Int J Clin Exp Med 2015;8(2):2197-2204
www.ijcem.com /ISSN:1940-5901/IJCEM0004306

*Original Article*

# Apparent diffusion coefficient measurements and Gd-DTPA enhanced-imaging in staging hepatic fibrosis in rats

Yi-Ping Zhao[1], Dong-Mei Guo[1], Hui Liu[2], Wen-Hong Liu[3], Wen-Ying Mu[1], Peng Zhang[1]

[1]*Department of Radiology, Second Affiliated Hospital, Dalian Medical University, Dalian 116027, China;* [2]*Department of Biomedical Engineering, Dalian University of Technology, Dalian 116024, China;* [3]*School of Electronic and Information Engineering, Shanghai Dianji University, Shanghai 201306, China*

Received November 30, 2014; Accepted January 29, 2015; Epub February 15, 2015; Published February 28, 2015

**Abstract:** To evaluate the utility of ADC values and Gd-DTPA equilibrium phase MR imaging in staging hepatic fibrosis in rats. 48 rats were allocated into experimental and control groups. Experimental rats were subcutaneously injected with a mixture of $CCl_4$. From 4th-12th weeks, MR images were obtained, which include pre-enhanced phase imaging, DWI and equilibrium phase imaging. Then the rat groups were subdivided according to the stages of fibrosis (S0, S1, S2, S3 and S4) after histopathological analysis. The original MRI data were forwarded to the workstation to obtain apparent diffusion coefficient (ADC) maps at b value of 500 s/mm$^2$. Pre-enhanced phase and equilibrium phase signal intensities and relative contrast enhancement index (RCEI) were measured as well. Lastly, the ADC values and RCEI of the experimental group were compared with each other and with the control group. All statistical analyses were carried out with SPSS, where $P < 0.05$ is considered to represent a significant difference. Hepatic ADC values are significantly different between the experimental and control groups ($P = 0$). There is a statistically significant difference between the experimental and control groups on RCEI ($P = 0$). Comparing the S1, S2, S3 and S4 groups, there is a statistically significant difference between the mild group (S1 and S2) and the severe group (S4) in terms of ADC values and RCEI (all $P < 0.05$). A statistically significant difference is also found between the moderate group (S3) and the severe group in ADC values. As the degree of fibrosis increases, there are a reduction in ADC values and an increase in RCEI. Comparing the groups with ADC values and enhancement index, there are statistically significant differences in sensitivity and specificity on diagnosis of hepatic fibrosis. The ADC values have the best sensitivity (93.1%) and specificity (83.3%). Quantitative ADC values and RCEI may be helpful to the staging of rat fibrosis, but their application in human is controversial.

**Keywords:** Hepatic fibrosis staging, magnetic resonance imaging, apparent diffusion coefficient, equilibrium phase imaging, rat model

## Introduction

Hepatic fibrosis can be prevented or reversed at the early stage by antifibrotic treatment or by eliminating the cause. Otherwise it would lead to end-stage liver diseases [1, 2]. Therefore, accurately staging hepatic fibrosis is important in choosing appropriate therapy to improve the prognosis of this disease. Hepatic biopsy is currently considered a gold standard for assessing the stages of fibrosis. But this invasive method is limited by inter- and intra-observer variability, sampling error and existing complications [3, 4]. Noninvasive, reproducible and reliable methods are greatly needed to assess hepatic fibrosis.

To date, a number of noninvasive methods including ultrasound, CT and MRI have been proposed for identification of hepatic fibrosis. Ultrasound and CT are difficult to stage hepatic fibrosis [5, 6]. MR imaging holds the promise of providing functional and biological information about hepatic pathology as it is related to future treatment of hepatic fibrosis. Earlier plain MRI study found that the signal intensity of the liver parenchyma using T1- and T2-weighted imaging appeared to be associated with the degree of histological severity in patients with chronic liver disease [7]. Gadolinium-enhanced MR images were reviewed to determine the enhancement patterns, and it was concluded that in patients with chronic hepatitis the presence of

