Table 2 Variables that predict HCC development: univariate and multivariate analyses

Variables	Univariate		Multivariate	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Male	0.56 (0.29–1.95)	0.755		
Age (per year)	1.06 (1.00–1.12)	0.039	1.08 (1.01–1.16)	0.024
Cirrhosis	14.37 (1.90–108.44)	0.009	3.54 (0.37–33.77)	0.231
HCV (vs HBV)	4.39 (0.58–33.17)	0.151		
Platelet count (per 10^{10}/L)	1.19 (1.06–1.33)	0.003	1.17 (1.03–1.35)	0.017
ALT (per IU/L)	1.00 (0.99–1.02)	0.423		
γ-GT (per IU/L)	1.00 (0.99–1.01)	0.688		
AFP >10 ng/mL	3.98 (1.47–10.77)	0.006	1.47 (0.49–4.33)	0.486
Non-clean liver	12.36 (4.68–32.61)	<0.001	9.41 (3.47–25.46)	<0.001

γ-GT, γ-glutamyltransferase; AFP, α-fetoprotein; ALT, alanine aminotransferase; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

DISCUSSION

THIS STUDY REVEALED presence of hypovascular hypointense liver nodules (non-clean liver) on gadoxetic acid-enhanced MRI, is a significant risk factor for subsequent development of typical HCC not only at the same sites but also at the different sites from the initial nodules. The incidence of development of typical HCC in the non-clean liver patients was more than 50% during a 3-year follow-up period, indicating that these higher risk patients should be rigorously investigated for the early detection of HCC during follow up.

In the present study, six of the 18 patients in the non-clean liver group developed typical HCC at the same site of the initial nodules during the subsequent 3 years (11.1%/year). Most of the hypovascular hypointense nodules on gadoxetic acid-enhanced MRI are considered precursor lesions of typical HCC, such as early HCC or high-grade dysplastic nodules, on histological examination,[13–15] while it has been reported that most hypovascular nodules exhibiting high-intensity to isointensity signals in the hepatocyte phase are benign hepatic nodules.[14,15] Recent studies have suggested that a reduction of organic anion-transporting polypeptide 1B3 (OATP 8) transporter expression begins at the earliest stage of hepatocarcinogenesis,[21,22] before changes in vascularity such as decreased portal flow or increased arterial flow. The progression rate of the small

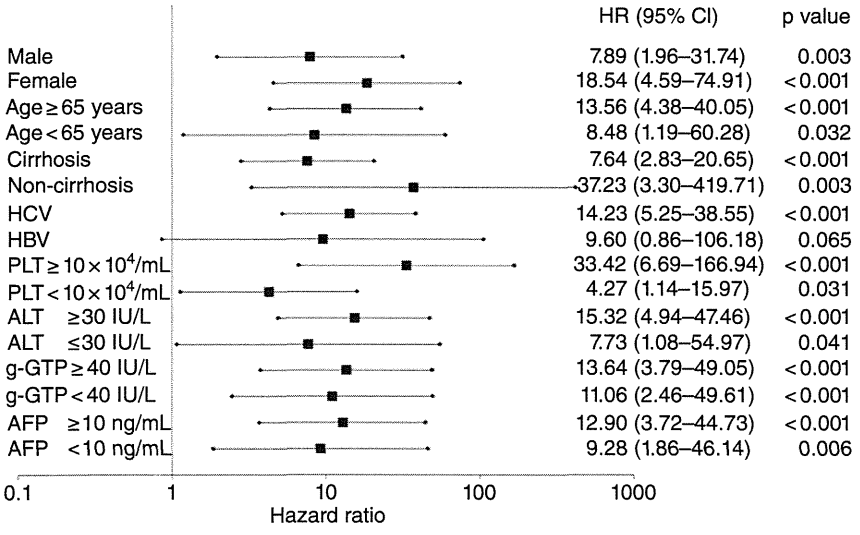

Figure 4 Stratified analyses of the non-clean liver as a risk factor for typical HCC development. AFP, α-fetoprotein; ALT, alanine aminotransferase; CI, confidence interval; g-GTP, γ-glutamyltransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; PLT, platelets.

hypovascular hypointense nodules to typical HCC was reported as 10–17%/year,[9,10] which is comparable to the present study. Typical HCC arose exclusively among the nodules of 8 mm or more, as in previous studies in which the larger hypovascular hypointense nodules were found to be the risk factor for progression to typical HCC in the initial MRI study.[9,10]

Hyperintensity on T2WI[12] or diffusion-weighted images (DWI)[11] also was reported to be useful for prediction of typical HCC progress in hypovascular hypointense nodules. In our patients, none of the nodules in the non-clean liver group showed hyperintensity on T2WI, suggesting that the hepatocyte phase is more sensitive for detecting the early stage of hepatocarcinogenesis.[15] DWI were not evaluated in this study because this usually detects pathologically advanced HCC of larger size or with hypervascularity.[23] Thus, it is reasonable that the hepatocyte phase can effectively recognize the earliest stage of HCC development without T2WI or DWI.

In 11 of 17 patients, typical HCC developed at sites other than the initially detected hypovascular hypointense nodules. As shown in Figure 3, the incidence rates of such HCC in the non-clean liver group was significantly higher than in the clean liver group ($P = 0.003$), indicating that a non-clean liver itself is a risk factor for HCC development, apart from the detectable hypovascular hypointense nodules. In addition, in four patients with nodules even below 8 mm, two developed HCC at different sites from the initial nodules during follow up (data not shown). Taken together, a non-clean liver has the higher potential for hepatocarcinogenesis or for undetectable precursor lesions. The non-clean liver may reflect more advanced genetic or epigenetic changes in the background hepatocytes, however, the detailed biological mechanism is not clear in this study.

Non-clean liver was an independent risk factor for the development of typical HCC, apart from well-documented risk factors (Table 2), such as cirrhosis,[24] ALT,[25] γ-GT,[26] age and AFP.[27] A non-clean liver is a significant risk for HCC development also for those without cirrhosis or with high platelet counts (Fig. 4). This means patients at increased risk of HCC development can be discerned as having a non-clean liver even among low-risk subgroups.

Conversely, patients without such nodules (clean liver group) showed a significantly lower risk of developing typical HCC than those with non-clean livers (0.0% vs 11.1% at 1 year, 6.8% vs 55.5% at 3 years of follow up; $P < 0.001$), suggesting that gadoxetic acid-enhanced MRI could detect precursor lesions sensitively enough to rule out immediate (within 1 year) development of typical HCC. Although seven patients in the clean liver group developed typical HCC only after 1 year, these patients had other risk factors for HCC development, including lower platelet counts, implying more advanced liver cirrhosis or high AFP (data not shown). Such HCC may arise from precursor lesions that cannot be visualized by current imaging techniques.

This study is a retrospective study and has some limitations. We included patients with HBV and HCV together, because gadoxetic acid-enhanced MRI findings or HCC development do not differ between these two groups and HBV or HCV infection is not an independent risk factor for typical HCC development. However, the number of HBV patients was too small ($n = 26$) to statistically confirm the current result when limited to HBV patients only. Prospective studies with larger numbers of patients who have uniform liver disease etiologies and imaging intervals are needed to verify our findings in different settings. Although the imaging interval of the non-clean liver group was shorter than the clean liver group (3 vs 4 months: $P = 0.015$), the median intervals between the initial MRI and HCC diagnosis was 16 months in the non-clean liver group and 21 months in the clean liver group. They are short enough for cumulative detection of HCC development for 3 years and it is assumed that there was little influence on the conclusions.

In conclusion, patients with chronic viral liver disease are at high risk for developing typical HCC at any sites of the liver if they have hypovascular hypointense nodules on gadoxetic acid-enhanced MRI. These patients should be closely followed up for developing typical HCC not only at the same site but also at different sites from the initial nodule.

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Hepatology Research

Hepatology Research 2014; 44: 720–727 doi: 10.1111/hepr.12179

Original Article

Prospective comparison of real-time tissue elastography and serum fibrosis markers for the estimation of liver fibrosis in chronic hepatitis C patients

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Aim: Real-time tissue elastography (RTE) is a non-invasive method for the measurement of tissue elasticity using ultrasonography. Liver fibrosis (LF) index is a quantitative method for evaluation of liver fibrosis calculated by RTE image features. This study aimed to investigate the significance of LF index for predicting liver fibrosis in chronic hepatitis C patients.

