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Role of Noninvasive Tests in Clinical Gastroenterology Practices to Identify Patients With Nonalcoholic Steatohepatitis at High Risk of Adverse Outcomes: Expert Panel Recommendations

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Nonalcoholic fatty liver disease (NAFLD) is generally considered a silent and potentially reversible condition. The subtype of NAFLD that can be classified as nonalcoholic steatohepatitis (NASH) can progress to advanced fibrosis and cirrhosis. Because of the metabolic nature of the pathogenic mechanism underlying NAFLD and NASH, it is often accompanied by common comorbidities such as obesity, insulin resistance, and type 2 diabetes mellitus. The increase in the prevalence of these comorbidities has resulted in a parallel increase in the prevalence of NAFLD and NASH, globally, nationally, and even in children. In recent years, it has been identified that the stage of fibrosis is the most important predictor of liver outcomes; therefore, identifying patients with NAFLD and NASH with more advanced stages of fibrosis can be essential for optimal management. Several noninvasive tools for diagnosing and staging NAFLD and NASH are available, but simple and straightforward recommendations on the use of these tools are not. Recognizing these unmet needs, hepatologists who are members of the American College of Gastroenterology and the Chronic Liver Disease Foundation created a practical decision tree/algorithm to risk stratify NAFLD/NASH as a resource in gastroenterology/hepatology clinical practices. This review will provide insight into how this algorithm was developed, describe it in detail, and provide recommendations for its use in clinical practice.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a common, generally silent, and potentially reversible condition defined as accumulation of fat in the liver, in the absence of other causes of liver disease or hepatic fat. A growing number of patients with unrecognized NAFLD progress to a more severe form of NAFLD called nonalcoholic steatohepatitis (NASH), which is manifested by steatosis, inflammation, and liver cell injury with or without fibrosis. Globally, NAFLD is a significant problem, with an estimated worldwide prevalence of 25% (1). Although the exact prevalence of NASH is not known, a reasonable estimate places the prevalence of NASH between 1.5% and 6.5% (2).

In the United States, NASH is a leading cause of cirrhosis in adults (3) and one of the most common predisposing factors for hepatocellular carcinoma (4). In addition, NASH-related cirrhosis is the second-leading indication for liver transplantation in adults (5,6) and the leading indication for liver transplantation in female patients (7,8).

Patients with NAFLD often have type 2 diabetes mellitus (T2DM), dyslipidemia, hypertension, and hypertriglyceridemia as associated conditions (9,10). It is, therefore, not surprising that cardiovascular disease is the leading cause of death in patients with NAFLD (1). Increasing age, obesity, and T2DM have also been identified as risk factors associated with advanced liver fibrosis (11). As the epidemics of these comorbidities increase worldwide, the prevalence of NAFLD and NASH are also increasing. In addition to the clinical sequel of NASH, cases with NASH, especially those associated with significant fibrosis, are associated with a significant economic burden to society and negative reported health-related quality of life for patients (Figure 1) (12,13).

Although NAFLD and NASH carry significant burdens to society, many unmet needs exist such as lack of screening methods/recommendations and US Food and Drug Administration (US FDA)–approved therapies. Gastroenterologists and hepatologists need simple, noninvasive tools to screen and stage the influx of NAFLD/NASH referrals that come from primary care practitioners and other medical specialists caring for patients at high risk of NAFLD. In the context of this growing unmet need, the Chronic Liver Disease Foundation (CLDF) and the American

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College of Gastroenterology (ACG) have partnered to create a straightforward practical diagnosis and staging decision tree/algorithm for gastroenterologists and hepatologists managing NAFLD/NASH. The initial data were presented by expert hepatologists, summarizing evidence during the NASH Leadership Forum organized by CLDF in October 2019. In addition, literature was reviewed and summarized to create a practical, easy-to-use algorithm that can be used in clinical practice.

THE SIGNIFICANCE OF FIBROSIS IN NAFLD AND NASH

Fibrosis stage has historically been important for monitoring the clinical risk of progression to cirrhosis with any liver disease (e.g., hepatitis B, hepatitis C, and alcoholic liver disease) (14). Recent studies have suggested that the stage of fibrosis, independent of any other histological feature, predicts mortality in NAFLD (13) and might in fact be the most important predictor of long-term outcome (1,15–17). A systematic review and meta-analysis by Dulai et al. pooled data from 5 adult NAFLD cohort studies reporting fibrosis stage-specific mortality. The study included 1,495 patients with NAFLD with 17,452 patient-years of follow-up. They found that, compared with patients with NAFLD with no fibrosis (stage 0), patients with NAFLD with fibrosis were at a higher risk of all-cause mortality, which increased with advancing stages of fibrosis, specifically at stage 2 or higher. Furthermore, the risk of liver-related mortality increased exponentially with each increase in the stage of fibrosis (12).

