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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Strain elastography for assessment of liver fibrosis and prognosis in patients with chronic liver diseases

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Abstract
Background Estimation of liver stiffness is essential in the treatment of liver diseases. Various procedures alternative to liver biopsy have been developed, and transient elastography using shear wave is an established method for evaluating liver stiffness and has been shown to be a prognostic indicator. In contrast, strain elastography (SE) has been applied to evaluate liver stiffness, however the significance remains uncertain.
Methods We retrospectively analyzed 598 patients who underwent SE to evaluate the ability of estimating liver stiffness and the prognosis. Elasticity index (EI) was evaluated as an indicator of liver stiffness in this study.
Results EI was increased as histological fibrosis advanced. EI was significantly different between mild fibrosis (F0–2) and advanced fibrosis (F3, 4). In contrast, EI was similar among those with different activity scores. EI showed better diagnostic performance in estimating advanced fibrosis than other serological markers and good reproducibility. Furthermore, EI was shown to be an independent prognostic factor in patients with chronic liver diseases and also with hepatocellular carcinoma (HCC) with advanced stage.
Conclusions SE could estimate advanced liver fibrosis without influence of liver inflammation unlike other serological liver fibrosis markers. SE might be a prognostic factor in chronic liver diseases and HCC.

Keywords Strain elastography · Liver stiffness · Liver biopsy · Hepatocellular carcinoma · Prognosis

Introduction

Estimating liver stiffness is essential in treating patients with chronic liver diseases because liver stiffness induced by progression of liver fibrosis is closely associated with the prognosis of chronic liver diseases [1]. Liver biopsy has been the gold standard for the assessment of liver fibrosis [2]. However, it is an invasive method, and has been reported to have problems such as sampling error and interobserver variability [3, 4]. Therefore, many efforts to develop noninvasive markers reflecting whole-liver stiffness have been made. Blood markers such as platelets, hyaluronic acid (HA), type 4 collagen 7S (4C7), or algorithm-based serum models such as FIB4 index or aminotransferase/platelet ratio index (APRI), have been tried for estimating liver fibrosis and reported to be effective for prediction of liver fibrosis [5]. However, such blood markers can be affected by various factors related or unrelated to the liver [6].

On the other hand, elastography has been developed as a procedure able to evaluate liver stiffness noninvasively. Especially, transient elastography using shear-wave speed techniques, FibroScan® (EchoSens, Paris, France) or acoustic radiation force impulse (ARFI) have been shown to be a useful noninvasive method of assessing liver fibrosis [7, 8]. Liver stiffness evaluated with shear-wave elastography is strongly associated with the degree of liver fibrosis in patients with chronic liver diseases [8, 9].

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However, shear-wave elastography has been reported to be limited in patients with severe obesity or ascites [10, 11]. Furthermore, the former requires special equipment and is expensive. On the other hand, real-time tissue strain elastography (SE) can be performed with a conventional ultrasound probe during a routine ultrasonography examination. SE has been shown to be effective, even in patents with ascites [12]. Several studies have also shown the effectiveness of SE to estimate liver fibrosis in patients with chronic liver diseases [13–16]. However, negative results as compared with shear-wave elastography have been reported [17, 18]. Thus, SE is relatively effective and easily obtained, but further research is still required to provide more evidence and to establish the standardized method [6, 19].

In this study, we evaluated the effectiveness of SE using a large cohort including patients with various degrees of liver fibrosis and its application in estimating the prognosis of chronic liver diseases.

Methods

Patients

We retrospectively evaluated 598 patients who were underwent ultrasonography and SE at our department between October 2013 and June 2015. As the reason of receiving ultrasonography, most of them were for the evaluation of chronic liver diseases. Other reasons were for the evaluation of metastatic liver tumor, biliary diseases, or other gastrointestinal diseases. Therefore, the present study included various livers with various stiffnesses from normal liver to cirrhosis, and then patients with normal liver were used as a normal control. As the etiology of liver diseases, we regarded patients with anti-hepatitis C virus (HCV) antibody and HCV-RNA as HCV, those with hepatitis B virus (HBV) surface antigen as HBV, those with alcohol drinking history ($\geqq$60 g/day in men and $\geqq$40 g/day in women for at least 5 years), improvement of liver enzymes by cessation of drinking and without other etiologies as alcoholic liver disease (ALD) [20], and those with steatosis and without alcohol drinking history (<30 g/day in men and <20 g/day in women) and other etiologies as non-alcoholic fatty liver disease (NAFLD) [21]. Autoimmune hepatitis (according to diagnostic criteria by an international autoimmune hepatitis group [22]), primary biliary cholangitis (according to the clinical practice guideline in Japan [23]) or drug-induced liver injury (according to the diagnostic scale in Japan [24]) were included as 'Others'. Patients with normal liver function and without definite etiology were defined as 'Normal'. Patients with superinfection of both HBV and HCV or liver dysfunction without definite etiology were not included in this study. Diagnosis of hepatocellular carcinoma (HCC) was confirmed by histological examination or radiological findings with increase of tumor markers such as α-fetoprotein or des-γcarboxyprothrombin. Finally, we assessed liver-related death, liver failure, and HCC in 598 cases who underwent SE. This retrospective study was approved by the institutional ethics committee. Written informed consent was obtained from all patients included in this study.

