# Quantified Terminal Ileal Motility during MR Enterography as a Biomarker of Crohn Disease Activity: Prospective Multi-Institution Study

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Conflicts of interest are listed at the end of this article.

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***Purpose:*** To evaluate the accuracy of MRI-quantified small bowel motility for Crohn disease activity against endoscopic and histopathologic reference standards.

***Materials and Methods:*** For this prospective study, 82 participants (median age, 31 years; range, 16 to 70 years; 42 males [median age, 31 years; range, 17 to 70 years] and 40 females [median age, 31 years; range, 16 to 63 years) underwent colonoscopy and MR enterography within 14 days (from October 2011 to March 2014) at two centers. The Crohn disease endoscopic index of severity (CDEIS), histopathologic activity score (endoscopic biopsy acute histologic inflammatory score [EAIS]), and MR index of activity (MaRIA) were scored in the terminal ileum. Terminal ileal motility was quantified by using an image registration based–motility assessment algorithm (hereafter, Motility). Sensitivity and specificity of Motility (<0.3 arbitrary units) and MaRIA (≥7 and ≥11) for disease activity (CDEIS ≥4 or EAIS ≥1) were compared by using the McNemar test. Receiver operating characteristic curves were constructed and areas under the curve were compared. Motility was correlated with reference standards by using Spearman rank estimates.

***Results:*** Terminal ileal Motility was negatively correlated with EAIS ($r = -0.61$; 95% confidence interval [CI]: 0.7, −0.5) and CDEIS ($r = -0.59$; 95% CI: 0.7, −0.4). With CDEIS as the standard of reference, Motility had higher sensitivity than did MaRIA (≥11) (93% vs 78%, respectively; $P = .03$), but lower specificity (61% vs 81%, respectively; $P = .04$). With EAIS as the standard of reference, Motility had higher sensitivity than did MaRIA (≥7) (92% vs 75%, respectively; $P = .03$) but similar specificity (71% vs 74%, respectively; $P > .99$). The area under the receiver operating characteristic curve for Motility was 0.86 and 0.87 with CDEIS and EAIS as the standard of reference, respectively.

***Conclusion:*** The terminal ileal Motility score showed good agreement with endoscopic and histopathologic activity in Crohn disease.



*Online supplemental material is available for this article.*

MR enterography is increasingly implemented for the diagnosis and monitoring of Crohn disease (1). In particular, MRI activity scores based on features such as wall thickness, T2 signal, ulceration, and contrast enhancement with gadolinium have been validated against a variety of reference standards including endoscopy, histologic analysis, and biochemical markers such as calprotectin (2–5), and can effectively depict treatment response (6–8). A limitation of current activity scores is that treatment changes may lag behind clinical response (9). Although inter- and intra-agreement data are reasonable (10), scoring is time consuming, which limits use in routine clinical practice.

An alternative to assessing activity by using bowel structure is to evaluate function, specifically segmental motility. Recent software innovations now allow rapid quantitation of segmental bowel motility (11–14) with minimal user input. Emerging evidence suggests that reduced segmental motility in affected bowel is directly associated with Crohn disease inflammatory activity (15,16). Furthermore, initial data suggests that improvements in motility in response to treatment may be better able to predict early treatment outcome compared with standard MRI activity scores (6).

Most prior studies evaluating bowel motility as a biomarker of Crohn disease activity have been single site and retrospective (15–18). The purpose of our study was to prospectively evaluate the accuracy of MRI quantified–small bowel motility for Crohn disease activity against endoscopic and histopathologic reference standards.

## Abbreviations

AUC = area under the receiver operating characteristic curve, CDEIS = Crohn disease endoscopic index of severity, CI = confidence interval, EAIS = endoscopic biopsy acute histologic inflammatory score, MaRIA = MR index of activity


## Summary

Quantified motility is an objective biomarker of endoscopic and histopathologic inflammatory activity in Crohn disease and is comparable to previously validated gadolinium-enhanced MRI activity scores.


## Implications for Patient Care

- Use of MRI as a noninvasive biomarker of Crohn disease activity may reduce the need for endoscopy.
- Software quantified–small bowel motility appears to be an objective indicator of inflammatory activity that is comparable to previously validated gadolinium-enhanced MRI activity scores.

# Materials and Methods

### Participants

Participants were recruited prospectively and enrolled at two European centers (center 1, University College London, United Kingdom; center 2, Academisch Medisch Centrum, the Netherlands) as part of the Virtual Gastrointestinal Tract, or VIGOR++, study (funded by the European Union's Seventh Framework Program, project no. 270379) that ran between June 2011 and March 2014. Ethical permission was obtained from the medical ethics committees of both institutions and written informed consent was obtained from each participant. The VIGOR++ study was designed to develop software analysis tools for bowel wall structure such as wall thickness and contrast enhancement to partly automate the evaluation of disease activity by using MRI (19–21). Recruited participants known to have or suspected of having Crohn disease underwent MR enterography and colonoscopy with biopsy sampling within 2 weeks of each other (as a convenience series). The funding agency had no influence on how the study was performed or reported.

