Journal of Crohn's and Colitis, 2022, **16**, 708–716
https://doi.org/10.1093/ecco-jcc/jjab168
Advance access publication 13 October 2021
Original Article

Fibrosis and MAGNIFI-CD Activity Index at Magnetic Resonance Imaging to Predict Treatment Outcome in Perianal Fistulizing Crohn's Disease Patients

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Abstract

Background and Aims: Characteristic magnetic resonance imaging [MRI] features associated with long-term perianal fistula closure are still being discussed. This study evaluated the predictive value of degree of fibrosis and disease activity (MAGNIFI-CD index) at MRI for long-term clinical closure of Crohn's perianal fistulas.

Methods: Crohn's disease [CD] patients treated with surgical closure following anti-tumour necrosis factor [anti-TNF] induction or anti-TNF alone for high perianal fistulas as part of a patient preference randomized controlled trial [PISA-II] between 2013 and 2020 with a post-treatment MRI and long-term clinical follow-up data were retrospectively included. Two radiologists scored the degree of fibrosis and MAGNIFI-CD index at pre- and post-treatment MRI. The accuracy of post-treatment MRI findings in predicting long-term clinical closure [12 months after the MRI] was evaluated using receiver operating characteristics [ROC] analysis.

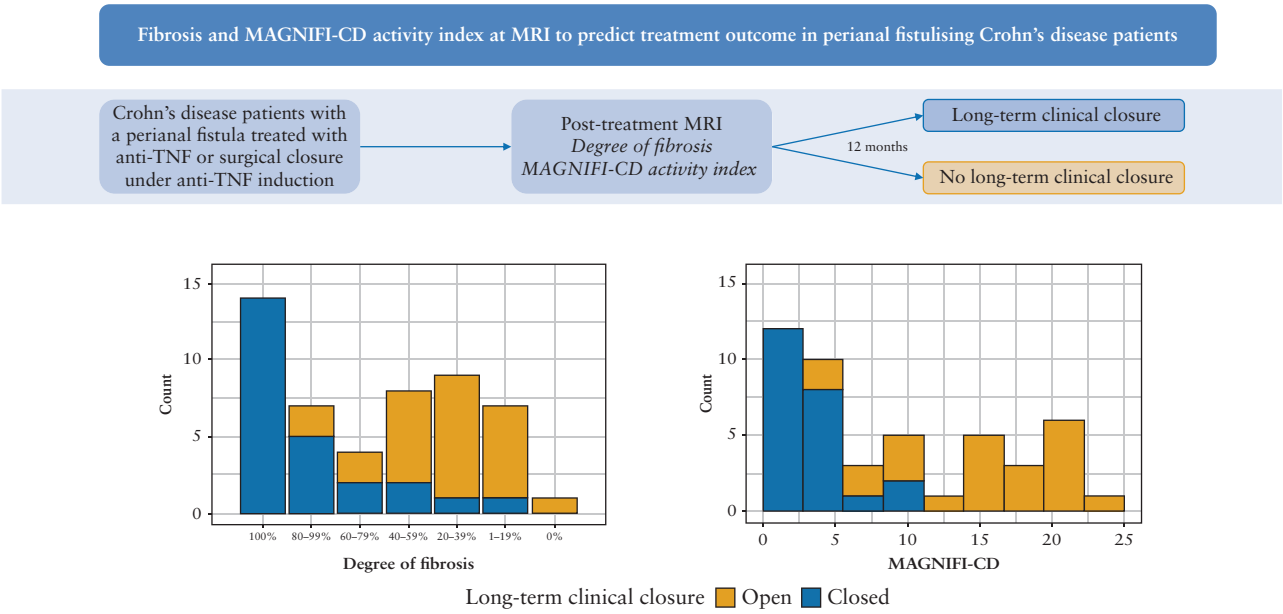
Results: Fifty patients were included: 31 female, median age 33 years (interquartile range [IQR] 26–45). Fourteen patients showed a 100% fibrotic fistula at post-treatment MRI, all of which had long-term clinical closure. Median MAGNIFI-CD index at post-treatment MRI was 0 [IQR 0–5] in 25 patients with long-term clinical closure and 16 [IQR 10-20] in 25 patients without. ROC analysis showed an area under the curve of 0.90 (95% confidence interval [CI] 0.82–0.99) for degree of fibrosis and 0.95 [95% CI 0.89–1.00] for the MAGNIFI-CD index, with a Youden cut-off point of 6 [91% specificity, 87% sensitivity].

Conclusions: Degree of fibrosis and MAGNIFI-CD index at post-treatment MRI are accurate in predicting long-term clinical closure and seem valuable in follow-up of perianal CD. A completely fibrotic tract at MRI is a robust indicator for long-term fistula closure.

EudraCT: 2013-002932-25 and 2018-002064-15

Key Words: Anal fistula; Crohn's disease; magnetic resonance imaging

Graphical Abstract



Fibrosis and MAGNIFI-CD acitivity index at MRI are predictive of long-term clinical fistula closure in Crohn's disease patients

1. Introduction

Perianal fistulas are a frequent complication in patients with Crohn's disease with a considerable impact on quality of life, occurring in about one-third of patients during their disease course.[1,2] Clinical guidelines currently advocate anti-tumour necrosis factor [anti-TNF] in combination with immunosuppressives as first-line treatment and suggest considering surgical closure in suitable patients.[3–5] However, as relapse occurs frequently and re-interventions are often required, evaluation of treatment response is needed to guide clinical management.[5–8]

Magnetic resonance imaging [MRI] is recommended by current guidelines as the imaging modality for evaluation of fistula activity and assessment of radiological healing.[5,9] However, characteristic features associated with long-term clinical fistula closure are still being discussed. Over the years, several MRI-based activity indices have been developed to evaluate response to therapy, of which the MAGNIFI-CD was developed with the most stringent methodology and is best validated.[10–12] This activity index has the potential to be used as a tool for clinical follow-up and as a reliable instrument in clinical trials, but its performance in predicting long-term response to treatment has not yet been evaluated.

