Minimally-invasive imaging of the small intestine

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Chapter 4

MR enteroclysis in refractory coeliac disease: Proposal and validation of a severity scoring system

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Abstract

Purpose

To determine magnetic resonance (MR) enteroclysis findings in patients with uncomplicated coeliac disease (CD), refractory CD type I (RCD I) and refractory CD type II (RCD II), to develop and validate a scoring system to identify patients with RCD II and to determine the diagnostic accuracy of MR enteroclysis to detect CD-related malignancies.

Materials and Methods

This study was performed with approval of the institutional review board. One radiologist blinded to clinical details retrospectively evaluated quantitative and qualitative criteria of 28 studies obtained in symptomatic patients with CD (uncomplicated CD, $n = 10$; RCD I, $n = 8$; RCD II, $n = 10$). A scoring-system was developed using parameters identified in multivariate analysis to be associated with RCD II, which two radiologists evaluated in a second group of 40 symptomatic patients with CD. Accuracy to detect malignancy was assessed in the total study group. Cumulative survival was evaluated in the total study group by using the Kaplan-Meier method.

Results

MR enteroclysis could not be used to discriminate between uncomplicated CD and RCD I. The presence of less than 10 folds per 5 cm jejunum, mesenteric fat infiltration and bowel wall thickening were associated with RCD II. A positive MR score was defined as the presence of two or more of these features. In the validation group, the MR score was positive in 13 of 15 patients with RCD II (sensitivity 0.87) and negative in 24 of 25 patients without RCD II (specificity 0.96). The 5-year survival rate was 95% in patients with a negative MR score and 56% in patients with a positive MR score ($p < 0.0001$). MR enteroclysis helped to identify the presence of seven of eight malignancies and to diagnose absence of malignancy in 58 of 60 studies.

Conclusion

MR enteroclysis can be used to investigate the presence of RCD II or malignancy in symptomatic patients with CD.

Introduction

Coeliac disease (CD) is an immune-mediated enteropathy induced by gluten in susceptible persons.[1] Although usually responsive to a gluten-free diet, CD can be associated with severe morbidity and mortality. Persisting or relapsing symptoms that occur while the patient is on a gluten-free diet may be caused by dietary mistakes, irritable bowel syndrome or conditions associated with CD, such as microscopic colitis or intussusception.[2, 3] A minority of patients experience severe symptoms including malabsorption, which if accompanied by intestinal villous atrophy, might indicate refractory CD (RCD).[4] RCD can be subdivided into type I (RCD I), which has a normal intraepithelial lymphocytes (IEL) phenotype, and RCD type II (RCD II), which has an abnormal IEL phenotype.[4, 5] Life expectancy in RCD I is similar to that in controls and patients with uncomplicated CD, whereas RCD II is associated with poor prognosis, mainly because of enteropathy-associated T-cell lymphoma.[6-8]

Symptoms caused by lack of dietary compliance usually resolve after these have been corrected, while other symptoms in uncomplicated CD usually require only supportive therapy. Therapeutic options in RCD I include immunosuppressive drugs.[6-9] RCD II may respond to chemotherapy or autologous haematopoietic stem cell transplantation.[10-12] Because of the important prognostic and therapeutic differences, discrimination between patients with or without RCD II is important. Determination of duodenal IELs is labour intensive, not widely available, and not aimed to diagnose malignancy.[13] Enteroscopy and video capsule endoscopy are invasive, often do not evaluate the complete small bowel and are associated with complications.[14-21]

One study on computed tomography (CT) enterography reported bowel wall thickening, lymphadenopathy, intussusception, low splenic volume and a decrease in splanchnic circulation to be associated with RCD II.[22] Although CT enteroclysis, magnetic resonance (MR) enterography and MR enteroclysis have successfully been used to diagnose CD or small-bowel neoplasms, these modalities have not been studied in patients suspected of having RCD.[23-33] In our institution, and in others, cross-sectional enteroclysis techniques are preferred when detailed intraluminal information is needed, because they usually result in better small-intestinal distension.[25, 33, 34]

The aim of our study was to determine MR enteroclysis findings in patients with uncomplicated CD, RCD I and RCD II, to develop and validate a scoring system to identify patients with RCD II, and to determine the diagnostic accuracy of MR enteroclysis to detect CD-related malignancies.

Materials and Methods

Patient population and study design

This retrospective study was approved by our institutional review board. The requirement for informed consent was waived. From our MR database, we identified 80 MR enteroclysis studies that were obtained between September 2004 and July 2009 in 72

adult patients with CD who experienced symptoms despite a gluten-free diet. CD was diagnosed based on the results of duodenal biopsies and positive serology for antihuman tissue-transglutaminase and anti-endomysium in all patients.[1, 35] Informed consent for the MR enteroclysis examinations had been obtained in all patients.

Follow-up studies (n = 12) obtained after chemotherapy and/or autologous haematopoietic stem cell transplantation for RCD or enteropathy-associated T-cell lymphoma were excluded. Consecutive studies obtained from September 2004 to December 2005 were included in the test group and used to construct a scoring system to predict RCD II. Consecutive studies obtained from January 2006 to July 2009 were included in the validation group and used to validate the scoring system (***figure 4.1***). Patient survival and diagnostic accuracy of MR enteroclysis to depict malignancy were investigated in the total study group. The total group comprised 68 patients (age range, 18–81 years; mean, 56 years; median, 56 years). There were 38 female patients (age range, 18–81 years; mean, 53 years; median, 54 years) and 30 male patients (age range, 33–81 years; mean, 60 years; median, 63 years). The age difference between male and female patients was statistically significant (p = 0.035).

