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DOI: 10.17235/reed.2018.5691/2018

Link: [PubMed \(Epub ahead of print\)](#)

Please cite this article as:

Faletti Riccardo, Ribaldone Davide Giuseppe, Gatti Marco, Perazzini Chiara, Robella Mattia, Angelino Francesca, Saracco Giorgio Maria, Astegiano Marco, Pellicano Rinaldo, Fonio Paolo. Apparent diffusion coefficient and enhancement patterns in MR imaging as markers of severe or moderate ileum inflammation in Crohn's disease. Rev Esp Enferm Dig 2018. doi: 10.17235/reed.2018.5691/2018.



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**OR 5691**

**Apparent diffusion coefficient and enhancement patterns in MR imaging as markers of severe or moderate ileum inflammation in Crohn's disease**

Riccardo Faletti<sup>1</sup>, Davide Giuseppe Ribaldone<sup>2</sup>, Marco Gatti<sup>1</sup>, Chiara Perazzini<sup>3</sup>, Mattia Robella<sup>3</sup>, Francesca Angelino<sup>3</sup>, Giorgio Maria Saracco<sup>2</sup>, Marco Astegiano<sup>4</sup>, Rinaldo Pellicano<sup>4</sup> and Paolo Fonio<sup>3</sup>

<sup>1</sup>Department of Surgical Sciences. Radiology Institute. University of Turin. Turin, Italy. <sup>2</sup>Department of Medical Sciences. Division of Gastroenterology. University of Torino. Torino, Italy. <sup>3</sup>Department of Diagnostic Imaging and Radiotherapy. S.C. Radiologia Universitaria. Università di Torino. Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino. Turin, Italy. <sup>4</sup>Department of General and Specialist Medicine. Gastroenterologia-U. Città della Salute e della Scienza di Torino. Turin, Italy

**Received:** 5/05/2018

**Accepted:** 13/07/2018

**Correspondence:** Davide Giuseppe Ribaldone. Department of Medical Sciences. Division of Gastroenterology. University of Torino. C.so Bramante, 88. 10126 Turin, Italy  
e-mail: davrib\_1998@yahoo.com

**ABSTRACT**

**Background and purpose:** magnetic resonance enterography has been increasingly used for the diagnosis and follow-up of Crohn's disease (CD). The purpose of the study was to compare the apparent diffusion coefficient (ADC) with wall enhancement for the differentiation of severe, moderate or no inflammation activity in the ileum.

**Methods:** a prospective, blinded study was conducted of 46 CD patients with a clinical Crohn's disease activity index (CDAI)  $\geq 220$  and a simple endoscopic score for Crohn's disease (ES-CD)  $\geq 7$ , which yielded 58 inflamed segments with CD. Twenty controls were also included. All segments were characterized by four ADC readings. The two different

enhancement patterns observed in inflamed segments, transmural or mucosal, were associated with severely (23) or moderately (35) active CD.

**Results:** the ADC value decreased from  $2.79 \pm 0.35 \times 10^{-3} \text{ mm}^2/\text{s}$  for normal segments to  $1.81 \pm 0.39 \times 10^{-3} \text{ mm}^2/\text{s}$  for the moderately inflamed segments and  $1.15 \pm 0.20 \times 10^{-3} \text{ mm}^2/\text{s}$  for severely inflamed segments ( $p \leq 0.0001$ ). ROC curve analysis on the basis of the three ADC distributions showed a very good discrimination capability with an area under the curve of 0.95. Three groups were defined as follows: normal ileum ADC  $> 2.4 \times 10^{-3} \text{ mm}^2/\text{s}$ , moderate stages of inflammation  $1.5 \times 10^{-3} \text{ mm}^2/\text{s} < \text{ADC} \leq 2.4 \times 10^{-3} \text{ mm}^2/\text{s}$  and severe stages of ADC  $\leq 1.5 \times 10^{-3} \text{ mm}^2/\text{s}$ .

**Conclusions:** the ADC value reliably discriminates between normal and inflamed ileum and also distinguishes between severe and moderate inflammation.

