Original Article

J Korean Soc Radiol 2020;81(2):365-378 https://doi.org/10.3348/jksr.2020.81.2.365 pISSN 1738-2637 / eISSN 2288-2928

# Quantitative Evaluation of Liver Fibrosis on T1 Relaxometry in Comparison with Fibroscan

Fibroscan과 비교를 통한 T1 MR Relaxometry를 이용한 간섬유화의 정량적 평가

### Byeong Hak Sim, MD<sup>1</sup> <sup>(D)</sup>, Suk Hee Heo, MD<sup>2</sup> <sup>(D)</sup>, Sang Soo Shin, MD<sup>1</sup> <sup>(D)</sup>, Seong Beom Cho, MD<sup>3</sup> <sup>(D)</sup>, Yong Yeon Jeong, MD<sup>2\*</sup> <sup>(D)</sup>

<sup>1</sup>Department of Radiology, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Korea Departments of <sup>2</sup>Radiology, <sup>3</sup>Gastroenterology, Chonnam National University Hwasun Hospital, Chonnam National University Medical School, Hwasun, Korea

**Purpose** This study was performed to determine whether the T1 relaxation time of gadoxetic acid-enhanced liver MR imaging is useful for detecting and staging liver fibrosis in patients with chronic liver disease.

**Materials and Methods** One hundred and three patients with suspected focal liver lesion underwent MR imaging and Fibroscan. Fibroscan was chosen as the reference standard for classifying liver fibrosis. T1 relaxation times were acquired before (preT1), 20 minutes after (postT1) contrast administration, and reduction rate of T1 relaxation time (rrT1) on transverse 3D VIBE (volumetric interpolated breath-hold examination) sequence using 3T MR imaging. The optimal cut-off values for the fibrosis staging were determined with ROC analysis.

**Results** PreT1 and postT1 increased and rrT1 decreased constantly with increasing severity of liver fibrosis according to the METAVIR score (F0–F4). There were statistically significant differences between F2 and F3 in preT1 (F2, 836.0  $\pm$  74.7 ms; F3, 888.6  $\pm$  77.5 ms, *p* < 0.05) and between F3 and F4 in postT1 (F3, 309.0  $\pm$  80.2 ms; F4, 406.6  $\pm$  147.7 ms, *p* < 0.05) and rrT1 (F3, 65.4  $\pm$  7.7%; F4, 57.3  $\pm$  11.4%, *p* < 0.05). ROC analysis revealed that combination test (preT1 + postT1) was the best test for predicting liver fibrosis.

**Conclusion** PreT1 and postT1 increased constantly with increasing severity of liver fibrosis. T1 mapping in gadoxetic acid-enhanced liver MR imaging could be a helpful complementary sequence to determine the liver fibrosis stage.

Index terms Liver; Liver Cirrhosis; Magnetic Resonance Imaging; Gadolinium DTPA; Humans

## 대한영상의학회지

Received January 21, 2019 Revised May 21, 2019 Accepted August 24, 2019

#### \*Corresponding author

Yong Yeon Jeong , MD Department of Radiology, Chonnam National University Hwasun Hospital, Chonnam National University Medical School, 42 Jebong-ro, Dong-gu, Gwangju 61469, Korea.

Tel 82-61-379-7102 Fax 82-61-379-7133 E-mail yjeong@jnu.ac.kr

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/ licenses/by-nc/4.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

#### ORCID iDs

Byeong Hak Sim D https:// orcid.org/0000-0003-4779-7355 Suk Hee Heo D https:// orcid.org/0000-0003-2175-4293 Sang Soo Shin D https:// orcid.org/0000-0002-5752-7431 Seong Beom Cho D https:// orcid.org/0000-0002-5734-1645 Yong Yeon Jeong D https:// orcid.org/0000-0001-6096-3130



#### INTRODUCTION

Liver cirrhosis occurs as a result of histologic transformation by repeated liver injury, which is caused by hepatitis B or C virus, alcohol abuse, or nonalcoholic steatohepatitis. Liver cirrhosis, which is the final stage of chronic liver disease, is associated with hepatocellular carcinoma, portal hypertension, and liver dysfunction, which is a substantial cause of mortality and morbidity (1, 2). If liver fibrosis is detected early and treatment is initiated, such complications can be prevented; thus, it is important to determine the stage of liver fibrosis accurately (3).

Liver biopsy is the gold standard for diagnosing and staging liver fibrosis. It is useful for staging and monitoring disease progression by sequential histological grading of liver fibrosis (4). However, liver biopsy is an invasive and painful procedure that can rarely cause life-threatening complications, including hemorrhage or infection. Furthermore, the accuracy of liver biopsy is limited owing to sampling errors (up to 30%) and inter-observer variability (5, 6).