Imaging protocol

After an overnight fast, a 9-French nasojejunal tube (Hospimed International, Zwolle, The Netherlands) was positioned distal to the duodenojejunal junction with fluoroscopic

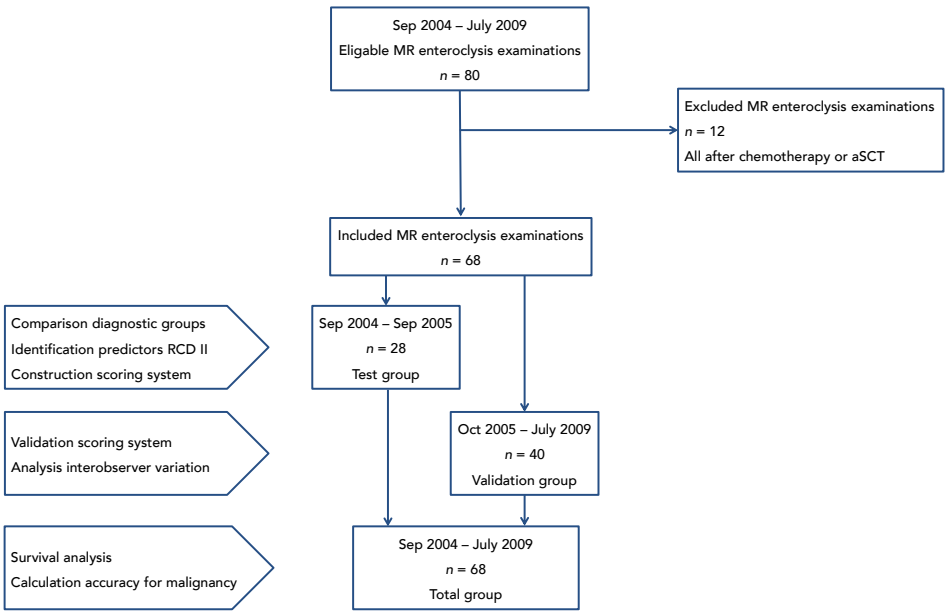

Figure 4.1: Flow chart shows the progress of patients who underwent MR enteroclysis studies as they passed through the study protocol. Large arrows indicate which calculations were performed per group. aSCT = autologous haematopoietic stem cell transplantation.

guidance. Next, during MR imaging, a minimum of 2000 ml 0.5% methylcellulose solution in water was infused through the tube, at a flow rate of 80–100 mL/min, using a MR-compatible infusion pump system (Watson Marlow, Falmouth, United Kingdom).

We performed 1.5-T MR imaging (Sonata; Siemens Medical Systems, Erlangen, Germany) with use of a 16-element phased-array surface coil. Gradient strength was 40 mT/m with a maximal gradient slope of 200 mT/m/msec. The imaging protocol consisted of multiple axial and coronal breath-hold true fast imaging with steady-state precession (FISP) sequences in multiple breath-hold series, to cover whole the abdomen. In between the true FISP sequences, a heavily T2-weighted half-Fourier acquisition single-shot fast spin-echo (HASTE) was performed 3 times with full abdominal coverage to follow infusion of the contrast agent. MR parameters of both sequences are summarized in ***table 4.1***. Images were acquired with patients in the prone position, to reduce the abdominopelvic volume.[36] Acquisition time per series was 20–25 sec. All series were repeated at least five times in a row. Imaging was stopped when optimal distension of the full small-bowel and caecum was obtained. The total imaging time per patient was approximately 30 minutes. No intravenous contrast material was used. Because of the short acquisition time of the true FISP sequence and the enteroclysis-related atonia of the small intestine, no antispasmodics were administered.[36] This protocol was used during the entire study period.

Image analysis

All MR readings were prepared by the study coordinator (S.J.B.V.W.) who de-identified the studies and presented them to the reader(s) in random order. The coordinator had no role in the reading of the MR studies. All studies were read within a 2-week period. The studies in the test group were considered pilot studies and were reviewed by one gastrointestinal radiologist (J.H.T.M.V.W.) with 8 years of MR enteroclysis experience (reader 1), who was blinded to clinical details and final diagnosis. True FISP images were used for diagnostic analysis. The number of jejunal folds and ileal folds per 5 cm was calculated by using the maximum value of three measurements for each loop.[23, 26, 37, 38] Jejunoileal fold pattern

Table 4.1: MR parameters.

Parameter	True FISP	HASTE
Repetition time (msec) / echo time (msec)	4.3/2.2	1000/90
Echo train length	—	224
Flip angle (degrees)	70	150
Section thickness (mm)	4	6
Intersection gap (mm)	0.8	3
Field of view (mm)	320–400	320–400
Matrix	288 × 512	388 × 512

Note: FISP = fast imaging with steady-state precession; HASTE = half-Fourier acquisition single-shot fast spin-echo.

reversal was defined as the presence of an equal or higher number of intestinal folds in the ileum compared with the jejunum.[24, 26, 38] Small-bowel wall thickening was considered to be present when the wall thickness of a distended small-bowel loop was more than 3 mm.[23, 26, 39] Intussusception was defined as a target mass or a complex layered mass within the bowel lumen.[40, 41] Ascites was evaluated by visual inspection. Lymph nodes larger than 1 cm in diameter in their shortest axis were considered enlarged.[42] Mesenteric vascular engorgement was defined as increased calibre of both mesenteric arteries and veins.[23, 26] Mesenteric fat infiltration (panniculitis) was defined as a decrease in signal intensity of the mesentery surrounding mesenteric vessels.[23, 43] Splenic volume was calculated by the following formula: 30 + (0.58 × length × width × height). The length was the longest splenic axis in the transverse plane, the width was the distance perpendicular to the length, and the height was the longest craniocaudal splenic axis.[44] Small-bowel masses were identified as well-defined soft-tissue masses with intra- and/or extraluminal growth or circumferential constriction or as focal full-thickness mural thickening.[45]

The studies in the validation group were reviewed independently by reader 1 and a second gastrointestinal radiologist (reader 2, M.R.M.) with 4 years of MR enteroclysis experience. Both were blinded for clinical details and final diagnosis. Only parameters identified in the test group as independent predictors of RCD II and the presence of masses were evaluated and noted for both readers.

After all studies had been evaluated, a consensus meeting was organized. During this meeting all studies for which the readers disagreed on one or more feature in their initial reading were presented, without clinical details being disclosed. Discrepancies were resolved during joint reading of the studies.

Standard of reference

Duodenal biopsy specimens, obtained within 3 months before or after MR enteroclysis, were examined by one of three specialized gastrointestinal pathologists, each with over 5 years of experience in evaluating small-intestinal biopsy specimens and graded according to the modified Marsh classification which describes the presence and extent of villous atrophy.[46, 47] T-cell flow cytometry was performed to determine the phenotype of small-intestinal IELs according to the method previously described in detail.[5] Abnormal phenotype was defined as > 20% surface CD3–, cytoplasmic CD3+ cells within the CD7+/CD45+ cells; and as CD3– CD7+ cells within the CD103+/CD45+ cells.

