings
de Voogd *et al*[2]	Prospective, single centre	16 UC, 22 CD	BWT, CDS, loss of haustration, bowel wall stratification, fatty wrapping	FCP	Baseline	Addition of FCP, decrease of FCP, or cutoff values for FCP did not improve the multivariate model (BWT, haustrations) to detect endoscopic remission, improvement, or response
St-Pierre *et al*[90]	Prospective, multicenter, observational cohort	18 UC, 123 CD	BWT, CDS	FCP	Baseline	Median FCP: IUS inactive inflammation: 50 μg/g, active inflammation 270 μg/g
Castellano *et al*[44]	Retrospective	44 pediatric IBD	CDS	FCP	Baseline	Median FCP low (median 92 μg/g) for low Doppler flow (≤ 2 /cm^2) and high (median 2286 μg/g) for high Doppler flow (≥ 3 /cm^2)

FCP: Fecal calprotectin; CDS: Color Doppler Signal; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn' disease; IUS: Intestinal ultrasound; BWT: Bowel wall thickness; NPV: Negative predictive value; CRP: C-reactive protein.

Table 8 Summary of studies evaluating correlation of colonoscopy and intestinal ultrasound in ulcerative colitis

Ref.	Study type	Number of patients	Treatment	IUS predictors	Colonoscopy score	Follow-up duration	Time points of IUS	Correlation with colonoscopy
Borthne *et al* [48]	Prospective	UC 4, CD 17 (pediatric)	NA	BWT, length, CDS, lymph nodes	-	Cross-sectional	Baseline	Sensitivity and diagnostic accuracy of IUS as compared to endoscopy: 93.3%
Bremner *et al* [49]	Prospective	12 UC (25 CD, 1 in determinate colitis, 6 normal	NA	BWT	Subjective assessment	Cross-sectional	Baseline	Colonic BWT > 2.9: Sensitivity for moderate/severe disease: 48%, specificity: 93%, PPV: 83%; ileal BWT > 2.5 mm: Sensitivity for moderate/severe disease: 75%, specificity: 92%, PPV: 88%
Chavannes *et al*[72]	Cross-sectional, single centre	33 children with suspected IBD (11 UC)	NA	Ileo-colonoscopy	UCEIS	Cross-sectional	Baseline	Colonic BWT > 1.9 mm: AUC: 0.743, sensitivity: 64%, specificity: 76% to detect inflamed bowel; agreement with colonoscopy: Prediction of IBD: 69.7%, kappa = 0.52; distribution of disease: 45.5%, kappa = 0.48
Haber *et al*[47]	Prospective	21 UC pediatrics (26 CD, controls)	NA	BWT, BWS, wall echo pattern	No, mild, severe	Cross-sectional	Baseline	AUC: 0.743, sensitivity: 64%, specificity: 76% to detect inflamed bowel
Parente *et al* [50]	Prospective	83 moderate to severe UC	High dose systemic steroids	BWT, CDS	Baron score	15 mo	Baseline, 3, 9, and 15 mo	Agreement with colonoscopy: Prediction of IBD: 69.7%, kappa = 0.52; distribution of disease: 45.5%, kappa = 0.48
Parente *et al* [51]	Prospective	83 moderate to severe UC	Same as above	BWT, CDS	Baron score	15 mo	Baseline, 3, 9, and 15 mo	Similar result as the study above
Yamada *et al* [62]	Prospective	26 UC	NA	SWE, SWD	UCEIS	Cross-sectional	-	SWE and UCEIS correlation: r = -0.404, P = 0.041. No significant correlation between SWD & UCEIS
Carter *et al*[53]	Retrospective	11 UC (167 CD)	NA	BWT, BWS, CDS, wall echogenicity, i-fat	NA	Cross-sectional	Baseline	Sensitivity 90%, specificity: 23% as compared to colonoscopy/MRE (combined CD and UC)
Antonelli *et al* [52]	Retrospective	51 moderate to severe UC	NA	BWT > 4 mm	Mayo score	Cross-sectional	-	BWT strongly correlated with CRP and endoscopic score
Allocca *et al* [16]	Prospective	53 UC	NA	BWT > 3 + CDS; BWT > 4.43 + no CDS	Mayo endoscopic score	Cross-sectional	Baseline	Sensitivity: 68%, specificity: 100%, accuracy: 83%, PPV: 100%, NPV: 73%
Kinoshita *et al* [54]	Prospective, multi centre (n = 5)	156 UC	NA	BWT, BWS, wall echogenicity	Matt's endoscopic classification	Cross-sectional	Baseline	Significant concordance between maximum grades (kappa = 0.47) and grades among all colonic segments (kappa = 0.55)
Luo *et al*[14]	Retrospective	50 UC, 50 CD, and 50 controls	NA	CDS	Active *vs* remission	Cross-sectional	Baseline	Higher Limberg's score in active disease (odds ratio: 26.325, P < 0.05)
Sathananthan	Prospective,	39 UC (35 CD)	5-ASA, immunomod-	BWT, CDS	MES	Cross-	Same day or	Same day colonoscopy (sensitivity 100%, specificity 100%, PPV 100%, NPV 100%,

