

Non-invasive methods for the diagnosis of nonalcoholic fatty liver disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is the commonest chronic liver disease and includes simple steatosis and nonalcoholic steatohepatitis (NASH). Since NASH progresses to cirrhosis more frequently and increases liver-related and cardiovascular disease risk substantially more than simple steatosis, there is a great need to differentiate the two entities. Liver biopsy is the gold standard for the diagnosis of NAFLD but its disadvantages, including the risk of complications

and sampling bias, stress the need for developing alternative diagnostic methods. Accordingly, several non-invasive markers have been evaluated for the diagnosis of simple steatosis and NASH, including both serological indices and imaging methods. The present review summarizes the current knowledge on the role of these markers in the diagnosis of NAFLD. Current data suggest that ultrasound and the fibrosis-4 score are probably the most appealing methods for detecting steatosis and for distinguishing NASH from simple steatosis, respectively, because of their low cost and relatively high accuracy. However, currently available methods, both serologic and imaging, cannot obviate the need for liver biopsy for diagnosing NASH due to their substantial false positive and false negative rates. Therefore, the current role of these methods is probably limited in patients who are unwilling or have contraindications for undergoing biopsy.

Key words: Nonalcoholic steatohepatitis; Steatosis; Fibrosis; Imaging; Nonalcoholic fatty liver disease

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Core tip: Current data suggest that ultrasound and the fibrosis-4 score are probably the most appealing methods for detecting steatosis and for distinguishing nonalcoholic steatohepatitis from simple steatosis, respectively, because of their low cost and relatively high accuracy. However, currently available methods, both serologic and imaging, cannot obviate the need for liver biopsy for diagnosing nonalcoholic steatohepatitis due to their substantial false positive and false negative rates. Therefore, the current role of these methods is probably limited in patients who are unwilling or have contraindications for undergoing biopsy.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of hepatic steatosis in the absence of other causes of hepatic fat accumulation^[1-3]. NAFLD includes simple steatosis, steatosis accompanied by varying degrees of inflammation and fibrosis [non-alcoholic steatohepatitis, (NASH)] and cirrhosis^[3]. NAFLD is the commonest chronic liver disease; the prevalence of simple steatosis and NASH in the general population is approximately 20%-30% and 5%-12%, respectively^[4-7]. However, in patients with obesity and type 2 diabetes mellitus (T2DM), NAFLD is substantially more common, affecting up to 70% of patients^[8,9].

Simple steatosis is associated with a relatively low risk for progression to cirrhosis^[10-12]. Moreover, it is unclear whether patients with simple steatosis have increased mortality compared with the general population^[13-15]. On the other hand, approximately 7% of patients with NASH will progress to cirrhosis within 3 years^[10-12]. In addition, several prospective studies showed that NASH is independently associated with increased mortality, from both liver disease-related and cardiovascular causes^[15,16]. Therefore, there is a clear need for differentiating patients with simple steatosis from those with NASH.

Liver biopsy remains the golden standard for the diagnosis of NAFLD and for distinguishing simple steatosis from NASH. However, biopsy is an invasive method carrying a small but not negligible risk of complications^[17,18]. Sampling bias has also been reported in patients with NAFLD and might affect both diagnosis and staging of the disease^[19]. Given these limitations of liver biopsy, several non-invasive markers have been evaluated for the diagnosis of simple steatosis and NASH, including both serological indices and imaging methods. The present review summarizes the current knowledge on the role of these markers in the diagnosis of NAFLD.

SEROLOGIC MARKERS

Serologic markers for detecting hepatic steatosis

Cytokeratin-18 (CK18) is the major intermediate filament protein in the liver and plasma levels of caspase-generated CK18 fragments reflects hepatocellular apoptosis, which is implicated in the pathogenesis of NAFLD^[20-22]. In an early study ($n = 157$ patients from Hong-Kong with biopsy-proven NAFLD), CK18 levels had an area under the receiving-operating characteristics curve (AUROC) 0.90 for detecting steatosis^[20]. However, a very recent large study ($n = 318$) performed in the United States reported a considerably lower AUROC

(0.77)^[21]. Similar results were observed in a smaller cohort from Germany^[22]. Different CK18 fragments reflecting total hepatocellular death do not appear to be more accurate^[20,22] (Table 1).

