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**Quantitative assessment of hepatic fibrosis in chronic hepatitis B and C: T1 mapping on Gd-EOB-DTPA-enhanced liver magnetic resonance imaging**

Pan S *et al*. Hepatic fibrosis assessment by Gd-EOB-DTPA-enhanced look-locker

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**Abstract**

***AIM***

To assess the accuracy of Look-Locker on Gd-EOB-DTPA-enhanced magnetic resonance imaging for staging liver fibrosis in chronic hepatitis B/C.

***Methods***

We prospectively included 109 patients with chronic hepatitis B (CHB) or C (CHC) who underwent a 3.0-Tesla magnetic resonance imaging (MRI) examination, including T1-weighted and Look-Locker sequences for T1 mapping. Hepatocyte fractions (HeF) and relaxation time reduction rate (RE) were measured for staging liver fibrosis. A receiver operating characteristic analysis using the area under the receiver operating characteristic curve (AUC) was used to compare the diagnostic performance in predicting liver fibrosis between HeF and RE.

***Results***

A total of 73 patients had both pathological results and MRI information. The number of patients in each fibrosis stage was evaluated semiquantitatively according to the METAVIR scoring system: F0, *n* = 23 (31.5%); F1, *n* = 19 (26.0%); F2, *n* = 13 (17.8%), and F3, *n* = 6 (8.2%). HeF by EOB enhancement imaging was significantly correlated with fibrosis stage (*r* = -0.808, *P* < 0.05). AUC values for diagnosis of any (≥ F1), significant (≥ F2), or advanced (≥ F3) fibrosis, and cirrhosis (F4) using HeF were 0.837 (0.733–0.913), 0.890 (0.795–0.951), 0.957 (0.881–0.990), and 0.957 (0.882–0.991), respectively. HeF measurement was more accurate than use of RE in establishing liver fibrosis staging, suggesting that calculation of HeF is a superior noninvasive liver fibrosis staging method.

***Conclusion***

A T1 mapping-based HeF method is an efficient diagnostic tool for the staging of liver fibrosis.

**Key words**: Liver fibrosis; Gd-EOB-DTPA; Look-Locker; magnetic resonance imaging relative enhancement; hepatocyte fraction; liver function

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**C****ore tip:** T1 mapping using the Look-Locker method with Gd-EOB-DTPA-enhanced magnetic resonance imaging at 3-Tesla by calculating the hepatocyte fraction is an efficient method for the assessment of liver fibrosis in patients with chronic hepatitis B and C, and that this method is superior to using reduction rate.

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**INTRODUCTION**

Chronic hepatitis B (CHB) and C (CHC) are major health problems[[1](#_ENREF_1),[2](#_ENREF_2)] and important factors globally in the development of hepatic fibrosis and even cirrhosis[[3](#_ENREF_3),[4](#_ENREF_4)]. Liver fibrosis is a diffuse pathological change caused by chronic liver disease. As fibrosis progresses, it leads to cirrhosis and even cancer[5]. Early diagnosis and monitoring of liver fibrosis, and intervention with timely and effective treatments, are critical for patients with liver disease. At present, liver biopsy is the gold standard for diagnosis of liver fibrosis. Tissue acquisition from a liver can be performed by endoscopic ultrasound-guided fine-needle aspiration[[6-8](#_ENREF_6)], particularly for the left lobe[[9](#_ENREF_9),[10](#_ENREF_10)]. This method is invasive with a risk of bleeding, increased tissue injury and the repeatability of the examination is poor[[11](#_ENREF_11),[12](#_ENREF_12)]. Therefore, noninvasive, comprehensive, and accurate methods of diagnosing liver fibrosis are required. In recent years, noninvasive methods have been increasingly used, such as serological examination[13], ultrasound based elastography[[14](#_ENREF_14)], diffusion-weighted imaging (DWI) [15], magnetic resonance enterography (MRE) [16], T1 rho[[17](#_ENREF_17)] and texture analysis[[18](#_ENREF_18)].

Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) is a liver-specific contrast agent that has a higher hepatocellular uptake rate than the traditionally used gadobenate dimeglumine (Gd-BOPTA)[[19](#_ENREF_19)]. In previous studies, Gd-EOB-DTPA-enhanced magnetic resonance imaging (MRI) was mainly used to diagnose focal liver lesions, especially hepatocellular carcinomas and even on functional MR cholangiography[[20-22](#_ENREF_20)]. It has been shown that the intracellular transport mechanisms of Gd-EOB-DTPA are mediated by organic anion-transporting polypeptides (OATPs)[[23](#_ENREF_23)]. Liver fibrosis obstructs the delivery of Gd-EOB-DTPA to hepatic cell surface transporters[24], contributing to a decline in OATP expression in the diseased liver[25], and consequently causing a decline in the T1-shortening effect of gadoxetic acid[[26](#_ENREF_26)]. Recording liver parenchymal T1 values before and after drug administration allows the T1 relaxation time reduction rate (RE) to be calculated, reflecting the functional hepatocyte-specific uptake of gadoxetic acid and, thus, the state of the liver[[27](#_ENREF_27)]. This method has been shown to have accurate diagnostic value in the assessment of liver fibrosis and is based on the traditional diagnostic method of Gd-EOB-DTPA-enhanced MR. Use of T1 mapping technology is a noninvasive, quantitative method for determining tissue T1 relaxation time. After liver fibrosis, excessive accumulation of extracellular matrix proteins occur, leading to T1 relaxation time changes in fibrotic tissues. Therefore, T1 mapping is theoretically applicable to studies of liver fibrosis such as the variable flip angle (VFA) T1 mapping technique[28], which has been shown to be effective in diagnosing liver fibrosis. T1 mapping using the Look-Locker method is one of the fastest, most efficient and reliable approaches to T1 quantification[29]. We proposed a method based on a simple pharmacokinetic model and ΔR1 values to calculate a hepatocyte fraction (HeF). In this method, changes to R1 in liver and spleen after EOB administration are calculated to obtain the HeF. In previous studies, the Look-Locker technique has mostly been used in the assessment of myocardial fibrosis and liver function[[30](#_ENREF_30)]. However, its application in the clinical diagnosis of liver fibrosis has not yet been reported.

