

ORIGINAL ARTICLE

Value of Texture Analysis on Gadoxetic Acid-enhanced MR for Detecting Liver Fibrosis in a Rat Model

Jia Xu¹, Xuan Wang^{1*}, Zhengyu Jin^{1*}, Yan You², Qin Wang¹,
Shitian Wang¹, Huadan Xue¹

¹Department of Radiology, ²Department of Pathology, Peking Union Medical College Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing 100730, China

Key words: liver fibrosis; magnetic resonance imaging; texture analysis; Entropy; T1 mapping

Objective To explore the ability of texture analysis of gadoxetic acid-enhanced magnetic resonance imaging (MRI) T1 mapping images, as well as T1-weighted (T1W), T2-weighted (T2W) and apparent diffusion coefficient (ADC) maps for distinguishing between varying degrees of hepatic fibrosis in an experimental rat model.

Methods Liver fibrosis in rats was induced by carbon tetrachloride intraperitoneal injection for 4–12 weeks ($n = 30$). In the control group ($n = 10$) normal saline was applied. The MRI protocol contained T2W, diffusion weighted imaging, pre- and post-contrast image series of T1W and T1 mapping images. METAVIR score was used to grade liver fibrosis as normal (F0), mild fibrosis (F1–2), and advanced fibrosis (F3–4). Texture parameters including mean gray-level intensity (Mean), standard deviation (SD), Entropy, mean of positive pixels (MPP), Skewness, and Kurtosis were obtained. Nonparametric Mann-Whitney U test was used to compare the average value of each texture parameter in each sequence for assessing the difference between F0 and $F \geq 1$ as well as F0–2 and F3–4. Receiver operating characteristic (ROC) curves were obtained to assess the diagnosing accuracy of the parameters for differentiating no liver fibrosis from liver fibrosis and rats with liver fibrosis grading F0–2 from those with grading F3–4. The area under ROC curve (AUC) was calculated to evaluate the diagnostic efficiency of texture parameters.

Results Finally, 20 rats completed MR T1 mapping image scan. The pathologic staging of these 20 rats was no fibrosis (F0, $n = 6$), mild fibrosis (F1–2, $n = 5$) and advanced fibrosis (F3–4, $n = 9$). On pre-contrast T1 mapping image, Entropy was seen to be statistically significant higher in the $F \geq 1$ group than that in the F0 group at each spatial scaling factor (SSF) setting ($P = 0.015, 0.015, 0.015, 0.013, 0.015$ and 0.018 respectively to SSF = 0, 2, 3, 4,

Received for publication January 21, 2019. Published online March 11, 2019.

*Corresponding author Xuan Wang Tel: 86-10-69157438, E-mail: dr_wangxuan@163.com; Zhengyu Jin Tel: 86-10-69155441, E-mail: jinzy_pumch@foxmail.com

Supported by the National Science Foundation of China (Grant No. 81501446) and the National Public Welfare Basic Scientific Research Program of Chinese Academy of Medical Sciences (2018PT32003 and 2017PT32004).

5, 6), and Mean of the $F \geq 1$ rats was statistically significant higher than that of the F0 rats at SSF 4, 5, 6 ($P=0.004$, 0.006, and 0.013, respectively). Entropy and Mean showed a moderate diagnostic performance in most SSF settings of T1 mapping pre-contrast images for differentiation of normal liver from liver fibrosis.

Conclusion Certain texture features of gadoxetic acid-enhanced MR images, especially the Entropy of non-contrast T1 mapping image, was found to be a useful biomarker for the diagnosis of liver fibrosis.

THE early detection and staging of hepatic fibrosis in population at risk become increasingly important, since timely diagnosis and appropriate therapies could slow or halt progression of liver damage and improve the prognosis of these patients.^[1-2] Percutaneous hepatic biopsy is currently served as a gold standard of reference for staging fibrosis, although there are several limitations including sampling bias, high inter-observer variability and risk of procedure-related complications especially bleeding.^[2] Thus, a global and non-invasive method with minimal risk and patient discomfort is of significant clinical importance in evaluating hepatic fibrosis and monitoring response to therapy.

