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AASLD Practice Guideline on non-invasive liver disease assessments of portal hypertension

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Abbreviations

AASLD American Association for the Study of Liver Diseases;

ALD alcohol-associated liver disease;

APRI aspartate aminotransferase–platelet ratio index;

ARFI acoustic radiation force impulse;

AUROC area under the receiver operating characteristic curve;

CI confidence interval;

CLD chronic liver disease;

CSPH clinically significant portal hypertension;

CT computerized tomography;

DAA direct-acting antiviral;

ELF enhanced liver fibrosis;

FIB-4 Fibrosis 4 index;

GRADE Grading of Recommendations, Assessment, Development, and Evaluations;

HCC hepatocellular carcinoma;

HBV hepatitis B virus;

HCV hepatitis C virus;

HR hazard ratio;

HVPG hepatic venous pressure gradient;

LSM liver stiffness measurement;

LSPS LSM-to-spleen/platelet score;

MASLD metabolic dysfunction-associated steatotic liver disease;

MRE magnetic resonance elastography;

NFS NAFLD fibrosis score;

NPV negative predictive value;

NILDA noninvasive liver disease assessment;

PICO patient, intervention, comparison, and outcome;

PBC primary biliary cholangitis;

PPV positive predictive value;

RR relative risk;

SSM spleen stiffness measurement;

SVR sustained virologic response;

SWE shear wave elastography;

TE transient elastography;

US ultrasound;

PURPOSE AND SCOPE

Chronic liver disease (CLD) leads to liver fibrosis, which leads to an estimated two million annual deaths worldwide with an enormous healthcare burden.[1, 2] The majority of liver-related outcomes, such as hepatic decompensation and complications from portal hypertension (variceal bleeding, hepatic encephalopathy, and ascites) and hepatocellular carcinoma (HCC), occur almost exclusively in those with cirrhosis. Therefore, it is critical to identify patients with fibrosis, especially those with significance to advanced fibrosis. Over the past few decades, multiple noninvasive blood biomarkers and imaging modalities or tests, termed here noninvasive liver disease assessments (NILDAs), have been developed to determine the presence and severity of liver fibrosis, steatosis, and clinically significant portal hypertension (CSPH).

NILDAs can generally be categorized as blood based and imaging based. The American Association for the Study of Liver Diseases (AASLD) Practice Guidelines Committee commissioned a diverse group of experts across multiple disciplines in the field of adult and pediatric liver disease to develop a systematic review and guideline to rigorously evaluate and address the use of NILDAs to identify CSPH. Specific clinically focused questions ("patient, intervention, comparison, and outcome" [PICO]) were examined (Table 1). Each blood-based[3] and imaging-based[4] NILDA to detect fibrosis and steatosis are discussed in separate guidelines.

RATIONALE FOR USE OF NILDAS TO DETECT PORTAL HYPERTENSION

Accurate assessment of portal hypertension is important in predicting prognosis and making treatment recommendations in patients with CLD. The reference standard for assessing portal hypertension in adults is direct hepatic venous pressure measurements, usually via the transjugular approach, to calculate the hepatic venous pressure gradient (HVPG), an indirect surrogate of portal pressure.[5, 6] However, as with liver biopsy, HVPG measurement is invasive and carries risks. HVPG measurement is also limited by the need for adequate experience, skill, and utilization of standardized measurement techniques. In the last 20 years, noninvasive methods for assessing portal hypertension utilizing blood- and imaging-based methods have been developed to reduce the need for invasive liver assessment procedures.

NILDAs are attractive to noninvasively assess portal hypertension for several reasons. First, because the presence and degree of portal hypertension is typically associated with poor clinical outcomes such as decompensation and death, the ability to use widely applicable noninvasive methods is critical to the management of patients with CLD. Moreover, NILDAs are most accurate in the detection of advanced forms of fibrosis (especially cirrhosis),[3, 4] and because portal hypertension is typically associated with more severe fibrosis, including cirrhosis, it follows that NILDAs should readily detect portal hypertension, especially CSPH. However, the correlation between fibrosis and portal hypertension is often not exact; that is to say that some patients with advanced fibrosis may not have portal hypertension. Moreover, when NILDAs have been used to predict the presence of esophageal varices, which is not addressed in this guideline (see de Franchis et al.[7] for review), the additional confounder—variation in the propensity to develop esophageal varices in the setting of portal hypertension—is difficult to overcome. Finally, the pathogenesis of severe portal hypertension is complex, and there are clinical settings in which the extent of fibrosis and degree of portal hypertension may not correlate.

METHODOLOGY

Overall approach

The guideline writing group consisted of a multidisciplinary panel of experts in both adult and pediatric hepatology, pathology, and radiology, as well as experts in systematic review and Grading of Recommendations, Assessment, Development, and Evaluations (GRADE; see below framework) evidence assessment methodology. Two complementary approaches were taken to answer the PICO questions. The first approach depended on a commissioned systematic review[8] conducted independently by the Mayo Clinic Evidence-Based Practice Center; this led to graded recommendations following the GRADE framework detailed in Table 2. The systematic review was performed following a priori protocol developed by the clinical practice guideline writing group designated by the AASLD. The reporting of this systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statements. The databases included Ovid MEDLINE and ePub Ahead of Print, In-Process and Other Non-Indexed Citations, and Daily, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted

by an experienced librarian with input from the study investigators. Controlled vocabulary supplemented with keywords was used to search for studies of NILDAs (the strategy utilized is available in the Appendix). These recommendations are followed by a section that describes the quality of evidence and other considerations. The writing group members also monitored the literature for studies published after the three systematic reviews' search date and included relevant studies through April 22, 2022.

To address several other important clinical questions that could not be answered by a systematic review due to sparse and/or indirect evidence, the second approach involved a thorough narrative review by the writing group to develop ungraded guideline statements. These statements considered this additional review and the clinical experience of the authors with regards to noninvasive assessments of portal hypertension. Because of the rapid evolution of the field and predetermined quality of studies incorporated in our systematic reviews, we did not include every published study on the topic. Studies with smaller sample size (<50 subjects in any one type of liver disease), those that did not have HVPG as the reference standard to assess CSPH, and studies with mixed etiologies of liver disease (except for hepatitis C virus [HCV] with co-existing human immunodeficiency virus [HIV]) or overlapping diseases were excluded.

ASSESSMENT OF DIAGNOSTIC PERFORMANCE OF NONINVASIVE MARKERS

We used several statistical tests and indices in our assessment of the performance of blood- and imaging-based NILDAs for prediction of CSPH (Table 3). Although several studies report test characteristics such as sensitivity and specificity at selected cutoffs (low to rule out and high to rule in CSPH), the positive predictive values (PPVs) and negative predictive values (NPVs) of the test are dependent on the prevalence of the condition (e.g., CSPH) in the population being studied.[9] The diagnostic odds ratio (DOR) is the ratio of the odds of disease in those that test positive to the odds of the disease in those that test negative (i.e., summarizing the odds of fibrosis in those with a positive test relative to those with a negative test) and provides a reliable estimate of a test's accuracy that is independent of the prevalence of the condition being tested. The area under the receiver operating characteristic curve (AUROC) analysis and c-statistic are other effective ways to summarize the overall diagnostic accuracy of the test. It takes values from 0 to 1, in which a value of 0 indicates a perfectly inaccurate test and a value of 1 reflects a perfectly accurate test. In general, an AUROC or c-statistic of 0.5 suggests no discrimination

(i.e., inability to diagnose patients with and without the disease or condition based on the test), 0.7–0.8 is considered acceptable, 0.8–0.9 is considered good, and more than 0.9 is considered excellent.

TYPES OF NONINVASIVE BIOMARKERS

Blood-based biomarkers

Blood-based markers have received extensive attention for the assessment of fibrosis,[3] and a limited number of studies have examined blood-based markers for assessment of portal hypertension. For assessment of CSPH, the blood-based marker that has received the most attention is the platelet count by virtue of the fact that portal hypertension causes splenomegaly, which in turn leads to platelet sequestration, and thrombocytopenia. However, blood-based tests (Table 4), including platelets, are limited by a variety of clinical factors (i.e., infection, splenectomy, bone marrow suppression, etc.; Table 5). Use of the platelet count to estimate the severity of portal hypertension may be particularly affected by systemic disorders that affect platelets, such as primary bone marrow diseases, which may also lead to thrombocytopenia. A detailed description of blood-based NILDA tests as well as variables affecting their accuracy are discussed in the AASLD guideline document on blood-based assessment of NILDAs.[10]

Imaging techniques

Imaging techniques have been utilized for many years in the evaluation of CLD; some basic characteristics across commercially available elastography techniques are summarized in Table 6. In clinical practice and in large epidemiologic studies, standard two-dimensional B-mode (grayscale) ultrasound (US) is frequently used to identify features of cirrhosis.[11] Features of general imaging studies to diagnose cirrhosis and portal hypertension include a nodular liver, dilated portal vein (>12 mm) or presence of collaterals, recanalization of the umbilical vein, splenomegaly (frequently defined as ≥13 cm but varies depending on patient sex, body habitus, and morphology), and (in the proper clinical setting) ascites. Importantly, routine imaging methods such as computed tomography (CT) and MRI, though they may identify features of portal hypertension, generally cannot reliably estimate the severity of portal hypertension (unless varices or hepatofugal flow are present). There has been an explosion of information about the use of elastography for liver stiffness measurement (LSM) and spleen stiffness measurement

(SSM) to assess for portal hypertension. Transient elastography (TE; FibroScan, Echosens, Paris, France) uses M-mode US to track the speed of propagation of a mild-amplitude and low-frequency (50 Hz) elastic wave produced by a mechanical vibrator included in the probe. Acoustic radiation force impulse techniques and shear wave elastography (SWE) assess liver stiffness based on tissue displacement from acoustic compression pulses. Magnetic resonance elastography (MRE) uses propagating mechanical shear waves generated with an acoustic passive plastic driver placed over the upper right quadrant. Similar to US-based techniques, the speed of propagation of the shear wave determines tissue stiffness. Further details about the different elastography techniques and variables affecting the accuracy and general considerations important for interpreting imaging-based NILDAs are discussed in the systematic review and practice guideline on the use of imaging tests in CLD.[3, 12]

In patients with portal hypertension, the abnormal pressure in the splenic circulation stimulates the spleen to undergo remodeling with enhanced angiogenesis and fibrogenesis,[13] along with lymphoid hyperplasia, and results in splenomegaly and increased spleen stiffness. Thus, SSM is particularly attractive as a tool to assess portal hypertension. Further, SSM is also able to capture portal hypertension that is due to presinusoidal or prehepatic causes that may not be detected by LSM.[14, 15] An additional potential benefit of SSM in the assessment of portal hypertension is that because spleen injury and fibrosis are likely to be driven primarily by pressure mechanics, changes in the hepatic parenchyma caused by variation in the underlying biology of liver disease (e.g., the severity of inflammation) or elimination of injurious agents are less likely to affect SSM than LSM and confound the relationship between intrahepatic biology and portal hypertension. On the other hand, splenic remodeling and fibrosis dynamics are poorly understood, and it remains unclear how these affect SSM, and clinical experience suggests that splenomegaly in the setting of portal hypertension resolves slowly or not at all after elimination of portal hypertension. Finally, it is important to recognize that SSM has a number of practical limitations–including the failure to obtain valid measurements in a significant number of patients (particularly with probes in which the spleen is not well visualized) and a lack of widespread operator experience.

