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eViralHepatitis Review
VOLUME 3, ISSUE 12

BEYOND BIOPSY: NEW DIRECTIONS IN NONINVASIVE LIVER DISEASE ASSESSMENT

In this Issue...

The need to perform invasive testing (ie, liver biopsy) to identify and stage the extent of liver disease in patients with viral hepatitis has long been a major barrier to the initiation of treatment for both clinicians and patients. New noninvasive methods, some currently available and others in the process of validation, represent significant progress in increasing diagnostic accuracy while reducing the need for liver biopsy.

In this issue, we review recent literature describing:

- the performance of transient elastography (TE) vs biomarkers
- the use of TE for screening the general population
- factors influencing liver stiffness in patients with chronic HCV infection
- comparative uses of shear-wave elastography vs TE in HBV carriers
- new research into spleen stiffness to predict clinical complications in HCV-related cirrhosis

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Describe the currently available noninvasive tests and their diagnostic value for staging liver fibrosis in patients with viral hepatitis.
- Outline the utility and limitations of noninvasive tests for staging liver fibrosis in patients with viral hepatitis.
- Describe the most effective evidence-based strategies for using noninvasive testing for managing patients with viral hepatitis.

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IMPORTANT CME/CE INFORMATION ▼ Program Begins Below

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STATEMENT OF NEED

Through discussions with experts in the specialty of HBV, a survey of participants from previous Johns Hopkins CME activities, and a review of current literature, the following core learning gaps have been identified:

HCV

- Clinicians do not adequately identify which of their patients are at highest risk for HCV infection or effectively interpret testing results.
- Clinicians need to understand best practices in how to identify and manage HCV treatment-related side effects.

Program Information

CME Info
Accreditation
Credit Designations
Intended Audience
Learning Objectives
Internet CME Policy
Faculty Disclosures
Disclaimer Statement

Length of Activity

1.0 hour Physicians
1.0 contact hour Nurses

Launch Date

July 31, 2014

Expiration Date

July 30, 2016

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Hepatitis C Association
SCALE HBV
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Length of Activity: 60 minutes

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- Clinicians need improved awareness of how newly emerging therapies impact therapeutic decision-making in HCV infected and HIV/HCV co-infected patients.
- Clinicians are unaware of new non-invasive techniques to stage liver disease.
- Clinicians need to understand best practices in identifying cirrhosis and HCC in patients infected with HCV.

HBV

- Clinicians do not effectively identify their patients at risk for HBV.
- Clinicians are unaware of new non-invasive techniques to stage liver disease.
- Clinicians need to understand best practices in identifying cirrhosis and HCC in patients infected with HBV.

INTENDED AUDIENCE

The target audience (clinicians) for the HBV curriculum includes:

- Primary: primary care physicians (PCPs), OB/GYNs, physician assistants (PAs), nurse practitioners (NPs), community gastroenterologists and others who care for patients of Asian and West African descent in areas of high HBV prevalence
- Secondary: gastroenterologists, infectious disease specialists, and other clinicians involved in the care of patients at risk for HBV

The target audience for the HCV curriculum includes:

- PCPs, OB/GYNs, NPs, PAs, hepatologists, gastroenterologists, infectious disease physicians, and others involved in the care of patients with hepatitis.

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IN THIS ISSUE

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Dr. Castera has indicated that he has received lecture fees from Echosens.

Unlabeled/Unapproved Uses

Dr. Castera has indicated that there will be no references to unlabeled/unapproved uses of drugs or products.

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COMMENTARY

Over the past decade, the development of noninvasive methods to assess liver fibrosis has advanced the practice of hepatology. The assessment of liver fibrosis degree and progression in patients with viral hepatitis B or C is important not only to determine prognosis but also to identify patients who require antiviral therapy. For many years, liver biopsy has been considered the gold standard for evaluation of hepatic fibrosis. There are clinically relevant endpoints: detection of significant fibrosis (METAVIR, F ≥ 2), which indicates that patients with hepatitis B or C should receive antiviral treatment, and detection of cirrhosis (METAVIR, F4), which indicates that patients should be monitored for complications related to portal hypertension and hepatocellular carcinoma.[1] Liver biopsy is, however, an invasive procedure with rare but potentially life-threatening complications and is prone to sampling errors. These limitations, as well as the availability of powerful new diagnostic tools and new antiviral drugs, have rapidly decreased the use of liver biopsy in viral hepatitis and led to the development of noninvasive methodologies for the assessment of fibrosis. Among the currently available noninvasive methods, there are two distinct approaches: 1) a biological approach based on the dosage of serum biomarkers of fibrosis and 2) a physical approach based on the measurement of liver stiffness using transient elastography (TE). Although complementary, these two approaches are based on different rationales and concepts: TE measures liver stiffness related to elasticity, which corresponds to a genuine and intrinsic physical property of the liver parenchyma, whereas serum biomarkers are combinations of several not strictly liver-specific blood parameters optimized to mimic fibrosis stages as assessed by liver biopsy.

