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ORIGINAL ARTICLE

Real time shear wave elastography in chronic liver diseases: Accuracy for predicting liver fibrosis, in comparison with serum markers

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Abstract

AIM: To evaluate the correlation between liver stiffness measurement (LSM) by real-time shear wave elastography (SWE) and liver fibrosis stage and the accuracy of LSM for predicting significant and advanced fibrosis, in comparison with serum markers.

METHODS: We consecutively analyzed 70 patients with various chronic liver diseases. Liver fibrosis was staged from F0 to F4 according to the Batts and Ludwig scoring system. Significant and advanced fibrosis was defined as stage F $\geqslant$ 2 and F $\geqslant$ 3, respectively. The accuracy of prediction for fibrosis was analyzed using receiver operating characteristic curves.

RESULTS: Seventy patients, 15 were belonged to F0-F1 stage, 20 F2, 13 F3 and 22 F4. LSM was increased with progression of fibrosis stage (F0-F1: 6.77 ± 1.72, F2: 9.98 ± 3.99, F3: 15.80 ± 7.73, and F4: 22.09 ± 10.09, $P < 0.001$). Diagnostic accuracies of LSM for prediction of F $\geqslant$ 2 and F $\geqslant$ 3 were 0.915 (95%CI: 0.824-0.968, $P < 0.001$) and 0.913 (95%CI: 0.821-0.967, $P < 0.001$), respectively. The cut-off values of LSM for prediction of F $\geqslant$ 2 and F $\geqslant$ 3 were 8.6 kPa with 78.2% sensitivity and 93.3% specificity and 10.46 kPa with 88.6% sensitivity and 80.0% specificity, respectively. However, there were no significant differences between LSM and serum hyaluronic acid and type Ⅳ collagen in diagnostic accuracy.

CONCLUSION: SWE showed a significant correlation with the severity of liver fibrosis and was useful and accurate to predict significant and advanced fibrosis, comparable with serum markers.

Key words: Elastography; Liver fibrosis; Liver stiffness; Liver biopsy; Serum markers

Core tip: This study showed that liver stiffness measurement by real time shear wave elastography was highly accurate to predict the biopsy-proven significant and advanced liver fibrosis and its accuracy was comparable with that of serum markers of hyaluronic acid and type Ⅳ collagen.

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INTRODUCTION

In patients with chronic hepatitis, the progression of inflammatory reactions and necrosis of hepatocytes causes hepatic fibrosis and leads to cirrhosis, which presents various clinical complications, including ascites, jaundice, or hepatocellular carcinoma[1]. The staging of liver fibrosis, therefore, is of major clinical concern because it informs the patient's prognosis and is a key factor when determining a treatment strategy. Particularly in cases of chronic viral hepatitis B and C, it is important to detect significant and advanced fibrosis, because these stages are the critical points for anti-viral treatment[2,3]. Traditionally, liver biopsy has been the gold standard for liver fibrosis staging[2]. However, this invasive procedure has potential complications, such as pain or hemorrhage, and the possibility of repeat examination is limited[3]. In addition, hepatic fibrosis affects the liver inhomogeneously, and biopsy specimens may be inadequate samples that do not represent the histology of the whole hepatic parenchyma; this can lead to inter-observer variation of 10%-20% in histologic measurements[4,5]. Non-invasive complementary tools, including traditional imaging using ultrasonography (US) or computerized tomography and blood tests using several serum markers, have been developed, but there is limited clinical evidence that these techniques are effective, particularly for predicting and diagnosing earlier stages of hepatic fibrosis[6-9].

Recently, non-invasive methods for measuring liver stiffness (LS), including transient elastography (TE), acoustic radiation force impulse imaging (ARFI), and magnetic resonance elastography have been developed, and several studies report good results in their ability to predict the degree of hepatic fibrosis[10-12]. More recently, real-time shear wave elastography (SWE), another method for measuring LS, has been developed[13]. Unlike TE, SWE measures tissue elasticity simultaneously during B-mode ultrasound examination, and elasticity values can be measured on the basis of anatomical information. In addition, SWE provides elastography color maps according to the degree of stiffness, allowing an assessment of homogeneity. As a result, SWE provides more accurate information about hepatic fibrosis staging than TE[14]. However, there are few studies comparing SWE results with histologic diagnosis using liver biopsy, and to our knowledge, there are no reports comparing SWE results with indirect serologic markers of hepatic fibrosis such as aspartate aminotransferase (AST) to platelet (PLT) ratio index (APRI), hyaluronic acid (HA), and type Ⅳ collagen[15].

Therefore, the aim of this study was to evaluate the correlation between LS measurement (LSM) using SWE and liver fibrosis stage determined histopathologically in patients with various chronic liver diseases, as well as to determine the diagnostic accuracy and clinical usefulness of SWE in predicting significant fibrosis and advanced liver fibrosis. We also compared LS values measured using SWE with serum markers that are also used to detect hepatic fibrosis.

