

Diffusion-weighted imaging and variable flip angle T1 mapping: a supplement for image-guided biopsy in follow-up analysis of liver fibrosis

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ABSTRACT

Purpose To evaluate the performance of diffusion-weighted imaging (DWI) and variable flip angle (VFA) T1 mapping as a supplement to image-guided biopsy in follow-up analysis of liver fibrosis.

Materials and Methods This prospective study was approved by the institution's committee on human research, and written informed consent was provided from the enrolled patients. We investigated five MRI parameters of DWI and VFA T1 mapping, collected from 11 patients who underwent serial ultrasound image-guided biopsy with follow-up MRI within 1.5 years after treatment for liver fibrosis/cirrhosis. For each patient, four consecutive MRI examinations were conducted, including baseline MRI before treatment and three follow-up MRI examinations after treatment at each 0.5-year interval. ADC values at four b values and T1 relaxation times were correlated to pathology-confirmed liver fibrosis stages, which were subsequently divided into two groups, stages F2–3 and F4. The receiver operating characteristic (ROC) analysis and repeated measurement analysis of variance were used for statistical analysis.

Results Among these ADC parameters, ADC value ($b = 500 \text{ s/mm}^2$) was the most consistent in differentiating between stage F2–3 and F4 liver fibrosis. Repeated measurement analysis showed that the intra-group and inter-group differences were 0.447 and 0.024, respectively. T1 relaxation time could not consistently differentiate between the F2–3 and F4 groups; however, it was repeatable, and the intra-group and inter-group differences were 0.410 and 0.042, respectively.

Conclusion MRI-ADC value at a b value of 500 s/mm^2 can be a promising biomarker for differentiating stages F2–3 and F4 liver fibrosis. A combination of this biomarker with repeatable T1 relaxation time may function as a non-invasive tool for follow-up liver fibrosis in patients who reject repeated image-guided biopsy.

Keywords: image-guided biopsy, MRI T1 mapping; diffusion-weighted imaging

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INTRODUCTION

Liver fibrosis caused by hepatitis B virus (HBV) infection is a worldwide health problem. The World Health Organization (WHO) 2015 report showed that nearly 240 million people are chronically infected with HBV and more than 780,000 people die every year due to complications of HBV, which include cirrhosis and liver cancer. Patients with fibrosis caused by HBV are much more likely to develop hepatocellular carcinoma than those without HBV infection (1).

Liver fibrosis was once thought to be an irreversible process. However, recent studies have shown that liver fibrosis can be reversed if its causes are removed (2-6). Thus, early diagnosis and adequate treatment are essential for those patients with liver fibrosis caused by HBV. Liver biopsy is the current gold standard of diagnosing and evaluating the efficacy of therapies of liver fibrosis. However, biopsy is an invasive modality with sampling error and intra- and inter-observer interpretation error (7,8). More critically, repeated biopsies for following up treated liver fibrosis are often rejected by patients.

Several magnetic resonance imaging (MRI)-based methods can be used for the assessment of liver fibrosis, such as magnetic resonance elastography (MRE), dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), magnetic resonance spectroscopy (MRS), diffusion-weighted imaging (DWI), and T1 mapping. MRE examination requires specific instruments to generate mechanical waves and corresponding software to generate elastograms (9). DCE-MRI examination requires the administration of a contrast agent with specific kinetic mode (10). Few studies have focused on MRS in the evaluation of liver fibrosis, and those that did have demonstrated that its application value is in dispute (11,12). Among these methods, both DWI and T1 mapping are non-invasive, available in routine clinical

practice, and easily acceptable by patients. In the present study, we aimed to explore DWI and T1 mapping for long-term follow-up of liver fibrosis caused by HBV.

PATIENTS AND METHODS

Patients

Our prospective study was approved by the Institution's Committee on Human Research, and informed written consent was given by each of the enrolled patients. The inclusion criteria were: (a) ages between 18 and 65 years; (b) a history of HBV infection with biopsy-confirmed liver fibrosis or clinically confirmed cirrhosis; (c) acceptance of antiviral treatment with or without interferon therapy for 1.5 years; and (d) agreement having a repeat biopsy at the end of follow-up from those patients whose liver fibrosis were initially confirmed by biopsy. The exclusion criteria were: (a) history of hepatitis C, human immunodeficiency virus infection, or other chronic liver disease; (b) progression to decompensated liver cirrhosis; and (c) new emergence of hepatocellular carcinoma and other malignant tumor.

