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American Gastroenterological Association Institute Technical Review on the Role of Elastography in Chronic Liver Diseases

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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: ascertain the evidence on comparative diagnostic performance of different noninvasive imaging modalities for detection of cirrhosis, and performance of different vibration-controlled transient elastography-based liver stiffness cut-offs for detection of cirrhosis and clinically significant portal hypertension in patients with chronic liver diseases, in different clinical and practice settings.

Chronic liver diseases (CLDs), due to chronic hepatitis C; hepatitis B; nonalcoholic fatty liver diseases (NAFLD); and alcoholic liver disease, are a leading cause of morbidity and mortality globally. Early identification of patients with cirrhosis at high risk of progression to liver-related complications may facilitate timely care and improve outcomes. With risks and misclassification associated with invasive tests, such as liver biopsy, noninvasive imaging modalities for liver fibrosis assessment have gained popularity. Therefore, the American Gastroenterological Association prioritized clinical guidelines on the role of elastography in CLDs, focusing on vibration-controlled transient elastography (VCTE) and magnetic resonance elastography (MRE). To inform these clinical guidelines, the current technical review was developed in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework for diagnostic accuracy studies. This technical review addresses focused questions related to: (1) comparative diagnostic performance of VCTE and MRE relative to nonproprietary, serum-based fibrosis markers for detection of cirrhosis in patients with hepatitis C virus (HCV), hepatitis B virus (HBV), NAFLD, and alcoholic liver diseases; (2) performance of specific VCTE-defined liver stiffness cutoffs as a test replacement strategy (to replace liver biopsy) in making key decisions in the management of patients with CLDs; and (3) performance of specific VCTE-defined liver stiffness cutoffs as a triage test to identify patients with low likelihood of harboring high-risk esophageal varices (EVs) or having clinically significant portal hypertension (for presurgical risk stratification). This technical review does not address performance of other noninvasive modalities for assessing fibrosis (eg, acoustic radiation force pulse imaging or shear wave elastography) or steatosis (controlled attenuation parameter or magnetic resonance imaging−estimated proton density fat fraction).

Keywords: Fibrosis; Noninvasive Imaging; Chronic Liver Diseases; Guidelines.

Globally >1.75 million deaths are attributed to chronic liver diseases (CLDs), which are an important source of health and economic burdens.[1] In the United States, nearly 150,000 people are diagnosed with CLDs annually (of which 20% are diagnosed with cirrhosis), and 36,000 patients die of CLDs, primarily attributable to complications of decompensated cirrhosis and/or hepatocellular cancer (HCC).[2,3] Annually, these generate approximately 5.9 million CLD-related ambulatory care visits and 759,000 CLD-related hospitalizations, with health care costs exceeding $1.5 billion.[3] HCC is the second leading cause of cancer-related death worldwide, and most patients with HCC will have underlying CLDs.[4] Globally, it is estimated that >185 million and 248 million people may be living with chronic HCV infection and chronic HBV infection, respectively; corresponding rates in the United States are approximately 4.7 million and 2 million, respectively.[5−7] NAFLD is a rapidly increasing cause of CLDs, with an estimated 13.5%−31.8% affected globally and 24.1% of adults in North America.[8] The burden of alcoholic liver disease is more difficult to determine, but one report estimated that alcohol-attributable liver cirrhosis was responsible for 493,300 deaths globally in 2010.[9]

Early identification of patients at high risk for progression to decompensated cirrhosis can help direct high-value care and decrease the morbidity and mortality attributed to CLDs.

Abbreviations used in this paper: **APRI, aspartate aminotransferase to platelet ratio index; AUROC, area under the receiver operating characteristic; CI, confidence interval; CLD, chronic liver disease; EGD, esophagogastroduodenoscopy; EVs, esophageal varices; FIB-4, fibrosis-4 index; FN, false negative; FP, false positive; HBV, hepatitis B virus; HCC, hepatocellular cancer; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IPD, individual participant data; kPa, kilopascal; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; PICO, patients; intervention, comparator and outcome; SVR, sustained virologic response; TN, true negative; TP, true positive; VCTE, vibration-controlled transient elastography.**

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AGA SECTION

One of the key determinants of progression to CLD-related complications is degree of liver fibrosis, and is often factored in making treatment and surveillance decisions (for HCC and/or esophageal variceal screening). Historically, liver biopsy has been the gold standard for diagnosis and staging of fibrosis, in addition to its role in identifying etiology of abnormal liver enzymes and assessing degree of inflammation. However, this procedure has several limitations. It is invasive and associated with an estimated morbidity (including severe pain) and mortality rate of 3% and 0.01%, respectively; in the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis trial, serious adverse events occurred in 29 of the 2740 (1.1%) biopsies performed and included 16 (0.6%) bleeding cases.[10,11] Liver biopsy is prone to sampling error resulting in misclassification of fibrosis stage in up to 25% of cases, and there is also considerable intra- and inter-observer variability in interpretation of histology, especially at lower stages of fibrosis.[12]

