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Research Article

Evaluation of The Diagnostic Effectiveness of Real Time Shear-Wave Elastography Technique in Chronic Viral and Autoimmune Hepatitis

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Abstract

Objectives: Real Time Shear-Wave Elastography (SWE) is a new non-invasive method in which shear wave sent by ultrasound probe for the assessment of the tissue stiffness.The purpose of this study to assess liver fibrosis by using Real Time Shear-Wave Elastography method in patients with chronic viral and autoimmune hepatitis.The reference method for diagnosis is determined as Knodell and Ishak scoring system.

Methods: The patients who had chronic hepatitis B, chronic hepatitis C, autoimmune hepatitis, cryptogenic hepatitis (n=135) and a control group (n=44) were included in the study. The liver measurements were taken from 6 different points from left to caudate lobe. During each measurement 1-5 MHz convex ultrasound probe was used. The SPSS (18.0) software was used for statistical analysis.

Results: The correlation of sonografic elastography values with the histological fibrosis stages was assessed using Spearman's correlation test. Our results showed a moderately strong correlation between liver stiffness and Knodell-Ishak histological scoring system. We found that SWE correlated with patient's Knodell score 14.3 kPa> and Ishak score 15.3 kPa> that may suggest significant fibrosis and therefore chronic liver disease.

By considering our study results one can conclude that Real Time SWE method as being noninvasive and accurate would replace the recurrent liver biopsies for detection of fibrosis in cases of chronic hepatitis.

Conclusion: According to our study results, it can be concluded that the Real Time SWE method is noninvasive and accurate and will replace repetitive liver biopsies in the detection of fibrosis in chronic hepatitis cases.

Keywords: Chronic Viral Hepatitis, liver fibrosis, shear-wave elastography

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Chronic viral hepatitis and autoimmune hepatitis are important health problems that causes serious morbidity and mortality worldwide.[1, 2] In particular, hepatitis B and C are two of the major infectious diseases that cause the most deaths in the world.[3] For this reason, it is very important to use the developing technology in the diagnostic methods first.

The amount of fibrosis in the liver plays an important role in determining the prognosis and management of the chronic viral hepatitis and autoimmune hepatitis.[1] Although liver needle biopsy is still considered the gold standard in the evaluation of fibrosis; it is invasive, painful, expensive and has limitations in its use.[4, 5] When evaluating liver fibrosis, that is influenced by many factors such as the accuracy of

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the liver biopsy area, sampling error and diversity of observers. In addition, in chronic hepatitis and autoimmune hepatitis, a biopsy may be required to re-evaluate the progression of the disease and this is not easily tolerated by patients.[6–10] These limitations in liver biopsy lead to the need to uncover non-invasive methods for measuring liver fibrosis.[11–13]

Real Time Shear-Wave Elastography (SWE) is a non-invasive method, a new ultrasound technique in which images are obtained by evaluating the tissue response to localized mechanical stimuli sent by ultrasonography probe. Real-time SWE technique enables us to make quantitative estimates about tissue hardness with the estimated values of the speeds of shear waves we create with mechanical stimulus in the tissue. In addition, this technique has the advantage of obtaining images related to liver stiffness in real time. Shear waves are created by mechanical compressions with an ultrasound probe.[12–15] In addition, the Real Time Elastography images to be acquired are also guided by high-resolution B-mode images obtained simultaneously and the most suitable images are obtained. Thus, Real Time SWE image which is obtained by the help of B-mode image would help us to score the degree of fibrosis in the tissue more accurately.[12–17]

In contrast to the one-point measurement of liver biopsy here is the advantage of placing as many ROI points as possible through liver parenchyma making measurements from multiple points from right to left lobe parenchyma and evaluating a larger area of the liver compared to biopsy.[16, 17]

The aim of this study is to evaluate the accuracy of the Real Time SWE method in comparison with histopathological Knodell and Ishak scoring systems, which are accepted as diagnostic reference methods in the evaluation of liver fibrosis of chronic hepatitis cases.