Guideline framework

We adopted the GRADE approach to develop guidelines (Table 2).[16, 17] The quality of evidence for each recommendation was rated as high, moderate, low, or very low. This was based on study design, risk of bias, precision and consistency of estimates, directness of evidence, and publication bias. We rated down for risk of bias if the majority of studies in a particular analysis had a high risk of bias. We rated down for imprecision when the confidence intervals (CIs) of sensitivity and specificity estimates overlapped at an arbitrary cutoff of 0.75. Strength of recommendations was based on the quality of evidence, balance of benefits and harms, burden of testing (access and financial), and feasibility of the recommended action. The "strength of recommendation" determination assumed that performing tests with good (>80%) or excellent (>90%) diagnostic accuracy is associated with improved patient outcomes. Accordingly, AASLD recommendations were graded as either strong (they apply to most patients with minimal variation and can be adapted as policy in most situations) or conditional (they apply to a majority of patients, but variation in care is acceptable). Because patient representation was not included in developing these guidelines, patient values and preferences beyond the experiences of the panel were not specifically addressed. Technical remarks and supporting evidence are included with recommendations to help reconcile the level of the recommendation with the quality of the evidence and to facilitate implementation.

Consensus process

For all guideline statements, we pursued a modified Delphi approach to define the final set of recommendations[18] using previously described methodology and also adapted by the AASLD practice metrics committee.[19] In the first round, each member rated the candidate statement independently based on the level of evidence. Candidate statements were ranked on a five-point scale (1, strongly disagree; 2, disagree; 3, neither agree nor disagree; 4, agree; and 5, strongly agree). Statements reaching ≥75% agreement for either 4 (agree) or 5 (strongly agree) were considered as acceptance of the statement. In the second round (video conference), the experts' rating (both individual and group) for each statement was discussed and then rerated. Statements with <75% agreement were rediscussed and included the following considerations: (i) review of the scores, (ii) discussion to identify the reasons for variation, (iii) revision of suboptimally worded statements for accuracy by consensus, (iv) deletion of statements that were deemed problematic or irrelevant by consensus, and (v) identification of additional statements deemed

necessary for inclusion in the list of statements. Any new statement after discussion with ≥75% agreement for 4 (agree) or 5 (strongly agree) was considered as acceptance of the statement. Guidance statements were not included in cases of continued disagreement, but the pertinent evidence and discussion were summarized in the text. The accompanying systematic review supports the guideline statements.[8]

TARGET AUDIENCE

These guidelines and guidance statements are intended primarily for adult healthcare providers who care for patients with CLD. Additionally, this document may inform policy decisions and payers regarding use of NILDAs in the evaluation and management of those with CLD. The key PICO questions developed focus on using blood-based tests, imaging-based tests, or the two combined to assess for portal hypertension (Table 1). Although HVPG measurement has been shown to be feasible and safe in children with severe liver disease,[20] its use in pediatrics is uncommon. Therefore, there is insufficient literature in children regarding the diagnostic performance of noninvasive methods for predicting the degree of portal hypertension based on the HVPG, hence the absence of a portal hypertension PICO assessment in children within this document.

GUIDELINE RECOMMENDATIONS

PICO 1: in adult patients with CLDs, what is the diagnostic performance of noninvasive methods (blood and/or imaging based) for predicting the presence and/or severity of portal hypertension, including CSPH (based on HVPG)?

Guideline statements

(1) In adults with CLD, the AASLD advises against using the currently available blood-based markers or thrombocytopenia alone for the detection of CSPH (defined as HVPG ≥ 10 mmHg; conditional recommendation, low-quality evidence).

(2) In adults with CLD, the AASLD suggests using the combination of LSM and platelet count to assess for the presence of CSPH (conditional recommendation, low-quality evidence).

(3) In adults with CLD, the AASLD suggests against using LSM to quantify higher degrees of portal hypertension (HVPG □□12 mmHg; conditional recommendation, low-quality evidence).

(4) The AASLD suggests that serial LSM and platelet count levels may be followed over time to monitor for progression to CSPH in adults with CLD without baseline CSPH, in whom the underlying etiology of cirrhosis is active/uncontrolled (ungraded statement).

(5) In adults with cirrhosis who are receiving treatment for their liver disease or known portal hypertension, the AASLD suggests caution around the use of LSM or SSM to detect longitudinal changes in portal hypertension (i.e., HVPG; conditional recommendation, low-quality evidence).

Technical remarks

- The most accurate single NILDA for the detection of CSPH in most etiologies of CLD appears to be LSM; further, LSM values of ≥25 kPa or ≤15 kPa can be used to rule in or rule out CSPH, respectively.
- In adults with CLD, combining the platelet count and the LSM value likely provides greater accuracy for ruling in or out CSPH than use of LSM alone and is most useful in patients with LSM values between 15 and 25 kPa. For example, an LSM ≥15 kPa and platelet count <110,000/mcl suggests the presence of CSPH but requires clinical judgement.
- SSM is rapidly evolving, and in adults with CLD, SSM >40 kPa may be used to detect CSPH.
- In adults with CLD, although thrombocytopenia (platelets < 150,000/mcl) has been recommended as a threshold for assessing for the presence of varices, the performance of platelet count and other blood-based NILDAs to detect CSPH is poor.
- In adults with CLD, and particularly in those with cirrhosis, studies of blood- and/or imaging-based NILDAs to predict CSPH are rapidly emerging in the setting of each (1) uncontrolled primary liver disease and (2) treated primary liver disease (i.e., eradicated HCV), and additional data are anticipated.
- Additional details on use of NILDAs in the treatment/management of CSPH can be found in the AASLD Guidance: Risk Stratification and Management of Portal Hypertension and Varices in Cirrhosis.[21]
- The use of imaging-based NILDAs to detect meaningful changes in portal hypertension (CSPH) following treatment of the underlying liver disease is currently poorly defined.

Background

The pathogenesis of portal hypertension is complex. In general, portal pressure increases progressively over time as a result of cellular and molecular derangement in the intrahepatic sinusoids, followed by increases in blood flow as the disease progresses. It is commonly accepted that portal pressure increases in proportion to the degree of fibrosis in relatively linear fashion over time, although the evidence to support this notion is weak. Nonetheless, in patients with cirrhosis and portal hypertension, HVPG is the reference standard technique to measure portal pressure and assess portal hypertension. Portal hypertension is defined as being present at an HVPG >5 mmHg, and CSPH is defined by a level of ≥10 mmHg.

HVPG is well established as an effective and valuable predictor of outcome.[22, 23] Further, in patents with compensated cirrhosis, HVPG predicts the risk of developing portal hypertension-related complications,[24] and patients with compensated cirrhosis and CSPH have a higher risk of clinical decompensation and death.[25] Additionally, it has been established that in compensated cirrhosis, an HVPG reduction of 10% or more after therapy is associated with a decreased risk of first variceal hemorrhage.[26, 27]

Evidence and rationale

Of all the types of clinical information available in patients with cirrhosis, HVPG is the single best predictor of outcome.[22, 23, 28] Unfortunately, the clinical use of HVPG measurement is limited by its invasiveness, availability, technical requirements, and cost. Therefore, the use of noninvasive methods to identify the presence of CSPH is an important area in contemporary hepatology practice. It should be noted that the presence of gastroesophageal varices on endoscopy, portosystemic collaterals, or hepatofugal flow on imaging is sufficient to diagnose CSPH, and in this clinical setting, noninvasive testing is not necessary.

The utilization of noninvasive techniques to assess portal pressure is limited by two major factors. First, although evidence suggests that esophageal varices develop only at an HVPG >10 mmHg, not all patients with this degree of portal hypertension develop esophageal varices. Furthermore, assessment of the presence and size of esophageal varices is subject to substantial interobserver variability. Secondly. much of the currently available data have been derived in

patients with active HCV (viremic), and it is not entirely clear whether portal hypertension in this disease is the same as in other forms of liver disease, such as NASH.

We acknowledge that there has been a recent multisociety endorsement of a nomenclature change from NAFLD to metabolic dysfunction–associated steatotic liver disease (MASLD). Although this is an important change that will impact of future of the study of this entity, all data utilized to develop these guideline statements were based on prior literature that utilized the previous NAFLD definition. Therefore, NAFLD is the term used throughout this document when referring to the existing literature. Current evidence indicates >98% overlap between patients who meet criteria for diagnosis of NAFLD/NASH and the new criteria for MASLD/metabolic dysfunction–associated steatohepatitis (MASH) in large cohort studies, indicating that the analyses and recommendations provided in these Guidelines for patients with NAFLD/NASH are likely to pertain to patients characterized by the new nomenclature of MASLD and MASH..

The topic of variceal screening was viewed to be beyond the scope of this guidance document and is intentionally not addressed here (see de Franchis et al.[7] and AASLD writing group[21] for review).

Blood-based NILDAs

Thrombocytopenia

Portal hypertension frequently leads to splenomegaly,[29] and due to splenic sequestration of platelets, platelets have been used as a surrogate marker for portal hypertension. Lower platelet count is significantly associated with HVPG.[30] However, a platelet count of <100,000 mcl had a sensitivity of only 78% for detection of CSPH, and a platelet count of >100,000 mcl had very poor specificity for exclusion of CSPH.[30] Consequently, thrombocytopenia alone is not a good marker for CSPH.

