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# How many times should we repeat measuring liver stiffness using shear wave elastography?: 5-repetition versus 10-repetition protocols

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ABSTRACT

The purpose of this study is to evaluate whether a 5-repetition liver stiffness (LS) measurement as the standard protocol of shear wave elastography (SWE) is comparable to a conventional 10-repetition measurement protocol and to identify factors that influence the reliability of the 5-repetition protocol. A total of 346 patients (mean, 48.0 years; range, 15–81 years, M:F = 192:154) who underwent SWE were enrolled. The median, first quartile, third quartile, and interquartile range divided by the median (IQR/M) of LS measurement were calculated and compared between 5-repetition and 10-repetition protocols. Subgroup analyses were also performed to identify factors associated with measurement reliability. The overall mean LS from the 10-repetition protocol was 7.97 kPa, which was not significantly different from the mean LS of the 5-repetition protocol (7.91 kPa; $p = 0.192$). However, the third quartile and IQR/M values of the two groups were significantly different from each other ($p = 0.003$ and <0.001). Subgroup analysis revealed that the 5-repetition results were significantly different from the 10-repetition results in the fatty liver and high LS subgroups. Therefore, the 5-repetition SWE measurement protocol can replace the conventional 10-repetition protocol, with the exception of patients with fatty liver disease or an LS value higher than 10 kPa.



## 1. Introduction

Elasticity imaging is now widely considered as a noninvasive and useful technique for the measurement of liver stiffness in the patients with liver cirrhosis replacing the liver biopsy [1]. Various elasticity imaging techniques have been developed using different methods based on dispersion of shear wave, such as magnetic resonance elastography [2], one-dimensional (1-D) transient ultrasound elastography [3], supersonic shear imaging (SSI) [4], shear wave dispersion ultrasound vibrometry (SDUV) [5], spatially modulated ultrasound radiation force (SMURF) imaging [6], ultrasound stimulated vibro-acoustography (USVA) [7], comb-push ultrasound shear elastography (CUSE) [8] and acoustic radiation force impulse (ARFI imaging) [9,10].

Among them, in terms of TE, a standard protocol for LS measurement was developed [11]. In this protocol, measurements are repeated 10 times at the same intercostal space. The median of these LS measurements is calculated and accepted when the interquartile range divided by the median (IQR/M) does not exceed 30%. This measurement protocol has become widely accepted as the gold standard. However, the validity of TE measurements has been questioned [11–16]. Moreover, a number of confounding factors have been shown to influence TE measurement of LS, including the depth of the subcutaneous fat layer, the presence of ascites, and fatty liver disease.

US-based elastography approaches, including shear wave elastography (SWE), are a hybrid type of elastography that combine conventional ultrasonography with elastography. A dedicated transducer induces an acoustic radiation force, generating shear waves that are detected and whose velocities are calculated [17]. In healthy livers, stiffness was 5.4 kPa using SWE [18], which was comparable to that of TE. In SWE, a color-coded stiffness image is used in combination with a grayscale US image to guide more accurate and more reliable measurement. This technique was expected to acquire more reliable results

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because a region-of-interest (ROI) was larger than TE and grayscale US image helped localizing the ROI at the proper area without large hepatic vessels. It could make the repetition of measurement reduced than that of TE, and also lessen a burden of time for LS measurement. Actually, many studies have suggested that fewer measurements (3–5) are required when using SWE [19–21]. However, no standard SWE protocol has yet been developed by which measurements as reliable as TE measurements can be obtained.

The purpose of this study was twofold: (1) to investigate whether a 5-repetition SWE protocol yields results comparable to those of a conventional 10-repetition SWE protocol, and (2) to identify the factors that influence the reliability of the 5-repetition protocol.

## 2. Materials and methods

### 2.1. Patients

The Institutional Review Board approved this retrospective study and the requirement for written informed consent was waived for all patients. Between September and December 2010, 380 patients underwent liver ultrasonography coupled with SWE on the same day. Of these 380 patients, all patients with unreliable LS measurements due to patient-related factors such as noncooperation or a thick subcutaneous layer of fat were considered to be measurement failures and were excluded from further analysis. The reasons for sonographic examination were as follows: viral hepatitis ($n = 79$); heavy alcoholism ($n = 25$); other liver abnormalities, including altered liver function test results ($n = 61$), focal hepatic lesions ($n = 11$), abdominal pain ($n = 20$), and suspected biliary disease ($n = 18$); routine scanning during renal examination in patients with diabetes ($n = 35$); regular assessment for individual health promotion and postoperative evaluation after surgical procedures such as cholecystectomy ($n = 126$); and other unspecified reasons ($n = 5$).