et al[58]	single centre		ulator, biologics, steriods			sectional	within 30 d	kappa = 1); colonoscopy within 30 d (sensitivity 92%, specificity 86%, PPV 92%, NPV 86%, kappa = 0.77 (MES ≥ 1). Extent: Sensitivity 92%, specificity 80%, PPV 88%, NPV 86%, kappa = 0.7
Sagami *et al* [57]	Single centre, prospective, cross-sectional	53 UC	5-ASA, immunomodulators, budesonide, anti-TNF	BWT, BWS, CDS	MES	Cross-sectional	Baseline	BWT > 4 mm trans-perineal USG (sensitivity: 100%, specificity: 45.8%, AUC: 0.904) to predict MES, better than trans-abdominal ultrasound (sensitivity: 96.3%, specificity: 12.5%, AUC: 0.667). Correlation of MES with rectal BWT (trans-perineal US): BWT and MES: $r = 0.7204$, $P < 0.0001$; CDS and MES: $r = 0.6619$, $P < 0.0001$
Kamel *et al*[56]	Prospective	14 UC (26 CD)	NA	BWT, CDS, BWS, i-fat, lymph nodes, stricture, abscess	NA	Cross-sectional	Baseline	100% agreement between colonoscopy and IUS
Allocca *et al* [17]	Prospective	43 UC	Details not available	BWT, CDS	Mayo endoscopic score	Cross-sectional	Baseline	MUC > 6.2 discriminated active UC (sensitivity 85%, specificity 94%, AUC 0.902); MUC > 8.2 100% specific; FCP no incremental value
Zhang *et al*[59]	Retrospective	103 UC	NA	BWT, CDS	Mayo endoscopic score	Cross-sectional	Baseline	Prediction of endoscopic activity: BWT: Not significant; CDS: OR = 2.492, $P < 0.001$
Bots *et al*[23]	Prospective	60 UC	Conventional therapy, biologic, tofacitinib, topical tacrolimus	BWT, vascularity, haustrations, fat wrapping	Mayo endoscopic score, UCEIS	Cross-sectional	Baseline	UC-IUS score has strong correlation with endoscopic disease activity (ρ = 0.83 for Mayo score, ρ = 0.76 for UCEIS score); BWT > 2.1 for Mayo 0 *vs* Mayo 1-3: Sensitivity: 82.6%, specificity: 93%, AUC: 0.91. BWT > 3.2 for Mayo 0-1 *vs* Mayo 2-3: Sensitivity: 89.1%, specificity: 92.3%, AUC: 0.946. BWT > 3.9 mm for Mayo 3 *vs* others: Sensitivity: 80.6%, specificity: 84.1, AUC: 0.909
Allocca *et al* [18]	Prospective	98 UC	NA	BWT, CDS	MES	Cross-sectional	Baseline	Significant correlation between MES and MUC ($r = 0.653$)
Bots *et al*[23]	Retrospective, single center	65 UC (280 CD)	Biologics, conventional therapy	BWT, CDS, BWS, i-fat, haustrations, lymph nodes, motility	MES	Cross-sectional	Baseline	Agreement with endoscopy: 86.3%. Correlation: 0.70. Kappa agreement: 0.61 (both UC and CD)
Miyoshi *et al* [61]	Retrospective	24 UC (31 CD, 10 IBS)	NA	BWT, BWS, CDS, modified Limberg's score, SMI	MES	Cross-sectional	≤ 15 d between IUS and colonoscopy	BWT < 3.75 mm and SMI < 49.7: Sensitivity: 70%, specificity: 97.7%, PPV: 95.5%, NPV: 82.7%, accuracy: 86.5%
de Voogd *et al* [2]	Prospective	30 UC	Tofacitinib	BWT	MES and UCEIS	8 wk	Baseline and 8 wk	BWT correlated with MES and UCEIS. Cutoff values for BWT: (1) 2.8 mm for endoscopic remission (AUC: 0.87, 95%CI: 0.74-1.00, $P = 0.006$) (sensitivity 73%, specificity 100%); (2) 3.9 mm for improvement (AUC: 0.92, 95%CI: 0.82-1.00, $P < 0.0001$) (sensitivity 81%, specificity 100%); and (3) Decrease of 32% for response (AUC: 0.87, 95%CI: 0.74-1.00, $P = 0.002$) (sensitivity 71%, specificity 90%). Correlation: ΔBWT and ΔMES: 0.50, $P = 0.009$; ΔBWT and ΔUCEIS: 0.68, $P < 0.0001$ (sigmoid); ΔBWT and ΔMES: 0.67, $P = 0.001$; ΔBWT and ΔUCEIS: 0.50, $P = 0.02$ (descending colon)
van Wassenaer *et al*[64]	Prospective cross-sectional	35 UC (pediatric)	NA	UC-IUS score, Civitelli index	Mayo endoscopic score	Cross-sectional	Baseline	UC-IUS score better than Civitelli index for both sensitivity (88%-100% *vs* 65-80%) and specificity (84%-87% *vs* 89-93%) (MES ≥ 2). Higher AUC in ascending colon (0.82 *vs* 0.76) and transverse colon (0.88 *vs* 0.77). No difference in descending colon (both 0.84)
Goodsall *et al*	Prospective	29 UC	NA	BWT, CDS, BWS,	UCEIS	Cross-	Baseline	MUC had significant correlation with UCEIS ($r = 0.32$; 95%CI: 0.14-0.49; $P < 0.001$)