Blood-based biomarkers. A limited number of NILDAs have been studied in the assessment of CSPH in patients with advanced fibrosis and cirrhosis.[31] For example, in a study of 130 patients with various types of liver disease (including 71% with cirrhosis), there was a weak but significant correlation between FibroTest (Table 4) and HVPG in cirrhosis (Pearson correlation coefficient = 0.24), although the correlation in patients with less advanced fibrosis was stronger.[32] Of note, correlation between FibroTest and HVPG was significantly higher when

there was severe portal hypertension (HVPG ≥ 12 mmHg). However, AUROCs for the diagnosis of severe portal hypertension were similar for platelets and Child-Turcotte-Pugh score. In a small study of 30 patients (including 21 with portal hypertension), the enhanced liver fibrosis (ELF) score correlated well with the entire population but did not correlate with HVPG in the subgroup of patients with CSPH.[33] In a study of 219 patients with compensated (N = 88) and decompensated (N = 131) alcohol-associated cirrhosis, the AUROC of aspartate aminotransferase–platelet ratio index (APRI) and Fibrosis 4 index (FIB-4) for the detection of CSPH were 0.64 and 0.65, respectively—substantially lower than for TE-LSM (0.85).[34] In aggregate, data suggest a correlation between abnormal blood-based NILDAs and the presence of CSPH, though this association is modest and is not as robust as with imaging-based NILDAs.

Imaging-based NILDAs

US-based elastography. Studies to date have focused on the ability of elastography to predict CSPH (Table 7[34–63]; see AASLD writing group,[8] Thiele et al.,[64] and You et al.[65] for review). As can be readily appreciated, LSM generally has good to excellent sensitivity and specificity for detection of CSPH. However, there are important caveats. First, the study populations examined have been extremely heterogenous, especially in terms of the disease studied, the severity of fibrosis, the presence of complications, elimination of the underlying cause of liver injury (e.g., antiviral therapy in hepatitis B virus [HBV]/HCV or alcohol cessation), variable exclusion of patients with test failures, or treatment with beta-blockers. All of these variables are clearly confounders in the interpretation of the data. Second, cut-off values used as a threshold for CSPH have been extremely variable, with LSM cutoffs as correlates for CSPH ranging widely—from relatively low (TE-LSM 8.7 kPa) to relatively high (TE-LSM 34.9 kPa) levels (Table 7).[34–41, 43–63] Many studies used their own population to set thresholds without a separate test set for threshold validation, thus potentially overestimating test accuracy. It is also critical to recognize that LSM cutoffs for the presence of CSPH vary substantially for different liver diseases, raising the possibility that there are intrinsic differences in the relationship between fibrosis and portal hypertension in different diseases. Finally, due to the tradeoff between sensitivity and specificity, there has been great variability in the thresholds used to rule in and rule out CSPH, such that the available data have established high accuracy primarily at threshold extremes. Unfortunately, this has led to inaccuracy at intermediate thresholds.

In a meta-analysis examining the diagnostic performance of TE-LSM for CSPH, there was high correlation between TE-LSM and HVPG (pooled correlation coefficient = 0.78, 95% CI 0.74–0.82).[65] In this analysis, individual studies using cutoffs between 13.6 and 18 kPa for CSPH had an aggregate sensitivity of 91% (95% CI 83%–96%) and specificity of 81% (95% CI 70%–89%) with an AUROC of 0.92, whereas cut-off values of 21–25 kPa had a sensitivity of 71% (95% CI 52%--85%) and specificity of 91% (95% CI 82%--96%) with an AUROC of 0.78. In another meta-analysis of 328 patients with cirrhosis who underwent two-dimensional[HK1][RS2] SWE and HVPG measurement, the majority of whom had decompensated cirrhosis due to HCV or alcohol-associated liver disease (ALD), the sensitivity of LSM to detect CSPH at 14.0 kPa (chosen as the optimal cutoff) was 91%, but the specificity was 37% (with a summary AUROC of 0.88).[64]

In the AASLD-sponsored systematic review examining NILDAs and HVPG for predicting the severity of portal hypertension,[8] which included nine studies with 2492 patients that examined blood-based tests and imaging-based tests, imaging-based NILDAs appeared to be superior to blood-based NILDAs for assessment of portal hypertension (APRI 56% and 68% sensitivity and specificity, respectively; and FIB-4 54% and 73% sensitivity and specificity, respectively) compared with imaging-based tests (TE-LSM) at 16–18.8 kPa, TE sensitivity was 92%--100%, and specificity was 48%–71% but varied with the disease studied. It is likely that emerging data examining other elastography techniques such as SWE will demonstrate equivalency to TE-LSM or, in the case of MRE, which allows for a large area of the liver to be assessed compared with other elastography methods, may show equivalence or superiority to TE-LSM. It is important to emphasize that there is substantial heterogeneity among studies with regard to liver disease studied and cut-off values used to detect CSPH and that these are important limitations when attempting to set thresholds.

Notwithstanding the limitations in the available literature, the NILDA with the best performance characteristics for assessment of CSPH appears to currently be LSM, and the data supporting the use of blood-based NILDAs are so limited that they cannot be recommended for assessment of CSPH. Based on existing data, the writing group concluded that for ALD, HCV (viremic), and NASH, LSM values of <10 kPa rule out CSPH in essentially all patients and that LSM values of >25 kPa rule in CSPH. LSM values between 11 and 24 are more problematic and may or may

not indicate CSPH. Based on other data not included in the formal analysis, LSM values may combined with platelet counts to enhance the noninvasive assessment of CSPH,[8] and an LSM ≤15 kPa plus a platelet count ≥150 × 10^3/mcl rules out CSPH with high confidence.

A specific important issue is whether LSM is equivalent across different etiologies of liver disease. In a multicenter retrospective study of 836 patients with compensated advanced CLD, including many previously reported in other studies, as well as a new cohort of 220 patients with NASH,[36] it was found that TE-LSM performed well in patients with ALD, chronic HBV, chronic untreated HCV, and NASH without obesity (with a PPV ≥90%) but not in patients with NASH and obesity, in whom the PPV was 63%, suggesting that patients with NASH and obesity cannot be adequately assessed for CSPH by TE-LSM alone. Other studies have suggested that TE-LSM cutoffs for detection of CSPH are higher in patients with ALD than in those with HCV, despite the fact that the range of HVPG in the various clinical cohorts is similar.[34, 60] This may reflect the inclusion of patients with active hepatocyte injury and inflammation, the latter of which confounds TE-LSM. It is notable that TE-LSM performs better for detection of CSPH than do blood-based tests.[33, 34]

An important caveat about the use of TE-LSM for assessment of HVPG is that the correlation is not highly dependable in patients with severe portal hypertension.[56, 62] This is consistent with the concept that the pathogenesis of portal hypertension at lower portal pressures is more directly linked to factors in the liver such as fibrosis, whereas at higher portal pressures (>12 mmHg), the degree of portal hypertension is more dependent on extrahepatic components, such as hyperdynamic circulation and splanchnic vasodilatation. It is also important to recognize that because current medical therapies (e.g., nonselective beta-blockers) reduce portal pressure by decreasing mesenteric blood flow and not by reducing fibrosis, elastography is unlikely to be useful in monitoring the hemodynamic response to drug therapy. For example, in a study of patients with Child-Turcotte-Pugh A/B cirrhosis (model for end-stage liver disease 9.5 ± 4.7) treated with carvedilol for 2 weeks, LSM failed to predict a reduction in HVPG,[66] though a change in SSM by point SWE (pSWE) was associated with a reduction in HVPG.

TE-LSM also appeared to correlate reasonably well with HVPG (again, at the level of CSPH rather than severe portal hypertension) in patients with HCV recurrence after liver transplantation[63] and in patients co-infected with HCV/HIV.[59]

Overall, it appears that LSM represents a viable approach to noninvasively assess CSPH, although a number of issues require further study (see below), and standardized liver stiffness thresholds for different types of liver diseases will need to be established.

MR-based elastography. Studies examining MRE in portal hypertension are currently limited. A recent systematic review evaluating liver and/or spleen stiffness measured with MRE using primarily indirect measures of portal hypertension (ascites, esophageal varices, and encephalopathy) found that the sensitivity, specificity, and AUROC values for MRE-LSM were 83% (95% CI 72%–90%), 80% (95% CI 70%–88%) and 0.88 (95% CI 0.85–0.91), respectively, at a mean cut-off value of 5.1 kPa.[67] Although the data suggest that MRE-LSM is attractive in the assessment of portal hypertension, further investigation is required.

US-based spleen elastography

As highlighted above, in portal hypertension, abnormal pressure in the splenic circulation leads to remodeling, angiogenesis, fibrogenesis, and lymphoid hyperplasia and ultimately results in splenomegaly not only with platelet sequestration but also with increased spleen stiffness. A substantial body of literature has examined SSM in patients with cirrhosis and portal hypertension, demonstrating that spleen stiffness is increased in the presence of portal hypertension (Table 8).[39, 44, 46, 47, 50, 52, 58, 68–70] As with LSM, variation in cut points used for CSPH have been wide. As with the study of CSPH using LSM, studies of SSM are also limited by inclusion of heterogeneous study populations (different diseases studied, the presence of complications, whether the underlying cause of liver injury has been eliminated or not [e.g., antiviral therapy in patients with HBV/HCV or ethanol cessation], or treatment with beta-blockers). Some studies have demonstrated that SSM is superior to LSM for identifying CSPH, whereas others have reported that LSM is superior to SSM (Table 8).

In a meta-analysis of nine studies examining SSM and HVPG for the detection of CSPH, the AUROC, sensitivity, specificity, and DOR were 0.92 (95% CI 0.89–0.94), 0.88 (95% CI 0.70–0.96), 0.84 (95% CI 0.72–0.92), and 38 (95% CI 17–84), respectively.[70] For the detection of severe portal hypertension, these values were 0.87 (95% CI 0.84–0.90), 0.92 (95% CI 0.82–0.96), 0.79 (95% CI 0.72–0.85), and 41 (95% CI 17–100), respectively. The summary correlation coefficient between SSM and HVPG was 0.72 (95% CI 0.63–0.80). This study was limited by

the inclusion of heterogeneous populations of patients, highly variable cut-off values, and utilization of different imaging techniques.

