European Radiology (2019) 29:3069–3078
https://doi.org/10.1007/s00330-018-5848-6

GASTROINTESTINAL

IVIM with fractional perfusion as a novel biomarker for detecting and grading intestinal fibrosis in Crohn's disease

Meng-Chen Zhang[1] · Xue-Hua Li[1] · Si-Yun Huang[1] · Ren Mao[2] · Zhuang-Nian Fang[1] · Qing-Hua Cao[3] · Zhong-Wei Zhang[4] · Xu Yan[5] · Min-Hu Chen[2] · Zi-Ping Li[1] · Can-Hui Sun[1] · Shi-Ting Feng[1]

Received: 28 July 2018 / Revised: 3 October 2018 / Accepted: 22 October 2018 / Published online: 13 December 2018

Abstract

Objectives Intravoxel incoherent motion (IVIM) diffusion-weighted magnetic resonance imaging (MRI) provides information on both perfusion and diffusion and has been used to evaluate Crohn's disease (CD) activity and fibrosis in children; however, there are no reports on its use in adults. We aimed to determine its value for detecting and grading intestinal fibrosis in adults with CD compared with contrast-enhanced imaging and traditional diffusion-weighted imaging using surgical histopathology as a reference standard.

Methods Twenty-four adults with CD underwent preoperative IVIM, traditional diffusion-weighted, and contrast-enhanced imaging. Region-by-region correlations between MRI findings and histologic findings of the surgical specimens were performed. Imaging parameters including fractional perfusion, perfusion coefficient, and diffusion coefficient for IVIM and apparent diffusion coefficient value for traditional diffusion-weighted imaging and contrast-enhanced parameter of 95 bowel lesions were measured. Intestinal fibrosis was histologically scored from 0 to 3.

Results The fractional perfusion ($r = -0.629$, $p < 0.001$) and apparent diffusion coefficient values ($r = -0.495$, $p < 0.001$) were significantly correlated with fibrosis scores. Fractional perfusion decreased following increases in fibrosis severity from mild, to moderate, to severe ($p < 0.001$). The area under the receiver operating characteristic curve for distinguishing moderate-severe from mild fibrosis was 0.876 ($p < 0.001$) for fractional perfusion, followed by 0.802 for apparent diffusion coefficient value ($p < 0.001$). Perfusion coefficient, diffusion coefficient, and contrast-enhanced parameter were uncorrelated with histological fibrosis.

Conclusions IVIM diffusion-weighted magnetic resonance imaging outperforms traditional diffusion-weighted and contrast-enhanced imaging in grading bowel fibrosis, and fractional perfusion may be a promising biomarker for fibrosis severity in adults with CD.

Key Points

- *Intravoxel incoherent motion diffusion-weighted MRI outperforms contrast-enhanced imaging and traditional diffusion-weighted MRI for detecting and grading intestinal fibrosis in adult Crohn's disease.*
- *The parameter fractional perfusion, a promising biomarker for fibrosis severity, may be beneficial for treatment planning and monitoring of bowel fibrosis in adult Crohn's disease.*
- *Perfusion coefficient, diffusion coefficient, and the percentage of enhancement gain between 70 s and 7 min were uncorrelated with histological fibrosis.*

Meng-Chen Zhang and Xue-Hua Li contributed equally to this work.

✉ Can-Hui Sun
canhuisun@sina.com

✉ Shi-Ting Feng
fengsht@mail.sysu.edu.cn

[1] Department of Radiology, The First Affiliated Hospital, Sun Yat-Sen University, 58 Zhongshan II Road, Guangzhou 510080, People's Republic of China

[2] Department of Gastroenterology, The First Affiliated Hospital, Sun Yat-Sen University, 58 Zhongshan II Road, Guangzhou 510080, People's Republic of China

[3] Department of Pathology, The First Affiliated Hospital, Sun Yat-Sen University, 58 Zhongshan II Road, Guangzhou 510080, People's Republic of China

[4] Department of Radiology, University of Florida, Gainesville, FL 32610, USA

[5] MR Collaboration NE Asia, Siemens Healthcare, Shanghai, People's Republic of China

Keywords Diffusion magnetic resonance imaging · Magnetic resonance imaging · Crohn disease · Fibrosis

Abbreviations

ADC	Apparent diffusion coefficient
AUCs	Areas under ROC curves
CD	Crohn's disease
CDAI	Crohn's disease activity index
CE	Contrast-enhanced
CRP	C-reactive protein
DWI	Diffusion-weighted imaging
ESR	Erythrocyte sedimentation rate
FOV	Field of view
ICCs	Intraclass correlation coefficients
IVIM	Intravoxel incoherent motion
MRE	Magnetic resonance enterography
MRI	Magnetic resonance imaging
ROC	Receiver operating characteristic
ROI	Region of interest
SI	Signal intensity
WSIs	Wall signal intensities

Introduction

Crohn's disease (CD) is a chronic relapsing inflammatory disorder of the gastrointestinal tract. CD causes progressive loss of bowel structure and function, and bowel inflammation and tissue remodeling over time can lead to mural collagen deposition and intestinal fibrosis [1, 2]. Detecting and grading the severity of mural fibrosis are essential because currently, no medical treatment can relieve severe bowel wall fibrosis and it requires endoscopic or surgical treatment [3]. Moreover, the detection of an early fibrotic stage might enable progress in new antifibrotic treatment and intestinal fibrotic prediction [4]. Distinguishing the early stage of fibrosis from severe fibrotic strictured CD requiring surgery is challenging. Many techniques, including conventional magnetic resonance imaging (MRI) and computed tomography, have been applied to this problem [2, 4, 5]. However, there is no standard for the accurate evaluation of bowel fibrosis [2, 4].

Pathologically, intestinal fibrosis in CD results from excessive extracellular matrix collagen deposition. This pathological change may affect blood perfusion and/or molecular diffusion of the involved bowel walls, providing a clue in the development of new makers for grading intestinal fibrosis. A conventional perfusion parameter of contrast-enhanced (CE) MRI, i.e., percentage of enhancement gain between 70 s and 7 min, has been reported to be helpful for assessing bowel fibrosis [6]. However, studies using CE imaging to assess bowel fibrosis of CD have produced conflicting results [6–8]. Traditional diffusion-weighted MRI (DWI) with apparent diffusion coefficient (ADC) value is a non-invasive technique sensitive to molecular diffusion in vivo and has been used to assess CD activity and fibrosis [9–14]. However, the motion of water molecules in tissues is a combination of true diffusion derived from random thermic molecular motion and perfusion resulting from blood microcirculation in the capillary network [15–17]. The superimposition of diffusion and perfusion in DWI complicates the biological interpretation and might limit its specificity.