Fibroblast growth factor 21 (FGF21) is involved in the regulation of glucose and lipid metabolism^[23-26]. Patients with steatosis have elevated FGF21 levels, which also correlate with the degree of steatosis^[23-26]. Moreover, in a recent prospective study, elevated FGF21 levels independently predicted the development of steatosis^[23]. However, in a comparative study, measurement of FGF21 levels was less accurate in diagnosing steatosis than CK18 fragments^[25].

In addition to these isolated markers, several algorithms incorporating multiple clinical and biochemical parameters have been evaluated for the diagnosis of simple steatosis. Perhaps the most promising is the fatty liver index (FLI), which incorporates readily available parameters [body mass index (BMI), waist circumference and serum levels of triglycerides and γ -glutamyl-transpeptidase (GGT)] to detect hepatic steatosis. In a study in the general population, this algorithm had an AUROC of 0.84 for detecting steatosis^[27]. The Lipid Accumulation Product (LAP) is an even simpler algorithm that takes into account gender, waist circumference and fasting triglyceride levels. However, in the same population where the FLI was developed, LAP had a smaller AUROC for identifying steatosis (0.79)^[28]. In addition, the diagnostic accuracy of the FLI was reported to be similar to that of a model including BMI and FGF21 levels^[23].

The Hepatic Steatosis Index is another panel of simple biomarkers [gender, history of T2DM, BMI, alanine transaminase (ALT) and aspartate transaminase (AST)] and had an AUROC of 0.81 for diagnosing NAFLD [defined as presence of fatty liver in ultrasound (US) in the absence of other causes of chronic liver disease] in the derivation study ($n = 5362$ Korean patients)^[29]. However, this algorithm had poor agreement with magnetic resonance spectroscopy (MRS) in the assessment of steatosis^[30]. Finally, the SteatoTest includes levels of α_2 -macroglobulin, apolipoprotein A-I, haptoglobin, total bilirubin, GGT, fasting glucose, triglycerides, cholesterol and ALT adjusted for age, gender and BMI^[31]. In addition to the cost of measuring the parameters included in the SteatoTest, this index has limited sensitivity and specificity for detecting steatosis (69% and 74%, respectively)^[31]. Moreover, the SteatoTest showed poor agreement with MRS in the assessment of steatosis^[30].

In summary, among the serologic markers that have been evaluated for the detection of steatosis, measurement of CK18 levels and the FLI appear to be the most accurate. Since the FLI is inexpensive and readily available in clinical practice, it appears to be more appealing than measuring CK18 levels. However, available data for this algorithm are rather limited and it should be validated in large studies in different populations.

Table 1 Accuracy of the most-well studied serologic markers for detecting steatosis and for differentiating simple steatosis from nonalcoholic steatohepatitis

Marker	AUROC	<i>n</i>	Ref.
Serologic markers for detecting steatosis			
CK18	0.90	157	[20]
	0.77	318	[21]
FLI	0.84	496	[27]
LAP	0.79	588	[28]
Hepatic steatosis index	0.81	5362	[29]
SteatoTest	0.79	69	[31]
Serologic markers for differentiating simple steatosis from nonalcoholic steatohepatitis			
APRI	0.60	190	[34]
CK18	0.82	838	[39]
NAFLD fibrosis score	0.82	733	[43]
Comparative studies of serologic markers for differentiating simple steatosis from nonalcoholic steatohepatitis			
FIB-4	0.86	145	[46]
NAFLD fibrosis score	0.81		
BARD score	0.77		
APRI	0.67		
FIB-4	0.96	165	[47]
NAFLD fibrosis score	0.94		
BARD score	0.84		
FIB-4	0.80	541	[48]
NAFLD fibrosis score	0.77		
BARD score	0.70		
APRI	0.73		
FIB-4	0.87	576	[49]
NAFLD fibrosis score	0.86		
APRI	0.79		
BARD score	0.76		

AUROC: Area under the receiving-operating characteristics curve; AST: Aspartate transaminase; CK18: Cytokeratin-18; FLI: Fatty liver index; LAP: Lipid accumulation product; APRI: AST/platelet ratio index; NAFLD: Non-alcoholic fatty liver disease; FIB-4: Fibrosis-4; BARD: BMI, AST/ALT Ratio, Diabetes; BMI: Body mass index; ALT: Alanine transaminase.