Although TE-based SSM is attractive in the assessment of portal hypertension, it has not gained widespread use outside of the research setting. This is likely due in part to some of its weaknesses, including the failure to obtain valid measurements in a substantial number of patients, technical limitations of current SSM probes, and a lack of widespread operator experience. Hepatologists have been primarily responsible for TE-LSM, and it has gained relatively widespread acceptance. However, currently, hepatologists are not as familiar with TE-SSM. In general, the failure rate of TE-SSM is higher than other imaging-based elastography measures,[71–75] which may be due to the lack of appropriate spleen visualization and/or lack of operator experience. It is possible that direct imaging-based elastography techniques, such as pSWE, will likely fare better than TE-SSM because with the former, the spleen can be directly visualized during the measurement process.

Combination techniques

Combining blood- and imaging-based NILDAs to detect portal hypertension is attractive, in particular to enhance specificity. In a retrospective multicenter study of 518 patients with compensated cirrhosis from five centers in Europe and Canada, the authors aimed to develop noninvasive test-based risk prediction models using TE-LSM, platelet count, and spleen diameter with calculation of an LSM-to-spleen/platelet score (LSPS) score and platelet–spleen ratio (PSR) with reference standard of HVPG measurement.[76] The study population included 229 patients with compensated cirrhosis who had TE-LSM and HVPG measurement and 179 patients with LSPS/PSR and HVPG measurement; the majority of patients had a viral etiology of cirrhosis and two-thirds had CSPH. The LSPS-based model had the best predictive value for CSPH (AUROC 0.88), followed by LSM >20 kPa (AUROC 0.82) and LSM >20 kPa plus platelet count <150 mcl (AUROC 0.85). However, there is clearly selection bias given the large proportion of patients with CSPH such that the thresholds used might not apply to a low-risk population. Also, the authors pointed out that the models could not identify patients at low risk of CSPH and therefore could not be used to rule it out. Another model, the Portal Hypertension Assessment Tool, which included TE-LSM, FIB-4, and sex, showed promising results in ruling out CSPH.[35]

In a multicenter retrospective study of 836 patients with advanced CLD, including many previously reported in other studies,[36] the authors examined two TE-based models to predict CSPH, one using LSM alone and one using LSM and platelet count. In 203 patients with LSM ≤15 kPa, 168 did not have CSPH, whereas in 117 patients with LSM ≤15 kPa and platelets ≥150 × 10^9/L, 113 did not have CSPH (NPV of 97%), suggesting that this combination (LSM ≤15 kPa and platelets ≥150 × 10^9/L) can be used to exclude CSPH in patients with most etiologies of CLD. The authors also proposed a new model for patients with NASH (termed the ANTICIPATE-NASH model) using body mass index, LSM, and platelet count to predict CSPH.

Combination imaging-based NILDA algorithms have also been proposed to improve the detection of portal hypertension. One study suggested that if sequential SWE-LSM was <16 kPa, an SWE-SSM threshold of 26.6 kPa could rule out CSPH in 99% of patients,[77] though such an approach was not validated in a follow-up study.[78]

Novel imaging techniques

Several novel imaging techniques are currently under investigation to noninvasively evaluate portal hypertension. In a recent study, a computational model based on CT angiographic images[79] had an AUROC of 0.83 for the detection of CSPH and a good correlation with HVPG (r = 0.61). Additionally, in a cohort of patients with cirrhosis, a radiomics signature was developed using contrast-enhanced CT[80] and had an AUROC of 0.85 for detection of CSPH.

Other techniques

Various other techniques such as measurement of total serum bile acid concentration, breath tests, and metabolic clearance tests have been used to noninvasively estimate liver function, typically in patients with advanced liver disease. As such, it is possible that some of these may be useful in the assessment of CSPH. However, despite the potential of these tests, they are generally complex to perform and have not been fully evaluated. Of the various tests proposed to evaluate CSPH (including caffeine elimination rate, antipyrine clearance, the hepatic conversion of lidocaine to monoethylglycinexylidide concentration, methionine breath test, galactose elimination capacity, dual cholate clearances and cholate shunt, perfused hepatic mass, and indocyanine green retention), the indocyanine green retention test is perhaps the best studied.[81] In a small study of patients with various causes of liver disease that examined TE-LSM, direct

portal pressure measurement, the dual cholate clearance and shunt test (also HepQuant SHUNT Test), FIB-4, LSM, and shunt percentage had AUROCs of 0.74, 0.80, and 0.86 for detection of CSPH,[82] respectively, suggesting that this liver function test holds promise as a noninvasive tool for patients with CLD.

NILDAS FOR THE DETECTION OF CHANGES IN PORTAL HYPERTENSION

Current evidence clearly indicates that fibrosis and even cirrhosis are reversible.[83, 84] Further, several studies have now demonstrated that eradication of HCV is associated with reductions in HVPG and liver stiffness.[45, 85] In a study of 112 liver transplant recipients with HCV who achieved sustained virologic response (SVR), it was shown that HVPG and LSM decreased significantly.[41] Interestingly, the ELF test also declined in parallel with HVPG and LSM. It should be emphasized that reductions in LSM must be interpreted with caution because such reductions can reflect improvements in inflammation rather than changes in fibrosis or portal pressures.[86, 87]

Additional evidence is emerging with regard to the use of NILDAs for assessment of CSPH in patients in whom the primary liver disease has been arrested or effectively treated. A study in European patients after HCV eradication that included patients from previous studies demonstrated that posttreatment LSM <12 kPa and platelets >150 × 10^3/mcl had a sensitivity of 99% for excluding CSPH, and the likelihood of having CSPH with an LSM ≥25 kPa was 94%.[88]

QUALITY OF EVIDENCE AND OTHER CONSIDERATIONS

Available evidence is limited by the fact that published studies have included extremely heterogeneous populations and small cohorts and have used wide cutoffs for detection of CSPH. The diagnostic utility of liver and SSMs for detection of CSPH has been studied primarily in patients with parenchymal liver disease (especially in those with HCV and ALD); thus, the use of these techniques may not be generalizable to other chronic fibrosing liver diseases. Analyses supporting PICO 1 provided very imprecise diagnostic estimates and were derived from a relatively small number of studies. The quality of evidence was judged to be low.

PICO 2: In adult patients with CLD and CSPH, what is the prognostic performance of NILDAs to predict liver-related clinical outcomes (decompensation and transplant-free survival) compared with HVPG?

Guidance statements

(6) In patients with CLD and CSPH, there is insufficient evidence to support the use of blood- or imaging-based NILDAs to predict clinical outcomes (ungraded statement).

Technical comments

- A systemic review was not performed to address this PICO question.
- Although data in adult patients with cirrhosis and CSPH are limited and confounded by underlying treatment, decompensation events are unlikely in patients who have an LSM below a certain threshold (i.e., 20 kPa).
- The clinical importance of change in NILDAs over time as compared with change in HVPG for predicting liver-related clinical outcomes (decompensation and transplant-free survival) is unclear.
- In the published literature on the use of NILDAs to predict clinical outcomes, there is great heterogeneity in cohorts, variation in endpoints, different periods of follow-up, and variability in cutoffs utilized—all of which limit comparisons of performance of NILDAs to predict liver-related clinical outcomes.
- Treatment of primary liver disease confounds interpretation of much of the available data on the use of NILDAs in predicting clinical outcomes when thresholds are poorly defined to rule in or rule out CSPH.
- Data in patients with CLD for whom their primary disease has been treated are rapidly emerging and will provide further insights about the ability of NILDAs to predict clinical outcomes.

Background

Although there is an association between NILDAs and diagnosis of portal hypertension, there is limited evidence assessing NILDAs in compensated cirrhosis for the prediction of subsequent liver-related clinical outcomes (Table 9).[49, 61, 62, 89–94] In contrast, HVPG measurements have relatively robust performance characteristics when used to predict clinical outcomes. In a meta-

analysis, baseline LSM (one study used MRE, otherwise LSM was obtained by TE) was associated with subsequent risk of decompensation (six studies, relative risk [RR] 1.07, 95% CI 1.03–1.11), HCC (nine studies, RR 1.11, 95% CI 1.05–1.18), and death (five studies, RR 1.22, 95% CI 1.05–1.43).[95] However, not all studies were limited to patients with cirrhosis or had comparison with HVPG.[96–98] It is critical to emphasize that there remain multiple issues that must be considered in interpreting available NILDA data for prediction of clinical outcome. For example, in the published literature, there is great heterogeneity in cohorts, variation in endpoints (HCC, complications of portal hypertension, hepatic decompensation, or combinations thereof), different periods of follow-up, and variability in cutoffs utilized—all of which limit direct comparisons of performance.

Evidence and rationale

Liver-related complications. In a prospective study of 100 patients with CLD (65% with cirrhosis) comparing baseline HVPG measurement with TE-LSM, the incidence of subsequent portal hypertension-related complications was 27% at a median follow-up of 16 months[91]; the performances of TE and HVPG were similar (AUROC 0.73 for each) for identifying portal hypertension-related complications. At a cutoff of LSM of 21.1 kPa and HVPG of 10 mmHg, respectively, the NPV was 100% for either modality for the development of portal hypertension-related complications. Of note, accurate measurements were not obtainable in 5% of the study population, primarily due to obesity.

In a subsequent study of 109 patients, including 93% with cirrhosis, the development of portal hypertension-related complications was assessed at baseline and over time.[49] The median baseline TE-LSM was higher in the 28 patients who developed portal hypertensive complications (41.9 vs. 23.1 kPa, $p = 0.001$). At a median follow-up of 15.1 months, HVPG >10 mmHg and TE-LSM >34.5 kPa predicted portal hypertensive complications with 100% and 75% sensitivity, 40% and 70% specificity, 43% and 53% PPV, and 100% and 86% NPV, respectively. Of note, portal hypertensive complications occurred in four patients with TE-LSM <21.1 kPa, including two with ascites and two with portal hypertension-related bleeding. A TE-LSM cutoff of 21.1 kPa had 40% PPV and 85% NPV for prediction of portal hypertensive complications.

