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Original Article

Correlation between shear wave elastography and vibration-controlled transient elastography of liver stiffness in chronic hepatitis B infection in Samut Sakhon Hospital

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Abstract

Background: Assessment of the liver stiffness to evaluate liver fibrosis in viral hepatitis has been an important factor in the management guideline. Due to limitations of liver biopsy, non-invasive assessments of liver stiffness become a more practical method. Vibration-controlled transient elastography (VCTE) has been widely used for a long time and the newcomer, 2D shear wave elastography (2D-SWE) was claimed to possess a strong correlation.

Objective: To assess agreement and correlation of liver stiffness measurement using VCTE and 2D-SWE in patients with viral hepatitis B.

Materials and Methods: 34 patients with a laboratory confirmation as viral hepatitis infected were included. Liver stiffness measurements were obtained using 2D-SWE with VCTE serving as the reference standard on the same occasion. The differences of two measurements were demonstrated by both Bland-Altman and scattered plot. We analyzed their mean differences, 95% limit of agreement, and Spearman correlation (rs) coefficient to determine the agreement and the correlation of the 2D-SWE compared to VCTE.

Results: For VCTE and 2D-SWE, the median elasticity was 5.35 kPa (IQR 4.57, 6.77) and 6.90 kPa (IQR 6.07, 8.25), respectively. The mean differences of the elasticity of tissue between VCTE and SWE were 0.50 kPa (S.D. 3.25 kPa) and 95% limit of agreement was between -6.87 and 5.87 kPa. There was a strong correlation (rs =0.659) between VCTE and 2D-SWE.

Conclusion: In this pilot experience of these two methods, the initial correlation test in real clinical setting has proved a strong measurement correlation between Shear wave elastography and VCTE in hepatitis B patients.

Keywords: 2D shear wave elastography (2D-SWE), Vibration-controlled transient elastography (VCTE), Liver fibrosis.

Introduction

Hepatocellular carcinoma is one of the most common malignant tumors in men and the third most common cancer in women in Thailand [1]. A delay in the diagnosis would lead to poorer prognosis [2]. Therefore, early detection of hepatocellular carcinoma is important for high-risk patients [3]. The most common causes of hepatocellular carcinoma were chronic hepatitis B infection (49.6%), followed by alcoholic cirrhosis (26%), chronic hepatitis C infection (19%), cryptogenic cirrhosis (16%) and non-alcoholic steatohepatitis (2.4%), respectively [1,4-5]. Chronic hepatitis B and C infection caused chronic inflammation and hepatocellular injury with subsequent liver fibrosis and hepatocyte proliferation,

promoting liver cirrhosis [4,6-8]. Liver fibrosis, defined as the excessive accumulation of extracellular matrix caused by chronic liver injury, is the key determinant for the prognosis of patients with chronic liver diseases (CLD) [9]. Prior studies suggested that liver stiffness measurement could be a useful predictor of hepatocellular carcinoma development in patient with chronic hepatitis B infection [3]. Because the patients with a mild degree of liver fibrosis or early liver cirrhosis were asymptomatic, the accurate assessment of the degree of liver fibrosis could assist with early diagnosis of liver cirrhosis, prediction of a better disease outcome, and influence on the indication for antiviral therapy [9,10].

Liver biopsy was known to be the gold standard for evaluation in the degree of liver fibrosis [11]. However, this procedure was considered invasive because of its complications. Moreover, equivocal diagnostic accuracy of liver biopsy depended on the sampling specimen [9]. Ideally, a non-invasive method for evaluation of liver fibrosis should be reliable, reproducible, inexpensive, easy to perform, helpful in monitoring disease progression and evaluating treatment efficacy [10]. Recently, liver stiffness measured by noninvasive methods such as transient elastography and 2D-shear wave elastography (2D-SWE) has been reported to be well correlated with liver biopsy [3,9-15]. Following validations in prior cross-sectional studies, transient elastography is now regarded as a reliable surrogate for liver biopsy for grading the severity of liver fibrosis in patients with chronic liver disease [16-18]. 2D-SWE was an excellent modality for evaluating liver fibrosis by itself and provided some strength compared with transient elastography [19, 20]. The aim of this study was to assess the agreement and correlation between 2D-SWE and vibration-controlled transient elastography (VCTE) in patients with hepatitis B virus infection.