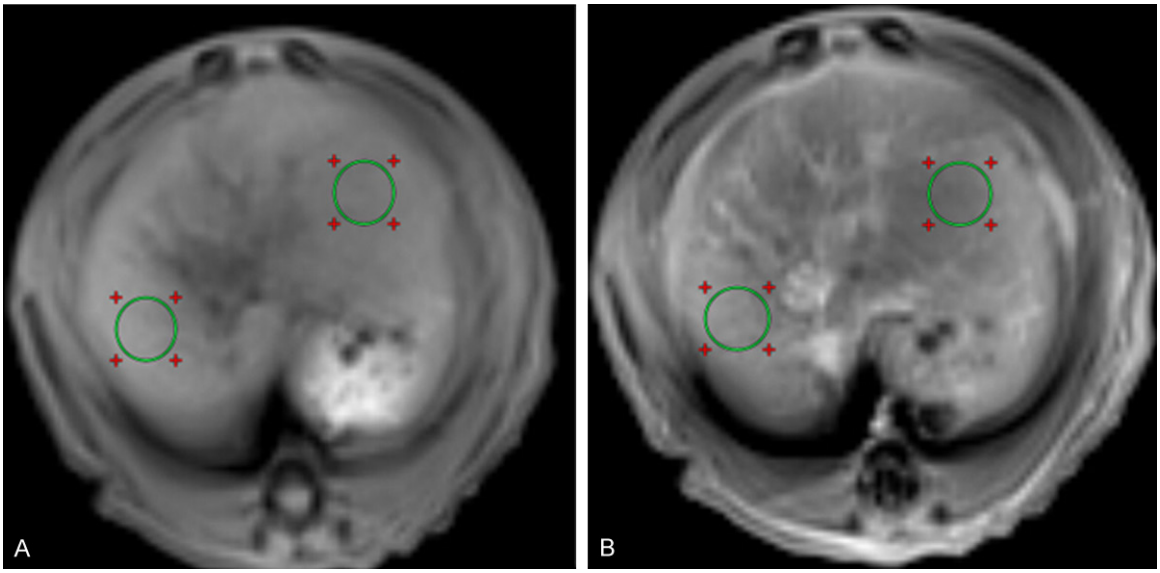


**Figure 1.** ROI of enhanced MR imaging. A is pre-enhanced phase T1WI; B is equilibrium phase imaging.

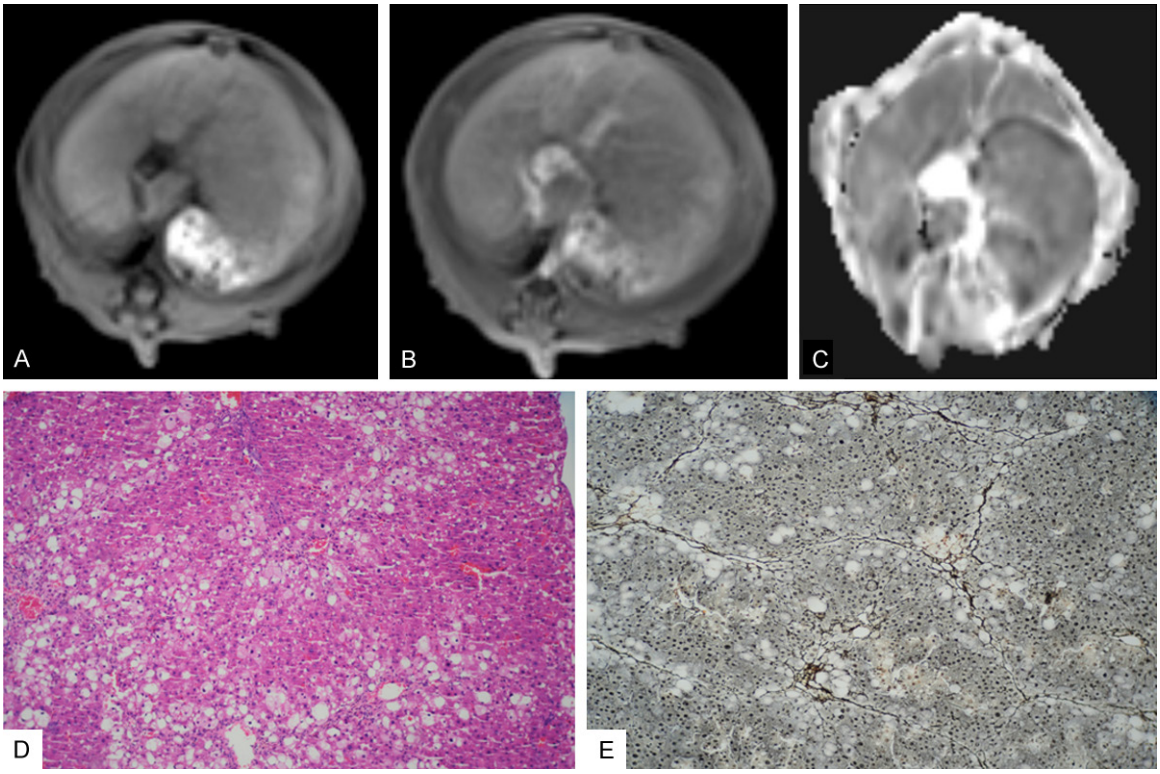


**Figure 2.** Hepatic fibrosis stage 2. A-C: T1WI, equilibrium phase, and ADC images (b values of 500 s/mm$^2$) respectively; it shows patchy enhancement. D, E: Photomicrograph (original magnification, × 100; Modified Gomori Methenamine-Silver) shows hepatic periportal fibrosis.

late linear enhancement indicates the presence of fibrosis, with a high degree of correlation