In a subset of patients with cirrhosis ($n = 258$, 68% CSPH, median HVPG 12 mmHg) in data combined from simtuzumab trials in NASH,[89] blood-based markers (ELF, FibroTest, NAFLD

fibrosis score [NFS], FIB-4, and APRI) were compared with HVPG (also repeated at weeks 48 and 96). Over 29 months, 19% of patients developed liver-related clinical events. Higher ELF at baseline (hazard ratio [HR] 2.11), FibroTest (HR 1.21), NFS (HR 1.78), FIB-4 (HR 1.24), and APRI (HR 1.88) were associated with development of clinical events. The risk of clinical events increased with higher baseline HVPG (HR per 1.15 mm Hg, 95% CI 1.09–1.21). Interestingly, among those with clinical events, 14% had an HVPG <10 mmHg at baseline.[89] In a single-center study in patients with cirrhosis (approximately 60% decompensated at baseline), HVPG, FIB-4, and APRI were all poor predictors of mortality within 3 months (AUROC 0.55–0.63 for HVPG, FIB-4, APRI, and Lok Index).[90]

In a validation cohort of patients with compensated cirrhosis (compensated advanced CLD), patients with an LSM <12 kPa and platelets >150 × 10^3/mcl were free of decompensation events within 3 years, whereas patients with a posttreatment LSM ≥25 kPa had a 3-year decompensation risk of 10%. Patients with an LSM between 13 and 24 kPa were viewed to be in a "gray" zone but also had a low rate (1%) of decompensating events over 3 years.[88] In another study, baseline LSM of <17.5 kPa along with improvements in LSM of at least 25% at 1 year after SVR with direct-acting antiviral (DAA) treatment (plus baseline albumin) was associated with no HCC development at 3 years.[99] Post-SVR TE-LSM >20 kPa (regardless of pretreatment values) has also been associated with development of decompensation, HCC, and need for liver transplantation.[100, 101] Another study with patients with HCV who achieved SVR with DAA treatment identified that TE-LSM (with or without a blood-based NILDA) had good to excellent accuracy in predicting decompensation.[102] Combinations of individual components of the FIB-4 and LSM into a single scoring system may identify patients with compensated liver disease at risk of developing complications of portal hypertension.[103]

Decompensation after partial hepatectomy. One study assessed predictors of accuracy of TE-LSM in predicting liver-related decompensation within 3 months after partial hepatectomy.[94] In univariate analysis, only elevated HVPG and LSM were associated with 3-month decompensation. In multivariate analysis, HVPG was the only variable associated with decompensation (OR 1.44, 95% CI 1.07–1.95). TE-LSM was less accurate than HVPG in predicting 3-month decompensation (AUROC 0.78 vs. 0.89); however, only 27 patients had both measured, and there was no significant difference between HVPG and LSM in predicting

decompensation (AUROC 0.88 vs. 0.81, $p = 0.21$). TE-LSM cutoff of 21 kPa had similar accuracy to HVPG (71% vs. 79%, respectively) to predict 3-month decompensation. Notably, no patients with LSM <13.6 kPa experienced decompensation. Splenomegaly and thrombocytopenia had poor accuracy of 58% to predict decompensation.

In a second study, direct puncture of the hepatic vein and portal vein were done to calculate portal pressures at the time of partial liver resection. Thirty-four patients had both HVPG and LSM measurements by TE-LSM. The majority with LSM >22 kPa (67%) developed complications after partial hepatectomy, and two patients died due to liver failure in the 90-day postoperative period.[93]

Change in LSM and SSM and relationship to outcomes. There are limited data on LSM change over time (particularly compared with HVPG) and prediction of clinical liver-related events. In one study, a change in SWE-LSM correlated with a change in HVPG.[104] Although ELF was not predictive of outcome, FibroTest, NFS, APRI, and change in FIB-4 (HR 1.10, 95% CI 1.01–1.21) from baseline were associated with liver-related clinical events. Change in HVPG had a similar magnitude of change (HR 1.15, 95% CI 1.09–1.22); however, prediction of clinical events was modest (c-statistic 0.65, 95% CI 0.57–0.74).[89] In a prospective multicenter study of patients ($n = 226$) with cirrhosis and CSPH who achieved SVR after antiviral therapy,[105] TE-LSM decreased with antiviral therapy but did not correlate with changes in HVPG. Overall, 8% of patients had decompensation during a median follow-up of 3.7 years. However, neither baseline LSM, change in HVPG, or change in LSM were associated with decompensation.

Other studies have assessed SSM for prediction of decompensation or portal hypertension-related outcomes. One study with median follow-up of 48 months showed that elevated SSM predicted hepatic decompensation and death.[106] SSM has also been shown to predict outcome after TIPS[107–109] and to predict recurrence of HCC after resection.[110]

OTHER CONSIDERATIONS AND LIMITATIONS

It is important to emphasize that these guidelines on NILDAs were developed based on evidence derived from patients with cirrhosis and a high prevalence of CSPH. Additionally, clinicians must consider what NILDA tools are available to them. Studies of TE-LSM and HVPG that have examined serial changes in NILDAs paired with changes in HVPG as predictors of clinical

outcomes remain limited and, unless under a research protocol, are likely to remain limited due to the invasive nature of HVPG. Among imaging-based NILDAs, most data are available for TE. Most of the studies are from single-center cohorts, and measurement of HVPG is generally not standardized or uniform. Further, there is spectrum bias (difference in prevalence of cirrhosis and CSPH across studies). In addition, the risk of future decompensation is variable, even among patients with cirrhosis, as it is contingent on where they lie on the compensated/decompensated spectrum, use of primary prophylaxis to reduce risks of complications, treated or untreated cirrhosis, and variable clinical practices for monitoring. Therefore, generalizability of published data is not possible. It is unclear whether TE-LSM (a surrogate for intrahepatic resistance to flow) is able to accurately predict decompensation given that extrahepatic factors (hyperdynamic circulation, splanchnic vasodilation, infection, and renal failure) in advanced cirrhosis modify outcomes. Variation in the prediction of outcomes is also almost certainly impacted by the presence of ongoing liver injury (i.e., as might be expected with continued reception of active ethanol or weight gain) as compared with arrested liver injury (for example, after DAA therapy or ethanol cessation).[111]

A SIMPLIFIED NILDA ALGORITHM FOR DETECTION OF CSPH

In an effort to facilitate incorporation of NILDAs into clinical practice, the AASLD NILDA writing group developed an algorithm intended to be used by clinicians to readily identify or exclude CSPH (Figure 1). Because blood-based NILDAs have not been shown to have sufficient sensitivity for detection of CSPH and blood-based NILDA levels consistent with fibrosis may falsely suggest CSPH, it is suggested that imaging-based NILDAs be the primary approach. An LSM <15 kPa combined with a platelet count >150,000 mcl essentially rules out CSPH. Conversely, in the absence of confounding clinical factors, such as right heart failure or severe hepatic inflammation, an LSM ≥25 kPa rules in CSPH. In those with LSM 10–15 kPa and platelet counts <150,000 mcl, or if LSM 15–25 kPa and platelet >150,000 mcl, CSPH may be possible; once alternative etiologies for thrombocytopenia have been excluded, additional testing, such as MRE (a value ≥5.1 kPa is suggestive of CSPH), SSM (a value ≥40 kPa is suggestive of CSPH), esophagogastroduodenoscopy (EGD) (for detection of varices which, if present, indicate CSPH), or direct HVPG. It should be noted that this algorithm is best applied to patients with active primary liver disease. For patients for whom their primary liver disease has

been treated or eliminated (i.e., patients with HBV or HCV who are receiving active drug or have received DAA therapy, respectively), it is likely that thresholds for LSM and/or platelets are different.

SUMMARY

The available data suggest that NILDAs are modestly effective at detecting CSPH—likely reflecting a balance between the fact that NILDAs are most accurate at detecting advanced fibrosis/cirrhosis (which is typically present in patients with CSPH) and the imprecise relationship between fibrosis and portal hypertension. The available data are limited because of a variety of methodological issues in currently available studies, including small sample sizes, examination of heterogeneous populations, and wide variability in study design. Although there is insufficient evidence to reliably recommend the use of blood-based NILDAs for detection of CSPH, and available data suggest that LSM (and perhaps SSM) are promising noninvasive tools for predicting CSPH, there are limitations. These include the fact that there are inherent technical limitations to performance of elastography, and accurate measurements are not always possible to obtain (particularly in patients with obesity and in those with ascites). Intrahepatic inflammatory activity appears to confound LSM assessment of fibrosis[3] and likely also confounds assessment of CSPH. Available data indicate that liver stiffness is more accurate at low HVPG levels than at higher levels. In clinical practice, because LSM has a high sensitivity (and specificity) for CSPH at high LSM (>25 kPa), patients with an LSM >25 kPa should be considered to have a very high likelihood of having CSPH and it being managed appropriately.[21] Addition of the platelet count to LSM likely improves the ability to detect CSPH, and thus, the platelet count appears to be complimentary to LSM. Further, combinations of individual components of the FIB-4 and LSM into a single scoring system may be able to more accurately predict CSPH. It must be pointed out that available data specifically in the NASH space are not as robust as in other CLDs, and NILDAs in this group must be used with caution. We conclude that the use of NILDAs for detection of CSPH is reasonable but is imperfect. MR-based LSM is also attractive but is limited by the fact that it is an expensive modality and has less availability than US-based modalities. Finally, the effectiveness of LSM/SSM in the setting of noncirrhotic portal hypertension and perhaps some parenchymal liver diseases such as primary biliary cholangitis or schistosomiasis is unknown.

