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

Papagianni M *et al.* Non-invasive methods for the diagnosis of NAFLD

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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 fatty liver disease; Nonalcoholic steatohepatitis; Steatosis; Fibrosis; Imaging

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**Core tip:** Current data suggest that ultrasound and the FIB-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 (nonalcoholic 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 (Table 1)**

***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].

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 α2-macroglobulin, apolipoprotein Α-Ι, 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.

***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 BARD (BMI, AST/ALT Ratio, Diabetes) 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 (NIKEI) 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 (PNPLA3) genotype and had an AUROC of 0.76 in a cohort of 380 obese Caucasian patients[54]. FibroTest-FibroSURE is composed of α2-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, α2-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 were 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*[60] (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***

**Ultrasound:** Ultrasound 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 ≥ 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 ≥ 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 ≥ 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 (≥ 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].

**1H-magnetic resonance spectroscopy:** 1H-magnetic 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 (Table 2)***

**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].

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 13,369 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 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 ≥ stage 1 and ≥ 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*[106]. 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 resonanceelastography (MRE) evaluates fibrosis by estimating liver elasticity through the application of mechanical excitation and motion-sensitive magnetic resonancesequences[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.

**REFERENCES**

1 **Farrell GC**, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology* 2006; **43**: S99-S112 [PMID: 16447287 DOI: 10.1002/hep.20973]

2 **Dowman JK**, Tomlinson JW, Newsome PN. Systematic review: the diagnosis and staging of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2011; **33**: 525-540 [PMID: 21198708 DOI: 10.1111/j.1365-2036.2010.04556.x]

3 **Chalasani N**, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. *Gastroenterology* 2012; **142**: 1592-1609 [PMID: 22656328 DOI: 10.1053/j.gastro.2012.04.001]

4 **Vernon G**, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 2011; **34**: 274-285 [PMID: 21623852 DOI: 10.1111/j.1365-2036.2011.04724.x]

5 **Younossi ZM**, Stepanova M, Afendy M, Fang Y, Younossi Y, Mir H, Srishord M. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. *Clin Gastroenterol Hepatol* 2011; **9**: 524-530.e1; quiz e60 [PMID: 21440669 DOI: 10.1016/j.cgh.2011.03.020]

6 **Williams CD**, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, Landt CL, Harrison SA. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. *Gastroenterology* 2011; **140**: 124-131 [PMID: 20858492 DOI: 10.1053/j.gastro.2010.09.038]

7 **Browning JD**, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004; **40**: 1387-1395 [PMID: 15565570 DOI: 10.1002/hep.20466]

8 **Leite NC**, Salles GF, Araujo AL, Villela-Nogueira CA, Cardoso CR. Prevalence and associated factors of non-alcoholic fatty liver disease in patients with type-2 diabetes mellitus. *Liver Int* 2009; **29**: 113-119 [PMID: 18384521 DOI: 10.1111/j.1478-3231.2008.01718.x]

9 **Targher G**, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, Day C, Arcaro G. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. *Diabetes Care* 2007; **30**: 1212-1218 [PMID: 17277038 DOI: 10.2337/dc06-2247]

10 **Wong VW**, Wong GL, Choi PC, Chan AW, Li MK, Chan HY, Chim AM, Yu J, Sung JJ, Chan HL. Disease progression of non-alcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years. *Gut* 2010; **59**: 969-974 [PMID: 20581244 DOI: 10.1136/gut.2009.205088]

11 **Dam-Larsen S**, Franzmann M, Andersen IB, Christoffersen P, Jensen LB, Sørensen TI, Becker U, Bendtsen F. Long term prognosis of fatty liver: risk of chronic liver disease and death. *Gut* 2004; **53**: 750-755 [PMID: 15082596 DOI: 10.1136/gut.2003.019984]

12 **Adams LA**, Sanderson S, Lindor KD, Angulo P. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. *J Hepatol* 2005; **42**: 132-138 [PMID: 15629518 DOI: 10.1016/j.jhep.2004.09.012]

13 **Haring R**, Wallaschofski H, Nauck M, Dörr M, Baumeister SE, Völzke H. Ultrasonographic hepatic steatosis increases prediction of mortality risk from elevated serum gamma-glutamyl transpeptidase levels. *Hepatology* 2009; **50**: 1403-1411 [PMID: 19670414 DOI: 10.1002/hep.23135]

14 **Targher G**, Bertolini L, Rodella S, Tessari R, Zenari L, Lippi G, Arcaro G. Nonalcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular events in type 2 diabetic patients. *Diabetes Care* 2007; **30**: 2119-2121 [PMID: 17519430 DOI: 10.2337/dc07-0349]

15 **Ekstedt M**, Franzén LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, Kechagias S. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology* 2006; **44**: 865-873 [PMID: 17006923 DOI: 10.1002/hep.21327]

16 **Adams LA**, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, Angulo P. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005; **129**: 113-121 [PMID: 16012941 DOI: 10.1053/j.gastro.2005.04.014]

17 **Myers RP**, Fong A, Shaheen AA. Utilization rates, complications and costs of percutaneous liver biopsy: a population-based study including 4275 biopsies. *Liver Int* 2008; **28**: 705-712 [PMID: 18433397 DOI: 10.1111/j.1478-3231.2008.01691.x]

18 **Cadranel JF**, Rufat P, Degos F. Practices of liver biopsy in France: results of a prospective nationwide survey. For the Group of Epidemiology of the French Association for the Study of the Liver (AFEF). *Hepatology* 2000; **32**: 477-481 [PMID: 10960438 DOI: 10.1053/jhep.2000.16602]

19 **Ratziu V**, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, Grimaldi A, Capron F, Poynard T; LIDO Study Group. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology* 2005; **128**: 1898-1906 [PMID: 15940625 DOI: 10.1053/j.gastro.2005.03.084]

