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Noninvasive Assessment of Liver Disease in Patients With Nonalcoholic Fatty Liver Disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is estimated to afflict approximately 1 billion individuals worldwide. In a subset of NAFLD patients, who have the progressive form of NAFLD termed ***nonalcoholic steatohepatitis*** (NASH), it can progress to advanced fibrosis, cirrhosis, hepatocellular carcinoma, and liver-related morbidity and mortality. NASH is typically characterized by a specific pattern on liver histology, including steatosis, lobular inflammation, and ballooning with or without peri-sinusoidal fibrosis. Thus, key issues in NAFLD patients are the differentiation of NASH from simple steatosis and identification of advanced hepatic fibrosis. Until now, liver biopsy has been the gold standard for identifying these 2 critical end points, but has well-known limitations, including invasiveness; rare but potentially life-threatening complications; poor acceptability; sampling variability; and cost. Furthermore, due to the epidemic proportion of individuals with NAFLD worldwide, liver biopsy evaluation is impractical, and noninvasive assessment for the diagnosis of NASH and fibrosis is needed. Although much of the work remains to be done in establishing cost-effective strategies for screening for NASH, advanced fibrosis, and cirrhosis, in this review, we summarize the current state of the noninvasive assessment of liver disease in NAFLD, and we provide an expert synthesis of how these noninvasive tools could be utilized in clinical practice. Finally, we also list the key areas of research priorities in this area to move forward clinical practice.

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.12.036.

Conflicts of interest

The authors disclose the following: Laurent Castera: speaker bureau of AbbVie, Echosens, Intercept, Gilead, and Sirtex. Advisory boards for Allergan, Gilead, MSD, Pfizer, and Servier. Mireen Friedrich-Rust: speaker honorarium from Echosens, Siemens. Advisory board for Toshiba. Research support for Echosens, Supersonic, and Siemens. Rohit Loomba: grants from Allergan, BMS, Boehringer Ingleheim, Eli Lily, Galectin, Galmed, GE, Genfit, Gilead, Intercept, Janssen, Madrigal, NGM, Prometheus, Siemens, Shire, Pfizer, advisory committees for Arrowhead Research, Conatus, Galmed, Gemphire, Gilead, Intercept, NGM, and Cirius. Consultant for Bird Rock Bio, BMS, Coh Bar, Celgene, Civi Bio, Conatus, Enanta, Gilead, GRI Bio, Ionis, Metacrine, NGM, Receptos, Sanofi, Salix, Kowa, and Median technologies. Co-founder of Liponexus Inc.

Keywords

NAFLD; Steatosis; NASH; Fibrosis; Noninvasive; VCTE; CAP; MRI-PDFF; MRE; Serum Biomarkers; ARFI; SWE

Nonalcoholic fatty liver disease (NAFLD) affects around one-fourth of the general population worldwide.[1] Nonalcoholic steatohepatitis (NASH), the active form of NAFLD, characterized by histological lobular inflammation and hepatocyte ballooning, is associated with faster fibrosis progression and affects around 1.5%–6.5% of the general population.[1] NAFLD is frequently associated with metabolic comorbidities, such as obesity (51%; 95% confidence interval [CI], 41%–61%), type 2 diabetes (22%; 95% CI, 18%–28%), hyperlipidemia (69%; 95% CI, 50%–83%), hypertension (39%; 95% CI, 33%–%46), and metabolic syndrome (42%; 95% CI, 30%–56%).[1] Although the most common cause of death in patients with NAFLD is cardiovascular disease, independent of other metabolic comorbidities, NAFLD is becoming a major cause of liver disease-related morbidity (eg, cirrhosis, end-stage liver disease, hepatocellular carcinoma, and liver transplantation), as well as mortality.[2,3] NAFLD is expected in the next decade to become the leading indication for liver transplantation in the United States.[4] It is estimated that liver-specific mortality and overall mortality among patients with NAFLD are 0.77 and 11.77 per 1000 person-years, whereas they are 15.44 and 25.56 per 1000 person-years among patients with NASH.[1]

The vast majority of NAFLD patients, however, will not progress, only a minority, namely those with NASH and advanced hepatic fibrosis, are at greatest risk of developing complications of chronic liver disease.[5] Indeed, advanced fibrosis has been shown to be the major driver for long-term outcome and mortality.[6–8] Thus, key issues in patients with NAFLD are the differentiation of NASH from simple steatosis and identification of advanced hepatic fibrosis. Given the huge number of at-risk patients, there is a substantial unmet need for efficient and cost-effective means for risk stratification of NAFLD patients for these 2 critical end points. Liver biopsy, the gold standard for identifying these 2 end points until now, appears unrealistic and unsuitable. In addition, it has well-known limitations, including invasiveness, poor acceptability, sampling variability, and cost. As a result, this has fueled the development of alternative noninvasive strategies, which have been an area of intensive research over the past decade.[9]

This review is aimed at discussing the performance, advantages, and limitations of noninvasive methods for the management of patients with NAFLD, including diagnosis and quantification of steatosis, differentation of NASH from simple steatosis, and identification of advanced hepatic fibrosis.

Currently Available Noninvasive Methods and Their Limitations

Noninvasive methods rely on 2 different approaches: a “biological” approach based on the quantification of biomarkers in serum samples or a “physical” approach based on the measurement of liver stiffness, using either ultrasound- or magnetic resonance-based elastography techniques. Although these approaches are complementary, they are based on different rationales. Liver stiffness corresponds to a genuine and intrinsic physical property

of liver parenchyma, whereas serum biomarkers indicate several, not strictly liver-specific, clinical and serum parameters that have been associated with NASH or fibrosis stage, as assessed by liver biopsy.

Serum Biomarkers

Current serum biomarkers (summarized in Table 1) include predictive models for diagnosing or grading steatosis (such as the Fatty Liver Index) or staging fibrosis (eg, NAFLD Fibrosis Score), direct measures of hepatocellular damage (eg, circulating keratin 18 fragments) to differentiate patients with NASH from those with simple steatosis and direct measures of fibrosis (eg, PIIINP or Pro-C3) to discriminate patients with advanced fibrosis. Some are specific of NAFLD (eg, BARD and NAFLD fibrosis scores) whereas some have been initially designed in hepatitis C (aspartate transaminase [AST]/alanine transaminase [ALT] ratio, Aspartate Transaminase-to-Platelet Ratio Index [APRI], FIB-4). A few are proprietary formulas (FibroTest, Fibrometer, Hepascore, and Enhanced Liver Fibrosis [ELF] score) but most are nonpatented.

The practical advantages of analyzing serum biomarkers include their high applicability (>95%), their good interlaboratory reproducibility, and their potential widespread availability (nonpatented). However, none are liver-specific—their results can be influenced by comorbid conditions and they require critical interpretation of results.

Imaging Techniques

Elastography.—There are 2 different kinds of elastography techniques: ultrasound-based or magnetic resonance-based. The first one uses ultrasound to detect the velocity of the microdisplacements (shear waves) induced in the liver tissue, whereas the latter uses the magnetic resonance scanner. The shear wave's velocity is then converted into a liver stiffness measurement (LSM), expressed in kilopascals (kPa) or in meters per second. Vibration-controlled transient elastography (TE) has been the pioneer ultrasound-based technique and is the most widely used worldwide, but newer elastography modalities like point shear wave elastography (pSWE), which includes acoustic radiation force impulse imaging (ARFI), or 2dimensional shear wave elastography (2D-SWE), integrated in conventional ultrasound systems, are emerging.[10–12] Their main characteristics, advantages, and limitations are summarized in Table 2. TE and magnetic resonance elastography (MRE) provide additional information in patients with NAFLD. The same machine can be used to determine whether steatosis is present: controlled attenuation parameter (CAP) for TE and calculation of the proton-density fat traction (PDFF) for MRE. Comprehensive technical details can be found in the Supplementary Material.

