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ORIGINAL ARTICLE

Utility of bowel ultrasound in assessing disease activity in Crohn's disease

Pradeep Kakkadasam Ramaswamy[1] · Kayal Vizhi N[1] · Amit Yelsangikar[1] · Anupama Nagar Krishnamurthy[1] · Vinay Bhat[2] · Naresh Bhat[1]

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Abstract

Background Gastrointestinal ultrasound (GIUS) has been used increasingly for monitoring inflammatory bowel disease (IBD) patients. The aim of this study was to assess the utility of GIUS in assessing disease activity in Crohn's disease (CD).

Methods Consecutive patients with CD (diagnosis established for at least 6 months) between July 2017 and July 2018 requiring assessment of disease activity were prospectively assessed by magnetic resonance enterography, colonoscopy (CS), and GIUS within a 2-week period and without any change in ongoing treatment. Features on GIUS which correlated with disease activity were assessed. Sensitivity and specificity of the GIUS in assessing disease activity and localization were calculated.

Results Thirty-five patients were enrolled in the study. Bowel wall thickness (BWT) ≥ 3 mm and Doppler activity ≥ 2 had the highest sensitivity (100% and 95.6%, respectively) for detecting active disease on CS. BWT ≥ 3 mm had sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 83.3%, 92%, and 100%, respectively for assessing active disease. Combination of median BWT, Doppler activity, and loss of bowel wall stratification correlated with simplified endoscopic score (SES) for CD ($r = 0.8$, p 0.009) and Harvey-Bradshaw index (HBI, $r = 0.76$, p 0.04). For localizing active disease in the ileum, GIUS had a sensitivity of 93.7%, 80% for lesions in the right colon, 100% for transverse colon, and 89% for the left colon. Specificity was 100% for ileal and colonic lesions.

Conclusion Loss of stratification, BWT, and Doppler activity in the bowel wall correlate with endoscopic and clinical disease activity in CD. GIUS is a sensitive modality in assessing disease activity in CD.

Keywords Biosimilars · Bowel ultrasound · Calprotectin · Crohn's disease · Crohn's disease activity index · Harvey Bradshaw score · Inflammatory bowel disease · Mucosal healing · Simplified endoscopic score

Introduction

Ileocolonoscopy is the gold standard for the assessment of disease activity in inflammatory bowel disease (IBD) patients, and several endoscopic scores have been developed and validated, which can be used to assess endoscopic disease activity [1–3]. However, in up to 15% of patients, ileal intubation is not achieved during colonoscopy (CS) [4]. Colonoscopy is a relatively invasive procedure associated with a risk of bowel perforation, it causes discomfort, and it is poorly tolerated by the patients [5, 6]. In up to 18% of patients with Crohn's disease (CD), colon and the terminal ileum may not be involved and hence may be missed on CS [7, 8]. Cross-sectional imaging modalities, such as computed tomographic enterography (CTE) and magnetic resonance enterography (MRE), are used to assess the small bowel and to determine complications like stenosis, fistulae, and abscesses [9–12]. However, these are expensive, time consuming, not readily available, and, especially CTE, not ideal for repeated use [11, 12]. Trans-abdominal gastrointestinal ultrasound (GIUS) or bowel ultrasound is a simple alternative imaging tool to assess the intestines and can be performed easily on patients in the out-patient clinic [13, 14]. GIUS is a rapid, non-invasive, inexpensive, safe, reproducible imaging modality. It

✉ Pradeep Kakkadasam Ramaswamy
drkrpradeep@gmail.com

[1] Department of Gastroenterology, Liver Diseases and Clinical Nutrition, Aster CMI Hospital, #43/2, International Airport Road, Sahakar Nagar, Bangalore 560 092, India

[2] Department of Surgery and Allied Sciences, Aster CMI Hospital, Bangalore 560 092, India

Bullet points of the study highlights

What is already known?