Many non-invasive tests such as measurement of serum markers [e.g. aspartate aminotransferase-to-platelet ratio index (APRI), FibroTest, FibroMeter], ultrasound elastography, and MR elastography (MRE) have been developed to evaluate liver fibrosis (7). One of the most widely used non-invasive tests for evaluating liver fibrosis is Fibroscan (US transient elastography), which is known to be reliable as a quantitative test (8-10). However, the Fibroscan technique is difficult to use for individuals with narrow intercostal space, obesity, and ascites (11, 12).

Gadoxetic acid is a hepatocyte-specific contrast agent that has a T1 shortening effect on MR imaging. Hepatocytes show uptake of gadoxetic acid through organic anion-transporting polypeptides (OATPs) and then excrete gadoxetic acid into the bile through multi-drug-resistant proteins (MRPs). As liver fibrosis progresses, the expression of OATPs decreases and that of MRPs increases, resulting in decreased uptake of gadoxetic acid (13-15). Attempts have been made to assess liver function and to diagnose liver fibrosis using the T1 shortening effect of gadoxetic acid (16-18). Also, as liver fibrosis progression, extracellular matrix proteins accumulate excessively in liver, leading to T1 relaxation time changes.

T1 mapping is a non-invasive, quantitative method for determining T1 relaxation time of targeted tissue. T1 relaxation time in liver MR imaging has received increasing attention as a method for quantitative evaluation of liver fibrosis, which is independent of many technical parameters (19-22). The purpose of this study was to determine whether the T1 relaxation time of gadoxetic acid-enhanced liver MR imaging is useful for detecting and staging liver fibrosis in patients with chronic liver disease.

#### MATERIALS AND METHODS

#### PATIENTS

This study was approved by the local Institutional Review Board of the Chonnam National University Hwasun Hospital, and this retrospective study was performed according to the relevant guidelines and regulations (IRB No. CNUHH-2019-230). From November 2016 to December 2017, a total of 154 patients underwent both gadoxetic acid-enhanced liver 3 Tesla (3T) MR imaging (Magnetom Skyra, Siemens Healthcare, Erlangen, Germany) and FibroScan 502<sup>®</sup> (Echosens, Paris, France) for the evaluation or detection of a focal liver lesion. Of the 154 pa-

tients, 51 patients were excluded for the following reasons: presence of multiple or infiltrative hepatocellular carcinoma (HCC) with limited parenchymal evaluation (n = 15), presence of acute parenchymal liver disease (n = 8), and history of treatment with radiofrequency ablation or transarterial chemoembolization for HCC (n = 28). Finally, 103 patients were included in the study population (Fig. 1). A detailed description of patient characteristics is given in Table 1.

#### CLASSIFICATION OF THE LIVER FIBROSIS STAGE USING FIBROSCAN

The setup of this study was designed similar Bensamoun et al. (23) study, which compared liver stiffness (LS) with values measured by two imaging techniques (Fibroscan and MRE). Bensamoun et al. (23) study used the Fibroscan exam as the reference technique to classify the level of liver fibrosis.

LS measurement was performed on the right lobe of the liver through the intercostal spaces in patients lying in the dorsal decubitus position with the right arm in maximal abduction. Fibroscan was performed within one week before and after liver MRI. LS values were measured by a single experienced technician, who was blinded to patient information, using a transient elastography device (FibroScan 502<sup>®</sup>). The results were expressed as kilopascals (kPa). The interquartile range (IQR) was defined as the index of intrinsic variability of LS values corresponding to the interval of LS results containing 50% of the valid measurements between the 25th and 75th percentiles. In the present study, LS values with  $\geq 10$  validated measurements and an

Fig. 1. Flow chart of selection of the research population.

HCC = hepatocellular carcinoma, RFA = radiofrequency ablation, TACE = transarterial chemoembolization



Patients who met the criteria (n = 103) were classified as follows according to liver Fibroscan (METAVIR score) F0-1 (n = 24); F2 (n = 27); F3 (n = 17); F4 (n = 35)

 Table 1. Demographic Characteristics of 103 Patients, Who Underwent both Gadoxetic Acid-Enhanced Liver

 MRI and Fibroscan, According to Their METAVIR Score

	Total ( <i>n</i> = 103)	F0-1 ( <i>n</i> = 24)	F2 ( <i>n</i> = 27)	F3 ( <i>n</i> = 17)	F4 (n = 35)
Sex (M/F)	86/17	19/5	22/5	15/2	30/5
Age (years)	$58.7\pm11.2$	$60.2\pm11.1$	$60.2\pm9.8$	$62.0\pm13.6$	$54.9 \pm 0.5$
AST	$45.0\pm31.0$	$30.0\pm7.8$	$38.8\pm19.8$	$59.5 \pm 25.6$	$66.8\pm38.8$
PLT	$159.1\pm70.5$	$191.6\pm56.1$	$161.2 \pm 66.3$	$161.41\pm92.0$	$133.9 \pm 63.6$

Underlying factors. Hepatitis B: 65 (63.1%), Hepatitis C: 12 (11.7%). Coinfection of hepatitis B and C: 1 (1%), Chronic alcoholism: 16 (15.5%). Others (arteriovenous shunt, adenoma, hemangioma): 9 (8.7%). Hepatocellular carcinoma: 56 (54.4%).