**Key words:** ADC. Crohn's disease. Diffusion-weighted imaging. Magnetic resonance enterography. Staging.

## INTRODUCTION

Crohn's disease (CD) is an inflammatory disorder that affects mainly people from a young age. The disease may involve any part of the gastrointestinal tract, although it more frequently affects the small bowel, in particular, the terminal ileum. Longstanding inflammation may cause several complications in the bowel including obstruction, stricture, fistula and abscesses (1). Magnetic resonance enterography (MR-E) has been increasingly used for the diagnosis and follow-up of CD. The advantages of this technique compared to computed tomography include the fact that ionizing radiation is not used, it is capable of multi-planar imaging and also affords a high-contrast resolution (2). The contrast enhancement pattern is an established index for the differentiation of inflammation and normal conditions. Furthermore, it has been shown that a transmural pattern of enhancement reflects histologic features of severe small bowel inflammation in CD (3), although there are conflicting reports in the literature (4). Besides, a low-signal-intensity halo is produced by fat hypertrophy and fibrosis of the submucosa in chronic inflammatory disease (5,6).

A new possibility to expand the capability of MR is via diffusion-weighted imaging (DWI) that

reflects the changes in water mobility caused by interactions with cell membranes, macromolecules and alterations of the tissue environment. Brownian motion causes the diffusion of water molecules in biological tissues (7); the diffusion of water molecules is restricted in inflamed tissues.

The apparent diffusion coefficient (ADC) is a quantitative expression of the diffusion characteristics of tissues, which decreases with increasing tissue cellularity or cell density. High ADC values represent free diffusion of water molecules and are typical of healthy tissues or benign pathologic processes, whereas low values reflect a restricted diffusion, which may indicate malignancy or high cellularity (7). In early severely active CD, inflammatory cells and lymphoid aggregates have a restricted diffusion due to increased cell density infiltrates of the lamina propria and submucosa. In addition to the increased number of inflammatory cells, dilated lymphatic channels, hypertrophied neuronal tissues and the development of granulomas in the bowel wall can further narrow the extracellular space, thus contributing to the restricted diffusion of water molecules (7). It is unclear whether fibrosis in late stages of CD may cause a decrease in the ADC values of the bowel wall, either due to severe wall inflammation, wall fibrosis or inflammation associated with fibrosis (7). Few studies (1,6-11) have confirmed that DWI sequences could be useful for distinguishing disease-active bowel segments from normal intestinal loops. The bowel wall with active inflammation is characterized by restricted diffusion and the ADC value of a disease-active terminal ileum is significantly lower than that of normal ileal loops. The aim of the study was to correlate the diagnostic value of the ADC with the enhancement patterns for the assessment of the level of ileal wall inflammation in patients with CD.

## **METHODS**

A prospective, blinded study of consecutive CD patients who underwent MR-E due to ileal Crohn's disease was performed. Inclusion criteria included: a histological diagnosis of small bowel CD; Crohn's disease activity index (CDAI)  $\geq 220$ ; an endoscopic examination in the last two weeks resulting in a simple endoscopic score for Crohn's disease (SES-CD)  $\geq 7$  (with at least ulcers in the ileum engaging  $> 10\%$  of the segment) and no contraindications to intravenous (i.v.) contrast medium. Controls were selected among patients who underwent MR-E due to occult bowel hemorrhage with a final diagnosis of a normal examination or

telangiectasia.

### **MR protocol**

Before undergoing the MR examination, the 46 CD patients and 20 controls (Table 1) had to drink 1 l of a polyethylene glycol (PEG) solution and water mixture in order to distend bowel loops and to contrast the lumen during the 45 minutes procedure. This was previously prepared by dissolving a granular powder containing 34.8 g of PEG 4,000 (Selg, Promefarm, Italy), 1.42 g sodium sulphate, 0.42 g sodium bicarbonate, 0.36 g sodium chloride and 0.18 g potassium chloride in 1,000 ml water.

After the radiologist had observed adequate bowel distension and if there were no contraindications, 10 ml/mg of N-hyoscine butylbromide were administered i.v. immediately after the scout acquisition and before the first sequence in order to reduce bowel peristalsis and related motion artefacts. MR-E was performed at Achieva 1.5T (Philips Medical System, Eindhoven, The Netherlands) using a maximum gradient strength of 30 mT/m. All patients were examined in the prone position using a phased array body coil (16 channels XL-Torso coil).

After acquiring a standard three-plane scout, the breath-hold sequence was followed, as shown in table 1. The last sequence (T1weighted high resolution isotropic volume excitation [THRIVE]) was performed before and 90 seconds after i.v. injection of 0.1 mmol/kg of gadolinium diethylenetriamine penta-acetic acid (Gadobutrol, Gadovist®, Bayer, Germany), followed by a bolus of saline.

### **Qualitative and quantitative analysis**

The MR Extended Work Space 2.6.3.4 software (Philips Medical Systems) was used for image interpretation. Two observers (R.F. and M.R., with three years' experience in MR) independently reviewed all images and were blinded to the results of each other but not blinded to the post-contrast images, in order to ensure that the same segments were sampled in the ADC maps. One of them repeated the analysis on a random selection of 50% of segments and were blinded to her/his original results and to the segment sequence.