Liver stiffness measurement

SE was performed by conventional ultrasonography equipment manufactured by GE Healthcare (Logic E9, USA) according to the manufacture's protocol and the guidelines published by the World Federation for Ultrasound in Medicine and Biology (WFUMB) [6]. Briefly, a linear probe (9L, 9 MHz) was used at the right lobe of the liver with right intracostal scanning. SE was acquired with little compression during brief breath-hold so that SE could be naturally generated by heartbeat. Adequate acquisition of SE was confirmed whether the indicator located at the upper left of panel kept green. When we analyzed the results, the value of the indicator was shown at the bottom of the panel with same color and the record of SE was accepted while the indicator was showing green. The target region of interest (ROI, E1) was placed inside the liver parenchyma at about 1 cm under the liver capsule to avoid large vessels. Tumor area such as HCC or metastatic liver tumor was also avoided by B-mode imaging. Because elastography was obtained as relative evaluation in the target lesion in this system, control ROI (E2) was placed at subcutaneous tissue in this study, and then the elasticity index (EI) was set up as E1/E2. Then, average EI for 5 s at three times and in three different points was finally recorded. Two hepatologists with over 15 years of experience (KT and KK) performed these procedures independently.

Histological assessment of liver stiffness

Histological assessment of liver fibrosis was evaluated by the results of ultrasound-guided liver biopsy or surgical resected specimens performed within 3 months of SE. Liver biopsy was performed with an 18-G needle, and specimens containing fewer than five portal areas were excluded from histologic analysis. Fibrosis was classified by the METAVIR system into four categories (F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis and few septa; F3, numerous septa without cirrhosis; F4, cirrhosis). Necroinflammatory activity was graded A0, absent; A1, mild; A2, moderate; and A3, severe [25].

Other markers for evaluation of liver stiffness

We evaluated blood platelet count, serum hyaluronic acid (HA), and type 4 collagen 7S (4C7) as liver fibrosis markers. Blood samples collected at the same day SE was done were used for these analyses. FIB4 index and aspartate aminotransferase platelet ratio index (APRI) were applied for the evaluation of liver stiffness [26, 27]. The FIB4 index was calculated by age × AST[IU/l]/(platelet count $[10^9/L] \times ALT[IU/l]^{0.5}$) [26], whereas APRI was calculated AST/upper normal limit/platelet count$[10^9/l] \times 100$ [27]. We then evaluated the relevance between these markers and EI.

Statistical analysis

We evaluated the correlation between fibrotic markers including EI by Spearman's correlation test. We compared the difference between the two groups using Student's *t* test. For the evaluation of diagnostic value, area under the receiver operating characteristic curve was assessed. Furthermore, we evaluated the intraclass correlation coefficient (ICC) among a part of cases ($n = 193$) between two observers (KT and KK) according to the etiology of liver diseases. The ICC was defined as follows: slight, $0 \leq ICC < 0.20$; fair, $0.21 \leq ICC < 0.40$; moderate, $0.41 \leq ICC < 0.60$; substantial, $0.61 \leq ICC < 0.80$; and almost perfect, $0.81 \leq ICC$ [28]. For calculation of survival time, Kaplan–Meier survival curve was evaluated and log-rank test was used in comparison of survival time between each of the groups. As for univariate and multivariate analysis for predicting the outcome of liver-related death, Cox regression analysis was employed. Statistical evaluation was performed with SPSS software, version 19.0 (SPSS). Statistical significance was defined as $p < 0.05$.