Materials and methods

Study subjects

Patients with a laboratory confirmation of HBV infection, in the special outpatient liver clinic of Samut Sakhon Hospital were recruited in the study. Patients were excluded for the following reasons (i) Ongoing CHF (ii) Having focal hepatic lesion (iii) Having ascites (iv) Previous history of hepatic intervention procedure (v) Prior history of antiviral therapy (vi) Performance of 2D-SWE by other radiologists and (vii) Inhomogeneous color map for SWE.

Preparation for vibration-controlled transient elastography (VCTE) and 2D-shear wave elastography (2D- SWE)

All subjects were required to fast at least 6 hours. Patients were placed in supine.

Vibration-controlled transient elastography (VCTE) protocol

Vibration-controlled transient elastography was performed using Fibroscan device (Echosens®) utilizing the medium transducer as per the manufacturer's recommendation. The median value of ten successful acquisitions liver stiffness measurements was calculated and the results were shown in kilopascals (kPa). Grading of liver fibrosis was described below; in Table 1. Because vibration-controlled transient elastography was a valid method to assess liver fibrosis, it was used as the reference method to compare with 2D shear-wave elastography. According to classification stage of liver fibrosis, the cut off values adopted the Metavir score of vibration-controlled transient elastography (Fibroscan) [21].

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Table 1. *The interpretation of Vibration-controlled transient elastography parameter in grading liver fibrosis.*

Liver fibrosis	Metavir score	Value (kPa)
No liver fibrosis	F0-F1	1.5-7.0
Non-advance fibrosis	F1-F2	7.1-8.6
Advance liver fibrosis	F2-F3	8.7-10.2
Cirrhosis	F3-F4	10.3-75

2D-shear wave ultrasound shear wave elastography protocol

2D-shear wave elastography was performed by a single radiologist using Toshiba Aplio® 500 and 550 on the same occasion with operator blind to the VCTE results. The radiologist had a 3-year experience in diagnostic radiology and a 2-year experience in ultrasound shear wave elastography and had performed at least 70 cases of ultrasound shear wave elastography before this study. The used probe was a curvilinear probe (5 MHz) via the right hepatic lobe through the intercostal space with the patient lying in a supine position with the right arm in maximal abduction. All patients held their breaths for 5-10 seconds to minimize breathing motion artifacts until obtaining the most adequate window for the liver. The sample box/region of interest (ROI) was located at least 1 cm below the liver capsule and was no more than 5 cm deep from skin with an avoiding area of artifacts and large blood vessel to obtain the best quantitative measurement with a single shot technique. Regions of interest measurements were taken in a circular motion and 1 cm in diameter for 5 times. The median value of five consecutive measurements of all patients was used for statistical analysis and the results were shown in kilopascal (kPa). The median/IQR ratio was less than 0.3 considered to ensure reliable measurement (Figure 1). Grading of liver fibrosis was described below (Table 2) according to the study of Ferraioli et al. [22].