The segments were first qualitatively analyzed via a visual assessment. The window setting could be altered at the discretion of the radiologist during the review of the THRIVE

sequences performed after the i.v. injection of contrast, in order to achieve the best conditions to recognize the ileum active-disease segments on the basis of the observed pathological enhancement. The normal ileum wall has a homogeneous enhancement that makes it different from disease-active segments (3). Disease-active segments were further subdivided as severe or moderate activity according to the different features of the enhancement. The segment was considered as severely inflamed if the enhancement involved the entire wall thickness (transmural), whereas moderate inflammation was considered if the enhancement involved the mucosa and muscularis mucosae (“halo sign”). The next step was the quantitative assessment of DWI via the determination of the apparent diffusion coefficient (ADC). The segments were studied on the images of the DWI sequences (b-values of 0 and 800 s/mm<sup>2</sup>) and ADC maps were automatically constructed using the manufacturers’ software. The reader drew four oval regions of interest (ROIs) of 2.5 mm<sup>2</sup> on the wall of each segment on the ADC maps (one ADC map sequence for each MR exam) and the average value of four pixels in the wall thickness were calculated for each.

### **Statistical analysis**

The statistical tests used to assess inter- and intra-rater agreement of the ADC measurements included Bland-Altman (BA) plots, Pearson’s linear coefficient, regression line and the Wilcoxon’s test. The difference between two uncorrelated variables was assessed with the ANOVA test and the Mann-Whitney non-parametric test. The differences among  $n > 2$  correlated samples were computed using the non-parametric Friedman test. In all cases, statistical significance was set at  $p < 0.05$ . The discriminatory ability of the ADC value to distinguish between different levels of inflammation was assessed using receiving operating characteristics (ROC) curves. Categorical variables were arranged in 2 x 2 contingency tables and analyzed by the Chi-square test with Yates correction and/or the Fisher’s test. This was used to compute the odds ratio (OR); statistical significance was set at  $p < 0.05$  and the OR 95% confidence interval excluding 1. The statistical analysis was performed using the MedCalc software (version 14.8.1).

### **Ethical considerations**

The study has been approved by the local ethics committee (“Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino - A.O. Ordine Mauriziano - A.S.L. Città di Torino”) and has been performed in compliance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients gave their informed consent prior to inclusion in the study.

## RESULTS

The study population included 46 consecutive cases, 30 males (65.2%) with a mean age of  $42.7 \pm 15.3$  years. Of the 20 controls, 15 were male (75%) with a mean age of  $49.7 \pm 18.4$  years. Fifty-eight inflamed segments were included in the analysis and were further subdivided on the basis of the contrast enhancement pattern as severe ( $n = 23$ ) or moderate ( $n = 35$ ). Twenty normal terminal ileum segments were included as a reference from the control group. Figure 1 illustrates a clinical case. The left image of the top panel is the THRIVE sequence; the inflamed segment appears hyper-enhanced and the inflammation involves the mucosa. The right image of the first line is the DWI ( $b800 \text{ s/mm}^2$ ); the inflamed segment appears as an area of a high signal corresponding to an area of low signal intensity on the ADC map. The middle and bottom panel are the ADC map where four oval ROIs were placed for the quantitative analysis, resulting in a moderately inflamed segment with an ADC average of 1.8.

The reliability of the qualitative and quantitative analyses was tested with regard to both inter and intra-rater variability (Fig. 2). The concordance of the qualitative evaluations by visual assessment of the enhancement patterns was unanimous.

Figure 2A is the regression line (solid), which has angular coefficient very close to 1 ( $0.96 \pm 0.08$ ), which practically coincides with the bisector. The  $\pm SE_{est} = \pm 0.36$  interval (limited by dotted lines) includes more than 80% of the points. Figure 2B is the Bland-Altman plot with a value of  $0.02 \pm 0.35$  and the corresponding region that is well centered at zero, and includes  $56/58 = 96.6\%$  of the points. The Pearson’s linear correlation coefficient is  $r = 0.82$ , with a standard error of 0.08 and 95% confidence intervals of 0.70-0.89. The result of the Wilcoxon test was  $p = 0.8$ .

