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GASTROINTESTINAL

Magnetic resonance elastography can predict development of hepatocellular carcinoma with longitudinally acquired two-point data

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Abstract

Objective To evaluate the usefulness of longitudinal observation of liver stiffness measured using magnetic resonance elastography (MRE) to stratify the risk of hepatocellular carcinoma (HCC) in patients with chronic liver disease.

Materials and methods We retrospectively reviewed data for 161 patients with chronic liver disease using the following inclusion criteria: two MRE examinations separated by at least a 12-month interval, no history of HCC, no development of HCC between the two examinations and availability of laboratory results. Liver stiffness was classified as low (< 3 kPa), moderate (3–4.7 kPa) or high (> 4.7 kPa). The patients were divided into three groups according to sequential changes in liver stiffness as follows: high on the first MRE (group A, $n = 60$), low on both MRE examinations (group C, $n = 36$) and other combinations (group B, $n = 65$). Cox analyses and Kaplan-Meier methods were used to determine the risk of developing HCC.

Results Forty-seven patients (29.2%) developed HCC during follow-up (46.7% [28/60] in group A, 26.2% [17/65] in group B, and 5.6% [2/36] in group C). There was a significant difference in the rate of development of HCC between groups A (45.1%), B (26.1%) and C (12.4%) at 3 years ($p = 0.0002$). The independent risk factors for development of HCC were group A classification, age and a high alanine aminotransferase level (risk ratio 1.018–6.030; $p = 0.0028$–0.0268).

Conclusion Longitudinal observation of liver stiffness using MRE can stratify the risk of HCC during follow-up of chronic liver disease.

Key Points

- *The results of MRE can stratify the risk for development of HCC during follow-up in patients with chronic liver disease.*
- *Patients with chronic liver disease and high liver stiffness (> 4.7 kPa) on a previous MRE examination are at high risk for developing HCC, regardless of current liver stiffness.*
- *Management of patients with chronic liver disease becomes more appropriate using longitudinally acquired two-point MRE data.*

Keywords Hepatocellular carcinoma · Magnetic resonance elastography · Risk assessment · Observation

Abbreviations

ALT	Alanine aminotransferase
DAA	Direct-acting antiviral
MRE	Magnetic resonance elastography
PIVKA-II	Protein induced by vitamin K absence or antagonists-II
SVR	Sustained virological response

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Introduction

Assessment of risk for development of hepatocellular carcinoma (HCC) is essential in the management of patients with chronic liver disease. Cirrhosis has been reported to be the most important risk factor [1]. Therefore, it is important to be able to detect advanced fibrosis or cirrhosis in patients with chronic liver disease to stratify the risk for development of

HCC. These patients should be followed up closely so that HCC can be detected at an early stage because curative treatment can prolong survival in patients with HCC [2]. Historically, staging of liver fibrosis required a liver biopsy followed by histopathological assessment. Biopsy can have complications, including severe pain, bleeding and biliary injury [3], so it is difficult to perform these repeatedly during follow-up. Moreover, it is difficult to assess intermediate stage of fibrosis by biopsy even though a skilled hepatopathologist evaluates a good quality biopsy specimen [4]. Routinely, many patients are diagnosed and monitored with a combination non-invasive tests, the most important being elastography. Elastography is a non-invasive method for measurement of liver stiffness using magnetic resonance imaging (MRI) or ultrasound (US) and is used for diagnosis of liver fibrosis/cirrhosis. Many types of US-based elastographic techniques have been used to evaluate liver fibrosis [5, 6]. Moreover, there are several studies that have addressed the ability of transient elastography to predict the development of HCC [7, 8]. Even if US-based methods are most frequently used, recent studies indicate that magnetic resonance elastography (MRE) is a highly reproducible and accurate method for staging of hepatic fibrosis [9, 10]. There is a good correlation between liver stiffness measured via MRE or US elastography and the stage of liver fibrosis [10, 11]. Little has been reported on the ability of MRE to predict the development of HCC [12]. Given that development of HCC subsequent to fibrosis is an event that occurs over a long period of time, data from more than one time point, i.e. chronological changes in liver stiffness, can be more useful than simple one-time observations of current status.