The VIGOR++ study identified a total of 158 recruited participants (69 at center 1 and 89 at center 2). Among these, 52 participants were excluded for the following reasons: diagnosis other than Crohn disease ($n$ = 18), greater than 14 days between MRI and colonoscopy ($n$ = 7), failure to comply with the oral contrast protocol ($n$ = 6), cancelled or aborted ileocolonoscopy ($n$ = 5), incomplete MRI protocol (eg, missing sequences and incomplete imaging; $n$ = 14), insufficient bowel cleansing ($n$ = 1), and noncompliance with breathing commands because of language barrier ($n$ = 1), leaving 106 participants suitable for analysis (37 at center 1 and 69 at center 2).

For inclusion in our study, we selected all participants from the VIGOR++ study who had a confirmed diagnosis of Crohn disease based on established criteria, good-quality motility images through the terminal ileum (see motility assessment section below) as judged by our study coordinator (A.M., a postdoctoral research fellow with 8 years of experience in MR enterography) and study radiologist (G.B., a consultant gastrointestinal radiologist with 9 years of experience) in consensus, and a terminal ileum biopsy available (22).

### MRI Protocol

An identical MRI protocol was used at both sites. Participants fasted for 4 hours before ingesting 800 mL of 2% mannitol 3 hours prior to the start of the examination to fill the colon. An additional 1600 mL of 2% mannitol was provided 1 hour before the examination start time and participants were instructed to drink to tolerance to distend the small bowel.

Participants were imaged in the supine position with 3.0-T systems (center 1, Achieva and center 2, Ingenia; Philips, Best, the Netherlands) by using the manufacturer's external body coils. Specific details of the imaging parameters are provided in Table E1 (online). In summary, small bowel motility was captured by using a two-dimensional, coronal, balanced turbo field-echo sequences acquired during a 22-second breath hold. The temporal resolution of the dynamic images was 1.1 seconds per section with a section thickness of 10 mm. After each breath-hold acquisition, radiographic technicians repositioned the acquisition block from anterior to posterior to cover the whole of the small bowel volume, ensuring at least one of the dynamic series was acquired through the terminal ileum.

Following motility sequences (Table E1 [online]), a spasmolytic agent (hyoscine butylbromide; Boehringer Ingelheim, Ingelheim am Rhein, Germany) was administered intravenously and before structural MRI (ie, T2-weighted and gadolinium-enhanced sequences) were acquired.

### Colonoscopy and Endoscopic Assessment of Inflammation

Ileocolonoscopy was performed by using standard bowel preparation and equipment within 2 weeks of the MRI by either a consultant gastroenterologist (with at least 10 years of experience) or senior gastroenterology trainee under direct supervision of the consultant gastroenterologist. The endoscopist was blinded to results from MRI except when balloon dilatation was considered for short strictures and MR images were used to determine the stricture length. The segmental Crohn disease endoscopic index of severity (CDEIS) was scored for all endoscopically intubated terminal ileum segments by using conventional definitions (23) within 20 cm of the ileocecal valve. Two to four biopsies were also taken from the last 5 cm of the terminal ileum. When colonoscopy was performed by a senior trainee, the CDEIS was assigned by the supervising consultant present. The CDEIS was selected as a reference standard because it is a widely used quantitative metric for Crohn disease activity.

### Histopathologic Assessment of Inflammation

Each terminal ileal biopsy was stained with hematoxylin-eosin and reviewed in face-to-face consensus by two experienced pathologists (M.R.J. and L.A.B., with 10 years and 15 years of experience, respectively) who were blinded to clinical information other than the diagnosis of Crohn disease. The endoscopic biopsy acute histologic inflammatory score

(EAIS) was used to semiobjectively evaluate typical morphologic features associated with Crohn disease activity as previously described (24,25). The EAIS score includes measures of epithelial damage, architectural changes in the mucosa, epithelial neutrophils, erosion and/or ulceration, and the presence of granulomas (Table E2 [online]). The biopsy with the highest score was used to grade the level of inflammation for each patient. The EAIS was selected as a reference standard because it is an alternative quantitative metric to CDEIS for measuring disease activity.

## Motility Assessment

Terminal ileal motility was quantified by using the methodology described by Menys et al (15). Specifically, the dynamic series for each participant were processed by the study coordinator with a previously validated registration algorithm designed for the assessment of bowel motility (13) (GI-Quant, version 2.0; Motilent, London, United Kingdom). Deformation fields generated with the registration were used to produce a surrogate motility metric defined as the standard deviation of the Jacobian determinant of the deformation fields in the terminal ileum (hereafter, Motility), with a score of zero representing no motility.