20 **Shen J**, Chan HL, Wong GL, Chan AW, Choi PC, Chan HY, Chim AM, Yeung DK, Yu J, Chu WC, Wong VW. Assessment of non-alcoholic fatty liver disease using serum total cell death and apoptosis markers. *Aliment Pharmacol Ther* 2012; **36**: 1057-1066 [PMID: 23066946 DOI: 10.1111/apt.12091]

21 **Cusi K**, Chang Z, Harrison S, Lomonaco R, Bril F, Orsak B, Ortiz-Lopez C, Hecht J, Feldstein AE, Webb A, Louden C, Goros M, Tio F. Limited value of plasma cytokeratin-18 as a biomarker for NASH and fibrosis in patients with non-alcoholic fatty liver disease. *J Hepatol* 2014; **60**: 167-174 [PMID: 23973932 DOI: 10.1016/j.jhep.2013.07.042]

22 **Joka D**, Wahl K, Moeller S, Schlue J, Vaske B, Bahr MJ, Manns MP, Schulze-Osthoff K, Bantel H. Prospective biopsy-controlled evaluation of cell death biomarkers for prediction of liver fibrosis and nonalcoholic steatohepatitis. *Hepatology* 2012; **55**: 455-464 [PMID: 21993925 DOI: 10.1002/hep.24734]

23 **Li H**, Dong K, Fang Q, Hou X, Zhou M, Bao Y, Xiang K, Xu A, Jia W. High serum level of fibroblast growth factor 21 is an independent predictor of non-alcoholic fatty liver disease: a 3-year prospective study in China. *J Hepatol* 2013; **58**: 557-563 [PMID: 23142063 DOI: 10.1016/j.jhep.2012.10.029]

24 **Li H**, Fang Q, Gao F, Fan J, Zhou J, Wang X, Zhang H, Pan X, Bao Y, Xiang K, Xu A, Jia W. Fibroblast growth factor 21 levels are increased in nonalcoholic fatty liver disease patients and are correlated with hepatic triglyceride. *J Hepatol* 2010; **53**: 934-940 [PMID: 20675007 DOI: 10.1016/j.jhep.2010.05.018]

25 **Shen J**, Chan HL, Wong GL, Choi PC, Chan AW, Chan HY, Chim AM, Yeung DK, Chan FK, Woo J, Yu J, Chu WC, Wong VW. Non-invasive diagnosis of non-alcoholic steatohepatitis by combined serum biomarkers. *J Hepatol* 2012; **56**: 1363-1370 [PMID: 22314419 DOI: 10.1016/j.jhep.2011.12.025]

26 **Dushay J**, Chui PC, Gopalakrishnan GS, Varela-Rey M, Crawley M, Fisher FM, Badman MK, Martinez-Chantar ML, Maratos-Flier E. Increased fibroblast growth factor 21 in obesity and nonalcoholic fatty liver disease. *Gastroenterology* 2010; **139**: 456-463 [PMID: 20451522 DOI: 10.1053/j.gastro.2010.04.054]

27 **Bedogni G**, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, Tiribelli C. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol* 2006; **6**: 33 [PMID: 17081293 DOI: 10.1186/1471-230X-6-33]

28 **Bedogni G**, Kahn HS, Bellentani S, Tiribelli C. A simple index of lipid overaccumulation is a good marker of liver steatosis. *BMC Gastroenterol* 2010; **10**: 98 [PMID: 20738844 DOI: 10.1186/1471-230X-10-98]

29 **Lee JH**, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, Kim YJ, Yoon JH, Cho SH, Sung MW, Lee HS. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. *Dig Liver Dis* 2010; **42**: 503-508 [PMID: 19766548 DOI: 10.1016/j.dld.2009.08.002]

30 **Guiu B**, Crevisy-Girod E, Binquet C, Duvillard L, Masson D, Lepage C, Hamza S, Krausé D, Verges B, Minello A, Cercueil JP, Hillon P, Petit JM. Prediction for steatosis in type-2 diabetes: clinico-biological markers versus 1H-MR spectroscopy. *Eur Radiol* 2012; **22**: 855-863 [PMID: 22101800 DOI: 10.1007/s00330-011-2326-9]

31 **Poynard T**, Ratziu V, Naveau S, Thabut D, Charlotte F, Messous D, Capron D, Abella A, Massard J, Ngo Y, Munteanu M, Mercadier A, Manns M, Albrecht J. The diagnostic value of biomarkers (SteatoTest) for the prediction of liver steatosis. *Comp Hepatol* 2005; **4**: 10 [PMID: 16375767 DOI: 10.1186/1476-5926-4-10]

32 **Fracanzani AL**, Valenti L, Bugianesi E, Andreoletti M, Colli A, Vanni E, Bertelli C, Fatta E, Bignamini D, Marchesini G, Fargion S. Risk of severe liver disease in nonalcoholic fatty liver disease with normal aminotransferase levels: a role for insulin resistance and diabetes. *Hepatology* 2008; **48**: 792-798 [PMID: 18752331 DOI: 10.1002/hep.22429]

33 **Mofrad P**, Contos MJ, Haque M, Sargeant C, Fisher RA, Luketic VA, Sterling RK, Shiffman ML, Stravitz RT, Sanyal AJ. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. *Hepatology* 2003; **37**: 1286-1292 [PMID: 12774006 DOI: 10.1053/jhep.2003.50229]

34 **Sebastiani G**, Castera L, Halfon P, Pol S, Mangia A, Di Marco V, Pirisi M, Voiculescu M, Bourliere M, Alberti A. The impact of liver disease aetiology and the stages of hepatic fibrosis on the performance of non-invasive fibrosis biomarkers: an international study of 2411 cases. *Aliment Pharmacol Ther* 2011; **34**: 1202-1216 [PMID: 21981787 DOI: 10.1111/j.1365-2036.2011.04861.x]

