

The Accuracy of a Non-invasive Liver Fibrosis Evaluation Method, Shear Wave Elastography: A Retrospective Pilot Study

Satoshi KOTANI¹⁾, Shuichi SATO²⁾, Naruaki KOHGE³⁾, Kosuke TSUKANO³⁾, Sayaka OGAWA³⁾, Satoshi YAMANOUCI³⁾, Ryusaku KUSUNOKI³⁾, Masahito AIMI³⁾, Yoichi MIYAOKA¹⁾, Hirofumi FUJISHIRO³⁾, Tomohiko YAMAMOTO⁴⁾, Hideyuki OHNUMA⁴⁾

¹⁾ Department of Endoscopy, Shimane Prefectural Central Hospital, Izumo, 693-8555, Japan

²⁾ Department of Gastroenterology and Hepatology, Shimane University Faculty of Medicine, Izumo, 693-8501, Japan

³⁾ Department of Gastroenterology, Shimane Prefectural Central Hospital, Izumo, 693-8555, Japan

⁴⁾ Department of Pathology, Shimane Prefectural Central Hospital, Izumo, 693-8555, Japan

(Received July 24, 2017; Accepted August 21, 2017)

Objective: We aimed to evaluate the diagnostic accuracy of shear wave elastography (SWE) for the assessment of liver fibrosis in patients with liver disease.

Methods: A total of 54 consecutive patients who underwent SWE measurement and liver biopsy were included. Receiver-operator characteristic (ROC) curves were constructed to calculate the area under the ROC curve (AUC) for F0-2 versus F3-4 and F0-3 versus F4. **Results:** Fibrosis scores estimated by SWE were F0 for 9 cases, F1 for 18 cases, F2 for 11 cases, F3 for 9 cases, and F4 for 7 cases. AUCs for severe fibrosis (F3 and F4) and cirrhosis (F4) were 0.931 ($P < 0.001$) and 0.916 ($P < 0.001$), respectively. Shear wave velocity correlated significantly with liver fibrosis obtained by liver biopsy ($r = 0.679$, $P < 0.001$).

Conclusion: SWE is a useful and non-invasive technology to estimate liver fibrosis in liver disease regardless of etiology.

Key words: chronic liver disease, liver fibrosis, shear wave elastography

INTRODUCTION

Liver fibrosis and cirrhosis occur as a result of chronic liver inflammation caused by viral, autoimmune, and metabolic diseases. It is very important to assess the degree of liver fibrosis to determine the prognosis and to decide whether treatment should be pursued. Liver biopsy is considered the gold standard for assessment of liver fibrosis and cirrhosis [1, 2]. However, it is an invasive procedure associated with morbidities, such as pain via examination, intraabdominal bleeding, and perforation of the intestine. In addition, liver biopsy has the limitations of sampling error and intra- and interobserver variability [3-5]. Because of these problems, liver biopsy is not an ideal method for repeated assessment of disease progression in patients with chronic liver diseases. Therefore, a non-invasive and accurate liver fibrosis assessment method is needed as an alternative to liver biopsy. Liver stiffness measurements using elastography for the non-invasive evaluation of liver fibrosis have been developed in the last few years [6-9]. Transient elastography (TE, Fibroscan[®]) is a useful test in almost any patient in whom a clinician wishes to stage liver fibrosis. However, technical limitations of the test preclude its use in patients with ascites and in obese individuals, in whom either the test cannot be performed or the results of the test are not reliable. Shear wave elastography (SWE) can calculate the velocity of shear waves, and this velocity can be used to assess tissue stiffness by the formula $E = \rho c^2$. E is tissue elasticity (kPa), ρ is tissue density (kg/m^3),

Corresponding author: Satoshi Kotani, MD

Department of Endoscopy, Shimane Prefectural Central Hospital, 4-1-1 Himebara, Izumo, 693-8555 Shimane, Japan

Tel: +81-853-22-5111

Fax: +81-853-21-2975

E-mail: ksoattaonsihi@gmail.com

and c is shear wave velocity (m/s) [10]. Several reports indicate that SWE is more accurate than TE in assessing significant fibrosis [10-12]. However, the usefulness of SWE has not been fully investigated.