Therefore, we proposed a working hypothesis that it was possible to diagnose liver fibrosis by calculating the HeF in the Look-Locker sequence by measuring Gd-EOB-DTPA-enhanced T1 signal intensity, and that this method would be superior to using RE. The purpose of this study, based on pathologic gold standards, was to quantitatively assess the level of hepatic fibrosis in hepatitis B and C patients by calculating the HeF and compare the results with traditional T1-enhanced test parameters with the aim of establishing a novel noninvasive diagnosis method for liver fibrosis.

**MATERIALS AND METHODS**

This cross-sectional, prospective study was performed between August 2016 and June 2017. The study was approved by our institutional review board, and written informed consent was obtained from the participants prior to the study.

***Patient population***

The subjects of the study were patients with suspected or known chronic liver disease attending our hospital's infectious disease department. The inclusion criteria were as follows: (1) over 18 years old; (2) chronic hepatitis diagnosed clinically (blood laboratory tests, ultrasound, or computed tomography scans showing morphological cirrhotic changes); (3) liver biopsy performed within 3 mo prior to the study or liver biopsy planned to obtain fibrosis staging; (4) Child–Pugh score < 7 (class A); (5) no magnetic resonance contraindications; and 6. signed informed consent. A total of 109 patients met the inclusion criteria; 84 had CHB and 25 had CHC. We excluded three patients due to discomfort during MR examination, seven patients due to poor imaging quality from improper breathing, and two with a mass that was too large. The remaining patients (*n* = 97) were scheduled for a liver biopsy within 1 wk of MRI. Of these 97, 20 did not undergo liver biopsy, and 4 were excluded due to poor liver biopsy quality. The standards for patient inclusion and exclusion are shown in Figure 1.

***MRI acquisition***

MR images were obtained with a 3-Tesla MRI system (Ingenia, Phillips Healthcare, Best, Netherlands) using a 32-channel torso phased-array coil. Patients were instructed to fast without water intake for 4-6 h before MR scanning. Before the examination, patients were trained to reduce breathing frequency or an abdominal binder was used to limit breathing frequency, to reduce interference during image acquisition. A volume of 0.025 mmol/kg Gd-EOB-DTPA (Bayer Healthcare, Berlin, Germany) was administered, at a rate of 1-2 mL/s. Following this, 30 mL saline was administered to flush the residual contrast reagent from the injection tube. T1WI and Look-Locker sequences were obtained twice; before and after Gd-EOB-DTPA administration. To obtain T1 relaxation time, enhanced images were recorded 18 min after Gd-EOB-DTPA injection. For T1 relaxation time, the enhanced images were obtained at 18 min after Gd-EOB-DTPA injection. The T1WI sequence was obtained using the following scan parameters: FOV = 356 mm × 262 mm, slice thickness = 7 mm, 24 slices, in-plane resolution = 1.6 mm × 1.96 mm, matrix = 220 × 133, TR/TE = 12/2.3 ms, band with = 361.9 kHz. Two-dimensional (2D) T1 maps were obtained using Look-Locker sequencing before and 20 min after Gd-EOB-DTPA administration[31]. A three-lead vector cardiogram was used for electrocardiogram gating. The T1 map was calculated from the Look-Locker sequence using the following scan parameters: 2D image with single slice, TE/TR = 1/6 ms, 3.5 mm × 3.5 mm × 8 mm acquisition resolution, and 1.37 mm × 1.37 mm × 8 mm for recon, FA = 7°, two shots TFE with TFE factor 16, shot interval = 5 s for full T1 relaxation, SENSE factor = 2, and scan time = 15 s, with breath holding. T1 maps were then automatically calculated using HepFract work-in-progress software (Phillips Healthcare).

***Assessment of pathological specimens***

Liver biopsy was performed under ultrasound guidance using an intercostal approach with a 14G disposable needle (MN1420; Bard Biopsy Systems, Tempe, AZ, United States) under local anesthesia. Liver specimens < 15 mm or containing < 11 portal tracts were excluded. Pathological sections of the biopsies were stained using the Masson method. Each pathologic section was read by two doctors with more than 10 years of pathologic diagnostic experience who were unaware of the patient serological or imaging diagnosis. If the opinion of the two pathologists differed, a final diagnosis was reached by, or after, discussion with a more senior pathologist. Fibrosis stage was evaluated semiquantitatively according to the METAVIR scoring system[32] , with grading on a 5-point scale as follows: F0, no fibrosis; F1, fibrous portal expansion but without septa formation; F2, few bridges or septa; F3, numerous septa formation without cirrhosis; and F4, cirrhosis[[33](#_ENREF_33)].

***MRI analysis***

As mentioned above, two doctors with more than 10 years of experience in the diagnosis of abdominal imaging—both of whom were unaware of the patient's laboratory results, pathologic grade, or clinical diagnosis prior to measurement—assessed the MR images, with any inconsistency finalized by a senior clinician.