Methods

Study Subjects and Design

The study was performed in the sonography unit of Marmara University Radiology Clinic, İstanbul. The study group included the patients with asymptomatic or symptomatic chronic viral hepatitis or autoimmune hepatitis in the age groups of ≥18 who had liver biopsy between May and October 2013. The total number of patients was 135. The patients with BMI>40, under 18 years of age, with concomitant liver mass lesion and difficulty in inspiration were excluded from the study. Healthy subjects were selected from patients who required USG for reasons other than liver disease.

Real Time SWE Technique

All SWE examinations were performed using an Philips IU22 Bothell WA, 98041 USA ultrasound device. Measurements were made with 1–5 MHz convex ultrasonography probe. The procedure required for at least 8 hours of fasting and an empty stomach as hepatobilier ultrasound examination was performed prior to the Real time SWE procedure. The study required no medication and ionizing radiation. The liver first viewed in B-mode inspected for lesions.Then the elastography mode was chosen and the shear-waves were created with pressures applied to the skin repeatedly with the ultrasound probe.

Real Time SWE images were obtained by a single radiologist. In each case for the liver; Measurements were taken from 8 different points, two from the left lobe and caudate lobe. One measurement was taken from each segment under the guidance of the Couinaud classification from the right lobe of the liver.[18–19] Real Time SWE measurements; the patient is in supine position and left decubitus position with the patient's right arm in full abduction; The subxiphoidal line, midclavicular line and midaxillary line were made from images obtained by holding breath to the patient through the intercostal and subcostal space. During these operations with B-mode, values in kPa (kilopascals) were obtained after each point measurement (Fig. 1). All measurements were obtained from liver parenchyma up to a depth of 8 cm. During the procedure, the values obtained by placing ROI in each segment of the liver (15x10 mm) avoiding vascular structures as much as possible. Standard square of ROI determined by the device was used in the measurements. Using the values measured from 8 points by the software installed in the device; after the procedure, arithmetic mean, median and standard deviation values were obtained. All patients were diagnosed histopathologically with tru-cut biopsy in the last year, and fibrosis scores of biopsy materials were determined using the Knodell and Ishak classification.

This study was conducted in accordance with the principles of the Declaration of Helsinki.The necessary written consents were taken from all participants and it was reviewed and approved by the Ethics Committee of the Marmara University Faculty of Medicine.

Statistical Analysis

Statistical analysis of the data collected in our study was performed using SPSS version 18 (SPSS, Chicago, IL, USA). Since elasticity values did not show normal distribution, non-parametric tests were used in the study and quantitative values were reported as median. Continuous variables were compared using the Mann-Whitney-U test, and cat-

