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Validation of Shear-wave Elastography Cutoff Values on the Supersonic Aixplorer for Practical Clinical Use in Liver Fibrosis Staging

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Abstract

The purpose of this study was to determine the validity of previously established ultrasound shear-wave elastography (SWE) cutoff values (F2 fibrosis) on an independent cohort of patients with chronic liver disease. In this IRB approved, HIPAA compliant cross-sectional study, a total of 338 patients undergoing liver biopsy underwent SWE using an Aixplorer ultrasound machine (Supersonic Imagine). Median SWE values were calculated from sets of 10 elastograms. A single blinded pathologist evaluated METAVIR fibrosis staging as the gold standard. 277 subjects with a mean age of 48 years were analyzed. On pathological examination, 212 (76.5%) subjects had F0–F1 fibrosis, while 65 had F2 fibrosis (23.5%). Spearman's correlation of fibrosis with SWE was 0.456 ($p < 0.001$). A cutoff value of 7.29 kPa yielded sensitivity of 95.4% and specificity of 50.5% for the diagnosis of METAVIR stage F2 liver fibrosis in patients with liver disease using the Supersonic Aixplorer SWE system.

Keywords

Liver biopsy; Noninvasive imaging; Fibrosis; Elastography; Validated cutoff values

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INTRODUCTION

Hepatitis C viral disease (HCV), hepatitis B viral disease (HBV), nonalcoholic fatty liver disease (NAFLD), autoimmune hepatitis (AIH) and alcoholic liver disease (ALD) are forms of chronic liver disease (CLD) that share a common pathway of progressive liver fibrosis, which may ultimately culminate in cirrhosis (Sebastiani et al. 2011). Management of these various forms of CLD is centered on attempts to reverse early fibrosis and prevent progression to cirrhosis. While non-focal liver biopsy is currently the reference standard for fibrosis staging in patients with known liver disease, it is invasive, expensive, morbid, and limited by inter-observer variability and sampling error (Regev et al. 2002).

Various imaging techniques including morphologic analysis, CT-perfusion analysis (Ronot et al. 2010), MR-perfusion analysis (Hagiwara et al. 2008), water diffusion imaging (Bonekamp et al.; Wang et al. 2012) and elastography have been shown to predict liver fibrosis stage with varying degrees of accuracy. As a noninvasive, inexpensive and portable technique, ultrasound elastography has shown promising results (Chon et al. 2012; Friedrich-Rust et al. 2012; Friedrich-Rust et al. 2008). In particular, shear-wave elastography (SWE) derived estimates of shear-wave speed and hepatic Young's modulus (eYM) have been shown to be related to liver fibrosis stage, (Beland et al. 2014a; Deffieux et al. 2015; Feng et al. 2016; Jeong et al. 2014; Sporea et al. 2014; Tada et al. 2015; Zheng et al. 2015) and cutoff eYM or shear-wave speed values for different liver fibrosis stages have been proposed in a number of studies (Beland et al. 2014b; Jeong et al. 2014; Samir et al. 2015). A recent meta-analysis of SWE studies summarizes this dilemma where in 12 manuscripts reviewed have generated 12 different cutoff values for variable sensitivities and specificities (Feng et al. 2016). To date, these cutoff values have not been prospectively validated in data sets independent of those used to generate the cutoff values making it extremely difficult for clinicians to decide on which set of values to base a clinical decision. A recent editorial by experts in the field has also pointed out these challenges from a clinical standpoint (Piscaglia et al. 2016).

The purpose of this study was to evaluate the validity of our previously established estimated liver Young's modulus (eYM) cutoff values for staging liver fibrosis (Samir et al. 2015) in an independent cohort of patients with diffuse liver disease.

MATERIALS AND METHODS

Design overview and study population

This prospective single institution study was approved by the institutional review board (IRB) and compliant with the Health Insurance Portability and Accountability Act (HIPAA). Patients with known or suspected diffuse liver disease scheduled for ultrasound guided non-focal liver biopsy between January 2014 and January 2015 underwent SWE. Patients less than 18 years of age were excluded. The IRB waived the requirement for informed consent as SWE examination is FDA approved and increasingly becoming standard of clinical care, while the liver biopsies were performed as a part of regular clinical care, not related to this research study. Blinded histopathologic assessment of liver fibrosis stage using the METAVIR scoring system was used as the reference standard.