Serologic markers for differentiating simple steatosis from NASH

Isolated markers have limited accuracy for the diagnosis of NASH. Thus, normal ALT levels do not exclude the presence of advanced fibrosis or cirrhosis and ALT levels do not correlate with the severity of fibrosis^[32,33]. Other simple markers, such as the AST/platelet ratio index (APRI), defined as (AST/upper limit of normal AST levels)*100/platelet count, also have very low accuracy (AUROC < 0.60)^[34,35]. In contrast with its satisfactory performance in detecting steatosis, CK18 fragments also have moderate accuracy (AUROC = 0.70-0.83) in the diagnosis of NASH^[20-22,36-38]. Moreover, measurement of CK18 has limited accuracy in distinguishing fibrosis stages^[21,22,37]. Different CK18 fragments reflecting total hepatocellular death do not appear to be more accurate^[20,22]. In a recent meta-analysis of 10 studies in patients with NASH (*n* = 838), uncleaved and caspase-cleaved CK18 fragments had an AUROC of 0.82 and 0.84 for diagnosing NASH, respectively^[39]. A recent study suggested that measuring serum levels of Fas, a regulator of apoptotic death, might improve the ability of CK18 to diagnose NASH but additional studies

are needed to validate these findings^[40]. Another marker used to detect steatosis, FGF21, is elevated in patients with NASH compared with controls^[25]. However, in a comparative study, measurement of FGF21 levels was less accurate in diagnosing NASH than CK18 fragments^[25]. Nevertheless, combining the measurement of FGF21 and CK18 improved the accuracy of CK18 alone^[25].

Given the suboptimal diagnostic performance of isolated markers for distinguishing NASH from simple steatosis, several algorithms that combine different parameters have been developed. Some of these panels include readily available variables. The BMI, AST/ALT ratio, diabetes (BARD) score takes into account BMI, AST/ALT ratio and the presence of T2DM and had a high negative predictive value for excluding advanced fibrosis (stages 3-4) in a population of obese patients from the United States^[41]. This score was validated in a Polish population where it showed similarly high negative predictive value (97%)^[42]. The NAFLD fibrosis score incorporates age, BMI, hyperglycemia (fasting glucose levels ≥ 110 mg/dL or previously diagnosed T2DM), platelet count, albumin and AST/ALT ratio and had an AUROC of 0.82 for detecting advanced fibrosis in the study in United States where it was developed (*n* = 733)^[43]. In a validation study in 162 Chinese patients with NAFLD, this score had 91% negative predicted value and obviated the need for 79% of liver biopsies^[44]. The Nippon score includes gender, age and history of T2DM or hypertension and had an AUROC of 0.78 for detecting severe fibrosis (stages 3-4) in the derivation study (*n* = 182 Japanese patients with biopsy-proven NAFLD)^[45].

Fibrosis-4 (FIB-4) appears to be the most promising simple scoring system for distinguishing NASH from steatosis and incorporates age, AST, ALT and platelet count. Indeed, in a comparative study from the United Kingdom (*n* = 145), FIB-4 had greater AUROC for detecting advanced fibrosis compared with the AST/ALT ratio, NAFLD fibrosis score, BARD score and APRI (0.86, 0.83, 0.81, 0.77 and 0.67, respectively)^[46]. In another study in 165 Caucasian patients with NAFLD, the FIB-4 score had similar accuracy with the NAFLD fibrosis score and greater than the BARD score (AUROC 0.96, 0.94 and 0.84, respectively)^[47]. In a larger study performed in the United States (*n* = 541), FIB-4 again was more predictive of advanced fibrosis than the latter scores, even though reported AUROCs were smaller (0.70-0.80)^[48]. Moreover, accuracies for detecting significant fibrosis (stage 2-4) were even lower (AUROC 0.68-0.75)^[48]. In a more recent large comparative study in 576 Japanese patients with NAFLD, FIB-4 again had better accuracy than the NAFLD fibrosis score, APRI, age/platelet index, AST/ALT ratio, BARD score and Nippon score for the diagnosis of advanced fibrosis (0.87, 0.86, 0.82, 0.81, 0.79, 0.76 and 0.71, respectively)^[49]. In the above-mentioned studies, the sensitivity and

specificity of a cut-off value of 1.30-1.45 of the FIB-4 score for detecting advanced fibrosis was 74%-90% and 64%-88%, respectively, whereas a cut-off value of 3.25 had sensitivity of 26%-40% and specificity of 95%-100%^[46-49]. However, in a retrospective study in 320 Caucasian patients with NAFLD, the NAFLD fibrosis score appeared to be a better indicator of the risk for development of liver-related complications or death than the FIB-4 and BARD scores and the APRI^[50].

