Noninvasive Methods for Assessing Liver Fibrosis and Steatosis

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Abstract: Accurate diagnosis and staging of liver fibrosis is crucial to the individualized management of patients with chronic liver disease. Liver biopsy remains the reference standard for the assessment of steatosis, necroinflammation, and fibrosis. However, over the past decade, there has been an exponential growth in noninvasive tests (NITs) designed to assess liver fibrosis and steatosis. These NITs range from serum biomarkers to imaging assessments of liver tissue stiffness. Current noninvasive methods overcome the limitations of nonspecific laboratory markers, conventional imaging, and invasive procedures, and are now starting to be adopted. The Fibrosis-4 index, Enhanced Liver Fibrosis test, and elastography have gained the strongest clinical footholds for the diagnosis of advanced fibrosis. There remains significant interest in demonstrating superiority of any specific test or, alternatively, optimizing a sequential algorithm to provide the most accurate diagnosis of fibrosis staging. This article reviews currently available noninvasive methods for assessing liver fibrosis and steatosis.

Keywords
Liver fibrosis, steatosis, noninvasive tests, biomarker, imaging, elastography

Chronic liver disease (CLD) is a global burden that affects approximately 1.5 billion people and accounts for 2 million deaths worldwide each year.[1] The cornerstone of CLD management is detecting and staging liver fibrosis as this enables therapeutic decision-making, prognostication, and evaluation of treatment response. Although liver biopsy is currently the gold standard for the identification and stratification of liver fibrosis, its use is limited by invasiveness, procedure risk, patient willingness, sampling error, and inter- and intraobserver variability.[2] Noninvasive tests (NITs) overcome many of these limitations and are quickly replacing liver biopsy as the preferred modalities for liver fibrosis and steatosis assessment. NITs identify and stage liver fibrosis by referencing histologic scores such as the METAVIR score, in which a score of at least F2 indicates a significant level of fibrosis.[3] Noninvasive diagnosis and stratification of liver fibrosis has rapidly evolved in recent years. This article reviews the tremendous strides made in fibrosis assessment and highlights key laboratory and imaging NITs that are currently available for clinical use.

Table 1. Serologic Tests Used in the Evaluation of Hepatic Fibrosis

Biomarker (with abbreviation)	Components	Chronic liver disease(s)
AST to Platelet Ratio Index (APRI)	(AST/AST upper limit of normal)/(platelet count [10^9/L]) × 100	HCV, HBV, alcohol-associated liver disease, MASLD
Fibrosis-4 (FIB-4) index	(Age [years] × AST [U/L])/([platelet count (10^9/L)] × √ALT [U/L])	HCV, HBV, alcohol-associated liver disease, MASLD
NAFLD Fibrosis Score (NFS)	1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelet count (10^9/L) − 0.66 × albumin (g/dL)	MASLD
FibroTest	Serum α2-macroglobulin, apolipoprotein A1, haptoglobin, total bilirubin, and GGT, adjusted for age and sex	MASLD, HCV, HBV, alcohol-associated liver disease
Enhanced Liver Fibrosis (ELF) test	Type III procollagen peptide, hyaluronic acid, and tissue inhibitor of metalloproteinase-1	MASLD/MASH

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transpeptidase; HBV, hepatitis B virus; HCV, hepatitis C virus; IFG, impaired fasting glucose; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease.

Biomarkers

Metabolic dysfunction-associated steatotic liver disease (MASLD; formerly known as nonalcoholic fatty liver disease [NAFLD]) is one of the most common causes of CLD and encompasses a spectrum of disease ranging from simple steatosis without inflammation to steatohepatitis, fibrosis, cirrhosis, and end-stage liver disease. Hepatic steatosis, defined as intrahepatic fat of at least 5% of liver weight, is the accumulation of triacylglycerols in the liver.[4] Abnormal serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels are nonspecific to liver disease etiology but are often attributed to hepatic steatosis in the absence of other apparent causes of acute or chronic liver injury. In simple hepatic steatosis, aminotransferase levels are often normal but sometimes associated with a significant increase in ALT.[5,6] Nevertheless, elevated AST and ALT alone are poor indicators for greater than 5% hepatic steatosis, with area under the curves (AUCs) of 0.64 and 0.71, respectively.[7]