AST = aspartate aminotransferase, PLT = platelet



IQR-to-median-value ratio (IQR/M) of < 0.3 were considered reliable.

In a way to avoid invasive procedures, Fibroscan was used as the reference standard for evaluating the degree of liver fibrosis based on METAVIR score (8-10, 23). Foucher et al. (24) had set up all of staging of liver fibrosis regardless of etiology for a positive predictive value of at least 90%. The degree of liver fibrosis was classified according to the METAVIR score as follows: F0–1, no to mild liver fibrosis; F2, moderate liver fibrosis; F3, severe liver fibrosis; and F4, liver cirrhosis (25).

#### **MR IMAGING**

MR imaging was performed with a clinical 3T imaging system (3T Magnetom Skyra, Seimens Healthinner, Erlangran, Germany) and a combination of body and spine array coil elements (18-channel body matrix coil and 32-channel spine matrix coil) for signal reception. The fat suppressed T1-weighted volume interpolated breath hold examination (VIBE) sequence was performed for obtaining images of the whole liver before gadoxetic acid administration. The VIBE sequence was repeated in 20 min hepatobiliary phase after gadoxetic acid administration. T1 map of the liver was obtained before and 20 min after gadoxetic acid administration (Primovist, Bayer Healthcare, Berlin, Germany) using modified 3 dimensional spoiled gradient echo sequence using flip angle (8°), with the routine imaging protocol. For the T1 map, the VIBE sequence is as follows: repetition time/echo time = 3/1.32 ms, voxel size =  $2.0 \times 2.0 \times 3.0$  mm, field-of-view =  $380 \times 320$  mm, slice thickness = 5 mm, number of excitation = 1, section number = 3, breath hold time = 14 sec. CAIPIRINHA was used as parallel imaging technique for higher acceleration. Gadoxetic acid (0.025 mmoL/kg body weight) was administered via bolus injection (flow rate: 1 mL/s, flushed with 20 mL normal saline).

#### ASPARTATE AMINOTRANSFERASE TO PLATELET RATIO INDEX (APRI)

Laboratory data including alanine aminotransferase and aspartate aminotransferase (AST) levels for all patients were collected. APRI was calculated as follows: APRI = (AST/upper limit of normal)/platelet  $\times$  100. APRI values were compared between each group classified according to the METAVIR score on Fibroscan.

#### **IMAGE ANALYSIS**

One radiologist, who was blinded to patient information, drew regions of interest along the edge of the liver on each section of the T1 maps before and after the administration of gadoxetic acid with the tool for calculating T1 relaxation time. During this process, major hepatic vessels, focal liver lesions, and imaging artifacts were avoided. The mean T1 relaxation time was calculated automatically and considered to represent the T1 value of the whole liver. The preT1 and postT1 relaxation times are the T1 values before and 20 min after the administration of gadoxetic acid. The preT1 and postT1 relaxation times comprised a total of 28 seconds, 14 seconds per sequence. The reduction rate of the T1 relaxation time (rrT1) between pre and postT1 relaxation time was calculated as follows:  $rrT1 = [(preT1-postT1)/preT1] \times 100$  (%).

#### STATISTICAL ANALYSIS

All statistical analyses were performed using IBM SPSS Statistics (version 23, IBM Corp.,

METAVIR Score	F0-1 (n = 24)	F2 (n = 27)	F3 (n = 17)	F4 (n = 35)	<i>p</i> -Value			
					F0-1 vs. F2	F2 vs. F3	F3 vs. F4	F0-1 vs. F4
Fibroscan (kPa)	$5.38\pm0.89$	$9.94 \pm 1.52$	$14.91\pm1.47$	$29.45 \pm 14.79$	< 0.001	< 0.001	< 0.001	< 0.001
PreT1 (ms)	$809.1\pm85.6$	$836.0 \pm 74.7$	$888.6 \pm 77.5$	$941.6 \pm 104.2$	0.326	0.007*	0.084	< 0.001
PostT1 (ms)	$272.5\pm60.9$	$296.0\pm61.5$	$309.0\pm80.2$	$406.6 \pm 147.7$	0.160	0.555	0.004*	< 0.001
rrT1 (%)	$66.2 \pm 6.9$	$64.6 \pm 6.9$	$64.4 \pm 7.7$	$57.3 \pm 11.4$	0.462	0.727	0.007*	< 0.001
APRI	$0.44\pm0.18$	$0.72\pm0.42$	$1.21\pm0.84$	$1.56\pm1.16$	0.01*	0.048*	0.238	< 0.001

#### Table 2. Fibroscan, Pre- and Post-Contrast T1 Relaxation Times, rrT1, and APRI According to the METAVIR Score

\**p* values are significant when < 0.05.