Shear-Wave Elastography (SWE)

SWE was performed using an Aixplorer US system (SuperSonic Imagine S.A., Aix-en-Provence, France) with a convex broadband probe (SC6-1). Liver tissue Young's modulus was expressed in kilopascal (kPa) and mapped as a color-coded two-dimensional SWE image with simultaneous conventional B-mode images. All patients were fasting overnight, as per the requirement of their clinically warranted liver biopsy. Multiple sonographers with varying ultrasound experience and trained in SWE image acquisition performed SWE acquisitions immediately prior to liver biopsy. Each SWE acquisition consisted of 10 sequential measurements obtained in the upper right hepatic lobe via an intercostal approach at end expiration. SWE measurements were obtained at least 1 cm deep to the liver capsule and at a depth of less than 6 cm from the skin surface. Sonographers placed a 10 mm region of interest in the hepatic parenchyma, avoiding blood vessels or portal tracts. The median of the 10 SWE measurements was calculated to represent the liver tissue Young's modulus.

SWE image review

A blinded reviewer with expertise in liver elastography (MD) evaluated all SWE images. An SWE acquisition was marked as poor quality if: (1) a minimum of 8 acquisitions were not made, (2) a poor ROI was placed, such as in the area immediately below the liver capsule (known to cause image artifact, Figure 1a) or images had limited SWE data (Figure 1b); in comparison to an example of a good quality SWE image acquisition with an appropriate ROI placement (Figure 1c). Analyses of SWE accuracy were performed with and without exclusion of cases marked as "poor quality."

Exclusion

Patients who had non-focal liver biopsies for the evaluation of liver allografts were excluded from the study. Subjects with rare diseases were also excluded from the study as there is literature suggesting these diseases confound SWE measurement (Trifanov et al. 2015). Finally, patients whose SWE image review was not satisfactory as defined above were also excluded.

Liver Biopsy

All biopsies were performed under US guidance by interventional radiology fellows in the department of abdominal imaging and intervention under the supervision of an attending physician. Patients gave informed consent and were given local anesthesia prior to the procedure. All biopsies were obtained from the upper right lobe using a 16-gauge BioPince™ (Full Core Biopsy Instrument; Medical Device Technologies Inc. Gainesville, FL) biopsy needle. It is standard practice in our department to acquire at least one 2 cm biopsy – however the number of biopsy cores obtained was not recorded at the time of biopsy.

Histological Examination

A single subspecialist pathologist (AKB) blinded to clinical history and SWE values reviewed the biopsy specimens. The length of each specimen in millimeters and the number of portal tracts visualized were recorded. Visualization of a minimum of three portal triads

and a minimum 1 cm biopsy sample was considered adequate for histological examination. Liver fibrosis was staged using the METAVIR staging system, utilizing fibrosis, steatosis and necroinflammatory score (Bedossa and Poynard 1996). Fibrosis was staged on a five-point ordinal scale from 0 to 4: (F0, absent; F1, enlarged fibrotic portal tract; F2, few portal-portal septa but intact architecture; F3, many septa with architectural distortion but no obvious cirrhosis; and F4, cirrhosis). Steatosis was classified as absent (S0), <5% (S1), 5–33% (S2), 34–66% (S3) and >66% (S4). Necroinflammatory score was calculated for each of the following; (a) Piecemeal/Interface Hepatitis (0–3) and (b) Lobular hepatitis (0–2) to provide a total necroinflammatory activity score of 0–3, also classified as A0–A3 (Bedossa and Poynard 1996).

Statistical Analysis

Statistical analysis was performed using SPSS (Release 21.0, IBM®) software. The diagnostic performance of SWE for differentiating higher grades of fibrosis (F2–F4) from lower grades of fibrosis (F0, F1) was calculated by plotting receiver operating characteristic (ROC) curves using the SWE values to obtain area under the ROC (AUROC). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR–), were computed for the previously derived SWE cutoff value of 7.29 kPa (Samir et al. 2015).

RESULTS

A total of 338 patients between January 2014 and January 2015 underwent SWE acquisitions just prior to non-focal liver biopsy. Sixty-one subjects were excluded from the study group per the exclusion criteria; 29 with allografts, one with granulomatous hepatitis, one with amyloidosis and 30 in whom elastograms were of poor quality (n=25) or inadequate number (n=5). A total of 277 subjects remained (Figure 2). These comprised 152 (54.9%) females and 125 (45.1%) males with a mean age of 48 ± 13.48 years (range: 18–82 years). Liver biopsy was performed for diagnosis in 154/277 (55.6%) and for assessment of known liver disease in 44.4% of patients (n=123) (Table 1).

