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Noninvasive Risk Stratification for Nonalcoholic Fatty Liver Disease Among Living Liver Donor Candidates: A Proposed Algorithm

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Abstract

To reduce waitlist mortality, living donor liver transplantation (LDLT) has increased over the past decade in the United States, but not at a rate sufficient to completely mitigate organ shortage. As a result, there are ongoing efforts to expand the living liver donor pool. Simultaneously, the prevalence of nonalcoholic fatty liver disease (NAFLD) in the general population has increased, which has significant implications on the pool of potential living liver donors. As such, a clinical assessment algorithm that exhaustively evaluates for NAFLD and fibrosis is critical to the safe expansion of LDLT. An ideal algorithm would employ safe and noninvasive methods, relying on liver biopsy only when necessary. While exclusion of NAFLD and fibrosis by noninvasive means is widely studied within the general population, there are no well-accepted guidelines for

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Nilay Danis acquired data, performed analysis and interpretation of data, and drafted the manuscript. Ihab R. Kamel, Azarakhsh Baghdadi, Maryam Ghadimi, Sharon R. Weeks, Tinsay Woreta, and Ahyoung Kim critically revised the manuscript for important intellectual content. Behnam Saberi acquired and interpreted data. Jacqueline Garonzik-Wang and Benjamin Philosophe were responsible for study concept and design, interpretation of data, and critical revision of the manuscript for important intellectual content. Ahmet Gurakar was responsible for study concept and design, acquisition of data, drafting of the manuscript, and critical revision of the manuscript. Rohit Loomba performed interpretation of data, critical revision of the manuscript for important intellectual content, and study supervision.

evaluation of living donors using these modalities. Here we review the current literature regarding noninvasive NALFD and fibrosis evaluation and propose a potential algorithm to apply these modalities for the selection of living liver donors.

To reduce waitlist mortality, living donor liver transplantation (LDLT) has increased over the past decade in the United States,[1] but not at a rate sufficient to completely mitigate organ shortage. As a result, there are ongoing efforts to expand the living liver donor pool. Simultaneously, the prevalence of nonalcoholic fatty liver disease (NAFLD) in the general population has increased from 15% to 25% since 2005,[2] which has significant implications on the pool of potential living liver donors. In the era of organ scarcity, the goal of expanding the donor pool stands in tension with the obesity epidemic which may compromise many potential donors as candidates to provide quality grafts due to NAFLD prevalence.

In light of increasing rates of obesity and resultant NAFLD, donor evaluation protocols demand modification to optimize donor selection. Obesity is rising in the United States and has been linked to NAFLD.[3,4] NAFLD prevalence is 91% among individuals with obesity (body mass index [BMI] ≥30 kg/m^2) and 67% among those who are overweight (BMI = 25–29 kg/m^2).[2,5] Among living donors who have undergone a preoperative liver biopsy, fatty liver changes are the most common pathological finding. In a study of 612 living related liver donor candidates, 32% of liver biopsies had pathological findings, with 44% of these pathological findings being fatty liver.[6] While liver biopsy is the gold standard to assess the liver tissue, it is an invasive procedure with associated risks.[7] Furthermore, its predictive value can be compromised by sampling error; fibrosis stage discordance of at least 1 has been reported to be as high as 41%.[8] Current guidelines for evaluation of NAFLD were developed for the general population rather than for living liver donation, where consequences may be far reaching.

A careful noninvasive approach to facilitate safe and expeditious evaluation of steatosis, steatohepatitis, and fibrosis is critical in the setting of increasing NAFLD in the potential donor pool. The aim of this paper is to review the literature for assessment of NAFLD and to propose a potential algorithm for evaluation of living liver donors for NAFLD and fibrosis.

Physical Examination and Serum Biomarkers for the Initial Evaluation of NAFLD Among Living Liver Donor Candidates

Initial evaluation of the living liver donors by physical examination and basic laboratory tests may indicate people at risk for NAFLD. Taken in isolation, however, this evaluation is neither sensitive nor specific enough to rule potential donors in or out of consideration. Noninvasive studies can also be used as surrogate markers to supplement the identification of underlying NAFLD.