While most studies focus on measuring changes in disease activity at MRI, there is little focus on radiological healing.[10–14] In previous studies, different definitions have been used.[15–18] Generally, a completely fibrotic tract is considered as radiological healing.[15,17] Although it has been shown that a completely fibrotic tract is associated with a longer flare-fee period,[17] one can speculate that a largely but not completely fibrotic tract at imaging may be the representation of a possibly irreversible process of fibrosis development. Therefore, a largely fibrotic tract may have a similar predictive value for future long-term closure comparable to that of completely fibrotic tracks. Confirmation of this hypothesis may be relevant for a valid definition of radiological fistula healing, which is, in itself, pivotal for treatment management.

So far, most studies regarding treatment monitoring with MRI have been performed in patients receiving anti-TNF therapy with few in patients after surgical closure, while both treatment options are relevant in clinical practice.[14,15,19–21] The course of perianal fistulas on MRI may differ between these treatments, indicating the need for evaluation of long-term treatment responses in a broad group of patients.

The aim of this study was to evaluate degree of fibrosis and disease activity using the MAGNIFI-CD index at MRI as predictors of long-term clinical fistula closure in Crohn's patients receiving anti-TNF therapy or surgical closure after anti-TNF induction therapy.

2. Materials and Methods

2.1. Study design

Clinical data and MRI scans were collected from the database of the patient preference randomized controlled trial [RCT] [PISA II] comparing anti-TNF treatment alone to anti-TNF plus surgical closure [unpublished data from the PISA II study]. This is a follow-up study of the prospective PISA-I study: an RCT comparing anti-TNF treatment to surgical closure following induction treatment of 4 months of anti-TNF and chronic seton drainage, all combined with 6-mercaptopurine [6-MP].[22,23] These trials were registered at the Dutch Trial Registry [NTR4137 and NL7625]. Patients were included between September 2013 and December 2019 and had previously signed informed consent. For the current study, ethical approval was waived by the Medical Ethical Committee at the Amsterdam UMC, location Academic Medical Centre [AMC]. To ensure patient privacy, the data underlying this article cannot be shared publicly. Anonymous data will be shared upon reasonable request.

2.2. Study group

We included data from adult patients, over 18 years old, with a high perianal Crohn's fistula with single internal opening

treated with anti-TNF or surgical closure combined with anti-TNF therapy from the PISA trial. In patients undergoing surgical closure, anti-TNF treatment was stopped after 4 months, unless luminal inflammation precluded stopping medication. Patients underwent seton drainage before the start of treatment and both treatments were combined with 6-MP for 1 year. The start of treatment was defined as the date of seton removal in the anti-TNF group and surgical closure date in the surgery group, as from this point on the fistula was able to close.

Patients were eligible if they had a post-treatment MRI between 3 and 24 months after the start of treatment without re-interventions between treatment initiation and the post-treatment MRI. This time window was chosen because we wanted to include the MRI scans at 18 months [allowed between 12 and 24 months] post-treatment according to the PISA trial protocol. However, if an MRI before 12 months was performed for a clinical indication, we deemed it relevant to find predictors for clinical closure from those MRI scans as well. In surgical closure patients it was previously shown that a post-treatment MRI as soon as 3 months after ligation of the intersphincteric tract was relevant to assess fistula healing.[21] Re-interventions were defined as a surgical intervention [e.g. seton placement or incision] or switch/stopping medical therapy.

MRI scans had to include at least a T2-weighted sequence in two directions and a T2-weighted sequence with fat-suppression and had to be of sufficient diagnostic quality. Also, clinical information regarding fistula closure 12 months after the post-treatment MRI had to be present. Excluded were patients with re-interventions or switch to another therapy between treatment initiation and the post-treatment MRI, and presence of active proctitis and/or a stoma.

2.3. MRI protocol

Pre-treatment MRI scans were collected to assess baseline MRI characteristics and were performed before start of anti-TNF treatment or surgical closure. Post-treatment MRI scans, defined as MRI scans performed after the start of treatment, were collected to assess the association of fibrosis and the MAGNIFI-CD index with treatment outcomes. The majority [81%] of the MRI scans had been performed at our tertiary inflammatory bowel disease [IBD] referral hospital [Amsterdam UMC, location AMC]. Scans at our centre were performed on a 1.5-T scanner [Magnetom Avanto, Siemens] or 3.0-T scanner [Intera, Philips]. Our local protocol consists of a sagittal, coronal and axial T2-weighted sequence, an axial T2-weighted sequence with fat suppression and a T1-weighted post-contrast sequence with fat suppression after intravenous administration of gadolinium. The coronal and transverse sequences were angled parallel and perpendicular to the anal canal, respectively. MRI scans from other centres had to include at least a T2-weighted sequence in two planes and a T2-weighted sequence with fat suppression. A T1 post-contrast sequence was not mandatory, as many of the MRI parameters, including fibrosis, could be assessed without this sequence.

2.4. MRI assessment

Two abdominal radiologists [JT and KH] with special interest and experience [10 and 17 years'] in MRI of Crohn's disease patients independently and blindly reviewed all MRI scans in a random order. They were blinded for clinical information and the time-point [pre- or post-treatment] of the MRI scans. Discrepancies between observers for all separate items were resolved by a third abdominal radiologist (expert in MRI of perianal fistulas [JS]; >25 years' experience).

Scoring items are shown in Table 1 and consisted of the degree of fibrosis and activity items according to the MAGNIFI-CD index.[12] The item degree of fibrosis was composed for the current study to gain insight into the effect of a partially fibrotic tract on long-term outcomes and has not been evaluated previously. It was evaluated by estimating the volume of the fistula tract that consisted of fibrosis on a T2-weighted sequence without fat suppression; fibrosis was defined as an absence of hyperintensity on all sequences. No actual fistula volumes were measured. Figure 1 shows examples of the different fibrosis grades. If there was no post-contrast T1-weighted sequence present, the MAGNIFI-CD index could not be calculated [post-contrast T1 sequences were absent in 12 pre-treatment scans and four post-treatment scans].