SWE Values and Pathological Examination

SWE values and liver biopsy was performed in all subjects without any adverse events. Median SWE values ranged from 3.65 kPa to 50.70 kPa with a mean of 10.35 kPa (95% CI: 9.51 to 11.19 kPa), median value of 8.4 kPa and a standard deviation of 7.09 kPa. On pathological examination, the biopsy samples ranged from 1–3.8 cm in size with a mean of 1.77 ± 0.56 cm and median value of 1.6 cm. A total of 212 subjects had either no fibrosis (F0; n=108, 39.0%) or F1 fibrosis (n=104, 37.5%) while 28 had F2 fibrosis (10.1%), 27 had F3 fibrosis (9.7%) and 10 had F4 fibrosis (3.6%) (Table 2).

The median SWE values for stages F0–F4 were 6.93 kPa, 7.7 kPa, 9.6 kPa, 13.95 kPa and 23.73 kPa, respectively. Subjects with F4 fibrosis showed the largest inter-subject variation (standard deviation = 12.6 kPa), while subjects with no fibrosis (F0) had the lowest inter-subject variation (standard deviation = 3.6 kPa). Figure 3 demonstrates the variation of median values in the form of a box and whisker plot.

Correlation with pathology

Spearman's correlation showed moderate correlation of fibrosis with elastography values ($r=0.456$, $p<0.001$). The distribution of steatosis grade amongst the cohort was S0 ($n=77$, 27.8%), S1 ($n=61$, 22.0%), S2 ($n=53$, 19.1%), S3 ($n=62$, 22.4%) and S4 ($n=24$, 8.7%) while that of inflammation was A0 ($n=102$, 36.8%), A1 ($n=134$, 48.4%), A2 ($n=31$, 11.2%) and A3 ($n=10$, 3.6%). Steatosis degree did not correlate with SWE values ($r=0.076$, $p=0.205$), while inflammation showed a fair correlation with SWE values ($r=0.362$, $p<0.001$). These results have been summarized in Table 3

Differentiating higher grades of fibrosis

Receiver operating characteristic (ROC) curves to differentiate higher grades of fibrosis from lesser grades of fibrosis (F0, F1) had an area under the ROC curve (AUROC) of 0.84 (95% CI: 0.78–0.89). A cutoff value of 7.29 kPa provided a sensitivity and specificity of 95% and 51%, respectively (Figure 4). The diagnostic accuracy at the cutoff value of 7.29 kPa was: sensitivity ($n = 62/65$, 95.4%; 95% CI: 86.2–98.8), specificity ($n = 107/212$, 50.5%; 95% CI: 43.6–57.4), positive predictive value ($n = 62/167$, 37.1%; 95% CI: 29.9–44.97), negative predictive value ($n = 107/110$, 97.27%; 95% CI: 91.65–99.29), positive likelihood ratio (1.93, 95% CI: 1.66–2.23) and negative likelihood ratio (0.09, 95% CI: 0.03–0.28).

DISCUSSION

Shear-wave elastography of the liver offers exciting potential for noninvasively differentiating patients with advanced liver fibrosis (F2–F4) from those with no or early fibrosis (F0, F1). This distinction is of critical clinical importance because advanced fibrosis at the time of diagnosis has been shown to correlate with long-term cirrhosis risk in patients with HCV and HBV (Di Bisceglie 1995; Kato et al. 1994; Park et al. 2007; Takano et al. 1995; Yamada et al. 1995).

Previous SWE studies have proposed various cutoff values for distinguishing different fibrosis stages, such as early/no fibrosis, advanced fibrosis and cirrhosis (Beland et al. 2014; Jeong et al. 2014; Samir et al. 2015; Sporea et al. 2014). Some of these studies have focused on identifying cutoff values for the diagnosis of METAVIR fibrosis stage F2 and higher (Beland et al. 2014; Jeong et al. 2014; Samir et al. 2015). However, these cutoff values have been generated from single data sets and have not, to our knowledge, subsequently been validated on independent cohorts. A recent meta-analysis of SWE studies published in the *Journal of Ultrasound in Medicine*, is a prime example where 12 studies in the meta-analysis have different sensitivities and specificities without validation in an independent cohort (Feng et al. 2016).

