ADVANCES IN HEPATOLOGY

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Highlights From the Recent AASLD Practice Guidelines on Noninvasive Assessment of Hepatic Fibrosis and Steatosis

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G&H Why were guidelines recently released on noninvasive assessment of hepatic fibrosis and steatosis, and how were they developed?

RS Understanding the fibrosis stage is paramount to managing patients with chronic liver disease. The stage of fibrosis not only can provide prognostic information, but also identifies patients who are at risk for developing complications of portal hypertension, such as ascites, hepatic encephalopathy, and variceal bleeding, as well as patients at risk for developing hepatocellular carcinoma. Additionally, the fibrosis stage is often considered when determining whether treatment is indicated, such as with metabolic dysfunction-associated steatotic liver disease (MASLD). The gold standard for fibrosis assessment is liver biopsy, but this is an invasive procedure that can be associated with pain, bleeding, and, rarely, puncture of other organs. It also is subject to sampling error. Liver biopsy is still used in certain situations, such as in patients with autoimmune hepatitis to confirm the diagnosis and determine whether it is safe to stop immune suppression and in liver transplant recipients to rule out rejection. I have said that the only things worse than doing a liver biopsy is having one done on yourself or teaching someone else how to do it. As such, more than 30 noninvasive tests have been developed and over the past 10 years, in most situations, noninvasive liver disease assessment (NILDA) has replaced liver biopsy in clinical practice. There have been nearly 10,000 studies and reviews on noninvasive tests of liver disease severity in the past 20 years.

I led the American Association for the Study of Liver Diseases (AASLD) group of experts that included adult and pediatric hepatologists, radiologists, and pathologists to select key clinical questions addressing the use of blood- and imaging-based NILDA to identify fibrosis, steatosis, and clinically significant portal hypertension. Working with the Mayo Clinic Evidence-Based Practice Center, 3 guidelines were developed using the patient, intervention, comparison, and outcome (PICO) approach as well as 3 accompanying systematic reviews. When there was not sufficient evidence from the systematic review for a guideline statement, ungraded guidance statements were developed. For each statement, technical remarks were included to provide context. The writing group also worked with other AASLD guideline groups, such as those involving autoimmune hepatitis, MASLD, and portal hypertension, to have a consistent message and to avoid contradictory recommendations. The purpose of the guidelines was to review the literature through April 2022 and provide an evidence-based approach on NILDA use in clinical practice.

It is important to acknowledge the recent multisociety endorsement of the nomenclature change from nonalcoholic fatty liver disease (NAFLD) to MASLD. Although this is an important change that will impact future study of this entity, all data utilized to develop these guideline statements were based on prior literature, which utilized the previous NAFLD definition.

G&H According to the guidelines, how accurate is blood-based NILDA for hepatic fibrosis staging?

RS Most blood-based NILDA was developed to identify patients with bridging fibrosis or cirrhosis, known as advanced fibrosis, and not to identify those with F2

or higher, known as significant fibrosis. The guidelines recommend that simple, nonproprietary blood-based NILDA (such as the Aspartate Aminotransferase to Platelet Ratio Index [APRI], Fibrosis-4 [FIB-4] index, and NAFLD Fibrosis Score [NFS]) be used over more complex, proprietary tests because the simple tests work as well and do not require additional costs. We found that the FIB-4 index works best for most liver diseases, including viral hepatitis and NAFLD. If two simple blood-based NILDA tests are congruent, say APRI or NFS with the FIB-4 index, the clinician can be more confident that their patient does or does not have advanced fibrosis.

Additionally, the guidelines recommend that patients who have blood-based NILDA results above the lower threshold undergo imaging-based NILDA. Given cost and availability, most clinicians will use ultrasound-based elastography. Overall, all NILDA work better ruling out advanced fibrosis at the lower thresholds than ruling it in at the upper thresholds.

G&H How accurate is imaging-based NILDA for the staging of fibrosis?

RS Overall, imaging-based NILDA performs better than blood-based NILDA, especially for ruling in advanced fibrosis. In patients with chronic untreated hepatitis C virus (HCV), hepatitis B virus (HBV), or NAFLD, the guidelines recommend that imaging-based NILDA be used to detect significant fibrosis (F2-F4), advanced fibrosis (F3-F4), and cirrhosis (F4).

Among the different modalities for imaging-based NILDA, magnetic resonance elastography (MRE) had the best performance compared with ultrasound-based NILDA. Of the various ultrasound-based elastography methods, vibration-controlled transient elastography and shear wave elastography perform about the same, so clinicians should use whichever they have access to. In NAFLD patients, transient elastography liver stiffness measurement (LSM) has acceptable sensitivity and specificity for detection of fibrosis but is limited by technical issues in certain patients (eg, those with obesity). Although less data exist for MRE-LSM, it is a reliable method to detect significant fibrosis and cirrhosis and is particularly useful for the discrimination of advanced fibrosis in NAFLD patients.

G&H Can serial blood- or imaging-based noninvasive tests be used to predict the natural history of progression or regression of fibrosis in response to treatment?

RS Based upon review of the available literature, the AASLD suggests against the use of imaging- or blood-based NILDA alone to assess regression or progression of liver fibrosis. Any reduction after therapy, such as viral eradication of HCV or viral suppression of HBV, may reflect reductions in inflammation and not fibrosis. However, I have found imaging-based NILDA useful to monitor steatosis after weight loss.