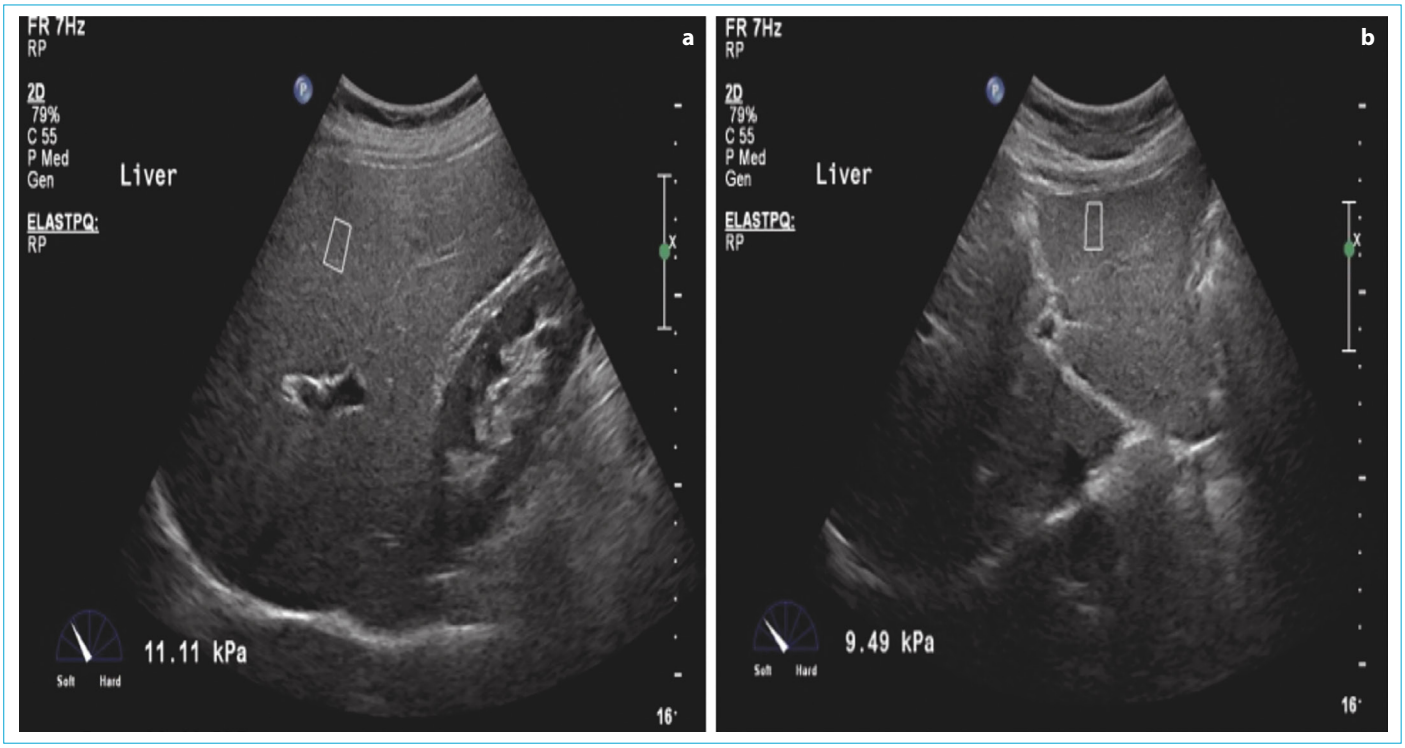

Figure 1. Ultrasound images show the stiffness values obtained in kPa in **(a)** right lobe and **(b)** left lobe by SWE (Shear-Wave Elastography) method.

egorical variables were compared using the chi-square test or "Fisher's exact test". The correlation between elasticity values and histological fibrosis stages was evaluated using the Spearman correlation test. The difference between the elasticity values of the right and left lobes of the liver was evaluated with "Wilcoxon paired test". Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated from the optimal threshold values obtained with the ROC curves. The diagnostic performance of elastography and the distinction between histopathological stages of fibrosis were evaluated according to the areas under the ROC curve (AUROC: areas under the ROC curve, accuracy) and p value <0.05 was considered statistically significant.

Results

The study included 135 patients; 83 were male and 52 were female. In addition, 21 of 44 healthy cases were female and 23 were male. The ages of 135 patients in our study ranged between 18–75 years (mean:46). The ages of healthy subjects ranged between 18 and 62 (mean:35). The study included 135 patients; 97 (71.9%) had history of chronic hepatitis B, 25 (18.5%) of chronic hepatitis C, 7 (5.2%) of autoimmune hepatitis, and 6 (4.4%) of cryptogenic hepatitis.

135 patients in our study were evaluated according to the Knodell and Ishak histopathological scoring system (Table 1). According to the Ishak histopathological fibrosis classification, significant fibrosis considered when Ishak F ≥2 which was in 79 (58.5%) of the patients.

Table 2 shows the liver stiffness values obtained by SWE and their distribution to histopathological scores. When comparing the liver stiffness medians in the Knodell scoring with the Mann-Whitney-U test, there was a difference between p=0.024 for F1-F3 and p=0.000 for F3-F4. Comparing liver stiffness medians in Ishak scoring, there was a difference between F4-(F5-6) and p=0.004.

According to Spearman correlation in our study, there was a significant, moderately strong correlation between liver stiffness in SWE values and Knodell scores (rs=0.405, p=0.000) (That is, as the scoring stage increases, liver stiffness also increases) (rs=correlation coefficient). Similarly, there was a significant, moderately strong correlation between liver stiffness in SWE and Ishak scores (rs=0.406, p=0.000) (as the scoring stage increases, liver stiffnes also increases).