Among a range of alternative non-invasive approaches currently available to the assessment of liver fibrosis, MRI techniques have drawn growing attention compared to other modalities, since they could offer evaluation of the entire liver with no radiation exposure and low operator-dependent variation. Texture analysis, as a mathematic method for quantification of heterogeneity by evaluating the distribution of pixel intensities within certain Regions of Interest (ROIs),^[3] has been employed to extract additional textural features from conventional and functional MR images recently. Several studies have found that texture analyses were useful in assessing hepatic fibrosis performed with T2-weighted as well as diffusion-weighted images.^[4-7] On the other hand, T1 relaxation time is considered to be a useful tool for comparing pre- and post-contrast enhancement.^[8-10] It has been reported that prolonged pre-contrast T1 relaxation time may suggest liver cirrhosis, while the T1 relaxation time measurement on gadoxetic acid-enhanced MRI images showed correlation with liver fibrosis staging scores.^[11-12] However, to the best of our knowledge, texture analyses using the T1 mapping images have not been reported in the evaluation of liver fibrosis.

Given the advantages of T1 relaxation time and the strengths of texture analyses technique, the purpose of the present study was to explore the ability of texture analyses of T1 mapping images for distinguish-

ing between varying degrees of hepatic fibrosis in an experimental rat model. We also assessed the textural features from T1-weighted, T2-weighted and apparent diffusion coefficient (ADC) maps for evaluating fibrosis as a comparison.

MATERIALS AND METHODS

Animal models

Forty healthy male Sprague-Dawley rats (180–220 g, 6–8 weeks old) were obtained from Beijing Vital River Laboratory Animal Technology Co., Ltd (China), and were maintained in the animal experiment center under standard conditions and controlled environment of 12-hour light/dark cycle at room temperature (23 °C). They were fed with standard laboratory food and water. After 1 week of adaptation, the rats were divided into the experimental ($n=30$) and control ($n=10$) groups. In the experimental group, a mixture of carbon tetrachloride (CCl_4 ; Sinopharm Chemical Reagent Co., Ltd, Shanghai, China) and olive oil (Sinopharm Chemical Reagent Co., Ltd) [2:3 (v/v)] was injected intraperitoneally twice a week at 0.3 ml/100 g body weight for 4 ($n=14$), 8 ($n=8$), or 12 ($n=8$) weeks to induce different stages of liver fibrosis. In the control group, normal saline was applied.

MR examination

MRI examinations were performed using a 3.0 T scanner (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany) with a 16-channel wrist coil. The rats received an intraperitoneal injection of 60 mg/kg body weight of pentobarbital sodium (Sigma, St. Louis, MI, US) for anesthesia before MRI examinations. The MRI protocol included axial T2-weighted Turbo Spin Echo (TSE) [repetition time (TR)/time echo (TE)=5000 ms/62 ms, field of view (FOV)=80 mm×160 mm, slice thickness=2.0 mm], diffusion weighted imaging (TR/TE=6000 ms/56 ms, FOV=260 mm×130 mm, slice thickness=4.8 mm, b-values of 50 and 800 s/mm²), contrast enhanced sequences and T1 mapping series. Contrast enhanced

sequences including pre-contrast and hepatobiliary phases (20 min and 60 min after contrast enhancement). A volume interpolated breath-hold examination (VIBE) sequence was used for multiple hepatobiliary phase acquisitions (TR/TE=4.50 ms/2.50 ms, FOV=140 mm×140 mm, slice thickness=2 mm). A dual-flip-angle T1 3D VIBE sequence was used for T1 mapping imaging (TR/TE=6.22 ms/2.46 ms, FOV=90 mm×200 mm, slice thickness=2.00 mm, flip angle 1=3°, flip angle 2=15°), including pre-contrast, 20 min and 60 min after contrast injection. Each rat received a bolus injection of gadoteric acid (Primovist, Bayer Schering Pharma AG, Berlin, Germany; 0.025 mmol Gd/kg body weight, concentration of 0.025 mmol/ml) *via* the tail vein within 3 s.

Pathological examination

After the MR examinations, each rat was euthanized by means of intravenous injection of pentobarbital sodium. Right lateral liver lobes of each rat were removed and stained with hematoxylin and eosin (H&E) and Masson trichrome for histopathological analysis after MR exams. METAVIR score was used to grade liver fibrosis (F0–F4): no fibrosis, portal fibrosis without septa, portal fibrosis with a few septa, numerous septa without cirrhosis, and cirrhosis, respectively.^[13] In this study, we defined F0 as no fibrosis, F1–2 as mild fibrosis, and F3–4 as advanced fibrosis.

Image analysis

Texture analysis was performed using the TexRAD commercial research software (TexRAD Ltd, www.texrad.com, part of Feedback Plc, Cambridge, UK). Images of T2WI, ADC map, contrast enhanced sequences (including pre-contrast, 20 min after contrast injection, and 60 min after contrast injection), T1 mapping sequences (including pre-contrast, 20 min after contrast injection, and 60 min after contrast injection) were transferred to the TexRAD software.