The purpose of this study was to evaluate the diagnostic accuracy of SWE technology from Toshiba for the assessment of liver fibrosis in patients with liver disease.

MATERIALS AND METHODS

Patients

Between December 2014 and March 2016, 68 patients were admitted to our hospital to undergo liver biopsy. Among these, 54 consecutive patients underwent SWE measurement with Aplio500 (Toshiba Medical Systems Corporation, Tochigi, Japan) at the time of liver biopsy. The remaining 14 patients had no space to measure SWE because of metastatic liver cancer. We gave each patient a full explanation of the study procedures prior to study entry, and the patients provided written informed consent at enrollment. This retrospective human study was approved by the Ethics Committee of the Shimane Prefectural Central Hospital, and complied with all of the provisions of the Declaration of Helsinki.

Measurement of shear wave elastography

We use the Aplio500 ultrasound (US) system with a convex broadband probe (3.5MHz). SWE measurements were performed on the right lobe of the liver, through the intercostal spaces, with patients in the supine position with the right hand abducted. The upper edge of the SWE box was placed about 2 cm from the body surface. The SWE box was away from intrahepatic vessels and the gallbladder. A circular region of interest (ROI) of size 1cm diameter was placed on the most homogeneous area within the SWE box. Each measurement was made at least twice, and the average shear wave velocity was recorded. We also measured the thickness of the body wall. No patient had ascites at the time of the SWE measurement.

Liver biopsy and histological assessment

The same intercostal space was used for both SWE measurement and liver biopsy. Liver biopsy and SWE measurement were performed on the same day. SWE measurements and liver biopsies were carried out consecutively by three physicians (SK, KT, and NK). An 18-gauge automatic biopsy gun (ACECUT, TSK LABORATORY, Tochigi, Japan) was used under US guidance. Liver biopsy specimens were read by two expert pathologists (TY and HO). Histological stages of liver fibrosis were diagnosed according to the new Inuyama classification of chronic hepatitis: F0, no fibrosis; F1, portal fibrosis widening; F2, portal fibrosis widening with bridging fibrosis; F3, bridging fibrosis plus lobular distortion; and F4, liver cirrhosis [13]. Liver inflammatory activity stages were staged as A0, no liver inflammation; A1, mild degree of liver inflammation; A2, moderate degree of liver inflammation; A3, severe degree of liver inflammation [13]. In this study, F3 and F4 were defined as severe fibrosis.

Statistical analysis

A receiver operating characteristic (ROC) curve was constructed to assess the accuracy of the SWE measurement and to identify an optimal cut-off value. Continuous variables were compared with the Kruskal-Wallis test. Correlation between groups was evaluated with Spearman's rank correlation coefficient test. Multiple regression analysis was carried out with a stepwise method. A P-value < 0.05 was considered statistically significant. Analysis was performed with SPSS version 21 software for Windows (IBM, Armonk, USA).

RESULTS

Patient characteristics

The baseline characteristics of the patients ($n = 54$) are shown in Table 1. The study population contained 20 men (37.0%) and 34 women (63.0%) with a median age of 65 years (range, 26-86 years). The final diagnosis of the 54 patients was as follows: hepatitis C virus infection in 13 cases (24.1%), non-alcoholic steatohepatitis (NASH) in 10 cases (18.5%), hepatitis B virus infection in 9 cases (16.7%), alcoholic liver disease (ALD) in 6

Table 1. Patient characteristics (n = 54). Data are expressed as number or median (range or percentage)

Age (range), years	65 (26-86)
Sex, male/female	20/34
Etiology of liver disease, n (%)	
Chronic hepatitis B	9 (16.7%)
Chronic hepatitis C	13 (24.1%)
Non-alcoholic steatohepatitis	10 (18.5%)
Alcoholic liver disease	6 (11.1%)
Primary biliary cirrhosis	5 (9.4%)
Other	11 (20.4%)
Liver histological findings	
Fibrosis, 0/1/2/3/4	9/18/11/9/7
Activity, 0/1/2/3	6/27/16/5

