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White Paper

Prospective Evaluation of Liver Fibrosis using S-Shearwave Imaging™

: Comparison with Magnetic Resonance Elastography

V8 ultrasound imaging system

Jeong Eun Lee, M.D., Ph.D., Kyung Sook Shin, M.D., Ph.D.

Department of Radiology, Chungnam National University Hospital,
Chungnam National University College of Medicine

Introduction

Background

Chronic liver diseases (CLDs) have become important health issues worldwide: chronic liver injury induces anatomical changes of liver and increase of liver stiffness (LS) [1, 2, 3]. Liver fibrosis may progress and eventually lead to severe clinical conditions including cirrhosis, portal hypertension, hepatic insufficiency, and hepatocellular carcinoma (HCC) [3]. With the rising prevalence of chronic liver disease, noninvasive estimation of liver fibrosis and early diagnosis of fibrosis stage are of utmost importance in public health [4].

Shear wave elastography (SWE) is the method currently satisfying these needs: non-invasive, easily accessible, cost effective, and safe. Generation of mechanical push and consecutive motion monitoring are all executed with ultrasound, without the need of an extra mechanical motor. These traits make SWE portable and feasible in various clinical environments. At the same time, SWE is required to produce reproducible estimations with low inter- and intra-operator variability with clinically significant cutoff values for fibrosis staging.

Objective

The purpose of this study is to prospectively investigate the diagnostic performance of S-Shearwave Imaging™ for liver fibrosis staging, with Magnetic Resonance Elastography (MRE) used as the reference method.

Materials and Methods

▪ Patients

The Institutional Review Board of Chungnam National University Hospital, Daejeon, Korea approved this prospective study, and written informed consent was obtained from each participant. A total of 148 patients with chronic liver disease were consecutively enrolled into the study between February 2021 and November 2021, of whom 133 patients met eligibility criteria and were included. Each participant underwent both 2D-SWE and MRE.

▪ 2D-SWE (S-Shearwave Imaging™)

In each participant, conventional liver ultrasound examination and two dimensional shear wave elastography (2D-SWE) examination were performed using an ultrasound system (V8, Samsung Medison Co., Ltd., Korea) with a convex probe (CA1-7S, 1-7 MHz, Samsung Medison Co., Ltd., Korea). S-Shearwave Imaging™ is the trade name 2D SWE implemented on V8 imaging system.

