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Role of Intestinal Ultrasound in Ulcerative Colitis: A Systematic Review

IUS in Ulcerative Colitis

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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

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

METHODS

99 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 ulcerative colitis (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 weeks). IUS correlates well with ileo-colonoscopy, 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, postoperative CD). Inter-observer agreement is acceptable and trained physicians have comparable diagnostic accuracy. Point of care ultrasound impacted management in 40-60%. Hand-held IUS (HHIUS) 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

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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 IBD physicians can

significantly influence clinical decisions, underscoring its potential for broader clinical adoption.

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 7,608 records between 1986 and April 2024 (PP and KP performed the search individually). We screened all the titles and abstracts including the full text of selected articles. Finally, 99 original research articles on IUS were included for scoping review excluding review articles/Letters to editors/editorial/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, Flow diagram). We summarized the evidence under each subheading based on the review of existing literature. In the areas where the literature was substantial, we represented it in a tabular form.

RESULTS

3.1 *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 USG probes used to diagnose IBD (table 1).[1, 3, 5, 6] Sensitivity was higher for the diagnosis of 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 82.6% sensitivity in a retrospective study of suspected pediatric IBD. The presence of all three parameters had 100% specificity and PPV.[7] the presence of any of the 3 parameters had 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 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]

3.1.2. 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 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), heterogenous 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]

3.2. *IUS in UC:*

3.2.1. Assessing disease activity:

Several IUS parameters are used to assess disease activity.[13, 14] Among them, the interclass correlation was perfect, substantial, moderate, and fair for bowel wall thickness (BWT), color Doppler signal (CDS) intensity, lymph node and mesenteric fat/Loss of haustrations/bowel wall stratification as shown in an inter-observer agreement study of 6 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.

3.2.2. 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 x BWT (mm) + 2x CDS (CDS = 1 if present, 0 if absent)] was highly predictive of endoscopic activity (Mayo Endoscopic score: MES ≥ 2) (sensitivity: 71%, specificity 100%, AUC: 0.891) with high inter-observer agreement (κ 0.86). The additional fecal calprotectin (FCP) increased sensitivity to

100%[16] In an external validation study (n = 43), MUC > 6.2 had 95% sensitivity and 94% specificity.[17] On 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 weeks (for UC on biologics) independently predicted endoscopic activity (MES ≤ 1) at 1 year (odds ratio: 5.8). A ≥ 2 reductions 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 fecal calprotectin ≥ 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 better 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]

3.2.3. UC-IUS index:

This index was developed based on a prospective study in which IUS and colonoscopy were done within 3 weeks (60 patients, 207 colonic segments). UC-IUS index (score 0-7) is based on BWT (score 1,2, 3 for > 2 mm, > 3 mm and > 4 mm respectively), CDS intensity (present: Score 1, stretches: Score 2), lack of haustrations (score 1, predict active disease) and fat wrapping (score 1, predict 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 respectively with excellent accuracy (area under the curve: 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 UCEIS (UC Endoscopic Index of Severity) (table 2) with substantial inter- and intra-rater agreement.[23]In the same study, a BWT > 2 mm and

fecal calprotectin (FCP)> 200 µg/g resulted in a sensitivity of 76.9% and specificity of 93.3% for detecting endoscopically active disease.[23]

3.2.4. Kyorin ultrasound criteria (KUC)/submucosal index (SMI):

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

3.3. ***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 (Dubbins *et al*, 1984) did not show any significant changes in BWT for UC treated with conventional therapy at 2-4 months as opposed to a significant reduction in CD (n = 19).[25] However, Maconi *et al* (1999) 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.[13] Further studies showed that early IUS response at 2-3 weeks (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 contrast-enhanced ultrasound (US) parameters, such as peak enhancement, and amplitude-dependent parameters with vedolizumab therapy at 14 weeks, 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 bowel wall thickness (BWT) in the descending/sigmoid colon which reduced significantly as early as 2 weeks preceding clinical and biomarker response. Normalization of BWT at 12 weeks 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 BWS) could predict immediate and subsequent treatment escalation over the next 6 months.[29]

A small (n = 31, 8 UC), retrospective study showed that a 16% improvement in BWT at 6 weeks and 10% improvement at 14 weeks predicted long-term treatment response at 46 weeks while 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 weeks of treatment intensification, transmural healing (TH) was achieved in 45-61% UC and transmural response (TR: ≥ 25% reduction or normalization of BWT) in 76% UC.[32]

