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Research Article

Comparison of the Accuracy of Shear Wave Elastography and Acoustic Radiation Force Impulse in Determining Liver Fibrosis among Patients with Chronic Liver Disease

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Abstract

Objective: Compare the accuracy of Shear Wave Elastography (SWE) and Acoustic Radiation Force Impulse (ARFI) in determining liver fibrosis among patients with chronic liver disease.

Methods: Prospective study conducted between March-July 2012. SWE, ARFI and ultrasound-guided liver biopsy were performed on 120 patients. Liver fibrosis using Knodell's histologic activity index and AUROC were determined for F0-F1 vs. F2-F4, F0-F2 vs. F3-F4, and F0-F3 vs. F4. SPSS 16.0, OpenEpi 2.3.1, and Stata 11.0 software were utilized in the statistical analysis.

Results: AUROCs were 0.858 (ARFI) and 0.893 (SWE), 0.944 (ARFI) and 0.95 (SWE), and 0.919 (ARFI) and 0.965 (SWE), between F0 - F1 vs. F2 - F4, F0 - F2 vs. F3 - F4, and F0 - F3 vs. F4, respectively. ARFI has a sensitivity and specificity of 87.5% (64 - 96.5) and 84.6% (76.5 - 90.3), 95.8% (79.8 - 99.3) and 78.1% (68.9 - 85.2), 91.3% (79.7 - 96.6) and 43.2% (32.6 - 54.6) for F4 vs. F0 - F3, F3 - F4 vs. F0 - F2, and F2 - F4 vs. F0 - F1. SWE has a sensitivity and specificity of 100% (80.6 - 100) and 83.7% (75.4 - 89.5), 95.8% (79.7 - 99.3) and 85.4% (77 - 91.1), and 78.3% (64.4 - 87.7) and 86.5% (76.9 - 92.5).

Conclusion: SWE is more accurate in assessing liver cirrhosis. Both sensitivity and specificity of ARFI and SWE increased with the severity of liver fibrosis. SWE is more sensitive between F4 vs. F0 - F3 and more specific between F3 - F4 vs. F0 - F2 and F2 - F4 vs. F0 - F1. ARFI is more specific between F4 vs. F0 - F3 and more sensitive between F2 - F4 vs. F0 - F1. Differences in estimates between SWE and ARFI were statistically significant between F0 - F1 and F2 - F4. Thus, both SWE and ARFI can be used as non-invasive tools in detecting liver fibrosis.

Keywords: *Shear Wave Elastography; Acoustic Radiation Force Impulse; Liver Fibrosis; Chronic Liver Disease*

Introduction

Background

The prognosis of chronic liver diseases (CLD) depends on the extent of liver fibrosis. Liver fibrosis is the excessive accumulation of extracellular matrix proteins including collagen that occurs in most types of chronic liver diseases. Advanced liver fibrosis results in cirrhosis, liver failure and portal hypertension and often requires liver transplantation [1]. The annual incidence of hepatocellular carcinoma, decompensation, and death is approximately 3%, 4%, and 3% respectively in patients with compensated liver cirrhosis.

Review of Literature

Liver biopsy is a cornerstone in the evaluation and management of patients with liver disease and has long been considered to be an integral component of the clinician's diagnostic armamentarium [2]. It is a generally safe but costly procedure that carries a small risk of severe complications. Sampling error is common because only 1/50,000 of the organ is analyzed, resulting in up to 30% of false-negative results. The emergence of new noninvasive techniques for assessment of liver fibrosis has posed a major challenge. Liver stiffness measurement (LSM) has been demonstrated to be a reliable tool for assessing hepatic fibrosis and cirrhosis mainly in patients with chronic hepatitis C but additional studies have evaluated the accuracy of LSM in diagnosing liver fibrosis in patients with chronic liver disease of various causes and in patients with cholestatic liver diseases.

Acoustic radiation force impulse (ARFI) imaging is a noninvasive method to evaluate liver fibrosis. It relies on the mechanical excitation of tissue by providing localized, impulsive, acoustic radiation force. This results in shear-wave propagation away from the region of excitation. However, it is also a one-dimensional technique but has been integrated onto a conventional ultrasound imaging system and it has other limitations such as:

- There is no elasticity map of tissue produced by this technique,
- The elasticity measurement is not real time,
- The elasticity measurement cannot be performed retrospectively,
- Only one single acquisition can be acquired at a time,
- The evaluated area of parenchyma is a small pre-determined size and cannot be modified,
- Only the average of the elasticity in the ROI is calculated, without any information on standard deviation,
- Excessive transducer heating is prevented by limiting the frequency and magnitude of push pulses, which in turn restricts the possible depth of the ROI.

Shear wave elastography (SWE) is a two-dimensional, real time, quantitative, imaging of tissue elasticity in combination with conventional ultrasound imaging. It relies on the measurement of the shear wave propagation speed in soft tissue; it does not require an external vibrator to generate the shear wave. It is based on the generation of a radiation force in the tissue to create the shear wave. The ultrasound probe of the device produces a very localized radiation force deep in the tissue of interest. This radiation force/push induces a shear wave, which then propagates from this focal point. Several focal points are then generated almost simultaneously, in a line perpendicular to the surface of the patient's skin creating a conical shear wave front, which sweeps the image plane, on both sides of the focal point. The progression of the shear wave is captured by the very rapid acquisition of ultrasound images (up to 20,000 images per second), called UltraFast imaging. The acquisition takes only a few milliseconds, thus the patient or operator movement does not impact the result. A high-speed acquisition is necessary to capture the shear wave as it moves at a speed in the order of 1 to 10 m/s. A comparison of 2 consecutive ultrasound images allows the measurement of displacements induced by the shear wave and creates a "movie" showing the propagation of the shear wave whose local speed is intrinsically linked to elasticity. The propagation speed of the shear wave is then estimated from the movie that is created and a real-time 2-dimensional color map is displayed, for which each color-codes the shear wave speed. This color map is accompanied by an anatomic reference gray scale (or B-mode) image. This imaging technique is a real-time imaging mode.