The scanned pre- and post-Look-Locker images were saved in PAR-REC format, with the files imported into the HepFract processing software (Philips Scientific Software). Regions of interest (ROIs) were defined manually. A spleen ROI of about 4–5 cm2 was drawn first, and three ROI of approximately 2-3 cm2 were selected and marked in the liver parenchyma, two in the right lobe and three in the left (Figure 2), avoiding visible macroscopic vascular areas, the bile duct, and the liver edge. No selection was made if the left lobe was too small or the image quality was insufficient. The HeF was calculated using the following formulas:

R1 change after EOB in both liver and spleen:

Δ𝑅1𝐿𝑖𝑣𝑒𝑟 = 1 – 𝜑𝐿𝑖𝑣𝑒𝑟 × Δ𝑹𝟏𝑯𝒆𝒑𝒂𝒕𝒐𝒃𝒊𝒍𝒊𝒂𝒓𝒚 + 𝜑𝐿𝑖𝑣𝑒𝑟 × Δ𝑹𝟏𝑩𝒍𝒐𝒐𝒅𝑬𝑬𝑺 and

Δ𝑅1𝑠𝑝𝑙𝑒𝑒𝑛 = 𝜑𝑠𝑝𝑙𝑒𝑒𝑛 × Δ𝑹𝟏𝑩𝒍𝒐𝒐𝒅𝑬𝑬𝑺,

Where 𝜑 = total tissue water content (blood and extracellular space (EES)), 𝜑𝐿𝑖𝑣𝑒𝑟 = 0.23, and 𝜑𝑠𝑝𝑙𝑒𝑒𝑛 = 0.3).

HeF:

(Δ𝑹𝟏𝑯𝒆𝒑𝒂𝒕𝒐𝒃𝒊𝒍𝒊𝒂𝒓𝒚)/(Δ𝑹𝟏𝑯𝒆𝒑𝒂𝒕𝒐𝒃𝒊𝒍𝒊𝒂𝒓𝒚 + Δ𝑹𝟏𝑩𝒍𝒐𝒐𝒅𝑬𝑬𝑺) × 100 (%),

Where Δ𝑹𝟏𝑯𝒆𝒑𝒂𝒕𝒐𝒃𝒊𝒍𝒊𝒂𝒓𝒚 = the T1 relaxation rate change of the liver parenchyma ROI before and after contrast reagent administration and Δ𝑹𝟏𝑩𝒍𝒐𝒐𝒅𝑬𝑬𝑺 = the T1 relaxation rate change of blood, which was estimated based on the comparison of T1 relaxation rate of spleen parenchyma and liver parenchyma ROIs.

RE image processing was performed using DICOM Viewer R3.0 SP3 software (Philips). Images at the same Look-Locker level were preferred. Three ROIs were selected from the T1 liver images before and after Gd-EOB-DTPA administration. The ROIs were selected according to anatomical signs and the ROI positions of the Look-Locker images as far as possible. Figure 3 shows ROI selection for the RE method. The RE was calculated according to the formula:

RE = () × 100 (%),

where Pre and Post were the average signal intensity of liver parenchyma ROIs before and after Gd-EOB-DTPA administration.

Finally, the averages of the HeF, RE, Post, and Pre calculations for the three ROIs were calculated.

***Statistical analysis***

After testing for normality with the Shapiro–Wilk test, HeF, RE, Post, and Pre were expressed as the mean ± standard deviation (SD). One-way analysis of variance followed by Bonferroni’s/Tamhane’s T2 post-hoc comparison were performed to compare the means. Spearman’s rank correlation coefficient (r) was used to show the correlation between HeF, RE, Post, Pre, and histological scores.

We performed receiver operating characteristic (ROC) analysis of the different stages of fibrosis and area under the ROC curve (AUC) analysis was used to evaluate the following classifications: F0 vs. F1–F4 (≥ F1); F0–F1 *vs* F2–F4 (≥ F2); F0–F2 *vs* F3–F4 (≥ F3); and F0–F3 vs. F4, using Pre, Post, the RE of the hepatobiliary phase (HBP) and the HeF, based on Look-Locker. The optimal discrimination thresholds for RE and HeF were determined by maximizing the sums of sensitivity and specificity. The cutoff values, sensitivity, specificity, negative predictive value, positive predictive value, positive likelihood ratio, and negative likelihood ratio were calculated. Comparisons of AUCs were carried out using the method proposed by DeLong *et al*[[34](#_ENREF_34)].

Data analysis was performed with SPSS software, version 17.0 (SPSS, Chicago, IL, United States) and Medcalc version 7.4.2.0 (Medcalc Software, Mariakerke, Belgium) statistical software. A *P* value < 0.05 was considered significant.

**RESULTS**

***Patient characteristics***

The epidemiological characteristics of the enrolled patients, based on the presence or absence of fibrosis, are summarized in Table 1. We included a total of 73 patients [47 (64%) male and 26 (36%) female] who were eligible for inclusion on histopathological findings. Of these, 62 (85%) were infected with CHB and 11 (15%) were infected with CHC. Patient age ranged from 19-67 years (40.8 ± 12.1 years). Among them, there were 23 patients (31.5%) without fibrosis and 50 patients (68.5%) with fibrosis. Mean body mass index (BMI) was 23.73 ± 4.65 kg/m2 for the overall sample, and 15 of the 73 patients (21%) were overweight/obese (> 25 kg/m2), nine with CHB and six with CHC.

***Differences in MRI at different levels of fibrosis***

The average Post, RE, and HeF (%) in patients without fibrosis was 356 ± 44, 0.94 ± 0.18, and 88.77 ± 5.10, respectively, which were significantly lower than patients with fibrosis (Post: 331 ± 45; RE: 0.79 ± 0.23; HeF (%): 76.31 ± 11.23), and these values were significantly different between fibrotic and non-fibrotic patients (*P* = 0.037, 0.009, and < 0.001, respectively). Pre was not significantly different between patients with or without fibrosis (*P* = 0.235). Pre, Post, RE, and HeF (%) (mean ± SD) in patients with different grades of fibrosis are summarized in Table 2.