Other simple algorithms for the detection of fibrosis have been studied less extensively. FibroMeter NAFLD includes age, weight, platelet count and ferritin, glucose, AST and ALT levels and had better accuracy than the NAFLD fibrosis score and the APRI for detecting significant fibrosis (AUROC 0.91, 0.86 and 0.84, respectively) in a French study ($n = 235$)^[51]. The Koeln-Essen index includes age, AST, AST/ALT ratio and total bilirubin levels and had similar AUROC with the FIB-4 score and the NAFLD fibrosis score (0.97, 0.93 and 0.96, respectively) but greater than the AST/ALT ratio and the BARD score (0.81 and 0.67, respectively) in a German study ($n = 267$)^[52].

In addition to these simple algorithms, other scoring systems incorporate more sensitive but less readily available and therefore more expensive variables. However, the latter scores do not appear to be more accurate in detecting NASH than the simple algorithms. The NAFLD liver fat score includes the history of T2DM or metabolic syndrome and serum ALT, AST and insulin levels and had an AUROC of 0.87 for detecting NAFLD (either simple steatosis or NASH) in the derivation study ($n = 470$ Caucasian patients)^[53]. This score showed similar accuracy in an independent cohort of Caucasian patients with NAFLD^[36]. The NASH score includes AST and fasting insulin levels as well as the patatin-like phospholipase domain containing-3 genotype and had an AUROC of 0.76 in a cohort of 380 obese Caucasian patients^[54]. FibroTest-FibroSURE is composed of $\alpha 2$ -macroglobulin, apolipoprotein A-I, haptoglobin, GGT and total bilirubin levels adjusted for sex and age^[55]. In the derivation study in 267 patients with NAFLD, the FibroTest had an AUROC of 0.81 for detecting significant fibrosis but only 0.59 for differentiating NASH from simple steatosis^[55]. Moreover, a more recent study ($n = 190$ Caucasian patients) reported a considerably smaller AUROC for detecting significant fibrosis (0.59)^[34]. The NashTest includes age, gender, height, weight and serum levels of triglycerides, total cholesterol, ALT, AST, total bilirubin, GGT, $\alpha 2$ -macroglobulin, haptoglobin and apolipoprotein AI and had an AUROC of 0.79 for detecting NASH in the derivation study ($n = 257$ French patients)^[56]. Another composite index developed by Palekar *et al*^[57] includes age, gender, BMI, AST, AST/ALT ratio and hyaluronic acid levels. In the small derivation study performed in the United States ($n = 80$), this index had an AUROC of 0.76 for distinguishing NASH from simple steatosis^[57].

Very few studies compared algorithms based on simple parameters and scoring systems that

incorporate more elaborate variables. The Antwerp NAFLD significant fibrosis score includes waist, AST and fasting C-peptide levels^[58]. In the Caucasian population where it was developed ($n = 313$), it had greater AUROC than the NAFLD fibrosis score, the FIB-4 score, the BARD score and the APRI^[58]. Interestingly, measurement of CK18 levels did not improve the accuracy of this algorithm^[58]. The enhanced liver fibrosis panel (ELF) consists of tissue inhibitor of matrix metalloproteinase 1, hyaluronic acid and aminoterminal peptide of pro-collagen III^[59]. In a pivotal study in 192 patients with NAFLD, ELF had an AUROC of 0.82 for identifying significant fibrosis^[59]. In a subgroup of patients ($n = 91$), the ELF and the NAFLD fibrosis score had comparable AUROCs (0.90 and 0.86, respectively) whereas the combination of the 2 scores marginally increased the AUROC to 0.93^[59]. Another algorithm, the NAFIC score, including serum ferritin, insulin and type IV collagen 7S levels, had an AUROC of 0.85 and 0.78 for distinguishing NASH from simple steatosis in the derivation and validation studies, respectively, in Japanese patients with biopsy-proven NAFLD ($n = 177$ and 442, respectively)^[60]. The AUROC for detecting significant and advanced fibrosis was 0.83 and 0.86, respectively^[60]. In the same study, the NAFIC score had greater AUROC for distinguishing NASH from simple steatosis than the BARD score, the Nippon score, the NAFLD fibrosis score and the score developed by Palekar *et al*^[57] (0.80, 0.63, 0.67, 0.68 and 0.73, respectively).