Liver fibrogenesis is a dynamic process characterized by excessive accumulation of extracellular matrix (ECM) proteins. ECM components include interstitial type I and III collagen, basement membrane type IV, microfibrillar type VI, pericellular type V, and noncollagenous proteins.[8,9] Thus, potential biomarkers relevant to hepatic fibrosis progression include collagen synthesis and degradation products, matrix synthesis and degradation enzymes, proteoglycans/glycosaminoglycans, and ECM glycoproteins.[10]

Overall, serum biomarkers predicting advanced fibrosis (Table 1) can be classified as indirect or direct.[10] Indirect tests are markers that reflect changes in hepatic function but do not directly reflect ECM metabolism. These include serum aminotransferases, total bilirubin, gamma-glutamyl transpeptidase, platelet count, coagulation parameters, α2-macroglobulin, and α2-globulin. Direct tests are markers that reflect ECM deposition and/or degradation. These include procollagen peptides, type I and IV collagen, hyaluronic acid, inflammatory glycoprotein, metalloproteinases, and tissue inhibitors of metalloproteinases (TIMP-1 and TIMP-2). Cytokines/chemokines directly associated with hepatic fibrosis, such as transforming growth factor (TGF-α and TGF-β) and platelet-derived growth factor, are also direct indicators of fibrosis.

Although many NITs have been developed for the assessment of hepatic fibrosis owing to various underlying diseases, only a handful are well validated and widely used in clinical practice (Table 1).

Conventional Tests

The AST to Platelet Ratio Index (APRI) and Fibrosis-4 (FIB-4) index are 2 serologic tests that have been extensively validated and are commonly used owing to their easy accessibility with readily available clinical data.[11,12] APRI (Table 1) is a simple model that was first constructed to predict significant fibrosis and cirrhosis in patients with hepatitis C virus (HCV) infection. Initial results in HCV demonstrated AUCs of 0.83 (95% CI,

Table 2. Prognostic Accuracy of Noninvasive Tests

Noninvasive test (with abbreviation)	Chronic liver disease or setting	AUC (95% CI)
Assessment of hepatic fibrosis		
AST to Platelet Ratio Index (APRI)	HCV	Significant fibrosis: 0.83 (0.78-0.88) Cirrhosis: 0.90 (0.86-0.94)[13]
	MASLD	0.65 (0.53-0.73) to 0.72 (0.65-0.80)[16]
Fibrosis-4 (FIB-4) index	HCV	Significant fibrosis: 0.85 (0.82-0.89) Cirrhosis: 0.91 (0.86-0.93)[17]
	MASLD	0.802 (0.76-0.85)[19]
NAFLD Fibrosis Score (NFS)	MASLD	Significant fibrosis: 0.84[19]
FibroTest	HCV, HBV, alcohol, MASLD	Significant fibrosis (initial validation in HCV infection): 0.84 (0.78-0.88)[15]
Enhanced Liver Fibrosis (ELF) test	MASLD	0.90 (0.84-0.96)[27]
FibroScan	HCV	Significant fibrosis (≥F2): 0.88 Cirrhosis: 0.99[46]
	MASLD	Significant fibrosis: 0.83 (0.79-0.87) Cirrhosis: 0.93 (0.90-0.97)[47]
FibroScan-AST (FAST) score	MASLD	0.85 (0.83-0.87)[50]
Acoustic radiation force impulse (ARFI)	MASLD	0.87 (0.79-0.92)[55]
Magnetic resonance elastography (MRE)	MASLD	Significant fibrosis: 0.93 (0.89-0.96) Cirrhosis: 0.94 (0.89-0.99)[59]
LiverMultiScan	High-risk MASH	NAS ≥4, ≥F2: 0.78 (0.74-0.82)[67]
Assessment of hepatic steatosis		
Controlled attenuation parameter (CAP)	>10% of hepatic steatosis >33% of hepatic steatosis >66% of hepatic steatosis	0.79 (0.74-0.84) 0.84 (0.80-0.88) 0.84 (0.80-0.88)[43]
Magnetic resonance imaging proton density fat fraction (MRI-PDFF)	Steatosis grade 2 Steatosis grade 3	0.90 (0.82-0.97) 0.92 (0.84-0.99)[63]
LiverMultiScan	Steatosis	0.69 (0.64-0.74)[67]