- Colonoscopy is gold standard for establishing active ileo-colonic Crohn's disease (CD).
- Magnetic resonance enterography computed tomographic enterography are most commonly used imaging modalities to assess disease activity in CD.

What is new in this study?

- Gastrointestinal ultrasound (GIUS) is accurate in determining disease extent and activity in CD, although assessment of the proximal small bowel and rectum are suboptimal.

What are the future clinical and research implications of the study findings?

- GIUS based scores for assessing disease activity in CD. GIUS may be useful for monitoring response to therapy in CD.

does not involve radiation, and a dynamic assessment of the bowel can be made; hence, it is a suitable modality for disease monitoring in IBD patients [14, 15]. GIUS has been used increasingly for monitoring IBD patients; however, there is limited availability of expertise in GIUS in India [13, 17]. There is no study from India so far assessing the utility of GIUS in IBD. The aim of this study was to assess the utility of GIUS in assessing disease activity in CD.

Methods

Consecutive patients with CD (diagnosis established for at least 6 months) between July 2017 and July 2018 requiring assessment of disease activity were prospectively assessed by MRE, CS, and GIUS within a 2-week period and without any change in ongoing treatment. Exclusion criteria were pregnancy, renal disease, known allergy to intravenous contrast or any contraindication to MRE, and patients who did not give consent. Patients underwent complete clinical assessment, and complete blood count (CBC), C-reactive protein (CRP), and a fecal calprotectin (FC) were monitored.

Endoscopic activity was scored by simplified endoscopic score for CD (SES-CD) [2] or by the Rutgeerts score (RS) [18] when appropriate. SES-CD score of ≥ 3 was defined as endoscopically active disease. The RS was used to assess postoperative recurrence, with a RS ≥ i2 defined as endoscopic recurrence. Colonoscopy was performed after standard bowel preparation by any one of the 4 endoscopists (NB, ANK, KVN, AY) with at least 5 years of experience, with a standard video endoscope (Olympus, Japan). Clinical disease activity was assessed by the Harvey-Bradshaw Index (HBI) [19], and a HBI of 5 or more was defined as active disease.

MRE interpretation was performed independently by two expert radiologists having more than 8 years of experience. In each segment, the following parameters were evaluated: wall thickening; wall enhancement after intravenous contrast, wall edema (hyperintensity in T2-weighted images), stricture with pre-stenotic dilation; fistula; and abscess. On MRE, intestinal wall thickening > 3 mm and hyperintensity of the involved intestinal segment on T2W images, stratified hyperenhancement of the intestinal wall, comb sign on gadolinium-enhanced T1W images, and diffusion restriction on diffusion-weighted imaging (DWI) were considered indicative of active disease. Patients were defined as having active disease if any one of the criteria was fulfilled (SES-CD ≥ 3, RS ≥ i2, or MRE showing active disease).

GIUS was performed using a Noblus ultrasound machine (Hitachi, Japan) with convex (1–5 MHz) and linear probes (3–7 MHz). Each GIUS was performed independently by a gastroenterologist (PKR) with 2 years of experience in GIUS, unaware of the results of other diagnostic procedures. Neither preparation nor intravenous contrast was used. The entire abdomen was systematically scanned, starting from the right iliac fossa. The following parameters were evaluated: bowel wall thickness (BWT), measured on the anterior wall of the bowel (or where it was better visible) in the longitudinal direction, avoiding haustrations and mucosal folds; measurement was taken from the interface between the mucosa and the lumen to the interface between the serosa and the muscularis propria layer. Bowel wall stratification was graded as present or absent. Doppler activity within the bowel wall was graded semi-quantitatively from 0 to 4 based on the Limberg scale [20]. Mesenteric fat (fatty wrapping) was considered abnormal if it covered more than half of the bowel circumference or thicker than 10 mm or was thicker than the normal bowel wall thickness. Peri-intestinal mesenteric fatty wrapping was

graded as present or absent. Strictures were defined as the presence of thickened and stiffened bowel wall with narrowing of the lumen (< 10 mm), with or without prestenotic dilatation. Fistulae were defined as hypoechoic duct-like structures with fluid or air content, communicating between two intestinal loops, or to other viscera or to the skin. Abscess was defined as an irregular, aperistaltic, hypoechoic area without vascularity and internal echoes indicating air within. Intestinal motility, presence of ascites, and enlarged mesenteric lymph nodes (short axis > 10 mm) were noted.