To overcome these limitations and inconvenience of an invasive test, noninvasive serum- and imaging-based methods of staging fibrosis have been developed. Although several proprietary and nonproprietary serum-based markers have been developed, they are nonspecific for the liver and may have inferior performance characteristics to imaging-based tests.[13] Among imaging tests, ultrasound-based VCTE has been studied most extensively and validated with high intra- and inter-observer reproducibility, and can be performed quickly, potentially at point of care.[14] In this technique, a piston vibrator placed in the intercostal space generates a shear wave, and then the velocity is measured in a region 25−65 mm below the skin surface with the standard adult M-probe and 35−75 mm with the XL probe for larger patients. The unit of measurement is kilopascals (kPa), and the device readings range from 2.5 to 75 kPa.

With recent recommendations for universal screening for HCV, availability of highly effective but expensive newer direct-acting agents against HCV, and rising prevalence of NAFLD, an increasing number of patients are seeking evaluation for CLDs, and fibrosis staging through noninvasive means has become increasingly important and appealing for physicians.[15,16] Patients also have a strong preference for VCTE over liver biopsy. In a Canadian survey of 422 patients, of whom 205 had undergone liver biopsy, approximately 95% patients preferred VCTE over liver biopsy, with the majority reporting no discomfort (84%), no feelings of anxiety (78%), short test duration and short time to result.[17] In its recent guidelines, the European Association for the Study of Liver Diseases and the Latin American Association for the Study of the Liver have recommended VCTE as a validated noninvasive standard for assessment of liver fibrosis, in patients with HCV and HBV, with >90% negative predictive value in ruling out cirrhosis.[18] However, these guidelines offer limited guidance on the diagnostic performance of specific cutoffs of VCTE-identified liver stiffness, in clinical contexts of high- and low-risk populations of patients with CLD, and its potential impact on downstream patient-important outcomes. Identifying specific cutoffs for liver stiffness corresponding to cirrhosis and advanced fibrosis could guide management decisions, including treatment for HCV and HBV and triage for preventive cirrhosis care. Therefore, the American Gastroenterological Association prioritized this topic for generation of clinical guidelines.

Objectives of This Review

This technical review addresses focused clinical questions on the diagnostic performance of VCTE (and MRE) in patients with HCV, HBV, NAFLD, and alcoholic liver disease, focusing specifically on: (1) overall performance relative to nonproprietary, serum-based fibrosis markers and (2) implications of specific liver stiffness cutoffs on downstream patient-important outcomes. Additionally, in this review we sought to evaluate the performance of specific liver stiffness cutoffs to assess portal hypertension to triage patients with compensated cirrhosis with low likelihood of high-risk EVs, as well as its role in presurgical risk stratification of patients with CLD.[19] This review does not address the performance and utility of other noninvasive imaging modalities, such as acoustic radiation force pulse imaging or shear wave elastography. Based on feedback during the public comment period, the technical review was updated with 2 additional questions on the comparative performance of VCTE and MRE in detection of cirrhosis in patients with HCV and NAFLD.

Methods

Formulation of Clinical Questions

The participants (including SS, AJM, DTD, and YFY) for this technical review were selected by the American Gastroenterological Association Clinical Guidelines Committee based on their clinical content and guidelines methodological expertise and went through a thorough vetting process for potential conflicts of interest. Through an iterative process, the participants developed focused clinical questions deemed relevant for clinical practice that the guideline would address and that related to the diagnostic performance and utility of VCTE in 5 different populations: adults with HCV, HBV, NAFLD, chronic alcoholic liver disease, and CLD suspected to have portal hypertension. From these focused questions, well-defined statements in terms of patients, intervention, comparator, and outcome (PICO) were defined, and these formed the framework for formulating the study inclusion and exclusion criteria and guided the literature search. The American Gastroenterological Association Governing Board approved the final set of questions and statements. The focused and PICO questions are shown in Table 1. Two questions on the role of MRE on detection of cirrhosis were added after the public comment period.

There were 2 broad themes for our focused questions. The first set of questions for each population of interest (HCV, HBV, NAFLD, and alcoholic liver diseases) were centered around the overall diagnostic performance (across a broad range of cutoffs) of VCTE in relation to commonly used, nonproprietary, noninvasive serum biomarkers of fibrosis in these conditions (aspartate aminotransferase to platelet ratio index [APRI] and fibrosis-4 index [FIB-4]) (PICO #1, 4, and 6).[13,20] Although proprietary serum-based fibrosis markers may have slightly higher diagnostic accuracy compared with nonproprietary markers, the latter are inexpensive, easy to calculate, and widely available.[18] After the public comment period, 2 questions (PICO #11 and 12) on the comparative performance of VCTE and MRE on