Objectives of the Study

Research Question

How accurate is SWE compared to ARFI imaging in detecting liver fibrosis among patients with chronic liver disease using liver biopsy as the reference standard?

General Objective

To compare the accuracy of SWE versus ARFI in determining liver fibrosis among patients with chronic liver disease.

Specific Objective

1. To determine the accuracy of ARFI in determining liver fibrosis using liver biopsy as the reference standard among patients with chronic liver disease.
2. To determine the accuracy of SWE in determining liver fibrosis using liver biopsy as the reference standard among patients with chronic liver disease.

Patients and Methods

Patients

This is a two center, prospective, cohort study. Between March 2012 and July 2012, 120 patients with confirmed history of chronic liver disease were enrolled in the study. Patients underwent a series of blood tests inclusive of complete blood count, prothrombin time, serum aminotransferases, bilirubin and alpha-fetoprotein. Patients with history of hepatitis B or C underwent hepatitis profile, HBV DNA, HCV RNA and genotyping whenever applicable. All patients included in the study underwent liver biopsy, ARFI and SWE in the Liver Disease and Transplant Center of St. Luke's Medical Center - Quezon City and Global City. Inclusion criteria were patients ages 18 and above, both of male and female sex and diagnosed to have chronic liver disease (Hepatitis B, Hepatitis C, Non-alcoholic fatty liver disease). Patients with severe comorbidities such as history of cerebrovascular disease, severely decompensated chronic liver disease (Child Pugh C), history of cancer of any source besides hepatocellular carcinoma and history of chemotherapy for other malignancies were excluded from enrollment. Patients' characteristics, epidemiological data and biochemical tests were recorded. Liver biopsy was performed within 3 months from the day SWE and ARFI imagings were done. Two hepatologists, independently performed the liver biopsy. Two liver pathologists independently interpreted the liver biopsy results. Two liver ultrasound technologists performed real-time SWE and ARFI imaging. All study personnel involved in the study were blinded to the patients' results. The Institutional Ethical Research Committee and the Institutional Scientific Research Committee approved the study protocol. Patients were enrolled after providing their written and informed consent. This study was not sponsored by any real-time SWE or ARFI imaging manufacturer.

Inclusion Criteria

1. Patients ages 18 and above
2. Male and female sex
3. Diagnosed with Chronic Liver Disease (Hepatitis B, Hepatitis C, Non-alcoholic fatty liver disease).

Exclusion Criteria

1. Serious comorbidities (cerebrovascular accident)
2. Severe decompensation of chronic liver disease (Child Pugh C)
3. History of cancer
4. History of chemotherapy.

Variables to be investigated

1. Age and sex
2. Liver stiffness using Knodell's Histologic Activity index and fibrosis scoring among SWE, ARFI and liver biopsy.

Liver Stiffness Measurement

Real-Time SWE and Acoustic Radiation Force Impulse imaging

Real-time SWE and ARFI imaging studies were performed using Supersonic Aixplorer and Siemens Acuson S2000 respectively. Measurements were performed on the right lobe of the liver, through intercostal spaces with the patient lying in supine position with the right arm in maximal abduction. The same intercostal space was used for SWE, ARFI and liver biopsy. Fibrosis on real time SWE and ARFI imaging were graded as follows: F0 - 1.0 m/s, F1 - 1.185 m/s, F2 - 1.215 m/s, F3 - 1.54 m/s, F4 - 1.94 m/s and F0 - 6 kPa, F1 - 7-8 kPa, F2 - 9-10.5 kPa, F3 - 11-12 kPa, F4 - 12.5 kPa, respectively. This modulus was extrapolated from previous literatures on SWE and ARFI and was validated. Fibrosis scores were defined as having no fibrosis (F0), mild fibrosis (F1), significant fibrosis (F2), severe fibrosis (F3) and cirrhosis (F4) [3].

Liver biopsy and Histopathology

Ultrasound guided liver biopsy was performed by two experienced hepatologists by using an intercostal approach. The same intercostal space, which was used for SWE and ARFI measurements, was used for liver biopsy. A disposable Sonopsy-C1 Hakko sonoguide Chiba biopsy needle type-C1 G18 or G21. Liver tissue samples obtained measured between 0.5 cm to 4.5 cm in length. Two liver pathologists blinded to the results of both ARFI and real-time SWE, but not to the patient's clinical and biochemical data read the specimens on site. Liver fibrosis was evaluated according to Knodell's histologic activity index and the Metavir score. Knodell's histologic activity index graded fibrosis as follows: 0 - no fibrosis, 1 - fibrous portal expansion, 3 - bridging fibrosis (portal-portal or portal-central linkage) and 4 - cirrhosis [4].