Table 2. Multiple regression analysis results

Factor	Unstandardized coefficients		Standardized		
	B value	Standard error	Beta value	T test	P-value
Constant	-0.688	0.606		-1.135	0.262
Shear wave velocity	1.587	0.221	0.664	7.172	0.000
Platelet count	-0.005	0.002	-0.293	-3.169	0.003

cases (11.1%), primary biliary cirrhosis (PBC) in 5 cases (9.3%), and other (including autoimmune hepatitis, drug-induced liver injury, elevated liver function tests of unknown cause, and metastatic liver cancer) in 11 cases (20.4%). The fibrosis score was F0 for 9 cases (16.7%), F1 for 18 cases (33.3%), F2 for 11 cases (20.4%), F3 for 9 cases (16.7%), and F4 for 7 cases (13.0%). There were 16 cases of severe fibrosis, 8 of them were NASH, 4 were ALD, 3 were hepatitis C virus infection and 1 was autoimmune hepatitis.

Correlation between shear wave velocity and liver fibrosis

The average shear wave velocity ranged from 1.51 to 3.69 m/s, with a median [first and third quartiles] of 2.01 [1.75-2.39] m/s. The correlation

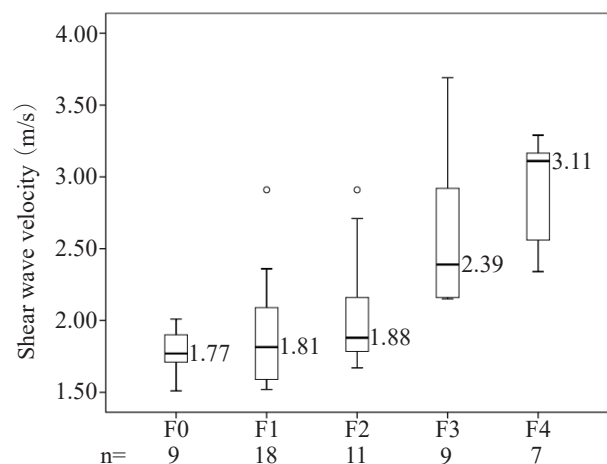


Fig. 1. Box-and-whisker plot of the shear wave velocity for each fibrosis stage of the liver in 54 patients who underwent liver biopsy. The top and bottom of the boxes are the first and third quartiles. The length of the box represents the interquartile range, covering 50% of the levels. The lines through the middle of the box and values besides the box indicate the median level. The error bars are the minimum and maximum levels.

between shear wave velocity and fibrosis stage obtained by liver biopsy was analyzed (Fig. 1). The median shear wave velocity in each type of fibrosis was 1.77 m/s in F0, 1.81 m/s in F1, 1.88 m/s in F2, 2.39 m/s in F3, and 3.11 m/s in F4. The shear wave velocity increased significantly according to the progression of liver fibrosis ($r = 0.679$, $P < 0.001$). We analyzed the diagnostic accuracy of shear wave velocity to predict severe fibrosis and liver cirrhosis by ROC. For predicting severe fibrosis, the area under the ROC curve (AUC) was 0.931 at an optimal cut-off value of 2.145 m/s (sensitivity, 100%; specificity, 81.6%; $P < 0.001$). For predict-

ing liver cirrhosis, the AUC was 0.916 at an optimal cut-off value of 2.475 m/s (sensitivity, 85.7%; specificity, 85.1%; $P < 0.001$) (Fig. 2).

Multiple regression analysis

To determine the independent factors affecting fibrosis, multiple regression analysis was conducted. Multiple regression analysis included age, body mass index (BMI), thickness of the body wall, shear wave velocity, aspartate aminotransferase (AST) level, alanine aminotransferase (ALT) level, platelet count, serum albumin level, fibrosis 4 index (FIB-4 index), and aspartate aminotransferase to platelet