The aim of this study was to evaluate the usefulness of longitudinal measurement of liver stiffness via MRE to stratify the risk for development of HCC in patients with chronic liver disease.

Materials and methods

Patients

This retrospective study was performed in accordance with the principles outlined in the Declaration of Helsinki and was approved by our institutional review board. The requirement for written informed consent was waived in view of the retrospective design. Between January 2010 and April 2014, 1,512 consecutive patients with chronic liver disease underwent MRE. They were required to satisfy the following inclusion criteria: two MRE examinations separated by an interval of at least 12 months; no prior history of HCC; no development of HCC between the two MRE examinations; and availability of laboratory results within 2 weeks before or after the second MRE examination. The primary endpoint of the study was development of hypervascular HCC, which was diagnosed based on pathological evidence or fulfilment of the criteria for HCC proposed by the American Association for the Study of Liver Diseases [13] and European Association for the Study of the Liver [14], i.e. arterial hypervascularity and washout in the venous or delayed phase on contrast-enhanced computed tomography (CT) images.

Magnetic resonance elastography

MRE was performed using either a 1.5-T magnetic resonance (MR) system with a superconducting magnet (Signa Excite HD MR 1.5 T; GE Medical Systems, Milwaukee, WI, USA) and an 8-channel phased-array coil or a 3.0-T MR system (Discovery 750; GE Medical Systems) with a 32-channel phased-array coil. The patient was placed in the supine position, and a cylindrical passive driver was attached to the right chest wall using a rubber belt. Pneumatic vibration was delivered through a plastic cylinder to a passive driver from a vibrator placed outside the imaging room. The passive driver then transferred the vibration to the liver via the chest wall [15]. The scanning position extended from above the gallbladder to below the subphrenic space in the liver. Patients were instructed to breath-hold after expiration to maintain a consistent position during image acquisition at each phase offset [16]. The following parameters were used: frequency of vibration, 60 Hz; axis of motion-sensitising gradient pulse, z-axis (perpendicular to the imaging plane); MR sequence for data acquisition, two-dimensional gradient echo; and acquisition time, 13–17 s. Table 1 summarises the MR sequence parameters. The MR scanners automatically generated liver stiffness maps by processing the acquired propagating shear-wave images according to a two-dimensional inversion algorithm [17], and shear stiffness of the tissue was translated to a pixel value (kPa) [18]. Based on the stiffness maps, one radiologist (S.I.) with 10 years' experience in abdominal radiology and blinded to the histopathological data placed a region of interest (ROI) in the right lobe of the liver of each patient. ROIs of at least 1.5 cm^2 were placed to exclude large blood vessels seen on a magnitude MRE image, to exclude the edge of the liver and to include a parallel waveform without interference on the phase images.

Statistical analysis

Liver stiffness was classified as low (< 3 kPa), moderate (3–4.7 kPa) or high (> 4.7 kPa) according to the previously reported cut-off values [9]. The cumulative incidence rate for development of HCC was compared between these three groups based only on the second MRE examination

Table 1 Sequence parameters of magnetic resonance elastography

Parameter	1.5-T system	3-T system
Sequence	Two-dimensional gradient echo T1-weighted imaging	Two-dimensional gradient echo T1-weighted imaging
Plane	Transverse	Transverse
Repetition time (ms)	100	50
Echo time (ms)	27	20
Matrix	256 × 64	256 × 80
Field of view (cm)	36 × 27	35 × 35
Section thickness/intersection gap (mm)	10/5	10/5
Number of signals acquired	1	1
Flip angle (°)	30	23
Acquisition time (s)	13	17
Frequency of driver (Hz)	60	60
Amplitude (%)	60	70
Axis of motion-sensitising gradient pulse	z	z

(method A, standard) using the Kaplan-Meier method and a Cox proportional hazards model. The cumulative incidence rate for development of HCC was also assessed on the basis of the first MRE examination (method B) and both MRE examinations to take into account the chronological change in liver stiffness between the first and second examinations (method C). For classification using method C, Kaplan-Meier curves were constructed for all combinations of the two MRE results (see Electronic Supplementary Material, 1). After a visual assessment of these curves, stiffness was classified using method C as follows: high stiffness on the first MRE examination (group A); low stiffness on both MRE examinations (group C), and other combinations (group B). The reference date for the Kaplan-Meier curves was set as the date of the second MRE examination for all classifications.

