NON-INVASIVE METHOD FOR PREDICTING HEPATOCELLULAR CARCINOMA IN PATIENTS WITH CHRONIC HEPATIC DISEASE BY MEASURING THE SHEAR WAVE VELOCITY

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Abstract

Aim : To evaluate the usefulness of acoustic radiation force impulse (ARFI) in predicting hepatocellular carcinoma (HCC) in patients with chronic hepatic disease (CHD).

Methods : A total of 230 patients participated in this study. They were subsequently classified into the "HCC group" and the "non-HCC group". We measured their liver stiffness and calculated the mean shear wave velocity (SWV) using ARFI.

Results : The mean SWV was significantly higher in the HCC group than in the non-HCC group. The cut-off value for the mean SWV with the best discrimination between the two groups was 1.36 (m/s). The area under the receiver operating characteristic curve (AUROC) was 0.807. The AUROCs of the aspartate-aminotransferase-to-platelet ratio and Fibrosis 4 score were 0.780, 0.728, respectively. The independent risk factors of HCC included the mean SWV and age. A further analysis, based on the individual causes of CHD, found that among the HCV and non-HBV and non-HCV (nBnC) cases, the mean SWV was significantly higher in the HCC group than in the non-HCC group.

Conclusion : Measuring the SWV using ARFI was a reliable method for predicting HCC in CHD patients, especially in HCV and nBnC patients.

Key words : acoustic radiation force impulse, shear wave velocity, receiver operating characteristic curves, hepatocellular carcinoma

Introduction

Liver cancer is the second most common cause of death : it accounted for nearly 746,000 deaths worldwide in 2012[1]. Thus, the prevention and early detection of hepatocellular carcinoma (HCC) are very important issues. The risk factors for HCC include hepatitis C virus (HCV) infection, hepatitis B virus (HBV) infection, alcohol consumption, obesity, and other factors ; however, the most important factor is progressive liver fibrosis, particularly the presence of cirrhosis[2]. When treating progressive liver disease, it is very important to provide appropriate to prevent HCC. Furthermore, it is important to evaluate the stage of liver fibrosis in order to predict HCC in patients with progressive chronic hepatic disease (CHD). A liver biopsy is considered to be the gold standard for liver fibrosis assessments ; however

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this method is invasive and is not suitable for screening examinations. After transient elastography (TE) using a FibroScan examination was applied in the clinical setting as a non-invasive assessment of liver stiffness, many studies have reported correlations between TE findings and liver fibrosis[3-6]. Acoustic radiation force impulse (ARFI) was recently developed as a new method for conducting non-invasive liver fibrosis assessments. ARFI is a non-invasive ultrasonographic technique that can be used to evaluate the degree of liver stiffness by measuring the shear wave velocity (SWV)[7]. Studies that compared of TE and ARFI have found ARFI to have a similar predictive value to or to be more accurate than TE in the diagnosis of severe fibrosis[7-14]. Furthermore, unlike TE, ARFI is said to not be influenced by the body mass index (BMI) (<27.7 kg/m^2) or the presence of ascites[15] and is able to assess liver fibrosis of both the right and left lobes[16].

Several studies have reported a correlation between liver fibrosis and stiffness (as measured by ARFI). However, few reports have evaluated the liver SWV in patients with CHD with respect to predicting HCC. The aim of this study was to compare the degree of liver stiffness between patients with and without HCC using ARFI and to evaluate the usefulness of this technique for predicting HCC in patients with CHD.

Materials and Methods

The present study was conducted in accordance with the principles of the Declaration of Helsinki and the study protocol was approved by the ethics committee of Akita University Graduate School of Medicine. We obtained informed consent from all patients prior to their entry into the study entry.

Patients

A total of CHD 230 patients who underwent the measurement of the SWV in the liver parenchyma at Akita University hospital between September 2009 and January 2014 were included in this study. Patients with HCC were classified into the "HCC group" ; those who had not previously been diagnosed with HCC were classified into the "non-HCC group."

Diagnosis and classification

The diagnosis of HCC was made using contrast-enhanced computed tomography, contrast-enhanced magnetic resonance imaging, contrast-enhanced ultrasonography with Sonazoid® and/or a tumor biopsy based on the guidelines proposed by the Japan Society of Hepatology[17]. HCC staging was performed according to the TNM classifications provided by the American Joint Committee on Cancer (AJCC)[18].

The assessment of liver stiffness

We used a Siemens ACUSON S2000 device (Mochida Siemens Medical Systems Co. Ltd., Tokyo, Japan) to measure the degree of tissue stiffness quantified by shear wave speed expressed in meters/second (m/sec) and calculated the SWV within the a 10×5 mm region of interest (ROI). In this study, the mean SWV was calculated within the ROI, which located in a segment of the right liver lobe 5, six times via the intercostal approach using a convex probe. The procedures were performed by the same experienced physicians. While performing B-mode imaging, we focused on the ROI at a depth of 2-5 cm below the liver capsule and selected a location without large vessels or bile ducts.

Other indexes of liver fibrosis

The aspartate aminotransferase/alanine aminotransferase ratio (AAR), aspartate-aminotransferase-to-platelet ratio (APRI) and Fibrosis 4 score (FIB-4) are existing formulae that are used for predicting the progression of liver fibrosis[19-21]. These formulae were used to measure liver fibrosis in each of the cases. The formulae are as follows :

AAR = AST (U/L)/ALT (U/L)

APRI = (AST [U/L]/
Upper normal limit for AST [U/L])/
Platelet count (10^9/L)×100

FIB-4 = (age [years]×AST [U/L])/
(Platelet count [10^9/L]×ALT [U/L]$^{0.5}$).

We compared each of the indexes with the SWV and examined the usefulness of the SWV.