These data have important implications in clinical practice because they suggest that, based on the stage of fibrosis, a patient-specific risk profile can be generated to help guide treatment decisions in NAFLD and NASH (12). According to the American Association for the Study of Liver Disease (AASLD) practice guidance, liver biopsy is the gold standard and most reliable approach to assess the stage of fibrosis in NAFLD and diagnose NASH (18). The information provided by this histopathological assessment also allows for the exclusion of other causes of liver disease and characterization of liver lesions and correlates the lesions with potential clinical outcomes in the context of the natural history of the disease (19,20). Unfortunately, practical considerations including cost, sampling errors, and procedure-related morbidity, and even mortality, limit the use of large-scale liver biopsies in clinical practice (21). Furthermore, as an invasive tool for staging the severity of underlying liver disease, liver biopsy has no effective role in population-based screening.

According to the AASLD practice guidance, liver biopsy should be considered in patients with suspected NAFLD for whom coexisting or competing diagnosis might be present (i.e., persistently high serum ferritin, increased iron saturation, homozygote or heterozygote C282Y Human Factors Engineering mutation, or autoimmune liver disease) (21). Liver biopsy should also be considered in patients with NAFLD who are at increased risk of having steatohepatitis, especially those with advanced fibrosis, which can be suspected when patients with NAFLD present with components of metabolic syndrome such as T2DM. In addition, one could potentially risk stratify patients with NAFLD using noninvasive tests (NITs) such as NAFLD Fibrosis Score (NFS) or Fibrosis-4 Index (FIB-4) or liver stiffness measured by elastography. By contrast, it is important to remember that histologic NASH might still be present even if patients do not meet the indication for liver biopsy. Although liver enzymes can be a marker of ongoing cellular injury in NASH, they might be normal in up to 70% of patients (22) and are insensitive for diagnosis of NASH (23). In this context, a meta-analysis by Younossi et al. found that NASH prevalence estimates among patients with NAFLD without an indication for biopsy (e.g., elevated liver enzymes and clinical signs of liver disease) were 6.67% (95% confidence interval: 2.17–18.73) in Asia and 29.85% (95% confidence interval: 22.72–38.12) in North America (1).

NITS FOR FIBROSIS

Current knowledge dictates that it is very important to evaluate patients with NAFLD for the possibility they might have significant liver fibrosis (24). This is based on the evidence that stage of fibrosis is the most important predictor of long-term outcomes. Given the aforementioned limitations of liver biopsy (1,21), there has been significant interest in recent years in developing NITs to screen for NAFLD and NASH to identify patients at risk of disease progression (i.e., those with significant liver fibrosis). Much progress has been made in this field, as indicated by Tables 1 and 2, which highlight the biomarkers (classified as serum or imaging biomarkers), and algorithms using serum biomarkers, which the panel believes have the strongest evidence for identifying fibrosis in NAFLD. Most of these NITs are designed to detect significant fibrosis, with the exception of an additional advantage of detecting steatosis using controlled attenuation parameter of transient elastography (TE) and proton density fat fraction of MRI. Nevertheless, it is important that liver biopsy remains the only method to diagnose NASH (because it detects inflammation and ballooning). In fact, steatohepatitis is a pathologic diagnosis that can only be made with a liver biopsy. Although histologic diagnosis of NASH indicates the potentially, progressive form of NAFLD, it is stage of fibrosis that surpasses all other current prognostic factors for predicting outcomes. In this context, NITs for liver fibrosis are attractive alternatives for disease risk stratification in NASH. In this section, the ACG-CLDF panel highlights the biomarkers that are recommended within the algorithm because these are the most broadly studied NITs that have been validated when compared with liver biopsy.