APRI = aspartate aminotransferase to platelet ratio index, rrT1 = the reduction rate of the T1 relaxation time

Table 3. Comparison of the Mean Values Measured with Pre- and Post-Contrast T1 Mapping and rrT1 on Fibroscan

Parameter	Spearman Coefficient	<i>p</i> -Value	
Fibroscan			
PreT1	0.392	< 0.001	
PostT1	0.367	< 0.001	
rrT1	-0.244	< 0.001	

rrT1 = the reduction rate of the T1 relaxation time

Armonk, NY, USA). The data are presented as mean  $\pm$  standard deviation (SD). For comparisons between the groups, Mann-Whitney non parametric test for independent variables and Wilcoxon signed rank test for dependent variables were used. PreT1, postT1, and rrT1 were included in the binary logistic regression analysis, for calculating predictive probability as an independent variable of the combination test. The correlations between the T1 relaxation time (PreT1, postT1, and rrT1) and Fibroscan were assessed using Spearman's test. Receiver operating characteristic (ROC) curve analyses were used to compare the diagnostic performance of each diagnostic test, and the optimal cut-off value was estimated according to the Youden index. The estimates for the area under the curve (AUC) and true classification rates were reported. All statistical tests were two-sided, and *p* values < 0.05 indicated statistical significance.

#### RESULTS

#### COMPARISON OF T1 RELAXATION TIME AND DEGREE OF LIVER FIBROSIS

The distribution of patients was classified on the basis of Fibroscan results: F0–1 (n = 24), F2 (n = 27), F3 (n = 17), and F4 (n = 35). Table 2 shows an increasing trend in the value of preT1, postT1, and APRI with increase in the liver fibrosis stage. The preT1, postT1 and the liver fibrosis stage measured using Fibroscan were positively correlated with moderate relationship (Table 3). Also rrT1 was negatively correlated with liver fibrosis stage measured using Fibroscan with relatively weak relationship.

In the determination of the degree of liver fibrosis, there was a statistically significant difference between F2 (preT1, 836.0  $\pm$  74.7 ms) and F3 (preT1, 888.6  $\pm$  77.5 ms) in the value of preT1 (p < 0.01). However, there was no significant difference between the other groups in terms of pre T1 (F0–1 to F2, p = 0.326; F3 to F4, p = 0.084) (Fig. 2).



Further, there was a significant difference between F3 (postT1, 309.0  $\pm$  80.0 ms) and F4 (postT1, 406.6  $\pm$  147.7 ms) in the value of postT1 (p < 0.01). However, there was no significant difference between the other groups in terms of postT1 (F0–1 to F2, p = 0.16; F2 to F3, p = 0.55) (Fig. 3).

The mean value of rrT1 in the determination of liver fibrosis stage was similar to postT1. There was a significant difference between F3 (rrT1, 64.4  $\pm$  7.7%) and F4 (rrT1, 57.3  $\pm$  11.4%) (p < 0.01). However, rrT1 did not show a statistically significant difference between the other groups (F0–1 to F2, p = 0.46; F2 to F3, p = 0.72) (Fig. 4).

#### ROC ANALYSIS FOR DETERMINATION OF THE DEGREE OF LIVER FIBROSIS

The ROC curves of the preT1, postT1, rrT1 and combination test (preT1 + postT1) for the diagnosis of the liver fibrosis stages are shown in Figs. 5 and 6. Corresponding cut-off, sensitivities and specificities are shown in Table 4. The AUC of combination test was greater than those of others. The best test for the diagnosis of  $F \ge 2$  was combination test (0.77), followed by preT1 (0.76), and postT1 (0.71), although the rrT1 was not statistically significant with respect





\*p-values < 0.05 are significant.





\*p-values < 0.05 are significant.

to the diagnosis of  $F \ge 2$ . The best test for the diagnosis of  $F \ge 3$  was combination test (0.79), followed by preT1 (0.78), postT1 (0.72) and rrT1 (0.64). The best test for the diagnosis of F4 was combination test (0.81), followed by postT1 (0.78), preT1 (0.77), and rrT1 (0.73).