Diagnosis and Grading of Steatosis

Serum Biomarkers

Several steatosis scores have been proposed for the detection of steatosis, including the SteatoTest,[13] Fatty Liver Index,[14] Hepatic Steatosis Index,[15] lipid accumulation product,[16] the Index of NASH,[17] and the NAFLD Liver Fat Score.[18] Their diagnostic performances have been summarized in a recent review.[19] Although SteatoTest, Fatty Liver Index NAFLD

Liver Fat Score, lipid accumulation product, and Hepatic Steatosis Index have been validated independently,[20–23] their diagnostic performances are difficult to compare, as they have been designed and validated against different standards: liver biopsy, ultrasonography, or magnetic resonance spectroscopy. Nevertheless, when the Fatty Liver Index, NAFLD Liver Fat Score, and Hepatic Steatosis Index were retrospectively compared in the same cohort of 324 patients with suspected NAFLD and liver biopsy, their area under the receiver operating characteristic (AUROC) values for the diagnosis of steatosis (>5%) did not differ (0.83, 0.80, and 0.81, respectively).[21] Further studies are needed, but it should be acknowledged that these scores have not gained much popularity, as they do not add much to the information provided by clinical, laboratory, and imaging studies done routinely in patients with suspected NAFLD.

Ultrasonography

Conventional ultrasonography is the most commonly used imaging method for the diagnosis of hepatic steatosis because it is widely available, well established, well tolerated, and cheap. Typical ultrasonography features are hyperechogenicity as compared to the right kidney parenchyma, distal attenuation, and the presence of areas of focal sparing.[24] The degree of steatosis can be subjectively scored as mild, moderate, and severe, or as reported in some studies by using ordinal ultrasonography scores.[25,26] In a large meta-analysis[24] (n = 34 studies, 2815 patients with suspected or known liver diseases), pooled sensitivities and specificities of ultrasonography to distinguish moderate-to-severe fatty liver from the absence of steatosis, taking liver biopsy as the reference, were 85% (80%–89%) and 93% (87%–97%), respectively. However, in clinical practice, mainly the presence or absence of steatosis is recorded and ultrasonography has the limitation that it can only detect steatosis with >2.5%–20% liver fat content[27] and, therefore, a relevant number of patients with steatosis starting at 5% liver fat content can be missed.[28] In addition, the accuracy of ultrasonography for diagnosis of liver steatosis is reduced in patients with obesity and coexistent renal disease.[29,30] Recent studies obtained better results using quantitative ultrasound.[28,31] Nevertheless, European guidelines for the management of NAFLD recommend using ultrasonography as first-choice imaging in adults at risk for NAFLD.[2]

Controlled Attenuation Parameter

In the initial study assessing its performances in 115 patients with chronic liver diseases (15% with NAFLD only), CAP was able to accurately detect steatosis ≥11%, ≥33%, and ≥66% with AUROCs of 0.91, 0.95 and 0.89, respectively.[32] Nevertheless, despite a good correlation with histological steatosis, overlapped results between different grades of steatosis suggest that CAP cannot differentiate adjacent grades of steatosis with good precision. A recent individual data meta-analysis[33] based on 19 studies using the M-probe and having included 2735 patients (537 with NAFLD; 19.6%) has reported for steatosis ≥11%, ≥33%, and ≥66%, AUROCs of 0.82, 0.86, and 0.88, respectively, sensitivities of 0.69, 0.77, and 0.88 and specificities of 0.82, 0.81 and 0.78, respectively. The authors proposed optimal cutoffs of 248 dB/m (95 % CI, 237–261 dB/m), 268 dB/m (95 % CI, 257–284 dB/m), and 280 dB/m (95% CI, 268–294 dB/m), respectively. Interestingly, CAP values were influenced by several covariates, including NAFLD, diabetes, and body mass index (BMI). Other authors, using magnetic resonance imaging (MRI)-PDFF as reference have

recently suggested 288 dB/m as an optimal cutoff for detection of ≥5% fat in the liver.[34] Table 3 summarizes the results of CAP in NAFLD patients.[35–45] Several comments can be made: most studies have been conducted in small sample size (<100 patients) and heterogeneous populations with variable BMI and diabetes prevalence; this may be an explanation for the differences in proposed cutoffs. However, the cutoff associated with significant steatosis (>33% of hepatocytes) is almost always >250 dB/m. Finally, most of these studies have been performed with the M-probe. In a recent US multicenter study, using the XL-probe, in 393 NAFLD patients, CAP had an AUROC of 0.76 for detecting steatosis >5% and a 96% positive predictive value at a cutoff of 263 dB/m.[45] In contrast, the accuracy of CAP for separating steatosis ≥33% and ≥66% was suboptimal.

Thus far only 2 studies[36,46] compared head to head the performance of CAP with M- and XL-probes, using liver biopsy as reference, with conflicting results. In one study (236 Western patients with chronic liver disease with a mean BMI 24.4 ± 6.3 kg/m^2), the performances and cutoff values were similar,[46] whereas in another study (57 NAFLD Chinese patients with a mean BMI 30.2 ± 5.0 kg/m^2), the performances were similar, but cutoff values were higher with the XL-probe.[36] Therefore, further studies are necessary before any firm conclusions can be drawn.

Only 2 studies have performed a head-to head comparison of CAP with ultrasonography, taking liver biopsy as reference: 1 in 72 patients with chronic liver disease[47] and the other 1 in 366 patients with chronic hepatitis B.[48] Both studies showed that the performance of CAP for detecting and grading liver steatosis was higher than that of ultrasonography, however, the rate of overestimation was significantly higher for CAP than for ultrasonography (30.5% vs 12.4%; $P < .05$).[48] More studies are needed before any firm conclusion can be drawn.

In the 3 studies[39,43,44] comparing CAP and PDFF magnetic resonance spectroscopy (MRS) for grading steatosis, using liver biopsy as reference, CAP was outperformed by MRI-PDFF. In a study in 78 American patients with NAFLD,[43] MRI-PDFF performed better than CAP for diagnosing all grades of steatosis (AUROC 0.99 vs 0.85, respectively; $P = .0091$). Similarly, in a study in 127 Japanese patients with NAFLD,[39] MRI-PDFF had better diagnostic accuracy than CAP, whatever the grade of steatosis. Finally, a study in 55 Dutch patients with NAFLD found similar results.[44]

Longitudinal studies are awaited. Recently, a study that followed up 4282 patients who had both a reliable LSM and ≥10 successful CAP measurements has shown that neither the presence nor the severity of hepatic steatosis predicted liver-related events, cancer, or cardiovascular events in the short term, while LSM and etiology independently predicted liver-related events.[49] Subgroup analyses of viral hepatitis (hepatitis B: 37.0%; hepatitis C: 2.9%) and NAFLD patients (40.7% of the entire cohort) revealed similar results.

In summary, CAP is a promising point-of-care technique for rapid and standardized steatosis quantification, but needs to be better validated in patients with NAFLD with the XL-probe. CAP is outperformed by MRI-PDFF, but should to be compared to ultrasonography, which, despite its limitations, remains the most widely used tool for first-line steatosis assessment.