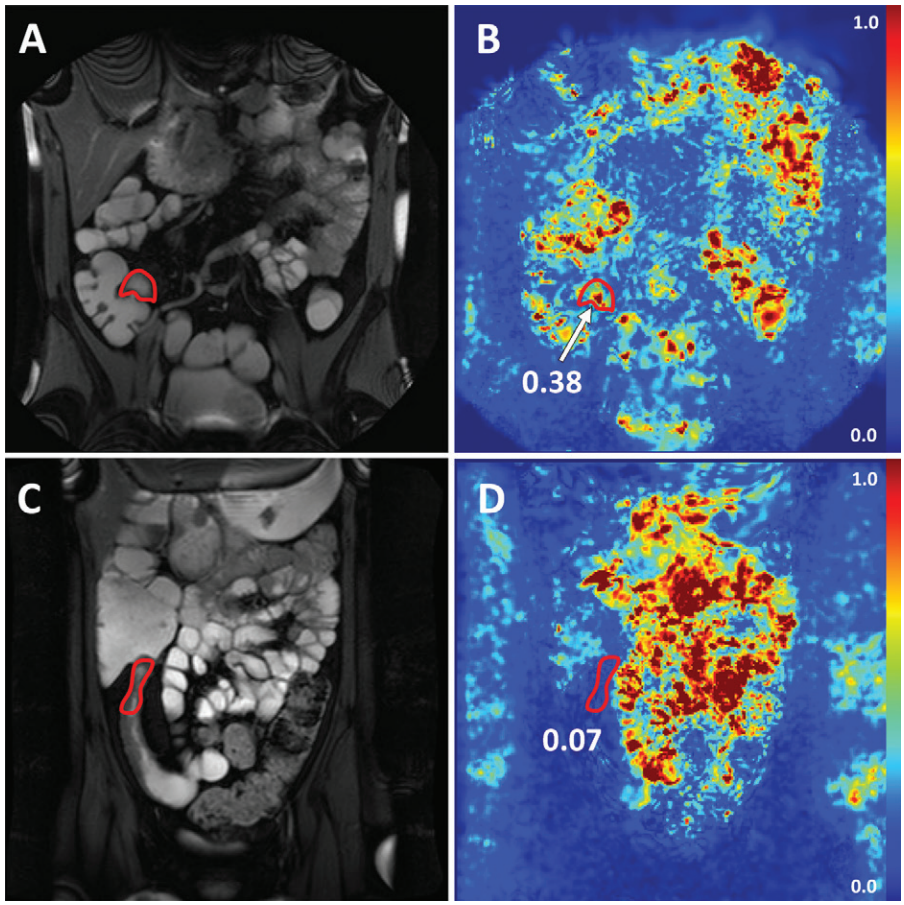


**Figure 1:** Anatomic reference MR images in, *A*, a healthy 32-year-old man and, *C*, a 19-year-old man with neoterminal ileal Crohn disease along with, *B*, *D*, corresponding Motility maps. Region of interest at terminal ileum is indicated in red along with Motility score depicting high motility (*B*) and low motility (*D*).

A single observer (G.B., who was independent to the observers who derived the MR index of activity [MaRIA] score) was presented with a single registration target image (selected automatically by the registration technique) containing the terminal ileum and was otherwise blinded to the motility data (including the cine series and Motility maps) and all clinical data. The observer used the automatically selected reference image to manually place a polygonal region of interest within the last 5 cm of terminal ileum in each participant to encompass the bowel wall and lumen (Fig 1). The region of interest was automatically applied to the parametric Motility map, each pixel of which was produced by taking the deformation fields standard deviation of its Jacobian determinant value, with the average pixel value taken from under the region of interest on the map to create the terminal ileal Motility score for that patient in arbitrary units (au). Because previous data has already shown good intraobserver agreement for this observer (6), this was not repeated for the current study.

## MaRIA Score

The terminal ileal MaRIA score within 5 cm of the ileocecal valve was calculated independently by two radiologists for participants imaged at their respective institutions (33 participants by D.P., with 10 years of experience at center 1; 49 participants by C.N., with 4 years of experience at center 2) by using the standard anatomic images as described by Rimola et al (4) and by using the following formula: MaRIA = [1.5 × wall thickness (mm)] + [0.02 × relative contrast enhancement] + [5 × edema] + [10 × ulcers].

## Statistical Analysis

The primary analysis tested the ability of Motility scores below a predefined cutoff to detect active inflammation by using both endoscopic and histologic standards of reference. A secondary analysis assessed the ability of Motility scores to quantify the severity of inflammation (again, judged by using both endoscopy and histologic scoring systems). The same analyses were calculated for the MaRIA score and compared with those of the Motility metric.

A predefined Motility metric cutoff of 0.30 au was applied to define the presence of active inflammation. This threshold was prespecified by using the optimal cutoff point from a previously published retrospective cohort (15) (Fig E1 [online]).

The sensitivity and specificity of a Motility score of less than 0.30 au for the presence of active inflammation, defined as either an CDEIS of greater than or equal to 4 (endoscopic

standard of reference) or EAIS score of greater than or equal to 1 (histopathologic standard of reference) was calculated. A CDEIS cutoff of greater than or equal to 4 was chosen given its utility as a marker of mucosal healing (7).

