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TITLE: Reliability of CT Enterography for Fibrostenosing Crohn Disease

ARTICLE TYPE: Original Research

SUMMARY STATEMENT:

Maximal associated small bowel dilation, stricture length, and maximal stricture wall thickness on CT enterography can reliably describe Crohn disease stricture severity and serve as eligibility/efficacy criteria in anti-fibrotic trials.

KEY RESULTS:

- In a retrospective study of CT enterography exams from patients (N=43) with Crohn Disease and terminal ileal strictures, 5 measurements and 6 observations demonstrated at least moderate inter-rater reliability (intraclass correlation coefficient ≥0.41) when assessed by four blinded abdominal radiologists.
- CT measurements included maximal associated small bowel dilation, stricture length, distance to ileocecal valve/anastomosis, maximal stricture wall thickness, maximal luminal stricture diameter; CT observations included sacculations, perienteric fat stranding, engorged vasa recta, mural hyperenhancement, ulceration, enhancement pattern.
- Stricture length, maximal stricture wall thickness, and maximal associated small bowel dilation were independently associated with stricture severity (*P*<.001–.003).

ABBREVIATIONS:

ICC, intraclass correlation coefficient; VAS, visual analog scale

ABSTRACT (299/300 words)

Background: Standardized methods to measure and describe Crohn disease strictures are needed for CT enterography to guide clinical decision-making and for use in therapeutic studies.

Purpose*:* To assess the reliability of CT enterography features to describe Crohn disease strictures and their correlation with stricture severity.

Materials and Methods*:* A retrospective study of 43 adult patients with symptomatic terminal ileal Crohn disease strictures who underwent standard-of-care CT enterography at a tertiary care center at the Cleveland Clinic between January 2008 and August 2016 was conducted. After training on standardized definitions, 4 blinded abdominal radiologists assessed imaging features of the most distal ileal stricture in 2 separate sessions (separated by ≥2 weeks) in random order. Acceptable reliability was an inter-rater intraclass correlation coefficient (ICC)≥0.41 (moderate reliability). Univariable and multivariable linear regression analysis identified reliable features associated with a visual analog scale of overall stricture severity. Significant, reliable features were assessed as components of a CT enterography-based model to quantitate stricture severity.

Results*:* Exams from 43 patients (mean age, 52 years ± 16 [SD]; 23 females) were evaluated. Five continuous measurements and 6 observations demonstrated at least moderate inter-rater reliability (inter-rater ICC range, 0.42 [95% CI 0.25, 0.57]–0.80 [95% CI 0.67, 0.88]). Of these, 10 were univariably associated, and 3 continuous measurements (stricture length (inter-rater ICC 0.64 [95% CI: 0.42, 0.81]), maximal associated small bowel dilation (inter-rater ICC 0.80 [95% CI: 0.67, 0.88]), and maximal stricture wall thickness (inter-rater ICC 0.50 [95% CI: 0.34, 0.62]) were independently associated (*P*<.001-.003) with stricture severity. These 3 measurements were used to derive a well-calibrated (optimism-adjusted calibration slope=1.00) quantitative model of stricture severity.

***Conclusion**:* Standardized CT enterography measurements and observations can reliably describe terminal ileal Crohn disease strictures. Stricture length, maximal associated small bowel dilation, and maximal stricture wall thickness are correlated with stricture severity.

INTRODUCTION (400/400)

Fibrostenotic strictures increase the risk of disease complications and surgery in patients with Crohn disease (1). Approximately 20% of patients present with a stricture at diagnosis and half will progress to a clinically apparent stricturing phenotype (1). Strictures likely precede the development of internal penetrating disease (1). Prevention and treatment of Crohn disease-associated strictures is an unmet medical need. No therapies are approved for this indication because drug development has been hampered by challenges inherent to stricture biology and a lack of consensus regarding optimal methods for diagnosing and defining stricturing disease, quantifying stricture severity, and assessing response to treatment (2).

Routine endoscopy does not provide comprehensive transmural evaluation of strictures, associated penetrating complications, nor frequently, their proximal extent. Impassable distal strictures often preclude assessment of more proximal strictures when multiple regions of narrowing are present. Finally, the reliability of endoscopic assessment of stenosis is poor (3).