Physical examination can certainly provide information regarding body habitus and obesity. BMI has also been used as a surrogate for underlying steatosis. In a study of 250 patients with NAFLD compared with a control population, the odds ratio for NAFLD was 21.8 for BMI between 23 and 25 kg/m^2, but 29.9 for BMI ≥25 kg/m^2.[9] There was no increased odds

ratio for patients with BMI <23 kg/m^2. Furthermore, obesity was associated with an elevated risk for liver fibrosis among patients with NAFLD.[10] Another study used <25, 25–28, and >28 kg/m^2 as BMI cutoffs and found that no patient with BMI <25 kg/m^2 had hepatic steatosis, 33% of patients with BMI of 25–28 kg/m^2 had steatosis on biopsy, and 76% of patients with BMI >28 kg/m^2 had steatosis proven by liver biopsy.[11] One recent study with 264 living donor liver candidates used <25, 25–29.9, and ≥30 kg/m^2 as BMI thresholds, and 83.3% of candidates with BMI <25 kg/m^2 had no steatosis; however, this ratio was 51.5% among candidates with BMI of 25–29.9 kg/m^2, and 31.9% among candidates with BMI ≥30 BMI kg/m^2 on the liver biopsy.[12] However, BMI alone is not a sufficiently precise predictor of NAFLD because both lean and obese patients with NAFLD can have similar metabolic profile for cardiovascular disease risk. Both lean and patients with obesity having NAFLD have abnormal plasma total cholesterol and triglycerides as well as elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyltransferase (GGT) levels.[13,14] Thus, BMI alone is not sufficiently robust to select ideal living liver donor candidates.

Serum biochemical studies are an important component of the living liver donor evaluation process and may give insight into the underlying liver dysfunction. These include evaluation of ALT, AST, GGT, alkaline phosphatase, complete blood count, international normalized ratio, total bilirubin, albumin, lipid profile, fasting glucose level, and hemoglobin A1c. Both ALT and GGT have a linear dose-response relationship with metabolic syndrome.[15–17] Based on a large systematic review, NAFLD is the most common cause of asymptomatic elevation of transaminases, found to be present in up to 25% of patients with elevated ALT or AST depending on the study population.[18,19]

However, there does not appear to be a dose-response relationship between ALT or AST level and severity of nonalcoholic steatohepatitis (NASH).

Total cholesterol, low-density lipoprotein-cholesterol, and triglyceride serum levels were statistically significantly higher in patients with hepatic steatosis. Furthermore, higher AST levels were associated with significant liver fibrosis.[20] Higher hemoglobin A1c was also indicated to predict the presence of NAFLD. Sixty-six of patients with NAFLD had an A1c greater than 5.7, whereas this ratio was 32% for controls.[21] However, the prevalence of NAFLD among patients with type 2 diabetes mellitus was demonstrated to be 55%, indicating that half of patients with type 2 diabetes mellitus do not necessarily have fatty liver disease.[22] Patients with liver fibrosis may also have normal serum aminotransferase levels.[23] Therefore, none of these biomarkers is sufficiently sensitive or specific to predict fat accumulation and fibrosis of the liver.

Scoring Systems for Liver Fibrosis

Given the associations found between various individual markers and NAFLD, several scoring systems for liver fibrosis have been developed on the basis of these relationships. The most studied of these scoring systems are fibrosis-4 (FIB-4), the NAFLD fibrosis score (NFS), and the enhanced liver fibrosis (ELF) test. The accuracy of these systems in identifying clinically relevant fibrosis is evaluated by calculating the area under the

receiver operating characteristic curve (AUROC) for distinguishing advanced fibrosis from less severe disease. Advanced fibrosis is defined by the NASH clinical research network score as F3, bridging fibrosis, or F4, cirrhosis.

The simplicity of FIB-4, a composite score utilizing AST, ALT, and platelet count, has made it widely accepted in clinical practice (Table 1). Its diagnostic accuracy for advanced fibrosis is 64.2%.[24] Another meta-analysis showed that FIB-4 prognostic accuracy for detecting progression to advanced fibrosis ranged from an area under the curve of 0.65 (95% confidence interval [CI], 0.54–0.76) to 0.81 (95% CI, 0.73–0.89).[25]

NFS, which in contrast to FIB-4, was designed specifically for NAFLD, requires serum albumin level and diabetes mellitus diagnosis, in addition to FIB-4 items.[26] Its performance to differentiate advanced fibrosis (F3-F4) from F0-F2 fibrosis is 80%.[27] Age has been suggested as a confounding factor for NFS and FIB-4, especially among the group 35 years of age or younger. Such living liver donor candidates could be potentially approached as intermediate risk[28] (Fig. 1).