Magnetic Resonance Imaging Proton-Density Fat Traction

Cross-Sectional Utility of Magnetic Resonance Imaging Proton-Density Fat Traction.—MRS has been employed in several large epidemiologic studies, and now with the development of MRI-PDFF, it has been more widely utilized in epidemiologic studies to classify presence of hepatic steatosis as well as to quantify the amount of liver fat.[50–53]

Longitudinal Comparison With Histology and Magnetic Resonance Spectroscopy.—A series of single-center studies suggested the utility of MRI-PDFF in the longitudinal assessment of changes in liver fat content with paired assessment with MRS and liver histology over a 24-week period.[54–56] These studies suggested that MRI-PDFF was more sensitive than liver histology in assessing changes in liver fat and has may be utilized in the setting of a clinical trial.[57] These data have since been confirmed in multicenter studies in both adult and pediatric populations.[58] These studies have shown that longitudinal change in MRI-PDFF robustly correlates with longitudinal change in MRS-PDFF (with correlation coefficients ranging from 0.96 to 0.99), when both the MRI and MRS measurements at each time points are meticulously colocalized.[55,57]

Role of Magnetic Resonance Imaging Proton-Density Fat Traction as an End Point in Early-Phase Nonalcoholic Steatohepatitis Trial.—Several early phase trials in NASH have adopted MRI-PDFF as an end point to examine efficacy of various drugs to assess treatment response. Le et al[54] followed by the MOZART (Magnetic Resonance Imaging and Elastography in Ezetimibe Versus Placebo for the Assessment of Response to Treatment in NASH) trial proposed the need for co-localization of regions of interests before and after treatment, as the liver fat is heterogeneously distributed.[54,55,57] MRI-PDFF is unable to assess liver inflammation, ballooning, or resolution of NASH or improvement in fibrosis.[59]

Clinical Utility of Amount of Decline in Liver Fat.—As the new trial data emerged, the experts started noticing a range of liver fat improvement in various trials. Using the paired MRI-PDFF and histology data from the MOZART trial, it appeared that, at a threshold of a relative 30% reduction in MRI-PDFF, one may start to appreciate significantly higher odds of a 2-point improvement in NAFLD Activity Score on liver histology.[60] These data require further validation, which is ongoing in the multicenter setting.[61] Higher liver fat content at baseline in patients without fibrosis has recently been shown to be associated with significantly higher odds of fibrosis progression than those patients who have lower liver fat content.[62] These emerging data suggest that liver fat content may have prognostic significance, especially early on the fibrosis progression cascade, but need to be confirmed. MRI-PDFF estimation methods have been successfully implemented in the clinical setting as a tool for fat quantification. They are Food and Drug Administration-approved and commercially available on the several MRI vendors, including GE Healthcare, Siemens, and Philips, and are now more readily available on newer scanners.[63]

Diagnosis of Nonalcoholic Steatohepatitis

Serum Biomarkers

Many serum biomarkers have been investigated for the diagnosis of NASH [64] but cytokeratin (CK)-18 is by far the one that has been the most widely investigated. CK-18 fragments come from apoptosis of hepatocytes accomplished by the enzyme caspase 3 and can be measured in serum by immunoassay. The M30 enzyme-linked immunosorbent assay measures the caspase-cleaved K18 fragments and detects apoptosis, which is a hallmark of steatohepatitis, whereas the M65 enzyme-linked immunosorbent assay detects total cell death. Since the initial study by Feldstein et al,[65] reporting circulating serum levels of CK-18 to be predictive of NASH in patients with NAFLD (with AUROC of 0.83 and sensitivity of 0.75 and specificity of 0.81 for a CK- 18 value of about 250 U/L), many studies[66–75] have confirmed these results, though in rather small populations. In 2 subsequent meta-analyses,[76,77] CK-18 had pooled AUROC of 0.82 (95% CI, 0.76–0.88) to predict NASH with a median sensitivity of 66%–78% and specificity of 82%–87%. There are however, several issues with CK-18: lack of a commercially available clinical test,[78] limited sensitivity at the individual level[79] and considerable variability in the suggested cutoffs and their respective diagnostic accuracy among studies, which makes choosing which threshold to use very difficult.[64] These limitations have resulted in limited clinical utility in practice so far. To increase CK-18 sensitivity, some authors have combined it with other biological parameters, such as sFas levels,[80] uric acid,[81] adiponectin and resistin (NASH diagnostics),[74,82] or ALT and presence of metabolic syndrome (Nice Model).[83] Other predictive models, combining clinical and laboratory parameters, have been proposed for the diagnosis of NASH, including HAIR (hypertension, increased ALT, and insulin resistance),[84] Palekar score (age, sex, AST, BMI, AST/ALT ratio, and hyaluronic acid),[85] Gholam score (AST and diabetes mellitus),[86] oxNASH (13-hydroxyl-octadecadienoic acid/linoleic acid ratio, age, BMI, and AST),[87] NAFIC score (ferritin, insulin and type IV collagen 7s),[88] and NashTest (Biopredictive, Paris, France), a proprietary formula including 12 variables (age, sex, height, weight, serum levels of triglycerides, cholesterol, $\alpha 2$-macroglobulin, apolipoprotein A1, haptoglobin, γ-glutamyltransferase, aminotransferases ALT, AST, and total bilirubin).[89] In a meta-analysis from the developer, in 494 obese patients with a prevalence of NASH of 17.2%, the weighted AUROC of NashTest was 0.84.[20] However, most of these models rely on small and highly selected populations (morbidly obese patients)[83,90–92] and have not been externally validated.[93] The diagnostic performances of these different models have been recently reviewed and are therefore not detailed in the present review.[78,64] Recently, several approaches using genetic biomarkers have been proposed, including single nucleotide polymorphisms located in *PNPLA3,* such as the NASH Score (PNPLA3 genotype, AST, and fasting insulin)[94] and the NASH ClinLipMet Score (glutamate, isoleucine, glycine, lysophosphatidylcholine 16:0, phosphoethanolamine 40:6, AST, fasting insulin, and PNPLA3 genotype),[95] but also expression of noncoding RNAs, specifically microRNAs, such as miR-122.[96,97] However, the information yielded has had moderate clinical utility.

In summary, none of the currently available serum marker are able to differentiate NASH from simple steatosis with high sensitivity and specificity, however, their diagnostic accuracy can be improved by combining different approaches.

Imaging Techniques

Studies on the ability of elastography to discriminate between isolated steatosis and NASH are limited to TE and MRE. The performances of MRE have been investigated in 5 studies[39,43,98–100] and those of TE in 4.[39,43,45,101] A wide range of AUROCS (0.35–0.93) and optimal cutoffs have been reported and likely depend on the prevalence of advanced fibrosis in the study population.[102] In the 2 studies[39,43] with head-to-head comparison, there was no difference between TE and MRE. Currently, neither modality can reliably discriminate NASH from simple steatosis, although MR-based modalities are showing promise, as discussed in the Other Magnetic Resonance-Based Methods section.