Cross-sectional imaging has therefore emerged as the preferred method for assessing stricturing small bowel Crohn disease (4). CT and MR enterography are mainstays for evaluation in clinical practice. Selection of modality varies according to various factors (5). CT enterography has high spatial resolution, facilitates rapid diagnosis, and is widely available; however, it exposes patients to ionizing radiation, and is predominantly used in symptomatic or older patients (6). Both modalities have high sensitivity (>85%) and specificity (>90%) for diagnosing Crohn disease strictures, provide useful adjunctive information (eg, length and number of strictures, presence of concurrent inflammation or penetrating complications (eg, fistulas or abscesses) (7), and are used routinely to plan subsequent intervention.

Consensus recommendations and expert panels define a Crohn disease small bowel stricture as luminal narrowing, bowel wall thickening, and an associated small bowel dilation ≥3 cm (2, 8). Standardized methods to measure and describe small bowel Crohn disease strictures could guide clinical decision-making and potentially define relevant eligibility and efficacy criteria for therapeutic studies. A continuous CT enterography-based measure of stricture severity composed of reliable and responsive features could improve the efficiency of drug development in low sample size studies (eg, proof-of-concept and dose-finding designs) (2). However, the reliability of CT enterography imaging features has not been systematically studied in patients with stricturing Crohn disease, and the correlation of these features with stricture severity is unknown. Thus, the aim of this study was to assess the reliability of CT enterography features to describe Crohn disease strictures and their correlation with stricture severity.

MATERIALS AND METHODS (799/800 words)

Study design and patients

This was a retrospective analysis of data from adult patients with terminal ileal stricturing Crohn disease who underwent standard-of-care CT enterography at a tertiary care center at the Cleveland Clinic between January 2008 and August 2016. The research ethics board approved (19-572) the CT enterography exams for clinical research. Patient written informed consent was waived. Alimentiv participated in study design; collection, analysis, and interpretation of data; report-writing; and the decision to submit the paper for publication. Financial support also included an unrestricted grant from Pfizer, Inc and funding from the Leona M. and Harry B. Helmsley Charitable Trust. All authors had control of the data and information submitted for publication.

Eligibility criteria included: (i) diagnosis of Crohn disease by a gastroenterologist, (ii) a terminal ileal stricture within 15 cm of the ileocecal valve or ileocolonic anastomosis meeting CONSTRICT criteria (**Supplemental Table 1**) (2), and (iii) symptoms consistent with a stricture within 3 months of CT enterography imaging. Patients with internal penetrating disease, malignancy, or non-ileal/neo-terminal ileal strictures were excluded.

Natural language processing of radiology reports was used to produce a list of patients who met the search criteria of “Crohn disease,” “prestenotic dilation,” “upstream dilation,” and who underwent a CT enterography exam between 2008 and 2016. Exams that met the eligibility criteria based on manual screening of potentially eligible candidates were forwarded to a gastrointestinal radiologist (MEB; 38 years of experience) for review. Patients with a spectrum of stricture severity, and who underwent subsequent surgery or conservative management were included. Exams from patients with radiologic evidence of a Crohn disease-related stricture and adequate diagnostic image quality were selected, of which, exams from patients with symptoms consistent with obstruction upon retrospective review (FR) were included. Exams from patients who contributed more than one exam were excluded. All CT enterography exams were performed on Sensation 16, Sensation 64, Definition, Definition AS+, or Definition FLASH (Siemens Healthineers) units (see **Supplemental Methods** for imaging protocol).

CT enterography stricture measurements and observations

Radiologic features assessed were derived from a previous study (2) (**Table 1**). A single stricture was defined as an area with continuous luminal narrowing; multiple areas of luminal narrowing connected by active bowel inflammation; or multiple areas with luminal narrowing ≤3 cm apart. A visual analog scale (VAS) was employed as a global measure of stricture severity. Scoring of the VAS was performed using a 100 mm continuous horizontal line ranging from 0 (completely normal) to 100 mm (worst disease ever seen). Central readers provided a global assessment of stricture severity by placing a mark on the horizontal line. **Supplemental Figure 1** provides a visual example of VAS severity scores for representative radiologic images.

Reader training and procedures

Central readers included four abdominal radiologists (CSS, NC, SAT, JR with 5-20 years as subspecialized academic staff) blinded to all patient information. Reader training involved review of a comprehensive module consisting of definitions for features under consideration and methods for use of an online reading platform (OsiriX, version 11.0.0), and a separate virtual session involving case study review. Study exams were independently read twice (separated by ≥2 weeks) in random order. The most distal terminal ileal stricture was assessed.

