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Comparison Liver Stiffness Measurement by Transient Elastography and Shear Wave Elastography

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Abstract

To compare liver stiffness (LS) values measured by transient elastography (TE), 2D-shear wave elastography (2D-SWE) and point shear wave elastography (p-SWE). 90 subjects were examined by Radiology department, Rajavithi hospital, Bangkok, Thailand and data was analyzed by SPSS version 17.0. The results found that the correlation of liver stiffness value between TE and 2D-SWE was the highest with r=0.84 (p-value=0.001). Then the simple linear regression equations for prediction liver stiffness value were LS(TE)=–6.08+2.09LS(2D-SWE) and LS(TE)=2.03+1.12 LS(p-SWE). Using area under receiver operating characteric curve (AUROC) to investigate significant fibrosis and cirrhosis, both shear wave elastography techniques, 2D-SWE and p-SWE, were appropriate to predict fibrosis than significant fibrosis. Furthermore, 2D-SWE was higher performance in prediction significant fibrosis and cirrhosis than p-SWE.

Keywords: liver stiffness, transient elastography, shear wave elastography, fibrosis, cirrhosis

INTRODUCTION

Liver fibrosis is a disease caused by liver inflammation from multiple chronic liver conditions such as chronic viral hepatitis (hepatitis B virus or HBV, hepatitis C virus or HCV), autoimmune, hereditary, metabolic, toxin-mediated liver disease and cholestasis liver disease [1]. These cause hepatocellular dysfunction, expansion of extracellular matrix, distortion hepatic architectural, portal hypertension and finally can lead to clinically significant fibrosis or liver cirrhosis [2]. Mild to moderate fibrosis is reversible while cirrhosis, the end stage outcome of fibrosis is irreversible. Severity or grading of liver fibrosis in chronic liver disease is significant for determine prognosis and treatment as antiviral therapy drug and in advanced liver fibrosis, cirrhosis patient for monitoring to screen for treat complications, esophageal varies [3]. Patient with chronic liver disease develops liver cirrhosis approximate 20-30% increasing due to increase patient chronic hepatitis C, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steotohepatitis (NASH). Up to recently, Liver biopsy has been considered gold standard for fibrosis staging and still reference method for assess fibrosis. It is invasive procedure with associated morbidity, minor complication as pain about 25% and severe complication, significant bleeding (0.05-5.3%). The limitation as inadequate sampling, intra-inter observer variability, heterogeneous distribution in liver fibrosis [4-7]. Non-invasive methods for evaluation liver fibrosis can be divided into two main groups: biomarker use blood serum [8-9] and physical parameter or imaging based methods evaluation elastography use ultrasound [10-19] and MRI [20]. Many guidelines included the European Federation for Societies for Ultrasound in Medicine and Biology, World Federation for Ultrasound in Medicine and Biology, Canadian Association for the study of the liver, National Institution for Health and Care Excellence have mention elastography for assessment of liver fibrosis in clinical guidelines [21-25]. Transient elastography (TE) or called fibroscan is the first ultrasound-based elastography technique and most extensive used and validated method for fibrosis staging [26]. The recent guidelines for management hepatitis C infection such as European Association for the Study of the Liver permit the use of TE instead of liver biopsy [27]. Shear wave elastography (SWE) technique has been implemented in conventional real-time ultrasound systems. Several studies have shown their accuracy on the assessment of liver fibrosis [28-31]. Compared with TE, these techniques have an advantage of the B-mode image guidance to choose best acoustic window for correctly performing examination in real time.

This study was performed to compare liver stiffness measurement by 2D shear wave elastography (2D-SWE) and point shear wave elastography (p-SWE) using TE as reference.

MATERIALS AND METHODS

1. Subjected and Study Design

This was a single center, cross-section retrospective study. Matching the patients in hepatobiliary and Gastroenterology unit from Rajavithi hospital, Thailand who were evaluated with