35 **Loaeza-del-Castillo A**, Paz-Pineda F, Oviedo-Cárdenas E, Sánchez-Avila F, Vargas-Vorácková F. AST to platelet ratio index (APRI) for the noninvasive evaluation of liver fibrosis. *Ann Hepatol* 2008; **7**: 350-357 [PMID: 19034235]

36 **Musso G**, Gambino R, Durazzo M, Cassader M. Noninvasive assessment of liver disease severity with liver fat score and CK-18 in NAFLD: Prognostic value of liver fat equation goes beyond hepatic fat estimation. *Hepatology* 2010; **51**: 715-717 [PMID: 19821531 DOI: 10.1002/hep.23255]

37 **Feldstein AE**, Wieckowska A, Lopez AR, Liu YC, Zein NN, McCullough AJ. Cytokeratin-18 fragment levels as noninvasive biomarkers for nonalcoholic steatohepatitis: a multicenter validation study. *Hepatology* 2009; **50**: 1072-1078 [PMID: 19585618 DOI: 10.1002/hep.23050]

38 **Malik R**, Chang M, Bhaskar K, Nasser I, Curry M, Schuppan D, Byrnes V, Afdhal N. The clinical utility of biomarkers and the nonalcoholic steatohepatitis CRN liver biopsy scoring system in patients with nonalcoholic fatty liver disease. *J Gastroenterol Hepatol* 2009; **24**: 564-568 [PMID: 19378390 DOI: 10.1111/j.1440-1746.2008.05731.x]

39 **Chen J**, Zhu Y, Zheng Q, Jiang J. Serum cytokeratin-18 in the diagnosis of non-alcoholic steatohepatitis: A meta-analysis. *Hepatol Res* 2014; **44**: 854-862 [PMID: 23834322 DOI: 10.1111/hepr.12197]

40 **Tamimi TI**, Elgouhari HM, Alkhouri N, Yerian LM, Berk MP, Lopez R, Schauer PR, Zein NN, Feldstein AE. An apoptosis panel for nonalcoholic steatohepatitis diagnosis. *J Hepatol* 2011; **54**: 1224-1229 [PMID: 21145805 DOI: 10.1016/j.jhep.2010.08.023]

41 **Harrison SA**, Oliver D, Arnold HL, Gogia S, Neuschwander-Tetri BA. Development and validation of a simple NAFLD clinical scoring system for identifying patients without advanced disease. *Gut* 2008; **57**: 1441-1447 [PMID: 18390575 DOI: 10.1136/gut.2007.146019]

42 **Raszeja-Wyszomirska J**, Szymanik B, Ławniczak M, Kajor M, Chwist A, Milkiewicz P, Hartleb M. Validation of the BARD scoring system in Polish patients with nonalcoholic fatty liver disease (NAFLD). *BMC Gastroenterol* 2010; **10**: 67 [PMID: 20584330 DOI: 10.1186/1471-230X-10-67]

43 **Angulo P**, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, Enders F, Saksena S, Burt AD, Bida JP, Lindor K, Sanderson SO, Lenzi M, Adams LA, Kench J, Therneau TM, Day CP. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology* 2007; **45**: 846-854 [PMID: 17393509 DOI: 10.1002/hep.21496]

44 **Wong VW**, Wong GL, Chim AM, Tse AM, Tsang SW, Hui AY, Choi PC, Chan AW, So WY, Chan FK, Sung JJ, Chan HL. Validation of the NAFLD fibrosis score in a Chinese population with low prevalence of advanced fibrosis. *Am J Gastroenterol* 2008; **103**: 1682-1688 [PMID: 18616651 DOI: 10.1111/j.1572-0241.2008.01933.x]

45 **Miyaaki H**, Ichikawa T, Nakao K, Yatsuhashi H, Furukawa R, Ohba K, Omagari K, Kusumoto Y, Yanagi K, Inoue O, Kinoshita N, Ishibashi H, Yano M, Eguchi K. Clinicopathological study of nonalcoholic fatty liver disease in Japan: the risk factors for fibrosis. *Liver Int* 2008; **28**: 519-524 [PMID: 17976158 DOI: 10.1111/j.1478-3231.2007.01614.x]

46 **McPherson S**, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. *Gut* 2010; **59**: 1265-1269 [PMID: 20801772 DOI: 10.1136/gut.2010.216077]

47 **Demir M**, Lang S, Nierhoff D, Drebber U, Hardt A, Wedemeyer I, Schulte S, Quasdorff M, Goeser T, Töx U, Steffen HM. Stepwise combination of simple noninvasive fibrosis scoring systems increases diagnostic accuracy in nonalcoholic fatty liver disease. *J Clin Gastroenterol* 2013; **47**: 719-726 [PMID: 23442837 DOI: 10.1097/MCG.0b013e3182819a89]

48 **Shah AG**, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ; Nash Clinical Research Network. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2009; **7**: 1104-1112 [PMID: 19523535 DOI: 10.1016/j.cgh.2009.05.033]

49 **Sumida Y**, Yoneda M, Hyogo H, Itoh Y, Ono M, Fujii H, Eguchi Y, Suzuki Y, Aoki N, Kanemasa K, Fujita K, Chayama K, Saibara T, Kawada N, Fujimoto K, Kohgo Y, Yoshikawa T, Okanoue T. Validation of the FIB4 index in a Japanese nonalcoholic fatty liver disease population. *BMC Gastroenterol* 2012; **12**: 2 [PMID: 22221544 DOI: 10.1186/1471-230X-12-2]

50 **Angulo P**, Bugianesi E, Bjornsson ES, Charatcharoenwitthaya P, Mills PR, Barrera F, Haflidadottir S, Day CP, George J. Simple noninvasive systems predict long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology* 2013; **145**: 782-729.e4 [PMID: 23860502 DOI: 10.1053/j.gastro.2013.06.057]