Staging of Liver Fibrosis

Serum Biomarkers

The diagnostic performances of serum biomarkers have already been summarized in several reviews[78,64,103] and, therefore, will not be detailed here. Briefly, as for nonpatented tests, a recent meta-analysis (based on 64 studies in 13,046 NAFLD patients) comparing BARD, APRI, FIB-4, and NAFLD fibrosis score (NFS) for diagnosing advanced fibrosis reported summary AUROCS of 0.76, 0.77, 0.84, and 0.84, respectively.[104] With an APRI threshold of 1.0 and 1.5, the sensitivities and specificities for advanced fibrosis were 50.0% and 84.0% and 18.3% and 96.1%, respectively. With a FIB-4 threshold of 2.67 and 3.25, the sensitivities and specificities for advanced fibrosis were 26.6% and 96.5% and 31.8% and 96.0%, respectively. The summary sensitivities and specificities of BARD score (threshold of 2), and NFS (threshold of −1.455) for advanced fibrosis were 0.76 and 0.61, 0.72, and 0.70, respectively. Among the 4 biomarkers, FIB-4 and NFS are the most accurate with high negative predictive values (>90%) for ruling out advanced fibrosis. They could therefore be used as first-line tools in primary health care setting to identify patients without advanced fibrosis who do not need further assessment. In that respect, FIB-4 may be more attractive to general practitioners, as it is based on widely available and simple parameters (age, transaminases, and platelets) and easier to calculate than NFS. There are, however, several limitations that should be acknowledged: first, performances of FIB-4 and NFS to rule in advanced fibrosis are rather inadequate, meaning that further assessment with another test is needed in case of positive results (Figure 1). Second, it is important to keep in mind that they have been mostly validated in liver clinics, where the prevalence of advanced fibrosis is much higher than in primary health care settings. Third, when using FIB-4 or NFS, a significant proportion of patients (around 30%) fall in the intermediate-risk cate- gory[105] (Figure 1) and cannot be correctly classified. This may lead to unnecessary referral of these patients to liver clinics for further assessment. Finally, new age-adjusted cutoffs have been proposed recently to improve the diagnostic performance of NFS and FIB-4 for advanced fibrosis.[106]

As for patented tests, no independent meta-analysis is available. A recent French study[107] from the developer comparing Fibrometer to other patented (FibroTest and Hepascore) and nonpatented (APRI, FIB-4, BARD, and NFS) serum biomarkers in 452 NAFLD patients, showed that Fibrometer (AUROC 0.82) outperformed all of the other tests for diagnosing advanced fibrosis. These results require further independent confirmation. Finally, novel markers, such as the PRO-C3, a commercially available assay that detects the synthesis of type III collagen, has been recently suggested to be superior to APRI, FIB-4, and NFS to identify patients with NAFLD and advanced fibrosis when combined with age, platelet, and diabetes.[108] These promising results require further validation. Finally, despite slight improvement in diagnostic accuracy over nonpatented biomarkers, the limited availability of patented tests and their cost might limit their wider application.

In summary, among the different serum biomarkers studied, NFS and FIB-4 have been the most extensively studied and validated in different NAFLD populations and with consistent results. These tests perform best at excluding advanced fibrosis (with negative predictive values >90%) and could therefore be used as a first-line triage to identify patients at low risk of advanced fibrosis in settings where more sophisticated tests are unavailable.[9]

Ultrasound-Based Elastography

Transient Elastography.—Several meta-analysis, mostly performed in viral hepatitis patients, have reported good (88%–89%) and excellent (93%–96%), accuracies of TE for diagnosing advanced fibrosis and cirrhosis, respectively.[11] Two meta-analysis performed in NAFLD patients have confirmed these results.[76,104] The meta-analysis by Kwok, based on 9 studies (8 with the M-probe) including a total of 1047 NAFLD patients, reported summary sensitivities of 85% and 92% and specificities of 82% and 92% for diagnosing advanced fibrosis and cirrhosis, respectively.[76] Table 4 summarizes the results of the most recent studies (since 2015),[39,43,107,109–112] as prior studies have been already summarized.[103] These results deserve several comments: 1) these studies have included heterogeneous populations with a rather limited number of cirrhotic patients (<20%) and wide range or BMI (27–40 kg/m^2); 2) the failure or unreliable results is lower when the XL-probe is used. Also, as shown in the most recent meta-analysis based on 19 studies (4 using the XL-probe) including a total of 2495 NAFLD patients from different ethnic back-grounds, summary AUROCs of TE did not differ between M- and XL-probes for diagnosing advanced fibrosis (0.87 vs 0.86) and cirrhosis (0.92 vs 0.94), respectively[104]; 3) apart from the type of probe used, the uneven distribution of fibrosis stages between studies may likely be an explanation for the observed differences between proposed cutoffs for a given end point, known as the spectrum bias.[113,114] Finally, it should be stressed that all of these studies have been conducted in tertiary referral centers, where the proportion of patients with advanced fibrosis is higher that in the general population, thus making it difficult to extrapolate the performance of TE if used to detect cirrhosis in large populations. Overall, these results suggest that TE could be of interest to exclude confidently advanced fibrosis and cirrhosis with high negative predictive value (around 90%) in these patients.[9] For instance, at a cutoff <8 kPa, TE had a 94%–100% negative predictive value.[112,115] Finally, TE is recommended in the current guidelines on management of NAFLD.[2,9]

Acoustic Radiation Force Imaging.—Meta-analyses of pSWE using ARFI imaging in patients with chronic liver disease reported diagnostic accuracies of 89%–91% for advanced fibrosis and 92%–93% for cirrhosis, with cutoffs ranging from 1.55–1.61 m/s for advanced fibrosis and 1.80–1.87 m/s for cirrhosis, respectively.[116,117] Other pSWE systems show comparable results to ARFI. However, different cutoffs are recommended for different systems.[10,118] Only a few studies have evaluated pSWE using ARFI in patients with NAFLD with diagnostic accuracies of 84%–98% for advanced fibrosis.[38,109,119–123] A systematic review of 7 studies having included 723 NAFLD patients, reported a summary diagnostic accuracy, sensitivity and specificity of 90%, 80% and 85%, respectively, for the detection of significant fibrosis.[124] However, significant fibrosis is not the most relevant end point and no data are available to date for advanced fibrosis and cirrhosis. Similarly, no data are available for the follow-up of NAFLD patients using pSWE. Therefore, pSWE is not included in the current guidelines on management of NAFLD.

Shear Wave Elastography.—A retrospective meta-analysis, evaluating 2D-SWE in 1340 patients with chronic liver diseases from 13 centers worldwide, reported diagnostic accuracies of 91% and 95% for advanced fibrosis and cirrhosis, and optimal cutoffs of 9.2, and 13.5 kPa, respectively.[125] In the subgroup of 172 NAFLD patients, diagnostic accuracies were 93% and 92% for advanced fibrosis and cirrhosis, respectively, with the same optimal cutoffs as for the overall group. When 2D-SWE was compared to TE in a subgroup of 91 NAFLD patients with reliable TE-values, 2D-SWE performed significantly better for diagnosing advanced fibrosis (AUROC difference of 12%; $P = .003$). In another study in 291 NAFLD patients, 2D-SWE had diagnostic accuracies of 89% and 88% for detecting advanced fibrosis and cirrhosis, respectively.[109] The cutoff values with sensitivity >90% were 8.3 kPa and 10.5 kPa for advanced fibrosis and cirrhosis, respectively. Interestingly, 2D-SWE outperformed TE and ARFI only for significant fibrosis. No data are available for the follow-up of NAFLD patients using 2D-SWE. Therefore, 2D-SWE is not included in the current guidelines on management of NAFLD.