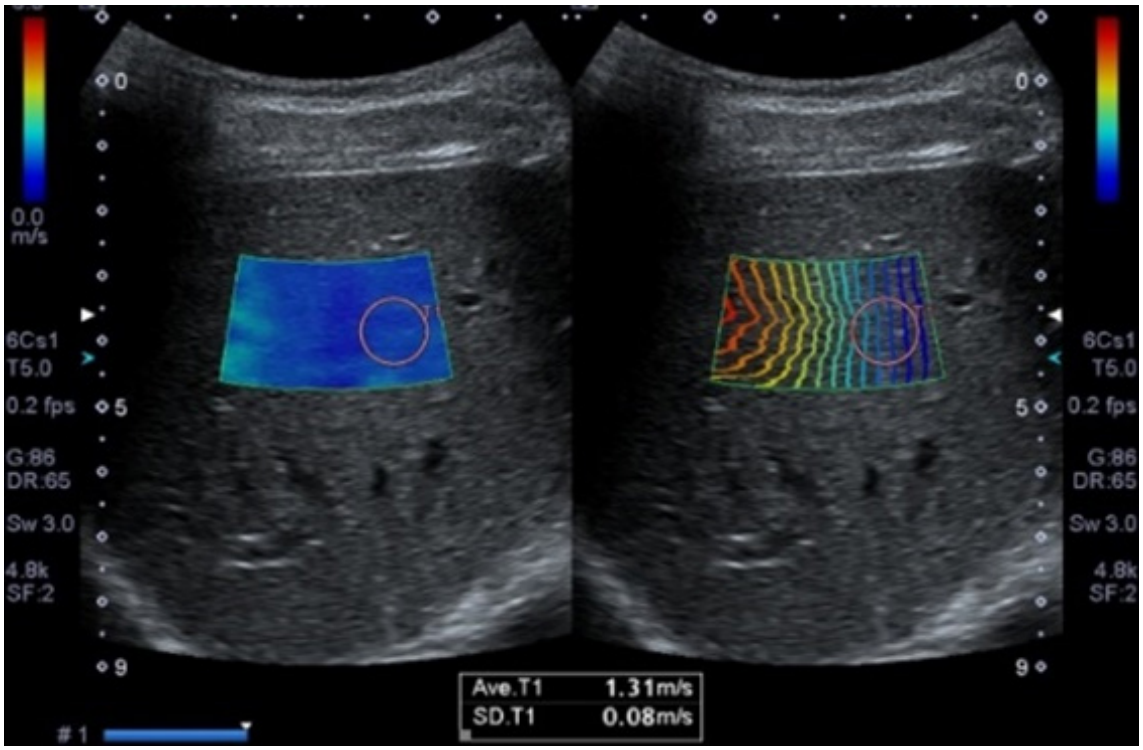

Figure 1. *Speed and propagation maps showing elastogram with 10 mm region of interest.*

Table 2. *Shear wave elastography parameter in grading liver fibrosis [22].*

Liver fibrosis staging	Metavir score	Value (kPa)
No/mild fibrosis	F0-F1	<7.0
significant fibrosis	F2-3	7.0-9.0
severe fibrosis	≥ F3-F4	> 9.0

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Statistical analysis

A data analysis was performed using SPSS version 17.0 (IBM Corporation, Chicago, IL, USA). Continuous data were analyzed to assess their normality using the Kolmogorov-Smirnov test and presented as mean and standard deviation or median and interquartile range (IQR) as appropriate. Categorical data were presented as frequency and percentage.

VCTE was used as the reference standard and 2D-SWE was assessed for the differences. Any observed differences between two measurements were analyzed using the Bland-Altman plot, mean difference and its 95% limit of agreement. The correlation between VCTE and 2D-SWE was demonstrated using scattered plot and evaluated for its Spearman's correlation coefficient (rs) using two-tailed significance at p-value of 0.01. Degree of Spearman's correlation coefficient was defined as the followings, 0.00-0.19 "very weak". 0.20-0.39 "weak", 0.40-0.59 "moderate", 0.60-0.79 "strong", and 0.80-1.0 "very strong", respectively.

Ethics consideration

The protocol was approved by the ethic committee of Samut Sakhon Hospital following the ethical guideline of the 1975 declaration of Helsinki and written informed consent was obtained from each patient.

Results

There were 34 patients with a laboratory confirmation of chronic viral hepatitis B infection (by gastroenterologist of Samut Sakhon Hospital), which included immune-tolerant chronic hepatitis B infection (normal or minimally elevated ALT and/or AST levels) or immune-active chronic hepatitis B infection (elevated ALT and/or AST levels), attended in the special outpatient liver clinic of Samut Sakhon Hospital on September 3rd, 2020. The patients were performed noninvasive assessments of liver stiffness using VCTE and 2D- SWE on the same occasion. There was one patient excluded from the study since he was performed 2D-SWE by other radiologists and another one was excluded due to inhomogeneous color map SWE. All in all, there were 32 patients included in this study (Figure 2).