[4]				MUC		sectional		
Lim *et al*[63]	Prospective cross-sectional	29 UC (22CD)	NA	BWT, BWS, i-fat, CDS	UCEIS	Cross-sectional	Baseline	Sensitivity: 50%, specificity: 100%, PPV: 100%, NPV: 84%; 100% sensitivity/specificity in transverse colon; correlation with endoscopic activity index: 0.648 ($P < 0.01$)
Maeda *et al* [20]	Retrospective	58 UC	5-ASA, topical therapy, anti-TNF, vedolizumab	BWT, CDS, BWS, enlarged lymph nodes, MUC	MES	3 mo	Baseline, 3, 6, 12 mo	MUC and MES: 0.61 (entire colon). Most severely affected segment: BWT and MES: 0.88; CDS and MES: 0.98; MUC and MES: 0.88. Accuracy of MUC > 6.2 to differentiate MES ≥ 1 and 0 (sensitivity: 24%, specificity: 100%, PPV: 100%, NPV: 0.47, AUC: 0.67)
Rispo *et al*[22]	Prospective	86 UC	5-ASA, steroids, IMS, biologics	Milan ultrasound criteria	Mayo endoscopic score	Cross-sectional	-	HHIUS MUC > 6.2: Sensitivity: 80%, specificity: 88%, PPV: 83%, NPV: 86%, accuracy: 84%; highest in sigmoid colon; lowest in rectum

TNF: Tumor necrosis factor; BWT: Bowel wall thickness; CDS: Color Doppler signal; IUS: Intestinal ultrasound; IUS: Intestinal ultrasound; SWE: Shear wave elastography; HHIUS: Hand-held intestinal ultrasound; 5-ASA: 5-amino salicylic acid; UC: Ulcerative colitis; PPV: Positive predictive value; NPV: Negative predictive value; IMS: Immunosuppressant; MUC: Milan ultrasound score; MES: Mayo endoscopic score; BWS: Bowel wall stratification; UCEIS: Ulcerative colitis endoscopic activity index; i-fat: Inflammatory fat; CD: Crohn's disease; CI: Confidence interval; AUC: Area under the curve; SMI: Submucosal index.

Gastroenterologist- or sonologist-led IUS

A pilot study showed that point-of-care IUS performed by gastroenterologists after limited training (200 supervised scans) can accurately identify disease activity and the extent, and presence of complications based on paired MRE ($n = 42$) and colonoscopy ($n = 38$)[80]. The cut-off for achieving competence to detect IBD complications (advanced competence) was shown to be even lower ($n = 97$) in a recent study (even lower in those with experience in gastrointestinal ultrasound, approximately 70)[81]. Similarly, after an existing IUS training curriculum, healthcare physicians could perform IUS with comparable diagnostic accuracy (AUC: 0.71-0.81) as radiologists (0.67-0.79)[68]. A feasibility study of 79 cases of suspected or established IBD showed that the sensitivity values of IUS to detect bowel wall thickening, stricture, and mass were 90%, 94%, and 75%, respectively, where cross-sectional imaging or endoscopic examination was done within 3 mo of IUS[53]. The sensitivity and specificity to detect active disease can be as high as 88% and 93%, respectively, even in a low-volume, non-expert center[82]. However, there are barriers to physician sonographers leading IUS service in IBD which include an unmet need for training opportunities, preference for alternate imaging modalities, lack of adequate support from management, increased workload, and protectionist behavior from radiologists. A United Kingdom survey showed that 70% of physician sonographers were not confident in doing IUS in IBD although there was high interest[83].

IOA with IUS: A study assessing IOA among six expert sonographers conducting IUS in 30 UC patients (25 active, 5 quiescent) showed perfect, substantial, moderate, and fair agreement for BWT (kappa = 0.96), CDS (kappa = 0.63), lymph nodes (kappa = 0.41), and inflammatory fat (kappa = 0.36)/bowel wall stratification (kappa = 0.24)/loss of haustrations (kappa = 0.26). The agreement for IUS disease severity and activity was perfect (kappa = 0.93) and substantial (kappa = 0.77), respectively[15]. In a study comparing the correlation of IUS with colonoscopy in UC ($n = 53$), the IOA between two expert operators was 0.83[84]. Another prospective study showed the highest IOA for terminal ileal wall thickness and the highest agreement for wall thickness (0.882) [> mesenteric hyperechogenicity (0.841) > wall stratification (0.685) > vascularity (0.681) > lymphadenopathy (0.633)][85]. The agreement (kappa) for the overall IUS score was 0.749 in another study with two experts blinded to clinical details[86]. In a study on IUS including children with suspected or established IBD in which physician gastroenterologists and radiologists performed IUS, the IOA (kappa) for disease activity in the terminal ileum, transverse colon, and descending colon was 0.58, 0.49, and 0.52, respectively[68]. An interesting prospective study evaluated IOA for new ($n = 11$) and relapsing CD ($n = 27$). The agreement for small bowel diseases was

Table 9 Summary of studies comparing intestinal ultrasound and magnetic resonance enterography

