Liver Stiffness Measurement by Point and 2D Elastography: A Comparison of the Relative Merits of using Mean or Median Values

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Background: *Chronic liver disease is a worldwide problem with many causes, and there are varying degrees of fibrosis that can develop into cirrhosis. Many methods have been used to evaluate the grading of fibrosis, such as liver stiffness measurement by ultrasound-based transient elastography and the newly-developed shear wave elastography, including point shear wave and 2D shear wave elastography.*

Objective: *To compare the use of mean and median values in liver stiffness measurements made by two shear wave elastography modalities: point shear wave and 2D shear wave elastography.*

Material and Method: *This was a retrospective study of 90 patients with liver disease in Rajavithi Hospital between March 2016 and January 2017, evaluated by means of transient elastography, point shear wave elastography and 2D shear wave elastography. Correlations between the mean and the median values of each study were examined using transient elastography (TE) as the reference method.*

Results: *Ninety patients with liver disease were included, with mean age±SD of 49.49±12.75 years (range 24 to 97). The ratio of males to females was 2: 3. The correlation (r) values of mean and median of point shear wave elastography were 0.675 and 0.635 respectively, while for 2D shear wave elastography they were 0.854 and 0.844 respectively.*

Conclusion: *There was no significant difference between correlations arrived at using mean and median values for liver stiffness measurement. The correlation between TE and 2D shear wave was more accurate than that of point shear wave elastography and TE.*

Keywords: *Liver stiffness, Shear wave elastography, Point shear wave elastography, 2D shear wave elastography, Mean, Median*

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There are many causes of chronic liver disease including chronic viral hepatitis B or C, autoimmune disease, and alcoholic or non-alcoholic hepatitis[1]. Evaluation of the severity of chronic liver disease is important in its management and in the determination of disease prognosis. Mild to moderate fibrosis is reversible while end-stage fibrosis, or cirrhosis, is not[2]. For many years, liver biopsy has been the gold standard method for evaluation of fibrosis, but it has limitations resulting from inadequate sampling, variability of interpretation and severe complications[3]. Non-invasive modalities for liver assessment are now being increasingly used.

Non-invasive assessment of liver fibrosis can be performed by biological test[4,5] or by elastography measurement. Recently, the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB)[6,7] and the Canadian Association for the Study of the Liver (CASL) have recommended elastography as a method of assessing liver fibrosis.

Elastographic methods can be divided into types: displacement techniques and shear wave speed techniques. The latter includes Transient Elastography (TE); fibroscan (EchoSens, Paris, France); point shear wave elastography (PSWE); the ElastPQ technique; Acoustic Radiation Force Impulse elastography (ARFI); and shear wave elastography imaging including 2D- and 3D-SWE[8-11].

For TE, the manufacturer recommends performing 10 valid liver stiffness (LS) measurements and calculating the median of these values.

For PSWE or ARFI, meta-analysis shows similar results to those of TE for evaluation of liver

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fibrosis. Some researchers use the mean[12] while others employ the median[13,14] for evaluation of liver stiffness. Recently, the manufacturers have recommended using the latter[15,16].

There is little data that can be used to determine whether 2D-SWE should use mean[18] or median[17,19,20] values for LS measurement.

This study aimed to analyse the relative merits of using mean or median values in PSWE and 2D-SWE for evaluation of liver stiffness compared to results found using TE.

Material and Method

The protocol of this research was reviewed and approved by the ethics committee of Rajavithi Hospital (No. 219/2559).

This was a single-center cross-sectional study. Matched patients who attended the hepatobiliary and Gastroenterology units of Rajavithi Hospital, Bangkok, Thailand between March 2016 and January 2017 were evaluated with transient elastography (fibroscan) and were subsequently also investigated with ultrasound of the upper abdomen in the Radiology department within an interval of less than 1 month.

In fasting condition, the patient was placed in the supine position with right arm in maximum abduction, after which measurements were taken of the right lobe of the liver through the intercostal spaces while subjects held their breath for a few seconds.