Statistical analysis

Summary statistics described baseline demographic data. Reliability was quantified using the intraclass correlation coefficient (ICC), with point estimates derived using a 2-way random effects analysis of variance model, with interaction between CT enterography exams and readers (9). Two-sided 95% CI were estimated using the non-parametric percentile cluster bootstrap method (10). Reliability based on ICC estimates was interpreted as follows: <0.00=poor; 0.00-0.20=slight; 0.21-0.40=fair; 0.41-0.60=moderate; 0.61-0.80=substantial; and >0.80=almost perfect (11).

Features with at least moderate inter-rater reliability were subjected to univariate analysis using *P*<.05 to select features for multivariable linear regression analysis. The VAS also served as the anchor for development of a model to quantitate stricture severity. A preliminary full model was developed with *P*≤.10 as the criterion for feature retention. A backwards step-down approach simplified the model, with *P*<.05 as the criterion for feature retention. *P* values were calculated using the Student's t-test. Exploratory bivariate analysis of the relationship between the VAS and candidate features was performed to guide coding. A final model incorporating continuous features with moderate reliability and correlation with the stricture severity VAS was constructed. Model stability and optimism-corrected performance was evaluated using the 0.632 bootstrap method (12). Model coefficients were standardized by dividing by the smallest coefficient and rounding to the nearest integer. Within-patient standard deviation (SD) for model features was calculated in exploratory analyses (**Supplemental Methods**).

Sample size calculation assumed a 1-way random effects model for estimation of ICC (10). Assuming an ICC of 0.75, evaluation of 43 exams by 4 central readers ensured that the 1-sided 95% CI would exceed 0.60 with 79.2% probability.

Analyses were conducted by ZW in SAS version 9.4 (SAS Institute).

RESULTS (727/1000)

Baseline patient characteristics and CT enterography imaging sequences

Of 649 patients who met the search criteria, 119 contrast-enhanced CT enterography exams that met the manual screening eligibility criteria were forwarded for review. Eighty-three exams from 68 patients with radiologic evidence of a Crohn disease-related stricture and adequate diagnostic image quality were initially selected. Of those, 50 originated from patients with symptoms consistent with obstruction. Seven exams that originated from patients who contributed more than one exam were excluded, resulting in a total of 43 contrast-enhanced CT enterography exams for analysis (**Figure 1**). Thus, 43 patients (mean age, 52 years ± 16 [SD]; 20 males, 23 females) underwent a contrast-enhanced CT enterography exam, met the eligibility criteria, and were included for analysis (see **Table 2** for baseline demographics of the final study sample). A total of 58% (25/48) of the patients had prior ileocecal resection with ileocolonic anastomosis. Median stricture length was 8.2 cm (IQR 3.3, 20.7 cm). Median maximal stricture wall thickness was 4.8 mm (IQR 4.0, 6.0 mm). Median maximal associated small bowel dilation was 25.0 mm (IQR 20.2, 33.0 mm). The median VAS of stricture severity score was 49 (IQR 35, 60). The VAS stricture severity scores for the final 43 patients were normally distributed (**Supplemental Figure 2**).

Assessment of reliability

Inter- and intra-rater ICCs for radiologic features potentially relevant for assessment of stricturing Crohn disease on CT enterography are summarized in **Table 3.** Reader level intra-rater reliability is summarized in **Supplemental Table 2.** There was substantial (ICC 0.61-0.80) inter-rater reliability for assessment of maximal associated small bowel dilation (ICC 0.80 [95% CI: 0.67, 0.88]), stricture length (ICC 0.64 [95% CI: 0.42, 0.81]), and stricture distance from the ileocecal valve or ileocolonic anastomosis (ICC 0.63 [95% CI: 0.33, 0.77]). Several features had moderate (ICC 0.41-0.60) inter-rater reliability, including maximal stricture wall thickness, maximal luminal diameter of stricture, sacculations, peri-enteric fat stranding, engorged vasa recta, mural hyperenhancement, ulceration, and enhancement pattern on enterographic phase. All remaining items had slight to fair inter-rater reliability, with the lowest ICC estimates for inter-rater reliability observed for the measurement of wall thickness of normal bowel (ICC 0.06 [95% CI: 0.01, 0.12]).

Intra-rater reliability for most CT enterography features was substantial to almost perfect. Specifically, almost perfect intra-rater reliability (ICC 0.81-1.0) was observed for maximal associated small bowel dilation, stricture length, maximal stricture wall thickness, and regional enlarged lymph nodes.

Inter-rater reliability was moderate (ICC 0.44 [95% CI: 0.23, 0.58]) and intra-rater reliability was substantial (ICC 0.78 [95% CI: 0.69, 0.84]) for scoring of the VAS of stricture severity.