MR images were evaluated by one trained operator with 2 years of experience in MRI and repeated the process four weeks later. The average value of two measurements for each texture parameter was calculated and recorded for statistical analysis afterward.

ROIs were drawn manually to cover the whole liver at the level of hepatic hilum, leaving a distance of 1–2 mm to the borderline and avoiding imaging artifacts, major vascular branches, and gallbladder. For texture analysis, image filtration was performed using

Laplacian of Gaussian spatial band-pass filter to extract image features of different sizes at different spatial scales within a ROI, and followed by texture quantification using histogram analysis. The spatial scaling factor (SSF) represents the size of the image features highlighted by the filter and ranges between object radii of 0, 2, 3, 4, 5, and 6 mm. SSF 0 indicates use of no filtration, SSF 2 indicates fine texture scale, 3–5 indicate medium texture scales, and 6 indicates coarse texture scale, respectively. **Figure 1** showed an illustration of ROI within the lesion and corresponding texture images.

Quantified texture parameters derived from histogram analysis included mean gray-level intensity (Mean, the average value of the pixels within the ROI), standard deviation (SD, the variation from the average), Entropy (irregularity of pixel intensity distribution), mean of positive pixels (MPP, only pixels greater than zero), Skewness (the asymmetry of the histogram), and Kurtosis (the sharpness of the histogram). The six parameters of ROI were recorded across each SSF.

Statistical analysis

Statistical analysis was performed using SPSS 23.0 (IBM, Armonk, New York, USA). Continuous variables were expressed as means ± standard deviation. Nonparametric Mann–Whitney *U* test was used to compare the average value of each texture parameter in each sequence for assessing the difference between F0 and F≥1 as well as F0–2 and F3–4. Receiver operating characteristic (ROC) curves were obtained to assess the diagnosing accuracy of the parameters for differentiating rats with F0 grading from those with F≥1 grading and rats of F0–2 grading from those having F3–4 grading. The point with the maximal sum of specificity plus sensitivity was regarded as the optimal diagnostic point. The area under ROC curve (AUC) was calculated to evaluate the diagnostic efficiency of texture parameters. *P*-value < 0.05 was considered statistically significant.

RESULTS

Eleven rats died from the intraperitoneal injection of CCl₄ or anesthesia before MR scanning. Three died during MR examination after contrast injection. In the end, 26 rats completed MR scan. The pathologic staging of these 26 rats were no fibrosis (F0, *n*=7), mild fibrosis (F1–2, *n*=9) and advanced fibrosis (F3–4, *n*=10). Six of them failed to obtain T1 mapping data due to temporary malfunction of the sequence. The

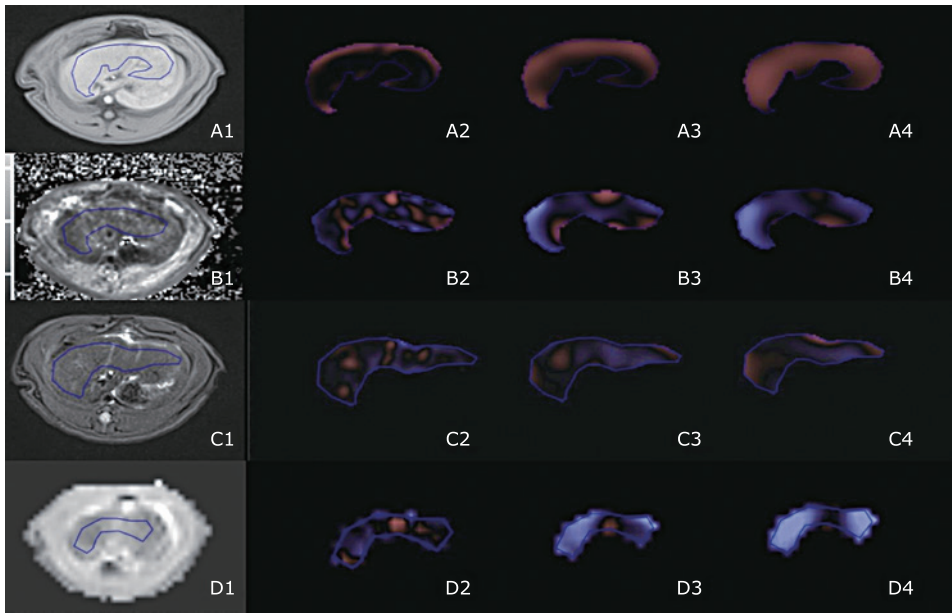


Figure 1. Texture analysis in a rat with mild liver fibrosis (F=1). Pre-contrast T1-weighted and T1 mapping images, as well as T2-weighted and apparent diffusion coefficient (ADC) images with Regions of Interest (ROIs) drawn around are showed in image A1, B1, C1 and D1 respectively. Color texture output are exhibited at fine (SSF=2, image A2–D2), medium (SSF=4, image A3–D3), and coarse (SSF=6, image A4–D4) filter levels.

pathologic staging of these 20 rats completed T1 mapping series was no fibrosis (F0, $n=6$), mild fibrosis (F1–2, $n=5$) and advanced fibrosis (F3–4, $n=9$).