All patients underwent regular follow-up at our outpatient clinic; the interval between visits was determined by the severity of symptoms, but no longer than 1 year. All patients underwent serological and endoscopic follow up, at intervals determined by the severity of symptoms. Uncomplicated CD was diagnosed if during follow-up clinical symptoms and villous atrophy improved without the need for immunosuppressive therapy. RCD I was diagnosed in case of persisting villous atrophy despite a gluten-free diet, but with normal phenotype IELs. RCD II was diagnosed in case of persisting villous atrophy with abnormal phenotype IELs.[6-8] The diagnosis of enteropathy-associated T-cell lymphoma

and adenocarcinoma were based on histologic analysis of biopsy or resection specimens, and were established according to international criteria.[48, 49]

Statistical analysis

We compared qualitative variables with the Fisher exact test or χ^2 test. Quantitative variables were compared with the two-sided Student *t* test or the Mann-Whitney *U* test. The comparisons between the three subgroups within the test group were exploratory and not corrected for multiple testing, because the main goal of our study was to identify characteristics associated with RCD II and not to investigate differences between the three diagnostic subgroups. Therefore the comparisons between uncomplicated CD and RCD I, uncomplicated CD and RCD II, and RCD I and RCD II should be interpreted as descriptive only. We compared findings in patients with uncomplicated CD and RCD I with the findings in patients with RCD II using multivariate logistic regression analysis. For this analysis, continuous MR enteroclysis features were dichotomized, by using cut-off levels determined by identifying the point where the sensitivity and specificity to detect RCD II were equal on the receiver operating characteristic curve. Because jejunoileal fold pattern reversal is a function of both the number of jejunal as ileal folds, this feature was not included in this analysis. *P* values less than 0.05 were considered to indicate a significant difference. By utilizing the independent predictors of RCD II, we constructed a scoring system for RCD II. We calculated the area under the curve for the proposed scoring system and determined its optimal cut-off value using receiver operating characteristic analysis.

We validated the scoring system by using the studies included in the validation group. For each parameter included in the scoring system interobserver agreement was assessed using κ statistics. A κ value ≥ 0.80 was considered to represent excellent agreement.[50] Performance characteristics (including 95% confidence intervals [CIs]) for the included parameters and the scoring system were calculated for each reader and for the results of the consensus meeting.

The survival period after MR enteroclysis was calculated with the Kaplan-Meier method. Differences in survival between patients with positive and negative scores were analysed with the log-rank test. Performance characteristics for the detection of malignancy were calculated for the total study group after discrepancies between the reviewers were resolved. Statistical analysis was performed with SPSS software (SPSS for Windows, version 17.0; SPSS, Chicago, Ill).

Results

Sixty-eight studies in 68 patients were included: 28 in the test group and 40 in the validation group (***table 4.2***). The mean length of follow-up was 28 months. The minimum length of follow-up for patients alive at the end of follow-up was 6 months. Except for the duration of follow-up, there were no statistical significant differences between both groups. The examinations were well tolerated and no adverse effects occurred.

Table 4.2: Clinical and histologic features of included patients.

Feature	Test group (*n* = 28)	Validation group (*n* = 40)	Total group (*n* = 68)	*P* value (test group *vs* validation group)
Mean age, y (range)	54 (22–67)	58 (18–81)	56 (18–81)	0.299*
Sex				0.621†
Female	17 (61)	21(53)	38 (56)	
Male	11 (39)	19 (47)	30 (44)	
Indication for MR enteroclysis				0.697‡
Weight loss	13 (46)	21 (53)	34 (50)	
Abdominal pain	10 (36)	11 (28)	21 (31)	
Vomiting	2 (7)	1 (3)	3 (4)	
Diarrhoea	2 (7)	3 (8)	5 (7)	
Other	1 (4)	4 (10)	5 (7)	
Duration of follow-up, months (SD)	42 (25)	18 (12)	28 (22)	< 0.001*
Small-bowel histology				0.683‡
Marsh 0	6 (21)	6 (15)	12 (18)	
Marsh 1	5 (18)	6 (15)	11 (16)	
Marsh 2	2 (7)	3 (8)	5 (7)	
Marsh 3 A	6 (21)	7 (18)	13 (19)	
Marsh 3 B	5 (18)	5 (13)	10 (15)	
Marsh 3 C	4 (14)	13 (33)	17 (25)	
Flow cytometry #				0.269‡
Not performed	6 (21)	6 (15)	12 (18)	
< 5% abnormal IELs	9 (32)	18 (45)	27 (40)	
5–19 abnormal IELs	5 (18)	2 (5)	7 (10)	
≥ 20 abnormal IELs	8 (29)	14 (28)	22 (32)	
Final diagnosis				0.845‡
Uncomplicated coeliac disease	10 (36)	16 (40)	26 (38)	
Refractory coeliac disease type I	8 (29)	9 (23)	17 (25)	
Refractory coeliac disease type II	10 (36)	15 (38)	25 (37)	
Ulcerative jejunitis	7 (25)	7 (18)	14 (21)	0.547†
EATL	2 (7)	3 (8)	5 (7)	1.000†
Small-bowel carcinoma	0 (0)	3 (8)	3 (4)	0.263†
aSCT during follow-up	4 (14)	3 (8)	7 (10)	0.435†
Death during follow-up	6 (21)	8 (20)	14 (21)	1.000†

Note: Unless otherwise indicated, data are number of patients and numbers in parentheses are rounded percentages. IEL = intraepithelial lymphocyte; EATL = enteropathy-associated T-cell lymphoma; aSCT = autologous haematopoietic stem cell transplantation

* Calculated with the two-sided Student *t* test.

† Calculated with the Fisher exact test.

‡ Calculated with the χ^2 test.

T-cell flow cytometry was not performed in 10 patients with uncomplicated CD and in 2 patients with RCD II, who both had ulcerative jejunitis and enteropathy-associated T-cell lymphoma.

Comparison between uncomplicated CD, RCD I, and RCD II in the test group

No MR parameter differed significantly between patients with uncomplicated CD or RCD I (***table 4.3***). The median number of jejunal folds per 5 cm was lower in patients with RCD II when compared to patients with uncomplicated CD or RCD I. Splenic volume was lower in patients with RCDII than in patients with RCD I (***figure 4.2***). Jejunoileal fold pattern reversal and diffuse bowel wall thickening were more frequently observed in RCD II than in uncomplicated CD. Mesenteric fat infiltration was more prevalent in patients with RCD II than in patients with RCD I.