MATERIALS AND METHODS

Study population

This was a single-center retrospective study, with data collected from 83 patients who consecutively underwent SWE, serum sampling for HA and type Ⅳ collagen and consequent liver biopsy between September 2010 and February 2013 at Hanyang University Guri Hospital. Thirteen of the 83 patients were excluded, 10 because of body mass indexes (BMI) greater than 30 kg/m^2, and 3 due to total bilirubin levels greater than 5 mg/dL. These two factors have been reported to cause unreliable results when performing TE measurements[16,17]. In total, 70 patients were included in the study. The diagnostic criteria of chronic viral hepatitis were as follows: (1) elevated serum alanine aminotransferase (ALT); (2) elevation of serum HBV DNA levels for longer than six months; and (3) positive serum antibody for HCV. Non-viral chronic liver diseases such as alcoholic liver disease and non-alcoholic fatty liver disease were diagnosed through patient history, physical examination, blood testing, abdominal ultrasonography, and liver biopsy. The study was approved by the institution's ethics committee (IRB 2012-06). All participants gave informed written consent for liver biopsy.

Patient examination

Body weight and height were measured for each patients on the day liver biopsy was performed, and BMI was calculated. Blood samples were taken the morning of the same day, after patients had fasted more than eight hours. Blood tests, which included hemoglobin, PLT, serum albumin, total bilirubin, AST, ALT, prothrombin time (PT; INR: international normalized ratio), gamma-glutamyltranspeptidase (GGT), type Ⅳ collagen, and HA were conducted. In addition, APRI [AST/upper limit of normal/PLT count (× 10^9/L) ×100], which is reportedly a non-invasive method for diagnosing hepatic fibrosis, was calculated using the same blood. HA (normal range: below 75 ng/mL) was measured by enzyme-linked binding protein assay using a hyaluronic acid plate kit (Corgenix, Inc., Westminster, CO, United States), and the serum concentration of type Ⅳ collagen (normal range: below 140 ng/mL) was calibrated by the Latex method (Fuji Chem, Ind. Ltd., Tokyo, Japan) using monoclonal antibody that recognizes different parts of type Ⅳ collagen. HA and type Ⅳ collagen were

Table 1 Baseline characteristics of patients

Characteristics	*n* = 70	
Age, yr (SD, range)	45.9	(15.7, 12.0-82.0)
Sex, male (%)	45	(64.3)
HBV/HCV/Alcohol/NAFLD/Other (%)	23 (32.9)/18 (25.7)/12 (17.1)/4 (5.7)/13 (18.6)	
Body mass index, kg/m^2(SD, range)	23.8	(2.9, 16.9-29.7)
Hemoglobin, g/dL (SD, range)	12.9	(2.2, 6.7-17.8)
Platelet count, 10^3/mm^3 (SD, range)	174.7	(55.3, 76.0-285.0)
Albumin, g/dL (SD, range)	3.9	(0.7, 1.6-5.3)
AST, U/L (IQR, range)	55	(31-111, 13-369)
ALT, U/L (IQR, range)	47	(24-99, 6-473)
Total bilirubin, mg/dL (IQR, range)	0.7	(0.5-1.1, 0.2-4.9)
GGT, U/L (IQR, range)	57	(31-157, 13-1569)
Prothrombin time, INR (IQR, range)	0.93	(0.87-1.00, 0.76-1.48)
APRI (IQR, range)	0.91	(0.51-1.35, 0.55-5.88)
Hyaluronic acid[1], ng/mL (IQR, range)	62	(23-176, 10-2796)
Type IV collagen[1], ng/mL (IQR, range)	182	(117-310, 66-2790)
Liver stiffness by SWE, kPa (IQR, range)	11.1	(7.3-18.4, 4.73-48.61)
Fibrosis stage (%)		
F0-1	15	(21.4)
F2	20	(28.6)
F3	13	(18.6)
F4	22	(31.4)

[1]*n* = 61. HBV: Hepatitis B virus; HCV: Hepatitis C virus; NAFLD: Nonalcoholic fatty liver disease; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma glutamyltranspeptidase; INR: International normalized ratio; SWE: Shear wave elastography; kPa: Kilopascals; SD: Standard deviation; IQR: Interquartile range.

not measured in 9 patients.

SWE was conducted using an Aixplorer US system (Supersonic Imagine S.A, Aix-en-Provence, France), and a convex probe. All SWE measurements were made by experienced abdominal radiologists (Y. Kim and W. K. Jeong). Shear wave was generated by a continuously repeated focused ultrasound beam to the target tissue along the direction the longitudinal wave propagated. The velocity of the generated shear wave was measured by performing an ultra-fast ultrasound scan at a very high frame rate (more than 4000 frames per second), and the liver stiffness of corresponding tissue was calculated by measuring the shear wave velocity generated. After gray-scale US, SWE was performed using the same probe. The curved transducer was placed intercostally at the level of the right lobe of the liver, with the target area was located in the right anterior hepatic segment at a depth of more than 2 cm from the hepatic capsule to avoid major vessels. LS was measured within a 5 s breath hold. The measurement was performed 10 times for each patient, and results were expressed in kilopascals (kPa). Median value was considered representative of the LS.

Liver biopsy was conducted percutaneously under US-guidance. Biopsy specimens were fixed in formalin and embedded in paraffin; 5-mm-thick sections were then cut and stained with hematoxylin-eosin. Masson-trichrome staining was also performed to more accurately analyze hepatic fibrosis. All histologic analyses were performed independently by one pathologist (Y. Oh). The hepatic fibrosis was staged on a 0-4 scale according to the classification suggested by Batts and Ludwig: F0 = no fibrosis; F1 = portal fibrosis; F2 = periportal fibrosis; F3 = septal fibrosis; and F4 = cirrhosis[18]. Hepatic fibrosis staged higher than F2 was considered significant fibrosis, and higher than stage F3 as advanced fibrosis[18].