The homogeneity of the segments was tested by comparing the ADC readings relative to four different ROIs. The result of Friedman’s test ( $p = 0.77$ ) warranted a good agreement

among the four correlated series of readings and allowed the characterization of each segment with one ADC value obtained by averaging the values of the four spots. The ADC values for the three samples of severe (23), moderate (35) and normal (20) segments were significantly different with wide 95% CI. The results were as follows: severe activity samples  $ADC_{sev} = 1.15 \pm 0.20 \times 10^{-3} \text{ mm}^2/\text{s}$  with 95% CI = 1.06-1.24; moderate activity samples  $ADC_{mod} = 1.81 \pm 0.39 \times 10^{-3} \text{ mm}^2/\text{s}$  with 95% CI = 1.67-1.94; and normal samples  $ADC_{norm} = 2.79 \pm 0.35 \times 10^{-3} \text{ mm}^2/\text{s}$  with 95% CI = 2.63-2.95. The comparison of the three values was performed using the ANOVA test and the Mann-Whitney test with a p value  $\leq 0.0001$ .

The distributions of the ADC values obtained for the three sets are shown in figure 3A. These were the basis for the construction of the two ROC curves used to measure the ability of ADC to distinguish severe from moderate activity and moderate from the normal segment.

The areas under the two ROC curves confirm the discriminant ability of ADC, the AUC was 0.95 with 95% CI = 0.90-1.0 for both. The ADC threshold between severe and moderate activity was set at  $1.5 \times 10^{-3} \text{ mm}^2/\text{s}$  (sensitivity = 82.9%, specificity = 91.3%, diagnostic accuracy = 86.2%), in accordance with the maximum of the harmonic mean of sensitivity and specificity, diagnostic accuracy and Cohen's coefficient k (Fig. 3B). The ADC threshold between moderate disease and the normal segments was set with the same procedure of maximization of the three parameters at  $2.4 \times 10^{-3} \text{ mm}^2/\text{s}$  (sensitivity = 80%, specificity = 91.4%, diagnostic accuracy = 88.9%).

The number of segments with ADC values  $\leq 1.50 \times 10^{-3} \text{ mm}^2/\text{s}$  was 23/23 (100%) in the severely inflamed sample compared to 8/35 (23%) in the moderately inflamed sample,  $p < 0.0001$ . The OR for severe activity was  $\geq 74$  (95% CI = 8.62-639.8), which was obtained by considering a minimum of one value  $> 1.50 \times 10^{-3} \text{ mm}^2/\text{s}$  for the severe segments. The number of the segments with ADC values  $> 2.40 \times 10^{-3} \text{ mm}^2/\text{s}$  was 15/20 (80%) for the normal segments compared to 3/35 (9%) for the moderately inflamed segments,  $p < 0.0001$  and OR for normal conditions was 32 (95% CI = 6.74-151.86).

## DISCUSSION

This study investigated the role of MR-E with DWI for the assessment of ileal wall inflammation in patients with CD. DWI and the corresponding ADC values were related with the different enhancement patterns and the corresponding severity of ileum wall

inflammation. Disease activity is usually assessed by a combination of clinical symptoms, physical findings, laboratory investigations, endoscopy and imaging tests. Over the last few years, specific findings on MR imaging such as mural signal intensity characteristics and contrast enhancement patterns have been proposed as accurate markers of disease activity (3,5,6). Few studies have explored the diagnostic value of MR-E with DWI and ADC value for the assessment of bowel loop inflammation (1,6-11). These studies have shown that MR-E with DWI can differentiate the intestinal loops with active inflammation from the normal intestinal segment.

Table 2 summarizes the key findings of these studies. The ADC values of normal and inflamed ileum vary according to the different technical parameters and diffusion gradient used (high b value = 600-1,000 s/mm<sup>2</sup>). In fact, the ADC value for normal ileum varies from  $2.28 \times 10^{-3}$  mm<sup>2</sup>/s (6) to  $3.69 \pm 0.40 \times 10^{-3}$  mm<sup>2</sup>/s (8) and varies from  $1.32 \pm 0.44 \times 10^{-3}$  mm<sup>2</sup>/s (8) and  $1.71 (1.43-2.31) \times 10^{-3}$  mm<sup>2</sup>/s for inflamed ileum (6). Moreover, there is no universally accepted ADC threshold for defining inflammation, the cut off has been calculated in several studies and the values range from 1.72 (11) to 2.4 (10).

