Original Article

Quantitative comparison of transient elastography (TE), shear wave elastography (SWE) and liver biopsy results of patients with chronic liver disease

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Abstract. [Purpose] The purpose of this study was to carry out a comparitive analysis of hepatic fibrosis results of the liver hardness of patients with chronic liver disease as measured by elastography (TE), shear wave elastography (SWE), and liver biopsy. [Subjects and Methods] This study was a retrospective analysis of 304 patients who underwent SWE and TE before and after liver biopsy, taken from among patients who had been checked for liver fibrosis by liver biopsy between August 2013 and August 2014. We used receiver operating characteristic (ROC) curve to prove the diagnostic significance of liver stiffness, and then analyzed the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of SWE and TE, as well as the kappa index through cross-analysis of SWE, TE, and liver biopsy. [Results] For liver hardness, the sensitivity of SWE was 84.39%, the specificity of SWE was 97.92%, the accuracy of SWE was 87.33%, the positive predictive value of SWE was 99.32%, and the negative predictive value of SWE was 63.51%. The sensitivity of TE was 94.80%, the specificity of TE was 77.08%, the accuracy of TE was 90.95%, the positive predictive value of TE was 93.97%, and the negative predictive value of TE was 80.43%. [Conclusion] It is our opinion that SWE and TE are non-invasive methods that are more effective than the invasive methods used for diagnosing liver hardness. Invasive methods cover only a section of liver tissue, and are more likely to cause side effects during biopsy.
Key words: TE, SWE, Sensitivity

INTRODUCTION

Chronic viral hepatitis is a disease that continuously expands inflammation and necrosis in the liver for years. If hepatocellular necrosis were to continue, it would cause fibrosis, and if widespread fibrosis were to surround normal hepatic lobules, it would cause liver cirrhosis that has a regenerative node[1]. During these processes of liver cirrhosis, there can be various complications[2–4]. Therefore, it is important to diagnose liver fibrosis in patients with chronic viral hepatitis in order to predict, cure, and prevent the progress of disease. Liver biopsy has for a long time been a standard method for diagnosing liver fibrosis, and for determining the treatment of patients with chronic liver disease[5, 6]. However, liver biopsy is invasive, and there are complications such as bleeding and pain that make it difficult to carry out a follow-up biopsy. Another disadvantage is that the small

liver sample taken during biopsy is limited to only one tissue per 50,000 in the total liver[7, 8]. In order to overcome these limitations, many studies into the development of various non-invasive liver fibrosis diagnosis methods are currently being conducted[9]. Methods such as transient elastography (TE), acoustic radiation force impulse imaging (ARFI), and magnetic elastography (MRE) have been developed. It has been proven by many studies that these methods are able to predict the degree of liver fibrosis with precision[10]. TE is fast, and easy and painless examination for the patient, and it has high reproducibility. Besides, TE represents about 1/500 of total hepatic parenchyma[11]. Another more recent method of measuring liver fibrosis is by shear wave elastography (SWE)[12]. Unlike TE, SWE enables the measurement of liver stiffness where it is desired, by watching a real-time image with B-mode ultrasound, and the measurement of stiffness based on anatomical information. In addition, SWE can assess the homogeneity of the liver, because SWE produces colour images corresponding to the varying degrees of hardness. Due to these advantages, SWE has been suggested as a more precise method of the measurement of liver hardness than TE[13]. However, only a few studies have compared these methods by performing TE, SWE and liver biopsy at the same time, and no study has compared haematological predictive factors of liver fibrosis using these methods.

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Therefore, this study carried out a comparitive analysis of the liver fibrosis of chronic liver disease patients, of the results of liver biopsy and liver hardness as measured by TE and SWE.