Statistical Analysis

Descriptive statistics were produced for demographic, clinical and laboratory characteristics for this study sample of patients. Data were presented as means and standard deviations or as medians and interquartile ranges; whichever was more appropriate, for continuous variables, and in frequencies and proportions for categorical variables. The Spearman's rank coefficient and Pearson's correlation coefficient tests were used to determine correlations between ordinal and continuous variables, respectively. The Kruskal Wallis and Friedman's tests were used to compare medians between real-time SWE and ARFI among different fibrosis stages. A frequency distribution was obtained for choosing optimal cut-off values of real-time SWE and ARFI to maximize the sum of sensitivity and specificity for different fibrosis thresholds: F0 - F1 (no to mild fibrosis) vs. F2 - F4 (significant fibrosis to cirrhosis), F0 - F2 (no to significant fibrosis) vs. F3 - F4 (severe fibrosis to cirrhosis) and F0 - F3 (no to severe fibrosis) vs. F4 (cirrhosis). Using receiver operating characteristic (ROC) curves and the area under the ROC (AUROC) curve analysis assessed the diagnostic performance of real-time SWE and ARFI, and their combinations. All tests were two-tailed and considered significant at $p < 0.05$. The SPSS 16.0, OpenEpi 2.3.1, and Stata 11.0 softwares were utilized in the statistical analysis.

Results

Patients

One hundred and thirty-nine patients were eligible during the recruitment period. A total of 19 patients were excluded because of the following: 1 patient had a cerebrovascular accident, 15 patients refused to undergo liver biopsy, 1 patient was not allowed by family members to undergo liver biopsy, 1 patient was diagnosed to have pancreatic cancer, and 1 patient had thrombocytopenia due to chronic liver disease. A total of 120 patients met the inclusion criteria. The demographic and biochemical profile of the 120 patients included are summarized in table 1. There were 48 men and 72 women. Mean length of liver biopsy specimens was 2 cm (range 0.8 - 4.0). Patients included were distributed to the following chronic liver diseases as follows: 38 had hepatitis B, 4 had hepatitis C, 2 had hepatitis B and C, 23 had hepatitis B and non-alcoholic steatohepatitis (NASH), 1 had hepatitis B, hepatitis C and NASH, 3 had hepatitis B and schistosomiasis, 1 had hepatitis B, NASH and schistosomiasis, 2 had autoimmune hepatitis, 1 had hepatic tuberculosis, 36 had NASH, 1 had NASH and auto-

immune hepatitis, 1 had NASH and schistosomiasis, 3 had schistosomiasis alone, 3 had cryptogenic cirrhosis and 1 had hemochromatosis. Table 2a shows that there is statistically significant correlation between ARFI and SWE with a Pearson correlation of 0.850 and a p value of < 0.001 and vice versa. The patient's INR, SGPT, total bilirubin and serum ferritin are positively correlated with ARFI values signifying that as these values increase, ARFI measurement increases and as the value decreases, ARFI measurement decreases. The patient's platelet count and albumin levels are negatively correlated with ARFI measurements signifying that as one value increases, the ARFI measurement decreases and vice versa. The patient's INR, SGPT and total bilirubin levels are positively correlated with SWE measurements. Similar with ARFI, the patient's platelet count and albumin levels are negatively correlated with the SWE measurements. Table 2b shows that statistically there are good correlation between ARFI and SWE fibrosis score with histopathology with a Spearman's rank coefficient ρ of 0.661.