With regard to the evaluation of ADC values, our data are in line with those previously published. The mean ADC value of the ileal loops with active inflammation was  $1.55 \pm 0.52 \times 10^{-3}$  mm<sup>2</sup>/s, which is significantly lower than that of the normal ileum ( $2.79 \pm 0.35 \times 10^{-3}$  mm<sup>2</sup>/s). Moreover, in our study, disease-active segments were further subdivided as severe or moderate activity and the DWI analysis with ADC values was useful for identifying different grades of inflamed segments (Fig. 3A). We were also able to derive ranges of ADC values that corresponded to different stages of CD.  $ADC_{sev} \leq 1.50 \times 10^{-3}$  mm<sup>2</sup>/s for the severe stage,  $1.50 \times 10^{-3}$  mm<sup>2</sup>/s <  $ADC_{mod} \leq 2.40 \times 10^{-3}$  mm<sup>2</sup>/s for the moderate stage and  $ADC_{norm} > 2.40 \times 10^{-3}$  mm<sup>2</sup>/s for the normal state. These thresholds can differentiate severe from moderate activity and moderate activity from normal segments with a high sensitivity, specificity and diagnostic accuracy. This last finding is crucial, as the therapy of CD is correlated with the current disease activity. (12).

However, despite the very good intra- and inter-observer agreement observed for DWI and ADC analysis that underlines the consistency of these sequences, it is not recommended to omit the use of intravenous contrast material in the routine clinic. Nevertheless, it has already been shown that DWI is not inferior to contrast-enhanced MR (CE-MR) for the

evaluation of inflamed bowel loops (13). The identification of Crohn's disease complications such as penetrating complications depends mainly on the anatomical details of the examination and in this specific task, DWI has been demonstrated to be inferior to CE-MR, probably due to their inherent poor spatial resolution.

This study has some limitations. First, it is a single center study which covers a limited number of patients. Second, the endoscopic evaluation of the ileum segments was performed only for the 46 terminal ileum segments and not for the 12 proximal segments (12 of the 46 patients had disease not only in the terminal ileum but also in a proximal ileum loop). In these segments, our diagnosis was based only on the MR findings. Third, we did not correlate the ADC value with CDAI and SES-CD. With regard to CDAI, it was not possible to make a one-to-one correlation since a group of our patients had more than one ileal segment involved with different disease activity. With regard to SES-CD, it was not possible to evaluate every segment with endoscopy. Moreover, even though endoscopy provides a direct view of the mucosal surface, it did not evaluate the full thickness inflammation of the bowel as the MRI does. Therefore, a correlation between endoscopy and MRI is lacking. However, this was not the aim of our study. The aim of our study was to directly correlate the DWI findings and the ADC value with wall enhancement in order to evaluate inflammation activity in the ileum.

In summary, there was an excellent agreement among our data and the literature confirming and reinforcing not only the diagnostic ability of ADC as an inflammatory state sentinel but also introducing the range of values corresponding to moderate and severe inflamed bowel loops and healthy conditions. The determination of the three ADC ranges identifying the three different ileum conditions (normal, moderate or severe inflammation) will be particularly useful, if further prospective studies confirm the reliability of ADC values obtained without the contrast enhanced sequences support. Furthermore, the possibility of a functional evaluation of the ileum wall by DWI and ADC, without the support of contrast enhancement for the diagnosis of the stage of CD, may be a great asset for patient management. Especially for patients that cannot be examined with the aid of the i.v. contrast medium due to different reasons such as chronic renal failure, severe renal failure and an allergy to contrast medium or to other substances.

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**Table 1. MR protocol**

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Axial single-shot T2

Axial T2 spectral adiabatic inversion recovery (SPAIR)

Coronal turbo spin echo T2

Coronal T2 SPAIR

Coronal balanced turbo field echo multiple sequential 2D (BTFE M2D)

Axial BTFE M2D

Axial echo planar T2 and diffusion weighted images (b values 0 and 800 s/mm<sup>2</sup>)

Axial 3D T1weighted high resolution isotropic volume excitation (THRIVE)

Coronal 3D T1w THRIVE

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**Table 2. Comparison of the studies of the role of MR-E with DWI**