For the purpose of analysis and in order to be able to compare findings, the ileo-colonic tract visualized at MRE/GIUS was divided into five segments: ileum, right colon (cecum, ascending colon including ileo-cecal valve), transverse colon, left colon (descending and-sigmoid colon), and rectum. The findings in the rectum were excluded from the final analysis. All patients gave informed consent for this study and ethical clearance from the Institutional Review Board was obtained.

Statistical analysis

Descriptive statistics of the baseline data are presented as medians or as percentages when appropriate. Sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of bowel US were calculated with a 95% confidence interval (CI), using CS + MRE findings (together) as a reference standard. Bivariate correlation was calculated by Pearson's correlation coefficient.

Results

A total of 35 consecutive patients with proven CD were included in the study. The baseline characteristics and clinical data of the study population are shown in Table 1. Seventeen (48.5%) patients had only small intestinal involvement, 12 (34.3%) had ileo-colonic, and 6 (17.2%) colonic involvement only. As per the SES-CD or RS score, 12 patients (34%) were in remission, 7 (20%) had mild endoscopic activity, 6 (17%) had moderate endoscopic activity, and 10 (29%) had severe endoscopic activity. Three patients had undergone an ileo-cecal resection, and one had a RS of i0; one patient had a tight stricture in the transverse colon, and the third patient had active disease in the left colon. As per the HBI, eighteen (51%) patients were in remission, 6 (17%) had mild, 8 (23%) had moderate, and 3 (9%) had severe disease. Complete CS could not be achieved in one patient due to an impassable stricture in the transverse colon.

Median BWT was greater in patients with active disease as compared to those in endoscopic remission (6 mm vs. 2.45 mm, $p < 0.01$). BWT ≥ 3 mm correlated with SES-CD ($r = 0.455$, p 0.007) and HBI ($r = 0.506$, p 0.002). Loss of bowel wall stratification correlated with SES-CD ($r = 0.432$, p 0.011) and HBI ($r =$ 0.483, p 0.003). Doppler activity correlated with SES-CD ($r =$ 0.494, p 0.003) and HBI ($r = 0.656$, p 0.001) (Table 2). Bowel wall thickness of ≥ 3 mm and a Doppler activity ≥ 2 had the highest sensitivity (100% and 95.6%, respectively) for detecting active disease on CS (Table 3, Fig. 1). Disease extent as evaluated by GIUS significantly correlated with the disease extent assessment at MRE (r 0.791, $p < 0.0001$). The sensitivity, specificity, accuracy, PPV, and NPV of GIUS alone, compared with CS plus MRE for localizing active disease was calculated (Table 4). For ileal lesions, the sensitivity was 93.7%, 80% for lesions in the right colon, 100% for transverse colon, and 89% for lesions in the left colon. The specificity was 100% for ileal and colonic lesions.

Table 1 Characteristics of patients

	Remission ($n = 12$)	Active disease ($n = 23$)
M:F	5:7	14:9
Median age (years)	33	34
Location (%)		
L1	8 (66.7)	9 (39.1)
L2	2 (16.65)	4 (17.4)
L3	2 (16.65)	10 (54.5)
Disease behavior (%)	7 (58.3)	10 (43.4)
B1	5 (41.7)	11 (47.9)
B2	0	2 (8.7)
B3	5 (41.7)	11 (47.9)
Previous surgery (%)	6 (5)	5 (21.7)
Treatment currently receiving, *n* (%)		
Steroids	0	3 (13)
Immunosuppressants	11 (91.6)	17 (73.9)
Biologicals	6 (50)	3 (13)
Median HBI	1	6
Hb (g/dL)	12.85	11.9
Platelets (lacs/cu mm)	2.78	3.88
CRP (IU/mL)	3.5	12
Fecal calprotectin (mcg/g)	11.5	192
Bowel USG features		
Median BWT (mm)	2.45	6
Loss of stratification	3 (25%)	17 (74%)
Doppler activity ≥ 2	4 (33.3%)	22 (95.6%)
Fatty wrapping	3 (25%)	20 (87%)
Reduced motility	4 (33.3%)	11 (47.8%)

