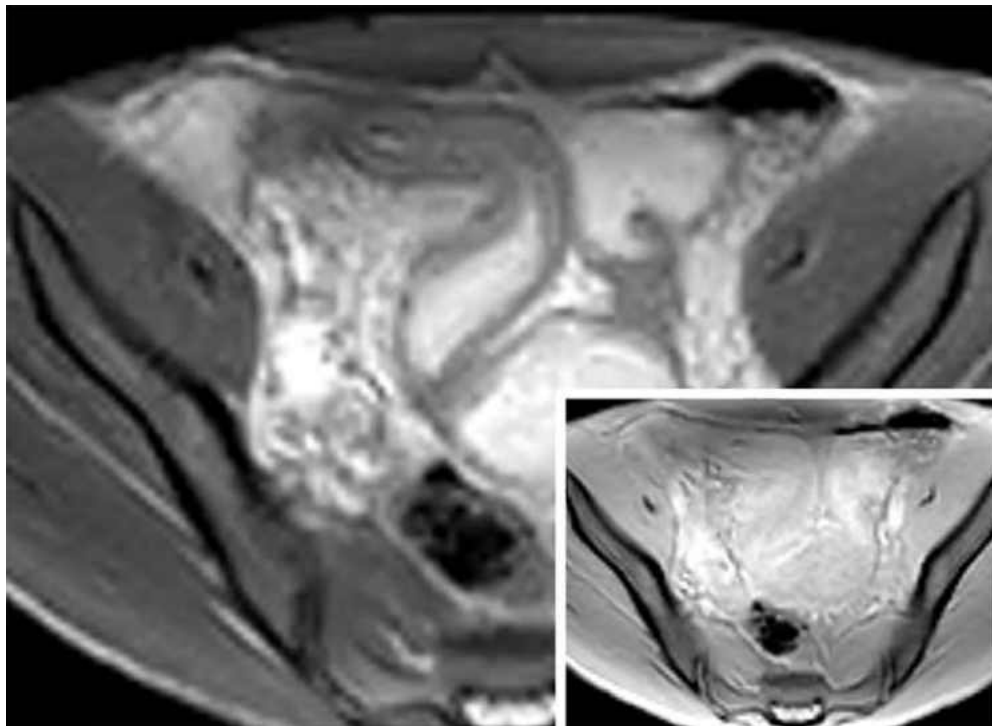


Crohn Disease Strictures: Multimodality Imaging to Identify Imaging Biomarkers

Safa Hoodeshenas, MD • Jonathan R. Dillman, MD, MSc • Stuart A. Taylor, MBBS • Jordi Rimola, MD, PhD • Bachir Taouli, MD, MHA
Kathryn A. Robinson, MD • Aiming Lu, PhD • David J. Bartlett, MD • David H. Bruining, MD • Catherine E. Hagen, MD • Ajit H. Goenka, MD
Shigao Chen, PhD • Florian Rieder, MD • Brian Feagan, MD • Mark E. Baker, MD • Joel G. Fletcher, MD

Author affiliations, funding, and conflicts of interest are listed at the end of this article.
See also the related articles by [Rieder and Ma et al](#) and [Rieder et al](#) in *Radiology*.



The morphologic imaging features of Crohn disease (CD) small bowel strictures have been defined by intersociety recommendations and expert panels. CD small bowel strictures result in penetrating and obstructing complications that often lead to surgery. Imaging biomarkers in fibrostenosing CD can be used to reproducibly diagnose and measure strictures and identify those at high risk for subsequent surgery. Emerging biomarkers seek to accurately and reproducibly identify and measure histopathologic correlates of fibrosis, inflammation, and smooth muscle hyperplasia or hypertrophy, as well as to reflect biomechanical properties such as stiffness. The authors review and define imaging features of small bowel strictures using routine MR and CT enterography, which should be incorporated into clinical reports to guide management decisions or to use in clinical trials. The most promising quantitative imaging biomarkers reflecting histopathologic composition of small bowel strictures are reviewed with a focus on MRI and US methods. Imaging is a critical tool for the management of patients with stricturing CD.

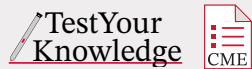
©RSNA, 2025 • radiographics.rsna.org

Introduction

Crohn disease (CD) is a transmural inflammatory bowel disease that can affect any location in the gastrointestinal tract. CD-related strictures are a particularly important complication of small bowel CD because their obstructive, penetrating, and other complications result in emergency room visits, hospitalizations, endoscopic intervention, surgery, cumulative bowel damage, and disability (1–3). Approximately 40% of patients with CD will develop strictures, and 80% ultimately will require

surgery (4). Reports indicate that 11% of patients diagnosed with CD had bowel strictures at the time of their initial diagnosis (5).

Imaging plays a critical role in the diagnosis, assessment, and monitoring of CD strictures. Strictures themselves often preclude endoscopic intubation and assessment of proximal inflammation, luminal narrowing, and proximal strictures, and endoscopic sampling can reach only the superficial bowel layers. Imaging, predominantly CT enterography (CTE) and MR enterography (MRE), but



RadioGraphics 2025; 45(11):e240226

<https://doi.org/10.1148/rg.240226>

Content Codes: GI, MR, US

Abbreviations: CD = Crohn disease, CONSTRUCT = Crohn's disease antifibrotic STRICTure Therapies, CTE = CT enterography, DWI = diffusion-weighted imaging, FAPI = fibroblast activation protein inhibitor, MaRIA = Magnetic Resonance Index of Activity Score, MRE = MR enterography, MT = magnetization transfer, SAR/AGA/SPR = Society of Abdominal Radiology, the American Gastroenterological Association, and the Society for Pediatric Radiology, STAR = Stenosis Therapy and Anti-Fibrotic Research Consortium.

TEACHING POINTS

- Multiple longitudinal retrospective studies have shown that maximum associated small bowel dilation, stricture length, and the development of new strictures are significantly associated with subsequent surgery in patients with fibrostenosing CD.
- A single stricture can be a single bowel segment with continuous luminal narrowing and bowel wall thickening, multiple narrowed segments connected by imaging findings of inflammation (eg, mesenteric border inflammation), or multiple narrowed segments separated by 3 cm or less.
- The histologic composition of strictures in CD tends to vary and encompasses differing combinations of inflammation, fibrosis, neuronal hyperplasia, and smooth muscle hyperplasia and hypertrophy.
- Multiple studies with well-defined histopathologic reference standards have demonstrated that MT-MRI using normalized MT ratios may distinguish nonfibrotic and mildly fibrotic strictures from strictures with greater degrees of fibrosis.
- Gallium-68 FAPI PET targets fibroblast activation protein, which acts as a biomarker for activated fibroblasts. Fibrostenotic lesions in CD have an increased fibroblast activation protein expression in intestinal myofibroblasts within the submucosa and smooth muscle layers.

also intestinal US, provide visualization of the perienteric mesentery, bowel wall deep to the mucosa, and penetrating and vascular complications.

Recent interdisciplinary consensus, including recommendations from the Society of Abdominal Radiology, the American Gastroenterological Association, and the Society for Pediatric Radiology (SAR/AGA/SPR) and an interdisciplinary expert panel, the Crohn's disease antifibrotic STRICTure Therapies (CONSTRUCT) group, has defined imaging features of CD small bowel strictures (6,7). Key features of both definitions include luminal narrowing, small bowel wall thickening, and associated proximal small bowel dilation of 3 cm or more (Fig 1). The consensus in terminology and identification of key diagnostic features has facilitated the use of imaging to more reliably identify and describe CD small bowel strictures in clinical practice (8,9). The Stenosis Therapy and Anti-Fibrotic Research (STAR) Consortium was established to provide clinical trial endpoints, including imaging, histopathologic analysis, and a patient reporting outcome tool, to facilitate the development and regulatory approval of drugs for fibrostenosing CD (10). Early prospective studies of these agents are underway now (11). Given these clinical and research advances in fibrostenosing CD, renewed attention is turning to imaging biomarkers for small bowel strictures (12).

Biomarkers describe characteristics that can be objectively, accurately, and reproducibly measured (quantitatively) or identified (qualitatively) and used as an indicator of normal biologic processes, disease processes, or response to pharmacologic therapies (13,14). Biomarkers in fibrostenosing CD can be classified in several ways. Existing biomarkers contribute to current clinical management and include diagnostic biomarkers and predictive (prognostic) biomarkers. Quantitative imaging biomarkers also can be categorized according to the histologic processes they reflect and the imaging modality used. This review aims to underscore the established CD biomarkers for clinical use and to critically evaluate promising biomarkers with potential for future application in clinical practice and clinical trials.

Existing CD Stricture Biomarkers

Current diagnostic and prognostic biomarkers of CD strictures are used in daily clinical practice and generally describe the morphology and inflammation associated with CD small bowel strictures.

Diagnostic Biomarkers

Diagnostic biomarkers establish or confirm stricture diagnosis and may be used to select a patient population for emerging clinical trials that examine the therapeutic efficacy of antifibrotic agents. Both the intersociety SAR/AGA/SPR consensus recommendations and CONSTRUCT criteria are used to diagnose CD small bowel strictures at CTE or MRE in clinical and research settings, and both currently require luminal narrowing, bowel wall thickening, and an associated small bowel dilation threshold of at least 3 cm (Fig 1, Table 1). Important differences between criteria highlight the weaknesses of each definition. The SAR/AGA/SPR consensus recommendations do not consider endoscopic findings (eg, inability of an endoscope to traverse a stricture). The CONSTRUCT group criteria do not address persistent regions of small bowel luminal narrowing and wall thickening that show luminal dilation below the threshold 3-cm criteria, even when segmental narrowing and wall thickening are persistent on multiple examinations or timepoints (termed *probable strictures* in the SAR/AGA/SPR recommendations). Persistent luminal narrowing on CTE or MRE images is the most sensitive imaging marker for strictures (15). It is anticipated that, over time, these discrepancies will be resolved, with these definitions incorporating both cross-sectional imaging and endoscopic criteria. The threshold for maximum associated small bowel dilation may be reduced if reliability is preserved, and lower thresholds still identify patients with stricture-related complications. In clinical trials of antifibrotic agents, these imaging criteria are, or will be, combined with other requirements, such as presence of patient symptoms, absence of penetrating complications, and location of strictures at specific locations (eg, within 15 cm of the ileocecal valve or anastomosis), which can be verified or interrogated with endoscopic examination.

Prognostic Biomarkers

Prognostic biomarkers predict the likelihood of a clinical event, such as surgical resection or strictureplasty, disease recurrence

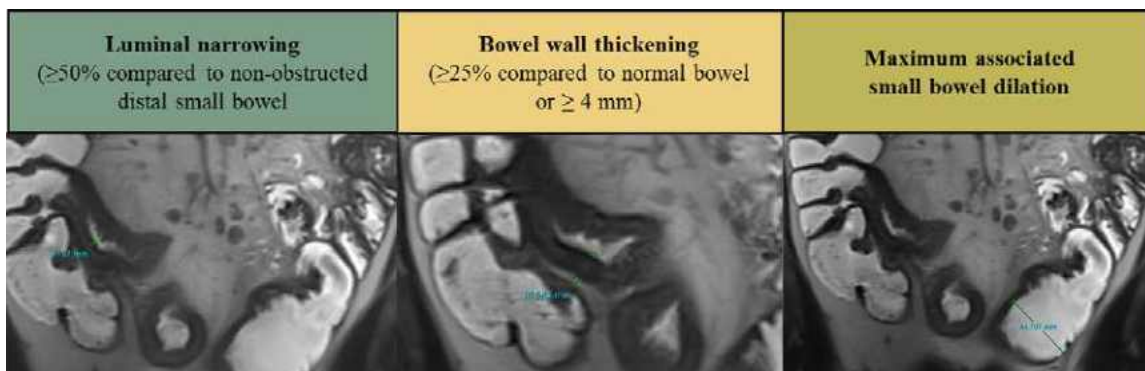


Figure 1. Strictures, by definition, require bowel luminal narrowing, bowel wall thickening, and maximum associated small bowel dilation of 3 cm or greater using either SAR/AGA/SPR or CONSTRUCT criteria. CONSTRUCT criteria additionally require the metrics listed in parentheses.

Table 1: SAR/AGA/SPR and CONSTRUCT Imaging Criteria for CD Small Bowel Strictures

Group Name	Definition
SAR/AGA/SPR	Luminal narrowing in area of CD with unequivocal upstream dilation of ≥ 3 cm Probable stricture: multiple pulse sequences, fluoroscopic observation, or serial imaging demonstrates fixed narrowing without unequivocal upstream dilation*
CONSTRUCT	Bowel wall thickening ($\geq 25\%$ increase in wall thickness) Localized luminal narrowing (luminal diameter reduction of $\geq 50\%$) Prestricture dilation (>3 cm) OR Inability to pass an adult or pediatric colonoscope (any size patient) [†]

* Unique only to the SAR/AGA/SPR definition.

[†] Unique only to the CONSTRUCT definition.

(eg, stricture recurrence), or progression in patients diagnosed with the disease (eg, development of penetrating complications, bowel obstruction requiring hospitalization) (14). Multiple longitudinal retrospective studies have shown that maximum associated small bowel dilation, stricture length, and the development of new strictures are significantly associated with subsequent surgery in patients with fibrostenosing CD (1,3,16–22). Table 2 summarizes imaging features that have been found to be associated with surgery and near-term surgery (ie, within 2 years). The primary contributions of CTE in terms of biomarkers are the prognostic morphologic assessments of stricture length, associated small bowel dilation, and identification of chronic mesenteric vein thrombosis and new strictures. The authors are not aware of other CTE biomarkers identified by multiple institutions in various CD populations. Nevertheless, these imaging features, which also can be identified at MRE and sometimes US, are strong predictors of subsequent surgery. In one meta-analysis of over 600 patients with strictures who underwent endoscopic dilation, a stricture length of 5 cm or less was associated with a surgery-free outcome, but every

1-cm increase of stricture length increased the hazard of need for surgery by 8% (hazard ratio, 1.04 [95% CI: 1.01, 1.07]) (18).