AST, aspartate aminotransferase; AUC, area under the curve; HBV, hepatitis B virus; HCV, hepatitis C virus; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD Activity Score.

0.78-0.88) and 0.90 (95% CI, 0.86-0.94), respectively.[13] APRI has demonstrated lower diagnostic accuracy in predicting advanced fibrosis in other etiologies of CLD. In patients with hepatitis B virus (HBV)-related CLD, summary AUCs for predicting advanced fibrosis and cirrhosis were 0.79 and 0.75, respectively. Sensitivity and specificity were variable depending on cutoff thresholds, with APRI values of 0.5, 1.5, and 2.0 having a sensitivity and specificity of 84% and 41%, 49% and 84%, and 28% and 87%, respectively, suggesting limited clinical utility.[14] Weaker performance of APRI was seen in CLD owing to alcohol, with an AUC of 0.59 (95% CI, 0.51-0.67) for differentiating F2 to F4 vs F0 to F1 and an AUC of 0.67 (95% CI, 0.59-0.75) for differentiating F4 vs F0 to F3.[15] In patients with MASLD, the prognostic accuracy of APRI for fibrosis was low, ranging from an AUC of 0.65 (0.53-0.73) to 0.72 (0.65-0.80) in various studies.[16]

The FIB-4 index (Table 1) is a well-studied, simple algorithm that was first validated in patients with HCV infection. It was compared against liver biopsy and FibroTest (FibroSure in the United States, LabCorp) (Table 1) in HCV-infected patients and patients with advanced

fibrosis and cirrhosis, with AUCs of 0.85 (95% CI, 0.82-0.89) and 0.91 (95% CI, 0.86-0.93), respectively.[17] A FIB-4 index less than 1.45 had a negative predictive value of 94.7% to exclude advanced fibrosis with a sensitivity of 74.3%. In another study, the FIB-4 index was compared against other fibrosis markers in patients with MASLD and demonstrated superior performance with an AUC of 0.802 (95% CI, 0.76-0.85), which was higher than the AUCs of the NAFLD Fibrosis Score (NFS) (0.77; 95% CI, 0.72-0.82; *P*=.09) and APRI (0.73; 95% CI, 0.68-0.78; *P*<.001).[18] A lower limit of 1.3 and upper limit of 2.67 were able to rule out and diagnose advanced fibrosis, respectively, with 82% sensitivity and 96% specificity.

The NFS was specifically established to assess and predict fibrosis in patients with MASLD. This test uses standard clinical data (Table 1), is easily calculated, and accounts for an underlying diagnosis of diabetes. The NFS was constructed and validated in a study of 733 patients with MASLD confirmed by liver biopsy.[19] The diagnosis of advanced fibrosis demonstrated an AUC of 0.82 in the validation cohort with a negative predictive value of 88% and positive predictive value of 82% when using cutoff values of -1.455 and 0.676, respectively. In a meta-analysis of 13,046 patients with MASLD, NFS and the FIB-4 index offered the best diagnostic performances for detecting advanced fibrosis with a pooled AUC of 0.84 for both tools.[20] In another meta-analysis, a head-to-head comparison of lower-end cutoffs for the FIB-4 index (threshold 1.3) and NFS (threshold -1.455) demonstrated a sensitivity of 76% (95% CI, 70-81) vs 67% (95% CI, 61-73), respectively, and a specificity of 81% (95% CI, 73-86) vs 64% (95% CI, 56-72), respectively.[21]