G&H How accurate are these tests for grading hepatic steatosis specifically in patients with MASLD?

RS Blood-based NILDA is not accurate for detection of steatosis in an individual patient. In adults, transient elastography controlled attenuation parameter (CAP) has good diagnostic accuracy to grade steatosis in clinical practice. We found that magnetic resonance imaging–proton density fat fraction (MRI-PDFF) was as good as histology and can be used as a reference standard for detecting steatosis.

G&H What do the guidelines note regarding NILDA thresholds for different liver diseases?

RS When using either blood- or imaging-based NILDA, 2 questions need to be considered: (1) What is the chance the patient does not have significant or advanced fibrosis at the lower threshold? and (2) What is the chance the patient has advanced fibrosis at the upper threshold? For example, in patients with untreated viral hepatitis, the lower threshold for the FIB-4 index is 1.45, whereas it is 1.3 for patients with NAFLD. Conversely, the upper thresholds appear to hold true for most diseases. For example, for the FIB-4 index, we found that the upper threshold of 2.67 for NAFLD works as well as the upper threshold of 3.25 used in viral hepatitis.

It should be pointed out that for most clinicians, the most common liver diseases seen are viral hepatitis,

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MASLD, and alcohol-associated liver disease. While the AASLD systematic reviews identified sufficient data for chronic untreated HCV, HBV, and MASLD, far fewer studies were identified for other diseases such as primary sclerosing cholangitis, primary biliary cholangitis, hemochromatosis, and alcohol-associated liver disease. Additionally, for patients with viral hepatitis, it is important to note that NILDA should be used prior to initiating treatment, as most improvements in NILDA soon after treatment are related to decreases in inflammation and not in fibrosis.

G&H What guidance is provided for using blood- and imaging-based NILDA in combination?

RS Although imaging-based NILDA outperformed blood-based NILDA overall in the AASLD's review, the guidelines recommend that both be used together in clinical practice. Noninvasive testing starts with simple blood-based NILDA such as APRI and the FIB-4 index, and, for MASLD, NFS can also be used. Patients with results below the lower thresholds, especially if more than one test agrees, have a very low chance of advanced fibrosis. For patients with results above the lower threshold, an imaging-based NILDA should be performed. If the result is above the upper threshold, then the patient may have advanced fibrosis, whereas patients with results in between the lower and upper cutoffs require closer follow-up or additional testing.

It is important to recognize that while the sensitivity and specificity of each test have been defined, the positive and negative predictive values will depend on the population. Therefore, NILDA may work differently in a primary care or general population, where the prevalence of advanced fibrosis is less than 5%, compared with a referral hepatology practice, where the prevalence of advanced fibrosis may be greater than 30%.

G&H According to the guidelines, is there a role for using blood- or imaging-based noninvasive tests in pediatric patients with chronic liver disease?

RS The data in the pediatric population were much less robust than in the adult population. Blood-based noninvasive tests in children vary widely in their accuracy, even in detecting F3 to F4 fibrosis, and have difficulty discriminating earlier stages of fibrosis. These tests also have different disease-specific thresholds that correlate with histopathologic fibrosis and differ from adults. APRI and the FIB-4 index have been the most-studied tests in children, but there is still insufficient evidence to recommend blood biomarkers as endpoints to monitor changes in fibrosis over time. Any blood-based NILDA that includes age should be used cautiously in children. We found insufficient evidence to recommend any single imaging test over another. We also found that there may be different thresholds in pediatric patients compared with adult patients.

G&H What are the future directions for noninvasive assessment of hepatic fibrosis?

RS Although substantial progress has been made in the area of NILDA, there are still many opportunities for future research. In the era of precision medicine, high-throughput technologies applied to experimental models will continue to generate a wealth of novel disease- and injury-specific blood-based biomarkers for dynamic fibrosis assessment. Selection and validation of candidate biomarkers for fibrosis assessment from these multi-omics databases will be challenging. Progress in this field requires a paradigm shift from using a static and semi-quantitative assessment of fibrosis as the reference standard toward developing dynamic disease-specific models of clinical relevance that are associated with outcomes. There is a need for broader awareness of the utility of imaging-based NILDA while considering greater dissemination of testing in various clinical settings, recognition of imaging-based NILDA accuracy by payors, and hardware/software cost reduction. Emerging tools such as machine learning could optimize imaging-based NILDA accuracy by considering clinical features and key blood tests readily accessible to any health care system. The guidelines identify specific areas for future research.

Disclosures

Dr Sterling has no relevant conflicts of interest to disclose.

Suggested Reading

Duarte-Rojo A, Taouli B, Leung DH, et al. Imaging-based non-invasive liver disease assessment for staging liver fibrosis in chronic liver disease: a systematic review supporting the AASLD Practice Guideline [published online March 15, 2024]. *Hepatology*. doi:10.1097/HEP.0000000000000852.

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Sterling RK, Duarte-Rojo A, Patel K, et al. AASLD Practice Guideline on imaging-based non-invasive liver disease assessments of hepatic fibrosis and steatosis [published online March 15, 2024]. *Hepatology*. doi:10.1097/HEP.0000000000000843.

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