On pre-contrast T1 mapping image, Entropy was seen to be statistically significant higher in the $F\geq 1$ group than that in the F0 group at every SSF value (0, no filtration; 2, fine; 3, 4 and 5, medium; 6, coarse texture scale) (all $P<0.05$). Mean was statistically sig-

nificant higher in the $F\geq 1$ groups than that in the F0 group at SSF 4, 5, 6 (all $P<0.05$). On 20 min-delayed T1 mapping image, Mean was statistically significant higher in the $F\geq 1$ groups than that in the F0 group at SSF 6 ($P=0.039$). On 60 min-delayed T1 mapping image, Kurtosis was statistically significant higher in the $F\geq 1$ group than that in the F0 group at SSF 6 ($P=0.025$) (**Table 1**).

Table 1. Texture parameters with significant differences between F0 and F1–4 and well as F0–2 and F3–4 comparisons on pre- and post- (60 min delay) contrast T1 mapping images

Comparison	Sequence	Texture parameter	SSF	<i>U</i> value	<i>P</i> value
F0 vs. F1–4	Pre-contrast T1 mapping	Mean	4	114.0	0.004
			5	113.0	0.006
			6	109.0	0.013
		Entropy	0	108.0	0.015
			2	107.5	0.015
			3	108.0	0.015
	Post-contrast T1 mapping (20 min)	Mean	4	114.0	0.013
			5	113.0	0.015
			6	109.0	0.018
		Kurtosis	6	21.0	0.039
			6	76.5	0.025
			6	103.0	0.036
F0–2 vs. F3–4	Pre-contrast T1 mapping	Skewness	4	103.0	0.036

SSF: spatial scaling factor.

On pre-contrast T1-weighted image, mean gray-level intensity was significantly lower in the $F \geq 1$ group than that in the F0 group at SSF 2, 3, 4 (all $P < 0.05$). MPP is significantly lower in the $F \geq 1$ group than that in the F0 group at SSF 3 and 4 (both $P < 0.05$). SD and Entropy were significantly higher in the $F \geq 1$ vs. F0 as well as F3–4 vs. F0–2 comparisons at SSF 0 in both 20 min-delayed (all $P < 0.05$) and 60 min-delayed (all $P < 0.05$) phases of T1-weighted images (**Table 2**).

No significant difference was found in texture parameters between different fibrosis stages on T2-weighted image and ADC map.

Table 3 showed the ROC analysis for texture parameters with significant differences of F0 vs. F1–4 and F0–2 vs. F3–4 comparisons on pre- and post- (60 min delay) contrast T1 mapping images. The results showed the AUCs of Mean and Entropy ranged from 0.805 to 0.857 in most SSF settings in pre-contrast T1 mapping for differentiation of F0 and F1–4. **Table 4** showed the ROC analysis for texture parameters with significant differences of F0 vs. F1–4 and F0–2 vs. F3–4 comparisons on pre- and post-contrast T1W

images. SD and Entropy showed an increasing tendency with fibrosis staging at SSF0 in post-contrast T1W image of both 20 min and 60 min delay, and the corresponding AUCs for differentiating F0 from F1–4 and F0–2 from F3–4 were high.

DISCUSSION

The focus of this study was to explore the diagnostic performance of texture analysis on T1 mapping images in assessing liver fibrosis in a rat model. As a result, Entropy of non-contrast T1 mapping image was found to be a useful biomarker in classifying normal liver parenchyma from those with an abnormal fibrosis stage in every SSF setting (SSF=0, 2, 3, 4, 5 and 6), while mean gray-level intensity also exhibited good diagnostic performance at several filter scales. On the other hand, only a few texture features at certain filter setting of post-enhanced T1 mapping images and T1-weighted image showed statistical differences.