Table 1. Scoring items and calculation of the MAGNIFI-CD index[12]

Item	Scoring options	
Degree of fibrosis [Fig 1]	100%	
	80–99%	
	60–79%	
	40–59%	
	20–39%	
	1–19%	
	0%	
MAGNIFI-CD		Weight
Number of tracts	0 = None	3
	1 = Single, unbranched	
	2 = Complex	
Hyperintensity on post-contrast	0 = Absent/mild 1 = Pronounced	2
T1-weighted images	0 = Fibrous 1 = Granulation tissue 2 = Fluid/pus	
Dominant feature	0 = <2.5 cm 1 = 2.5–5 cm 2 = >5 cm	2
Fistula length	0 = Absent 1 = Horseshoe 2 = Infralevatoric/supralevatoric	2
Extension		2
Inflammatory mass	0 = Absent	1
	1 = Focal	
	2 = Diffuse	
	3 = Collections, small	
	4 = Collections, medium	
	5 = Collections, large	
Total MAGNIFI-CD		Range 0-25

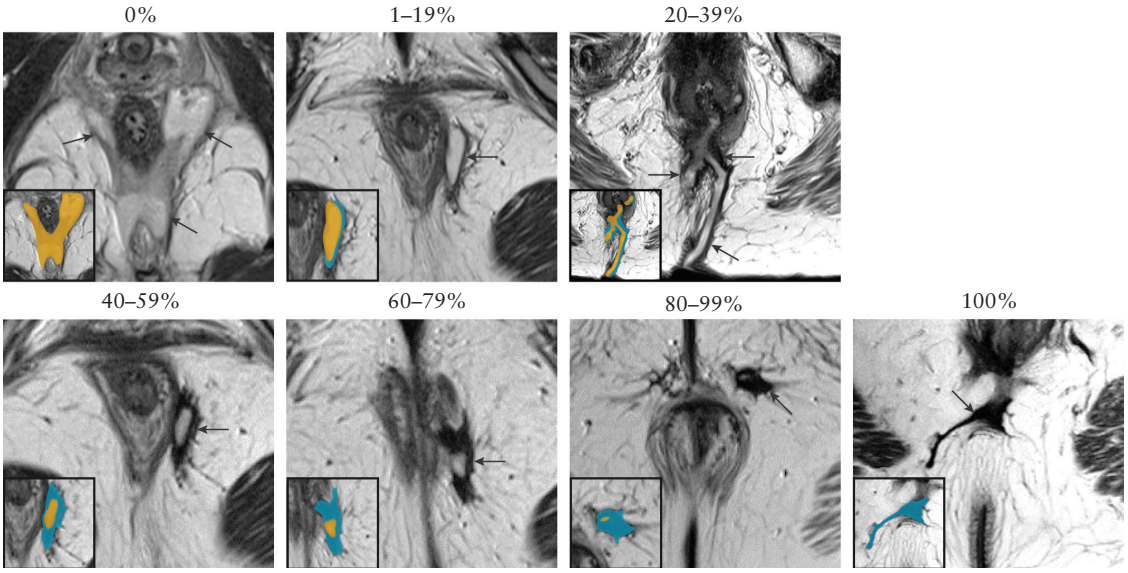


Figure 1. Degree of fibrosis examples. Axial T2-weighted images illustrating the different degrees of fibrosis that were scored. An enlarged image of the fistula is also shown with colour-coding according to the type of tissue, with fibrosis in blue and inflammation in yellow.

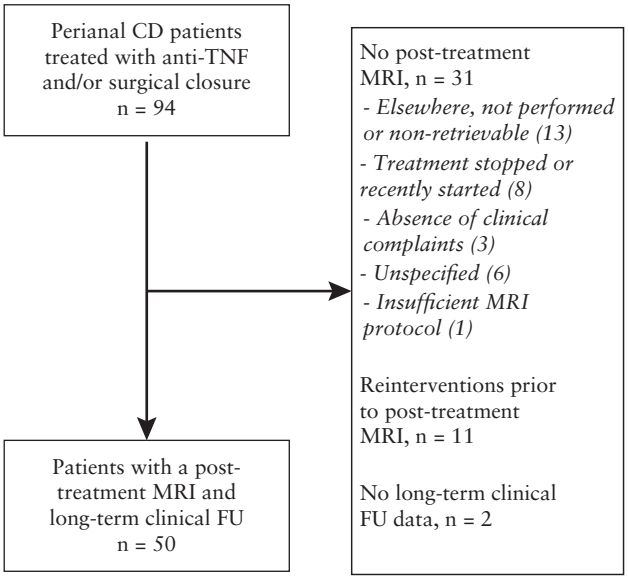


Figure 2. Flowchart of inclusion. CD = Crohn's disease; FU = follow-up.

2.5. Long-term clinical closure

Long-term clinical closure at 12 months after the post-treatment MRI [range 10–14 months] was assessed based on clinical notes of an IBD gastroenterologist and/or IBD surgeon in the electronic patient record. Most of these notes were prospectively recorded in the PISA trial and were assessed retrospectively for the current study; in eight patients clinical closure was assessed from regular clinical notes. The two study coordinators [KR and EM] reviewed the notes in consensus while they were blinded for MRI outcomes; in case of disagreement the cases were discussed with an IBD surgeon [CB]. Clinical closure was defined as no patient-reported drainage and no production on palpation[24] and an absence of surgical or medical re-interventions in the 12 months after the post-treatment MRI. If information on either patient-reported drainage or production on palpation was missing, one of the two was accepted. All other fistulas were defined as open. Additionally, recurrences and re-interventions after the post-treatment MRI were noted, defined as the re-opening of the external fistula opening or renewed production of the fistula after it had been closed and

Table 2. Baseline characteristics. LIFT = ligation of the intersphincteric tract; MAF = mucosal advancement flap

Total *n* = 50	***N* [%] or median [IQR]**
Sex, female	33 [66%]
Age in years	33 [26–45]
Smoking	15 [30%]
Disease location	
Terminal Ileum [L1]	30 [60%]
Colon [L2]	9 [18%]
Ileocolon [L3]	11 [22%]
Number of external openings	
One	38 [76%]
Two	11 [22%]
Three	1 [2%]
Treatment	
Anti-TNF	28 [56%]
Surgical closure under anti-TNF induction	22 [44%]
LIFT	12 [24%]
MAF	5 [10%]
Fistulotomy	5 [10%]
Pre-treatment MRI characteristics [n = 48]	
Transsphincteric fistula tract	34 [71%]
Complex fistula [single, branched tract or multiple tracts]	29 [60%]
Infra- or supralevatoric extension	23 [48%]
Degree of fibrosis <40%	38 [79%]
Predominantly granulated tissue	26 [54%]
Abscess	8 [17%]
Proctitis	7 [15%]
MAGNIFI-CD	16 [9–20]

the need for a surgical or medical intervention of the treated fistula tract, respectively.