with histopathological findings [8]. A researcher used hepatocyte-specific gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MR imaging to assess early hepatic cirrhosis. The research showed that hepatocyte phase RCEI values are

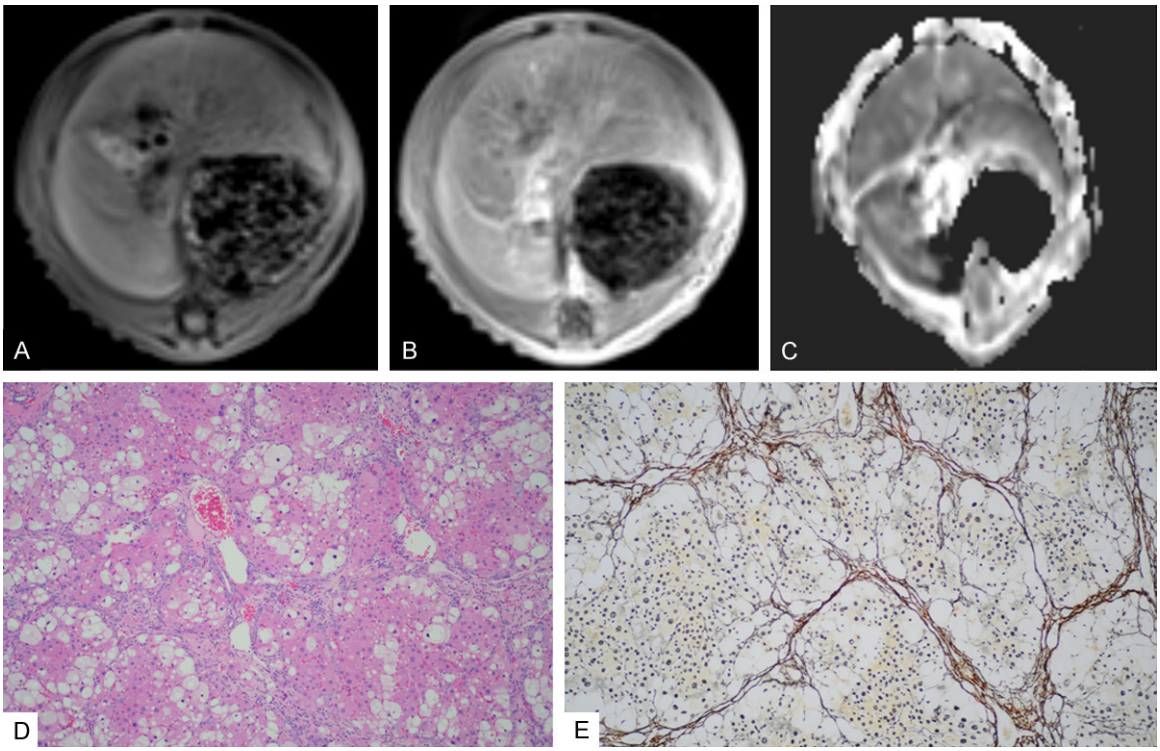


**Figure 3.** Hepatic fibrosis stage 3. A-C: T1WI, equilibrium phase, and ADC images (b values of 500 s/mm$^2$) respectively; it shows prominent linear enhancement. D, E: Photomicrograph (original magnification, × 100; Modified Gomori Methenamine-Silver) shows hepatic septal fibrosis.