Identifying, Measuring, and Reporting Using Biomarkers

There are practical obstacles to implementing current diagnostic and prognostic biomarkers into clinical practice—principally, the lack of guidance in how key imaging features of strictures like stricture length and proximal (or maximal associated) small bowel dilation should be measured, and the way in which other key imaging features can be described.

The STAR consortium recently systematically established imaging definitions and conventions, which were used by three panels of radiologists in evaluating two populations of symptomatic CD patients with MRE and a third population with CTE (23,24). Symptomatic patients had a terminal ileal stricture at CTE or MRE using CONSTRUCT criteria and had no penetrating complications other than a blind-ending sinus tract. According to these authors, a single stricture can be a single bowel segment with continuous luminal narrowing and bowel wall thickening, multiple narrowed segments connected by imaging findings of inflammation (eg, mesenteric border inflammation), or multiple narrowed segments separated by 3 cm or less (Fig 2). Their rationale for this decision reflects the amount of bowel at risk for surgical resection in the setting of fibrostenosing CD because bowel segments with multiple areas of luminal narrowing adjacent to each other or connected by inflammation would be included in a single resection. Maximum associated small bowel dilation was measured orthogonal to the luminal axis of the bowel either proximal to or within a stricture by using the maximum dilation in any plane, including when the dilated bowel loop is oval and not round (Fig 3). Measurements were taken from the mid-bowel wall to the opposite mid-bowel wall. Using these methods, the interrater intraclass correlation coefficient for stricture length was 0.85–0.91 using MRE, and 0.64 at CTE. Similarly, the interrater intraclass correlation coefficient for maximum associated small bowel dilation was 0.73–0.74 at MRE and 0.80 at CTE. Table 3 lists these and other selected imaging features at MRE and CTE that demonstrated at least moderate reliability, which likely have clinical utility, along with the STAR operational definitions. Unlike prior studies

Table 2: Studies Highlighting the Imaging Features of Small Bowel CD Strictures Associated with Surgery and Near-Term Surgery

Feature	Reference Number(s)
Stricture length	1, 3, 18, 19, 21
Maximum small bowel dilation	19–21
Penetrating complications	3, 19, 20
New strictures at subsequent imaging	3
Luminal narrowing	17
Ratio of dilation to narrowing	16
Simplified MaRIA Score*	16, 17
Chronic mesenteric vein thrombosis	22 [†]

Note.—Except for the Simplified Magnetic Resonance Index of Activity (MaRIA) Score, these imaging features can be identified at both CTE and MRE.

* The Simplified MaRIA Score requires evaluation of the following: small bowel wall thickening greater than 3 mm, intramural edema, fat stranding, and luminal ulcerations.

[†] Cohort study that demonstrated that chronic mesenteric vein thrombosis is associated with subsequent stricture development and surgery, so the time interval to development of stricture and surgery is not within the 2-year time frame.

describing active inflammatory small bowel inflammation, luminal ulcerations in small bowel strictures were detected with only moderate reproducibility at CTE but not detected reliably at MRE (23,24).

Strengths, Weaknesses, and Use of Biomarkers

Although there are limited reproducibility data on using the formalized intersociety SAR/AGA/SPR or CONSTRICT definitions for a CD small bowel stricture and differences between CTE and MRE, these conventions are used routinely now in clinical practice and research. Given what is known about the weaknesses of using a specified threshold for small bowel dilation, it makes sense to implement the intersociety SAR/AGA/SPR definition of a probable stricture when persistent luminal narrowing is seen with multiple MRE sequences or across imaging timepoints, especially if associated with dilation of small bowel loops. Certainly, the CONSTRICT criteria use of endoscopic information can be incorporated readily into reports by simply correlating imaging findings with endoscopic findings (eg, “the terminal ileal stricture, which prohibited endoscopic passage...”).

Prior intersociety SAR/AGA/SPR recommendations for interpretation of CTE and MRE images have specified that when a small bowel stricture is present, radiologists should mention not only stricture location (including proximity to any enteric anastomosis) and the presence of any penetrating complications but also stricture length, associated bowel dilation, and imaging findings of inflammation. Radiology practices should consider implementing the operationalized STAR definitions for how to reproducibly describe these parameters. The requirement for reproducibility simplifies what is reported for specific features (eg, restricted diffusion is present or absent, not the pattern within the bowel

wall). Because the STAR definition incorporates strictures with multiple regions of luminal narrowing, it reduces the number of strictures that need to be described. In the STAR experience, over 95% of patients had only a single stricture that extended to within 15 cm of the ileocecal valve or ileocolonic anastomosis. Table 4 summarizes these practical recommendations for incorporation of diagnostic and prognostic biomarkers into clinical imaging practice.

In the future, multiple imaging features may be combined to form a single stricture score, which could be reproducible, as well as responsive to change for novel and efficacious CD stricture therapies (eg, similar to the Magnetic Resonance Index of Activity [MaRIA] or London Score for CD-related active small bowel inflammation) (25). Inflammation severity scores at MRE generally have been incorporated into research studies but not into clinical practice. However, they do identify the imaging features, which radiologists reproducibly identify, and this information can be used by radiologists and societies in deciding which imaging findings to report. In the future, the development of semiautomated tools is anticipated, in clinical trials and hopefully in clinical practice. This will reduce interobserver variability in identifying and measuring small bowel strictures.

Histopathologic and Physiologic Targets for Imaging Biomarkers

CD is a chronic inflammatory disorder characterized by a pattern of relapsing inflammation, with tissue damage initiating tissue reparative responses that overwhelm normal regulatory mechanisms. This disruption of normal regulatory mechanisms leads to a cascade of events that results in increased collagen-rich extracellular matrix, smooth muscle hypertrophy and hyperplasia, and ultimately, fibrosis.

The histologic composition of strictures in CD tends to vary and encompasses differing combinations of inflammation, fibrosis, neuronal hyperplasia, and smooth muscle hyperplasia and hypertrophy (Fig 4). *Smooth muscle hyperplasia* generally refers to smooth muscle in the muscularis mucosa or submucosa, and *smooth muscle hypertrophy* refers to marked thickening of the muscularis propria layer in the bowel wall (26). These factors lead to the pathologic thickening of all layers of the bowel wall, luminal narrowing, and ultimately, obstruction (27).

Accurate assessment of the burden of fibrosis, inflammation, smooth muscle hypertrophy and hyperplasia, and other components within small bowel strictures is crucial to the development of new therapies and likely beneficial for patient management. Because no standardized histopathologic method to describe Crohn strictures has been validated for use in clinical practice or trials (28,29), biomarker studies reflecting histopathologic targets use different grading schemes and quantitation methods to demonstrate the relationship of imaging features to fibrosis, muscular hypertrophy and hyperplasia, and stiffness.

Fibrosis

Fibrosis is characterized by the excessive production of extracellular matrix, including collagen, and triggered by the

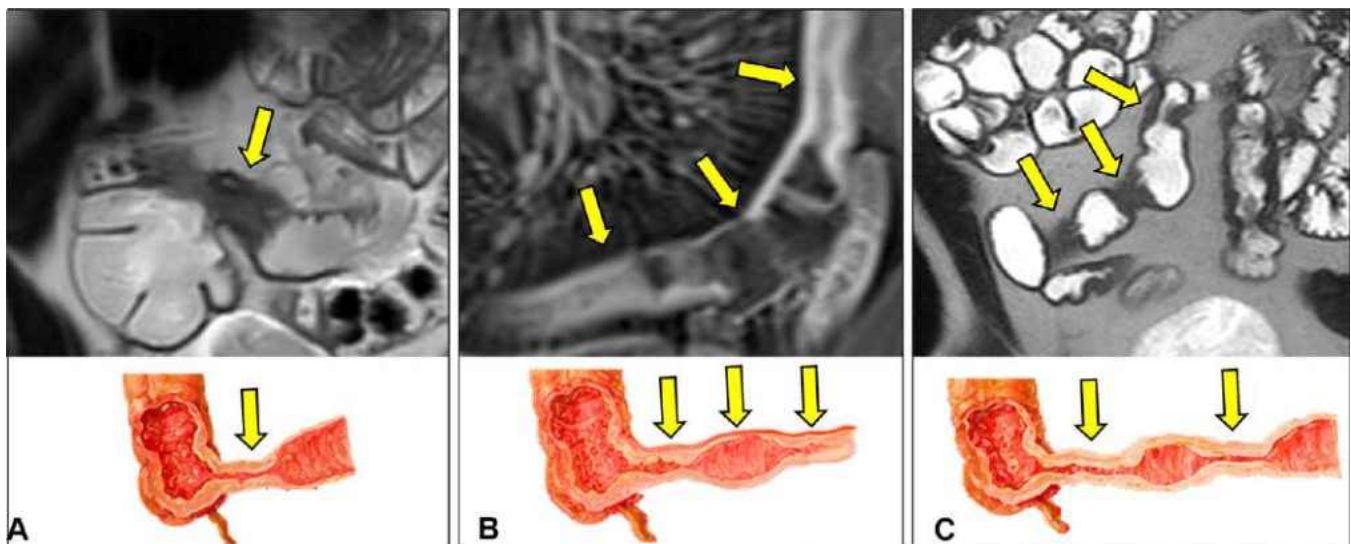


Figure 2. STAR Consortium definition of a single stricture. **(A)** Coronal MR image and illustration show a single bowel segment with continuous luminal narrowing and bowel wall thickening (arrows). **(B)** Coronal MR image and illustration show multiple narrowed segments linked by imaging findings of inflammation, such as mesenteric border inflammation (arrows). **(C)** Coronal MR image and illustration show multiple narrowed segments (arrows) separated by 3 cm or less.

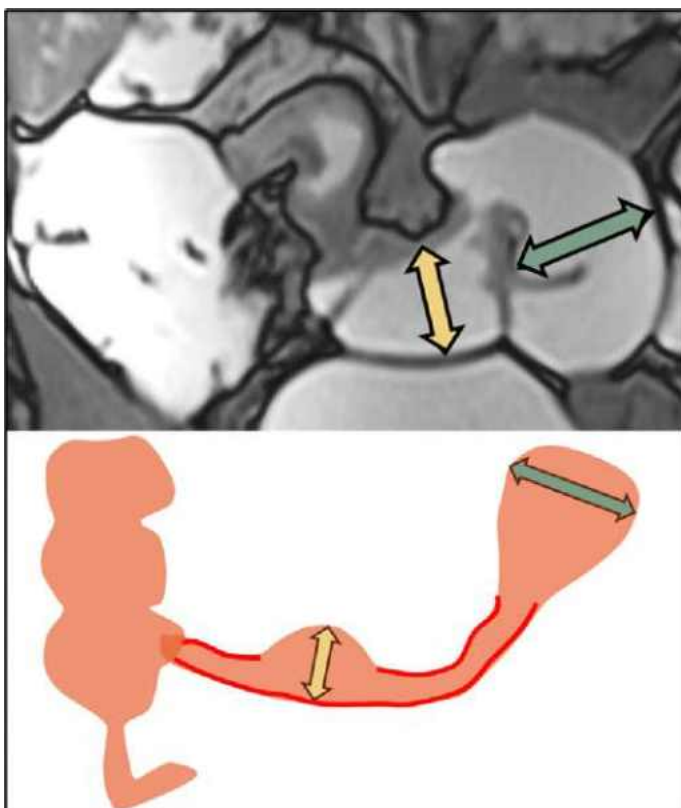


Figure 3. Measurement of maximum associated small bowel dilation. Coronal MR image and illustration show that maximum dilation is measured perpendicular to the center line or axis of the small bowel, from the midpoint of one bowel wall to the midpoint of the opposite bowel wall (as shown). Some strictures may exhibit multiple areas of severe narrowing within the stricture itself. Therefore, the maximum associated small bowel dilation might be found within the stricture (yellow double-headed arrows) rather than proximal to it (green double-headed arrows). In such cases, the larger dilation should be measured.

release of cytokines, growth factors, and other inflammatory products, which activate, proliferate, and differentiate cells involved in synthesizing the extracellular matrix. Myofibroblasts play a central role in this process, and various cell types, including epithelial, endothelial, stellate cells, fibroblasts, and bone marrow stem cells can differentiate into myofibroblasts, which contributes to the overproduction of extracellular matrix (30,31). In patients with CD, these factors and mechanisms ultimately lead to the pathologic thickening of all layers of the intestinal wall, from the mucosa and muscularis mucosa to the muscularis propria (27). Fibrosis can be described by the depth and location of fibrosis within the bowel wall (32).

Muscle Hypertrophy and Hyperplasia

Strictures in many patients with CD primarily result from smooth muscle hyperplasia in the submucosa and hypertrophy of the muscularis propria rather than fibrosis (26,33). Using quantitative histopathologic measurements of smooth muscle and collagen, Wagner et al (34) demonstrated that bowel wall thickness, MaRIA and Clermont scores, and fistulas were associated with ileal segments in which smooth muscle hypertrophy was predominant over fibrosis.