In summary, a large number of algorithms have been developed for differentiating between simple steatosis and NASH. Among the existing algorithms, the FIB-4 score appears to be the most accurate. Moreover, this algorithm has been validated in several studies and consists of readily available and inexpensive variables. More elaborate and costly algorithms appear to be less accurate than the FIB-4 score but comparative studies are limited.

IMAGING METHODS

Imaging methods for detecting hepatic steatosis

US: US is a widely available and inexpensive method for evaluating the presence of steatosis that does not expose the patient to radiation and allows repeated examinations. However, US has several drawbacks: it is operator-dependent and cannot provide information regarding fibrosis^[61-63]. In US, a diffuse increase in hepatic echogenicity (bright liver) suggests the presence of steatosis^[61]. Additional sonographic features, such as hepatorenal contrast (*i.e.*, the difference in echogenicity between liver and right kidney cortex) or blurring of hepatic vein have similar sensitivity with hepatic echogenicity whereas other characteristics such as portal vein blurring or posterior attenuation have lower sensitivity^[61]. However, the combined evaluation of hepatic echogenicity and portal vein blurring improved the sensitivity of US^[61]. In a recent study in 79 patients

(21 with NAFLD) who underwent both US and liver biopsy, the sensitivity and specificity of the US for detecting macrovesicular steatosis $\geq 5\%$ of total hepatocyte area were 82% and 100%, respectively, but the sensitivity and specificity for detecting microvesicular steatosis were only 59% and 74%, respectively^[61]. In patients with steatosis $\geq 20\%$ of total hepatocyte area, sensitivity increased to 96% for macrovesicular steatosis but only to 67% for microvesicular steatosis; specificity decreased to 98% and 66%, respectively^[61]. In contrast, a larger study in 94 patients with NAFLD reported an AUROC of 0.98 of US for detecting steatosis; the sensitivity and specificity was 92% and 100%, respectively^[64]. In a meta-analysis of 49 studies ($n = 4720$), US had an AUROC of 0.93 for detecting steatosis; the sensitivity and specificity was 85% and 94%, respectively^[65]. Moreover, in 5 small comparative studies ($n = 215$), US was as accurate as computed tomography (CT), magnetic resonance imaging (MRI) and MRS for detecting steatosis and had a sensitivity and specificity of 94% and 80%, respectively^[65].

CT: CT provides an objective evaluation of the presence of steatosis but is more expensive than US and exposes the patient to radiation. Similar to US, CT cannot distinguish NASH from simple steatosis^[63]. In a comparative study, CT was less accurate than dual gradient-echo MRI and MRS for identifying steatosis $\geq 5\%$ whereas the latter 2 methods had similar accuracy (AUROC 0.65, 0.88 and 0.85, respectively)^[66]. Notably, at higher degrees of steatosis ($\geq 30\%$), the accuracy of the 3 methods was similar (AUROC 0.92, 0.99 and 0.91, respectively)^[66]. In the same study, CT was also less accurate than US^[66]. However, other studies reported similar accuracy of MRI, CT and US in assessing steatosis^[63,65].

MRI: In patients with NAFLD, MRI has shown excellent accuracy for detecting steatosis^[67-70], which is similar with the accuracy of MRS^[66,71-73] and superior or similar compared with US and CT^[63,65,74]. However, in patients with advanced fibrosis or cirrhosis, MRI appears to be less reliable for grading steatosis^[67,73]. Compared with CT, MRI has the advantage that it does not expose the patient to radiation and can therefore be used for follow-up. On the other hand, MRI is more expensive than CT, it cannot be performed in patients with claustrophobia and the measurements are affected by hepatic iron deposition, which is frequently present in patients with NAFLD^[75,76]. MRI also does not provide information regarding the presence of fibrosis. Indeed, in a small study in 10 patients with NAFLD, chemical-shift MRI was very accurate in identifying steatosis but could not differentiate between NASH and isolated steatosis^[77]. A larger study in 25 patients with NAFLD also showed that MRI is not useful in distinguishing NASH from simple steatosis^[63].