FUTURE RESEARCH

It is clear that much more study of the utility of NILDAs in assessment of portal hypertension is needed. Because NILDAs have replaced invasive testing in clinical practice in many situations, the collection of robust data comparing NILDAs directly with HVPG is likely to be limited. Notwithstanding, not only is more work required to assess whether currently available noninvasive tests such as LSM can be used alone or in combination with other tests to determine which patients have CSPH, but further study of novel noninvasive techniques (particularly those that utilize current imaging methods) is needed. SSM as NILDAs for portal hypertension holds promise and requires further study. Finally, although research in this area will be limited by the invasiveness of measuring HVPG, this issue should not preclude much needed further investigation. Our writing group identified several major areas for future research that are needed, which are as follows:

- Research is needed on the generalizability of NILDAs across different populations and disease states.
- Research is needed on the use of NILDAs to assess CSPH in pediatric populations.
- The performance and threshold of blood- and imaging-based NILDAs for CSPH in MASLD need to be defined.
- Studies using combination techniques, including combinations of imaging-based and/or blood-based NILDAs, are required.
- Further study of the integration of NILDAs in management algorithms for CSPH that are tied to clinical outcomes is required.
- Utilization of artificial intelligence and machine learning should allow for incorporation of demographics and clinical data with NILDAs to improve diagnosis and management of portal hypertension and CLD.
- Longitudinal studies of NILDAs to assess the natural history of portal hypertension, specific liver diseases, clinical outcomes, and changes with therapy are needed. Study of the utility of NILDAs in real-time disease management is also needed.
- Further study of the utility of SSM for the prediction of CSPH is required.
- Cost-effectiveness studies of NILDAs in patient care paradigms are required.
- Novel noninvasive techniques for the assessment of CSPH are needed.

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FIGURE 1 A simplified NILDA algorithm for detection of CSPH. Because blood-based NILDAs have not been shown to have sufficient sensitivity for detection of CSPH (defined as HVPG ≥10 mmHg) and blood-based NILDAs consistent with fibrosis may falsely suggest CSPH, it is suggested that imaging-based NILDAs be the primary approach to assess CSPH. It should be noted that the majority of data informing noninvasive assessment of CSPH has been obtained with TE-LSM, but other LSM techniques are likely to be equivalent. An LSM value of <15 kPa largely excludes CSPH (with the exception of patients with low platelet counts, which raises the possibility of portal hypertension–induced splenomegaly), and a value ≥25 kPa indicates that CSPH is highly likely to be present. For patients with an LSM value of <15 kPa, a platelet count ≥150,000/mcl further suggests the absence of CSPH. For those with an LSM value of <15 kPa and a platelet count <150,000/mcl, CSPH is uncertain. Patients with LSM values between 15 and 25 kPa are considered to be in the "gray zone," and clinical judgement is required; here, other testing is likely to be helpful. For example, the platelet count may be helpful to indicate whether portal hypertension is present or not. In those with a platelet count ≤110,000/mcl, CSPH is more likely, as it is for those with an LSM ≥20 kPa and a platelet count <150,000/mcl. Note, the integration of platelet counts into this algorithm in patients with primary hematologic or splenic disorders is not possible. For centers with the capability to further assess these patients (i.e., with MRE, SSM, esophagogastroduodenoscopy, or direct HVPG), further evaluation may be warranted. This algorithm is based on studies in patients with active primary liver disease. For patients in whom the primary liver disease has been treated or eliminated (i.e., patients with HBV or HCV who are on active drug treatment or have received DAA therapy), it is likely that thresholds for LSM and/or platelets will vary. Abbreviations: CSPH, clinically significant portal hypertension; DAA, direct-acting antiviral; HBV, hepatitis B virus; HCV, hepatitis C virus; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; NILDA, noninvasive liver disease assessment; SSM, spleen stiffness measurement; TE, transient elastography.

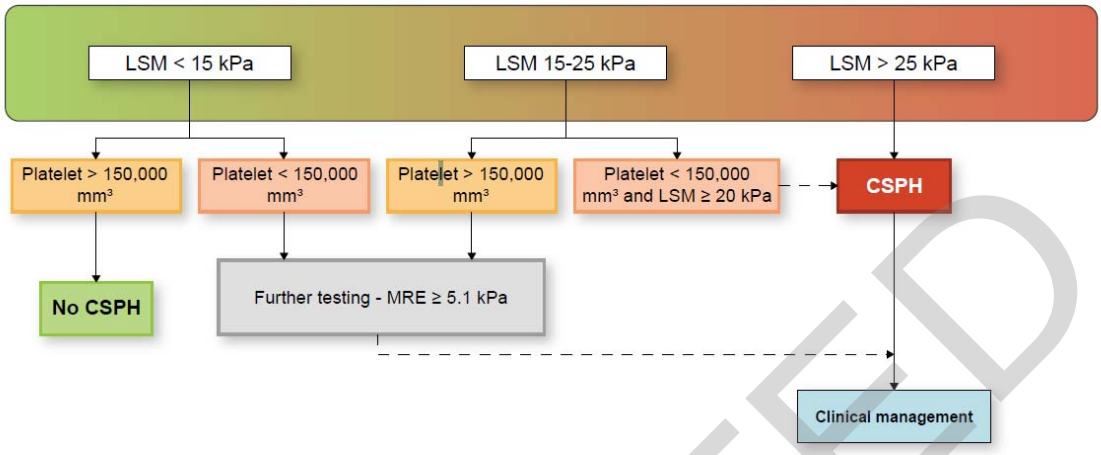

TABLE 1 PICO questions in NILDAs

Imaging based with or without being blood based for portal hypertension in adults	
PICO 1	In adult patients with chronic liver diseases, what is the diagnostic performance of noninvasive methods (blood and/or imaging based) for predicting the presence and/or severity of portal hypertension, including CSPH (based on HVPG)?
PICO 2	In adult patients with CLD and clinically significant portal hypertension, what is the prognostic performance of noninvasive assessments of liver fibrosis for predicting liver-related clinical outcomes (decompensation and transplant-free survival) compared with HVPG?

Abbreviations: CLD, chronic liver disease; CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; NILDA, noninvasive liver disease assessment; PICO, patient, intervention, comparison and outcome.

TABLE 2 GRADE system approach[a]

1. Rating the quality of evidence			
Study design RCT Observational	Initial rating of quality of evidence High Moderate Low Very low	Rate down when there is Risk of bias Inconsistency Imprecision Indirectness Publication bias	Rate up when there is Large effect size (e.g., RR 0.5) Very large effect (e.g., RR 0.2) Dose response gradient All plausible confounding that would increase the association.
2. Determinants of strength of a recommendation			
Quality of evidence Balance of benefits and harms Patient values and preferences Resources and costs			
3. Implications of the strength of a recommendation			

Strong Population: most people in this situation would want the recommended course of action and only a small proportion would not. Healthcare workers: most people should receive the recommended course of action. Policy makers: the recommendation can be adopted as policy in most situations. Conditional Population: the majority of people in this situation would want the recommended course of action, but many would not. Healthcare workers: be prepared to help patients make a decision that is consistent with their values using decision aids and shared decision making. Policy makers: there is a need for substantial debate and involvement of stakeholders.

Abbreviations: GRADE, Grading of Recommendation Assessment, Development and Evaluation; RCT, randomized controlled trial; RR, relative risk.

[a]This table was modified from Guyatt et al.[112]

TABLE 3 Diagnostic performance indices used in NILDAs

Diagnostic index	Calculation	Comments
Sensitivity	TP/(TP + FN)	Usually independent on the prevalence of the disease. Correctly detects patients who have the condition; does not miss the disease.
Specificity	TN/(TN + FP)	Usually independent on the prevalence of the disease. A high specificity means a test is useful for ruling in disease and does not falsely assign the disease.
Accuracy	(TP +TN)/(P + N)	—
PPV	TP/(TP + FP) × 100	Used to "rule in" disease.
NPV	TN/(TN + FN) × 100	Important for screening studies to not miss disease.
AUROC	Graph values of test performance from 0 (a perfectly inaccurate test) to 1 (a perfect test). Plots the diagnostic ability of a binary classifier system as its discrimination threshold is varied.	Summarizes the overall diagnostic accuracy of a test. In general, an AUROC of 0.5 suggests no discrimination (i.e., ability to diagnose patients with and without the disease or condition based on the test), 0.7–0.8 is considered acceptable, 0.8–0.9 is considered excellent, and >0.9 is considered outstanding.
c-statistic	The probability that a randomly selected subject who experienced the outcome will have a higher predicted probability of having the outcome occur than a	A value of 0.5 means that the model is no better than predicting an outcome than random chance. Values >0.7 indicate a good model. Values >0.8 indicate a strong model.

	randomly selected subject who did not experience the outcome.	

The ratio of odds of positivity of those with disease relative to odds of positivity in those without disease is demonstrated. The higher the diagnostic odds ratio, the better the test.

Abbreviations: AUROC, area under the receiver operating characteristic curve; FN, false negative; FP, false positive; N, all negative; NILDA, noninvasive liver disease assessment; NPV, negative predictive value; P, all positive; PPV, positive predictive value; TN, true negative; TP, true positive.

TABLE 4 Components of blood-based biomarker algorithms for fibrosis and portal hypertension[a]

Blood-marker panel, year	Study cohort	Clinical variables	Indirect markers	Direct markers	Model algorithm
APRI, 2003[113]	HCV	—	AST, platelets	—	[(AST level/ULN)/platelet count (10^9/L)] × 100
FIB-4, 2006[114]	HIV-HCV	Age	AST, ALT, platelets	—	Age (years) × AST (U/L) platelet count (10^9/L) × √ALT (U/L)
NFS, 2007[115]	NAFLD	Age, BMI, IFG/diabetes	AST, ALT, platelets, albumin	—	−1.675 + (0.037 × age) + (0.094 × BMI) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × (AST/ALT ratio) − (0.013 × platelets) − (0.66 × albumin)
FibroTest, 2001[116]	HCV	—	□2M, GGT, total bilirubin, haptoglobin, ApoA-I	—	Proprietary
ELF, 2004[117]	Mixed	Age	—	HA, PIIINP, TIMP-1	Proprietary

FibroSpect II, 2004[118]	HCV	—	□2M	HA, TIMP-1	Proprietary
FibroMeter, 2005[119]	Mixed	Age	Platelets, prothrombin index, urea, AST, □2M	HA	Proprietary

Abbreviations: □2M,□□2-macroglobulin; ALT, alanine aminotransferase; APoA-1, apolipoprotein A-1; APRI, aspartate aminotransferase–platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; ELF, enhanced liver fibrosis; FIB-4, Fibrosis 4 index; GGT, gamma-glutamyl transferase; HA, hyaluronic acid; IFG, impaired fasting glucose; NFS, NAFLD fibrosis score; PIIINP, amino-terminal propeptide of type III procollagen; TIMP-1, tissue inhibitor matrix metalloproteinase 1; ULN, upper limit of normal.