Stiffness

Chronic inflammation, increased smooth muscle hypertrophy and hyperplasia, and fibrosis are primary factors influencing mechanical remodeling induced by injuries to the bowel wall. Muscular hyperplasia, hypertrophy, and fibrosis increase the bowel wall stiffness with subsequent decreased reduced deformability and motility (35–38). Moreover, the biomechanical characteristics of the cellular environment significantly impact fibroblast behavior. For example, augmented rigidity prompts fibroblasts within the human colon to adopt a fibrogenic phenotype. These characteristics may perpetuate intestinal fibrosis independent of inflammation,

Table 3: Imaging Features That Demonstrated at Least Moderate Reliability in Studies by the STAR Consortium

Imaging Feature	Interrater ICC	STAR Definition
Measurement		
Stricture length	MRE: 0.85, 0.91 CTE: 0.64	Single stricture defined as a single segment with continuous luminal narrowing and bowel wall thickening, multiple areas of luminal narrowing connected by active inflammation, or multiple areas with luminal narrowing ≤ 3 cm apart; measured from the most proximal to the most distal region of luminal narrowing
Maximal associated small bowel dilation	MRE: 0.74, 0.73 CTE: 0.80	Maximum diameter of small bowel proximal to or within a stricture with multiple areas of luminal narrowing; measured orthogonal to the luminal axis
Maximal stricture wall thickness within stricture	MRE: 0.58, 0.57 CTE: 0.50	Select thickest region; report average of three measurements (in mm)
Observation		
Mural hyperenhancement	MRE: 0.44 CTE: 0.46	Rated as mild (greater than normal bowel), moderate (less than vascular structures), or severe (approaches vascular structures)
Sacculation along the antimesenteric border	MRE: 0.46 CTE: 0.56	Rated as present or absent
MRE only: restricted diffusion	0.48, 0.48	Rated as present or absent; pattern of signal within bowel wall (eg, stratified) is not described
MRE only: intramural T2 signal intensity on fat-suppressed images	0.40	Rated as absent (similar to normal bowel), mild (minor increase; dark gray similar to skeletal muscle), moderate (light gray similar to liver or spleen), or severe (nearly similar to luminal content)
MRE only: pattern of enhancement on delayed 7-min images	0.48, 0.44	Rated as homogeneous or not homogeneous (ie, layered)
CTE only: ulceration	0.43	Focal depression or irregularity in inner surface of thickened intestinal wall; linear enhancing tracts within bowel wall should be considered fissures (linear ulcers); measured as absent or present
CTE only: perienteric fat stranding	0.51	Loss of normal sharp interface between bowel wall and mesentery, with edema and/or fluid and/or enhancement in perienteric fat; measured as absent or present

Sources.—References 23, 24.

Note.—Two interrater intraclass correlation coefficients (ICCs) are reported for MRE imaging features to reflect values reported in two populations and radiologist reader panels. *Moderate reliability* is defined as ICC greater than 0.41.

Table 4: Imaging Features of Biomarkers to Incorporate into Clinical Reports

Biomarker	Rationale
Stricture length	Longer lengths increase risk of surgery; lengths <5 cm can be endoscopically dilated
New penetrating complications	Associated with increased surgical risk within 2 years; treatment with biologic and antibiotic therapy can heal enteroenteric fistulas in some patients
New strictures (on serial imaging examinations)	Associated with increased surgical risk within 2 years
Imaging findings reflecting more severe inflammation*	Reflects increased enteric inflammation, which may be treated to decrease obstructive symptoms
Stricture associated with enteric anastomosis	Potentially associated with increased surgical risk; potential for superimposed ischemia
Maximum associated small bowel dilation	Reproducible, but not always associated with near-term surgery; decrease may reflect response with therapy

* Severe inflammation is reflected by diffusion restriction, mural ulcerations, mural edema on T2-weighted images, increased wall thickness, increased Doppler US signal or increased flow with microvessel imaging with US.

which contributes to the intractable nature of CD-associated fibrosis (38). The role of fat-wrapping and cumulative bowel damage in stiffness is in the early stages of investigation (33,39).

Quantitative Modality-based Imaging Biomarkers

Quantitative biomarkers in CD strictures generally reflect underlying histopathologic processes or targets, such as fibrosis

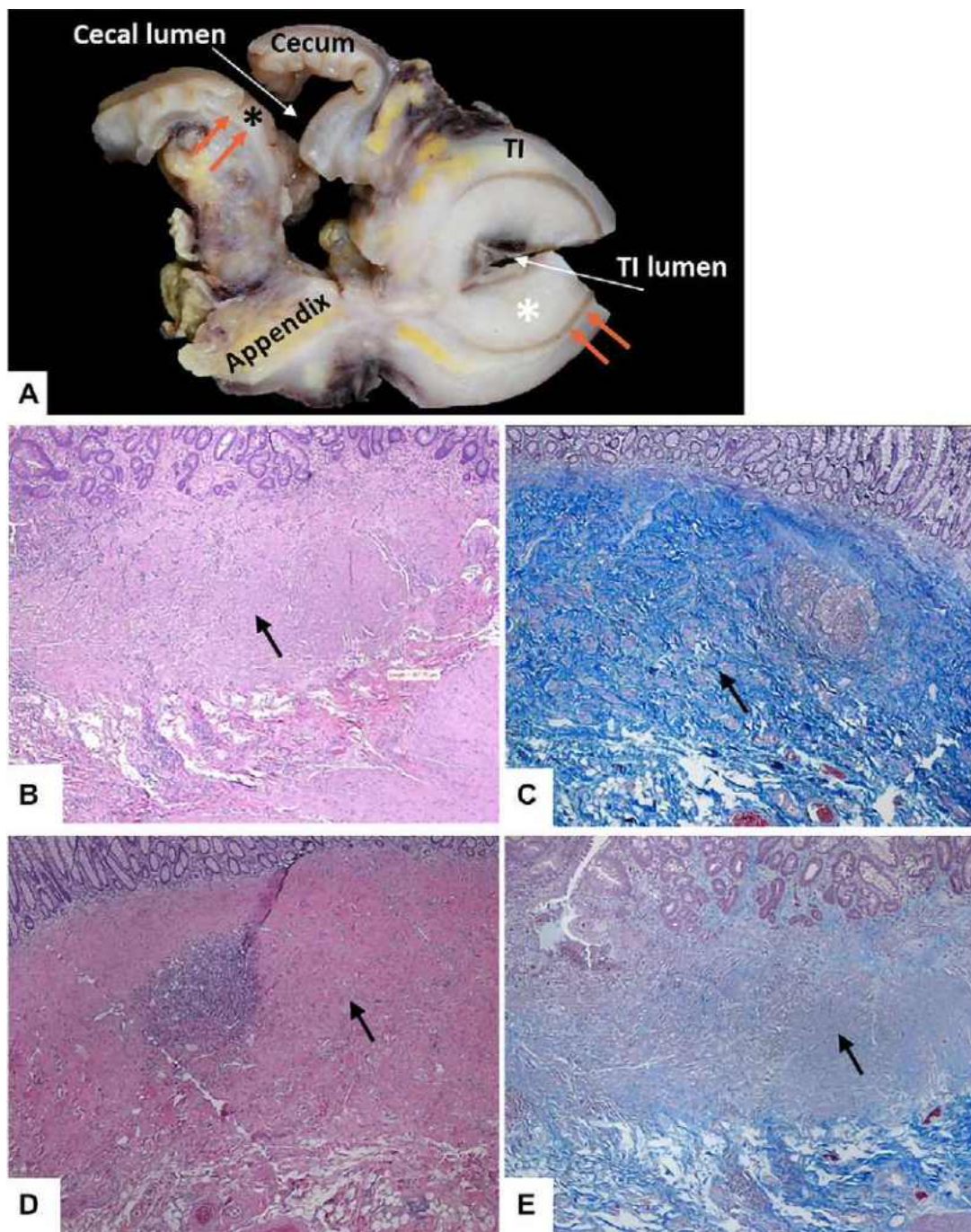


Figure 4. Manifestation of CD strictures in different patients. **(A)** Photograph of the gross specimen shows the submucosa (black *) and the dual layers of the muscularis propria (orange arrows) within the cecum. Conversely, in the terminal ileum (TI), the submucosa (white *) appears considerably thickened and is situated between the lumen (white arrows) and the muscularis propria. **(B, C)** Photomicrographs in a different patient show wall thickening attributed predominantly to submucosal fibrosis (arrow in **B**). (Hematoxylin-eosin [H-E] stain; original magnification, $\times 4$.) This is indicated by the royal blue collagen staining with the trichrome stain (**C**). (Masson trichrome stain; original magnification, $\times 4$.) **(D, E)** In another patient, photomicrograph **(D)** shows that the wall thickening primarily results from submucosal muscular hyperplasia (arrow in **D**). (H-E stain; original magnification, $\times 4$.) The submucosal muscular hyperplasia (arrow in **E**) is highlighted by the pale gray-red hue with the trichrome stain (**E**). (Masson trichrome stain; original magnification, $\times 4$.)

or fibroblasts, or physical properties of the bowel wall, such as stiffness or motility.

MRI Biomarkers

Quantitative biomarkers for CD strictures have been developed and are in various stages of validation. However, none have been incorporated into routine clinical practice, at present.

MRI-Magnetization Transfer.—Pools of hydrogen nuclei that contribute to generating the MR signal consist of a free pool, encompassing free water, and a bound pool, comprising bound water and macromolecules. Protons located deep in the macromolecules and those tightly bound have limited mobility, which leads to rapid signal decay. In magnetization transfer (MT) MRI, by using a specific radiofrequency pulse (MT-pulse), energy is injected into the macromolecular pool and is then transferred to the free pool, a process called *magnetization transfer*. The MT-pulse saturates macromolecular protons, and because of the interaction between pools, protons in the free water pool become indirectly saturated, as well (Fig 5).

In response to subsequent routine radiofrequency pulses and gradients, voxels containing both pools show signal intensity loss (40). MR images with the MT-pulse show signal loss within a stricture in which water molecules are bound by macromolecules. MR images without the MT-pulse show iso-intense signal within a stricture. The resulting signal difference reflects the magnitude of the MT effect (Fig 6).

Tissue macromolecules such as collagen, larger extracellular matrix proteins, actin, and myosin enhance the MT effect. This phenomenon is present in bowel segments containing increased smooth muscle and fibrosis. Biomarker studies examining MT-MRI often use the comparison of changes in bowel wall signal intensity to that of skeletal muscle for normalization.

Multiple studies with well-defined histopathologic reference standards have demonstrated that MT-MRI using normalized MT ratios may distinguish nonfibrotic and mildly fibrotic strictures from strictures with greater degrees of fibrosis (32,41). Another recent study has shown that MT ratio is associated with the need for surgical intervention in stricturing and penetrating ileal CD (17).

MRI Delayed Gadolinium Enhancement.—Rimola et al (42) found significant positive correlation between the presence of fibrosis in resected CD small bowel strictures and both delayed contrast medium enhancement (at 7 minutes) and the percentage of gadolinium enhancement from 70 seconds to 7 minutes at MRE. Additionally, they discovered that a homogeneous pattern observed during the delayed phase frequently is associated with more advanced stages of fibrosis. This delay in the diffusion of intravenous contrast material into the extravascular space is attributed to the deposition of fibrosis (42). Unfortunately, these findings have not been reproduced in larger studies (43,44).

Multiple studies, including that by Rimola et al (42), have shown that the majority of small bowel strictures have both

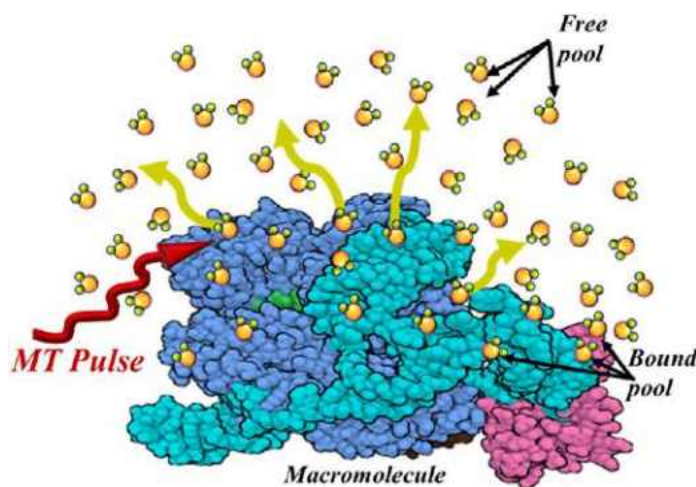


Figure 5. Illustration of MT-MRI. Hydrogen nuclei contributing to the MR signal include a free pool (free water) and a bound pool (bound water and macromolecule). In MT-MRI, the MT-pulse targets the bound pool and injects energy that subsequently transfers to the free pool. This pulse saturates the protons within the macromolecular pool and indirectly saturates those in the free water pool, as well. Following this, routine radiofrequency pulses and gradients cause a decrease in signal intensity in areas containing both pools. (Created with BioRender.com.)

inflammation and fibrosis. Intramural edema on T2-weighted images can be used to estimate inflammation along with restricted diffusion, whereas delayed 7-minute postgadolinium-enhanced images can be used in conjunction with other imaging findings in clinical practice (Figs 7, 8).

Qualitative and Quantitative Assessment of Diffusion-weighted Imaging.

Diffusion-weighted imaging (DWI) quantifies water proton movement within a voxel of tissue and provides insights into tissue microstructure and cellularity. Reduced tissue cellularity or disruption of cell membranes facilitates water molecule mobility. The measured diffusion within a volume is affected by the collective movement of water protons across its various tissue compartments (ie, intra- and extracellular).

DWI is a T2-weighted MRI sequence enhanced by a diffusion sensitizing gradient. Water proton movement along the gradient direction results in signal loss, whereas restricted diffusion increases DWI signal. The apparent diffusion coefficient quantifies this effect, which reflects the diffusion rate. Although several studies have noted a negative correlation between apparent diffusion coefficient values and fibrosis (45–47), it does not adequately differentiate fibrosis from inflammation, especially as inflammation increases (45).

