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Small Bowel Motility Quantified by Cine MRI to Predict Longer-Term Response in Patients with Crohn's Disease Commencing Biological Therapy: The Motility Study

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Background: Small bowel Crohn's disease (SBCD) is increasingly treated with biological therapies. Predicting response or remission (RoR) for individual patients is difficult and complicates treatment strategy. We aimed to determine if motility magnetic resonance imaging (mMRI) is superior to CRP and fecal calprotectin (FC) for the prediction of RoR at 1 year in patients commencing biologics for SBCD.

Methods: Prospective, multicenter ($n = 13$) cohort study of patients with active non-stricturing SBCD requiring anti-TNFα or anti-IL-12/23 treatment. We measured mMRI and CRP at baseline and post-induction (visit 2: 12-30 weeks), and FC in a subset. RoR was assessed at 1 year using clinical and structural magnetic resonance enterography parameters. We compared sensitivity, specificity, and area under the receiver operating characteristic curve (ROC-AUC) of changes in mMRI and CRP to predict RoR at 1 year. Secondary outcomes compared mMRI with FC, and prediction of improved quality of life (QoL).

Results: Eighty-six participants completed all assessments. Stable or improved mMRI at visit 2 was more sensitive than normalization of CRP for RoR (mMRI:71.0%, 95%CI 52.0-85.8; CRP:45.2%, 95%CI 27.3-64.0%, $P = .008$) but less specific (mMRI:30.9%, 95%CI 19.1-44.8; CRP:67.3%, 95%CI 53.3-79.3%, $P < .001$). There was no significant difference in ROC-AUC (mMRI:0.48; CRP:0.53, $P = .65$). Similar results were obtained for FC. None of mMRI, CRP, or FC predicted patient QoL at 1 year.

Conclusions: Although improved mMRI is more sensitive than CRP and FC to predict RoR at 1 year, it is less specific. No factor predicted patient QoL. Motility MRI remains a marker of disease activity at given timepoints.

Lay Summary

Changes in CRP, fecal calprotectin level, or small bowel motility as quantified by MRI do not reliably predict response or remission to biological therapy at 1 year. Motility MRI is a useful marker of active small bowel inflammation.

Key Words: biologics (IBD), Crohn's disease, inflammatory bowel disease, radiology/imaging, small intestine

Key Messages

What is already known?

Motility MRI (mMRI) is associated with active small bowel inflammation, and retrospective data suggests its early improvement might be a predictor of longer-term response to biological therapy.

What is new here?

In this prospective multicenter study, we showed that none of the early changes in mMRI, C-reactive protein, or fecal calprotectin levels were reliably able to predict response or remission to biological therapy at 1 year.

How can this help patient care?

Early changes in mMRI parameters should not be used to make decisions about longer-term biological treatment, as they do not reliably identify long-term treatment responders.

Introduction

Crohn's disease (CD) treatment has been revolutionized by biological drugs, chiefly antibodies directed against tumor necrosis factor-α (anti-TNFα), as they are widely available, low risk, and highly efficacious.[1] A major shortcoming of current first-line biological therapies is that they do not work for all patients; either not at all (ie, primary non-response, PNR), or after an initial period of response, they become ineffective (ie, loss of response, LOR). Although a proportion of patients with LOR can be "rescued" with increased drug dosing and/or supplementary immunomodulation, ultimately, in real-world practice, only around 35-40% of patients achieve remission at 1 year. This falls to less than one-third by 3 years, with nearly 50% of patients changing treatment due to reduced efficacy.[2,3] Early identification of patients who are unlikely to achieve sustained response or remission would be of significant value, as it would facilitate replacing ineffective agents with alternatives. Prognostication is increasingly relevant as the variety of available treatments has broadened in both number and mechanism of action.[4] However, presently it is not possible to reliably predict in advance, or after treatment induction, which individuals are likely to achieve longer-term response or remission, and which patients are at higher risk of treatment failure (therefore requiring more intensive surveillance of disease status and inflammatory activity).

Biochemical markers of inflammation such as blood C-reactive protein (CRP) have some predictive value; in one study, 76% of patients with elevated CRP responded to infliximab vs. 46% with normal CRP.[5] A post-hoc analysis of the ACCENT-1 trial of infliximab maintenance treatment showed that 64% of patients whose CRP fell to less than < 5 mg/L post-induction, had sustained response at one year, compared to 38% of those with persistently raised CRP.[6] Fecal calprotectin has reasonable sensitivity and specificity for active inflammation for patients with CD[7,8] and shows promise as an early predictor of longer-term response. For example, a post-hoc analysis of week 6 calprotectin levels after treatment with ustekinumab showed reasonable predictive ability for endoscopic remission at 52 weeks.[9] A

separate multicenter retrospective cohort study showed that post-induction reductions in FC were associated with higher treatment response levels in both CD and ulcerative colitis (UC),[10] implying FC may also have value as a predictor of response.

Magnetic resonance imaging, typically performed with an oral solution to distend the small bowel (enterography, MRE), is widely used to assess CD, as it facilitates diagnosis, permits activity assessment, maps disease distribution along the whole gut, and detects complications.[11] Interpretation turns on a morphological assessment of bowel wall characteristics which can be translated into subjective activity scores that quantify inflammation, and have been validated against endoscopy and/or the stool inflammatory biomarker calprotectin.[12] However, MRI structural changes typically lag behind clinical, biological, and endoscopic improvements, limiting utility for response assessment and prediction. Conversely, modern MRI techniques combined with suitable post-processing software can assess bowel function quantitively, specifically peristalsis.[13,14] Motility MRI (mMRI) is potentially a sensitive, rapidly responsive test, as it measures gut function rather than structure. Quantified motility is known to accurately reflect inflammatory burden[15] and improves rapidly in response to treatment.[16] Therefore, it is possible that improved motility after treatment induction may predict which patients are likely to achieve longer-term response or remission.

We hypothesized that mMRI measurements before and after induction are more prognostic of longer-term response to treatment in patients commencing biological therapy for small bowel CD than currently used biochemical markers. We performed a multicenter prospective clinical trial that compared the predictive ability of mMRI to blood CRP and fecal calprotectin for therapeutic response in eligible patients, at 1-year follow-up.

Materials and Methods

Study Design

This was a multicenter, prospective cohort study comparing the predictive accuracy of mMRI and CRP for response to anti-TNFα and anti-IL-12/23 agents, at 1 year. The study is ethically approved (NHS West Midlands Research Ethics Committee: 17/WM/0106), registered (ISRCTN14481560), and the protocol is publicly available (https://www.isrctn.com/editorial/retrieveFile/18aadd81-26ad-48d6-ab3e-6d90eb5b2d06/33110).