Intravoxel incoherent motion (IVIM) imaging, a novel technique based on DWI, is used to quantitatively assess blood perfusion and pure molecular diffusion. It may be superior to both CE imaging and traditional DWI with regard to combining the advantages of diffusion and perfusion and providing independent information about diffusion and perfusion without intravenous enhancement [15]. In a previous study [16], IVIM-DWI was used to evaluate liver fibrosis, and decreased perfusion was noted in the cirrhotic liver group compared with that in the healthy liver group, suggesting that IVIM-DWI might help evaluate intestinal fibrosis in CD.

Previously, IVIM-DWI was reported to be able to assess CD activity or fibrosis [17–19]. To our knowledge, no study has investigated the efficacy of IVIM-DWI for evaluating bowel fibrosis in adults with CD, using surgical histopathology as the reference standard. This study aimed to determine the value of IVIM-DWI for detecting and grading bowel wall fibrosis in adults with CD compared with that of CE imaging and traditional DWI, using surgical histopathology as the reference standard. We hypothesized that the perfusion-related parameters derived from IVIM-DWI outperformed CE imaging and traditional DWI for grading intestinal fibrosis.

Materials and methods

Patients

From July 2016 to January 2017, 26 consecutive adult patients with CD scheduled for elective surgery were recruited from our institute. The inclusion criteria were patients aged ≥ 18 years with a diagnosis of CD based on standard clinical, imaging, endoscopic, and histological criteria, who were non-responsive to medical treatment (non-response was defined for those patients who did not achieve treatment goals as a ▵CD activity index ≥ 100 points) [20]; preoperative magnetic resonance enterography (MRE) within 15 days of elective surgery; and pathological bowel segments identified on MRI at the same location as the histologic findings. The exclusion criteria were inadequate MRE image quality of IVIM-DWI, traditional DWI, or CE imaging; and/or the presence of other bowel diseases, such as adenocarcinoma. The institutional

ethics review board approved this prospective study, and written informed consent was obtained from all patients.

MRI protocol

Bowel preparation was performed as described previously [11]. Briefly, patients ingested a polyethylene glycol electrolyte solution for 6–8 h, followed by 1600–2000 mL of 2.5% mannitol solution as an oral contrast agent 1 h before MRE. Ten milligrams of raceanisodamine hydrochloride (Minsheng Pharmaceutical Group Co.) was injected intramuscularly into the buttocks 10 min before MRE.

MRE (Table 1) was performed on a 3-T MR system (Magnetom Trio; Siemens Healthineers) equipped with eight-channel phased-array body coils, including (1) T2-weighted imaging for locating the abnormal bowels; (2) IVIM-DWI sequence; the ADC map of traditional DWI was reconstructed from the original IVIM-DWI data using selected *b*-values of 0–1000 s/mm^2 with a monoexponential model; and (3) CE imaging sequence before and at 15 s, 70 s, and 7 min after an intravenous injection of 0·2 mL/kg gadopentetate dimeglumine (Gd-DTPA) at a rate of 2 mL/s.

MRI analysis

IVIM-DWI and traditional DWI analysis

IVIM-DWI data calculation was performed with prototype post-processing software based on MATLAB (Math Works Inc.). The IVIM-DWI data were fitted with a biexponential model to generate three parameter maps quantifying diffusion and perfusion properties: the diffusion coefficient, representing molecular diffusion resulting from Brownian motion (units 10^{-3} mm^2/s); the perfusion coefficient, representing molecular perfusion resulting from blood microcirculation in the capillary network due to the pseudorandom orientation of capillaries at the voxel level (unit 10^{-3} mm^2/s); the fractional perfusion, determined as the fractional microcirculation volume of the voxel involving only capillaries with blood flow (percentage). The IVIM-DWI parameters were calculated using $S_b/S_0 = (1\text{-}F)\bullet\exp(-b\bullet D) + F\bullet\exp(-b\bullet D^*)$, where S_b is the signal intensity of the image at a certain *b*-value, S_0 is the baseline signal intensity without applying a diffusion gradient, F is the fractional perfusion, D is the diffusion coefficient, and D^* is the perfusion coefficient [15].

Three IVIM-DWI parameters and ADC values were measured by two radiologists with 5 (M.Z.) and 8 (X.L.) years of experience in gastrointestinal radiology, who were blinded to the clinical and pathological information. Three regions of interest (ROIs) were drawn in the abnormal bowel walls, excluding the bowel content, on the original IVIM-DWI images by both radiologists independently. The ROIs were copied and pasted into the three calculated IVIM maps and the ADC maps to measure the quantitative parameters. The average values of the six ROIs from both radiologists were used in the subsequent analysis.

CE parameter analysis

The wall signal intensities (WSIs) on CE images acquired at 70 s and 7 min were measured in the same region within the abnormal bowel walls by two radiologists with 5 (M.Z.) and 8 (Z.F.) years of experience in bowel MRI; they had no knowledge of the clinical or pathological information. Three ROIs were placed on the full thickness of the bowel walls in the case of homogeneously transmural enhancement or on the submucosa-muscularis layer in the case of stratified enhancement. The average WSIs of the six ROIs were recorded. The percentage of enhancement gain

Table 1 MRI sequences and parameters

Parameter	T2WI HASTE	IVIM-DWI SS-SE-EPI	VIBE
Orientation	2D axial	2D axial	3D coronal
Acquisition matrix	320 × 194	132 × 132	320 × 217
Flip angle (°)	160		13
Slice thickness (mm)	4	5	2
Echo time (ms)	87	80	1.37
Repetition time (ms)	1200	3200	4.37
Number of slices	18	18	80
Respiratory control	Breath-hold	Free-breathing	Breath-hold
b factors (s/mm^2)		0, 10, 20, 40, 60, 80, 100, 150, 300, 600, 1000, 1500, 2000	
Acquisition time (s)	24	308	28

HASTE, half-Fourier acquisition single-shot turbo spin echo; *IVIM-DWI*, intravoxel incoherent motion diffusion-weighted magnetic resonance imaging; *SS-SE-EPI*, single-shot spin-echo echo-planar imaging; *VIBE*, volumetric interpolated breath-hold examination; *2D*, two-dimensional; *3D*, three-dimensional

between 70 s and 7 min was calculated using the following equation [6]: % gain = [(WSI 7 min–WSI 70 s)/(WSI 70 s)] × 100.