Results

Patient characteristics

The characteristics of patients enrolled in this study are shown in Table 1. As shown, 93 patients with normal liver were included in this study. Thus, 505 patients with chronic liver injury including 276 patients with liver cirrhosis were enrolled. For the diagnosis of liver cirrhosis, it was clinically diagnosed by symptoms (e.g., ascites, esophageal varices, hepatic coma), blood test (e.g., platelet, AST/ALT ratio) or radiological findings (e.g., splenomegaly, liver atrophy, liver surface pattern). As the etiology of liver injury, most were caused by HCV ($n = 238$) followed by ALD + NAFLD, HBV, and Normal. Other etiologies, such as autoimmune hepatitis, primary biliary cholangitis, or drug-induced liver injury), were few in this study. Fourteen patients, who had been obtained sustained viral response (SVR) within 2 years before the SE examination, were included in the HCV group. Twelve patients with HCV were successfully treated by direct-acting antivirals and received SVR after the SE examination. This study cohort included 265 patients with HCC (44.3% in the total of 598 cases). Regarding the stage of HCC, Barcelona-Clinic Liver Cancer (BCLC) staging O-A, B, C and D was 112, 69, 73, and 11 patients, respectively [29]. Thus, relatively advanced cases with HCC were included in this study. Histological evaluation of liver fibrosis was determined in 167 cases using METAVIR score (F0, 18 cases; F1, 52 cases; F2, 23 cases; F3, 20 cases; F4, 54 cases). Activity of inflammation was assessed in 98 cases (A0, two cases; A1, 39 cases; A2, 50 cases; A3, seven cases).

Acquisition of the elasticity index

We obtained the EI as shown in Fig. 1. Soft tissues are shown in red, whereas hard tissues are shown in blue as their stiffnesses progress. Subcutaneous tissue is shown as soft tissues with red color. Average SE in control subcutaneous ROI (yellow circle and yellow line) was 1.16 ± 0.46 in whole 598 cases. In the liver with low chronicity, liver parenchyma is shown in red to yellow, and the EI was around 2 in the liver with F1 (Fig. 1a). In contrast, in cirrhotic liver, liver parenchyma is shown in green to blue, and the EI was over 4 in the liver with F4 (Fig. 1b).

Correlation between EI and liver fibrosis

Next, we evaluated the association between the EI and liver histological fibrosis. The EI was increased as liver fibrosis was advanced (Fig. 2a). When we divided patients into two groups, namely those with mild fibrosis (F0, F1, and F2 in METAVIR score) and those with advanced fibrosis (F3 and F4 in METAVIR score), EI was significantly different between the two groups (mild fibrosis vs. advanced fibrosis: 2.53 vs. 3.70, $p < 0.001$). In contrast, EI was similar among those with different activity score A0 to A3 (Fig. 2b).

When we analyzed the association between EI and histological fibrosis score according to the etiology of liver diseases, significant differences between mild fibrosis and advanced fibrosis were found in HCV infection and ALD/NAFLD (2.56 vs. 4.05, $p < 0.001$; 2.58 vs. 4.08, $p < 0.001$, respectively) (Fig. 2c and e). However, no significant difference was found in HBV infection (2.94 vs. 3.51, $p = 0.10$) (Fig. 2d). In HBV infection, the EI was relatively high in the mild fibrosis group. When we

Table 1 Characteristics of patients

Factors	Number or average ± SD
Gender (male/female)	369/229
Age (years)	66.3 ± 13.2
Body mass index (kg/m^2)	24.5 ± 1.5
Clinical diagnosis (NL/CLD/LC)	93/229/276
Etiology (HCV/HBV/ALD + NAFLD/others/normal)	238/102/116/50/92
HCC (present/absent)	265/333
Platelet count ($\times 10^4$/μl)	17.3 ± 8.9
Serum ALT (IU/l)	48.8 ± 52.2
Hyaluronic acid (ng/ml)	382.0 ± 654.7
Type 4 collagen 7S (ng/ml)	7.5 ± 4.1
APRI	1.6 ± 3.1
FIB4 index	4.1 ± 3.9
Elasticity index	3.11 ± 1.03
Fibrosis (F0/F1/F2/F3/F4)	18/52/23/20/54
Activity (A0/A1/A2/A3)	2/39/50/7

NL normal liver, *CLD* chronic liver disease, *LC* liver cirrhosis, *HCV* hepatitis C virus, *HBV* hepatitis B virus, *ALD* alcoholic liver disease, *NAFLD* non-alcoholic fatty liver disease, *HCC* hepatocellular carcinoma, *ALT* alanine aminotransferase, *APRI* aspartate aminotransferase platelet ratio index, *SD* standard deviation

evaluated the mismatched cases between EI and histological fibrosis, HBV infection or higher BMI might be associated the dissociation (Supplementary Table 1). Evaluation using surgically resected specimens might also be associated because fibrosis around HCC might be different from the part distant from the tumor. Collectively, the EI could diagnose advanced fibrosis, especially in HCV infection and ALD/NAFLD.