The above analysis was repeated by using the MaRIA score. A MaRIA score of less than 7 has been previously associated with mucosal healing (score ≥7 representing active disease) and a score of less than 11 has been associated with ulcer healing (score ≥11 representing the presence of ulceration) (4). Both cutoffs were tested in the analysis.

The differences in sensitivity and specificity between Motility scores and the MaRIA scores were assessed with McNemar test, where the null hypothesis was no difference existed between the two scores.

Thereafter, linear correlation between Motility scores and the MaRIA scores, and both EAIS and CDEIS, was performed with Spearman rho. Finally, receiver operating characteristic curves of Motility and the MaRIA score to detect inflammation based on both EAIS and CDEIS were constructed and area under the receiver operating characteristic curve (AUC) calculated. The AUC for Motility and MaRIA score against both standards of reference were compared (DeLong method [26]). The optimal Motility and MaRIA cutoffs were derived from the receiver operating characteristic curves for the current study data automatically (top-left method).

All statistical analysis was performed in R (R Foundation for Statistical Computing, Vienna, Austria) and receiver operating characteristic analysis was performed with the pROC package in R (27).

The sensitivity and specificity of both the Motility score and MaRIA score against the endoscopic and histopathologic standard was assessed separately according to recruitment site.

## Results

Overall, 24 participants were further excluded from our study because of missed terminal ileum on dynamic sequences ($n$ = 11), poor dynamic imaging quality ($n$ = 6), or recent use of motility-altering medication (prokinetics and opioid analgesia; $n$ = 7) (Fig 2).

Eighty-two participants were eligible for our study (33 at center 1 and 49 at center 2; median age, 31

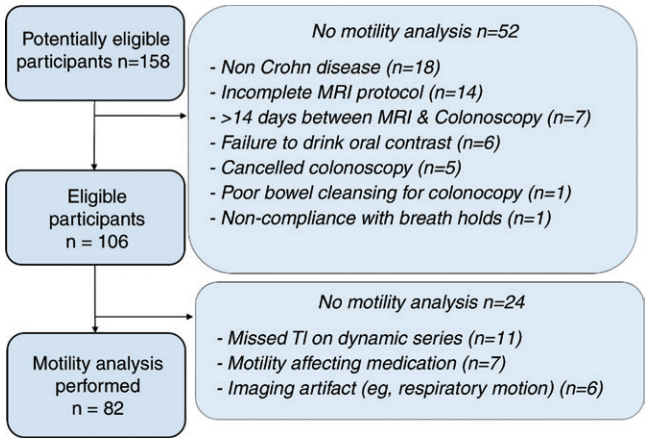


**Figure 2:** Diagram shows flow of participants. TI = terminal ileum.

**Table 1: Participant Demographics**

| Characteristic | Center 1 ($n$ = 33) | Center 2 ($n$ = 49) |
|---|---|---|
| Sex* | | |
| Male | 12 (36) | 30 (61) |
| Female | 21 (64) | 19 (39) |
| Age (y) | 27 (16–63) | 35 (19–70) |
| Female | 29 (16–63) | 35 (20–59) |
| Male | 25 (17–43) | 36 (19–70) |
| At diagnosis | 22 (6–53) | 24 (13–56) |
| Disease duration (y) | 4 (0–30) | 8 (0–42) |
| Montreal classification of disease location* | | |
| L1 | 7 (21) | 27 (55) |
| L2 | 5 (15) | 5 (10) |
| L3 | 21 (64) | 17 (35) |
| No. of previous surgical procedures* | | |
| 0 | 26 (84) | 30 (61) |
| 1 | 5 (16) | 1 (2) |
| 2 | … | 2 (4) |
| ≤3 | … | 16 (33) |
| Medication* | | |
| Steroid | 2 (7) | 10 (20) |
| 5-aminosalicylic acid or immunomodulators† | 15 (50) | 12 (25) |
| Biologic | 6 (20) | 16 (33) |
| C-reactive protein‡ | 2 (0–68) | 4 (0–40) |
| Harvey-Bradshaw index | 4 (0–9) | 6 (0–38) |
| CDEIS | 0 (0–31) | 9 (0–36) |
| 0 | 24 | 21 |
| >7 | 2 | 9 |
| >11 | 7 | 19 |
| EAIS | 0 (0–4) | 2 (0–4) |
| 0 | 17 | 17 |
| 1 | 6 | 2 |
| 2 | 6 | 17 |
| 3 | 1 | 6 |
| 4 | 3 | 7 |
| Loperimide | 1 | 3 |

Note.—Unless otherwise specified, data are medians, with ranges in parentheses. CDEIS = Crohn disease endoscopic index of severity, EAIS = endoscopic biopsy acute histologic inflammatory score.