Methods: In this prospective study, 115 patients with chronic hepatitis C who underwent liver biopsy were included, and the diagnostic accuracy of LF index and serum fibrosis markers was evaluated.

Results: RTE imaging was successfully performed on all patients. Median LF index in patients with F0–1, F2, F3 and F4 were 2.61, 3.07, 3.54 and 4.25, respectively, demonstrating a stepwise increase with liver fibrosis progression ($P < 0.001$). LF index (odds ratio [OR] = 5.3, 95% confidence interval [CI] = 2.2–13.0) and platelet count (OR = 0.78, 95% CI = 0.68–0.89) were independently associated with the presence of advanced fibrosis (F3–4). Further, LF index was independently associated with the presence of minimal fibrosis (F0–1) (OR = 0.25, 95% CI = 0.11–0.55). The area under the receiver–operator curve (AUROC) of LF index for predicting advanced fibrosis (0.84) was superior to platelets (0.82), FIB-4 index (0.80) and aspartate aminotransferase/platelet ratio index (APRI) (0.76). AUROC of LF index (0.81) was superior to platelets (0.73), FIB-4 index (0.79) and APRI (0.78) in predicting minimal fibrosis.

Conclusion: LF index calculated by RTE is useful for predicting liver fibrosis, and diagnostic accuracy of LF index is superior to serum fibrosis markers.

Key words: chronic hepatitis C, fibrosis, liver fibrosis index, real-time tissue elastography

INTRODUCTION

AN ADVANCED STAGE of liver fibrosis in chronic hepatitis C (CHC) is associated with hepatocellular carcinoma development and complications such as esophageal variceal bleeding and liver failure.[1,2] Therefore, accurate evaluation of the stage of liver fibrosis is most important in clinical practice. Liver biopsy is considered to be the golden standard for diagnosis of liver fibrosis.[3–5] However, this method may be inaccurate because of sampling errors and interobserver variations.[6,7]

Improvements in a variety of non-invasive methods for evaluating liver fibrosis have recently emerged as alternatives to liver biopsy. Liver fibrosis was reportedly predicted by measurement of liver stiffness using transient elastography[8,9] and acoustic radiation force impulse (ARFI).[10,11] As assessed by blood laboratory tests, the aspartate aminotransferase (AST)/alanine

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Conflict of interest: The authors who have taken part in this study declare that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Received 28 January 2013; revision 20 May 2013; accepted 29 May 2013.

aminotransferase (ALT) ratio,[12] AST/platelet ratio index (APRI),[13,14] and FIB-4 index[15,16] have been reported to be useful for the prediction of liver fibrosis. We previously reported that the FIB-4 index is useful for the prediction of liver fibrosis progression.[17]

Real-time tissue elastography (RTE) is a non-invasive method for the measurement of tissue elasticity using ultrasonography.[18] RTE calculates the relative hardness of tissue from the degree of tissue distortion and displays this information as a color image. RTE was recently reported to be useful for predicting liver fibrosis.[19,20] To increase the objectivity of the evaluation, an image analysis method to evaluate the strain image features and a new algorithm to deliver an index were proposed. Liver fibrosis (LF) index is a quantitative method for evaluation of liver fibrosis that is calculated by nine RTE image features, and the significance of LF index for predicting liver fibrosis has been reported.[21,22]

In the present study, we prospectively investigated the significance of LF index calculated by RTE for the prediction of liver fibrosis in CHC patients. Further, diagnostic accuracy for liver fibrosis was compared between LF index and serum fibrosis markers.

METHODS

Patients

A TOTAL OF 127 consecutive patients with CHC were prospectively investigated. All patients underwent liver biopsy at Musashino Red Cross Hospital between February 2011 and November 2012. Exclusion criteria comprised the following: (i) co-infection with hepatitis B virus ($n = 1$); (ii) co-infection with HIV ($n = 1$); (iii) history of autoimmune hepatitis or primary biliary cirrhosis ($n = 3$); (iv) alcohol abuse (intake of alcohol equivalent to pure alcohol ≥40 g/day) ($n = 0$); (v) portal tracts of biopsy sample of less than five ($n = 7$); and (vi) presence of serious heart disease ($n = 0$). After exclusion, 115 patients were enrolled in this study. Written informed consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the institutional ethics review committees (application no. 24007).

Histological evaluation

Liver biopsy specimens were laparoscopically obtained using 13-G needles ($n = 93$). When laparoscopy was not conducted due to a history of upper abdominal surgery, percutaneous ultrasound-guided liver biopsy was performed using 15-G needles ($n = 22$). Specimens were fixed, paraffin-embedded, and stained with hematoxylin–eosin and Masson-trichrome. A biopsy sample with minimum portal tracts of five was required for diagnosis. All liver biopsy samples were independently evaluated by two senior pathologists who were blinded to the clinical data. Fibrosis staging was categorized according to the METAVIR score:[23] F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis. Activity of necroinflammation was graded on a scale of 0–3: A0, no activity; A1, mild activity; A2, moderate activity; and A3, severe activity. Percentage of steatosis was quantified by determining the average proportion of hepatocytes affected by steatosis and graded on a scale of 0–3: grade 0, no steatosis; grade 1, 1–33%; grade 2, 34–66%; and grade 3, 67% and over.

Clinical and biological data

The age and sex of the patients were recorded. Serum samples were collected within 1 day prior to liver biopsy and the following variables were obtained through serum sample analysis: AST, ALT and platelet count. FIB-4 index and APRI were calculated according to the published formula appropriate to each measure.[13,15]

RTE and LF index

Real-time tissue elastography was performed using HI VISION Preirus (Hitachi Aloka Medical, Tokyo, Japan) and the EUP-L52 linear probe (3–7 MHz; Hitachi Aloka Medical) within 3 days of liver biopsy. RTE was performed on the right lobe of the liver through the intercostal space. An RTE image was induced by heartbeats. Five RTE images were collected for each patient and analyzed to calculate nine image features. RTE method and the equation that calculates LF index using nine image features has been previously detailed.[22] Results are expressed as mean LF index of all measurements. Two hepatologists (N. T. and K. Tsuchiya, with 8 and 16 years of experience, respectively) performed RTE. In 32 patients with CHC, LF index was measured independently by two examiners. The correlation coefficient of LF index between two examiners was 0.85 ($P \leq 0.001$).

Statistical analysis

Correlations between LF index and histological fibrosis stage were analyzed using Spearman's rank correlation coefficients. Categorical variables were compared using Fisher's exact test, and continuous variables were compared using Mann–Whitney *U*-test. $P < 0.05$ was considered statistically significant. Logistic regression was

used for multivariate analysis. Receiver–operator curves (ROC) were constructed, and the area under the ROC (AUROC) was calculated. Optimal cut-off values were selected, to maximize sensitivity, specificity and diagnostic accuracy. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated by using cut-offs obtained by ROC. SPSS software ver. 15.0 (SPSS, Chicago, IL, USA) was used for analyses.

RESULTS

Patient characteristics

THE CHARACTERISTICS OF all 115 patients are listed in Table 1. F0–1 was diagnosed in 52 cases (45%), F2 in 31 (27%), F3 in 20 (17%) and F4 in 12 (11%). Mean values of LF index of F0 (2.62) and F1 (2.60) were not significantly different ($P = 0.9$), and only six patients with F0 were included in this study. Therefore, patients with F0 and F1 were integrated for the analysis. RTE imaging was successfully performed in all patients, and LF index was calculated.

Relationship between histological findings and LF index by RTE

The median value of LF index compared with the METAVIR fibrosis stage is shown in Figure 1. Median LF index in patients with F0–1, F2, F3 and F4 were 2.61, 3.07, 3.54 and 4.25, respectively, demonstrating a stepwise increase with liver fibrosis progression ($P < 0.001$). LF index of each fibrosis stage significantly differed from each other (F0–1 vs F2, $P < 0.001$; F0–1 vs F3, $P < 0.001$; F0–1 vs F4, $P < 0.001$; F2 vs F3, $P = 0.009$; F2 vs F4, $P = 0.001$). On the other hand, mean values of LF index in patients with steatosis grade 0, 1 and 2 were 2.99, 3.29 and 2.60, respectively, demonstrating no significant correlation (Fig. 2a). LF index was compared with steatosis grade for each fibrosis stage. LF index was not significantly different between patients with steatosis and without steatosis (Fig. 2b).

