Liver fibrosis staging using T1 mapping on gadoxetic acid-enhanced MRI compared with DW imaging

Y. Ding, S.-X. Rao, T. Zhu, C. Chen, R. Li, M.-S. Zeng

Department of Radiology, Zhongshan Hospital of Fudan University, No180, Fenglin Road, Xuhui District, Shanghai, China, 200032,

*Guarantor and correspondent: S.-X. Rao, Department of Radiology, Zhongshan Hospital of Fudan University, No.180, Fenglin Road, Xuhui District, Shanghai, China, 200032. Tel.: +86-021-64041990-2130.

E-mail address: raoxray@163.com

ABSTRACT

AIM: To evaluate the utility of T1 mapping on gadoxetic acid-enhanced magnetic resonance imaging (MRI) and diffusion-weighted imaging (DWI) for staging liver fibrosis.

MATERIALS AND METHODS: This retrospective study was approved by the institutional review board and included 145 patients (mean age: 54 years old; 115 men and 30 women). Necro-inflammatory activity grade (G) and liver fibrosis stage (S) were histopathologically determined. T1 relaxation time and apparent diffusion coefficient (ADC) of the liver were measured and the reduction rate of the T1

relaxation time ($\Delta\%$) was calculated. T1 relaxation time measurements were compared with ADC values according to S/G scores.

RESULTS: Unenhanced hepatobiliary phase (HBP) and $\Delta\%$ of T1 relaxation times showed significant correlations with S/G scores (ρ : 0.28, 0.51, -0.35 for the S score, 0.26, 0.39, -0.26 for the G score, respectively, $p < 0.05$). ADC values showed significant correlation with the S score (ρ : -0.17 , $p = 0.04$) and did not correlate significantly with the G score (ρ : -0.07 , $p = 0.39$). The areas under receiver operator characteristics (AUC) curve of unenhanced HBP, $\Delta\%$ T1 relaxation time, and the ADC value were 0.68, 0.82, 0.71, 0.61 for the identification of $S \geq 3$, and 0.63, 0.68, 0.62, 0.52 for the identification of $G \geq 3$, respectively. The HBP T1 relaxation time was better than that of ADC for identification of $S \geq 3$ ($p = 0.0005$) and $G \geq 3$ ($p = 0.014$).

CONCLUSIONS: The HBP T1 relaxation time measurement on gadoteric acid-enhanced MRI images might be a potential biomarker in the staging of hepatic fibrosis, and was more accurate than the ADC measurement.

INTRODUCTION

Fibrosis is an innate part of the wound-healing response that occurs in injured tissues. Within the liver, fibrosis is characterised by the deposition of extracellular matrix. Liver fibrosis may be represented by variable clinical manifestations and is the main cause of morbidity in patients with chronic liver disease[1]. In China, the most common cause of chronic liver disease is hepatitis B virus (HBV); however, recently, the rate of non-alcoholic fatty liver has been increasing [2]. The end stage of liver fibrosis is liver

cirrhosis and it usually progresses irreversibly to a decompensated stage, which is characterised by liver functional impairment and portal hypertension. Cirrhosis substantially increases the risk of hepatocellular carcinoma (HCC), cirrhotic complications, and death. The risk of complications as a result of liver fibrosis starts to increase in F3 fibrosis. In a cohort of 2125 patients with chronic viral hepatitis, the relative risk of developing cirrhosis and HCC in patients with F3 fibrosis was 6.3% and 4.4% compared with those with F1 and F2 fibrosis[3]. Until the end stage, the progression of fibrosis to cirrhosis has a number of sequelae. First, it will distort the hepatic architecture and vasculature; second, it will have a deleterious effect on hepatic function; and third, it will increase the propensity for neoplastic transformation. Many studies have showed that liver fibrosis could be reversed, for example, by administering antiviral treatment for chronic viral hepatitis[4,5]. In addition, the severity of liver fibrosis affects the prognosis of liver cancer surgery. Therefore, it is important to detect liver fibrosis early, which has significant clinical implications.