Texture analysis provides an objective, quantitative assessment of target tissue heterogeneity by analyzing the distribution and relationship of pixel or

Table 2. Texture parameters with significant differences between F0 and F1–4 as well as F0–2 and F3–4 on pre- and post-contrast T1W images

Comparison	Sequence	Texture parameter	SSF	U value	P value
F0 vs. F1–4	Pre-contrast T1W	Mean	2	39.0	0.045
			3	35.0	0.025
			4	37.0	0.034
		MPP	3	34.0	0.021
			4	33.0	0.018
	Post-contrast T1W (20 min)	SD	0	98.0	0.013
			0	94.5	0.023
		Kurtosis	2	98.5	0.011
F0–2 vs. F3–4	Post-contrast T1W (60 min)	SD	0	40.0	0.018
			0	39.5	0.028
		MPP	3	6.0	0.040
			4	6.0	0.040
		Skewness	3	41.0	0.010
			4	40.0	0.018
	Pre-contrast T1W	Skewness	0	122.0	0.041
	Post-contrast T1W (20 min)	SD	0	112.0	0.004
			0	101.5	0.027
		Kurtosis	2	103.0	0.023
	Post-contrast T1W (60 min)	SD	0	52.0	0.004
			0	51.5	0.004

MPP: mean of positive pixels; SD: standard deviation.

Table 3. Receiver operating characteristic (ROC) analysis for texture parameters with significant differences of F0 vs. F1-4 and F0-2 vs. F3-4 comparisons on pre- and post-contrast T1 mapping images

Sequence	Comparison	Texture parameter	SSF	AUC	95%CI	P value	Threshold	Sensitivity	Specificity
Pre-contrast T1 mapping	F0 vs. F1-4	Mean	4	0.857	0.711, 1.000	0.006	>-391.855	0.684	1.000
			5	0.850	0.701, 0.999	0.007	>-608.24	0.789	1.000
			6	0.820	0.635, 1.000	0.014	>-745.89	0.789	0.857
		Entropy	0	0.812	0.638, 0.986	0.016	>5.305	0.632	1.000
			2	0.808	0.631, 0.985	0.018	>5.655	0.632	0.857
			3	0.812	0.636, 0.988	0.016	>5.210	0.632	0.857
			4	0.816	0.641, 0.991	0.015	>5.185	0.632	0.857
			5	0.812	0.637, 0.987	0.016	>5.225	0.632	0.857
			6	0.805	0.629, 0.980	0.019	>5.170	0.632	0.857
Post-contrast T1 mapping (60 min)	F0-2 vs. F3-4	Skewness	4	0.747	0.554, 0.939	0.037	>-0.265	0.900	0.625
		Kurtosis	6	0.797	0.592, 1.000	0.028	>-0.390	0.833	0.750

Table 4. ROC analysis for texture parameters with significant differences of F0 vs. F1-4 and F0-2 vs. F3-4 comparisons on pre- and post-contrast T1W images

Sequence	Comparison	Texture parameter	SSF	AUC	95%CI	P value	Threshold	Sensitivity	Specificity	
Pre-contrast T1W	F0 vs. F1-4	Mean	2	0.745	0.556, 0.934	0.043	<131.57	0.765	0.556	
			3	0.771	0.586, 0.856	0.025	<186.005	0.706	0.778	
			4	0.758	0.561, 0.955	0.033	<255	0.647	0.556	
	MPP	3	0.778	0.592, 0.964	0.022	<227.22	0.706	0.778		
		4	0.784	0.600, 0.969	0.019	<320.61	0.765	0.667		
Post-contrast T1W (20 min)	F0 vs. F1-4	SD	0	0.817	0.642, 0.991	0.014	>53.785	0.667	1.000	
		Entropy	0	0.788	0.599, 0.976	0.026	>5.04	0.667	0.825	
		Kurtosis	2	0.821	0.644, 0.998	0.013	>0.700	0.600	0.875	
	F0-2 vs. F3-4	SD	0	0.848	0.689, 1.000	0.005	>53.785	0.727	0.833	
		Entropy	0	0.769	0.572, 0.966	0.029	>5.04	0.727	0.750	
		Kurtosis	2	0.780	0.582, 0.979	0.023	>0.155	0.818	0.593	
	Post-contrast TIW (60 min)	F0 vs. F1-4	SD	0	0.909	0.739, 1.000	0.019	>36.375	0.909	1.000
			Entropy	0	0.898	0.735, 1.000	0.022	>4.920	0.727	1.000
			MPP	3	0.864	0.670, 1.000	0.037	<303.140	0.909	0.750
F0-2 vs. F3-4		Skewness	4	0.864	0.671, 1.000	0.037	<351.545	0.818	1.000	
			3	0.932	0.794, 1.000	0.013	>-0.115	0.909	1.000	
			4	0.909	0.754, 1.000	0.019	>-0.160	0.818	1.000	
			SD	0	0.929	0.782, 1.000	0.005	>37.345	1.000	0.857
F0-2 vs. F3-4	Entropy	0	0.920	0.781, 1.000	0.007	>4.920	0.875	0.857		
		3	0.804	0.569, 1.000	0.049	>6.050	0.750	0.857		
		4	0.804	0.573, 1.000	0.049	>6.095	0.625	0.857		