In our previous cross-sectional study with SWE performed by a single sonographer and image post-processing performed by a post-doctoral fellow, we reported sensitivity of 91.4% and specificity of 52.5% for a cutoff value of 7.29 kPa for the diagnosis of METAVIR fibrosis stage F2 (Samir et al. 2015). In this study, we validate the diagnostic performance of this cutoff value with an independent dataset acquired by multiple sonographers at our

institution, and without any additional image processing. We chose this method to determine whether our proposed cutoff values would generalize to a more typical clinical ultrasound scenario, where the number of sonographers acquiring elastograms is greater than one, and a sonographer selects the ROI rather than a researcher. Furthermore, as SWE increasingly becomes part of standard clinical care, it is important to establish cutoff values that have higher sensitivities despite a tradeoff in specificity. This, from a clinical standpoint, allows radiologists to provide the clinician information regarding concern for higher degree of fibrosis with great certainty. A low specificity (50.5%, 95%CI: 43.6 – 57.4), high sensitivity (95.4%, 95%CI: 86.2 – 98.8), and high negative predictive value (97.3%, 95%CI: 91.65–99.29) implies that a large cohort of patients can with certainty be classified as “healthy” and ~50% who may not have higher grade of fibrosis will still need further work-up. In a current climate where liver biopsy is the gold standard, this becomes a very practical approach in clinical practice. The viewpoint that arbitrary cutoff values without validation is concerning in the field of elastography has been echoed in a recent editorial article by experts in the field (Piscaglia et al. 2016).

Other studies of SWE have demonstrated varying areas under the ROC curves (0.81–0.92) and proposed various cutoff values for F2 fibrosis in patients with diffuse liver disease (Table 4). Variation in proposed cutoff values makes comparison of sensitivity, specificity and other accuracy markers challenging. Moreover, differences in subject distribution across liver fibrosis stages can bias reported test performance. For example, if a cohort contains many subjects with F0 and F4 disease and relatively few with F1 or F2 disease, then the AUROC for distinguishing fibrosis stages (F0 and F1) from stages (F2, F3 and F4) is expected to be higher than the AUROC in a study cohort that contains a relatively greater proportion of F1 and F2 subjects. This confounding variable, termed spectrum bias, can be mitigated to some degree by statistical weighting techniques, such as the DANA correction (Poynard et al. 2007). However, generalizing test performance is likely to require careful comparison of expected and actual distribution of fibrosis stages in cutoff value generation and validation cohorts. Our initial cutoff value generation cohort (Samir et al. 2015) had 25.7% F2 cases and the cohort presently under analysis had 23.4% F2 cases.

In this study, we validated our proposed cutoff value of 7.29 kPa (Samir et al. 2015), deriving similar estimates of sensitivity (95%) and specificity (51%) for the diagnosis of METAVIR fibrosis stage F2 in patients with chronic diffuse liver disease in an independent patient cohort with a similar spectrum of fibrosis stages (Table 5).

The validation cohort represents the typical subject population for our institution – a busy quaternary Hepatology referral center that manages patients with a diverse range of chronic liver diseases. Our validated results are likely to generalize to other similar institutions, but it is important for practitioners to carefully consider whether the expected distribution of liver fibrosis stages in their practice environments might differ substantially from ours. This is important because variations in NPV and PPV might occur if the prevalence of F2 fibrosis in their practices varies from ours, and should be accounted for in making clinically relevant decisions. The consistent test performance achieved with multiple sonographers acquiring elastograms and selecting ROIs also validates the generalizability of this technique to conventional radiology clinic settings.

The limitations of the study include: (1) Inclusion of many forms of chronic liver disease (HCV, HBV, NAFLD, AIH, ALD), which may result in heterogeneous liver elasticity measurements, (2) Inclusion of a smaller proportion of patients with higher grades of fibrosis compared to those with lower grades, (3) A single subspecialist pathologist reviewed all pathology samples for purposes of the research study in order to mitigate inter-observer variability. In conventional clinical practice, multiple different pathologists may review samples, and significant inter-observer variability may exist in assigned liver fibrosis stages. This difference could conceivably reduce the generalizability of our conclusions to conventional clinical contexts. However, alternative, and more resource-intensive, study designs such as panel-based pathology reviews also suffer from the same limitation, (4) Usage of the METAVIR liver fibrosis staging system. The METAVIR system was originally designed only for the staging of viral hepatitis. However, this system is used as a measure of liver fibrosis stage throughout the SWE literature, and was used here to facilitate comparison across studies.

In conclusion, we have validated the test performance of a cutoff value of 7.29 kPa on liver SWE using the Supersonic Aixplorer system to distinguish higher stages of liver fibrosis (METAVIR stages F2–F4) from lower stages of fibrosis (METAVIR stages F0, F1) in patients with chronic liver disease.