The within-patient SD for maximal associated small bowel dilation, stricture length, and maximal stricture wall thickness was 9.9 mm, 9.2 cm, and 1.6 mm, respectively. Within-patient SD for maximal associated small bowel dilation and stricture length was relatively small compared to the actual maximal associated small bowel dilation and stricture length, whereas the within-patient SD was relatively large compared to the actual measurement for maximal stricture wall thickness (**Figure 2**).

Univariable and multivariable linear regression for development of a model to quantitate stricture severity

Univariable linear regression of reliable CT enterography measurements and observations determined that stricture length, maximal stricture wall thickness, maximal associated small bowel dilation, mural hyperenhancement, ulceration, maximal luminal diameter of stricture, engorged vasa recta enhancement pattern enterographic phase, peri-enteric fat stranding, and sacculations were significantly correlated with the VAS of stricture severity (*P* <.001–.03) (**Supplemental Table 3)**. A full multivariable model including three continuous features (stricture length, maximal stricture wall thickness, and maximal associated small bowel dilation) independently associated with VAS of stricture severity (*P* <.001–.003) was constructed (**Supplemental Table 4)**. The relationships between the model features and the VAS are summarized in **Supplemental Figure 3**. The R^2 of the model was 0.71 and was 0.65 after optimism correction. The optimism-corrected calibration slope was 1.00.

Using standardized coefficients, stricture severity may be calculated as the sum of stricture length (cm), maximal associated small bowel dilation (mm), and five times the maximal stricture wall thickness (mm). The model had substantial inter-rater (ICC 0.72 [95% CI: 0.62, 0.78]) and almost-perfect intra-rater (ICC 0.92 [95% CI: 0.87, 0.96]) reliability. Mean (SD) and median (IQR) stricture severity scores for the final 43 patients based on the model were 66 (22) and 63 (50, 81). Scores ranged from 17 to 125. Images for a representative patient are shown in **Figure 3**.

DISCUSSION

CT enterography is routinely used to evaluate small bowel stricturing Crohn disease and provides complementary cross-sectional information beyond symptoms or ileocolonoscopy. Although surgical assessment and endoscopy are consensus reference standards in inflammatory and perianal Crohn disease (13, 14), they have limited utility in fibrostenosing disease. Endoscopic evaluation is constrained in the presence of impassable strictures, has poor accuracy for evaluating stricture length, and is limited to observation of luminal disease (8, 15). Histologic evaluation of fibrosis also inadequately describes the extent or degree of stricturing disease, both of which contribute to the pathophysiologic impact of the disease, and reproducible histopathologic assessments of Crohn disease fibrostenosis severity are lacking (16, 17). Identification of accurate and reliable methods for describing Crohn disease small bowel strictures on CT enterography is a clinical and research priority given the substantial proportion of patients with Crohn disease who develop this phenotype, the attendant complications and negative prognostic implications, and the lack of approved treatments for this indication (1). We aimed to assess the reliability of CT enterography features to describe Crohn disease strictures as well as their correlation with stricture severity. Three common features (maximal associated small bowel dilation, maximal stricture wall thickness, and stricture length) were identified in this study as reliably assessed (inter-rater ICC≥.041) and correlated with stricture severity ($P<.05$). These features may have value in clinical practice to guide therapeutic decision-making and in clinical trials of anti-fibrotic therapies to define eligibility and efficacy criteria.

The three model features are relevant to stricture morphology and associated with clinically meaningful outcomes. Studies have demonstrated an association between prestenotic dilation and a two- to three-fold increased risk of resection (18-20). Increased bowel wall thickness, which may result from inflammation, accumulation of extracellular matrix, and expansion of mesenchymal cells (21), strongly discriminates active terminal ileal Crohn disease from normal bowel, and is correlated with endoscopic and histologic Crohn disease activity (22, 23). Finally, stricture length is likely a function of disease extent, severity, and duration. Longer strictures are less likely to respond to endoscopic balloon dilation; a meta-analysis including 676 patients with Crohn disease found an 8% increase in hazard for surgery ($P=.008$) with each 1 cm increase in stricture length (20). Stricture length was additionally a predictor for shorter time to intervention (balloon dilation or surgery) (24).

CT enterography has high sensitivity and specificity for diagnosing Crohn disease-related strictures when post-surgical histopathology is used as the reference standard (4). Bowel wall thickness and prestenotic dilation are among several radiologic features previously proposed for assessment of stricturing Crohn disease (25-27), and current North American and European guidelines recommend the routine description of stricture length, presence of upstream dilation, and wall thickness in radiology reports for patients with small bowel stricturing Crohn disease and for diagnostic assessment of inflammatory bowel disease (8, 15).