Statistical analysis

The values are expressed as the mean ± standard deviation. The statistical analyses were performed using the non-parametric Wilcoxon-Mann-Whitney *U*-test for continuous data, χ^2 or Fisher's exact test for qualitative data and the one-way analysis of variance for the multi-group data. The correlations between the mean SWV and the fibrosis indexes were assessed according to Spearman's correlation coefficient. Receiver operating characteristic (ROC) curves were used to assess the diagnostic performance of ARFI, and the area under the ROC curve (AUROC), sensitivity, specificity and cut-off values were calculated. ROC curves represent sensitivity versus 1-specificity for all possible cut-off values for the prediction of HCC. An AUROC value close to 1.0 indicated high diagnostic accuracy. Risk factors for HCC were identified using a multiple logistic regression analysis. *P*-values of <0.05 were considered to indicate statistical significance.

Results

Patient characteristics

A total of 230 patients were included in the current study (male, $n=132$; female, $n=98$; mean age, 61.6± 13.3 years). In terms of the cause of CHD, 98 patients developed HCV infection (HCV cases), 68 patients developed HBV infection (HBV cases) and 64 patients were found to have a non-HBV and non-HCV status (nBnC cases). Among the 230 patients, 47 had HCC (HCV, $n=33$; HBV, $n=5$; nBnC, $n=9$). Table 1 shows all of the patients' characteristics and a comparison of the HCV cases, HBV cases, and nBnC cases. There were significant differences in the age, the number of males, the mean SWV, and the APRI and FIB-4 values of the HCV cases and the HBV and nBnC cases. Regarding the tumor size and the number of tumors in the HCC patients, 27 of the HCV patients had a tumor size of ≤5 cm and 26 had ≤3 tumors. Four of the HBV patients had a tumor size of ≤5 cm and 4 had ≤3 tumors. Eight of the nBnC patients had a tumor size of ≤5 cm and 8 had ≤3 tumors. Almost of the HCC patients were classified as stage I or II (Table 2).

Table 1. The patient characteristics (mean±standard deviation)

Characteristics	All ptaients	HCV cases	HBV cases	nBnC cases
n	230	98	68	64
Age (years)	61.6 ± 13.3	65.7 ± 11.2*†	57.9 ± 13.4	59.2 ± 14.5
Male, *n* (%)	132 (57)	49 (50)*	53 (78)	30 (47)
HCC cases, *n* (%)	47 (20)	33 (34)*†	5 (7)	9 (14)
Mean SWV of liver S5 (m/s)	1.42 ± 0.57	1.56 ± 0.60*†	1.19 ± 0.31	1.44 ± 0.66
AST (U/L)	38 ± 30	41 ± 33*	29 ± 17	41 ± 34
ALT (U/L)	37 ± 35	38 ± 35	30 ± 21	44 ± 45
PLT ($\times10^9$/L)	161 ± 64	139 ± 53*†	168 ± 57	190 ± 75
AFP (ng/mL)	26.3 ± 155.6	48.2 ± 222.8*	2.8 ± 1.4	15.1 ± 56.8
PIVKA II (mAU/mL)	2,051 ± 16,938	3,490 ± 22,589	29 ± 48	874 ± 2,762
AAR	1.13 ± 0.37	1.2 ± 0.36	1.08 ± 0.324	1.09 ± 0.42
APRI	0.77 ± 1.31	1.06 ± 1.87*†	0.47 ± 0.37	0.62 ± 0.61
FIB-4	3.41 ± 4.41	4.53 ± 5.95*†	2.35 ± 2.02	2.76 ± 2.76

*$P<0.05$ vs HBV cases, †$P<0.05$ vs nBnC cases.
AST : Asparate transaminase ; ALT : Alanine transaminase ; AFP : Alpha-fetoprotein ; PIVKA-II : protein induced by Vitamin K absence or antagonists-II ; AAR : Aspartate aminotransferase/alanine aminotransferase ratio ; APRI : aspartate-aminotransferase-to-platelet ratio ; FIB-4 : Fibrosis 4 score.

Table 2. The clinical characteristics of the 47 hepatocellular carcinoma patients.

	HCV cases	HBV cases	nBnC cases
n	33	5	9
Tumor size			
≤5 cm	27	4	8
>5 cm	6	1	1
Tumor number			
≤3	26	4	8
>3	7	1	1
TNM stage			
Stage I + II	29	4	9
Stage III (IIIa + IIIb + IIIc)	3	0	0
Stage IV (IVa + IVb)	1	1	0

The correlation between the SWV values and the AAR, APRI and FIB-4 values

The mean SWV was significantly correlated with the AAR (r=0.293, P<0.0001) (Fig. 1a). Significant correlations were found between the mean SWV values and the APRI (r=0.503, P<0.0001) and FIB-4 (r=0.522, P<0.0001) values (Fig. 1b, c).

Comparison of the HCC and non-HCC groups

The mean SWV values in the HCC and non-HCC groups were 1.82 ± 0.61 (m/s) and 1.31 ± 0.50 (m/s), respectively. The mean SWV was significantly higher in the HCC group than in the non-HCC group (Table 3). Age, the AST, ALT and AFP levels and the APRI and FIB-4 values were significantly higher and the platelet count was significantly lower in the HCC group than in the non-HCC group (Table 3). The cut-off value, sensitivity, specificity, positive predictive value (PPV) and the negative predictive value (NPV) which exhibited the best discrimination for the mean SWV were 1.36 (m/s), 0.79, 0.75, 0.45 and 0.93 respectively (Fig. 2a). The AUROC was 0.807. The AUROCs for the APRI and FIB-4, were 0.780 and 0.728, respectively (Fig. 2b, 2c). These data indicate that the SWV is a more reliable predictor of HCC than the APRI and FIB-4.