[a]Original study cohorts are referenced.

TABLE 5 Clinical factors affecting performance of blood- and imaging-based noninvasive assessment of portal hypertension and fibrosis

Clinical condition	Tools affected	Comments
Obesity[120–125]	TE MRE pSWE/2D-SWE	Although an XL probe can remediate TE-LSM failure in most cases with skin-to-(liver) capsule distance ≥25 mm, extreme obesity (BMI ≥40 kg/m^2) can result in TE-LSM failure. Depending on body frame, extreme obesity can also affect transmission of mechanical wave leading to MRE failure. SWE acoustic signal transmission can also be affected by obesity, resulting in failure.
Narrow intercostal space	TE	If not corrected by repositioning, this can lead to failure or falsely elevated LSM estimation.
Ascites[121]	TE pSWE	Transmission of vibration and mechanical signals are affected, leading to failure.
Splenectomy	APRI FIB-4 FibroIndex FibroMeter NFS SSE	As these tools use platelets as a biomarker of portal hypertension, attenuated thrombocytopenia from splenectomy gives a falsely higher fibrosis estimation. Spleen stiffness cannot be assessed after splenectomy.
Thrombocytopenia (not related to portal hypertension)	APRI FIB-4 FibroIndex FibroMeter NFS	Thrombocytopenia from other conditions gives a falsely higher estimation of the degree of portal hypertension.
Iron overload[126]	MRE	T2 signaling is affected, leading to failure.

Steatosis[127–129]	TE SWE	Although its clinical impact is unclear, moderate to severe steatosis causes TE-LSM to overestimate LSM.
Active alcohol use[130]	FibroTest Hepascore	GGT increases, leading to falsely elevated fibrosis estimation.
Hepatic venous outflow tract obstruction[131]	TE MRE pSWE/2D-SWE	Retrograde vascular congestion results in increased stiffness of hepatic parenchyma and falsely elevated LSM estimation.
Obstructive cholestasis[132]	TE MRE pSWE/2D-SWE	Large bile duct obstruction results in increased stiffness of hepatic parenchyma and falsely elevated LSM estimation.
Hepatic infiltration[133]	TE MRE pSWE/2D-SWE	Amyloid or tumoral infiltration results in increased stiffness of hepatic parenchyma and falsely elevated LSM estimation.
Elevated ALT and/or AST (inflammatory hepatitis)[130, 134, 135]	APRI FIB-4 FibroIndex FibroMeter TE NAFLD fibrosis score	Elevated aminotransferases occurring in relation to acute or acute-on-chronic hepatitis lead to falsely elevated fibrosis and/or LSM estimation.
Chronic kidney disease[136–138]	FibroIndex APRI FIB-4 FibroMeter TE	Elevated urea levels can result in falsely lower fibrosis estimation. Patients with hemodialysis tend to have lower ALT and AST levels, resulting in falsely lower fibrosis estimation. Hemofiltration can result in higher stiffness in patients with baseline fluid overload.

Malnutrition	NFS	Albumin reduction that is disproportionate to liver dysfunction results in falsely elevated fibrosis estimation.
Inflammatory condition	FibroTest FibroIndex Hepascore FibroMeter	Can result in increased α2-macroglobulin levels and falsely elevated FibroTest, and increased α-globulin and falsely elevated FibroIndex.
Hemolysis	FibroTest	Haptoglobin levels are decreased and total bilirubin is increased, leading to falsely elevated fibrosis estimation.
Gilbert syndrome and other cholestatic diseases	FibroTest Hepascore	Increased total bilirubin and falsely elevated fibrosis estimation can occur.
Postprandial[139]	TE NFS	Liver stiffness increases of up to 26% have been described for TE-LSM 2 hours after a meal. A rise in postprandial glucose (>110 mg/dl) falsely elevates NAFLD fibrosis score. Similar effects are expected with other forms of liver stiffness measurement (SWE and MRE).
Gastrectomy[140]	FibroSpect Hepascore ELF	Increases in hyaluronic acid result in falsely elevated fibrosis estimation.
Extrahepatic fibrosing conditions[141]	FibroMeter FibroSpect ELF	Conditions such as interstitial lung disease can increase collagen turnover markers, resulting in falsely elevated fibrosis estimation.
Acute sickle cell crisis[142]	FibroTest TE	The results are related to hemolysis (as above). Acute vaso-occlusive crisis increases LSM.
Critically ill[143]	TE	Deceased liver donors in the ICU may have falsely elevated LSM, which is potentially related to fluid overload and nonspecific or ischemia-related elevations in aminotransferases.

Abbreviations: 2D, two-dimensional; ALT, alanine aminotransferase; APRI, aspartate aminotransferase–platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; ELF, enhanced liver fibrosis; FIB-4, Fibrosis 4 index; GGT, gamma-glutamyl transferase; ICU, intensive care unit; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; NFS, NAFLD fibrosis score; pSWE, point shear wave elastography; SSE, spleen stiffness elastography; SWE, shear wave elastography; TE, transient elastography; XL, extra large.

TABLE 6 Operational characteristics of imaging-based techniques for assessment of fibrosis and portal hypertension

Method	**Availability**	**Cost**	**Evidence**	**ROI size**	**ROI placement**	**Failure rate**	**Reasons for failure**	**Units**
TE	Widespread in hepatology offices	Low	Well validated	Small	Restricted—no guidance	<5%–15%	High BMI (M probe) ascites	Young's modulus (kPa)
ARFI methods	Moderate	Low	Moderate validation	Small (pSWE) Medium (2D-SWE)	Flexible up to 8-cm depth with US guidance	<5%–15%	High BMI	SWE: Young's modulus (kPa) pSWE: wave speed (ms^{-1})
MRE	Limited	High	Limited validation	Large	Whole organ coverage	<5%	Liver iron deposition, large ascites, high BMI, 3T (for 2D GRE)	Shear modulus (kPa)

Abbreviations: 2D, two-dimensional; ARFI, acoustic radiation force impulse; BMI, body mass index; GRE, gradient recalled echo; MRE, magnetic resonance elastography; pSWE, point shear wave elastography; ROI, region of interest; SWE, shear wave elastography; TE, transient elastography; US, ultrasound; 3T, 3 Tesla.

TABLE 7 Estimation of CSPH using LSM

Author (year)	Liver disease[a]	Technique	Total *N*	Cirrhosis, *N* (%)	CSPH, *N* (%)[b]	Cut off (kPa or m/s)[c]	AUROC[c]	Sens (%)	Spec (%)	PPV (%)	Comments
Carrion et al. (2006)[63]	HCV	TE	124	19 (15)	15 (12)	8.7	0.94	NA	NA	NA	HCV was recurrent after liver transplant.
Vizzutti et al. (2007)[62]	HCV	TE	61	61 (100)	47 (77)	13.6	0.99	97	92	97	Correlation of LSM and HVPG was poor at HVPG ≥12 mm Hg.
Bureau et al. (2008)[61]	Mixed	TE	144	89 (59)	76 (51)	13 21	NA 0.95	93 90	84 93	84 93	—

Lemoine et al. (2008)[60]	HCV	TE	44	44 (100)	34 (77)	20.5	0.76	63	70	88	Active HCV therapy, PVT, and treatment with beta-blockers were excluded.
	ALD	TE	48	48 (100)	40 (83)	34.9	0.94	90	88	97	
Sanchez-Conde et al. (2011)[59]	HCV/ HIV	TE	38	17/28 (61)	28 (74)	14	0.80	93	50	84	Patients without histological cirrhosis had clinical evidence suggestive of cirrhosis.
Colecchia et al. (2012)[58]	HCV	TE	100	100 (100)	65 (65)	16 24.2	0.92 0.92	95 52	69 97	NA NA	SSM was also performed; SSM, but not LSM, predicted clinical

											decompensation.
Llop et al. (2012)[57]	Mixed	TE	79	79 (100)	32 (40)	136	0.84	91	57	59	Cirrhosis was compensated with resectable liver lesions.
Reiberger et al. (2012)[56]	Mixed ETOH	TE TE	502 NA	NA NA	276 (55) NA	18 19	0.8 0.8	83 89	82 73	86 89	Patients with active ETOH consumption were excluded; there is no information on antiviral therapy.
Berzigotti et al. (2013)[55]	Mixed	TE	117	117 (100)	78 (67)	17.4	0.88	82	77	88	LSPS was also examined, which was slightly

											more accurate in predictio n of CSPH than LSM alone.
Hong et al. (2013)[54]	Mixe d	TE	59	59 (100)	42 (71)	22	0.85	83	74	87	At a cutoff of 24 kPa, the AUROC for HVPG ≥12 mm Hg was 0.88.
Salzl et al. (2014)[53]	Mixe d	TE ARFI	59 (10 0%)	59 (100)	42 (71)	16. 8 2.6 m/s [c]	0.87 0.86	90 71	75 88	88 94	The failure rate of TE was 25%. Patients who received beta-blockers

											were excluded.
Attia et al. (2015)[46]	Mixed	ARFI	78	67 (86)	67 (86)	2.2 m/s[c]	0.93	97	89	99	SSM was also performed.
Cho et al. (2015)[34]	ALD	TE	88	88 (100)	44 (50)	21.8	0.85	72	70	72	LSM and LSPS (AUROC 0.82) were better than APRI and FIB-4.
Elkrief et al. (2015)[47]	Mixed	SWE	77	77 (100)	69 (90)	24.6	0.87	81	89	98	SSM was also performed. VCTE and SWE were both performed. Failure of VCTE was high for both

											LSM and SSM.
Kim et al. (2015)[48]	Mixed	SWE	92	92 (100)	77 (84)	15.2	0.82	86	80	96	Patients with advanced liver failure were excluded, and patients being treated with vasoactive drugs were excluded.
Kitson et al. (2015)[49]	Mixed	TE	95	88 (93)	70 (74)	29	0.90	72	100	100	LS <25.0 kPa and a platelet count >150 × 10^9/L excluded CSPH with 92% sensitivity.