Post, RE, and HeF were significantly different among different grades of liver fibrosis (all *P* < 0.05). In the comparison of HeF in different groups of patients with different levels of fibrosis, each pair comparison was significantly different (*P* < 0.001), except for F1 and F2 (F1 *vs* F2 = 84.23 ± 6.99 *vs* 79.71 ± 8.09, *P* = 0.065). RE was not significantly different between the comparison groups F0 *vs* F1, F0 *vs* F2, and F1 *vs* F2 (*P* = 0.365, 0.490, 0.912, respectively), but was significantly different between other comparison groups (*P* < 0.05). Post was statistically significantly different between patients with liver cirrhosis (F4) and patients without liver fibrosis (F0) (F4 vs. F0 = 356 ± 44 *vs* 305 ± 50, *P* < 0.001), and was not significantly different between any other comparison groups (*P* > 0.05). Pre was not significantly different among different levels of liver fibrosis *(P* > 0.05). Figure 4 shows the HeF images in different stages of liver fibrosis.

***Correlation analysis***

RE and HeF were not correlated with BMI or age (Spearman’s correlation test, *r* = 0.034, 0.247, *P* = 0.847, 0.071, respectively), and did not differ between males and females (RE: 0.81 ± 0.27 *vs* 0.83 ± 0.16; HeF (%): 84.29 ± 8.17 *vs* 86.29 ± 6.10; both *P* > 0.05 for the independent samples *t*-test).

HeF and RE showed a strong correlation with fibrosis stage (RE: *r* = -0.773 (-0.852–0.661); HeF: *r* = 0.808 (-0.875–0.709); both *P* < 0.001). Post was moderately associated with grade of liver fibrosis [r = -0.525 (-0.674–0.336), *P* < 0.001]. Pre was not related to fibrosis grade [r = 0.188 (-0.045–0.4003), *P*= 0.112]. Correlation between Pre, Post, RE, and HeF (%) with fibrosis ratings is summarized in Table 3 and Figure 5. RE was moderately correlated to HeF [*r*= 0.539, (0.353–0.684), *P* < 0.001].

***ROC analysis***

The AUC values, optimal cutoff values, and the respective diagnostic performances for liver fibrosis measured by RE and HeF are summarized in Table 4 and Figure 6. The AUC values for HeF and RE were significantly higher than those for Pre and Post for detection of all fibrosis stages (*P* < 0.05). In the AUC comparison of HeF and RE, HeF had slightly higher AUCs than RE for discriminating ≥ F1 (HeF *vs* RE = 0.837 *vs* 0.678, *P* = 0.028), ≥ F2 (HeF *vs* RE = 0.890 *vs* 0.723, *P* = 0.008). HeF and RE for ≥ F3 and F4 stage AUC showed no significant difference (HeF *vs* RE= 0.957 *vs* 0.921, *P* = 0.418; HeF *vs* RE = 0.957 *vs* 0.962, respectively).

**DISCUSSION**

The results of our study indicated that T1 parameters from pre- or post-contrast T1 maps (HeF) and RE had good diagnostic value in the assessment of CHB, CHC, and liver fibrosis. HeF and RE both had good diagnostic performance in advanced liver fibrosis and cirrhosis (≥ F3 and F4) (AUC > 0.9). In diagnosis at ≥ F1 and ≥ F2 stages, HeF was better than RE.

Previous studies have used RE[35], liver-to-spleen ratio[[36](#_ENREF_36)], contrast enhancement index[37] or dynamic measurements[[38](#_ENREF_38)] based on Gd-EOB-DTPA-enhanced MRI, to quantify parenchymal enhancement. In recent years, T1 mapping technology based on Gd-EOB-DTPA enhancement has been used mainly in the study of liver disease diagnosis. Katsube *et al*[39], first reported that evaluation of hepatic uptake of Gd-EOB-DTPA using T1 mapping of liver parenchyma could help estimate liver function. Kiyohisa *et al*[[40](#_ENREF_40)] showed similar results in their study, which also demonstrated the diagnostic value of T1 mapping in liver disease. At present, T1 mapping is used to evaluate the degree of hepatic fibrosis, but only a few studies have focused on liver fibrosis caused by chronic viral hepatitis (CHB, CHC). Li *et al*[28] found that, in CCl4-induced liver fibrosis in New Zealand rabbits, using the T1-mapping technique based on a series of liver acquisition volume acceleration sequences, AUCs in ≥ F1, ≥ F2, and ≥ F3 stages from the ROC analysis were 0.803, 0.712, and 0.696, respectively. However, the study did not include F4 data. Our HeF results were based on clinical patients, which have better reference values than animal experiments, and results for all the fibrosis stages were obtained. Yang *et al*[[41](#_ENREF_40)]used 3D gradient-echo imaging on a 1.5-T MRI scanner to study volumetric interpolated breath-hold examination in liver fibrosis after CHB infection. They found that reduction in T1 relaxation time 20 min after gadoxetic acid injection (△T1, △R1%) compared with before injection and the contrast uptake rate (KHep) decreased significantly as the fibrosis score increased. In that study, △R1% had the highest correlation with fibrosis stage (*r* = -0.626), followed by KHep (*r* = -0.527), and △T1 (*r* = 0.513). The above mentioned studies were based on 1.5-T MR, while our images were acquired using 3.0-T MR with better image quality, assisting in image analysis and processing. Banerjee *et al*[[42](#_ENREF_42)] explored the relationship between corrected T1 parameter (cT1) and hepatic fibrosis Ishak rank, based on a shortened modified Look-Locker inversion (shMOLLI) recovery sequence T1 mapping technique, and found that cT1 was strongly correlated with increased liver fibrosis (cT1 *vs* Ishak [n = 84, r = 0.68], AUC of F ≥ 1 stage = 0.94). While the AUC values for the most of the fibrosis groups were similar to those of our study, the correlation reported by Banerjee *et al*[[42](#_ENREF_42)] was stronger than what was observed in this study where the AUC value for F ≥ 1. Banerjee’s study enrolled a total of 84 patients. While the causes of liver fibrosis in their study were from different types of chronic liver disease, 31 cases were caused by virus[[42](#_ENREF_42)]. A lack of research into viral hepatitis highlights the importance of studying changes in the degree of liver fibrosis caused by different types of liver disease. Ruo Fan Sheng et al have compared T1 mapping with RE on Gd-EOB-DTPA-enhanced MRI in the field of liver fibrosis assessment. The result showed that Gd-EOB-DTPA-enhanced T1 mapping might provide a reliable diagnostic tool in staging liver fibrosis, whereas it was a research on rabbits[[43](#_ENREF_43)]. As our study applies to human, which clinical significance is superior to animal studies.