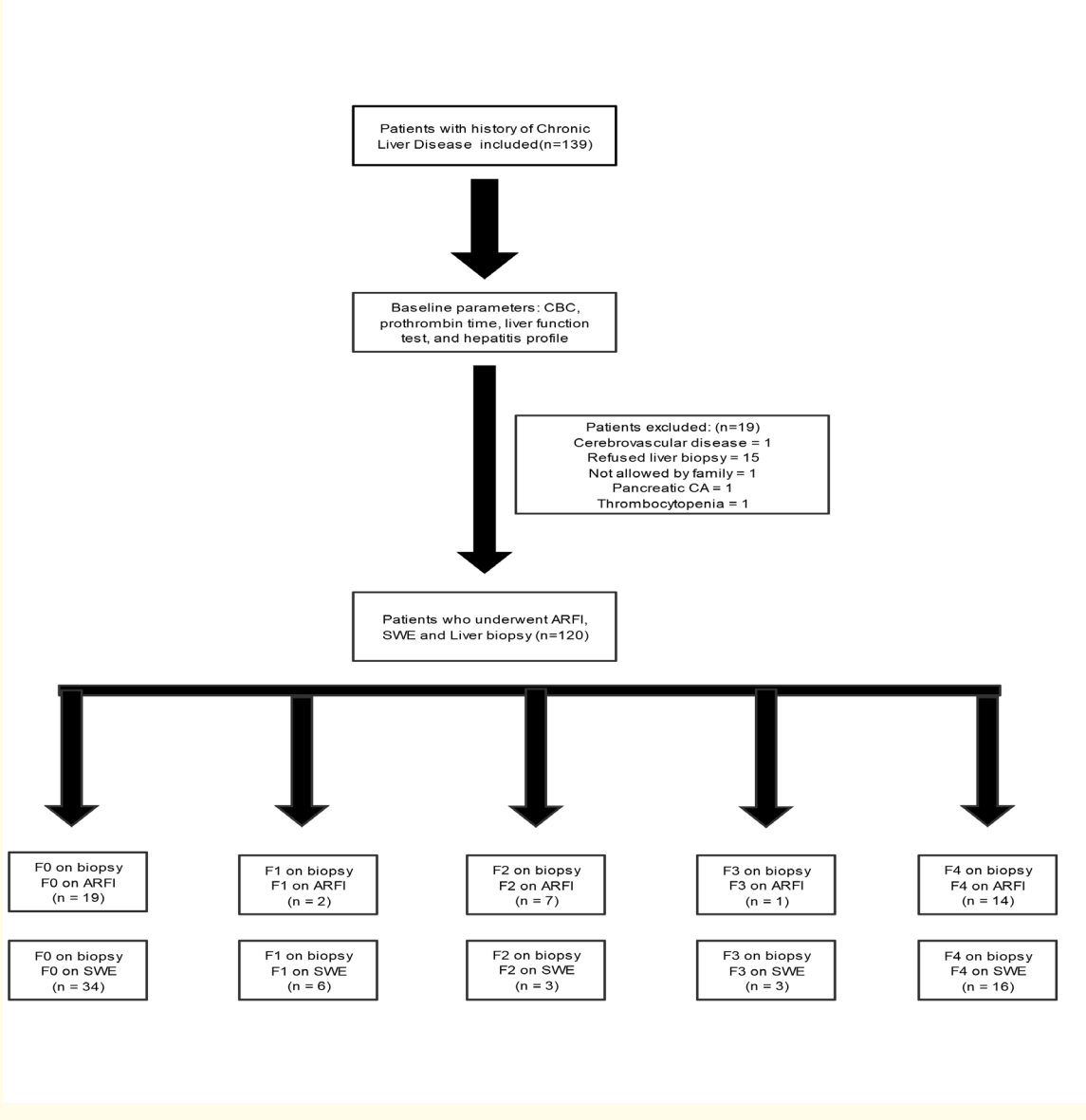


Figure 1: *Data Collection and Processing.*

Characteristic	N= 120
Age, years (SD; range)	48.8 (12.9; 21.0 - 77.0)
Sex, male (%)	48 (40)
Sex, female (%)	72 (60)
BMI, kg/m^2 (IQR; range)	25.7 (23.0 - 29.1; 15.6 - 45.8)
Platelet (SD; range)	219,858 (71,666.3; 61,200 - 380,000)
INR (IQR; range)	1.0 (1.0 - 1.1; 0.9 - 1.9)
SGPT, U/L (IQR; range)	60 (44 - 94; 23 - 661)
Total bilirubin, mg/dl (IQR; range)	0.7 (0.5 - 1.1; 0.2 - 18.7)
Albumin, g/dl (IQR; range)	3.8 (3.5 - 4.0; 1.9 - 4.6)
Alpha fetoprotein, ng/ml (IQR; range)	3.3 (2.2 - 6.5; 0.9 - 67,496)
ARFI, m/s (IQR; range)	1.4 (1.2 - 1.9; 1.0 - 4.1)
SWE, kPa (IQR; range)	7.5 (6.2 - 13.6; 4.2 - 57.5)
HBV DNA IU/ml (%)	
< 2,000	25 (36.8)
2,000 - 20,000	8 (11.8)
20,001 - 2,000,000	5 (7.4)
> 2,000,000	6 (8.8)
DNA not detected	18 (26.5)
HCV RNA (%)	
< 800,000	1 (14.3)
> 800,000	3 (42.9)
HCV RNA not detected	1 (14.3)
Length of liver biopsy specimen, cm (Mean; range)	2 (0.8 - 4.0)
ARFI fibrosis score	
F0 (%)	27 (22.5)
F1 (%)	9 (7.5)
F2 (%)	40 (33.3)
F3 (%)	14 (11.7)
F4 (%)	30 (25.0)
SWE fibrosis score	
F0 (%)	51 (42.5)
F1 (%)	23 (19.2)
F2 (%)	9 (7.5)
F3 (%)	4(3.3)
F4 (%)	33 (27.5)
Histopathology fibrosis score	
F0 (%)	48 (40.0)
F1 (%)	25 (20.8)
F2 (%)	22(18.3)
F3 (%)	8 (6.7)
F4 (%)	17 (14.2)

Table 1: *Demographic and biochemical profile of patients.*

Biochemical tests	N	ARFI, m/s		SWE, kpa	
		Pearson Correlation	p value	Pearson Correlation	p value
Platelet	119	-0.429	< 0.001	-0.379	< 0.001
INR	119	0.519	< 0.001	0.537	< 0.001
SGPT, U/L	120	0.279	0.002	0.213	0.020
Total bilirubin, mg/dl	120	0.356	< 0.001	0.311	0.001
Albumin, g/dl	120	-0.475	< 0.001	-0.602	< 0.001
GGT	3	0.997	0.051	0.548	0.631
Serum ferritin	76	0.331	0.004	0.220	0.057
Alpha fetoprotein, ng/ml	116	-0.017	0.860	-0.033	0.723

Table 2a: *Correlation between ARFI or SWE measurements and biochemical tests.*

Tests	N	Spearman's rank coefficient rho	p value
Histopathology and ARFI fibrosis score	120	0.661	< 0.001
Histopathology and SWE fibrosis score	120	0.689	< 0.001