Ref.	Study type	Number of patients	Follow-up duration	Comparator	IUS parameters	Gold standard	Results
Kamel *et al*[56]	Prospective	40 (14 UC, 26 CD)	Cross-sectional	Bowel ultrasound and MRE	BWT, CDS, mesenteric fat and lymph nodes, complications	MRE and colonoscopy	Accuracy of IUS (in IBD): 85% ileum, 70% large bowel, 100% correlation with MRI/colonoscopy with respect to active disease (in IBD) (no separate analysis for UC)
Ziech *et al* [8]	Prospective	28 suspected IBD pediatric	Cross-sectional	MR colonography	BWT, CDS, BWS, i-fat, haustrations, lymph nodes, motility	MR colonography	Sensitivity IUS: 55%; MR colonography: 57%; Specificity IUS: 100%; MR colonography: 75%; cannot effectively differentiate UC and CD unless terminal ileum is involved
Barber *et al*[71]	Retrospective	53 children	Cross-sectional	MRE	Scoring based on METRIC trial	Combined consensus score based imaging and clinical scores	Clinical correlation of IUS score (0.657) > MRE score (0.598). Agreement for IUS scoring: Lin coefficient 0.95 > MRE 0.60

CD: Crohn's disease; UC: Ulcerative colitis; MRE: Magnetic resonance enterography; CTE: Computed tomography enterography; TI: Terminal ileum; BWT: Bowel wall thickness; BWS: Bowel wall stratification; AUC: Area under the curve; IBUS-SAS: International bowel ultrasound segmental activity score; HR-US: High resolution ultrasound.

Table 10 Summary of studies correlating histology with intestinal ultrasound

Ref.	Study type	Number of patients	Treatment	IUS predictors	Histologic score	Correlation
Scholbach *et al*[66]	Single center, cross-sectional	12 pediatric UC	NA	Dynamic tissue perfusion measurement (DTPM)	No score Parameters: crypt abscess, neutrophils and lymphocytic invasion, wall edema	Wall perfusion on DTPM positively correlated with crypt abscess, neutrophils, and lymphocytic invasion. Negative correlation with wall edema
Romanini *et al*[42]	Prospective	18 UC, 15 CD	NS	Peak intensity, time to peak, regional blood volume and flow	Vascular density	High vascular density (CD 34+; > 265 vessels per high power field, 40 ×) correlated with IUS and CEUS (higher and earlier peak, higher blood flow and volume)
Kinoshita *et al*[54]	Prospective	156 UC	NS	BWT, CDI, BWS, wall echogenicity	Matt's histological grade (1-5)	$r = 0.35$, $P < 0.001$
Sagami *et al* [57]	Single center, prospective, cross-sectional	53 UC	5-ASA, immunomodulators, budesonide, anti-TNF	BWT, BWS	Robarts histopathology index and Nancy histological index	Only BWT independently predicted histological activity in rectum; BWT > 4 highest sensitivity (95.5%), specificity 41.6%, and AUC 0.869 to predict NHI >1; specificity (76.2%) higher and sensitivity (59.1%) lower with Limberg's score ≥ 2 (AUC: 0.812)
Goodsall *et al*[4]	Prospective	19 UC (29 paired data)	NS	Milan ultrasound criteria (MUC), BWT, CDI, BWS	NHI	Coefficient: 0.14, $P = 0.011$; MUC > 6.3 and/or FCP ≥ 100 μg/g for NHI > 1 sensitivity 88%, specificity 90%, PPV 95%, NPV 57%

PPV: Positive predictive value; NPV: Negative predictive value; UC: Ulcerative Colitis; CD: Crohn' disease; CDI: Color Doppler intensity; BWT: Bowel wall thickness; AUC: Area under the curve; NHI: Nancy histologic index; BWS: Bowel wall stratification; IUS: Intestinal ultrasound.

Table 11 Summary of studies on intestinal ultrasound in pediatric inflammatory bowel disease

