United European Gastroenterology Journal

WILEY

UNITED EUROPEAN GASTROENTEROLOGY ueg journal

ORIGINAL ARTICLE OPEN ACCESS

Volumetric Changes in Perianal Fistulizing Crohn's Disease Measured by Magnetic Resonance Is Feasible and Could Be a Potential Biomarker to Predict Clinical Outcomes

Berta Caballol[1,2,3] | Ingrid Ordás[1,2,3] | Carolina Saavedra[3] | Julia Saidman[3] | Maria Carmen Masamunt[1,2,3] | Marta Gallego[1] | Rebeca Barastegui[1] | Agnès Fernández-Clotet[1,2,3] | Alex Menys[4] | Julian Panés[3] | Elena Ricart[1,2,3] | Jordi Rimola[2,3,5]

[1]IBD Unit, Gastroenterology Department, Hospital Clinic de Barcelona, Barcelona, Spain | [2]Centro de Investigación Biomédica en Red Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain | [3]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain | [4]Motilent Limited, London, UK | [5]IBD Unit, Radiology Department, Hospital Clinic de Barcelona, Barcelona, Spain

Correspondence: Jordi Rimola (jrimola@clinic.cat)

Received: 3 October 2024 | **Revised:** 10 November 2024 | **Accepted:** 8 December 2024

Funding: Julia Saidman is supported by a grant from the EU commission HLTH-2022-DISEASE-06-02. This work was supported by Leona M. and Harry B. Helmsley Charitable Trust (#2008-04050).

Keywords: biological treatment | biologics | fistula | imaging | medical | MRI | pelvic | prediction | remission | volume

ABSTRACT

Background and Aim: Changes in 3D volumetry of perianal fistulas in patients with Crohn's disease (CD) measured by MRI could be an imaging biomarker of interest. The objective of the study was to determine the value of volumetric changes in CD perianal fistulas after medical treatment to predict outcomes.

Methods: This is a retrospective single-center pilot study evaluating CD patients with active perianal fistulas who started biological therapy between 2012 and 2021. Eligible patients were those who had both pre- and post-treatment pelvic MRI and clinical follow-up of 2–5 years. Patients were categorized as clinically active or in remission based on fistula drainage. Using specific software, we calculated the 3D volume of the fistulas, and their active and fibrotic components. We evaluated MRI volumetric changes between assessments and analyzed their predictive value for clinical remission.

Results: We included 24 patients (83.3% with complex fistulas), of which 13 were in clinical remission at the last follow-up. Logistic regression analysis identified the percentage of relative change in the volumetric active component as an independent predictor of clinical remission (OR 0.92 [0.86–0.98] $p = 0.013$). The area under receiver operating characteristic (ROC) curve was 85.3% ($p < 0.0001$). A reduction of ≥ 16% in the volumetric percentage of the active component has a sensitivity of 84.6 and specificity of 81% in predicting clinical remission during follow-up.

Conclusion: Changes in the 3D MRI volumetry of perianal fistulas might have value in predicting clinical remission. Specifically, the reduction in the volumetry of the active component emerges as a promising biomarker for assessing therapeutic response.

Abbreviations: Cc, cubic centimeters; CD, Crohn's disease; ICC, intraclass correlation coefficient; IQR, interquartile range; MRI, magnetic resonance imaging; OR, odds ratio; PFD, perianal fistulizing disease.

Berta Caballol and Ingrid Ordás have contributed equally.

Summary

- Summarize the established knowledge on this subject
  - Perianal fistulizing disease is a common and disabling complication in Crohn's disease.
  - Magnetic resonance imaging is the preferred radiological tool for the assessment and classification of perianal fistulas.
  - MRI based Indices for perianal fistulizing disease such Van Assche index or the MAGNIFI index have demonstrated responsiveness properties for measuring therapeutic response but well-defined cut-offs for clinical response and remission are lacking.
- What are the significant and/or new findings of this study?
  - Our results suggest that a reduction in the volume of the active component of the fistula tract predicts clinical remission in patients who receive biological treatment.
  - Volumetric assessment of perianal fistulas is a promising and reliable metric tool for predicting clinical outcomes.
  - Based on our observations, the volume reduction in the active component could be a biomarker for defining therapeutic targets in perianal fistulizing disease.

1 | Introduction

Perianal fistulizing disease (PFD) occurs in up to one third of patients with Crohn's disease (CD) and is associated with a more severe clinical course [1]. Managing PFD poses considerable challenges, with a high risk of clinical recurrence (44% within the first 18 months after fistula healing) leading to disabling symptoms with a significant negative impact on patients' quality of life [2]. According to the AGA PFD classification, the majority (80%) of perianal fistulas are categorized as complex, characterized by lower healing rates, higher and quicker relapses, and greater treatment requirements to achieve fistula healing compared with simple fistulas [1, 3]. The current medical management of PFD is challenging and still faces considerable unmet treatment needs [4].

Magnetic resonance imaging (MRI) is a precise and non-invasive method recommended by international clinical guidelines for the assessment and classification of perianal fistulas in CD [1, 5–7]. Clinical assessment of perianal disease activity is based on fistula drainage. However, MRI allows for a more comprehensive assessment of the fistula tracts in terms of their anatomy (simple vs. complex) as well as in the evaluation of the degree of inflammation and/or fibrosis. Currently, optimal assessment of fistula severity and therapeutic response in clinical practice and clinical trials is evolving. Assessment of fistula activity by MRI is commonly performed based on T2 hyperintensity [8, 9]. A T2-weighted sequence with fat suppression is the optimal MRI sequence for the identification of the active component of perianal fistulas and its associated complications. Additionally, gadolinium-enhanced sequences are useful in distinguishing pus from granulation tissue [7].