Among the serum biomarkers, the most widely used and validated are the APRI (a free, nonpatented index) and the FibroTest® (Biopredictive; Paris, France) (a patented test that is not widely available).[2] The practical advantages of analyzing serum biomarkers include their high applicability (> 95%) and interlaboratory reproducibility, as well as their potential widespread availability. However, none is liver-specific – their results can be influenced by comorbid conditions, and they require critical interpretation of results. For instance, FibroTest® produces false-positive results in patients with Gilbert's syndrome or hemolysis, because these patients have hyperbilirubinemia. Similarly, acute hepatitis can produce false-positive results in the aspartate-to-platelet ratio index (APRI).

As for the measurement of liver stiffness, transient elastography (TE) (FibroScan®, Echosens; Paris, France) has become the standard to be beaten. Advantages of TE include a short procedure time (< 5 minutes), immediate results, and the ability to perform the test at the bedside or in an outpatient clinic (it is not a difficult procedure to learn). However, accurate results require careful interpretation of data according to quality criteria (at least 10 validated measurements, a success rate (the ratio of valid measurements to the total number of measurements) above 60%, and an interquartile range (IQR) of less than 30% of the median value). Although TE analysis has excellent inter- and intraobserver agreement, its applicability (80%) is not as good as that of serum

biomarkers. Failure to obtain any measurement has been reported in 3% of cases, and unreliable results (not meeting previous recommendations) have been reported for 16%, mostly because of patient obesity or limited operator experience.[3] Overestimation of liver stiffness values has been reported with several confounding factors, including ALT flares, extrahepatic cholestasis, and congestive heart failure.[2] Thus, noninvasive tests should always be interpreted by specialists in liver disease, according to the clinical context and the results of other tests (biochemical, radiological and endoscopic), and should take into account the recommended quality criteria for each test and its possible pitfalls.

Noninvasive tests have been initially studied in chronic hepatitis C and can now be considered well-validated in viral hepatitis. For instance, in patients with HCV who are treatment-naïve HCV with no comorbidities such as alcoholism or nonalcoholic fatty liver disease, noninvasive tests can be used as first-line assessment of fibrosis stage. In that respect, the use of either TE or patented biomarkers was recommended after an independent systematic review by the French Health Authorities and moreover has been endorsed by the European Association for Study of Liver Clinical Practice guidelines.[1] However, the HCV genotype should also be considered, along with local availability of noninvasive methods and clinical relevance, and clinicians should note that a liver biopsy might be necessary if there are discordant results from TE and biomarker before a treatment decision is made. Also, with the development of direct-acting agents, particularly with next-generation direct-acting agents or interferon-free regimens, which produce higher rates of sustained virologic response, discriminating between fibrosis stages F0-F1 and above F2 might not be relevant in determining treatment indications.

Noninvasive tests have been less well-incorporated into HBV management than HCV management because there have been fewer studies and because liver inflammation might confound interpretation of test results. For example, strategies to combine noninvasive tests such as TE and biomarkers have been shown to increase diagnostic accuracy in patients with HCV but have not yet been validated in patients with HBV. Serum levels of aminotransferases should also be taken into account when interpreting results from TE in patients with hepatitis B to avoid the risk of false-positive results. Some authors have proposed to adapt TE cutoffs based on levels of ALT.[4] In patients who are treatment-naïve, noninvasive tests could be used for patients with levels of ALT > 2-fold the upper limit of normal and levels of HBV DNA > 20,000 IU/mL (for HBeAg-positive patients) or > 2000 IU/mL (for HBeAg-negative patients.[5]

Noninvasive testing was introduced in France several years ago for managing patients with hepatitis C in routine practice and has significantly reduced the need for liver biopsy; this trend has since been observed in most countries where these methods have been implemented. However, noninvasive tests will reduce but not completely eliminate the need for liver biopsy. Liver biopsies and noninvasive methods should be used as an integrated system to allow more efficient evaluation of patients with hepatitis B or C.[6] Finally, there is increasing evidence that noninvasive tests, particularly TE, can be used to identify patients with cirrhosis who are at risk of disease progression.[7] The potential of TE for predicting clinical outcomes seems to be greater than that of liver biopsy: probably the noninvasive tests measure continuing pathophysiologic processes and functions that a biopsy cannot. Assays for serum biomarkers and TE over histologic scoring systems also provide a range of continuous values, instead of a limited number of categories.