The reliability of EI

Among cases evaluating ICC ($n = 193$), the EI showed good reproducibility (ICC: 0.835). This tendency was also confirmed in cases with HCV infection (ICC: 0.859), whereas cases with HBV infection and ALD/NAFLD showed relatively weak reproducibility between each observer (ICC: 0.792 and 0.703, respectively) (Supplementary Table 2). In the ALD/NAFLD group, body mass index (BMI) was significantly higher as compared with other groups (vs. HCV and HBV, $p < 0.001$ and $p = 0.001$, respectively).

The relationship between EI and other fibrosis markers

Diagnostic performance assessed by receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC) analysis showed relatively good diagnostic ability for F4 and advanced fibrosis (F3 and 4) (AUC: 0.768 and 0.774, respectively). Especially the EI showed better AUC in predicting advanced fibrosis (F3 and F4). Furthermore, EI showed better diagnostic value as compared to other fibrosis makers such as HA, 4C7, APRI, and the FIB4 index (Fig. 3a and b).

The association between EI and serum fibrosis marker was also evaluated. As shown in Fig. 3c, the EI showed good associations with other fibrosis markers. However, the EI was not relevant to serum ALT consistent with the result of histological findings.

Thus, the EI had a better diagnostic performance for predicting advanced fibrosis than serum fibrosis markers and could distinguish advanced liver fibrosis independent of liver inflammatory activities.

EI and prognosis

We assessed whether EI could predict the prognosis of patients. During the observation period (median, 2.1 years, range, 1.1–4.1 years), death was found in 64 cases. Among them, liver-related death (liver failure, HCC) was found in 44 cases (7.4%, among 598 cases; 23 cases with liver failure and 21 cases with HCC). Among these 44 cases, 41 (93.2% in cases with liver-related death) had HCC. As for non-liver-related death, other malignancy was found in ten cases, cerebral vascular accident in four cases, myocardial infarction in two cases, pneumonia in two cases, and unknown sudden death in two cases.

As for hepatic decompensation, it was found in 24 cases in the entire cohort. Hepatic decompensation was found in seven cases without HCC, and average EI of them was significantly higher than that of cases without hepatic decompensation (4.04 vs. 2.79, $p = 0.02$). In BCLC-O-A

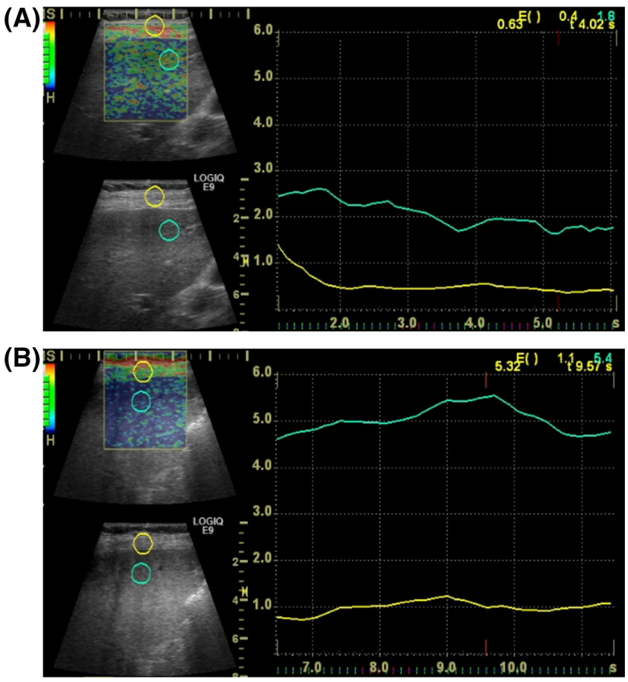

Fig. 1 Acquisition of the elasticity index (EI). The target region of interest (ROI, E1, *green*) was placed inside the liver parenchyma at about at about 1 cm under liver capsule to avoid large vessels. Control ROI (E2, *yellow*) was placed at subcutaneous tissue. The procedures were performed with light compression and breath-hold. The EI was recorded to keep stable acquisition of EI while the indicator located at the *upper left of panel* shows *green* (the status of the indicator is shown in the *bottom of the panel*, representative data). The EI was set up as E1/E2. Then average EI for 5 s at three times was finally recorded. **a** Case with mild liver fibrosis, a 67-year-old female, chronic hepatitis due to hepatitis C virus infection, A1F1. EI: 2.0. **b** A 65-year-old female with liver cirrhosis due to hepatitis C virus infection, A1F4. EI: 5.0

HCC cases, recurrence was found in 32 cases during the observation period. The EI in HCC recurrence cases was higher than cases without recurrence (3.77 vs. 3.21, $p = 0.02$). HCC developed in one case (EI: 3.8) who had no HCC at SE examination. Thus, high EI might be associated with not only hepatic decompensation but also HCC development.