TE and patients were investigated ultrasound upper abdomen in Radiology department interval less than one month. Patients in fasting condition, supine position with right arm in maximum abduction, measurement in the right lobe of the liver through intercostal spaces and measurements were performed in while holding their breath for a few seconds. Fibroscan device (EchoSens, Paris, France), which incorporate 15-MHz ultrasound transducer probe vibrator for generated a completer painless vibration (50 Hz frequency and 2 mm amplitude) for induced and elastic shear wave propagation through skin and subcutaneous tissue to the liver. The wave velocity is tracked by coaxial ultrasound transducer and calculated by the device and expressed in kilopascals. In each patient 10 valid TE measurement were performed. Reliable measurement defined as success rate (SR=ratio of the number of successful acquisition divided but the total number of acquisitions) more than 60% and interquartile range interval (IQR=the difference between the 75th and 25th percentile, essential the range of the middle 50% of the data) less than 30%, then median value of the 10 valid measurement were calculated. Ethics Committee of Rajavithi Hospital has approved and informed consent to the above investigation according to study about the liver stiffness measurement by transient elastography and shear wave elastography. The data have not been published in whole or in part elsewhere.

2. Shear Wave Elastography (SWE)

The patients from Gastrointestinal unit were sent to Radiologic department for evaluation upper abdomen with ultrasound. After finished B scan examination upper abdomen, the patients were performed evaluation elastography by using the EPIQ7 ultrasound system (Philips Healthcare, Bothell, WA, USA) with convex broad base probe the Elast PQ technique and GE LogiQ E9(GE healthcare, Wauwatosa,WI,USA) in same session.

2.1 2D-Shear Wave Elastography (2D-SWE)

2D-SWE was performed by LOGIQ E9 (GE Healthcare, Wauwatosa, WI, USA) using R5.1.0 software and the C1-6-D probe to obtained a quantitative elasticity map of the medium. Using ultrafast, ultrasonic scanner generated the mechanical shear wave by focusing ultrasound at given location and image the medium during wave propagation at level high frame rate and displaced in unit of velocity, meter per second (m/s) or converted into kPa. The region of interested (ROI) was placed at least 1 cm below liver capsule and free of vessel. The circular measurement, approximately 1 cm in diameter, 12 measurement regions were placed on difference shear wave image. The system calculated the median and IQR value of the valid measurement. Measurement in homogenous area with IQR less than 30% was considered valid measurement.

2.2 Point shear wave elastogrphy (p-SWE)

The p-SWE is one of evaluation elastography using the EPIQ7 ultrasound system, Elast PQ technique, this method generated shear wave inside the liver using radiation force from a focus ultrasound beam. The ultrasound machine monitors the shear wave propagation and measurement the velocity of shear wave then the shear wave velocity is displayed in meters per second (m/s) or in kilopascal (kPa). Using real time image selected the vessel free area, at least 1.5 cm from liver capsule, fixed region of interest of 0.5x1.5 cm was placed while patients hold their breast, and 10 valid measurements were performed and the median and IQR value were calculated. Measurement in homogenous area with IQR less than 30% was considered valid measurement.

4. Statistical Analysis

The demographic and clinical history was summarized in descriptive statistics. The statistical analysis was generated by SPSS version 17.0. The categorical variable was reported as number of patients (percent). Student's t-test and paired t-test was used for group comparison of continuous variables (the results of liver stiffness) with assumption of normal distribution. The Pearson's correlation coefficient (r) was used to assess the relation of liver stiffness (LS) but means of 2D-SWE (GE logiq9E) and p-SWE (Elast PQ) with TE. Simple linear regression (SLR) model was fitted the LS between 2D-SWE and TE, p-SWE (Elast PQ). Area under receiver operating characteric (AUROC) curve were built for 2D-SWE and p-SWE to identify cut off value for significant fibrosis (F≥2) and liver cirrhosis (F=4). The study was approved by the Local Ethics Committee and performed by accordance with the Helsinki Declaration of 1975.

RESULTS AND DISCUSSION

LS measurement was evaluated by SWE, 2D-SWE and p-SWE, and TE with valid measurement 90 subjects. The main subjected characteristics presented in Table 1. Correlation of LS by elastography: TE, 2D-SWE and p-SWE were presented in Table 2.

Table 1 Descriptive statistics of the subjects.