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DIAGNOSTIC ACCURACY OF FIBROSCAN VS LIVER FIBROSIS BIOMARKERS: (THE FIBROSTIC STUDY)

Degos F, Perez P, Roche B, et al. Diagnostic accuracy of FibroScan and comparison to liver fibrosis biomarkers in chronic viral hepatitis: a multicenter prospective study (the FIBROSTIC study). *J Hepatol*. 2010; 53: 1013-1021.

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The noninvasive assessment of liver fibrosis relies either on the measurement of liver stiffness, using TE, or on the dosage of serum biomarkers. Very few studies have directly compared the performances of these 2 approaches.[1] In this multicenter, prospective cross-sectional study conducted in 23 French university hospitals, Degos and colleagues compared the performance for detecting significant fibrosis and cirrhosis of TE with that of most popular patented (FibroTest®, Fibrometre®, and Hepascore®) and nonpatented (APRI) biomarkers in 1307 patients with viral hepatitis, taking liver biopsy as the reference. Most patients were men (69.2%), with a mean age of 47 years and mean BMI of 23.8 kg/m2 ; 913 had chronic hepatitis C and 284 chronic hepatitis B; the median size of liver biopsy was 24 mm and distribution of histological fibrosis stage was as follows : F0 8.6%, F1 34.3%, F2 28.4%, F3 14.8%, F4 13.8%.

Diagnostic accuracy of noninvasive methods was high for cirrhosis but poor to moderate for significant fibrosis. The AUROC values for significant fibrosis ranged from 0.72 to 0.78, with no significant differences between TE and biomarkers. Conversely, the accuracy of transient elastography was high (AUROC 0.90) and significantly higher ($P < 0.0075$-0.0001) than that of biomarkers in predicting cirrhosis (AUROC 0.77 — 0.86).

This study is the largest to date, independent from the companies marketing TE and serum biomarkers, and funded by the French Ministry of Health. Its results confirm on a large scale that TE is currently the most accurate noninvasive method to detect cirrhosis, although it is better at ruling out than ruling in cirrhosis.[2] For instance, at a cutoff of 12.5 kPa, TE had a high negative predictive value (95.3%) but a rather low positive predictive value (53.3%); raising the cutoff to 17 kPa increased the predictive value to 72%. However, this study did not assess the performance of combining TE with serum biomarkers as others have, suggesting that the combination increases diagnostic accuracy for significant fibrosis in chronic hepatitis C.[1,3]

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TE FOR FIBROSIS AND CIRRHOSIS IN PATIENTS > 45 YEARS

Roulot D, Costes JL, Buyck JF, et al. Transient elastography as a screening tool for liver fibrosis and cirrhosis in a community-based population aged over 45 years. *Gut*. 2011; 60: 977-984.

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The use of noninvasive testing could represent a very attractive strategy for screening liver fibrosis and cirrhosis in risk groups or in the general population. As TE is a simple and painless technique that can be rapidly performed on an outpatient basis, it seems particularly suited as a screening tool. Roulot et al were the first to investigate using such a strategy in a large, community based-population over 45 years of age (n = 1358) seen for a free medical checkup in France. The authors showed that in all individuals with liver stiffness values > 8 kPa (n = 89; around 8%), a cause of liver disease could be evidenced nonalcoholic fatty liver disease (NAFLD being the leading cause) and fibrosis was present in 26 of the 27 patients who underwent a liver biopsy. Interestingly, almost half of these 89 patients had normal liver function tests. Finally, TE had an excellent positive predictive value (100%) for cirrhosis (diagnosed in 0.7% of the population).