Serum biomarkers and associated algorithms

The AASLD guidance document highlights the use of 2 algorithms, both constructed from routine clinical and laboratory values, to assess for fibrosis: the FIB-4 and NFS. These are described as "clinically useful tools for identifying patients with NAFLD with higher likelihood of having advanced hepatic fibrosis (bridging fibrosis [stage 3] or cirrhosis [stage 4]) (21). Online or smart phone calculators are available and can readily generate, on entry of the necessary data, a FIB-4 or NFS as a point-of-care risk stratifier (25,26).

The FIB-4 is an algorithm based on a noninvasive panel that relies on age and levels of platelets, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) to indicate the presence or absence of advanced fibrosis (27). FIB-4 was previously validated in patients with hepatitis C virus infection (28), and later, data became available on its utility in patients with NAFLD. A study found that, using the FIB-4 threshold values of <1.3 and >2.67 for the absence and presence of advanced fibrosis, respectively, would have avoided a liver biopsy in 78% of the evaluated patients with NAFLD (29). Many other studies have shown the accuracy of FIB-4 in assessing patients with NAFLD and stratifying them to those with advanced fibrosis vs none (30,31).

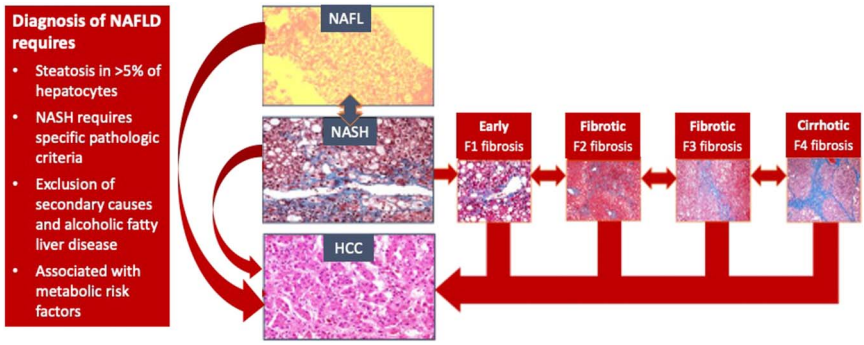

Figure 1. The spectrum of NAFLD (13,21,59,67–69). HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Similar to the FIB-4, the NFS takes not only age, platelets, and AST and ALT ratio into consideration but also factors in albumin levels, body mass index (BMI), and whether the patient has impaired fasting glucose/diabetes (26). The AST/ALT ratio is an important component of the NFS because it can detect advanced fibrosis even if the actual AST and ALT levels are normal (often seen with cirrhosis). A study in patients with NAFLD found that applying a low cutoff score of <-1.455 excluded advanced fibrosis with high accuracy (negative predictive value of 93% and 88% in the estimation and validation groups, respectively) and applying a high cutoff score of >0.675 diagnosed the presence of advanced fibrosis with high accuracy (positive predictive value of 90% and 82% in the estimation and validation groups, respectively). Furthermore, investigators found that using the NFS would have avoided liver biopsy in 549 (75%) of the 733 patients studied, with correct prediction in 496 (90%) (11).

The Enhanced Liver Fibrosis (ELF) score is an extracellular matrix marker set consisting of tissue inhibitor of metalloproteinases 1, amino-terminal propeptide of type III procollagen, and hyaluronic acid. Unlike FIB-4 and NFS, this serum biomarker requires a specialized laboratory service that provides the score after analyzing a patient's blood sample (32). To date, the ELF score demonstrates good correlations with progression of fibrosis in a number of chronic liver diseases (33–37). About NAFLD and NASH, in a recent study of 122 patients with NAFLD, ELF demonstrated good accuracy for detection or exclusion of advanced fibrosis in NAFLD; however, the cutoffs differed slightly from those identified in hepatitis C virus-infected patients (34). In another study of 162 patients with biopsy-proven NASH cirrhosis and portal hypertension, mean baseline ELF was significantly higher among patients with liver-related outcomes vs those without these outcomes (11.3 ± 1.1 vs 10.6 ± 1.2, $P < 0\,01$). In addition, ELF was associated with increased risk of liver-related outcomes, and baseline ELF had higher prediction to detect 1-year liver-related outcomes, when compared with FIB-4, model for end-stage liver disease, and Child-Turcotte-Pugh. Finally, patients with an ELF >11.3 showed a significantly greater (2.3-fold, $P = .016$) increase in risk of liver-related outcomes over the next 52 weeks (35). At the time of the completion of this article, ELF testing has not been approved in the United States. Nevertheless, ELF is becoming a potentially attractive biomarker and is considered by the expert panel to have promise as a screening tool for advanced hepatic fibrosis once approved. Although the exact cutoff for ELF is not fully validated in patients with NASH from real-world clinical practice, a threshold of 10.51 has been suggested; however, cutoff values will be defined when ELF testing is approved in the United States (36).