Liver fibrosis index was compared with histological activity. A significant correlation existed between histological activity and fibrosis stage. Therefore, the relationship between LF index and histological activity was examined by each fibrosis stage. In patients with F0–1, the mean LF index of A1, A2 and A3 was 2.60, 2.58 and 2.40, respectively, demonstrating no significant correlation. Similarly, in patients with F2, F3 and F4, there was no significant correlation between LF index and histological activity (Fig. 3).

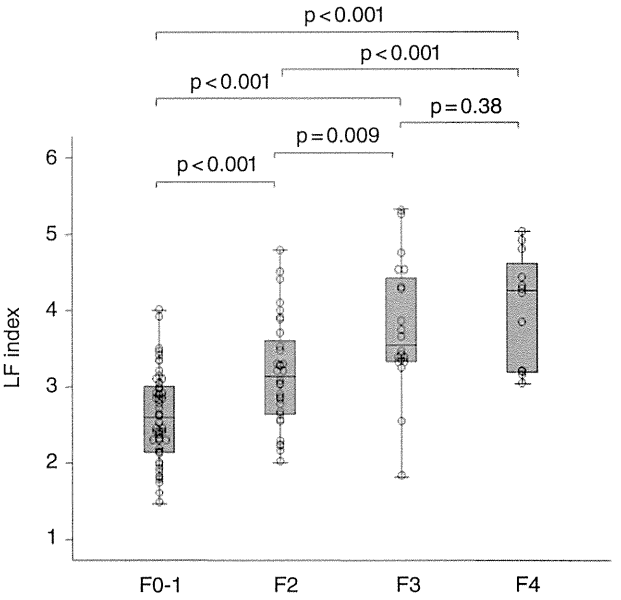

Figure 1 Correlation between liver fibrosis (LF) index calculated by real-time tissue elastography and fibrosis stage. Box plot of the LF index is shown according to each fibrosis stage. The bottom and top of each box represent the 25th and 75th percentiles, giving the interquartile range. The line through the box indicates the median value, and error bar indicates minimum and maximum non-extreme values.

Table 1 Patient characteristics

Characteristics	Patients ($n = 115$)
Female/male	68/47
Age (years)	57.9 ± 10.9
AST (IU/L)	55.7 ± 44.9
ALT (IU/L)	63.2 ± 56.3
Platelet counts ($\times 10^9$/L)	162 ± 53
Portal tracts of biopsy samples	12.6 ± 5.0
Fibrosis stage	
F0–1 (%)	51 (44)
F2 (%)	32 (28)
F3 (%)	20 (17)
F4 (%)	12 (11)
Histological activity	
A0 (%)	0 (0)
A1 (%)	75 (65)
A2 (%)	34 (30)
A3 (%)	6 (5)
Steatosis grade	
Grade 0 (%)	65 (57)
Grade 1 (%)	47 (41)
Grade 2 (%)	3 (2)
Grade 3 (%)	0 (0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

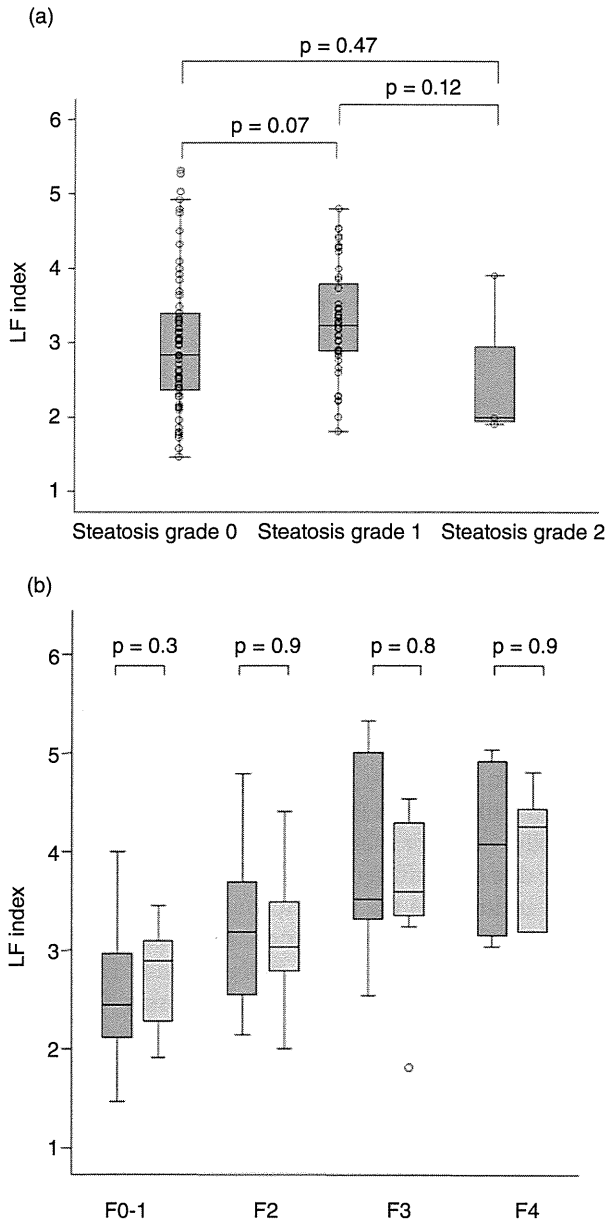

Figure 2 (a) Correlation between liver fibrosis (LF) index and steatosis grade. Box plot of the LF index is shown according to each steatosis grade. The bottom and top of each box represent the 25th and 75th percentiles, giving the interquartile range. The line through the box indicates the median value, and error bar indicates minimum and maximum non-extreme values. (b) Box plot of LF index for each fibrosis stage in relation to degree of steatosis grade. The bottom and top of each box represent the 25th and 75th percentiles, giving the interquartile range. The line through the box indicates the median value, and error bar indicates minimum and maximum non-extreme values. Dark grey bar chart indicates steatosis grade 0. Light grey bar chart indicates steatosis grade 1–2.

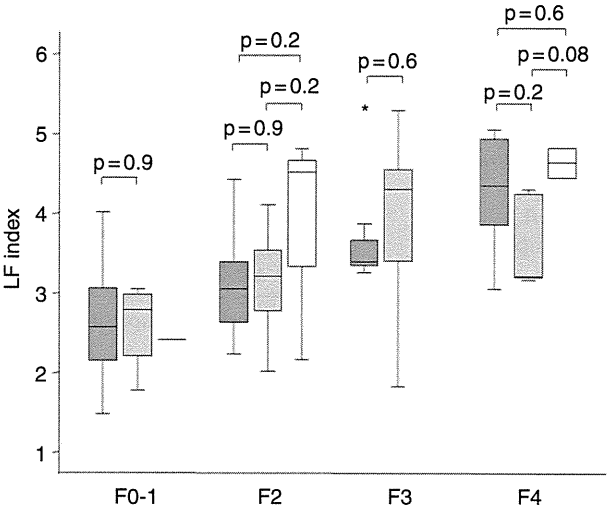

Figure 3 Box plot of liver fibrosis (LF) index for each fibrosis stage in relation to degree of necroinflammatory activity. The bottom and top of each box represent the 25th and 75th percentiles, giving the interquartile range. The line through the box indicates the median value, and error bar indicates minimum and maximum non-extreme values. Dark grey bar chart indicates activity grade 1. Light grey bar chart indicates activity grade 2. White bar chart indicates activity grade 3.

Comparison of variables associated with the presence of advanced fibrosis (F3–4) by univariate and multivariate analysis

Variables associated with the presence of advanced fibrosis (F3–4) were assessed by univariate and multivariate analysis (Table 2). The variables of age ($P = 0.03$) and LF index ($P < 0.001$) were significantly higher, and the variable of platelets ($P < 0.001$) was significantly lower in patients with advanced fibrosis than in patients with F0–2. Multivariate analysis showed that LF index (odds ratio [OR] = 5.3, 95% confidence interval [CI] =2.2–13.0) and platelets (OR = 0.78, 95% CI = 0.68–0.89) were independently associated with the presence of advanced fibrosis.

Comparison of variables associated with the presence of minimal fibrosis (F0–1) by univariate and multivariate analysis

Variables associated with the presence of minimal fibrosis (F0–1) were assessed by univariate and multivariate analysis (Table 3). The variables of age ($P < 0.001$), AST ($P = 0.02$) and LF index ($P < 0.001$) were significantly lower, and the variable of platelets ($P < 0.001$) was significantly higher in F0–1 patients than F2–4 patients.