In multivariate analysis, presence of HCC, high 4C7, and high EI were independently associated with liver-related death (Table 2). Regarding platelet count, it was controversially associated with liver-related mortality. Further investigation was required for evaluating the prognostic value of platelets for liver-related death. Among this cohort involving a considerable number of patients with HCC, EI showed good prognostic value for liver-related death except for the presence of HCC. In the cohort without HCC, liver-related death (liver failure) was found in three cases, and they all showed high EI (EI: 3.8, 4.1, and 5.7). In the HCC cohort, BCLC staging was the strongest predictor of the prognosis because survival curves were clearly stratified according to BCLC stage (Supplementary Fig. 1). In the cohort with BCLC-C HCC, high ALT and high EI were independently associated with survival (Table 3). EI was a more powerful indicator for predicting survival than ALT in BCLC-C HCC. In other BCLC stages, EI could not show statistical significance in multivariate analysis whereas statistical significance was found in univariate analysis (data not shown). Thus, EI could be a prognostic indicator in patients with BCLC-C. In other BCLC stages, except for BCLC-C, some confounding factors such as therapeutic effect might be found.

Discussion

In this study, SE was effective in predicting advanced fibrosis of the liver as well as the prognosis. Our results showed the effectiveness of SE as compared with other fibrotic blood markers using a large cohort including normal liver. In previous studies for the prediction of liver stiffness with SE, SE had good performance if adequate procedure was performed. The ROI with 2.5 × 2.5 cm should be placed deep to the liver capsule and avoid large vessels so that uniform images could be generated [13, 30–32]. Our study was also performed to be included adequate size of liver parenchyma according to such guidelines of SE. Because EI, which had been used as an indicator in this study, showed good associations with histological fibrosis and other fibrosis markers, our results were meaningful. Our analytic method used in this study is based on relative evaluation of liver stiffness, and therefore was concerned with the sensitivity of liver stiffness evaluation. Our results showed that EI could not fully distinguish between liver cirrhosis (F4) and advanced liver fibrosis (F3 ad 4). However, in a past largest study including 295 cases with HCV ad HBV from Japan, SE showed an accurate diagnosis rate for ≥F3 and F4 with 78.3 and 78.4%, respectively [13]. In another study of SE using HCV patients from Japan, the specificity for diagnosis of ≥F3 and F4 was 96.4 and 91.5%, respectively [14]. Furthermore, another study using HBV patients from China, the diagnostic accuracy of SE by AUROC for ≥F3 and F4 was 0.84 and 0.66, respectively [33]. In a study of SE using HCV patients from Italy, the sensitivity for diagnosis for ≥F3 and F4 was 91.7 and 66.7%, respectively [17]. Thus, previous studies, as well as our results, indicated that SE might have relatively weak performance to distinguish between F3 and F4. SE might be suitable for diagnosing advanced fibrosis easily, not but cirrhosis. In a study comparing SE, shear-wave elastography, and ARFI, failure or inconsistent results occurred in 12.5% of the attempts at shear-wave elastography, but in none of the attempts at SE and ARFI [34]. SE can evaluate liver