Additional algorithms are available to stage the degree of fibrosis in patients with NAFLD/NASH. The AST:platelet ratio index uses AST, AST and upper limit of normal and platelet counts, which are entered into an online calculator (37). The results demonstrate the opposing relationship between fibrosis stage and AST level and platelet count (38). Hepascore is calculated from a panel that includes age, sex, bilirubin, γ-glutamyl transferase, and components involved in hepatic fibrogenesis (i.e., hyaluronic acid and α2-macroglobulin) (39). FibroTest (FibroSure in the United States) consists of an algorithm of 5 fibrosis markers: α2-macroglobulin, apolipoprotein A1, total bilirubin, haptoglobin, and γ-glutamyl transferase (40). Scores correspond to the 0–4 point METAVIR liver fibrosis scale (41). Finally, FibroMeter is an algorithm that calculates results based on patient clinical data (age and weight) and 5 blood biomarkers: platelet count, AST, ALT, ferritin, and glucose (42). The recommended cutoffs for the algorithms summarized in this section are listed in Table 1.

In the context of noninvasive algorithms, the ACG-CLDF panel feels that FIB-4 is probably the most studied simple noninvasive algorithm and endorsed by liver societies that can be used for risk stratification in clinical practice. Nevertheless, this test will most likely be most valuable as a combination of sequential NITs that can identify patients at risk. NFS also is well studied and endorsed by guidance societies; however, it includes several variables associated with diabetes (and the presence of diabetes itself), which likely lead to an overestimate of risk when selectively applied to the population with diabetes (43).

As described, FIB-4 and NFS have 2 cutoff values to detect advanced fibrosis vs non-fibrosis, which leaves the clinician with a range of values in between (called indeterminate zone) (Figure 2). This is when a second NIT can be performed, a concept termed as sequential testing that has proven to narrow this indeterminate zone (31,44,45). Finally, it is important to recognize that the strength of these tests is their ability to exclude those with advanced fibrosis. For example, patients with NAFLD with FIB-4 <1.3 are less likely to have significant hepatic fibrosis. Nevertheless, the validity and clinical utility of these tests in specific patient populations such as T2DM require additional data.

Imaging

Several imaging techniques are available to noninvasively assess hepatic steatosis, as described in Table 2. Liver stiffness measure

Table 1. Noninvasive serum biomarkers or algorithms for assessing fibrosis

Biomarkers/algorithms	Details
FIB-4[a]	<1.3 excludes significant fibrosis
NFS[a]	< −1.455 excludes significant fibrosis
APRI[a]	A meta-analysis of 40 studies in HCV indicated that APRI score >1.0 had a sensitivity of 76% and specificity of 72% for predicting cirrhosis and APRI >0.7 had a sensitivity of 77% and specificity of 72% for predicting significant hepatic fibrosis (70).
ELF	More data are needed on cutoff values to indicate the presence or absence of clinical fibrosis.
Hepascore®	A meta-analysis of 21 studies indicated a cut point of 0.50–0.61 had a summary sensitivity of 81% and a summary specificity of 74% to predict advanced fibrosis. Hepascore® has better diagnostic ability for advanced fibrosis in HCV, HBV, and alcoholic liver disease than for NAFLD (71).
FibroTest® (FibroSure® in the United States) (40)	Surrogate marker (S) 0.0–1.0 indicates liver fibrosis (Metavir F0–F4), hepatic steatosis (0.0–1.0, S0–S3), and NASH (0.0–0.75, N0–N2). The absence of steatosis (S < 0.38) precludes the diagnosis of NASH. Interpret with caution in those with Gilbert syndrome or hemolysis (72).
FibroMeter® (73)	Scores between 0.85 and 0.9 indicate ≥ F2 A score of ≥0.91 indicates F4

APRI, aspartate aminotransferase to platelet ratio index; ELF, enhanced liver fibrosis; FIB-4, Fibrosis-4 Index; NFS, NAFLD Fibrosis Score.
[a]Scores that incorporate data typically readily available with minimal or no additional costs.