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Figure 2.
Patient selection

Figure 3.
Shear-wave elastography (SWE) values of different fibrosis stage

Figure 4.

Receiver operating characteristic (ROC) curves of SWE to differentiate higher grades of fibrosis (F 2) from lesser grades of fibrosis (F0, F1)

Table 1

Patient demographics and reason for liver biopsy

Demographic and Reason for biopsy		
Gender	Male (n=125)	Female (n=152)
Age	46.16 ± 13.5 (18–78)	50 ± 12.27 (18–82)
Race and Ethnicity		
Race	White	217
	Asian	14
	Black	14
	Hispanic/Latino	8
	American Indian	2
	Spanish	1
	Unknown/Declined	20
Reason for Liver Biopsy		
Follow-up of Known Liver Disease	Chronic HCV	43
	NAFLD/NASH	30
	AIH, AIH Overlap	17
	PBC	16
	Chronic HBV	8
	PSC	2
	Alcoholic hepatitis	2
	HCV, HBV	2
	Giant cell hepatitis	1
	Alpha 1 antitrypsin	1
	Autoimmune cholangiopathy	1
Diagnostic	Elevated LFT's, Cirrhosis on Imaging/Varices, Drug toxicity, Rule out hemochromatosis	154

Table 2

Number, median, range, standard deviation (Std. Dev.), first and third quartiles for mean SWE values obtained from RUL for fibrosis stages (F0–F4) in all patients.

Fibrosis Grade	F0	F1	F2	F3	F4
Total	108 (39%)	104 (37.5%)	28 (10.1%)	27 (9.7%)	10 (3.6%)
Median	6.93	7.7	9.6	13.95	23.73
Mean	8.09	9.29	10.98	16.97	26.01
Std. Dev.	3.6	6.1	4.8	9.4	12.6
Min.	3.65	3.90	5.80	8.75	12.80
Max.	25.10	41.3	28.40	50.10	50.70
1st Quartile	6.0	6.21	8.69	10.8	14.28
3rd Quartile	9.24	9.7	11.31	18.85	35.26

Table 3

Distribution of steatosis and inflammation in the cohort with correlation to Median SWE values.

Histopathology	N (%)	Correlation with Median SWE (r, p)
Steatosis	S0 77 (27.8%)	r=0.076, p=0.205
	S1 61 (22.0%)	
	S2 53 (19.1%)	
	S3 62 (22.4%)	
	S4 24 (8.7%)	
Inflammation	A0 102 (36.8%)	r=0.362, p<0.001
	A1 134 (48.4%)	
	A2 31 (11.2%)	
	A3 10 (3.6%)	

Table 4

Prior studies of SWE in hepatitis C (HCV) and chronic liver disease (CLD)

Study	Etiology	N	GS	%	F2	Meas	AUROC	F2 Cutoff	Sens	Spec	PPV	NPV
Ferraioli et al. ²⁶	HCV	121	ME	58.7%	5	0.92	7.1	90.0	87.5	91.3	85.7	
Cassinotto et al. ²⁷	CLD	336	ME	61.3%	3	0.89	8	83	82	88	75	
Defieux et al. ¹¹	CLD	118	ME	48%	10	0.81	8.9	77	79	77	79	
Sporea et al. ²⁸	CLD	237	ME	NA	5	NA	7.1	79.1	70.4	70.1	79.3	

Abbreviations: GS – Gold standard; ME – METAVIR; AUROC – Area under the Receiver Operating Curve; Sens. – Sensitivity; Spec. – Specificity; PPV – Positive predictive value; NPV – Negative predictive value

Table 5

Comparison of sensitivity and specificity between the initial cohort and the independent validation cohort

	Initial Cohort¹⁸	Validation Cohort
Number	136	277
Mean Age (Range)	49 years (18–74 years)	48 years (18–82 years)
Cutoff value for METAVIR F2 fibrosis	7.29 kPa	7.29 kPa
AUROC	0.77 (0.68 – 0.86)	0.84 (0.78–0.89)
Sensitivity	91.4% (95%CI: 75.6 – 97.8)	95.4% (95%CI: 86.2 – 98.8)
Specificity	52.5% (95%CI: 42.3 – 62.4)	50.5% (95%CI: 43.6 – 57.4)
PPV	40.0% (95%CI: 29.4 – 51.6)	37.1% (95%CI: 29.9 – 44.97)
NPV	94.6% (95%CI: 84.2 – 98.6)	97.3% (95%CI: 91.65–99.29)