	<i>Oto et al.</i>	<i>Kiryu et al.</i>	<i>Oto et al.</i>	<i>Caruso et al.</i>	<i>Foti et al.</i>	<i>Hordonnea et al.</i>	<i>Tielbeck et al.</i>	<i>Present Study</i>
	(2009)	(2009)	(2011)	(2014)	(2015)	(2015)	(2015)	(2018)
DWI b-value (s/mm <sup>2</sup> )	0.60	0.80	0.60	50.10	0.80	0.800	0.600	0.800
ADC normal ileum (10 <sup>-3</sup> mm <sup>2</sup> /s)	2.74 ± 0.68	2.61 ± 0.62	3.11 ± 0.56	n.a.	3.69 ± 0.40	2.53 ± 0.43	2.28 (1.99-2.78)	2.79 ± 0.35
ADC inflamed ileum (10 <sup>-3</sup> mm <sup>2</sup> /s)	1.59 ± 0.45	1.69 ± 0.43	1.98 ± 0.55	n.a.	1.32 ± 0.44	1.37 ± 0.37	1.71 (1.43-2.31)	1.55 ± 0.52
ADC cut-off normal vs inflamed ileum (10 <sup>-3</sup> mm <sup>2</sup> /s)	2.0	n.a.	2.4	1.72	n.a.	1.9	n.a.	2.4*/1.5 <sup>†</sup>
ROC curve (AUC)	0.94	n.a.	0.92	0.98	n.a.	n.a.	n.a.	0.95*/0.95 <sup>†</sup>
Sensitivity (%)	84%	n.a.	94%	91%	n.a.	94%	n.a.	80%*/83% <sup>†</sup>
Specificity (%)	91%	n.a.	88%	100%	n.a.	96%	n.a.	91%*/91% <sup>†</sup>

n.a.: not applicable. \*Between moderate inflamed ileum and normal segment. <sup>†</sup>Between severe

and moderate inflamed ileum.

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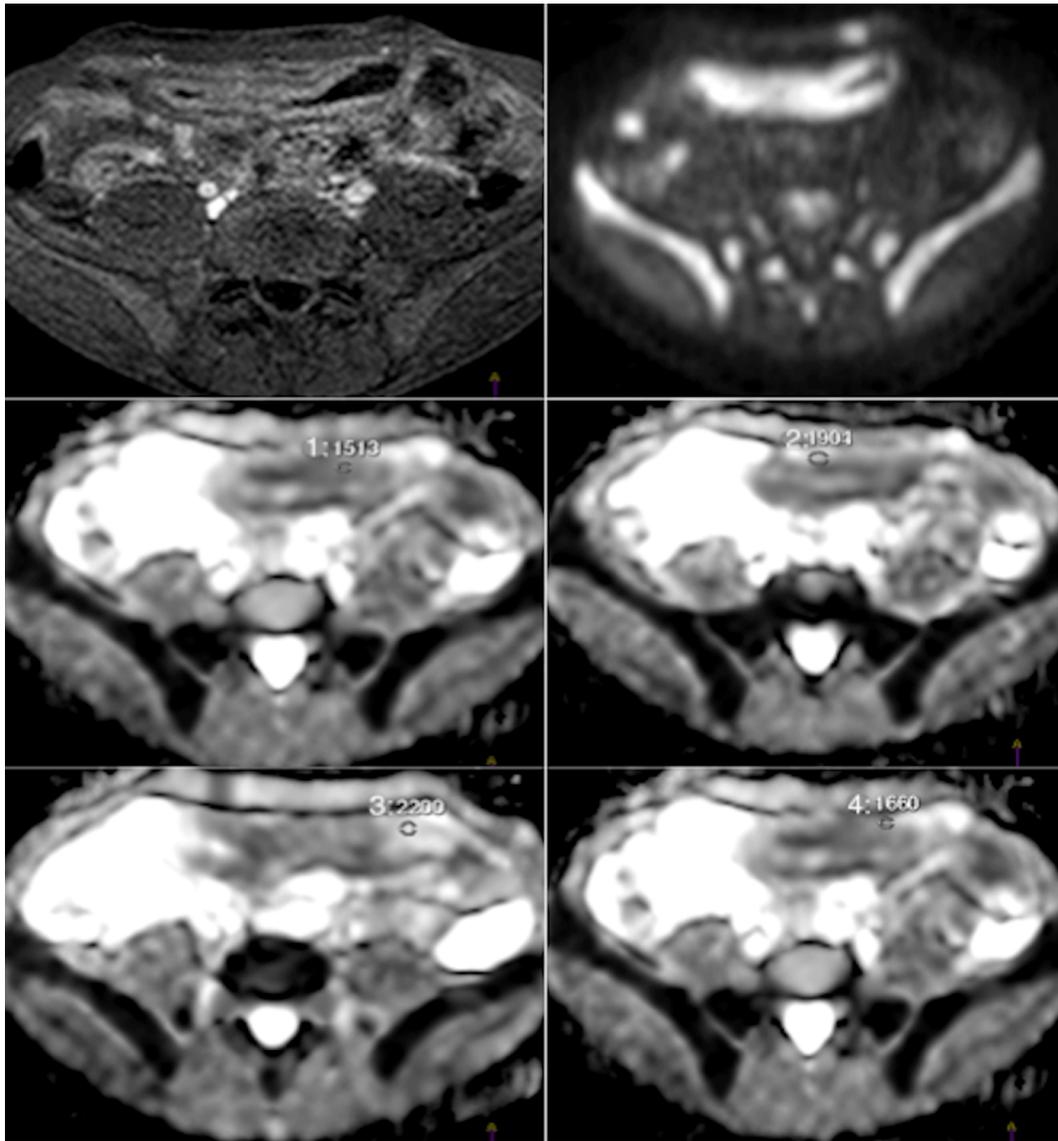