Statistical analysis

Statistical analysis was performed using the SPSS software package version 18.0 for Windows (SPSS, Chicago, IL, United States), and Medcalc, version 9.1 (Medcalc software, Ostend, Belgium). Statistical significance was defined as $P < 0.05$.

The results of each examination were described either as mean ± SD or median value inter-quartile range (IQR). Kruskal-Wallis' one-way analysis of variance by ranks was used the test differences between measured LS values, and the Tukey test was used for post-hoc comparison. The diagnostic performance of SWE was accessed using receiver operating characteristic (ROC) curves and area under the ROC (AUROC) curve analysis. Diagnostic cut-off value for the diagnosis of significant fibrosis, advanced fibrosis and cirrhosis was determined as the maximum combined values of sensitivity and specificity. Spearman's coefficient was used to test the correlation between stage of hepatic fibrosis and each variable. Additionally, AUROC analysis was also performed to access the efficacy of LS values measured by SWE and serum markers for the prediction of hepatic fibrosis in chronic liver disease.

RESULTS

Clinical characteristics of patients

The clinical characteristics of the patients are summarized in Table 1. The mean age of 70 total patients was

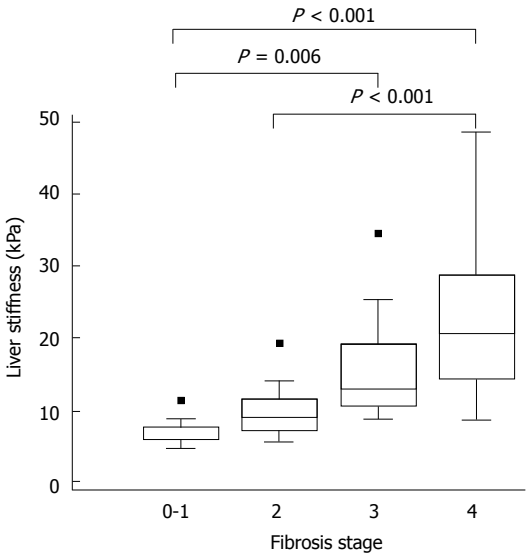

Figure 1 Score values of liver stiffness by according to fibrosis stage (*n* = 70). Boxplots summarize the liver stiffness by shear wave elastography (SWE) for each fibrosis classification. For each box, the box gives the interquartile range, that is, the 25th to 75th percentiles of liver stiffness by SWE, with line inside the box denoting the median, the 50th percentile of data. Statistical significant test was done by Tukey test using ranks.

Table 2 Liver stiffness cut-off values for the diagnosis of significant (≥ F2) and advanced (≥ F3) fibrosis and cirrhosis (F4) (*n* = 70)

Value	≥ F2	≥ F3	= F4
Number of patients, *n* (%)	55 (78.6)	35 (50.0)	22 (31.4)
Optimal cut-off[1] (kPa)	8.60	10.46	14.00
Sensitivity (%)	78.20	88.60	77.30
Specificity (%)	93.30	80.00	85.40
Negative likelihood ratio	11.73	4.43	5.30
Positive likelihood ratio	0.23	0.14	0.27

[1]Cut-off value was calculated to maximize the sum of sensitivity and specificity. kPa: Kilopascals.

45.9 ± 15.7 years, and the majority (64.3%) was male. The causes of chronic liver disease were HBV (*n* = 23, 32.9%), HCV (18, 25.7%), alcohol (12, 17.1%), non-alcoholic liver disease (4, 5.7%), and other diseases including autoimmune hepatitis and unknown causes (13, 18.6%). The mean length of liver biopsy specimens was 16.2 ± 2.3 mm.

The stage of hepatic fibrosis in the patients showed a relatively even distribution, as follows: F0-1, *n* =15 (21.4%); F2, 20 (28.6%); F3, 13 (18.6%); and F4, 22 (31.4%). Median measured value of LS was 11.1 (IQR: 7.3-18.4) kPa.

Correlation between LSM and hepatic fibrosis

Figure 1 show the correlation between LS measured using SWE and hepatic fibrosis diagnosed by biopsy. The mean LSM values according to hepatic fibrosis stage were as follows: F0-1, 6.77 ± 1.72 kPa; F2, 9.98 ± 3.99 kPa; F3, 15.80 ± 7.73 kPa; and F4, 22.09 ± 10.09 kPa. The correlation between LSM and hepatic fibrosis stage was significant (r = 0.774, P < 0.001). When comparing LS values at different hepatic fibrosis stages, significant differences were found between F0-1 and F3 (P = 0.006), between F0-1 and F4 (P < 0.001), and between F2 and F4 (P < 0.001). However, there were no significant differences between the other hepatic fibrosis stages.