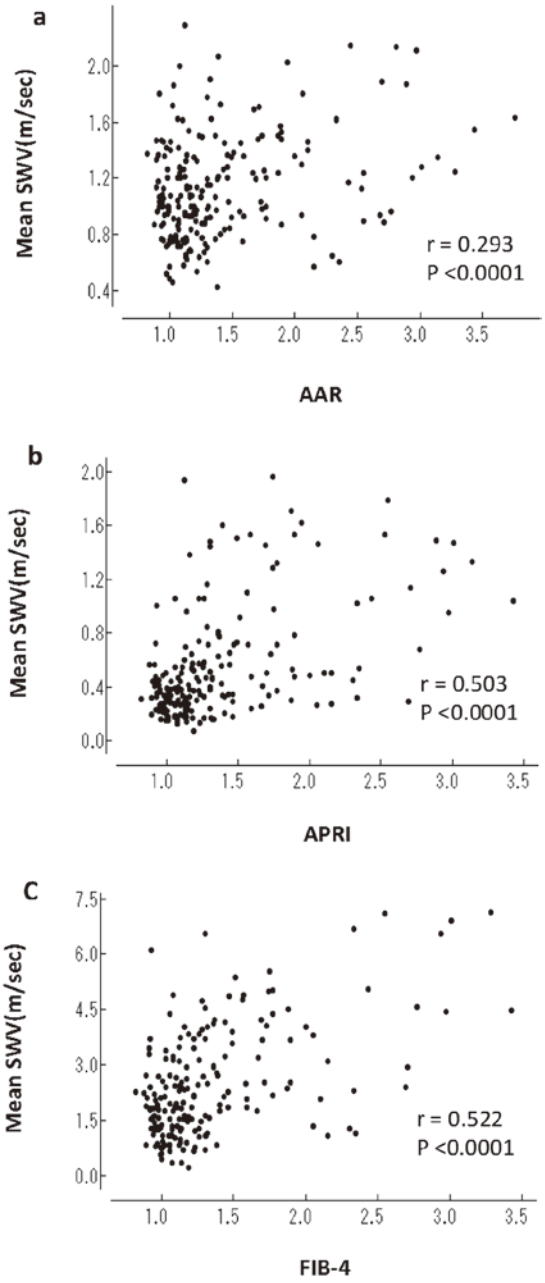

Fig. 1. The correlation between the SWV values and other parameters of fibrosis
(a) The mean SWV was significantly correlated with the AAR (r=0.293, P<0.0001). (b) The mean SWV was significantly correlated with the APRI (r=0.503, P<0.0001). (c) The mean SWV significantly correlated with the FIB-4 (r=0.522, P<0.0001).

Table 3. The comparison of all patients in the HCC and non-HCC groups (mean±standard deviation)

	HCC	non-HCC
n	47	183
Age (years)	70.4 ± 9.0*	59.3 ± 13.3
Male, *n* (%)	26 (55)	106 (58)
HCV cases, *n* (%)	33 (70)*	65 (36)
HBV cases, *n* (%)	5 (11)*	63 (34)
Mean SWV of liver S5 (m/s)	1.82 ± 0.61*	1.31 ± 0.50
AST (U/L)	57 ± 43*	33 ± 24
ALT (U/L)	55 ± 42*	33 ± 31
PLT ($\times 10^9$/L)	137 ± 61*	168 ± 59
AFP (ng/mL)	96.1 ± 311.4*	4.7 ± 7.7
PIVKA II (mAU/mL)	5,677 ± 30,053	407 ± 1,253
AAR	1.17 ± 0.41	1.12 ± 0.33
APRI	1.44 ± 1.92*	0.60 ± 1.05
FIB-4	5.70 ± 4.64*	2.82 ± 4.17

*$P<0.05$ vs non-HCC groups. AST : Asparate transaminase ; ALT : Alanine transaminase ; AFP : Alpha-fetoprotein ; PIVKA-II : protein induced by Vitamin K absence or antagonists-II ; AAR : Aspartate aminotransferase/alanine aminotransferase ratio ; APRI : aspartate-aminotransferase-to-platelet ratio ; FIB-4 : Fibrosis 4 score.

A multivariate analysis for discriminating between the HCC and non-HCC groups

The discriminative value of the patient characteristics in the HCC and non-HCC groups was evaluated using a multivariate logistic regression analysis. Consequently, the mean SWV and age were found to be statistically significant (Table 4).

The HCV cases in the HCC and non-HCC groups

The mean SWV values for the HCV cases in the HCC and non-HCC groups were 1.87±0.57 (m/s) and 1.41±0.57 (m/s), respectively. The mean SWV was significantly higher in the HCC group than in the non-HCC group. The AST, ALT and AFP levels and the APRI and FIB-4 values were significantly higher and the platelet count was significantly lower in the HCC group than in the non-HCC group (Table 5). The cut-off value which exhibiting the best discrimination for the mean SWV between the HCC group and the non-HCC group was 1.32 (m/s). The AUROC values were 0.778. The mean SWV showed a sensitivity of 0.88, a specificity of 0.65, a PPV of 0.56, and an NPV of 0.91 for detecting HCC ($P<0.0001$) (Fig. 3a).

The HBV cases in the HCC and non-HCC groups

The mean SWV values for the HBV cases in the HCC and non-HCC groups were 1.50±0.45 (m/s) and 1.17±0.28 (m/s), respectively (Table 5). Unfortunately, the difference was not statistically significant. This was attributed to the number of HBV cases in the HCC group, which was smaller than the numbers of HCV and nBnC cases. However, the mean SWV cut-off value for the HBV cases (1.67 [m/s]) showed the best discrimination between the HCC and non-HCC groups. Furthermore, the AUROC value was 0.708, and the mean SWV showed a sensitivity of 0.60, a specificity of 0.95, a PPV of 0.50 and an NPV of 0.97 for detecting HCC ($P=0.0007$) (Fig. 3b).