51 **Calès P**, Lainé F, Boursier J, Deugnier Y, Moal V, Oberti F, Hunault G, Rousselet MC, Hubert I, Laafi J, Ducluzeaux PH, Lunel F. Comparison of blood tests for liver fibrosis specific or not to NAFLD. *J Hepatol* 2009; **50**: 165-173 [PMID: 18977552 DOI: 10.1016/j.jhep.2008.07.035]

52 **Demir M**, Lang S, Schlattjan M, Drebber U, Wedemeyer I, Nierhoff D, Kaul I, Sowa J, Canbay A, Töx U, Steffen HM. NIKEI: a new inexpensive and non-invasive scoring system to exclude advanced fibrosis in patients with NAFLD. *PLoS One* 2013; **8**: e58360 [PMID: 23555578 DOI: 10.1371/journal.pone.0058360]

53 **Kotronen A**, Peltonen M, Hakkarainen A, Sevastianova K, Bergholm R, Johansson LM, Lundbom N, Rissanen A, Ridderstråle M, Groop L, Orho-Melander M, Yki-Järvinen H. Prediction of non-alcoholic fatty liver disease and liver fat using metabolic and genetic factors. *Gastroenterology* 2009; **137**: 865-872 [PMID: 19524579 DOI: 10.1053/j.gastro.2009.06.005]

54 **Hyysalo J**, Männistö VT, Zhou Y, Arola J, Kärjä V, Leivonen M, Juuti A, Jaser N, Lallukka S, Käkelä P, Venesmaa S, Simonen M, Saltevo J, Moilanen L, Korpi-Hyövalti E, Keinänen-Kiukaanniemi S, Oksa H, Orho-Melander M, Valenti L, Fargion S, Pihlajamäki J, Peltonen M, Yki-Järvinen H. A population-based study on the prevalence of NASH using scores validated against liver histology. *J Hepatol* 2014; **60**: 839-846 [PMID: 24333862 DOI: 10.1016/j.jhep.2013.12.009]

55 **Poynard T**, Lebray P, Ingiliz P, Varaut A, Varsat B, Ngo Y, Norha P, Munteanu M, Drane F, Messous D, Bismut FI, Carrau JP, Massard J, Ratziu V, Giordanella JP. Prevalence of liver fibrosis and risk factors in a general population using non-invasive biomarkers (FibroTest). *BMC Gastroenterol* 2010; **10**: 40 [PMID: 20412588 DOI: 10.1186/1471-230X-10-40]

56 **Poynard T**, Ratziu V, Charlotte F, Messous D, Munteanu M, Imbert-Bismut F, Massard J, Bonyhay L, Tahiri M, Thabut D, Cadranel JF, Le Bail B, de Ledinghen V. Diagnostic value of biochemical markers (NashTest) for the prediction of non alcoholo steato hepatitis in patients with non-alcoholic fatty liver disease. *BMC Gastroenterol* 2006; **6**: 34 [PMID: 17096854 DOI: 10.1186/1471-230X-6-34]

57 **Palekar NA**, Naus R, Larson SP, Ward J, Harrison SA. Clinical model for distinguishing nonalcoholic steatohepatitis from simple steatosis in patients with nonalcoholic fatty liver disease. *Liver Int* 2006; **26**: 151-156 [PMID: 16448452 DOI: 10.1111/j.1478-3231.2005.01209.x]

58 **Francque SM**, Verrijken A, Mertens I, Hubens G, Van Marck E, Pelckmans P, Michielsen P, Van Gaal L. Noninvasive assessment of nonalcoholic fatty liver disease in obese or overweight patients. *Clin Gastroenterol Hepatol* 2012; **10**: 1162-1168; quiz e87 [PMID: 22796457 DOI: 10.1016/j.cgh.2012.06.019]

59 **Guha IN**, Parkes J, Roderick P, Chattopadhyay D, Cross R, Harris S, Kaye P, Burt AD, Ryder SD, Aithal GP, Day CP, Rosenberg WM. Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: Validating the European Liver Fibrosis Panel and exploring simple markers. *Hepatology* 2008; **47**: 455-460 [PMID: 18038452 DOI: 10.1002/hep.21984]

60 **Sumida Y**, Yoneda M, Hyogo H, Yamaguchi K, Ono M, Fujii H, Eguchi Y, Suzuki Y, Imai S, Kanemasa K, Fujita K, Chayama K, Yasui K, Saibara T, Kawada N, Fujimoto K, Kohgo Y, Okanoue T. A simple clinical scoring system using ferritin, fasting insulin, and type IV collagen 7S for predicting steatohepatitis in nonalcoholic fatty liver disease. *J Gastroenterol* 2011; **46**: 257-268 [PMID: 20842510 DOI: 10.1007/s00535-010-0305-6]

61 **Dasarathy S**, Dasarathy J, Khiyami A, Joseph R, Lopez R, McCullough AJ. Validity of real time ultrasound in the diagnosis of hepatic steatosis: a prospective study. *J Hepatol* 2009; **51**: 1061-1067 [PMID: 19846234 DOI: 10.1016/j.jhep.2009.09.001]

62 **Mathiesen UL**, Franzén LE, Aselius H, Resjö M, Jacobsson L, Foberg U, Frydén A, Bodemar G. Increased liver echogenicity at ultrasound examination reflects degree of steatosis but not of fibrosis in asymptomatic patients with mild/moderate abnormalities of liver transaminases. *Dig Liver Dis* 2002; **34**: 516-522 [PMID: 12236486 DOI: 10.1016/S1590-8658(02)80111-6]