#### DISCUSSION

An increase in the ratio of free to bound water and augmented hepatic water content occurs in the early stage of hepatic fibrosis and in the process of tissue remodeling in liver fibrogenesis. This phenomenon causes increased T1 relaxation time in the early stages of liver cirrhosis (26). However, in the advanced stage of liver cirrhosis, deposition of paramagnetic macromolecules such as copper, manganese, and collagen increases and total water content decreases; this results in a decreased T1 relaxation time in advanced liver cirrhosis (27-29). Because of these differences, several studies failed to identify any statistically significant relationship between the liver fibrosis stage and preT1 relaxation time (17, 30, 31). However, the present study showed that preT1 increases gradually with progressive liver fibrosis, although there was only statistically significant differences between F2 and F3. Also ROC analysis showed that preT1 was greater than postT1 and rrT1 for predicting fibrosis F  $\geq$  2 and F  $\geq$  3.

Gadoxetic acid is a contrast medium with T1-shortening effects (30). The generated T1 maps indicated the absolute values of T1 relaxation times, which did not vary considerably at various points of measurement and thus led to low values of SD. In the present study, F0–1 had the lowest values of T1 relaxation times after administration of gadoxetic acid compared with higher stages of hepatic fibrosis. These values showed a constant significant increase of postT1 relaxation times from patients with normal liver up to patients with liver cirrhosis. The present study showed that the mean value of postT1 increased gradually with progressive hepatic fibrosis score in all groups, although there was only statistically significant differences between F3 and F4.

As liver fibrosis progresses, the expression of OATPs decreases and that of MRPs increases in hepatocytes, resulting in decreased deposition of gadoxetic acid on hepatobiliary phase (15). Using this characteristic, several studies have been performed to evaluate global liver

Fig. 4. Boxplots of the rrT1 based on the METAVIR score on Fibroscan. rrT1 indicates rrT1 from pre- to post-contrast T1. Data are expressed as mean rrT1  $\pm$  standard deviation. \**p*-values < 0.05 are significant. rrT1 = the reduction rate of the T1 relaxation time



#### Quantitative Evaluation of Liver Fibrosis by T1 Relaxometry Compared with Fibroscan



function and to assess liver cirrhosis using postT1 relaxation time. Several studies have reported the relationship between signal intensities following the injection of gadoxetic acid and several liver function scores such as MELD or Child-Pugh score (31, 32). Previous studies suggest that postT1 may present a useful method to evaluate global liver function or liver cirrhosis (17-19). Another study had examined the relationship between postT1 relaxation time and histologically proven stages of liver fibrosis (18, 33). All previous studies except Pan et al. (33),

Fig. 5. ROC curves showing diagnostic performances for liver fibrosis staging of pre- and post-contrast T1 and the combination test (pre-contrast T1 + post-contrast T1).

A-C. ROC curves with a threshold of F2 (A), F3 (B), and F4 (C) are shown. ROC = receiver operating characteristic



it was observed that hepatic parenchymal enhancement is lower in patients with liver fibrosis than in normal people with statistical differences. The present study showed that there was a significant difference between F3 and F4 (p < 0.01) in postT1, although postT1 did not differ significantly between the other groups. ROC analysis showed that postT1 was greater than preT1 and rrT1 for predicting fibrosis F4.

대한영상의학회지

Fig. 6. ROC curves showing diagnostic performances for liver fibrosis staging of the reduction rate of T1.

A. ROC curve with a threshold of F2 is shown ( $\geq$  F2, p = 0.06).

**B.** ROC curve with a threshold of F3 is shown ( $\geq$  F3; cut-off: 66.3%, AUC: 0.64, p = 0.013).

C. ROC curve with a threshold of F4 is shown (F4; cut-off: 59.9%, AUC: 0.73, p < 0.001).

AUC = area under the curve, CI = confidence interval, ROC = receiver operating characteristic





METAVIR Score	Cut-Off	Sensitivity (%)	Specificity (%)	AUC
PreT1 (ms)				
$\geq$ F2	832.2	78.2	64.0	0.76
$\geq$ F3	859.7	78.2	70.2	0.78
= F4	867.4	76.9	64.4	0.77
PostT1 (ms)				
$\geq$ F2	271.0	78.2	56.0	0.71
$\geq$ F3	290.0	76.4	57.9	0.72
= F4	298.3	79.5	60.3	0.78
Combination test (pr	eT1 + postT1)			
$\geq$ F2	0.698	78.2	64.0	0.77
$\geq$ F3	0.453	78.2	68.4	0.79
= F4	0.420	66.7	79.5	0.81
rrT1 (%)				
$\geq$ F2	-	-	-	-
$\geq$ F3	66.3	60.0	63.0	0.64
= F4	59.9	60.3	74.2	0.73

Table 4. Cut-Off Values of Pre- and Post-Contrast T1 and Reduction Rate of T1 in Liver Fibrosis Staging

The data were considered significant when p values were < 0.05. The p values of all data in the above table were less than 0.05, except for diagnosis of F  $\ge$  2 in rrT1.