Composite indices based on MRI findings for the adult population, such as the Van Assche index (VAI) and its modified version (mVAI) or the MAGNIFI index, were proposed for grading fistula severity [10–12]. These indices combine anatomical and inflammatory features as markers of disease activity and severity [13]. They represent a valuable tool for clinical follow-up and are reliable instruments for measuring therapeutic response in clinical trials since they have demonstrated responsiveness properties [10]. However, although the radiological indices were demonstrated to be responsive and reliable tools, well-defined cut-offs for the assessment of clinical response and remission are lacking [14].

Previous studies have reported that an active fistula tract evaluated by MRI may persist even after clinical healing (absence of drainage or even closure of the external opening) [3, 15, 16]. This suggests that radiological healing usually lags behind clinical remission [17]. Despite the slower pace of radiological healing and the relatively low rates of radiological response, there is growing evidence suggesting that achieving fistula healing, identified by means of MRI, may be a desirable endpoint due to its association with prolonged periods of clinical remission [15, 18, 19]. The definition of fistula healing on MRI is usually based on the disappearance of the T2 hyperintense signal. A reduction in inflammation of the fistula tract is accompanied by an increase in fibrosis and a higher fibrotic component is associated with better outcomes in terms of prolonged clinical remission. Recently, the degree of fibrosis assessed by visual impression and a MAGNIFI-CD activity score < 6, after PFD medical treatment, was correlated with long-term clinical closure [20]. The MAGNIFI-CD index descriptors include subjective assessment of the primary component of the fistula subjectively [10]. However, each component, either active inflammation or fibrosis, can also be quantified using specialized software to provide objective and more reliable metrics as a measure of treatment efficacy [21].

The aim of this pilot study was to assess the feasibility of objectively calculating the total volume of perianal fistulas, along with active inflammation and fibrosis components, using specific segmentation software. Additionally, we aimed to evaluate changes in fistula volumetry following biological treatment and its predictive value for subsequent clinical remission.

2 | Patients and Methods

2.1 | Study Design and Patients

This is a pilot observational unicentric and retrospective study performed at a tertiary IBD referral center. We included adult patients ($\geq$ 18 years) with established diagnosis of CD according to European Crohn's and Colitis Organisation (ECCO) definitions and associated PFD confirmed by MRI who started biological treatment (anti-TNF, vedolizumab or ustekinumab) at our center between 2012 and 2021. Eligible patients included those who had an active draining perianal fistula confirmed by medical physical examination and underwent a pre-treatment

(baseline) MRI within 6 months preceding the initiation of biological treatment, a post-treatment MRI performed between 3 and 18 months after treatment initiation, and clinical follow-up ranging from at least 2–5 years. The time window between both pelvic MRIs was selected based on previous evidence to identify predictors of fistula clinical closure [15, 20]. Patients with ileoanal pouches were excluded from the study. Patient identification was conducted by reviewing our IBD unit database. Three distinct time-points (TP) of interest were established: TP-0 (baseline) before the initiation of biological treatment, TP-1 when PFD was radiologically evaluated after treatment initiation and TP-2 representing the moment of the last clinical follow-up (Figure S1).

2.2 | Clinical Data and Outcome Definitions

Clinical data were extracted by reviewing each patient medical records. Epidemiological data and IBD characteristics including the disease duration, Montreal classification, date of PFD diagnosis, rectal involvement, previous medical treatments, and surgeries for both luminal and perianal diseases were recorded for each patient. At each time point of the study, we assessed luminal disease activity using the Harvey–Bradshaw index (HBI) and perianal-related symptoms—specifically fistula drainage. Treatment information, including biological therapy, concomitant treatments including antibiotics, immunosuppressants, biological therapy, and perianal surgical procedures were also documented at each time point. During follow-up (TP-1 and TP-2), according to fistula drainage assessment (FDA), patients were categorized as either being in “perianal remission”, defined as absence of external opening fistula drainage, or “perianal non-remission” in case of persistent drainage [22].

2.3 | Pelvic MRI Protocol

MRI examinations were performed according to our institution's protocol using 1.5-T magnet scans (either Signa Explorer, General Electric, or Aera, Siemens). Our local pelvic MRI protocol for assessing perianal fistulas remained unchanged with no significant changes throughout the study period and included sagittal, coronal, and axial T2-weighted sequences, axial T2-weighted sequences with fat suppression, T1-weighted axial sequences with fat suppression pre-contrast followed by T1-weighted axial, and coronal with fat suppression postcontrast sequences after intravenous administration of gadolinium. Supplementary Table 1 reports in detail the characteristics of the fistula MRI acquisition protocol. The coronal and axial sequences were angled parallel and perpendicular to the anal canal, respectively.

2.4 | Readers and Pelvic MRI Assessment

2.4.1 | Readers

A single radiologist (JR), with more than 15 years of experience in IBD imaging, evaluated all pelvic MRI at baseline and follow up and their characteristics and calculated the fistula volumetry in all assessments. The radiologist was blinded to clinical assessments and outcomes. The information obtained from the interpretation of this radiologist was used for the statistical analysis of this study.

To determine the inter-observer agreement of the fistula volumetry, a second radiologist (MS) with 4 years (after having finished residency) of experience in abdominal radiology calculated the volumetry of 10 pairs of pelvic MRIs randomly selected.

2.5 | Pelvis MRI Assessments

Perianal fistulas were defined as tracts connecting the anus or rectum and the perianal skin or other organs according to the ECCO-ESGAR recommendations [6, 23]. Typically, these fistulas feature a single internal opening and one or more external openings. Fistula characteristics included fistula classification based on AGA recommendations (simple or complex) as well as according to Parks' classification. The VAI and the MAGNIFI indices were calculated at both pre- and post-treatment assessments. Additionally, the radiologist subjectively evaluated the percentage of fibrotic component of each fistula.