voxel gray levels in the biomedical image.^[3, 14] Statistical-based technique is the most common method of texture analysis. It enables quantification of the

gray-level patterns, pixel interrelationships, and the spectral properties of the target area, thus extracts inherent properties which are imperceptible to the hu-

man visual system. Texture analysis has been widely applied in the analysis of a series of different diseases and organ systems including liver, lungs, brain, thyroid, breasts, kidneys and prostate.^[3] In liver it has been used to detect and analyse chronic liver disease,^[5-6, 15] evaluate different hypervascular focal lesions,^[16-17] predict prognosis and treatment response in patients with hepatocellular carcinoma,^[18-19] and differentiate benign from malignant portal vein thrombus,^[20] and correlation has also been reported between imaging texture features and tumor molecular markers.^[21] These robust and widespread applications of texture analysis exhibit its promising potential to provide additional relevant data in clinical practice.

Several studies have been performed to evaluate liver fibrosis with texture analysis technique in the past decade, many of them were focused on CT images.^[15, 22-23] However, the risk of ionizing radiation remains as the main consideration for applying all CT-based methods. Besides, a previous study compared different types of datasets acquired with CT and MR modalities showed that MR images was superior to CT images in classifying liver fibrosis.^[24] There were also some studies based on MR images,^[4-7] in which texture analyses of T2-weighted images, diffusion-weighted images and double contrast-enhanced images have been proved useful in assessing hepatic fibrosis. Compared to these studies, a strength of our study includes that we evaluated the texture features of T1 mapping images and identified Entropy of pre-contrast images in its capacity to differentiate between normal and fibrosis groups with statistical significance in all filter settings. Moreover, all subjects in this study were performed with *in vivo* imaging setting and pathologic assessment, making the results presented in this work more convictive and feasible to be generalized.

The result that Entropy of pre-contrast T1 mapping images exhibited better diagnostic performance than post-contrast ones was beyond our expectation. In previous researches, gadoxetic acid-enhanced MRI using T1 mapping was reported to be more useful in estimation of liver function^[8-10] and evaluation of liver fibrosis staging^[11] compared to pre-contrast images. Some factors may account for this result. One possible reason is that the degree of fibrosis is not always paralleled with the impairment of liver function in each subject despite the overall decreasing trend, and the change of T1 relaxation time reflects hepatocyte

intracellular gadoxetic acid uptake, which is directly corresponded to the function of hepatocytes instead of the degree of fibrosis. Besides, Entropy represents the irregularity as it describes the variation in a volume histogram.^[3] Since liver fibrosis is a complicated course with progressive changes in tissue composition and architecture, the Entropy of T1 mapping images and T1 relaxation time may present different pathological features of this course.

Besides, it is noticeable that several texture parameters extracted from post-contrast T1 weighted images showed highest AUCs compared to the T1 mapping ones in the diagnosis of liver fibrosis, also more parameters showed diagnostic difference in T1 weighted images. One possible reason is that we applied a high resolution T1W sequence with a voxel size of 0.5 mm × 0.5 mm × 2 mm, while in T1 mapping sequence the voxel size was 0.8 mm × 0.8 mm × 2 mm. Moreover, six rats failed to obtain T1 mapping data due to temporary malfunction of the sequence. Thus the sample size of T1 mapping is smaller than T1 weighted images (20 vs. 26). Further studies with novel T1 mapping sequence need to be performed to validate its diagnostic effectiveness. Nevertheless, the result of our research also exhibited the promising potential of gadoxetic acid-enhanced T1 weighted images in the assessment of liver fibrosis.

Different from previous studies, we found no statistical difference of the Entropy of the hepatic ADC values between the normal and fibrosis groups.^[4-5] One possible explanation is that this study was performed with a rat model with a clinical 3.0 Tesla scanner instead of high-resolution small animal MR modality, diffusion images were sensitive to magnetic susceptibility artifacts and suffered from distortion and limited spatial resolution, thus the results were affected ever since.