Table 3 Correlation between noninvasive serum markersand histologic fibrosis in chronic liver disease (*n* = 70)

Fibrosis stage	*r*	*P* value
Age	0.344	0.004
Hemoglobin	-0.281	0.018
Platelet	-0.514	< 0.001
Albumin	-0.505	< 0.001
AST	0.215	0.074
ALT	-0.087	0.475
Total bilirubin	0.302	0.011
GGT	0.236	0.049
Prothrombin time (INR)	0.479	< 0.001
APRI	0.390	0.001
Hyaluronic acid[1]	0.708	< 0.001
Type IV collagen[1]	0.691	< 0.001
Liver stiffness by SWE	0.774	< 0.001

[1]*n* = 61. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma glutamyltranspeptidase; INR: International normalized ratio; APRI: Aspartate aminotransferase to platelet ratio index; SWE: Shear wave elastography.

Diagnostic performance of LSM using SWE for the prediction of hepatic fibrosis

The AUROCs for LSM using SWE were 0.915 (95%CI: 0.824-0.968, P < 0.001), 0.913 (95%CI: 0.821-0.967, P < 0.001), and 0.878 (95%CI, 0.778-0.944, P < 0.001) for the diagnosis of significant fibrosis (≥ F2), advanced fibrosis (≥ F3) and cirrhosis (F4), respectively. Optimal cut-off values for the different levels of hepatic fibrosis by ROC curve analysis for SWE measurement were as follows: significant fibrosis, 8.6 kPa (sensitivity 78.2%, specificity 93.3%); advanced fibrosis, 10.46 kPa (sensitivity 88.6%, specificity 80.0%); and cirrhosis, 14.0 kPa (sensitivity 77.3%, specificity 85.4%) (Figure 2, Table 2).

Correlation between serum markers and hepatic fibrosis

When analyzing paired combinations, hepatic fibrosis showed a significant negative correlation with platelet (r = -0.514, P < 0.001) and albumin (r = -0.505, P < 0.001) levels, and a significant positive correlation with PT (INR) (r = 0.479, P < 0.001), HA (r = 0.708, P < 0.001), and type Ⅳ collagen (r = 0.691, P < 0.001). There were only weak correlations between hepatic fibrosis and hemoglobin (r = -0.281, P = 0.018), serum total bilirubin (r = 0.302, P = 0.011), GGT (r = 0.236, P = 0.049), and APRI (r = 0.390, P = 0.001). AST and ALT showed no significant correlation with hepatic fibrosis stage (Table 3). When analyzing paired combinations of hepatic fibrosis with serum markers and LSM, LSM showed the

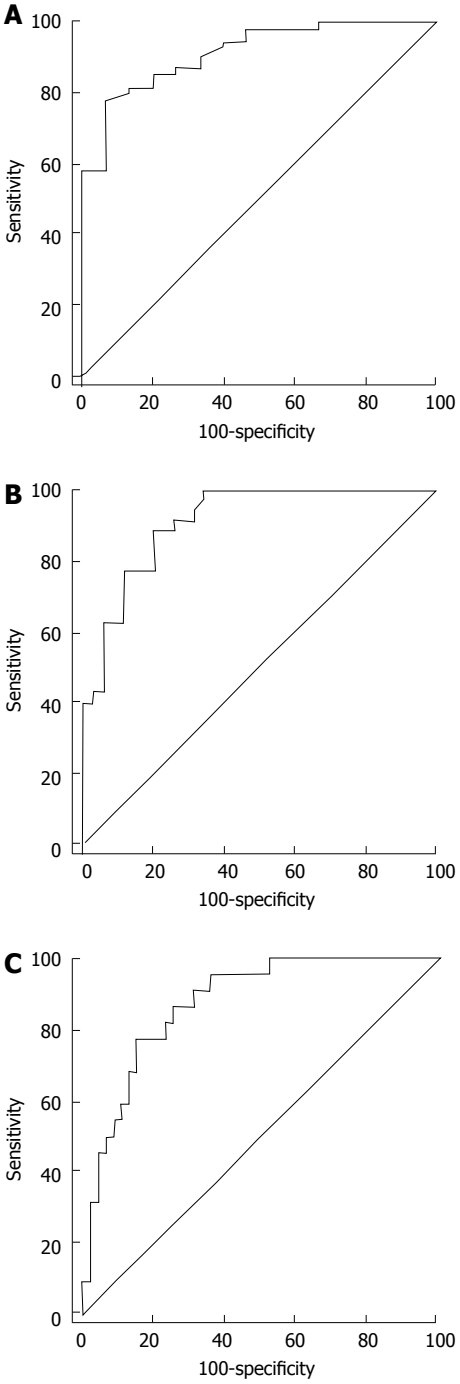

Figure 2 Receiver-operating characteristic curves of liver stiffness determined by shear wave elastography for diagnosis of significant fibrosis (F0-1 *vs* F2-4, A), advanced fibrosis (F0-2 *vs* F3-4, B) and cirrhosis (F0-3 *vs* F4, C) (*n* = 70).