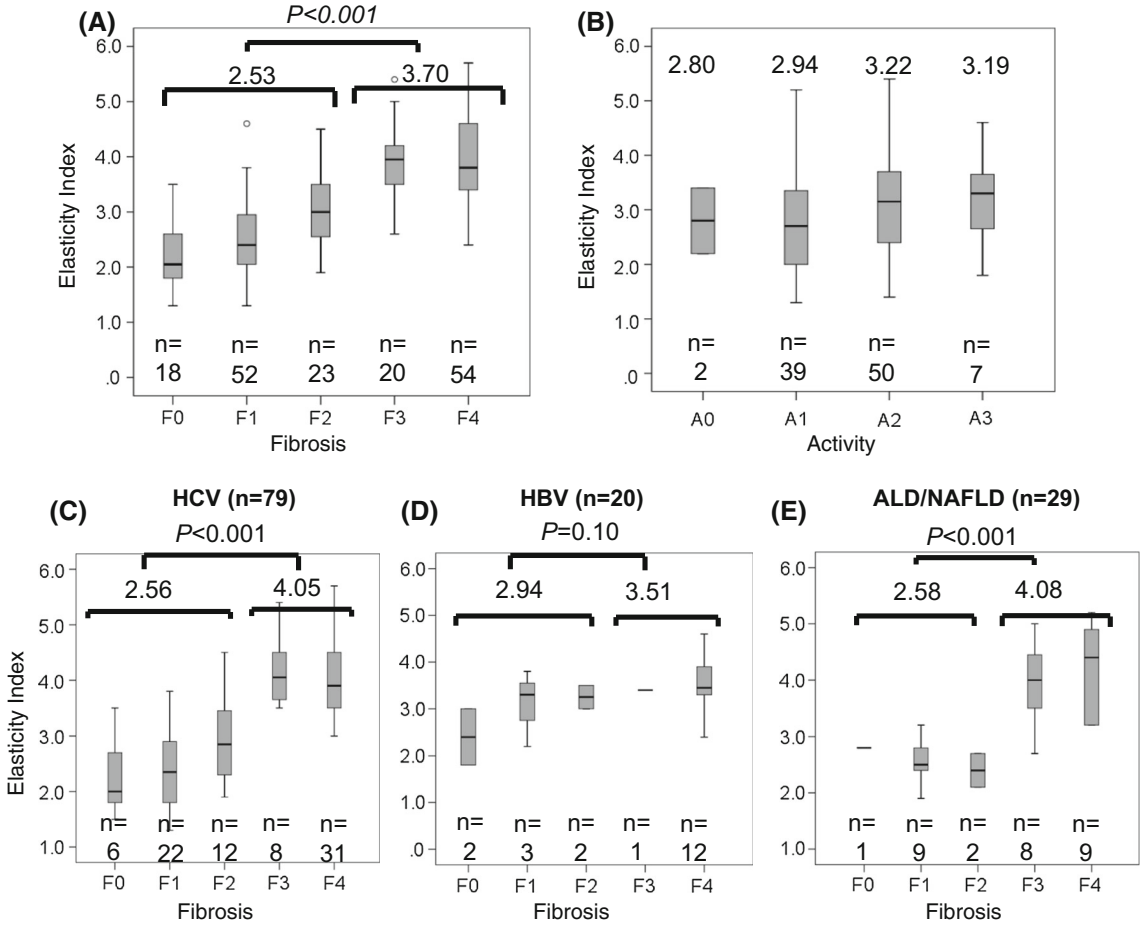

Fig. 2 Correlation between EI and histological-proven fibrosis. **a** Fibrosis and the EI. The *Y*-axis indicates the EI value and the *X*-axis represents the METAVIR score F0 to F4 confirmed histologically. The *number at the top of box* represents the average EI of indicated groups (2.53 in no-advanced fibrosis group, F0–F2; 3.70 in advanced fibrosis group, F3 and 4). **b** Inflammatory activity and the EI. The *Y*-axis indicates the EI value and the *X*-axis represents the activity score A0 to A3. The *number of the top of box* represents each average EI. **e–g** The relationship of EI and fibrosis score in each etiology. The *number at the top of box* represents the average EI of indicated groups. The *number at the top of column* represents the *p* value. **c** HCV infection, $N = 79$. **d** HBV infection, $N = 20$. **e** ALD/NAFLD, $N = 29$

fibrosis without being affected by liver inflammation, jaundice, and blood congestion [6]. Furthermore, SE could be evaluated in patients with ascites [12]. SE might be suitable as a comprehensive procedure for estimation of advanced liver fibrosis.

As for prediction of the prognosis of liver disease, liver-stiffness measurements using shear-wave elastography were shown to be useful in predicting disease progression such as death, liver decompensation, liver cancer, worsening of liver reserve function, or portal hypertension-related complications [35–40]. However, few data are found regarding the prognostic capacity of SE. Our data showed that SE could independently predict liver-related death (HR 1.631, Table 2). Furthermore, SE could also predict death in HCC patients with BCLC-C (HR 2.205, Table 3). Because our cohort included many patients with advanced HCC, liver-related death was found in such patients. Therapeutic cure could be obtained in BCLC-0, A, and B patients. However, therapeutic cure is hardly found in BCLC-C HCC patients [29]. Also in previous studies, ALT had been shown to be a prognostic factor regarding HCC recurrence in HCC patients [41, 42]. Although further investigations on how EI is contributing to the clinical course in HCC patients should be required, we might consider the possibility of recurrence or progression of HCC in patients with high EI. Collectively, EI might be a prognostic factor in liver diseases, and also might be a possible prognostic factor in HCC patients. Further investigations are desired.