The nBnC cases in the HCC and non-HCC groups

The mean SWV values of the nBnC cases in the HCC and non-HCC groups were 1.94±0.80 (m/s) and 1.35±0.59 (m/s), respectively. The mean SWV value was sig-

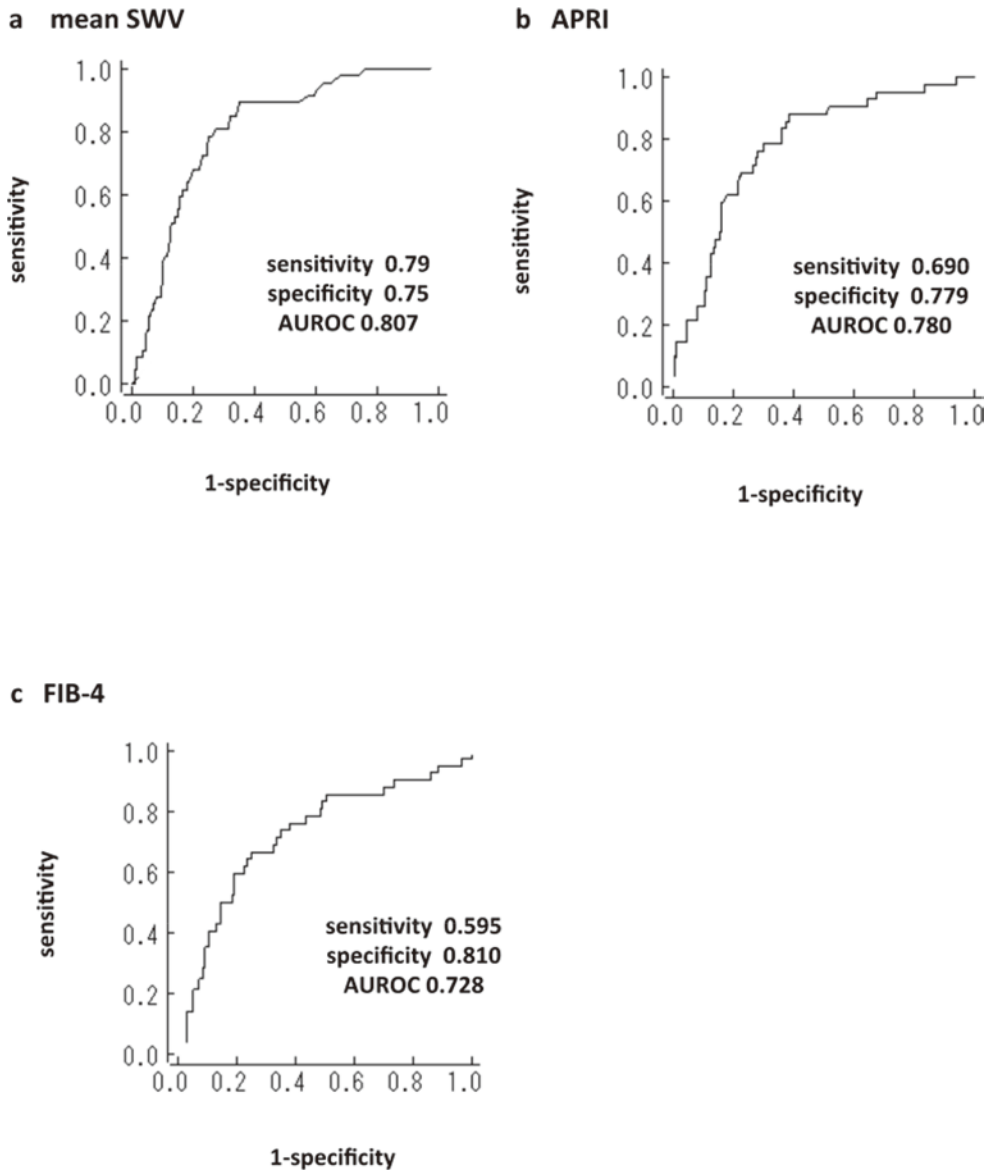

Fig. 2. The ROC curves for the mean SWV (a), APRI (b) and FIB-4 (c). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), AUROC and the cut-off value exhibiting the best discrimination for each of the data are shown, respectively.

nificantly higher in the HCC group than in the non-HCC group. The age and FIB-4 values were significantly higher in the HCC group than in the non-HCC group (Table 5). The cut-off value exhibiting the best discrimination for the mean SWV between the HCC and non-HCC groups was 1.59 (m/s). The AUROC value was 0.803. The mean SWV showed a sensitivity of 0.67, a specificity of 0.84, a PPV of 0.38, and an NPV of 0.94 for detecting HCC (P=0.0040) (Fig. 3c).

Table 4. A multivariate logistic regression analysis of the risk factors for hepatocellular carcinoma.

Variables	OR	95% CI	*P*-value
Age	1.113	1.057-1.173	<0.0001
Mean SWV of the liver S5	2.411	1.036-5.615	0.0412

OR : odd's ratio ; CI : confidence interval.