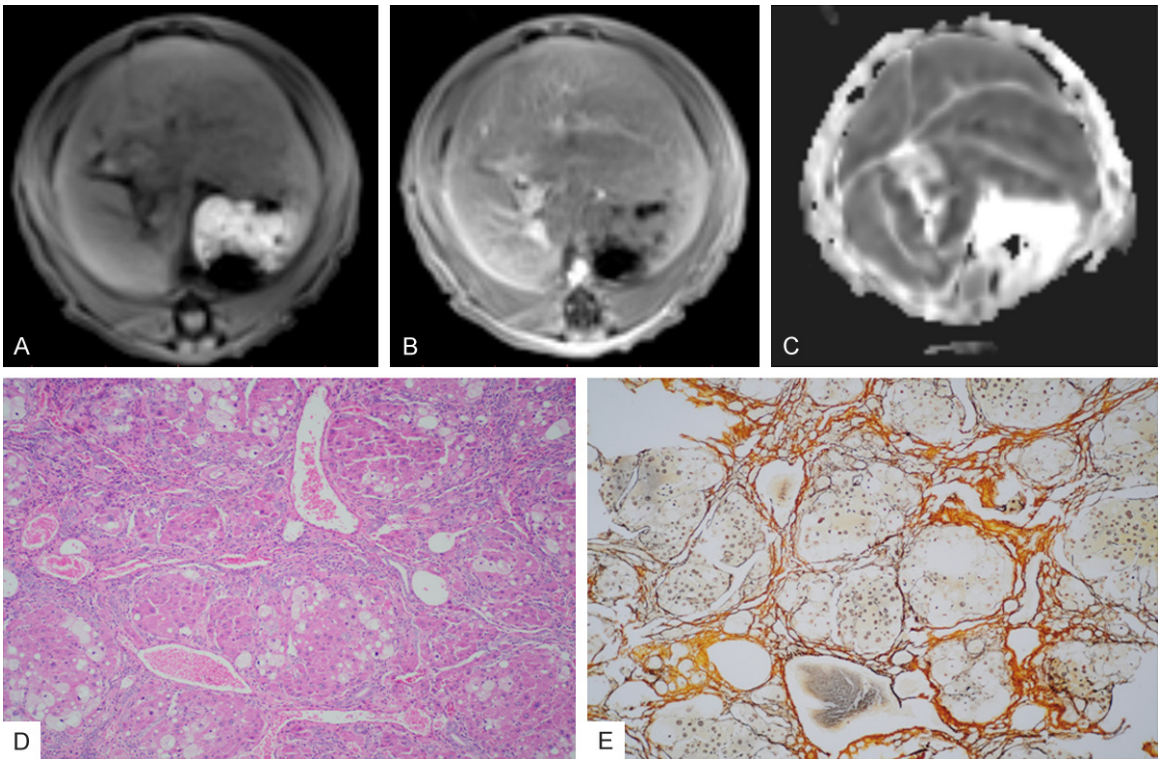


**Figure 4.** Hepatic fibrosis stage 4. A-C: T1WI, equilibrium phase, and ADC images (b values of 500s/mm$^2$) respectively; it shows grid enhancement. D, E: Photomicrograph (original magnification, × 100; Modified Gomori Methenamine-Silver) shows hepatic cirrhosis.