MRI acquisition

For each patient, four consecutive MRI examinations were conducted, namely, baseline MRI before treatment and three follow-up MRI examinations after treatment at each 0.5-year interval. The interval between biopsy and MRI examination was no more than 1 week. Ultimately, 44 MRI examinations were obtained and each MRI examination included breath-hold DWI and variable flip angle (VFA) T1 mapping. Overnight fasting was required for each patient prior to MRI examination to avoid any influence on apparent diffusion coefficient (ADC) values from a meal. All of the MRI data were acquired with a 3.0-T MRI scanner (Signa HDxt, General Electric Medical Systems, Waukesha, WI, USA).

The parameters of the breath-hold DWI sequence included b value, 200 s/mm², 500 s/mm², 700 s/mm², and 1000 s/mm²; TR, 1800 ms; TE, 56.1 msec, 56.6 msec, 60.5 msec, and 60.7 msec; field of view, 38 × 38 cm; matrix, 96 × 130; slice thickness, 7.0 mm; and slice interval, 2.0 mm.

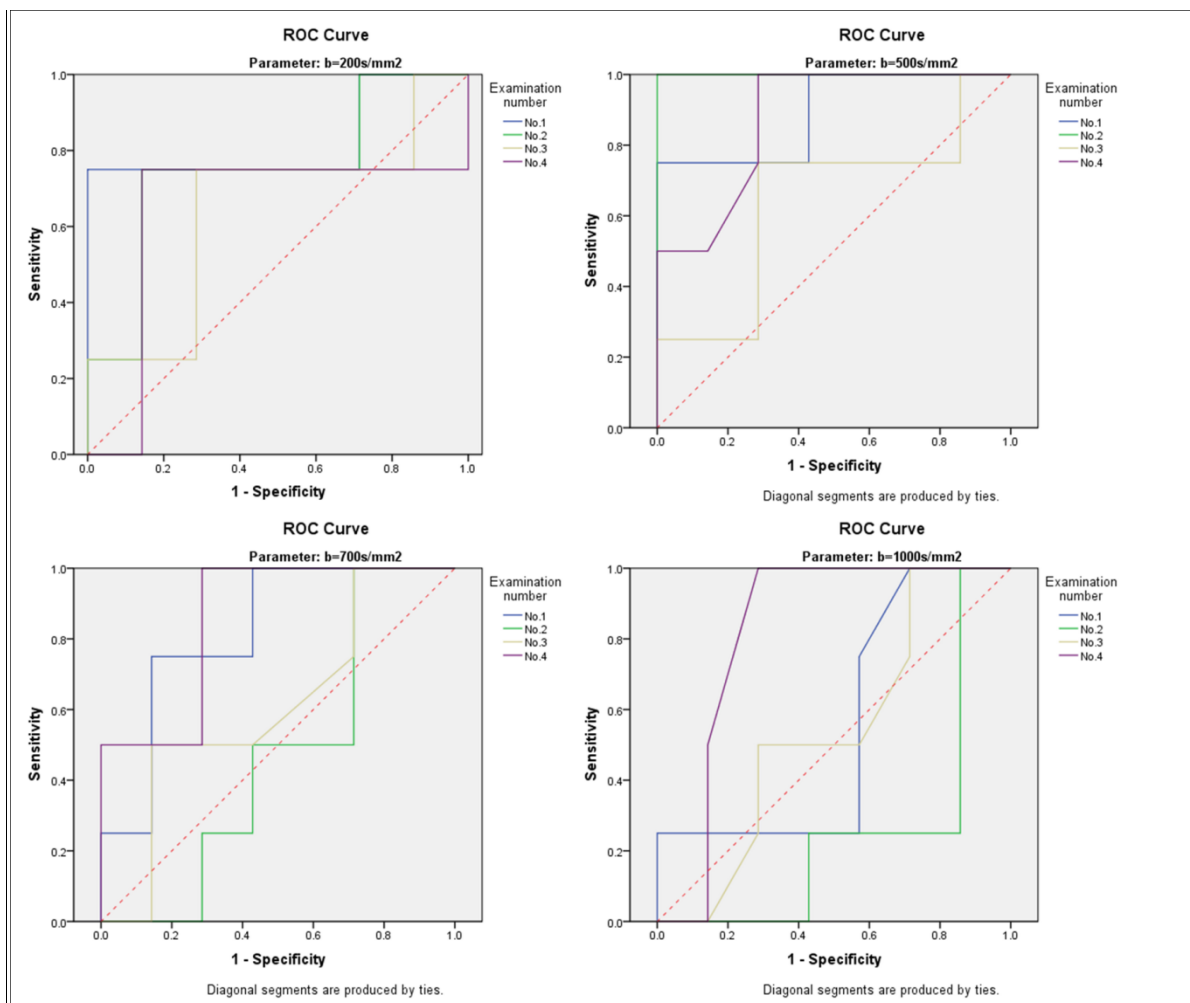


Figure 1 Area under the ROC curve (AUC) of ADC values at four time points, showing that the performance of the AUC values at a b value of 500 s/mm² was the best.

The parameters of VFA T1 mapping using a series of breath-hold liver acquisition volume acceleration (LAVA) were flip angles 3, 6, 9, 12, and 15°; TR/TE, 2.48/1.17 msec, 2.48/1.17 msec, 2.48/1.17 msec, 2.60/1.19 msec, 2.79/1.23 msec; bandwidth, 125 Hz/pixel; matrix, 256 × 192; slice thickness, 8 mm; slice interval, 0 mm; and field of view, 38 × 38 cm.

Imaging analysis

All of the DWI data were transferred to a commercially available software package (Functool 9.3.01g, GE Medical Systems) and the ADC maps were automatically generated. Nine round- or oval-shaped regions of interest (ROI) (approximately 200 mm²) were placed in different slices of the right lobe of liver with an effort to avoid artifacts, vessels and extremely areas. The final result was the average ADC value of the nine ROIs.