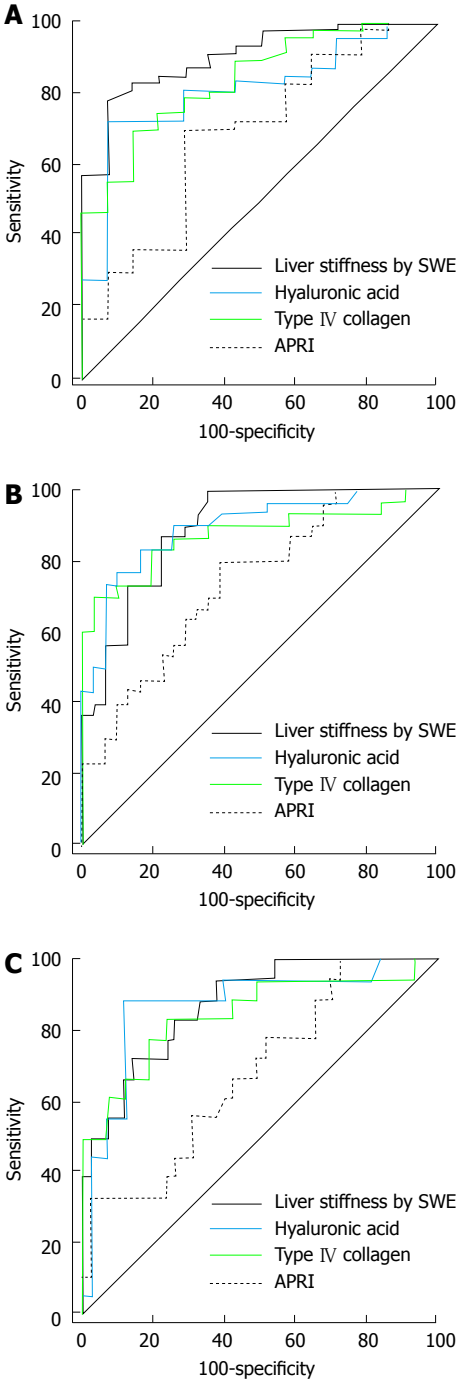

Figure 3 Receiver operating characteristic curves of noninvasive serum markers for discriminating F0-1 *vs* F2-4 (significant fibrosis, A), F0-2 *vs* F3-4 (advanced fibrosis, B) and F0-3 *vs* F4 (cirrhosis, C) (*n* = 61). SWE: Shear wave elastography; APRI: Aspartate aminotransferase to platelet ratio index.

highest correlation ($r = 0.774$, $P < 0.001$).

Comparison of LSM with serum markers for the prediction of hepatic fibrosis in the whole patients

Figure 3 shows the ROC curves for APRI, HA, type Ⅳ collagen and LSM by SWE for the diagnosis of significant fibrosis, advanced fibrosis and liver cirrhosis. The AUROC value for the diagnosis of significant fibrosis was higher in SWE (0.908) than serum markers (APRI = 0.691, HA = 0.812, type Ⅳ collagen = 0.841), but the results were not statistically significant (HA, $P = 0.081$; and type Ⅳ collagen, $P = 0.189$), except in the case of APRI ($P = 0.003$). The AUROC value for the diagnosis of advanced fibrosis was also significantly higher in SWE (0.893) than APRI (0.743) ($P = 0.032$). However, LSM showed no significant differences between the other 2 markers (HA = 0.897 and type Ⅳ collagen = 0.876; P = 0.974 and 0.631, respectively). Finally, the AUROC value

Table 4 Comparison of diagnostic performance between noninvasive serum marker for discriminating F0-1 *vs* F2-4 (significant fibrosis), F0-2 *vs* F3-4 (advanced fibrosis) and F0-3 *vs* F4 (cirrhosis) (n = 61)

	AUROC	95%CI	Pairwise comparison of ROC curves		
			Factor	Difference between areas (95%CI)	*P* value
Significant fibrosis					
SWE	0.908	0.806-0.967	HA	0.097 (-0.012-0.205)	0.081
			Type Ⅳ	0.067 (-0.003-0.167)	0.189
			APRI	0.217 (0.074-0.359)	0.003
HA	0.812	0.691-0.900	Type Ⅳ	0.030 (-0.092-0.152)	0.634
			APRI	0.120 (-0.041-0.281)	0.145
Type Ⅳ	0.841	0.725-0.922	APRI	0.150 (-0.006-0.305)	0.059
APRI	0.691	0.560-0.803			
Advanced fibrosis					
SWE	0.893	0.787-0.957	HA	0.004 (-0.093-0.101)	0.939
			Type Ⅳ	0.017 (-0.080-0.113)	0.735
			APRI	0.150 (0.013-0.287)	0.032
HA	0.897	0.792-0.960	Type Ⅳ	0.020 (-0.074-0.115)	0.671
			APRI	0.154 (0.014-0.293)	0.031
Type Ⅳ	0.876	0.767-0.947	APRI	0.133 (-0.010-0.277)	0.069
APRI	0.743	0.615-0.846			
Cirrhosis					
SWE	0.877	0.768-0.947	HA	0.002 (-0.114-0.118)	0.974
			Type Ⅳ	0.027 (-0.084-0.138)	0.631
			APRI	0.194 (0.031-0.358)	0.002
HA	0.879	0.770-0.948	Type Ⅳ	0.029 (-0.072-0.130)	0.571
			APRI	0.196 (0.022-0.371)	0.027
Type Ⅳ	0.850	0.736-0.928	APRI	0.167 (-0.003-0.338)	0.055
APRI	0.683	0.551-0.796			

ROC: Receiver-operating characteristic curves; AUROC: Area under the ROC curve; SWE: Shear wave elastography; HA: Hyaluronic acid; Type Ⅳ: Type Ⅳ collagen; APRI: Aspartate aminotransferase to platelet ratio index.