Setting and Participants

Target population and recruitment sites

The study recruited patients with Crohn's disease who had recently commenced, or were scheduled to commence, anti-TNFα or anti-IL-12/23 therapy for active small bowel disease, either as a first-line treatment or after prior treatment (including alternative biologic agents). We recruited from 13 NHS sites with established IBD services and expertise in MRE. There was no stipulation for prior experience with mMRI, although radiologists had to be affiliated to the British Society of Gastrointestinal and Abdominal Radiology.

Inclusion and exclusion criteria

Eligible patients were aged 16 years or more with small bowel Crohn's disease, with or without colonic disease. All patients gave written informed consent. Inclusion required all of (1) active small bowel disease on ileocolonoscopy, video capsule endoscopy (VCE) or imaging (MRE, computed tomography (CT), intestinal ultrasound (IUS) or barium follow-through (BaFT), sufficient in the opinion of the clinical care team to commence, recommence, or change biological therapy; (2) documented disease distribution and activity within 90 days prior to commencing biological therapy or within 14 days of first treatment dose; (3) the primary target of therapy in the opinion of the treating physician was small bowel disease, rather than colonic or perianal disease; and (4) planned treatment to be an anti-TNFα (eg, infliximab or adalimumab, including biosimilars) or anti-IL 12/23 agent (eg, ustekinumab). Exclusion criteria were any of (1) planned treatment with other biological or small molecule therapies (eg, anti-integrins such as vedolizumab); (2) a primary treatment target of colonic or perianal disease; (3) contra-indications to MRI; (4) small bowel surgery within 90 days of recruitment; (5) stricturing disease, defined as a fixed small bowel narrowing with upstream luminal dilatation of > 50%; or (6) any disorder precluding informed consent.

Assessments and Procedures

At the initial visit (visit 1), disease activity was assessed using available clinical parameters including the Harvey-Bradshaw Index (HBI), contemporaneous blood tests, and findings from ileocolonoscopy and/or imaging within 90 days of starting biologics. Potentially eligible participants without documented baseline disease activity on ileocolonoscopy, MRE or VCE (eg, those with active small bowel disease requiring biologics based on findings from other imaging modalities) underwent either ileocolonoscopy or MRE to document disease status to facilitate subsequent response assessment at 1 year.

Participants provided blood and stool samples for serum CRP and fecal calprotectin (FC) at visit 1. All patients also underwent mMRI regardless of whether or not they had previously completed conventional (morphological) MRE; however, we permitted both standard MRE and mMRI to be performed at the same visit. Participants completed the EQ-5D-5L quality of life score as well as two disease-specific patient-recorded outcome measures (PROMs); the Crohn's and Ulcerative Colitis Questionnaire 8 (CUCQ-8[17,18]) and IBD-Control.[19]

Following initial biological treatment, participants were re-assessed at 12-30 weeks (visit 2), and at study completion at 44-78 weeks (visit 3). At visits 2 and 3, HBI was documented, serum CRP and FC were repeated, and PROMs were also repeated. We stipulated repeat mMRI at visit 2 but not at visit 3 since it was irrelevant for study outcomes. Sites were encouraged to undertake visit 2 assessments as close to 12 weeks as possible, but a wider window was permitted to allow for dose optimization, if performed, and the impact of the Covid pandemic on outpatient hospital care and research. Ileocolonosocopy was encouraged at both visit 1 and visit 3 if clinically indicated but was not stipulated (as, by definition, recruits had small bowel disease which was not necessarily amenable to endoscopic assessment). All clinical site data were collected by local investigators using paper case report forms (CRFs) and entered into the study database (MACRO; InferMed, UK). Radiological data from MRE scan interpretation were entered into electronic data capture forms (RedCAP; Tennessee, USA) by site staff and radiologists.

Assessment of whether or not each individual participant had responded to treatment was performed at visit 3. We divided patients into responders and non-responders to calculate the primary outcome. Those who had responded were further subdivided into those with remission, and those with response but non-remission. Because small bowel disease was not always accessible to endoscopy, we used a combination of ileocolonoscopy and MRE morphological parameters; ileocolonoscopy prevailed where these were discrepant. We used the simple endoscopic score for Crohn's disease (SES-CD[20]) to quantify endoscopic activity and the London index[21] to quantify MRE activity. Remission was defined as a SES-CD score of 0 to 2[22,23] and a London index of ≤4.1[21]; for patients not undergoing ileocolonsocopy, the MRE index alone was used (Table S1). The response was defined as a ≥50% drop in either SES-CD[22,23] or the London Index between visits 1 and 3 (Figure 1). Non-response was defined as either failure to achieve the criteria above or, after visit 2, any of (1) enteric surgery for target small bowel disease; (2) necessity to change or stop biological therapy because of lost efficacy in the opinion of the treating physician; or (3) steroid rescue therapy needed for active luminal Crohn's disease confirmed by at least one objective test documenting active inflammation (including biochemical, imaging, or endoscopic indices). SES-CD scores were assigned by site gastroenterologists at the time of ileocolonoscopy; MRE activity scores were assigned by one of a pool of five independent consultant radiologists with individual experience of over 300 MRE examinations, blinded to all clinical information. Radiologists did not view any motility MRI images.

Conduct and Analysis of mMRI

Motility MRI was performed using standard MRI units (1.5 Tesla or greater), coils, and sequence parameters at each individual site. Following a 4-6-hour fast and ingestion of oral contrast identical to that used for standard MRE, rapid cine acquisition MR images were acquired that encompassed the entire small bowel volume (see Table S2 for technical parameters). All mMRI scans were pseudonymized with the participant trial ID, transferred electronically to a central repository, and underwent post-processing using a standard algorithm (GIQuant; Motilent, London, UK). Quantitation of mMRI motility values was automated but required a radiologist to delineate the region of abnormal bowel via a region-of-interest (ROI) tool. ROIs were placed by two experienced central readers, one of whom was randomly designated to determine the primary outcome, the other assessment being used to measure inter-observer variability. Central radiologists were blinded to all clinical information when placing ROIs, other than knowing the relevant enteric segment (terminal ileum, ileum, or jejunum), based on which segment had been evaluated by the radiologist deriving the morphological London disease activity score (Figure 2). To mirror how mMRI would be performed in clinical practice, the central radiologists had access to limited anatomical sequences to aid ROI placement, and for each patient placed ROIs across all MREs at the same read to ensure anatomical registration between ROIs from different patient visits. Recruitment sites were blinded to mMRI-derived measurements of small bowel motility to prevent this biasing clinical care. Images were not reported clinically but instead were reviewed at each recruitment site for urgent unsuspected findings that, if present, were divulged for ethical and patient safety concerns.