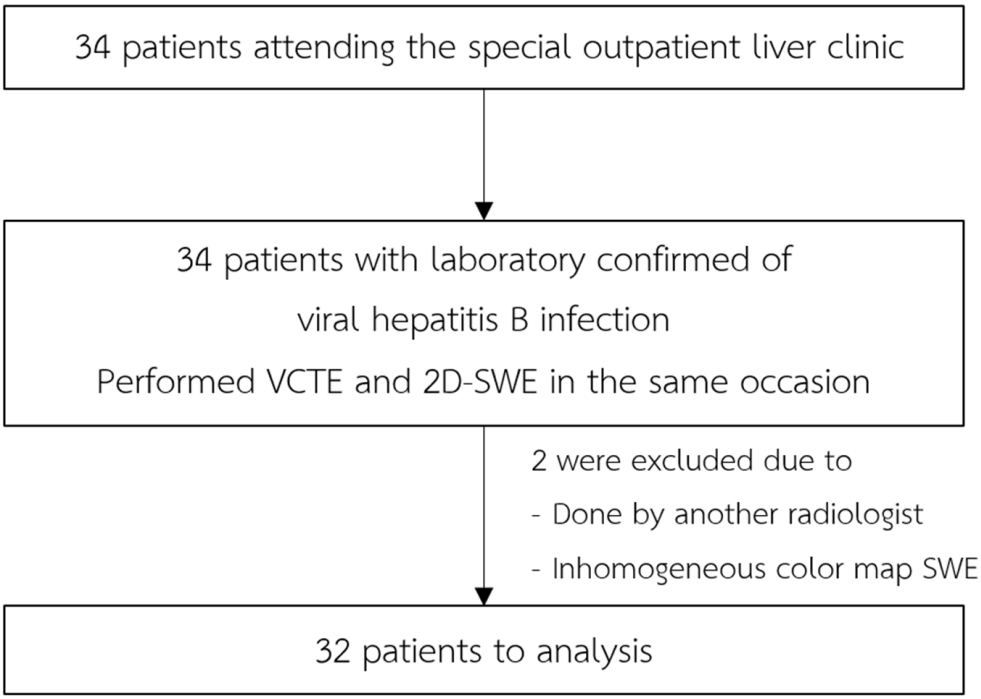

Figure 2. *Flow diagram outlining patient inclusion in this study.*

Among the 32 subjects who were included in the study, there were 10 (31.2%) males and 22 (68.8%) females with the mean age (±standard deviation) of 52.7 years ± 10.5 years. The mean body mass index was 24.5± 3.2 kg/m2. The mean intercostal thickness was 16.7±2.9 mm. The mean AST and ALT were 30±11 IU/L and 30±25 IU/L, respectively (Table 3).

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Table 3. *Baseline characteristics of the study subjects.*

Variables	Number (%)	
Sex		
Male	10 (31.2)	
Female	22 (68.8)	
Age (years)		
15-59	23 (71.9)	
≥ 60	9 (28.1)	
Mean (± SD)		52.7 (±10.5)
BMI (kg/m2)		
<25	15 (46.9)	
≥25	12 (37.5)	
No data	5 (15.6)	
Mean (±SD)		24.5 (±3.2)
Intercostal thickness (mm)		
< 25	32(100)	
≥25	0 (0)	
Mean (±SD)		16.9 (±2.9)
AST (IU/L)		
Mean (±SD) IU/L		30 (±11)
ALT (IU/L)		
Mean (±SD) IU/L		30 (±25)

Overall agreement of liver stiffness values between VCTE and 2D-SWE

For VCTE and 2D-SWE, the median elasticity was 5.35 kPa (IQR 4.57, 6.77) and 6.90 kPa (IQR 6.07, 8.25), respectively. The agreement of VCTE and 2D-SWE was elucidated using Bland-Altman plot (Figure 3). The mean differences of the elasticity of tissues between VCTE and 2D-SWE were 0.50 kPa (S.D. 3.25 kPa) and 95% limit of agreement was between -6.87 and 5.87 kPa.