Table 2 Variables associated with the presence of advanced fibrosis (F3–4) by univariate and multivariate analysis

	F0–2 ($n = 83$)	F3–4 ($n = 32$)	*P*-value (Univariate)	Odds ratio (95% CI) (Multivariate)
Age (years)	56.6 ± 10.9	61.3 ± 10.4	0.03	
Sex (female/male)	51/32	17/15	0.41	
AST (IU/L)	52.3 ± 43.3	64.4 ± 48.3	0.19	
ALT (IU/L)	62.9 ± 60.6	63.9 ± 44.2	0.93	
Platelets ($\times 10^9$/L)	179 ± 47	117 ± 42	<0.001	0.78 (0.68–0.89)
LF index	2.81 ± 0.69	3.86 ± 0.81	<0.001	5.30 (2.16–13.0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; LF, liver fibrosis.

Multivariate analysis showed that LF index was independently associated with the presence of minimal fibrosis (OR = 0.25, 95% CI = 0.11–0.55).

Diagnostic accuracy of RTE and serum fibrosis markers

Receiver-operator curves of LF index, platelets, FIB-4 index and APRI for predicting advanced fibrosis (F3–4), and minimal fibrosis (F0–1) were plotted, as shown in Figure 4. AUROC of LF index for predicting advanced fibrosis (0.84) was superior to platelets (0.82), FIB-4 index (0.80) and APRI (0.76). Similarly, for predicting minimal fibrosis, AUROC of LF index (0.81) was superior to platelets (0.73), FIB-4 index (0.79) and APRI (0.78). The corresponding sensitivities, specificities, PPV and NPV are detailed in Table 4.

DISCUSSION

IMPROVEMENTS IN VARIOUS methods for prediction of liver fibrosis have recently emerged as alternatives to liver biopsy. RTE is a non-invasive method for the measurement of tissue elasticity using ultrasonography. The utility of RTE for evaluating liver fibrosis is reported in a few studies.[18–22] However, for utilizing LF index, one of the equations used to calculate tissue elasticity by RTE is still unclear. The aim of this study was to investigate the significance of LF index for the prediction of liver fibrosis in CHC patients.

In this prospective study, we found that LF index is a useful predictive factor for diagnosis of the fibrosis stage in CHC patients. Increase in LF index significantly correlated with progression of the fibrosis stage and LF index was able to predict the presence of advanced fibrosis and minimal fibrosis. Previous studies reported the utility of LF index for prediction of the liver fibrosis stage.[21,22] In this study, LF index differed significantly between patients with F0–1 and F2; thus, LF index was especially useful for prediction of minimal fibrosis. This may be due to a sufficient number of patients with F0–1 and F2 included in the present study. This is an advantage of LF index because other quantitative methods by RTE could not discriminate patients with F0–1 and F2.[19,20] On the other hand, there is a possibility that a similar result may be obtained for differentiation of F3 and F4 if a large number of patients with advanced fibrosis was included.

Previous studies did not compare the diagnostic accuracy of LF index and serum fibrosis markers. We revealed that LF index performed better than serum fibrosis

Table 3 Variables associated with the presence of minimal fibrosis (F0–1) by univariate and multivariate analysis

	F0–1 ($n = 51$)	F2–4 ($n = 64$)	*P*-value (Univariate)	Odds ratio (95% CI) (Multivariate)
Age (years)	54.0 ± 11.9	61.0 ± 9.0	<0.001	
Sex (female/male)	31/20	37/27	0.74	
AST (IU/L)	44.5 ± 42.6	64.6 ± 44.9	0.02	
ALT (IU/L)	53.0 ± 56.3	71.3 ± 55.5	0.08	
Platelets ($\times 10^9$/L)	186 ± 47	142 ± 50	<0.001	
LF index	2.60 ± 0.59	3.51 ± 0.84	<0.001	0.25 (0.11–0.55)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; LF, liver fibrosis.

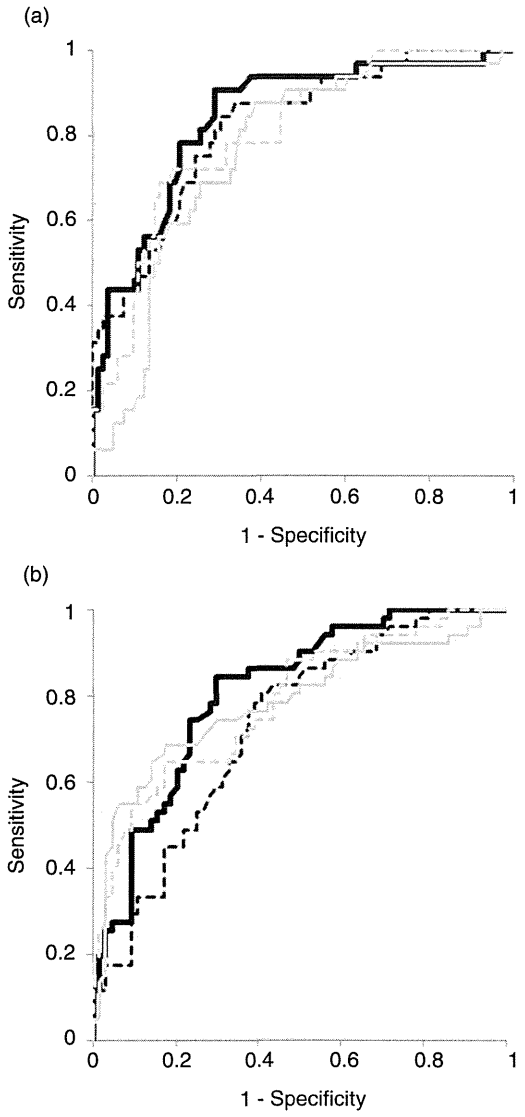

Figure 4 Receiver–operator curves (ROC) of liver fibrosis (LF) index and serum fibrosis markers. (a) ROC for diagnosis of significant fibrosis (F3–4). (b) ROC for diagnosis of minimal fibrosis (F0–1). —, LF index; ----, platelets; ——, aspartate aminotransferase-to-platelet ratio index; ·····, FIB-4 index.

markers based on blood laboratory tests for predicting liver fibrosis.

Transient elastography has been most commonly used to measure liver stiffness and is established in clinical practice to evaluate liver fibrosis.[8,9] RTE exhibits some advantages compared with transient elastography. In this study, RTE imaging was successfully performed in all patients, and LF index was calculated. Although transient elastography has high diagnostic capabilities when it comes to liver fibrosis, measurements are sometimes impossible in patients with severe obesity and ascites.[24] Reproducibility of transient elastography was reportedly lower in patients with steatosis, inflammation, increased body mass index and lower degrees of liver fibrosis.[25–27] On the other hand, LF index is measured by ultrasound guidance that facilitates the identification of a suitable location for elastographic measurement, thereby resulting in a higher number of patients with valid results.

Unlike transient elastography, another advantage of LF index is that the results are not influenced by the presence of inflammation and steatosis. It was reported that LF index is not useful in patients with steatosis.[22] However, LF index was not significantly different between patients with and without steatosis in the present study even after stratification by fibrosis stage. Thus, LF index was useful for prediction of fibrosis in CHC patients regardless of steatosis. Because LF index of each activity grade and steatosis grade did not differ from each other, estimation of liver fibrosis by LF index demonstrated higher reproducibility than transient elastography.

In previously reports, diagnostic accuracy of liver fibrosis using RTE was inferior to transient elastography;[28] however, other studies have reported contrasting results.[19] The reason for this variability is probably because RTE technology and the equations used to calculate tissue elasticity are rapidly changing. The utility of elastic ratio, another RTE method for evaluation of liver fibrosis, was reported.[20] The elastic ratio is the ratio between the tissue compressibility of the liver and that of the intrahepatic small vessel. The AUROC of elastic ratio for predicting advanced fibrosis was 0.94 and was superior to LF index. Further, ARFI and real-time shear wave elastography were reported to have a high diagnostic accuracy of liver fibrosis.[10,11,29] There are currently no studies that directly compare LF index and those methods for diagnostic value of liver fibrosis. Therefore, further studies are needed to fully explore the potential of RTE, especially with regard to LF index.

Our study had several limitations. The number of patients with advanced fibrosis was small. The potential of LF index to differentiate patients with F3 and F4 needs to be explored with a large number of patients. Further, validation study is needed to evaluate the diagnostic accuracy of fibrosis stage, especially in comparison with other modalities.