VFAs T1 mapping was transferred to a non-commercial software package (Omni-Kinetics, GE Healthcare) and T1 maps were automatically generated. Freehand ROIs including hepatic parenchyma and excluding areas close to the liver margins and larger vessels were placed in five consecutive slices of the middle portion of the liver. The final result was the average T1 relaxation time of the five ROIs.

Statistical analysis

All of the 44 MRI examinations were subdivided into two fibrosis stage groups: the F2–3 group and the F4 group. SPSS v.19 analysis software (IBM, USA) was used for the statistical computations. The receiver operating characteristic (ROC) analyses

were calculated to differentiate between the F2–3 and F4 groups. Repeated measures analyses of variance were calculated to test the repeatability of ADC value and T1 relaxation time. For intra-group differences, $P > 0.05$ indicated the parameter was repeatable during the follow-up; for inter-group differences, $P < 0.05$ indicated that the staging performance of the parameter was stable.

RESULTS

Patient characteristics

Eleven patients with complete follow-up data were recruited to the study, including four males and seven females, age range 38–61 years. Of the 11 patients, 6 had clinically confirmed cirrhosis (F4), while the liver biopsies of the other 5 patients showed liver fibrosis at different stages according to the METAVIR system, namely, three patients at F2, one at F3, and one at F4 (cirrhosis) stages.

DWI finding

Area under the ROC curve (AUC) of ADC values at four b values are listed in Table 1. Repeated ROC analyses at four time points were used to differentiate the F2–3 group and F4 group. ADC value ($b = 500$ s/mm²) was the most consistent in differentiating between F2–3 and F4 staged liver fibrosis. The AUC of four time points were 0.893 (95% CI: 0.675–1.000, cutoff value: 0.00118 mm²/s) for baseline, 1.000 (95% CI: 1.000–1.000, cutoff value: 0.00119 mm²/s) at 0.5 yr follow-up, 0.643 (95% CI: 0.269–1.000, cutoff value: 0.00125 mm²/s) and 1.0 yr follow-up, and 0.875 (95% CI: 0.661–1.000, cutoff value: 0.00105 mm²/s) at 1.5 yr follow-up. The second best performance was the ADC values of $b = 200$ s/mm², followed by the ADC values at b values of 700 s/mm² and 1000 s/mm² (Figure 1).