Construction of the scoring system

The continuous variables were dichotomized using the cut-off levels for optimal diagnosis of RCD II (***table 4.4***). The categorical parameters, except for jejunoileal fold pattern reversal, were entered as variables in the multivariate analysis. Multivariate analysis showed the presence of less than 10 folds per 5 cm jejunum, diffuse bowel wall thickening and mesenteric fat infiltration to be independently associated with RCD II (***table 4.5, figures 4.3–4.5***). We devised a scoring system for the diagnosis of RCD II using these three parameters (***table 4.6***) and applied this to the test set. At the optimal cut-off value of 2, none of the 10 patients with RCD II were missed with the scoring system (sensitivity, 1.00; 95% CI, 0.66–1.00), and the absence of RCD II was correctly diagnosed in 15 of the 18 patients without RCD II (specificity 0.83; 95% CI, 0.58–0.96) (***figure 4.6***).

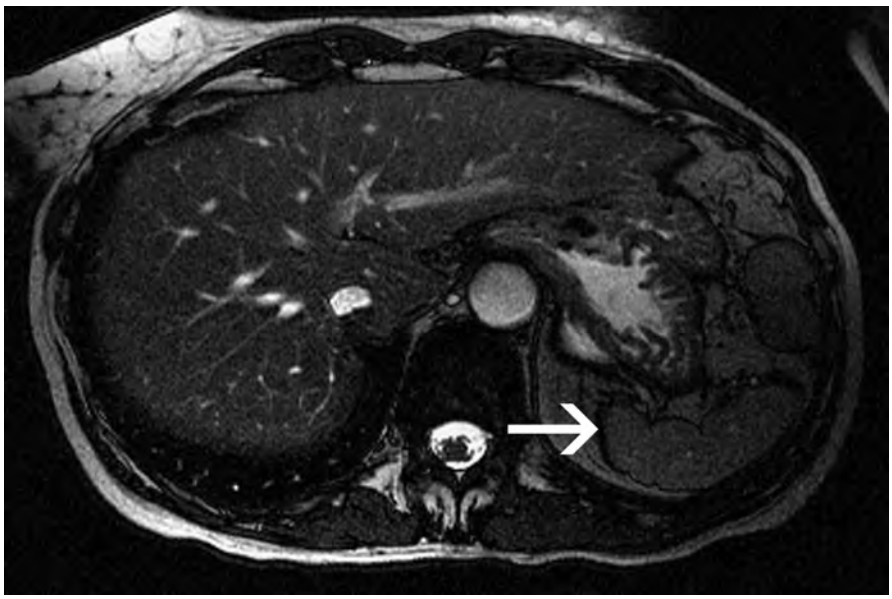

Figure 4.2: Axial true FISP image (4.3/2.2, 70° flip angle) in a 64-year-old woman with RCD II shows a small spleen, with a calculated volume of 65 cm^3.

Table 4.3: MR enteroclysis findings according to final diagnosis in patients in the test group.

	Group			*P* value		
Finding	**uncomplicated CD (*n* = 10)**	**RCD I (*n* = 8)**	**RCD II (*n* = 10)**	**uncomplicated CD *vs* RCD I**	**uncomplicated CD *vs* RCD II**	**RCD I *vs* RCD II**
Median number (IQ-range) of jejunal folds per 5 cm	10.5 (8.8–11.3)	9.5 (7.3–11.5)	5.5 (2.8–9.0)	0.420 *	0.002 *	0.018*
Median number (IQ-range) of ileal folds per 5 cm	6.0 (4.8–7.8)	7.5 (5.0–10.8)	7.5 (7.0–9.3)	0.369 *	0.055 *	0.753*
Jejunoileal fold pattern reversal	2 (20)	4 (50)	8 (80)	0.321	0.023	0.321
Bowel wall thickness > 3 mm	2 (20)	2 (25)	8 (80)	1.000	0.023	0.054
Intussusception	1 (10)	1 (12)	1 (10)	1.000	1.000	1.000
Mesenteric vascular engorgement	8 (80)	4 (50)	8 (80)	0.321	1.000	0.321
Mesenteric fat infiltration	3 (30)	1 (12)	8 (80)	0.588	0.070	0.015
Largest mesenteric lymph node > 10 mm	1 (10)	0 (0)	3 (30)	1.000	0.582	0.216
Ascites	0 (0)	0 (0)	1 (10)	1.000	1.000	1.000
Mean splenic volume (cm^3) ± standard deviation	218 ± 128	218 ± 76	130 ± 63	0.999 †	0.710 †	0.019†

Note: Unless otherwise indicated, data are number of patients and numbers in parentheses are rounded percentages. CD = coeliac disease; RCD I = refractory coeliac disease type I; RCD II = refractory coeliac disease type II; IQ = interquartile. *P* values are calculated with the Fisher exact test except when otherwise indicated.
* Calculated with the Mann-Whitney *U* test.
† Calculated with the Student *t* test.

Table 4.4: Results of receiver operator characteristics curves analysis for continuous variables to detect refractory coeliac disease type II.

	No refractory coeliac disease type II (*n* = 18)		Refractory coeliac disease type II (*n* = 10)				
MR enteroclysis finding	**Mean**	**Median**	**Mean**	**Median**	***P* value**	**AUC***	**Optimal cut-off value†**
Number of jejunal folds per 5 cm	10.0 (8.8–11.2)	10.0 (8.0–11.3)	5.6 (3.4–7.8)	5.5 (2.8–9.0)	0.001	0.88 (0.74–1.00)	< 10
Number of ileal folds per 5 cm	7.3 (5.7–8.9)	6.5 (5.0–10.0)	8.1 (7.0–9.2)	7.5 (7.0–9.3)	0.175‡	0.66 (0.46–0.86)	> 6
Splenic volume in cm^3	218 (166–271)	212 (126–278)	130 (84–175)	117 (65–184)	0.023#	0.79 (0.62–0.97)	< 160

Note: For mean and area under the curve (AUC), data in parentheses are 95% CIs, and for median, data in parentheses are interquartile ranges.
* AUC of the estimated receiver operating characteristic curve generated to discriminate between patients with and patients without refractory coeliac disease type II.
† The optimal cut-off levels were determined by identifying the point where the sensitivity and specificity were equal on the estimated receiver operating characteristic curve.
‡ Calculated with the Mann-Whitney *U* test.
# Calculated with the Student *t* test.

Table 4.5: Multivariate analysis of MR enteroclysis findings between patients with and those without RCD II in the test group.