Liver biopsy has been regarded as the “reference standard” test for the diagnosis of liver fibrosis for many years[6]; however, liver biopsy does have limitations. In large studies of patients undergoing liver biopsy, pain has been reported in 20% and severe complications reported in 0.57%[7]. The patient will have to undergo numerous liver biopsies, and this will increase the rate of potentially life-threatening complications (haemorrhage in 0.3% of patients and mortality in 0.01%)[8]. Additionally, due to sampling errors, liver biopsy is hindered by an approximately 24% false-negative rate for the diagnosis of cirrhosis[9]. Liver biopsy also has inherent problems such as high

interobserver variability and low patient acceptance.

There are a range of alternative methods to non-invasive assess liver fibrosis currently available, such as the indirect markers of liver injury, computed tomography (CT), transient elastography (TE), and magnetic resonance imaging (MRI). Dual-energy CT, with its proven ability to discriminate between different tissue types, may offer a viable alternative for imaging-based characterisation and quantification of liver fibrosis, but the radiation dose and use of iodinated contrast agents are its major drawbacks. Recent advances in MRI techniques have led to growing interest in optimising and applying functional MRI to assess the stage of liver fibrosis[10]. Perfusion-weighted imaging has also been used to predict the stage of liver fibrosis[11], but is limited due to a lack of standardisation of acquisition techniques, complex mathematical modelling, and breathing motion artefacts during imaging acquisition. Diffusion-weighted imaging (DWI), which is easily incorporated into a routine MRI protocol, has been used to distinguish the different stages of liver fibrosis[12]. DWI is based on the random Brownian motion of water molecules within the voxel. Li *et al.*[13] showed that hepatic MRI-DWI played a key role in evaluating liver fibrosis following transcatheter arterial chemoembolisation (TACE) with low doses of chemotherapy. Tokgoz *et al.*[14] reported that the relationship between apparent diffusion coefficient (ADC) values and degree of fibrosis was not statistically significant in chronic liver disease.

Gadoxetic acid (Primovist, Bayer-Schering Pharma, Berlin, Germany) is a hepatocyte MRI contrast medium, which could be used to evaluate the hepatobiliary system. Previous studies showed that patients with liver dysfunction presented with reduction

of liver parenchymal enhancement using gadoxetic acid-enhanced HBP MRI by the methods of direct measurement of liver parenchymal signal intensity or calculation of perfusion parameters[15,16].

In theory, the T1 relaxation time of the liver parenchyma is directly correlated with the concentration of gadoxetic acid, and it may be more reliable and less subjective. Compared with the other methods, such as CT and perfusion-weighted imaging, the T1 relaxation time does not deliver a radiation dose or require complex mathematical formulae. Moreover, the direct measurement of the T1 relaxation time is easier than the calculation of the relative enhancement[15] or enhancement index[16] of the liver parenchyma by measuring the signal intensity. Haimer *et al.*[17] demonstrated that gadoxetic acid-enhanced MRI using T1 mapping could help estimate the liver function according to the Child–Pugh score in patients with chronic liver disease or cirrhosis. A previous study also showed that gadoxetic acid-enhanced MRI was useful to evaluate non-alcoholic fatty liver disease in an animal model by T1 relaxation time measurement. To the authors' knowledge, the T1 relaxation time has not been reported in the evaluation of liver fibrosis staging.

Therefore, the purpose of the present study was to evaluate whether there were correlations between the T1 relaxation time of the liver parenchyma and liver fibrosis stage (S)/necro-inflammatory activity grade (G) score, the potential for liver fibrosis staging, and to compare the results of T1 relaxation time measurement with DWI-ADC measurement.

MATERIALS AND METHODS

Patients

Retrospective data collection and analysis were approved by the Institutional Review Board of Fudan University. Between January 2012 and September 2014, 510 patients who were suspected of having focal hepatic lesions and underwent a preoperative gadoxetic acid-enhanced MRI examination were included. In 201 of 510 patients, G and S scores were histopathologically determined with hepatectomy conducted to treat hepatic tumours. Fifty-six of 210 patients were excluded from the study because of previous hepatic resection ($n=41$) and other diffuse liver disease such as primary sclerosing cholangitis and primary biliary cirrhosis ($n=15$).

The final study group comprised 145 patients with an age range of 24~75 years (mean age 54 years old); 115 of the 145 patients were men and 30 were women. The mean time interval between surgical resection and the MRI examination was 3 days (range 2~7 days). The flow chart for the enrolment of the study population was presented in Fig. 1.