resonance spectroscopy is an accurate method for evaluating hepatic steatosis^[66,72,73,78,79]. Furthermore, MRS is operator-independent and fast^[66,78,79]. However, MRS has some important disadvantages, including limited availability and high cost^[66,78,79]. The results might also be affected by respiratory movements, since MRS is a free-breathing method^[66]. Some studies also suggested that advanced fibrosis is also associated with less accurate evaluation of steatosis using MRS^[73]. Claustrophobia and the presence of implanted devices are additional limitations in the use of MRS^[66,78,79].

In summary, the different imaging methods for detecting steatosis appear to have comparable accuracy. Since US is the least expensive, readily available, does not expose the patient to radiation and can be used for repeat evaluations, it appears to represent the most useful imaging method for detecting steatosis.

Imaging methods for differentiating simple steatosis from NASH

Transient elastography: In transient elastography (TE), an M-probe that includes an ultrasonic transducer is used. The transducer is placed above the right lobe of the liver through an intercostal space and produces a vibration that generates a wave, which is transmitted through the skin into the liver. The velocity of the wave correlates directly with liver stiffness. In turn, liver stiffness correlates inversely with the degree of fibrosis^[80-82]. In a large study ($n = 246$ patients with NAFLD), TE had an AUROC of 0.84 and 0.93 for detecting significant and severe fibrosis, respectively^[83]. In the same study, TE was more accurate in identifying fibrosis than APRI, FIB-4 score, NAFLD fibrosis score and BARD score^[83]. Other smaller studies in Caucasian and Japanese patients with NAFLD also reported similarly high accuracies of TE in detecting significant and severe fibrosis^[79,82,84,85] (Table 2).

Liver stiffness evaluation with TE is considered reliable when the interquartile range/median ratio of measurements is ≤ 0.30 ^[86]. Unreliable measurements are more frequent in older subjects and in overweight or obese patients^[83,87,88]. In a large study that analyzed 13369 examinations of liver stiffness using TE (13.7% with NAFLD), 15.8% of the examinations yielded unreliable measurements^[89]. In overweight and obese patients, 24% and 35% of measurements, respectively, were considered unreliable^[89]. Obesity not only hampers the measurement of liver stiffness but also increases liver stiffness independently of the presence of fibrosis^[90]. The presence of steatosis also appears to affect liver stiffness evaluation, particularly in non-cirrhotic patients^[80,81,88]. To overcome these limitations, another probe has been developed, the XL-probe, which provides more reliable measurements in obese patients^[84,87,91,92]. The XL-probe generates a lower frequency (1.75 MHz vs 3.5 MHz with the M-probe) and higher amplitude (3 mm and 2 mm, respectively) vibration resulting in greater measurement depth (3.5-7.5 cm vs 2.5-6.5 cm, respectively) and yields

¹H-magnetic resonance spectroscopy: ¹H-magnetic

Table 2 Accuracy of imaging methods for differentiating simple steatosis from nonalcoholic steatohepatitis

Imaging method	AUROC	n	Ref.
Imaging methods for differentiating simple steatosis from nonalcoholic steatohepatitis			
TE	0.84	246	[83]
	0.87	75	[84]
ARFI	0.86	77	[101]
	0.90	172	[100]
RTE	0.85	181	[106]
MRE	0.93	58	[110]
	0.95	142	[111]
Comparative studies of imaging methods for differentiating simple steatosis from nonalcoholic steatohepatitis			
TE	0.99	54	[104]
ARFI	0.97		
TE	0.73	13	[108]
ARFI	0.71		
RTE	0.51		

TE: Transient elastography; ARFI: Acoustic radiation force impulse; RTE: Real-time shear wave elastography; MRE: Magnetic resonance elastography; AUROC: Area under the receiving-operating characteristics curve.

reliable results in approximately 57%-63% of patients with unreliable M-probe measurements^[84,87,92,93]. Therefore, the combined use of both probes enables assessment of liver stiffness in > 90% of patients^[87]. Even though liver stiffness values are lower when the XL probe is used, both probes yield similar results regarding the presence of fibrosis^[84,87,92,94]. However, even when the XL probe is used, both the reliability of measurements and the accuracy of detecting fibrosis are decreasing with the increase of BMI^[87,91,93,95].