63 **Saadeh S**, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, Mullen KD, Cooper JN, Sheridan MJ. The utility of radiological imaging in nonalcoholic fatty liver disease. *Gastroenterology* 2002; **123**: 745-750 [PMID: 12198701 DOI: 10.1053/gast.2002.35354]

64 **Hamaguchi M**, Kojima T, Itoh Y, Harano Y, Fujii K, Nakajima T, Kato T, Takeda N, Okuda J, Ida K, Kawahito Y, Yoshikawa T, Okanoue T. The severity of ultrasonographic findings in nonalcoholic fatty liver disease reflects the metabolic syndrome and visceral fat accumulation. *Am J Gastroenterol* 2007; **102**: 2708-2715 [PMID: 17894848 DOI: 10.1111/j.1572-0241.2007.01526.x]

65 **Hernaez R**, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, Clark JM. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. *Hepatology* 2011; **54**: 1082-1090 [PMID: 21618575 DOI: 10.1002/hep.24452]

66 **Lee SS**, Park SH, Kim HJ, Kim SY, Kim MY, Kim DY, Suh DJ, Kim KM, Bae MH, Lee JY, Lee SG, Yu ES. Non-invasive assessment of hepatic steatosis: prospective comparison of the accuracy of imaging examinations. *J Hepatol* 2010; **52**: 579-585 [PMID: 20185194 DOI: 10.1016/j.jhep.2010.01.008]

67 **Permutt Z**, Le TA, Peterson MR, Seki E, Brenner DA, Sirlin C, Loomba R. Correlation between liver histology and novel magnetic resonance imaging in adult patients with non-alcoholic fatty liver disease - MRI accurately quantifies hepatic steatosis in NAFLD. *Aliment Pharmacol Ther* 2012; **36**: 22-29 [PMID: 22554256 DOI: 10.1111/j.1365-2036.2012.05121.x]

68 **Tang A**, Tan J, Sun M, Hamilton G, Bydder M, Wolfson T, Gamst AC, Middleton M, Brunt EM, Loomba R, Lavine JE, Schwimmer JB, Sirlin CB. Nonalcoholic fatty liver disease: MR imaging of liver proton density fat fraction to assess hepatic steatosis. *Radiology* 2013; **267**: 422-431 [PMID: 23382291 DOI: 10.1148/radiol.12120896]

69 **Hatta T**, Fujinaga Y, Kadoya M, Ueda H, Murayama H, Kurozumi M, Ueda K, Komatsu M, Nagaya T, Joshita S, Kodama R, Tanaka E, Uehara T, Sano K, Tanaka N. Accurate and simple method for quantification of hepatic fat content using magnetic resonance imaging: a prospective study in biopsy-proven nonalcoholic fatty liver disease. *J Gastroenterol* 2010; **45**: 1263-1271 [PMID: 20625773 DOI: 10.1007/s00535-010-0277-6]

70 **Mennesson N**, Dumortier J, Hervieu V, Milot L, Guillaud O, Scoazec JY, Pilleul F. Liver steatosis quantification using magnetic resonance imaging: a prospective comparative study with liver biopsy. *J Comput Assist Tomogr* 2009; **33**: 672-677 [PMID: 19820490 DOI: 10.1097/RCT.0b013e318199d883]

71 **Yokoo T**, Bydder M, Hamilton G, Middleton MS, Gamst AC, Wolfson T, Hassanein T, Patton HM, Lavine JE, Schwimmer JB, Sirlin CB. Nonalcoholic fatty liver disease: diagnostic and fat-grading accuracy of low-flip-angle multiecho gradient-recalled-echo MR imaging at 1.5 T. *Radiology* 2009; **251**: 67-76 [PMID: 19221054 DOI: 10.1148/radiol.2511080666]

72 **Noworolski SM**, Lam MM, Merriman RB, Ferrell L, Qayyum A. Liver steatosis: concordance of MR imaging and MR spectroscopic data with histologic grade. *Radiology* 2012; **264**: 88-96 [PMID: 22723561 DOI: 10.1148/radiol.12110673]

73 **McPherson S**, Jonsson JR, Cowin GJ, O'Rourke P, Clouston AD, Volp A, Horsfall L, Jothimani D, Fawcett J, Galloway GJ, Benson M, Powell EE. Magnetic resonance imaging and spectroscopy accurately estimate the severity of steatosis provided the stage of fibrosis is considered. *J Hepatol* 2009; **51**: 389-397 [PMID: 19505740 DOI: 10.1016/j.jhep.2009.04.012]

74 **Fishbein M**, Castro F, Cheruku S, Jain S, Webb B, Gleason T, Stevens WR. Hepatic MRI for fat quantitation: its relationship to fat morphology, diagnosis, and ultrasound. *J Clin Gastroenterol* 2005; **39**: 619-625 [PMID: 16000931 DOI: 10.1097/00004836-200508000-00012]

75 **Bugianesi E**, Manzini P, D'Antico S, Vanni E, Longo F, Leone N, Massarenti P, Piga A, Marchesini G, Rizzetto M. Relative contribution of iron burden, HFE mutations, and insulin resistance to fibrosis in nonalcoholic fatty liver. *Hepatology* 2004; **39**: 179-187 [PMID: 14752836 DOI: 10.1002/hep.20023]

76 **Chitturi S**, Weltman M, Farrell GC, McDonald D, Kench J, Liddle C, Samarasinghe D, Lin R, Abeygunasekera S, George J. HFE mutations, hepatic iron, and fibrosis: ethnic-specific association of NASH with C282Y but not with fibrotic severity. *Hepatology* 2002; **36**: 142-149 [PMID: 12085358 DOI: 10.1053/jhep.2002.33892]

77 **Kalra N**, Duseja A, Das A, Dhiman RK, Virmani V, Chawla Y, Singh P, Khandelwal N. Chemical shift magnetic resonance imaging is helpful in detecting hepatic steatosis but not fibrosis in patients with nonalcoholic fatty liver disease (NAFLD). *Ann Hepatol* 2009; **8**: 21-25 [PMID: 19221529]