(LSM) is a promising surrogate biomarker of liver fibrosis stage and can be measured using elastography. As such, the expert panel believes the most accurate noninvasive methods to assess LSM and to classify the patient into advanced vs nonadvanced fibrosis involve elastography. The techniques recommended in our algorithms are TE, magnetic resonance elastography (MRE), and ultrasound-based 2D shear wave elastography (2D-SWE).

One-dimensional TE is an ultrasound-based method in which a probe generates a low-frequency, acoustic shear wave that travels through the liver. The velocity of the wave is captured, thus providing an idea of the liver's elasticity. The-higher the value, the greater the degree of liver stiffness; LSM values range from 1.5 to 75 kPa (46). TE (marketed as FibroScan) is noninvasive and reliable and provides a rapid, bedside LSM. Furthermore, an extra-large probe is available, which has significantly reduced the high failure rate previously observed in patients with BMI >28 kg/m^2 (47–49). One-dimensional TE can also be combined with an assessment of hepatic steatosis by measuring the ultrasonic attenuation of the echo wave called controlled attenuation parameter score.

Another elastography technique, 2D-SWE, produces shear waves by a focused ultrasound beam that travel through the liver tissue. Similar to TE, the propagation velocity of the shear waves correlates with the elasticity of tissue (50). Unlike TE, 2D-SWE can be performed using a conventional ultrasound scanner and can create a real-time, 2D quantitative map of liver tissue stiffness under the guidance of very high frame rate B-mode imaging (51).

MRE is also considered a clinically useful tool for evaluating the stages of fibrosis (18). MRE uses MRI to propagate acoustic shear waves into the liver and computes cross-sectional images of the liver using a mathematical algorithm, thereby allowing for assessment of steatosis and detection of fibrosis (38,52–54). Data demonstrates the utility of both MRE (38,40) and 2D-SWE in patients with NAFLD, but costs are significantly greater than TE (39,42,47,55), and many practitioners simply do not have access to this advanced technology. It is worth mentioning that a study showed higher accuracy of MRE in comparison with TE (56,57). Nevertheless, given the limitation in access and cost, TE is the best point-of-care test. On the other hand, in patients with severe abdominal obesity, MRE might be the modality of choice. We refrain from discussing MRE and 2D-SWE cutoffs, given their limited availability and the higher cost of MRE, but additional information has been published (46,50,54,58).

PRACTICAL ALGORITHM TO IDENTIFY PATIENTS AT HIGH RISK OF NASH IN GASTROENTEROLOGY/HEPATOLOGY PRACTICES

Primary care practitioners should be further assessing patients with elevated ALT (>30 μ/mL for male subjects or >20 μ/mL for female subjects). If a patient has ≥3 risk factors associated with NAFLD (BMI ≥25, hypertension, T2DM, polycystic ovarian syndrome, obstructive sleep apnea, or hyperlipidemia) (59) or a family history of cirrhosis and/or hepatocellular carcinoma, further evaluation, including referral to experts, should be considered.

To establish the diagnosis of NAFLD/NASH, clinicians need to decide the following (1): whether the patient has NAFLD by documentation of fatty liver and exclusion of excessive alcohol consumption; (2) whether there are other etiologies of chronic liver disease (e.g., viral hepatitis, autoimmune liver disease, medications) (1,60); (3) whether the patient is likely to have underlying NASH; (4) whether fibrosis is present; and (5) whether fibrosis is at an advanced stage (13).

Given the importance of staging hepatic fibrosis in NASH and the limitations of liver biopsy, accurate, noninvasive diagnostic algorithms are urgently needed (13,61). Nevertheless, a number of currently available NITs that can be used for risk stratification, screening, and staging NASH (Tables 1 and 2) are available. The CLDF and ACG expert panel has developed a straightforward practical diagnosis and staging decision tree algorithm for NAFLD/NASH (Figure 2), which is recommended for use by gastroenterologists and hepatologists.