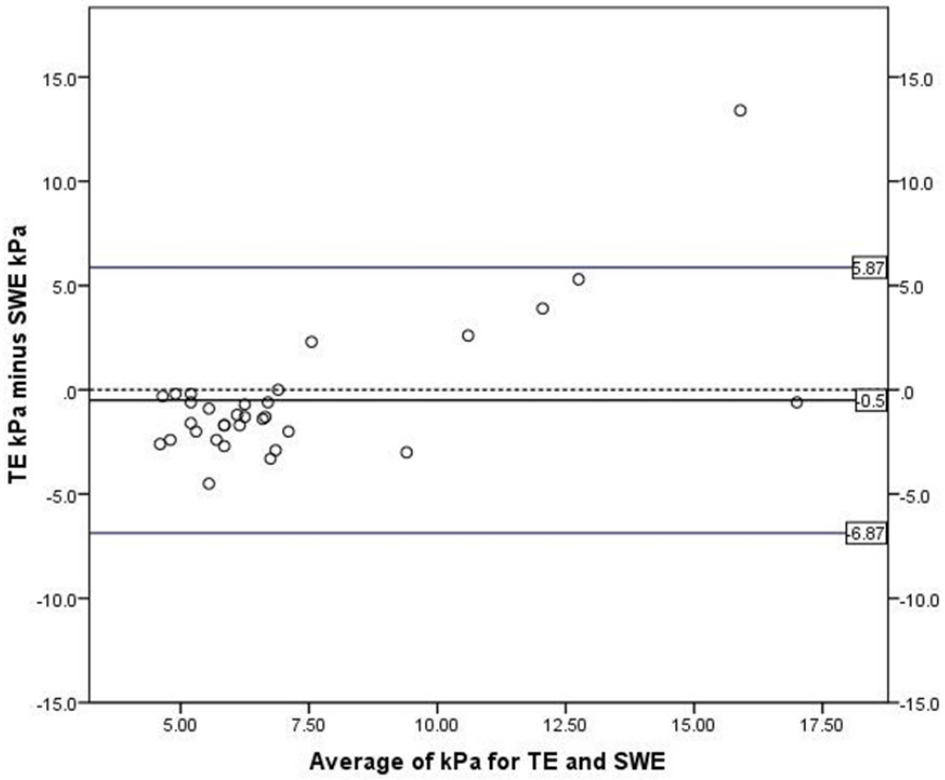

Figure 3. *Bland-Altman plot of VCTE versus 2D-SWE, showing line of mean difference of 0.92 and its 95% limit of agreement.*

The correlation of VCTE and 2D-SWE was demonstrated using scatterplot (Figure 4). Spearman's correlation coefficient was 0.659 (p-value < 0.001), signifying the strong correlation between both tests.