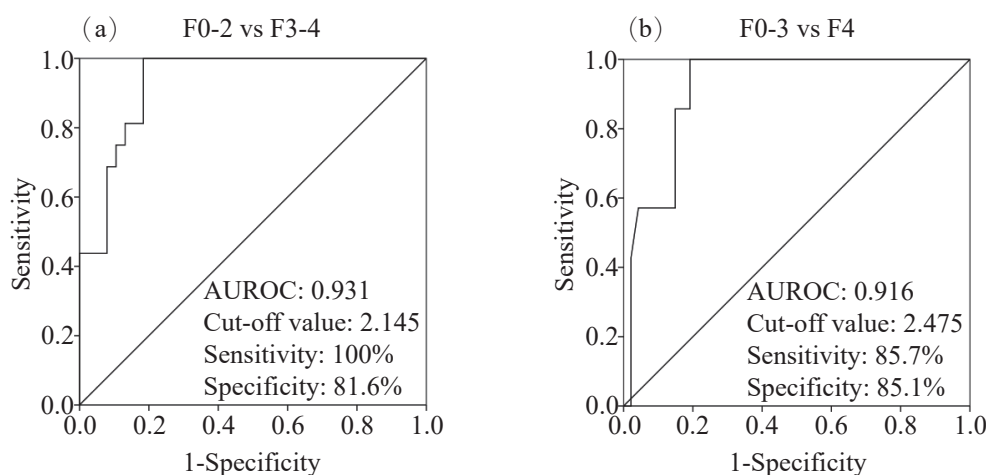


Fig. 2. Receiver operating characteristic (ROC) curve analyses for predicting severe fibrosis (F3 or F4) and cirrhosis (F4). (a) F0-2 vs F3-4. (b) F0-3 vs F4.

Table 3. Correlation between groups was evaluated with Spearman's rank correlation coefficient test. Correlation between the shear wave velocity and laboratory parameters

Variable	r	P-value
Age	0.192	0.165
Liver fibrosis	0.679	<0.001
Liver inflammation	0.303	<0.05
AST (U/L)	0.366	<0.05
ALT (U/L)	0.294	<0.05
Platelet count ($\times 10^9/L$)	-0.312	<0.05
Serum albumin (g/L)	-0.058	0.676
FIB-4 index	0.455	<0.005
APRI	0.486	<0.001
BMI (kg/m^2)	0.406	<0.005
Thickness of the body wall (mm)	0.524	<0.001

AST: aspartate aminotransferase; ALT: alanine aminotransferase; APRI: aspartate aminotransferase to platelet ratio index; BMI: body mass index; FIB-4 index: fibrosis 4 index

ratio index (APRI). Table 2 demonstrates that the effects of shear wave velocity and platelet count were statistically significant. The regression equation was as follows: $Y = -0.688 + 0.664X_1 - 0.293X_2$, where X_1 is shear wave velocity (m/s) and X_2 is platelet count ($\times 10^9/L$). These results suggested that the contribution of these two predictors to the regression equation was in the following descending order: shear wave velocity > platelet count.

Correlation between shear wave velocity and laboratory parameters

Shear wave velocity was positively correlated with the level of AST, ALT, FIB-4 index, APRI, BMI and the thickness of the body wall (Table 3). The thickness of the body wall showed the highest correlation ($r = 0.524$, $P < 0.001$), followed by APRI ($r = 0.486$, $P < 0.001$), FIB-4 index ($r = 0.455$, $P < 0.005$), BMI ($r = 0.406$, $P < 0.005$), AST level ($r = 0.366$, $P < 0.05$), liver inflammation ($r = 0.303$, $P < 0.05$) and ALT level ($r = 0.294$, $P < 0.05$). It was negatively correlated with platelet count ($r = -0.312$, $P < 0.05$). No correlation was found between shear wave velocity and age or serum albumin level.

DISCUSSION

In this study, we evaluated the diagnostic accuracy of SWE with Aplio500 for liver fibrosis in liver disease. The results demonstrated that SWE was reliable for assessing severe fibrosis and cirrhosis.