Another proposed scoring system for NAFLD is ELF. A disadvantage of this test is the need for additional measurements that are not routinely collected (tissue inhibitor of metalloproteinase-1 [TIMP-1], procollagen type 3 N-terminal propeptide [PIIINP], and hyaluronic acid [HA]).[29] A recently published meta-analysis showed that ELF test has a high sensitivity of 93% but limited specificity to exclude advanced and significant fibrosis at a low cutoff (7.7).[30]

There are also new scoring systems based on serum biomarkers to detect advanced fibrosis. They are alleged to be superior to FIB-4 and NFS, such as the Hepamet Fibrosis Scoring System and the serum metabolomics panel.[31,32] The Hepamet Fibrosis Scoring System utilizes the homeostatic model assessment for insulin resistance in addition to AST, albumin, and platelets to estimate advanced fibrosis.[32] In a study of 2452 patients with NAFLD, diagnostic accuracy of the Hepamet Fibrosis Scoring System was found to discriminate between patients with and without advanced fibrosis with an AUROC curve value of 0.85.[32] This diagnostic accuracy compares favorably with NFS or FIB-4, with AUROC of 0.80 ($P = 0.001$).[32] By contrast, in a comparative study, 10 serum metabolite panels had a combined AUROC value of 0.94 (95% CI, 0.90–0.98) for detection of advanced fibrosis, whereas these values were 0.78 (95% CI, 0.67–0.89; $P = 0.002$) for FIB-4 and 0.84 (95% CI, 0.72–0.93; $P = 0.02$) for NFS.[31]

Scoring Systems for Liver Steatosis

There are also other scoring systems proposed to predict hepatic steatosis. Prominent ones are (i) Fatty Liver Index, (ii) Hepatic Steatosis Index, and (iii) NAFLD Liver Fat Score. Their reported AUROC scores, sensitivity, and specificity were 0.84, 0.81, and 0.87; 87%, 93%, and 86%; and 86%, 92%, and 71%, respectively.[33–36] By contrast, SteatoTest has an acceptable AUROC score, sensitivity, and specificity rates compared with liver biopsy. However, SteatoTest needs additional serum biomarkers, such as alpha-2-macroglobulin, and

apolipoprotein A1.[37] These scoring systems are well summarized by Stern and Castera[33] (Table 2).

Image-Based Evaluation of Living Liver Donor Candidates

Recent advances in image-based modalities have allowed for improved assessment of steatosis and fibrosis.

MAGNETIC RESONANCE

Magnetic resonance (MR) spectroscopy is the most reliable imaging technique to evaluate fat content of the liver and is considered the reference standard for fat quantification in the liver.[38–40] However, the technique is not widely utilized due to its limited availability, the need for special sequences, relatively small voxel-based measurement, time-consuming acquisition, and complicated postprocessing techniques.[38]

MR cholangiopancreatography is necessary for accurate mapping of the biliary tree of living liver donors for surgical planning. Adding a reliable, safe MR sequence for fat quantification that does not carry the limitations of MR spectroscopy is desirable to ensure adequate assessment of the liver parenchyma. Several studies have shown that proton density fat fraction (MRI-PDFF) has high accuracy in quantifying liver fat content of living donor candidates. MRI-PDFF differentiate moderate or severe steatosis from mild or no steatosis with 93% sensitivity and 85% specificity.[38,41,42] The imaging technique is widely available and is now commonly performed in liver imaging.

COMPUTED TOMOGRAPHY

Compared with MR, computed tomography (CT) has less accuracy in detecting hepatic steatosis, especially in cases with low fat deposition.[43,44] Other disadvantages such as ionizing radiation and semiquantitative technique make CT a less desirable technique for fat quantification in the liver.[38]

ULTRASOUND

Ultrasound is commonly used as an initial imaging technique for evaluation of the margins of the liver, as well for detection of masses, altered echogenicity, and changes in blood flow. However, it does not have an acceptable performance for detecting liver fat content and is therefore not routinely performed on living liver donor candidates. Controlled attenuation parameter (CAP) is a new parameter that can measure hepatic fat using vibration-controlled transient elastography (VCTE; FibroScan, Echosens, Paris, France) M probe. But head-to-head studies comparing CAP and MRI-PDFF showed the latter to have better results in estimating liver fat accumulation, with a good diagnostic accuracy (AUROC, 0.80; 95% CI, 0.70–0.90) for ≥5% liver fat accumulation and with an AUROC of 0.87 (95% CI, 0.80–0.94) for ≥10% liver fat accumulation[38,45,46] (Table 3).