**Table 1.** ADC values and RCEI ratios of rat hepatic tussues

| | ADC values | | RCEI ratios | |
|---|---|---|---|---|
| Fibrosis stage (n) | mean | SD | mean | SD |
| S0 (10) | 3.083 | 0.032 | 0.326 | 0.009 |
| S1 (5) | 2.707 | 0.009 | 0.573 | 0.010 |
| S2 (12) | 1.999 | 0.022 | 0.738 | 0.007 |
| S3 (8) | 1.889 | 0.027 | 1.011 | 0.014 |
| S4 (8) | 1.394 | 0.034 | 1.309 | 0.023 |

helpful to early diagnosis of hepatic cirrhosis [9]. Recently, magnetic resonance elastography (MRE) has been developed as a noninvasive functional MR imaging method for detecting and staging hepatic fibrosis. The study had shown that MRE had greater predictive ability in distinguishing the stages of liver fibrosis [10].

Diffusion-weighted imaging (DWI) is a type of functional magnetic resonance technique. DWI had emerged for detecting fibrosis [11, 12]. Some studies have shown that ADC values of the liver are lower in patients with cirrhosis compared with control subjects, which is thought to reflect a restriction of the motion of water molecules in fibrotic tissues [11]. Nevertheless, ADC values obtained in the previous experiences for studying hepatic fibrosis widely varied because of the employed settings of so-called b-values [12]. Zhu's [13] and Ozkurt H's [14] researches proved that DWI is a useful clinical tool in the quantitative evaluation of hepatic fibrosis and in the prediction of the process of hepatic fibrosis with the recommendable b values. Zhu's study showed that when b value was 500 s/mm$^2$, the sensitivity and specificity of DWI for diagnosis of liver fibrosis were the highest. Ozkurt H's findings suggested that the mean hepatic ADC values of patients with hepatic fibrosis were significantly lower than those of patients without hepatic fibrosis; there were statistically significant differences between S1, S2 and S1, S3 at b-values of 750 s/mm$^2$ and 1000 s/mm$^2$.

The use of hepatocyte-specific contrast agent and MRE holds promise as a non-invasive imaging procedure in detecting and staging liver fibrosis in patients with chronic liver disease and has the potential to replace liver biopsy in some patients. But they are hard to be widely used because the hepatocyte-specific contrast agent is very expensive and MRE needs special equipment. Gd-DTPA enhanced MRI and DWI are routine methods in clinic to detect chronic liver disease and the images are easily available. To our knowledge, there have been a few data focusing on the correlation between ADC value and triple-phase dynamic MRI to stage hepatic fibrosis [15].

Our purpose is using routine MRI methods to diagnose the stages of hepatic fibrosis. And this research is also prepared for the next step to diagnose the stages of hepatic fibrosis with computer-assisted diagnosis system.

## Materials and methods

### *Animal model*

Animals were used in full compliance with the National Council of Animal Care guidelines. The protocol was approved by the Committee of the Ethics of Animal Experiments of our institute.

48 healthy male Sprague-Dawley rats, weighted 174-280 g, were obtained from the Experimental Animal Center of Dalian Medical University. They were fed in cages and randomly assigned to the experimental group (n = 36) and the control group (n = 12). The experimental group rats were subcutaneously injected with a mixture of carbon tetrachloride (Baiyin Reagent Factory, Shanghai) and olive oil (50% v/v) at a dose of 0.3 ml/100 g of body weight, twice per week (12 weeks in total), and the first dose was 0.5 ml/100 g. The control group rats were subcutaneously injected with physiologic saline with the same dose.

### *MRI technique*

From 4th to 12th weeks, 4 experimental rats and 1-2 control rats were randomly selected every week for MR examination. The rats were fasted for 6 hours prior to the MRI examinations. MRI was performed using the Siemens Magnetom Verio Tim 3.0T MR scanning with a rat coil (3.0T, Chenguang medicine technology corporation, Shanghai). After the rats had been anesthetized by an intraperitoneal injection of chloral hydrate (40%) at a dose of 4 mL/100 g of body weight for the experimental rats and 2-4 ml/100 g of body weight for the control rats, the rats were positioned prostrate at the center of the coil. Firstly, Pre-enhanced phase T1WI and DWI were obtained. Secondly, Gd-DTPA was inserted through a tail vein cath-