Methods to assess the development of liver fibrosis are valuable. Morphological changes are observed on ultrasonography, computed tomography and magnetic resonance imaging. Irregular surface and atrophy of the liver [14-17], dilatation of the portal and hepatic veins, splenomegaly and ascites are often observed in patients with advanced chronic liver disease. However, the diagnostic accuracy of these findings is not high. Recently, various biological markers based on clinical and biological data have been reported to be useful predictors of liver fibrosis in patients with liver disease. These include hyaluronic acid, type IV collagen 7S, type III procollagenN-peptide (P-III-P) levels, fucosylated haptoglobin and Mac2 binding protein. In addition,

combinations of biochemical markers, such as in the APRI, the FIB-4 index and the FibroTest, have been reported to be associated with liver fibrosis [18-23]. In recent years, advances in imaging technology have enabled quantitative and non-invasive measurements of liver stiffness with various US-based elastographic methods, including Real-time Tissue Elastography (RTE), TE, Acoustic Radiation Force Impulse Imaging (ARFI), and SWE. Among these methods, SWE is a new real-time technique that uses measurements of acoustically generated tissue shear wave propagation velocity to derive estimates of liver stiffness. RTE, TE, and ARFI have been evaluated in several meta-analyses for their roles in staging liver fibrosis, and were shown to be useful methods with high accuracy for the diagnosis of cirrhosis but intermediate accuracy for differentiating between mild and moderate liver fibrosis [24]. TE, however, has limitations, because in a considerable percentage of patients with obesity, it was unsuccessful. In addition, in spite of the limited function of the TE machine, which only measures TE, the machine is very expensive. Other machines that do not measure TE include two techniques, imaging examination and estimation of liver elasticity. Aplio500 for SWE was just released in 2014, so few reports have evaluated the diagnostic accuracy of SWE using Aplio500. Iijima *et al.* evaluated the diagnostic accuracy of SWE for liver fibrosis with Aplio500, and they also demonstrated the reliability of SWE. However, the cut-off value of cirrhosis in their report was 2.20 m/s, which was significantly lower than our cut-off value [11]. Thus, we have investigated the reason for this difference. A comparison of the patient groups in Iijima's report and in our case revealed that while the cases of chronic hepatitis C in Iijima's reports had accounted for about two-thirds of the population, in our report, hepatitis C represented only 24% of the population. In addition, Iijima's population contained only once case of NASH, while there were 10 cases of NASH in our report. Thus, it is considered that the difference in the proportions of patients with these diseases appeared to be the reason for the difference in the cut-off values. As described in the Results section, SWE was correlated with BMI and the thickness of the body wall. Furthermore, patients with

NASH tend to have greater BMI and body wall thickness compared to patients with other diseases. Therefore, in patients with NASH, there is a possibility that SWE will be higher than the degree of fibrosis. Grgurevic *et al.* also reported that the reliability of SWE was significantly lower in patients with high BMI [25].

A limitation of this study is that the number of patients is small. Therefore, we could not verify the correlation between liver fibrosis and SWE for each disease group. It is necessary to accumulate more cases to verify it.

CONCLUSION

Although an accurate evaluation might be difficult in obese patients, especially those with NASH, SWE is a useful method to evaluate liver fibrosis non-invasively.

The authors state that they have no Conflict of Interest (COI).