2.6. Statistical analysis

Receiver operating characteristic [ROC] analysis was used to evaluate the performance of degree of fibrosis and the MAGNIFI-CD index at post-treatment MRI in predicting long-term clinical closure. The area under the curve [AUC] with a 95% confidence interval [CI] was calculated to express accuracy. For the MAGNIFI-CD, a cut-off point maximizing Youden's index was calculated, with its sensitivity and specificity. Although not the primary aim of this study, we also described the pre-treatment MAGNIFI-CD index in relation to long-term clinical closure. Interobserver variability between the two observers was expressed as weighted kappa statistics for ordinal variables and intraclass correlation coefficients [ICCs] for continuous variables. Interpretation was performed according to Landis and Koch[25]: <0 equals poor, 0.01–0.20 equals slight, 0.21–0.40 equals fair, 0.41–0.60 equals moderate, 0.61–0.80 equals substantial and 0.81–1.00 equals almost perfect. MRI and clinical features are presented as frequencies with percentages or medians with interquartile ranges [IQRs].

3. Results

3.1. Baseline characteristics

Scans and data from 50 patients could be included (31 female, median age 33 years [IQR 26–45]). Figure 2 shows the flowchart of inclusion and Table 2 shows the baseline characteristics of the included patients. In total, 98 MRI scans were assessed; in two patients no pre-treatment MRI was present. All 98 MRI scans had good diagnostic quality. The pre-treatment MRI was performed median 4 months [IQR 1–6] before treatment and the post-treatment MRI at a median of 7 months [IQR 4–15] after treatment.

Twenty-five [50%] patients had a clinically closed fistula at long-term follow-up and 25 [50%] had an open [persistently draining] fistula. Of the patients with an open fistula, this was considered as recurrence [reopening] in six patients as they previously were demonstrated to have clinical closure. A total of 15 patients needed a re-intervention after the post-treatment MRI.

3.2. Pre-treatment MRI

The pre-treatment MRI characteristics are presented in Table 2. At pre-treatment MRI, the majority of patients [79%] had less than 40% fibrosis. The overall median MAGNIFI-CD index was 16 [IQR 9–20]. The median pre-treatment MAGNIFI-CD index was 11 [IQR 7–18] in patients who reached long-term clinical closure after their treatment and 19 [IQR 15–23] in patients who did not.

3.3. Post-treatment degree of fibrosis and MAGNIFI-CD index in relation to long-term clinical closure

In Figure 3 the degree of fibrosis at the post-treatment MRI is shown for patients who had long-term clinical closure and those who did not. All 14 patients who had a 100% fibrotic fistula at their post-treatment MRI showed long-term clinical closure [Figure 4 shows an example of a patient who has a completely fibrotic tract at post-treatment MRI]. In patients with 0% fibrosis, only open fistulas were present at long-term follow-up. In all other categories, both patients with and without long-term clinical closure were present. ROC analysis shows an AUC of 0.90 [95% CI: 0.82–0.99] accuracy in predicting long-term clinical closure.

Figure 5 shows the MAGNIFI-CD index at post-treatment MRI in relation to long-term clinical closure. In four patients no MAGNIFI-CD could be calculated because there was no post-contrast T1 sequence. The median MAGNIFI-CD index was 0 [IQR 0–5] in patients with long-term clinical closure and 16 [IQR 10–20] in patients without. ROC analysis shows an AUC of 0.95 [95% CI: 0.89–1.00] accuracy in predicting long-term clinical closure. The Youden threshold to determine long-term clinical closure was a MAGNIFI-CD index of 6, with a 91% specificity and 87% sensitivity.

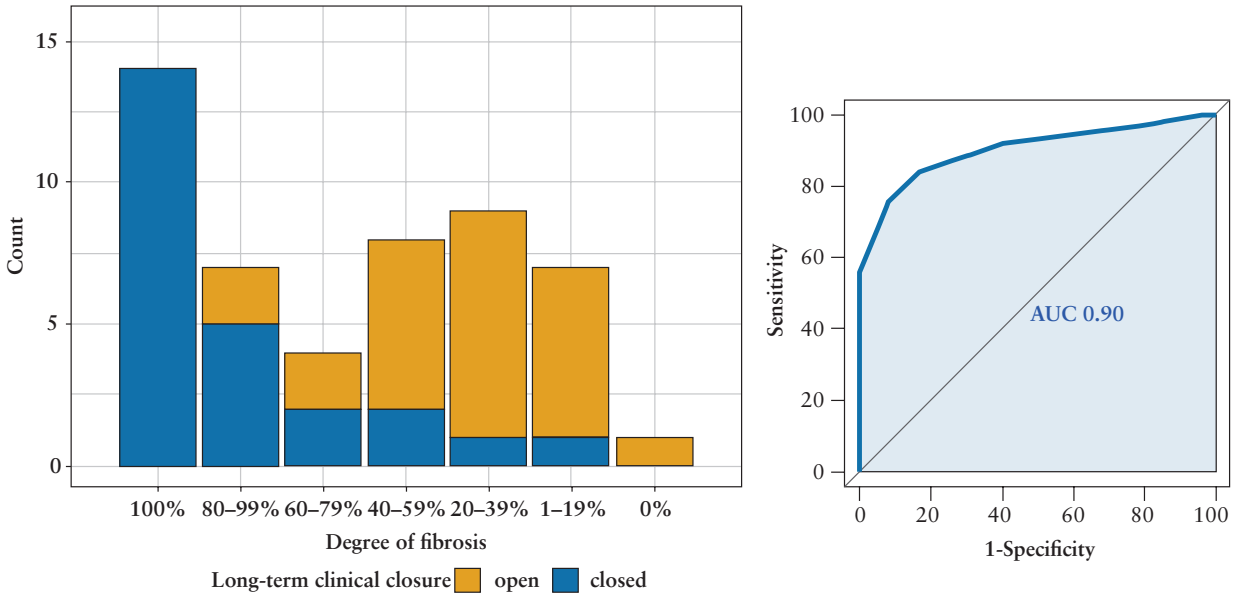


Figure 3. Degree of fibrosis at the post-treatment MRI in relation to long-term clinical closure.

