JAMA Diagnostic Test Interpretation

Vibration-Controlled Transient Elastography for Diagnosing Cirrhosis and Staging Hepatic Fibrosis

Julius Wilder, MD, PhD; Steve S. Choi, MD; Cynthia A. Moylan, MD, MHS

A 68-year-old man was diagnosed with chronic hepatitis C genotype 1b 5 years ago. He had no evidence of advanced liver disease (eg, thrombocytopenia). Liver ultrasound showed no signs of cirrhosis, such as nodularity. Vibration-controlled transient elastography (VCTE) performed prior to treatment was negative for signficant fibrosis at 6.7 kPa. Hepatitis C was cured, based on viral load, with simeprevir and sofosbuvir for 12 weeks. He presents for follow-up. Laboratory studies and VCTE were performed (**Table 1**).

HOW DO YOU INTERPRET THESE RESULTS?

A. The patient has cirrhosis.

B. The patient has a healthy liver.

C. The patient has minimal fibrosis.

D. The patient requires a liver biopsy to confirm fibrosis stage.

Table 1. Patient's Test Results

Laboratory Test	Patient Values	Reference Standard
International normalized ratio	1.1	0.9-1.1
White blood cell count, $\times 10^3/\mu L$	9.1	3.5-11.0
Hemoglobin, g/dL	14.2	12.0-16.0
Platelet count, $\times 10^3/\mu L$	250	140-400
Albumin, g/dL	4.0	3.5-5.5
Aspartate aminotransferase, U/L	23	9-34
Alanine aminotransferase, U/L	28	6-41
Total bilirubin, mg/dL	0.6	0.1-1.1
Alkaline phosphatase, U/L	66	37-116
Creatinine, mg/dL	1.1	0.49-1.12
Liver stiffness measurement, kPa	20.0	2.3-6.1

SI conversion factors: to convert alanine aminotransferase, alkaline phosphatase, and aspartate aminotransferase to μkat/L, multiply by 0.0167; bilirubin to μmol/L, multiply by 17.104; creatinine to μmol/L, multiply by 88.4.

Answer

A. The patient has cirrhosis.

Test Characteristics

Cirrhosis is the end result of chronic liver injury and progressive fibrosis.[1] In the United States, the most common causes of cirrhosis and end-stage liver disease among adults awaiting liver transplantation are chronic hepatitis C (35%), alcoholic liver disease (18%), and nonalcoholic fatty liver disease (16%).[2]

VCTE measures liver fibrosis (stiffness) noninvasively (Medicare national reimbursement, $41.04).[3] VCTE measurements correlate with METAVIR, a histopathological 5-stage scoring system of fibrosis (stage 0 [no fibrosis] to stage 4 [cirrhosis]).[4] VCTE was first validated against biopsy for detecting hepatitis C cirrhosis.[5] The VCTE ultrasound transducer probe generates both an elastic shear wave that traverses the liver and a pulse echo that measures wave velocity through the liver. More fibrotic tissue is stiffer and resistant to deformation from the shear wave. Thus, higher wave velocities indicate greater liver fibrosis. Results are expressed as liver stiffness measurement (LSM; 1.5 kPa [no stiffness] to 75 kPa [greatest stiffness]).[4,6] VCTE is more accurate for diagnosing cirrhosis than for staging fibrosis but is often considered a method of staging fibrosis.

VCTE has limitations. First, postprandial increases in portal blood flow increase velocity. Therefore, patients should fast at least 3 hours prior to VCTE.[5] Second, VCTE should not be performed in patients with ascites, alanine aminotransferase greater than 100 U/L, or acute liver injury (eg, acute hepatitis or ischemia) because poor wave transmission and inflammation cause falsely elevated results. Third, alcohol consumption, cholestasis, heart failure, and tumor infiltration increase hepatic venous pressure and wave attenuation, which leads to increased velocity and subsequent misdiagnosis of advanced fibrosis stage or cirrhosis.[4,6] Fourth, VCTE may be uninterpretable due to poor transmission quality caused by small intercostal spaces or large body habitus. Fifth, VCTE cannot reliably distinguish between fibrosis stages (ie, stage 1 vs stage 2). Approximately 1% to 5% of adults undergoing VCTE have unreliable or inaccurate results, subsequently requiring liver biopsy.

Despite limitations, LSM is highly accurate compared with the reference standard of liver biopsy for diagnosing cirrhosis. Diagnostic thresholds, sensitivity, and specificity for cirrhosis vary by underlying liver disease due to differences in hepatic venous pressure, cholestasis, inflammation, and fibrosis pattern (**Table 2**).[4,5] Area under the receiver operating characteristic curves for cirrhosis range from 0.93 to 0.99 (Table 2).[5]

Table 2. Sensitivity, Specificity, and AUROC for Cirrhosis Assessed by Vibration-Controlled Transient Elastography

Liver Disease	Threshold, kPa[a]	Sensitivity	Specificity	AUROC
Hepatitis C virus	12.5	0.84	0.94	0.93
Hepatitis B virus	11	0.75	0.90	0.94
Primary biliary cholangitis	16.9	0.93	0.99	0.99
Primary sclerosing cholangitis	14.3	1.00	0.88	0.95
Nonalcoholic fatty liver disease	10.5	0.78	0.96	0.94

Abbreviation: AUROC, area under the receiver operating characteristic curve.