Outcome Measures

The primary outcome was the difference in sensitivity between changes in mMRI and serum CRP between baseline and early reassessment to predict longer-term response or remission (RoR; defined as per the previous section) at one year (visit 3 time). We regarded mMRI as predicting RoR if the motility score obtained from the affected small bowel segment was either stable or improved (ie, increased) at visit 2, when compared with visit 1, based on earlier retrospective work which identified this as the optimal threshold.[16] We regarded

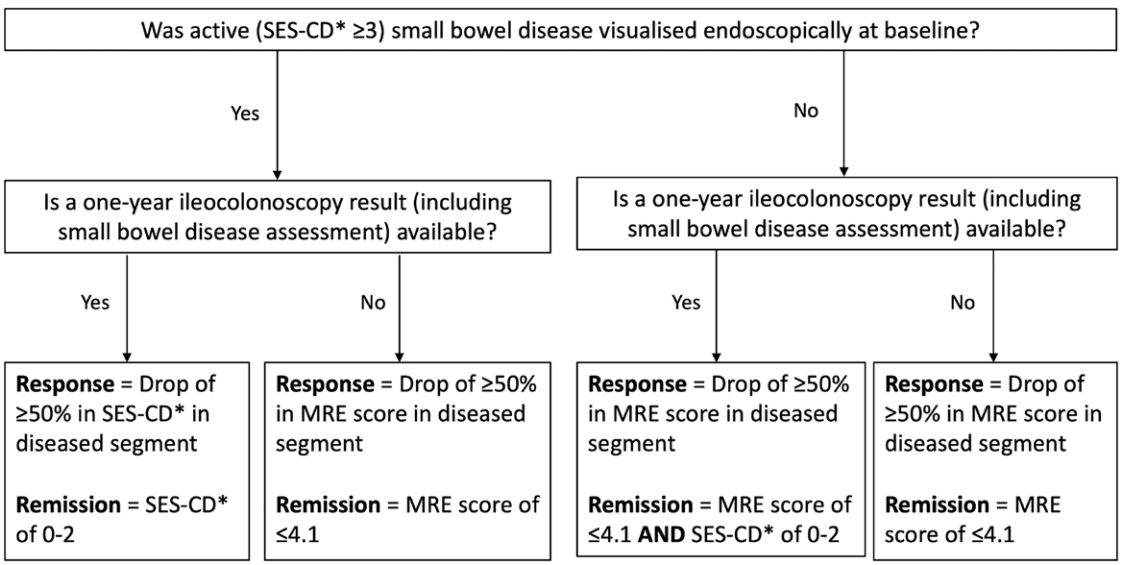

Figure 1. Assessment of disease response or remission for participants who had not met clinical criteria for non-response. *SES-CD = simple endoscopic score for Crohn's disease; MRE score = magnetic resonance enterography London Score (see Table S1 for details of calculation). Clinical criteria for non-response were any of: (1) requirement for enteric surgery for small bowel disease, (2) need to change or stop biological therapy because of loss of efficacy, or (3) requirement for steroid rescue for active luminal Crohn's disease.

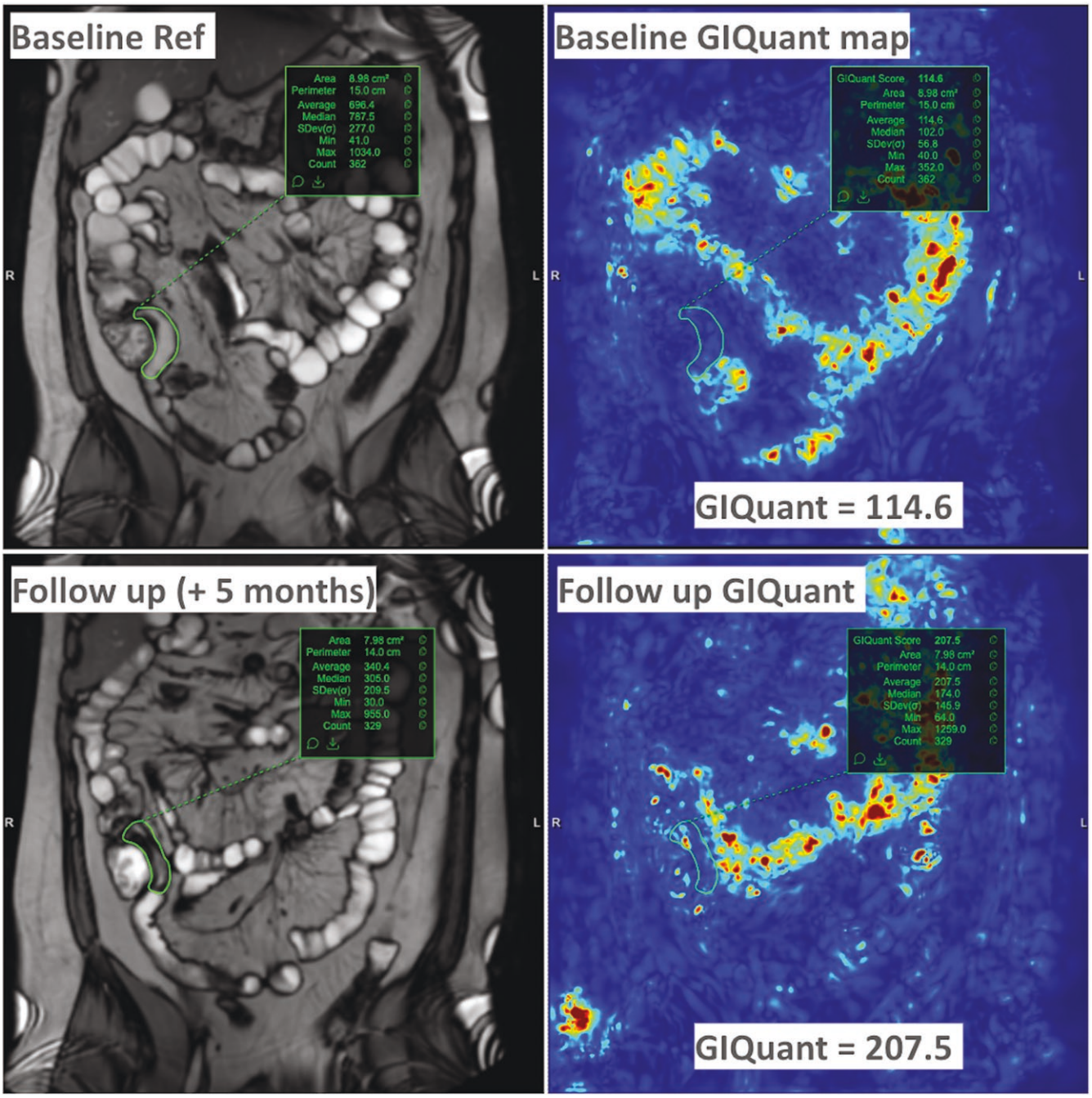

Figure 2. Procedure for mMRI ROI placement. Top left panel shows a segment of terminal ileum (green crescent-shaped region of interest) and its corresponding motility score of 0.07 in the top right panel (labeled GIQuant = 114.6). Radiologist readers were provided with mMRI scans from each visit and were instructed to draw a single ROI on an affected segment of bowel at each visit. Radiologists were instructed to ensure similar size and configuration of ROIs between visits; as shown in this example (bottom left panel). In this example, the GIQuant score at follow-up had increased to 207.5.