Among the T1 mapping techniques, Look-Locker has several advantages. It is efficient compared with conventional techniques, which only sample one point for each inversion pulse. In addition, Look-Locker is less sensitive to B1 heterogeneity and less prone to error compared with the VFA method[[44](#_ENREF_44),[45](#_ENREF_45)].

Some research into the relationship between RE and liver fibrosis has been conducted. The earliest discussion of the relationship between relative T1 values and fibrosis was reported by Smith et al. in 1981[[46](#_ENREF_46)]. However, subsequent studies did not confirm the correlations[[47](#_ENREF_47)]. Verloh *et al*[[26](#_ENREF_26)] in a study of the relationship between RE and liver fibrosis, found strong correlations between the uptake characteristics of Gd-EOB-DTPA with RE and the grade of fibrosis/cirrhosis, classified using the Ishak scoring system. The inclusion criteria for this experiment did not limit the type of chronic liver disease that led to liver fibrosis. Feier et al. showed a strong correlation between the RE and METAVIR score (*r* = -0.65), which was consistent with our results (*r* = -0.773). Among their results, the AUC in the ≥F1 and ≥F2 stages was higher than our results (≥ F1: 0.81 *vs* 0.68; ≥ F2: 0.82 *vs* 0.72). The reasons for this difference in results are as follows. First, Feier *et al*[[35](#_ENREF_35)] did not focus on liver fibrosis caused by chronic viral hepatitis (CHB, CHC); instead, they included patients with alcoholic liver disease and autoimmune hepatitis leading to liver fibrosis. Second, in our study, the F3 and F4 groups were small, which could have led to bias. Third, RE measurement is relatively simple and direct; however, some disadvantages are also obvious. MRI signal intensity is influenced by many factors, and the collection method of the image may make statistical analysis difficult. Look-Locker sequencing ensures consistent image acquirement and analysis. T1 maps obtained using Look-Locker sequencing may be more robust than simple signal intensity (SI) measurements on the HBP[48], as T1 maps are less affected by MR parameters at the same magnetic field strength than SI measurements.

In contrast to the current international consensus on the diagnosis of liver fibrosis using MRE technology, our results showed that, based on Gd-EOB-DTPA-enhanced T1 mapping technology, HeF and METAVIR classification of liver fibrosis were significantly correlated (*r* = -0.808), although slightly lower than with the MRE technique (*r* = 0.899). Comparing the AUCs of the ≥ F1, ≥ F2, ≥ F3, and F4 groups, the AUCs for MRE were 0.84, 0.88, 0.93, and 0.92, respectively[[49](#_ENREF_49)]. Our HeF results were consistent with previous studies. Compared with MRE technology, which requires a special hardware installation, Gd-EOB-DTPA-enhanced Look-Locker scanning can be operated on standard clinically used MR equipment, an important advantage making it a popular choice. In contrast, the results of studies using the apparent diffusion coefficient (ADC) value in conjunction with DWI to assess hepatic fibrosis were quite different, and the use of ADC values in diagnosis remains controversial. For example, Tokgöz *et al*[[50](#_ENREF_49)] showed that ADC values in the different grades of fibrosis were not significantly different. A meta-analysis of DWI studies analyzing the use of ADC in liver fibrosis staging included a cumulative total of 613 patients in 10 studies[51]. It reported an AUC of 0.86 for F ≥ 1, 0.83 for F ≥ 2, and 0.86 for F ≥ 3, and concluded that DWI had a good diagnostic value for degree of liver fibrosis. Ding *et al*[[52](#_ENREF_52)] compared DWI with Gd-EOB-DTPA enhanced RE in the diagnosis of liver fibrosis; the results showed that RE was better than ADC. In our experiments, HeF was of superior diagnostic value than RE, so we can predict that HeF for liver fibrosis staging is of greater diagnostic value than DWI. Because different b values affect the results of ADC, they cannot be compared between studies because liver fibrosis staging is difficult to establish.

T1 mapping of gadoxetic acid-enhanced MR images using Look-Locker sequencing can be achieved using breath-holding and simplifying the image processing. We believe that this practical method has potential in the quantitative estimate of liver fibrosis and can be used as an important complementary sequence in clinical Gd-EOB-DTPA-enhanced MRI in patients with chronic liver disease.

Our study had some limitations. First, the sample size of this study was small, especially for the F3 stage category. Compared to similar studies which have shown inconsistency in hepatocellular function in the F ≥ 3 stage group (AUC: 0.63, 0.85, 0.87, and 0.93)[[53](#_ENREF_53)], a larger sample size was needed for the F3 stage category. Second, the study only examined the information obtained at 20 min after Gd-EOB-DTPA administration, and did not analyze HeF measured at other times, such as 5 or 10 min. Third, the Look-Locker sequence was a 2D sequence that did not contain information about the whole liver. When the HeF scan is part of an examination, an enhanced sequence of the whole liver should be added to the scanning protocol because of its value in clinical diagnosis. Furthermore, mismatches between pre- and post-contrast images were observed due to motion and the long gap between scans. To improve accessibility for future clinical use, further development in fast multi-slice or 3D volume quantitative T1 mapping is needed with liver-specific motion registration.