Table 2b: *Correlation between histopathology scores and ARFI or SWE.*

Liver Stiffness and Measurement

Median values, IQR, range and p values of measurements obtained for each fibrosis stage with SWE and ARFI are shown in Table 3. Table 4a and 4b shows the concordance rate of real-time SWE and ARFI versus histopathology fibrosis score. Overall, ARFI imaging correctly classified 35.8% of patients and SWE correctly classified 51.7% of patients. ARFI imaging correctly classified 19 out of 50 (70.4%) F0 patients, 2 out of 24 (22.2%) F1 patients, 7 out of 22 (17.5%) F2 patients, 1 out of 8 (7.1%) F3 patients and 14 out of 16 (46.7%) F4 patients. SWE on the other hand, correctly classified 34 out of 50 (66.7%) F0 patients, 6 out of 24 (26.1%) F1 patients, 3 out of 22 (33.3%) F2 patients, 3 out of 8 (75%) F3 patients and 16 out of 16 (48.5%) F4 patients. The concordance rates were relatively higher for SWE than ARFI imaging. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, positive likelihood ratio (+LR), and negative likelihood ratio (-LR) of the optimal cut-off values for each fibrosis stage are found in Table 5. Figures 3A to C shows the receiver operating characteristics (ROCs) for cirrhosis (F4), severe and significant fibrosis (F3, F2), mild and no fibrosis (F1, F0). ARFI presents to be a good test in determining liver fibrosis with an AUC of 0.858 for F0-F1 (no to mild fibrosis) vs. F2 - F4 (significant fibrosis to cirrhosis), AUC of 0.944 for F0 - F2 (no to significant fibrosis) vs. F3 - F4 (severe fibrosis to cirrhosis) and AUC of 0.919 for F0-F3 (no to severe fibrosis) vs. F4 (cirrhosis). SWE presents to be an excellent test in determining liver fibrosis with an AUC of 0.893 for F0-F1 (no to mild fibrosis) vs. F2 - F4 (significant fibrosis to cirrhosis), AUC of 0.950 for F0 - F2 (no to significant fibrosis) vs. F3 - F4 (severe fibrosis to cirrhosis) and AUC of 0.965 F0 - F3 (no to severe fibrosis) vs. F4 (cirrhosis). The accuracy of both ARFI and SWE in detecting liver fibrosis increased as the degree of liver fibrosis increased. Table 6 shows the ROCs for each level of fibrosis by real-time SWE over ARFI. Overall, ARFI and SWE have good to excellent accuracy in determining the presence of significant fibrosis, severe fibrosis and cirrhosis. However, SWE was more accurate in determining significant fibrosis (F2 - F4), severe fibrosis (F3 - F4) and cirrhosis (F4) over ARFI and a statistically significant improvement was only observed in determining cirrhosis (F4) with a p value of 0.041.

Elastography by histopathology score	Valid N	Median	IQR	Range	Friedman p value
All stages					< 0.001
ARFI, m/s	50	1.2	1.1 - 1.4	1.0 - 2.7	
SWE, kpa	50	6.3	5.2 - 7.2	4.2 - 39.4	
Fibrosis score					
F0					< 0.001
ARFI, m/s	50	1.2	1.1 - 1.4	1.0 - 2.7	
SWE, kpa	50	6.3	5.2 - 7.2	4.2 - 39.4	
F1					< 0.001
ARFI, m/s	24	1.3	1.2 - 1.5	1.0 - 1.9	
SWE, kpa	24	6.9	6.0 - 8.8	4.9 - 14.1	
F2					< 0.001
ARFI, m/s	22	1.5	1.3 - 2.0	1.0 - 2.7	
SWE, kpa	22	10.2	7.4 - 16.7	5.8 - 28.0	
F3					0.002
ARFI, m/s	8	2.4	2.0 - 3.1	1.4 - 4.1	
SWE, kpa	8	14.9	11.4 - 24.6	7.7 - 48.3	
F4					< 0.001
ARFI, m/s	16	2.5	2.0 - 3.0	1.6 - 4.1	
SWE, kpa	16	30.7	24.4 - 38.3	13.5 - 57.5	

Table 3: *Median values, IQR, range and p values of Measurements obtained for each Fibrosis stage with SWE and ARFI.*

Elastography	Histopathology fibrosis score					Total	Concordance rate (95% CI)
	F0 (n = 50)	F1 (n = 24)	F2 (n = 22)	F3 (n = 8)	F4 (n = 16)		
ARFI							
F0	19	6	2	0	0	27	70.4% (51.4% - 85.2%)
F1	5	2	2	0	0	9	22.2% (3.9% - 56.2%)
F2	23	9	7	1	0	40	17.5% (8.0% - 31.6%)
F3	1	7	3	1	2	14	7.1% (0.4% - 30.5%)
F4	2	0	8	6	14	30	46.7% (29.5% - 64.4%)
SWE							
F0	34	12	5	0	0	51	66.7% (52.9% - 78.5%)
F1	12	6	4	1	0	23	26.1% (11.3% - 46.6%)
F2	2	4	3	0	0	9	33.3% (9.3% - 66.8%)
F3	0	1	0	3	0	4	75.0% (24.2% - 98.8%)
F4	2	1	10	4	16	33	48.5% (31.9% - 65.3%)