CRP changes as predicting RoR if CRP had normalized (defined as a reduction from ≥ 5.0 mg/L at visit 1 to < 5.0 mg/L at visit 2). Secondary outcomes included (1) the difference in specificity between mMRI and CRP for predicting RoR, (2) differences in area under the receiver-operating characteristic curve (ROC AUC) for changes in mMRI and CRP at visit 1 and visit 2 when predicting RoR, (3) relative accuracy of the two tests to predict improved quality of life measures (ie, PROMs) at 1 year, and (4) both (a) the absolute prognostic accuracy of mMRI versus CRP and (b) the incremental prognostic value of mMRI in addition to CRP to predict RoR at one year. We also performed corresponding analyses comparing mMRI to fecal calprotectin. Prognostic modeling was conducted in accordance with the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) statement.[24] Finally, we calculated inter-observer variability of mMRI measurements between the two central readers.

Sample Size and Statistical Analysis

The study sample size was based on the primary outcome and assumed a paired design in which all patients underwent both tests, using a patient-level unit of analysis. We assumed 40% sensitivity of CRP normalization to predict RoR[6] versus 60% for mMRI, a conservative estimate from previous studies.[16] We assumed the prevalence of RoR at one year was 50%, based on provisional data from the PANTS cohort[2] and a moderate 50% correlation between mMRI and CRP. At 5% alpha, we required 140 patients to achieve 90% power. We assumed a loss to follow-up of 10%, aiming to recruit 156 patients, but the COVID-19 pandemic prevented many patients from attending protocol-specified procedures. Consequently, interim data monitoring identified a loss to follow-up of approximately 30%, necessitating a revised recruitment of 200 patients.

Statistical analysis followed a pre-specified statistical analysis plan (SAP). In brief, the primary outcome was assessed using McNemar's test to compare paired proportions, with prespecified subgroup analyses for, (a) patients with previous surgery, (b) biologic-naïve patients, and (c) those in whom RoR had been defined using MRE rather than ileocolonoscopy (ie, SES-CD). Corresponding calculations were performed to compare specificity and to compare mMRI with FC. Receiver operating characteristic curves were constructed using percentage change in mMRI scores and absolute changes in CRP and FC from visit 1 to visit 2, to predict RoR. Differences in prognostic accuracy for PROMs (EQ-5D-5L, CUCQ-8, and IBD control) were quantified using multivariable regression models using PROM change as the outcome variable and either percentage change in mMRI, change in CRP, or change in FC from visit 1 to visit 2 as continuous explanatory variables; age (continuous), sex (binary), history of previous surgery (binary), presence of perianal disease (binary), and presence of a stoma (binary) were used as covariates in the prediction model. The absolute prognostic accuracy of mMRI, CRP, and FC, and the incremental prognostic value of mMRI over CRP and FC, was estimated using multivariable prognostic models using binary logistic regression with RoR at 1 year as the outcome variable and changes in each test from visit 1 to visit 2 as the main predictor variables. Additional predictor covariates included age at diagnosis (continuous), Montreal disease classification (categorical), current tobacco use (binary), and presence of perianal disease (binary). Model comparison used the Akaike information criterion (AIC), with smaller AIC values indicating better model fit. Interobserver agreement between radiologists was quantified using the intraclass correlation coefficient. Analyses were performed using Stata/MP 18.0 (StataCorp LLC, Texas, USA), and statistical significance was assigned at $P < .05$.

Exploratory Analyses

After the study inception, a newer MRI activity score (sMARIA) was derived, validated, and has been widely used.[25,26] We therefore repeated the primary analysis using sMARIA as the MRE reference standard to define RoR instead of the London score, using the following criteria: either sMARIA of < 2 (ie, 0 or 1) at visit 3 (denoting remission); or a drop of ≥ 50% from visit 1 to visit 3 (denoting response).[27] We also calculated correlation between MRE activity scores and mMRI at each patient visit, and overall.

Role of Funding Source

The funder had no role in study design, data collection, data analysis, data interpretation, or report writing. All authors had access to the final study data and statistical reports, reviewed and approved the final report, and took responsibility for the data and its analysis. The corresponding author had final responsibility for the decision to submit for publication.

Results

Participant Characteristics

Recruitment was August 30, 2017 until April 25, 2022 inclusive. The study flow chart is shown in Figure 3. Of 219 patients screened, 199 were eligible and began biologic therapy within the protocol-specified time period. Ninety-three patients did not complete all visit 1 assessments, including 27 in whom MRI was not performed (largely due to the COVID-19 pandemic) and 27 patients who withdrew (largely due to COVID-19 "shielding"). A further 18 patients were excluded from analysis due to trial assessments at visits 1 and/or 2 being conducted outside the stipulated timescale. A total of 86 patients completed all protocol-stipulated assessments and were analyzed.

The baseline characteristics of analyzed and excluded populations are shown in Table 1. Most analyzed patients were biologic-naïve (70/86, 81.4%) and had no previous intestinal surgery (57/86, 66.3%). As stipulated by our protocol, all patients had ileal (L1) or ileocolonic (L3) disease; only 6 (7.0%) had co-existent perianal disease.

At the end of follow-up, 31 of 86 patients (36.0%) had achieved RoR. Two of the 86 patients had been defined as non-responders based on clinical grounds (both of whom had to switch biologic due to ongoing evidence of active disease) and the remainder had their response status categorized using morphological London index MRE parameters. No patient had both baseline and end-of-trial ileocolonoscopy for response assessment using SES-CD.

Comparison Between mMRI and CRP

Stable or improved mMRI at visit 2 was achieved in 60 of 86 patients (70.0%), and was significantly more sensitive than normalization of CRP for the prediction of RoR at 1 year; 71.0% (95%CI 52.0-85.8%) vs. 45.2% (95%CI 27.3-64.0%), $P = .008$. However, mMRI was significantly less specific; 30.9% (95%CI 19.1-44.8%) vs. 67.3% (95%CI 53.3-79.3%), $P < .001$; Table 2. The area under the curve (AUC) of the receiver operating characteristic (ROC) for the two tests was not significantly different ($P = .65$), at 0.48 for MRI and 0.53 for CRP (Figure 4). Neither mMRI nor CRP added any significant incremental prognostic value over and above simpler clinical models to predict gains in patient-recorded quality of life at one year (Table 3). Although we had planned to compare pre-specified subgroups based on prior biological and surgical history, the number of patients reaching RoR in each group was too small for meaningful analysis.