In conclusion, LF index calculated by RTE is useful for predicting liver fibrosis, and diagnostic accuracy of LF index is superior to that of serum fibrosis markers.

Table 4 Diagnostic performance of LF index and serum fibrosis markers

	F0–2 vs F3–4					F0–1 vs F2–4				
	AUROC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUROC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
LF index	0.84	90.6	71.1	54.7	95.2	0.81	84.3	70.3	69.4	84.9
Platelets	0.82	87.5	66.3	50.0	93.2	0.73	80.4	59.4	61.2	79.2
FIB-4 index	0.80	71.9	81.9	60.5	88.3	0.79	54.9	90.6	82.3	71.6
APRI	0.76	87.5	61.4	46.7	92.7	0.78	64.7	85.9	78.6	75.3

APRI, aspartate aminotransferase/platelet ratio index; AUROC, area under the receiver–operator curve; NPV, negative predictive value; PPV, positive predictive value.

ACKNOWLEDGMENT

THIS STUDY WAS supported by a Grant-in-Aid from Ministry of Health, Labor, and Welfare, Japan.

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J Gastroenterol (2014) 49:1175–1182
DOI 10.1007/s00535-013-0877-z

The Japanese Society of Gastroenterology

Liver stiffness measurement by acoustic radiation force impulse is useful in predicting the presence of esophageal varices or high-risk esophageal varices among patients with HCV-related cirrhosis

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Received: 5 August 2013 / Accepted: 23 August 2013 / Published online: 5 September 2013

Abstract
Background Screening and periodic surveillance for esophageal varices (EVs) by esophagogastroduodenoscopy (EGD) are recommended for cirrhotic patients. We investigated non-invasive liver stiffness measurement using acoustic radiation force impulse (ARFI) for the diagnosis of EV presence and high-risk EVs among patients with HCV-related cirrhosis.
Methods Among 181 consecutive patients with HCV-related cirrhosis, we studied 135 patients who had received EGD and ARFI. Serum fibrosis markers [platelet count, FIB-4, and aspartate aminotransferase-to-platelet ratio index (APRI)] were measured in a training set of 92 patients and compared with ARFI in the diagnostic performance for EV presence and high-risk EVs. Furthermore, the obtained optimal cutoff values of ARFI were prospectively examined in a validation set of 43 patients.
Results In the training set, the ARFI value increased with the EV grade ($p < 0.001$). The ARFI value for high-risk EVs was significantly higher than that for low-risk EVs ($p < 0.001$). AUROC values for diagnosis of EV presence and high-risk EVs by ARFI were 0.890 and 0.868, which had the highest diagnostic performance among factors including serum fibrosis markers. The optimal cutoff value of ARFI for EV presence was 2.05 m/s with good sensitivity (83 %), specificity (76 %), PPV (78 %), and NPV (81 %), and that for high-risk EVs was 2.39 m/s with good sensitivity (81 %), specificity (82 %), PPV (69 %), and NPV (89 %). These cutoff values obtained in the training cohort also showed excellent performance in the validation set.
Conclusions Liver stiffness measurement by ARFI is useful in predicting EV presence or high-risk EVs among patients with HCV-related cirrhosis.

Keywords Acoustic radiation force impulse · Esophageal varices · HCV-related cirrhosis · Portal hypertension · Liver stiffness

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Introduction

Esophageal varices (EVs) resulting from portal hypertension are present in approximately 50 % of patients with cirrhosis [1], and variceal bleeding is life-threatening with a 14 % mortality for hospitalized patients [2, 3]. The risk of bleeding has been shown to be related to the size of the varices, the presence of red signs, and the stage of liver insufficiency as evaluated by the Child–Pugh score [2, 4, 5]. Patients with high-risk EVs require prophylactic treatment to prevent variceal bleeding [1, 6]. Among patients with cirrhosis, the rate of EV incidence was reported to be 5 % at 1 year, 17 % at 2 years, and 28 % at 3 years, and the rate of EV progression from a small to a large size was found to be 12 % at 1 year, 25 % at 2 years, and 31 % at 3 years [7]. Therefore, cirrhotic patients should undergo periodic surveillance for EVs.

Esophagogastroduodenoscopy (EGD) is the gold standard for the diagnosis of EVs. American Association for the Study of Liver Diseases (AASLD) guidelines and Baveno V consensus strongly recommend screening EGD for all patients who are diagnosed with cirrhosis [1, 6]; the recommended intervals are 2–3 years for patients without varices and 1–2 years for those with small varices [6]. However, EGD causes psychological distress for patients when not performed under sedation, resulting in poor acceptance by patients. Furthermore, repeated EGD examinations can lead to complications and entail high costs. Therefore, instead of EGD, the development of non-invasive methods which can be useful in evaluating EVs is very important.

Several non-invasive markers such as platelet count, FIB-4 index, aspartate aminotransferase-to-platelet ratio index (APRI), and FibroTest have been examined as predictors of the accumulation of fibrosis and have been reported to predict the presence of EVs and large EVs in cirrhotic patients [8–10]. However, their performance values were not sufficiently accurate to support the use of these markers as alternatives to EGD. On the other hand, the platelet count/spleen diameter ratio (PSR) with a cutoff value of 909 has shown to have high sensitivity (100 %) and specificity (93 %) [11]. However, the PSR cutoff value (909) has not shown good accuracy for the prediction of EVs in a recent study [12].

As a non-invasive and ultrasound-based method, transient elastography (TE) has shown excellent diagnostic accuracy for the estimation of liver fibrosis [13, 14]. In addition, TE is useful for predicting portal hypertension [15]. However, TE measurements are difficult to perform with obese patients and when ascites is present, and the interfering structures such as blood vessels can not to be avoided in TE measurement [16]. On the other hand, acoustic radiation force impulse (ARFI), a new ultrasound imaging modality for evaluation of liver stiffness, can be performed for these patients, and a high level of accuracy of ARFI for predicting liver fibrosis has been reported over the last few years [17–19].

The aim of this study was to investigate whether ARFI can be useful in selecting patients with hepatitis C virus (HCV)-related cirrhosis who need screening EGD for the diagnosis of EV and who need EGD at short intervals for the diagnosis of the progression to high-risk EVs.

Patients and methods

The 181 consecutive patients with HCV-related cirrhosis visited in our hospital between April 2009 and January 2013. Among them, 40 patients did not undergo ARFI and 6 patients did not undergo EGD. Finally, 135 patients who had undergone both EGD and ARFI were enrolled in this study. ARFI was measured less than 6 months before or after the EGD examination. HCV infection was diagnosed by a real-time PCR method. Diagnosis of cirrhosis was done by histologic examination or combined physical, laboratory, and radiologic findings. Patients with a history of endoscopic treatment for EVs, portal thrombosis, β-blocker use, post-liver transplantation, co-infection with HBV, or other causes of liver disease [autoimmune hepatitis, alcoholic liver disease, non-alcoholic steatohepatitis (NASH), primary biliary cirrhosis, etc.] were excluded from the study.

The patient characteristics and the following biochemical tests were recorded at the time of ARFI: platelet count, prothrombin time, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and albumin. Data were collected on the presence or absence of ascites, hepatic encephalopathy, and hepatocellular carcinoma (HCC). The Child–Pugh scores were also determined.

The training set comprised 92 patients who had undergone EGD and ARFI measurements between April 2009 and September 2012. The validation set comprised 43 patients who had undergone EGD and ARFI measurements from October 2012 to January 2013. We examined the diagnostic performance of ARFI for the presence of EVs and high-risk EVs and conducted comparative analysis with several serum non-invasive markers in the training set. The obtained optimal cutoff values of ARFI were prospectively examined in the validation set.

This study was approved by the institution's ethics committee and was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki amended in 2008. Written informed consent was obtained from all study patients.

Non-invasive serum markers

The relationships were examined for three established serum markers of liver fibrosis, i.e., platelet count, FIB-4, and APRI, and the presence of EVs or the risk of variceal bleeding. Serum liver fibrosis scores were calculated according to previously published formulas: FIB-4 = [age (years) × AST (IU/L)]/[platelet count (10^9/L) × ALT (IU/L)$^{1/2}$]; APRI = [(AST/ULN) × 100]/platelet count 10^9/L (ULN = the upper limit of normal) [20, 21].