DWI captures water proton dynamics across various tissue compartments and the microcirculation of blood, with signal attenuation arising from both perfusion and diffusion. This dual influence can be distinguished by using bi-exponential modeling of DWI data, which distinguishes true tissue diffusion from perfusion effects, particularly at higher *b*-values, and is known as intravoxel incoherent motion. Intravoxel incoherent motion can differentiate between diffusion and perfusion contributions and offers insights

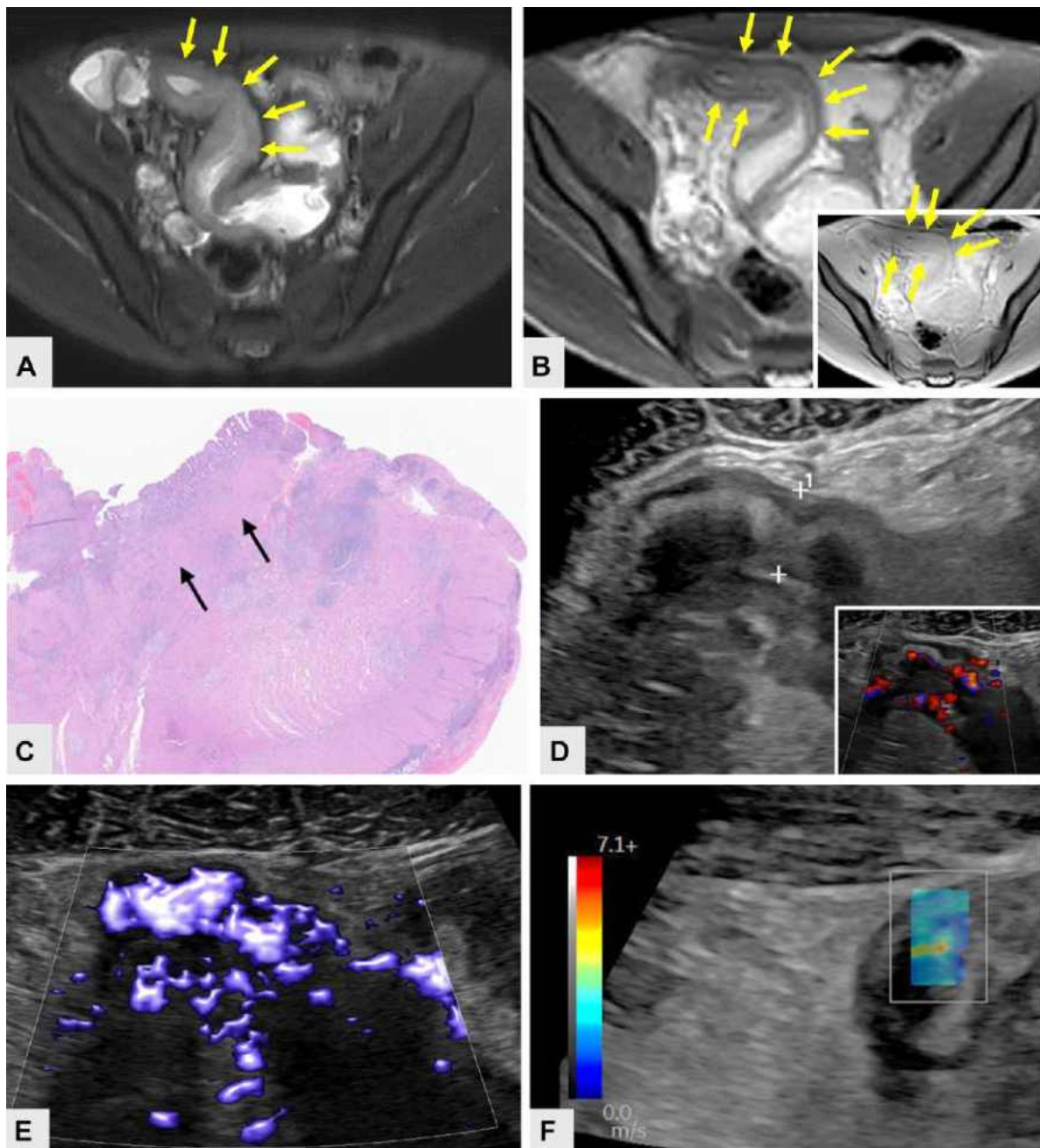


Figure 6. CD in a 29-year-old man who presented with ongoing postprandial symptoms of pain and abdominal cramping and a normal colonoscopy result. **(A)** Axial single-shot fast spin-echo fat-saturated MR image shows a stricture (arrows) with inflammation and intramural T2-weighted edema. **(B)** Corresponding axial two-dimensional MT image with MT-pulse applied shows substantial loss of signal intensity in the stricture wall (arrows). Inset shows the stricture without MT-pulse with high signal intensity in the stricture wall (arrows in inset). **(C)** Photomicrograph of the histopathologic specimen shows submucosal fibrosis and smooth muscle hyperplasia (arrows) in a stricture with inflammation and fibrosis. (H-E stain; original magnification, $\times 2$.) **(D, E)** US images show wall thickening on the gray-scale image **(D)**, with increased vascularity reflecting inflammation on the Doppler US image (inset in **D**), which is more pronounced on the corresponding US microvessel image **(E)**. **(F)** Shear-wave elastogram shows the involved bowel segment.

into tissue characteristics and vascular behavior crucial for clinical assessments. Biexponential modeling using various b -values enables differentiation of these components and allows for the derivation of intravoxel incoherent motion parameters, including D (the true diffusion coefficient), PF (the perfusion fraction), and D^* (the pseudo-diffusion coefficient) (Fig 9) (48).

Intravoxel incoherent motion may help define the degree of inflammation and fibrosis by measuring contributions of microperfusion. Zhang et al (49) found that fractional perfusion (the percentage of voxel volume that contains capillaries) is decreased in fibrotic segments and might be a good parameter reflecting the severity of collagen deposition, but this work has not been replicated by others.

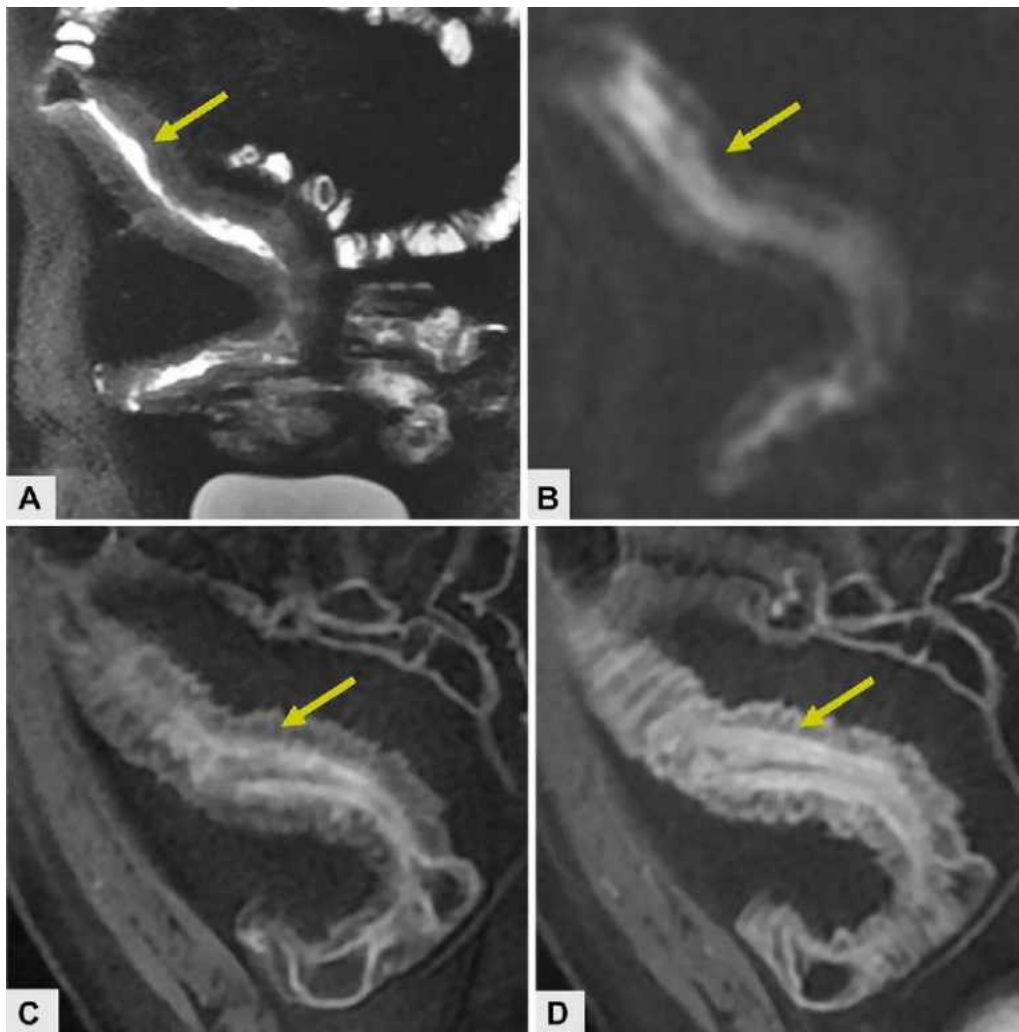


Figure 7. CD stricture with inflammation in a 32-year-old man. **(A)** Coronal T2-weighted single-shot fast spin-echo fat-saturated MRE image shows ileal luminal narrowing (arrow) with mild-to-moderate intramural edema. **(B)** Coronal diffusion-weighted MRE image shows restricted diffusion along the inner wall of the stricture (arrow). **(C, D)** Coronal contrast-enhanced fast spoiled gradient-echo fat-saturated MRE images show a layered pattern of intramural enhancement at 70 seconds **(C)** and 7 minutes **(D)**, as well as enhancement gain, which is most characteristic of strictures (arrow) with high levels of inflammation, as well as fibrosis.

Quantified Small Bowel Motility.—CD affects small bowel motility (50), which leads to decreased peristalsis compared with unaffected segments. Quantified small bowel motility with MRI is a reproducible parameter and can be measured from cine MR images (51). Menys et al (52) showed that quantitative bowel motility negatively correlates with histopathologic and imaging findings of inflammation. Quantified intestinal motility MRI also can be used to reliably predict anti-inflammatory treatment response (as early as 12 weeks) using a continuous GIQuant (Motilent) score, from 0 to 1000 (53,54). Small bowel motility is significantly reduced within strictures and, to a lesser extent, the dilated proximal small bowel, in comparison with normal-appearing proximal loops without disease (Fig 10) (55). Although quantified small bowel motility does not quantify fibrosis or distinguish it from inflammation, changes in motility within strictures may indicate progression or response to treatment or underlying pathophysiologic condition (eg, fibrosis

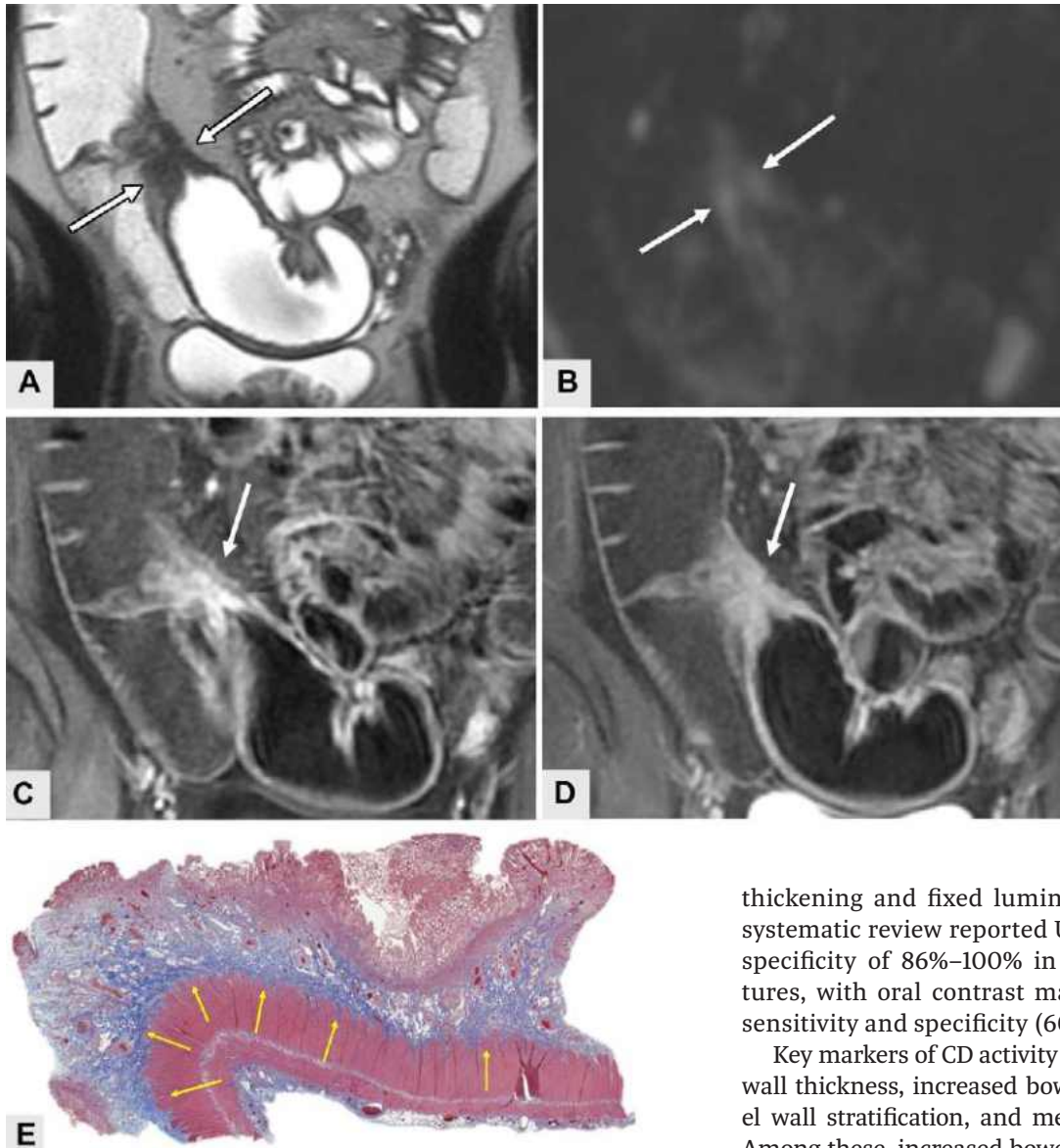
predominant). This technique can be applied to real-time US as well.

T1 Mapping

The T1 relaxation time is the time constant for the net magnetization vector to return to its equilibrium state. A T1 map quantifies the T1 relaxation time for each pixel in the image (56). Currently, modified Look-Locker inversion recovery imaging is the most used sequence for T1 measurement. Changes in tissue structure and composition cause variations in T1 values, which can be detected by T1 mapping.