Comparison Between mMRI and Fecal Calprotectin

In total, 43 participants had both mMRI and FC data available at all relevant time points to permit analysis. Similarly to the comparison with CRP, mMRI was significantly more sensitive than normalization of FC to predict RoR at 1 year

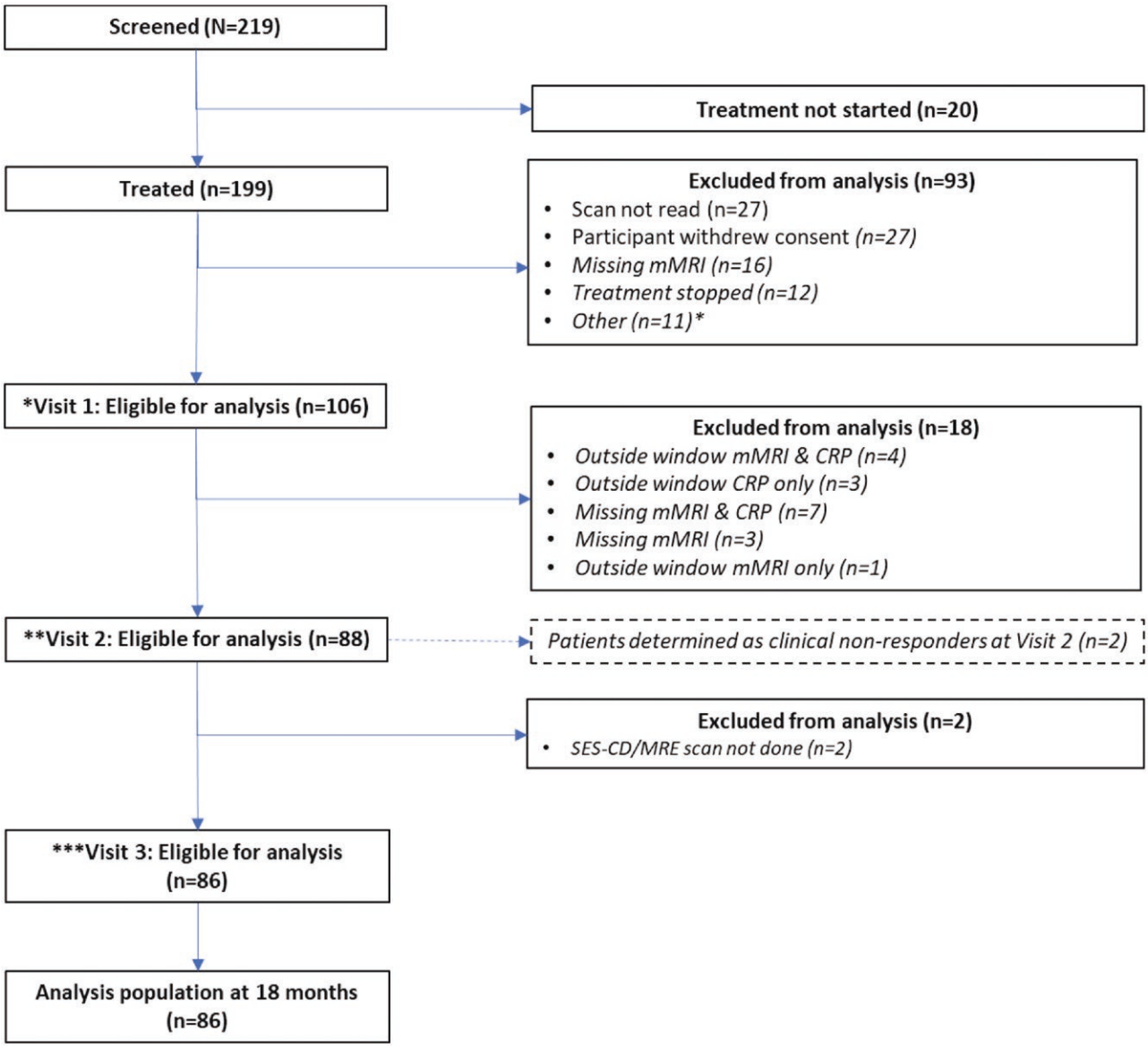

Figure 3. Study flowchart.

(mMRI: 64.3%, 95%CI 35.1-87.2%; FC: 7.1%, 95%CI 0.2-33.9%, $P = .02$), but significantly less specific (mMRI: 31.0%, 95%CI 15.3-50.8%; FC: 79.3%, 95%CI 60.3 to 92.0%, $P = .001$). ROC AUC for mMRI and FC were 0.58 and 0.67, respectively; a non-significant difference ($P = .41$, Figure 5). Prognostic modeling showed no significant predictive ability of either mMRI or FC to predict improved quality of life at 1 year (Table 4).

Exploratory Analyses

When using sMARIA to define RoR, overall results were similar. In total, 32 patients (37.2%) were judged to have achieved RoR. The sensitivity of mMRI was 81.3% (95%CI 63.6-92.8), significantly greater than CRP at 46.9% (95%CI 29.1-65.3%, $P = .007$). Again, the specificity of mMRI was significantly less than CRP; 37.0% (95%CI 24.3-51.3%) vs. 68.5% (95%CI 54.4-80.5%, $P = .001$; Table S3). There was no significant difference in the area under the ROC curve (MRI: 0.60; CRP: 0.57, $P = .71$; Figure S1).

Quantified mMRI scores showed a moderate negative correlation with MRE-measured disease activity in that segment and consistent associations across all visits, with correlation coefficients of –0.39 (all visits), –0.29 (visit 1), –0.41 (visit 2), and –0.32 (visit 3); Figure S2.

Interobserver Variability

A total of 299 mMRI scans from 104 patients were read by two expert readers; the discrepancy in the number of patients interpreted for the primary outcome is because some participants were lost to follow-up before completing the study but had already provided mMRI data. The intraclass correlation coefficient was 0.75 (95%CI 0.68-0.80), indicating good interobserver variability between the two experts when measuring segmental mMRI.

Table 1. Demographics and baseline characteristics of the analyzed and excluded population.