The model features were also found to be significantly associated with stricture severity in a companion MR enterography study, potentially suggesting the interchangeability of CT and MR enterography for assessment of Crohn disease stricture severity in research and clinical practice. Although MR enterography avoids ionizing radiation and may provide imaging findings better correlated with inflammation versus fibrostenosis (28-31), there are practical and technical advantages to CT enterography that may also be important in the clinical trial setting, including simplicity, widespread availability, reduced cost, shorter image acquisition time, and higher spatial resolution. The ability of CT enterography to expand the network of sites that can participate in clinical trials may be crucially important as the development of anti-stricture therapies proceeds to large, phase 3 programs.

Our study had several important strengths. We systematically evaluated the reliability of CT enterography features in patients with stricturing Crohn disease and used robust methodology to develop a model with face validity that reflects stricture severity. We also developed scoring conventions and a training program for CT enterography based assessment of Crohn disease-related strictures. The included patients in our study were symptomatic with a broad spectrum of non-penetrating terminal ileal Crohn disease strictures and are representative of patients eligible for participation in clinical trials. The model features are also relevant for disease assessment in clinical trials employing MR enterography and could potentially foster inclusion of younger patients by avoiding radiation exposure. Although our study was conducted with subspecialized abdominal radiologists, the model and conventions used to define the proximal and distal extent of a stricture and to measure maximal associated small bowel dilation may also be translatable to clinical care.

We also acknowledge several limitations. First, stricture length was measured using curvilinear multiplanar reconstruction (MPR). Although this method provides the greatest accuracy for assessment of stricture length, we acknowledge that MPR may not currently be broadly feasible in routine clinical practice. However, algorithms are frequently added to workstations once clinical utility has been established, and our study may be a first step towards that goal. Second, given the limitations of endoscopy, histopathology, and patient symptoms to serve as reference standards for stricture severity, a VAS (of stricture severity) was used as the dependent variable for model development. However, there is precedent for this approach in index development in Crohn disease for other modalities (e.g., endoscopy, patient-reported outcomes) (32, 33) and anatomic locations (perianal disease) (34, 35), and for use of a VAS to identify independent variables correlated with disease severity (34, 35). Finally, there is a long history of regulatory acceptance of VAS-derived indices (32, 33, 36). Third, our model requires external validation ideally using both CT enterography and MR enterography. Specifically, model responsiveness must be demonstrated when applied to treatment of known efficacy. No effective medical therapies currently exist for this indication, although several promising agents are in development (37, 38). Fourth, although we provide optimism-adjusted estimates, the generalizability of our model requires empiric assessment.

In conclusion, we evaluated the reliability of CT enterography features for describing fibrostenosing ileal Crohn disease and developed a model for quantitating stricture severity based on maximum associated small bowel dilation, stricture length, and maximal stricture wall thickness, all of which can be reliably measured by abdominal radiologists using standardized definitions and methods. These features can be assessed in routine clinical care and on MR enterography images, and may potentially be used as inclusion and efficacy criteria in clinical trials of anti-fibrotic therapy.

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TABLES

Table 1. Definitions of features for scoring of Crohn disease-related terminal ileal strictures on CT enterography.

Feature	Definition
Stricture length	Length of stricture, measured in cm[a]
Stricture distance from ileocecal valve or ileocolonic anastomosis	Distance from the most distal part of the most distal stricture to the ileocecal valve or site of ileocolonic anastomosis, measured in cm
Luminal diameter of stricture	Maximum caliber of bowel lumen within stricture, measured in mm (3 measurements)
Luminal diameter of normal-appearing bowel	Caliber of normal, adjacent, appropriately distended ileal bowel loop, measured in mm (3 measurements)
Maximal associated small bowel dilation	Measurement of maximum dilation in prestenotic bowel, measured in mm, selecting the view/plane with the maximal diameter (3 measurements)
Maximal stricture wall thickness	Maximally thickened area, measured in mm (3 measurements)
Wall thickness of normal bowel	Adjacent appropriately distended ileal bowel loop, measured in mm (3 measurements)
Mural hyperenhancement	Increased uptake of contrast in a well-distended bowel segment relative to nearby normal-appearing loops, measured as absent or present
Enhancement pattern at the enterographic phase	Inner wall hyperenhancement or halo sign, assessed as homogeneous, mucosal only, or target pattern
Ulceration	Areas of depression/ irregularity in the inner surface of a thickened intestinal wall; linear enhancing tracts within the bowel wall should be considered fissures (linear ulcers), measured as absent or present
Creeping fat	Adherence of mesenteric fibrofatty tissue over the circumference of a thickened bowel loop which displaces strictures, measured as absent or present
Peri-enteric fat stranding	Loss of normal sharp interface between the bowel wall and mesentery, with edema and/or fluid and/or enhancement in the peri-enteric fat, measured as absent or present
Engorged vasa recta	Increased and prominent peri-enteric vasa recta that supply a bowel loop, measured as absent or present
Asymmetric inflammation	Asymmetric in cross-sectional or longitudinal direction compared to the lumen, measured as absent or present
Regional enlarged lymph nodes	Presence of lymph nodes >10 mm diameter in short axis
Sacculations	Broad-based outpouchings along the mesenteric border of the bowel, resulting from shortening along the mesenteric border, which are identified in either plane