The results were compared between patients with and without occurrence of hypervascular HCC during follow-up using a Cox proportional hazards model to identify factors that were independently associated with development of HCC. The following variables were analysed: age, sex, body weight, aetiology of hepatitis, chronological change in liver stiffness, the interval between the first and second MRE examination, platelet count, aspartate aminotransferase level, alanine aminotransferase (ALT) level, albumin level, total bilirubin level, lactate dehydrogenase level, alkaline phosphatase level, gamma-glutamyl transferase level, prothrombin activity, alpha-fetoprotein level, PIVKA-II (protein induced by vitamin K absence or antagonists-II) level, Child-Pugh classification and achievement of SVR. All statistical analyses were performed using JMP version 10.0.2 software (SAS Institute, Cary, NC, USA). p-values < 0.05 were considered statistically significant.

Results

Patients

Finally, 161 patients (102 male; 59 female; mean age 65.3 [range, 60–88] years) were included in the study (see Electronic Supplementary Material, 2). The aetiologies of chronic liver disease were hepatitis C (n = 100), hepatitis B (n = 36), alcoholic steatohepatitis (n = 10), primary biliary cholangitis (n = 6), non-alcoholic steatohepatitis (n = 1), autoimmune hepatitis (n = 1) and uncertain liver disease with elevated liver enzyme levels (n = 7). The mean interval between the two MRE examinations was 17.9 (range 12–46.8) months. All patients were followed up at our institution. The median duration of follow-up after the second MRE examination was 32.7 (range 3.8–52.7) months. During follow-up, 44 (32.4%) of 136 patients who had hepatitis C or B were treated with antiviral therapy, 25 of whom achieved a sustained virological response (SVR).

Occurrence of HCC

Forty-seven (29.2%) of the 161 patients developed HCC during the follow-up period. Hypervascular HCC was diagnosed based on pathological evidence in 13 cases (biopsy, n = 7; resection, n = 6) and on CT images in 34 cases. According to method A, 49 (30.4%), 63 (39.1%) and 49 (30.4%) patients had low, moderate and high liver stiffness. Among them, 6 (12.2%), 20 (31.7%) and 21 (42.9%) developed HCC (p = 0.0033). The incidence rates for development of HCC at 3 years in the high, moderate and low liver stiffness groups were 17.7%, 29.0% and 44.9%, respectively (p = 0.0033; Fig. 1a). According to method B, 44 (27.3%), 57 (35.4%) and 60 (37.5%) patients had low, moderate and high liver stiffness.

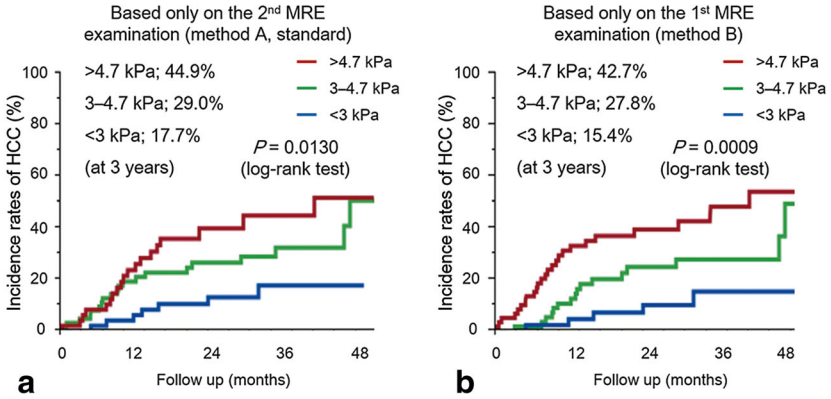

Fig. 1 Cumulative incidence rate for development of HCC. (**a**) Kaplan-Meier analysis comparing the three groups based only on the second MRE examination (method A, standard). (**b**) Kaplan-Meier analysis comparing the three groups based only on the first MRE examination by setting the date of the second MRE examination as the reference date (method B). The results were similar for methods A and B, but the separation was slightly better when using method B than when using method A. *HCC* hepatocellular carcinoma, *MRE* magnetic resonance elastography