Liver stiffness measurements

Liver stiffness was measured by ARFI, using the Siemens ACUSON S-2000 ultrasound system. ARFI is based on the measurement of the acoustic shear wave induced by an ultrasonic push pulse to assess the elastic properties of target tissues [22]. During real-time B-mode imaging, a region of interest (ROI) was set in the right hepatic lobe at a depth of 2 cm below the liver capsule. Patients were

examined in a supine position with short intervals of breath-holding. The operator performing the ARFI measurements was blinded to the EGD results. The velocity of the shear wave was quantified, and the results are expressed in meters per second (m/s). The mean values of 10 valid measurements for each patient were used for further analyses.

Endoscopic evaluation of EVs

EGD examination was performed by endoscopists who were blinded to the AFRI results. Consensus was reached for discrepancies in the diagnosis of varices during endoscopic conferences. EVs were recorded according to the general rules of the Japanese Society for Portal Hypertension [23]. The grade of EVs was classified as follows: F0, lesions assuming no varicose appearance; F1, straight small-calibered varices; F2, moderately enlarged, beady varices; F3, markedly enlarged, nodular, or tumor-shaped varices. Red color (RC) signs included red wale marking, cherry red spot, or hematocytic spot. We categorized varices as presence (grade $\geq$ F1) or absence (grade = F0). Patients were then divided into two groups according to the risk of EV bleeding; high-risk EVs (grade $\geq$ F2 or F1 with RC signs) and low-risk EVs (F0 or F1 without RC signs).

Statistical analysis

Quantitative demographic data are expressed as mean ± standard deviation. The non-parametric Mann–Whitney test was used to compare various subgroups. The relationship between the ARFI value and the grade of varices was assessed by the Jonckheere–Terpstra test. The diagnostic performance of ARFI, platelet count, APRI, and FIB-4 was assessed by using curves of receiver operating characteristics (ROC) and analysis of the area under the ROC (AUROC) curve. The optimal cutoff values were determined to maximize the sum of sensitivity (Se) and specificity (Sp). Se, Sp, positive predictive value (PPV), and negative predictive value (NPV) were calculated. AUROCs were compared using the DeLong test. The 95 % confidence intervals (95 % CIs) were calculated for each predictive test and a p value less than 0.05 was regarded as significant for each statistical test. All statistical analyses were performed with SPSS software, version 19 (SPSS, Chicago, IL, USA) and MedCalc software (MedCalc, Ostend, Belgium).

Results

The characteristics of the patients in the training and validation sets are presented in Table 1. ARFI was successfully performed in all patients. In the training set, EVs were found on conducting EGD in 47 patients (51.1 %): 19 with F1, 22 with F2, and 6 with F3. RC signs were present in 24 patients (26.1 %). There were 31 (33.7 %) and 61 (66.3 %) patients with high-risk and low-risk EVs, respectively. In the validation set, EVs were present on EGD in 27 (62.8 %) patients. High-risk EVs were present in 12 patients (27.9 %). The median ARFI values of the training set and the validation set were 2.12 m/s [interquartile range (IQR) 1.56–2.69] and 2.28 m/s (IQR 1.69–2.61).

Table 1 Baseline characteristics of patients in training and validation sets

Factor	Training set	Validation set
Number	93	43
Age (year)	68.8 ± 9.3	72.6 ± 6.9
Sex (male/female)	48/45	26/17
BMI (kg/m^2)	22.7 ± 3.2	22.3 ± 3.2
Child–Pugh class		
A	60 (64.5 %)	31 (72.1 %)
B	31 (33.3 %)	11 (25.6 %)
C	2 (2.2 %)	1 (2.3 %)
HCC		
No	47 (50.5 %)	12 (27.9 %)
Yes	46 (49.5 %)	31 (72.1 %)
Ascites		
No	82 (88.2 %)	35 (81.4 %)
Yes	11 (11.8 %)	8 (18.6 %)
Platelet ($\times 10^4$/mm^3)	9.63 ± 4.94	9.85 ± 4.30
AST (IU/L)	54.0 ± 29.9	38.6 ± 22.6
ALT (IU/L)	48.9 ± 32.9	53.4 ± 38.6
Albumin (g/dl)	3.59 ± 0.59	3.67 ± 0.56
Total bilirubin (mg/dl)	1.06 ± 0.86	1.02 ± 0.61

Results are given as mean ± standard deviation or n (%)

BMI body mass index, *HCC* hepatocellular carcinoma, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

ARFI measurements and EV grades

The median ARFI values for patients without EVs and with EVs were 1.59 m/s (IQR 1.27–2.07) and 2.63 m/s (IQR 2.14–3.03) and the ARFI value for patients with EVs was significantly higher than that without EV ($p < 0.001$) (Fig. 1a). The median ARFI values according to the grade of EVs were as follows: F0, 1.59 m/s (IQR 1.27–2.07); F1, 2.23 m/s (IQR 1.95–2.66); F2, 2.74 m/s (IQR 2.47–3.12); F3, 3.02 m/s (IQR 2.89–3.16) (Fig. 1b). The ARFI value increased with the grade of EVs ($p < 0.001$). The median ARFI value for low-risk and high-risk EVs were 1.74 m/s (IQR 1.40–2.24) and 2.84 m/s (IQR 2.48–3.15), and the

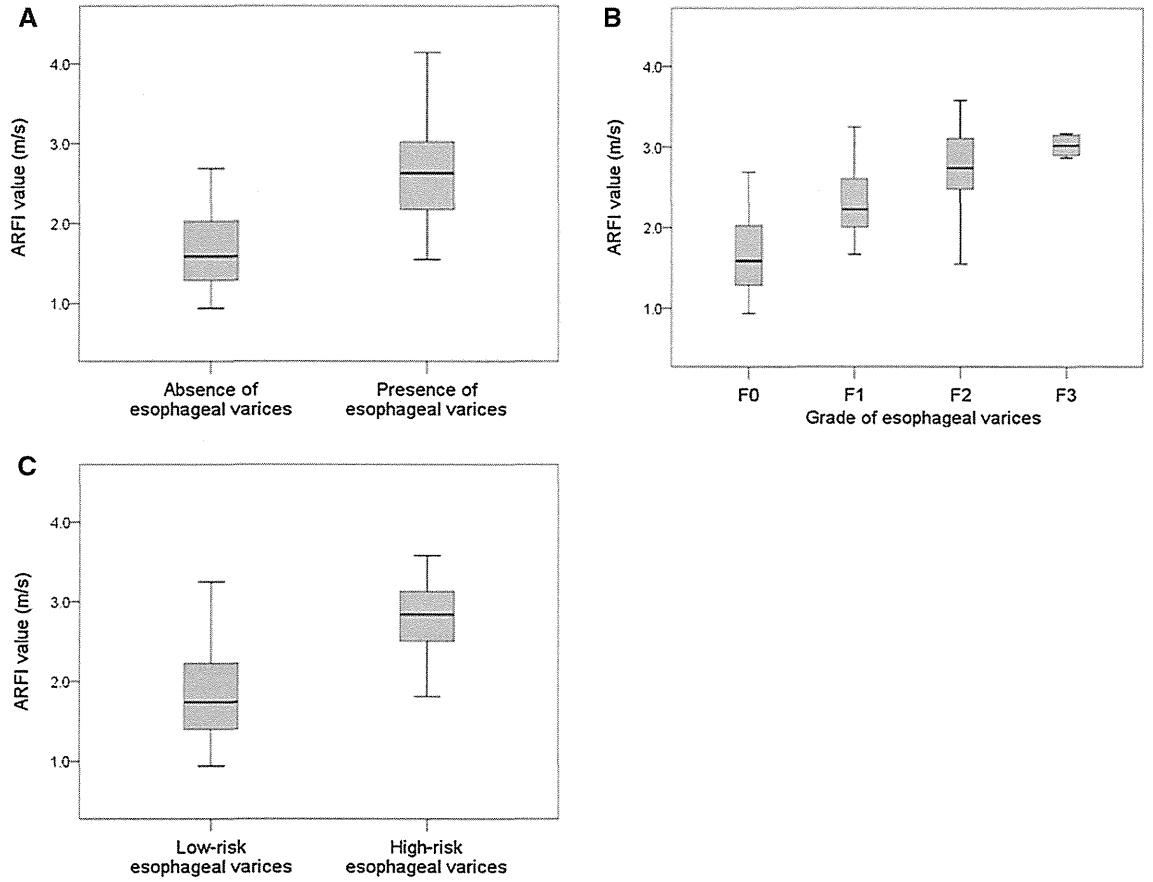

Fig. 1 Correlation between ARFI values and esophageal varices. The *top* and *bottom* of each *box* represent the first and third quartiles, respectively. The *middle line* represents the median. Correlation between ARFI values and **a** the presence or absence of esophageal varices, **b** the grade of esophageal varices, **c** low-risk esophageal varices or high-risk esophageal varices

ARFI value with high-risk EVs was significantly higher than that with low-risk EVs ($p < 0.001$) (Fig. 1c).