Fistula volume was calculated using dedicated software (Entrolytics, Motilent, UK) after manual segmentation of the fistula tract. This software enabled the calculation of the volume of both the active and fibrotic components within each tract of the perianal fistulas.

The active component was defined as the sections presenting hypersignal in the T2-weighted sequences with fat suppression, interpreted as either fluid or granulation tissue, while the fibrotic component was defined as the area presenting hypo signal in T2-weighted sequences with and without fat suppression. To determine the volume of the active component, we utilized T2-weighted sequences with fat suppression in the axial plane. For the volume of the fibrotic component, we employed T2-weighted sequences without fat suppression in the axial plane. Following the manual segmentation of each component separately (active and fibrotic), the software automatically generates a three-dimensional model. This enables the user to ascertain whether any overlaps or gaps have been generated between the two components during the segmentation process and to correct them if necessary (Figure 1).

The area was calculated for each section where the fistula was identified including its extensions. If there was a seton within the fistula, visible as a hypointense structure on T2, it was excluded from the volumetry. The volume in cubic centimeters (cc) of each component, whether active or fibrotic, was obtained by summing the area in each section. Based on these determinations, we obtained the following parameters for each assessment: total fistula volume, representing the sum of the active and the fibrotic volumes; the percentage (%) of active and fibrotic components (active volume/total volume * 100; fibrosis volume/total volume * 100).

2.6 | Volumetric Changes Between Assessments

Volume changes for each component (active and fibrotic) and total volume were calculated by subtracting the baseline volume from the post-treatment volume. The percentage of change in fistula volume between the two MRIs was calculated using the following formula: (% baseline volume − % post-treatment volume/% baseline volume) * 100.

As the fibrotic tissue tends to compact over time [24], we calculated the relative changes relative to baseline of the % in the active component (% active baseline − % active post-treatment/% active baseline * 100) as well as in the fibrotic component (% fibrotic post-treatment − % fibrotic baseline/fibrotic baseline * 100), respectively.

2.7 | Statistical Analysis

Since it was designed as a pilot study, no formal sample-size calculation was performed. Patient's demographics and baseline clinical characteristics are reported as frequencies and percentages for categorical variables, and continuous data are reported by means (SD) or medians and interquartile intervals [IQR: percentile 25th–75th]. Continuous variables have been compared using parametric *t*-test and non-parametric Mann-Whitney test, while Chi-squared analysis and Fisher's exact test has been used for categorical variables. A *p*-value less than 0.05 was considered statistically significant.

For the primary analysis of the study, we compared the volumetric changes between baseline (TP-0) and post-treatment (TP-1) pelvic MRIs based on clinical outcomes observed at TP-2. In addition, we conducted an exploratory analysis to assess the association between baseline volumetric measurements and clinical outcomes. Univariate logistic regression analyses were used to predict clinical remission during follow-up and the best predictor was selected using a multivariate stepwise logistic regression using time between MRIs as the controlling variable. Data are presented as odds ratios (OR) with 95% confidence intervals (CIs). Receiver operating characteristic (ROC) curve analysis was used to calculate the area under the curve (AUC) for the best predictor variable and to determine the best cutoff value for identifying clinical remission in the long term.

The inter-observer correlation between the two radiologists for volumetric assessment was measured using the intraclass correlation coefficient (ICC). Subsequent analysis of fistula volume was performed using data from the main reader. Inter-reader agreement was assessed as follows: < 0.50, poor; 0.5–0.75, moderate; 0.75–0.90, good; and > 0.90 excellent [25]. The analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

2.8 | Ethics

The institutional review board approved the study (HCB/2021/0380). Due to the retrospective nature of the study, the requirement for informed consent was waived. The study was conducted according to the good clinical practice guidelines of the European Medicines Agency.

3 | Results

3.1 | Patients' Characteristics

A total of 33 patients met the study inclusion criteria. However, volumetric assessment was feasible in only 24 patients due to technical problems in uploading MRI images to the Motilent platform as a consequence of a cyber attack affecting our institution, being this the final study sample size. Figure 2 shows the flow chart of the patients who were finally included in the volumetric analysis. Among them, 13 achieved perianal remission, while 11 did not. We observed differences in patient

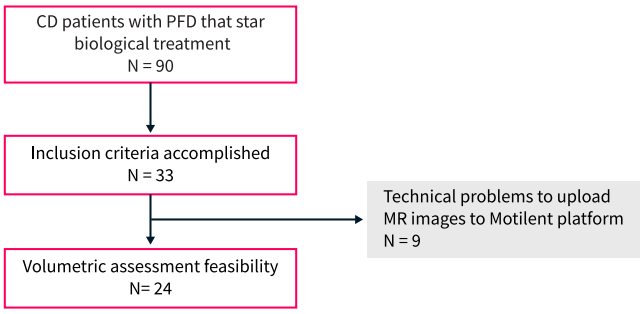

FIGURE 2 | Flow-chart of patients included in the study.