More recently, IUS was shown to be a good surrogate marker for endoscopic response and remission in moderate to severe UC. In a study of 30 patients started on tofacitinib induction therapy were monitored using IUS, colonoscopy, and Robert's histological index (RHI) at baseline and after 8 weeks. BWT cutoffs of 2.8 mm and 3.9 mm had excellent accuracy (AUC > 0.85) for endoscopic remission (Mayo Endoscopic Score: 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 weeks can effectively rule out endoscopic activity at 1 year (negative predictive value 96%) in UC on biologic therapy. A 2-point decrease in MUC predicted eMS ≤ 1 with 89% sensitivity and 71% specificity.[19]A prospective study demonstrated

that BWT, CDS, and SMT predicted endoscopic parameters (improvement and remission) by 6 weeks. Hence IUS can be used as a surrogate marker for endoscopy. BWT reduced significantly at 2 weeks on infliximab and tofacitinib whereas it took longer time (6 weeks) for vedolizumab. After 8 weeks, there was no difference between the different agents regarding changes in BWT.[33]

3.3.1 IUS in acute severe ulcerative colitis

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 hours after IV steroid predicted clinical response (partial Mayo score decrease > 30%) and need for rescue therapy at day 7.[34] Similarly, a

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 Milan Ultrasound criteria (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]

3.3.2. IUS to detect appendiceal inflammation in UC

Regardless of the extent of UC, IUS findings of transverse appendicular diameter (TAD) ≥ 6 mm are seen in 43% 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 it might help to select patients who would benefit from an appendectomy. However, future validation is warranted by incorporating histologic findings in appendectomy specimens.

3.3.3. 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) (see table 4)[38-41] However, the clinical usefulness of such findings is currently questionable.

3.3.4. Contrast-enhanced ultrasound (CEUS)

Three studies (2 prospective and 1 retrospective) evaluated CEUS in UC/IBD. The retrospective study was discussed earlier (Zhang *et al* for differentiation of colonic cancer and IBD).[11] 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 (CD 34+).[42]

3.4. *Correlation of IUS with other modalities*

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

3.4.1. Correlation with biomarkers (*e.g.*, fecal calprotectin: FCP/CRP):

A recent retrospective study has shown that FCP and 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 (LRG) (> 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 a combination of fecal immunochemical testing (FIT > 100 ng/mL) and BWT > 2 mm predicted mucosal inflammation (MES > 0) with good accuracy (Area under the curve: FIT: 0.93, BWT: 0.84-0.97).[46]

3.4.2. IUS 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, includes 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 days.[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 significant correlation of 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 fecal calprotectin.[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 handheld IUS (dual probe 5-7.5 MHz) (V san, General Electric Co.) had 84% accuracy (highest sigmoid colon and lowest rectum).[22]

Shear wave elastography showed a significant negative correlation (-0.404) with UCEIS.[62] IUS scores after 3 months of high-dose steroids in severe UC also correlated with future risk of endoscopic activity at 15 months.[50, 51] In a recent study, the median FCP was lower in those with inactive IUS (dian 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 sigmoid (MES: 0.50, UCEIS: 0.68) and descending colon (MES: 0.67, UCEIS: 0.50).[2] Combination of BWT < 3.75 mm and submucosal index (submucosal thickness divided by BWT %) < 49.7 has 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 pseudo polyposis in a small series (n-12 both UC and CD) with high sensitivity (75%) and specificity (100%).[65]

3.4.3. IUS 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 7). The accuracy of IUS in large bowel was 70% with MRI as the gold standard with a 100% correlation for active disease.[56] In suspected pediatric IBD, sensitivity of IUS and MR colonography were similar (55% IUS, 57% MR) whereas IUS was more specific (100% *vs* 75% MR). Differentiation between UC and CD was not possible with either method except in cases where the terminal ileum was involved.[8]

3.4.4. IUS histologic correlation:

An earlier single-center, cross-sectional study showed that dynamic tissue perfusion in the inflamed intestine positively correlated with crypt abscess, neutrophil, 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 early 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] Milan ultrasound criteria (MUC) positively correlated with 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.[4] Rectal BWT > 4 mm on trans-perineal USG had 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]

3.5. IUS and transmural healing:

Transmural healing 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 transmural healing (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 3 definitions of TH. Transmural response (TR: ≥ 25%

reduction or normalization of BWT) was achieved in 76% of UC. Based on various definitions, TH was achieved in 45-61% of UC.[32]

3.6. *IUS in special populations*

3.6.1. 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 (CCE) 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, 7 studies 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, endoscopic (77% sensitivity, 83% specificity), and histologic severity (75% sensitivity and 82% specificity) of the disease.[47] The cut-off for 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 fecal calprotectin 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 ASUC as discussed earlier.[35] A combination of grayscale, color doppler, and shear wave ultrasound was shown to increase diagnostic accuracy (92%) with 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]

3.6.3. 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 including 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 fecal calprotectin (r = 0.73). IUS identified active disease with 84% sensitivity and 98% specificity. Treatment response was detected with 80% sensitivity and 92% specificity.[75] A case series (n = 5, UC post-ileal-pouch anal anastomosis: IPAA) has shown that fecal calprotectin and intestinal ultrasound can help detect inflammatory pouch complications in pregnancy after ileal-pouch anal anastomosis avoiding pouchoscopy.[76]

3.6.4. IUS in IBD management during COVID-19 pandemic:

Bedside IUS could lead to a change in clinical management in up to 80% of IBD patients with acute symptoms or suspected of IBD as shown in a prospective, observational study during the COVID-19 pandemic when access to endoscopic services was limited.[77] Another prospective, multi-center study showed the point of care IUS in urgent care pathway showed active disease in 65% 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.