Magnetic Resonance Elastography

2D-MRE has been shown in a prospective cohort of 117 patients with biopsy-proven NAFLD to have a high diagnostic accuracy for the detection of advanced fibrosis.[99] The AUROCs for the detection of any fibrosis, advanced fibrosis, and cirrhosis were 0.84, 0.92, and 0.89, respectively, with an optimal cutoff for advanced fibrosis of 3.64 kPa. These results have been confirmed in a meta-analysis based on 9 studies and 232 NAFLD patients.[126] In another recent meta-analysis based on 5 studies and 628 NAFLD patients, the pooled AUROC of 2D-MRE for advanced fibrosis was 0.96.[104]

In a head-to-head comparison between 3D-MRE vs 2D-MRE, 3D-MRE at 40 Hz was superior to 2D-MRE at 60 Hz with an AUROC for the detection for advanced fibrosis of 0.98 (3D-MRE) vs 0.92 (2D-MRE).[100] However, processing of 3D-MRE takes a much longer time and has yet not been applied in multicenter studies. 3D-MRE appears to be an extremely promising tool for longitudinal changes in fibrosis assessment. Further studies are needed to determine its role in fibrosis assessment in routine clinical practice.

Other Magnetic Resonance-Based Methods.—A novel method called LiverMultiScan (Perspectum Diagnostics) has been proposed recently as a noninvasive, imaging-based biomarker to measure liver fat and correlate it with liver iron content, fibrosis, and inflammation. The 3 parameters included in the proprietary algorithm are liver fat assessment, T2*, and corrected T1 decay on advanced MRI.[127] A pilot proof-of-concept study has shown promising data, and further larger validation of these parameters in patients with biopsy-proven NAFLD, and its utility in assessment of treatment response in NASH trials is being actively assessed.[127]

Recent novel data suggest that addition of damping ratio in addition to 2D-MRE and perhaps MRI-PDFF may help further advance the assessment of both inflammation and fibrotic components of disease activity and severity of NAFLD.[128] Further studies are needed to examine the exact utility and applicability of these approaches in assessment of NAFLD severity.

Comparison and Combination of Approaches

Among clinical available modalities, MRE has the highest diagnostic accuracy in the detection of advanced fibrosis in NAFLD,[129] but the evidence is based on a limited number of selected patients (n < 700) in highly specialized tertiary centers. In a head-to-head comparison with 7 serum fibrosis markers, including FIB-4, in 102 patients with NAFLD, 2D- MRE performed better than all serum markers for the detection of advanced fibrosis.[130] When compared head to head with serum markers (FIB-4, NFS, APRI, BARD, Fibr- ometer, and FibroTest) in large cohorts of NAFLD patients (n = 452 and n = 761), TE outperformed all other serum markers,[115] apart from Fibrometer.[107] Some authors have proposed strategies combining TE with FIB-4 or NFS, either in a paired or in a serial fashion.[111,115] Such serial strategy, however, increased the diagnostic performance with an accuracy around 70%, but at the price of an uncertainty area (around 20%) and a 10% rate of misclassified patients.[115] MRE and TE have been compared head to head in patients with biopsy-proven NAFLD in 3 studies[39,43,110] with conflicting results. Chen et al[110] have shown in 111 patients with morbid obesity (mean BMI, 40.3 kg/m^2) that MRE performed better than TE for detecting advanced fibrosis in intention to diagnose, but not in per-protocol, analysis. In 2 other studies, 1 in 142 Japanese patients (mean BMI, 28.1 kg/m^2), using only the M-probe[39] and 1 in 104 American patients (mean BMI, 30.4 kg/m^2), using both M and XL-probes,[43] there was no statistical difference between MRE and TE for the detection of advanced fibrosis. Differences in the studied populations might account for this discrepancy. Recent data suggest that, when staging fibrosis taking liver biopsy as reference, BMI is significantly associated with discordance of findings between MRE and TE, the degree of discordancy increasing with BMI.[131] Finally, a recent individual patient meta-analysis (based on 230 patients) found that MRE had a statistically significantly higher diagnostic accuracy than vibration-controlled TE in assessing each stage of fibrosis in patients with biopsy-proven NAFLD.[132] Therefore, further studies are needed before any firm conclusion can be drawn. As for comparison with pSWE using ARFI, 2D-MRE has been shown to be superior to pSWE for the detection of any fibrosis, but not for advanced fibrosis.[119] In addition, pSWE underperformed in the setting of obesity and higher liver fat content.

In summary, all of these modalities have a role in clinical practice and understanding the caveats associated with their utility (summarized in Table 2) are helpful in optimal clinical use of these tools.

Use in Clinical Practice

In patients with suspected NAFLD (presence of steatosis on ultrasound or abnormal liver tests [transaminases/γ-glutamyltransferase] in patients with risk factors such as obesity, type 2 diabetes, or metabolic syndrome), noninvasive tests can be used in clinical practice for risk stratification. Whatever the approach, serum biomarkers or elastography, each modality is most reliable in excluding the presence of advanced fibrosis. As shown in Figure 1, the choice of noninvasive tools to be used should be guided by local availability and context of use. In primary health care setting, simple inexpensive and widely available serum biomarkers, such as FIB-4 or NAFLD fibrosis scores, with high negative predictive value (>90%) for ruling out advanced fibrosis should be used as first-line. Patients with low risk (FIB-4 <1.3 or NAFLD Fibrosis score < −1.455; 55% to 58% of cases) of having advanced fibrosis do not need further assessment. They should be offered lifestyle modifications and exercise. Those with intermediate (FIB-4 = 1.3 to 3.25 or NFS = −1.455 to 0.672; 30% of cases) and high risk (FIB-4 >3.25 or NFS >0.672; 12% to 15% of cases, positive predictive value 75% to 90%) should be sent to a referral center for further assessment. Patented serum biomarkers (FibroTest, Fibrometer, or ELF) could be considered in patients with intermediate risk according to local availability. Otherwise TE, as the most widely available and best evaluated point-of-care technique, appears to be the tool of choice, although ARFI and SWE are becoming increasingly available. XL-probe should be used in patients with skin-liver capsule distance >25 mm in order to minimize the TE failure rate (<7%). Patients at low risk of having advanced fibrosis (LSM <8 kPa; negative predictive value 94%–100%) should be offered lifestyle modifications and reevaluation after 1 year. For those with intermediate (LSM = 8–10 kPa) or high risk (LSM ≥10 kPa, positive predictive value 47%–70%) of having advanced fibrosis should be considered for liver biopsy. However, confounders should be carefully excluded to minimize the risk of false positive. In case of TE failure despite the use of XL-probe or high BMI (≥35 kg/m^2), alternative techniques such as MRE or SWE/ARFI may be considered according to local availability. However, although SWE and ARFI seem to be as promising as TE, data are currently limited for these modalities regarding the determination of advanced fibrosis in NAFLD. As for MRE, despite its high accuracy, cost and limited availability are limitations to its use in practice. Its role as a surrogate of fibrosis improvement in therapeutic trials remains to be demonstrated. In any case, these patients should be offered lifestyle modifications and exercise and vitamin E (in nondiabetics) and pioglitazone may be considered, as recommended by recent European Association for the Study of the Liver or American Association for the Study of Liver Diseases clinical practice guidelines.[2,3] Finally, patients identified as having advanced fibrosis or cirrhosis should be screened for portal hypertension and liver cancer, given the increased risk of this disease in these individuals.

Special Populations and Controversies

Patients with type 2 diabetes mellitus are known to be at increased risk for NAFLD and advanced fibrosis. Noninvasive screening strategies for NAFLD, NASH, or advanced fibrosis have been proposed in diabetic patients, including the use of routinely available clinical variables,[133] TE,[134,135] MRE,[52] or combination of TE and ELF.[136] It is noteworthy that most studies on noninvasive tests in NAFLD patients have not been stratified for the presence of diabetes. Several recent studies suggested that noninvasive tests, which were developed and validated in nondiabetic cohorts, underperformed when applied to diabetic patients.[137–139] Thus, caution is requested when extrapolating results of noninvasive tests from nondiabetic populations to patients with diabetes. Also the role of ethnicity may be important to take into account,[140,141] as most available studies have been done in Caucasians. Further studies are needed to address these issues.