In conclusion, this study showed a strong correlation between HeF and liver fibrosis stage in CHB and CHC. Although HeF and RE are used to generate quantitative measurements to distinguish between different grades of liver fibrosis, HeF performed better than RE. This study showed that the T1 mapping-based HeF method is an efficient diagnostic tool for the staging of liver fibrosis.

**Article Highlights**

***Research background***

Chronic hepatitis B (CHB) and C (CHC) are both leading causes of liver related morbidity and mortality and predisposes patients to liver fibrosis, the excessive accumulation of extracellular matrix proteins. As fibrosis progresses, it leads to cirrhosis and even cancer. Early diagnosis and monitoring of liver fibrosis, and intervention with timely and effective treatments, are critical for patients with liver disease. At present, liver biopsy is the gold standard for diagnosis of liver fibrosis. Invasive methods have a risk of bleeding, increased tissue injury and the repeatability of the examination is poor. Therefore, noninvasive, comprehensive, and accurate methods of diagnosing liver fibrosis are required.

***Research motivation***

Currently, noninvasive methods have been increasingly used, such as serological examination, ultrasound based elastography, diffusion-weighted imaging (DWI), magnetic resonance enterography (MRE), and texture analysis. None of these methods can replace the biopsy. T1 mapping via the Look-Locker method is one of the fastest approaches to T1 quantification, and is the most time efficient method for T1 mapping and less affected by MR parameters than other methods. We proposed a method based on a simple pharmacokinetic model and ΔR1 values to calculate a hepatocyte fraction (HeF). Furthermore, mismatches between pre- and post-contrast images were observed due to motion and the long gap between scans. To improve accessibility for future clinical use, further development in fast multi-slice or 3D volume quantitative T1 mapping is needed with liver-specific motion registration.

***Research objectives***

We aimed to quantitatively assess the level of hepatic fibrosis in hepatitis B and C patients by calculating the HeF and compare the results with traditional T1-enhanced test parameters. In the future, more imaging methods should be compared with HeF, such as MRE, DWI.

Research methods

One hundred and nine patients were included in the study. MR images were obtained with a Gd-EOB-DTPA-enhanced 3-Tesla MRI system, including T1-weighted and Look-Locker sequences for T1 mapping. HeF and RE were calculated for staging hepatic fibrosis. Area under the receiver operating characteristic curve (AUC) was used to compare the diagnostic performance in predicting liver fibrosis between HeF and RE.

***Research results***

We included a total of 73 patients who were eligible for inclusion on histopathological findings. The results of our study indicated that T1 parameters from pre- or post-contrast T1 maps (HeF) and RE had good diagnostic value in the assessment of CHB, CHC, and liver fibrosis. HeF and RE both had good diagnostic performance in advanced liver fibrosis and cirrhosis (≥ F3 and F4) (AUC > 0.9). In diagnosis at ≥F1 and ≥F2 stages, HeF was better than RE.

***Research conclusions***

This study showed a strong correlation between HeF and liver fibrosis stage in CHB and CHC. The methods use HeF and RE to generate quantitative measurements to distinguish different grades of liver fibrosis, but HeF performed better than RE. This study showed that the T1 mapping-based HeF method is an efficient diagnostic tool for the staging of liver fibrosis.

***Research perspectives***

Due to the limited number of patients included, further studies are needed to assess the performance of the HeF in hepatic fibrosis. More imaging methods should be compared in the field of liver fibrosis diagnosis.

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Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **No fibrosis (*n* = 23)** | **Liver fibrosis (*n* = 50)** | **All (*n* = 73)** |
| Age (yr), mean ± SD | 39.5 ± 11.1 | 41.3 ± 12.5 | 40.8 ± 12.1 |
| Gender  Male  Female | 17 (74)  6 (26) | 30 (60)  20 (40) | 47 (64)  26 (36) |
| Height (m), mean ± SD | 1.72 ± 0.09 | 1.70 ± 1.21 | 1.71 ± 1.15 |
| Weight (kg), mean ± SD  BMI (kg/m 2), mean ± SD | 77.21 ± 17.32  24.09 ± 4.91 | 78.23 ± 16.12  22.06 ± 4.57 | 78.10 ± 16.64  23.73 ± 4.65 |
| CHB | 21 (34) | 41 (66) | 62 (85) |
| CHC | 2 (18) | 9 (82) | 11 (15) |

**Table 1 Patients’ characteristics *n* (%)**

BMI: body mass index; CHB: chronic hepatitis B; CHC: chronic hepatitis C.

**Table 2 Pre, Post, reduction rate of T1 relaxation time, and hepatocyte fraction (%) of patients at different METAVIR fibrosis stages**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Fibrosis stage (METAVIR)** | **F0 (*n* = 23)** | **F1 (*n* = 19)** | **F2 (*n* = 13)** | **F3 (*n* = 6)** | **F4 (*n* = 12)** | **Total (*n* = 73)** |
| Mean pre-T1 liver, mean ± SD | 180 ± 28 | 188 ± 19 | 174 ± 17 | 192 ± 22 | 200 ± 24 | 186 ± 24 |
| Mean post-T1 liver, mean ± SD | 356 ± 44 | 355 ± 38 | 316 ± 34 | 336 ± 43 | 305 ± 50 | 338 ± 46 |
| RE, mean ± SD | 0.94 ± 0.18 | 0.89 ± 0.20 | 0.94 ± 0.16 | 0.71 ± 0.17 | 0.52 ± 0.15 | 0.84 ± 0.23 |
| HeF (%), mean ± SD | 88.77 ± 5.10 | 84.23 ± 6.99 | 79.71 ± 8.09 | 70.90 ± 7.27 | 62.80 ± 7.01 | 80.24 ± 11.30 |

HeF: hepatocyte fraction; RE: reduction rate of T1 relaxation time.