Ref.	Study type	Number of patients	Follow-up duration	Gold standard	Comparator	Results
Borthne *et al*[48]	Prospective	43 children with suspected IBD	3 wk	Endoscopy	Endoscopy	Sensitivity and accuracy of IUS compared to endoscopy: 93.3%
Bremner *et al*[49]	Prospective	12 UC (25 CD, 1 indeterminate colitis, 6 normal)	Cross-sectional	ileo-colonoscopy	Ileo-colonoscopy	Colonic BWT > 2.9: Sensitivity for moderate/severe disease: 48%, specificity: 93%, PPV: 83%; ileal BWT > 2.5 mm: Sensitivity for moderate/severe disease: 75%, specificity: 92%, PPV: 88%
Haber *et al*[47]	Prospective	21 UC pediatrics (26 CD, controls)	Cross-sectional	Ileo-colonoscopy	Ileo-colonoscopy	Sensitivity and specificity of IUS as compared to endoscopy: 77% and 83%, respectively
Ziech *et al*[8]	Prospective	28 suspected IBD pediatrics	Cross-sectional	Ileocolonoscopy and endoscopy	MR colonography	Sensitivity IUS: 55%; MR colonography: 57%. Specificity IUS: 100%; MR colonography: 75%; cannot effectively differentiate UC and CD unless terminal ileum is involved
Barber *et al*[71]	Retrospective	53 children	Cross-sectional	Combined consensus score based imaging and clinical scores	MRE	Clinical correlation of IUS score (0.657) > MRE score (0.598); agreement for IUS scoring: Coefficient 0.95
Chavannes *et al* [72]	Cross-sectional, single centre	33 children with suspected IBD (1 UC)	Cross-sectional	Ileo-colonoscopy	Ileo-colonoscopy	Colonic BWT > 1.9 mm: AUC 0.743, sensitivity: 64%. specificity: 76% to detect inflamed bowel. Agreement with colonoscopy: Prediction of IBD: 69.7%, kappa = 0.52; distribution of disease: 45.5%, kappa = 0.48
Dell'Era *et al*[7]	Retrospective	113 suspected pediatric IBD	1 year	Ileo-colonoscopy and 1 year follow-up	Ileo-colonoscopy	IUS bowel pattern, mesenteric hypertrophy, and BWT > 3; all 3 sensitivity: 57.5%; specificity: 100%
Scarallo *et al*[35]	Single centre, retrospective	25 acute severe UC patients	Cross-sectional	NA	PUCAI > 45 at day 3; PUCAI > 65 day 5	At day 3 BWT > 3.4 mm and loss of BWS are independent predictors of steroid failure; BWT > 3.4 mm 92% sensitivity and 52% specificity for steroid resistance; PUCAI > 45 at day 3: 80.6% sensitivity and 45.5% specificity; PUCAI > 65 at day 5: 33.3% sensitivity and 90% specificity
van Wassenaer *et al*[68]	Prospective cross-sectional	22 UC	Cross-sectional	Ileo-colonoscopy	Physicians *vs* radiologists	Moderate inter-observer agreement for disease activity in terminal ileum (kappa = 0.58), descending colon (kappa = 0.52), and transverse colon (kappa = 0.49) between radiologists (AUC: 0.67-0.79) and gastroenterologists (AUC: 0.71-0.81)
Hudson *et al*[69]	Cross-sectional study	35 CD,15 UC,4 IBD	Cross-sectional	SES-CD, Mayo endoscopic score	MRE and endoscopy	High patient and caregiver satisfaction. Preferred over MRE and colonoscopy. No concern about IUS findings in those with co-existing anxiety
van Wassenaer *et al*[64]	Prospective cross-sectional	35 UC (pediatric)	Cross-sectional	Mayo endoscopic score	Endoscopy	UC-IUS score better than Civitelli index for both sensitivity (88-100% *vs* 65%-80%) and specificity (84%-87% *vs* 89%-93%) (MES ≥ 2); higher AUC in ascending colon (0.82 *vs* 0.76) and transverse colon (0.88 *vs* 0.77). No difference in descending colon (both 0.84)
Mohamed *et al* [74]	Prospective	40 IBD	Cross-sectional	Clinical and fecal calprotectin	Clinical activity	Combined gray scale ultrasound, color Doppler, and shear wave elastography increase accuracy (92%) with 100% accuracy
Otani *et al*[73]	Retrospective	40 UC	Cross-sectional	Colonoscopy and fecal calprotectin	Fecal calprotectin	Accuracy of sum of adjusted bowel wall thickness was higher than fecal calprotectin for detecting moderate colonic inflammation (Mayo endoscopic score 2)
Spyropoulou *et al* [70]	Prospective	32 UC	cross-sectional	Colonoscopy	Colon capsule endoscopy, fecal calprotectin	Sensitivity, specificity, PPV, and NPV of US are 85%, 92%, 94%, and 79%, respectively. Noninvasive approach combining CCE, FCP, and IUS better tolerated than colonoscopic monitoring

CD: Crohn's disease; UC: Ulcerative colitis; TI: Terminal ileum; IUS: Intestinal ultrasound; HRUS: High resolution ultrasound; MRI: Magnetic resonance imaging; MRE: Magnetic resonance enterography; BWT: Bowel wall thickness; PCD: Pediatric Crohn's disease; UC-IUS: Ulcerative colitis intestinal ultrasound score; PCDAI: Paediatric Crohn Disease Activity; CCE: Colon capsule endoscopy; FCP: Fecal calprotectin; AUC: Area under curve; IBD: Inflammatory bowel disease; PUCAI: Pediatric ulcerative colitis activity index, PPV: Positive predictive value; NPV: Negative predictive value.

substantial for both new (kappa = 0.64) diagnosis and relapsing (kappa = 0.63) cohort. Agreement for colonic disease in new and relapsed diseases was fair (kappa = 0.27) and moderate (kappa = 0.56), respectively[87].

So overall, IOA is substantial for several IUS parameters with the highest agreement for BWT which varies by region of the bowel involved. The agreement may be higher for colonic involvement in established disease over new diagnosis.

Point-of-care IUS and clinical decision-making: POCUS has been shown to influence real-time management of IBD in several studies, impacting management in 40%-60%of cases[86,88]. Clinically inactive disease can have activity detectable by IUS. The impact on management varied from escalation/de-escalation of therapy and making surgical decisions[60]. POCUS has moderate agreement with MRE and ileo-colonoscopy. POCUS has a good correlation with MRE and also colonoscopy in detecting the presence, extent, and complications of the disease in CD and UC (Table 13)[80].

Clinical decision-making based on IUS has been shown to effectively treat inflammation based on follow-up of the patients in a retrospective cohort study in the United States (108 CD; 39 UC, 14 active disease, 25 in remission)[89]. IUS plays an important role in therapeutic optimization. A prospective study including both UC and CD patients (89 UC, 28 CD) showed that BWT and CDS intensity independently predicted immediate therapeutic intensification whereas loss of bowel wall stratification along with BWT predicted subsequent therapeutic optimization[29]. A similar study during the COVID-19 pandemic (123 CD, 18 UC) showed that clinical assessment with IUS resulted in an acute management change in 57% of cases and avoiding/delaying colonoscopy in 85%[90].