**Table 2.** Receiver operating curve analyses of ADC values and RCEI for prediction of different fibrosis stages

| Cutoff values (ADC) | Stage differences | AUC | *P* values | 95% confidence intervals (AUC) |
|---|---|---|---|---|
| 2.715 | S0 vs. S > 0 | 0.986 | 0.000 | 0.961-0.992 |
| 2.050 | S ≤ 1 vs. S > 1 | 0.741 | 0.058 | 0.723-0.762 |
| 1.875 | S ≤ 2 vs. S > 2 | 0.934 | 0.017 | 0.906-0.961 |
| 1.505 | S ≤ 3 vs. S > 3 | 0.993 | 0.025 | 0.986-0.999 |
| Cutoff values (RCEI) | | | | |
| 0.450 | S0 vs. S > 0 | 0.975 | 0.001 | 0.958-0.993 |
| 0.645 | S ≤ 1 vs. S > 1 | 0.623 | 0.064 | 0.616-0.684 |
| 0.880 | S ≤ 2 vs. S > 2 | 0.921 | 0.036 | 0.904-0.977 |
| 1.045 | S ≤ 3 vs. S > 3 | 0.568 | 0.066 | 0.550-0.598 |

eter with Spectris Solaris MR injection system (Medrad corporation, USA) and equilibrium phase imaging was obtained 180 s after injection of Gd-DTPA (0.2 ml/100 g).

The parameters of pre-enhanced phase T1WI and equilibrium phase imaging are the same. (t1_vibe_fs_tra_p2): TR/TE = 5.4/1.8 ms; Slice thickness 3.0 mm; Spacing slice 2.2 mm; Matrix 133 × 192; FOV 81 × 99 mm.

DWI (ep2d_diff_3scan_trace_p2): TR/TE = 7700/86ms; Slice thickness 2.0 mm; Spacing slice 2.2 mm; Matrix 260 × 260; FOV 160 × 160 mm (The value of b:500 s/mm$^2$).

*Histopathology*

After the MR examinations, the rats were scarified and whole liver of each rat was fixed in 10% buffered formaldehyde solution for 24 hrs to obtain common pathological sections for hematoxylin and eosin (H&E) and Modified Gomori Methenamine-Silver for histopathological analysis. The stages of hepatic fibrosis in the samples were then confirmed semi-quantitatively according to the human METAVIR classification system. This scoring system has a five-point scale: stage 0, no fibrosis; stage 1, portal fibrosis; stage 2, periportal fibrosis; stage 3, septal fibrosis; and stage 4, cirrhosis. Two experienced pathologists scored the use of pathological specimens, and any discrepancies between the two observers were settled by consensus.

*MR image analysis*

With reference to pathological findings, the region of interest (ROI) was drown by two radiologists. Artifact, diaphragm and intrahepatic vasculature were avoided, and the ROI area was 0.1-0.2 cm$^2$ (**Figure 1**). ROIs of identical size and shape were placed at the same location for images obtained before and after Gd-DTPA administration. The average value of three signal intensities (SIs) of the liver parenchyma was used for data analysis. The relative contrast enhancement index (RCEI) ratio was calculated from the SI measurements before ($SI_{-pre}$) and equilibrium phase after ($SI_{-post}$) intravenous Gd-DTPA administration as follows: RCEI = ($SI_{-post}$-$SI_{-pre}$)/$SI_{-pre}$.

The original MRI data were directly interfaced and forwarded to the workstation (Siemens syngo MutiModality Workplace, Germany) to obtain ADC maps at b value of 500 s/mm$^2$. The ADC value of each ROI as well as the ADC map was automatically generated. The ADC values of the two ROIs in each slice were averaged to give an estimate of ADC value for this slice. Respective ADC values of the three slices were averaged to obtain a final estimate of the liver ADC value to be used for data analysis.

*Statistical analyses*

All statistical analyses were carried out with SPSS (version 17.0). $P < 0.05$ is considered to represent a significant difference. The ADC values and RCEI data were expressed as X ± SD. Comparisons among groups were analyzed by one-way analysis of variance. Spearman's correlation analyses were used to assess the correlation between RCEI and fibrosis stage, or between the ADC values and fibrosis stage. The cutoff value and area under the curve (AUC) of RCEI or ADC values were determined with receiver-operating characteristic (ROC) analysis for predicting different hepatic fibrosis stages. The sensitivity and specificity of RCEI and ADC values were compared.