### 2.2. Liver stiffness measurement

Liver stiffness measurement was performed with a US machine equipped with a shear wave elastography module (Aixplorer version 3, Supersonic imagine, Aix-en-Provence, France) and a convex broadband probe (SC6-1). In SWE, a focused ultrasound beam penetrates the tissue to generate shear waves in the liver and the speed of these waves is measured to deduce the tissue elasticity. SWE enables the visualization of 2-dimensional color-coded grayscale US images to display tissue viscoelasticity. LS measurement was performed by one of three abdominal radiologists (W.K.J., Y. K., and M.Y.K.), each of whom has more than 9 years of clinical experience in abdominal radiology and has obtained LS measurements from more than 100 patients.

The measurement protocol was as follows: After fasting, LSM was performed through the right intercostal window. Depending on the location of the region of interest, a scan was acquired at a location deeper than 2 cm from the hepatic capsule to avoid reverberation artifacts. In addition, the scan was acquired away from large vessels to avoid erroneous measurement. After obtaining the SWE images, sequential frames were recalled until the elasticity color map was saturated without any large defect areas (Fig. 1). The round Q-box™ was then positioned in the center of the saturated color map to measure the mean elasticity value and its standard deviation. The size of Q-box™ was maximum 20 mm; its size was user-adjustable depending on the area of measurable parenchyma and the locations of the vessels and hepatic capsule.

LSM was repeated 10 times, and the median value was taken as the LS of the patient. In addition, the first quartile (1Q), third quartile (3Q), and interquartile range (IQR) of each LS value was determined. To evaluate LSM reproducibility, the IQR divided by the median (IQR/M) was also calculated [22].

### 2.3. Comparison of 5-repetition versus 10-repetition liver stiffness measurement protocols

As mentioned above, ten consecutive measurements were obtained for each patient. Patients were then divided into two groups. In the first group, only the first five measurements were used. In the second group, all 10 measurements were used (Fig. 2). In each group, the median, 1Q, 3Q, and IQR/M values were calculated. The median value of each group was taken as the LS value for the given TE protocol [23]. Next, the LS, Q1, Q3, and IQR/M values were compared between the two groups. Subgroup analyses were also performed. If the LS, Q1, Q3, and IQR/M values were not different from each other, this finding would indicate that the 5-repetition method could replace the conventional TE protocol. According to known factors that potentially influence measurement reliability [24–27], subgroup analyses were performed according to sex (male vs. female), age ($\geqslant$65 years old vs. <65 years old; older vs. younger group), and laboratory findings, including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin levels. For the laboratory findings, patients were divided into those with values higher than two times the upper normal limit [$\geqslant$80 U/L for AST (high AST group), $\geqslant$80 U/L for ALT (high ALT group), and $\geqslant$3.0 mg/dL for total bilirubin (high bilirubin group)] versus those with values lower than this cutoff.

Fatty liver syndrome and underlying disease were also considered to be factors potentially related to reliable measurement. Sonographic images were used to record the presence of moderate fatty liver disease (fatty liver group). Moderate fatty liver on US was defined as in a previous study [28]. Specifically, the loss of echoes from the portal vein walls, particularly from the peripheral branches, was described. Underlying disease was classified into normal, chronic hepatitis B, chronic hepatitis C, and alcoholic liver disease.

In addition, the 5-repetition and 10-repetition measurement protocols were also compared in the subgroup in which the first 5 LS measurements were lower than 10 kPa.

### 2.4. Statistical analysis

The paired $t$-test was performed to compare the mean LS values and IQRs of the 5-repetition protocol with those of the 10-repetition protocol. Differences of the parameters between the two methods were also calculated with 95% confidence intervals. Then, linear regression analyses were performed to determine the relationships of LS and IQR/M between the two methods. If the regression coefficient (beta) was found to be approximately 1 and the $y$-intercept was found to be 0, i.e. the linear equation of the 5-repetition vs the 10-repetition methods formed a line with a slope of 1 that passed through the origin, these two methods of measurement could be considered to yield equivalent results. These statistical methods were also used for subgroup comparisons, as well as for comparisons of the overall groups. In the subgroup analyses, the regression coefficient differences and the intercepts of the various subgroups were also investigated by linear regression analysis to determine whether the coefficients and intercepts were the same between different subgroups. To compare the proportions of numbers in different subgroups (i.e. according to sex or age), Fisher's exact test and the chi-square test were performed.

$P$-values <.05 were considered to indicate statistical significance. Statistical analyses were conducted using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).