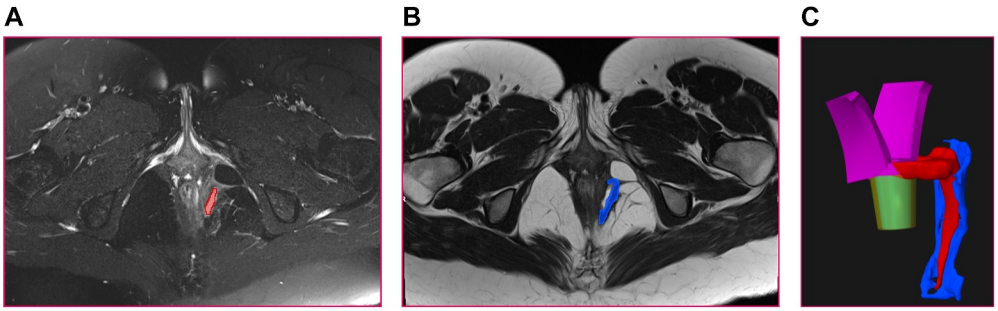

FIGURE 1 | Example of manual segmentation of a perianal fistula for volume evaluation using dedicated software (Entrolytics). Figure A displays an axial T2-weighted image with fat suppression revealing a complex fistula. The active component of the fistula is highlighted in red. In Figure B, the same fistula is visible on an axial T2-weighted image, with the fibrotic component manually segmented and now highlighted in blue. Figure C depicts the three-dimensional representation of the fistula, which includes the schematic anal-sphincter complex and both components of the fistula: in red the active fistula component, in blue the fibrotic fistula component, in purple the elevator plate, and in yellow the sphincters.

phenotype and rates of clinical responses ($p = 0.02$). Baseline patient and fistula characteristics are detailed in Table 1.

The biological treatment started at TP-0 was infliximab in 11 (45.8%) patients, adalimumab in 5 (20.8%) and ustekinuamb in 8 (33.3%) patients, without statistically significant differences between treatment's response ($p = 0.506$). 10 patients (41.7%) were on concomitant treatment with azathioprine, 1 (4.2%) with methotrexate and 3 with tacrolimus (12.5%). At TP-0 (baseline), 10 patients (41.7%) also received a course of antibiotics, 6 patients (25%) required abscess drainage, two of them (8.3%) with seton placement, and two (8.3%) additional patients with seton placement. Until TP-1 no changes in concomitant immunosuppressant treatment were done, 7 (29.2%) patients had received at least one more cycle of antibiotics (maximum of two) and in 1 (4.1%) patient a new seton placement was performed.

3.2 | Changes in Volumetric Assessments Between Radiological Evaluations and Predictors of Clinical Remission

The mean time-window between MRI at TP-0 and MRI at TP-1 was 10.8 (± 5.51) months for patients who did not achieve perianal remission and 9.38 (± 3.69) months for the group patients who achieved remission, without statistically significant differences ($p = 0.504$) between groups.

Table 2 summarizes the changes in MRI measurements observed between the two radiological assessments (TP-0 and TP-1). Only the change in the % of the active component, and the change in the % of relative active and fibrotic components were responsive to clinical changes induced by medical treatment. We have not observed differences in the volumetric changes between medical therapies and the percentage of relative active ($p = 0.203$) or fibrotic ($p = 0.692$) components.

When including the MRI volumetric variables associated with clinical remission into the logistic regression model, only the percentage of change in the relative active component was found to be a predictor for achieving clinical remission during follow-up (OR = 0.92 [95%CI 0.86–0.98] $p = 0.013$) (Table 3).

The model for predicting long-term clinical remission, which includes only one variable (% of change of relative active component), achieved an AUROC of 0.85 (Figure 3). The ROC curve analyses indicated that a reduction in the percentage of the relative active component of the perianal fistula ≥ 16% was the best predictor for achieving long-term clinical remission, with a sensitivity of 84.6% and a specificity of 81.8%.

3.3 | Baseline Volumetric Assessment and Clinical Outcome

Table 4 shows the differences observed in baseline volumetric assessments and clinical outcomes. The results indicate that subjects who achieved clinical remission had lower baseline volumes of both the total and active components as well as a lower volume of fibrotic component. The volume of the active component was found to be the best predictor of subsequent clinical remission (OR = 0.94 [95%CI 0.90–0.99], $p = 0.02$).

3.4 | Reproducibility of Volumetric Assessment

The inter-observer and the intra-observer correlation of volumetric assessments between readers was almost perfect for the active, fibrotic, and total fistula volumes (Table S2).

4 | Discussion

Our study shows that volumetric MRI is a feasible and reliable technique for measuring perianal fistula volume in patients with CD. The observed results suggest that a reduction in the volume of the active component of the fistula tract, whether it comprises granulation tissue or fluid, may help to predict clinical remission in patients who receive biological treatment. Therefore, volumetric changes in PFD hold potential as imaging biomarkers, given their predictive value for fistula clinical outcomes. Volumetric assessment of perianal fistulizing CD can also aid in the identification of new therapeutic targets for PFD. Furthermore, our findings indicate minimal variation in volume measurement between observers, highlighting its consistency and reliability as a metric tool.

Currently, there are no established therapeutic targets for managing PFD in CD. Some authors propose that the goal of fistula treatment should be to achieve deep remission, which is defined as the absence of fistula drainage and complete radiological healing of the fistula tracts. However, complete healing of fistula tracts may require several months, or even years of medical treatment. Therefore, there is a need to develop new surrogate endpoints in clinical research for a more precise evaluation of therapeutic response in PDF. The results of this study suggest the potential utility of an objective, feasible and reproducible method as a surrogate endpoint for early evaluation of treatment efficacy in PFD. Specifically, the findings indicate that reducing the active component of the fistula tract, rather than increasing the fibrotic component, predicts the achievement of clinical remission.

MRI is widely considered as the gold standard tool for assessing PFD in CD because of its ability to provide a virtual map of the fistulas and associated complications such as collections [7, 8, 26–29]. However, subjective evaluations are frequently employed to interpret the severity of PFD or the response to therapeutic interventions. Various MRI indices have been used in clinical research, including the VAI and MAGNIFI indices [10, 11]. Although changes in the VAI or MAGNIFI scores have a good correlation with clinical response to medical treatment, they have not been fully validated.