There are several limitations in this study. At first, EI, the indicator used in this study to show liver stiffness, was a relative evaluation of liver stiffness. In the guidelines of the WFUMB, objective assessment can be made only by the use of the liver fibrosis (LF) index [30] because only

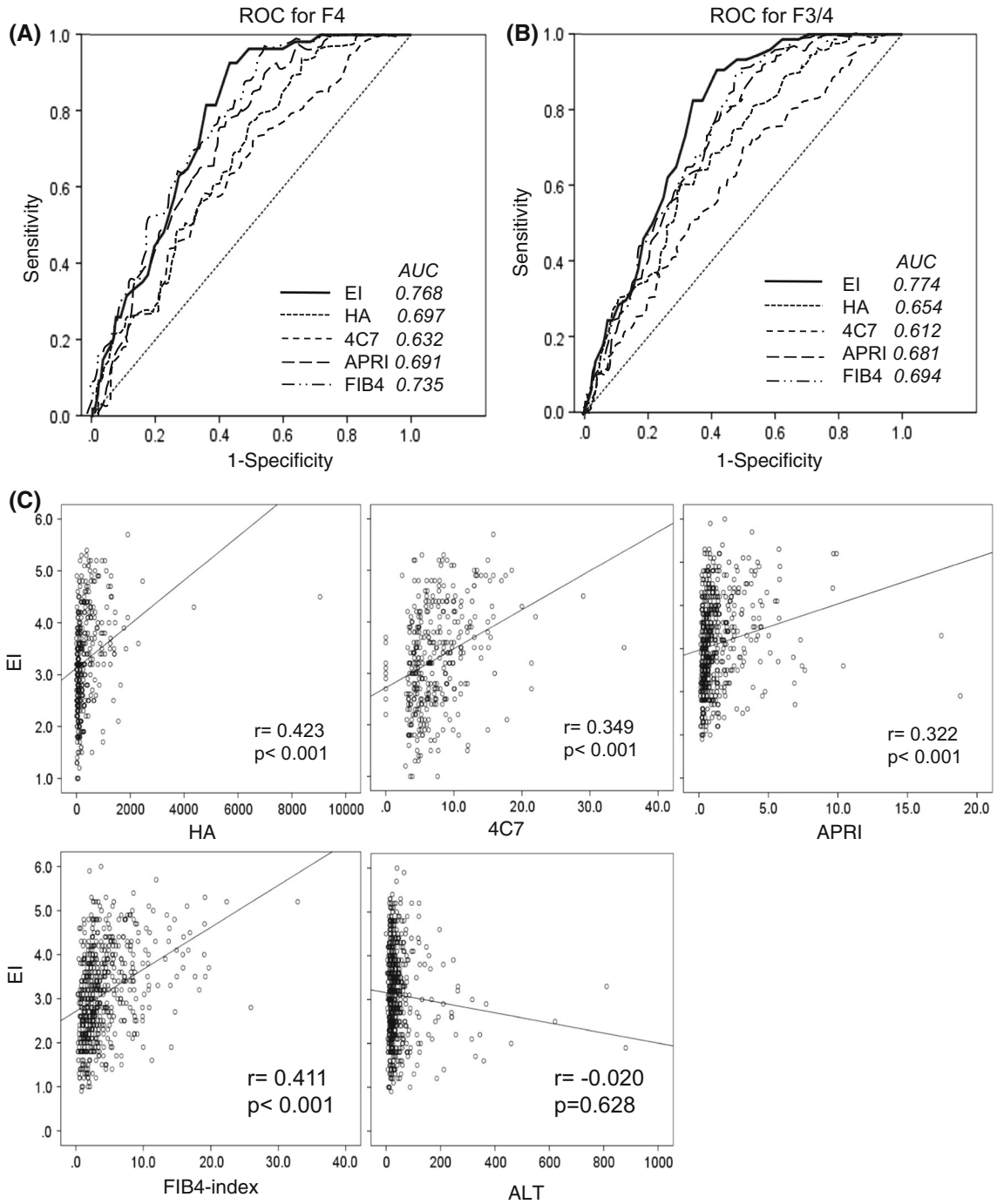

Fig. 3 Relationship between the EI and other liver fibrosis markers. **a**, **b** Receiver operating characteristic (ROC) curve for EI and other fibrosis markers for diagnosis of F4 (**a**) and advanced fibrosis (F3 and 4) (**b**). The *X*-axis represents specificity and the *Y*-axis represents sensitivity. The *italic number in the box* represents the area under the ROC curve (AUC). **c** *Scattered plot* between EI and fibrosis markers. *Numbers shown in each box* represent a correlation coefficient (*r*) and *p* value (*p*). *EI* elasticity index, *HA* hyaluronic acid, *4C7* type 4 collagen 7S, *APRI* aspartate aminotransferase platelet ratio index, *ALT* alanine aminotransferase