Table 5. The HCV, HBV and nBnC cases between in the HCC and non-HCC groups. (mean ± standard deviation)

	HCV cases		HBV cases		nBnC cases	
	HCC	non-HCC	HCC	non-HCC	HCC	non-HCC
n	33	183	5	63	9	55
Age (years)	70.1 ± 9.6*	63.4 ± 11.4*	66.8 ± 9.0	57.2 ± 13.5	73.3 ± 6.6†	56.8 ± 14.1†
Male, *n* (%)	17 (52)	32 (49)	4 (80)	49 (78)	6 (67)	24 (44)
Mean SWV of liver S5 (m/s)	1.87 ± 0.57*	1.41 ± 0.57*	1.50 ± 0.45	1.17 ± 0.28	1.94 ± 0.80†	1.35 ± 0.59†
AST (U/L)	62 ± 45*	31 ± 20*	37 ± 31	28 ± 15	54 ± 29	38 ± 34
ALT (U/L)	60 ± 45*	27 ± 21*	30 ± 21	25 ± 19	54 ± 18	42 ± 45
Platelets ($\times 10^9$/mL)	115 ± 44*	151 ± 53*	169 ± 53	151 ± 82	188 ± 88	190 ± 64
AFP (ng/mL)	117.5 ± 356.6*	7.9 ± 19.1*	4.0 ± 2.0	2.7 ± 1.3	80.1 ± 137.9	2.1 ± 7.1
PIVKA-II (mAU/mL)	6,836 ± 33,571	832 ± 2,290	53 ± 101	25 ± 30	—	—
AAR	1.13 ± 0.39	1.23 ± 0.33	1.50 ± 0.2*	1.04 ± 0.28*	1.22 ± 0.46	1.07 ± 0.36
APRI	1.75 ± 2.18*	0.73 ± 1.63*	0.81 ± 0.51	0.44 ± 0.34	0.85 ± 0.67	0.59 ± 0.60
FIB-4	6.08 ± 5.15*	3.78 ± 6.20*	5.61 ± 4.86	2.04 ± 1.25	4.39 ± 2.04†	2.49 ± 2.77†

*$P<0.05$, †$P<0.05$. AST : Asparate transaminase ; ALT : Alanine transaminase ; AFP : Alpha-fetoprotein ; PIVKA-II : protein induced by Vitamin K absence or antagonists-II ; AAR : Aspartate aminotransferase/alanine aminotransferase ratio ; APRI : aspartate-aminotransferase-to-platelet ratio ; FIB-4 : Fibrosis 4 score.

Discussion

In the present study, we evaluated the efficacy of the mean SWV of the liver in predicting HCC in CHD patients. The APRI and FIB-4 values have been shown to be correlated with the degree of liver fibrosis in previous studies[5,20-25] and were found to be correlated with the mean SWV in this study. In addition, by comparing each of the AUROCs, we found that the ARFI was more useful for predicting HCC than the APRI and FIB-4. Based on the results of meta-analyses, some studies have reported that the results of ARFI elastography to have a good correlation with the extent of liver fibrosis[15,26-31], and the ARFI values have been demonstrated to differ between patients with and without a sustained viral response (SVR) after antiviral treatment for chronic hepatitis C (CHC)[32]. Some researchers have reported that liver stiffness, as measured by TE using a FibroScan examination, was a predictor of HCC, and have shown high liver stiffness values in HCC patients[3,33,34]. However, few studies have reported the efficacy of predicting HCC by measuring the SWV using ARFI. Vermehren *et al.* reported that the AUROC for diagnosing HCC was 0.54 for ARFI, but did not present the cut-off value in cirrhosis patients[13]. In the present study, the mean SWV was significantly higher in the HCC group than in the non-HCC group (1.82 [m/s] vs. 1.31 [m/s]), and the cut-off value was 1.36 (m/s) with a good AUROC (0.807). This result indicates that potential for HCC increased in association with advances in liver fibrosis in CHD patients. The age and α-fetoprotein (AFP) and transaminase levels were also significantly higher and the platelet count was significantly lower in the HCC group than in the non-HCC group. A decreased platelet count was re-