HBI Harvey-Bradshaw index, *CRP* C-reactive protein, *USG* ultrasonography, *M*: male, *F*: female, *Hb*: hemoglobin, *CRP*: C-reactive protein, *IU*: international unit, *USG*: ultrasound, *BWT*: bowel wall thickness

Table 2 Correlation of gastrointestinal ultrasound features to endoscopic and clinical disease activity scores

	SES-CD	HBI
BWT ≥ 3 mm	0.45 (p 0.007)	0.50 (p 0.002)
Loss of bowel wall stratification	0.43 (p 0.01)	0.483 (p 0.003)
Doppler activity ≥ 2	0.49 (p 0.003)	0.65 (p 0.001)
Combining all 3 features	0.8 (p 0.009)	0.76 (p 0.04)

SES-CD simple endoscopic score- Crohn's disease, *HBI* Harvey-Bradshaw index, *BWT* bowel wall thickness

Table 3 Gastrointestinal ultrasound parameters in assessing disease activity

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)	PLR (95% CI)	NLR (95% CI)
BWT ≥ 3 mm	100 (CI 85–100)	83.3 (51 to 97.9)	92 (76 to 97)	100	94.2 (80 to 99)	6	0
BWT ≥ 4 mm	100 (85 to 100)	91.67 (61.5 to 99.7)	95.8 (77.2 to 99.9)	100	97.1 (85 to 99.8)	12	0
Doppler activity ≥ 2	95.6 (78 to 99)	66.67 (35 to 90)	84.6 (71 to 92)	88.9 (53 to 98)	85.7 (69.7 to 95)	2.87	0.07
Loss of stratification	73.9 (51.5 to 89.7)	75 (42.8 to 94.5)	85 (67.3 to 93.9)	60 (41 to 76)	74.3 (56 to 87)	2.96	0.3
Fatty wrapping	86.9 (66.4 to 97.2)	75 (42.8 to 94.5)	86.9 (71 to 94.7)	75 (49.8 to 90)	82.8 (66.3 to 93.4)	3.48	0.17
Reduced motility	47.8 (26.8 to 69.4)	66.6 (35 to 90)	73.3 (52.2 to 87)	40 (27.5 to 53.8)	54.3 (36.6 to 71.1)	1.43	0.78

PPV positive predictive value, *NPV*, negative predictive value, *CI* confidence interval, *PLR* positive likelihood ratio, *NLR* negative likelihood ratio, *BWT* bowel wall thickness

Stricture was identified in 12 patients on MRE, of which GIUS was able to identify the stricture in 9 patients. The sensitivity and specificity of GIUS for assessing strictures were 75% and 100%, respectively. Two patients with ileal strictures and one with IC valve stricture were not identified by GIUS. One patient with an intra-abdominal abscess (Fig. 2) and 2 with enterocutaneous fistulae were accurately detected by GIUS. Three patients had jejunal involvement, and in all 3 cases GIUS was able to localize disease activity.