MRI protocol

MRI was performed using a 1.5 T MRI system (Magnetom Aera, Siemens Medical Solution, Erlangen, Germany) equipped with phased-array coils. For T1 mapping using Syngo MapIt, a dual flip angle three-dimensional (3D) gradient-echo sequence with volumetric interpolated breath-hold examination (VIBE) was performed before and after injection of gadoxetic acid (Primovist, Bayer-Schering). The parameters were

as follows: 4.38 ms/1.93 ms (repetition time/echo time), 2° and 12° flip angle, 380–400×300–324 mm field of view (FOV), 216×288 matrix, 200 cm slab thickness resulting in an interpolated 5 mm section thickness. A parallel imaging technique ($R=2$) was performed using generalised autocalibrating partially parallel acquisition (GAPPA). In all patients, 0.025 mmol/kg body weight of gadoxetic acid was injected manually at approximately 1 ml/s, as recommended, by one investigator through a 20 G intravenous catheter placed in a cubical or cephalic vein. Immediately afterwards, a 20 ml saline flush was administered at the same injection rate. T1 mapping was obtained before and at 20 min after gadoxetic acid administration for HBP.

Three scan trace free-breath DWI images were obtained prior to gadoxetic acid injection using a single-shot spin-echo echo planar imaging sequence (3200 ms/56 ms TR/TE, 5.5 mm section thickness, 84×128 matrix size, 380–400×300–324 mm FOV) with b-values of 0 and 500 s/mm². A parallel imaging technique ($R=2$) was performed using GAPPA.

Imaging analysis

Quantitative T1 relaxation time maps and ADC maps were derived automatically on a voxel-by-voxel basis. The MRI data sets were transferred to a workstation (Leonardo, Siemens, Erlangen, Germany) to measure the T1 relaxation time and ADC values of the liver parenchyma using operator-defined regions of interest (ROI). The ROIs were manually drawn covering the whole right lobe of the liver on the same mid-liver section of the T1-weighted images and high b-value ($b=500$ s/mm²) DWI images (except for

any visible lesions, the border of the liver [to avoid partial volume effects], major hepatic veins, and the inferior vena cava) were then copied to corresponding T1 maps and ADC maps (Fig. 2). Two radiologists with more than 10 years of experience in abdominal MRI retrospectively analysed the images. The readers had no knowledge of the clinical results. In addition, the reduction rate of the T1 relaxation time between the unenhanced and HBP images was calculated by

$$\text{reduction rate } (\Delta\%) = 100 \times (T1_{\text{pre}} - T1_{\text{post}}) / T1_{\text{pre}}$$

where $T1_{\text{pre}}$ and $T1_{\text{post}}$ are the T1 relaxation time of the liver before and after gadoxetic acid injection.

Reference standard

All surgical specimens were evaluated by a senior hepatopathologist with 10 years of experience, blinded to the radiological diagnoses. Necro-inflammatory activity grades and fibrosis stages were determined semi-quantitatively. Criteria for the necro-inflammatory activity grades were as follows: G0, no activity; G1, slight activity; G2, mild activity; G3, moderate activity; and G4, severe activity[18]. Criteria for the fibrosis stages were as follows: S0, no fibrosis; S1, fibrous portal expansion; S2, bridging fibrosis; S3, bridging fibrosis with architectural distortion; and S4, cirrhosis[18].

Statistical analyses

Statistical analyses were performed using MedCalc (MedCalc for Windows, version 11.5.0.0, www.medcalc.be). The correlations between MRI measurements (ADC and pre-, post-, and $\Delta\%$ measurements of the T1 relaxation time) and S and G scores were assessed using Spearman's rank-correlation test. The ADC and pre-, post-, and $\Delta\%$ measurements of the T1 relaxation time, respectively, were compared between S scores (≤ 2)/G scores (≤ 2), and S scores (≥ 3)/G scores (≥ 3) using a Student's *t*-test when normally distributed or Mann–Whitney *U*-test when not normally distributed. In addition, receiver operating characteristics (ROC) analyses were constructed to determine the potential diagnostic performance for differentiating S scores (≤ 2)/G scores (≤ 2) from S scores (≥ 3)/G scores (≥ 3). Corresponding areas under the ROC curve (AUCs), sensitivities, specificities, positive likelihood ratio (+LR), and negative likelihood ratio (–LR) with 95% confidence intervals (CI) were calculated. The difference in diagnostic performance was analysed by comparing the ROC curves. Differences in AUCs were analysed by comparing the ROC curves according to the method of DeLong *et al.*[19]. Differences with $p < 0.05$ were considered statistically significant.