Prognosis

Several recent studies have shown the ability of liver stiffness, measured using TE,[107] or serum biomarkers[107,142,143] to predict clinical decompensation as well as survival in patients with NAFLD. A meta-analysis[144] based on 17 studies in 7058 patients with chronic liver diseases (mainly related to viral hepatitis) has shown that baseline liver stiffness, measured using TE, was associated significantly with risk of hepatic decompensation (6 studies; relative risk [RR], 1.07; 95% CI, 1.03–1.11), hepatocellular carcinoma (9 studies; RR, 1.11; 95% CI, 1.05–1.18), death (5 studies; RR, 1.22; 95% CI, 1.05–1.43), or a composite of these outcomes (7 studies; RR, 1.32; 95% CI, 1.16–1.51). In a nationwide study (National Health and Nutrition Examination Survey cohort)[143] in 11,154 participants (34% with NAFLD) with a median follow-up of 14.5 years, those with a high probability of advanced fibrosis using APRI (>1.5), NFS (>0.676), or FIB-4 (>2.67), had a 69% increase in mortality compared to subjects without fibrosis (for NFS: hazard ratio, 1.69; 95% CI, 1.09–2.63; for APRI: hazard ratio, 1.85; 95% CI, 1.02>3.37; for FIB-4: hazard ratio, 1.66; 95% CI, 0.98>2.82) after adjustment for other known predictors of mortality.

Future Directions

There is a wealth of data that are informing clinicians regarding the utility and limitations of each of the diagnostic modalities in the assessment of NAFLD. However, further advances are needed to refine clinical management and more accurate identification of patients at risk for fibrosis progression and those who need to be treated in the setting of a clinical trial without subjecting them to a liver biopsy evaluation. The key research priorities in the field are listed in Table 5. Addressing these gaps in knowledge would greatly impact the field.

Recently, efforts concentrating on “omics” approaches (lipidomics, proteomics, and metabolomics) using high- throughput technologies have shown promising results to identify novel biomarkers of NAFLD, NASH, and advanced fibrosis.[145] For instance, several studies based on lipidomics approaches have shown circulating oxidized fatty acids and products of arachidonic acid metabolism to be predictive of NASH.[146–148] Similarly, proteomics have been used to identify NAFLD patients with active fibrosis, by measuring extracellular matrix

remodeling rates in tissue and blood.[149] Using a metabolomic approach,[150] subtypes of NAFLD with specific serum metabolomic profiles that differentiate steatosis from NASH in each subtype could be identified and might be used to monitor disease progression and identify therapeutic targets for patients. Finally, omics technologies have been used for the profiling of gut microbiota and identification of fecal-microbiome–derived metagenomic signatures associated with NASH and fibrosis in several human studies.[151,152] It should be stressed, however, that these findings rely on small cross-sectional studies with a lack of external validation. In addition, the complicated methodology involved in omics platforms as well as reproducibility between centers and stability of samples and high cost prevent far widespread application in clinical practice.

Finally, given the high prevalence of NAFLD in the general population, noninvasive tests could be used as screening tools to identify patients with NAFLD at high risk of progression.[153] Recently, several studies have screened systematically for liver fibrosis, using either serum biomarkers[154] or TE,[155–157] the general population or at-risk populations,[158] or diabetics or those with a family history of NAFLD cirrhosis.[51,134] Their results suggest an alarmingly high prevalence of chronic liver diseases, mainly related to NAFLD, ranging between 5% and 8% in the general adult population and between 18% and 27% among individuals with risk factors.[159] Thus, screening programs for liver fibrosis in the general population, using TE for identifying patients with presymptomatic chronic liver diseases susceptible to interventions should be further assessed.

Conclusions

Significant progress has been made regarding the noninvasive assessment of liver disease in patients with NAFLD. Use of noninvasive tests should be tailored according to the setting (primary heath care, tertiary referral center, trial) and clinical needs (screening, staging of fibrosis, follow-up). Regarding detection and grading of steatosis, MRI-PDFF is the most accurate method but appears better suited for assessment and follow-up of selected patients in clinical trials, whereas conventional ultrasound, and if no steatosis is shown, CAP, as a point of care technique, could be used as triage in large unselected populations. Regarding NASH, no highly sensitive and specific blood tests are available to differentiate NASH from simple steatosis. Neither imaging modality can reliably discriminate NASH from simple steatosis, although MR-based modalities are showing promise. As for the identification of advanced fibrosis, MRE, TE, as well as FIB-4 and NFS are the most accurate and validated methods. FIB-4 and NFS are best suited as first-line tools in primary health care setting to confidently exclude advanced fibrosis, whereas TE and MRE are more suited for referral centers to select the patients who require a liver biopsy. Finally, there is increasing evidence that serum markers and liver stiffness, measured using TE, accurately identify the subgroup of patients with NAFLD at a higher risk to reach the outcome of liver-related complications and death/liver transplantation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ALT	alanine transaminase
APRI	Aspartate Transaminase-to-Platelet Ratio Index
ARFI	acoustic radiation force imaging
AST	aspartate transaminase
AUROC	area under the receiver operating characteristic
BMI	body mass index
CAP	controlled attenuation parameter
CI	confidence interval
CK	cytokeratin
2D-SWE	2-dimensional shear wave elastography
ELF	Enhanced Liver Fibrosis
kPa	kilopascals
LSM	liver stiffness measurement
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
MRE	magnetic resonance elastography
NFS	nonalcoholic fatty liver disease fibrosis score
PDFF	proton density fat fraction
pSWE	point shear wave elastography