Current MRI scoring systems do not include the volume of the fistula. The MAGNIFI index considers the predominant component of the fistula (fibrosis, granulation tissue, or pus) that occupies more than 50% of the total fistula [10]. However, this assessment is subjective and prone to inter-observer variability. The calculation of the fistula volume and its components

TABLE 1 | Patients and fistula characteristics before treatment initiation stratified by perianal outcome.

	No remission (n = 11)	Remission (n = 13)	p-value
Age at inclusion, mean (SD)	46.5 ± 12.9	39.0 ± 15.2	0.21
Smoking status, n (%)			0.15
Non-smoker	4 (36.4%)	8 (61.5%)	
Smoker	4 (36.4%)	5 (38.5%)	
Ex-smoker	3 (27.2%)	0 (0.0%)	
CD phenotype at inclusion, n (%)			0.02
Inflammatory	2 (18.2%)	10 (76.9%)	
Stricturing	4 (36.4%)	1 (7.7%)	
Penetrating	5 (45.5%)	2 (15.4%)	
CD location at inclusion, n (%)			0.66
Ileal	5 (45.4%)	3 (23.1%)	
Ileocolonic	4 (36.4%)	6 (46.2%)	
Colonic	2 (18.2%)	4 (30.8%)	
Rectal involvement any time, n (%)			0.42
Yes	5 (50.0%)	9 (56.5%)	
PFD duration (years), mean (SD)	6.3 ± 5.1	4.3 ± 4.2	0.31
Luminal CD surgery, n (%)			0.01
Yes	8 (72.7%)	2 (15.4%)	
Type of luminal surgery, n (%)			
Intestinal resection	8 (72.7%)	2 (15.4%)	0.01
Intra-abdominal abscess drainage	2 (18.2%)	1 (7.7%)	0.58
Ostomy	2 (18.2%)	0 (0.0%)	0.20
Perianal-related hospitalization,[a] n (%)			0.68
Yes	3 (27.3%)	5 (38.5%)	
PFD surgery, n (%)			0.09
Yes	8 (72.7%)	5 (38.5%)	
Number of perianal surgeries	2.5 ± 2.3	2.5 ± 1.4	1.0
Type of perianal surgery, n (%)			
Abscess drainage	6 (54.6%)	4 (30.8%)	0.41
Seton placement	6 (54.6%)	4 (30.8%)	0.41
Fistulotomy	1 (9.1%)	2 (15.4%)	1.0
Stem cell therapy	1 (9.1%)	1 (7.7%)	1.0
Diverting stoma	0 (0.0%)	0 (0.0%)	—
Previous treatments, n (%)			
Steroids	10 (90.9%)	11 (84.6%)	1.0
Azathioprine/Mercaptopurine	9 (81.8%)	8 (61.5%)	0.39
Methotrexate	3 (27.3%)	0 (0.0%)	0.08
Tacrolimus	6 (54.6%)	4 (30.8%)	0.41
Infliximab	2 (18.2%)	1 (7.7%)	0.58
Adalimumab	5 (45.4%)	6 (46.1%)	0.97
Vedolizumab	3 (27.3%)	0 (0.0%)	0.08
Ustekinumab	3 (27.3%)	1 (7.7%)	0.30

(Continues)

TABLE 1 | (Continued)

	No remission (n = 11)	Remission (n = 13)	p-value
AGA Classification, n (%)			0.1
Simple	0 (0.0%)	4 (30.8%)	
Complex	11 (100%)	9 (69.2%)	
Type of fistula-parks classification			
Transsphincteric	7 (63.6%)	4 (30.8%)	0.23
Suprasphincteric	1 (9.1%)	1 (7.7%)	
Intersphincteric	3 (27.3%)	8 (61.5%)	
MAGNIFI score, mean (SD)	18.5 ± 4.2	11.7 ± 4.9	0.001
Van assche index, mean (SD)	16.1 ± 2.8	13.8 ± 4.2	0.15

Abbreviations: AGA: American Gastroenterology Association; CD: Crohn's disease; SD: standard deviation.
[a]This includes admissions for surgery.

TABLE 2 | MRI changes associated with long-term clinical remission.

MR changes	No remission (n = 11)	Remission (n = 13)	p value
Standard evaluation			
Delta MAGNIFI	−1 (−7–2)	−3 (−8 to −2)	0.282
Relative change of the % of subjective fibrotic component	100 (0–500)	200 (66,7–400)	0.663
Volumetric evaluation			
Total reduction volume (%), median (IQR)	0.5 (−64.5–41.5)	−35.6 (−50.8 to −12.4)	0.354
% of change of active component, median (IQR)	−38.7 (−73.3–31)	−82.5 (−89.0 to −72.5)	0.007
% of change of fibrotic component, median (IQR)	14.4 (−5.1–131.8)	39.4 (11.9–145.5)	0.325
% of change of relative active component, mean (SD)	−25.5 ± 30.6	−68.2 ± 21.2	0.001
% of change of relative fibrotic component, median (IQR)	34.1 (8.4–117.3)	119.7 (74.3–181.9)	0.032
Delta total volumen (cc), median (IQR)	0.03 (−5.82–1.11)	−0.542 (−0.806 to −0.226)	0.817
Delta active component (cc), median (IQR)	−0.53 (−4.17–0.26)	−0.599 (−1.286 to −0.47)	0.908
Delta fibrotic component (cc), median (IQR)	0.23 (−0.14–1.19)	0,13 (0.03–0.55)	0.885

TABLE 3 | MRI volumetric changes predictors of long-term clinical remission.