RESULTS

Characteristics of patients

A total of 145 patients were underwent partial hepatectomy with the following pathological results: HCC, $n=103$; intrahepatic cholangiocarcinoma, $n=8$;

haemangioma, $n=7$; cirrhosis, $n=7$; focal nodular hyperplasia, $n=5$; colorectal liver metastases, $n=6$; inflammatory nodules, $n=3$; degenerative nodule, $n=3$; angiomyolipomas, $n=2$; hepatocellular adenoma, $n=1$. Necro-inflammatory activity grade and fibrosis stage of the patients are summarised in Fig. 1. Fifty-three patients were classified as mild fibrosis stage (S score ≤ 2) and 92 patients were classified as severe fibrosis stage (S score ≥ 3). Sixty-four patients were classified as mild necro-inflammatory activity grade (G score ≤ 2) and 81 patients were classified as severe necro-inflammatory activity grade (G score ≥ 3).

MRI measurements and S/G scores

Table 1 showed the relationships between T1 relaxation time measurement or ADC value and S/G scores. Unenhanced T1 relaxation time ($\rho=0.28$, $p=0.0007$), HBP T1 relaxation time ($\rho=0.51$, $p<0.0001$), and $\Delta\%$ of T1 relaxation time ($\rho=-0.35$, $p<0.0001$) showed significant correlations with the S score. Similarly, unenhanced T1 relaxation time ($\rho=0.26$, $p=0.002$), HBP T1 relaxation time ($\rho=0.39$, $p<0.0001$), and $\Delta\%$ of T1 relaxation time ($\rho=-0.26$, $p=0.002$) showed significant correlations with the G score. Conversely, the ADC value ($\rho=-0.17$, $p=0.04$) showed significant correlation with the S score, but did not correlate significantly with the G score ($\rho=-0.07$, $p=0.39$).

The mean values for the T1 relaxation time measurements (unenhanced, HBP, and $\Delta\%$) are provided in Table 2. The T1 relaxation time decreased after administration of gadoxetic acid, from a mean of 682.2 ms to 194.9 ms and 697.3 ms to 214.6 ms,

respectively, in mild S/G scores and from a mean of 743.9 ms to 253.4 ms and 740.3 ms to 52.6 ms in severe S/G scores. Mean values of unenhanced, HBP, and $\Delta\%$ T1 relaxation times showed a significant difference between mild and severe S/G scores ($p<0.0001$ and $p=0.0006$, $p<0.0001$ and $p=0.001$, $p<0.0001$ and $p=0.01$, respectively). The ADC value was not significantly different between mild and severe G scores ($p=0.63$), but was significantly different between mild and severe S scores ($p=0.01$).

Diagnostic performance for assessment of severe S/G scores

The ROC curves performed to compare the diagnostic performance of pre-, HBP, $\Delta\%$ T1 relaxation time for assessment of severe S/G scores are shown in the Figs. 3 and 4. Corresponding sensitivities, specificities, +LR, and –LR are provided in Tables 3 and 4. AUCs of unenhanced, HBP, $\Delta\%$ T1 relaxation time, and ADC values were 0.68, 0.82, 0.71, 0.61 for identification of $S\geq 3$, and 0.63, 0.68, 0.62, 0.52 for identification of $G\geq 3$, respectively. The comparison of ROC analyses on $S\geq 3$ / $G\geq 3$ using T1 relaxation times and ADC values are shown in Table 5. HBP T1 relaxation time (AUC, 0.82 and 0.68, respectively) was better than that of ADC (AUC, 0.61 and 0.52, respectively) for identification of $S\geq 3$ ($p=0.0005$) and $G\geq 3$ ($p=0.014$).

DISCUSSION

The results of the present study revealed that HBP T1 relaxation time measurement on gadoxetic acid-enhanced MRI significantly correlated with the S/G scores ($\rho=0.51$ for S score, $\rho=0.39$ for G score, respectively) and had high accuracy for

identification of $S \geq 3$ with a AUC of 0.82, while relative low accuracy for identification of $G \geq 3$ (AUC:0.68). HBP T1 relaxation time measurement showed significantly higher accuracy than DWI-ADC measurement for liver fibrosis staging.