When screening a large population, the sensitivity of the test used is crucial to minimize the risk of false negative cases, since missed cases may lead to individual disasters. The present study confirms the poor sensitivity of liver function tests for detecting fibrosis. Indeed, 43% of the 89 patients with presumed liver disease had normal transaminase and gamma-glutamyl transferase values. NAFLD was the most frequent cause of liver disease, and it is well known that severe fibrosis may be present in patients with NAFLD despite normal liver tests. Conversely, TE had high sensitivity for detecting liver fibrosis and cirrhosis. Fibrosis was present in 17 of the 18 patients with liver stiffness values > 8 kPa who underwent liver biopsy, and cirrhosis was confirmed in all 9 patients with liver stiffness values>> 13 kPa, most of whom had no clinical signs suggestive of cirrhosis and normal platelet counts (> 100 000/ mm3). Therefore, TE appears an accurate tool for detecting cirrhosis, not only in patients with liver diseases but also in healthy subjects without overt liver disease.

However, the choice of appropriate cutoffs for diagnosing fibrosis and cirrhosis is a key issue and still a matter of debate. The original cutoffs were defined in small, selected populations of patients with chronic liver disease seen in tertiary care centers and may be not applicable to the general population, where the prevalence of chronic liver disease is much lower. In an effort to overcome such limitation, the authors used a cutoff for detecting significant fibrosis (8 kPa) that corresponded to the upper normal limit proposed in nonobese men in a previous exploratory study defining liver stiffness values in "normal individuals."[1] For cirrhosis, they used the cutoff (13 kPa) suggested as optimal by the largest metaanalysis at that time.[2] Although these choices could be further debated, they seem wise and sensible.

In conclusion, this important study opens up new perspectives: it is the first to suggest the value of TE for detecting undiagnosed chronic liver disease in apparently healthy subjects and for screening for cirrhosis in the general population. These challenging findings must, however, be confirmed in other cohorts. Also, comparison of strategies using either TE or biomarkers (or their combination) in the same population should be studied. Finally, the cost-effectiveness of such screening strategy must be further evaluated before implementation.

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FACTORS INFLUENCING LIVER STIFFNESS IN PATIENTS WITH CHRONIC HCV INFECTION

Arena U, Lupsor Platon M, Stasi C, et al. Liver stiffness is influenced by a standardized meal in patients with chronic hepatitis C virus at different stages of fibrotic evolution. *Hepatology* 2013; 58: 65-72.

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The risk of overestimating liver stiffness values has been reported with various confounding factors, including ALT flares, extrahepatic cholestasis, and congestive heart failure. In 2009, the potential influence of food intake was also suggested.[1] In this 2013 report, the authors prospectively investigated the influence of food intake on liver stiffness measurement, using transient elastography in 125 HCV patients at different stages of fibrotic evolution (F0-F1 n = 50; F2-F3 n = 35; F4 n = 40). Liver stiffness values were obtained after overnight fasting and 15, 30, 45, 60, and 120 minutes after the onset of a standardized liquid meal (400 mL, 600 Kcal, 16.7% protein, 53.8% carbohydrates, 29.5% fat). An increase in liver stiffness values was observed 15 to 45 minutes after the onset of the meal (from 16% in F4 patients to 33% in F0-F1) with return to baseline premeal levels within 120 minutes in all patients. Changes in liver stiffness values after a test meal are likely a consequence of the adaptation of the hepatic microcirculation to an increased portal blood flow and are in overall agreement with the observation that postprandial hyperemia is associated with a greater increase in portal pressure in patients with cirrhosis.

The 2009 study by Mederacke et al[1] was the first to investigate the effect of food intake on liver stiffness values in a pilot study in eight patients with HCV. However, this study had several limitations, including lack of standardization in the administration of the test meal, measurement of liver stiffness values at time points not clearly related to postprandial hyperemia (immediately and 60 minutes after the onset of the meal), and the lack of histological staging. The results of the present study provide definitive evidence of the confounding effect of a meal on the accuracy of liver stiffness measurements, and suggest that a fasting period of 120 minutes should be observed before the performance of TE. These results have since been confirmed by at least two other groups.[2,3] Thus, the preponderance of evidence indicates that, in 2014, TE should be performed in patients who are fasting.

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COMPARISON OF SHEAR-WAVE ELASTOGRAPHY AND TRANSIENT ELASTOGRAPHY IN CHRONIC HBV CARRIERS

Leung VY, Shen J, Wong VW, et al. Quantitative elastography of liver fibrosis and spleen stiffness in chronic hepatitis B carriers: comparison of shear-wave elastography and transient elastography with liver biopsy correlation. *Radiology*. 2013; 269: 910-918.