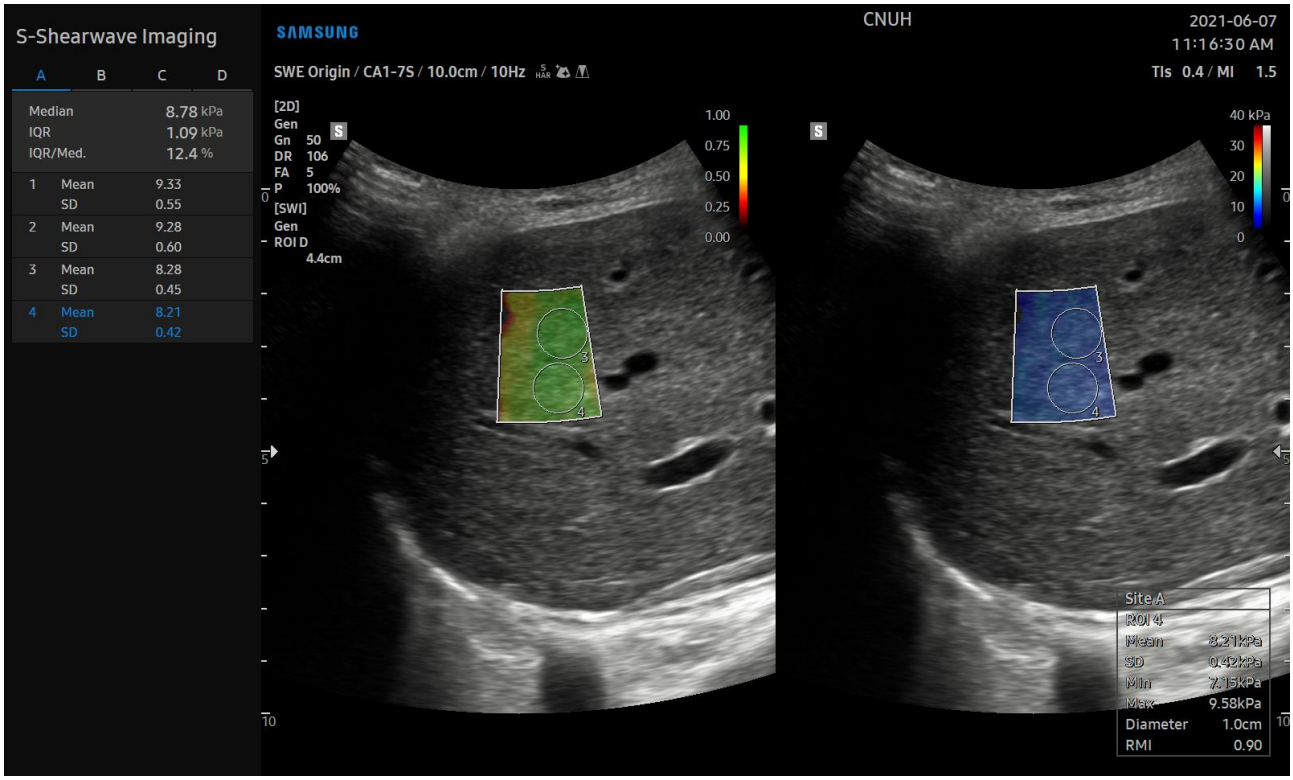


Figure 1. A sample S-Shearwave Imaging™ output image. RMI (on the left) and stiffness (on the right) are displayed on top of B-mode images.

All participants were asked to fast for at least 6 hours before the US examination. Radiologists performed data acquisitions in the right lobe of the liver by using a right intercostal plane. The participants were placed in the supine position with the right arm abducted during the data acquisitions.

A sample S-Shearwave Imaging™ output image is shown in Figure 1, where 2D maps of elasticity (Young's modulus or shear wave speed) and reliability (RMI: Reliable Measurement Index) are superimposed on top of B-mode images. RMI (on the left) is between 0 and 1, and stiffness map (on the right) is scalable by users either in kPa (measured in Young's modulus) or m/s (in shear wave speed). Several frames of S-Shearwave Imaging™ were obtained for each patient to reduce noise and variability. A 2D-SWE measurement was considered reliable if ROI showed fairly homogeneous RMI values above 0.4. Figure 2 shows an example of the stiffness values of several independent measurements. IQR/Med (Interquartile range/Median) was used to quantify the variability, where the condition IQR/Med <0.3 was considered to be trustable. Median elasticity over ten consecutive measurements were calculated for each patient.