HBP T1 relaxation time measurement on gadoxetic acid-enhanced MRI was better than ADC for distinguishing mild S/G scores from severe S/G scores, which was in keeping with a previous study. Watanabe *et al.*[20] indicated that the contrast enhancement index with gadoxetic acid-enhanced MRI was an efficient biomarker in the staging of liver fibrosis and was more accurate than ADC values. It is clinically useful to determine the stage of fibrosis to manage patients with chronic liver disease appropriately. The risks of various complications would increase dramatically if patients reached the stage of cirrhosis. In a cohort of 188 Korean chronic hepatitis B patients followed up for nearly 10 years, the cumulative probability of developing cirrhosis for patients with Metavir stage F0 or F1 fibrosis at baseline was 0%, 11%, and 11% at 5, 10, and 15 years, respectively. The probabilities were increased significantly with baseline fibrosis at stage F3 (22%, 47%, and 65% at 5, 10, and 15 years respectively)[21]. Therefore, unenhanced, HBP and $\Delta\%T1$ relaxation times could be used to differentiate mild and severe fibrosis, which was very useful for the patients both regarding treatment and effective follow-up. During stage S0/G0 liver fibrosis to cirrhosis, the liver parenchyma is characterised by architectural disruption, aberrant hepatocyte regeneration, nodule formation, and vascular changes[22]. The signal intensity of the liver parenchyma changes during the process. The T1 relaxation time is an absolute value, which appears more reliable and less subjective than the direct

hepatic signal intensity[23]. Syngo MapIt enables fast MRI sequencing using 3D-VIBE and has high resolution[24]; therefore, it is included in routine liver MRI at the authors' institution. DWI enables the visualisation of Brownian molecular motion, which is based on the motion of water molecular in the extracellular space[25]. This motion can be quantified through the ADC of protons, which depends on the tissue structure. It is significantly influenced by technical parameters, such as the b-value, ghosting artefacts and low spatial resolution using respiratory-triggered DWI. Thus, the results of ADC are poorly reproducible and the lack of a definitive cut-off value limits its use in clinical practice. Unenhanced, $\Delta\%$ T1 relaxation times significantly correlated with the S/G scores and were significantly different between mild S/G scores and severe S/G scores. Conversely, the AUCs of unenhanced, $\Delta\%$ T1 relaxation times were relatively low for identification of $S \geq 3$ and $G \geq 3$. A previous study also indicated that unenhanced T1 relaxation times could not predict the stage of non-alcoholic fatty liver disease in an animal model[26]. According to the calculating formula, the results of $\Delta\%$ T1 relaxation time were much more affected by the results of the unenhancedT1 relaxation times than those of the HBP. Therefore, the result of the HBP T1 relaxation time was more accurate.

Another finding was that the AUCs on HBP T1 relaxation times for differentiating between S2 and S3 were better than those for differentiating between G2 and G3. The reasons for this may be as follows: (1) histological staging of fibrosis is a combinatorial assessment of the amount of fibrosis and architectural disorganisation. It is based on semi-quantitative scoring systems, including the histological activity index, the Ishak's

score, etc.[27]; however, necro-inflammation is a continuous process. It could be evaluated by portal tract inflammation, interface hepatitis, and lobular inflammation. It may be a past event that has stabilised or even regressed, or is an ongoing process that may worsen[28]. Therefore, it is difficult to divide the stage clear. (2) Gadoteric acid is a liver-specific MRI contrast agent with hepatocyte-selective properties. When the hepatocytes are dysfunctional, the dose will decrease on the HBP and the signal intensity will change. Conversely, several variables, such as a decreasing number of hepatocytes, hepatocyte necrosis, and inflammatory change would affect the signal intensity of the liver parenchyma, as well as the T1 relaxation time[29]. The T1 relaxation time is a robust parameter to distinguish the different changes occurring in the dysfunctional hepatocytes.

There were some limitations in the present study. First, the present study could not avoid sampling bias because of its retrospective nature. There were relatively small patients who were at G3/G4 and relatively large patients who were at stage of S4. Second, in the present study b-values of 0 and 500 s/mm² were used to calculate the ADC, which may have affected the accuracy of the ADC values. Some researchers recommend a b-value of 700 s/mm²[30]. In addition, another new technique called intravoxel incoherent motion MRI (IVIM) has been used, which is a measurement of numerous points of the ADC at different b-values.