Repeated measures analyses of variance demonstrated that no significant intra-group differences of ADCs were found in F2–3 and F4 groups for parameters at b values of 500 s/mm², 700 s/mm², and 1000 s/mm² ($P > 0.05$). Significant inter-group differences between the F2–3 group and the F4 group were found only in the ADCs at a b value of 500 s/mm² ($P < 0.05$) (Table 2 and Figure 2).

Table 1 Area under the ROC curve (AUC) of ADC values at the four time points.

b value (s/mm ²)	Examination number	AUC	Cutoff value (mm ² /s)
200	1	0.821	0.001755
	2	0.750	0.001995
	3	0.643	0.001250
	4	0.643	0.001455
500	1	0.893	0.001180
	2	1.000	0.001185
	3	0.643	0.001250
	4	0.875	0.001050
700	1	0.821	0.001085
	2	0.464	0.000915
	3	0.607	0.001065
	4	0.857	0.000945
1000	1	0.554	0.000945
	2	0.250	0.000875
	3	0.536	0.000860
	4	0.821	0.000930

Table 2 Repeated measures analyses of variance of four b values.

b value (s/mm ²)	P value	
	Intra-group difference	Inter-group difference
200	0.025	0.098
500	0.447	0.024
700	0.161	0.277
1000	0.229	0.581

Table 3 Area under the ROC curve (AUC) of T1 relaxation times.

Parameter	Examination number	AUC	Cutoff value (msec)
T1 relaxation time	1	0.071	589
	2	0.179	525
	3	0.071	608
	4	0.250	476

T1 mapping finding

Repeated ROC analyses at the four time points showed that the AUC of four time points was 0.071 (95% CI: 0.000–0.232, cutoff value: 589 msec) at baseline, 0.179 (95% CI: 0.000–0.501, cutoff value: 525 msec) at 0.5 yr follow-up, 0.071 (95% CI: 0.000–0.236, cutoff value: 608 msec) at 1.0 yr follow-up, and 0.250 (95% CI: 0.000–0.563, cutoff value: 476 msec) at 1.5 yr follow-up (Table 3 and Figure 3).

Repeated measures analyses of variance demonstrated that no significant intra-group differences of T1 relaxation times were found in the F2–3 and F4 groups ($P > 0.05$); and the significant inter-group difference between F2–3 and F4 groups was observed in T1 relaxation times as well ($P < 0.05$) (Table 4 and Figure 4).