78 **Roldan-Valadez E**, Favila R, Martínez-López M, Uribe M, Ríos C, Méndez-Sánchez N. In vivo 3T spectroscopic quantification of liver fat content in nonalcoholic fatty liver disease: Correlation with biochemical method and morphometry. *J Hepatol* 2010; **53**: 732-737 [PMID: 20594607 DOI: 10.1016/j.jhep.2010.04.018]

79 **Karlas T**, Petroff D, Garnov N, Böhm S, Tenckhoff H, Wittekind C, Wiese M, Schiefke I, Linder N, Schaudinn A, Busse H, Kahn T, Mössner J, Berg T, Tröltzsch M, Keim V, Wiegand J. Non-invasive assessment of hepatic steatosis in patients with NAFLD using controlled attenuation parameter and 1H-MR spectroscopy. *PLoS One* 2014; **9**: e91987 [PMID: 24637477 DOI: 10.1371/journal.pone.0091987]

80 **Ziol M**, Kettaneh A, Ganne-Carrié N, Barget N, Tengher-Barna I, Beaugrand M. Relationships between fibrosis amounts assessed by morphometry and liver stiffness measurements in chronic hepatitis or steatohepatitis. *Eur J Gastroenterol Hepatol* 2009; **21**: 1261-1268 [PMID: 19478678 DOI: 10.1097/MEG.0b013e32832a20f5]

81 **Gaia S**, Carenzi S, Barilli AL, Bugianesi E, Smedile A, Brunello F, Marzano A, Rizzetto M. Reliability of transient elastography for the detection of fibrosis in non-alcoholic fatty liver disease and chronic viral hepatitis. *J Hepatol* 2011; **54**: 64-71 [PMID: 20932598 DOI: 10.1016/j.jhep.2010.06.022]

82 **Lupsor M**, Badea R, Stefanescu H, Grigorescu M, Serban A, Radu C, Crişan D, Sparchez Z, Iancu S, Maniu A. Performance of unidimensional transient elastography in staging non-alcoholic steatohepatitis. *J Gastrointestin Liver Dis* 2010; **19**: 53-60 [PMID: 20361076]

83 **Wong VW**, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, Choi PC, Kowo M, Chan AW, Merrouche W, Sung JJ, de Lédinghen V. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. *Hepatology* 2010; **51**: 454-462 [PMID: 20101745 DOI: 10.1002/hep.23312]

84 **Myers RP**, Pomier-Layrargues G, Kirsch R, Pollett A, Duarte-Rojo A, Wong D, Beaton M, Levstik M, Crotty P, Elkashab M. Feasibility and diagnostic performance of the FibroScan XL probe for liver stiffness measurement in overweight and obese patients. *Hepatology* 2012; **55**: 199-208 [PMID: 21898479 DOI: 10.1002/hep.24624]

85 **Yoneda M**, Yoneda M, Mawatari H, Fujita K, Endo H, Iida H, Nozaki Y, Yonemitsu K, Higurashi T, Takahashi H, Kobayashi N, Kirikoshi H, Abe Y, Inamori M, Kubota K, Saito S, Tamano M, Hiraishi H, Maeyama S, Yamaguchi N, Togo S, Nakajima A. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with nonalcoholic fatty liver disease (NAFLD). *Dig Liver Dis* 2008; **40**: 371-378 [PMID: 18083083 DOI: 10.1016/j.dld.2007.10.019]

86 **Boursier J**, Zarski JP, de Ledinghen V, Rousselet MC, Sturm N, Lebail B, Fouchard-Hubert I, Gallois Y, Oberti F, Bertrais S, Calès P; Multicentric Group from ANRS/HC/EP23 FIBROSTAR Studies. Determination of reliability criteria for liver stiffness evaluation by transient elastography. *Hepatology* 2013; **57**: 1182-1191 [PMID: 22899556 DOI: 10.1002/hep.25993]

87 **de Lédinghen V**, Wong VW, Vergniol J, Wong GL, Foucher J, Chu SH, Le Bail B, Choi PC, Chermak F, Yiu KK, Merrouche W, Chan HL. Diagnosis of liver fibrosis and cirrhosis using liver stiffness measurement: comparison between M and XL probe of FibroScan®. *J Hepatol* 2012; **56**: 833-839 [PMID: 22173167 DOI: 10.1016/j.jhep.2011.10.017]

88 **Fraquelli M**, Rigamonti C, Casazza G, Conte D, Donato MF, Ronchi G, Colombo M. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. *Gut* 2007; **56**: 968-973 [PMID: 17255218 DOI: 10.1136/gut.2006.111302]

89 **Castéra L**, Foucher J, Bernard PH, Carvalho F, Allaix D, Merrouche W, Couzigou P, de Lédinghen V. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. *Hepatology* 2010; **51**: 828-835 [PMID: 20063276 DOI: 10.1002/hep.23425]

90 **Baba M**, Furuya K, Bandou H, Kasai K, Sadaoka K. Discrimination of individuals in a general population at high-risk for alcoholic and non-alcoholic fatty liver disease based on liver stiffness: a cross section study. *BMC Gastroenterol* 2011; **11**: 70 [PMID: 21669003 DOI: 10.1186/1471-230X-11-70]

91 **Wong VW**, Vergniol J, Wong GL, Foucher J, Chan AW, Chermak F, Choi PC, Merrouche W, Chu SH, Pesque S, Chan HL, de Lédinghen V. Liver stiffness measurement using XL probe in patients with nonalcoholic fatty liver disease. *Am J Gastroenterol* 2012; **107**: 1862-1871 [PMID: 23032979 DOI: 10.1038/ajg.2012.331]