Utility of IUS

Patient acceptability: Patient acceptability is one of the unique aspects of IUS. The acceptability of IUS, MRE, and colonoscopy was 99%, 88%, and 60%, respectively. However, patients emphasized that test accuracy is more important than discomfort[91]. Similarly, another international study with 37 participants revealed that noninvasive monitoring strategies like IUS were preferred although they were willing for invasive modalities like colonoscopy if warranted. They stressed the importance of patient involvement in shared decision-making[92]. For pediatric patients, both patients and caregivers preferred IUS over other modalities and found it more informative to understand their disease[69].

Cost-effectiveness: Although IUS seems to be cost-effective over other modalities of monitoring, it has not been studied extensively. A cost-effectiveness study performed in the United Kingdom showed that up to 55% of MREs and 28% of colonoscopies/sigmoidoscopies could be avoided by the introduction of IUS. The potential lesions to be missed were colonic polyps (n = 2) seen on colonoscopy and upper GI/extra-intestinal manifestations (EIM) in MRE. However, there was no upper GI involvement and the EIMs were of limited significance. The projected annual cost savings was £ 500000 [93]. As compared to MRE, the cost (5 times lower) and scheduling time (2 times shorter) for IUS are significantly lower based on a retrospective survey in the United Kingdom[94]. It is important to recognize that cost-effectiveness and billing strategies differ in several parts of the world.

Survey on widespread adoption of IUS: Three studies from the United Kingdom performed at different timelines have shown that IUS is increasingly being adopted but still, there is a need for expansion. In the first study published in 2014, IUS was performed only for younger patients (< 40 years) with low suspicion of CD in 44% of radiology departments[95].

Table 12 Summary of studies on transperianal ultrasound in ulcerative colitis

Ref.	Study type	Number of patients	Follow-up duration	Comparator	USG parameters	Results
Sagami *et al*[57]	Cross-sectional	55 UC	Cross-sectional	Endoscopy, Histopathology	BWT, CDS, BWS	BWT ≤ 4 MM predicts endoscopic healing (MES ≤ 1), AUC = 0.904. BWT ≤ 4 MM predicts rectal histologic mucosal healing, AUC = 0.869. Better than FCP
Sagami *et al*[78]	Prospective, single centre	100 UC	Cross-sectional	FCP, CRP	BWT, CDS	Rectal ΔBWT at 1 wk predicted remission at 8 wk (odds ratio for 1 mm increase is 1.9); FCP did not predict remission

MES: Mayo endoscopic score; UC: Ulcerative colitis; FCP: Fecal calprotectin; CRP: C- reactive protein; BWT: Bowel wall thickness; CDS: Color Doppler signal; AUC: Area under the curve; BWS: Bowel wall stratification.

Table 13 Summary of studies evaluating role of point-of-care ultrasound in inflammatory bowel disease

Ref.	Study type	Comparator	Follow-up duration	Number of patients	Impact on management
Bots *et al*[60]	Retrospective	MRI, colonoscopy	MRE within 8 wk of IUS	345 (280 CD and 65 UC)	POCUS changed management in 60%; change in medications 48%; correlation with IUS 86.3%; correlation with MRI 80%; reduced use of MRI with increased adoption of IUS
Sathananthan *et al*[58]	Prospective	Ileocolonoscopy	POCUS & ileocolonocscopy within 30 d of one another	74 (CD 35; UC 39)	Correlation with same day colonoscopy (sensitivity 100%, specificity 100%, PPV 100%, NPV 100%, kappa 1); correlation with colonoscopy within 30 d (sensitivity 92%, specificity 86%, PPV 92%, NPV 86%, kappa 0.77 (MES ≥ 1); extent: Sensitivity 92%, specificity 80%, PPV 88%, NPV 86%, kappa 0.7
Carter *et al*[53]	Retrospective	MRE	Cross-sectional	11 UC (167 CD)	Sensitivity 90%; specificity: 23% as compared to colonoscopy/MRE (combined CD and UC); impact on management not evaluated
de Voogd *et al*[2]	Prospective, single centre cohort	Clinical activity and FCP	Prospective, single centre cohort study	16 UC, 22 CD	Impact on management (56.25%); treatment escalation: *n* = 6 (UC); continue same treatment: *n* = 3 (UC)
Saleh *et al*[89]	Retrospective	Clinical (UCAI ≤ 5 and partial Mayo ≤ 2) and biomarker remission (ESR ≤ 40 mm/h and CRP ≤ 10 mg/L and fecal calprotectin ≤ 50 μg/mg and fecal lactoferrin ≤ 30 μg/mL)	Mean time between follow-up IUS 203 d	39 UC, 108 CD	25 active UC on IUS; change in plan: 13; continue therapy: 11; deescalate therapy: 1; 14 inactive UC; 80.7% continued therapy (overall IBD); 5.2% deescalated therapy; 14% change in therapy Treatment change more in those with higher BWT (≥ 5 mm, < 5 mm-> 3 mm, ≤ 3 mm); Treatment change did not differ by CDS (Limberg's score 0, 1, ≥ 2)
Lu *et al*[77]	Prospective, observational	Sigmoidoscopy, FCP, CTE/MRE	1 year	UC-16 (CD-46)	Change in management in 80% with IUS only (all IBD); Sigmoidoscopy + IUS 83% change in management

CD: Crohn's disease; MRE: Magnetic resonance enterography; IUS: Intestinal ultrasound; UC: Ulcerative colitis; MRI: Magnetic resonance imaging; BWT: Bowel wall thickness; POCUS: Point-of-care intestinal ultrasound; HHIUS: Hand-held intestinal ultrasound.