SUBJECTS AND METHODS

We carried out a retrospective analysis of 304 patients who underwent SWE and TE before and after liver biopsy, among patients who had been checked for liver fibrosis by liver biopsy between August 2013 and August 2014. All the participants signed an informed consent form approved by the Institutional Review Board of the Asan Medical Center. Serologic tests showed patients with chronic hepatitis B were positive with hepatitis B surface antigen (HBsAg) for more than 6 months, patients with chronic viral hepatitis C were positive with anti-hepatitis C virus (HCV) as well as in HCV genetic material (RNA) for more than 6 months, and patients with alcoholic hepatitis were also positive. Other causes of hepatitis were labeled as "unknown" and were excluded from the study. After exclusions, 211 subjects remained comprising 144 hepatitis B virus (HBV) patients, 71 HCV patients, and six alcoholic patients. There were 125 males (56.6%) and 96 females (44.3%). The average age of the subjects was 54.79 ± 11.46 years. Percutaneous ultrasound guided biopsy was performed and the sample was fixed with formalin solution, treated with paraffin, and sectioned at 5 μm. Masson-trichrome and hematoxylin-eosin staining were performed in order to have a precise under-standing of the liver fibrosis. For the SWE measurement of liver hardness, we used the 1–6 MHz convex probe of Aixplorer (SuperSonic Imagine, France). This device creates a shear wave by centralizing an ultrasonic wave repetitively on the tissue's region of interest, at short intervals in the longitudinal wave's direction of progress. The shear wave velocity is measured at over 4,000 frames per second us-ing a rapid ultrasound scan, in order to calculate the liver hardness in the region of interest. The test was performed after verifying the location with a general ultrasound scan. During the test, patients were asked to lie down with their right arms raised above their heads, and ultrasound scanning of the right lobe of the liver was performed first, to select the location where the liver thickness becomes 60 mm, excluding a large part of the blood vessel structure within the hepatic parenchymal. Patients were asked to hold their breath for about five seconds, while the stiffness of the re-gion of interest was measured. In order to improve the accu-racy, five measurements were made for each patient and the mean average value of those measurements was recorded in kiloPascals (kPa: metric) (Fig. 1). For the TE measurement of liver stiffness, a FibroScan (Echosens, Paris, France) was used. This device creates a low-frequency acoustic wave to an ultrasonic transducer, we measure its speed first with an ultrasound imaging, and using the measured speed, the tissue's stiffness is computed where the acoustic wave pen-etrates[14]. When a liver biopsy had already been performed, the liver stiffness was measured within a year of the biopsy, and the result was expressed in kPa. In order to measure the stiffness, the patients were asked to lie down with their right arms raised to their heads, and the probe was placed verti-
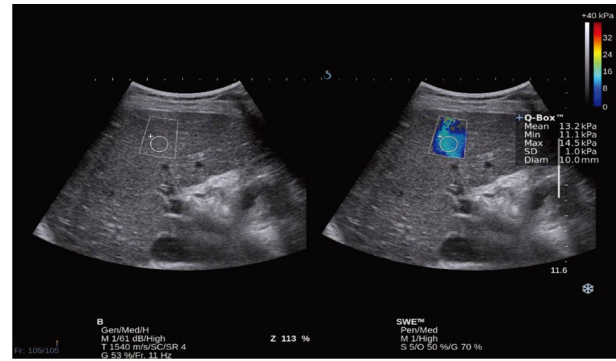
Fig. 1. Ultrasound Shear Imaging of liver stiffness measurement

cally on their skin on the intercostal of the right lobe of the liver. The lung area and intercostal areas were avoided when using FibroScan's ultrasonic TM mode (time-motion) and A-mode (amplitude mode) images. The probe direction was chosen as that with a lesion that did not have a large blood vessel structure within a thickness of 6 cm of the right lobe of the liver. The liver parenchyma's stiffness was measured between 2.5 to 6.5 cm under skin by pressing the probe's oscillator button. The measurements were ended when 10 successful values had been obtained for each patient, and the examination time was about five minutes. Stiffness was determined as the average value of the 10 measurements, af-ter excluding the highest and the lowest values. The success rate was defined as the number of successful results divided by the total number of examinations. The presence of ascites was determined with an abdomen ultrasound scan on the day of the FibroScan. For the statistical analysis, the receiver operating characteristic (ROC) curve was computed, and the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value, of SWE and TE were deter-mined. The kappa index was calculated in a cross-section analysis of the results of SWE, TE, and the liver biopsy. Statistical analysis was performed using SPSS version 18.0 software (SPSS Inc, Chicago, USA), and significance was accepted for values of $p<0.05$.

RESULTS

For liver hardness, the sensitivity of SWE was 84.39%, the specificity of SWE was 97.92%, the accuracy of SWE was 87.33%, the positive predictive value of SWE was 99.32%, and the negative predictive value of SWE was 63.51%. The sensitivity of TE was 94.80%, the specificity of TE was 77.08%, the accuracy of TE was 90.95%, the positive predictive value of TE was 93.97%, and the negative predic-tive value of TE was 80.43% (Table 1). SWE was low in sensitivity compared to TE but high in specificity compared to TE. For the AUC (area under the curve) of SWE and TE, the ROC curve was located close to the upper right corner, and the area under the ROC curve was close to 1, showing a 95% confidence interval. The 95% approximation confi-dence interval for SWE was from 0.870 to 0.953, and its cut-off value was 0.912. The 95% approximation confidence interval for TE was from 0.786 to 0.933, and its cut-off value

Table 1. Sensitivity and specificity of each test for liver cirrhosis

Division	Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value
SWE	84.4	97.9	87.3	99.3	63.5
TE	94.8	77.1	90.9	93.7	80.4

SWE: shear wave elastography, TE: elastography

Table 2. Cross tabulation and kappa coefficients of SWE, TE, and biopsy

Division		Biopsy Normal	Liver cirrhosis	Total	Kappa Coefficient
SWE	Normal	47	27	74	0.73
	Liver cirrhosis	1	146	147	
Total		48	173	221	
TE	Normal	37	9	46	0.688
	Liver cirrhosis	11	164	175	
Total		48	173	221	