Many conventional calculations for assessing advanced fibrosis have been developed. Although the APRI, NFS, and FIB-4 scores are widely studied, FIB-4 is the most validated and carries the highest prognostic accuracy (Table 2). The FIB-4 index is one of the most robust NITs for excluding advanced fibrosis and is included in the latest American Association for the Study of Liver Diseases (AASLD) guidance with 90% sensitivity and specificity at thresholds of at least 3.48 and less than 1.67.[22]

Tests That Include Extracellular Matrix Assessment

Beyond the simple algorithms utilizing readily available clinical data, there are several commercially available panels for the evaluation of advanced fibrosis. FibroTest is a frequently used multimarker panel that was first designed and validated in patients with HCV infection. In its initial validation, the AUC for predicting advanced fibrosis was 0.84 (95% CI, 0.78-0.88).[15] Its sensitivity and specificity for detecting hepatic fibrosis in patients with chronic HBV infection was 60% to 75% and 80% to 90%, respectively.[23] FibroTest was shown to be an effective alternative to liver biopsy in patients with CLD secondary to HCV, HBV, MASLD, and alcohol with a pooled mean AUC of 0.84 (95% CI, 0.83-0.86).[24]

The Enhanced Liver Fibrosis (ELF) test is a newer, proprietary algorithm that utilizes direct markers of fibrosis: type III procollagen peptide, hyaluronic acid, and TIMP-1.[25] The ELF test was validated in a cohort of patients with biopsy-proven metabolic dysfunction-associated steatohepatitis (MASH; formerly known as nonalcoholic steatohepatitis) and demonstrated an AUC of 0.90 (95% CI, 0.84-0.96) for distinguishing advanced fibrosis.[26] In a meta-analysis estimating the accuracy of the ELF test against liver biopsy, the ELF test had high sensitivity for diagnosing fibrosis (>0.90) but poor specificity to exclude advanced fibrosis at low cutoffs.[27] The performance of the ELF test was recently evaluated in a retrospective, cross-sectional study of 829 patients with MASLD. The AUC for identifying patients with advanced fibrosis diagnosed by biopsy was 0.81 (95% CI, 0.77-0.85), with a similar performance observed among patients with MASLD who had diabetes or who were age 65 years or older.[28] Although the ELF test may be reliably used to diagnose advanced fibrosis in patients with MASLD, its current clinical utility is limited by the need for specialty laboratory processing.

The utilization of chemokines/cytokines associated with hepatocyte death and apoptosis, oxidative stress, and inflammation for the assessment of fibrosis is being evaluated. Cytokeratin-18 (CK-18) was evaluated in a cohort of 139 patients with biopsy-proven MASH cross-matched with healthy controls by age, and showed an AUC of 0.83 (95% CI, 0.75-0.91) with a sensitivity of 0.75 (95% CI, 0.64-0.83) and specificity of 0.81 (95% CI, 0.61-0.93) for a CK-18 threshold level of 246 U/L.[29] C-X-C motif chemokine ligand 10 is a proinflammatory cytokine involved in the pathogenesis of diabetes and obesity and has been shown to be moderately accurate for differentiating MASH from simple steatosis (AUC, 0.68; 95% CI, 0.59-0.77) and from non-MASH (AUC, 0.77; 95% CI, 0.70-0.84).[30] PRO-C3, a marker that detects synthesis of type III collagen, has recently been suggested to be superior to the FIB-4 index, NFS, and APRI in patients with MASLD.[31,32] Although these biomarkers appear promising, they are still being evaluated and are not yet ready for prime time.