3.4. Post-treatment MRI per treatment group in relation to long-term clinical closure

The treatment consisted of anti-TNF in 28 patients and surgical closure following anti-TNF induction in 22 patients. At pre-treatment MRI, the median MAGNIFI-CD index was 18 [IQR 12–21] in the anti-TNF group and 13 [IQR 7–20] in the surgical group. Figure 6 shows the degree of fibrosis and MAGNIFI-CD index at post-treatment MRI in relation to long-term clinical closure per patient group.

If more than 60% fibrosis was present, two-thirds of the patients in the anti-TNF group had long-term clinical closure as opposed to all patients in the surgical closure group. In the anti-TNF group, only if the fistula tract was completely fibrotic were all fistulas closed at long-term clinical follow-up. The MAGNIFI-CD index in the anti-TNF group with a closed fistula at long-term clinical follow-up had a median of 5 [IQR 3–5], while in the surgical closure group this was 0 [IQR 0–2]. When the fistula was open at long-term clinical follow-up, the median MAGNIFI-CD index was 16 [IQR 9–18] in the anti-TNF group and 18 [IQR 16–20] in the surgical closure group.

3.5. Interobserver agreement

Interobserver agreement ranged from 'moderate' to 'almost perfect' for the individual items [Table 3]. For the degree of fibrosis, interobserver agreement was 'substantial' and for the MAGNIFI-CD index as a whole this was 'almost perfect'.

4. Discussion

This study shows that the degree of fibrosis and the MAGNIFI-CD index at post-treatment MRI are predictive of long-term clinical fistula closure after anti-TNF treatment and surgical closure following anti-TNF induction. In patients with a completely fibrotic tract at MRI, long-term clinical closure was observed in all patients, indicating that this should be considered as the definition of radiological fistula healing.

Our finding that a completely fibrotic tract at MRI is associated with long-term clinical closure is consistent with previous findings.[17] Chambaz *et al*. found that deep remission, as defined by clinical remission and a completely fibrotic tract at MRI, was associated with higher rates of flare-free survival in patients receiving anti-TNF.[17] However, no previous studies have focused on different grades of fibrosis to predict long-term outcomes. Our results show that a higher degree of fibrosis is predictive for long-term clinical closure, indicating that fibrosis reflects the process of healing. However, only when a tract was completely fibrotic, long-term clinical closure was observed in patients after all treatments, indicating that residual activity on MRI may later result in a flare-up. This may be one of the causes for the recurrence rate of 47% after cessation of anti-TNF therapy in a study by Tozer *et al*., where the definition of radiological healing included subtle residual tracts.[16]

We also found high accuracy in predicting long-term clinical closure using the MAGNIFI-CD index, showing that changes in fistula activity as measured by the MAGNIFI-CD index are related to the long-term outcome. We propose a cut-off point of a MAGNIFI-CD index of 6 to predict long-term clinical closure with high specificity and sensitivity [91% and 87%]. This index has only been applied in one previous study [except for the study in which it was developed], which showed that fistula length and dominant feature at diagnosis were predictive of the disease course in a paediatric population.[26] However, that study focused on MRI at diagnosis, while in the current study we focused primarily on post-treatment MRI. The high accuracy of the MAGNIFI-CD index at post-treatment MRI to determine long-term clinical closure suggests that this is a useful tool for treatment monitoring in clinical practice and clinical trials. The impact of post-treatment MRI features on long-term clinical outcomes for different treatments is highly relevant as it may orientate further therapeutic strategy, such as the need for optimization or the possibility of de-escalation.

In this study, both patients who received anti-TNF treatment and who underwent surgical closure after anti-TNF induction were included. Most previous studies evaluating treatment responses at MRI have focused on anti-TNF treatment and few on surgical closure.[14–16,20,21] Our results suggest that the behaviour of perianal fistulas after the two treatments is different. A completely fibrotic tract was achieved in 14% of the patients receiving anti-TNF treatment vs 50% of the patients after surgical closure under anti-TNF induction. Also, with more than 60% fibrosis, two-thirds of patients receiving anti-TNF treatment reached long-term closure as opposed to all patients in the surgical closure group. One can speculate that after surgical closure following anti-TNF induction there is a more clear-cut response; the fistula will either heal or there is no healing at all. In the anti-TNF group, the decrease in fistula activity may be more gradual over time and complete radiological healing is reached less often. We suggest that radiological follow-up should be adjusted to the treatment that patients have received, but to draw firm conclusions on this, a prospective study with different treatments comparing serial MRI scans at predefined time points should be performed.

While not the primary focus of this study, the fistula activity measured with the MAGNIFI-CD at pre-treatment MRI was also evaluated and showed a possible difference between patients having an open and closed fistula at long-term clinical follow-up. The MAGNIFI-CD index was higher in patients with an open fistula at long-term clinical follow-up, which suggests that more severe activity before treatment may have an effect on the late response to treatment. Finding MRI predictors for long-term clinical closure at pre-treatment MRI is an interesting focus for follow-up studies.

A supporting finding for the use of the MRI features that we evaluated was that the interobserver agreement for most individual items was substantial and for the MAGNIFI-CD index as a whole it was almost perfect. Nevertheless, in daily clinical practice, in some situations it might be more practical to focus on describing changes in activity and fibrosis instead of calculating an index for every patient.