Region-by-region correlations between MRI and surgical specimens

The surgical specimens were dissected by a radiologist (S.H.), who was not blinded to the imaging and surgical information. Similar to the previous studies [6, 14, 21], the specimens were sectioned at 4- to 5-cm intervals to obtain matching bowel segments for histologic and MRI evaluations (Fig. 1). Three to five specimens were obtained from every patient according to the number of resected bowel segments and the disease extent.

Histopathological examination

The samples were fixed in formalin, embedded in paraffin, and then sliced into 4-μm-thick sections. One section was stained with Masson trichrome to assess the bowel fibrosis. Histological fibrosis in the most severe pathological areas was scored as described previously [21–23] by a pathologist (Q.C.) without knowledge of the clinical or MRI information (Table 2). The fibrosis was then further divided into mild (scores 0–1) and moderate-severe (scores 2–3) groups.

Statistical analysis

The statistical analysis was performed with two-sided comparisons using SPSS version 20.0 software (SPSS Inc.). $P < 0.05$ was considered statistically significant. Normally distributed quantitative data are presented as means and standard deviations, whereas non-normally distributed quantitative data are presented as medians and interquartile ranges. The bivariate correlations between MRI parameters and histological fibrosis grades were analyzed using Spearman's rank correlation. A correlation coefficient (r) < 0.01 was considered none, 0.01–0.24 minimal, 0.25–0.49 fair, 0.50–0.74 moderate to good, and 0.75–1.00 very good to excellent. Differences in IVIM parameters and ADC values among different histological fibrosis grades were assessed with the Kruskal-Wallis test. One-way analysis of variance was performed to analyze differences in CE parameters between different fibrosis groups. The Wilcoxon test was used for bivariate comparisons. The areas under the receiver operating characteristic (ROC) curves (AUCs) were analyzed to determine the optimal threshold according to the Youden index. Multiple linear regression was performed by the stepwise method using the dependent variable (fibrosis score) and the independent variables (IVIM-DWI parameters, ADC value, and CE parameter) to test whether a combined index could have better predictive value for grading bowel fibrosis. Interobserver agreement evaluated using intraclass correlation coefficients (ICCs) was classified as poor (< 0.40), fair (0.40–0.59), good (0.60–0.74), or excellent (0.75–1.00).

Results

Demographic and clinical data

Of 26 patients, 2 were excluded from the analysis because of inadequate MRI quality due to insufficient intestinal distension in one and resected bowel segment containing adenocarcinoma in the other. The final enrolled population comprised 24 patients (14 men, 10 women; mean age 30 [26.50, 40.75] years) and 95 specimens from 37 resected bowel segments. The average wall thickness of the 95 specimens was 7.43 ± 3.82 mm on CE images. The demographic characteristics are shown in Table 3.

IVIM-DWI, ADC value, and CE parameter for bowel fibrosis evaluation

IVIM-DWI and ADC values

There was a good negative correlation between fractional perfusion (0.33 ± 0.13) and histological fibrosis score ($r = -0.629$, $p < 0.001$; Table 4). The pairwise comparison showed significantly lower fractional perfusion in severe fibrosis (0.23 [0.19, 0.27]; Fig. 2) than in moderate (0.29 [0.23, 0.33]; $\chi^2 = 17.01$, $p = 0.02$) and mild (0.43 [0.35, 0.60]; $\chi^2 = 46.99$, $p < 0.001$) fibrosis. The fractional perfusion of moderate fibrosis was also significantly ($\chi^2 = 29.97$, $p < 0.001$) lower than that of mild fibrosis (Fig. 3a). There was no significant correlation of perfusion coefficient ([9.10 ± 5.55] × 10^{-3} mm^2/s; $r = -0.194$, $p = 0.059$) or diffusion coefficient ([0.89 ± 0.25] × 10^{-3} mm^2/s; $r = -0.035$, $p = 0.740$) with histological fibrosis grade (Table 4).

There was a fair negative correlation between ADC values ([1.75 ± 0.75] × 10^{-3} mm^2/s) and histological fibrosis grade ($r = -0.495$, $p < 0.001$; Table 4). The ADC values of moderate fibrosis (1.35 [1.20, 1.89] × 10^{-3} mm^2/s) were significantly lower than those of mild (1.96 [1.58, 2.87] × 10^{-3} mm^2/s; $\chi^2 = 24.67$, $p < 0.001$) fibrosis. Significantly lower ADC values were noted in severe fibrosis (1.28 [1.28, 1.44] × 10^{-3} mm^2/s) than in mild fibrosis ($\chi^2 = 36.64$, $p < 0.001$). However, there was no significant difference in the ADC values between severe and moderate fibrosis ($\chi^2 = 7.066$, $p = 0.09$) (Fig. 3b).

Fractional perfusion had a high accuracy, with an AUC of 0.876 (95% confidence interval [CI] 0.79–0.96, $p < 0.001$) for differentiating moderate-severe from mild bowel wall fibrosis; ADC values ranked next in accuracy (AUC = 0.802; 95% CI, 0.71–0.90; $p < 0.001$) (Fig. 4). Using a threshold fractional perfusion of 0.33, the sensitivity and specificity values were 92.60% and 82.40%, respectively. The regression model (intestinal fibrosis score = [3.210–3.969 × fractional perfusion;