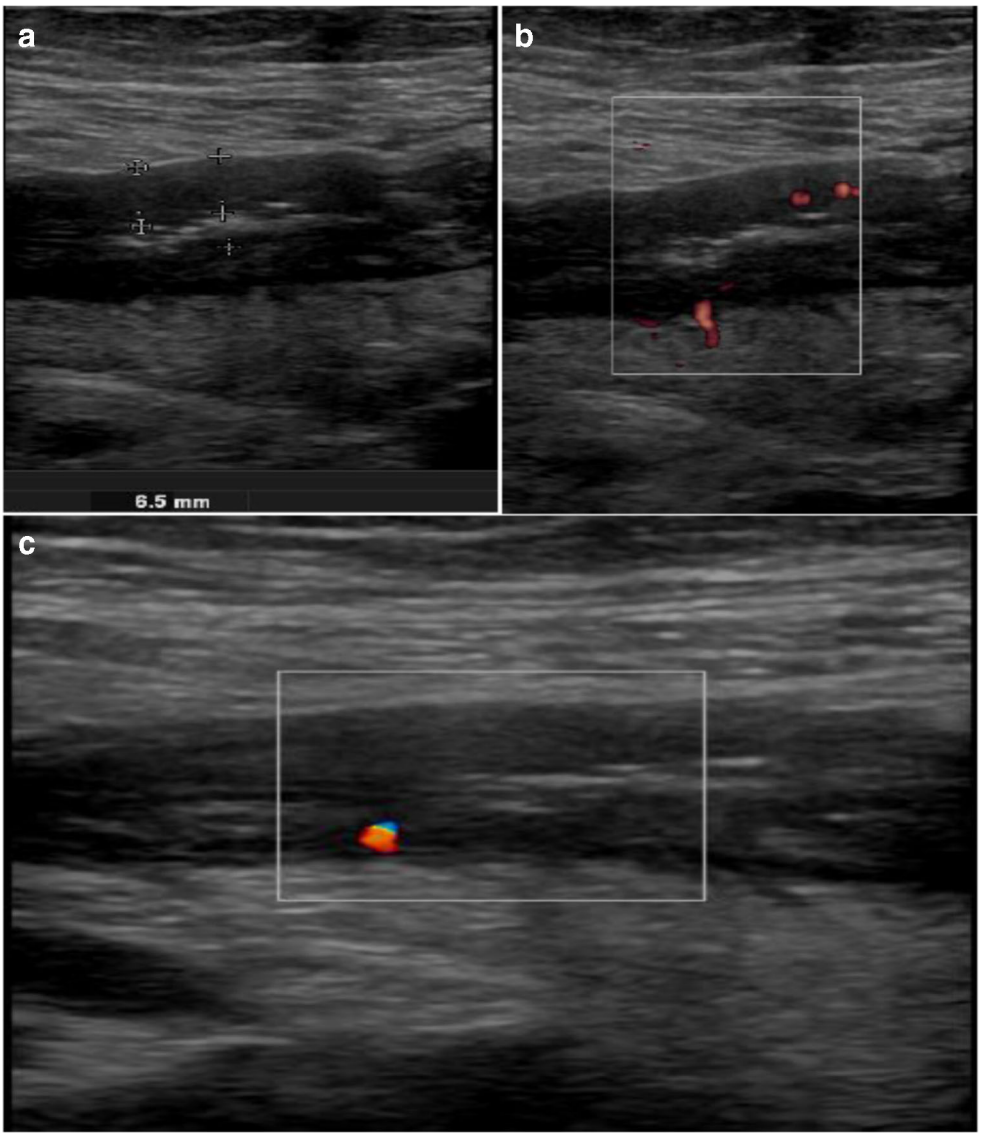

Fig. 1 **a** Thickened ileal loop with loss of bowel wall stratification and peri-intestinal fatty wrapping. **b**, **c** Thickened ileal loop with loss of bowel wall stratification and increased Doppler activity with peri-intestinal fatty wrapping

Table 4 Performance of gastrointestinal ultrasound compared with magnetic resonance enterography in combination with colonoscopy for localizing active disease

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
Ileum	93.75 (69 to 99)	100 (63 to 100)	100	88.9 (54.5 to 98)	95.8 (78.8 to 99.8)
Right colon	80 (44 to 97.5)	100 (78 to 100)	100	88.2 (68 to 96.2)	92 (74 to 99)
Transverse colon	100 (54 to 100)	100 (80 to 100)	100	100	100
Left colon	88.9 (51 to 99)	100 (66.4 to 100)	100	90	94.4 (72.7 to 99.8)