92 **Friedrich-Rust M**, Hadji-Hosseini H, Kriener S, Herrmann E, Sircar I, Kau A, Zeuzem S, Bojunga J. Transient elastography with a new probe for obese patients for non-invasive staging of non-alcoholic steatohepatitis. *Eur Radiol* 2010; **20**: 2390-2396 [PMID: 20526777 DOI: 10.1007/s00330-010-1820-9]

93 **Şirli R**, Sporea I, Deleanu A, Culcea L, Szilaski M, Popescu A, Dănilă M. Comparison between the M and XL probes for liver fibrosis assessment by transient elastography. *Med Ultrason* 2014; **16**: 119-122 [PMID: 24791843 DOI: 10.11152/mu.201.3.2066.162.rs1is2]

94 **Friedrich-Rust M**, Romen D, Vermehren J, Kriener S, Sadet D, Herrmann E, Zeuzem S, Bojunga J. Acoustic radiation force impulse-imaging and transient elastography for non-invasive assessment of liver fibrosis and steatosis in NAFLD. *Eur J Radiol* 2012; **81**: e325-e331 [PMID: 22119555 DOI: 10.1016/j.ejrad.2011.10.029]

95 **Myers RP**, Pomier-Layrargues G, Kirsch R, Pollett A, Beaton M, Levstik M, Duarte-Rojo A, Wong D, Crotty P, Elkashab M. Discordance in fibrosis staging between liver biopsy and transient elastography using the FibroScan XL probe. *J Hepatol* 2012; **56**: 564-570 [PMID: 22027584 DOI: 10.1016/j.jhep.2011.10.007]

96 **Shen F**, Zheng RD, Mi YQ, Wang XY, Pan Q, Chen GY, Cao HX, Chen ML, Xu L, Chen JN, Cao Y, Zhang RN, Xu LM, Fan JG. Controlled attenuation parameter for non-invasive assessment of hepatic steatosis in Chinese patients. *World J Gastroenterol* 2014; **20**: 4702-4711 [PMID: 24782622 DOI: 10.3748/wjg.v20.i16.4702]

97 **de Lédinghen V**, Vergniol J, Foucher J, Merrouche W, le Bail B. Non-invasive diagnosis of liver steatosis using controlled attenuation parameter (CAP) and transient elastography. *Liver Int* 2012; **32**: 911-918 [PMID: 22672642 DOI: 10.1111/j.1478-3231.2012.02820.x]

98 **Myers RP**, Pollett A, Kirsch R, Pomier-Layrargues G, Beaton M, Levstik M, Duarte-Rojo A, Wong D, Crotty P, Elkashab M. Controlled Attenuation Parameter (CAP): a noninvasive method for the detection of hepatic steatosis based on transient elastography. *Liver Int* 2012; **32**: 902-910 [PMID: 22435761 DOI: 10.1111/j.1478-3231.2012.02781.x]

99 **Palmeri ML**, Wang MH, Dahl JJ, Frinkley KD, Nightingale KR. Quantifying hepatic shear modulus in vivo using acoustic radiation force. *Ultrasound Med Biol* 2008; **34**: 546-558 [PMID: 18222031 DOI: 10.1016/j.ultrasmedbio.2007.10.009]

100 **Palmeri ML**, Wang MH, Rouze NC, Abdelmalek MF, Guy CD, Moser B, Diehl AM, Nightingale KR. Noninvasive evaluation of hepatic fibrosis using acoustic radiation force-based shear stiffness in patients with nonalcoholic fatty liver disease. *J Hepatol* 2011; **55**: 666-672 [PMID: 21256907 DOI: 10.1016/j.jhep.2010.12.019]

101 **Friedrich-Rust M**, Nierhoff J, Lupsor M, Sporea I, Fierbinteanu-Braticevici C, Strobel D, Takahashi H, Yoneda M, Suda T, Zeuzem S, Herrmann E. Performance of Acoustic Radiation Force Impulse imaging for the staging of liver fibrosis: a pooled meta-analysis. *J Viral Hepat* 2012; **19**: e212-e219 [PMID: 22239521 DOI: 10.1111/j.1365-2893.2011.01537.x]

102 **Ebinuma H**, Saito H, Komuta M, Ojiro K, Wakabayashi K, Usui S, Chu PS, Umeda R, Ishibashi Y, Takayama T, Kikuchi M, Nakamoto N, Yamagishi Y, Kanai T, Ohkuma K, Sakamoto M, Hibi T. Evaluation of liver fibrosis by transient elastography using acoustic radiation force impulse: comparison with Fibroscan(®). *J Gastroenterol* 2011; **46**: 1238-1248 [PMID: 21779759 DOI: 10.1007/s00535-011-0437-3]

103 **Boursier J**, Isselin G, Fouchard-Hubert I, Oberti F, Dib N, Lebigot J, Bertrais S, Gallois Y, Calès P, Aubé C. Acoustic radiation force impulse: a new ultrasonographic technology for the widespread noninvasive diagnosis of liver fibrosis. *Eur J Gastroenterol Hepatol* 2010; **22**: 1074-1084 [PMID: 20440210 DOI: 10.1097/MEG.0b013e328339e0a1]

104 **Yoneda M**, Suzuki K, Kato S, Fujita K, Nozaki Y, Hosono K, Saito S, Nakajima A. Nonalcoholic fatty liver disease: US-based acoustic radiation force impulse elastography. *Radiology* 2010; **256**: 640-647 [PMID: 20529989 DOI: 10.1148/radiol.10091662]

105 **Poynard T**, Munteanu M, Luckina E, Perazzo H, Ngo Y, Royer L, Fedchuk L, Sattonnet F, Pais R, Lebray P, Rudler M, Thabut D, Ratziu V. Liver fibrosis evaluation using real-time shear wave elastography: applicability and diagnostic performance using methods without a gold standard. *J Hepatol* 2013; **58**: 928-935 [PMID: 23321316 DOI: 10.1016/j.jhep.2012.12.021]

