Journal of Liver

Kotani et al., J Liver 2017, 6:3
DOI: 10.4172/2167-0889.1000212

Research Article OMICS International

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

Satoshi Kotani[1*], Shuichi Sato[2], Naruaki Kohge[3], Kousuke Tsukano[3], Sayaka Ogawa[3], Satoshi Yamanouchi[3], Ryusaku Kusunoki[3], Masahito Aimi[3], Youichi Miyaoka[1], Hirofumi Fujishiro[3], Tomohiko Yamamoto[4] and Hideyuki Ohnuma[4]

[1]Department of Endoscopy, Shimane Prefectural Central Hospital, Japan

[2]Department of Gastroenterology and Hepatology, Shimane University School of Medicine, Japan

[3]Department of Gastroenterology, Shimane Prefectural Central Hospital, Japan

[4]Department of Pathology, Shimane Prefectural Central Hospital, Japan

[*]Corresponding author: Satoshi Kotani, Department of Endoscopy, Shimane Prefectural Central Hospital, 4-1-1 Himebara, Izumo 693-8555, Shimane, Japan, Tel: 81-853-225111; E-mail: ksoattaonsihi@gmail.com

Received date: May 08, 2017; **Accepted date:** May 13, 2017; **Published date:** May 15, 2017

Abstract

Objective: Liver stiffness measurements using shear wave elastography (SWE) for the non-invasive evaluation of liver fibrosis have been developed in the last few years. However, the usefulness of SWE has not been fully investigated. We aimed to evaluate the diagnostic accuracy of 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. 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. 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.

Keywords 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 has been considered the gold standard for assessment of liver fibrosis and cirrhosis so far [1,2]. However, it is an invasive procedure associated with morbidities, such as pain via examination, intra-abdominal bleeding, and perforation of the intestine [3]. In addition, liver biopsy has the limitations of sampling error and intra- and inter-observer variability [4-6]. 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 [7-10]. 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), and c is shear wave velocity (m/s) [11]. Several reports indicate that SWE is more accurate than TE in assessing significant fibrosis [11-13]. 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.

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. We gave each patient a full explanation of the study procedures prior to study entry, and the patients provided written informed consent at enrolment. 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 (3.5 MHz). 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 [14]. 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 [14]. 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 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%).

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

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 between shear wave velocity and fibrosis stage obtained by liver biopsy was analyzed (Figure 1).

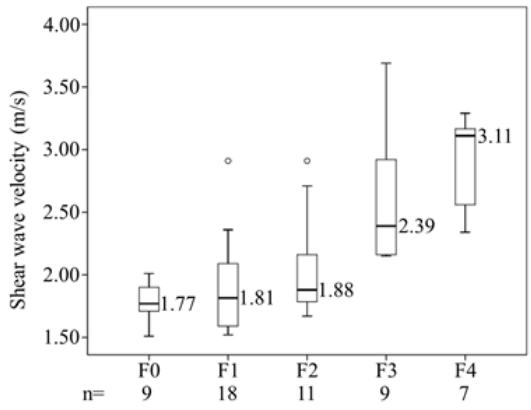

Figure 1: Box-and-whisker plot of the shear wave velocity for each fibrosis stage of the liver in 54 patients who underwent liver biopsy. The top and bottom of the boxes are the first and third quartiles. The length of the box represents the interquartile range, covering 50% of the levels. The lines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

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 predicting 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) (Figure 2).

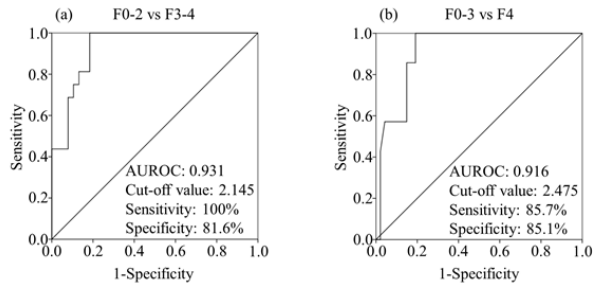

Figure 2: Receiver operating characteristic (ROC) curve analyses for predicting severe fibrosis (F3 or F4) and cirrhosis (F4). (a) F0-2 vs. F3-4. (b) F0-3 vs. F4.

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 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+0.664X1-0.293X2, where X1 is shear wave velocity (m/s) and X2 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.

	Unstandardized Coefficients		Standardized Coefficient		
Factor	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

Table 2: Multiple regression analysis results.

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.

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 (× 109/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

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

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 [15-18], 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 [19-24]. In recent years, advances in imaging technology have enabled quantitative and noninvasive 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 [25]. 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 [12]. 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 [26].

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 noninvasively.