Once the diagnosis of NAFLD/NASH is made (e.g., after imaging and ruling out other causes), staging of fibrosis is indicated, especially for patients at risk of NASH and fibrosis (e.g., T2DM or multiple other components of metabolic syndrome). Fibrosis can be staged by using noninvasive

Table 2. New imaging tests for assessing fibrosis and estimating hepatic steatosis

Imaging Tests	Details	Cutoff values	Considerations
TE (46)	The velocity of the wave that travels through the liver indicates LSM; the higher the LSM, the greater the degree of liver stiffness. Noninvasive, reliable, rapid, and able to be used in obese patients. Excellent negative predictive value. Sensitivity decreased by several factors including nonfasting state, increased liver enzymes, obesity, and cardiac congestion. CAP score available to quantitate steatosis.	Significant fibrosis is unlikely: <6.0 kPa F2: ≥8.2 kPa F3: ≥9.7 kPa F4: ≥13.6 kPa	Do not use: • When here is ascites • When there are other causes that can lead to increased stiffness such as congestive hepatopathy Additional consideration: • kPa ≥20 might suggest clinically significant portal hypertension, particularly in those patients with platelet count <150/mm^3 (74)
SWE	The propagation velocity of the shear wave that travels through the liver correlates with the elasticity of tissue; a higher velocity indicates increasing LSM. Validated cutoffs are only available for HCV.	F1: >7.1 kPa ≥F2: >7.8 kPa F3: >8 kPa F4: >11.5 kPa (75)	• More research in patients with NAFLD/NASH is needed.
Magnetic resonance techniques	MRE propagates acoustic shear waves into the liver and computes cross-sectional images using a mathematical algorithm, thereby allowing for detection of fibrosis (50). It is expensive, and availability is not widespread but probably more accurate than TE in obese patients. MRI shows fat and water proton, and the precession differences allow for detection of volumetric liver fat. MRI is regarded as the most definitive imaging tool to qualitatively and quantitatively evaluate hepatic steatosis (76). MRS measures proton signals as a function of their resonance frequency, allowing for quantification of signal intensities which correspond to water or fat, allowing for quantification of fat in the liver. MRS is sensitive to even trace amounts of liver fat but requires expert assessment, is restricted in spatial coverage, is associated with sampling errors, is time consuming, and is not widely available (54).	MRE (46): Any (≥stage 1): 2.61 kPa Significant (≥stage 2): 2.97 kPa Advanced fibrosis (≥stage 3): 3.61 kPa Cirrhosis (≥stage 4): 4.69 kPa MRI-PDFF ≥15.7% indicates fibrosis progression (77) MRS: PDFF cutoff value of 3% (78)	• Contraindicated in patients with claustrophobia and with some pacemakers Cost can be an issue Further data are needed on MRI-PDFF cutoffs
FAST score	Score that combines LSM, CAP, and AST. A 3-yr study of 350 patients with suspected NAFLD found that FAST provides an efficient way to noninvasively identify patients at risk of progressive NASH (79).	0.35 for sensitivity ≥0.90 0.67 for specificity ≥0.90	• Attention should be drawn to the LSM value regardless of the FAST score values • Best to be used in clinical trials
ARFI	ARFI is an ultrasound-based technique that evaluates the wave propagation speed and allows the assessment of tissue stiffness (80). ARFI is a fairly new technique, but results are promising for evaluating degrees of severity of NAFLD and hepatic fibrotic stages in NAFLD rat models (81).	Using a predictive shear stiffness threshold of 4.24 kPa, shear stiffness distinguished low (stage 0–2) from high (stage 3–4) fibrosis stages with a sensitivity of 90% and a specificity of 90% (AUC of 0.90) (79)	• More research is needed in this area

ARFI, acoustic radiation force impulse; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; CT, computed tomography; FAST, FibroScan-AST; HCV, hepatitis C virus; LSM, liver stiffness measure; MRE, magnetic resonance elastography; MRS, magnetic resonance spectroscopy; NAFLD, nonalcoholic fatty liver disease; PDFF, proton density fat fraction; SWE, shear wave elastography; TE, transient elastography.