Transient elastography was performed with Fibroscan device (EchoSens, Paris, France), which incorporates a 1.5-MHz ultrasound transducer probe vibrator in order to generate a more complete and painless vibration (50 Hz frequency and 2 mm amplitude) to induce elastic shear wave propagation through the skin and subcutaneous tissue to the liver. The wave velocity is tracked by a coaxial ultrasound transducer and is calculated by the device and expressed in kilopascals.

For each patient, 10 valid TE measurements were performed. Reliable measurement was defined as success rate (SR = ratio of the number of successful acquisitions divided by the total number of acquisitions) >60% and interquartile range interval (IQR = the difference between the 75^{th} and 25^{th} percentile; essentially, the range of the middle 50% of the data) <30%. After this, the median values of the 10 valid measurements were calculated.

Shear wave elastography

Each patient from the GI unit was sent to the radiology department for evaluation of upper abdomen with ultrasound. After Hepatitis B scan examination of the upper abdomen, elastography of the same patient was performed using the EPIQ7 ultrasound system (Philips Healthcare, Bothell, WA, USA) with convex broad base probe (Elast PQ technique). Evaluation by 2D shear wave elastography using GE LOGIQ 9E (GE Healthcare, Wauwatosa, WI, USA) was carried out later in the same session.

This method, point shear wave elastography using EPIQ7 with Elast PQ technique generates shear waves inside the liver using radiation force from a focused ultrasound beam. The ultrasound machine monitors the shear wave propagation and the measurement of the velocity of the shear waves which is displayed in meters per second (m/s) or in kilopascal (kPa). Using real time imaging to select the vessel-free area, at least 1.5 cm from the liver capsule, the fixed region of interest of 0.5x1.5 cm was set with the patients holding their breath, and then 10 valid measurements were performed.

The system calculated the mean and median values and the IQR of the valid measurements, and a homogenous area with IQR of less than 30% was considered a valid measurement[21,22].

2D shear wave elastography was performed by LOGIQ 9E (GE Healthcare, Wauwatosa, WI, USA) using R5.1.0 software and a C1-6-D probe to obtain a quantitative elasticity map of the medium. An ultrafast, ultrasonic scanner was used to generate a mechanical shear wave by focusing ultrasound at the given location and imaging the medium during the wave propagation at a high frame rate, and tissue elasticity was displayed in units of velocity, meters per second (m/s) or converted into kilopascal. The region of interest (ROI) was located at least 1 cm below the liver capsule and clear of the vessels. Using circular measurement, approximately 1 cm in diameter, 10 measurement regions were placed on different shear wave images, and then the system calculated the mean and median values and the IQR of valid measurements. Measurements in homogenous areas with IQR less than 30% were considered valid.

The study was approved by Ethics Committee Rajavithi Hospital and was performed in accordance with the provisions of the Helsinki Declaration of 1975.

Statistical analysis

Demographic data and clinical history were summarized using descriptive statistics, and analysis was performed using SPSS, version 17.0 (IBM

statistics). Categorical variables were reported as number of patients (percent). Student's t-test and paired t-test were used for group comparison of continuous variables (the results of liver stiffness measurement) with normal distribution. Pearson's correlation coefficient (r) was used to assess the correlation of mean and median LS measurement by point shear wave elastography (PSWE using ElastPQ) and 2D shear wave elastography (2D-SWE by GE LOGIQ 9E) with those arrived at using TE (transient elastography).

Results

Liver stiffness was evaluated by shear wave elastography (PSWE and 2D-SWE) and transient elastography (fibroscan) using valid measurements from 90 subjects. The mean age of the subjects was 49.49±12.75 years. The ratio of males to females was 2: 3 and 36.9% and 41.1% of subjects had chronic hepatitis B and hepatitis C respectively. The main subject characteristics are presented in Table 1.

The correlations of LS measurements are presented in Table 2. 2D-SWE showed slightly better correlation with TE than PSWE. There was no significant difference between the mean and median values, which were as follows: mean PSWE 7.1051±5.5165 kPa, median PSWE 7.0970±6.0330 kPa; mean 2D-SWE 7.6500±3.6548 kPa, median 2D-SWE 7.6121±3.6558 kPa.