Fig. 1. Evidence of mucous enhancement after injection of gadobutrol in a moderate CD patient and four higher ADC values (average = 1.8).

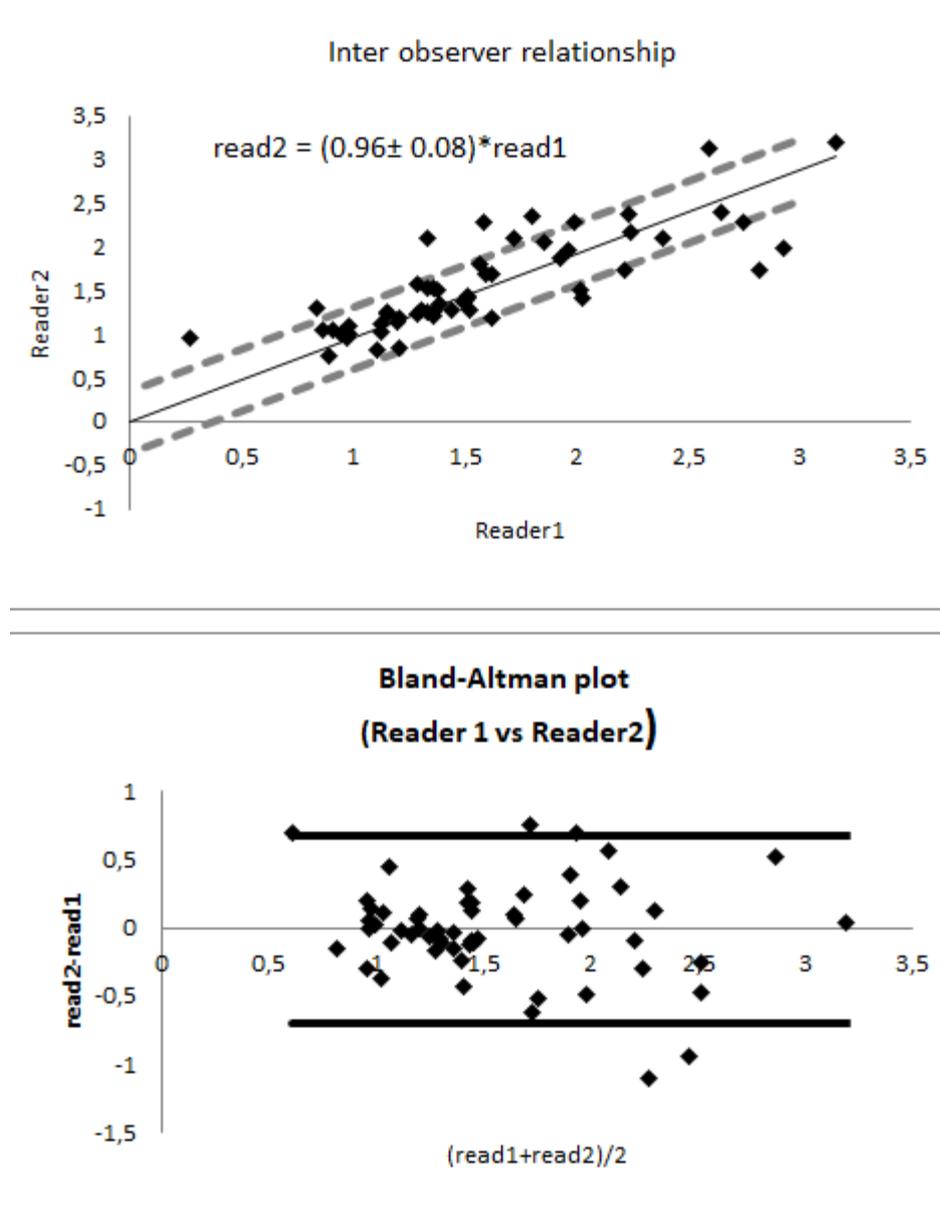


Fig. 2. A. Scatter plot of ADC values according to reader2 *versus* values according to reader1.  
B. Bland-Altman plot of the same data.