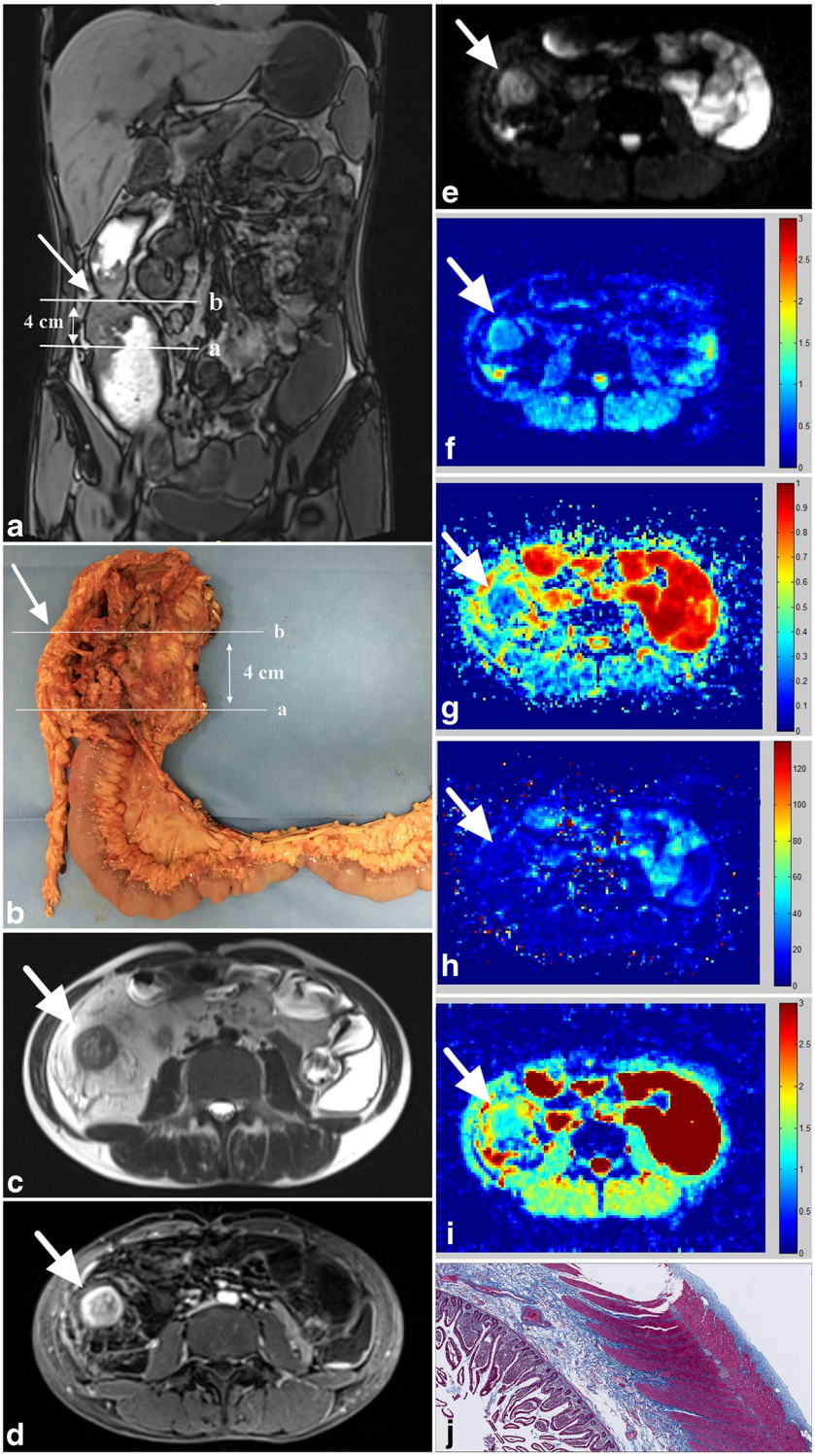

Fig. 1 Region-by-region correlations between MRI and surgical specimens in a 34-year-old man with severe CD of the ileocecum and ascending colon. One specimen (line a) from the prominently thickened bowel wall corresponding to the same level of the ileocecal valve and another specimen (line b) from the most stenosed segment (arrow) in the ascending colon at 4 cm distal to the ileocecal valve are localized on both coronal fat-saturated T1-weighted image (**a**) and the surgically resected intestine (**b**) for correlation. Axial T2-weighted (**c**) and CE fat-saturated T1-weighted (**d**) images showed marked bowel wall thickening (arrows) and luminal narrowing with bowel wall hyperenhancement (enhancement gain between 70 s and 7 min = 54%). Axial IVIM-DWI (**e**) (b = 0), calculated IVIM-DWI parameters including diffusion coefficient (**f**), fractional perfusion (**g**), perfusion coefficient (**h**), and ADC value (**i**) from traditional DWI showed diffusion coefficient = 0.85 × 10^{-3} mm^2/s, fractional perfusion = 0.29, perfusion coefficient = 13.6 × 10^{-3} mm^2/s, and ADC = 1.29 × 10^{-3} mm^2/s. Masson trichrome staining depicting transmural fibrosis (**j**) (blue area: score = 2, indicating moderate fibrosis, × 2 magnification). CD, Crohn's disease; MRI, magnetic resonance imaging

$F = 28.14$, $p < 0.001$]) indicated that fractional perfusion was the only significant explanatory variable to reflect bowel fibrosis.

The interobserver agreement was fair to good, with ICCs of 0.851 (95% CI, 0.77–0.91), 0.855 (95% CI, 0.77–0.91), 0.719 (95% CI, 0.56–0.82), and 0.832 (95% CI, 0.72–0.90) for the fractional perfusion, diffusion coefficient, perfusion coefficient, and ADC values, respectively (all $p < 0.001$).

Percentage of enhancement gain between 70 s and 7 min

The correlation between the percentage of enhancement gain (0.23 ± 0.21) and bowel fibrosis score was non-significant ($r = -0.051$, $p = 0.683$; Table 4). There was also no significant difference in this CE parameter among mild (0.23 ± 0.22), moderate (0.26 ± 0.23), and severe (0.19 ± 0.19) fibrosis ($F = 0.616$, $p = 0.543$).

Table 2 Histologic scoring for bowel fibrosis of Crohn's disease

Score	Fibrosis
0 (none)	No fibrosis
1 (mild)	Minimal fibrosis in the submucosa or subserosa, or increased submucosal fibrosis, septa into the muscularis propria
2 (moderate)	Septa through the muscularis propria, increase in subserosal collagen
3 (severe)	Significant transmural scar, marked subserosal collagen

Histological evaluation

The bowel fibrosis was graded as none ($n = 0$), mild ($n = 27$), moderate ($n = 45$), or severe ($n = 23$), resulting in 27 mild and 68 moderate-severe fibrotic bowel segments. Vascular sclerosis with wall thickening and lumen narrowing was found in the resected bowel walls with the most severe pathology.

Discussion

Our study demonstrates that fractional perfusion, which is derived from IVIM and linked to the blood volume of the microcirculation in the capillary network, correlates with the degree of intestinal fibrosis in adult CD patients. Perfusion is decreased in fibrotic bowel wall and might therefore be a good parameter for the severity of collagen deposition.