PPV positive predictive value, *NPV* negative predictive value, *CI* confidence interval

Discussion

In CD, current treatment strategies are aimed at mucosal healing, which is best assessed by CS [21]. However, CS assesses only the mucosal aspect and the extra-mural complications of the CD cannot be assessed. MRE is the current standard for assessing the small bowel and complications in CD, and it has been suggested that it may be used to supplement CS in assessing disease activity [11, 12]. Other biomarkers like fecal calprotectin and C-reactive protein have limited reliability in assessing CD activity [10, 22, 23]. This prospective study assessed the utility of GIUS in assessing disease activity in CD patients in comparison with standard clinical, endoscopic, or radiological criteria.

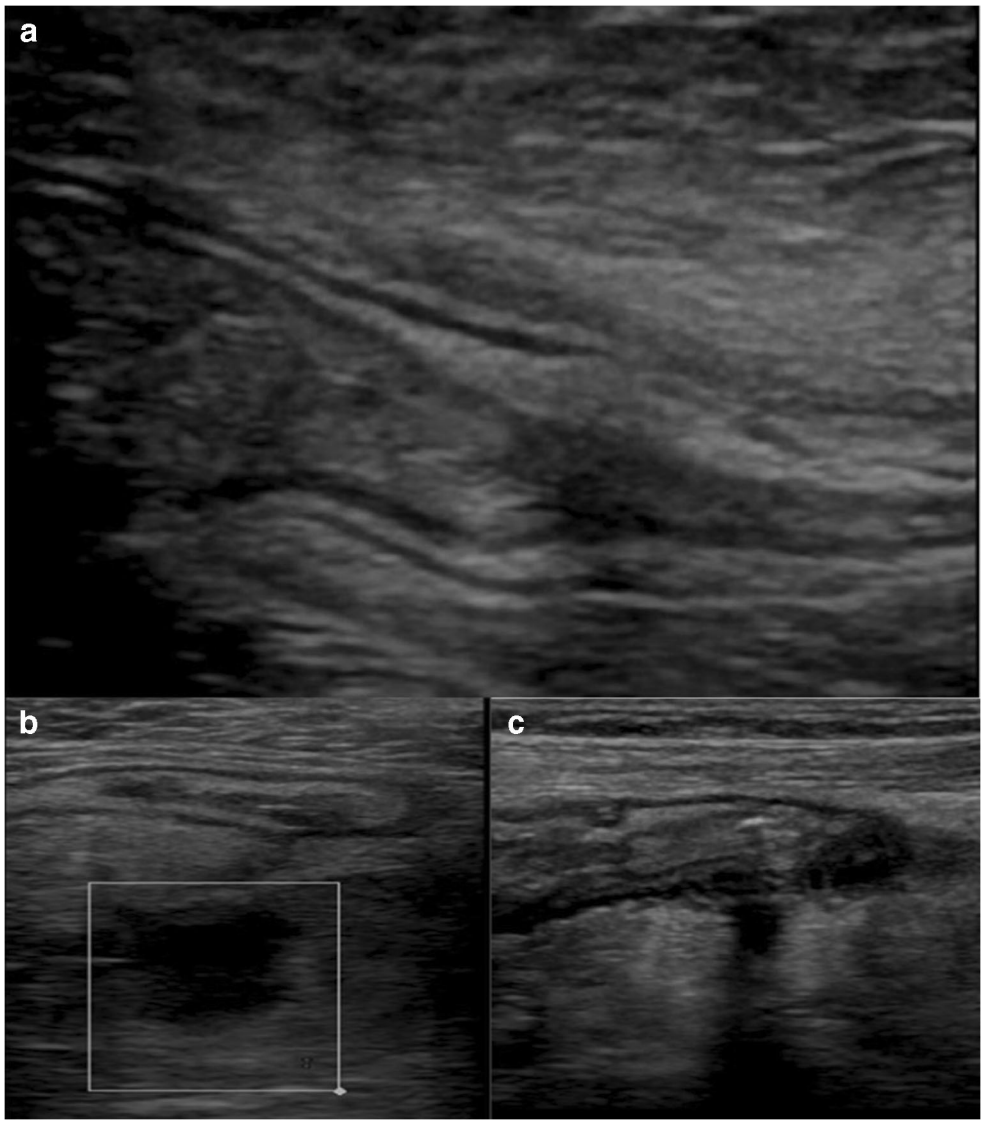

Fig. 2 **a** Fibrotic stricture with prestenotic dilatation of bowel. **b** Intra-abdominal abscess with thickened ileal loop. **c** Thickened colonic loop with fistulous tract

Bowel wall thickening has been shown to be the best indicator of inflammatory activity in CD [15]. A BWT of 3 mm has been shown to have 88% sensitivity and 93% specificity for diagnosing IBD [24]. When using a cut-off of 4 mm, the specificity increases by up to 97% [25]. This has been reproduced in this study, in which BWT of > 3 mm had a sensitivity and specificity of 100% and 83%, respectively, for detecting active CD; BWT of > 4 mm had a specificity of 91.6%. Increased bowel wall vascularity as indicated by increase Doppler signals correlates with endoscopic disease activity in CD [25, 26] and clinical disease activity [27]. In this study, increased Doppler signals had a sensitivity of 95% and specificity of 66.6% for detecting active CD. Persistence of increased vascularity after treatment has been shown to be a marker for increased risk of relapse [28]. Mesenteric fibrofatty proliferation ("creeping fat" or "fatty wrapping"), reduced bowel peristalsis, and loss of bowel stratification are other parameters on GIUS, which have been used to assess disease activity. Mesenteric fatty wrapping has a reported sensitivity and specificity of > 83% for detecting active CD, when compared with a CT scan [29]. It has also been shown that the mesenteric fat wrapping decreases in patients who have responded to treatment [29]. Absent or reduced peristalsis may be seen in involved segments of bowels; however, as it is a subjective parameter, it is not well standardized [15, 30]. Focal or extensive loss of bowel wall layers on GIUS suggests severe disease [15].