[a]Strictures start and end where luminal narrowing starts and stops. Two areas, each with wall thickening and luminal narrowing, separated by ≤3 cm of normal-appearing bowel were marked as a single stricture.

Table 2. Baseline patient demographics

Characteristic	N=43
Age, years	
Mean (SD)	52.5 (16.2)
Median (IQR)	48.0 (38.0, 67.0)
Range	28, 87
Age at symptom onset, years[a]	
Mean (SD)	26.0 (12.6)
Median (IQR)	22.0 (16.5, 34.0)
Age at Crohn disease diagnosis, years	
Mean (SD)	24.1 (11.5)
Median (IQR)	21 (15, 34)
Male sex, n (%)	20 (46.5)
Race, n (%)[b]	
White	41 (95.3)
Asian	2 (4.7)
Weight, kg	
Mean (SD)	67.5 (15.1)
Median (IQR)	68.5 (53.8, 77.2)
Height, cm	
Mean (SD)	170.7 (8.9)
Median (IQR)	170.2 (162.6, 177.8)
Body mass index[c]	
Mean (SD)	23.0 (3.9)
Median (IQR)	22.0 (20.2, 26.2)
Smoking status, n (%)	
Never	21 (48.8)
Former	10 (23.3)
Current	12 (27.9)
Prior ileocecal resection, n (%)	25 (58.1)

[a]Nine patients with missing data.

[b]As recorded in chart history and self-reported

[c]Calculated as weight in kilograms divided by the square of height in meters

Table 3. Inter- and intra-rater reliability of radiologic items for Crohn disease-related strictures

Item[a]	Inter-rater ICC (95% CI)	Intra-rater ICC (95% CI)
CT enterography imaging measurements		
Maximal associated small bowel dilation (mm)	0.80 (0.67, 0.88)	0.92 (0.87, 0.95)
Stricture length (cm)	0.64 (0.42, 0.81)	0.93 (0.89, 0.97)
Stricture distance from ileocecal valve or ileocolonic anastomosis (cm)	0.63 (0.33, 0.77)	0.75 (0.65, 0.92)
Maximal stricture wall thickness (mm)	0.50 (0.34, 0.62)	0.89 (0.81, 0.94)
Luminal diameter of stricture (mm)	0.43 (0.31, 0.53)	0.76 (0.67, 0.85)
Luminal diameter of normal bowel (mm)	0.40 (0.26, 0.54)	0.68 (0.57, 0.76)
Wall thickness of normal bowel (mm)	0.06 (0.01, 0.12)	0.64 (0.54, 0.72)
CT enterography imaging observations		
Sacculations	0.56 (0.35, 0.71)	0.62 (0.41, 0.80)
Peri-enteric fat stranding	0.51 (0.32, 0.66)	0.71 (0.57, 0.83)
Engorged vasa recta	0.47 (0.33, 0.61)	0.72 (0.62, 0.81)
Mural hyperenhancement	0.46 (0.27, 0.66)	0.76 (0.60, 0.88)
Ulceration	0.43 (0.26, 0.57)	0.75 (0.63, 0.84)
Enhancement pattern enterographic phase	0.42 (0.25, 0.57)	0.78 (0.68, 0.85)
Creeping fat	0.31 (0.18, 0.44)	0.72 (0.62, 0.82)
Regional enlarged lymph nodes	0.23 (0.09, 0.36)	0.84 (0.73, 0.96)
Asymmetric inflammation	0.25 (0.13, 0.36)	0.62 (0.47, 0.74)
Visual analog scale[b]		
Severity	0.44 (0.29, 0.58)	0.78 (0.69, 0.84)

Abbreviations: ICC, intraclass correlation coefficient.