Bowel fibrosis is a hallmark of severe CD and a major contributor to medical treatment failure and hospitalization with surgical resection. Currently, intestinal fibrosis is considered a dynamic and reversible disease instead of a static and irreversible entity [2, 4, 24]. Available biomarkers for detecting early fibrotic stage and accurately grading intestinal fibrosis might allow for new antifibrotic agents and intestinal

Table 4 Correlations between MRI parameters and intestinal fibrosis scores

MRI parameters	*r*	*p*
IVIM-DWI		
Diffusion coefficient	- 0.035	0.740
Perfusion coefficient	- 0.194	0.059
Fractional perfusion	- 0.629	< 0.001
Traditional DWI		
ADC value	- 0.495	< 0.001
CE parameter: percentage of enhancement gain between 70 s and 7 min	- 0.051	0.683

ADC, apparent diffusion coefficient; *CE*, contrast-enhanced; *DWI*, diffusion-weighted imaging

Table 3 Baseline demographic and clinical characteristics of the patients

	$n = 24$
Gender: female/male	10/14
Age, medians (IQR), years	30 (26.50, 40.75)
Disease duration, medians (IQR), months	30 (16.50, 120.00)
The interval between MRE and surgery, medians (IQR), days	7 (2.75, 12.75)
Less than 7 days	7
Between 7 and 15 days	17
Surgery type, *n* (%)	
Partial small bowel resection	4 (16.67%)
Terminal ileum and ileocecum resection	6 (25.00%)
Partial colectomy	4 (16.67%)
Partial small bowel resection and partial colectomy	8 (33.33%)
Partial small bowel resection and colectomy	2 (8.30%)
Number of bowel specimens, *n* (%)	
Terminal ileum	34 (35.79%)
Proximal ileum + jejunum	22 (23.16%)
Colon	39 (41.05%)
CDAI, medians (IQR)	293.20 (148.42, 323.25)
CRP, medians (IQR), mg/L	25.15 (3.65, 38.25)
ESR, medians (IQR), mm/h	40 (16.25, 53.75)

Values are presented as median (interquartile range) or *n* (%)

CDAI, Crohn's disease activity index; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *IQR*, interquartile ranges

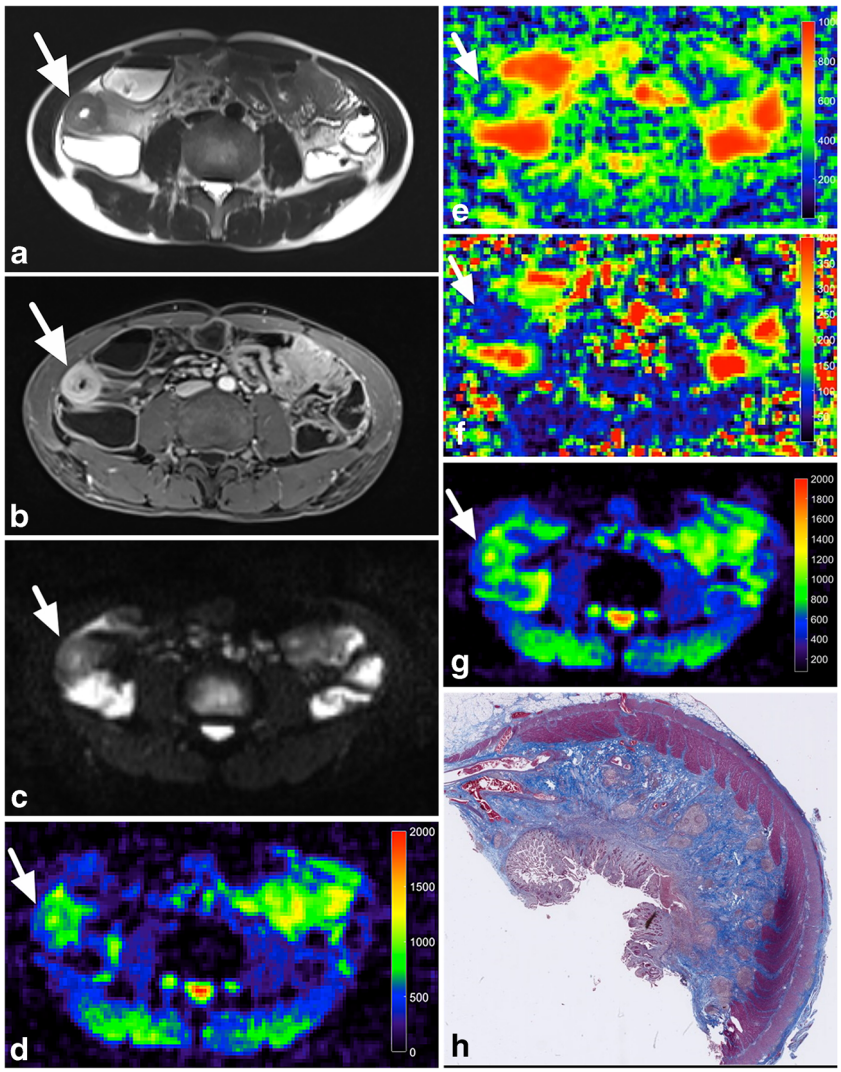

Fig. 2 A 41-year-old man with severe CD of the proximal ileum. **a** Axial T2-weighted and **b** CE fat-saturated T1-weighted images showed marked bowel wall thickening (arrows) and luminal narrowing with mural hyperenhancement (the percentage of enhancement gain between 70 s and 7 min = 27%). **c** Axial IVIM-DWI ($b = 0$), calculated IVIM-DWI parameters including **d** diffusion coefficient, **e** fractional perfusion, **f** perfusion coefficient, and **g** ADC value from traditional DWI showed diffusion coefficient = 0.67×10^{-3} mm^2/s, fractional perfusion = 0.26, perfusion coefficient = 8.94×10^{-3} mm^2/s, and ADC = 1.09×10^{-3} mm^2/s. **h** Masson trichrome staining depicting transmural fibrosis (blue area: score = 3, indicating severe fibrosis, × 0.45 magnification). ADC, apparent diffusion coefficient; CD, Crohn's disease; CE, contrast-enhanced; DWI, diffusion-weighted imaging; IVIM, intravoxel incoherent motion; MRE, magnetic resonance enterography; MRI, magnetic resonance imaging

fibrosis prediction. Conventional imaging is still insufficient for detecting bowel fibrosis [7, 23, 25]. Magnetization-transfer MRI enables intestinal fibrosis assessment in human CD [21]. However, multicenter and large-sample data to verify its effectiveness are still required. The utility of ultrasound elastography for bowel fibrosis is limited by the operator and is observer-dependent [26]. Although several novel imaging approaches have been studied, no single modality, currently, can accurately assess bowel fibrosis.