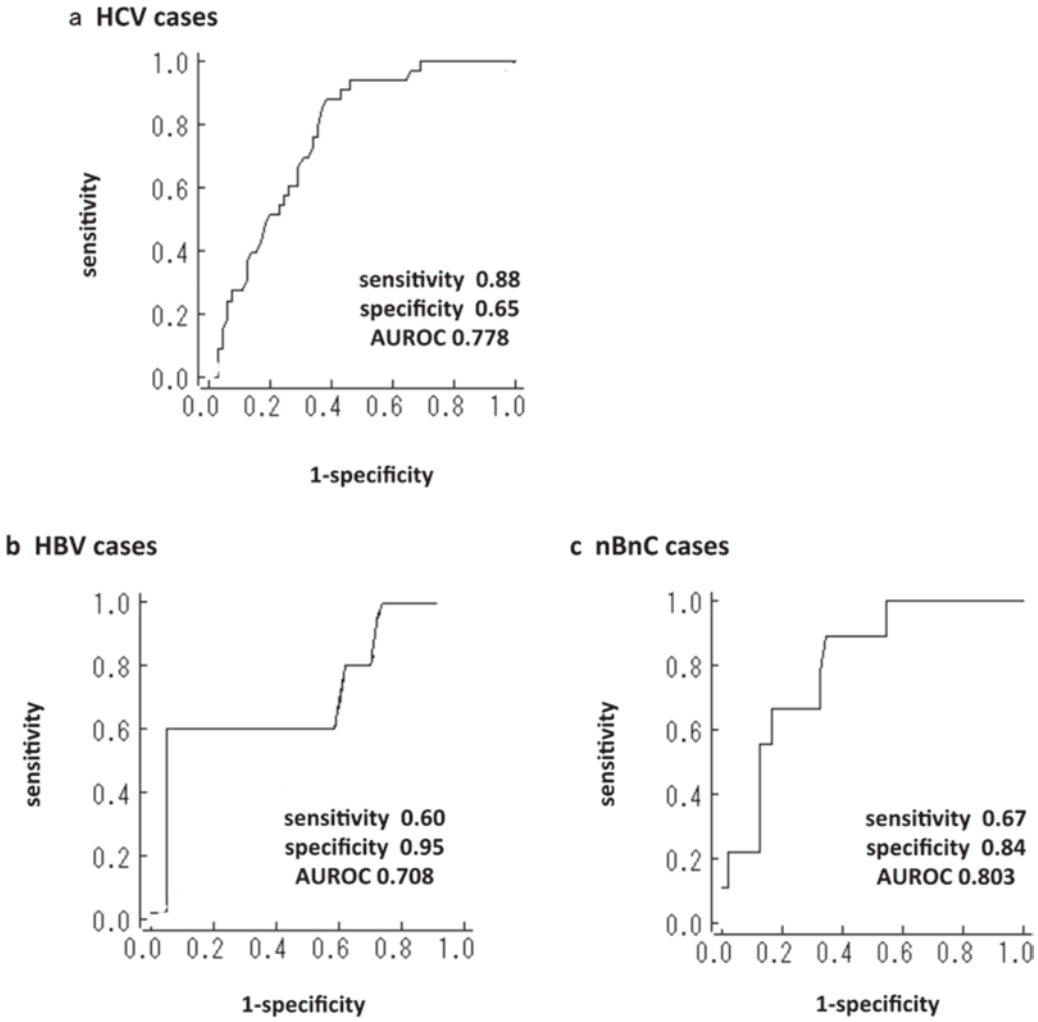

Fig. 3. The ROC curves for the mean SWV of the HCV cases (a), HBV cases (b), and nBnC cases (c). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), AUROC and the cut-off value exhibiting the best discrimination for the each case are shown, respectively.

ported to be a predictor of hepatic fibrosis[35]. We employed a multiple logistic regression analysis to assess the relationships between the presence of HCC and the patient variables. Consequently, age and the mean SWV were found to be independent risk factors for HCC, with odds ratios (95% confidence intervals) of 1.113 (1.057–1.173), and 2.411 (1.036–5.615), respectively. In previous studies, age[2] and liver stiffness[33] were found to be risk factors for HCC. The mean SWV reflected the liver stiffness and we showed that the mean SWV was an independent risk factor for HCC. Furthermore, ARFI has an advantage over Fibroscan, in that the SWV can be evaluated while scanning the liver with the B mode.

In the present study, the mean SWV of the HCV cases was significantly higher in the HCC group than in the non-HCC group (1.87 [m/s] vs. 1.41 [m/s]). The cut-off value was 1.32 (m/s) and good AUROC values for detecting HCC were observed (0.778). These data indicate that HCV-positive patients develop HCC via mechanisms such as chronic hepatitis and cirrhosis. Yoshida *et al.*[36]

and Inoue *et al.*[37] reported similar findings to the present study when they noted that the incidence of HCC increased with the degree of liver fibrosis in CHC patients.

In the HBV cases, the mean SWV tended to be higher in the HCC group than in the non-HCC group (1.50 [m/s] vs. 1.17 [m/s]) ; however, the difference did not reach significance due to the small number of HCC cases. However, the liver stiffness values determined by ARFI have been shown to be reliable predictors of liver fibrosis in patients with chronic hepatitis B (CHB)[38]. In addition, Jung *et al*. examined TE using FibroScan and reported that liver stiffness was a risk factor for HCC in patients with CHB[39]. Taken together, it seems reasonable to hypothesize that an increased number of HBV patients would allow us to obtain a significant difference in the mean SWV between the HCC and non-HCC groups.

In the nBnC cases, the mean SWV was significantly higher in the HCC group than in the non-HCC group (1.94 [m/s] vs. 1.35 [m/s]), and good AUROC values for detecting HCC were noted (0.803). Several studies have reported that the liver stiffness values determined by ARFI are reliable predictors of liver fibrosis in patients with autoimmune hepatitis[31] and nonalcoholic fatty liver disease[28]. Among the nBnC cases in the present study, the difference in the cut-off values between the HCC and non-HCC groups were significant. This is a very important finding, as no previous studies have reported the efficacy of ARFI in detecting HCC in nBnC patients.

In a multicenter study performed by Sporea *et al*., the cut-off values for ARFI that were predictive of the various stages of fibrosis were as follows : 1.19 (m/s) (AUROC = 0.779) for F≥1, 1.33 (m/s) (AUROC=0.792) for F≥2, 1.43 (m/s) (AUROC=0.829) for F≥3 and 1.55 (m/s) (AUROC=0.842) for F=4[40]. In the current study, the cut-off values which showed the best discrimination between the HCC and non-HCC groups were 1.36 (m/s) (AUROC=0.807), 1.32 (m/s) (AUROC=0.778) and 1.59 (m/s) (AUROC=0.803) for all cases, the HCV cases and the nBnC cases, respectively. Considering the above findings, the cut-off values for SWV which were predictive of HCC were equivalent to the F2 stage in all cases and the HCV cases and the F4 stage in the nBnC cases. We hypothesize that the cut-off value of the HCV cases in our study was lower than that in the nBnC cases due to the effects of the different mechanisms promoting HCC in HCV and nBnC as well as the strict follow-up that was provided in the HCV cases.

ARFI is a non-invasive and simple method for measuring the degree of liver stiffness. In the future, ARFI is expected to become more widely used in the clinical setting and may become a reliable method for predicting HCC in CHD patients, resulting in the prediction and subsequent treatment of the disease in the early stage. In conclusion, the assessment of the SWV by ARFI may reliably predict HCC in patients with CHD, especially in HCV and nBnC patients.