MR enteroclysis finding	Patients without RCD II* (*n* = 18)	Patients with RCD II (*n* = 10)	*P* value
< 10 jejunal folds per 5 cm†	7 (39)	10 (100)	0.001
> 6 ileal folds per 5 cm†	9 (50)	8 (80)	0.128
Bowel wall thickness > 3mm	4 (22)	8 (80)	0.002
Intussusception	2 (11)	1 (10)	0.931
Mesenteric vascular engorgement	12 (67)	8 (80)	0.473
Mesenteric fat infiltration	4 (22)	8 (80)	0.002
Largest mesenteric lymph node > 10 mm	1 (6)	3 (30)	0.082
Ascites	0 (0)	1 (10)	0.185
Splenic volume < 160 square cm†	6 (33)	7 (70)	0.066

Note: Data are number of patients. Numbers between parentheses are rounded percentages.
* Represents grouped findings of patients with either uncomplicated CD and those with RCD I.
† The optimal cut-off levels of the continuous MR enteroclysis features were determined by identifying the point where the sensitivity and specificity to detect RCD II were equal on the estimated receiver operating characteristic curve.

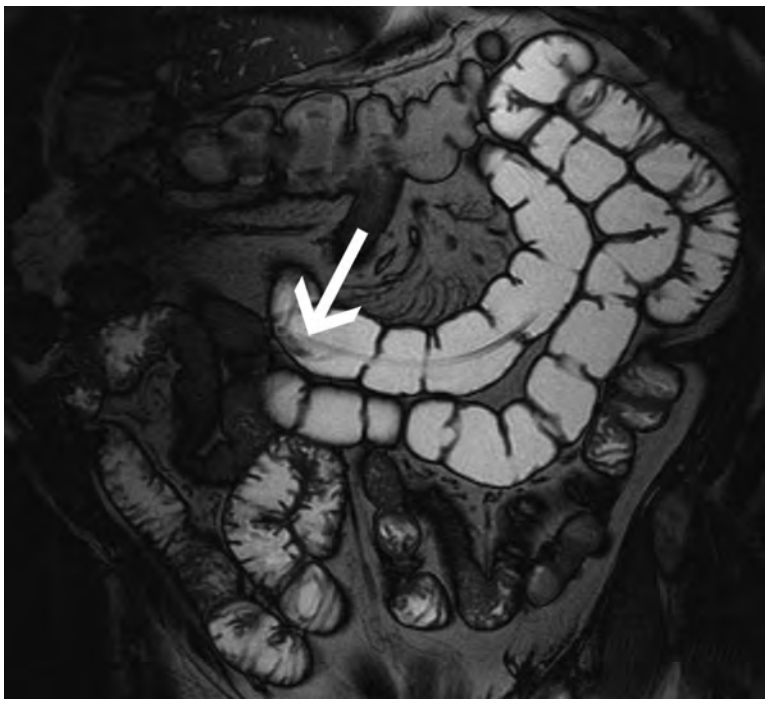

Figure 4.3: Coronal true FISP image (4.3/2.2, 70° flip angle) in a 77-year-old man with RCD II. The number of jejunal folds is decreased (left upper quadrant), whereas the number of ileal folds is increased (right lower quadrant). Arrow = distal end of the enteroclysis tube.

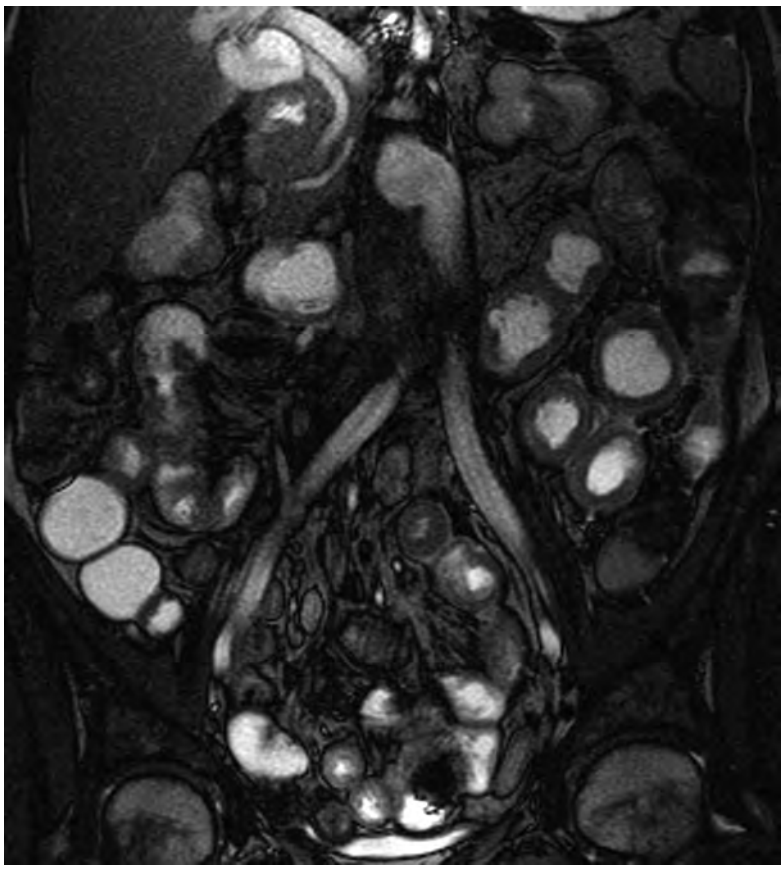

Figure 4.4: Coronal true FISP image (4.3/2.2, 70° flip angle) in a 57-year-old woman with RCD II shows a diffusely thickened small-bowel wall.

Table 4.6: Calculation of the proposed RCD II score.

Parameter	Points
Number of jejunal folds / 5 cm	
≥ 10	0
< 10	1
Mesenteric fat infiltration	
Absent	0
Present	1
Diffuse bowel wall thickening	
Absent	0
Present	1

Note: The score is calculated by adding the total number of points.