Noninvasive Imaging Modalities

Conventional noninvasive imaging tests such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) can detect moderate to severe hepatic steatosis. Ultrasonography in the detection of

severe hepatic steatosis demonstrated an AUC of 0.93 (95% CI, 0.91-0.95).[33] Detection of hepatic steatosis of at least 5% is much less accurate, with AUCs of 0.761 and 0.807 for ultrasonography and CT, respectively.[34] Although these imaging tests can assess for nodular hepatic surface, caudate lobe hypertrophy, changes in vasculature and spleen size, and morphologic changes seen in cirrhosis, the tests are unable to assess for early stages of fibrosis.[35]

Ultrasound and magnetic resonance elastography (MRE) are newer technologies that detect and stage fibrosis. Via Young's modulus, a physical principle that describes the relationship between stress, or applied mechanical force, and strain, or the deformation of that result, it is possible to characterize the elasticity of a material.[36] This principle can be applied to liver tissue; by applying a known mechanical or acoustic force, shear waves are generated.[37] Shear wave velocity, calculated by measuring the degree of liver displacement that occurs, is directly related to liver stiffness; higher velocity is seen in stiffer tissue.[38]

Ultrasound-based Imaging

Transient elastography (TE) uses shear wave imaging to estimate liver stiffness measurement.[39] The application of mechanical vibration pulses generates low frequency (5 Hz) elastic waves in the liver, and ultrasound is used to track elastic wave propagation velocity by measuring liver tissue displacement.[40] This velocity, measured in kilopascals (kPa), is an estimate of liver elasticity with higher values indicating increased tissue stiffness, providing a surrogate quantitation of liver fibrosis. TE via FibroScan (Echosens) is a widely used modality and carries marked advantages over percutaneous liver biopsy, including portability, inexpensiveness, short procedure time, immediate results, and reproducibility.

Controlled attenuation parameter (CAP) is a noninvasive tool available on the FibroScan system for the quantification of liver steatosis. By quantifying ultrasound attenuation through hepatic tissue, hepatic fat can be estimated while simultaneously measuring liver elasticity by TE.[41] In a prospective study examining the accuracy of CAP in patients with biopsy-confirmed MASH, the diagnosis of steatosis greater than 10%, greater than 33%, and greater than 66% had AUCs of 0.79 (95% CI, 0.74-0.84; *P*<.001), 0.84 (95% CI, 0.80-0.88; *P*<.001), and 0.84 (95% CI, 0.80-0.88; *P*<.001), respectively.[42] CAP values appear to correlate with the histologic NAFLD Activity Score (NAS) with a Spearman rho of 0.51 (*P*<.00005).[43] The AUC for CAP was 0.81 (95% CI, 0.74-0.88) compared with an AUC of 0.65 (95% CI, 0.57-0.74; *P*=.02) with the hepatic steatosis index and an AUC of 0.72 (95% CI, 0.63-0.82; *P*=.12) with the fatty liver index.[43] In a meta-analysis of 1297 patients across 9 studies, CAP exhibited good diagnostic value for mild and moderate steatosis with mean AUCs of 0.96 (standard error [SE], 0.0135; Q index, 0.9027) and 0.82 (SE, 0.0368; Q index, 0.7569), respectively. However, CAP also demonstrated lower accuracy in identifying severe steatosis, with a mean AUC of 0.70 (SE, 0.0278; Q index, 0.6469), pooled sensitivity of 76% (95% CI, 0.71-0.8), and pooled specificity of 58% (95% CI, 0.55-0.61).[44]