Conflict of Interest

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

References

1. Saadeh S1, Cammell G, Carey WD, Younossi Z, Barnes D, et al. (2001) The role of liver biopsy in chronic hepatitis C. Hepatology 33: 196-200.
2. Gebo KA, Herlong HF, Torbenson MS, Jenckes MW, Chander G, et al. (2002) Role of liver biopsy in management of chronic hepatitis C: a systematic review. Hepatology 36: S161-S172.
3. Tobkes AI1, Nord HJ (1995) Liver biopsy: review of methodology and complications. Dig Dis 13: 267-274.
4. Regev A1, Berho M, Jeffers LJ, Milikowski C, Molina EG, et al. (2002) Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 97: 2614-2618.
5. Bedossa P1, Dargère D, Paradis V (2003) Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology 38: 1449-1457.
6. Maharaj B, Maharaj RJ, Leary WP, Cooppan RM, Naran AD, et al. (1986) Sampling variability and its influence on the diagnostic yield of percutaneous needle biopsy of the liver. Lancet 1: 523-525.
7. Tsochatzis EA1, Gurusamy KS, Ntaoula S, Cholongitas E, Davidson BR, et al. (2011) Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. J Hepatol 54: 650-659.
8. Cassinotto C, Lapuyade B, Aït-Ali A, Vergniol J, Gaye D, et al. (2013) 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 269: 283-292.
9. Lin SH, Ding H, Mao F, Xue LY, Lv WW, et al. (2013) Non-invasive assessment of liver fibrosis in a rat model: shear wave elasticity imaging versus real-time elastography. Ultrasound Med Biol 39: 1215-1222.
10. Mak TM, Huang YP, Zheng YP (2013) Liver fibrosis assessment using transient elastography guided with real-time B-mode ultrasound imaging: a feasibility study. Ultrasound Med Biol 39: 956-966.
11. Ferraioli G, Tinelli C, Dal Bello B, Zicchetti M, Filice G, et al. (2012) Liver Fibrosis Study Group. (2012) Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Hepatology 56: 2125-2133.
12. Iijima H, Yoshida M, Hashimoto M, Nakano C, Aoki T, et al. (2014) Superiority of a new shear wave elastography in evaluation of liver fibrosis. Kanzo 55: 771-773.
13. Shan QY1, Liu BX1, Tian WS1, Wang W1, Zhou LY1, et al. (2016) Elastography of shear wave speed imaging for the evaluation of liver fibrosis: A meta-analysis. Hepatol Res 46: 1203-1213.
14. Ichida F, Tsuji T, Omata M, Ichida T, Inoue K, et al. (1996) New Inuyama classification; new criteria for histological assessment of chronic hepatitis. Int Hepatol Commun 6:112-119.
15. Khan KN, Yamasaki M, Yamasaki K, Inoue O, Yatsuhashi H, et al. (2000) Proposed abdominal sonographic staging to predict severity of liver diseases: analysis with peritoneoscopy and histology. Dig Dis Sci 45: 554-564.
16. Rofsky NM1, Fleishaker H (1995) CT and MRI of diffuse liver disease. Semin Ultrasound CT MR 16: 16-33.
17. Liu P, Li P, He W, Zhao LQ (2009) Liver and spleen volume variations in patients with hepatic fibrosis. World J Gastroenterol 15: 3298-3302.
18. Yu JS, Shim JH, Chung JJ, Kim JH, Kim KW (2010) Double contrast-enhanced MRI of viral hepatitis-induced cirrhosis: correlation of gross morphological signs with hepatic fibrosis. Br J Radiol 83: 212-217.
19. Yamasaki K, Tateyama M, Abiru S, Komori A, Nagaoka S, et al. (2014) Elevated serum levels of Wisteria floribunda agglutinin-positive human Mac-2 binding protein predict the development of hepatocellular carcinoma in hepatitis C patients. Hepatology 60: 1563-1570.
20. Younossi ZM1, Page S, Rafiq N, Birerdinc A, Stepanova M, et al. (2011) A biomarker panel for non-alcoholic steatohepatitis (NASH) and NASH-related fibrosis. Obes Surg 21: 431-439.
21. Tawara S, Tatsumi T, Iio S, Kobayashi I, Shigekawa M, et al. (2016) Evaluation of Fucosylated Haptoglobin and Mac-2 Binding Protein as Serum Biomarkers to Estimate Liver Fibrosis in Patients with Chronic Hepatitis C. PLoS One 11: e0151828.
22. de Oliveira AC, El-Bacha I, Vianna MV, Parise ER (2016) Utility and limitations of APRI and FIB4 to predict staging in a cohort of nonselected outpatients with hepatitis C. Ann Hepatol 15: 326-332.
23. Castéra L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, et al. (2005) Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 128: 343-350.

24. Yoneda M, Mawatari H, Fujita K, Yonemitsu K, Kato S, et al. (2007) 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 42: 375-381.

25. Kobayashi K1, Nakao H, Nishiyama T, Lin Y, Kikuchi S, et al. (2015) Diagnostic accuracy of real-time tissue elastography for the staging of liver fibrosis: a meta-analysis. Eur Radiol 25: 230-238.

26. Grgurevic I, Puljiz Z, Brnic D, Bokun T, Heinzl R, et al. (2015) 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 25: 3214-3221.