Clinical Gastroenterology and Hepatology 2015;13:772–779

# Accuracy of Fibroscan, Compared With Histology, in Analysis of Liver Fibrosis in Patients With Hepatitis B or C: A United States Multicenter Study

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**BACKGROUND & AIMS:** **Liver biopsy is invasive and associated with complications, sampling errors, and observer variability. Vibration-controlled transient elastography (VCTE) with FibroScan can be used to immediately assess liver stiffness. We aimed to define optimal levels of liver stiffness to identify patients with chronic viral hepatitis and significant fibrosis, advanced fibrosis, or cirrhosis.**

**METHODS:** **In a prospective, 2-phase study, patients with chronic hepatitis C or B underwent VCTE followed by liver biopsy analysis from January 2005 through May 2008 at 6 centers in the United States. In phase 1 we identified optimal levels of liver stiffness for identification of patients with stage F2−F4 or F4 fibrosis (the development phase, n = 188). In phase 2 we tested these cutoff values in a separate cohort of patients (the validation phase, n = 560). All biopsies were assessed for METAVIR stage by a single pathologist in the phase 1 analysis and by a different pathologist in the phase 2 analysis. Diagnostic performances of VCTE were assessed by area under the receiver operating characteristic curve (AUROC) analyses.**

**RESULTS:** **In phase 1 of the study, liver stiffness measurements identified patients with ≥F2 fibrosis with AUROC value of 0.89 (95% confidence interval, 0.83–0.92) and identified patients with F4 fibrosis with AUROC value of 0.92 (95% confidence interval, 0.87–0.95). Liver stiffness cutoff values (kPa) in phase 1 were 8.4 for ≥F2 (82% sensitivity, 79% specificity) and 12.8 for F4 (84% sensitivity, 86% specificity). In the phase 2 analysis, the liver stiffness cutoff values identified patients with ≥F2 fibrosis with 58% sensitivity ($P < .0001$ vs phase 1) and 75% specificity (nonsignificant difference vs phase 1); they identified patients with F4 fibrosis with 76% sensitivity ($P < .0001$ vs phase 1) and 85% specificity (nonsignificant differences vs phase 1). VCTE had an interobserver agreement correlation coefficient of 0.98 (n = 26) and an intraobserver agreement correlation coefficient of 0.95 (n = 34).**

**CONCLUSIONS:** **In a large U.S. multicenter study, we confirmed that VCTE provides an accurate assessment of liver fibrosis in patients with chronic viral hepatitis. Our findings are similar to those from European and Asian cohorts.**

*Keywords:* Liver Disease; HBV; HCV; Diagnosis; Diagnostic.

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Liver inflammation and cellular injury lead to fibrosis with progression to cirrhosis and complications of decompensated end-stage liver disease such as hepatocellular carcinoma. Currently, liver biopsy is the

*Abbreviations used in this paper:* APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; AUROC, area under receiver operating characteristic curve; BMI, body mass index; CHC, chronic hepatitis C; ICC, intraclass correlation coefficient; LSM, liver stiffness measurement; VCTE, vibration-controlled transient elastography.