* Data are the number of participants, with percentages in parentheses.

† Immunomodulators including methotrexate, azathioprine, and 6-mercaptopurine.

‡ Normal level <5 mg/L.

years [range, 16 to 70 years]) with demographics shown in Table 1. An example of a participant with an inflamed terminal ileum and Motility map overlay is provided in Figure 3.

## Detection of Inflammation

*Endoscopic reference.*—The sensitivity and specificity of Motility and the MaRIA score for identifying endoscopic activity (CDEIS ≥4) is shown in Table 2. The median CDEIS across the cohort was 6 (range, 0 to 36).

Motility score achieved a greater sensitivity for active disease (93% [95% confidence interval {CI}: 81, 99]) than did MaRIA score (78% [95% CI: 62, 89]) by using a cutoff of greater than or equal to 11 ($P$ = .03). The sensitivity of Motility score was not different compared to MaRIA score (85% [95% CI: 71, 94]) when using a cutoff greater than or equal to 7 ($P$ = .26).

Overall, Motility score identified 38 of 41 (93%) participants with active disease based on CDEIS compared with 35 of 41 (85%) for MaRIA score greater than or equal to 7 and 32 of 41 (78%) for MaRIA score greater than or equal to 11.

The specificity of Motility score (61% [95% CI: 45, 76]) was lower than was MaRIA score (81% [95% CI: 65, 91]) most notably at the cutoff of greater than or equal to 11 ($P$ = .04) and also at the cutoff of greater than or equal to 7 (76% [95% CI: 60, 88]; $P$ = .05).

*Histopathologic reference.*—The sensitivity and specificity of Motility score and MaRIA score for identifying histopathologic inflammation (EAIS ≥1) is shown in Table 3. The median EAIS across the cohort was 1 (range, 0 to 4).

Motility score achieved higher sensitivity (92% [95% CI: 80, 98]) than did MaRIA score greater than or equal to 7 (75% [95% CI: 60, 86]; $P$ = .03) and MaRIA score greater than or equal to 11 (71% [95% CI: 56, 83]; $P$ = .006) at both cutoffs. The specificity of Motility score (71% [95% CI: 56, 87]) was similar to that of MaRIA score greater than or equal to 7 (74% [95% CI: 56, 77]; $P$ = 1) and at the cutoff of greater than or equal to 11 (82% [95% CI: 66, 93]; $P$ = .25).

Overall, Motility score identified 44 of 48 (92%) participants with active disease based on EAIS compared with 36 of 48 (75%) for MaRIA greater than or equal to 7 and 34 of 48 (71%) for MaRIA score greater than or equal to 11.

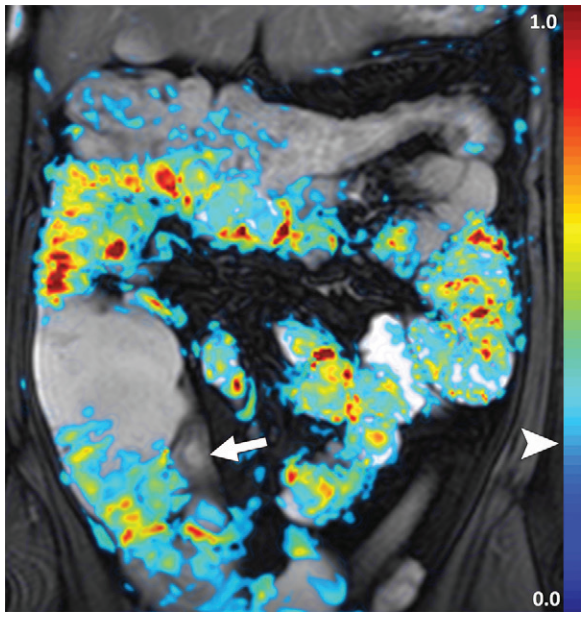


**Figure 3:** Motility map overlay shows morphologically normal bowel and inflamed terminal ileum (arrow) in a 34-year-old woman. Participant showed reduced Motility of 0.05, Crohn disease endoscopic index of severity score of 18, and endoscopic biopsy acute histologic inflammatory score of 2. Arrowhead on color bar indicates transparency threshold for Motility map overlay.

**Table 2: Sensitivity and Specificity of Motility and MaRIA Score for Active Disease Based on an Endoscopic Standard of Reference (CDEIS) at Two Cutoffs**

| Parameter | Sensitivity (%) ($n$ = 82)* | 95% Confidence Interval | $P$ Value† | Specificity (%) ($n$ = 82)‡ | 95% Confidence Interval | $P$ Value† |
|---|---|---|---|---|---|---|
| Motility <0.30 (au) | 93 (38 + 3) | 81, 99 | … | 61 (25 + 16) | 45, 76 | … |
| MaRIA score ≥7 | 85 (35 + 6) | 71, 94 | .26 | 76 (31+10) | 60, 88 | .05 |
| MaRIA score ≥11 | 78 (32 + 9) | 62, 89 | .03 | 81 (33 + 8) | 65, 91 | .04 |

Note.—CDEIS = Crohn disease endoscopic index of severity, MaRIA = MR index of activity.
* Data in parentheses are true-positive results and false-negative results, respectively.
† Indicates significance against Motility.
‡ Data in parentheses are true-negative results and false-positive results, respectively.