Transient elastography can also be used in the evaluation of steatosis by calculating the controlled attenuation parameter (CAP) using an algorithm included in the system. CAP has an AUROC of 0.79-0.93 and 0.76-0.94 in identifying steatosis \geq stage 1 and \geq stage 2, respectively^[79,94,96-98]. In comparative studies, it had similar accuracy with MRS^[79] and better accuracy than US^[97]. CAP also had better or similar accuracy with the FLI and better accuracy than the hepatic steatosis index and the SteatoTest^[97,98]. However, the accuracy of CAP appears to be lower in patients with more advanced fibrosis^[98].

Acoustic radiation force impulse imaging: Acoustic radiation force impulse (ARFI) imaging is an US-based elastography method integrated in conventional US machines where a region of interest in the liver is mechanically excited with an acoustic pulse inducing localized tissue displacement, which results in shear wave propagation^[99]. The velocity of wave propagation correlates with liver stiffness and fibrosis^[100]. In a meta-analysis of 4 early studies in patients with NAFLD ($n = 77$), ARFI imaging had an AUROC of 0.86 for diagnosing both significant and advanced fibrosis^[101]. In a more recent large study in 172 patients with biopsy-diagnosed NAFLD, the AUROC of the method

for detecting advanced fibrosis was 0.90^[100]. Compared with TE, ARFI has similar accuracy but lower rates of measurement failures^[101-104].

Real-time shear wave elastography: Real-time shear wave elastography (RTE) is based on the same principle with TE but provides real-time measurements of liver stiffness^[105]. In a recent study in 181 patients with NAFLD, RTE had an AUROC of 0.85 and 0.88 for detecting advanced and severe fibrosis, respectively^[106]. In the same study, RTE had similar accuracy with the FIB-4 score for detecting all stages of fibrosis and better accuracy than the NAFLD fibrosis score, BARD score and the score developed by Palekar *et al.*^[57]. Smaller studies reported similar accuracy rates^[107]. However, in a small comparative study that included 13 patients with NAFLD, RTE had lower accuracy in detecting advanced fibrosis than TE and ARFI, whereas the latter two methods had comparable accuracy (AUROC 0.51, 0.73 and 0.71, respectively)^[108]. Failure rates are similar with RTE and TE^[105].

Magnetic resonance elastography: Magnetic resonance elastography (MRE) evaluates fibrosis by estimating liver elasticity through the application of mechanical excitation and motion-sensitive magnetic resonance sequences^[109]. In a study in 72 patients with biopsy-proven hepatic fibrosis (8 with NASH), MRE had an AUROC of 0.91, 0.92 and 0.97 for detecting fibrosis stage ≥ 1 , ≥ 2 and ≥ 3 , respectively^[109]. In a more recent study in 58 patients with NAFLD, MRE had an AUROC of 0.93 for discriminating NASH from isolated steatosis^[110]. In a larger study in 142 patients with NAFLD, MRE had superior accuracy for detecting advanced fibrosis than the FIB-4 score, NAFLD fibrosis score, APRI and BARD score (AUROC 0.95, 0.83, 0.79, 0.74 and 0.71, respectively)^[111]. Compared with RTE, MRE has similar accuracy in excluding the presence of fibrosis and lower rates of unreliable measurements^[112].

In summary, among the different imaging methods for distinguishing simple steatosis from NASH, TE has been studied more extensively and appears to be more or equally accurate compared with the other techniques. However, very few studies compared these imaging methods with serological markers and it is unclear whether imaging is more accurate than the less expensive and more widely available serological algorithms.

CONCLUSION

A large number of serologic markers and imaging methods have been evaluated for the diagnosis of simple steatosis and NASH. However, most serologic markers have not been validated in independent cohorts whereas very few studies compared the different imaging methods. Current data suggest that US and the FIB-4 score are probably the most appealing methods

for detecting steatosis and for distinguishing NASH from simple steatosis, respectively, because of their low cost and relatively high accuracy. However, currently available methods, both serologic and imaging, cannot obviate the need for liver biopsy for diagnosing NASH due to their substantial false positive and false negative rates. The current role of these methods is probably limited in patients who are unwilling or have contraindications for undergoing biopsy.

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