In conclusion, T1 relaxation time measurement on gadoteric acid-enhanced MRI could be used to accurately evaluate liver fibrosis; thus, this measurement may be a potential biomarker in staging hepatic fibrosis. T1 relaxation time measurement was

more accurate than ADC measurement in staging fibrosis.

ACKNOWLEDGEMENTS

This project was supported by the National Science Foundation of China (Grant No. 81371543).

REFERENCES

1. Wong GL, Chan HL, Chan HY, *et al.* Accuracy of risk scores for patients with chronic hepatitis B receiving entecavir treatment. *Gastroenterology*. 2013;144:933-944.
2. Yu XY, Zhao Y, Song XX, Song ZY. Association between non-alcoholic fatty liver disease and arterial stiffness in the non-obese, non-hypertensive, and non-diabetic young and middle-aged Chinese population. *J Zhejiang Univ Sci B*. 2014;15:879-887.
3. Ikeda K, Saitoh S, Suzuki Y, *et al.* Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation of 2215 patients. *J Hepatol*. 1998;930-938.
4. Shen X, Cheng S, Peng Y, Song H, Li H. Attenuation of early liver fibrosis by herbal compound "Diwu Yanggan" through modulating the balance between epithelial-to-mesenchymal transition and mesenchymal-to-epithelial transition. *BMC Complement Altern Med*. 2014;14:418.
5. Liaw YF. Reversal of cirrhosis: an achievable goal of hepatitis B antiviral therapy. *J Hepatol*. 2013;59:880-881.

-
6. Bedossa P, Carrat F. Liver biopsy: the best, not the gold standard. *J Hepatol.* 2009;50:1-3.
 7. Castera L, Negre I, Samii K, Buffet C. Patient-administered nitrous oxide/oxygen inhalation provides safe and effective analgesia for percutaneous liver biopsy: a randomized placebo-controlled trial. *Am J Gastroenterol.* 2001;96:1553-1557.
 8. Casteral L. Invasive and non-invasive methods for the assessment of fibrosis and disease progression in chronic liver disease. *Best Pract Clin Gastroenterol.* 2011;25:291-303.
 9. Aube C. Imaging modalities for the diagnosis of hepatic fibrosis and cirrhosis. *Clin Res Hepatol Gastroenterol.* 2015;39:38-44.
 10. Dvorak K, Stritesky J, Petrtyl J, *et al.* Use of non-invasive parameters of non-alcoholic steatohepatitis and liver fibrosis in daily practice-an exploratory case-control study. *Plos One.* 2014;9:e111551.
 11. Hagiwara M, Rusinek H, Lee VS, *et al.* Advanced liver fibrosis: diagnosis with 3D whole-liver perfusion MR imaging—initial experience. *Radiology.* 2008;246:926-934.
 12. Lewis S, Dyvorne H, Cui Y, Taouli B. Diffusion-weighted imaging of the liver: techniques and applications. *Magn Reson Imaging Chli N Am.* 2014;22:373-395.
 13. Li H, Li N, Xiang Q, Zhou Y. Value of hepatic diffusion-weighted magnetic resonance imaging in evaluating liver fibrosis following transarterial chemoembolization with low doses of chemotherapy. *Exp Ther Med.* 2014;8:642-646.
 14. Tokgoz O, Unal I, Turgut GG, Yildiz S. The value of liver and spleen ADC measurements in the diagnosis and follow up of hepatic fibrosis in chronic liver

disease. *Acta Clin Belg.* 2014;69:426-32

15. Saito K, Ledsam J, Sourbron S, *et al.* Measuring hepatic functional reserve using low temporal resolution Gd-EOB-DTPA dynamic contrast-enhanced MRI: a preliminary study comparing galactosyl human serum albumin scintigraphy with indocyanine green retention. *Eur Radiol.* 2014;24:112-119.

16. Jang YJ, Cho SH, Bae JH, *et al.* Noninvasive assessment of hepatic fibrosis using gadoxetate-disodium-enhanced 3T MRI. *Ann Hepatol.* 2013;12:926-34.