Among them, 4 (9.09%), 16 (28.1%) and 27 (45.0%) developed HCC ($p = 0.0004$). The incidence rates for development of HCC at 3 years in the high, moderate and low liver stiffness groups were 15.4%, 27.8% and 42.7%, respectively ($p = 0.0009$; Fig. 1b). The Kaplan-Meier analysis showed similar results between methods A and B; however, method B showed slightly better separation between the three groups than method A. Using classification method B, there was a significant difference in the incidence rate for development of HCC between the three groups ($p = 0.0444$–0.0001, Table 2). However, using method A, there was a significant difference in incidence rate between patients with high liver stiffness and those with low liver stiffness and between patients with moderate liver stiffness and those with low liver stiffness ($p = 0.0026$ and $p = 0.0354$, respectively; Table 2), but not between patients with high liver stiffness and those with moderate liver stiffness ($p = 0.2458$).

According to method C, 60 (37.3%), 36 (22.5%) and 65 (40.4%) patients had high stiffness on the first MRE examination (group A), low stiffness on both MRE examinations (group C) and other combinations (group B) (Fig. 2). Among them, 28 (46.7%), 17 (26.2%) and two (5.6%) patients in groups A, B and C developed HCC ($p < 0.0001$; Fig. 3). The incidence rates for development of HCC at 3 years in groups A, B and C were 45.1%, 26.1% and 12.4%, respectively ($p = 0.0002$; Fig. 4). Using method C, there were significant differences in the incidence rates for development of HCC between the three groups ($p = 0.0335$ to $p < 0.0001$; Table 2). Figures 5 and 6 provide clinical details for specific clinical cases.

Factors associated with the development of HCC

Univariate analyses revealed that age, liver stiffness on first and second MRE, chronological change in liver stiffness between the two MRE examinations, platelet count and ALT level were associated with development of HCC (hazard ratio (HR) 0.994–7.080; $p < 0.0001$–0.0335; Tables 2 and 3). Aetiology of hepatitis did not show a significant difference ($p = 0.1613$–0.4047).

Multivariate analyses were performed three times (one for each method (method A, B or C)) of these factors. In multivariate analysis in included method A, age (HR, 1.043; 95% confidence interval (CI), 1.007–1.080; $p = 0.0145$) and ALT level (HR, 1.018; 95% CI, 1.005–1.032; $p = 0.0143$) were

Table 2 Hazard ratio for development of hepatocellular carcinoma between groups

Variable	Hazard ratio	95% CI	*p*-value
Classification method A			
High vs. moderate	1.456	0.769–2.746	0.2458
High vs. low	3.489	1.526–8.961	0.0026*
Moderate vs. low	2.397	1.059–6.117	0.0354*
Classification method B			
High vs. moderate	1.913	1.030–3.658	0.0401*
High vs. low	5.000	2.077–14.83	0.0001*
Moderate vs. low	2.614	1.023–7.997	0.0444*
Classification method C			
Group A vs. group B	2.185	1.194–4.106	0.0112*
Group A vs. group C	7.080	2.489–29.72	< 0.0001*
Group B vs. group C	3.240	1.087–13.87	0.0335*

Liver stiffness was grouped into high (>4.7 kPa), moderate (3.0–4.7 kPa) and low stiffness (<3.0 kPa). The classifications were based on the second (or most recent) MRE (method A, standard method of assessment), first (or previous) MRE that was performed >1 year before the second MRE (method B), and combinations of the two MRE examinations (method C)