Which predict the fibrosis values of the compared Knodell and Ishak scores and the optimal liver stiffness cut-off values, sensitivity, specificity, PPV, NPV and accuracy values, obtained as a results in our study are shown in Table 3. (Other names of Accuracy are diagnostic performance, AUROC (Area under ROC), discriminative ability, concordance index (c-index). It can take a value between 0.5–1, 1 is the

Table 1. Knodell and Ishak scoring of liver fibrosis in patients

Knodell	Frequency	Percent, %	Ishak	Frequency	Percent, %
F0	23	17.0	F0	23	17.0
F1	59	43.7	F1	33	24.4
F3	41	30.4	F2	26	19.3
F4	12	8.9	F3	29	21.5
			F4	12	8.9
			F5-6	12	8.9
Total	135	100.0	Total	135	100.0%

highest level of accuracy.)

Finally, during our study, the stiffness values of the right and left lobes of the liver were compared in the same Knodell and Ishak stage and there was no statistical difference (Table 4).

Discussion

Currently, the gold standard accepted method for the diagnosis and evaluation of liver fibrosis is liver biopsy.[20–22] However, liver biopsy is interventional method with a risk of complications and requires a trained physician.[4–5, 23] In a situation that has been learned to be a dynamic process and known that most of the etiology of hepatitis shows continuity throughout life (mainly chronic hepatitis b, chronic hepatitis c), the necessity of performing repeated liver biopsies has arisen.[4–10] The disadvantages mentioned have led researchers to work on methods that do not require intervention to detect liver fibrosis.[11–14]

Elastography; is a new non-invasive method, an ultrasound technique in which images are obtained by evaluating the tissue response to localized mechanical stimuli sent by ultrasonography probe. It is examined under two titles: Real Time Strain Elastography and Real Time SWE.[24, 25] There is also a method called Transient Elastography, which is partly similar to Real Time Shear-wave Elastography.[26] Real-time SWE technique allows us to make quantitative estimates about the stiffness of the velocity of the shear waves we create with mechanical stimulus in the tissue.[12–17, 27–28] In

Table 2. Liver SWE stiffness values and distribution according to scores

Knodell	Liver stiffness values, Median (IQR) (range)	Ishak	Liver stiffness values, Median (IQR) (range)
Control group (n=44)	5.8 (2.3) (2.6–14.9)	Control group (n=44)	5.8 (2.3) (2.6–14.9)
F0	10.3 (5.8) (3.5–31.2)	F0	10.3 (5.8) (3.5–31.2)
F1	11.8 (4.9) (4.5–21)	F1	11.8 (5.5) (4.5–21.0)
		F2	11.8 (3.6) (6.2–19.6)
F3	13.8 (7.7) (4.8–40.2)		
		F3	13.2 (6.5) (4.8–25.3)
F4	30.4 (16.7) (15.3–57.7)		
		F4	15.6 (7.6) (10.0–40.2)
		F5-F6	30.4 (16.7) (15.3–57.7)

SWE: Shear-wave elastography; IQR: Interquartile range.

Table 3. Optimal liver stiffness cut-off values, sensitivity, specificity, PPV, NPV and accuracy values

	Knodell (n=pos/neg group)			Ishak (n=pos/neg group)				
	F≥1 (n=112/23)	F≥3 (n=53/82)	F=4 (n=12/123)	F≥1 (n=112/23)	F≥2 (n=79/56)	F≥3 (n=53/82)	F≥4 (n=24/111)	F=5-6 (n=12/123)
Real Time SWE liver stiffness cut-off (kPa)	>7.9	>14.3	>15.3	>7.9	>10	>14.3	>14.4	>15.3
Sensitivity	93.7	58.5	91.7	93.7	84.8	58.5	79.2	91.7
Specificity	30.4	78.0	75.6	30.4	42.9	78.0	74.8	75.6
PPV	86.8	63.3	26.8	86.8	67,7	63.3	40.4	26.8
NPV	49.7	74.4	98.9	49.7	66.7	73.4	94.3	98.9
Accuracy	0.636	0.713	0.945	0.636	0.659	0.713	0.826	0.945

SWE: Shear-wave elastography; PPV: Positive predictive value; NPV: Negative predictive value.