The effectiveness of T1 mapping has been shown primarily in cardiac and hepatic fibrosis (57,58). Intestinal T1 mapping is being investigated as a biomarker for assessing intestinal inflammation and fibrosis (Fig 11). In a pilot study, Dillman et al (59) demonstrated that bowel wall T1 relaxation times are significantly prolonged in patients newly diagnosed with CD compared with healthy controls and can change in response

Figure 8. Imaging patterns of a neoterminal ileum CD stricture in a 17-year-old male patient. **(A)** Coronal T2-weighted single-shot fast spin-echo image shows a short terminal ileal stricture (arrows). **(B)** Coronal diffusion-weighted image shows faint diffusion restriction (CD stricture; arrows). **(C, D)** Coronal postcontrast MRE images show a layered enhancement pattern of the bowel wall at 70 seconds (CD stricture; arrow) **(C)**, which progressively becomes homogeneous at 7 minutes (CD stricture; arrow) **(D)**. This likely indicates a fibrotic component to the stricture. **(E)** Photomicrograph of the histologic section shows submucosal fibrosis (arrows) of the involved segment. (Masson trichrome stain; original magnification, $\times 2$.)



to medical therapy. A reduction in T1 relaxation times was observed. There is limited data on T1 mapping in CD strictures, and its ability to distinguish between inflammation and fibrosis is unknown.

Small Bowel US

US offers several advantages for frequent follow-up evaluations in individuals with CD because it is readily available, noninvasive, and does not require ionizing radiation. US-based studies generally define a stricture when bowel wall thickening exceeds 3 mm, the lumen is narrowed less than 1 cm, and there is upstream dilation greater than 2.5 cm (60). However, many US studies do not require oral contrast material or prestenotic dilation in the presence of bowel wall

thickening and fixed luminal narrowing (60,61). A recent systematic review reported US sensitivity of 68%–100% and specificity of 86%–100% in diagnosing small bowel strictures, with oral contrast material further enhancing both sensitivity and specificity (60).

Key markers of CD activity assessed using US include bowel wall thickness, increased bowel wall vascularity, loss of bowel wall stratification, and mesenteric inflammatory fat (60). Among these, increased bowel wall thickness is the most sensitive sonographic marker for diagnosing inflammatory bowel disease. Bowel wall thickness is measured across the five layers of the bowel wall, with the outer muscularis propria and inner muscularis mucosa being hypoechoic, and the submucosa being hyperechoic (Fig 12). Given the operator dependency of US, reproducibility is crucial. Studies have shown good reproducibility for assessing bowel wall thickness (61,62).

US performance can be influenced by the location and complexity of disease. For instance, transabdominal US assessments may face limitations in examining pelvic loops because of their deep location, but such challenges potentially can be addressed using perineal or transvaginal US in women.

Inflammation increases angiogenesis in the bowel wall of patients with CD, as shown on histologic and angiographic examinations (64), yet many other studies suggest decreased

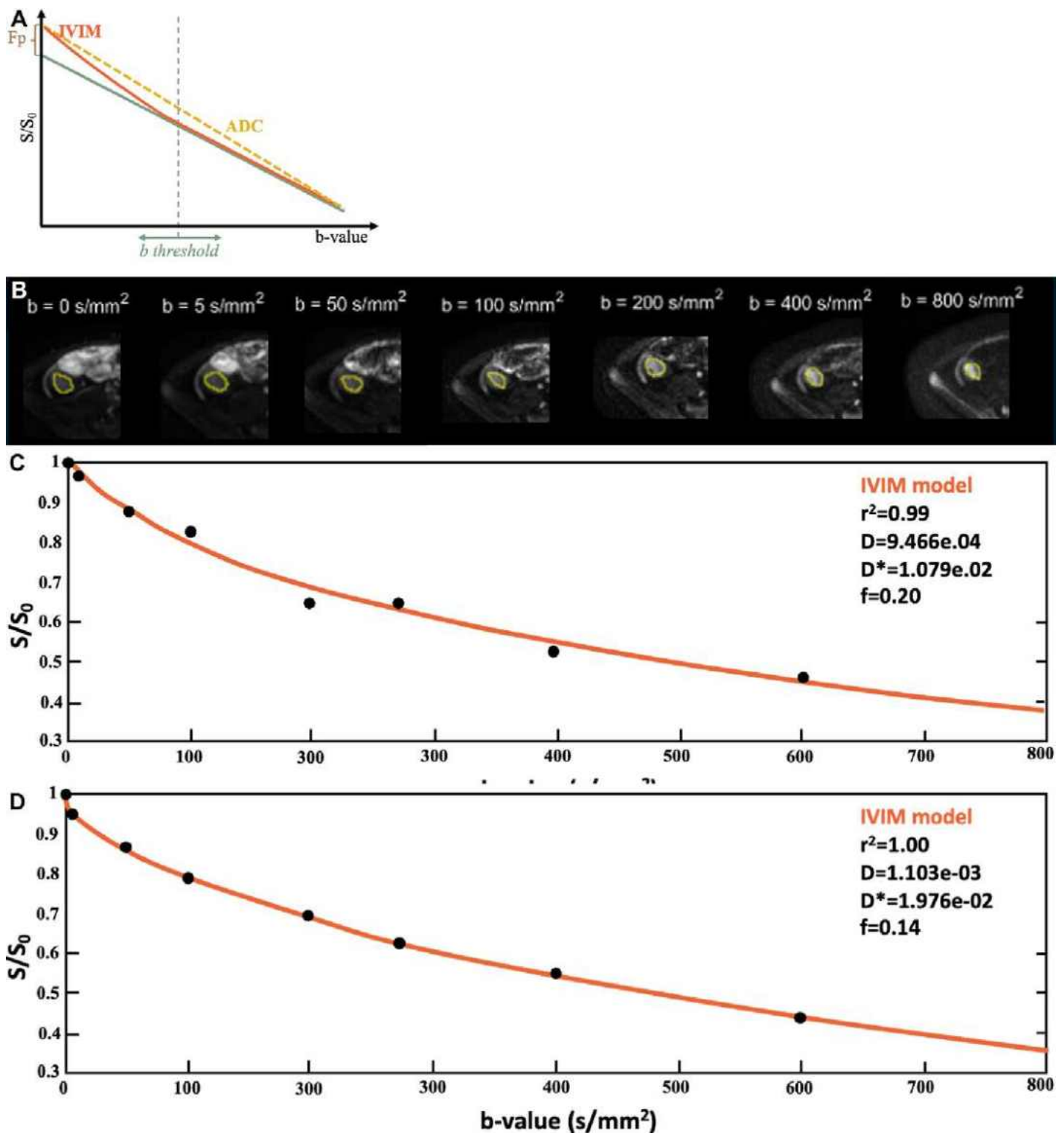


Figure 9. Application of intravoxel incoherent motion (IVIM) imaging in a 17-year-old patient with newly diagnosed ileal CD. **(A)** Graph shows two modeling approaches for analyzing DWI data acquired at multiple b values. The yellow dashed line represents a monoexponential model estimating apparent diffusion coefficient (ADC), whereas the orange line illustrates the IVIM model, which uses a biexponential function to account for both diffusion and perfusion components. The IVIM analysis provides key parameters, including perfusion fraction (f), true diffusion coefficient (D), and pseudodiffusion coefficient (D^*). Note that the IVIM effect is best observed at the low b values. **(B)** IVIM images were acquired at multiple b values ranging from 0 to 800 sec/mm^2 (selected b values shown). Regions of interest were placed in the terminal ileum at the site of the bowel wall thickening and luminal narrowing. **(C, D)** Signal intensity versus b -value plots from IVIM imaging at diagnosis **(C)** and 6 weeks after initiation of biologic therapy **(D)**. IVIM model shows that the perfusion fraction was low at baseline and minimally lower at follow-up, potentially indicating that fibrosis was present before the start of therapy and did not change significantly. The diffusion coefficient, which tracks with ADC, also increased with treatment. S/S_0 = normalized signal intensity.

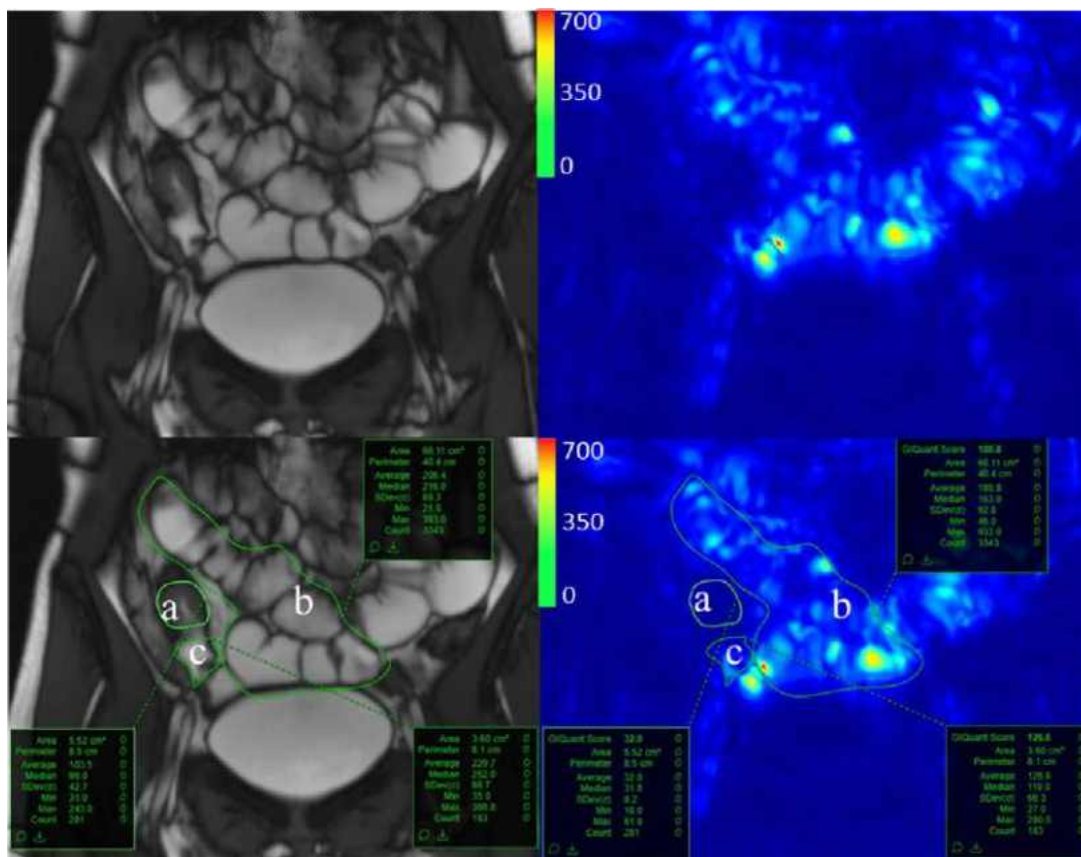


Figure 10. Quantified small bowel motility in a patient with terminal ileal CD. Anatomic reference True-FISP (fast imaging with steady-state precession; Siemens) MR images are on the left, with the corresponding color motility maps at the same location on the right. The bottom row of images shows regions of interest (green lines) drawn over three anatomic locations, as follows: over the terminal ileal stricture (*a*), over the uninvolved ileum (*b*), and just proximal to the stricture segment (*c*). The motility scores, derived from the GIQuant system, reveal a score of 32 at the stricture, in contrast to the uninvolved loop (score, 181), and just proximal to the stricture (score 127).

vessel density in active CD. Consequently, qualitative and quantitative evaluation of the bowel wall perfusion emerges as a valuable metric. Assessment of macroscopic vessel density using Doppler US in affected bowel segments has revealed a significant relationship with disease activity (65) (Fig 12). However, the ability to detect slow blood flow is limited using conventional color and power Doppler US (66).

US microvessel imaging is an emerging technique distinguished for its high sensitivity to blood vessels (Fig 13). Vessel-to-length ratio, calculated as the number of vessel pixels seen in a bowel wall segment using US microvessel imaging normalized to the segment length, can stage disease activity, and Lok et al (67) have shown using detailed histopathologic analysis of surgical specimens that US microvessel imaging vessel-to-length ratio correlates with histologic inflammation in Crohn strictures.

Elastography

Tissue stiffness as a biomarker for fibrosis can be quantified by elastography techniques at MRI and US (Fig 12). Strain and shear-wave US elastography investigations show widely varying results for detecting predominantly fibrotic intestinal segments (35,68). Shear-wave US elastography has shown

better performance for evaluating intestinal stenosis using endoscopic and histologic findings as reference standard. However, standardized assessment criteria and thresholds remain to be established (69).

MR elastography is used routinely to detect and monitor liver fibrosis. Propagation of waves within hollow organs has been challenging, but one group recently demonstrated increased bowel stiffness with MR elastography compared with a visual analog score using other pulse sequences (70).

Both US and MR elastography have demonstrated promise in identifying increased stiffness of mesenteric fat (35,71).