3.6.5. Trans-perineal and transvaginal USG:

Trans-perineal ultrasound (TPUS) with micro convex 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 fecal calprotectin.[57] Moreover, a decrease in rectal wall thickness within 1 week assessed by TPUS predicted clinical remission at 8 weeks (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 (> 5mm) and modified Limberg score ≥ 1 predicted endoscopic activity with high accuracy (AUC: 0.968 and 1 respectively.[79]

3.7. *Gastroenterologist or sonologist led IUS*

A pilot study showed that point-of-care intestinal US performed by gastroenterologists after limited training (200 supervised scans) can accurately identify disease activity, extent, and presence of complications based on paired magnetic resonance enterography (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~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 or mass were 90%, 94%, and 75% respectively where cross-sectional imaging or endoscopic examination was done within 3 months 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% were not confident in doing IUS in IBD although there was high interest.[83]

3.7.1. Inter-observer agreement (IOA) with IUS:

A study assessing IOA among 6 expert sonographers conducting IUS in 30 UC patients (25 active, 5 quiescent) showed perfect, substantial, moderate, and fair agreement for BWT (k -0.96), CDS (k-0.63), lymph nodes (k-0.41) and inflammatory fat (k-0.36)/bowel wall stratification (k-0.24) /Loss of haustrations (k-0.26). The agreement for IUS disease severity and activity was perfect (k-0.93) and substantial (k-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) > was stratification (0.685)> vascularity (0.681)> lymphadenopathy (0.633)].[85] The agreement (k) for the overall lUS score was 0.749 in another study with 2 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 (k value) for disease activity in the terminal ileum, transverse colon and descending colon were 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 substantial for both new (k-0.64) diagnosis and relapsing (k-0.63) cohort. Agreement for colonic disease in new and relapsed diseases was fair (k-0.27) and moderate (k-0.56) respectively.[87]

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

3.7.2. Point of care intestinal ultrasound and clinical decision-making:

Point of care ultrasound (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 validation based on follow-up of the patients treated based on IUS in a retrospective cohort study in the United States (108 CD; 39 UC, 14 active diseases, 25 remissions).[89] IUS plays an important role in therapeutic optimization. A prospective study including both UC and CD (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 57% acute management change avoiding/delaying colonoscopy in 85%.[90]

3.8. *Utility of IUS*

3.8.1. Patient acceptability:

Patient acceptability is one of the unique aspects of IUS. The acceptability of IUS, MRE, and colonoscopy were 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]

3.8.2. 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 UK showed that up to 55% of MREs and 28% of colonoscopy/sigmoidoscopy 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.

3.8.3. Survey on widespread adoption of IUS:

Three studies from the United Kingdom (UK) 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] 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 weeks) (MRI 4-6 weeks).[97] A survey of stakeholders identified (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 the unmet needs and shortcomings of existing evidence.

Prospective studies indicate that intestinal ultrasound (IUS) is a valuable diagnostic tool for suspected inflammatory bowel disease (IBD) and ulcerative colitis (UC),

particularly in patients with low-risk gastrointestinal symptoms where it helps to exclude irritable bowel syndrome. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of IUS in suspected IBD vary, with sensitivity ranging between 55-85% and specificity between 95-100%. Sensitivity is higher for diagnosing Crohn's disease (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 inter-observer agreement study among expert sonographers.[15] Various scoring systems, such as the Milan Criteria (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 fecal calprotectin (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 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 Kyorin ultrasound criteria (KUC), which use BWT and submucosal thickness, provide a high positive predictive value 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 weeks even before clinical and biochemical response.[28] The timeline for assessing therapeutic response is drug-dependent, ie. 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 Milan Ultrasound Criteria (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% 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 C-reactive protein (CRP), and histological activity. IUS correlates well with colonoscopy findings, with BWT showing consistent accuracy in reflecting endoscopic severity scores such as the Mayo Endoscopic Score (MES) and the Ulcerative Colitis Endoscopic Index of Severity

(UCEIS). The Milan Ultrasound Criteria (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 Crohn's Disease (CD) remains challenging without ileal involvement.[56] The ability of IUS to monitor transmural healing (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 fecal calprotectin. 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, 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 weeks. IUS has the potential to replace MRE and ileo-colonoscopy given its high accuracy, except for upper GI, jejunal, 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 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.

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