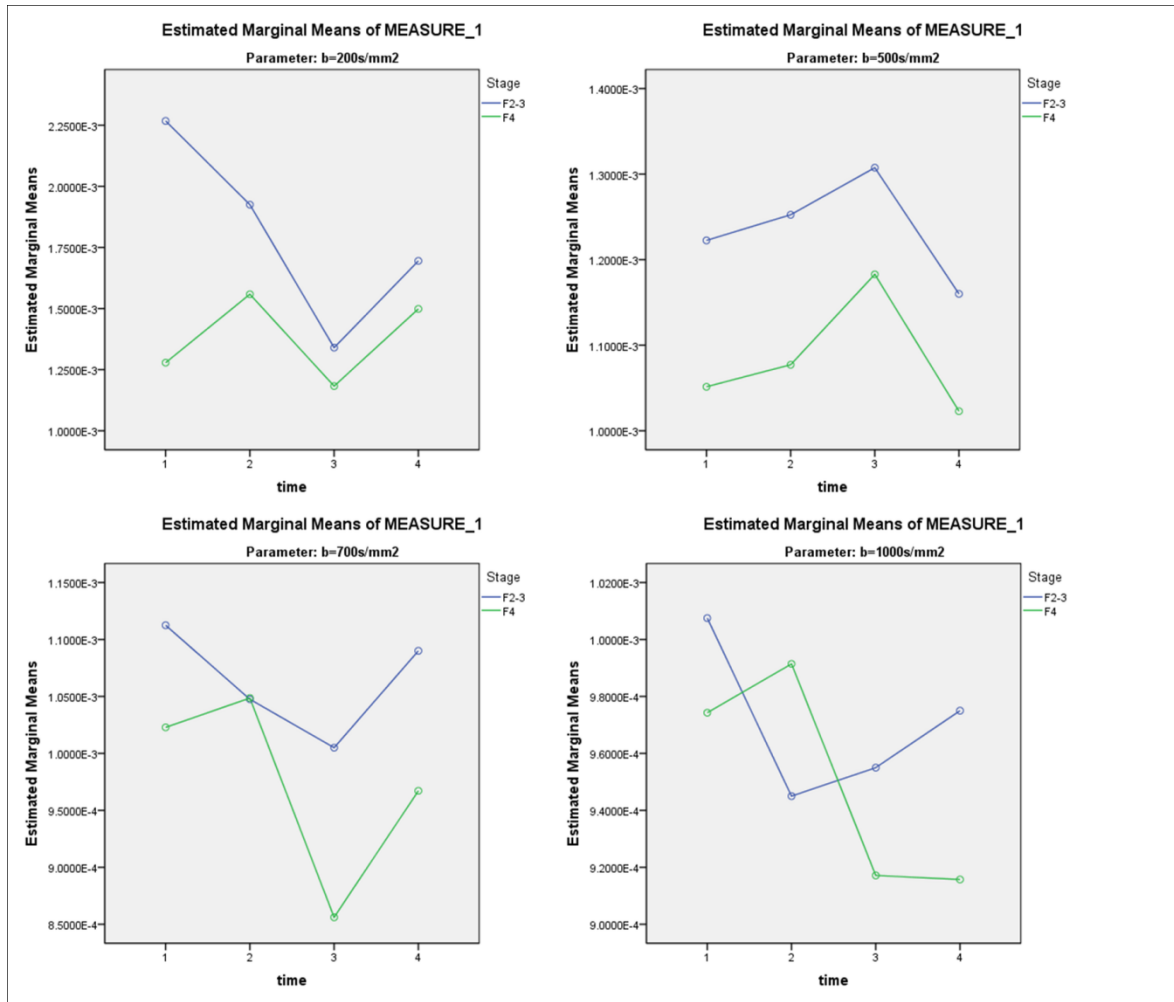


Figure 2 Estimated marginal means of four b values in differentiation of the F2–3 group and F4 group, showing that only the AUC values at a b value of 500 s/mm² were repeatable.

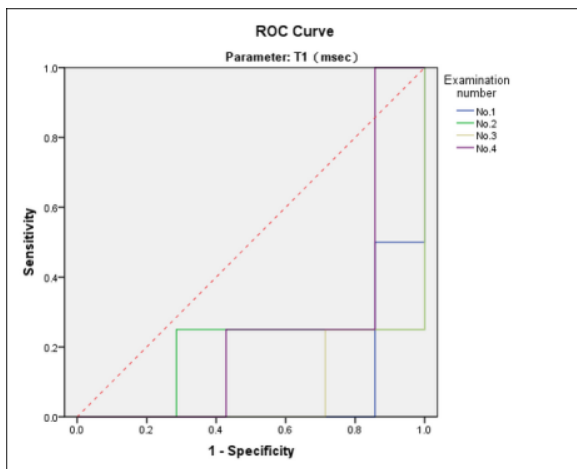


Figure 3 Area under the ROC curve (AUC) of T1 relaxation times, showing that the T1 relaxation times could not be used in differentiating between the F2–3 group and F4 group.