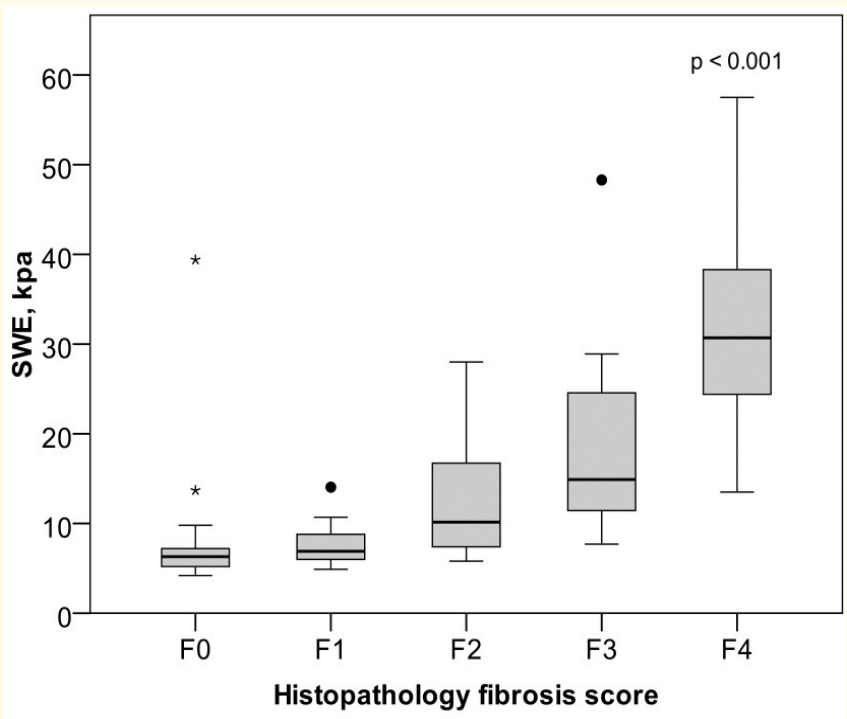
Table 4a: *Concordance rates of ARFI and SWE versus histopathology fibrosis score.*

	ARFI (95% CI)	SWE (95% CI)
Overall concordance rate	35.8% (28.9% - 43.3%)	51.7% (44.2% - 59.1%)
Kappa	0.187	0.340
P value	< 0.001	< 0.001

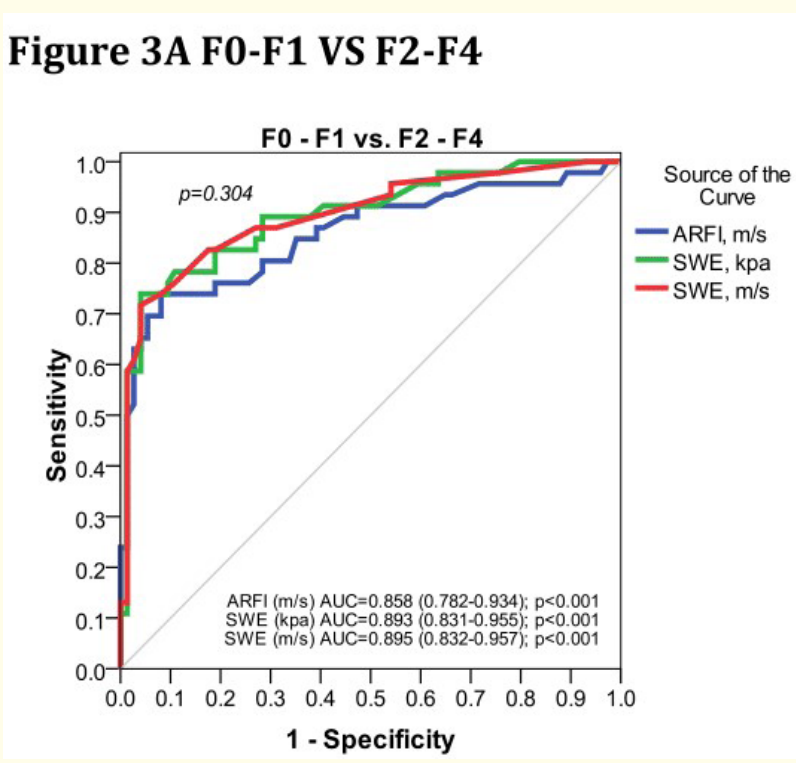
Table 4b: *Overall Concordance rates of ARFI and SWE versus histopathology fibrosis score.*