PET/MR Enterography

PET/MRE is a hybrid imaging modality integrating molecular, functional, and anatomic data from both PET and MRI modalities (72). The promise of PET/MRE for assessing CD-related strictures lies in its potential for improving the ability to distinguish between inflammation and fibrosis. Catalano et al (73) demonstrated that PET/MRE biomarkers combining elements of both modalities showed significant differences in 19 patients with small bowel strictures who underwent subsequent surgical resection between predominantly fibrotic strictures, strictures with combined fibrosis and active

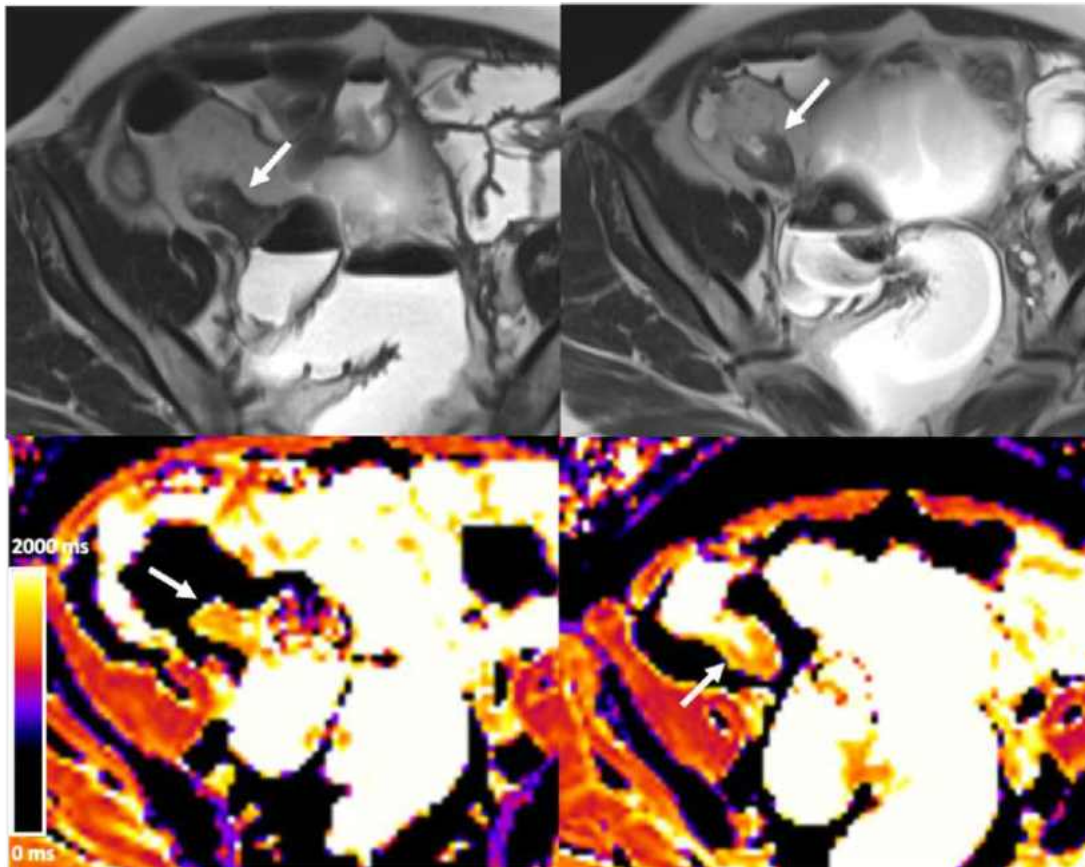


Figure 11. T1-mapping images of a CD stricture in the neoterminal ileum in a 41-year-old woman with an ileosigmoid anastomosis. Axial T2-weighted MR images in the top row show a thickened bowel wall (arrows). The bottom row contains corresponding axial parametric maps of the ileum produced from native T1 relaxometry (modified Look-Locker inversion recovery), with arrows pointing to the same stricture. The parametric maps are color coded according to T1 values of the tissue (inset, bottom left): yellow and orange represent higher T1 values. Bowel wall T1 estimates are increased in patients with ileal CD compared with uninvolved segments. In this case, endoscopic findings showed a short-segment stricture, which could be traversed with a pediatric endoscope, and 5 cm of endoscopic inflammation proximally.

inflammation, and strictures with predominantly active inflammation, with overall accuracy of 0.71.

Fibroblast Activation Protein Inhibitor PET

Gallium-68 fibroblast activation protein inhibitor (FAPI) PET targets fibroblast activation protein, which acts as a biomarker for activated fibroblasts (74). Fibrostenotic lesions in CD have an increased fibroblast activation protein expression in intestinal myofibroblasts within the submucosa and smooth muscle layers (75) (Fig 14). One investigation has shown a significant positive correlation between increasing maximum standardized uptake value and fibrosis at histopathologic evaluation of strictures (76). Li et al (77) found that fluorine-18 (^{18}F)-F-FAPI PET/CT is equivalent to MT-MRI in detecting intestinal fibrosis severity but more accurate than ^{18}F -FDG PET/CT. Additionally, ^{18}F -F-FAPI PET/CT outperforms both in identifying early-stage intestinal fibrosis (77). These studies suggest that FAPI PET may be useful in clinical trials to quantify fibrotic burden before treatment with antifibrotic agents. Further, FAPI PET potentially could identify intestinal segments with early fibrosis, which do not yet demonstrate typical imaging findings of a stricture at CTE or MRE.

Conclusion

Recent consensus underscores the efficacy of diagnostic and prognostic biomarkers derived from conventional MRE, CTE, and intestinal US in both routine clinical settings and therapeutic trials. Despite the potential of numerous biomarkers to reflect the pathophysiologic nuances of CD, their widespread adoption is impeded by a lack of standardization, reproducibility issues, and difficulty in distinguishing between inflammation, smooth muscle hypertrophy or hyperplasia, and fibrosis. Prognostic biomarkers reflecting Crohn stricture morphology and detected or measured at CTE and MRE can be incorporated into clinical practice. Meanwhile, emerging research methodologies are in various stages of development and validation, yet they signify promising advances in this field. As CD biomarkers are incorporated into clinical practice and research studies, more lessons will be learned relating to potential false positive measurements and observations, potentially relating to interpretation (eg, underestimating associated small bowel dilation by not looking at all acquired MRI sequences) and quantitative pitfalls of biomarkers (eg, a quantitative biomarker reflecting overlap of muscular hypertrophy and fibrosis or collagen).

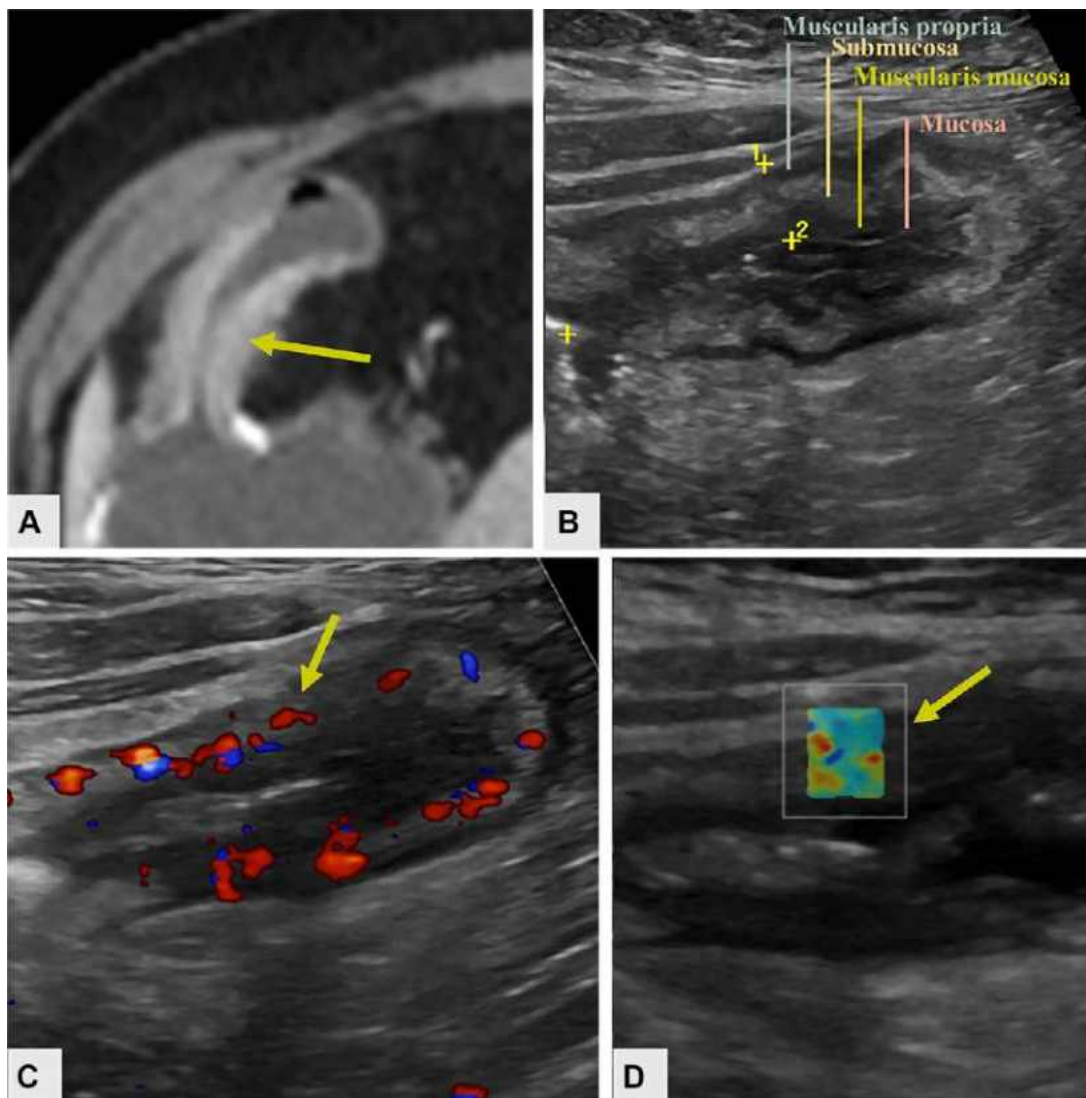


Figure 12. Short-segment stricture with inflammation involving the neoterminal ileum in a 42-year-old woman with prior ileocecal resection. **(A)** Axial contrast-enhanced CT image shows a 5-cm long stricture (arrow) with inflammation in the distal neoterminal ileum, which is characterized by 9-mm wall thickening, mural enhancement, and luminal narrowing. **(B)** Longitudinal gray-scale US image shows bowel wall thickening with mainly an expanding submucosal layer. **(C, D)** Additional longitudinal images with color Doppler US **(C)** and shear-wave elastography **(D)** show enhanced vascularity (arrow in **C**) and increased stiffness of the involved segment (arrow, inset in **D**), respectively.

Of particular importance is the development of accurate and dependable biomarkers for intestinal strictures, which are essential for identifying patients likely to respond to antifibrotic therapies. These biomarkers will be vital for improving the management of CD by enabling precise patient stratification and rigorous monitoring in clinical trials of innovative antifibrotic drugs (78).

Author affiliations.—From the Department of Radiology (S.H., K.A.R., A.L., D.J.B., A.H.G., S.C., J.G.F.), Division of Gastroenterology and Hepatology (D.H.B.), and Department of Laboratory Medicine and Pathology (C.E.H.), Mayo Clinic, 200 First St SW, Rochester, MN 55905; Department of Radiology, Cincinnati Children’s Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio (J.R.D.); Center for Medical Imaging, University College London, London, UK (S.A.T.); IBD Unit, Department of Radiology, Hospital Clínic Barcelona, IDIBAPS, University of Barcelona, Barcelona, Spain (J.R.); Department of Diagnostic, Molecular, and Interventional Radiology, Icahn School of Medicine at Mount Sinai, New York, NY (B.T.); Department of Inflammation and Immunity, Lerner Research Institute, Cleve-

land Clinic, Cleveland, Ohio (F.R.); Department of Gastroenterology, Hepatology and Nutrition, Digestive Diseases and Surgery Institute and Program for Global Translational Inflammatory Bowel Disease Research, Cleveland Clinic, Cleveland, Ohio (F.R.); Alimentiv, London, Ontario, Canada (B.F.); Department of Medicine and Department of Epidemiology and Statistics, University of Western Ontario, London, Ontario, Canada (B.F.); and Imaging Institute, Digestive Diseases and Surgery Institute, Cleveland Clinic, Cleveland, Ohio (M.E.B.). Presented as an education exhibit at the 2023 RSNA Annual Meeting. Received August 7, 2024; revision requested September 4 and received October 9; accepted October 29. **Address correspondence to** J.G.F. (email: Fletcher.Joel@mayo.edu).

Acknowledgments.—The authors wish to thank Dr Tom Smyrk for his assistance and guidance in understanding the pathology of fibrostenosing Crohn disease and providing relevant examples. They also wish to thank Dr U-Wai Lok for providing examples of US microvessel imaging.

Funding.—Supported in part by grants from The Leona M. and Harry B. Helmsley Charitable Trust (Stenosis Therapy and Anti-Fibrotic Research [STAR] Consortium) and Mayo Clinic funds. **S.C.** supported by a National Institutes of Health (NIH) grant (R01-DK120559). **F.R.** supported by NIH grants (R01-DK123233, R01-132038).

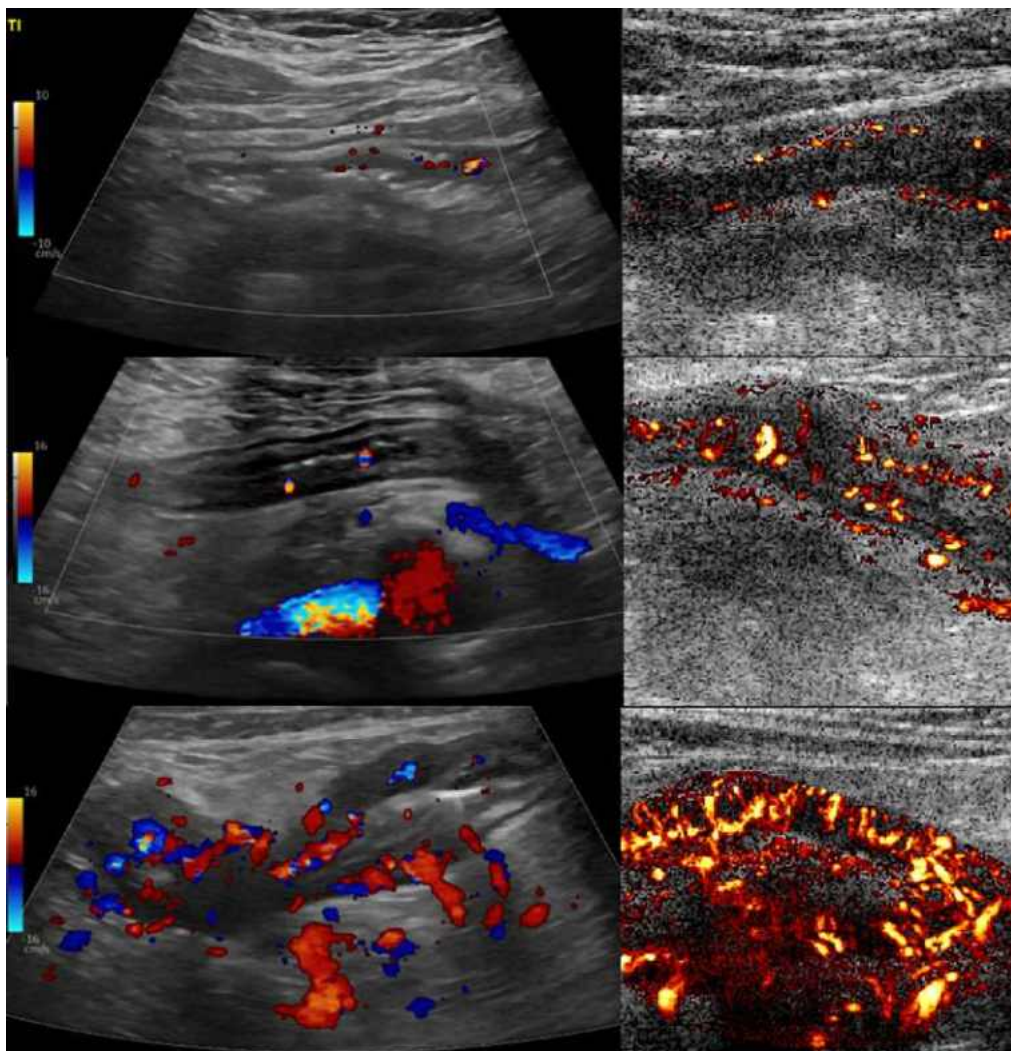


Figure 13. Color Doppler US images (left) and US microvessel images (right) in three patients with ileal CD. The top row shows a 32-year-old man with a vessel-to-length ratio (VLR) score of 0.36 based on UMI. The middle row shows a 44-year-old woman with a VLR of 4.42. The bottom row shows a 27-year-old man with a VLR of 12.81. Histopathologic evaluation of the involved segments indicated mild, moderate, and severe inflammation, respectively.