SWE: shear wave elastography, TE: elastography

was 0.859. The approximated significance probabilities of SWE and TE were 0.000 each (p < 0.05). In a cross-section analysis of the results of SWE and biopsy, SWE diagnosed 47 out of 48 normal patients as "normal" and diagnosed liver cirrhosis in 146 out of 173 patients with liver cirrhosis. TE diagnosed 37 out of 48 normal patients as "normal" and diagnosed liver cirrhosis in 164 out of 173 patients with liver cirrhosis. The kappa index value for SWE was 0.730 with 0.00 of significance probability, which proves that the two diagnostic methods have a significant conformity (p < 0.05). For TE, the kappa index value was 0.688 with 0.000 of significance probability, which proves that the two diagnostic methods have a significant conformity (p<0.05) (Table 2). SWE appears to have a higher precision since it had a higher kappa index value.

DISCUSSION

As liver fibrosis progresses, liver stiffness increases and blood flow is impeded, causing liver cirrhosis. Therefore, distinguishing the degree of liver fibrosis with precision is an important factor in treatment planning and prognosis for patients with chronic viral hepatitis type C. Even though liver biopsy is a useful way of measuring liver fibrosis, due to its invasiveness, the non-invasive alternatives of SWE and TE (that uses FibroScan) are now being widely used. Most studies of patients with chronic liver disease have compared liver biopsy with TE or liver biopsy with SWE, and most of them have been carried out on patients with chronic viral hepatitis type C. In this study, the clinical usefulness of SWE and TE was investigated by comparing the results of liver biopsy with those of TE and SWE of patients with chronic hepatitis. TE is now being widely used because it is a non-invasive method with a high reproducibility, that quantifies liver hardness, can be used to compute cut-off values, and predicts various complications of liver cirrhosis according to the numerical value of elasticity[10, 15]. Since TE is non-invasive, fast, painless, with high reproducibility, representative of 1/500 of total liver parenchyma, and measures liver stiffness directly without damaging other organs[16], it is a popular technique. The FibroScan equipment also measures liver fibrosis by a non-invasive approach. Its diagnostic usefulness for the liver fibrosis of patients with chronic liver disease has been reported by several studies since it was introduced by Sandrin et al[10]. Although most studies were conducted using patients with chronic viral hepatitis type C[17–20], Foucher et al.[21] included subjects with chronic viral hepatitis, alcoholic hepatitis and steatohepatitis, and reported a significant correlation between liver stiffness and the degree of liver fibrosis diagnosed by biopsy. However,

only a few studies have covered the liver biopsies of Asians, whose liver hepatitis has other causes, to investigate the clinical usefulness of liver stiffness measured by FibroScan. Kim et al.[21] measured the liver stiffness of 228 patients with chronic hepatitis B. Inactive HBsAg gave a value of 7.0±2.7 kPa, chronic hepatitis gave a value of 8.3±5.3 kPa, compensated liver cirrhosis gave a value of 15.9±8.3 kPa, non-compensated liver cirrhosis gave a value of 31.8±20.3 kPa, and hepatocellular carcinoma gave a value of 45.1±34.5 kPa, indicating that there are significant differences in the hardnesses of the lesion of different the liver disease. Ziol et al.[17] the reported diagnosis of liver cirrhosis was very accurate when using the liver stiffness measurement (LSM) value of Fibroscan. Castera et al. compared the usefulness of FibroScan's LSM value, Fibrotest, and APRI in terms of diagnosing liver fibrosis. FibroScan was the most accurate at diagnosing cirrhosis[16]. In our present study of the reliability of liver cirrhosis diagnosis, sensitivity of SWE was 84.39%, the specificity of SWE was 97.92%, the accuracy of SWE was 87.33%, the positive predictive value of SWE was 99.32%, and the negative predictive value of SWE was 63.51%. The sensitivity of TE was 94.80%, the specificity of TE was 77.08%, the accuracy of TE was 90.95%, the positive predictive value of TE was 93.97%, and the negative predictive value of TE was 80.43%. Both TE and SWE showed a high diagnostic accuracy in this study, confirming that when a patient with chronic viral cirrhosis in a real clinical trial shows over 7.2 kPa based on TE, there is an 86% probability that that patient has more than F2 liver fibrosis. In order to conduct a coincident analysis of liver biopsy, SWE, and TE, measurements were made, and as a clinical procedure, we have replaced liver biopsy with non-invasive SWE and TE to measure liver cirrhosis precisely without affecting other diagnostic results. Considering the fact that invasive liver biopsy covers only some parts of the tissue and has side effects during the biopsy, it is better and more effective to use these two non-invasive methods.

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