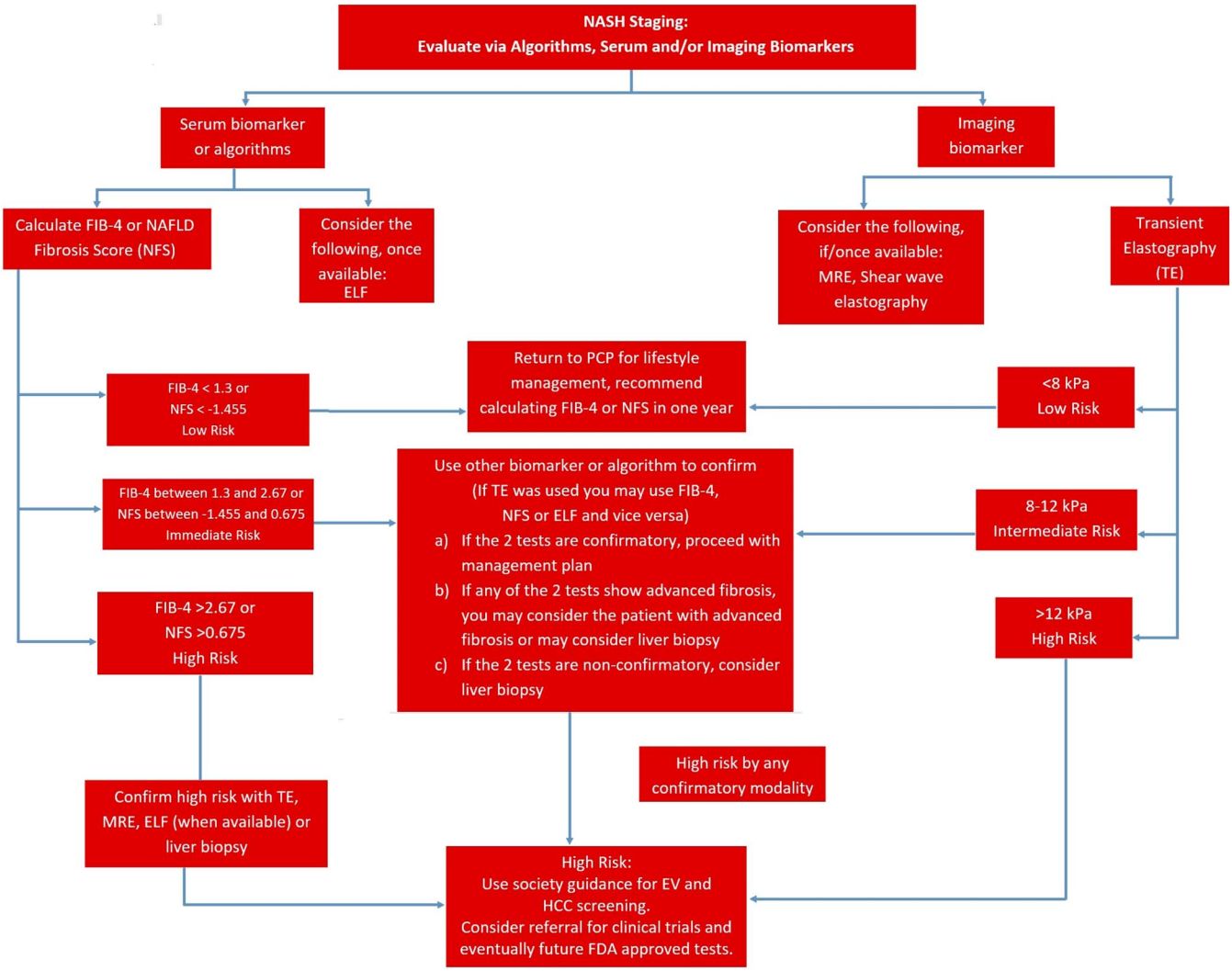

Figure 2. Algorithm to identify patients with NASH at high risk of adverse outcomes. ELF, enhanced liver fibrosis; EV, esophageal varices; FDA, US Food and Drug Administration; FIB-4, Fibrosis-4 Index; HCC, hepatocellular carcinoma; kPa, kilopascals; MRE, magnetic resonance elastography; NFS, NAFLD fibrosis score; NASH, nonalcoholic steatohepatitis; PCP, primary care physician; TE, transient elastography.

algorithms, such as FIB-4 and NFS, followed by other NITs such as ELF (when available), imaging-based testing (e.g., TE or MRE), or preferably by combining of serum biomarkers and imaging (Figure 2). If FIB-4 or NFS is chosen for screening and their values are <1.3 or < -1.455, respectively, fibrosis is likely ruled out. The patient is considered low risk of NAFLD/NASH and might follow-up with their primary care provider, with recommendations of weight loss, exercise, and yearly FIB-4 and NFS reassessment. On the other hand, if FIB-4 and NFS values are >2.67 or >0.675, respectively, the patient most likely has advanced fibrosis and should be followed by a specialist; a second NIT can be performed to reduce the area of uncertainty. Patients with these high NIT values might have NASH with significant fibrosis and might be referred to a clinical trial or treated with the US FDA-approved medications in the future, in addition to losing weight and exercising. Screening for esophageal varices and hepatocellular carcinoma might be considered for those with advanced fibrosis (F3 and F4) according to society guidelines (21).