To overcome the limitations of ultrasound-based techniques, computer-assisted quantitative techniques were also developed. The most promising one is Hepatorenal Index, which estimates liver fat content by using the ratio of mean brightness level within a region of

interest in the liver and in the right kidney. This technique is reported to have high diagnosis accuracy, sensitivity, and specificity (AUROC, 0.99; 100% sensitivity; 91% specificity using a cutoff of 1.49).[33] This method is also considered when MR-based techniques are not accessible or when MR is contraindicated. However, there is a no head-to-head comparison of this technique and MR-based techniques. To date, MRI-PDFF seems to be the best noninvasive choice for estimating liver fat content among the living liver donor candidates.

Further Evaluation

In a small proportion of donors with liver fat content <10%, fibrosis may need to be excluded. In such cases, some other noninvasive tests may be needed. In addition to the aforementioned serum biomarkers, assessment of fibrosis could be further analyzed with noninvasive imaging studies. MR elastography (MRE) is currently the most accurate technique (AUROC, 0.97) compared with ultrasound-based techniques including VCTE and acoustic radiation force impulse (ARFI) imaging/shear wave elastography (SWE).[38,47,48] Both VCTE and ARFI/SWE could reveal incorrect results especially in patients with obesity.[47] The discordance of findings between MRE and VCTE increases especially in patients with high BMI and despite the use of extra large ultrasound transducers with larger vibration amplitude and greater depth of measurements.[49] More recently, MRE combined with FIB index (MEFIB index; MRE ≥3.3 kPa and FIB-4 ≥1.6) has been proposed to identify those who have significant fibrosis and NASH with a high positive predictive value.[50] However, the MEFIB index is less valuable in the setting of LDLT due to the low likelihood of fibrosis in patients with MRI-PDFF <10%.

In conclusion, in living liver donors, MRI is the modality of choice for the detection of hepatic steatosis and fibrosis. The combination of MRI-PDFF and MRE provides a noninvasive and accurate assessment of the liver parenchyma without the need for biopsy. Moreover, these imaging techniques can be repeated as clinically indicated to assess for changes in liver steatosis and fibrosis over time. Candidates who have MRI-PDFF ≥10% and MRE ≥3 kPa may have NASH with fibrosis. MRE of 3 kPa has a diagnostic accuracy of 83% for detection of fibrosis with a 90% cross-validated specificity and a positive predictive value of 89%.[51] These patients may have high likelihood of having fibrosis and hence may need lifestyle interventions prior to serving as a donor or might be considered for a liver biopsy assessment to further assess their risk. These donor candidates may be placed on a hypocaloric diet and lifestyle interventions to lose weight, as approximately 5%–7% weight loss may improve liver fat and liver stiffness over 24 weeks.[52] After weight loss and further workup in NAFLD clinics, these donor candidates may be re-evaluated with MRI-PDFF and MRE and may be considered on a case-by-case basis.

Experience with Steatotic Living and Deceased Donor Liver Grafts

Living liver donor experience in using steatotic grafts has also been recently reported. A retrospective study from India compared 92 right lobe grafts with 10%–20% macrosteatosis with 531 grafts with <10% macrosteatosis and found no differences in donor and recipient outcomes.[53]

Among deceased donor liver grafts, Wong et al.[54] retrospectively compared >60% macrovesicular steatotic liver grafts with ≤60% steatotic grafts. They found out that early allograft dysfunction and 30-day mortality, and 1- and 3-year overall survival rates were similar between the 2 groups, as long as used with caution. A recent study has compared deceased donors with ≥30% graft steatosis to grafts with <30% steatosis, and recipient BMIs ≤35 versus >35 kg/m^2. Both high BMI and steatotic grafts were found to be associated with higher 30-day mortality following transplantation.[55]

Regarding living liver donors, some centers have advocated for the safety of using steatotic right lobe grafts, provided there is (i) appropriate size match between the recipients and donors, (ii) the recipients have Model for End-Stage Liver Disease scores ≤15, and (iii) grafts are from relatively younger donors, defined as ≤40 years of age.[53,56] However, steatotic grafts from living liver donors are still considered to be controversial and should be used with extreme caution.