**Table 3 Correlation of** **reduction rate of T1 relaxation time, hepatocyte fraction, and METAVIR fibrosis stages**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Pre** | **Post** | **RE** | **HeF** |
| r (95%CI) | 0.188 (-0.045 to 0.4003) | -0.525 (-0.674 to 0.336) | -0.773 (-0.852 to 0.661) | -0.808 (-0.875 to 0.709) |
| *P* value | 0.112 | 0.001 | < 0.001 | < 0.001 |

HeF: hepatocyte fraction; RE: reduction rate of T1 relaxation time.

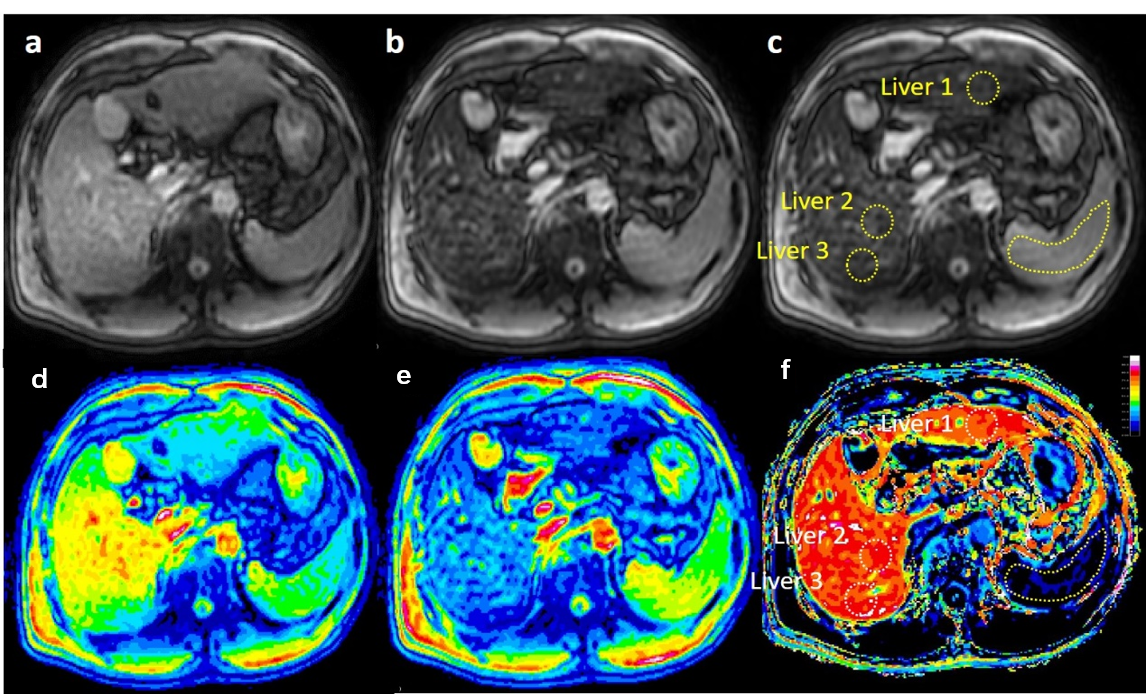
**Table 4 Performance of the mean reduction rate of T1 relaxation time and hepatocyte fraction for the prediction of METAVIR fibrosis stages according to cutoff values**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameters** | **≥ F1** | **≥ F2** | **≥ F3** | **= F4** |
| Cut-offs | | | | |
| HeF (%) | 82.93 | 79.24 | 74.37 | 74.37 |
| RE | 0.75 | 0.73 | 0.72 | 0.72 |
| AUC | | | | |
| HeF (%) | 0.837 (0.733-0.913) | 0.890 (0.795-0.951) | 0.957 (0.881-0.990) | 0.957 (0.882-0.991) |
| RE | 0.678 (0.559-0.783) | 0.723 (0.606-0.821) | 0.921 (0.834-0.971) | 0.962 (0.889-0.993) |
| Sensitivity, (%) | | | | |
| HeF(%) | 72.0 (57.5-83.8) | 77.4 (58.9-90.4) | 94.4 (72.7-99.9) | 100.0 (73.5-100.0) |
| RE | 44.0 (30.0-58.7) | 58.1 (39.1-75.5) | 88.9 (65.3-98.6) | 100.0 (73.5-100.0) |
| Specificity (%) | | | | |
| HeF (%) | 82.6 (61.2-95.0) | 92.9 (80.5-98.5) | 92.7 (82.4-98.0) | 85.3 (73.8-93.0) |
| RE | 100.0 (85.2-100.0) | 92.9 (80.5-98.5) | 92.7 (82.4-98.0) | 86.9 (75.8-94.2) |
| PPV (%) |  |  |  |  |
| HeF (%) | 90.0 (76.3-97.2) | 88.9 (70.8-97.6) | 81.0 (58.1-94.6) | 57.1 (34.0-78.2) |
| RE | 100.0 (84.6-100.0) | 85.7 (63.7-97.0) | 80.0 (56.3-94.3) | 60.0 (36.1-80.9) |
| NPV (%) |  |  |  |  |
| HeF (%) | 57.6 (39.2-74.5) | 84.8 (71.1-93.7) | 98.1 (89.7-100.0) | 100.0 (93.2-100.0) |
| RE | 45.1 (31.1-59.7) | 75.0 (61.1-86.0) | 96.2 (87.0-99.5) | 100.0 (93.3-100.0) |
| PLR |  |  |  |  |
| HeF (%) | 4.14 (1.7-10.3) | 10.84 (3.6-32.8) | 12.99 (5.0-33.6) | 6.78 (3.7-12.4) |
| RE | \_ | 8.13 (2.6-25.2) | 12.22 (4.7-31.8) | 7.62 (4.0-14.5) |
| NLR |  |  |  |  |
| HeF (%) | 0.34 (0.2-0.5) | 0.24 (0.1-0.5) | 0.060 (0.009-0.4) | \_ |
| RE | 0.56 (0.4-0.7) | 0.45 (0.3-0.7) | 0.12 (0.03-0.4) | \_ |

AUC: area under the curve; HeF: hepatocyte fraction; RE: reduction rate of T1 relaxation time; NLR: negative likelihood ratio; NPV: negative predictive value; PLR: positive likelihood ratio; PPV: positive predictive value.