Table 5 Comparison of diagnostic performance between shear wave elastography and noninvasive serum markers for discriminating F0-1 *vs* F2-4 (significant fibrosis) and F0-2 *vs* F3-4 (advanced fibrosis) in patients with chronic viral hepatitis (n = 36)

	AUROC	95%CI	Pairwise comparison of ROC curves		
			Factor	Difference between areas (95%CI)	*P* value
Significant fibrosis					
SWE	0.935	0.800-0.989	HA	0.277 (0.070-0.485)	0.009
			Type Ⅳ	0.158 (-0.009-0.325)	0.063
			APRI	0.077 (-0.066-0.220)	0.289
HA	0.658	0.482-0.807	Type Ⅳ	0.119 (-0.084-0.326)	0.257
			APRI	0.200 (-0.029-0.429)	0.086
Type Ⅳ	0.777	0.608-0.898	APRI	0.081 (-0.126-0.288)	0.445
APRI	0.858	0.701-0.951			
Advanced fibrosis					
SWE	0.914	0.771-0.980	HA	0.094 (-0.054-0.243)	0.214
			Type Ⅳ	0.120 (-0.030-0.271)	0.118
			APRI	0.086 (-0.061-0.234)	0.250
HA	0.819	0.656-0.927	Type Ⅳ	0.026 (-0.120-0.172)	0.725
			APRI	0.008 (-0.168-0.183)	0.931
Type Ⅳ	0.793	0.626-0.909	APRI	0.034 (-0.153-0.221)	0.722
APRI	0.827	0.665-0.932			

ROC: Receiver-operating characteristic curves; AUROC: Area under the ROC curve; SWE: Shear wave elastography; HA: Hyaluronic acid; Type Ⅳ: Type Ⅳ collagen; APRI: Aspartate aminotransferase to platelet ratio index.

for the diagnosis of liver cirrhosis was also significantly higher in LSM (0.877) than APRI (0.683) (P = 0.032), but there were no significant differences between LSM and the other serum markers (HA = 0.879 and type Ⅳ collagen = 0.850; P = 0.974 and 0.631, respectively) (Table 4).

Comparison of LSM with serum markers in a subgroup of patients with chronic viral hepatitis

Figure 4 shows the ROC curves for APRI, HA, type Ⅳ collagen and LSM for the diagnosis of significant hepatic fibrosis, advanced fibrosis and liver cirrhosis in 36 patients with chronic viral hepatitis. The AUROC value

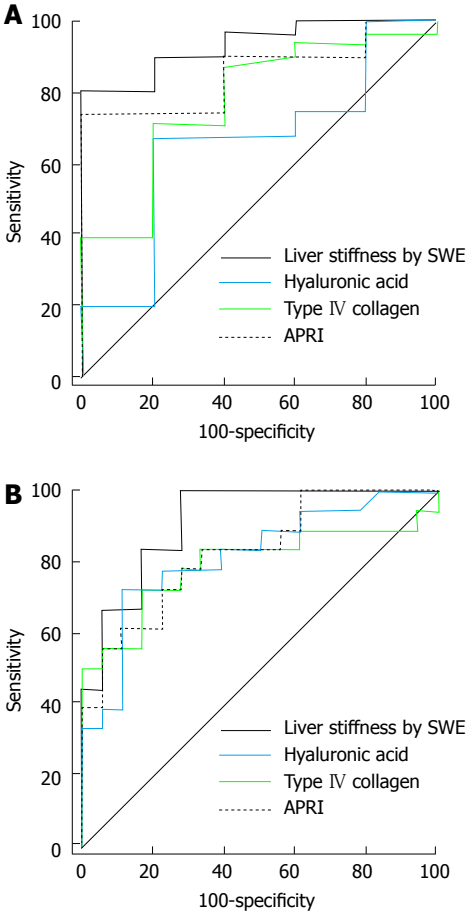

Figure 4 Comparison of receiver-operating characteristiccurves of non-invasive serum markers for discriminating F0F1 *vs* F2-4 (significant fibrosis, A) and F0-2 *vs* F3F4 (advanced fibrosis, B) in 36 patients with chronic viral hepatitis. ROC: Receiver-operating characteristic curves; SWE: Shear wave elastography; APRI: Aspartate aminotransferase to platelet ratio index.