References

1) Ferly, J., Soerjomataram, I., Ervik, M., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D.M., Forman, D. and Bray, F. (2013) GLOBOCAN 2012 v1.0, Liver Cancer Estimated Cancer Incidence, Mortality and Prevalence World wide : IARC CancerBase No. 11 [Internet]. Lyon, France : International Agency for Research on Cancer. Available from : http://globocan.iarc.fr, Accessed 8/October/2014.
2) Yang, J.D. and Roberts, L.R. (2010) Hepatocellular carcinoma : A global view. *Nat. Rev. Gastroenterol. Hepatol.*, **7**, 448-458.
3) Masuzaki, R., Tateishi, R., Yoshida, H., *et al*. (2012) Assessment of disease progression in patients with transfusion-associated chronic hepatitis C using transient elastography. *World J. Gastroenterol.,* **18**, 1385-1390.
4) Karlas, T., Neuschulz, M., Oltmanns, A., *et al*. (2012) Non-Invasive evaluation of cystic fibrosis related liver disease in adults with ARFI, transient elastography and different fibrosis scores. *PloS one*, **7**, e42139.
5) Khairy, M., Abdel-Rahman, M., El-Raziky, M., El-Akel, W., Zayed, N., Khatab, H. and Esmat, G. (2012) Non-invasive prediction of hepatic fibrosis in patients with chronic HCV based on the routine pre-treatment workup. *Hepat. Mon.,* **12**, e6718.
6) Bota, S., Herkner, H., Sporea, I., Salzl, P., Sirli, R., Neghina, A.M., Peck-Radosavljevic, M. (2013) Meta-analysis : ARFI elastography versus transient elastography for the evaluation of liver fibrosis.

Liver int., **33**, 1138–1147.

7) Friedrich-Rust, M., Wunder, K., Kriener, S., *et al*. (2009) Liver Fibrosis in viral Hepatitis : Noninvasive Assessment with Acoustic Radiation Force Impulse Imaging versus Transient Elastography. *Radiology,* **252**, 595–604.

8) Rizzo, L., Nunnari, G., Berretta, M. and Cacopardo, B. (2012) Acoustic Radial Force Impulse as an effective tool for a prompt and reliable diagnosis of hepatocellular carcinoma–preliminary data. *Eur. Rev. Med. Pharmacol. Sci.*, **16**, 1596–1598.

9) Rizzo, L., Calvaruso, V., Cacopardo, B., *et al*. (2011) Comparison of transient elastography and acoustic radiation force impulse for non-invasive staging of liver fibrosis in patients with chronic hepatitis C. *Am. J. Gastroenterol.*, **106**, 2112–2120.

10) Chen, S.H., Li, Y.F., Lai, H.C., Kao, J.T., Peng, C.Y., Chuang, P.H., Su, W.P. and Chiang, I.P. (2012) Effects of patient factors on noninvasive liver stiffness measurement using acoustic radiation force impulse elastography in patients with chronic hepatitis C. *BMC Gastroenterol.*, **12**, 105.

11) Sporea, I., Sirli, R., Bota, S., Popescu, A., Sendroiu, M. and Jurchis, A. (2012) Comparative study concerning the value of acoustic radiation force impulse (ARFI) in comparison with transient elastography (TE) for the assessment of liver fibrosis in patients with hepatitis B and C. *Ultrosound Med. Biol.*, **38**, 1310–1316.

12) Kircheis, G., Sagir, A., Vogt, C., Vom Dahl, S., Kubitz, R. and Häussinger, D. (2012) Evaluation of acoustic force impulse imaging for determination of liver stiffness using transient elastography as a reference. *World J. Gastroenterol.*, **18**, 1077–1084.

13) Vermehren, J., Polta, A., Zimmermann, O., Herrmann, E., Poynard, T., Hofmann, W.P., Bojunga, J., Sarrazin, C., Zeuzem, S. and Friedrich-Rust, M. (2012) Comparison of acoustic radiation force impulse imaging with transient elastography for the detection of complications in patients with cirrhosis. *Liver Int.,* **32**, 852–858.

14) Sporea, I., Badea, R., Sirli, R., Lupsor, M., Popescu, A., Danila, M., Focsa, M. and Deleanu, A. (2011) How efficient is acoustic radiation force impulse elastography for the evaluation of liver stiffness? *Hepat. Mon.,* **11**, 532–538.

15) Bota, S., Sporea, I., Sirli, R., Popescu, A., Danila, M., Jurchis, A. and Gradinaru-Tascau, O. (2014) Factors associated with the impossibility to obtain reliable liver stiffness measurements by means of Acoustic Radiation Force Impulse (ARFI) elastography–Analysis of cohort of 1031 subject. *Eur. J. Radiol.*, **83**, 268–272.

16) Toshima, T., Shirabe, K., Takeishi, K., Motomura, T., Mano, Y., Uchiyama, H., Yoshizumi, T., Soejima, Y., Taketomi, A. and Maehara, Y. (2011) New method for assessing liver fibrosis based on acoustic radiation force impulse : a special reference to the difference between right and left liver. *J. Gastroenterol.*, **46**, 705–711.

17) The Japan Society of Hepatology. (2010) Clinical Practice Guidelines for Hepatocellular Carcinoma–The Japan Society of Hepatology 2009 update. *Hepatol. Res.*, **40**, 6–7.

18) Edge, S.B., Byrd, D.R., Compton, C.C., Fritz, A.G., Greene, F.L. and Trotti, A. (2010) AJCC Cancer Staging Manual. 7th ed. Springer : New York, 191–200.

19) Sheth, S.G., Flamm, S.L., Gordon, F.D., Chopra, S. (1998) AST/ALT ratio predicts cirrhosis in patients with chronic hepatitis C virus infection. *Am. J. Gastroenterol.*, **93**, 44–48.

20) Wai, C.T., Greenson, J.K., Fontana, R.J., Kalbfleisch, J.D., Marrero, J.A., Conjeevaram, H.S. and Lok, A.S. (2003) A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology*, **38**, 518–526.

21) Sterling, R.K., Lissen, E., Clumeck, N., *et al*. (2006) APRICOT Clinical Investigators. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology*, **43**, 1317–1325.