In clinical practice, the long-term outcome that we used—consisting of an open or closed fistula—is a simplification of the clinical setting. From a patient perspective, a completely closed fistula at MRI does not necessarily have to be the desired outcome as long as symptoms have decreased substantially. Therefore, the treatment goal should include patient satisfaction and not only a completely fibrotic fistula tract at MRI. However, it is valuable as a clinician to keep in mind that residual fistula activity at MRI may flare, for example when considering ceasing medical therapy. Future studies should focus on linking differences in the MAGNIFI-CD index to a clinically relevant change in fistula

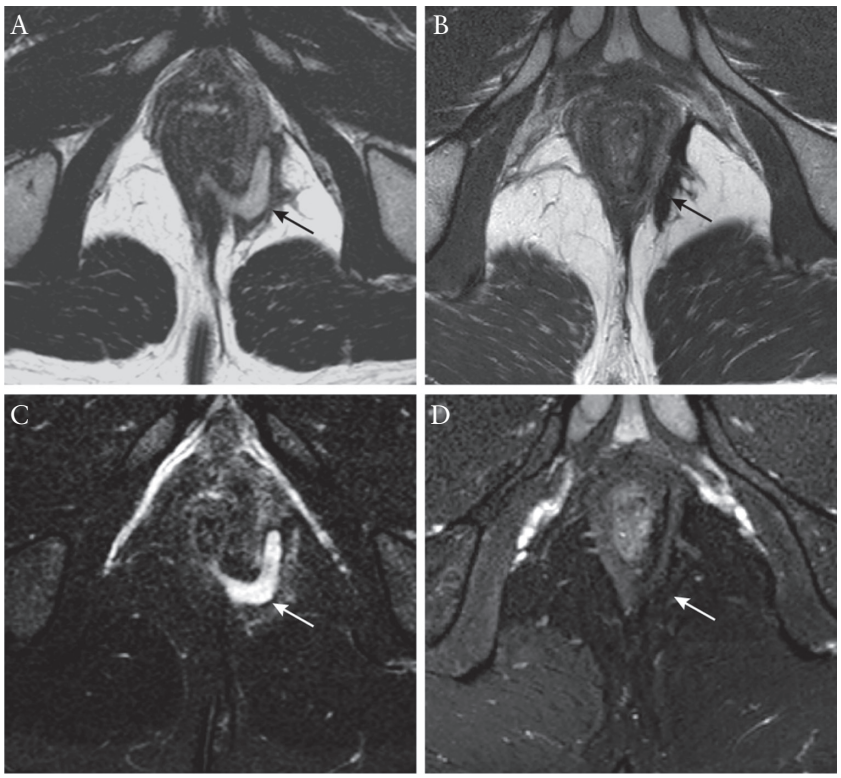


Figure 4. A completely fibrotic fistula tract at post-treatment MRI, 15 months after surgical closure. Axial T2-weighted images [A and B] and axial fat-suppressed T2-weighted images [C and D] at pre-treatment MRI [A and C] and at post-treatment MRI [B and D]. MRI shows a hyperintense, active fistula tract with predominantly granulated tissue before treatment, and a completely hypointense, fibrotic fistula tract 15 months after surgical closure.

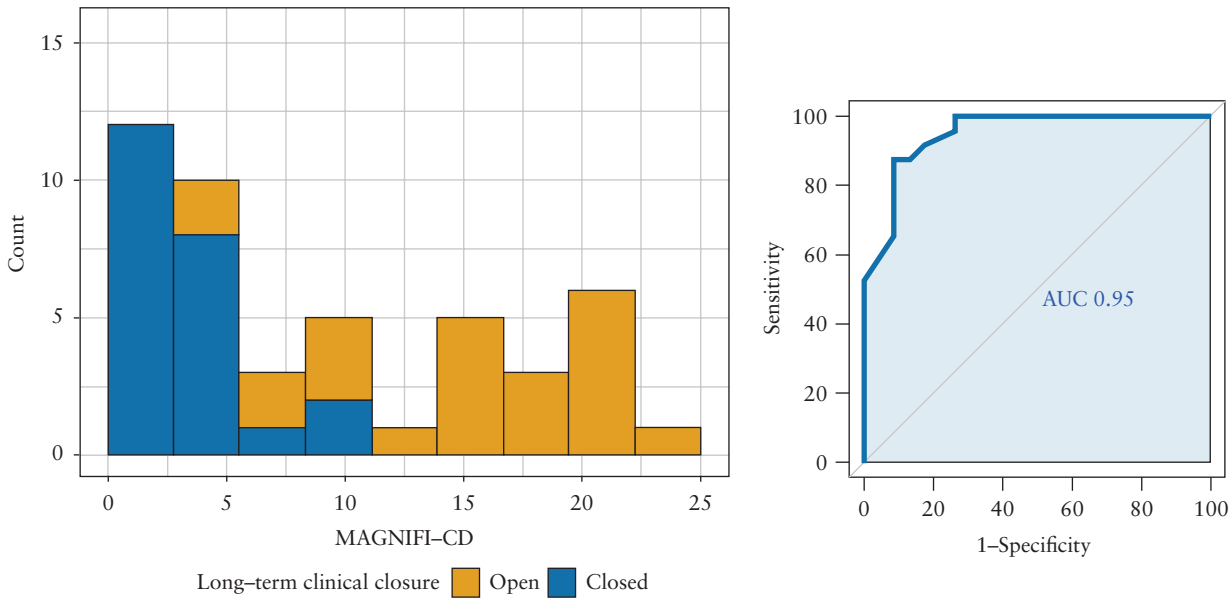


Figure 5. MAGNIFI-CD index at the post-treatment MRI in relation to long-term clinical closure.

activity incorporating patient perspective, for example by using quality of life scores.