Baseline characteristics	Trial population		
	Primary analysis population *N* = 86	Population not analyzed *N* = 113	Total *N* = 199
	Mean (SD)	Mean (SD)	Mean(SD)
Age (years)	39.0 (13.8)	36.8 (14.3)	37. (14.1)
SES-CD score	6.0 (4.9)	4.9 (3.4)	5.5 (4.3)
MRE score	6.4 (1.7)	5.9 (2.2)	6.3 (1.8)
C-reactive protein (mg/l)	10.9 (13.0)	12.2 (14.8)	11.6 (14.0)
EQ-5D-5L	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)
CUCQ-8	32.5 (22.1)	37.2 (24.2)	35.1 (23.4)
IBD-Control-8	8.3 (3.3)	8.5 (3.3)	8.4 (3.3)
Fecal calprotectin (µg/g)	140.9 (164.1)	209.9 (355.4)	166.6 (253.0)
	n (%)	*n* (%)	*n* (%)
Smoking Status			
Non-smoker	39 (45.35)	59 (52.21)	98 (49.25)
Current smoker	13 (15.12)	17 (15.04)	30 (15.08)
Ex-smoker	13 (15.12)	18 (15.93)	31 (15.58)
Missing	21 (24.42)	19 (16.81)	40 (20.10)
Previous bowel surgery			
No surgery	57 (66.28)	69 (61.06)	126 (63.32)
Single surgery	17 (19.77)	26 (23.01)	43 (21.61)
Multiple surgeries	12 (13.95)	18 (15.93)	30 (15.08)
History of biological therapy			
No	70 (81.40)	105 (92.92)	175 (87.94)
Yes	16 (18.60)	8 (7.08)	24 (12.06)
Age at diagnosis (years)			
A1 (<= 16)	6 (6.98)	16 (14.16)	22 (11.06)
A2 (17–40)	65 (75.58)	77 (68.14)	142 (71.36)
A3 (> 40)	15 (17.44)	18 (15.93)	33 (16.58)
Missing	0 (0)	2 (1.77)	2 (1.01)
L1 (ileal)			
No	22 (25.58)	27 (23.89)	49 (24.62)
Yes	59 (68.60)	70 (61.95)	129 (64.82)
Missing	5 (5.81)	16 (14.16)	21 (10.55)
L2 (colonic)			
No	61 (70.93)	70 (61.95)	131 (65.83)
Yes[a]	1 (1.16)	1 (0.88)	2 (1.01)
Missing	24 (27.91)	42 (37.17)	66 (33.17)
L3 (ileocolonic)			
No	39 (45.35)	44 (38.94)	83 (41.71)
Yes	28 (32.56)	40 (35.40)	68 (34.17)
Missing	19 (22.09)	29 (25.66)	48 (24.12)
L4 (upper digestive modifier)			
No	61 (70.93)	69 (61.06)	130 (65.33)
Yes	0 (0)	2 (1.77)	2 (1.01)
Missing	25 (29.07)	42 (37.17)	67 (33.67)
Behavior			
B1 (non-stricturing, non-penetration)	45 (52.33)	55 (48.67)	100 (50.25)
B2 (stricturing)	29 (33.72)	39 (34.51)	68 (34.17)

Table 1. Continued

Baseline characteristics	Trial population		
	Primary analysis population *N* = 86	Population not analyzed *N* = 113	Total *N* = 199
	Mean (SD)	Mean (SD)	Mean(SD)
B3 (penetrating)	11 (12.79)	10 (8.85)	21 (10.55)
Missing	1 (1.16)	9 (7.96)	10 (5.03)
Perianal disease modifier (p)			
No	79 (91.86)	95 (84.07)	174 (87.44)
Yes	6 (6.98)	6 (5.31)	12 (6.03)
Missing	1 (1.16)	12 (10.62)	13 (6.53)

[a]One participant had been classified as L1 and L2 disease on the site CRF; for the purposes of analysis, this individual was taken to have L3 (ileocolonic) disease.

Discussion

The ability to predict which patients are likely to achieve medium- or long-term response to biological therapy shortly after initiation would have considerable clinical value, as it would permit early switching to alternatives in those destined to not benefit. However, we found that changes in mMRI, CRP, and FC were unable to predict response or remission (RoR) reliably at 1 year. This implies that although these measures have clinical utility when assessing CD at specific time points, they do not have prognostic utility. Our study was limited by lower than expected sample size due to the COVID-19 pandemic.

When compared with either CRP or FC, we found that stable or improved bowel motility measured by mMRI was significantly more sensitive but significantly less specific for RoR. Most participants had either stable or improved mMRI scores post-induction, which was our pre-specified threshold for predicting RoR based on prior literature.[16] However, it is not the case that the poor predictive performance of mMRI was simply due to the selection of an incorrect threshold to predict RoR; inspection of the ROC curves shows that no particular percentage change in mMRI scores from baseline to post-induction has adequate sensitivity and specificity.

mMRI is an intuitively attractive tool to predict therapeutic response, since it measures gut function (ie, peristaltic activity) and we anticipated functional recovery would occur earlier than structural recovery. Previous work investigating mMRI has concentrated largely on its association with disease activity at specific time points (compared to various reference standards, including histological[28] and endoscopic[15]); or for stricture assessment.[29,30] Indeed, we were able to confirm a moderate negative correlation between mMRI scores and disease activity as quantified by morphological MRE parameters, as expected given prior research. However, we could not translate this attribute into a reliable, longer-term prediction method using an MRE structural activity score as the standard of reference. Loss of response is complex and (for anti-TNF agents at least) is strongly associated with low drug levels and anti-drug antibodies, which can be partly mitigated by concomitant use of immunomodulators.[2] These are factors that inevitably cannot be captured by measurement of mMRI post-induction.

In the PANTS cohort, remission at 14 weeks was associated with sustained remission at 1 year (and at 2 and 3 years). It is interesting that we did not identify a similar observation. There are several possibilities; the PANTS cohort was broad, whereas our patients were restricted to those with primarily small bowel disease, and reference standards for RoR were different. By necessity, we used MRE to judge disease response, requiring an arbitrary 50% improvement in imaging scores to denote response. Presently, there is no consensus regarding the most appropriate threshold to denote treatment response using MRE activity scores; other investigators have chosen a more lenient 25% improvement.[27] It is, therefore, possible that some patients with improved mMRI at visit 2, and therefore predicted as responders, were instead classified as non-responders based on failure to achieve our more stringent criterion of a 50% or greater MRE improvement. We had intended that most patients would have response assessed by ileocolonoscopy at both baseline and 1 year, but this proved impossible, largely due to the COVID-19 pandemic and the resultant impact on both endoscopy services and patient visits.