In the initial study evaluating significant fibrosis (≥F2) and cirrhosis in patients with HCV, the AUCs were 0.88 and 0.99, respectively.[39] Numerous prospective studies evaluating the diagnostic accuracy of FibroScan for staging fibrosis in varying etiologies of CLD have been performed. In a meta-analysis evaluating the diagnostic accuracy of TE in assessing fibrosis, the pooled sensitivity and specificity were 0.70 (95% CI, 0.67-0.73) and 0.84 (95% CI, 0.80-0.88), respectively.[45] In a large meta-analysis of 50 studies assessing overall performance of TE for the diagnosis of significant fibrosis, severe fibrosis, and cirrhosis, the AUCs were 0.84 (95% CI, 0.82-0.86), 0.89 (95% CI, 0.88-0.91), and 0.94 (95% CI, 0.93-0.95), respectively.[46] The diagnostic accuracy of TE staging of advanced fibrosis and cirrhosis was similarly demonstrated in a prospective study of patients with MASLD, with AUCs of 0.83 (95% CI, 0.79-0.87) and 0.93 (95% CI, 0.90-0.97), respectively.[47] In patients with MASLD, TE outperformed the FIB-4 index and NFS in the detection of advanced fibrosis, with AUCs of 0.85 (95% CI, 0.84-0.86) vs 0.76 (95% CI, 0.74-0.77) and 0.73 (95% CI, 0.71-0.75), respectively.[48] For detecting cirrhosis in patients with HCV, TE demonstrated a pooled sensitivity of 84% (95% CI, 81%-86%) and pooled specificity of 91% (95% CI, 90%-92%) with an AUC of 0.954.[49]

The FibroScan-AST (FAST) score combines FibroScan technology with AST level to detect advanced fibrosis. In a prospective derivation and global validation study, the pooled AUC of external patient cohorts was 0.85 (95% CI, 0.83-0.87).[50] The FAST score outperformed the FIB-4 index and NFS with AUCs of 0.85, 0.74, and 0.68, respectively.[51]

FibroScan offers the advantages of low cost, portability, accessibility, and patient tolerability. It also carries some significant disadvantages, including limited accuracy in patients with obesity, narrow intercostal spaces, ascites, congestive hepatopathy, and nonfasting states. The classic FibroScan M probe has high failure rates (17%) in patients with a body mass index (BMI) of at least 30.[52] Use of the XL probe in patients with a BMI of at least 28 resulted in lower FibroScan failure rates, 1.1% vs 16% with the M probe, and was more often reliable, 73% vs 50% with the M probe (both *P*<.00005).[53]

Acoustic radiation force impulse (ARFI) elastography is a 2-dimensional modality that measures tissue elasticity using the same underlying physical principle as TE. Rather than relying on mechanical vibration, ARFI utilizes ultrasound waves in both the pulsatile-focused generation of shear elastic waves (2.67 MHz) and the detection of shear wave propagation velocity (3.08 MHz).[54,55] ARFI elastography has several advantages, including real-time results, 2-dimensional elasticity measurements, simultaneous real-time ultrasound imaging, and implementation in existing diagnostic ultrasound systems and transducers.[37]

In a large meta-analysis that included 8 studies and 518 patients, ARFI diagnosis of at least F2, at least F3, and cirrhosis demonstrated AUCs of 87%, 91%, and 93%, respectively.[54] In a different meta-analysis, pooled diagnostic sensitivity for cirrhosis was 0.87 (95% CI, 0.79-0.92) and pooled specificity was 0.87 (95% CI, 0.81-0.91).[55] This accuracy dropped slightly in identifying significant fibrosis (≥F2), where pooled sensitivity and specificity were 0.74 (95% CI, 0.66-0.80) and 0.83 (95% CI, 0.85-0.89), respectively. These results were similarly reflected in a review of chronic HBV and HCV patients, which found that pooled sensitivity and specificity were 0.79 (95% CI, 0.76-0.83) and 0.86 (95% CI, 0.85-0.88), respectively, and that, overall, diagnostic accuracy was higher for identifying severe fibrosis and cirrhosis.[56] The accuracy of ARFI was not limited by patient weight, unlike TE, in which obese patients with a BMI greater than 30 had limited results with less diagnostic accuracy than normal-weight patients. In a study of 172 patients with MASLD in which greater than 60% had a BMI over 30, the sensitivity and specificity of identifying cirrhosis were both 90% with an AUC of 0.9.[57] The use of variable depth measurement relies on adjusting the focal depth, which can influence result accuracy.[54]