In light of the evidence for various means to assess NAFLD in the potential donors, we propose an algorithm to select the ideal living liver donor. Initially, to rule out liver fibrosis of the donor candidate, we suggest beginning with a liver fibrosis scoring system: either FIB-4 or NFS. If donor candidate emerges in low-risk profile (FIB-4 <1.3 or NFS <−1.455), we suggest proceeding with MRI-PDFF to determine liver fat accumulation. Living donor candidates with low liver fat accumulation (<%10) are ideal and may proceed with complete evaluation for liver donation. Donor candidates with intermediate- or high-risk profile by FIB-4 or NFS (FIB-4 ≥1.3 or NFS ≥−1.455) should undergo evaluation with MRI-PDFF and MRE. After this imaging study, if a donor candidate's liver fat accumulation and MRE scores are above the cutoff levels (MRI-PDFF with liver fat accumulation >10% ± MRE ≥3 kPa), we suggest considering diet, weight loss and then re-evaluation. Figure 1 summarizes our proposal for selecting appropriate living liver donor candidates.

Conclusion

As the obesity epidemic worsens in the United States, evaluation and clearance of potential living liver donors will require careful consideration and evaluation of NALFD. Here we review the available literature on methods for NAFLD assessment and propose a simple and logical, potential algorithm for the assessment of NAFLD among living liver donor candidates. This algorithm may help us assess an increasingly obese donor pool and aid in the expansion of LDLT in the United States.

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Abbreviations:

A2M	alpha-2-macroglobulin
ALT	alanine aminotransferase
ApoA1	apolipoprotein A1
ARFI	acoustic radiation force impulse
AST	aspartate aminotransferase
AUROC	area under the receiver operating characteristic curve
BMI	body mass index
CAP	controlled attenuation parameter
ELF	enhanced liver fibrosis
FIB-4	fibrosis-4
GGT	gamma-glutamyltransferase
HA	hyaluronic acid
HOMA	homeostatic model assessment
LDLT	living donor liver transplantation
MEFIB	MRE combined with FIB
MRE	magnetic resonance elastography
MRI-PDFF	magnetic resonance proton density fat fraction
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NFS	NAFLD fibrosis score
PIIINP	procollagen type 3 N-terminal propeptide
SWE	shear wave elastography
TIMP-1	tissue inhibitor of metalloproteinase-1
VCTE	vibration-controlled transient elastography