Predicting outcomes for Crohn's disease is challenging. A 2021 systematic review[31] concluded that research for individual prognostic biomarkers was poor quality, rating 92% of studies at high risk of bias. Here, we aimed to predict a response to treatment (rather than a longer-term adverse clinical outcome), but even so, our biomarkers were unsuccessful. Although a recent randomized trial[32] found that top-down biological therapy was superior to rapid step-up treatment, the predefined primary outcome was to test a novel prognostic blood-based biomarker based on T-cell transcriptional signatures, with the endpoint being steroid- and surgery-free remission at week 48. The researchers found that the biomarker had no prognostic utility, with identical outcomes for both top-down and rapid step-up groups regardless of biomarker status. We are not aware of any biochemical or imaging-based indicator that permits early, reliable identification of individuals who are likely to achieve remission or response with biologic treatment. In the PANTS-E cohort, higher drug levels after induction were associated with higher rates of response at 3 years,[2] but whether this translates to accurate prediction on a per-patient basis is unclear.

Table 2. 2 × 2 contingency table for the primary outcome (sensitivity) and first secondary outcome (specificity) of both stable or improved mMRI and CRP normalization for response or remission (RoR) at 1 year.

	mMRI				
	Response	**No response**	**Total**	**Sensitivity (%) (95% CI)**	**Specificity (%) (95% CI)**
RoR at 1 year	22	9	31	71.0 (52.0–85.8)	30.9 (19.1–44.8)
No RoR at 1 year	38	17	55		
Total	60	26	86		
	CRP				
RoR at 1 year	14	17	31	45.2 (27.3–64)	67.3 (53.3–79.3)
No RoR at 1 year	18	37	55		
Total	32	54	86		
McNemar's test *P*-value				.0078	.0005

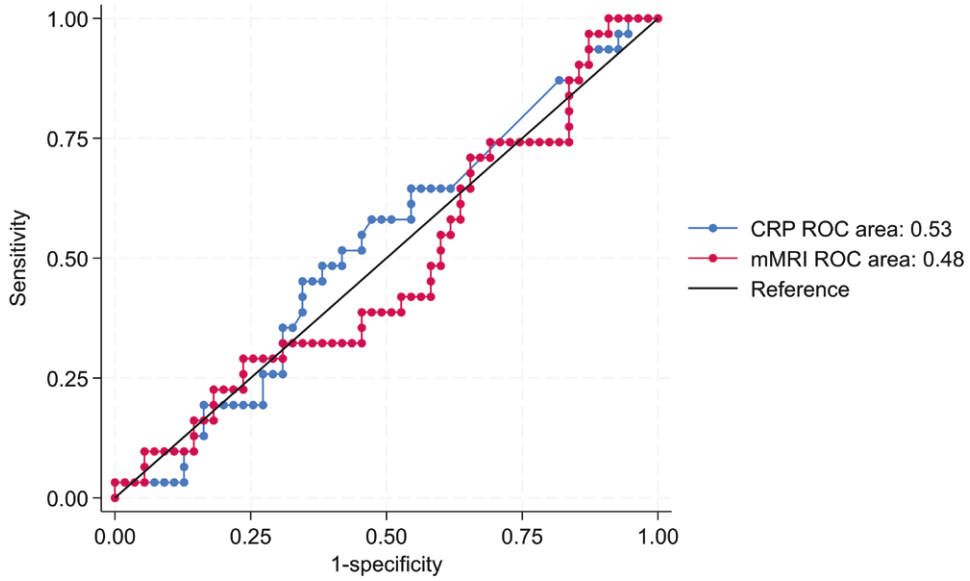

Figure 4. Receiver operating characteristic curve and area under the curve for percentage change in mMRI and change in CRP from baseline to visit 2 for response or remission (RoR) at 1 year.

Table 3. Prognostic models of the change in continuous mMRI small bowel motility score and change in CRP to predict improved quality of life.

Quality of Life measure	***N***	**mMRI**			**CRP**		
		Coefficient (95% CI)	***P*-value**	**AIC**	**Coefficient (95% CI)**	***P*-value**	**AIC**
EQ-5D-5L	72	0.0001 (−0.0003, 0.001)	.52	−58	−0.001 (−0.004, 0.001)	.16	−60
CUCQ-8	76	0.04 (−0.002, 0.08)	.07	642	0.13 (−0.07, 0.33)	.18	644
IBD-Control 8	65	0.004 (−0.01, 0.01)	.39	361	0.05 (0.01, 0.10)	.03	357

Abbreviations: AIC = Aikake Information Criterion; smaller values indicate a better model fit; CUCQ-8 = Crohn's and Ulcerative Colitis Questionnaire 8 item; EQ-5D-5L = European Quality of Life 5 dimension, 5 level;
IBD-Control = Inflammatory Bowel Disease Control.
Model covariates: age at diagnosis, sex, history of previous surgery, presence of perianal disease, presence of a stoma.

Strengths of our study include a prospective, multicenter design, and the use of pre-specified thresholds for response or remission and for mMRI. All imaging was interpreted in a manner reflecting normal clinical practice and compared against well-established biomarkers, namely CRP and FC. Moreover, we measured outcomes using both structural parameters (ie, MRE) and symptoms, including quality of life (ie, PROMs). Our main limitation was the unavoidable loss to follow-up imposed by the Covid-19 pandemic, necessitating a reduction in the recruited number of patients

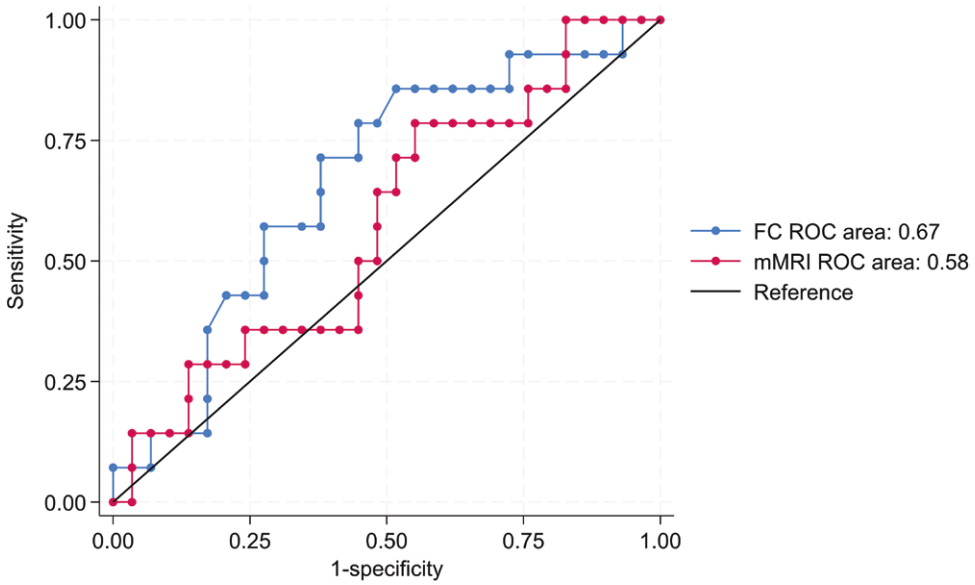

Figure 5. Receiver operating characteristic and area under the curve for percentage change in mMRI and change in fecal calprotectin from baseline to visit 2 for response or remission (RoR) at 1 year.