17. Haimer M, Verloh N, Zeman F, *et al.* Assessment of clinical signs of liver cirrhosis using T1 mapping on Gd-EOB-DTPA-enhanced 3T MRI. *PLoS One.* 2013;8:e85658.

18. Ichida F, Tsuji T, Omata M, *et al.* New Inuyama classification: new criteria for histological assessment of chronic hepatitis. *Int Hepatol Commun.* 1996;6:112- 119.

19. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics.* 1988;44: 837-45.

20. Watanabe H, Kanematsu M, Goshima S, *et al.* Staging hepatic fibrosis: comparison of gadoxetate disodium-enhanced and diffusion-weighted MR imaging—preliminary observations. *Radiology.* 2011;259:142-150.

21. Park BK, Park YN, Ahn SH, *et al.* Long-term outcome of chronic hepatitis B based on histological grade and stage. *J Gastroenterol Hepatol.* 2007;22:383-388.

22. Friedman SL. Liver fibrosis-from bench to bedside. *J Hepatol.* 2003;38:S38-53.

23. Bae KE, Kim SY, Lee SS, *et al.* Assessment of hepatic function with Gd-EOB-DTPA-enhanced hepatic MRI. *Dig Dis.* 2012;30:617-622.

-
24. Yoshimura N, Saito K, Saguchi T, *et al.* Distinguishing hepatic hemangiomas from metastatic tumors using T1 mapping on gadoxetic-acid-enhanced MRI. *Magn Reson Imaging.* 2013;31:23-27.
 25. Tam HH, Collins DJ, Wallace T, *et al.* Segmental liver hyperintensity in malignant biliary obstruction on diffusion weighted MRI: associated MRI findings and relationship with serum alanine aminotransferase levels. *Br J Radiol.* 2012;85:22-28.
 26. Ding Y, Rao SX, Meng T, Chen C, Li R, Zeng MS. Usefulness of T1 mapping on Gd-EOB-DTPA-enhanced MRI in assessment of non-alcoholic fatty liver disease. *Eur Radiol.* 2014;24:959-966.
 27. Mannan R, Misra V, Misra SP, *et al.* A comparative evaluation of scoring systems for assessing necro-inflammatory activity and fibrosis in liver biopsies of patients with chronic viral hepatitis. *J Clin Diagn Res.* 2014;8:FC08-12.
 28. Guido M, Mangia A, Faa G, *et al.* Chronic viral hepatitis: the histology report. *Dig Liver Dis.* 2011;43(Suppl.):S331-343.
 29. Nilsson H, Blomqvist L, Douglas L, *et al.* Gd-EOB-DTPA-enhanced MRI for the assessment of liver function and volume in liver cirrhosis. *Br J Radiol.* 2013 Jun;86(1026):20120653. doi: 10.1259/bjr.20120653. Epub 2013 Feb 12.
 30. Padhani AR, Liu G, Koh DM, *et al.* Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. *Neoplasia.* 2009;11:102-125.

Figure 1 Flow diagram of the study enrolment population during the 33-month study period.

Figure 2. Examples of placement of ROIs in the same area of liver parenchyma on the HBP image (a) and the corresponding T1 map to measure the T1 relaxation time (b) and on high b-value DWI images (c) and the corresponding ADC map (d).

Figure 3. ROC and AUC values for prediction of severe S scores using T1 relaxation times and ADC values. Numbers in parentheses represent 95% confidence intervals. Pre, precontrast phase; HBP, hepatobiliary phase; $\Delta\%$, reduction rate; ADC, apparent diffusion coefficient

Figure 4 ROC and AUC values for prediction of severe G scores using T1 relaxation times and ADC values. Numbers in parentheses represent 95% confidence intervals. Pre, precontrast phase; HBP, hepatobiliary phase; $\Delta\%$, reduction rate; ADC, apparent diffusion coefficient

Table 2. Mean values and standard deviation (SD) of T1 relaxation time and ADC values of the liver parenchyma