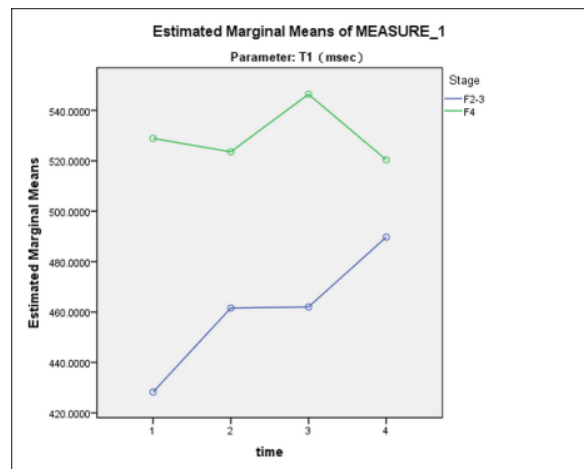


Figure 4 Estimated marginal means of T1 relaxation times in differentiating between the F2–3 group and F4 group, showing that the T1 relaxation times were repeatable during follow-up.

Table 4 Repeated measures analyses of variance of T1 relaxation times.

Parameter	P value	
	Intra-group difference	Inter-group difference
T1 relaxation time	0.410	0.042

DISCUSSION

Approximately 80% of hepatocellular carcinoma (HCC) occurs due to cirrhosis and 50% of HCC cases are caused by HBV infection throughout the world (13-15). In the present study, DWI and T1 mapping were demonstrated to be promising modalities in follow-up of liver fibrosis caused by HBV infection and correlated with ultrasound-guided biopsy.

Performance of DWI

With the progression of liver fibrosis, increased collagen fiber, glycosaminoglycans, and proteoglycans deposit in the extravascular extracellular space, which greatly restricts the diffusion motion of water molecules in the liver. All of these changes can be reflected by the decrease of ADC values (16-19).

Previous studies have shown that DWI can be used in staging liver fibrosis. Kocakoc et al. found that ADC values could be used to detect liver fibrosis, especially in identifying significant liver fibrosis when the b value of 1000 s/mm² was used (20). The results of Hu et al. demonstrated that ADC values of rats correlated with liver fibrosis when the b value of 800 s/mm² was used (21). In the current study, we found that the ADC value at a b value of 500 s/mm² was useful not only in differentiation between the F2-3 group and the F4 group, but also in follow-up of liver fibrosis.

However, the repeated measures analyses of variance showed that the ADC values at a b value of 200 s/mm² were not repeatable and stable in differentiating between the F2-3 group and F4 group. This perhaps was due to the fact that the ADC values at a low b value are influenced by microcirculation (22).

The performances of ADC values at b values of 700 s/mm² and 1000 s/mm² were not as good as expected. These values could not differentiate between the F2-3 group and F4 group and were not repeatable during the follow-up as well. The possible reasons for this include: (a) ADC values of liver are

easily affected by several factors and the reported inter-scanner and intra-scanner variability were approximately 5-15% (23-25); and b) the image quality of breath-hold DWI sequences are sensitive to magnetic susceptibility artifacts caused by tissue/air interface when higher b values are used (26,27).

Performance of T1 mapping

T1 relaxation time is a tissue-specific parameter, presented as the changes of tissue signal intensity. To date, measurement of T1 relaxation time has been used in different conditions including liver fibrosis (28-33). Heya et al. found that the T1 relaxation time of cirrhotic liver was significantly higher than healthy livers (34). Li et al. demonstrated that VFA T1 mapping could be used in the diagnosis of liver fibrosis of rabbit model, as the T1 relaxation time increased with the progression of liver fibrosis (33).

In the present study, the T1 relaxation times of the F4 group were higher than the F2-3 group. However, the AUCs of the four time points were not consistent between the two groups, thus T1 relaxation time could not be used to differentiate between the F2-3 group and F4 group. Nonetheless, repeated measures analyses of variance showed that T1 relaxation times were repeatable during the follow-up of liver fibrosis, and thus the T1 relaxation time still can be used as a biomarker in follow-up if baseline data are acquired.

CONCLUSION

In conclusion, DWI and VFA T1 mapping are both non-invasive and convenient MRI-based techniques, and they can be used in follow-up of liver fibrosis of patients who reject invasive repeated image-guided biopsy.

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