Diagnostic performances and optimal cutoff values for the presence of EVs

The ROC curves for diagnosis of the presence of EVs by ARFI, platelet count, FIB-4, and APRI are shown in Fig. 2. AUROCs (95 % CIs) were as follows: ARFI, 0.890 (0.825–0.955); platelet count, 0.735 (0.632–0.838); FIB-4, 0.745 (0.642–0.848); APRI, 0.684 (0.573–0.795). ARFI had the best diagnostic performance for predicting EVs compared with all other parameters (ARFI vs. platelet counts, $p = 0.0047$; ARFI vs. FIB-4, $p = 0.0041$; ARFI vs. APRI, $p = 0.0001$).

Table 2 shows the Se, Sp, NPV, and PPV of the optimal cutoff values for diagnosis of the presence of EVs. The optimal cutoff value of ARFI was 2.05 m/s with the best performance of Se (83 %), Sp (76 %), PPV (78 %), and NPV (81 %) compared with those of platelet count, FIB-4, and APRI.

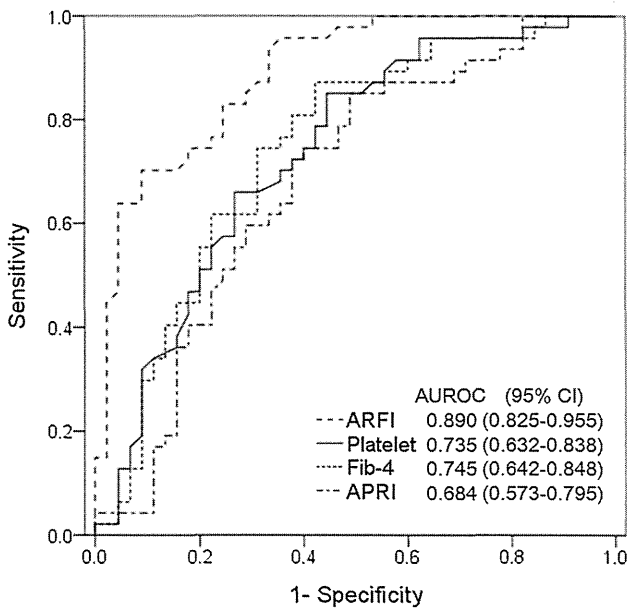

Fig. 2 Receiver operating characteristics curves of ARFI, platelet count, FIB-4, and APRI for detecting the presence of esophageal varices

Table 2 Diagnostic performance of ARFI, platelet count, FIB-4, and APRI for detecting the presence of esophageal varices

	Cutoff	Se (%)	Sp (%)	PPV (%)	NPV (%)
ARFI	2.05	83	76	78	81
Platelet	8.25	67	67	71	67
FIB-4	6.21	71	69	73	69
APRI	1.50	59	64	67	64

Se sensitivity, *Sp* specificity, *PPV* positive predictive value, *NPV* negative predictive value

Diagnostic performances and optimal cutoff values for high-risk EVs

The ROC curves for diagnosis of high-risk EV by ARFI, platelet count, FIB-4, and APRI are shown in Fig. 3. AUROCs (95 % CIs) were as follows: ARFI, 0.868 (0.792–0.943); platelet count, 0.659 (0.547–0.771); FIB-4, 0.741 (0.635–0.847); APRI, 0.669 (0.555–0.784). ARFI had the best diagnostic performance for predicting EV compared with all other parameters (ARFI vs. platelet count, $p = 0.0004$; ARFI vs. FIB-4, $p = 0.0109$; ARFI vs. APRI, $p = 0.0002$).

Table 3 shows the Se, Sp, PPV, and NPV of the optimal cutoff values for diagnosis of high-risk EVs. The optimal cutoff value of ARFI was 2.39 m/s with the best performance of Se (81 %), Sp (82 %), PPV (69 %), and NPV (89 %) compared with those of platelet count, FIB-4, and APRI.

Diagnostic performance of ARFI cutoff value in validation set

In the validation set, the optimal cutoff values of ARFI analyzed by the training set for diagnosis of the presence of EVs (2.05 m/s) and high-risk EVs (2.39 m/s) were prospectively analyzed. The ARFI cutoff value for the presence of EVs showed good performance with Se (85 %), Sp (81 %), PPV (89 %), and NPV (77 %), and that for high-risk EVs with Se (83 %), Sp (77 %), and NPV (92 %), but not PPV (59 %) (Table 4). Thus, the diagnostic performance of ARFI for the presence of EVs and high-risk EVs in the validation set were almost equal to those in the training set.

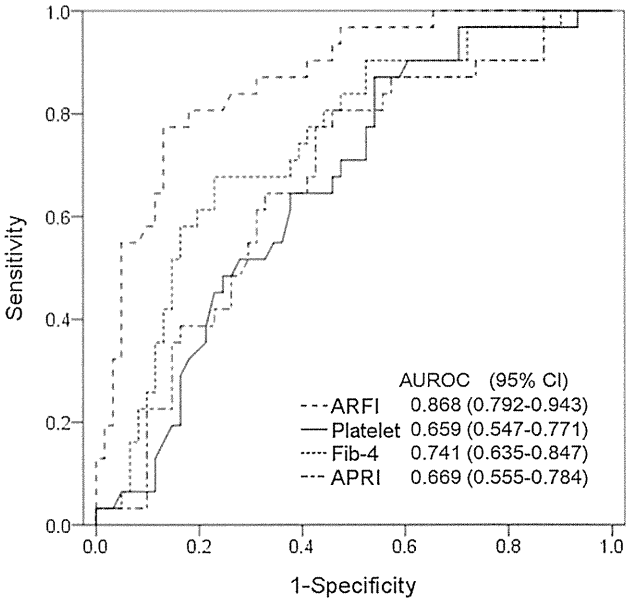

Fig. 3 Receiver operating characteristics curves of ARFI, platelet count, FIB-4, and APRI for diagnosis of high-risk esophageal varices

Table 3 Diagnostic performance of ARFI, platelet count, FIB-4, and APRI for detecting high-risk esophageal varices

	Cutoff	Se (%)	Sp (%)	PPV (%)	NPV (%)
ARFI	2.39	81	82	69	89
Platelet	7.95	64	63	49	63
FIB-4	7.70	67	78	63	78
APRI	1.62	64	68	53	68

Se sensitivity, *Sp* specificity, *PPV* positive predictive value, *NPV* negative predictive value

Table 4 Diagnostic performance of ARFI for detecting the presence of esophageal varices and high-risk esophageal varices in training and validation sets

	Cutoff	Set	Se (%)	Sp (%)	PPV (%)	NPV (%)
Presence	2.05	Training	83	76	78	81
		Validation	85	81	89	77
High-risk	2.39	Training	81	82	69	89
		Validation	83	77	59	92

Se sensitivity, *Sp* specificity, *PPV* positive predictive value, *NPV* negative predictive value

Discussion

Screening EGD for EVs is clinically important in the management of patients with cirrhosis. However, EGD is an examination that is not readily accepted by patients [24]. Therefore, there has been increasing interest in developing non-invasive methods for prediction of EVs. Recently, several serum markers and imaging methods have been shown to correlate well with liver fibrosis and can replace liver biopsy in the diagnosis of liver fibrosis [18]. Several of these methods have been tried for non-invasive assessment of EV prediction. Another simple test, the platelet count, has not been a good predictor of the presence of EVs in patients with cirrhosis (AUROC 0.63) [8]. In a large cirrhotic cohort, FIB-4 showed an AUROC of 0.64 for the

presence of EVs and 0.63 for large EVs, and APRI showed an AUROC of 0.57 for the presence of EVs and 0.60 for large EVs [9]. In the present study, the diagnostic performances for the presence of EVs and high-risk EVs by platelet count (AUROC 0.735 and 0.659, respectively), FIB-4 (AUROC 0.745 and 0.741, respectively), and APRI (AUROC 0.684 and 0.669, respectively) were superior to those by previously reported findings [8, 9]. Nevertheless, ARFI showed better diagnostic performances (AUROC 0.890 and 0.868, respectively) than these serum fibrosis markers in this study.