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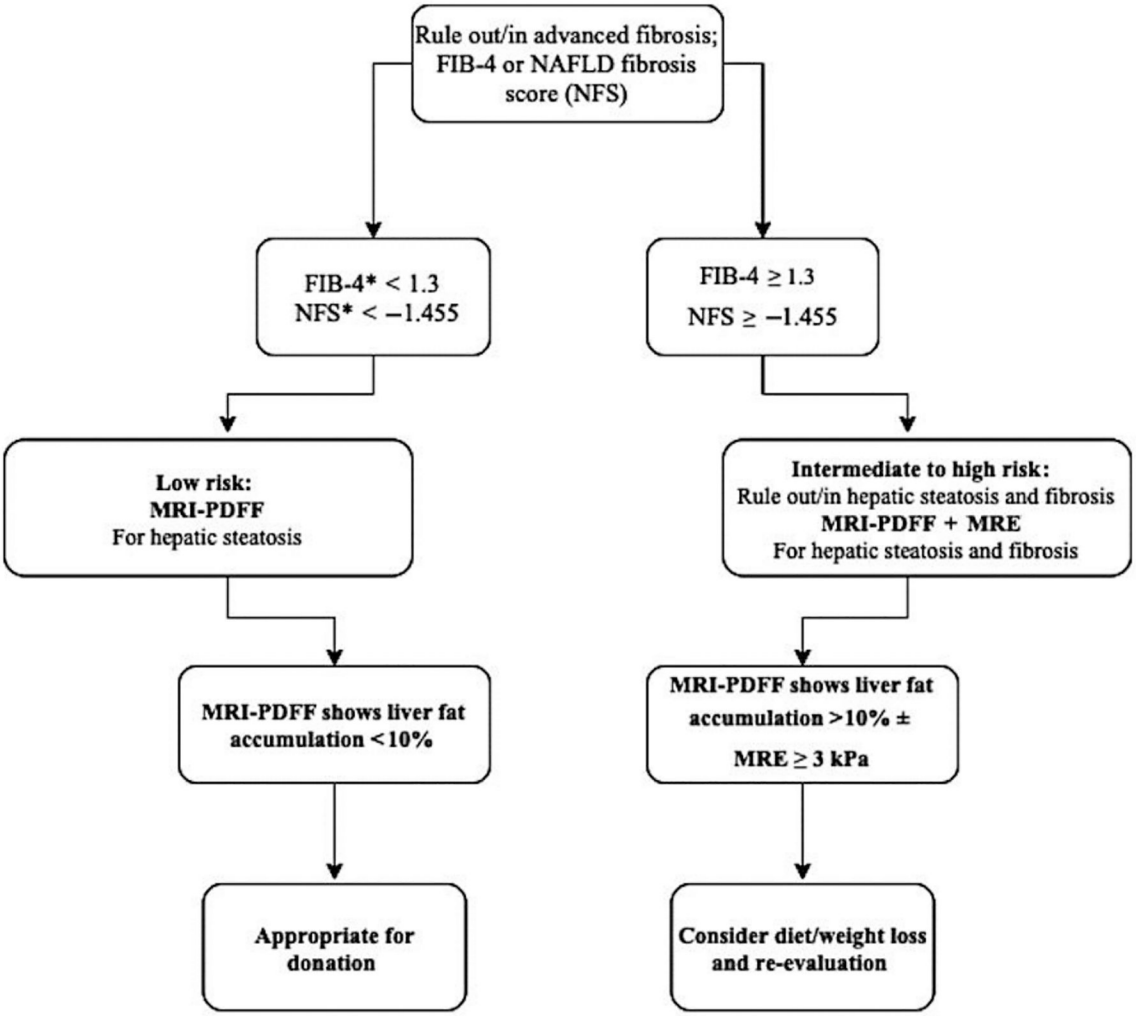

FIG. 1.
LDLT workup. *If discordant, proceed as intermediate to high risk.

TABLE 1.

Noninvasive Scores Using Serum Biomarkers Screening for the Presence of Fibrosis in NAFLD

Noninvasive Test	Parameter Used	Lower Threshold to Rule Out Advanced Fibrosis	Upper Threshold to Rule Out in Advanced Fibrosis
FIB-4	FIB-4 = age (years) × AST (U/L)/(platelets [10^9/L] × (ALT [U/L])1/2)	1.3	2.67
NFS	NFS = −1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × impaired fasting	−1.455	−0.676
	Glucose/diabetes mellitus (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelet (×10^9/L) − 0.66 × albumin (g/dL)		
ELF*	ELF = 2.494 + 0.846 In (CHA) + 0.735 In (CPIIINP) + 0.391 In (CTIMP-1)	9.8	11.3
Hepamet	https://www.hepamet-fibrosis-score.eu/	0.12	0.47

NOTE: See Refs. 25,29.

*Not widely commercially available.

TABLE 2.

Noninvasive Scores Using Serum Biomarkers Screening for Steatosis in NAFLD

Noninvasive Test	Parameters Used
Fatty liver index	BMI, triglyceride, waist circumference, GGT
Hepatic steatosis index	BMI, presence of diabetes mellitus, AST/ALT
NAFLD Liver Fat Score	Presence of metabolic syndrome, diabetes mellitus, insulin, AST/ALT
SteatoTest	Age, glucose, ALT, GGT, total bilirubin, total cholesterol, triglyceride, A2M, ApoA1, haptoglobin

NOTE: See Ref. 33.

TABLE 3.

Characteristics of Different Modalities for Diagnosis of Steatosis and Fibrosis

	Steatosis*		Fibrosis†	
	MRI-PDFF	**CAP**	**MRE**	**VCTE**
AUROC	0.99	0.85	0.93	0.83
Sensitivity	95.8	71.8	82.1	82.1
Specificity	100	85.7	89.8	77.6

NOTE: See Refs. 46,47.

*Grade 1–3 versus grade 0.

†Clinically significant fibrosis (stage 2–4) versus stage 0–1.