## Results

*Histopathological findings*

3 rats in the experimental group and 2 in the control group died during the experiment. Based on the pathological findings for the

**Table 3.** Analyses of different methods of ADC values and RCEI

| | | ADC values | | RCEI | |
|---|---|---|---|---|---|
| | | + | - | + | - |
| Gold standard | + | 27 | 2 | 23 | 3 |
| | - | 2 | 10 | 4 | 11 |
| Sensitivity (%) | | 93.1 | | 88.4 | |
| Specificity (%) | | 83.3 | | 73.3 | |
| Positive predictive value (%) | | 93.1 | | 85.2 | |
| Negative predictive value (%) | | 83.3 | | 78.6 | |
| False positive rate (%) | | 16.7 | | 26.7 | |
| False negative rate (%) | | 6.9 | | 11.6 | |

experimental group, the hepatic fibrosis group consisted of 33 rats: 5 in S1 stage, 12 in S2 stage (**Figure 2**), 8 in S3 stage (**Figure 3**), and 8 in S4 stage (**Figure 4**). The control group consisted of 10 rats (S0 stage).

*ADC values corresponding to stages of hepatic fibrosis*

ADC values corresponding to the stages of hepatic fibrosis are illustrated in **Table 1**. There is a decrease in liver ADC values with the increasing degree of fibrosis with b = 500 s/mm$^2$ ($P < 0.05$). There is negative correlation between ADC values and the stages of hepatic fibrosis (r = -0.903 and $P = 0$). There are significant differences between stage 0 and stages 1-4 (S0 = 3.083 ± 0.032, S1 = 2.707 ± 0.009, S2 = 1.999 ± 0.022, S3 = 1.889 ± 0.027, S4 = 1.394 ± 0.034; $P = 0$). ADC values can not differentiate stage 1 from stage 2 ($P = 0.057$), which are called mild hepatic fibrosis groups. But there are significant differences among mild hepatic fibrosis groups, S3 (moderate group) and S4 (severe group) (all $P < 0.05$).

*RCEI analyses in the control group and the hepatic fibrosis groups*

As shown in **Table 1**, RCEI ratios exhibit an increasing trend from the control group to the hepatic fibrosis groups (S0 = 0.326 ± 0.009, S1 = 0.573 ± 0.010, S2 = 0.738 ± 0.007, S3 = 1.011 ± 0.014, S4 = 1.309 ± 0.023). There is positive correlation between RCEI and the stages of hepatic fibrosis (r = 0.963 and $P = 0$). And there are significant difference between the control group and the hepatic fibrosis groups ($P = 0$). RCEI can not differentiate stage 1 from stage 2 ($P = 0.061$) and stage 3 from stage 4 ($P = 0.052$). The differences in RCEI ratios between mild and severe hepatic fibrosis groups are statistically significant ($P < 0.05$).

*Analyses of ADC values compared with RCEI*

Analyses of ROC show that ADC values and RCEI could predict different fibrosis stages with different cutoff values, respectively (**Table 2**). We also find that there is a higher diagnostic performance for ADC values compared with RCEI for prediction of stages 3 and 4. The AUC of ADC is better than RCEI in all fibrosis stages. However, ADC values can not differentiate S1 from S2 ($P > 0.05$). Besides, ADC values and RCEI have different specificity and sensibility. The ADC values have the best sensitivity (93.1%) and specificity (83.3%) for predicting fibrosis (**Table 3**).

## Discussion

Hepatic fibrosis is now regarded as a dynamic process with potential for regression. It can be prevented or reversed at the early stage, so hepatic fibrosis staging is important. Ultimately, hepatic fibrosis leads to cirrhosis, and is associated with nodule formation and organ contraction [16-18]. Some studies have indicated that, among non-invasive techniques to assess hepatic fibrosis, DWI could be a useful technique for staging it [19].