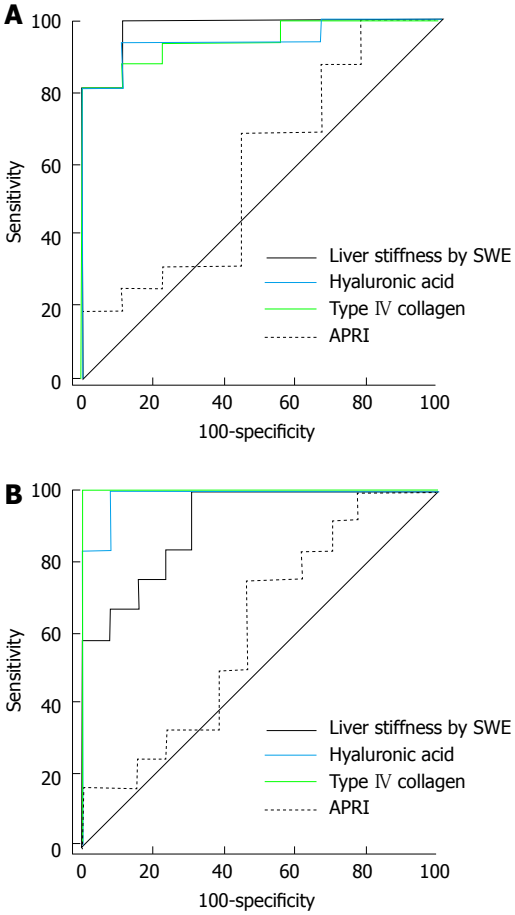

Figure 5 Comparison of receiver-operating characteristic curves of noninvasive marker for discriminating F0F1 *vs* F2-4 (significant fibrosis, A) and F0-2 *vs* F3F4 (advanced fibrosis, B) in 25 patients with non-viral chronic liver diseases. ROC: Receiver-operating characteristic curves; SWE: Shear wave elastography; APRI: Aspartate aminotransferase to platelet ratio index.

for the diagnosis of significant hepatic fibrosis was higher in SWE (0.935) than the serum markers (APRI = 0.858, HA = 0.658, type Ⅳ collagen = 0.777), but the difference was only significant between SWE and HA (P = 0.009; APRI and type Ⅳ collagen P values were 0.289 and 0.063, respectively). The AUROC value for the diagnosis of advanced fibrosis (≥ F3) was also higher in SWE (0.914) than the serum markers (APRI = 0.827, HA = 0.819, type Ⅳ collagen = 0.793), but the result was not statistically significant (Table 5).

Comparison of LSM with serum markers in a subgroup of patients with non-viral chronic liver disease

Figure 5 shows the ROC curves for APRI, HA, type Ⅳ collagen and LSM for the diagnosis of significant fibrosis, advanced fibrosis and cirrhosis in 25 patients with non-viral chronic liver disease. AUROC values for the diagnosis of significant fibrosis were higher in LSM (0.979) than the serum markers (APRI = 0.590, HA = 0.944, type Ⅳ collagen = 0.944), but there was no statistical significance (HA, P = 0.465; and type Ⅳ collagen, P = 0.429, respectively), except in the case of APRI (P = 0.001) (Table 6). AUROC value for the diagnosis of advanced fibrosis (≥ F3) was also significantly higher for LSM (0.910) than APRI (0.615) (P = 0.014). The AUROC value of LSM was lower than HA (0.987) and type Ⅳ collagen (1.000), but the results were not statistically significant (P = 0.206 and 0.156, respectively) (Table 6).

DISCUSSION

We assessed the clinical usefulness of LSM using SWE in patients with various chronic liver diseases in predicting the degree of hepatic fibrosis by comparing SWE with histopathological results. The results clearly showed LS values measured using SWE were significantly correlated with severity of hepatic fibrosis (r = 0.774, P < 0.001). Furthermore, the results indicated that the diagnostic accuracy of LSM using SWE for the detection of significant fibrosis (≥ F2) and advanced fibrosis (≥ F3) was very high (AUROC values of 0.915 and 0.913, respectively), suggesting that SWE offers excellent diagnostic performance. Our results are consistent with previously published studies. Bavu *et al*[14] compared the results of SWE with that of TE after grading hepatic fibrosis into F0-1, F2, F3, and F4 using serologic examination without

Table 6 Comparison of diagnostic performance between shear wave elastography and noninvasive serum markers for discriminating F0-1 *vs* F2-4 (significant fibrosis) and F0-2 *vs* F3-4 (advanced fibrosis) with non-viral chronic liver diseases (n = 25)

	AUROC	95%CI	Pairwise comparison of ROC curves		
			Factor	Difference between areas (95%CI)	*P* value
Significant fibrosis					
SWE	0.979	0.826-0.988	HA	0.035 (-0.058-0.128)	0.465
			Type Ⅳ	0.035 (-0.051-0.121)	0.429
			APRI	0.389 (0.163-0.615)	0.001
HA	0.944	0.773-0.993	Type Ⅳ	0.000 (-0.103-0.103)	1.000
			APRI	0.354 (0.137-0.572)	0.001
Type Ⅳ	0.944	0.773-0.993	APRI	0.354 (0.130-0.578)	0.002
APRI	0.590	0.378-0.781			
Advanced fibrosis					
SWE	0.910	0.726-0.985	HA	0.077 (-0.042-0.196)	0.206
			Type Ⅳ	0.090 (-0.034-0.214)	0.156
			APRI	0.295 (0.060-0.530)	0.014
HA	0.987	0.839-1.000	Type Ⅳ	0.013 (-0.034-0.060)	0.593
			APRI	0.372 (0.155-0.589)	0.001
Type Ⅳ	1.000	0.862-1.000	APRI	0.385 (0.160-0.609)	0.001
APRI	0.615	0.401-0.801			

ROC: Receiver-operating characteristic curves; AUROC: Area under the ROC curve; SWE: Shear wave elastography; HA: Hyaluronic acid; Type Ⅳ: Type Ⅳ collagen; APRI: Aspartate aminotransferase to platelet ratio index.

performing liver biopsies. In that study, LS measured using SWE increased according to the severity of hepatic fibrosis, and AUROC values for the diagnosis of significant fibrosis, advanced fibrosis and cirrhosis were 0.948, 0.962 and 0.968, respectively. Ferraioli *et al*[15] also compared SWE with TE in chronic hepatitis C patients using liver biopsy specimens, and LS measured using SWE also increased according to hepatic fibrosis stage. In their study, AUROC values for the diagnosis of significant fibrosis, advanced fibrosis and liver cirrhosis were 0.92, 0.98 and 0.98, respectively. Taken together, these results suggest that SWE is a promising tool for non-invasively predicting various degrees of hepatic fibrosis in patients with chronic liver diseases.