Magnetic Resonance–based Imaging

MRE generates shear elastic waves, and in a synchronized MR pulse sequence with motion encoding gradients, wave propagation through the liver can be mapped in 3 dimensions.[58] Liver stiffness is approximated by measuring micron-level tissue displacement over time, and particular anatomic areas of interest can be identified on elastograms. This allows for visualization of the heterogeneous pattern of liver fibrosis.[58] In a meta-analysis of MRE for the diagnosis of advanced fibrosis and cirrhosis in patients with MASLD, AUCs were 0.93 (95% CI, 0.89-0.96) and 0.94 (95% CI, 0.89-0.99), respectively.[59] For each liver fibrosis stage 1 to 4, pooled sensitivity was 0.77, 0.87, 0.89, and 0.94, and pooled specificity was 0.90, 0.86, 0.84, and 0.75, respectively.[60] When comparing MRE with TE, MRE had significantly higher diagnostic accuracy with an AUC of 0.94 (95% CI, 0.89-0.99) vs 0.84 (95% CI, 0.73-0.94) for TE (P=.005).[59] This was further supported in a cross-sectional study of 142 patients with biopsy-proven MASLD in which the diagnosis of at least F2 by TE had an AUC of 0.82 (95% CI, 0.74-0.89), whereas the AUC with MRE was 0.91 (95% CI, 0.86-0.96; P=.001).[61]

Proton density fat fraction (PDFF) is an MRI-calculated fraction between the liver fat signal over the total signal, which relies on the difference between the resonant frequency of water compared with triglycerides, the predominant content of hepatic fat.[62] This imaging modality is used to assess the degree of hepatic steatosis and is most often calculated in conjunction with MRE. MRI-PDFF was found to be excellent in the diagnosis of all steatosis stages; the AUCs were 0.90 (95% CI, 0.82-0.97) and 0.92 (95% CI, 0.84-0.99) for steatosis grades 2 and 3, respectively.[63] The AUC of hepatic steatosis identification by MRI-PDFF was 0.99 (95% CI, 0.98-1.00) vs 0.85 (95% CI, 0.75-0.96) for CAP. In a cross-sectional study of 142 patients with MASLD, the diagnosis of hepatic steatosis of at least grade 2 by CAP had an AUC of 0.74 (95% CI, 0.64-0.81), whereas the AUC with PDFF was 0.90 (95% CI, 0.82-0.97) (P<.001).[61] The value of PDFF was applied to predict liver fibrosis progression and compared with liver biopsy. Higher fat content (PDFF >15.7%) was more significantly associated with progression of fibrosis, with 38.1% of patients with higher fat content developing liver fibrosis compared with 11.8% of patients with lower fat content (P=.067).[64]

LiverMultiScan is a noninvasive modality that uses MRI to quantify hepatic fibroinflammatory injury, fat, and iron in order to assess CLD.[65] By quantifying characteristics such as liver fat, iron content, and extracellular water, estimations of liver fibrosis, steatosis, and hemosiderosis can be made.[66,67] Although MRE is highly accurate, limitations to its use include the requirement of specialized equipment and inaccurate measurements in patients with hemosiderosis.[68] Multiparametric MR is estimated by T1 relaxation after correcting for iron content, called cT1 mapping, while fat is estimated using cardiac-triggered proton spectroscopy.[66] In pooled comparisons of multiparametric MR vs histologic scores for steatosis, lobular inflammation, and composite NAS, the AUC of the diagnostic accuracy of cT1 was 0.78 (95% CI, 0.74-0.82) and was 0.78 for MRI liver fat (95% CI, 0.73-0.82).[67] When analyzing both cT1 and liver fat, the AUC significantly improved to 0.82 (95% CI, 0.78-0.85) (P<.001).[67] The identification of high-risk MASH using cT1 with an optimal cutoff of 825 milliseconds had a pooled AUC of 0.78 (95% CI, 0.74-0.82), whereas MRI liver fat was significantly less reliable at 0.69 (95% CI, 0.64-0.74) (P<.001).[67]

Although these MR-based methods are more diagnostically accurate and precise than other imaging

modalities, these studies are more expensive, time-intensive, and are often more difficult for patients to tolerate.[63] A summary of the prognostic accuracy of imaging modalities is listed in Table 2.