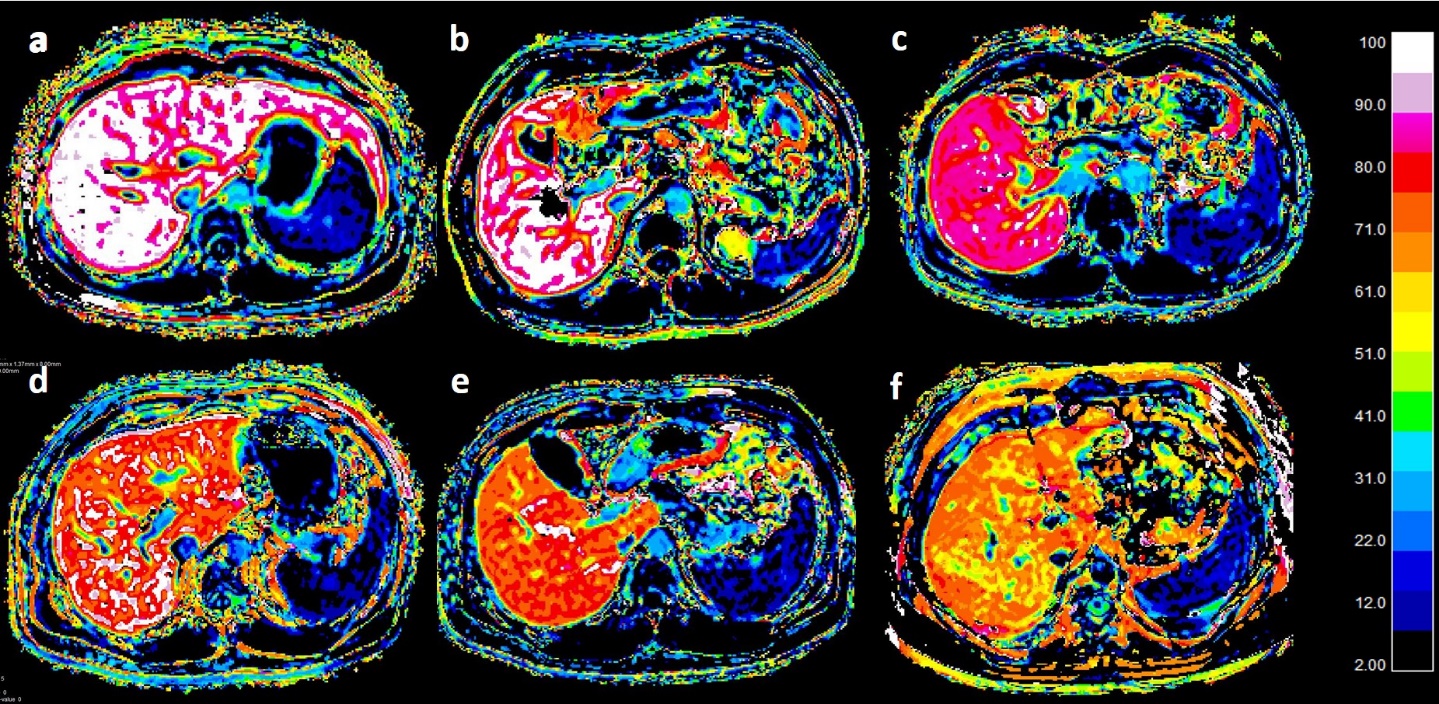
**Figure 1 Flow chart to demostrate patient selection procedure.**



**Figure 2 Pre-contrast (a, d) and post-contrast (b, e) T1 maps in a 72-year-old male with a METAVIR score of F4.** The hand-drawn regions of interest of the liver and spleen are shown (dotted closed curves).HeF image (f) is shown, and HeF liver 1, HeF liver 2, and HeF liver 3 values were 68.13%, 72.46%, and 70.45%, respectively, resulting in a HeF liver average of 70.34%. HeF: hepatocyte fraction.



**Figure 3 Pre-contrast (a) and post-contrast (b) T1-weighted images in a 72-year-old male with a METAVIR score of F4.** The hand-drawn regions of interest of the liver are shown (dotted closed curves). RE was 0.45. RE: reduction rate of T1 relaxation time.



**Figure 4 Representative images from patients with liver fibrosis at F0–F4 METAVIR stages.** (a) F0, HeF = 97.16%; (b) F1, HeF = 89.21%; (c) F2, HeF = 79.92%; (d) F2, HeF = 72.94%; (e) F3, HeF= 69.17%; (f) F4, HeF = 62.43%. HeF: hepatocyte fraction.



**Figure 5 Box-and-whisker plots of T1 values.** RE and HeF are shown for each METAVIR stage in relation to CHB and CHC.T1 values are reported on the y-axis, and METAVIR stage of fibrosis is reported on the x-axis. HeF: hepatocyte fraction; RE: reduction rate of T1 relaxation time; CHB: chronic hepatitis B; CHC: chronic hepatitis C.



**Figure 6 Comparison of the receiver operating characteristic curves of Pre, Post, RE, and HeF for different fibrosis thresholds.** From left to right: F0 *vs* F1–F4 (≥ F1), F0–F1 *vs* F2–F4 (≥ F2), F0–F2 *vs* F3–F4 (≥ F3), and F0–F3 *vs* F4 (≥ F4). The numbers in the boxes indicate the AUC values and 95%Cis. HeF: hepatocyte fraction; RE: reduction rate of T1 relaxation time.