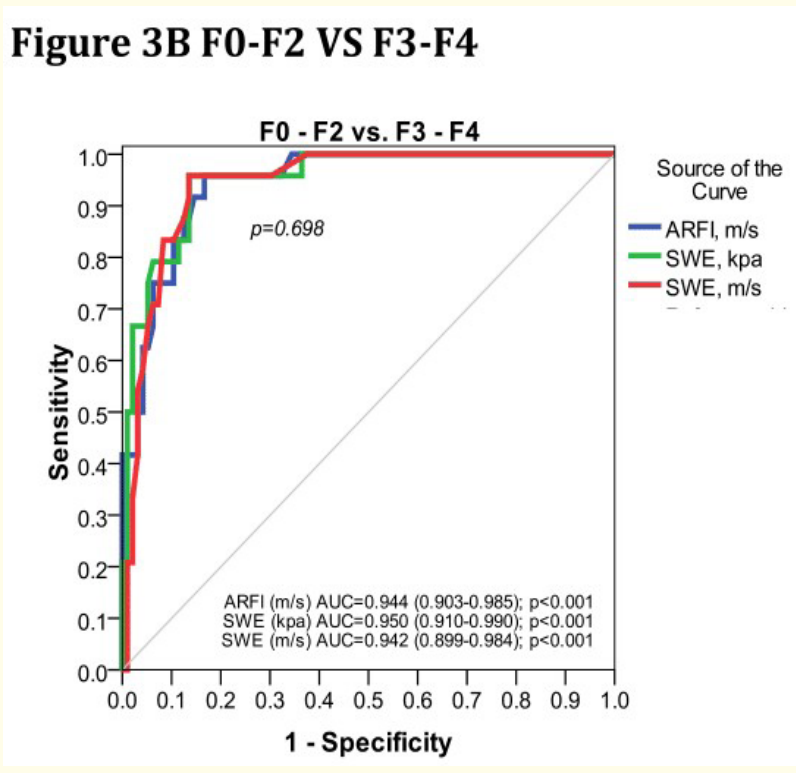
Elastography	Histopathology fibrosis score		Total	Sn (95% CI)	Sp (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)	LR+ (95% CI)	LR - (95% CI)
	F4	F0 - F3								
ARFI				**87.5%** (64.0 - 96.5)	**84.6%** (76.5 - 90.3)	46.7% (30.2 - 63.9)	97.8% (92.3 - 99.4)	85.0% (77.5 - 90.3)	5.69 (4.92 - 6.56)	0.15 (0.06 - 0.40)
F4	14	16	30							
F0 - F3	2	88	90							
Total	16	104	120							
SWE				**100.0%** (80.6 - 100.0)	**83.7%** (75.4 - 89.5)	48.5% (32.5 - 64.8)	100.0% (95.7 - 100.0)	85.8% (78.5 - 91.0)	6.12 (5.45 - 6.86)	0.00 (0.0 - '?')
F4	16	17	33							
F0 - F3	0	87	87							
Total	16	104	120							
	F3 - F4	**F0 - F2**								
ARFI				**95.8%** (79.8 - 99.3)	**78.1%** (68.9 - 85.2)	52.3% (37.9 - 66.2)	98.7% (92.9 - 99.8)	81.7% (73.8 - 87.6)	4.38 (3.98 - 4.83)	0.05 (0.01 - 0.38)
F3 - F4	23	21	44							
F0 - F2	1	75	76							
Total	24	96	120							
SWE				**95.8%** (79.7 - 99.3)	**85.4%** (77.0 - 91.1)	62.2% (46.1 - 75.9)	98.8% (93.5 - 99.8)	87.5% (80.4 - 92.3)	6.57 (5.69 - 7.59)	0.05 (0.01 - 0.35)
F3 - F4	23	14	37							
F0 - F2	1	82	83							
Total	24	96	120							
	F2 - F4	**F0 - F1**								
ARFI				**91.3%** (79.7 - 96.6)	**43.2%** (32.6 - 54.6)	50.0% (39.5 - 60.5)	88.9% (74.7 - 95.6)	61.7% (52.7 - 69.9)	1.61 (1.53 - 1.69)	0.20 (0.11 - 0.36)
F2 - F4	42	42	84							
F0 - F1	4	32	36							
Total	46	74	120							
SWE				**78.3%** (64.4 - 87.7)	**86.5%** (76.9 - 92.5)	78.3% (64.4 - 87.7)	86.5% (76.9 - 92.5)	83.3% (75.6 - 88.9)	5.79 (4.69 - 7.15)	0.25 (0.21 - 0.31)
F2 - F4	36	10	46							
F0 - F1	10	64	74							
Total	46	74	120							

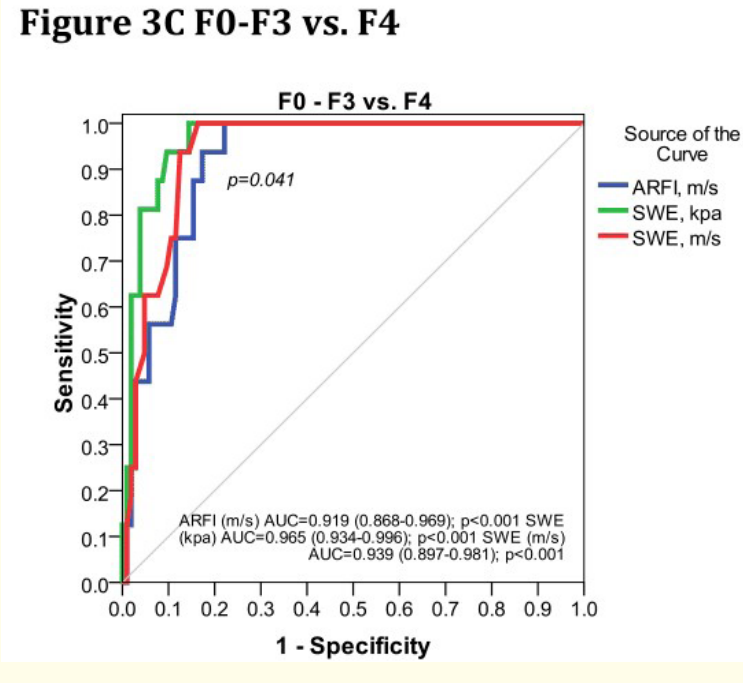
Table 5: *Diagnostic performance of ARFI and SWE versus histopathology fibrosis scores.*



Figures 2A and 2B: *The Box-and-Whisker plots of (2A) ARFI and (2B) SWE values for each histopathology score in relation to fibrosis. Liver stiffness values measured in kpa are on the y-axis and histopathology fibrosis scores are on the x-axis. The central box represents values from the lower to upper quartile (25th- 75th percentile). The line through each box represents the median. Error bars show minimum and maximum non-extreme values. * and •, extreme values or outliers.*







Figures 3A-C: *Ahows the ROCs for cirrhosis (F4), severe and significant fibrosis (F3, F2), and mild to no fibrosis (F1, F0).*

Test	AUC	95% CI AUC	P value*	Comparison of AUC
				p value
F0 - F1 vs. F2 - F4				**0.304**
ARFI (m/s)	0.858	0.782 - 0.934	<0.001	0.124
SWE (kpa)	0.893	0.831 - 0.955	<0.001	0.170
F0 - F2 vs. F3 - F4				**0.698**
ARFI (m/s)	0.944	0.903 - 0.985	<0.001	0.648
SWE (kpa)	0.950	0.910 - 0.990	<0.001	0.847
F0 - F3 vs. F4				**0.04**1
ARFI (m/s)	0.919	0.868 - 0.969	<0.001	0.024
SWE (kpa)	0.965	0.934 - 0.996	<0.001	0.284