22) Attallah, A., El-Far, M., Omran, M.M., Farid, K., Albannan, M.S. and El-Dosoky, I. (2013) Noninvasive diagnosis of liver fibrosis and cirrhosis in chronic hepatitis C patients. *J. Clin. Lab. Anal.*, **27**, 121–129.

23) Yilmaz, Y., Yonal, O., Kurt, R., Bayrak, M., Aktas, B. and Ozdogan, O. (2011) Noninvasive assessment of liver fibrosis with the asparate transaminase to platelet ratio index (APRI) : usefulness in patients with chronic liver disease. *Hepat Mon*, **11**, 103–106.

24) Yamada, R., Hiramatsu, N., Oze, T., *et al*. (2014) Significance of Liver Stiffness Measurement by Acoustic Radiation Force Impulse (ARFI) Among Hepatitis C patients. *J. Med. Virol.*, **86**, 241-247.

25) Castéra, L., Vergniol, J., Foucher, J., Le Bail, B., Chanteloup, E., Haaser, M., Darriet, M., Couzigou, P. and De Lédinghen ,V. (2005) Prospective comparison of transient elastography, Fibrotest, APRI, and Liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gstroenterology*, **128**, 343-350.

26) Haque, M., Robinson, C., Owen, D., Yoshida, E.M. and Harris, A. (2010) Comparison of acoustic radiation force impulse imaging (ARFI) to liver biopsy histologic scores in the evaluation of chronic liver disease : A pilot study. *Ann. Hepatol.*, **9**, 289-293.

27) Goertz, R.S., Sturm, J., Zopf, S., Wildner, D., Neurath, M.F. and Strobel, D. (2014) Outcome analysis of liver stiffness by ARFI (acoustic radiation force impulse) elastometry in patients with chronic viral hepatitis B and C. *Clin. Radiol.*, **69**, 275-279.

28) Palmeri, M.L., Wang, M.H., Rouze, N.C., Abdelmalek, M.F., Guy, C.D., Moser, B., Diehl, A.M. and Nightingale, K.R. (2012) Noninvasive Evaluation of Hepatic Fibrosis using Acoustic Radiation Force-Based Shear Stiffness in Patients with Nonalcoholic Fatty Liver Disease. *J. Hepatol*., **55**, 666-672.

29) Nierhoff, J., Chávez Ortiz, A.A., Herrmann, E., Zeuzem, S. and Friedrich-Rust, M. (2013) The efficiency of acoustic radiation force impulse imaging for staging of liver fibrosis : a meta-analysis. *Eur. Radiol.*, **23,** 3040-3053.

30) Nishikawa, T., Hashimoto, S., Kawabe, N., *et al*. (2014) Factors correlating with acoustic radiation force impulse elastography in chronic hepatitis C. *World J. Gastroenterol.*, **20**, 1289-1297.

31) Righi, S., Fiorini, E., De Molo, C., Cipriano, V., Cassani, F., Muratori, L., Lenzi, M., Morselli Labate, A.M. and Serra, C. (2012) ARFI elastography in patients with chronic autoimmune liver diseases : A preliminary study. *J. Ultrasound*, **15**, 226-231.

32) Forestier, N., Gaus, A., Herrmann, E., *et al*. (2012) Acoustic Radiation Force Impulse imaging for evaluation of antiviral treatment response in chronic hepatitis C. *J. Gastrointestin Liver Dis.*, **21**, 367-373.

33) Kuo, Y.H., Lu, S.N., Hung, C.H., Kee, K.M., Chen, C.H., Hu, T.H., Lee, C.M., Changchien, C.S. and Wang, J.H. (2010) Liver stiffness measurement in the risk assessment of hepatocellular carcinoma for patients with chronic hepatitis. *Hepatol. Int.*, **4**, 700-706.

34) Akima, T., Tamano, M., Hiraishi, H. (2011) Liver stiffness measured by transient elastography is a predictor of hepatocellular carcinoma development in viral hepatitis. *Hepatol. Res.*, **41**, 965-970.

35) Poynard, T. and Bedossa, P. (1997) Age and platelet count : a simple index for predicting the presence of histological lesions in patients with antibodies to hepatitis C virus. *J. Viral. Hepat.*, **4**, 199-208.

36) Yoshida, H., Shiratori, Y., Moriyama, M., *et al*. (1999) Interferon therapy reduces the risk for hepatocellular carcinoma : national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. *Ann. Intern. Med.*, **131**, 174-181.

37) Inoue, A., Tsukuma, H., Oshima, A., Yabuuchi, T., Nakao, M., Matsunaga, T., Kojima, J. and Tanaka, S. (2000) Effectiveness of interferon therapy for reducing the incidence of hepatocellular carcinoma among patients with type C chronic hepatitis. *J. Epidemiol*., **10**, 234-240.

38) Ye, X., Ran, H.T., Cheng, J., Zhu, Y.F., Zhang, D.Z., Zhang, P. and Zheng, Y.Y. (2012) Liver and Spleen Stiffness Measured by Acoustic Radiation Force Impulse Elastography for Noninvasive Assessment of Liver Fibrosis and Esophageal Varices in Patient With Chronic Hepatitis B. *J. Ultrasound Med.*, **31,** 1245-1253.

39) Jung, K.S., Kim, S.U., Ahn, S.H., Park, Y.N., Kim do, Y., Park, J.Y., Chon, C.Y., Choi, E.H. and Han, K.H. (2011) Risk assessment of hepatitis B virus-related HCC development using liver stiffness measurement (FibroScan). *Hepatology*, **53**, 885-894.

40) Sporea, I., Bota, S., Peck-Radosavljevic, M., *et al*. (2012) Acoustic Radiation Force Impulse elastography for fibrosis evaluation in patients with chronic hepatitis C : An international multicenter study. *Eur. J. Radiol.*, **81**, 4112-4118.