An Italian study showed that 24% of ultrasound referrals were for bowels with equal distribution of suspected and confirmed GI diseases[96]. A recent survey showed that 30% had IUS service (100% had MRI service) with a shorter average reporting time (1-4 wk) (MRI 4-6 wk)[97]. A survey of stakeholders (*n* = 14) identified perceived barriers and benefits of the implementation of IUS services (Table 14)[98]. A survey in Australia among 121 IBD patients showed that IUS was the preferred monitoring tool which improved IBD-specific knowledge[99]. In a Dutch retrospective cohort study, the use of POCUS increased over time for IBD monitoring along with the decline in the use of MRI[60].

DISCUSSION

The systematic scoping review highlights the role of IUS from diagnosis in suspected IBD/UC to monitoring and prediction tools in known UC. We have summarized the current evidence behind each indication of IUS and highlighted

Table 14 Summary of studies on implementation of intestinal ultrasound services

Ref.	Year	Country	Survey participants	Main results
Maconi *et al* [96]	2011	Italy	12 sonographers	24% of ultrasound referrals were for bowel ultrasound; 78% referred by gastroenterologists; half for suspected bowel disease and half for follow-up
Hafeez *et al* [95]	2014	United Kingdom	63 radiology and 73 gastroenterology departments	Barium meal follow through and CT preferred for luminal and extraluminal complications; IUS mainly for young patients with low suspicion of Crohn's disease; used in 44% of radiology departments
Rajagopalan *et al*[99]	2019	Australia	121 patients	IUS scored highest in the visual analogue scale as compared to colonoscopy, stool/blood sampling/imaging; IUS improved patient IBD specific knowledge of the need for medical therapy and disease extent
Radford *et al* [97]	2022	United Kingdom	103 IBD physicians	30% have IUS service (100% had MRI service); average time to reporting; USG (1-4 wk) (MRI: 4-6 wk); 59.6% confident in clinical decision-making using USG (MRI: 97%)
Radford *et al* [98]	2023	United Kingdom	14 stakeholders	Barriers to implement IUS service: (1) Reliance on existing imaging pathways; (2) Reluctance to change; (3) Perceived lack of precision; and (4) Initial financial and time outlay. Perceived benefits: (1) Reduced waiting time; (2) Earlier diagnosis and treatment allocation; (3) Reduced hospital appointments; and (4) Better understanding of disease

CT: Computed tomography; USG: Ultrasonography; IBD: Inflammatory bowel disease; MRI: Magnetic resonance imaging; IUS: Intestinal ultrasound.

the unmet needs and shortcomings of existing evidence.

Prospective studies indicate that IUS is a valuable diagnostic tool for suspected IBD and UC, particularly in patients with low-risk gastrointestinal symptoms where it helps to exclude irritable bowel syndrome. The sensitivity, specificity, PPV, and NPV of IUS in suspected IBD vary, with sensitivity ranging between 55%-85% and specificity between 95%-100%. Sensitivity is higher for diagnosing CD (84%) compared to UC (38%-66%), and higher for ileal (92%-96%) and left colonic lesions (81%-87%) compared to duodenal/jejunal (29%-33%) and rectal lesions (14%-15%). The loss of stratification among IUS parameters has the highest sensitivity (78.3%), and combining parameters improves diagnostic accuracy. Despite its promise, IUS has limitations, particularly in differentiating UC from its mimics, and more studies are needed to standardize its application, improve its sensitivity, especially in challenging anatomical areas, and validate its use in different clinical scenarios[1,3].

Assessing disease activity in IBD using IUS involves several parameters, with BWT and CDS intensity being the most reliable indicators according to an IOA study among expert sonographers[15]. Various scoring systems, such as the MUC and UC-IUS index, have been developed and validated to correlate IUS findings with endoscopic activity. The Milan criteria uses BWT and CDS to predict endoscopic activity with high accuracy, and its predictive value is enhanced when combined with FCP. MUC has shown efficacy in predicting adverse outcomes and endoscopic remission in UC patients. The UC-IUS index incorporates BWT, CDS intensity, lack of haustrations, and fat wrapping, demonstrating an excellent correlation with endoscopic scores and substantial inter- and intra-rater agreement[17]. IUS parameters with or without FCP can even predict histologic response[2,4]. The KUC, which use BWT and SMT, provide a high PPV for endoscopic improvement, highlighting the utility of IUS in non-invasive disease monitoring and management. Although several such scoring systems have been developed for UC and pediatric IBD, only a few are validated (*e.g.*, MUC) for treatment response and outcome prediction[4].

Monitoring therapeutic response and disease course in UC using IUS has demonstrated significant utility across various studies. The short-term goal of UC management focuses on clinical response, with intermediate and long-term goals targeting the normalization of biomarkers and mucosal healing, including histologic healing. Recent research, such as the TRUST UC study, confirmed that IUS parameters like BWT could predict clinical flare and treatment response, with normalization preceding clinical and biomarker improvements[28]. Prospective studies have reinforced the role of IUS in predicting treatment escalation and monitoring therapeutic responses over various timeframes. For instance, the IUS response to therapy can be detected as early as 2 wk even before clinical and biochemical response[28]. The timeline for assessing therapeutic response is drug-dependent, *i.e.*, response to Janus Kinase inhibitors and steroids can often be assessed by IUS within days; however, other medications would be recommended to be reassessed at a longer interval [33]. Additionally, IUS is a reliable surrogate for endoscopic outcomes, with specific criteria like the MUC effectively predicting disease severity, corticosteroid failure, and the need for colectomy. In acute severe UC, IUS parameters such as a > 20% reduction in BWT soon after initiating IV steroids were predictive of clinical response and the necessity for rescue therapy, underscoring the importance of IUS in acute settings[35]. Overall, IUS emerges as a valuable, non-invasive tool for monitoring disease activity, therapeutic response, and predicting long-term outcomes in UC. POCUS can alter the management of IBD in 40%-60% of cases although more data is required to support a "treat to target strategy" based on POCUS[86].