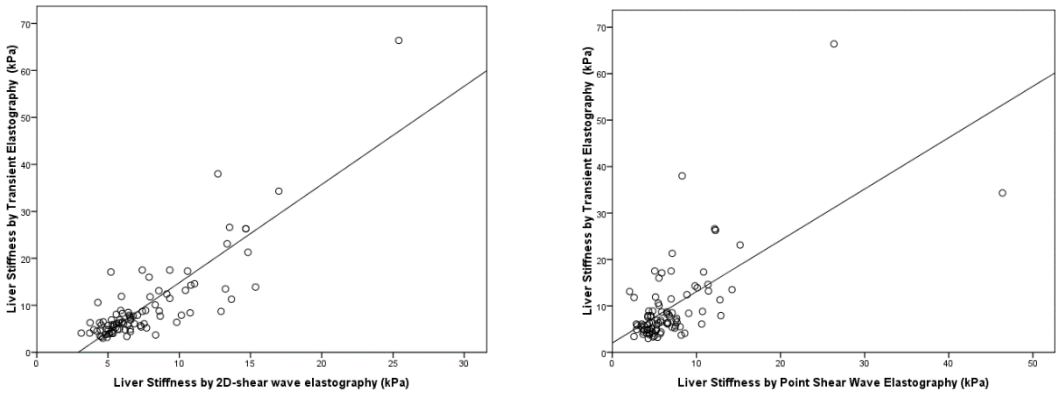
Parameter		Number of subjects
Total subjects		90 (100%)
Gender	– Male	36 (40%)
	– Femal	54 (60%)
Age (years)	– Mean±SD	49.49±12.75
	– Minimum	24
	– Maxunyn	97
Indication	– Chronic hepatitis B (HBV)	33 (36.7%)
	– Chronic hepatitis B (HCV)	37 (41.1%)
	– Chronic non-viral hepatitis (NAFLD)	9 (10%)
	– Others	11 (12.22%)

Table 2 Comparison of LS between mean LS using paired t-test obtained by means of TE, 2D-SWE, p-SWE and Pearsons' correlation coefficient (r).

LS measurement (kPa)	**Mean**	**SD**	**Median**	**Min**	**Max**	**p-value**		
						1 VS 2	**1 VS 3**	**2VS 3**
(1) TE	9.86	9.04	6.70	3.00	66.40	0.001*	<0.001*	0.193
(2) 2D-SWE	7.62	3.64	6.46	3.12	25.40		**r**	
(3) p-SWE	7.09	5.49	5.62	2.05	46.40	0.84	0.67	0.71

*Significance level at 0.01.

According to Table 2, LS measurement by TE ranged from 3.00-66.4 kPa, 2D-SWE ranged from 3.12-25.4 kPa and p-SWE ranged from 2.05-46.4 kPa. Means LS value by TE was the highest and the lowest one was p-SWE. Significant correlation between TE and 2D-SWER was found with r=0.84 (p-value=0.001) whereas correlation between TE and p-SWE was significantly with r=0.67 (p-value=0.001).



(a) (b)

Figure 1 Scatter plot between TE and SWE in 90 subjects; (a) TE and 2D-SWE, (b) TE and p-SWE.

As Figure 1(a), the scatter plots showed linear correlation between liver stiffness measurement value by transient elastogrpahy or LS(TE) and 2D-shear wave elastography or LS(2D-SWE) with r=0.84 (p-value=0.001) and SLR equation for prediction LS(TE) was following:

$$LS(TE) = -6.08 + 2.09\ LS(2D\text{-}SWE)$$

Therefore, the scatter plots illustrated linear correlation LS(TE) and point shear wave elastography or LS(p-SWE) with r=0.67 (p-value<0.001) in Figure 1(b) and SLR equation for prediction LS(TE) was following:

$$LS(TE) = 2.03 + 1.12\ LS(p\text{-}SWE)$$

Table 3 Staging of liver stiffness by transient elastography.

Staging	AUROC (F)	LS(TE) (kPa)	Number
No significant fibrosis	<2	<7	48 (53.3%)
Significant fibrosis	≥2	7-13	23 (25.6%)
Cirrhosis	4	>13	19 (21.1%)