*$p < 0.05$

CI confidence interval

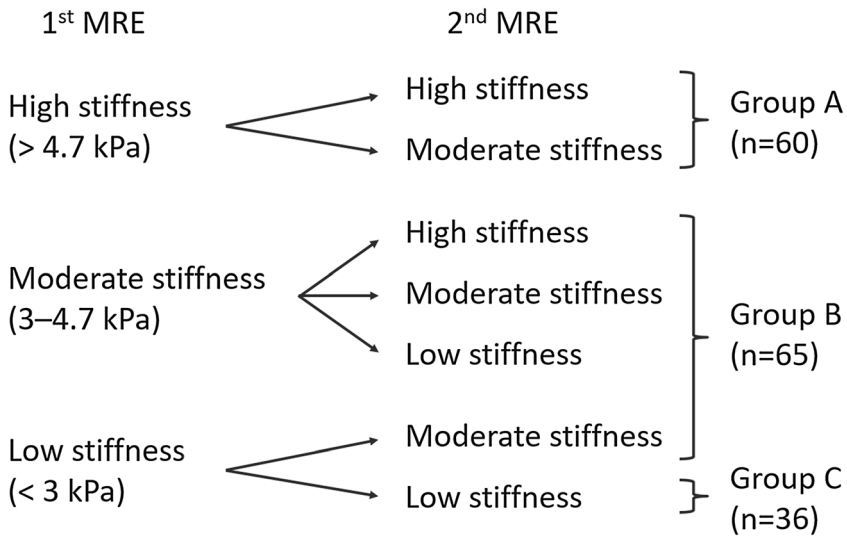

Fig. 2 Classification criteria for change in liver stiffness between the two MRE examinations. Group A, high stiffness on both examinations or high stiffness on the first examination and moderate stiffness on the second examination; Group C, low stiffness on both examinations; and Group B, other combinations. There were no patients with the combination of high stiffness on the first examination and low stiffness on the second examination or low stiffness on the first examination and high stiffness on the second examination. *MRE* magnetic resonance elastography

identified as independent risk factors for development of HCC. Classification of liver stiffness did not show a significant difference (p = 0.1174–0.6248). In multivariate analysis in included method B, age (HR, 1.046; 95% CI, 1.010–1.083; p = 0.0087), high liver stiffness (HR, 4.379; 95% CI, 1.523–14.59; p = 0.0053 compared with low liver stiffness) and ALT level (HR, 1.017; 95% CI, 1.004–1.032; p = 0.0195) were identified as independent risk factors for development of HCC. There was no significant difference between high and moderate liver stiffness (p = 0.1012). In multivariate analysis in included method C, age (HR, 1.043; 95% CI, 1.008–1.081; p = 0.0154), group A classification (HR, 6.030; 95% CI, 1.780–27.84; p = 0.0028 and HR, 2.164; 95% CI, 1.092–4.354; p = 0.0268 compared with group C and B, respectively) and ALT level (HR, 1.018; 95% CI, 1.003–1.032; p = 0.0196) were identified as independent risk factors for development of HCC (Table 4). Hazard ratios of MRE results in multivariate analysis that included method C were the highest among the three methods.

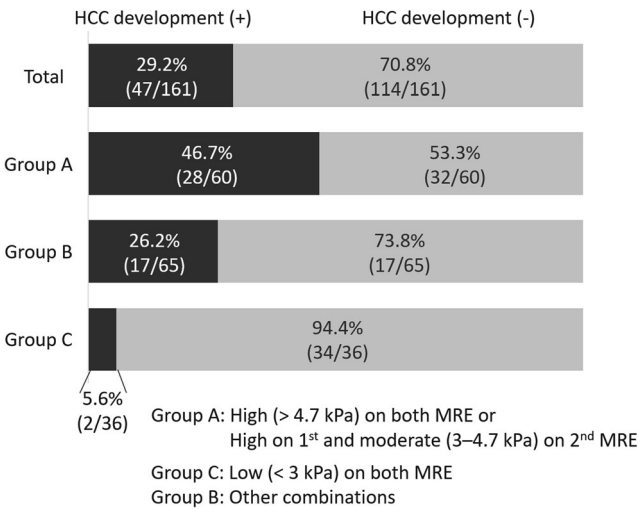

Fig. 3 Development of HCC during follow-up. Forty-seven (29.2%) of 161 patients developed HCC during follow-up (28 [46.7%] of 60 in group A; 17 [26.2%] of 65 in group B; and 2 [5.6%] of 36 in group C). *HCC* hepatocellular carcinoma

Discussion

In our study, the more recent liver stiffness values recorded on the second MRE examination were associated with development of HCC. However, our results also suggested that the