[a] Performance characteristics of liver stiffness measurement thresholds for cirrhosis relate to the prevalence of liver disease. Hence, thresholds are not universally accepted.

Application to This Patient

The patient's LSM of 20.0 kPa is consistent with cirrhosis because it is greater than the diagnostic threshold for cirrhosis (12.5 kPa). Liver biopsy is not required. VCTE is greater than 94% specific for cirrhosis when LSM is greater than the threshold and consistent with other findings of cirrhosis (ie, thrombocytopenia). Liver biopsy could confirm cirrhosis when uncertainty about the validity of VCTE exists or when histologic features are important for diagnosis. VCTE reliably detects cirrhosis in chronic hepatitis B, alcoholic liver disease, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis, and nonalcoholic fatty liver disease.[5] VCTE is approved for use in adults and children by the US Food and Drug Administration.[4,5]

What Are Alternative Diagnostic Approaches?

Although liver biopsy is the reference standard, biopsy size (sampling error) and interobserver variation among pathologists affect fibrosis staging.[5] One noninvasive test alternative is magnetic resonance elastography, which uses magnetic resonance imaging rather than ultrasound to measure stiffness and has superior sensitivity and specificity for fibrosis staging. However, magnetic resonance elastography is more expensive, labor intensive, and has limited availability. Other noninvasive tests include blood tests, such as the aspartate aminotransferase-to-platelet ratio index and other serologic fibrosis markers, which are readily available but diagnose cirrhosis less accurately than VCTE.[5]

Patient Outcome

VCTE diagnosed cirrhosis, thus the patient underwent testing for cirrhosis complications such as portal hypertension and liver cancer. Subsequently, upper endoscopy revealed large esophageal varices and the patient began taking a nonselective β-blocker to prevent variceal bleeding. Because of cirrhosis, he undergoes liver ultrasound every 6 months to evaluate for hepatocellular carcinoma. His liver function remains stable 2 years after cirrhosis diagnosis.

Clinical Bottom Line

- Vibration-controlled transient elastography (VCTE) accurately confirms the presence or absence of cirrhosis in many etiologies of chronic liver disease.
- Liver stiffness measurement (LSM) should be interpreted within the clinical context for each patient, and results should be corroborated with other noninvasive tests or liver biopsy if questions persist regarding LSM accuracy.
- Clinicians must be aware of the limitations of VCTE in order to use and interpret results correctly.

ARTICLE INFORMATION

Author Affiliations: Division of Gastroenterology, Duke University Health System, Durham, North Carolina (Wilder, Choi, Moylan); Duke Clinical Research Institute, Durham, North Carolina (Wilder); Durham Veterans Affairs Medical Center, Durham, North Carolina (Choi, Moylan).

Corresponding Author: Cynthia Moylan, MD, MHS, Duke University School of Medicine, 905 S Lasalle St, GSRB1, DUMC 3256, Durham, NC 27710 (cynthia.moylan@duke.edu).

Section Editor: Mary McGrae McDermott, MD, Senior Editor.

Published Online: October 31, 2018. doi:10.1001/jama.2018.13073

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Moylan reports receipt of grants from Madrigal, Taiwan J, Gilead, Intercept, and Genfit, and consulting fees from NuSirt outside the submitted work. No other disclosures were reported.

Additional Contributions: We thank the patient for sharing his experience and for granting permission to publish it.

REFERENCES

1. Udell JA, Wang CS, Tinmouth J, et al. Does this patient with liver disease have cirrhosis? *JAMA*. 2012;307(8):832-842. doi:10.1001/jama.2012.186

2. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology*. 2015;148(3):547-555. doi:10.1053/j.gastro.2014.11.039

3. Centers for Medicare & Medicaid Services. Physician Fee Schedule Look-Up Tool, 2018. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PFSlookup/. Accessed April 2, 2018.

4. Mueller S, Sandrin L. Liver stiffness: a novel parameter for the diagnosis of liver disease. *Hepat Med*. 2010;2:49-67. doi:10.2147/HMER.S7394

5. Afdhal NH, Bacon B R, Patel K, et al. Accuracy of fibroscan, compared with histology, in analysis of liver fibrosis in patients with hepatitis B or C: a United States multicenter study. *Clin Gastroenterol Hepatol*. 2015;13(4):772-779.e1-3.

6. Wilder J, Patel K. The clinical utility of FibroScan as a noninvasive diagnostic test for liver disease. *Med Devices (Auckl)*. 2014;7:107-114.