Table 4. Comparison of both liver lobe stiffness values according to Knodell and Ishak scoring

	Knodell	Liver stiffness value Median (IQR)	p
F0 (n=23)	Right lobe Left lobe	10.4 (5.3) (3.8–31.8) 8.7 (6.7) (2.0–27.5)	0.394
F1 (n=59)	Right lobe Left lobe	11.8 (5.4) (4.4–20.2) 9.9 (8.2) (2.7–45.7)	0.526
F3 (n=41)	Right lobe Left lobe	12.8 (7.8) (4.7–38.4) 10.8 (12.5) (3.89–49.1)	0.582
F4 (n=12)	Right lobe Left lobe	31.1 (22.1) (16.0–51.3) 29.5 (27.4) (6.1–89.6)	0.583
	Ishak	**Liver stiffness value Median (IQR)**	**p**
F0 (n=23)	Right lobe Left lobe	10.4 (5.3) (3.8–31.8) 8.7 (6.7) (2.0–27.5)	0.394
F1 (n=33)	Right lobe Left lobe	11.8 (5.9) (4.4–20.2) 11.0 (8.3) (2.7–45.7)	0.796
F2 (n=26)	Right lobe Left lobe	11.8 (5.1) (5.9–19.9) 9.6 (6.2) (5.2–24.3)	0.238
F3 (n=29)	Right lobe Left lobe	12.8 (7.2) (4.7–25.9) 10.3 (13.0) (3.9–48.7)	0.658
F4 (n=12)	Right lobe Left lobe	14.3 (8.3) (10.2–38.4) 13.1 (12.4) (7.1–49.1)	0.937
F5-6 (n=12)	Right lobe Left lobe	31.1 (22.1) (16.0–51.3) 29.5 (27.4) (6.1–89.6)	0.583

IQR: Interquartile range.

addition, the most important advantages of the method are that it gives quantitative values similar to the Transient Elastography method and that it is done with B-mode accompaniment.[12, 25, 27] Real time SWE method with B-mode allows ROI points to be placed in any part of the liver parenchyma and away from vascular structures, increasing the reliability of the results obtained.

Ferraioli et al.[12] reported a sensitivity of 67–99% and a specificity of 75–99% in detecting and scoring liver fibrosis in a pilot study involving 121 cases using Real Time SWE method in chronic hepatitis C patients.During this study, they considered liver biopsy as a reference. During the same study, Real Time SWE method and Transient Elastography method were compared and found that Real Time SWE method gave more accurate results in F2 (significant fibrosis) and F3 phases according to METAVIR scoring (85.7% for SWE and 67.2% for TE.

Marginean et al.[29] found a significant difference between chronic liver disease and NASH clinic cases and control group in a single-center study in 103 cases using Real Time SWE method to evaluate liver fibrosis in children by elastography (p=0.0032, p=0.0216). All patients with chronic liver disease had a history of liver biopsy before. As a result, they stated that there was a correlation between the histopathological fibrosis stages of patients with chronic liver disease and NASH clinic and the values obtained by using Real Time SWE method.

In the studies of Grgurevic I et al.[30] consisting of 123 patients with shear-wave elastography method in patients with viral fibrosis and cirrhosis due to viral hepatitis, liver stiffness was successfully measured in 79.7%. Histopathologically based on the Ishak classification, liver stiffness was

correctly separated between stages of liver disease, with cut-off values of 8.1 (AUC 0.991) for F ≥ 3, 10.8 KPA (AUC 0.954) for F ≥ 5, and 27 KPA (AUC 0.961) for decompensated LC.