One of the limitations of the current study was the relatively small sample size, which limits the ability to draw firm conclusions regarding the predictive value of MRI features. Furthermore, the partially retrospective design of the study resulted in different intervals between the start of treatment and the post-treatment MRI, which may limit generalizability of the MRI predictors for all follow-up time points. However, a heterogeneous follow-up is also characteristic for perianal fistulizing Crohn's disease patients, who often have a complex clinical course. The time point at which we determined clinical closure was always 12 months after the MRI, which allowed us to evaluate the relationship with post-treatment MRI findings and long-term clinical closure. Furthermore, clinical closure was assessed from medical records, and most of the data in the medical records were prospectively recorded within the PISA trial but some data were

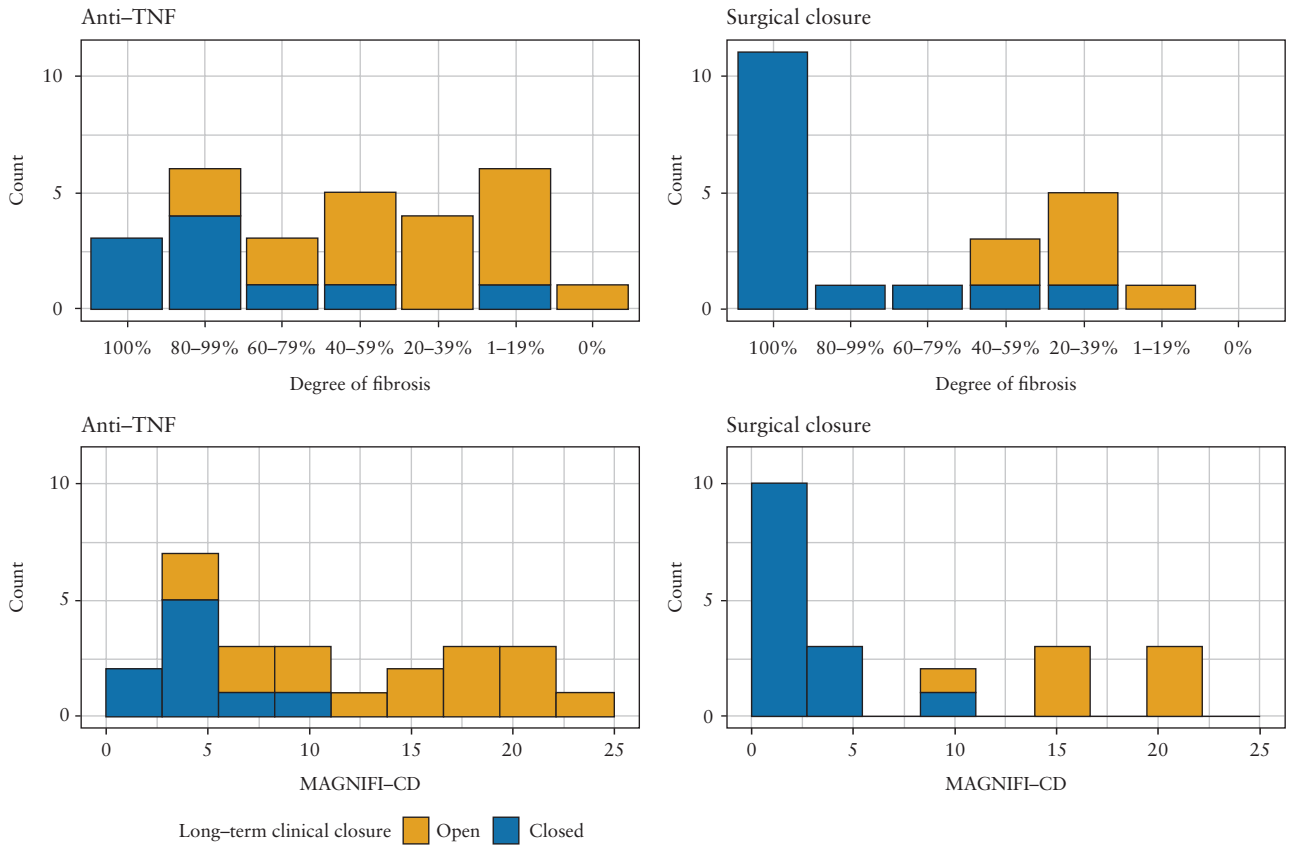


Figure 6. Degree of fibrosis and MAGNIFI-CD index at post-treatment MRI in relation to long-term clinical closure per treatment group. The degree of fibrosis was assessed on all 50 scans [28 anti-TNF and 22 surgical closure] and the MAGNIFI-CD index on the 46 scans [25 anti-TNF and 21 surgical closure] which had a post-contrast sequence.

Table 3. Interobserver agreement

Item	κ or ICC [95% CI]
Degree of fibrosis	0.77 [0.64–0.89]
Number of tracts	0.76 [0.64–0.88]
Hyperintensity T1	0.71 [0.56–0.87]
Dominant feature	0.56 [0.42–0.70]
Fistula length	0.85 [0.79–0.91]
Extension	0.62 [0.47–0.77]
Inflammatory mass	0.64 [0.45–0.82]
MAGNIFI-CD index	0.88 [0.79–0.93]

assessed retrospectively, which may have influenced the reliability of clinical outcomes in some patients. Also, MRI scans were performed for different indications, which could have introduced selection bias. We chose to score MRI scans in a random order to obtain an objective reflection of both the degree of fibrosis and the MAGNIFI-CD index. Although this is methodologically more robust, it might have been preferable to review changes between a pre- and post-treatment MRI, which would be more similar to the clinical setting.

We have shown that post-treatment degree of fibrosis and the MAGNIFI-CD index can predict long-term clinical closure. Our data suggest that a completely fibrotic tract at post-treatment MRI should be considered as radiologically healed. These findings can be valuable in treatment monitoring of Crohn's perianal fistulas with MRI in clinical practice and in clinical trials.

Funding

No funding was received for this study. The PISA-I and PISA-II studies received funding from the Netherlands Organisation for Health Research and Development [ZonMW] and Broad Medical Research Program funding.

Conflict of Interest

KLR, EMMP, PB, KH, HJS and JAWT have nothing to declare. GD has no disclosures associated with this study. KBG has received grants from Pfizer Inc. and Celltrion; consultancy fees from AbbVie, Arena Pharmaceuticals, Galapagos, Gilead, ImmunicTherapeutics, Janssen Pharmaceuticals, Novartis, Pfizer Inc., Samsung Bioepis and Takeda; and speaker's honoraria from Celltrion, Ferring, Janssen Pharmaceuticals, Novartis, Pfizer Inc., Samsung Bioepis, Takeda and Tillotts. CJB has an unrestricted grant from Boehringer Ingelheim and has received consultancy fees and/or speaker's honoraria from AbbVie, MSD, Tillotts, and Takeda. JS has a research agreement with Takeda not related to this topic.