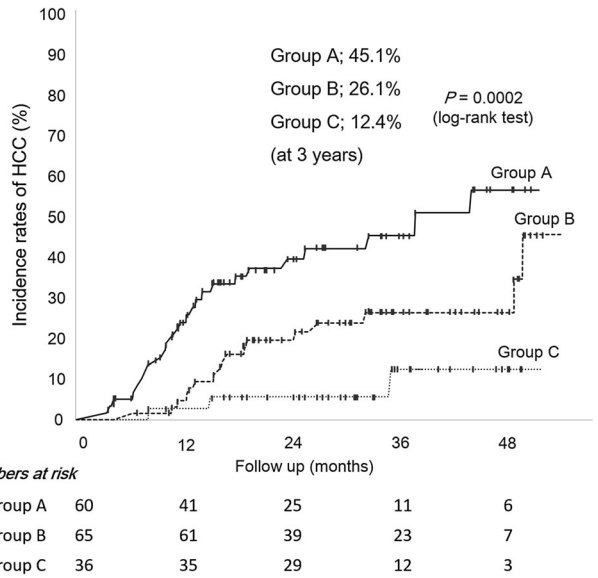

Fig. 4 Cumulative incidence rate for development of HCC in the three subgroups. The incidence rate was higher in group A than in the other subgroups and that in group C was lower than in the other groups. The incidence rate for development of HCC at 3 years in groups A, B and C was 45.1, 26.1 and 12.4%, respectively (p = 0.0002). *HCC* hepatocellular carcinoma

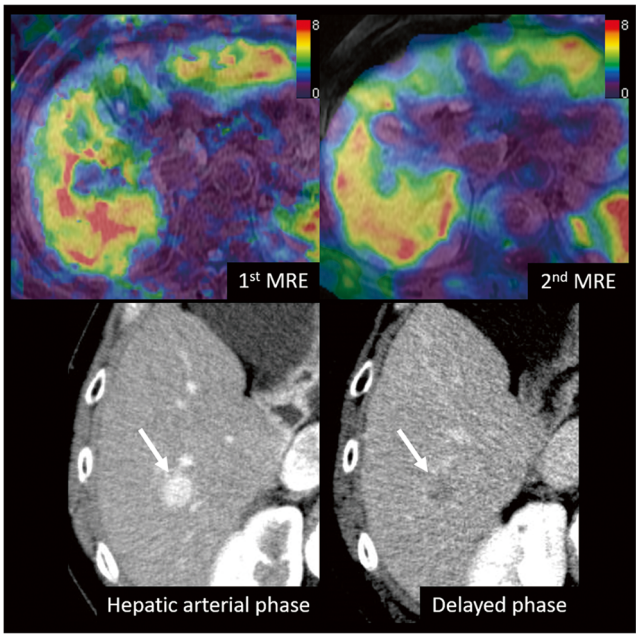

Fig. 5 Imaging findings in a 69-year-old man with hepatitis C. Liver stiffness was high on both the first and second MRE examinations (6.3 kPa and 6.2 kPa, respectively); 22.8 months after the second MRE examination, hypervascular hepatocellular carcinoma was observed on dynamic computed tomography. *MRE* magnetic resonance elastography

results of the first MRE examination, i.e. the earlier liver stiffness value, are also important, especially if liver stiffness had been found to be high more than a year earlier. It was also useful to take account of the chronological change in liver stiffness for estimation of the risk for development of HCC. A previous study focused on chronological change in liver stiffness measured by transient elastography, in which the authors indicated that patients with baseline and serial high liver stiffness had a higher risk of portal hypertension progression [19]. Our results were consistent with their results.