Table 6: *Receiver Operating Characteristic (ROC) for the different stages of fibrosis.*

Discussion

In this study, the diagnostic accuracy of real-time SWE and ARFI in determining liver fibrosis was compared to histopathology among patients with chronic liver disease. Real-time SWE was more accurate compared to ARFI in assessing significant fibrosis, severe fibrosis and cirrhosis. However, real-time SWE demonstrated statistically significant improvement in determining cirrhosis over ARFI. The AUCs in differentiating cirrhosis (F4) from no or severe fibrosis (F0 - F3) were 0.910 and 0.965, respectively with a significant p value of 0.041. No significant difference was observed between AUCs of ARFI and real-time SWE for significant fibrosis (0.858 and 0.893, respectively) and severe fibrosis (0.944 and 0.950, respectively). These results suggest that real-time SWE can be used in the same way as ARFI is being used for the assessment of significant and severe fibrosis with the benefit of improved assessment of cirrhosis. Both real-time SWE and ARFI are integrated into a conventional diagnostic ultrasound system and can make use of real-time B-mode imaging for the assessment of morphologic changes or detection of focal liver lesions such as hepatocellular carcinoma. The use of the B-mode image for guidance is also helpful to improve variability in stiffness measurements. Real-time SWE has two advantages over ARFI. First, real-time SWE has improved separation of fibrosis stages as a result of the use of shear waves with greater bandwidths. Secondly, it provides a real-time quantitative map of liver tissue stiffness. The spatial heterogeneity of liver stiffness can be visualized, and the size of the region used for a measurement can be selectively placed or adjusted. This results in physiological variations of liver fibrosis that can be averaged to better represent the fibrosis state. The region of interest for liver stiffness measurements can be adjusted in size and location to avoid artifacts, such as those arising around larger pulsating blood vessels. The real-time acquisition of real-time SWE enables user adjustment during acquisition for targeting a homogenous region of liver tissue. This ensures that excessive liver motion is avoided during real-time SWE acquisitions [5].

This study demonstrated that real-time SWE correctly classifies cirrhosis (F4) from no to severe fibrosis (F0 - F3) with a sensitivity of 100% and specificity of 83.7%, severe fibrosis to cirrhosis (F3 - F4) from no to significant fibrosis (F0 - F2) with a sensitivity of 95.8% and specificity of 85.4%, and significant fibrosis to cirrhosis (F2 - F4) from no to mild fibrosis (F0 - F1) with a sensitivity of 78.3% and specificity of 86.5%. It also shows that ARFI correctly classifies cirrhosis (F4) from no to severe fibrosis (F0 - F3) with a sensitivity of 87.5% and specificity of 84.6%, severe fibrosis to cirrhosis (F3 - F4) from no to significant fibrosis (F0 - F2) with a sensitivity of 95.8% and specificity of 78.1%, and significant fibrosis to cirrhosis (F2 - F4) from no to mild fibrosis (F0 - F1) with a sensitivity of 91.3% and specificity of 43.2%. It has been suggested that most discordant results between elastography and histopathology were caused by histology measurement failures. Even though, liver biopsy is still considered as the benchmark for validation of noninvasive techniques aimed at assessing degree of liver fibrosis, sampling errors and intra- and inter-observer variability challenge the accuracy of liver biopsy examination. Although distribution of fibrosis in the liver is heterogeneous, histological staging is based on a biopsy specimen that represents,

at most 1/50,000th of the total liver mass [6]. Determining the severity of liver fibrosis aids in the decision whether treatment should be initiated in a patient with chronic liver disease. Prompt treatment is warranted among patients with advanced fibrosis and should be strongly considered for those with significant fibrosis.

The limitations of the study are as follows: first, there is a variable distribution of patients for the different stages of fibrosis, particularly for F3. Second, there are a relatively small number of patients included in the study, hence, it is recommended to validate these results on larger studies.

Conclusion

The results of this study show that real-time SWE was more accurate than ARFI in assessing liver cirrhosis (F4). The accuracy, sensitivity and specificity of both ARFI and SWE increased as the degree of liver fibrosis increased. ARFI and SWE had equal sensitivity in the determining liver fibrosis between F3 - F4 (severe fibrosis to cirrhosis) vs. F0 - F2 (no to significant fibrosis) while ARFI had a higher specificity in determining liver fibrosis between F4 (cirrhosis) vs. F0 - F3 (no to severe fibrosis) and a higher sensitivity in determining liver fibrosis between F2 - F4 (significant fibrosis to cirrhosis) vs. F0 - F1 (no to mild fibrosis). SWE has a higher sensitivity compared to ARFI in detecting liver fibrosis between F4 (cirrhosis) vs. F0 - F3 (mild to severe fibrosis). SWE also has a higher specificity compared to ARFI in detecting liver fibrosis between F3 - F4 (severe fibrosis to cirrhosis) vs. F0 - F2 (no to significant fibrosis) and F2 - F4 (significant fibrosis to cirrhosis) vs. F0 - F1 (no to mild fibrosis). However, differences in estimates between ARFI and SWE in comparing liver fibrosis were only statistically significant between F0 - F1 (no to mild fibrosis) and F2 - F4 (significant fibrosis to cirrhosis). Thus, both SWE and ARFI can be used as a non-invasive tool in detecting liver fibrosis.

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