In this study, we performed a study focusing on the correlation between the stages of hepatic fibrosis and RCEI or ADC values by comparing the performance of sensitivity and specificity, and determining how DWI and RCEI could predict the stages of hepatic fibrosis. We found that only RCEI increases from stage 0 to stage 4. Our results are almost consistent with published studies [20]. But it is different with other researches [9]. It is may be of different mechanism with two kinds of contrast agents. Gd-EOB-DTPA is a newly developed hepatocyte-specific MRI contrast agent. Because of its specific hepatocyte uptake, Gd-EOB-DTPA has been used for the evaluation of hepatic function [21]. In addition to enhanced MRI, ADC value would be another indicator to quantitatively evaluate hepatic fibrosis. We find that ADC values tend to decrease from stage 0 to stage 4 and there is negative correlation between ADC values and the stages of fibrosis (r = -0.903 and $P = 0$), which are consistent with previous studies [13,

22]. Most of the researches show that the mechanism of diffusion restriction in the liver is deemed to be multifactorial, possibly associated with swelling of hepatic cell; and there is the presence of increased collagen fibers, which limited the motion of water molecules in the liver. The more deposition of collagen fibers in the extracellular space, the worse hepatic fibrosis gets, and the more significantly ADC value decreases. Our result of this change is consistent with the present study [23]. And there is positive correlation between RCEI and the stages of fibrosis ($r = 0.963$ and $P = 0$). However, Boulanger et al [24] found that there was no correlation between the histological stages of fibrosis and ADC using small b values of 50-250 s/mm$^2$, and we could presume that the difference in ADC values between normal and fibrotic livers could not be found by using the small b values because the ADC values obtained by the small b values could be prone to be influenced by hepatic perfusion [25].

There is no difference between ADC values and RCEI in mild hepatic fibrosis stages (all $P > 0.05$). In comparison with RCEI, we find that ADC values obtained with b = 500 s/mm$^2$ could be better predictors of hepatic fibrosis stage > 0, 2 and 3 by using different cutoff values (AUC = 0.986, 0.934 and 0.993, respectively). Moreover, ADC values have the sensitivity (93.1%) and specificity (83.3%) of more than 80%. It is possible that ADC maps are less contaminated by perfusion effects. Taken together, we conclude that ADC measured on DWI with b = 500 s/mm$^2$ could be recommended preferentially for predicting stages of hepatic fibrosis.

Compared with previous studies, the advantage of this study might be more persuasive to confirm that DWI and RCEI could be used to predict stages of hepatic fibrosis. That is because the experimental animals used in this study had been confirmed to have no fibrosis, hepatic fibrosis by pathology diagnosis. According to Angulo et al [26], most patients with acute hepatic diseases and even with chronic hepatic cirrhosis remained asymptomatic until decompensation occurred. There might be a long interval between patients undergoing hepatic biopsy and undergoing MRI, and the stage of hepatic fibrosis might change during the interval, which would potentially affect the prognosis. It is very crucial to find a noninvasive method to predict patients in the early stage of hepatic fibrosis.

There are some limitations in this study. Firstly, the sample size is relatively small. There are only 5 rats in stage 1 and it may lead to statistical bias. Therefore, further studies involving a larger number of samples are needed to evaluate the RCEI and ADC values for predicting different hepatic fibrosis stages. Secondly, this study is based on an animal experiment, so our findings maybe provide some declinational information. We will conduct further studies with patients to confirm the results. Thirdly, we can not evaluate the influence of inflammation grade, steatosis, iron overload, and edema on stiffness. Fourthly, Gd-DTPA is not a hepatic-specific contrast agent, and maybe it does not reflect the real signal intension of hepatic parenchyma.

In conclusion, ADC values and RCEI might be used to predict different stages of hepatic fibrosis. RCEI could predict normal and severe fibrosis groups with similar $P$ values (all $< 0.05$) compared with ADC values. ADC values with b = 500 s/mm$^2$ might be better predictors for normal, moderate and severe groups. Besides, ADC values can earn a higher diagnostic accuracy. This study might provide noninvasive methods for predicting different stages of hepatic fibrosis.

## Acknowledgements

This work is supported in part by the National Science Foundation of China, NO. 61003175. This work is supported by Shanghai Dianji University Leading Academic Discipline Project under Grant, No. 10XKF01.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Dong-Mei Guo, Department of Radiology, Second Affiliated Hospital, Dalian Medical University, Dalian 116027, China. E-mail: drguodong@163.com

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