Pathologically, long-standing disease with the excessive deposition of collagen fibers in the extracellular matrix causes vascular sclerosis with a characteristic vascular wall thickening and lumen narrowing [27, 28]. These vascular changes might cause a reduction in blood perfusion within the fibrotic bowel walls [27, 28]. A previous study using CE ultrasound demonstrated a decrease in blood volume in fibrotic CD compared with no CD and inflammatory CD [29]. Hence, the quantification of blood perfusion within the bowel walls might help to grade intestinal fibrosis.

IVIM is a non-invasive MRI technique that can provide quantitative information about blood perfusion via fractional perfusion and perfusion coefficient without contrast administration. Fractional perfusion has been shown to decrease with increasing liver fibrosis stages [30], and the perfusion coefficient in the cirrhotic liver, compared with that in the healthy liver, was shown to be reduced [16]. In IVIM characterizing CD, previous investigators found a significantly lower fractional perfusion, higher perfusion coefficient, and no significant difference in the diffusion coefficient of the enhanced compared with that of the non-enhanced bowel wall of children with CD [17]. Reduced fractional perfusion in bowel segments with inflammatory activity with CD was found in other studies [18, 19]. However, the evaluation of intestinal fibrosis using the IVIM technique in adult CD has not been well studied.

Our study demonstrated a negative correlation between fractional perfusion and histologic fibrosis in adult CD. This might be partly explained by the reason that the bowel fibrosis causes vascular damage, increases resistance to blood flow,

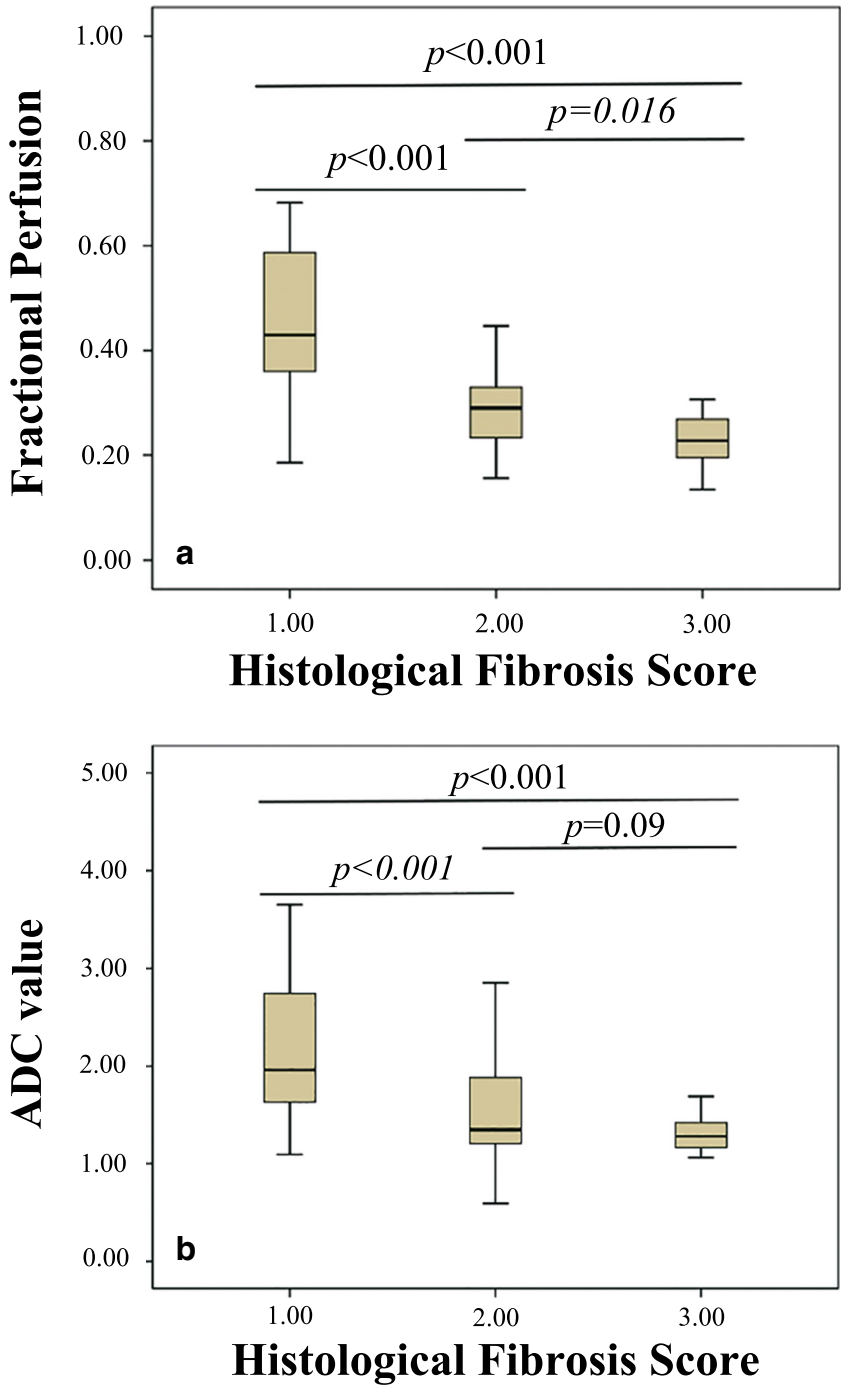

Fig. 3 **a** Box plot showing significantly decreasing fractional perfusion with increasing intestinal fibrosis. **b** The differences in ADC values between mildly and moderately fibrotic bowel walls and between mildly and severely fibrotic bowel walls were significant. There was no statistical difference in ADC values between moderately and severely fibrotic bowel walls. ADC, apparent diffusion coefficient

and leads to decreased perfusion within the affected bowel walls [27, 28]. Moreover, fractional perfusion was accurate for differentiating moderate-severe fibrosis from mild fibrosis. Consequently, fractional perfusion might be a promising biomarker for grading intestinal fibrosis and provides benefits for treatment planning and monitoring of bowel fibrosis in adult CD. However, inconsistent with the result of a previous study on liver fibrosis [16], no correlation between bowel fibrosis and perfusion coefficient was demonstrated in our study. This may be due to the low signal-to-noise ratio of the reconstructed perfusion coefficient images [31, 32].