Table 4. Prognostic models of the change in continuous mMRI small bowel motility score and change in fecal calprotectin to predict improved quality of life.

Quality of Life measure	*N*	mMRI (95% CI)	*P*-value	AIC	FC (95% CI)	*P*-value	AIC
EQ-5D-5L	42	0.0002 (−0.0004, 0.0007)	.54	−31.7	0.0001 (−0.0001, 0.0003)	.20	−33.3
CUCQ-8	41	−0.04 (−0.05, 0.04)	.87	340.6	−0.02 (−0.37, −0.001)	.04	335.3
IBD-Control 8	36	0.00002 (−0.02, 0.02)	.99	215.5	−0.01 (−0.13, −0.003)	.00	204.8

Abbreviations: AIC = Aikake Information Criterion; smaller values indicate a better model fit; CUCQ-8 = Crohn's and Ulcerative Colitis Questionnaire 8 item; EQ-5D-5L = European Quality of Life 5 dimension, 5 level; IBD-Control = Inflammatory Bowel Disease Control.
Modeling was conducted without adjustment for covariates due to the small number of events.

and the use of a MRE-based definition of disease RoR rather than ileocolonoscopic SES-CD. In particular, the number of patients with available data for analysis of fecal calprotectin in particular was very small, and these results should be regarded as exploratory. We were also not able to assess for potential alternative causes of elevated CRP or FC (eg, intercurrent infection), which may have underestimated their prognostic utility. These weaknesses are mitigated somewhat by our using two different MRE indices to define RoR, and by the fact that we did not identify any benefit of using mMRI as a predictor variable for patient quality of life when measured by our three PROMs. Given that mMRI is more expensive than both CRP and FC and is not superior in predicting quality of life, the use of such simpler and patient-centered measures should be encouraged.

In conclusion, although improved mMRI after induction is significantly more sensitive than CRP or FC to predict response or remission to biologics for CD at 1 year, it is significantly less specific. Neither mMRI, CRP, nor FC can predict 1-year RoR reliably when using an MRE-based reference standard. Motility MRI remains a clinically useful marker of disease activity at individual timepoints but does not appear to have prognostic utility.

Supplementary data

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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Author Contributions

A.A.P., G.M., T.A., S.B., A.H., I.J., A.M., S.T., S.H., and S.A.T. conceived the study and completed the funding applications. These authors with PM and DT designed the study, wrote the trial protocol, and obtained ethical permission, with assistance from A.W., S.P., K.C., and N.A. A.B., G.B., D.B., J.F., A.G., M.H., E.H., F.H.-A., R.H., Y.K., S.K., H.L., M.M., A.P., S.R., N.S., H.S., and E.T. assisted with participant recruitment and interpreted MRI scans. S.A., U.B.C., N.B., T.B., H.F., H.G., E.G., A.G., A.H., E.I., K.B.K., S.L., M.P., J.P., KamaP, KamiP, N.P., R.Pp., R.Pr., C.R., and N.T. recruited participants, performed study procedures and completed participant follow-up and assessment. K.C. and N.A. analyzed the data, assisted by S.A. A.A.P. and S.A.T. drafted the manuscript, which was edited by all coauthors.

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Conflicts of Interest

G.M. has served as a speaker, a consultant, and/or an advisory board member for Abbvie, Alimentiv, Pfizer, and Satisfai Health and has received research funding from AstraZeneca, Bristol Myers Squib, Jansen, and Pfizer. T.A. has served as a speaker, a consultant, and/or an advisory board member for Amgen, Celltrion, Eli Lilly, and Janssen; and has received research funding from AbbVie, Biogen, Celgene, F Hoffmann-La Roche, Galapagos, Hospira (Pfizer), MSD, Napp Pharmaceuticals, Nova Pharmaceuticals, Takeda, and Pfizer. A.H. has served as a speaker, a consultant, and/or an advisory board member for Abbvie, Bristol Myers Squib, Celltrion, Galapagos, Johnson & Johnson, Lilly, Pfizer, Roche, and Takeda. A.M. is an employee of Motilent and owns stocks and shares in Motilent. P.M. has served as a speaker, a consultant, and/or an advisory board member for Takeda. S.T. has served as a speaker, a consultant and/or an advisory board member for Abbvie, Apexian, Bioclinica, Bristol Myers Squib, ChemoCentryx, Cosmo, Endpoint Health, Enterome, Equilium, Ferring, GSK, Genentech, Immunocore, Immunometabolism, Janssen, Lilly, Mestag, Novartis, Pfizer, Protagonist, Roche, Sanofi, Satisfai Health, Sensyne, Spyre, Sun Pharma, Takeda, TR1X, UCB, VHSquare, Vifor, and Violicom; has received research funding from Abbvie, IOIBD, Lilly, UCB, Vifor, Norman Collisson Foundation, Pfizer, UKIERI, ECCO, Helmsley Trust and GSK; and owns stocks and shares in Satisfai Health Inc. G.B. has served as a speaker, a consultant, and/or an advisory board member for Alimentiv; is an employee of Motilent; owns stocks and shares in Motilent; and owns patent in P295276.US.02, system to characterize topology and morphology of fistulae from medical imaging data. E.G. has served as a speaker, a consultant, and/or an advisory board member for Bayer and Olympus. K.B.K. has served as a speaker, a consultant, and/or an advisory board member for Abbvie, Falk, Galapagos, Janssen, and Takeda. M.P. has served as a speaker, a consultant, and/or an advisory board member for Janssen and Takeda; and has received research funding from AstraZeneca, Galapagos, Gilead, and Pfizer. J.P. is an employee of Hexarad and owns stocks and shares in Hexarad. K.P. has served as a speaker, a consultant and/or and advisory board member for Abbvie, Alfasigma, Celltrion, DrFalk, Ferring, Galapagos, Janssen, PreddictImmune, Pfizer, Takeda, and Tillotts; and has received research funding from Abbvie. C.R. has served as a consultant for Perspectum. S.H. has served as an advisory board member for the National Screening Committee multicancer detection, adult reference and AI task groups, and the HTA Prioritization Board. S.T. has served as a speaker, a consultant, and an advisory board member for AstraZeneca, has received research funding from Takeda, and owns stocks and shares in Motilent. All other authors report no personal interests.

Ethical Considerations

Ethical approval: NHS West Midlands Research Ethics Committee: 17/WM/0106

Patient consent: All patients provided informed written consent

Permission to reproduce material: Will be considered by the Chief Investigators

Clinical trial registration: ISRCTN14481560

Data Availability

Requests for data will be considered by the Chief Investigators.

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