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Transient elastography for measuring liver stiffness is being challenged by several other ultrasound-based techniques, such as acoustic radiation force impulse imaging (ARFI) and shearwave elastography (SWE). Like ARFI, SWE has the advantage of being implemented on a commercially available ultrasound machine (Aixplorer®, Supersonic Imagine, Aix en Provence, France) with results expressed either in m/sec or in kPa with a wide range of values (2-150). Preliminary results in patients with chronic hepatitis C suggest that it might perform better than TE for the diagnosis of significant fibrosis but not for cirrhosis.[1] The authors compared the accuracy of SWE to that of TE, taking liver biopsy as reference, in 226 Chinese patients with chronic hepatitis B. In addition, 171 healthy individuals were studied as controls. Among patients with HBV, 65% were men with a mean age of 48.8 years and a median BMI of 24.2 kg/m2; the median size of liver biopsy was 18 mm and distribution of histological fibrosis stage was F0 17%, F1 23%, F2 25%, F3 20%, and F4 15%. In normal control subjects, the mean liver stiffness, using SWE, was 5.5 ± 0.7 kPa, with a range of 3.7 — 6.7 kPa. Men had significantly higher values than did women (5.7 ± 0.5 vs 5.4 ± 0.7, kPa, respectively; P = .02). There was excellent correlation in repeated measurements made by the operators. The intraclass correlation coefficient (ICC) for the three operators in three different sections of the liver ranged from 0.86 to 0.98, and the 95% confidence interval ranged from 0.71 to 0.99. Additionally, there was very good reproducibility among the three operators (ICC, 0.85; 95% confidence interval 0.70, 0.94). SWE had higher successful rate than TE (98.9% vs 89.6%). In patients with chronic hepatitis B, AUROCs of SWE were significantly higher than those of TE for both significant fibrosis (0.88 vs. 0.78) and cirrhosis (0.98 vs. 0.92).

Overall, these results suggest that SWE provides more accurate correlation of liver elasticity with liver fibrosis stage than transient elastography, especially in identifying stage F2 or greater. The main limitations of this study are that the interval between SWE and liver biopsy could be up to 12 months and the population was exclusively Chinese people with low BMI. These promising results must therefore be confirmed in cohorts of Western patients with higher BMI and in others with chronic liver disease before the exact place of SWE can be defined in clinical practice.

Reference

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SPLEEN STIFFNESS MEASUREMENT TO PREDICT CLINICAL COMPLICATIONS IN COMPENSATED HCV-RELATED CIRRHOSIS:

Colecchia A, Colli A, Casazza G, et al. Spleen stiffness measurement can predict clinical complications in compensated HCV-related cirrhosis: a prospective study. *J Hepatol* .2014; 60: 1158-1164.

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Liver stiffness and hepatic venous pressure gradient (HVPG) have been shown to predict clinical outcome in patients with cirrhosis.[1,2] Recently, spleen stiffness, measured using TE, has been shown to be closely correlated with the degree of portal hypertension, as measured by HVPG, from the early up to the most advanced stages of portal hypertension, and with the presence of esophageal varices.[3] In this prospective study, the authors assessed the predictive value of spleen stiffness for clinical decompensation compared to HVPG and liver stiffness in an initial cohort of 124 patients with HCV-related compensated cirrhosis followed for two years. In the study report, only 92 patients were included (12 were excluded because of inconclusive TE results and 20 did not completed the follow-up). Most patients were male (69%) with a median age of 56.5 years. Forty-three of 92 (46.7%)

patients had no varices (stage 1) while the majority (53.3%) were in stage 2 (presence of varices, F1, but no ascites). Patients in stage 2 had significantly lower platelet counts, larger spleens, and greater MELD scores, liver stiffness, spleen stiffness and HVPG values. During follow-up, 30 of 92 (32.6%) patients developed clinical decompensation (ascites n = 26; variceal bleeding n = 4). At multivariate analysis, only spleen stiffness (P = 0.0001) and MELD (P = 0.014) resulted as predictive factors. For instance, patients with spleen stiffness below 54 kPa were very unlikely to develop clinical decompensation within two years (3%) whereas those above 54 kPa had a 50% risk.

This study is the first to suggest the prognostic value of spleen stiffness in the context of cirrhosis, allowing differentiation of patients with low risk of decompensation from those with high risk, for whom further, more intensive testing should be reserved. However, the results of the present study need to be confirmed in larger cohorts of patients with other chronic liver diseases and longer follow-up. Also, TE may not be the most appropriate technique for measuring spleen stiffness because of the need to perform measurement with ultrasound assistance, as well as the high rate of failure (around 10%). Some alternative techniques, such as ARFI that overcomes this limitations, have been proposed.[4]

References

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