Gastroenterology 2017;152:1536–1543

AGA SECTION

American Gastroenterological Association Institute Guideline on the Role of Elastography in the Evaluation of Liver Fibrosis

Joseph K. Lim,[1] Steven L. Flamm,[2] Siddharth Singh,[3] Yngve T. Falck-Ytter,[4] and the Clinical Guidelines Committee of the American Gastroenterological Association

[1]Section of Digestive Diseases and Yale Liver Center, Yale University School of Medicine, New Haven, Connecticut; [2]Departments of Medicine and Surgery, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; [3]Division of Gastroenterology, University of California-San Diego, La Jolla, California; and [4]Division of Gastroenterology and Hepatology, Cleveland VA Medical Center and University Hospitals, Case Western Reserve University, Cleveland, Ohio

This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e19. Learning Objective: Upon completion of this CME activity successful learners will be able to: (1) describe the role of vibration-controlled transient elastography (VCTE) in the diagnosis of cirrhosis in adults with chronic hepatitis C, chronic hepatitis B, nonalcoholic fatty liver disease, and chronic alcoholic liver disease; (2) determine appropriate liver stiffness thresholds for the diagnosis of cirrhosis and clinically significant portal hypertension; (3) describe the role of magnetic resonance elastography (MRE) compared with vibration controlled transient elastography (VCTE) in the diagnosis of cirrhosis in adults with chronic hepatitis C and non-alcoholic fatty liver disease; and (4) understand the limitations of VCTE and MRE relevant to its application to clinical practice.

This document represents the official recommendations of the American Gastroenterological Association (AGA) on the role of vibration-controlled transient elastography (VCTE) in the evaluation of liver fibrosis. The guideline was developed by the Clinical Guidelines Committee and approved by the AGA Governing Board. The guideline was developed utilizing a process outlined elsewhere.[1] Briefly, the AGA process for developing clinical practice guidelines incorporates Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology,[2] as outlined by the Institute of Medicine.[3]

GRADE methodology was utilized to prepare the background information for the technical review and guideline. Optimal understanding and application of this guideline will be improved by reading applicable portions of the technical review. Four members of the guideline panel and AGA support staff met in person with the authors of the technical review on May 20, 2016. The information in the technical review was discussed in a systematic manner facilitating subsequent creation of guideline recommendations addressing each focused question. The strength of each recommendation rated as either strong or conditional.[4]

The assessment of liver fibrosis represents a critical component in the evaluation of chronic liver disorders. Liver biopsy represents the gold standard diagnostic tool for liver fibrosis assessment,[5] although noninvasive techniques are commonly used as a surrogate to the liver biopsy. Since the first description of the percutaneous liver biopsy in 1923,[6] histologic assessment of the liver has been used in the diagnosis and staging of liver disorders such as hepatitis C, hepatitis B, fatty liver disease, autoimmune hepatitis, primary biliary cirrhosis, and hemochromatosis.[7–12] However, liver biopsy has intrinsic limitations that dampen the enthusiasm of patients and clinicians for their routine incorporation in clinical practice. Although generally safe, liver biopsy is invasive, associated with significant pain in up to 30% of patients,[6] severe bleeding in <1% of patients,[13] requires hospitalization in 2%−3% of patients,[14] and has a mortality rate of up to 0.33%.[15] Furthermore, liver biopsy is subject to sampling error and both intra-observer and inter-observer variability in interpretation,[16] and is difficult to repeat for serial assessments over several points in time. In this context, the role of noninvasive tests for the assessment of liver fibrosis has increased in the United States and worldwide, and has been incorporated into clinical practice guidelines in Europe and Latin America.[17] A wide spectrum of fibrosis assessment tools has emerged, including direct and indirect serum markers of liver fibrosis, and several imaging-based methods, such as transient elastography, 2-dimensional shear wave elastography, acoustic radiation force impulse imaging or point shear wave elastography, and magnetic resonance elastography (MRE).

Vibration-controlled transient elastography (VCTE) is the most commonly used imaging-based fibrosis assessment method in the United States. It can be performed at bedside in an ambulatory office setting, is rapid to perform, has a wide range of scores (2.5−75 kPa), is associated with acceptable intra-observer and inter-observer reproducibility, and has been validated in large cohorts worldwide in a spectrum of liver diseases, including hepatitis B, hepatitis C, fatty liver disease, and autoimmune liver disorders, among others. By applying a probe to the intercostal skin in

Abbreviations used in this paper: **AGA, American Gastroenterological Association; APRI, aspartate aminotransferase to platelet ratio index; CI, confidence interval; FIB-4, fibrosis-4 index; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; SVR, hepatocellular carcinoma; VCTE, vibration-controlled transient elastography.**

Most current article

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2017.03.017

the 9th to 11th intercostal space in a region 25−65 mm (M-probe) or 35−75 mm (XL-probe) below the skin surface, a minimum of 10 valid liver stiffness measurements are obtained to derive a composite score used to estimate stage of liver fibrosis, which is determined to be of adequate quality if there are at least 10 validated measurements and the interquartile range/median value of liver stiffness is ≤30%.[18] VCTE has several limitations, including technical limits for performance (diameter of intercostal space, obesity), variable diagnostic performance across liver conditions with differing cutoffs to establish significant or advanced liver fibrosis or cirrhosis, inaccurate readings in patients with acute hepatitis, alcohol abuse, food intake within 2–3 hours, congestive heart failure, and extrahepatic cholestasis.