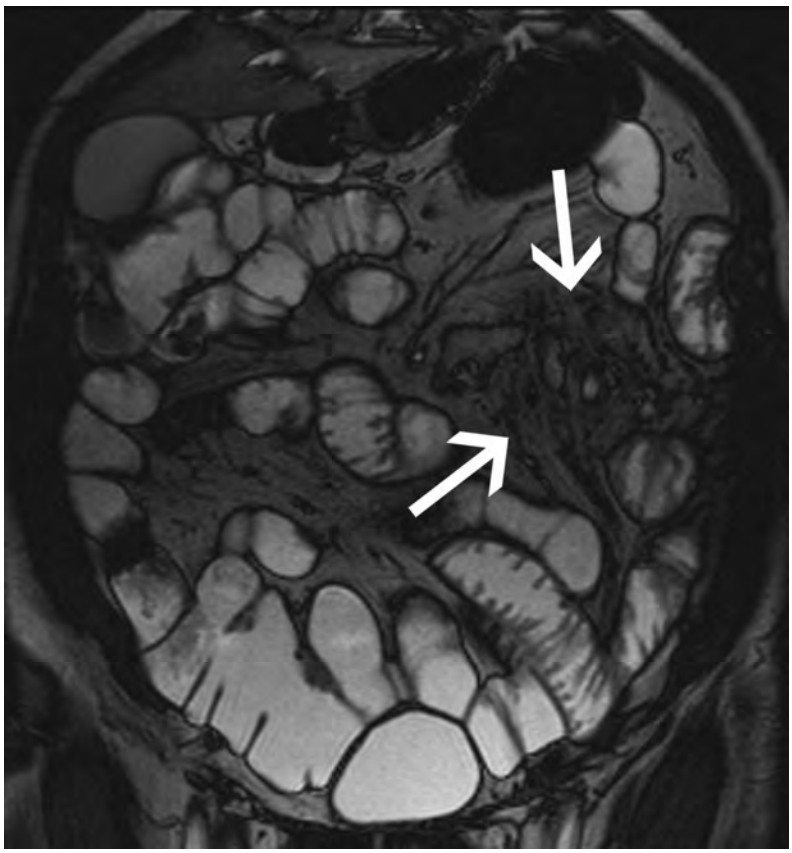

Figure 4.5: Coronal true FISP image (4.3/2.2, 70° flip angle) in a 64-year-old man with RCD II shows diffuse infiltration of the mesenteric fat (arrows).

Validation of the scoring system

We evaluated the three individual parameters and the scoring system in the validation group, which consisted of 15 patients with RCD II and 25 patients with either uncomplicated CD (n = 16) or RCD I (n = 9) (***table 4.7***). For the scoring system, the area under the receiver operating characteristic curve was 0.97. At the cut-off value of 2, two of the 15 patients with RCD II were missed with the scoring system (sensitivity, 0.87; 95% CI, 0.58–0.98) and the absence of RCD II was correctly diagnosed in 24 of the 25 patients without RCD II (specificity, 0.96; 95% CI, 0.78–1.00).

For nine of the 40 studies, the readers' interpretation disagreed on one feature. Six of nine discrepancies occurred in patients with RCD II (p = 0.040). For bowel wall thickening, the interpretation of the readers agreed in 37 of 40 studies (κ = 0.81; 95% CI, 0.60–1.00). For the presence of less than 10 jejunal folds, the readers agreed in 37 of 40 studies (κ = 0.85; 95% CI, 0.68–1.00). For mesenteric fat infiltration, the readers agreed

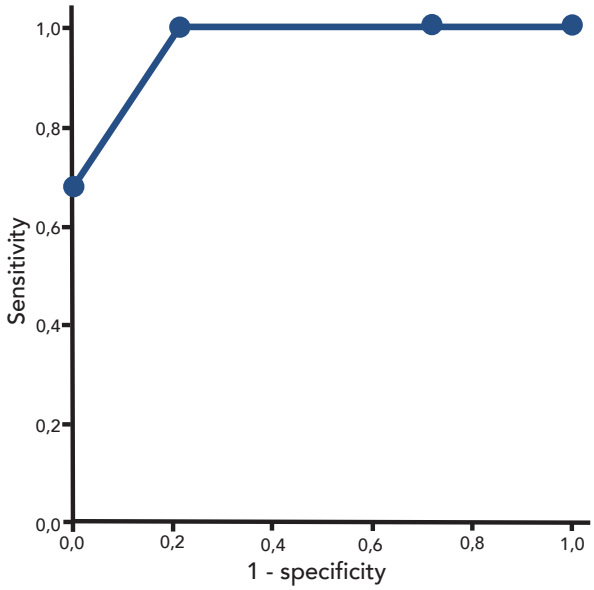

Figure 4.6: Receiver operator characteristic curve of the proposed MR enteroclysis score for RCD II. The area under the curve is 0.97. A = presence of none or more of the three parameters included in the scoring system (sensitivity 1.00; specificity 0.00, corresponding to 10 of 28 correctly classified cases). B = presence of one or more of the three parameters included in the scoring system (sensitivity 1.00; specificity 0.33, corresponding to 16 of 28 correctly classified cases). C = presence of two or more of the three parameters included in the scoring system (sensitivity 1.00; specificity 0.83, corresponding to 25 of 28 correctly classified cases). D = presence of all three parameters included in the scoring system (sensitivity 0.60; specificity 1.00, corresponding to 24 of 28 correctly classified cases).

in 37 of 40 studies (κ = 0.85; 95% CI, 0.68–1.00). In general, the consensus followed the interpretation of the more experienced reader (reader 1).

Survival analysis and detection of CD-related malignancies

Fourteen of 68 patients died during follow-up; among these were two of 41 patients with a MR score of less than 2 and 12 of 27 patients with a MR score of 2 or greater (***figure 4.7***). In all but one of these patients, the diagnosis was RCD II. Causes of death were enteropathy-associated T-cell lymphoma (n = 8), sepsis (n = 2), meningo-encephalitis (n = 2), disseminated small-bowel carcinoma (n = 1), and malabsorption (n = 1). The 5-year cumulative survival rate was 95% in patients with a MR score of less than 2 compared with 56% in patients with a MR score of 2 or greater ($p < 0.0001$).

Eight patients had a histologically confirmed CD-related malignancy at the time of MR enteroclysis. Enteropathy-associated T-cell lymphoma was diagnosed in five patients (***figure 4.8***), intraluminal small-bowel adenocarcinoma was diagnosed in two patients (***figure 4.9***) and a lymph node metastasis after resection of small-bowel adenocarcinoma

Table 4.7: Performance characteristics for score elements and total score for detection of RCD II in the validation group.