Author Contributions

KLR, EMMP, HJS, CJB and JS were involved in the conception and design of the study. KLR, EMMP and HJS acquired

the data. All authors were involved in analysis and interpretation of the data. All authors critically revised the article for intellectual content and all authors approved the final version to be submitted.

Acknowledgements

None.

References

1. Ng SC, Shi HY, Hamidi N, *et al*. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2017;**390**:2769–78.
2. Schwartz DA, Loftus EV Jr, Tremaine WJ, *et al*. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. *Gastroenterology* 2002;**122**:875–80.
3. Schwartz DA, Ghazi LJ, Regueiro M, *et al*.; Crohn's & Colitis Foundation of America, Inc. Guidelines for the multidisciplinary management of Crohn's perianal fistulas: summary statement. *Inflamm Bowel Dis* 2015;**21**:723–30.
4. Torres J, Bonovas S, Doherty G, *et al*. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohns Colitis* 2020;**14**:4–22.
5. Gecse KB, Bemelman W, Kamm MA, *et al*.; World Gastroenterology Organization, International Organisation for Inflammatory Bowel Diseases IOIBD, European Society of Coloproctology and Robarts Clinical Trials; World Gastroenterology Organization International Organisation for Inflammatory Bowel Diseases IOIBD European Society of Coloproctology and Robarts Clinical Trials. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. *Gut* 2014;**63**:1381–92.
6. Bemelman WA, Warusavitarne J, Sampietro GM, *et al*. ECCO-ESCP consensus on surgery for Crohn's Disease. *J Crohns Colitis* 2018;**12**:1–16.
7. Molendijk I, Nuij VJ, van der Meulen-de Jong AE, van der Woude CJ. Disappointing durable remission rates in complex Crohn's disease fistula. *Inflamm Bowel Dis* 2014;**20**:2022–8.
8. Bouguen G, Siproudhis L, Gizard E, *et al*. Long-term outcome of perianal fistulizing Crohn's disease treated with infliximab. *Clin Gastroenterol Hepatol* 2013;**11**:975–81.e1–4.
9. Maaser C, Sturm A, Vavricka SR, *et al*.; European Crohn's and Colitis Organisation [ECCO] and the European Society of Gastrointestinal and Abdominal Radiology [ESGAR]. ECCO-ESGAR guideline for diagnostic assessment in IBD Part 1: initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis* 2019;**13**:144–64.
10. Van Assche G, Vanbeckevoort D, Bielen D, *et al*. Magnetic resonance imaging of the effects of infliximab on perianal fistulizing Crohn's disease. *Am J Gastroenterol* 2003;**98**:332–9.
11. Samaan MA, Puylaert CAJ, Levesque BG, *et al*. The development of a magnetic resonance imaging index for fistulising Crohn's disease. *Aliment Pharmacol Ther* 2017;**46**:516–28.
12. Hindryckx P, Jairath V, Zou G, *et al*. Development and validation of a magnetic resonance index for assessing fistulas in patients with Crohn's Disease. *Gastroenterology* 2019;**157**:1233–1244.e5.
13. Savoye-Collet C, Savoye G, Koning E, Dacher JN, Lerebours E. Fistulizing perianal Crohn's disease: contrast-enhanced magnetic resonance imaging assessment at 1 year on maintenance anti-TNF-alpha therapy. *Inflamm Bowel Dis* 2011;**17**:1751–8.
14. Karmiris K, Bielen D, Vanbeckevoort D, *et al*. Long-term monitoring of infliximab therapy for perianal fistulizing Crohn's disease by using magnetic resonance imaging. *Clin Gastroenterol Hepatol* 2011;**9**:130–6.
15. Ng SC, Plamondon S, Gupta A, *et al*. Prospective evaluation of anti-tumor necrosis factor therapy guided by magnetic resonance imaging for Crohn's perineal fistulas. *Am J Gastroenterol* 2009;**104**:2973–86.
16. Tozer P, Ng SC, Siddiqui MR, *et al*. Long-term MRI-guided combined anti-TNF-α and thiopurine therapy for Crohn's perianal fistulas. *Inflamm Bowel Dis* 2012;**18**:1825–34.
17. Chambaz M, Verdalle-Cazes M, Desprez C, *et al*. Deep remission on magnetic resonance imaging impacts outcomes of perianal fistulizing Crohn's disease. *Dig Liver Dis* 2019;**51**:358–63.
18. Panés J, García-Olmo D, Van Assche G, *et al*.; ADMIRE CD Study Group Collaborators. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial. *Lancet* 2016;**388**:1281–90.
19. Gecse KB, Sebastian S, Hertogh Gd, *et al*. Results of the fifth scientific workshop of the ECCO [II]: clinical aspects of perianal fistulising crohn's disease-the unmet needs. *J Crohns Colitis* 2016;**10**:758–65.
20. van Rijn KL, Lansdorp CA, Tielbeek JAW, *et al*. Evaluation of the modified Van Assche index for assessing response to anti-TNF therapy with MRI in perianal fistulizing Crohn's disease. *Clin Imaging* 2020;**59**:179–87.
21. Meima-van Praag EM, Rijn KL, Monraats MA, *et al*. Magnetic resonance imaging after ligation of the intersphincteric fistula tract for high perianal fistulas in Crohn's disease: a retrospective cohort study. *Color Dis* 2021;**23**:169–77.
22. de Groof EJ, Buskens CJ, Ponsioen CY, *et al*. Multimodal treatment of perianal fistulas in Crohn's disease: seton versus anti-TNF versus advancement plasty (PISA): study protocol for a randomized controlled trial. *Trials* 2015;**16**:366.
23. Wasmann KA, de Groof EJ, Stellingwerf ME, *et al*. Treatment of perianal fistulas in crohn's disease, seton versus anti-TNF versus surgical closure following anti-TNF [PISA]: a randomised controlled trial. *J Crohns Colitis* 2020;**14**:1049–56.
24. Present DH, Rutgeerts P, Targan S, *et al*. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999;**340**:1398–405.
25. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;**33**:159–74.
26. Hwa Kim P, Kim SH, Ah Cho Y, *et al*. Ability of pelvic magnetic resonance imaging to predict clinical course of perianal fistula in pediatric Crohn's disease patients. *J Crohn's Colitis* 2021;**0**:1–14.