RR	relative risk
SWE	shear wave elastography
TE	transient elastography

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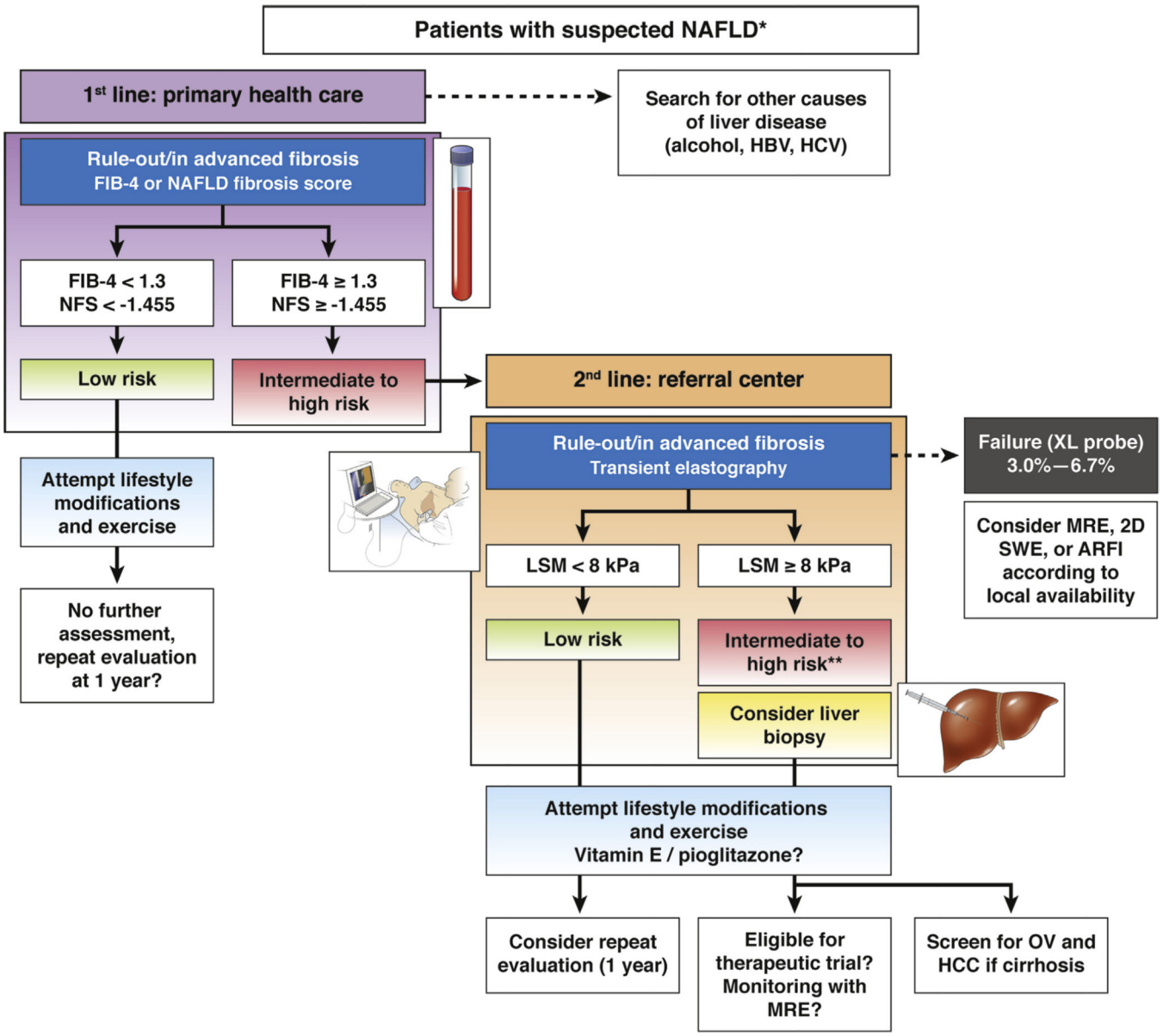

Figure 1.

A suggested algorithm for the use of noninvasive tests for risk stratification of patients with suspected NAFLD in clinical practice. *Suspicion of NAFLD is based on the presence of steatosis on ultrasound or abnormal liver tests (transaminases/γ-glutamyltransferase) in patients with risk factors (obesity, type 2 diabetes, or metabolic syndrome). Significant alcohol consumption and secondary causes of steatosis should be excluded. The proposed algorithm is based on expert opinion. The choice of noninvasive tools should be sequential, guided by local availability and the context of use: in primary health care setting, simple inexpensive and widely available serum biomarkers, such as FIB-4 or NFS, with high negative predictive value (88%−95%) for ruling out advanced fibrosis should be used as first-line. Patients with low risk (FIB-4 <1.3 or NAFLD Fibrosis score < −1.455; 55 to 58% of cases) do not need further assessment. They should be offered lifestyle modifications and

exercise. Those with intermediate (FIB-4 = 1.3 to 3.25 or NFS = −1.455 to 0.672; 30% of cases) and high risk (FIB-4 >3.25 or NFS >0.672; 12%–15% of cases, positive predictive value 75%–90%) of having advanced fibrosis should be addressed to a referral center for LSM, using TE, in fasting condition, using M-probe for patients with skin-liver capsule distance <25 mm otherwise with the XL-probe. Patients at low risk of having advanced fibrosis (LSM <8 kPa; NPV 94%–100%) should be considered for a repeat evaluation within 1 year. Those with intermediate (LSM = 8–10 kPa) or high risk (LSM ≥10 kPa, PPV 47%–70%) of having advanced fibrosis should be considered for liver biopsy. However, confounders for liver stiffness should be carefully excluded to minimize the risk of false positive results. **Also patented serum biomarkers (FibroTest, Fibrometer, or ELF) could be considered in patients with intermediate risk according to local availability. In case of TE failure, alternative such as SWE/ARFI, MRE (particularly when BMI >35 kg/m^2) may be considered according to local availability. In any case, all patients should be offered lifestyle modifications and exercise. As recommended by recent European Association for the Study of the Liver or American Association for the Study of Liver Diseases clinical practice guidelines, vitamin E (in non-diabetics) and pioglitazone may be considered in these patients. Also patients with cirrhosis should be screened for esophageal varices (OV) and hepatocellular carcinoma (HCC). In those with a liver biopsy, follow-up during treatment of LSM, using MRE, is the most promising noninvasive approach but requires further validation. NPV, negative predictive value; PPV, positive predictive value.

Table 1.

Available Serum Biomarkers for Diagnosing Steatosis or for Staging Fibrosis in Patients With Nonalcoholic Fatty Liver Disease

Index (ref)	Items, n	Age	Sex	BMI	Diabetes	Platelet count	AST level	ALT level	AST/ALT ratio	GGT level	TG level	Other components
Steatosis												
FLI[14]	4			X						X	X	Waist circumference
HSI[15]	3			X	X				X			—
SteatoTest[13]	12	X	X	X				X		X	X	A2M, ApoA1, haptoglobin, T bilirubin, cholesterol, and glucose
LAP[16]	3		X								X	Waist circumference
ION[17]	3/4		X					X			X	Waist-to-hip ratio (male yes; female no), and HOMA
NAFLD-LFS[18]	4				X				X			Metabolic syndrome and insulin
Fibrosis												
APRI[160]	2					X	X					—
FIB-4[161]	4	X				X	X	X				—
FibroTest[162]	8	X	X	X						X		A2M, ApoA1, haptoglobin, and total bilirubin
Fibrometer NAFLD[163]	7	X				X	X	X				glucose, ferritin and body weight
ELF[164]	3											Hyaluronic acid, PIIINP and TIMP-1
Hepacore[165]	6	X	X							X		A2M, hyaluronic acid and total bilirubin
BARD score[166]	3			X	X				X			—
$_{NFS}$[167]	6	X	X		X	X			X			Albumin

A2M, α2-macroglobulin; APOA1, apolipoprotein A1; FLI, fatty liver index; GGT, γ-glutamyltransferase; HSI, Hepatic Steatosis Index; ION, Index of NASH; LAP, lipid accumulation product; NAFLD-LFS, NAFLD liver fat score; NFS, NAFLD fibrosis score.

Table 2.

Respective Characteristics, Advantages, and Limitations of the 4 Available Elastography Techniques for Liver Fibrosis Staging

Techniques	Performed by	Units (range)	Steatosis grading	Quality criteria	Failure rate, %	Confounders			Evidence in NAFLD study patients	Cost	Point of care
						Inflammation	Obesity	Others			
TE	Hepatologist, trained	kPa (2–75)	Yes	Well-defined	3–27	++	++	Congestion steatosis?	n = 25	$	Yes
	nurse or technician		CAP	IQR/M <30%			XL-probe		3862		
MRE	Radiologist	kPa[a] (2–11)	Yes	Emerging QIBA	0–2	+	-	Congestion iron overload	n = 6	$$$	No
			PDFF	consensus			+		676		
				statement			+				
pSWE/ARFI	Radiologist or	m/s (0.5–4.4)	No	Not well-defined	2	+ ?	+ ?	Similar to TE?	n = 8	$$	No
	ultrasonographer					limited data	limited data	limited data	834		
2D-SWE	Radiologist or	kPa (2–150)	No	Not well-defined	13 ?	+ ?	+ ?	Similar to TE?	n = 2	$$	No
	ultrasonographer					limited data	limited data	limited data	447		

IQR/M, interquartile range/median; QIBA, Quantitative Imaging Biomarkers Alliance.