	Univariate[a]			Multivariate[a]		
MRI volumetric changes	Odds ratio	CI (95%)	p-value	Odds ratio	CI (95%)	p-value
% of change of active volume	0.94	0.89–0.99	0.027			
% of change of relative active component	0.92	0.86–0.98	0.013	0.92	0.86–0.98	0.013
% of change of relative fibrotic component	1.00	1.00–1.01	0.517			

Abbreviation: cc: cubic centimeters.
[a]Time between MRIs has been used as the controlling variable.

(active/fibrotic) would enable a more direct, objective, and potentially more reliable quantification of fibrosis and active components using MRI.

To the best of our knowledge, only one study has utilized volumetric changes in MRI to evaluate perianal fistulas. Lung et al. assessed the association between the percentage of fistula volume changes and subjective consensus agreement of response in 18 patients [30]. In our study, we have taken this further by measuring not only the total fistula volume but also the changes in each component of the fistula tract, either active or fibrotic and their predictive value in the assessment of clinical remission after a therapeutic intervention. Although the concept of fistula activity or fibrosis assessed by MRI, defined as the presence or absence of hypersignal on T2 sequences, respectively, is not validated against histology, it is used as an endpoint associated with clinical outcomes in different studies; therefore, we have considered it as a valid and applicable concept [8, 15, 23, 31].

The distinct demarcation between the high signal intensity of the fistula tract and the surrounding low signal intensity of fat or scar tissue (fibrosis) facilitates objective measurement of the active volume. In contrast, the difference in signal intensity between the low signal fibrotic components and the surrounding high signal intensity fat on T2 sequences without fat saturation makes it easier to measure the volume of the fibrotic component. Consequently, there was a high level of agreement among observers in measuring both components.

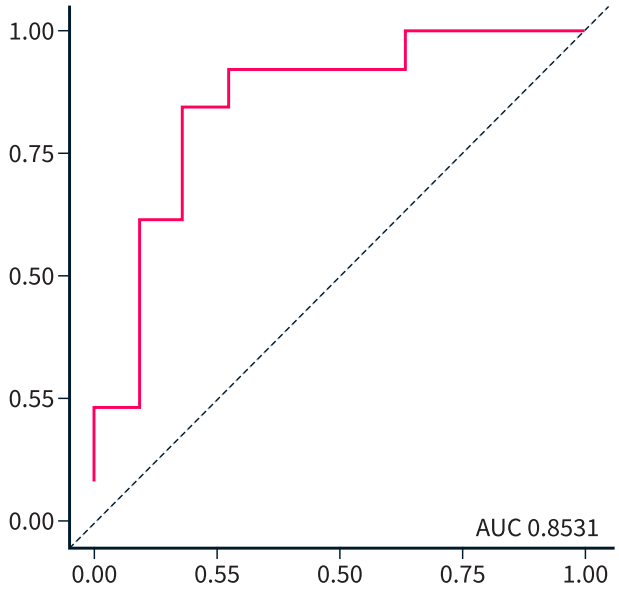

FIGURE 3 | ROC curve for the resulting model for predicting long-term clinical remission.

TABLE 4 | Baseline volumetric assessment associated with long-term clinical remission in response to biological therapy.

Baseline volumetric parameters	No remission ($n = 11$)	Remission ($n = 13$)	p value
Active—volume (cc), median (IQR)	4.18 (9.6–5.94)	0.72 (0.60–1.43)	0.013
Fibrosis—volume (cc), median (IQR)	2.77 (0.33–3.34)	0.42 (0.26–1.06)	0.049
Total volume (cc), median (IQR)	7.231 (1.29–9.27)	1.203 (0.97–2.58)	0.015
% Active—fistula, mean (SD)	66.4 ± 18.2	61.1 ± 20.7	0.520
% fibrosis—fistula, mean (SD)	33.6 ± 18.2	38.9 ± 20.7	0.516

Abbreviations: cc: cubic centimeters; IQR: interquartile range; SD: standard deviation.

While we have noted volumetric differences in baseline MRI among various clinical outcomes, our primary analysis has centered on longitudinal changes between the two assessments. Although informative, we believe this evaluation should include a larger sample size. Because of the inclusion criteria, our cohort comprises a relatively small sample size which hampers the identification of an optimal cutoff point for predicting therapeutic response.

This study has some limitations, including the small sample size and retrospective design. However, it was conceptualized as a pilot study to evaluate the feasibility of the technique (volumetry) and its potentiality to evaluate therapeutic response. The post-treatment MRI evaluation covers a relatively broad period, reflecting the variability of reassessing patients in clinical practice due to the absence of standardized recommendations for monitoring internal changes of PFD. Therefore, before providing recommendations in this regard, the results of this study should be validated in a larger cohort of patients with a more uniform clinical and radiological follow-up.

In conclusion, our observations suggest that changes in 3D volumetry on MRI of PFD may have value in predicting clinical response, specifically, the decrease in the active component rather than the increase in the fibrotic one. The volume reduction in the active component could therefore be considered as a biomarker for defining therapeutic targets in PFD in patients with CD.

Author Contributions

B.C., I.O., J.P. and J.R.: study design, project coordination and writing of the manuscript. B.C., I.O., J.R. and C.S. contributed to the analysis and interpretation of data. C.S. provided statistical analysis support. B. C., I.O., M.G., R.B., M.C.M., A.F.C., E.R., J.S. and J.R. contributed to patients' recruitment and data acquisition. All the authors approved the final version of the manuscript.

Acknowledgments

Motilent has graciously allowed us to use Entrolytics to develop this study.