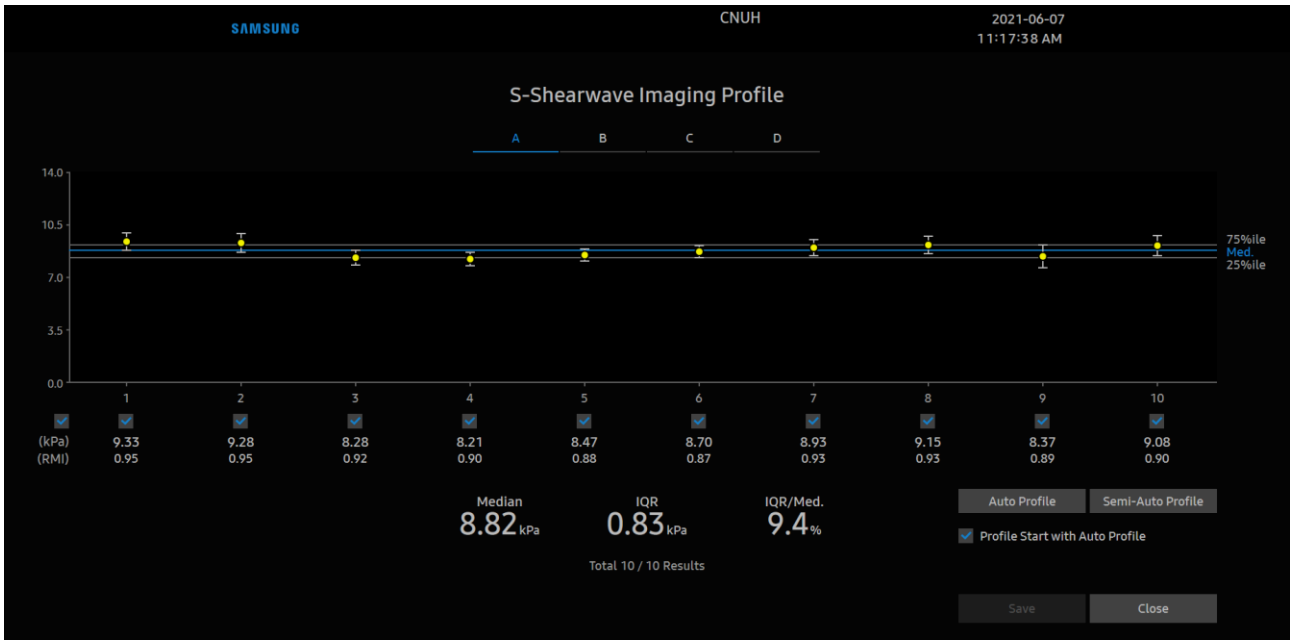


Figure 2. Young's moduli from several independent measurements of a patient.

- ## Transient Elastography (TE)

All patients underwent TE using a Fibroscan (Echosens, Paris, France) on the same day of the 2D-SWE examination. LS measurements were performed through the intercostal spaces at the right lobe of the liver in a supine position with the same method of 2D-SWE. An examination

was considered reliable if 10 valid measurements had acquired a success rate of at least 60% and an IQR < 30%. The median was considered as the representative value

▪ Serologic markers

Serological tests were performed with overnight fasting on the same day as the LS measurements. The following serological markers were routinely assessed: AST, alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin, r-glutamyl transferase (r-GT), and platelet count (PLT). As an indicator of the noninvasive serologic fibrosis marker test, the APRI (AST to Platelet Ratio Index) was calculated using the following formula: APRI = (AST/AST_{ULN} ×100)/PLT, where AST_{ULN} is defined as the upper limit of the normal AST value (40 IU/L) [5].

▪ MR Elastography

Blinded to the 2D-SWE results of each patient, an abdominal radiologist manually performed liver MRI with MR elastography (MRE) examinations using a 3T MR scanner (Discovery™ MR750w, GE Healthcare) on all 133 participants. METAVIR fibrosis staging was done on all the patients using MRE cutoff values of 2.61 kPa for ≥F1, 2.97 kPa for ≥F2 (significant fibrosis), 3.62 kPa for ≥F3 (advanced fibrosis), and 4.69 kPa for F4 (cirrhosis) following the systematic review and pooled analysis by Hsu et al. [6].

▪ Statistical analysis

All statistical analyses were performed using MedCalc for Windows (MedCalc Software, Mariakerke, Belgium). Correlations between the results of 2D-SWE, TE and APRI scores and MRE were analyzed using Spearman correlation coefficients. A correlation was considered to be strong if the absolute value of the correlation coefficient (r) was 0.7 to 1.0 and moderate if r was 0.4 to 0.7. The diagnostic performance of 2D-SWE for staging liver fibrosis was investigated using receiver operating characteristic (ROC) curve analysis. The respective cut-off values were determined using a common optimization step that maximized the Youden index [7]. A p-value of less than 0.05 was considered statistically significant.

Results

▪ Participants distribution and elasticity measurements

Distribution of participants and MRE measurements are summarized in Table 1 below. Age ranged from 20 to 84 with mean of 54.7. Seventy-eight patients were male and fifty-five were female. Fibrosis distribution of the participating patents turned out 83 for F0, 6 for F1, 15 for F2, 10 for F3, and 19 for F4. The patients' volume was a bit heavy for F0/F1, as is quite common in Korean population. However, sample size from F2 to F4 was still big enough to produce meaningful shear wave cutoff values.