In this study, we examined patients with HCV infection. A large study evaluating the performance of TE for diagnosis of cirrhosis showed variation in optimal liver stiffness cutoff values depending on the underlying cause of HCV infection, HBV infection, and alcoholic liver disease or NASH [25]. The factors which contribute to increasing liver stiffness other than fibrosis were reported as follows: severe inflammation which was characterized by ALT elevation often displayed in patients with chronic HBV infection [26–29], perisinusoidal fibrosis which was common in patients with alcoholic liver disease and NASH [25], and alcohol consumption characterized by AST elevation [30]. In addition, pooled meta-analysis suggested lower diagnostic performance for liver fibrosis in patients with chronic HBV infection. That is, the AUROC of diagnosis of the fibrosis (METAVIR fibrosis score $\geq$2) by ARFI in patients with chronic HBV infection was lower than that in those with chronic HCV infection (AUROC 0.79 vs. 0.88) [19]. This result could be related to architectural abnormalities, characterized by inhomogeneous liver fibrosis and macronodular cirrhosis, which is common in patients with HBV-related cirrhosis [25]. Thus, we suggest that liver stiffness measurement (LSM) for diagnosis of liver fibrosis should be evaluated according to the underlying disease, and the patients who were limited to HCV-related cirrhosis were examined in this study.

Recently, prediction of the presence of EVs and large or high-risk EVs by TE or ARFI has been reported in several studies [28, 31–36]. However, the diagnostic performances differed greatly among these reports; AUROC for the presence of EVs was from 0.58 to 0.84 and that for large or high-risk EVs was from 0.58 to 0.83 [28, 31–36]. The reason for these differences of AUROCs is considered to arise as a result of the underlying liver disease. In fact, Pritchett et al. [31] reported that the AUROC for predicting large varices by TE in patients with only HCV-related cirrhosis was higher than those with various cirrhosis etiologies except HCV-related (AUROC 0.78 vs. 0.72). Thus, as well as the evaluation of the LSM for diagnosis of liver fibrosis, the correlation between EVs and the liver stiffness by ARFI should be evaluated according to the specific etiology of liver diseases.

Our study is the first assessment of the prediction of EVs by ARFI for a patient group with homogeneous cirrhotic disease of HCV etiology. This led to the very good diagnostic performance for predicting the presence of EVs or high-risk EVs (AUROC 0.890 or 0.868, respectively) in the training cohort, and these results were also confirmed to prospectively validate another cohort of HCV-related cirrhosis patients whose characteristics differed from the training cohort. The results of our study showed better diagnostic performance than those of the past studies described above. Only one report showed high diagnostic performance of TE for the presence of EVs and high-risk EVs among patients with only HCV (AUROC 0.87 and 0.84, respectively) [37]. TE can show diagnostic performance for EVs comparable to ARFI. However, ARFI may have some advantages over TE for LSM. For one, the rate of unsuccessful TE was reported to be as high as 18.9 %, mostly because of obesity, ascites, and patients with narrow intercostal spaces [16]. On the other hand, ARFI is not limited by these conditions and the rate of unsuccessful results was reported to be 2.9 % overall [19]. In the present study, ARFI could be successfully performed in all patients. Moreover, ARFI is superior in terms of its convenience because it is integrated into a conventional ultrasonography (US) system using conventional probes and can be performed during standard US examinations. In addition, the ROI, which is 10 mm long and 6 mm wide, is smaller than that of TE and can be chosen while performing real-time B-mode imaging. Therefore, we can see the ROI while avoiding nearby interfering structures such as blood vessels and minimize the measurement error. Further study is needed to clarify whether ARFI surpasses TE in LSMs.

In recent studies, the relationship between spleen stiffness and the presence of EVs and high-risk or large EVs has been assessed. Takuma et al. [36] reported the high diagnostic performance of spleen stiffness for the presence of EVs and high-risk EVs (AUROC 0.933 and 0.930, respectively). On the other hand, Vermehren et al. [34] showed that the diagnostic performance of spleen stiffness for predicting large EVs was low (AUROC 0.58). Thus, the diagnostic values of EVs or portal hypertension by spleen stiffness remain controversial. The mechanism of spleen stiffness arising as portal hypertension develops should be investigated.

The limitation of our study is that a serial prospective study by ARFI for the development of EVs for a specific individual was not done. Therefore, the ideal interval for ARFI measurement to follow-up on EVs remains unclear. Further study is needed.

In conclusion, for patients with HCV-related cirrhosis, we showed that LSM by ARFI can non-invasively predict the presence of EVs or high-risk EVs. This indicates that the non-invasive ARFI can be useful in selecting patients with HCV-related cirrhosis who need screening EGD or EGD at short intervals for the diagnosis of the progression to high-risk EVs.

Acknowledgement Dr. Kanto belongs to an endowed department sponsored by MSD. Dr. Takehara received donations from MSD and Chugai Pharmaceutical Co., Ltd.

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

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JOURNAL OF VIRAL HEPATITIS JVH

Journal of Viral Hepatitis, 2014 doi:10.1111/jvh.12289

The real impact of telaprevir dosage on the antiviral and side effects of telaprevir, pegylated interferon and ribavirin therapy for chronic hepatitis C patients with HCV genotype 1

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Received April 2014; accepted for publication May 2014

SUMMARY. Triple therapy with telaprevir, pegylated interferon and ribavirin has been reported to improve antiviral efficacy but have potentially severe adverse effects in patients with chronic hepatitis C. To avoid the severe effects of telaprevir, lowering the dose has been suggested. However, impact of dosage changes on antiviral and adverse effects remains unclear. One hundred and sixty-six Japanese patients with HCV genotype 1 were treated with triple therapy. The drug exposure of each medication was calculated by averaging the dose actually taken. The overall SVR rate was 82%. The telaprevir discontinuation rate was 26%. The factors associated with discontinuation were an older age (≥65 y.o.) and a higher average dose during treatment. The telaprevir discontinuation rates were 42%, 25% and 14% in patients at ≥35, 25–35 and <25 mg/kg/day of telaprevir and 58% in older patients at ≥35 mg/kg/day of TVR. The factors associated with SVR were treatment-naïve, relapse to previous treatment, higher average telaprevir dose during treatment and completion of treatment. The SVR rate was higher, at 91%, in patients at 25–35 mg/kg/day of telaprevir than the 71% and 78% observed in those at <25 and ≥35 mg/kg/day of drug. In Japanese patients, a mean telaprevir dose of 25–35 mg/kg/day during treatment can augment its efficacy in triple therapy for patients with HCV genotype 1.

Keywords: chronic hepatitis C, discontinuation rate, drug adherence, older patients, telaprevir with pegylated interferon and ribavirin.

INTRODUCTION

Antiviral therapy for patients with chronic hepatitis C virus (HCV) genotype 1 infection has changed from interferon (IFN) monotherapy to dual therapy with pegylated interferon (Peg-IFN) and ribavirin (RBV) and even triple therapy with protease inhibitor (PI), Peg-IFN and RBV [1]. Although clinical trials of triple therapy with telaprevir (TVR), which is a first-generation PI, Peg-IFN and RBV have reported that the addition of TVR leads to a substantial improvement in sustained virologic response (SVR) [2–9], adverse effects caused by TVR, such as the rapid progression of anaemia, severe rash and renal dysfunction, have also been reported [2,3,8–11]. Patients with a high risk of hepatocellular carcinoma (HCC), such as older patients and patients with advanced liver fibrosis, should be treated with antiviral therapy as early as possible to eliminate HCV.

A 2250 mg/day fixed-dose regimen was selected for TVR worldwide [12,13], although the safety was inferior in Japan compared with Europe and the United States

Abbreviations: c-EVR, complete early virologic response; CH-C, chronic hepatitis C; EOT, end of treatment; ETR, end of treatment response; Hb, haemoglobin; HCV, hepatitis C virus; IFN, interferon; Peg-IFN, pegylated interferon; PI, protease inhibitor; RBV, ribavirin; RVR, rapid virologic response; SMV, simeprevir; SVR, sustained virologic response; TVR, telaprevir; WBC, white blood cell.

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