Decreased ADC values with increasing intestinal fibrosis were demonstrated in our study, which was in accordance with prior studies [13, 14]. However, in our study, ADC values failed to distinguish severe from moderate fibrosis and was inferior to fractional perfusion in further grading intestinal fibrosis. The fact that ADC value was influenced by both diffusion and perfusion effects [15] might limit its specificity

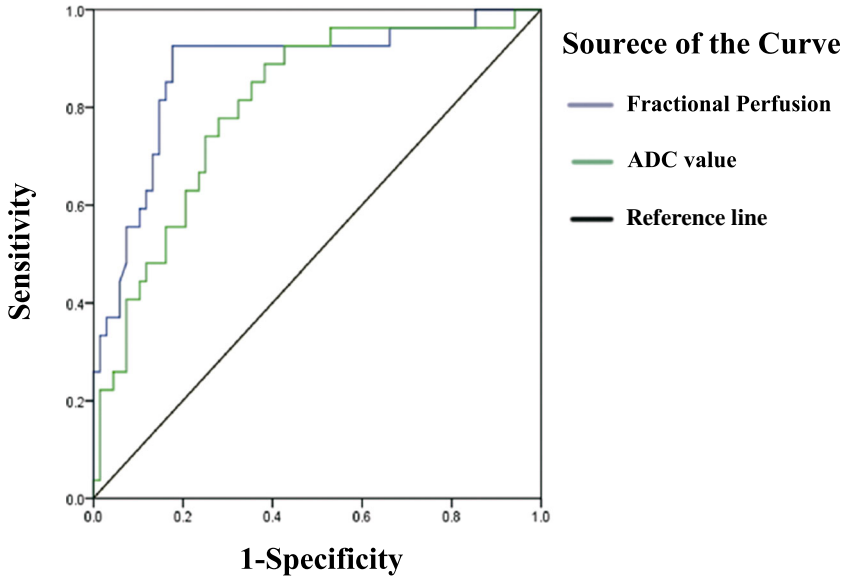

Fig. 4 The ROC curve demonstrates that fractional perfusion has a high accuracy, with an AUC of 0.876, for differentiating between mild and moderate-severe bowel wall fibrosis, followed by ADC value with an AUC of 0.802. ADC, apparent diffusion coefficient; AUC, area under ROC curve; ROC, receiver operating characteristics

for CD fibrosis. Moreover, our result demonstrated that diffusion coefficient showed poor performance in detecting bowel fibrosis compared with ADC values, indicating that reduced blood perfusion, instead of the restricted diffusion of water molecules, correlates with tissue fibrosis [15, 16, 30]. In other words, the negative correlation between ADC value and intestinal fibrosis might be due to the component of blood perfusion in ADC value besides diffusion coefficient [15, 16, 30]. Hence, perfusion-related parameters (e.g., fractional perfusion) may be more suitable for the assessment of bowel fibrosis. In addition, although the percentage of enhancement gain has been reported to be able to discriminate between mild-moderate and severe fibrosis [6], no correlation between this CE parameter and intestinal fibrosis was found in our study, which was consistent with the results of other studies [6, 7]. Fractional perfusion outperformed CE imaging and ADC value in grading bowel fibrosis and might be a clinically applicable alternative non-invasive tool and an important supplement to traditional MRE in intestinal fibrosis assessment. After accurately locating the CD lesions by traditional MRE, IVIM-DWI provides a perfusion index for detecting bowel fibrosis of the lesions.

Our study has some limitations. First, because most of the surgical specimens were severely fibrotic, the comparison of IVIM-DWI parameters between fibrotic and non-fibrotic bowel walls was compromised by the absence of non-fibrotic specimens. The efficacy of IVIM-DWI for assessing bowel fibrosis in an earlier stage of CD needs to be further clarified. Second, we only analyzed bowel fibrosis after excluding the assessment of bowel inflammation in this preliminary study to create a more focused object to test IVIM-DWI. Third, bowel peristalsis made it difficult to obtain precise point-by-point correlations between MRI and surgical specimens. With hypotonic bowel preparation and a short interval between MRI and surgery, we achieved region-by-region correlations between MRI and the specimens by identifying the anatomical structure or gross lesion in the same slice. Lastly, the reproducibility and certainty of the perfusion coefficient were not excellent, as demonstrated by the fair interreader agreement. This limitation has also been reported by other investigators [31, 32].

In conclusion, fractional perfusion, derived from IVIM-DWI without contrast administration, outperformed ADC value and CE imaging in accurately grading intestinal fibrosis in adult patients with CD. Fractional perfusion is a potential biological marker of bowel perfusion and may be beneficial for treatment planning and monitoring of bowel fibrosis in adult CD.

Acknowledgements The authors thank Professor Margaret H. Pui, a radiologist from Conde de S. Januario Central Hospital in Macau, for reading and commenting on the paper. We also thank Xiaolei Zhu, an MR collaboration scientist from Siemens Healthcare, for providing valuable suggestions regarding this paper.

Funding This study has received funding by the National Natural Science Foundation of China (81770654, 81600508, 81571750, 81771908, 81500501).

Compliance with ethical standards

Guarantor The scientific guarantors of this publication are Can-hui Sun and Shi-Ting Feng.