Table 1. Participants' characteristics

Parameters	Value (n=133)
Age (years)	
Mean ± SD	54.71 ± 15.55
Range	20–84
BMI (kg/m²)	
Mean ± SD	26.51 ± 4.92
Range	15.26–40.76
Sex	
Male	78 (58.6%)
Female	55 (41.4%)
Fibrosis Stage by MRE	
F0	83 (62.4 %)
F1	6 (4.5 %)
F2	15 (11.3 %)
F3	10 (7.5 %)
F4	19 (14.3 %)
Mean 2D-SWE (kPa)	
F0	5.05 ± 1.06
F1	6.79 ± 1.65
F2	8.32 ± 1.66
F3	12.33 ± 4.19
F4	16.58 ± 4.79
MRE (kPa)	
Mean ± SD	3.02 ± 1.66
Range	1.60–11.00

▪ Correlations between the results of 2D-SWE, TE and APRI

Figure 3 shows correlation of Young's moduli (in kPa by V8 S-Shearwave Imaging™) against shear moduli (in kPa by MRE) for all the patients in the study. Overall, 2D-SWE was well correlated with MRE measurements (Pearson R=0.926).

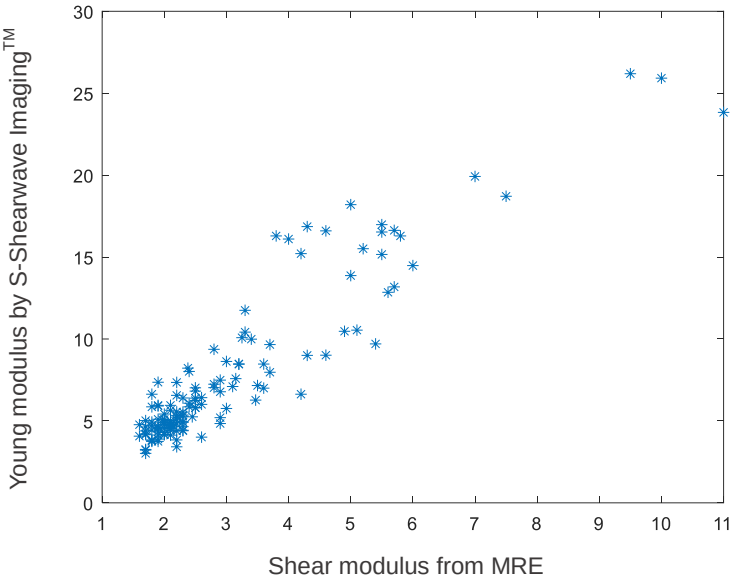


Figure 3. Correlation of Young's modulus by S-Shearwave Imaging™ against MRE by Discovery™ MR750w for the entire patient set. The coefficient was as high as 0.926 (p<0.001).

Table 2 shows the correlation of liver stiffness among non-invasive test; 2D-SWE (V8 S-Shearwave Imaging™), TE and APRI. MRE showed a very strong positive correlation with 2D-SWE (r = 0.926, p<0 .001),a strong positive correlation with TE (r = 0.763, p< 0.001) and moderate positive correlation with APRI score (r = 0.453, p< 0.001).

Table 2. Correlation of liver stiffness between MRE and other measurements

Correlation between MRE and other measurements	2D-SWE	TE	APRI
Correlation (r)	**0.926**	**0.763**	**0.453**
P -value	<.001	<.001	<.001

At the same time, inter-observer variability of 2D-SWE was experimented for 121 patients by two radiologists and the agreement was found to be excellent with an ICC of 0.962 [95% confidence interval, 0.945 to 0.973].

▪ Comparison of the Diagnostic Performance of 2D-SWE, TE, and APRI

Figure 4 shows the diagnostic performance of 2D-SWE (V8 S-Shearwave Imaging™), TE, and APRI. The AUROC values of 2D-SWE for the diagnosis of each stage of fibrosis were higher than those of TE and APRI. The AUROCs for 2D-SWE in differentiating mild fibrosis (≥ F1), significant fibrosis (≥ F2), advanced fibrosis (≥ F3), and cirrhosis (F4) were 0.966 (95% CI 0.920–0.990, $p < 0.001$), 0.978 (95% CI 0.937–0.996, $p < 0.001$); 0.982 (95% CI 0.942–0.997, $p < 0.001$); and 0.974 (95% CI 0.931–0.994, $p < 0.001$), respectively. For TE, the corresponding values were 0.909 (95% CI 0.847–0.952); 0.911 (95% CI 0849–0.953, $p < 0.001$); 0.966 (95% CI 0.920–0.990, $p < 0.001$); and 0.973 (95% CI 0.929–0.993, $p < 0.001$), respectively. The corresponding figures for APRI scores were 0.809 (95% CI 0.732–0.872); 0.842 (95% CI 0.769–0.900, $p < 0.001$); 0.828 (95% CI 0.753–0.888, $p < 0.001$); and 0.864 (95% CI 0.794–0.917, $p < 0.001$), respectively.