**Table 3: Sensitivity and Specificity of Motility and MaRIA Score for Active Disease Based on a Histopathologic Standard of Reference (EAIS ≥1)**

| Parameter | Sensitivity (%) ($n$ = 82)* | 95% Confidence Interval | $P$ Value† | Specificity (%) ($n$ = 82)‡ | 95% Confidence Interval | $P$ Value† |
|---|---|---|---|---|---|---|
| Motility <0.30 (au) | 92 (44 + 4) | 80, 98 | … | 71 (24 + 10) | 56, 87 | … |
| MaRIA score ≥7 | 75 (36 + 12) | 60, 86 | .03 | 74 (25 + 9) | 56, 77 | >.99 |
| MaRIA score ≥11 | 71 (34 + 14) | 56, 83 | .006 | 82 (28 + 6) | 66, 93 | .25 |

Note.—EAIS = endoscopic biopsy acute histologic inflammatory score, MaRIA = MR index of activity.
* Data in parentheses are true-positive results and false-negative results, respectively.
† Indicates significance against Motility.
‡ Data in parentheses are true-negative results and false-positive results, respectively.

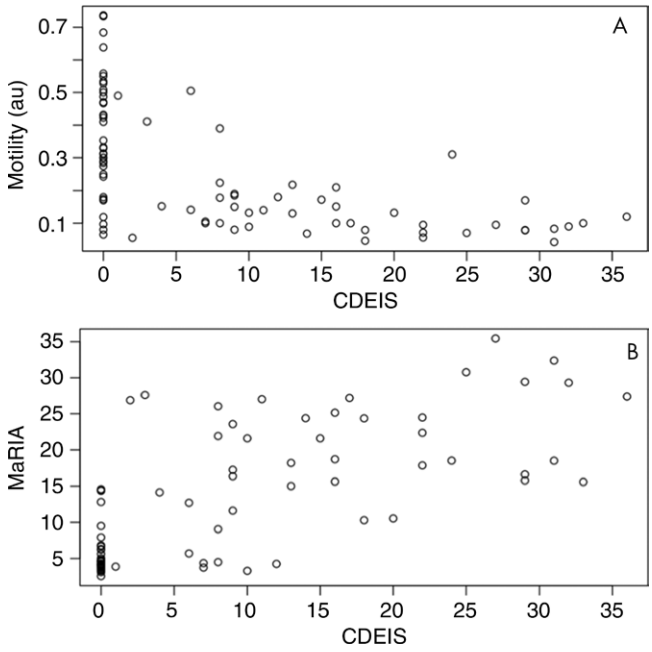


**Figure 4:** Graphs show Spearman rank correlation between, *A,* Motility and Crohn disease endoscopic index of severity (CDEIS) ($r = -0.59$; $P < .001$) and, *B,* MR index of activity (MaRIA) score and CDEIS ($r = 0.71$; $P < .001$).

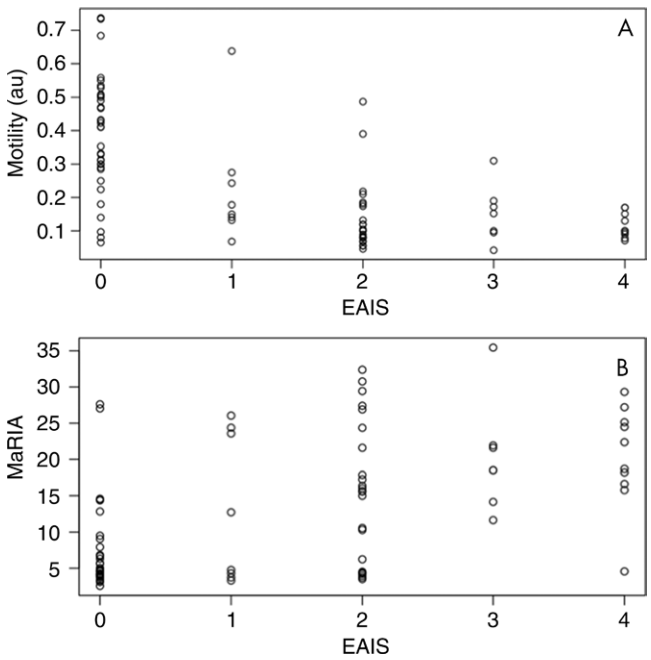


**Figure 5:** Graphs show Spearman rank correlation between, *A,* Motility and endoscopic biopsy acute histologic inflammatory score (EAIS) ($r = -0.61$; $P < .001$) and, *B,* MR index of activity (MaRIA) and EAIS ($r = 0.54$; $P < .001$).