REFERENCES

- 1) Saadeh S, Cammell G, Carey WD, Younossi Z, Barnes D, Easley K. The role of liver biopsy in chronic hepatitis C. *Hepatology* 2001;33:196-200.
- 2) Gebo KA, Herlong HF, Torbenson MS, *et al.* Role of liver biopsy in management of chronic hepatitis C: a systematic review. *Hepatology* 2002;36 (5 Suppl 1):S161-72.
- 3) Regev A, Berho M, Jeffers LJ, *et al.* Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol* 2002;97:2614-8.
- 4) Bedossa P, Dargère D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology* 2003;38:1449-57.
- 5) Maharaj B, Maharaj RJ, Leary WP, *et al.* Sampling variability and its influence on the diagnostic yield of percutaneous needle biopsy of the liver. *Lancet* 1986;1:523-5.
- 6) Tsochatzis EA, Gurusamy KS, Ntaoula S, Cholongitas E, Davidson BR, Burroughs AK. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. *J Hepatol* 2011;54:650-9.
- 7) Cassinotto C, Lapuyade B, Ait-Ali A, *et al.* Liver fibrosis: noninvasive assessment with acoustic radiation force impulse elastography--comparison with FibroScan M and XL probes and FibroTest in patients with chronic liver disease. *Radiology* 2013;269:283-92.
- 8) Lin SH, Ding H, Mao F, *et al.* Non-invasive assessment of liver fibrosis in a rat model: shear wave elasticity imaging versus real-time elastography. *Ultrasound Med Biol* 2013;39:1215-22.
- 9) Mak TM, Huang YP, Zheng YP. Liver fibrosis assessment using transient elastography guided with real-time B-mode ultrasound imaging: a feasibility study. *Ultrasound Med Biol* 2013;39:956-66.
- 10) Ferraioli G, Tinelli C, Dal Bello B, Zicchetti M, Filice G, Filice C; Liver Fibrosis Study Group. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. *Hepatology* 2012;56:2125-33.
- 11) Iijima H, Yoshida M, Hashimoto M, *et al.* Superior of a new shear wave elastography in evaluation of liver fibrosis. *Kanzo* 2014;55:771-3. (Eng Abstr)
- 12) Shan QY, Liu BX, Tian WS, *et al.* Elastography of shear wave speed imaging for the evaluation of liver fibrosis: a meta-analysis. *Hepatol Res* 2016;46:1203-13.
- 13) Ichida F, Tsuji T, Omata M, *et al.* New Inuyama classification; new criteria for histological assessment of chronic hepatitis. *Int Hepatol Commun* 1996;6:112-9.
- 14) Khan KN, Yamasaki M, Yamasaki K, *et al.* Proposed abdominal sonographic staging to predict severity of liver diseases: analysis with peritoneoscopy and histology. *Dig Dis Sci* 2000;45:554-64.
- 15) Rofsky NM, Fleishaker H. CT and MRI of diffuse liver disease. *Semin Ultrasound CT MR* 1995;16:16-33.
- 16) Liu P, Li P, He W, Zhao LQ. Liver and spleen volume variations in patients with hepatic fibrosis. *World J Gastroenterol* 2009;15:3298-302.
- 17) Yu JS, Shim JH, Chung JJ, Kim JH, Kim KW. Double contrast-enhanced MRI of viral hepatitis-induced cirrhosis: correlation of gross morpho-

- logical signs with hepatic fibrosis. *Br J Radiol* 2010;83:212-7.
- 18) Yamasaki K, Tateyama M, Abiru S, *et al.* Elevated serum levels of Wisteria floribunda agglutinin-positive human Mac-2 binding protein predict the development of hepatocellular carcinoma in hepatitis C patients. *Hepatology* 2014;60:1563-70.
- 19) Younossi ZM, Page S, Rafiq N, *et al.* A biomarker panel for non-alcoholic steatohepatitis (NASH) and NASH-related fibrosis. *Obes Surg* 2011;21:431-9.
- 20) Tawara S, Tatsumi T, Iio S, *et al.* Evaluation of fucosylated haptoglobin and Mac-2 binding protein as serum biomarkers to estimate liver fibrosis in patients with chronic hepatitis C. *PLoS One* 2016;11:e0151828. doi: 10.1371/journal.pone.0151828.
- 21) de Oliveira AC, El-Bacha I, Vianna MV, Parise ER. Utility and limitations of APRI and FIB4 to predict staging in a cohort of nonselected outpatients with hepatitis C. *Ann Hepatol* 2016;15:326-32.
- 22) Castéra L, Vergniol J, Foucher J, *et al.* Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005;128:343-50.
- 23) Yoneda M, Mawatari H, Fujita K, *et al.* Type IV collagen 7s domain is an independent clinical marker of the severity of fibrosis in patients with nonalcoholic steatohepatitis before the cirrhotic stage. *J Gastroenterol* 2007;42:375-81.
- 24) Kobayashi K, Nakao H, Nishiyama T, *et al.* Diagnostic accuracy of real-time tissue elastography for the staging of liver fibrosis: a meta-analysis. *Eur Radiol* 2015;25:230-8.
- 25) Grgurevic I, Puljiz Z, Brnic D, *et al.* Liver and spleen stiffness and their ratio assessed by real-time two dimensional-shear wave elastography in patients with liver fibrosis and cirrhosis due to chronic viral hepatitis. *Eur Radiol* 2015;25:3214-21.