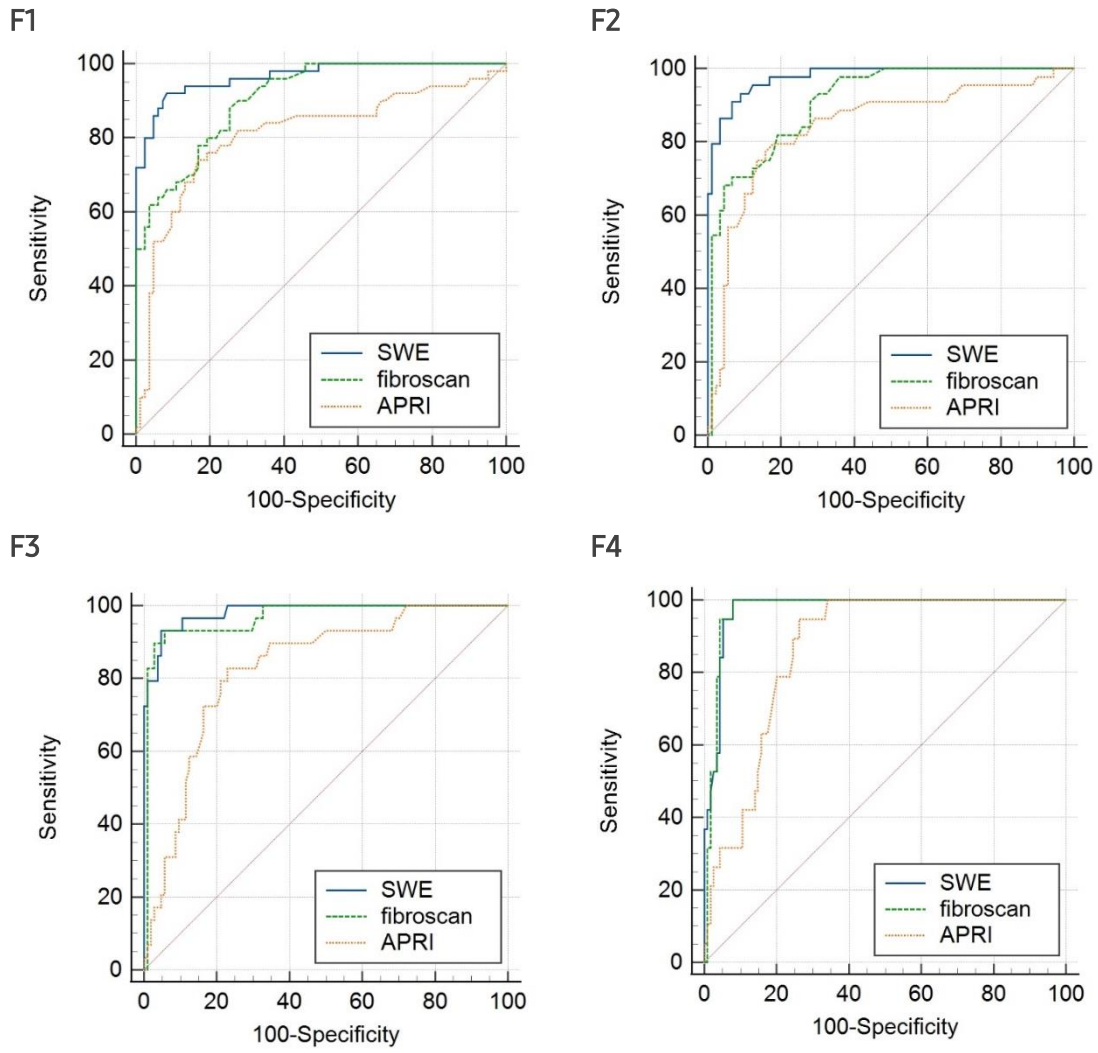


Figure 4. Diagnostic performance of SWE, TE, and APRI using MRE as reference method.