### Quantification of Inflammation

CDEIS and EAIS were positively correlated (Spearman $r$ = 0.75; 95% CI: 0.6, 0.8) (Fig E2 [online]).

Motility demonstrated a moderate negative correlation against the CDEIS score ($r = -0.59$; 95% CI: 0.7, 0.4), whereas MaRIA score showed a strong positive correlation with CDEIS ($r = 0.71$; 95% CI: 0.6, 0.8) (Fig 4).

Motility had a moderate negative relationship with the EAIS score ($r = -0.61$; 95% CI: 0.7, 0.5), whereas MaRIA score had a moderate positive correlation with EAIS ($r = 0.54$; 95% CI: 0.4, 0.7) (Fig 5).

Receiver operating characteristic curves generated for endoscopic grading (CDEIS ≥4) and histopathologic grading of activity (EAIS ≥1) are presented in Figure 6, *A* and *B*, respectively. Against CDEIS, Motility produced an AUC of 0.84 (95% CI: 0.7, 0.9) and MaRIA score generated an AUC of 0.84 (95% CI: 0.8, 0.9). The two receiver operating characteristic curves were not significantly different ($P = .72$). Against EAIS, Motility produced an AUC value of 0.87 (95% CI: 0.8, 0.1) and MaRIA score produced an AUC value of 0.78 (95% CI: 0.7, 0.9). The two receiver operating characteristic curves were not significantly different ($P = .125$).

In this prospective data, the optimal cutoff point for Motility score detecting disease activity against CDEIS is 0.23 and against EAIS is 0.22 based on the current study data shown in Table E3 [online]. The optimal cutoff point for MaRIA score against CDEIS was 9.9 and against EAIS was also 9.9.

The sensitivity of Motility and MaRIA score against CDEIS and EAIS according to recruitment site is shown in Table E4 (online).

## Discussion

In our study, we examined the relationship between terminal ileal motility and Crohn disease activity assessed with both an endoscopic severity index (CDEIS) and histopathologic score (EAIS). We found that for both endoscopically defined and histologically defined active inflammation, reduced Motility (<0.30 au) was highly sensitive (92% and 92%, respectively) at the cost of modest specificity (61% and 71%, respectively), and our results are an important step in validating the Motility score and software.

Indeed, the sensitivity of Motility score reduction for inflammation was greater than that in the previous retrospective evaluation (15), likely because of our prospective study design using a consistent bowel preparation, and supervision of the imaging protocol by a study scientist. Motility reduction was significantly more sensitive than was a previously validated activity score (MaRIA) for histopathologic inflammation by using previously published thresholds (7), suggesting it may serve as a rapid, reproducible, and simple means of excluding terminal ileal inflammation in patients with known Crohn disease. Against an endoscopic activity score, Motility score had similar sensitivity (93%) to the MaRIA score (using a cutoff of ≥7) but lower specificity (61%). Comparison of receiver operating characteristic curves of Motility score and MaRIA score against the endoscopic and histopathologic standards respectively showed no significant differences in AUC value, suggesting diagnostic performance for disease activity is governed here by choice of cutoff value. For example, based on the data in the current study, against CDEIS, a Motility score cutoff of 0.22 au gave 92% sensitivity for active disease and 76% specificity, whereas a MaRIA cutoff of 9.9 gave 83% sensitivity and 81% specificity (Table E3 [online]). These

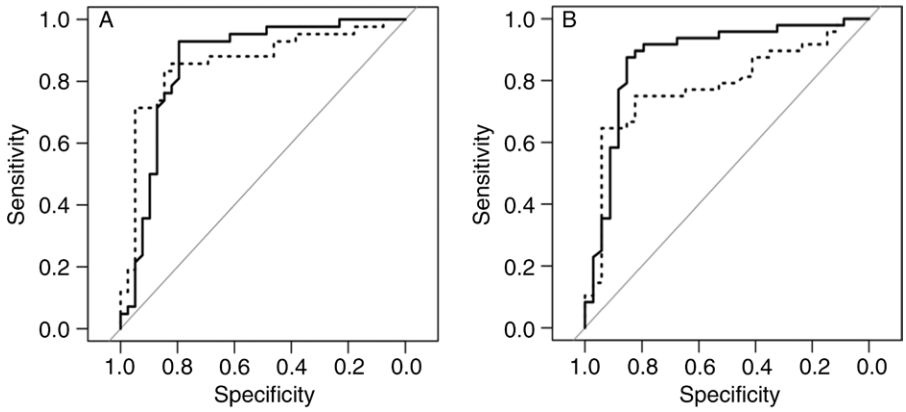


**Figure 6:** Graphs show Motility (solid black line) and MR index of activity (MaRIA) (dotted line) area under the receiver operating characteristic curves (AUC) for, *A,* endoscopic (Motility AUC, 0.84 [95% confidence interval {CI}: 0.7, 0.9] and MaRIA score AUC, 0.84 [95% CI: 0.8, 0.9]) and, *B,* histopathologic activity (Motility AUC, 0.87 [95% CI: 0.8, 0.1] and MaRIA score AUC, 0.78 [95% CI: 0.7, 0.9]).

cutoffs differ from those we prospectively defined for testing (Motility au $<0.30$ au and MaRIA $\geq 7$ and $\geq 11$) and it is important that imaging indicators of activity are reliable across the whole range of disease activity.