[a]Descriptive text that accompanied item assessment is included in **Table 1.**

[b]Scoring of the VAS was performed using a 100 mm continuous horizontal line ranging from 0 (completely normal) to 100 mm (worst disease ever seen). Central readers provided a global assessment of stricture severity by placing a mark on the horizontal line.

Reliability based on ICC estimates was interpreted as follows: <0.00=poor; 0.00-0.20=slight; 0.21-0.40=fair; 0.41-0.60=moderate; 0.61-0.80=substantial; and >0.80=almost perfect.

Table 4. Multivariable development of the CT enterography model of stricture severity.

Candidate model feature	**Full model *P*-value***	**Four-feature model coefficients**	***P*-value***	**Three-feature[a] model coefficients**	***P*-value***
Stricture length	.004	0.61	.003	0.76	<.001
Luminal diameter of stricture	.42				
Maximal associated small bowel dilation	<.001	0.71	<.001	0.66	<.001
Maximal stricture wall thickness	.04	3.33	<.001	3.2	.003
Perienteric fat stranding	.56				
Mural hyperenhancement	.38				
Enhancement pattern at the enterographic phase	.63				
Engorged vasa recta	.96				
Presence of radiographic ulceration	.93				
Sacculation	.01	8.9	.004		
Model performance					
R^2		0.77		0.71	
R^2 in validation		0.68		0.65	
Optimism between R^2 and R^2 in validation		0.09		0.07	
Optimism-corrected calibration slope		0.97		1.00	
Calibration intercept		1.61		-0.39	

*Calculated using the Student's t-test
[a]Restricted to features measured on a continuous scale.

FIGURE LEGENDS

Figure 1. Selection of exams. Natural language processing of radiology reports was used to produce a list of patients who met the search criteria of “Crohn disease,” “prestenotic dilation,” “upstream dilation,” and who underwent a CT enterography exam performed between 2008 and 2016. Exams that met the eligibility criteria based on manual screening of potentially eligible candidates were forwarded to a gastrointestinal radiologist for review. Exams from patients with radiologic evidence of a Crohn disease-related stricture and adequate diagnostic image quality were selected, of which, exams from patients with symptoms consistent with obstruction upon retrospective review were included. Exams that originated from patients who contributed more than one exam were excluded.

Figure 2. Central reader measurements for (A) maximal associated small bowel dilation (mm), (B) stricture length (cm), and (C) maximal stricture wall thickness (mm) for each patient in the final study sample (n=43). Black dots indicate the mean measurement value for each patient. For each variable, patient values are displayed from the smallest to largest. The dotted horizontal line (Panel B) indicates an arbitrary threshold for stricture length of 5.0 cm. Note that measurement variability in maximal associated small bowel dilation remains relatively constant.

Figure 3. Contrast-enhanced CT enterography imaging findings of a Crohn disease small bowel stricture in a 79-year-old male patient included in the study population. Figure panels A and B correspond to axial CT enterography images showing the presence of a long stricture (arrow) with a maximally thickened area of the wall (6.8 mm; white line in panel A) and marked maximal associated small bowel dilation (60.3 mm; white line in panel B). Curvilinear multiplanar reconstruction (panel C) focused on the same small bowel stricture allows measurement of the total length of the stricture (10.2 cm; white line).

SUPPLEMENTAL MATERIAL

SUPPLEMENTAL FIGURE LEGENDS

Supplemental Figure 1. Visual analog scale[a] of stricture severity scores for 3 representative cases. Corresponding mean (SD) values for stricture length and maximum associated small bowel dilation are also provided.

Abbreviations: VAS, visual analog scale; max, maximum.

[a]Scoring of the VAS was performed using a 100 mm continuous horizontal line ranging from 0 (completely normal) to 100 mm (worst disease ever seen). Central readers provided a global assessment of stricture severity by placing a mark on the horizontal line.

Supplemental Figure 2. Distribution of VAS[a] of stricture severity scores in the final study sample (n=43).

Abbreviation: VAS, visual analog scale.

[a]Scoring of the VAS was performed using a 100 mm continuous horizontal line ranging from 0 (completely normal) to 100 mm (worst disease ever seen). Central readers provided a global assessment of stricture severity by placing a mark on the horizontal line.

Supplemental Figure 3. Bivariate relationship between CT enterography model features and the VAS[a] of stricture severity.