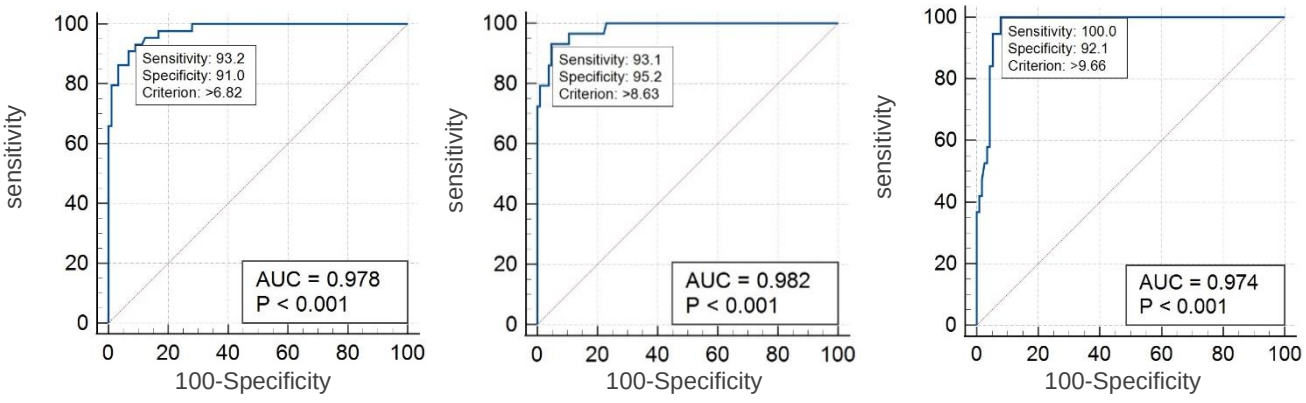
▪ Diagnostic Accuracy and Cut-Off Values of 2D-SWE

The results is summarized in Table 3 with corresponding ROC curves shown in Figure 5. The cutoff values for the diagnosis of significant fibrosis, advanced fibrosis and cirrhosis were found to be 6.82 kPa for ≥ F2, 8.63 kPa for ≥ F3, and 9.66 kPa for F4, respectively. All these parameter values assure a very confident classifier with excellent agreement with MRE.

Table 3. Diagnostic accuracy and optimal cutoff values of 2D-SWE for the diagnosis of liver fibrosis

Fibrosis Stage	≥F2	≥F3	F4
Cutoff, kPa	**6.82**	**8.63**	**9.66**
AUROC (95% CI)	0.978 (0.937 - 0.996)	0.982 (0.942 - 0.997)	0.974 (0.931 – 0.994)
P-value	<0.001	<0.001	<0.001
Sensitivity, %	93.2	93.1	100.0
Specificity, %	91.0	95.2	92.1

Abbreviation: AUROC= Area under ROC curve analysis, CI=Confidence Interval



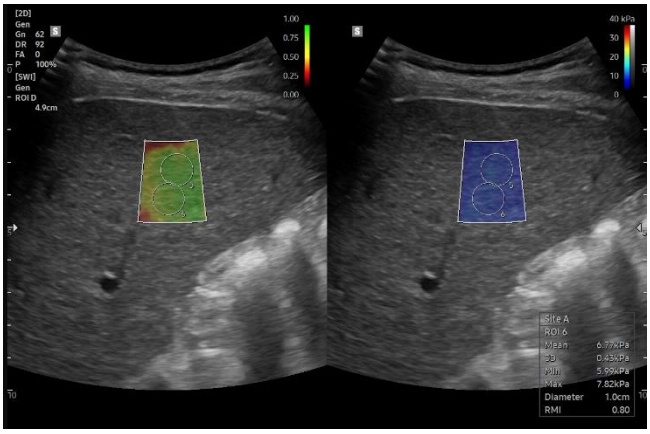
(a) F0-F1 versus F2-F4 (≥F2) Cutoff value=6.82 kPa