The current technical review and guideline were developed to provide clinicians with evidence-based guidance on the specific role of VCTE in clinical practice, and addressed focused clinically relevant questions reviewed by the Technical Review Committee.

Question 1. Should VCTE vs aspartate aminotransferase to platelet ratio index (APRI) be used to diagnose cirrhosis in adults with chronic hepatitis C?

Question 2. Should VCTE vs fibrosis-4 index (FIB-4) be used to diagnose cirrhosis in adults with chronic hepatitis C?

The pooled effect estimates of test characteristics for the diagnosis of cirrhosis in patients with chronic hepatitis C were obtained from 36 studies evaluating VCTE, 24 studies evaluating APRI, and 2 studies evaluating FIB-4. The test characteristics for these noninvasive fibrosis assessment tools were as follows: VCTE: sensitivity, 0.89; 95% confidence interval [CI], 0.84−0.92; specificity, 0.91; 95% CI, 0.89−0.92; APRI: sensitivity, 0.77; 95% CI, 0.73−0.81; specificity, 0.78; 95% CI, 0.74−0.81; and FIB-4: sensitivity, 0.87; 95% CI, 0.74−0.94; specificity, 0.91; 95% CI, 0.89−0.92. In adults with chronic hepatitis C, VCTE demonstrated superior sensitivity and specificity compared with FIB-4 and APRI for the diagnosis of cirrhosis. The AGA did not review the utility of other proprietary serum fibrosis assays for the diagnosis of cirrhosis, although available evidence does not support a significant advantage of these assays over nonproprietary tests (ie, APRI and FIB-4). Furthermore, other imaging-based fibrosis assessment tools were not evaluated within this review. The identification of cirrhosis remains a vital step in the pretreatment assessment of patients with chronic hepatitis C infection, and directly impacts treatment choice, duration, and potential need for ribavirin, as well as the requirement for variceal and hepatocellular carcinoma surveillance. VCTE is superior to noninvasive serum tests in the detection of cirrhosis, although caution should be exercised in the reliance of any one fibrosis assessment tool in ruling in or ruling out cirrhosis, which should incorporate all available clinical information.

Recommendation: In patients with chronic hepatitis C, the AGA recommends VCTE, if available, rather than other nonproprietary, noninvasive serum tests (APRI, FIB-4) to detect cirrhosis.
GRADE: *Strong recommendation, moderate quality evidence.*

Question 3. In adults with hepatitis C virus (HCV) undergoing VCTE, at what liver stiffness cutoff can we accurately diagnose cirrhosis (and initiate downstream management), obviating the need for liver biopsy?

In assessing the diagnostic performance of particular cutoffs for assessing liver stiffness, the context (or pretest probability) in which these are applied is important to define. For this question, 2 illustrative scenarios were chosen: one of a low prevalence of cirrhosis (5%, as can be seen in patients with HCV detected in primary care clinics during routine age-appropriate screening) and another of a high prevalence of cirrhosis (30%, as can be seen in patients with HCV with comorbid obesity, diabetes, excessive alcohol use, or co-infection with human immunodeficiency virus or chronic hepatitis B infection). The pooled effect estimates of test characteristics of a liver stiffness cutoff of 12.5 (±1) kPa for the diagnosis of cirrhosis in patients with HCV were obtained from 17 studies with 5812 patients. Using a cutoff for cirrhosis of 12.5 (±1) kPa, which is optimized to keep the rate of missing cirrhosis low, the pooled sensitivity was 0.86 (95% CI, 0.83−0.88) and pooled specificity was 0.91 (95% CI, 0.89−0.92). Using these values, it can be estimated that a cutoff of 12.5 kPa may misclassify <5% of patients as not having cirrhosis (when they indeed have cirrhosis), and <10% of patients as having cirrhosis (when they do not have cirrhosis). The evidence base to support the use of a liver stiffness cutoff of 12.5 kPa for the detection of liver cirrhosis was derived from cross-sectional diagnostic accuracy studies, as opposed to studies comparing different cutoffs and their effect on downstream patient-important outcomes related to impact of cirrhosis diagnosis (or misdiagnosis); therefore, false-positive and false-negative rates were considered surrogate measures of downstream patient important outcomes, and evidence was rated down for indirectness. Considerable heterogeneity was observed in pooled estimates of sensitivity and specificity, and studies reporting performance of a cutoff of 12.5 (±1) kPa were selectively chosen. On this basis, caution should be exercised in solely utilizing a cutoff of 12.5 kPa to diagnose cirrhosis, and the result of VCTE should be considered in context of other clinical information to guide management.

In summary, by selecting a cutoff of 12.5 kPa, the guideline panel made a conscious decision to minimize false-negative tests, thus making a judgment that the harm of missing cirrhosis is greater than the harms of overdiagnosis. However, although this strategy will result in a significant number of patients falsely labeled at high risk for