Conflicts of Interest

B.C. has received financial support for educational activities from Kern, Jansen, Takeda, Pfizer, Ferring and Lilly. I.O. has served as a speaker and/or consultant or has received educational funding from MSD, Abbvie, Pfizer, Takeda, Janssen, Faes Farma, and Chiesi; she has also received research funding from Abbvie and Faes Farma. A.F.C. has served as a speaker or has received educational funding from Dr. Falk, Janssen, Takeda, Chiesi, and Pfizer. J.P. received consultancy fees/honorarium from AbbVie, Alimentiv, Athos, Atomwise, Boehringer Ingelheim, Celsius, Ferring, Galapagos, Genentech/Roche, GlaxoSmithKline, Janssen, Mirum, Nimbus, Pfizer, Progenity, Prometheus, Protagonist, Revolo, Sanofi, Sorriso, Surrozen, Takeda, and Wasserman, and has served on a data safety monitoring board for Alimentiv, Mirum, Sorriso, Sanofi, and Surrozen. E.R. has received financial support for research and conference attendance, speaker fees, or consulting fees from MSD, Abbvie, Ferring, Janssen, Otsuka, Pfizer, Takeda, Galapagos, Kern Pharma, Lilly, Faes Pharma and Fresenius Kabi. J.R. has received research grants from Abbvie and Genentech and lecture or consultancy fees from Origo Biopharma, Gilead, Takeda, and Janssen; he is on the advisory boards of Takeda, TiGenix, Gilead, Lument, and Alimentiv. The rest of the authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Data Availability Statement

The data underlying this article are available in the article and in its online supplementary material.

References

1. G. R. Lichtenstein, E. V. Loftus, K. L. Isaacs, M. D. Regueiro, L. B. Gerson, and B. E. Sands, "Acg Clinical Guideline: Management of Crohn's Disease in Adults," *American Journal of Gastroenterology* 113, no. 4 (2018): 481–517, https://doi.org/10.1038/ajg.2018.27.

2. D. A. Schwartz, E. V. Loftus, W. J. Tremaine, et al., "The Natural History of Fistulizing Crohn's Disease in Olmsted County, minnesota," *Gastroenterology* 122, no. 4 (2002): 875–880, https://doi.org/10.1053/gast.2002.32362.

3. S. J. Bell, A. B. Williams, P. Wiesel, K. Wilkinson, R. C. G. Cohen, and M. A. Kamm, "The Clinical Course of Fistulating Crohn's Disease," *Alimentary Pharmacology and Therapeutics* 17, no. 9 (2003): 1145–1151, https://doi.org/10.1046/j.1365-2036.2003.01561.x.

4. T. Sharma, C. Ma, R. Sedano, et al., "Placebo Response Rates in Randomized Controlled Trials for Perianal Crohn's Disease: A Systematic Review and Meta-Analysis," *Journal of Crohns Colitis* 17, no. 4 (2023): 644–658, https://doi.org/10.1093/ecco-jcc/jjac160.

5. K. B. Gecse, W. Bemelman, M. A. Kamm, et al., "A Global Consensus on the Classification, Diagnosis and Multidisciplinary Treatment of Perianal Fistulising Crohn's Disease," *Gut* 63, no. 9 (2014): 1381–1392, https://doi.org/10.1136/gutjnl-2013-306709.

6. C. Maaser, A. Sturm, S. R. Vavricka, et al., "Ecco-esgar Guideline for Diagnostic Assessment in Ibd Part 1: Initial Diagnosis, Monitoring of Known Ibd, Detection of Complications," *Journal of Crohns Colitis* 13, no. 2 (2019): 144–164, https://doi.org/10.1093/ecco-jcc/jjy113.

7. S. Halligan, D. Tolan, M. M. Amitai, et al., "Esgar Consensus Statement on the Imaging of Fistula-In-Ano and Other Causes of Anal Sepsis," *European Radiology* 30, no. 9 (2020): 4734–4740, https://doi.org/10.1007/s00330-020-06826-5.

8. M. C. Greer and S. A. Taylor, "Perianal Imaging in Crohn Disease: Current Status With a Focus on Mri, From the Ajr Special Series on Imaging of Inflammation," *American Journal of Roentgenology* 218, no. 5 (2022): 781–792, https://doi.org/10.2214/ajr.21.26615.

9. S. P. Sheedy, D. H. Bruining, E. J. Dozois, W. A. Faubion, and J. G. Fletcher, "Mr Imaging of Perianal Crohn Disease," *Radiology* 282, no. 3 (2017): 628–645, https://doi.org/10.1148/radiol.2016151491.

10. P. Hindryckx, V. Jairath, G. Zou, et al., "Development and Validation of a Magnetic Resonance Index for Assessing Fistulas in Patients With Crohn's Disease," *Gastroenterology* 157, no. 5 (2019): 1233–1244, https://doi.org/10.1053/j.gastro.2019.07.027.

11. G. Van Assche, D. Vanbeckevoort, D. Bielen, et al., "Magnetic Resonance Imaging of the Effects of Infliximab on Perianal Fistulizing Crohn's Disease," *American Journal of Gastroenterology* 98, no. 2 (2003): 332–339, https://doi.org/10.1111/j.1572-0241.2003.07241.x.

12. M. A. A. Samaan, C. A. J. A. J. Puylaert, B. G. G. Levesque, et al., "The Development of a Magnetic Resonance Imaging Index for Fistulising Crohn's Disease," *Alimentary Pharmacology & Therapeutics* 46, no. 5 (2017): 516–528, https://doi.org/10.1111/apt.14190.

13. J. Panes and J. Rimola, "Perianal Fistulizing Crohn's Disease: Pathogenesis, Diagnosis and Therapy," *Nature Reviews Gastroenterology & Hepatology* 14, no. 11 (2017): 652–664, https://doi.org/10.1038/nrgastro.2017.104.