the LF index had a validation study [13]. The WFUMB recommends that further multicenter studies are needed for validation of SE [13]. The European and Romanian elastography guidelines also suggest that further research concerning SE is required [43, 44]. Standardized analytic method in SE should be established in future larger multicenter studies. Second, the heterogeneity of EI was found according to the etiology of liver diseases. EI could predict advanced fibrosis in HCV and ALD/NAFLD but could not in HBV. This may be due to that our study cohort included

Table 2 Univariate and multivariate analysis for predicting the prognosis in the entire cohort

Univariate			Multivariate	
Factors	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age (year)	1.036 (1.007–1.065)	0.014	1.010 (0.973–1.048)	0.596
Gender (female)	0.668 (0.349–1.276)	0.221		
HCC (absent)	0.049 (0.015–0.159)	<0.001	0.107 (0.032–0.361)	<0.001
Platelet ($\times 10^4/\mu l$)	0.945 (0.905–0.986)	0.009	1.047 (1.005–1.090)	0.027
ALT (IU/l)	0.998 (0.993–1.003)	0.505		
HA (ng/ml)	1.001 (1.000–1.001)	<0.001		
4C7 (ng/ml)	1.105 (1.056–1.156)	<0.001	1.080 (1.007–1.160)	0.032
APRI	1.022 (0.974–1.072)	0.380		
FIB4	1.105 (1.057–1.156)	<0.001	0.989 (0.896–1.160)	0.834
EI	2.211 (1.629–3.001)	<0.001	1.631 (1.070–2.487)	0.023

CI confidential interval, *HCC* hepatocellular carcinoma, *ALT* alanine aminotransferase, *HA* hyaluronic acid, *4C7* type 4 collagen 7S, *APRI* aspartate aminotransferase platelet ratio index, *FIB4* FIB4 index, *EI* elasticity index

Table 3 Univariate and multivariate analysis for predicting the prognosis in BCLC-C HCC cohort

Univariate			Multivariate	
Factors	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age (/year)	1.009 (0.964–1.057)	0.696		
Gender (female)	0.779 (0.232–2.616)	0.686		
Platelet ($\times 10^4/\mu l$)	0.999 (0.953–1.047)	0.958		
ALT (IU/l)	1.018 (1.009–1.028)	<0.001	1.015 (1.002–1.028)	0.019
HA (ng/ml)	1.000 (0.999–1.001)	0.837		
4C7 (ng/ml)	1.134 (0.997–1.289)	0.056		
APRI	1.371 (1.097–1.715)	0.006	1.077 (0.797–1.456)	0.628
FIB4	1.061 (0.973–1.158)	0.181		
EI	2.124 (1.215–3.711)	0.008	2.025 (1.111–3.690)	0.021

HCC hepatocellular carcinoma, *BCLC* Barcelona-Clinic Liver Cancer, *CI* confidential interval, *ALT* alanine aminotransferase, *HA* hyaluronic acid, *4C7* type 4 collagen 7S, *APRI* aspartate aminotransferase platelet ratio index, *FIB4* FIB4 index, *EI* elasticity index

a small number of HBV cases with histological results. On the other hand, ICC was low in patients with obesity in our study. Successful SE depends on the clarity of B-mode images [13]. Our results showed that acquisition of EI might be unstable with thick subcutaneous tissue cases. Furthermore, severe irregularity of liver parenchyma by B-mode echogram was found in HBV infection [45], which might have some effects in EI in HBV. Further investigations about HBV are required. Third, our study was only a retrospective study. Further observation is desirable in analyses of survival time in HCC patients with early stages and in evaluation of HCC recurrence. Prospective studies with longer observation periods are needed to clarify the significance of EI as the prognostic factor in HCC.

In conclusion, our study showed that SE using EI could predict advanced liver fibrosis easily. Our study also confirmed that SE is not affected by liver inflammation. SE might be a prognostic factor in chronic liver diseases and in HCC.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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