We found a moderate negative correlation between the EAIS and Motility score that was similar to that described in Menys et al and Cullman et al (15,16), and also similar to that achieved by the MaRIA score. To the best of our knowledge, this is the first time these observations have been reproduced prospectively in a multi-institution setting. It is perhaps intuitive that as the bowel wall thickens in response to inflammatory activity, the contractile potential of the bowel should decrease. Indeed, this has previously been observed in retrospective studies against histopathologic and structural markers of disease activity (15). Motility also had a moderate negative correlation with endoscopic scored activity, although a little lower than that of MaRIA.

The differing diagnostic performance of the two MRI techniques may reflect their derivation. MaRIA has been developed and validated against endoscopy, whereas Motility score has been predominantly validated against histopathologic analysis. The tested Motility score threshold for activity was defined based on a previous comparison with the EAIS, and its diagnostic performance against CDEIS is improved by a small change in this threshold to less than 0.22 (based on the current study data). Nonetheless, these data strongly suggest that motility as a biomarker can be used both for disease detection and for activity quantification. In this study, we used a CDEIS cutoff of 4 to define active disease because such a score has been advocated as the best predictor of mucosal healing (7). However, we acknowledge that a CDEIS of below 3 has also been used to define inactive disease. Only a single participant in our cohort had a CDEIS of 3, so our cutoff will not impact the overall study findings.

The terminal ileal Motility score describes a functional aspect of gut physiology that is not conveyed through other existing parameters based on bowel structure. Motility is an important aspect of normal physiology and our data suggests it provides at least comparable accuracy as MRI assessment of bowel structure. Indeed, recent data demonstrates its potential value as a biomarker to indicate early response to biologic therapy (6) and beyond this, a link between aberrant motility in normal bowel and patient symptom load has been described (28,29). Crucially in terms of clinical uptake, motility sequences can be easily added to existing MR enterography protocols with a small time penalty. This raises the intriguing possibility of combining structural and functional assessments into a single combined index, which would draw on the strengths of both (for example, using elements of structural MRI activity scores in combination with quantified Motility score assessment).

Segmental motility score assessment is quantitative, objective, and relatively easy to perform, requiring a single region of interest at the area of interest, placement of which generally takes a few seconds. A high level of interobserver agreement for the technique has been demonstrated (6,12). We acquired motility data at temporal resolution of 1.1 second; recent work has shown that in terms of motility metrics, more rapid acquisitions hold no advantage (30). Existing MRI activity scores based on bowel structure, although reproducible (10), are time consuming, particularly those requiring drawing of multiple regions of interest, which limit use in routine clinical practice. A disadvantage of motility analysis is that specialized postprocessing software is needed to analyze the data, although this is increasingly available to the clinical community.

Our study had limitations. We used a breath-hold protocol that may only capture a so-called snapshot of bowel motility. A future approach might be to acquire for an extended duration to average out transient variability in motility patterns (12,6). We were unable to perform the motility analysis in some recruited participants (because of poor bowel distension or missing motility sequences), but there were no technical failures of the algorithm. We used two reasonable reference standards well described in the literature—histology and endoscopy, although both have limitations. For example, histologic scores are subject to sampling errors from the site of biopsy. Furthermore, both scores mainly assess the mucosal changes, whereas Crohn disease affects the full bowel wall thickness. It is likely fibrosis will affect motility as it does existing structural MRI activity scores. Indeed, the influence of fibrosis on motility is an important consideration that we were unable to address in the current study. In the absence of validated noninvasive biomarkers of fibrosis, it is only possible to assess its influence by comparing to full-thickness histologic sampling of surgical resection specimens. The aim of the current study was to evaluate Motility score as a marker of disease activity, and to this end we used recognized independent scores of activity as our standard of reference. Because data were obtained from a larger study, a formal power calculation was not conducted. Although we included a reasonable number of data sets, future work should

include consideration of study power and effect size. Finally, where we analyzed data according to recruitment site, the results suggested higher specificity for both motility and MaRIA at center 2 (Academisch Medisch Centrum). This likely reflects the spectrum of disease across the two sites. In particular, participants recruited from Academisch Medisch Centrum tended to have more active disease.

In summary, the quantified Motility score is an objective biomarker of endoscopic and histopathologic inflammatory activity in Crohn disease and is comparable to previously validated MRI activity scores. By obviating the need for gadolinium injection and multiple manual measurements, it potentially has advantages over existing MRI activity scores based on evaluation of bowel structure and contrast enhancement.

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