[a]MRE is reported as shear modulus, while ultrasound elastography techniques are reported in Young modulus. The Young modulus is 3 times the shear modulus.

Table 3.

Performances of Controlled Attenuation Parameter for the Diagnosis and Grading of Steatosis in Patients With Nonalcoholic Liver Disease, Taking Liver Biopsy as Reference

Authors	Year	Design	Patients, n	Male sex, %	Age, *y*	Diabetes, %	BMI, *kg/m*^{2}	Steatosis grading, %	Steatosis prevalence, %	CAP probe	Failure rate, %	AUC	CAP cutoff, *dB/m*	Se, %	Sp, %
Friedrich-Rust[38]	2012	P	57	53	45 ± 14		28.0 ± 5.5	≥33	74	M	19	0.78	245	97	67
								≥66	46			0.72	301	76	68
Kumar[41]	2013	P	63	73	37[a]	—	25.1 ± 2.0	≥33	59	M	—	0.79	258	78	73
								≥66	11			0.77	283	71	68
Chan[35]	2014	P	105	51	50 ± 11	52	29.4 ± 3.9	≥5	97	M	4	0.97	263	92	94
								≥33	64			0.86	281	97	68
								≥66	14			0.75	283	100	53
Karlas[40]	2014	P	50 (11 C)	50	55 ± 9	28	31.1 ± 4.2	≥5	100	M	8	0.93	233	93	87
								≥33	62			0.94	268	97	81
								≥66	24			0.82	301	82	76
de Ledinghen[37]	2016	R	261	59	56 ± 12	59	30.2 ± 5.1	>33	72	M	24	0.80	310	79	71
								>66	32			0.66	311	87	47
Imajo[39]	2016	P	142 (10 C)	57	57 ± 15	50	28.1 ± 4.6	≥5	83	M	11	0.88	236	82	91
								>33	58			0.73	270	78	80
								>66	17			0.70	302	64	74
Park[43]	2017	P	104	43	51 ± 15	28	30.4 ± 5.2	≥5	91	M	—	0.85	261	72	86
								>33	43	XL	6.7	0.70	305	63	69
								>66	15			0.73	312	64	70
Runge[44]	2017	P	55	73	52[a]	—	27.8[a]	≥5	91	M	0	0.77	260	90	60
								>33	47			0.78	296	92	55
								>66	16			0.78	334	78	76
Chan[36]	2017	R	57 (22 C)	49	50 ± 10	—	30.2 ± 5.0	≥5	98	M	6	0.94	260	91	87
								>33	76	XL	2	0.80	266	91	87
								>66	26			0.69	267	100	47

Authors	Year	Design	Patients, n	Male sex, %	Age, *y*	Diabetes, %	BMI, *kg/m*^{2}	Steatosis grading, %	Steatosis prevalence, %	CAP probe	Failure rate, %	AUC	CAP cutoff, *dB/m*	Se, %	Sp, %
Naveau[42]	2017	R	194	22	41 ± 01	18	44.0 ± 0.4	≥5	85	XL	—	0.85	308	68	69
								>33	59			0.59	335	65	79
								>66	39			0.39	341	74	74
		P	123	26	40 ± 01	22	44.0 ± 0.6	≥5	81	XL	—	0.81	298	78	83
								>33	58			0.58	303	90	69
								>66	37			0.37	326	83	71
Siddiqui[45]	2018	P	393	32	51 ± 11	43	34.4 ± 6.4	≥5	95	M	5.0	0.76	285	80	77
								>33	57	XL		0.70	311	77	57
								>66	27			0.58	306	80	40

C, controls; P, prospective; R, retrospective; Se, sensitivity; Sp, specificity.

[a]Median.

Table 4.

Performances of Transient Elastography for the Diagnosis of Advanced Fibrosis and Cirrhosis in Adult Patients With Nonalcoholic Fatty Liver Disease, Taking Liver Biopsy as Reference

Authors	Year	Design	Patients, n	Age, *y*	BMI, *kg/m²*	Scoring system	End point	Prevalence, *%*	Cutoff, *kPa*	AUC	Se, *%*	Sp, *%*	Failure or unreliable, *%*	Probe
Petta[111]	2015	R	179	45 ± 13	29.3 ± 4.1	Kleiner	F3-F4	23	7.9/9.6	0.86	85	81	13.0	M
			142	44 ± 12	27.4 ± 3.7		F3-F4	20	7.9/9.6	0.85	68	86	23.0	M
Cassinotto[109]	2016	P	291	57 ± 12	32.1 ± 6.0	NASH-CRN	F3-F4	43	8.2/12.5	0.86	90/57	61/90	22.0	M
							F4	17	9.5/16.1	0.87	92/65	62/90		
Tapper[112]	2016	P	164	51 ± 13	32.2[a]	Brunt	F3-F4	18	9.9	0.93	95	77	26.8	M
							F4	—						
Boursier[107]	2016	R	452	56 ± 12	31.1 ± 5.2	NASH-CRN	F3-F4	38	8.7	0.83	88	63	14.1	M
							F4	13	—	0.87	—	—		
Imajo[39]	2016	P	142 (10 C)	57 ± 15	28.1 ± 4.6	Brunt	F3-F4	32	11.4	0.88	86	84	11.0	M
							F4	8	14.0	0.92	100	76		
Petta[115]	2017	R	324	54 ± 13	—	Kleiner	F3-F4	35	10.1	0.86	78	78	—	M
Park[43]	2017	P	104	51 ± 15	30.4 ± 5.2	NASH-CRN	F3-F4	20	7.3	0.80	78	72	—	M
							F4	8	6.9	0.69	63	66	6.7	XL
Chen[110]	2017	P	111	48[a]	40.3	Brunt	F3-F4	20	7.6	0.87	84	64	—	M
							F4	10	14.6	0.92	82	92	18.7	XL
Petta[168]	2017	R	761	51 ± 13	29.6 ± 4.9	Kleiner	F3-F4	31	7.9/9.6	0.86	90/74	65/81	—	M
Siddiqui[45]	2018	P	393	51 ± 11	34.4 ± 6.4	NASH-CRN	F3-F4	32	8.6	0.83	80	74	—	M
							F4	9	13.1	0.93	89	86	5.0	XL

AUC, area under the curve; C, controls; NASH-CRN, nonalcoholic steatohepatitis clinical research network; P, prospective; R, retrospective; Se, sensitivity; Sp, specificity.

[a]Median.

Table 5.

Research Priorities and Unmet Needs in the Field

Cut point for each modality with the context of use needs to be determined (eg, screening in primary care or screening in a diabetes clinic)
Validation of quality criteria for each modality
Cost-effectiveness of sequential use of clinical prediction rules (eg, FIB-4) followed by TE/SWE/ARFI followed by MRE
Clinically meaningful increase/decrease in liver stiffness that is linked to a clinical outcome in NAFLD
Clinically meaningful increase in liver stiffness that is associated with a 1-stage increase in liver fibrosis
Clinically meaningful decrease in liver stiffness that is associated with a 1-stage decrease in liver fibrosis
Cut point for liver stiffness for each modality that is associated with a need to treat varices in patients with NAFLD
Clinically meaningful decrease in liver stiffness that is linked to a clinical outcome in NAFLD
Does reduction in liver stiffness in cirrhosis is associated with reduction in the risk of liver decompensation despite no change in fibrosis stage