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● *Original Contribution*

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) cut-off values (≥F2 fibrosis) on an independent cohort of patients with chronic liver disease. In this cross-sectional study, approved by the institutional review board and compliant with the Health Insurance Portability and Accountability Act, 338 patients undergoing liver biopsy underwent SWE using an Aixplorer ultrasound machine (SuperSonic Imagine, Aix-en-Provence, France). Median SWE values were calculated from sets of 10 elastograms. A single blinded pathologist evaluated METAVIR fibrosis staging as the gold standard. The study analyzed 277 patients with a mean age of 48 y. On pathologic examination, 212 patients (76.5%) had F0–F1 fibrosis, whereas 65 (23.5%) had ≥F2 fibrosis. Spearman's correlation of fibrosis with SWE was 0.456 ($p < 0.001$). A cut-off 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 Imagine Aixplorer SWE system. (E-mail: dhyani.manish@mgh.harvard.edu) © **2017 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Liver biopsy, Noninvasive imaging, Fibrosis, Elastography, Validated cut-off values.**

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. Although non-focal liver biopsy is currently the reference standard for fibrosis staging in patients with known liver disease, it is invasive and expensive, and is 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. 2011; Wang et al. 2012) and elastography have been shown to predict liver fibrosis stage with varying degrees of accuracy. As a non-invasive, inexpensive and portable technique, ultrasound (US) elastography has shown promising results (Chon et al. 2012; Friedrich-Rust et al. 2008, 2012). In particular, shear wave elastography (SWE) derived estimates of shear wave speed and hepatic Young's modulus, measured in kilopascal (kPa) have been shown to be related to liver fibrosis stage (Beland et al. 2014; Deffieux et al. 2015; Feng et al. 2016; Jeong et al. 2014; Sporea et al. 2014; Tada et al. 2015; Zheng et al. 2015). Cut-off eYM or shear wave speed values for different liver fibrosis stages have been proposed in a number of studies (Beland et al. 2014; Jeong et al.

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2014; Samir et al. 2015). A recent meta-analysis of SWE studies summarizes this dilemma wherein 12 manuscripts reviewed have generated 12 different cut-off values for variable sensitivities and specificities (Feng et al. 2016). To date, these cut-off values have not been prospectively validated in data sets independent of those used to generate the cut-off 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 eYM cut-off 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 and compliant with the Health Insurance Portability and Accountability Act. Patients with known or suspected diffuse liver disease scheduled for US-guided non-focal liver biopsy between January 2014 and January 2015 underwent SWE. Patients younger than 18 y were excluded. The institutional review board waived the requirement for informed consent as SWE examination is approved by the US Food and Drug Administration and increasingly becoming the standard of clinical care, whereas 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.

SWE. SWE was performed using an Aixplorer US system (SuperSonic Imagine, 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 required for their clinically warranted liver biopsy. Several sonographers with varying US experience who were trained in SWE image acquisition performed SWE acquisitions immediately before liver biopsy. Each SWE acquisition consisted of 10 sequential measurements obtained in the upper right hepatic lobe *via* an intercostal approach at end expiration. The 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 (M.D.) evaluated all SWE images. An SWE acquisition was marked as poor quality if: (i) a minimum of eight acquisitions were not made, or (ii) a poor ROI was placed. A poor ROI was defined as placed in the area immediately below the liver capsule (known to cause image artifact as evident in Fig. 1a) or as images which had limited SWE data (Fig. 1b), in comparison with an example of a good quality SWE image acquisition with an appropriate ROI placement (Fig. 1c). Analyses of SWE accuracy were performed with and without exclusion of cases identified as "poor quality."

Exclusion. Patients who had non-focal liver biopsies for the evaluation of liver allografts were excluded from the study. Patients with rare diseases were also excluded from the study as literature suggests these diseases confound SWE measurement (Trifanov et al. 2015). Finally, patients whose SWE image review was unsatisfactory 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 before the procedure. All biopsies were obtained from the upper right lobe using a 16-gauge BioPince Full Core Biopsy Instrument biopsy needle (Argon Medical Devices, Plano, TX, USA). 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.

Histologic examination. A single subspecialist pathologist (A.K.B.) 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 histologic 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 5-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: (i) piecemeal/interface hepatitis (0–3) and (ii) lobular hepatitis (0–2) to provide a total necroinflammatory activity score of 0–3, also classified as A0–A3 (Bedossa and Poynard 1996).