In a meta-analysis of fifteen studies involving 1558 patients, the overall pooled sensitivity for GIUS in detecting active CD was 88%, specificity was 97%, and the diagnostic odds ratio was 121.7, and the area under the curve was 0.94 indicating good diagnostic accuracy. In the same study, meta-regression and subgroup analysis showed that the disease location may be a major contributor to the heterogeneity of the results [31]. In CD, GIUS has the highest sensitivity for detecting active disease in the terminal ileum and the least sensitivity for proximal small bowel and the rectum. GIUS can identify active ileal CD with sensitivity of 92.7% and specificity of 88.2%, and colonic CD with 81.8% sensitivity and 95.3% specificity [24–26]. In our study, GIUS had a specificity of 100% for detecting ileal and colonic disease, whereas the sensitivity varied from 80% to 100%. In our study, disease extent as evaluated by GIUS significantly correlated with the disease extent assessment at MRE (r 0.791, $p < 0.0001$). This corroborates with data from other studies, in which the correlation between disease extent evaluated by GIUS and by radiological/surgical evaluations ranged from 0.49 to 0.83 [15]. GIUS is useful for the assessment of CD-related complications like strictures, fistulae, and abscesses. The pooled sensitivity for the detection of stenosis on GIUS is 79% and specificity is 92% [24]. The sensitivity for detecting stenoses in CD may be increased to 89% by using small intestinal contrast ultrasound (SICUS) [15, 24]. In our study, GIUS was able to identify stenosis in 9 out of 12 patients (75%). For the diagnosis of fistulae in CD, GIUS has been shown to have a sensitivity of 74% and specificity of 95% [24]. Intestinal abscesses can also be detected on GIUS, with sensitivity of 83% to 100% and specificity of 84% to 94% [24]. In our study, GIUS accurately diagnosed 2 patients with enterocutaneous fistula and one with an intra-abdominal abscess. In the postoperative setting, in CD, BWT > 3 mm on GIUS done 1 year after surgery has been shown to have a sensitivity of 77% to 81% and specificity of 86% to 95% for the detection of recurrence [16, 24]. In our study, 3 patients had undergone an ileo-colic resection and GIUS was able to accurately diagnose it in all the 3 patients.