Parameter and Reader	No. of MR studies with positive parameter		Performance characteristics			
	Patients without RCD II (*n* = 25)	Patients with RCD II (*n* = 15)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
< 10 jejunal folds / 5 cm						
Reader 1	3	14	0.93 (0.66–1.00)	0.88 (0.68–0.97)	0.82 (0.56–0.95)	0.96 (0.76–1.00)
Reader 2	4	12	0.80 (0.51–0.95)	0.84 (0.63–0.95)	0.75 (0.47–0.92)	0.88 (0.67–0.97)
Consensus	3	14	0.93 (0.66–1.00)	0.88 (0.68–0.97)	0.82 (0.56–0.95	0.96 (0.76–1.00)
Mesenteric fat infiltration						
Reader 1	5	13	0.87 (0.58–0.98)	0.80 (0.59–0.92)	0.72 (0.46–0.89)	0.91 (0.69–0.98)
Reader 2	5	10	0.67 (0.39–0.87)	0.80 (0.59–0.92)	0.67 (0.39–0.87)	0.80 (0.59–0.92)
Consensus	5	13	0.87 (0.58–0.98)	0.80 (0.59–0.92)	0.72 (0.46–0.89)	0.91 (0.69–0.98)
Diffuse bowel wall thickening						
Reader 1	2	7	0.47 (0.22–0.73)	0.92 (0.72–0.99)	0.78 (0.40–0.96)	0.74 (0.55–0.87)
Reader 2	4	8	0.53 (0.27–0.78)	0.84 (0.63–0.95)	0.67 (0.35–0.89)	0.75 (0.55–0.89)
Consensus	4	7	0.47 (0.22–0.73)	0.84 (0.63–0.95)	0.64 (0.32–0.88)	0.72 (0.53–0.87)
Positive score*						
Reader 1	1	13	0.87 (0.58–0.98)	0.96 (0.78–1.00)	0.93 (0.64–1.00)	0.92 (0.73–0.99)
Reader 2	2	11	0.73 (0.45–0.91)	0.92 (0.72–0.99)	0.85 (0.54–0.97)	0.85 (0.65–0.95)
Consensus	1	13	0.87 (0.58–0.98)	0.96 (0.78–1.00)	0.93 (0.64–1.00)	0.92 (0.73–0.99)

Note: Data in parentheses are 95% CIs.
* Defined as the presence of two or more of the following parameters: Diffuse bowel wall thickening, less than 10 jejunal folds per 5 cm, mesenteric fat infiltration.

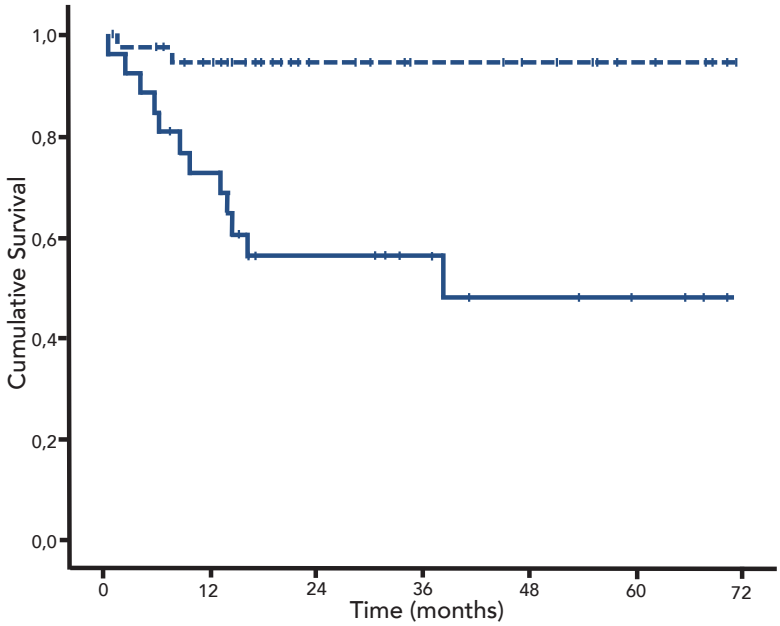

Figure 4.7: Graph shows survival by means of Kaplan-Meier method according to the MR score for RCD II. Dashed and solid curves = overall survival in patients with a negative MR score (score < 2) and patients with a positive MR score (score ≥2), respectively. + = censored.

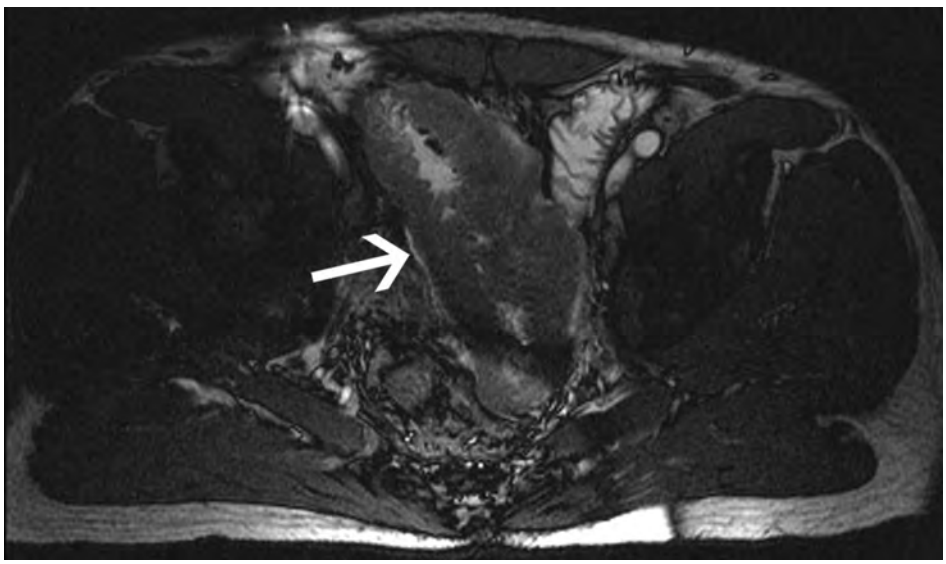

Figure 4.8: Axial true FISP image (4.3/2.2, 70° flip angle) of a 65-year-old man with RCD II, complicated by an enteropathy-associated T-cell lymphoma. Marked, asymmetric bowel wall thickening of the proximal jejunum can be observed (arrow).