14. S. K. Vuyyuru, V. Solitano, S. Singh, et al., "Scoring Indices for Perianal Fistulising Crohn's Disease: A Systematic Review," *Journal of Crohn's and Colitis* 18, no. 6 (2024): 836–850, https://doi.org/10.1093/ecco-jcc/jjad214.

15. S. C. Ng, S. Plamondon, A. Gupta, et al., "Prospective Evaluation of Anti-tumor Necrosis Factor Therapy Guided by Magnetic Resonance Imaging for Crohn's Perineal Fistulas," *American Journal of Gastroenterology* 104, no. 12 (2009): 2973–2986, https://doi.org/10.1038/ajg.2009.509.

16. P. Tozer, S. C. Ng, M. R. Siddiqui, et al., "Long-term Mri-Guided Combined Anti-tnf and Thiopurine Therapy for Crohn's Perianal Fistulas," *Inflammatory Bowel Diseases* 18, no. 10 (2012): 1825–1834, https://doi.org/10.1002/ibd.21940.

17. T. Lee, E. Yong, and N. S. Ding, "Radiological Outcomes in Perianal Fistulizing Crohn's Disease: A Systematic Review and Meta-Analysis," *JGH Open* 4, no. 3 (2020): 340–344, https://doi.org/10.1002/jgh3.12295.

18. C. Savoye-Collet, G. Savoye, E. Koning, J. N. Dacher, and E. Lerebours, "Fistulizing Perianal Crohn's Disease: Contrast-Enhanced Magnetic Resonance Imaging Assessment at 1 Year on Maintenance Anti-tnf-alpha Therapy," *Inflammatory Bowel Diseases* 17 (2011): 1751–1758, https://doi.org/10.1002/ibd.21568.

19. P. H. Kim, S. H. Kim, Y. A. Cho, et al., "Ability of Pelvic Magnetic Resonance Imaging to Predict Clinical Course of Perianal Fistula in Paediatric Crohn's Disease Patients," *Journal of Crohns Colitis* 15, no. 7 (2021): 1152–1160, https://doi.org/10.1093/ecco-jcc/jjab004.

20. K. L. van Rijn, E. M. Meima-van Praag, P. M. Bossuyt, et al., "Fibrosis and Magnifi-Cd Activity Index at Magnetic Resonance Imaging to Predict Treatment Outcome in Perianal Fistulizing Crohn's Disease Patients," *Journal of Crohns Colitis* 16 (2022): 708–716.

21. R. G. Beets-Tan, G. L. Beets, A. G. van der Hoop, et al., "Preoperative Mr Imaging of Anal Fistulas: Does it Really Help the Surgeon?," *Radiology* 218, no. 1 (2001): 75–84, https://doi.org/10.1148/radiology.218.1.r01dc0575.

22. A. Losco, C. Vigano, D. Conte, B. M. Cesana, and G. Basilisco, "Assessing the Activity of Perianal Crohn's Disease: Comparison of Clinical Indices and Computer-Assisted Anal Ultrasound," *Inflammatory Bowel Diseases* 15, no. 5 (2009): 742–749, https://doi.org/10.1002/ibd.20826.

23. T. Kucharzik, J. Tielbeek, D. Carter, et al., "Ecco-esgar Topical Review on Optimizing Reporting for Cross-Sectional Imaging in Ibd," *Journal of Crohns Colitis* 16, no. 4 (2022): 523–543, https://doi.org/10.1093/ecco-jcc/jjab180.

24. Q. Liu, X. Zhang, H. M. Ko, et al., "Constrictive and Hypertrophic Strictures in Ileal Crohn's Disease," *Clinical Gastroenterology and Hepatology* 20, no. 6 (2022): e1292, https://doi.org/10.1016/j.cgh.2021.08.012.

25. T. K. Koo and M. Y. Li, "A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research," *Journal of Chiropractic Medicine* 15, no. 2 (2016): 155–163, https://doi.org/10.1016/j.jcm.2016.02.012.

26. J. D. Feuerstein, E. Y. Ho, E. Shmidt, et al., "Aga Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease," *Gastroenterology* 160, no. 7 (2021): 2496–2508, https://doi.org/10.1053/j.gastro.2021.04.022.

27. A. M. Parian, M. Obi, P. Fleshner, and D. A. Schwartz, "Management of Perianal Crohn's Disease," *American Journal of Gastroenterology* 118, no. 8 (2023): 1323–1331, https://doi.org/10.14309/ajg.0000000000002326.

28. Da Schwartz, L. J. Ghazi, M. Regueiro, et al., "Guidelines for the Multidisciplinary Management of Crohn's Perianal Fistulas," *Inflammatory Bowel Diseases* 21, no. 4 (2015): 723–730, https://doi.org/10.1097/mib.0000000000000315.

29. G. Sciaudone, C. Di Stazio, P. Limongelli, et al., "Treatment of Complex Perianal Fistulas in Crohn Disease: Infliximab, Surgery or Combined Approach," *Canadian Journal of Surgery* 53 (2010): 299–304.

30. P. F. C. Lung, K. Sahnan, D. Burling, et al., "Volume Assessment Magnetic Resonance Imaging Technique for Monitoring Perianal Crohn's Fistulas," *Therapy Advance Gastroenterology* 11 (2018): 1756284818793609, https://doi.org/10.1177/1756284818793609.

31. E. M. Meima-van Praag, K. L. van Rijn, K. Wasmann, et al., "Short-Term Anti-tnf Therapy With Surgical Closure Versus Anti-tnf Therapy in the Treatment of Perianal Fistulas in Crohn's Disease (Pisa-ii): A Patient Preference Randomised Trial," *Lancet Gastroenterology Hepatology* 7 (2022): 617–626.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.