Procopet et al. (2015)[50]	Mixed	TE	43	43	NA	13.6	0.93	91	71	NA	SSM was also performed. LSM was higher (median 36 kPa) and more variable with decompensation.
			43	43	NA	21.0	0.93	64	95	NA	
		SWE	46	46	NA	15.4	0.94	90	90	NA	
Schwabl et al. (2015)[51]	Mixed	TE	226	124 (55)	72 (32)	16.1	0.96	95	87	76	A total 76% of the patients had viral etiology.
Zykus et al. (2015)[52]	Mixed	TE	107	102 (95)	78 (73)	17.4	0.95	88	88	96	SSM was also performed.
Mandorfer et al. (2016)[45]	HCV (post-SVR)	TE	60	60 (100)	41 (68)	27.2	NA	59	90	94	All patients were treated with

											DAA therapy; 84% were in CTP group A.
Jansen et al. (2017)[44]	Mixed	SWE	155	155 (100)	104 (67)	24.6	0.86	68	80	88	SSM was also performed.
Kumar et al. (2017)[43]	Mixed	TE	326	326 (100)	278 (85)	21.6	0.74	79	67	93	There was poorer performance as HVPG rose above >10 mmHg.
Wagner et al. (2018)[40]	Mixed	MRE	33	10 (29)	9 (27)	5.8	0.74	55	91	NA	Perfusion metrics were most accurate. SSM was also

											performed; SSM did not correlate with HVPG.
Mauro et al. (2018)[41]d	HCV	TE	112	37 (33)	NA	11.3	0.89	76	94	58	HCV was post-OLT.
Salavrakos et al. (2019)[38]	ALD	TE	118	45 (38)	28 (24)	30.6	0.92	81	94	NA	Patients had been actively drinking ETOH up to 2 weeks prior to TE.
Zhu et al. (2019)[39]	HBV	SWE	104	104 (100)	84 (81)	16.1	0.72	78	72	NA	SSM was also performed.
Zhu et al.	HBV	ARFI	64	64 (100)	NA	1.8 m/s	0.67	79	56	74	Performance was better in

(2020)[37]											patients with "advanced cirrhosis." SSM had no correlation with HVPG.
Pons et al. (2021)[36]	ALD HCV NASH HBV	TE TE TE TE	203 358 248 27	203 (100) 358 (100) 248 (100) 27 (100)	169 (83) 210 (59) 97 (39) 16 (63)	20 25 20 25 20 25 20 25	NA NA NA NA NA NA NA NA	92 85 75 57 79 59 82 64	65 82 80 93 75 89 100 100	93 96 84 92 67 77 100 100	Patients were from multiple centers, including some from earlier studies. Patients had "compensated advanced chronic liver disease."

Banini et al. (2022)[35]	Mixed	TE	142	85 (60)	16 (11)	21.3	0.68	56	74	21	Cohort was primarily patients with NASH.

Abbreviations: ALD, alcohol-related liver disease; ARFI, acoustic radiation force impulse; AUROC, area under the receiver operating characteristic curve; CSPH, clinically significant portal hypertension; CTP, Child-Turcotte-Pugh; DAA, direct-acting antiviral; ETOH, ethanol; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; LSPS, LSM–spleen/platelet score; MRE, magnetic resonance elastography; NA, not available; OTL, orthotopic liver transplant; PPV, positive predictive value; Sens, sensitivity; Spec, specificity; SVR, sustained viral response; SWE, shear wave elastography; TE, transient elastography.

[a]Populations studied have been widely variable in terms of each liver disease etiology and degree of underlying fibrosis. Adult studies only are included here.

[b]In some studies, the number of patients with CSPH was estimated based on descriptions of the cohorts provided.

[c]AUROC is used to predict CSPH (HVPG ≥ 10 mm Hg) at the specified cutoff.

[d]Posttransplant recipients

TABLE 8 Estimation of CSPH using SSM

Author (year)	Liver disease[a]	Technique	Total *N*	Cirrhosis, *N* (%)	CSPH by HVPG, *N* (%)[b]	Cutoff (kPa unless otherwise noted)	AUROC[c]	Sensitivity (%)	Specificity (%)	PPV	Comparison of SSM and LSM
Hiroka et al. (2011)[68]	Mixed	RTE	60	48 (80)	28 (47)	8.2	0.98	NA	NA	NA	AUROC for SSM was higher than LSM (AUROC 0.83).
Colecchia et al. (2012)[58]	HCV	TE	100	100 (100)	65 (65)	40 52.8	0.97 0.97	99 77	74 97	NA NA	LSM and SSM had similar performance

											characteristics.
Attia et al. (2015)[46]	Mixed	ARFI	78	67 (86)	70 (90)	2.32 m/s	0.97	96	89	96	LSM had similar performance characteristics.
Elkrief et al. (2015)[47]	Mixed	2D-SWE	77	77 (100)	69 (90)	34.7	0.64	40	100	100	LSM had better performance characteristics.
Procopet et al. (2015)[50]	Mixed	SWE	55	55 (100)	28 (51)	NA	0.73	NA	NA	NA	LSM had better performance characteristics. SSM failed in 34% of

											patients.
Zykus et al. (2015)[52]	Mixed	TE	99	95 (95)	NA	47.6	0.85	77	79	92	LSM had better performance characteristics.
Takuma et al. (2016)[69]	Mixed	ARFI	60	60 (97)	35 (57)	3.10 m/s	0.94	97	58	75	—
Jansen et al. (2017)[44]	Mixed	SWE	112	112 (100)	75 (67)[a]	26.3	0.84	80	84	91	LSM had similar to slightly poorer performance characteristics.
Zhu et al.	HBV	SWE	104	104 (100)	84 (81)	25.3	0.81	85	79	NA	AUROC for SSM

(2019)[39]											was higher than LSM.

Abbreviations: 2D, two-dimensional; ARFI, acoustic radiation force impulse; AUROC, area under the receiver operating characteristic curve; CSPH, clinically significant portal hypertension; HBV, hepatitis B virus; HCV, hepatitis C virus; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; NA, not available; PPV, positive predictive value; RTE, real-time elastography; SSM, spleen stiffness measurement; SWE, shear wave elastography; TE, transient elastography.

[a]Populations studied have been widely variable in terms of each liver disease etiology and degree of underlying fibrosis.

[b]In some studies, the number of patients with CSPH was estimated based on descriptions of the cohorts provided.

[c]AUROC is used to predict CSPH (HVPG ≥ 10 mm Hg) at the specified cutoff.

TABLE 9 Studies comparing HVPG and blood- or imaging-based NILDAs in patients with cirrhosis to predict decompensation events, portal hypertension-related outcomes, or death

Blood-based NILDA											
Author (year)	**Method**	**Population**	**Total *N***	**F/u (months)**	**Outcome**	**Incidence of decompensation**	**Marker**	**Cutpoint**	**Se**	**Sp**	**AUROC or other summary statistic**
Sanyal et al. (2019)[89]	Blood marker	NASH cirrhosis enrolled in simtuzumab trials	258	31 (median)	Liver disease–related complications: ascites,	50 (19 %)	HVPG	10 mm Hg	—	—	c-statistic 0.72
							ELF[a]	11.3	51	72	c-statistic 0.68

					varices, HE, increase in CTP score, and death						
Hsieh et al. (2018)[90]	Blood marker	Cirrhosis, 42% child A	242	6 (endpoint)	Death	7 (3%)	HVPG	—	—	—	0.61
							APRI	—	—	—	0.59
							FIB-4	—	—	—	0.64
							Lok Index	—	—	—	0.73
Imaging-based NILDA											

Author (year)	Method	Population	Total *N*	F/u (months)	Outcome	Incidence of decompensation	Marker	Cut point	Se	Sp	AUROC or other summary statistic
Robic et al. (2011)[91]	TE-LSM	100 patients with HVPG and TE (65% with cirrhosis)	100 (96 with TE)	24 (endpoint)	PHT complications: ascites and VB	18 (18 %)[b]	HVPG	10 mmHg	100	60	0.83
						—	LSM	21.1 kPa	100	65	0.84
					Liver disease–related complications: VB, ascites, HE,	41 (41 %)[b]	HVPG	10 mmHg	83	71	0.81
							LSM	21.1 kPa	82	76	0.84

					HCC, sepsis, LT, and death						
Colecchia et al. (2014)[92]	TE-LSM and SSM	Patients with HCV and cirrhosis, 100% (untreated)	92	24 (endpoint)	PHT complications: ascites, VB, and HE	30 (33%)	HVPG	10 mmHg	—	—	0.83 (accuracy)
							SSM	54.0 kPa	97	—	0.85 (accuracy)
							LSM	Not independently associated with outcome			
Kitson et al. (2015)[49]	TE-LSM	95 patients with HVPG and TE, 88 (93% cirrhosis)	90 with F/u	15.1 (median)	PHT compensated	28 (31%)	HVPG	10 mmHg	100	40	PPV 43%
							LSM	21.1 kPa	82	45	PPV 40%
								34.5	75	69	PPV 52%

							LSM	kPa			
Rajakannu et al. (2017)[93]	TE-LSM	HCC	102, 56 (49%) with cirrhosis)	3 (endpoint)	Decompensation after hepatectomy: ascites, jaundice, and HE	Mortality 5 (4.7%)	HVPG	10 mmHg	29	96	0.71
						Decompensation 9 (8.5%)	LSM	22 kPa	43	93	0.81
Procopet et al. (2018)[94]	TE-LSM	HCC	51 (27 with both HVPG and LSM)	3 (endpoint)	Decompensation after hepatectomy: ascites, VB,	15 (29%)[b]	HVPG	—	—	—	0.88
							LSM	—	—	—	0.81

					HE, jaundice, and AKI						

Abbreviations: AKI, acute kidney injury; APRI, aspartate aminotransferase–platelet ratio index; AUROC, area under the receiver operating characteristic curve; CTP, Child-Turcotte-Pugh; ELF, European Liver Fibrosis; FIB-4, Fibrosis 4 index; F/u, follow-up; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; LT, liver transplant; NILDA, noninvasive liver disease assessment; PHT, portal hypertension; PPV, positive predictive value; Se, sensitivity; Sp, specificity; SSM, spleen stiffness measurement; TE, transient elastography; VB, variceal bleeding.

[a]Data were not given on FibroSure, NAFLD fibrosis score, FIB-4, or APRI, although they were measured.

[b]The percent decompensation in the subset analyzed with both HVPG and LSM is unclear.