Furthermore, texture parameters of T2-weighted images failed to separate different fibrosis stages in our study, while in a previous study texture analysis of T2-weighted image exhibited capability of differentiating between cirrhotic patients and healthy volunteers.^[25] This is presumably because of the more prominent reticular patterns of hepatic fibrosis and the existence of regenerative nodules in cirrhosis compared to fibrosis, which lead to more significant changes in texture parameters. Besides, the image quality and the pixel numbers of ROI were also limited in this animal study compared to that human research.

We acknowledge several limitations to our study. First, the sample size was relative small and potentially weakened the statistical power of some parameters, further researches with a larger study population and the enrollment of clinical patients need to be performed. Second, texture analysis was only evaluated on a single slice at the level of hepatic hilum rather than the entire volume. However, previous studies have shown that a single slice of the largest cross-sectional area be used as an alternative to whole volume analysis for sampling and extracting subtle features.^[26-27] Third, we applied a 3D gradient-echo, VIBE with a dual flip-angle for T1 mapping measurement, more accurate sequences such as modified look-locker inversion recovery (MOLLI) has been used for T1 mapping in investigating liver disease.^[28-29]

In summary, certain texture features of gadoteric acid-enhanced MR images, especially the Entropy of non-contrast T1 mapping image, was found to be a useful biomarker for the diagnosis of liver fibrosis.

Acknowledgement

We thank Dr. Hui Liu for his kind help and valuable advices on the MR sequence setting.

Conflict of interest statement

The authors have no conflict of interest to disclose.

REFERENCES

1. Afdhal NH, Nunes D. Evaluation of liver fibrosis: a concise review. *Am J Gastroenterol* 2004; 99(6):1160-74. doi: 10.1111/j.1572-0241.2004.30110.x.
2. Nguyen D, Talwalkar JA. Noninvasive assessment of liver fibrosis. *Hepatology* 2011; 53(6):2107-10. doi: 10.1002/hep.24401.
3. Lubner MG, Smith AD, Sandrasegaran K, et al. CT texture analysis: definitions, applications, biologic correlates, and challenges. *RadioGraphics* 2017; 37(5):1483-503. doi: 10.1148/rg.2017170056.
4. Fujimoto K, Tonan T, Azuma S, et al. Evaluation of the mean and entropy of apparent diffusion coefficient values in chronic hepatitis C: correlation with pathologic fibrosis stage and inflammatory activity grade. *Radiology* 2011; 258(3):739-48. doi: 10.1148/radiol.10100853.
5. Barry B, Buch K, Soto JA, et al. Quantifying liver fibrosis through the application of texture analysis to diffusion weighted imaging. *Magn Reson Imaging* 2014; 32(1):84-90. doi: 10.1016/j.mri.2013.04.006.
6. Bahl G, Cruite I, Wolfson T, et al. Noninvasive classification of hepatic fibrosis based on texture parameters from double contrast-enhanced magnetic resonance images. *J Magn Reson Imaging* 2012; 36(5):1154-61. doi: 10.1002/jmri.23759.
7. Jirák D, Dezortová M, Taimr P, et al. Texture analysis of human liver. *J Magn Reson Imaging* 2002; 15(1):68-74.
8. Katsube T, Okada M, Kumano S, et al. Estimation of liver function using T1 mapping on Gd-EOB-DTPA-enhanced magnetic resonance imaging. *Invest Radiol* 2011; 46(4):277-83. doi: 10.1097/RLI.0b013e318200f67d.
9. Zhou ZP, Long LL, Huang LJ, et al. Gd-EOB-DTPA-enhanced MRI T1 mapping for assessment of liver function in rabbit fibrosis model: comparison of hepatobiliary phase images obtained at 10 and 20 min. *Radiol Med* 2017; 122(4):239-47. doi: 10.1007/s11547-016-0719-1.
10. Zhou ZP, Long LL, Qiu WJ, et al. Comparison of 10- and 20-min hepatobiliary phase images on Gd-EOB-DTPA-enhanced MRI T1 mapping for liver function assessment in clinic. *Abdom Radiol (NY)* 2017; 42(9):2272-8. doi: 10.1007/s00261-017-1143-2.
11. Ding Y, Rao SX, Zhu T, et al. Liver fibrosis staging using T1 mapping on gadoteric acid-enhanced MRI compared with DW imaging. *Clin Radiol* 2015; 70(10):1096-103. doi: 10.1016/j.crad.2015.04.014.
12. Pan S, Wang XQ, Guo QY. Quantitative assessment of hepatic fibrosis in chronic hepatitis B and C: T1 mapping on Gd-EOB-DTPA-enhanced liver magnetic resonance imaging. *WJG* 2018; 24(18):2024-35. doi: 10.3748/wjg.v24.i18.2024.
13. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. *Hepatology* 1994; 20(1 Pt 1):15-20.
14. Ganeshan B, Miles KA. Quantifying tumour heterogeneity with CT. *Cancer Imaging* 2013; 13(1):140-9. doi: 10.1102/1470-7330.2013.0015.
15. Lubner MG, Malecki K, Kloeke J, et al. Texture analysis of the liver at MDCT for assessing hepatic fibrosis. *Abdom Radiol (NY)* 2017; 42(8):2069-78. doi: 10.1007/s00261-017-1096-5.
16. Raman SP, Schroeder JL, Huang P, et al. Preliminary data using computed tomography texture analysis for the classification of hypervascular liver lesions: generation of a predictive model on the basis of quan-