AUC = area under the curve, rrT1 = the reduction rate of the T1 relaxation time

The present study showed that rrT1 gradually decreased with progression of liver fibrosis with statistically significant differences between F3 and F4. However, unlike the previous report, this study did not show significant differences between F0–1 and F2 and between F2 and F3 in rrT1 (17). ROC analysis of rrT1 in the present study revealed sensitivities  $\geq$  59.9% and sensitivity of  $\geq$  60% for the differentiation of fibrosis stages, except for differentiating between F0–1 and F2–F4, for which a relatively weak relationship was observed compared with previous studies (18).

Present study showed that the best tests for the diagnosis of  $F \ge 2$  and  $F \ge 3$  were the combination test similar to the preT1. And also the best test for the diagnosis of F4 was the combination test similar to postT1. However present study showed relatively weak relationship for differences between groups compared previous studies in ROC analysis, although T1 maps showed a clear association with liver fibrosis (18, 31, 32). Recently Pan et al. (33) reported that postT1 decreased with progression of liver fibrosis contrary to previous studies, but out study show the same results as previous studies. Haimerl et al. (18) had examined the relationship between T1 relaxation time and histologically proven stages of liver fibrosis in 65 patients. Haimerl et al. (18) did not show a significant difference between adjacent groups in preT1, and between F1 and F2, F3 and F4 in postT1.

Several MRI-based techniques have been developed for quantitative assessment of liver fibrosis. These techniques include MRE, diffusion-weighted imaging, texture analysis, perfusion imaging, hepatocellular function imaging, strain imaging, and T1 relaxation time (34-37). Of the many suggested techniques, MRE is the most standardized and has been most widely adopted in clinical practice (38). MRE of the liver is subject to artifacts caused by inadequate

breath hold and needs additional hardware. Signal may be poor in moderate to severe iron overload, leading to failed liver MREs. In contrast, T1 relaxation map does not require hardware to be added to the MR system and has been used on most scanners as a research tool. Further, unlike MRE, it is less affected by biological confounders such as postprandial state, steatosis, or iron load (39).

Patients with liver fibrosis have an increased risk of hepatocellular carcinoma or cholangiocarcinoma, as well as reduced liver function. Many institutes have been using liver MR imaging as an initial screening or monitoring test for early detection of cancer in patients with chronic liver disease. T1 relaxation time can be measured by adding one sequence to the existing liver MR imaging without additional equipment or requirement of a technician. It took only 28 seconds to obtain preT1 and postT1 in present study.

The present study had several limitations. First, the present study included patients with liver fibrosis due to various etiologies, such as hepatitis B and C virus, alcohol, and nonalcoholic steatohepatitis. In particular, the patient group in the present study differed from that in the previous study because a significant number of patients in this study had underlying HCC and hepatitis B. Further studies should be performed in a homogenous patient population because the etiology of liver fibrosis influences parenchymal changes, which influences T1 relaxation time. Second, the present study used Fibroscan instead of liver biopsy as a reference standard. Although Fibroscan is known to be reliable for evaluating hepatic fibrosis, the cut-off value of Fibroscan can be affected by the etiology of liver fibrosis. To minimize this influence, this study used a cut-off value of liver fibrosis that was set in patients with liver fibrosis due to various etiologies (24). Also, because the biopsy was not performed, inflammatory activity of the liver was not reflected. Finally, the present study was a single-center study that may have limited patient population.

The present study showed that pre and postT1 relaxation times showed a constant increase with increase in the severity of liver fibrosis. rrT1 showed a constant decrease with increase in the severity of liver fibrosis. In conclusion, T1 mapping in gadoxetic acid enhanced liver MR imaging could be a helpful complementary sequence to determine the liver fibrosis stage.

#### **Author Contributions**

Conceptualization, J.Y.Y.; investigation, S.B.H.; methodology, S.B.H.; project administration, C.S.B.; supervision, J.Y.Y., S.S.S., H.S.H.; validation, J.Y.Y., S.S.S., H.S.H.; visualization, S.B.H.; writing—original draft, S.B.H.; and writing—review & editing, J.Y.Y., S.S.S., H.S.H.

#### **Conflicts of Interest**

The authors have no potential conflicts of interest to disclose.

#### REFERENCES

- 1. Byass P. The global burden of liver disease: a challenge for methods and for public health. *BMC Med* 2014;12:159
- Sohrabpour AA, Mohamadnejad M, Malekzadeh R. Review article: the reversibility of cirrhosis. Aliment Pharmacol Ther 2012;36:824-832
- Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011;53:1020-1022
- 4. Schuppan D, Kim YO. Evolving therapies for liver fibrosis. J Clin Invest 2013;123:1887-1901



- Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos NT, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 2002;97:2614-2618
- 6. Bedossa P, Dargère D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology* 2003;38:1449-1457
- 7. Lucero C, Brown RS Jr. Noninvasive measures of liver fibrosis and severity of liver disease. *Gastroenterol Hepatol (N Y)* 2016;12:33-40
- 8. Pang JX, Zimmer S, Niu S, Crotty P, Tracey J, Pradhan F, et al. Liver stiffness by transient elastography predicts liver-related complications and mortality in patients with chronic liver disease. *PLoS One* 2014;9:e95776
- Degos F, Perez P, Roche B, Mahmoudi A, Asselineau J, Voitot H, et al. Diagnostic accuracy of FibroScan and comparison to liver fibrosis biomarkers in chronic viral hepatitis: a multicenter prospective study (the FI-BROSTIC study). J Hepatol 2010;53:1013-1021
- Mueller S, Sandrin L. Liver stiffness: a novel parameter for the diagnosis of liver disease. *Hepat Med* 2010;2:49-67
- 11. Nguyen D, Talwalkar JA. Noninvasive assessment of liver fibrosis. *Hepatology* 2011;53:2107-2110
- Pang JX, Pradhan F, Zimmer S, Niu S, Crotty P, Tracey J, et al. The feasibility and reliability of transient elastography using Fibroscan<sup>®</sup>: a practice audit of 2335 examinations. *Can J Gastroenterol Hepatol* 2014;28: 143-149
- **13.** Tsuda N, Harada K, Matsui O. Effect of change in transporter expression on gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging during hepatocarcinogenesis in rats. *J Gastroenterol Hepatol* 2011;26:568-576
- 14. Kim T, Murakami T, Hasuike Y, Gotoh M, Kato N, Takahashi M, et al. Experimental hepatic dysfunction: evaluation by MRI with Gd-EOB-DTPA. *J Magn Reson Imaging* 1997;7:683-688
- 15. Tsuda N, Matsui O. Cirrhotic rat liver: reference to transporter activity and morphologic changes in bile canaliculi--gadoxetic acid-enhanced MR imaging. *Radiology* 2010;256:767-773
- 16. Yoon JH, Lee JM, Kim E, Okuaki T, Han JK. Quantitative liver function analysis: volumetric T1 mapping with fast multisection B1 inhomogeneity correction in hepatocyte-specific contrast-enhanced liver MR imaging. *Radiology* 2016;282:408-417
- 17. Haimerl M, Verloh N, Zeman F, Fellner C, Müller-Wille R, Schreyer AG, 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. Haimerl M, Utpatel K, Verloh N, Zeman F, Fellner C, Nickel D, et al. Gd-EOB-DTPA-enhanced MR relaxometry for the detection and staging of liver fibrosis. *Sci Rep* 2017;7:41429
- 19. Haimerl M, Schlabeck M, Verloh N, Zeman F, Fellner C, Nickel D, et al. Volume-assisted estimation of liver function based on Gd-EOB-DTPA-enhanced MR relaxometry. *Eur Radiol* 2016;26:1125-1133
- **20.** Heye T, Yang SR, Bock M, Brost S, Weigand K, Longerich T, et al. MR relaxometry of the liver: significant elevation of T1 relaxation time in patients with liver cirrhosis. *Eur Radiol* 2012;22:1224-1232
- 21. Haimerl M, Verloh N, Fellner C, Zeman F, Teufel A, Fichtner-Feigl S, et al. MRI-based estimation of liver function: Gd-EOB-DTPA-enhanced T1 relaxometry of 3T vs. the MELD score. *Sci Rep* 2014;4:5621
- 22. Yamada A, Hara T, Li F, Fujinaga Y, Ueda K, Kadoya M, et al. Quantitative evaluation of liver function with use of gadoxetate disodium-enhanced MR imaging. *Radiology* 2011;260:727-733
- 23. Bensamoun SF, Leclerc GE, Debernard L, Cheng X, Robert L, Charleux F, et al. Cutoff values for alcoholic liver fibrosis using magnetic resonance elastography technique. *Alcohol Clin Exp Res* 2013;37:811-817
- 24. Foucher J, Chanteloup E, Vergniol J, Castéra L, Le Bail B, Adhoute X, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. *Gut* 2006;55:403-408
- 25. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. *Hepatology* 1996; 24:289-293
- 26. Thomsen C, Christoffersen P, Henriksen O, Juhl E. Prolonged T1 in patients with liver cirrhosis: an in vivo MRI study. Magn Reson Imaging 1990;8:599-604
- 27. Bataller R, Brenner DA. Liver fibrosis. J Clin Invest 2005;115:209-218
- Rodríguez-Moreno F, González-Reimers E, Santolaria-Fernández F, Galindo-Martín L, Hernandez-Torres O, Batista-López N, et al. Zinc, copper, manganese, and iron in chronic alcoholic liver disease. *Alcohol* 1997; 14:39-44
- 29. Kim KA, Park MS, Kim IS, Kiefer B, Chung WS, Kim MJ, et al. Quantitative evaluation of liver cirrhosis using T1

relaxation time with 3 tesla MRI before and after oxygen inhalation. J Magn Reson Imaging 2012;36:405-410