1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2014.12.014

reference technique for determining the extent of hepatic fibrosis and inflammation. However, the procedure is invasive and can result in occasional significant complications. Limitations of biopsy also include variability in tissue sampling and interobserver and intraobserver variability that result in incorrect staging of disease.[1] Because of the limitations of several liver biopsy imaging methods that are based on the principle of elastography have been evaluated for staging liver disease, which aims at measuring the stiffness of the liver. Several manufacturers have developed technologies evaluating liver stiffness such as the Virtual Touch Tissue Quantification system[2] (Siemens, Munich, Germany), the Shear Wave Elastography system[3] (SuperSonic Imagine, Aix en Provence, France), or the Vibration-Controlled Transient Elastography system (VCTE) implemented on the FibroScan[4] (Echosens, Paris, France). VCTE using the FibroScan device is the most validated and commonly used elastography method worldwide and was recently approved in the United States by the Food and Drug Administration.[5,6] This technology is based on a rapid measure of shear wave velocity and subsequent calculation of liver stiffness, which correlates with severity of fibrosis. Data suggest VCTE is reliable in diagnosing cirrhosis in patients with chronic liver disease,[7] advanced fibrosis in patients with alcoholic and nonalcoholic fatty liver disease,[8,9] and significant fibrosis in patients with chronic hepatitis C (CHC)[10] and in biliary diseases.[11] However, some factors such as patient body mass index (BMI) were reported to be associated with lower applicability of VCTE, but they caused unreliable measurements or examination failures.[12] Despite this limitation, a meta-analysis of 50 studies evaluating VCTE in comparison with liver biopsy as a reference showed that this technique has good diagnostic accuracy in detecting cirrhosis, regardless of the underlying cause of liver disease.[13]

In addition to these imaging techniques, other noninvasive methods to assess fibrosis are based on a biological approach that uses direct and indirect blood markers.[14–17] Among them, aspartate aminotransferase-to-platelet ratio index (APRI), which is based on aspartate aminotransferase (AST) and platelets, and FIB-4, which is based on age, AST, alanine aminotransferase, and platelets, are commonly used because the required blood parameters are inexpensive and routinely assessed for the management of patients with chronic liver disease. In addition, both APRI and FIB-4 exhibit good diagnostic performance for exclusion of cirrhosis in CHC patients.[18–20]

The primary objective of the study was to (1) identify optimal liver stiffness measurement (LSM) cutoff values for staging significant fibrosis, advanced fibrosis, and cirrhosis in a development cohort of U.S. patients with chronic viral hepatitis and (2) to validate these LSM cutoff points in an independent validation cohort. Secondary objectives were to (1) assess the intraoperator and interoperator reproducibility of LSM performed by VCTE, (2) identify the factors independently associated with LSM, (3) evaluate the potential influence of patient's BMI on the diagnostic performances of VCTE for significant fibrosis and cirrhosis assessment, and (4) to compare the diagnostic performance of VCTE versus the fibrosis biomarkers APRI and FIB-4 in the validation cohort.

## Methods

Consecutive adult male or female patients with chronic hepatitis B or CHC who were undergoing liver biopsy were prospectively included in this study. Enrollment was from January 2005 through May 2008 at 6 centers in the United States.

### *Study Design*

The study was conducted in 2 phases. Phase 1 was designed to identify the optimal LSM thresholds to stage significant liver fibrosis ($\geq$ F2), advanced fibrosis ($\geq$F3), and cirrhosis (F4). Phase 2 was designed to validate the selected LSM thresholds from phase 1. Assessment included interobserver and intraobserver variations in LSM, and liver biopsy served as the reference in staging fibrosis or cirrhosis.

The time between the FibroScan reading and the biopsy was not to exceed 6 months for phase 1 and 6 weeks for phase 2. The FibroScan operator was blinded to the fibrosis stage, and only the study pathologist, data center (Duke Clinical Research Institute), and sponsor had access to the centralized liver biopsy results.

### *Vibration-Controlled Transient Elastography*

LSMs were performed by using FibroScan device powered by VCTE (Echosens) as previously described (Supplementary Materials), equipped with the standard M probe.

### *Intraoperator and Interoperator Variability of Liver Stiffness*

Intraoperator and interoperator variability of LSM was performed on a subgroup of patients randomly selected from phase 2. For interoperator variability analysis, 2 LSMs were performed by 2 separate trained operators before liver biopsy on the same day and in the same anatomic location. Subjects enrolled in the intraoperator analysis had a second examination performed within 6 weeks by the same operator. In both interoperator and intraoperator analyses, the initial LSMs were considered the efficacy data, and the second measurements were variability data.

### *Liver Biopsy*

All liver biopsies were evaluated by the central pathology lab at Beth Israel Deaconess Medical Center according