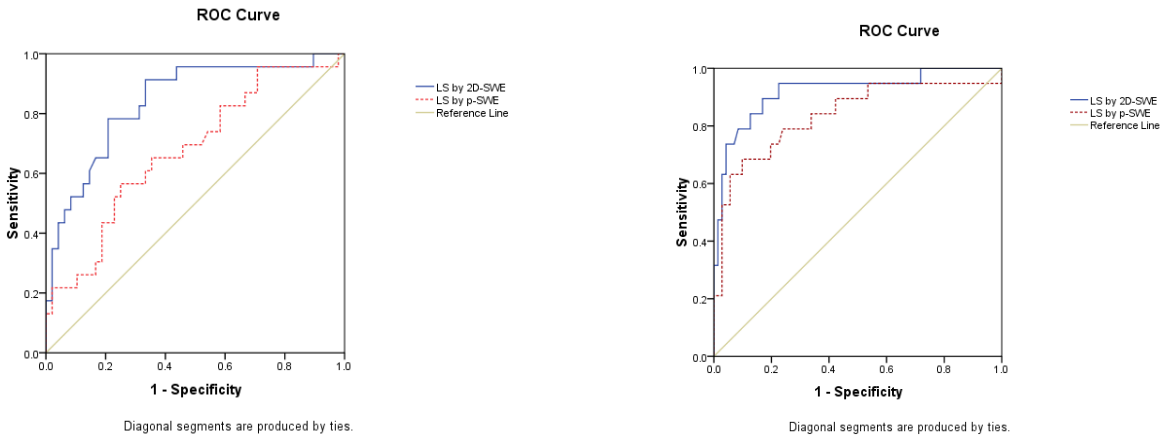
The number of patients was demonstrated on Table 3 for evaluation staging of group of patient significant fibrosis and cirrhosis.

Considering TE technique, cut off point liver stiffness value is 7-13 kPa or F≥2 for significant fibrosis and 13 kPa or F=4 for significant cirrhosis. Patients with significant fibrosis 23 subjects (25.6%) and significant cirrhosis 19 subjects (21.1%) are observed.

Considering 2D-SWE technique, cut off point liver stiffness value using 2D-SWE is 6.4 kPa (sensitivity 78%, specificity 79.2%, AUROC=0.84 (p-value<0.05)) for fibrosis (Figure 2(a)) and 8.5 kPa (sensitivity 78.9%, specificity 87.3%, AUROC=0.92 (p-value=0.05)) for cirrhosis (Figure 2(b)).

Considering p-SWE technique, cut off point liver stiffness value using 2D-SWE is 5.4 kPa (sensitivity 65.2%, specificity 64.62%, AUROC=0.67 (p-value<0.05)) for fibrosis (Figure 2(a)) and 7 kPa (sensitivity 73.7%, specificity 77.5%, AUROC=0.84 (p-value<0.05)) for cirrhosis (Figure 2(b)).

Both techniques, 2D-SWE and p-SWE, have better prediction for fibrosis more than significant fibrosis as 2D-SWE technique has better prediction than p-SWE technique in patients with significant fibrosis and cirrhosis.



(a) (b)

Figure 2 AUROC for 2D-SWE and p-SWE; (a) assessing liver fibrosis (LS in TE range from 7-13 kPa), (b) assessing liver cirrhosis (LS in TE more than 13 kPa).

DISCUSSION

In the past, liver biopsy as gold standard for evaluation liver fibrosis. In the recent yeasts non-invasive evaluation liver fibrosis using ultrasound base-elastography are increasing use in many countries and many guidelines for clinical application. The transient, the oldest technique, was endorsed in the recommendation of management of viral hepatitis such as the European Association for the Study of the Liver [1]. The quite expensive machine can use only evaluate fibrosis and fat but cannot perform in ascites patient. 2D-SWE and p-SWE are integrated in ultrasound machines and use ultrasound imaging to selected the region of interest and can use elastography evaluation in several organs (liver, breast, thyroid, kidney, spleen). The machines still use examination gray scale ultrasound, Doppler ultrasound.

Sporea et al. [32] compare 3 elastography techniques which are TE, 2D-SWE and p-SWE on 322 adult patients for feasibility of their use liver fibrosis evaluation showed significant higher percentage or reliable measurement for p-SWE than for TE and 2D-SWE (92.1% versus 72.2% ($p<0.0001$) and 92.1% versus 71.3% ($p<0.0001$) [10]. This study compared LS measurement by SWE techniques, 2D-SWE and p-SWE, and TE. A high significant correlation was found with r=0.84 for 2D-SWE and r=0.67 for p-SWE but LS was significant lower than obtained by TE. The liver stiffness using transcient elastography was predicted by the simple linear regression equations. The first one using 2D-SWE technique was LS(TE) = –6.08 + 2.09 LS(2D-SWE) and the second on using p-SWE technique was LS(TE) = 2.03 + 1.12 LS(p-SWE). The result of this study depicted the LS by 2D-SWE for predicting significant fibrosis and cirrhosis (F.2:6.4 kPa, F=4:8.5 kPa) which lower than manufactures' recommendation (F>0:5.48 kPa, F>1:8.29 kPa, F>2:9.4 kPa, F>3:11.9 kPa) [33]. These different could be many factors, for examples, software version, different in subject group, underlying etiology disease, difference time of study of TE and 2D-SWE, etc. Felix et al. [43] use 2D-SWE, GE for predicting stage of liver fibrosis found LS by 2D-SWE, GE lower than TE, and cut off point liver staging lower than manufactures' recommendation, no different from our study.