- **30.** Seale MK, Catalano OA, Saini S, Hahn PF, Sahani DV. Hepatobiliary-specific MR contrast agents: role in imaging the liver and biliary tree. *Radiographics* 2009;29:1725-1748
- Verloh N, Haimerl M, Zeman F, Schlabeck M, Barreiros A, Loss M, et al. Assessing liver function by liver enhancement during the hepatobiliary phase with Gd-EOB-DTPA-enhanced MRI at 3 Tesla. *Eur Radiol* 2014; 24:1013-1019
- **32.** Tamada T, Ito K, Higaki A, Yoshida K, Kanki A, Sato T, et al. Gd-EOB-DTPA-enhanced MR imaging: evaluation of hepatic enhancement effects in normal and cirrhotic livers. *Eur J Radiol* 2011;80:e311-316
- 33. 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. *World J Gastroenterol* 2018;24:2024-2035
- 34. Sandrasegaran K, Akisik FM, Lin C, Tahir B, Rajan J, Saxena R, et al. Value of diffusion-weighted MRI for assessing liver fibrosis and cirrhosis. *AJR Am J Roentgenol* 2009;193:1556-1560
- **35.** Bakan AA, Inci E, Bakan S, Gokturk S, Cimilli T. Utility of diffusion-weighted imaging in the evaluation of liver fibrosis. *Eur Radiol* 2012;22:682-687
- **36.** Hagiwara M, Rusinek H, Lee VS, Losada M, Bannan MA, Krinsky GA, et al. Advanced liver fibrosis: diagnosis with 3D whole-liver perfusion MR imaging--initial experience. *Radiology* 2008;246:926-934
- 37. Chen BB, Hsu CY, Yu CW, Wei SY, Kao JH, Lee HS, et al. Dynamic contrast-enhanced magnetic resonance imaging with Gd-EOB-DTPA for the evaluation of liver fibrosis in chronic hepatitis patients. *Eur Radiol* 2012; 22:171-180
- **38.** Tapper EB, Loomba R. Noninvasive imaging biomarker assessment of liver fibrosis by elastography in NAFLD. *Nat Rev Gastroenterol Hepatol* 2018;15:274-282
- 39. Venkatesh SK, Yin M, Ehman RL. Magnetic resonance elastography of liver: technique, analysis, and clinical applications. *J Magn Reson Imaging* 2013;37:544-555



# Fibroscan과 비교를 통한 T1 MR Relaxometry를 이용한 간섬유화의 정량적 평가

심병학1·허숙희2·신상수1·조성범3·정용연2\*

**목적** 본 연구는 gadoxetic acid 조영증강 간 자기공명영상에서 T1 이완시간이 만성간질환을 가진 환자에서 간섬유화의 발견과 병기설정에 유용한지 알아보고자 한다.

대상과 방법 국소간병변이 의심되는 103명 환자들이 간 자기공명영상과 Fibroscan을 시행하였다. Fibroscan은 간섬유화의 정도를 분류하는 참조표준검사로 사용되었다. T1 이완시간은 조영제 주입 전(preT1)과 주입 20분 후(postT1), 그리고 이들 간의 T1 이완시간 감소율(rrT1)을 3 테슬라 자기공명영상의 횡단 3D VIBE 시퀀스 하에 측정하였다. Receiver operating characteristic (이하 ROC) 분석을 통해 간섬유화 병기설정을 위한 최적의 cut-off 값이 결정 되었다.

**결과** METAVIR score (F0-F4)에 따른 간섬유화 병기가 증가함에 따라, preT1과 postT1은 증가하였고, rrT1은 감소하였다. PreT1의 F2와 F3 사이(F2, 836.0 ± 74.7 ms; F3, 888.6 ± 77.5 ms, *p* < 0.05), postT1의 F3와 F4 사이(F3, 309.0 ± 80.2 ms; F4, 406.6 ± 147.7 ms, *p* < 0.05), 그리고 rrT1의 F3와 F4사이(F3, 65.4 ± 7.7%; F4 57.3 ± 11.4%, *p* < 0.05)에서 통계적 유의미한 차이를 보였다. ROC 분석은 preT1과 postT1의 병용검사가 간섬유화 병기설정에 있어 가장 유용한 검사라는 것을 보여준다.

**결론** preT1과 postT1은 간섬유화 병기가 증가함에 따라 증가하며, T1 mapping이 gadoxetic acid 조영증강 간 자기공명영상에서 간섬유화 병기설정에 있어 유용한 보조적 시퀀스로 사용될 수 있다.

<sup>1</sup>전남대학교 의과대학 전남대학교병원 영상의학과, 전남대학교 의과대학 화순전남대학교병원 <sup>2</sup>영상의학과, <sup>3</sup>소화기내과