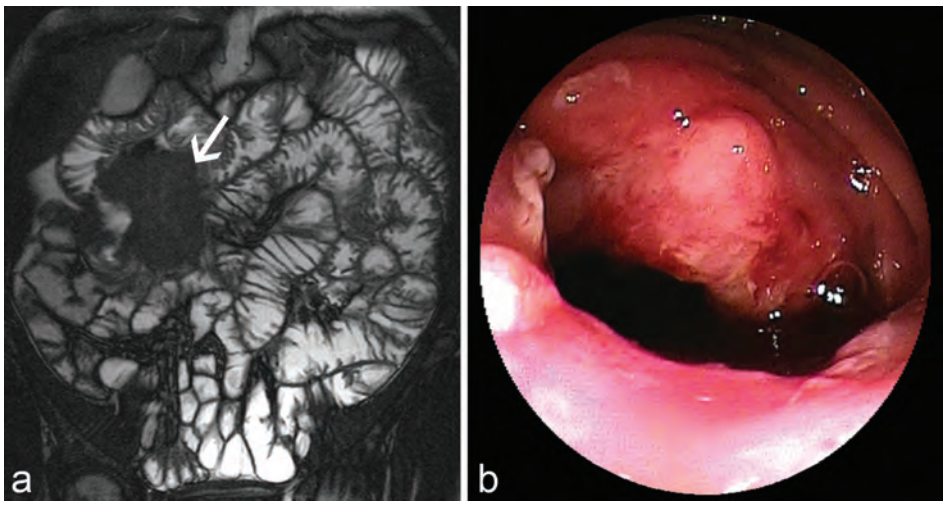

Figure 4.9: Images in 49-year-old woman with RCD I with weight loss and abdominal pain. (a) Coronal true FISP image (4.3/2.2, 70° flip angle) shows a 60 × 60-mm large mass in the proximal jejunum (arrow). (b) Endoscopic image of the tumour in the proximal jejunum. Histopathologic examination showed the lesion was adenocarcinoma.

was diagnosed in one patient. One case of diffuse enteropathy-associated T-cell lymphoma was not recognized at MR enteroclysis. Two MR studies were incorrectly interpreted as depicting a small-bowel neoplasm. Probable causes for these false-positive MR findings were severe ulcerative jejunitis (n = 1) and a stenotic anastomosis after resection of a small-bowel adenocarcinoma (n = 1). Sensitivity and specificity in the diagnosis of small-bowel malignancy were 0.88 (95% CI, 0.47–0.99) and 0.97 (95% CI, 0.87–0.99), respectively, resulting in a positive predicting value of 0.78 (95% CI, 0.40–0.96) and a negative predictive value of 0.98 (95% CI, 0.90–1.00).

Discussion

Our results indicate that MR enteroclysis may be a valuable modality in the investigation of patients with CD experiencing symptoms despite a gluten-free diet. We found no differences between studies in patients with uncomplicated CD or RCD I. Diffuse bowel wall thickening, the presence of less than 10 jejunal folds per 5 cm, and mesenteric fat infiltration were independent predictors of RCD II. The interobserver agreement for these parameters was good. We developed an MR scoring system with a sensitivity of 0.87 and a specificity of 0.96 in detecting RCD II in patients. Additionally, we demonstrated that the diagnostic accuracy for the diagnosis of small-bowel malignancy was high.

Although enteroclysis is more invasive than enterography, it prevents collapse of the jejunum during image acquisition.[51] We therefore prefer enteroclysis when high intraluminal detail is necessary. Although the features we found relevant to the diagnosis of RCD II can

also be assessed using CT, the use of ionizing radiation is a major drawback of CT, especially if repeated examinations are necessary. To our knowledge, at this moment there are no studies comparing MR with CT or enterography with enteroclysis in patients with (refractory) CD.

We studied patients with proven CD and relapsing or persisting symptoms despite a gluten-free diet. Therefore, our results cannot be directly compared with the findings of Soyer and co-workers, who observed jejunoileal fold pattern reversal, bowel wall thickening, and fold thickening more frequently in patients with untreated CD, than in patients without CD.[23] Additionally, it is difficult to compare our findings to those studies using enterography techniques in the diagnosis of CD.[26, 30, 52] To our knowledge, only one study has investigated imaging features in patients with RCD. By using CT enterography, Mallant and co-workers detected bowel wall thickening, lymphadenopathy, intussusception, absence of increased splanchnic circulation and a smaller splenic volume more frequently in patients with RCD II or enteropathy-associated T-cell lymphoma.[22] Jejunal or ileal folds could not be assessed in 54% of the patients, probably because of the enterography technique. We too found bowel wall thickening to be associated with RCD II. Although we observed lymphadenopathy, decreased splanchnic circulation and low splenic volume more often in patients with RCD II, these differences were not statistical significant in multivariate analysis.

Our MR protocol did not include contrast-enhanced sequences. It might be possible that the use of such sequences improves the diagnostic accuracy of MR enteroclysis in CD-related malignancies. However, recent studies showed that an MR enteroclysis protocol without contrast-enhancement had similar accuracy for the detection of small-intestinal neoplasms to that of a protocol that included contrast-enhancement.[25, 33] A recent article showed dynamic contrast-enhanced MR-imaging to be a promising tool in the investigation of uncomplicated CD.[31] Future studies should investigate this for RCD as well.

The proposed scoring system is based on the results of MR enteroclysis in symptomatic patients with CD despite a gluten-free diet. Therefore, our proposed scoring system should only be used in such patients, especially because two of its components, diffuse small-bowel wall thickening and mesenteric fat infiltration are rather unspecific findings.

For small-bowel wall thickening it should be noted that it contributes to the scoring system because of its high specificity, but that its sensitivity is too low to use this feature as a sole parameter for RCD II. The most experienced reader performed better than the less experienced reader, especially regarding the sensitivity for detecting mesenteric fat infiltration. This probably reflects a long learning curve, which could limit the generalizability of our results to nonreferral centres for small-intestinal disease, including complicated CD. Alternatively, this could have been caused by learning bias, because reader 1 had also evaluated the MR studies from the test group. Because of the large time frame between the original diagnostic reading of the studies and the readings for this study, we do not think memory bias could have significantly influenced our results.

Our study has several other limitations. First, because of the retrospective design, we cannot exclude a possible selection bias. It is possible that physicians ordered the MR

enteroclysis examinations because of abnormal findings noted at other investigations such as double-balloon endoscopy or capsule endoscopy. Second, the prevalence of RCD was high in our population, reflecting the tertiary referral setting of our study; this might have resulted in an overestimation of diagnostic accuracy. Third, despite the relative high prevalence of RCD II in this study, the sample size of our study is small, which is the result of the low prevalence (0.06 per 100000 person-years) of this condition.[53]

In conclusion, our findings demonstrate MR enteroclysis can be used to discriminate patients with RCD II from other patients with CD and persisting or relapsing symptoms despite a gluten-free diet. MR enteroclysis might be used to select patients in whom more invasive examinations like double-balloon endoscopy are needed in order to obtain material for histological verification. Further, prospective multicentre studies of a larger size are needed to determine the value of MR enteroclysis in symptomatic patients with CD and to externally validate our proposed scoring system for RCD II.

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