In the last years the technique 2D-SWE is implemented on several ultrasound machines (Supersonic Imaging, General Electric Healthcare, and Toshiba). Several studies have been published demonstrated that Supersonic Imaging 2D-SWE, SSI is useful tool for evaluating staging liver fibrosis, non-inferior to TE [34-36]. Jiang et al. published meta-analysis for diagnostic accuracy of 2D-SWE for liver fibrosis severity. The results showed sensitivity and specificity for detection significant fibrosis; F>2 were 0.84 and 0.83 consequently, for detection cirrhosis F=4 were 0.89 and 0.88 respectively [37]. All study used Aixplorer, Supersonic Imaging, Aix-en-Provence, France but this study used GE Logic E9 which less data about 2D-SWE on General Electric Healthcare (2D-SWE-GE). The result showed the cut off value LS by p-SWE, F>2:5.4, F4=7 which lower than recommendations' manufacture, (F0:2.0-45, F4.5-5.7, F2-3:5.7-12, F3-4:12-21 kPa). These different could be many factors: difference software version, different in subject group, underlying etiology disease and difference time of study of TE and p-SWE. Many factors influence liver stiffness such as different technique and vendors, measurement location, patient factors as inflammatory activity, biliary obstruction, liver steatosis, hepatic venous congestion, deep inspiration, food intake, body habitus. p-SWE with acoustic radiation force impulse ARFI has been introduced by many companies (Siemens, Phillips). Sporea et al. [34] published a meta-analysis compared the diagnostic performance of p-SWE and TE for assessment liver fibrosis using liver biopsy (gold standard) for detection significant fibrosis sensitivity 74%, specificity 78%, for diagnosis fibrosis F=4, sensitivity 87%, specificity 87% [38].

Most of previous study cut off value were presented in unit m/s [39-42]. The cut off value in Friedrich's meta-analysis were F>2:1.34 m/s, F>3:1.55 m/s, F= 4:1.8 m/s. The cut of value in Sprorea's multicenter study were F>2:1.33 m/s, F>3:1.43 m/s, F=4:1.55 m/s. The advantage of 2D-SWE and p-SWE technique comparison with TE is that they guided by B-mode imaging choose place to place ROI, visualize liver during measurement far from capsule and large vessels and stop breathing. Compare 2D-SWE and p-SWE for measurement liver stiffness, 2D-SWE is better correlation with TE than p-SWE. 2D-SWE measure ROI in the most homogenous area and use color homogeneity for qualitative criteria for selection. The performing p-SWE were required to hold breathing for several second and multiple times.

The limit of our study is limited in number of subjects, each staging (F0-F4) especially advance fibrosis. Limits study of TE is ascites so patient with ascites patient excluded from this study. Main limited study of this study is lack of liver biopsy as gold standard and using transient elastography as reference. Less study using 2D-SWE by General electric ultrasound so cut of value of staging liver fibrosis was found. Felix B et al. suggested cut of value for prediction F.2:6.7 kPa, F>3:8.9 kPa, and F=4:9.3 kPa. Further multicenter study and liver biopsy for reference method is recommended for more accurate cut off value for predicting stages of liver fibrosis by 2D-SWE-GE.

Three elastrography techniques (TE, 2D-SWE and p-SWE) have good correlation but give difference LS value each technique, each vendors. Liver stiffness measurement by 2D-SWE and p-SWE were significant lower than liver stiffness measurement by TE. The suggestion of predicting cut off value LS for significant fibrosis and cirrhosis for 2D-SWE are 6.4 kPa and 8.5 kPa. For p-SWE are 5.4 kPa and 7 kPa. Conflict interest: none.

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Authors' contributions: SJ designed for the study. SJ and CB collected and analyzed data. SJ, CB and JM interpreted the data. JM made the article draft. SJ and CB commented and approved the version to be published.

Conflict of interest: None declared.

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