Tada T et al.[31] in their study comparing liver fibrosis indices such as FIB-4 index, AST/platelet ratio index (APRI) and Forns' index in addition to liver biopsy, the SWE technique has an excellent ability to diagnose significant liver fibrosis in chronic hepatitis C (CHC) even when patients with cirrhosis are excluded. The diagnostic performance of SWE was superior compared to the three liver fibrosis indices.

In Dhyani M et al.[32] study, the correlation between SWE values and degree of fibrosis was strong in the pediatric group whose recent biopsies were evaluated with the METAVIR scoring system (r=0.58, p=0.003) Estimation of liver stiffness and fibrosis stage showed a strong correlation in pediatric cases using convex probe with real-time SWE method.

In another study aimed at assessing liver fibrosis compared to liver biopsy in patients with chronic hepatitis C using the SWE method, Ali Z and colleagues found a strong correlation between SWE fibrosis staging and liver biopsy. In addition to being noninvasive and its accuracy, SWE can reduce the complication rate associated with liver biopsy, in addition, it is also expressed in its superiority compared to transient elastography in the same study.[33]

Although the METAVIR histopathological scoring system was frequently used in previous years, other scoring systems have also started to be used in current and ongoing studies.[13, 15, 28–33] Based on this idea, we compared the elastography values in our study using two different histopathological scoring systems. The correlation is between elasticity values and histological fibrosis stages was assessed using Spearman's correlation test. In our study, between liver stiffness and Knodell-Ishak histological scorings a significant correlation was moderately strong. Although we achieved close results, we found that Knodell scoring was more successful in early fibrosis stages and Ishak scoring in late fibrosis stages. In our study, when evaluating the accuracy of the Real Time SWE method, our comparison with the two histopathological scoring systems (Knodell, Ishak) stood out as a difference compared to other studies. According to our study, in patients who underwent real-time SWE due to chronic viral hepatitis and autoimmune hepatitis, values with 14.3 kPa> in the parenchyma according to Knodell score and 15.3 kPa> according to Ishak score may suggest significant fibrosis and therefore chronic liver disease. For this reason, we think that SWE measurements should be made in addition to routine ultrasound examination in chronic viral hepatitis and autoimmune hepatitis.

The limiting factors in our study include performing elastography procedures by a single radiologist and the relatively low number of patients. Another limiting factor was the fact that few studies on liver stiffness and fibrosis have been performed with Real Time SWE, which we can compare the results we obtained in the literature.[12, 25, 29–35] Another limitation was that the dimensions of the ROI point measured during the examination could not be changed. In the light of new studies and technological advances, a significant portion of the restrictive factors mentioned above will be overcome.

Conclusion

The use of Real Time SWE, Real Time Strain Elastography and Transient Elastography methods for the detection of liver stiffness and fibrosis is increasing day by day. Although the Real Time SWE method has a newer modality compared to the other two methods, it stands out because it gives quantitative values and can be done simultaneously with B-mode. Real Time SWE is a new non-invasive method, an ultrasound technique in which images are obtained by evaluating the tissue response to shear-wave sent by ultrasonography probe. Contrary to a single point measurement in liver biopsy, the Real Time SWE method has the advantage of placing as many ROI points as possible in the liver parenchyma, and measuring a wider area of the liver. In a situation that has been found to be a dynamic process and known to have a persistent lifetime of most hepatitis etiology, it is a much simpler and wiser choice to apply Real time SWE to patients instead of repetitive liver biopsies.With the Real Time SWE method, which has begun to enter clinical use in many centers, patients are evaluated in a shorter time and at a more affordable cost. With the new studies to be carried out, increasing the clinical use of the Real Time SWE method will prevent unnecessary liver biopsies.

Disclosures

Ethics Committee Approval: The ethics committee of Marmara University Faculty of Medicine provided the ethics committee approval for this study (28.03.2013-09.2013.0050).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – E.K., D.T.; Design – E.K., D.T.; Supervision – E.K., D.T.; Materials – E.K.; Data collection &/or processing – E.K., O.T.; Analysis and/or interpretation – E.K., O.T.; Literature search – E.K.; Writing – E.K., O.T.; Critical review – E.K., O.T.

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