- titative spatial frequency measurements—a work in progress. *J Comput Assist Tomogr* 2015; 39(3):383-95. doi: 10.1097/RCT.0000000000000217.
17. Cannella R, Rangaswamy B, Minervini MI, et al. Value of texture analysis on gadoxetic acid-enhanced MRI for differentiating hepatocellular adenoma from focal nodular hyperplasia. *AJR Am J Roentgenol* 2019; 212(3):538-46. doi: 10.2214/AJR.18.20182.
 18. Mulé S, Thieffn G, Costentin C, et al. Advanced hepatocellular carcinoma: pretreatment contrast-enhanced CT texture parameters as predictive biomarkers of survival in patients treated with sorafenib. *Radiology* 2018; 288(2):445-55. doi: 10.1148/radiol.2018171320.
 19. Chen S, Zhu Y, Liu Z, et al. Texture analysis of baseline multiphasic hepatic computed tomography images for the prognosis of single hepatocellular carcinoma after hepatectomy: a retrospective pilot study. *Eur J Radiol* 2017; 90:198-204. doi: 10.1016/j.ejrad.2017.02.035.
 20. Canellas R, Mehrkhani F, Patino M, et al. Characterization of portal vein thrombosis (neoplastic *versus* bland) on CT images using software-based texture analysis and thrombus density (Hounsfield Units). *AJR Am J Roentgenol* 2016; 207(5):W81-7. doi: 10.2214/AJR.15.15928.
 21. Sadot E, Simpson AL, Do RKG, et al. Cholangiocarcinoma: correlation between molecular profiling and imaging phenotypes. *PLoS One* 2015; 10(7):e0132953. doi: 10.1371/journal.pone.0132953.
 22. Dagainawala N, Li B, Buch K, et al. Using texture analyses of contrast enhanced CT to assess hepatic fibrosis. *Eur J Radiol* 2016; 85(3):511-7. doi: 10.1016/j.ejrad.2015.12.009.
 23. Romero-Gómez M, Gómez-González E, Madrazo A, et al. Optical analysis of computed tomography images of the liver predicts fibrosis stage and distribution in chronic hepatitis C. *Hepatology* 2008; 47(3):810-6. doi: 10.1002/hep.22112.
 24. Zhang X, Gao X, Liu BJ, et al. Effective staging of fibrosis by the selected texture features of liver: which one is better, CT or MR imaging? *Comput Med Imaging Graph* 2015; 46 Pt 2:227-36. doi: 10.1016/j.compmmedimag.2015.09.003.
 25. Jiráček D, Dezortová M, Taimr P, et al. Texture analysis of human liver. *J Magn Reson Imaging* 2002; 15(1):68-74.
 26. Lubner MG, Stabo N, Lubner SJ, et al. CT textural analysis of hepatic metastatic colorectal cancer: pre-treatment tumor heterogeneity correlates with pathology and clinical outcomes. *Abdom Imaging* 2015; 40(7):2331-7. doi: 10.1007/s00261-015-0438-4.
 27. Ng F, Kozarski R, Ganeshan B, et al. Assessment of tumor heterogeneity by CT texture analysis: can the largest cross-sectional area be used as an alternative to whole tumor analysis? *Eur J Radiol* 2013; 82(2):342-8. doi: 10.1016/j.ejrad.2012.10.023.
 28. Yoon JH, Lee JM, Paek M, et al. Quantitative assessment of hepatic function: modified look-locker inversion recovery (MOLLI) sequence for T1 mapping on Gd-EOB-DTPA-enhanced liver MR imaging. *Eur Radiol* 2016; 26(6):1775-82. doi: 10.1007/s00330-015-3994-7.
 29. Yoon JH, Lee JM, Kang H-J, et al. Quantitative assessment of liver function by using gadoxetic acid-enhanced MRI: hepatocyte uptake ratio. *Radiology* 2019; 290(1):125-33. doi: 10.1148/radiol.2018180753.