A persistently high liver stiffness value could be a greater risk factor for hepatocarcinogenesis than a single point measurement of current moderate-to-high liver stiffness. Formation of new abnormal vessels (angiogenesis) is a key mechanism in the pathogenesis of chronic liver disease, and angiogenesis increases with the progression of fibrosis and hepatocarcinogenesis. Liver hypoxia is a major trigger for angiogenesis. There are many causes of liver hypoxia associated with cirrhosis, including compression of the portal tract by abnormal scarring with fibrous tissue, intrahepatic arterioportal shunts that decrease arterial oxygenation and impairment of oxygen exchange by capillarisation of hepatic sinusoids [20, 21]. Therefore, persistently high liver stiffness could be a greater risk factor for HCC than elevation of liver stiffness, given that a sustained state of cirrhosis is important for hepatocarcinogenesis. Calculations using a hidden Markov model showed that it can take 24.99–178.92 months for chronic liver disease to progress to liver cirrhosis, depending on the cause, and 15.63–48.91 months for cirrhosis to progress to HCC [22].

Interestingly, in our study, the Kaplan-Meier curve for the patients who had moderate liver stiffness on the first MRE and high liver stiffness on the second MRE (Fig. 1) showed that the incidence rate for development of HCC was the same as that in group A approximately 48 months later. Although the observation period in our study may not have been long enough, the risk for development of HCC may increase several years after liver stiffness increases to a cirrhotic level.

Recently, MRE has emerged as a superior modality for evaluation of liver fibrosis. MRE is a very applicable method for liver imaging not only for evaluation of liver fibrosis, but also for the assessment of degree of portal hypertension [23, 24], risk of hepatic decompensation or progression of cirrhosis [25, 26], characterisation of hepatic lesions [27, 28] and assessment of post-treatment state [29–31]. In general, it is well validated that liver stiffness by MRE is highly correlated with liver fibrosis stage. Liver cirrhosis is pathologically defined as a diffuse replacement of the normal lobule by abnormal nodules and fibrous septa [32]. Although cirrhosis is considered to be an end-stage liver disease, clinical severity and prognosis

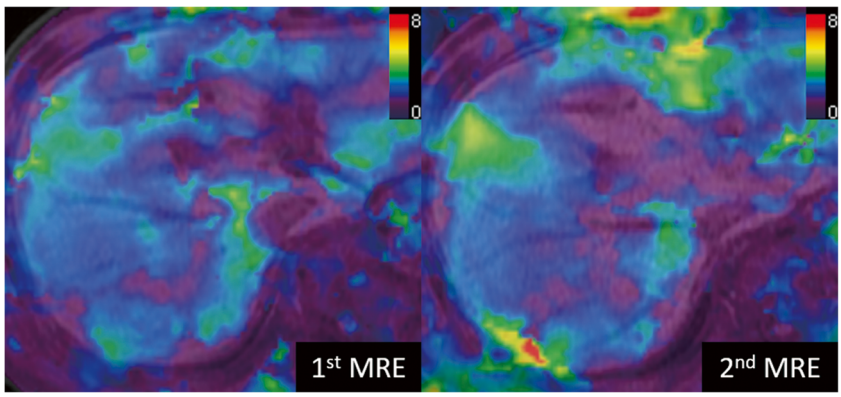

Fig. 6 Imaging findings in a 58-year-old man with hepatitis B. Liver stiffness was low on both the first and second MRE examinations (2.4 kPa and 2.3 kPa, respectively). No development of hepatocellular carcinoma was observed at 50.5 months after the second MRE examination. *MRE* magnetic resonance elastography

Table 3 Univariate analysis of Cox proportional hazards model

Variable	Hazard ratio	95% CI	*p*-value
Age	1.036	1.005–1.071	0.0241*
Sex (male vs. female)	1.630	0.879–3.212	0.1238
Body weight	1.001	0.981–1.020	0.6467
Aetiology of hepatitis			
HCV vs. HBV	1.353	0.677–3.015	0.4047
HCV vs. others	1.977	0.783–6.644	0.1613
HBV vs. others	1.458	0.473–5.539	0.5226
Interval between 1st and 2nd MRE	1.001	0.999–1.001	0.4150
Platelet count	0.994	0.999–0.999	0.0261*
AST	1.005	0.998–1.010	0.1165
ALT	1.016	1.003–1.027	0.0114*
Albumin	0.663	0.407–1.101	0.1102
Total bilirubin	1.059	0.591–1.653	0.8279
LDH	1.002	0.997–1.007	0.4257
ALP	1.000	0.998–1.000	0.6751
GGT	1.001	0.995–1.005	0.8381
Prothrombin activity	0.997	0.976–1.022	0.8219
Alpha-fetoprotein	1.000	0.999–1.000	0.1742
PIVKA-II	1.000	0.999–1.000	0.7500
Child-Pugh classification (class B vs. A)	0.711	0.245–1.640	0.4519
Achieved SVR (yes vs. no)	0.620	0.214–1.423	0.2823