The correlation of IUS with other diagnostic modalities in UC demonstrates its potential as a comprehensive non-invasive tool for disease assessment. Several studies have highlighted the strong association between IUS parameters, such as BWT and CDS, with clinical indices, biomarkers like FCP and CRP, and histological activity. IUS correlates well with colonoscopy findings, with BWT showing consistent accuracy in reflecting endoscopic severity scores such as the MES and UCEIS. The MUC and UC-IUS scores further enhance the predictive capability of IUS, with studies indicating significant agreement with endoscopic assessments and histological grades[4]. IUS correlates well with ileo-colonoscopy except in the rectum. Trans-perineal and trans-vaginal ultrasound have shown promise in evaluating rectal involvement

in UC, offering high accuracy in predicting endoscopic and histological healing[57]. Additionally, IUS demonstrates comparability with MRE in evaluating large bowel inflammation, though differentiation between UC and CD remains challenging without ileal involvement[56]. The ability of IUS to monitor TH provides a valuable therapeutic target, supporting its integration into routine clinical practice for managing UC. Overall, these findings underscore the utility of IUS in providing a reliable, non-invasive alternative for comprehensive disease monitoring and therapeutic response evaluation in UC patients[32]. More evidence is required to conclusively prove that change in decision-making based on IUS improved clinical outcomes.

IUS is proving to be a versatile and effective tool in managing UC across special populations, including pediatric patients, pregnant women, and during the COVID-19 pandemic. In children, IUS offers a non-invasive alternative to colonoscopy and MRI, showing high accuracy in assessing disease location and severity with a favorable patient experience. Studies indicate that IUS can predict steroid responsiveness and provide valuable insights into disease activity and histological severity, often correlating well with biomarkers such as FCP. Pediatric IUS scores need to be validated further with age-specific cut-offs. For pregnant women, IUS serves as a safe, radiation-free method to monitor IBD, although its feasibility decreases in the third trimester as a gravid uterus can hinder the evaluation of the sigmoid colon and terminal ileum[75]. During the COVID-19 pandemic, IUS facilitated changes in clinical management and reduced the need for endoscopic procedures, highlighting its role in urgent care settings. These findings underscore the growing utility of IUS as a non-invasive, effective diagnostic and monitoring tool across diverse patient groups and clinical scenarios.

The utility of IUS in managing IBD/UC is multifaceted, with high patient acceptability, potential cost-effectiveness, and growing adoption in clinical practice. Patients overwhelmingly prefer IUS due to its non-invasive nature, despite valuing test accuracy over comfort, with pediatric patients and caregivers also favoring it for its informativeness[69]. Cost-effectiveness studies suggest significant savings by reducing the need for MRE and colonoscopies, although these findings need broader validation[93]. Surveys indicate that while IUS adoption is increasing, with shorter scheduling and reporting times compared to MRI, there remain barriers to its widespread implementation. Barriers to the implementation of gastroenterologist-led ultrasound were a lack of widespread training programs, increased workload, and protectionist behavior from the radiologist[83]. Hand-held IUS can help in the widespread dissemination of IUS and was shown to be as good as conventional IUS[22]. Studies underscore the necessity for patient involvement in decision-making, and research highlights a preference for IUS, reflecting its growing role in routine IBD monitoring and its capacity to enhance patient knowledge and reduce reliance on more invasive procedures.

CONCLUSION

IUS is an emerging, non-invasive, radiation-free, highly sensitive, and dynamic tool for monitoring UC. Current indications include diagnosis of IBD, assessment of disease activity/complications, and monitoring and prediction of therapeutic response or clinical outcomes in UC. IUS can predict endoscopic response and even histologic healing in UC. IUS parameters can predict response to biologics and small molecules as early as 2 wk. IUS has the potential to replace MRE and ileo-colonoscopy given its high accuracy, except for upper GI, jejunal, and rectal lesions, and surveillance of colitis-associated neoplasia. IUS is also helpful in special situations such as pregnancy and pediatric UC. IUS by trained gastroenterologists is as accurate as that by radiologists. POCUS alters management in a substantial number of patients although comparative studies with standard management for the “treat to target” strategy are lacking.

Future research should focus on the long-term outcomes of IUS-based management to establish its efficacy and sustainability in routine clinical practice. Comparative studies with traditional management strategies are necessary to confirm the benefits of IUS in a "treat to target" approach. Additionally, expanding research on IUS's effectiveness in detecting upper GI, jejunal, and rectal lesions, as well as its role in the surveillance of colitis-associated neoplasia, is essential. Investigating the integration of IUS into telemedicine and remote monitoring could also broaden its accessibility and utility. Ultimately, addressing the existing knowledge gaps and gray areas will solidify IUS's position as a cornerstone in the management of UC.

FOOTNOTES

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