Previous studies have reported that serologic examinations using serum markers or TE more accurately diagnose liver cirrhosis rather than intermediate stages of fibrosis (F2-3)[8,11]. However, in our study, the AUROC value (0.878) of LSM using SWE for detecting cirrhosis was slightly lower, but not significantly, than the values for detecting fibrosis staged ≥ F2 and ≥ F3 (which were 0.915 and 0.913, respectively). We are not currently able to explain this difference. A small sample size and heterogeneous causes of chronic liver diseases may explain the result. Therefore, large prospective studies in patients with homogenous disease causes are needed. Nonetheless, a recent study showed no significant difference between LSM using SWE for detection of intermediate stage fibrosis and cirrhosis, and, in addition, reported that SWE was superior to TE in detecting significant fibrosis[17]; our findings suggest that SWE may diagnose intermediate stages of fibrosis more accurately than other modalities.

We did not compare SWE with TE in this study. However, we performed additional serologic examinations, and included various serum markers of hepatic fibrosis, such as APRI, HA, and type Ⅳ collagen, as well as other serum parameters [hemoglobin, serum bilirubin, PT (INR), GGT]. Levels of all the listed serum markers were positively correlated with hepatic fibrosis stage. On the other hand, platelet and serum albumin were negatively correlated, and AST and ALT showed no significant correlations. These results are consistent with other published data[15,19,20]. The results of LSM using SWE showed the highest correlation with hepatic fibrosis stage (r = 0.774, P < 0.001) of all the tested parameters.

When we compared the results of SWE and serum markers, the AUROC value for the detection of significant fibrosis was higher in SWE than the other serum markers, although the only significant difference was between SWE and APRI. The AUROC value for the detection of advanced fibrosis was also significantly higher using SWE than APRI, but the AUROC value of SWE was similar to both HA and type Ⅳ collagen. To our knowledge, there are no previous studies that compare SWE with serum fibrosis markers such as APRI, HA, and type Ⅳ collagen. In previous studies, TE was reportedly superior to serum markers for detecting hepatic fibrosis in hepatitis C patients[6,9,21,22]; additionally, SWE was superior to TE in detecting significant fibrosis, but similar to TE in detecting advanced fibrosis and liver cirrhosis[15]. In sum, the diagnostic performance of SWE is similar or superior to that of serum markers in detecting hepatic fibrosis. Furthermore, when we analyzed the results more specifically according chronic liver disease causes, SWE consistently showed AUROC values greater than 0.9, whereas the AUROC values of APRI, HA and type Ⅳ collagen varied according to disease cause. This suggests that SWE is a promising single method for detecting hepatic fibrosis, regardless of cause.

This study has several limitations. Firstly, it was a retrospective study of a relatively small number of patients

conducted in a single institution. To overcome this limitation, we consecutively collected subjects for the study, but there were lost data from serologic examinations of some patients, including HA and type Ⅳ collagen; and the results of these patients were excluded from the statistical analysis when comparing SWE and serum markers. Secondly, AUROC values of LS measured using SWE tended to be lower in our study than previously reported studies. This could be explained by the inclusion of heterogeneous subjects with various causes of chronic liver disease. Finally, we could not compare SWE to other recently developed imaging modalities, such as TE and ARFI.

In conclusion, LS measured using SWE positively correlates to hepatic fibrosis stage assessed by liver biopsy, and SWE is a very useful and accurate method for detecting significant fibrosis and advanced fibrosis, with diagnostic accuracy comparable to serum HA and type Ⅳ collagen. Prospective studies of a large cohort of patients with a homogeneous cause of chronic liver disease should be undertaken in the near future.

COMMENTS

Background

The staging of liver fibrosis, therefore, is of major clinical concern because it informs the patient's prognosis and is a key factor when determining a treatment strategy. Particularly in cases of chronic viral hepatitis B and C, it is important to detect significant and advanced fibrosis, because these stages are the critical points for anti-viral treatment.

Innovations and breakthroughs

This study was to evaluate the correlation between liver stiffness measurement (LSM) using shear wave elastography (SWE) and liver fibrosis stage determined histopathologically in patients with various chronic liver diseases, as well as to determine the diagnostic accuracy and clinical usefulness of SWE in predicting significant fibrosis and advanced liver fibrosis.

Applications

SWE is a very useful and accurate method for detecting significant fibrosis and advanced fibrosis, with diagnostic accuracy comparable to serum HA and type Ⅳ collagen.

Peer review

In this study authors evaluated the correlation between LSM byreal-time SWE and liver fibrosis stage. They enrolled 70 consecutive patients with various chronic liver diseases (hepatitis B virus, hepatitis C virus, alcohol, non-alcoholic liver disease and other diseases including autoimmune hepatitis and unknown cause). The major result is that LSM by SWE showed a significant correlation with the severity of liver fibrosis, maximally identifying moreadvanced degrees of disease.

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