Sequential Algorithms

Combined or sequential application of noninvasive serum biomarkers with elastography offers higher diagnostic accuracy than either individual test. Numerous studies have evaluated varying combinations of NITs. In a retrospective study of 577 patients with biopsy-proven MASH, several 2-step methods were evaluated, with the most clinically relevant technique, the FIB-4 index in tandem with TE, yielding an AUC of 0.81.[69] In a large meta-analysis evaluating the diagnostic performance of NITs in patients with MASLD, sequential combination of the FIB-4 index (cutoffs <1.3; ≥2.67) followed by TE (cutoffs <8.0; ≥10.0 kPa) in the diagnosis of fibrosis had sensitivities and specificities of 66% (95% CI, 63-68) and 86% (95% CI, 84-87), respectively.[48] In a prospective study that included 234 patients with biopsy-confirmed MASLD, MRE combined with the FIB-4 index (MEFIB) was compared head-to-head with the FAST score in 2 cohorts. One cohort demonstrated statistically higher diagnostic accuracy of MEFIB compared with the FAST score, with AUCs of 0.86 (95% CI, 0.81-0.91) and 0.76 (95% CI, 0.69-0.82), respectively (P=.005). Similar results were demonstrated in the other cohort, with AUCs of 0.89 and 0.72, respectively (P<.001).[70]

Based on the currently available tools and data, our general approach to assess hepatic steatosis and fibrosis is with a sequential algorithm combining the FIB-4 index and FibroScan with CAP. The FIB-4 index is easily calculated based on already available laboratory data, and the calculation is incorporated into our electronic medical record system. FibroScan with CAP, along with an experienced operator, is readily available in our clinic; thus, we also utilize the imaging modality for noninvasive assessment of hepatic steatosis and fibrosis.

Future Directions

Genetic testing may have a role in the assessment of hepatic fibrosis in patients with MASH. Many gene variants are being evaluated, and a sequence variation in the *PNPLA-3* gene, rs 738409, is strongly associated with the progression of MASH.[71] Additionally, gut microbiome–based metagenomics signatures may play a role in detecting advanced fibrosis.[72] However, these potential diagnostic targets require further study and validation in the clinical setting.

Imaging models are also being investigated to develop artificial intelligence– and deep machine learning–based processes. These models aim to identify unique imaging biomarkers termed radiomics, which are characteristics of images that may not be identified by the human eye.[73] The benefit of using such artificial intelligence– or machine learning–imaging models is that these computational biomarkers can be additive algorithms to existing imaging. Development of reproducible and accurate radiomics is limited by heterogeneity and quality of patient images.

Conclusion

The accurate assessment of liver fibrosis is crucial for appropriate liver disease management, prognostication, and treatment monitoring. Noninvasive serum biomarkers and imaging modalities have demonstrated high diagnostic accuracy for the detection of advanced fibrosis. Algorithms such as APRI, the FIB-4 index, and NFS utilize readily available patient demographics and laboratory data, and thus are easy to use in the clinical setting. Although screening of the general population is not recommended, the newest published guidance by the AASLD recommends primary risk assessment using the FIB-4 index, the most validated NIT, in patients who are at risk of progression of MASLD.[22] TE and MRE are newer imaging modalities that can detect advanced fibrosis while avoiding complications associated with liver biopsy. Combining elastography and anatomic imaging can provide thorough assessment of not only hepatic steatosis and fibrosis but can also evaluate for malignancy while avoiding the risks of ionizing radiation and invasive testing. Sequential algorithms have shown promising results, further increasing the sensitivity and specificity of these studies.

Disclosures

The authors have no relevant conflicts of interest to disclose.

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