Conflict of interest The authors of this manuscript declare relationships with the following companies: Author (Xu Yan) from a commercial company, Siemens Healthcare, was an MR collaboration scientist performing technical support in this study under the Siemens collaboration regulation without any payment and personal concern regarding to this study. All other authors declare no conflict of interest.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- Prospective
- Observational
- Performed at one institution

References

1. Rieder F, Fiocchi C (2013) Mechanisms of tissue remodeling in inflammatory bowel disease. Dig Dis 31:186–193
2. Rieder F, de Bruyn JR, Bao TP et al (2014) Results of the 4th Scientific Workshop of the ECCO (Group II): markers of intestinal fibrosis in inflammatory bowel disease. J Crohns Colitis 8:1166–1178
3. Latella G, Di Gregorio J, Flati V, Rieder F, Lawrance IC (2015) Mechanisms of initiation and progression of intestinal fibrosis in IBD. Scand J Gastroenterol 50:53–65
4. Rieder F, Latella G, Magro F et al (2016) European Crohn's and Colitis Organisation topical review on prediction, diagnosis and management of fibrostenosing Crohn's disease. J Crohns Colitis 10:873
5. Taylor SA, Avni F, Cronin CG et al (2017) The first joint ESGAR/ESPR consensus statement on the technical performance of cross-sectional small bowel and colonic imaging. Eur Radiol 27(6):1–13
6. Rimola J, Planell N, Rodríguez S et al (2015) Characterization of inflammation and fibrosis in Crohn's disease lesions by magnetic resonance imaging. Am J Gastroenterol 110:432–440
7. Wilkens R, Hagemann-Madsen RH, Peters DA et al (2018) Validity of contrast enhanced ultrasonography and dynamic contrast enhanced MR enterography in the assessment of transmural activity and fibrosis in Crohn's disease. J Crohns Colitis 12:48–56
8. Punwani S, Rodriguez-Justo M, Bainbridge A et al(2009) Mural inflammation in Crohn disease: location-matched histologic validation of MR imaging features. Radiology 252:712–720
9. Li XH, Sun CH, Mao R et al (2017) Diffusion-weighted MRI enables to accurately grade inflammatory activity in patients of ileocolonic Crohn's disease: results from an observational study. Inflamm Bowel Dis 23:244–253
10. Seo N, Park SH, Kim KJ et al (2015) MR Enterography for the evaluation of small-bowel inflammation in Crohn disease by using diffusion-weighted imaging without intravenous contrast material: a prospective noninferiority study. Radiology 278:762
11. Li XH, Sun CH, Mao R et al (2015) Assessment of activity of Crohn disease by diffusion-weighted magnetic resonance imaging. Medicine (Baltimore) 94:e1819
12. Hordonneau C, Buisson A, Scanzi J et al (2014) Diffusion-weighted magnetic resonance imaging in ileocolonic Crohn's disease: validation of quantitative index of activity. Am J Gastroenterol 109:89–98
13. Tielbeek JA, Ziech ML, Li Z et al (2014) Evaluation of conventional, dynamic contrast enhanced and diffusion weighted MRI for quantitative Crohn's disease assessment with histopathology of surgical specimens. Eur Radiol 24:619–629
14. Catalano OA, Gee MS, Nicolai E et al (2017) Evaluation of quantitative PET/MR enterography biomarkers for discrimination of inflammatory strictures from fibrotic strictures in Crohn disease. Radiology 278:150566
15. Le Bihan D (2008) Intravoxel incoherent motion perfusion MR imaging: a wake-up call. Radiology 249:748–752
16. Luciani A, Vignaud A, Cavet M et al (2009) Liver cirrhosis: intravoxel incoherent motion MR imaging – pilot study. Radiology 249:891
17. Freiman M, Perez-Rossello JM, Callahan MJ et al (2013) Characterization of fast and slow diffusion from diffusion-weighted MRI of pediatric Crohn's disease. J Magn Reson Imaging 37:156–163
18. Bairdain S, Freiman M, Pérez-Rosselló JM et al (2016) Incoherent-motion magnetic resonance imaging and pediatric Crohn disease. Arch Clin Exp Surg 5:116–120
19. Hectors SJ, Gordic S, Semaan S et al (2018) Diffusion and perfusion MRI quantification in ileal Crohn's disease. Eur Radiol. https://doi.org/10.1007/s00330-018-5627-4
20. Gomollón F, Dignass A, Annese V et al (2016) 3rd EUROPEAN Evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management. J Crohns Colitis. 2017 11(1):3–25
21. Li XH, Mao R, Huang SY et al (2018) Characterization of degree of intestinal fibrosis in patients with Crohn disease by using magnetization transfer MR imaging. Radiology 287(2):494
22. Huang SY, Li XH, Huang L et al (2018) T2* mapping to characterize intestinal fibrosis in Crohn's disease. J Magn Reson Imaging. https://doi.org/10.1002/jmri.26022
23. Adler J, Punglia DR, Dillman JR et al (2012) Computed tomography enterography findings correlate with tissue inflammation, not fibrosis in resected small bowel Crohn's disease. Inflamm Bowel Dis 18:849–856
24. Latella G, Sferra R, Speca S, Vetuschi A, Gaudio E (2013) Can we prevent, reduce or reverse intestinal fibrosis in IBD? Eur Rev Med Pharmacol Sci 17:1283–1304
25. Barkmeier DT, Dillman JR, Al-Hawary M et al (2016) MR enterography – histology comparison in resected pediatric small bowel Crohn disease strictures: can imaging predict fibrosis? Pediatr Radiol 46:498–507
26. Baumgart DC, Müller HP, Grittner U et al (2015) US-based real-time elastography for the detection of fibrotic gut tissue in patients with stricturing Crohn disease. Radiology 275:889–899
27. Hultén L, Lindhagen J, Lundgren O, Fasth S, Ahrén C (1977) Regional intestinal blood flow in ulcerative colitis and Crohn's disease. Gastroenterology 72:388–396
28. Kruschewski M, Busch C, Dörner A, Lierse W (1995) Angioarchitecture of the colon in Crohn disease and ulcerative colitis. Light microscopy and scanning electron microscopy studies with reference to the morphology of the healthy large intestine. Langenbecks Arch Chir 380:253
29. Nylund K, Jirik R, Mezl M et al (2013) Quantitative contrast-enhanced ultrasound comparison between inflammatory and fibrotic lesions in patients with Crohn's disease. Ultrasound Med Biol 39:1197–1206
306. França M, Martí-Bonmatí L, Alberich-Bayarri Á et al (2017) Evaluation of fibrosis and inflammation in diffuse liver diseases using intravoxel incoherent motion diffusion-weighted MR imaging. Abdom Radiol (NY) 42:468–477
31. Dyvorne HA, Galea N, Nevers T et al (2013) Diffusion-weighted imaging of the liver with multiple b values: effect of diffusion gradient polarity and breathing acquisition on image quality and intravoxel incoherent motion parameters – a pilot study. Radiology 266:920
32. Joo I, Lee JM, Yoon JH, Jang JJ, Han JK, Choi BI (2014) Nonalcoholic fatty liver disease: intravoxel incoherent motion diffusion-weighted MR imaging – an experimental study in a rabbit model. Radiology 270:131–140