The VAS of stricture severity scores for the CT enterography features were evaluated according to ranges of values for each feature (shown on the y-axis). Linear relationships were present between increments in the VAS stricture severity scores and each CT enterography feature. Scores for these features were therefore treated as continuous variables for model development.

Abbreviation: VAS, visual analog scale

[a]Scoring of the VAS was performed using a 100 mm continuous horizontal line ranging from 0 (completely normal) to 100 mm (worst disease ever seen). Central readers provided a global assessment of stricture severity by placing a mark on the horizontal line.

SUPPLEMENTAL TABLES

Supplemental Table 1. CONSTRICT stricture criteria

Criterion	Definition
Localized luminal narrowing	Luminal diameter reduction of at least 50%, measured relative to the normal adjacent bowel loop
Bowel wall thickening	A 25% increase in wall thickness relative to the adjacent nonaffected bowel
Pre-stricture dilation	Luminal diameter greater than 3 cm

Supplemental Table 2. Intra-rater reliability according to central reader.

Variable	Reader 1	Reader 2	Reader 3	Reader 4
Stricture length (cm)	0.93	1.00	0.86	0.91
Stricture distance (cm)	0.73	0.99	0.48	0.89
Luminal diameter of stricture (mm)	0.78	0.92	0.66	0.27
Luminal diameter of normal bowel (mm)	0.69	0.99	0.66	0.30
Maximal stricture wall thickness (mm)	0.83	0.98	0.79	0.76
Maximal associated small bowel dilation	0.95	0.97	0.91	0.86
Wall thickness of normal bowel (mm)	‥*	0.76	0.24	0.40
Creeping fat	0.39	1.00	0.62	0.67
Perienteric fat stranding	0.53	0.90	0.77	0.62
Mural hyperenhancement	0.66	‥*	0.91	0.70
Enhancement pattern at the enterographic phase	0.55	0.98	0.73	0.69
Engorged vasa recta	0.65	0.86	0.52	0.77
Asymmetric inflammation	0.42	0.73	0.49	0.83
Presence of radiographic ulceration	0.74	0.85	0.81	0.59
Regional enlarged lymph nodes	0.54	0.90	‥*	0.91
Sacculations	0.55	0.87	0.53	0.54
VAS severity[a]	0.77	0.91	0.72	0.50

Abbreviation: VAS, visual analog scale

*Little or no variance in assessment observed, resulting in ICC values approaching zero

[a]Scoring of the VAS was performed using a 100 mm continuous horizontal line ranging from 0 (completely normal) to 100 mm (worst disease ever seen). Central readers provided a global assessment of stricture severity by placing a mark on the horizontal line.

Supplemental Table 3. Univariable linear regression analysis of reliable CT enterography features with the visual analog scale[a] of stricture severity.

Candidate model feature	***P*-value***
Stricture length	<.001
Maximal stricture wall thickness	<.001
Maximal associated small bowel dilation	<.001
Mural hyperenhancement	.001
Ulceration	.001
Luminal diameter of stricture	.005
Engorged vasa recta	.02
Enhancement pattern at the enterographic phase	.02
Perienteric fat stranding	.03
Sacculations	.03
Stricture distance	.08

*Calculated using the Student's t-test

[a]Scoring of the VAS was performed using a 100 mm continuous horizontal line ranging from 0 (completely normal) to 100 mm (worst disease ever seen). Central readers provided a global assessment of stricture severity by placing a mark on the horizontal line.

SUPPLEMENTAL METHODS

CT enterography image acquisition and reconstruction

Patients ingested 1200 mL of neutral enteric contrast (VoLumen, Bracco Diagnostics) over 45 minutes followed by 200 mL of water just before the exam, one hour after the start of contrast ingestion. Exams were performed in the portal venous phase (70 seconds after the start of the injection) after intravenous administration of 150 mL iodinated contrast media (Ultravist-300, iopromide, 300 mg/mL, Bayer HealthCare). Exams included the top of the diaphragm and the perineum using the following technique: 120 kVp, quality mAs adjusted to weight (1 mAs per pound) using automated exposure control; 3 mm contiguous slices reconstructed in the axial and coronal planes. Exams were hosted on a secure remote server for central reader viewing after de-identification of DICOM images.

Calculation of within-patient standard deviation for model features

Useful radiologic features should also be minimally variable to detect clinically meaningful changes. Random effects models were used to estimate the within-patient variance, where the continuous measurements were the outcome variables, and the patient was the random effect. The first reading of each radiologist was used for these analyses. Within-patient standard deviation was calculated as the square root of the within-patient variance.