Disclosures of conflicts of interest.—**J.R.D.** Research support from Motilent, Perspectum, Philips Healthcare, GE HealthCare, Guerbet, Bracco Imaging. **S.A.T.** Research funding from Takeda. Consultant to AstraZeneca. Shareholder for Motilent. **J.R.** Research grants from Abbvie, Genentech. Lecture or consultancy fees from Origo Biopharma, Agomab, Alimentiv, Ferring, Gilead, Takeda, Lument, Janssen. Member of advisory board of TiGenix. Former member of advisory board of Alimentiv. **B.T.** Research support from Bayer, Takeda, Regeneron, Helio Health, Echosens, Guerbet, Siemens. Consulting for Bayer, Guerbet, Ascelia. **D.H.B.** Medical consulting for Janssen. **A.H.G.** Principal Investigator on institutional research grant from Sofie Biosciences, Novartis. Paid consultant to Bayer Healthcare, Candel Therapeutics, Ferronova, UWorld. **S.C.** Potential financial interest related to patents and pending patent applications in shear wave elastography and microvessel imaging. Royalties from licensed US shear wave elastography technology. **F.R.** Consultant or Advisory Board for Adiso, Adnovate, Agomab, Abbvie, Arena, AstraZeneca, Bausch & Lomb, Boehringer-Ingelheim, Celgene/BMS, Celltrion, CDISC, Celsius, Cowen, Eugit, Ferring, Galapagos, Galmed, Genentech, Gilead, Gossamer, Granite, Guidepoint, Helmsley, Horizon Therapeutics, Image Analysis Limited, Index Pharma, Landos, Janssen, Koutif, Mestag, Metacrine, Mirum, Mopac, Morphic, Myka Labs, Organovo, Origo, Palisade, Pfizer, Pliant, Prometheus Biosciences, Receptos, RedX, Roche, Samsung, Sanofi, Surmodics, Surrozen, Takeda, Techlab, Teva, Theravance, Thetis, Trlx Bio, UCB, Ysios, 89Bio. **B.F.** Consultant for Abbvie, Abivax, Adiso, AgomAB Therapeutics, Alliantera, Amgen, AnaptysBio, Arena Pharma, Avoro Capital Advisors, Atomwise, BioJamp, Biora Therapeutics, Blackbird Laboratories, Boehring-

er-Ingelheim, Boxer Capital, Celsius Therapeutics, Celgene/BMS, Celltrion, Connect BioPharma, Cytokine, Disc Medicine, Duality, EcoRI, Eli Lilly, Equillum, Ermium, First Wave, Forbion, Galapagos, Galen Atlantica, Genentech/Roche, Gilead, Gossamer Pharma, GSK, Hinge Bio, Index Pharma, Imhotex, Immunic Therapeutics, Intercept, JAKAcademy, Janssen, Japan Tobacco, Kaleido Biosciences, Klick Health, Landos Biopharma, Lenczner Slaght, LifeSci Capital, Lument AB, Mage Biologics, Mestag, Millennium, MiroBio, Monte Rose Tx, Morgan Lewis, Morphic Therapeutics, Mylan, Nexys Therapeutics, Nimbus Therapeutics, OM Pharma, OrbiMed Origo BioPharma, Orphagen, Pandion Therapeutics, Pendopharm, Pfizer, Prometheus Therapeutics and Diagnostics (Merck), Progenity, Protagonist, PTM Therapeutics, Q32 Bio, Rebiotix, REDX, Roche, Roivant/Televant, Sandoz, Sanofi, Seres Therapeutics, Silverback Therapeutics, Sobi, Spyre Therapeutics, Surrozen Inc., Sun Pharma, Synedgen, Takeda, Teva, Thelium, Tigenix, Tillotts, Triastek, TRIX Inc. Ventyx Biosciences, Zagbio, Zealand Pharma. Speakers Bureau for AbbVie, Janssen, Takeda, Pfizer, Biora, Celgene/BMS, Eli Lilly, Roche, Merck, Sanofi. Payment for expert testimony from Belmore Law, Morgan Lewis. Data Safety Monitoring or Advisory Board member for Belmore Law, Morgan Lewis. Support for travel from Abbvie, Takeda, Janssen, Sanofi, Roche, Eli Lilly, Pfizer, Enveda, Merck. Member, Scientific Advisory Board, DSMB for AbbVie, Amgen, AMT, AnaptysBio, Boehringer-Ingelheim, Celgene/BMS Eli Lilly, Genentech/Roche, Janssen, MiroBio, Origo BioPharma, Pfizer, Prometheus, REDX Pharma, Sanofi, Takeda, Tillotts Pharma, Teva, Progenity, Index, EcoRI Capital, Morphic, GSK, Axio Research. Stock shareholder for Connect BioPharma, EnGene. Senior Scientific Director, Alimentiv. **M.E.B.** Grants to institution from The Leona

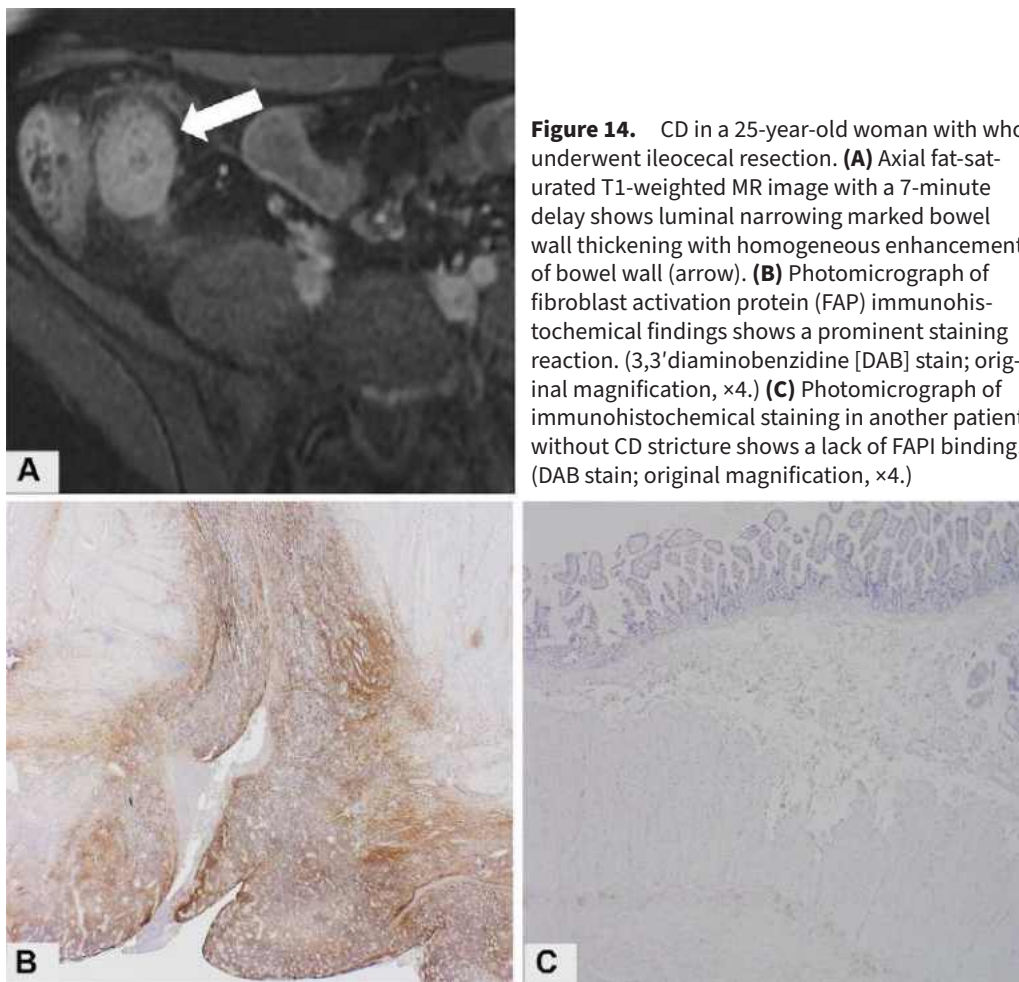


Figure 14. CD in a 25-year-old woman with who underwent ileocecal resection. **(A)** Axial fat-saturated T1-weighted MR image with a 7-minute delay shows luminal narrowing marked bowel wall thickening with homogeneous enhancement of bowel wall (arrow). **(B)** Photomicrograph of fibroblast activation protein (FAP) immunohistochemical findings shows a prominent staining reaction. (3,3'-diaminobenzidine [DAB] stain; original magnification, $\times 4$.) **(C)** Photomicrograph of immunohistochemical staining in another patient without CD stricture shows a lack of FAPI binding. (DAB stain; original magnification, $\times 4$.)

M. and Harry B. Helmsley Charitable Trust, Pfizer, J.G.F. Grants to institution from Siemens Healthineers, Alimientiv, Pfizer. Grant co-investigator for grant from Motilent. Consulting with funds to institution from Genentech, Boehringer Ingelheim, Glaxo Smith Kline, Janssen, Medtronic, Takeda, Alimientiv, Red X Pharma, Agomab. All other authors, the editor, and the reviewers have disclosed no relevant relationships.

References

- El Ouali S, Baker ME, Lyu R, et al. Validation of stricture length, duration and obstructive symptoms as predictors for intervention in ileal stricturing Crohn's disease. *United European Gastroenterol J* 2022;10(9):958–972.
- Hunaut T, Peyrin-Biroulet L, Le Bozec A, et al. Long-term neoplastic risk associated with colorectal strictures in Crohn's disease: a multicenter study. *Gastro Hep Adv* 2024;3(6):731–737.
- Inoue A, Bartlett DJ, Shahraki N, et al. Predicting risk of surgery in patients with small bowel Crohn's disease strictures using computed tomography and magnetic resonance enterography. *Inflamm Bowel Dis* 2022;28(11):1677–1686.
- Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011;140(6):1785–1794.
- Louis E, Collard A, Oger AF, Degroote E, Aboul Nasr El Yafi FA, Belaiche J. Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. *Gut* 2001;49(6):777–782.
- Bruining DH, Zimmermann EM, Loftus EV Jr, et al. Consensus recommendations for evaluation, interpretation, and utilization of computed tomography and magnetic resonance enterography in patients with small bowel Crohn's disease. *Gastroenterology* 2018;154(4):1172–1194.
- Rieder F, Bettenworth D, Ma C, et al. An expert consensus to standardize definitions, diagnosis and treatment targets for anti-fibrotic stricture therapies in Crohn's disease. *Aliment Pharmacol Ther* 2018;48(3):347–357.
- Guglielmo FF, Anupindi SA, Fletcher JG, et al. Small bowel Crohn disease at CT and MR enterography: imaging atlas and glossary of terms. *Radiographics* 2020;40(2):354–375.
- Bettenworth D, Bokemeyer A, Baker M, et al. Assessment of Crohn's disease-associated small bowel strictures and fibrosis on cross-sectional imaging: a systematic review. *Gut* 2019;68(6):1115–1126.
- Lin SN, Mao R, Qian C, et al. Development of antifibrotic therapy for stricturing Crohn's disease: lessons from randomized trials in other fibrotic diseases. *Physiol Rev* 2022;102(2):605–652.
- Agomab Spain S.L. STENOVA—a study to evaluate safety, tolerability, PK and PD of AGMB-129 in patients with fibrostenotic Crohn's disease. *ClinicalTrials.gov* identifier: NCT05843578. <https://classic.clinicaltrials.gov/show/NCT05843578>. Updated February 18, 2025. Accessed April 29, 2025.
- Rimola J, Beek KJ, Ordás I, Gecse KB, Cuatrecasas M, Stoker J. Contemporary Imaging assessment of strictures and fibrosis in Crohn disease, with focus on quantitative biomarkers: from the *AJR* Special Series on Imaging of Fibrosis. *AJR Am J Roentgenol* 2024;222(4):e2329693.
- European Society of Radiology (ESR). White paper on imaging biomarkers. *Insights Imaging* 2010;1(2):42–45.
- National Center for Advancing Translational Sciences (NCATS). Understand translational research tools: biomarkers. NCATS toolkit for patient-focused therapy development. <https://toolkit.ncats.nih.gov/module/discovery/developing-translational-research-tools/biomarkers/>. Accessed April 29, 2025.
- Stocker D, King MJ, El Homsy M, et al. Luminal narrowing alone allows an accurate diagnosis of Crohn's disease small bowel strictures at cross-sectional imaging. *J Crohn's Colitis* 2021;15(6):1009–1018.
- Debnath P, Epstein KN, Kocaoglu M, Towbin AJ, Denson LA, Dillman JR. Imaging and clinical predictors of surgery in stricturing ileal Crohn's disease: a retrospective study from a large pediatric hospital. *Abdom Radiol (NY)* 2024;49(10):3354–3363.
- Dillman JR, Tkach JA, Fletcher JG, et al. MRI and blood-based biomarkers are associated with surgery in children and adults with ileal Crohn's