Table 1. Baseline characteristics (n = 90)

Characteristics	n (%)
Gender	
Male	36 (40.0)
Female	54 (60.0)
Age (years)	
Mean ± SD	49.49±12.75
Min-Max	24 to 97
Indication	
Chronic hepatitis B (HBV)	33 (36.7)
Chronic hepatitis C (HCV)	37 (41.1)
Chronic non-viral hepatitis (NAFLD)	9 (10.0)
Others	11 (12.2)

Values are represented as n (%), mean ± SD, min-max

Discussion

Many studies of the accuracy of elastography measurement including the ARFI, PSWE and 2D-SWE techniques, have found high rates of accuracy and good correlation. Many published studies of PSWE and 2D-SWE have used the median value of liver stiffness in line with the practice of transient elastography. In the past, the manufacturers of 2D-SWE and PSWE suggested using the mean value for assessment of liver stiffness, but they now recommend utilizing the median value.

Our study analyzed mean and median values of elastography for LS measurement with both PSWE and 2D-SWE in order to determine which one should be used in clinical practice.

For TE the manufacturers have specified a clear protocol for calculating LS, using the median value of 10 measurements.

For shear wave elastography, there is some variation in the number of measurements taken and the use of mean or median to determine the grading of fibrosis. For ARFI elastography, published studies have used varying numbers of measurements, some using 5[13], 6[23], 10[14,21-25], 12[26] and even 20 measurements[27]. At present, the consensus is to use the median value of 10 valid measurements.

For 2D-SWE, some published studies have used 3[28], 4[17], or 5[29-31] valid measurements. A number of reports have utilized the mean value of LS measurement[20,24], while others have preferred the median[30].

One limitation of this study was its small

Table 2. The correlation between LS value measurement by TE and pSWE and TE with 2D-SWE

Measurement	Correlation with TE (r)	*p*-value	Paired t-test	*p*-value
Mean of pSWE	0.675	<0.001*	0.96	0.341
Median of pSWE	0.639	<0.001*		
Mean of 2D-SWE	0.854	<0.001*	0.07	0.945
Median of 2D-SWE	0.844	<0.001*		

TE=Transient elastography, pSWE = Point shear wave elastography, 2D-SWE = 2D shear wave elastography
* = Significant at $p<0.05$

number of subjects in each staging (F0-F4) especially in advanced fibrosis. The patients with ascites were excluded due to some limitations of TE and the lack of biopsy for use as the gold standard reference. This study used transient elastography, which is recognized as a valid technique for reference[1]. In order to attain a more accurate measurement, further studies should be performed with a larger number of subjects, and with liver biopsy as the reference.

Conclusion

This study demonstrated no difference in using mean or median in shear wave elastography, including point shear wave and 2D shear wave elastography. The latter's correlation with TE is better than that of point shear wave elastography.

What is already known on this topic?

Elastography, especially transient elastography, is an accurate method which is used in many guidelines. The accuracy of ARFI and 2D-SWE is also good, but there is still controversy about the relative merits of using mean or median values for assessing fibrosis staging.

Recent guidelines recommend EPSUM using ultrasound elastography.

There are several different ultrasound methods for estimating liver fibrosis such as TE (fibroscan), ARFI (ElastPQ, Virtual Touch Siemen), 2D-SWE (supersonic, GE).

A clear protocol for the use of TE has been set by the manufacturers.

The present consensus for ARFI is to use the median of 10 measurements.

No consensus has been reached regarding 2D, and both mean or median are still used.

There is little published data about new machines such as the LOGIQ 9E.

There is a lack of data for comparison of the merits of point shear wave and 2D shear wave elastography.

What this study adds?

No significant difference was detected between using mean or median values in measurement by point and 2D shear wave elastography.

No significant difference was found between using mean or median for evaluation of grade of liver fibrosis.

The correlation between 2D shear wave elastography and TE was better than that of point shear wave elastography and TE.

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Potential conflicts of interest

None.

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