		S scores			G scores		
		≤2	≥3	<i>p</i> -Value	≤2	≥3	<i>p</i> -Value
		(<i>n</i> =53)	(<i>n</i> =92)		(<i>n</i> =64)	(<i>n</i> =81)	
T1 relaxation time (ms)							
Precontrast		682.2	743.9	<0.0001	697.3	740.3	0.006
SD		90.9	94.6		83.2	104.2	
HBP		194.9	253.4	<0.0001	214.6	52.6	0.001
SD		32.4	55.3		245.8	54.8	
Δ%		0.71	0.66	<0.0001	0.69	0.67	0.01
SD		0.05	0.07		0.07	0.06	
ADC(×10 ⁻³ mm/s ²)		1.50	1.43	0.01	1.46	1.45	0.63
SD		0.18	0.18		0.18	0.19	

ADC, apparent diffusion coefficient; HBP, hepatobiliary phase; Δ%, reduction rate; G, necro-inflammatory activity grade; S, fibrosis stage.

Table 3. Diagnostic performance for T1 relaxation time and apparent diffusion coefficient (ADC) value in assessing fibrosis stage $S \geq 3$ by receiver operating characteristics (ROC) analyses.

	AUC	Sensitivity	Specificity	+LR	–LR	Cut-off
Pre	0.68	75.0	60.4	1.89	0.41	>679.0
95%CI	0.60-0.79	64.9-83.4	46.0-73.5	1.5-2.4	0.3-0.7	
HBP	0.82	65.2	90.6	6.91	0.38	>224.9
95%CI	0.75-0.88	54.6-74.9	79.3-96.9	5.8-8.2	0.2-0.9	
$\Delta\%$	0.71	58.7	73.6	2.22	0.56	≤ 0.676
95%CI	0.63-0.78	47.9-68.9	59.7-84.7	1.8-2.8	0.3-0.9	
ADC	0.61	30.4	90.6	3.23	0.77	$\leq 1.32 \times 10^{-3}$
95%CI	0.52-0.69	21.3-40.9	79.3-96.9	2.3-4.4	0.3-1.8	

AUC, area under the ROC curve; +LR, positive likelihood ratio; –LR, negative likelihood ratio; Pre, precontrast phase; HBP, hepatobiliary phase; $\Delta\%$, reduction rate; 95% CI, 95% confidence interval.

Table 4. Diagnostic performance for T1 relaxation time and apparent diffusion coefficient (ADC) value in assessing necro-inflammatory activity grade G $\geq$ 3 by receiver operating characteristics (ROC) analyses.

	AUC	Sensitivity	Specificity	+LR	–LR	Cut-off
Pre	0.63	38.3	90.6	4.08	0.68	>759.0
95%CI	0.54-0.71	27.7-49.7	80.7-96.5	3.1-5.4	0.3-1.5	
HBP	0.68	59.3	79.7	2.92	0.51	>227.0
95%CI	0.60-0.76	47.8-70.1	67.8-88.7	2.3-3.6	0.3-0.9	
$\Delta\%$	0.62	59.3	68.8	1.90	0.59	≤ 0.676
95%CI	0.54-0.70	47.8-70.1	55.9-79.8	1.5-2.4	0.4-0.9	
ADC	0.52	84.0	26.6	1.14	0.60	$\leq 1.60 \times 10^{-3}$
95%CI	0.44-0.61	74.1-91.2	16.3-39.1	0.8-1.7	0.4-1.0	

AUC, area under the ROC curve; +LR, positive likelihood ratio; –LR, negative likelihood ratio; Pre, precontrast phase; HBP, hepatobiliary phase; $\Delta\%$, reduction rate; 95% CI, 95% confidence interval.

Table 5. Comparison of receiver operating characteristics (ROC) analyses on necro-inflammatory activity grade/fibrosis stage $G \geq 3/S \geq 3$ using T1 relaxation time and apparent diffusion coefficient (ADC) values

		S ≥ 3 (<i>p</i> -Value)	G ≥ 3 (<i>p</i> -Value)
Compared groups			
Pre	HBP	0.0058	0.2782
versus			
Pre	$\Delta\%$	0.6783	0.9540
versus			
Pre	ADC	0.2692	0.1049
versus			
HBP	$\Delta\%$	0.0010	0.0702
versus			
HBP	ADC	0.0005	0.0139
versus			
$\Delta\%$	ADC	0.1288	0.0173
versus			
Pre, precontrast phase; HBP, hepatobiliary phase; $\Delta\%$, reduction rate.

Figure 1

Figure 2a

Figure 2b

Figure 2c

Figure 2d

Figure 3

Figure 4