(b) F0-F2 versus F3-F4 (≥F3) Cutoff value=8.63 kPa

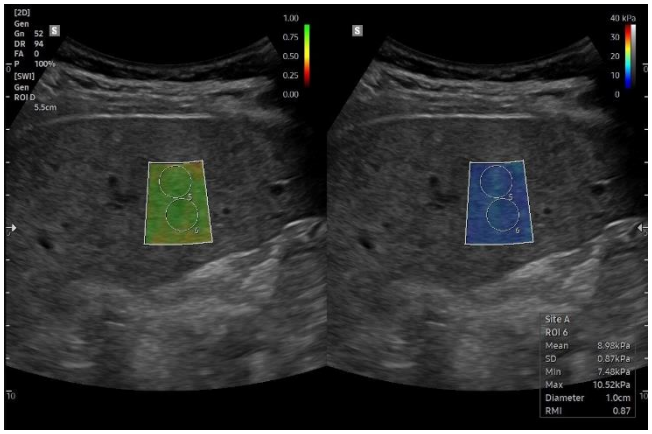
(c) F0-F3 versus F4 Cutoff value=9.66 kPa

Figure 5. ROC curves for 2D-SWE for difference fibrosis stage

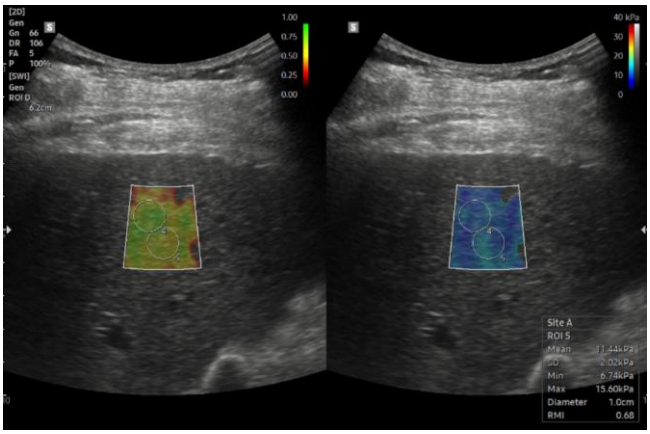
Figure 6 shows some sample images of S-Shearwave Imaging™ for different fibrosis stages.



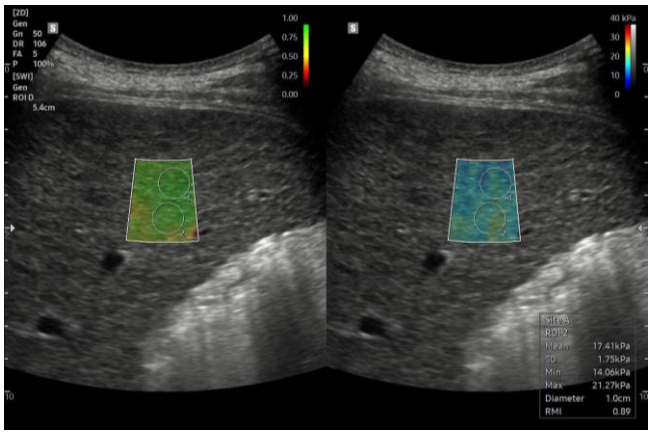
(a) F1 patient with median stiffness of 6.78 kPa



(b) F2 patient with median stiffness of 8.48 kPa



(c) F3 patient with median stiffness of 9.55 kPa



(d) F4 patient with median stiffness of 16.29 kPa

Figure 6. Some sample images of 2D-SWE and median stiffness values by V8 S-Shearwave Imaging™ (a) F1, (b)F2, (c) F3, and (d) F4.

Conclusion

S-Shearwave Imaging™ measurements showed excellent reproducibility and correlation with MRE values. In addition, S-Shearwave Imaging™ demonstrates diagnostic performance better than that of TE and APRI. In conclusion, V8 S-Shearwave Imaging™ is a good and reliable tool in estimating liver fibrosis, and helpful in medical practices in many clinical environments.

Supported Systems

- V8/XV8
- H8/XH8
- RS9/XR9
- V7/XV7

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