*$p < .05$

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CI* confidence interval, *GGT* gamma-glutamyl transferase, *LDH* lactate dehydrogenase, *MRE* magnetic resonance elastography, *PIVKA-II* protein induced by vitamin K absence or antagonists-II, *SVR* sustained virological response

Table 4 Multivariate analysis of Cox proportional hazards model

Variable	Hazard ratio	95% CI	*p*-value
Included method A			
Age	1.043	1.007–1.080	0.0145*
Classification of liver stiffness			
High vs. low	2.206	0.824–6.425	0.1174
High vs. moderate	1.184	0.599–2.335	0.6248
Moderate vs. low	1.864	0.782–4.947	0.1647
Platelet count	0.998	0.992–1.004	0.6015
ALT	1.018	1.005–1.032	0.0143*
Included method B			
Age	1.046	1.010–1.084	0.0087*
Classification of liver stiffness			
High vs. low	4.379	1.523–14.59	0.0053*
High vs. moderate	1.773	0.894–3.582	0.1012
Moderate vs. low	2.471	0.927–7.781	0.0715
Platelet count	1.001	0.995–1.007	0.7226
ALT	1.018	1.004–1.032	0.0195*
Included method C			
Age	1.043	1.008–1.081	0.0154*
Chronological change in liver stiffness			
Group A vs. C	6.030	1.780–27.84	0.0028*
Group A vs. B	2.164	1.092–4.354	0.0268*
Group B vs. C	2.787	0.892–12.27	0.0807
Platelet count	1.002	0.996–1.007	0.6110
ALT	1.018	1.003–1.032	0.0196*

*$p < 0.05$

ALT alanine aminotransferase, *CI* confidence interval

can vary [33]. Since most type C hepatitis, a major cause of cirrhosis, can be cured by antiviral treatments, the liver fibrosis can change or resolve over time [34]. That means that a simple point assessment of pathology-based fibrosis staging is not able to accurately stratify the risk of HCC development. Laennec's staging system can be used to assess the degree of cirrhosis, liver function and the risk of liver-related event occurrence among patients with cirrhosis [35, 36]. There are several reports using this staging system and ultrasound elastography [37, 38]; however, there is no report using this staging system and MRE.

The major limitation of our study was its retrospective design. The most appropriate method for assessment of risk factors for HCC would be a prospective study with longitudinal observation of a sufficient number of patients, in which the endpoint is the incidence of HCC. The incidence rate of HCC in this study was higher than that in previous studies [39, 40], suggesting that the population in our study may be skewed towards very high-risk patients probably due to the retrospective study design that included patients who were referred to MRI. Another potential limitation is that we did not assess the activity of hepatitis. Previous research has suggested that the activity of hepatitis may be a confounder of liver stiffness measurement during staging of fibrosis using MRE [41–43]. Finally, the observation period may have been too short, given that direct-acting antiviral (DAA) agents became available in the course of the study. These new agents are highly effective in the treatment of HCV infection and can be used safely in treatment-naïve patients with HCV and in patients who have been treated unsuccessfully, so HCV cure rates have increased dramatically [44, 45]. There are several reports suggesting that DAA therapy might reduce the risk of HCC [46, 47]. Achievement of an SVR was not associated with development of HCC in this study, but such an association might have been found had the observation period been longer.

In conclusion, longitudinal observation of liver stiffness via MRE examination can be useful to stratify the risk for development of HCC.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Hiroshi Onishi.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Some study subjects or cohorts have been previously reported in an earlier report (Ichikawa S, et al. J Magn Reson Imaging 2017;46(2):375-382.). Data of magnetic resonance elastography (MRE) for 42 patients in this study were included in the paper; however, the results for two MRE examinations for these patients have not been reported previously.

Methodology
- Retrospective
- Observational
- Performed at one institution

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