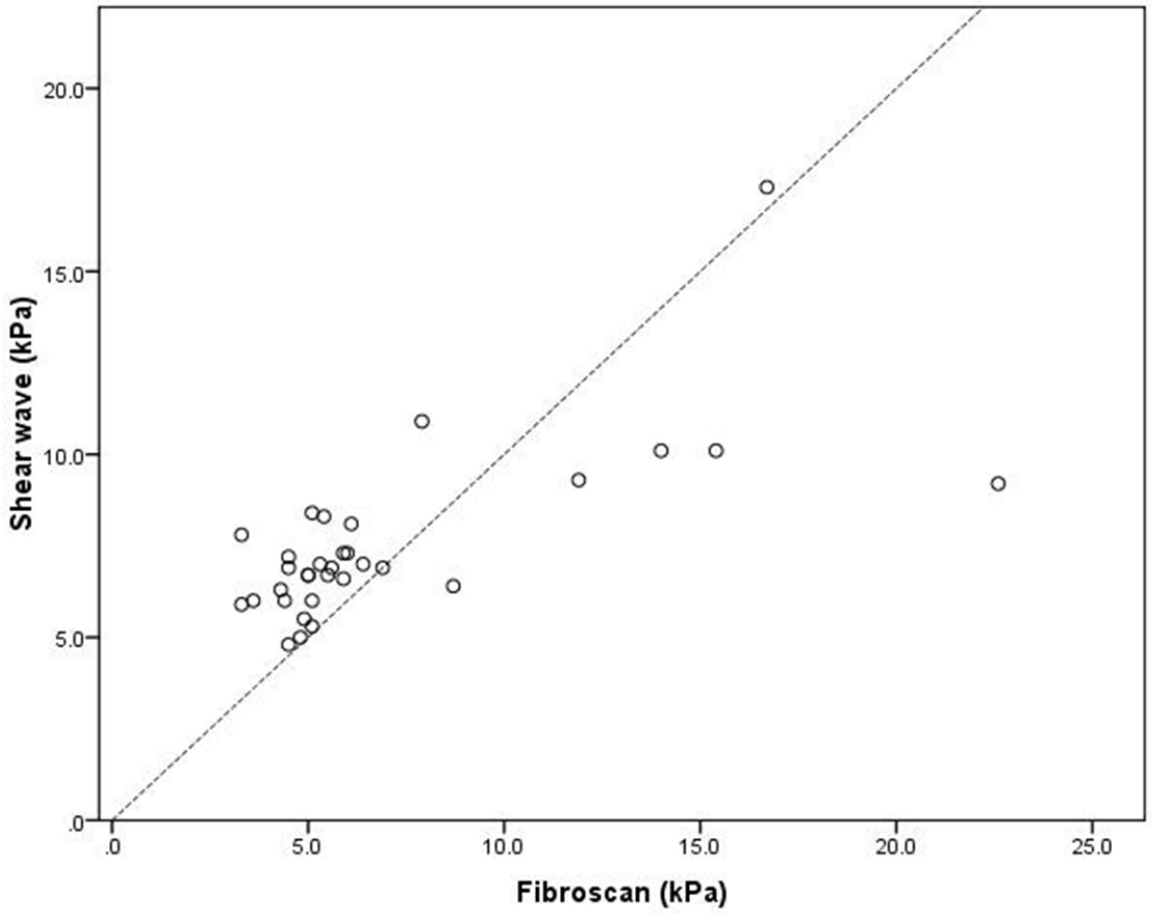

Figure 4. *Scatterplot of transient elastography (VCTE) versus shear wave elastography (SWE) kilopascals demonstrating the line of equal values.*

Discussion

Liver stiffness and fibrosis staging is crucial for treatment of patients with chronic liver disease. In the past, liver biopsy was traditionally used in the indication of fibrosis staging of liver cirrhosis. Nevertheless, the adoption of liver biopsy had its own limitations including sampling errors, bleeding complications and interobserver variations. Instead of liver biopsy, non-invasive measurement (VCTE) has become a more practical technique for assessment of the liver stiffness and fibrosis since 2003 and was considered to be the gold standard non-invasive method. 2D-SWE was a relatively new technique that can be utilized as part of the standard ultrasound examination to asses liver fibrosis. Its agreement and correlation compared to standard VCTE in Thai population were limited for detection of liver fibrosis.

By closely looking into the Bland-Altman plot in our study (Figure 3), we found that the differences between the test tended to be low in the subjects who had low liver stiffness, and the degree of difference tended to be higher as the liver stiffness was higher. This demonstrated the less deviation of liver stiffness (kPa) measured by SWE in no/mild liver fibrosis group (F0-F1, <7 kPa) patients, while in a higher stage of cirrhosis (F2-F4, ≥7.1 kPa), SWE tended to have higher deviation in kPa measured by VCTE. We summarized that SWE had reliable results and helped exclude significant fibrosis.

Our study results revealed that the liver stiffness from 2D-SWE technique achieved a strong correlation (rs =0.659) to the liver stiffness from VCTE technique. Compared to the previous studies, Noola et al [23] and Bende et al [24], who reported strong and very strong correlation (rs=0.66, and 0.83 respectively), our results showed a comparable correlation between the two tests. There were several limitations in this study. One of them is there was a small sample size and most of the recruited subjects were in no fibrosis or an early stage of liver fibrosis groups. Second, when we explored the raw data of the outlier subject, who had liver stiffness of 9.2 kPa and 22.6 kPa, whether measured by SWE or VCTE, respectively, both of the tests graded the patients to the same METAVIR score F3-F4, that did not alter its management on hepatitis B treatment. Third, 2D-SWE is also

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operator-dependent and our study did not assess the inter-operator and intra-operator variability, which, of course, could to be one of the objectives in the future study.

The advantage of 2D-SWE over vibration-controlled transient elastography (VCTE) is that the 2D-SWE is conducted by radiologists who can use the B-mode ultrasound to evaluate liver parenchyma and real-time choosing the region which is homogeneous parenchyma in the grey scale ultrasound and the color homogeneity in shear wave mode. 2D-SWE can avoid the region of intrahepatic vessels, bile ducts and the liver capsule when the box of region of interest (ROI) is placed. However, there were also limitations of 2D-SWE in patients who had ascites, a thick abdominal wall and could not hold their breaths long enough for the measurement.

Conclusion

In this pilot experience of these two methods, the initial correlation test in the real clinical setting has proved a strong measurement correlation between Shear wave elastography and VCTE in hepatitis B patients.

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