106 **Ochi H**, Hirooka M, Koizumi Y, Miyake T, Tokumoto Y, Soga Y, Tada F, Abe M, Hiasa Y, Onji M. Real-time tissue elastography for evaluation of hepatic fibrosis and portal hypertension in nonalcoholic fatty liver diseases. *Hepatology* 2012; **56**: 1271-1278 [PMID: 22488593 DOI: 10.1002/hep.25756]

107 **Orlacchio A**, Bolacchi F, Antonicoli M, Coco I, Costanzo E, Tosti D, Francioso S, Angelico M, Simonetti G. Liver elasticity in NASH patients evaluated with real-time elastography (RTE). *Ultrasound Med Biol* 2012; **38**: 537-544 [PMID: 22341049 DOI: 10.1016/j.ultrasmedbio.2011.12.023]

108 **Chung JH**, Ahn HS, Kim SG, Lee YN, Kim YS, Jeong SW, Jang JY, Lee SH, Kim HS, Kim BS. The usefulness of transient elastography, acoustic-radiation-force impulse elastography, and real-time elastography for the evaluation of liver fibrosis. *Clin Mol Hepatol* 2013; **19**: 156-164 [PMID: 23837140 DOI: 10.3350/cmh.2013.19.2.156]

109 **Asbach P**, Klatt D, Schlosser B, Biermer M, Muche M, Rieger A, Loddenkemper C, Somasundaram R, Berg T, Hamm B, Braun J, Sack I. Viscoelasticity-based staging of hepatic fibrosis with multifrequency MR elastography. *Radiology* 2010; **257**: 80-86 [PMID: 20679447 DOI: 10.1148/radiol.10092489]

110 **Chen J**, Talwalkar JA, Yin M, Glaser KJ, Sanderson SO, Ehman RL. Early detection of nonalcoholic steatohepatitis in patients with nonalcoholic fatty liver disease by using MR elastography. *Radiology* 2011; **259**: 749-756 [PMID: 21460032 DOI: 10.1148/radiol.11101942]

111 **Kim D**, Kim WR, Talwalkar JA, Kim HJ, Ehman RL. Advanced fibrosis in nonalcoholic fatty liver disease: noninvasive assessment with MR elastography. *Radiology* 2013; **268**: 411-419 [PMID: 23564711 DOI: 10.1148/radiol.13121193]

112 **Yoon JH**, Lee JM, Woo HS, Yu MH, Joo I, Lee ES, Sohn JY, Lee KB, Han JK, Choi BI. Staging of hepatic fibrosis: comparison of magnetic resonance elastography and shear wave elastography in the same individuals. *Korean J Radiol* 2013; **14**: 202-212 [PMID: 23483022 DOI: 10.3348/kjr.2013.14.2.202]

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Serologic markers for detecting steatosis** | | | |
| **Marker** | **AUROC** | ***n*** | **Ref.** |
| Cytokeratin-18 | 0.90  0.77 | 157  318 | 20  21 |
| Fatty Liver Index | 0.84 | 496 | 27 |
| Lipid Accumulation Product | 0.79 | 588 | 28 |
| Hepatic Steatosis Index | 0.81 | 5,362 | 29 |
| SteatoTest | 0.79 | 69 | 31 |
| **Serologic markers for differentiating simple steatosis**  **from nonalcoholic steatohepatitis** | | | |
| **Marker** | **AUROC** | ***n*** | **Ref.** |
| AST/platelet ratio index | 0.60 | 190 | 34 |
| Cytokeratin-18 | 0.82 | 838 | 39 |
| NAFLD fibrosis score | 0.82 | 733 | 43 |
| **Comparative studies of serologic markers**  **for differentiating simple steatosis from nonalcoholic steatohepatitis** | | | |
| **Marker** | **AUROC** | ***n*** | **Ref.** |
| FIB-4  NAFLD fibrosis score  BARD score  AST/platelet ratio index | 0.86  0.81  0.77  0.67 | 145 | 46 |
| FIB-4  NAFLD fibrosis score  BARD score | 0.96  0.94  0.84 | 165 | 47 |
| FIB-4  NAFLD fibrosis score  BARD score  AST/platelet ratio index | 0.80  0.77  0.70  0.73 | 541 | 48 |
| FIB-4  NAFLD fibrosis score  AST/platelet ratio index  BARD score | 0.87  0.86  0.79  0.76 | 576 | 49 |

AUROC: Area under the receiving-operating characteristics curve; AST: Aspartate transaminase; NAFLD: Non-alcoholic fatty liver disease; FIB-4: Fibrosis-4; BARD: BMI, AST/ALT Ratio, Diabetes.

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Imaging methods for differentiating simple steatosis**  **from nonalcoholic steatohepatitis** | | | |
| **Imaging method** | **AUROC** | ***n*** | **Ref.** |
| Transient elastography | 0.84  0.87 | 246  75 | 83  84 |
| Acoustic radiation force impulse | 0.86  0.90 | 77  172 | 101  100 |
| Real-time shear wave elastography | 0.85 | 181 | 106 |
| Magnetic resonanceelastography | 0.93  0.95 | 58  142 | 110  111 |
| **Comparative studies of imaging methods**  **for differentiating simple steatosis from nonalcoholic steatohepatitis** | | | |
| **Imaging method** | **AUROC** | ***n*** | **Ref.** |
| Transient elastography  Acoustic radiation force impulse | 0.99  0.97 | 54 | 104 |
| Transient elastography  Acoustic radiation force impulse  Real-time shear wave elastography | 0.73  0.71  0.51 | 13 | 108 |

AUROC: Area under the receiving-operating characteristics curve.