Gastrointestinal ultrasound can be used routinely in the gastroenterology out-patient clinic in addition to history and physical examination. Dedicated training in bowel ultrasound is necessary and should be performed following training in general abdominal ultrasound [14, 15]. Three levels of training requirements have been defined [14]. On level 1, the operator should be able to recognize the small and large bowel and major focal intestinal abnormalities including obstruction. On level 2, the investigator should be able to perform a comprehensive examination of the GI tract: evaluation of the small bowel for focal or diffuse disease, the large bowel for the presence of diverticular disease and its complications (tumors and obstruction), the peritoneal cavity, mesentery and the omentum for the presence of infectious or malignant diseases. On level 3, the 3 practitioners should spend the majority of their time undertaking GIUS or teaching, research, and development and be an expert in this area. According to the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB), gastroenterologists should perform 5–10 examinations per week, reaching a minimum of 300 examinations before performing US unsupervised in practice and these examinations should be supervised by a level 2 practitioner (or a level 1 practitioner with at least 2 years of experience) [32].

The utility of GIUS in obese individuals can be limited; however, currently there is no cut-off body mass index (BMI) above which GIUS is not recommended. A thick abdominal wall with sub-cutaneous adipose tissue, presence of ascites, and intra-abdominal fat also interfere with the accuracy of GIUS. The sensitivity of GIUS in detecting active rectal disease and active proximal small bowel disease is low, and hence, in our study we have excluded GIUS of the rectum in the final analysis. Finally, there is no evidence of GIUS in detecting colitis-associated dysplasia and hence it cannot replace CS for cancer surveillance [14, 15, 24]. Our study is the first prospective study from India studying the utility of GIUS in IBD patients; only patients with an established diagnosis of CD on follow-up for at least 6 months

were included; all the patients underwent bowel US, CS, and/or MRE within 2 weeks without any change in treatment. All GIUS studies were performed by a single gastroenterologist with 2 years of experience in GIUS. The main limitation of the study is the small number of patients. This study is a preliminary experience, and we propose that GIUS can be used to assess disease activity in CD. GIUS is complementary to other imaging modalities such as MRE and CTE and also to endoscopy. GIUS performed by trained gastroenterologists performs equally to MRE, and in the absence of good quality MRE in resource-limited settings like India it can be a very useful tool. In conclusion, GIUS is accurate in localizing active disease in CD and may also be useful to assess the complications of CD. In the future, GIUS can be used to monitor disease activity and response to treatment replacing the need for biomarkers and expensive investigations like MRE. There is a need for larger studies from India and to develop GIUS-based scores for assessing disease activity and severity in CD.

Author contributions All authors contributed to the study conception and design. Concept, design of the study, manuscript writing: Pradeep Kakkadasam Ramaswamy, Naresh Bhat. Data acquisition, analysis, and interpretation: Amit Yelsangikar, Kayal Vizhi N, Anupama Nagar Krishnamurthy, Vinay Bhat. The first draft of the manuscript was written by Pradeep Kakkadasam Ramaswamy, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest PKR, KVN, AY, ANK, VB, and NB declare that they have no conflict of interest.

Ethics statement The study was performed conforming to the Helsinki declaration of 1975, as revised in 2000 and 2008 concerning human and animal rights, and the authors followed the policy concerning informed consent as shown on Springer.com.

All patients gave their informed consent for this study and Institutional Review Board ethical clearance was obtained.

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