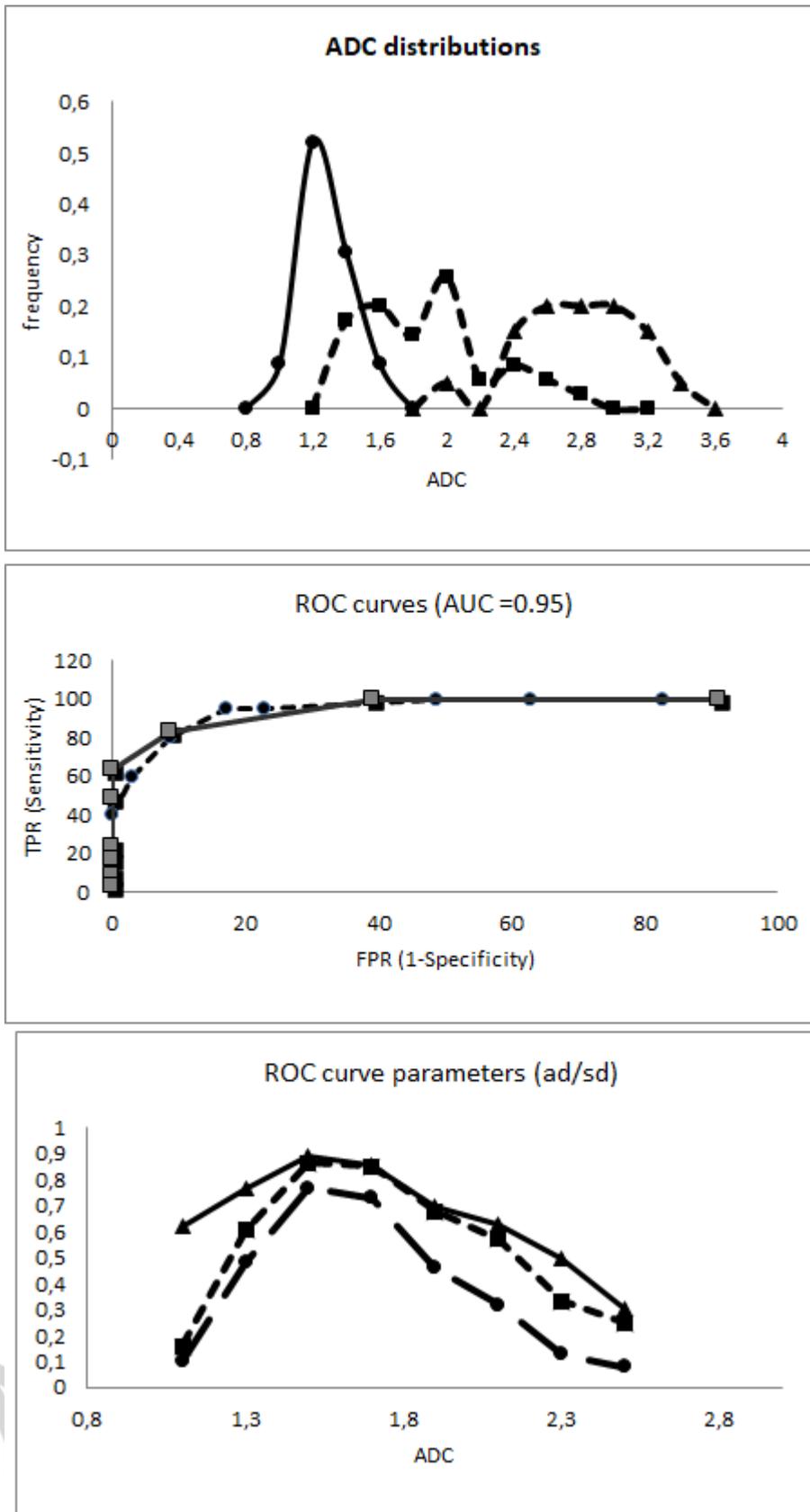


Fig. 3. A. ADC value frequency distributions for severe disease (full line), moderate disease

(dashed) and normal state (dotted). B. ROC curves for the differentiation between normal and moderate disease (dashed black line) and between moderate and severe disease (grey full line). C. Determination of the cut-off between severe and moderate disease by maximization of the Cohen's coefficient  $k$  (dashed line) diagnostic accuracy DA (solid line) and harmonic mean of sensitivity and specificity HM (dotted line).

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