- disease. *Inflamm Bowel Dis* 2024. 10.1093/ibd/izae101. Published online May 13, 2024.
18. Bettenworth D, Gustavsson A, Atreja A, et al. A pooled analysis of efficacy, safety, and long-term outcome of endoscopic balloon dilation therapy for patients with stricturing Crohn's disease. *Inflamm Bowel Dis* 2017;23(1):133–142.
 19. Bouhnik Y, Carbonnel F, Laharie D, et al. Efficacy of adalimumab in patients with Crohn's disease and symptomatic small bowel stricture: a multicentre, prospective, observational cohort (CREOLE) study. *Gut* 2018;67(1):53–60.
 20. Grass F, Fletcher JG, Alsughayer A, et al. Development of an objective model to define near-term risk of ileocecal resection in patients with terminal ileal Crohn disease. *Inflamm Bowel Dis* 2019;25(11):1845–1853.
 21. Maehata Y, Nagata Y, Moriyama T, et al. Risk of surgery in patients with stricturing type of Crohn's disease at the initial diagnosis: a single center experience. *Intest Res* 2019;17(3):357–364.
 22. Naik Viatti N, Viatti Violi N, Schoepfer AM, et al. Prevalence and clinical importance of mesenteric venous thrombosis in the Swiss Inflammatory Bowel Disease Cohort. *AJR Am J Roentgenol* 2014;203(1):62–69.
 23. Rieder F, Baker ME, Bruining DH, et al. Reliability of MR enterography features for describing fibrostenosing Crohn disease. *Radiology* 2024;312(2):e233039.
 24. Rieder F, Ma C, Hanzel J, et al. Reliability of CT enterography for describing fibrostenosing Crohn disease. *Radiology* 2024;312(2):e233038.
 25. Seo N. Comprehensive review of magnetic resonance enterography-based activity scoring systems for Crohn's disease. *Invest Magn Reson Im* 2025;29(1):1–13.
 26. Chen W, Lu C, Hirota C, Iacucci M, Ghosh S, Gui X. Smooth muscle hyperplasia/hypertrophy is the most prominent histological change in Crohn's fibrostenosing bowel strictures: a semiquantitative analysis by using a novel histological grading scheme. *J Crohns Colitis* 2017;11(1):92–104.
 27. Rieder F, Fiocchi C, Rogler G. Mechanisms, management, and treatment of fibrosis in patients with inflammatory bowel diseases. *Gastroenterology* 2017;152(2):340–350.e6.
 28. Gordon IO, Bettenworth D, Bokemeyer A, et al. Histopathology scoring systems of stenosis associated with small bowel Crohn's disease: a systematic review. *Gastroenterology* 2020;158(1):137–150.e1.
 29. Gordon IO, Bettenworth D, Bokemeyer A, et al. International consensus to standardise histopathological scoring for small bowel strictures in Crohn's disease. *Gut* 2022;71(3):479–486.
 30. Rieder F, Zimmermann EM, Remzi FH, Sandborn WJ. Crohn's disease complicated by strictures: a systematic review. *Gut* 2013;62(7):1072–1084.
 31. D'Haens G, Rieder F, Feagan BG, et al. Challenges in the pathophysiology, diagnosis, and management of intestinal fibrosis in inflammatory bowel disease. *Gastroenterology* 2022;162(1):26–31.
 32. Li XH, Mao R, Huang SY, et al. Characterization of degree of intestinal fibrosis in patients with Crohn disease by using magnetization transfer MR imaging. *Radiology* 2018;287(2):494–503.
 33. Liu Q, Zhang X, Ko HM, et al. Constrictive and hypertrophic strictures in ileal Crohn's disease. *Clin Gastroenterol Hepatol* 2022;20(6):e1292–e1304.
 34. Wagner M, Ko HM, Chatterji M, et al. Magnetic resonance imaging predicts histopathological composition of ileal Crohn's disease. *J Crohn's Colitis* 2018;12(6):718–729.
 35. Abu-Ata N, Dillman JR, Rubin JM, et al. Ultrasound shear wave elastography in pediatric stricturing small bowel Crohn disease: correlation with histology and second harmonic imaging microscopy. *Pediatr Radiol* 2023;53(1):34–45.
 36. Stidham RW, Xu J, Johnson LA, et al. Ultrasound elasticity imaging for detecting intestinal fibrosis and inflammation in rats and humans with Crohn's disease. *Gastroenterology* 2011;141(3):819–826.e1.
 37. Stewart DC, Berrie D, Li J, et al. Quantitative assessment of intestinal stiffness and associations with fibrosis in human inflammatory bowel disease. *PLoS One* 2018;13(7):e0200377.
 38. Johnson LA, Rodansky ES, Sauder KL, et al. Matrix stiffness corresponding to strictured bowel induces a fibrogenic response in human colonic fibroblasts. *Inflamm Bowel Dis* 2013;19(5):891–903.
 39. Rimola J, Alfaro I, Fernández-Clotet A, et al. Persistent damage on magnetic resonance enterography in patients with Crohn's disease in endoscopic remission. *Aliment Pharmacol Ther* 2018;48(11-12):1232–1241.
 40. Henkelman RM, Stanisz GJ, Graham SJ. Magnetization transfer in MRI: a review. *NMR Biomed* 2001;14(2):57–64.
 41. Fang ZN, Li XH, Lin JJ, et al. Magnetisation transfer imaging adds information to conventional MRIs to differentiate inflammatory from fibrotic components of small intestinal strictures in Crohn's disease. *Eur Radiol* 2020;30(4):1938–1947.
 42. Rimola J, Planell N, Rodríguez S, et al. Characterization of inflammation and fibrosis in Crohn's disease lesions by magnetic resonance imaging. *Am J Gastroenterol* 2015;110(3):432–440.
 43. Coimbra A, Rimola J, Cuatrecasas M, et al. Magnetic resonance enterography and histology in patients with fibrostenotic Crohn's disease: a multicenter study. *Clin Transl Gastroenterol* 2022;13(7):e00505.
 44. Caruso A, Angriman I, Scarpa M, et al. Diffusion-weighted magnetic resonance for assessing fibrosis in Crohn's disease. *Abdom Radiol (NY)* 2020;45(8):2327–2335.
 45. Li XH, Mao R, Huang SY, et al. Ability of DWI to characterize bowel fibrosis depends on the degree of bowel inflammation. *Eur Radiol* 2019;29(5):2465–2473.
 46. Grassi G, Laino ME, Fantini MC, et al. Advanced imaging and Crohn's disease: an overview of clinical application and the added value of artificial intelligence. *Eur J Radiol* 2022;157:110551.
 47. Tielbeek JA, Ziech ML, Li Z, et al. Evaluation of conventional, dynamic contrast enhanced and diffusion weighted MRI for quantitative Crohn's disease assessment with histopathology of surgical specimens. *Eur Radiol* 2014;24(3):619–629.
 48. Le Bihan D. What can we see with IVIM MRI? *Neuroimage* 2019;187:56–67.
 49. Zhang MC, Li XH, Huang SY, et al. IVIM with fractional perfusion as a novel biomarker for detecting and grading intestinal fibrosis in Crohn's disease. *Eur Radiol* 2019;29(6):3069–3078.
 50. Guglielmo FF, Mitchell DG, O'Kane PL, et al. Identifying decreased peristalsis of abnormal small bowel segments in Crohn's disease using cine MR enterography: the frozen bowel sign. *Abdom Imaging* 2015;40(5):1150–1156.
 51. Menys A, Taylor SA, Emmanuel A, et al. Global small bowel motility: assessment with dynamic MR imaging. *Radiology* 2013;269(2):443–450.
 52. Menys A, Puylaert C, Tutein Nolthenius CE, et al. Quantified terminal ileal motility during MR Enterography as a biomarker of Crohn disease activity: prospective multi-institution study. *Radiology* 2018;289(2):428–435.
 53. Plumb AA, Menys A, Russo E, et al. Magnetic resonance imaging-quantified small bowel motility is a sensitive marker of response to medical therapy in Crohn's disease. *Aliment Pharmacol Ther* 2015;42(3):343–355.
 54. Dillman JR, Tkach JA, Imbus R, Towbin AJ, Denson LA. MRI-based characterization of intestinal motility in children and young adults with newly diagnosed ileal Crohn disease treated by biologic therapy: a controlled prospective study. *AJR Am J Roentgenol* 2022;219(4):655–664.
 55. Menys A, Helbren E, Makanyanga J, et al. Small bowel strictures in Crohn's disease: a quantitative investigation of intestinal motility using MR enterography. *Neurogastroenterol Motil* 2013;25(12):967–e775.
 56. Taylor AJ, Salerno M, Dharmakumar R, Jerosch-Herold M. T1 Mapping: basic techniques and clinical applications. *JACC Cardiovasc Imaging* 2016;9(1):67–81.
 57. Hamilton-Craig CR, Strudwick MW, Galloway GJT. T1 Mapping for myocardial fibrosis by cardiac magnetic resonance relaxometry—a comprehensive technical review. *Front Cardiovasc Med* 2017;3:49.
 58. Hoad CL, Palaniyappan N, Kaye P, et al. A study of T1 relaxation time as a measure of liver fibrosis and the influence of confounding histological factors. *NMR Biomed* 2015;28(6):706–714.
 59. Mahalingam N, Tkach JA, Denson LA, Dillman JR. Bowel wall MRI T1 relaxation estimates for assessment of intestinal inflammation in pediatric Crohn's disease. *Abdom Radiol (NY)* 2022;47(8):2730–2738.
 60. Lu C, Rosentretter R, Parker CE, et al. Stenosis Therapy and Anti-Fibrotic Research (STAR) consortium. International expert guidance for defining and monitoring small bowel strictures in Crohn's disease on intestinal ultrasound: a consensus statement. *Lancet Gastroenterol Hepatol* 2024;9(12):1101–1110.
 61. Lu C, Rosentretter R, Delisle M, et al. Systematic review: defining, diagnosing and monitoring small bowel strictures in Crohn's disease on intestinal ultrasound. *Aliment Pharmacol Ther* 2024;59(8):928–940.
 62. Dillman JR, Smith EA, Sanchez R, et al. Prospective cohort study of ultrasound-ultrasound and ultrasound-MR enterography agreement in the evaluation of pediatric small bowel Crohn disease. *Pediatr Radiol* 2016;46(4):490–497.
 63. Fraquelli M, Sarno A, Girelli C, et al. Reproducibility of bowel ultrasonography in the evaluation of Crohn's disease. *Dig Liver Dis* 2008;40(11):860–866.
 64. Danese S, Sans M, de la Motte C, et al. Angiogenesis as a novel component of inflammatory bowel disease pathogenesis. *Gastroenterology* 2006;130(7):2060–2073.
 65. Spalinger J, Patriquin H, Miron MC, et al. Doppler US in patients with Crohn disease: vessel density in the diseased bowel reflects disease activity. *Radiology* 2000;217(3):787–791.
 66. Gong P, Song P, Kolbe AB, et al. Quantitative inflammation assessment for Crohn disease using ultrasensitive ultrasound microvessel imaging: a pilot study. *J Ultrasound Med* 2020;39(9):1819–1827.
 67. Lok UW, Tang S, Gong P, et al. Quantitative assessment of ultrasound microvessel imaging in Crohn's disease: correlation with pathological inflammation. *Eur Radiol* 2025;35(5):2806–2817.

68. Dal Buono A, Faita F, Peyrin-Biroulet L, Danese S, Allocca M. Ultrasound elastography in inflammatory bowel diseases: a systematic review of accuracy compared with histopathological assessment. *J Crohn's Colitis* 2022;16(10):1637–1646.
69. Grażyńska A, Kufel J, Dudek A, Cebula M. Shear wave and strain elastography in Crohn's Disease—a systematic review. *Diagnostics (Basel)* 2021;11(9):1609.
70. Avila F, Caron B, Hossu G, et al. Magnetic resonance elastography for assessing fibrosis in patients with Crohn's disease: a pilot study. *Dig Dis Sci* 2022;67(9):4518–4524.
71. Jensen LJ, Loch FN, Kamphues C, et al. Feasibility of *in vivo* magnetic resonance elastography of mesenteric adipose tissue in Crohn's disease. *Quant Imaging Med Surg* 2023;13(8):4792–4805.
72. Olson MC, Navin PJ, Welle CL, Goenka AH. Small bowel radiology. *Curr Opin Gastroenterol* 2021;37(3):267–274.
73. Catalano OA, Gee MS, Nicolai E, et al. Evaluation of quantitative PET/MR enterography biomarkers for discrimination of inflammatory strictures from fibrotic strictures in Crohn disease. *Radiology* 2016;278(3):792–800.
74. Karbhari A, Mosessian S, Trivedi KH, et al. Gallium-68-labeled fibroblast activation protein inhibitor-46 PET in patients with resectable or borderline resectable pancreatic ductal adenocarcinoma: a phase 2, multicenter, single arm, open label non-randomized study protocol. *PLoS One* 2023;18(11):e0294564.
75. Rovedatti L, Di Sabatino A, Knowles CH, et al. Fibroblast activation protein expression in Crohn's disease strictures. *Inflamm Bowel Dis* 2011;17(5):1251–1253.
76. Scharitzer M, Macher-Beer A, Mang T, et al. Evaluation of intestinal fibrosis with ⁶⁸Ga-FAPI PET/MR enterography in Crohn disease. *Radiology* 2023;307(3):e222389.
77. Li Z, Chen Z, Zhang R, et al. Comparative analysis of [¹⁸F]F-FAPI PET/CT, [¹⁸F]F-FDG PET/CT and magnetization transfer MR imaging to detect intestinal fibrosis in Crohn's disease: a prospective animal model and human cohort study. *Eur J Nucl Med Mol Imaging* 2024;51(7):1856–1868.
78. Steiner CA, Berinstein JA, Louissaint J, et al. Biomarkers for the prediction and diagnosis of fibrostenosing Crohn's disease: a systematic review. *Clin Gastroenterol Hepatol* 2022;20(4):817–846.e10.