Alternatively, if the clinician chooses a TE for initial NASH staging, certain cutoffs can be applied: LSM $\geq$8 kPa has been shown to correlate with histologic stage $\geq$F2, which is associated with increased liver-related morbidities and mortality. On the other hand, the expert panel considers patients with LSM $<$8 kPa, especially those with $<$6 kPa, at low risk of progressive liver disease and recommends they be followed up by their primary care provider for management of cardiometabolic risk factors through weight loss and exercise and annual fibrosis assessment. Although TE is the preferred point-of-care method for fibrosis assessment, other NITs such as FIB-4 can also be used, and a value of >1.3 should trigger further assessment by experts. A recent analysis demonstrated the cost-effectiveness of screening with TE to diagnose high-risk patients with NAFLD $\geq$ F2 (with $\geq$8 kPa cutoff), followed by 1-year of intensive lifestyle interventions (62). A separate study demonstrated that the use FIB-4 and NFS over 1 year increases early detection of advanced liver fibrosis, reduces unnecessary referral of patients with mild disease, and results in cost savings (63).

The expert panel considers patients with values of 8–12 kPa as intermediate risk and those with ≥12 kPa as high risk. For those with a kilopascal in the intermediate range, the panel recommends the patient receive another type of NIT (e.g., serum biomarker). As noted before, if ≥F2 is suspected, the patient can be considered a patient at high risk of NASH and should be referred for further evaluation, including entry into clinical trials and treatment with the US FDA-approved medications when they become available, in addition to weight loss and exercise. Similarly, in patients with LSM ≥12 kPa, a second NIT (such as serum based) can be considered for additional evidence of the degree of fibrosis, and these patients should be recommended for referral to clinical trials or treatment with the future US FDA-approved medications, in addition to weight loss and exercise. Furthermore, these patients might also need to be considered for screening for esophageal varices and hepatocellular carcinoma according to society guidelines.

It is noteworthy that the algorithm allows for liver biopsy under certain circumstances: (i) concern for competing or superimposed diagnoses with NASH such as autoimmune liver disease; (ii) serum biomarkers and imaging biomarkers of advanced fibrosis yield disparate results, or the results are inconclusive after 2 NITs; and (iii) LSM ≥12 kPa in the absence of clinical, laboratory, and radiographic features of advanced liver disease. In addition, there are circumstances where patients or clinicians might want to be absolutely sure about the stage of liver disease. Finally, liver biopsy and histologic documentation of NASH and stage of fibrosis is currently required for entry into phase 3 clinical trials of medications being considered for NASH.

SUMMARY AND CONCLUSIONS

As data accumulate on the growing severity of NAFLD and NASH, the need for prompt identification and assessment of fibrosis, timely specialists' referrals, and effective interventions are apparent (64). The most important step at this time is for clinicians to use NITs through an algorithm to risk stratify and identify patients with NASH who are at highest risk of adverse clinical outcomes. This initial step can occur in the primary care or other specialty practice setting where patients at risk of NASH are seen (endocrinology, cardiology, and gastroenterology) (65,66). Once this group is identified, the next step is to maximize the effort to potentially change the course of liver disease through weight loss and exercise and consideration for clinical trials and potential drugs that could be approved for NASH. Nevertheless, many issues regarding NAFLD and NASH remain to be defined including the role of diet vs many promising therapies currently in development, whether combination therapy will be required, and how patients who are likely to respond to these therapies will be identified. It is our hope that future clinician-led initiatives similar to this one will allow for healthcare professionals to make the best clinical use of the information that we currently have and to provide updates as more information becomes available.

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CONFLICTS OF INTEREST

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Study Highlights

WHAT IS KNOWN

- ✓ The spectrum of NAFLD includes its potentially progressive subtype of NASH.
- ✓ NASH can progress to advanced fibrosis and cirrhosis.
- ✓ The stage of fibrosis in NASH is the most important predictor of liver-related outcomes.
- ✓ NASH and fibrosis must be identified and managed appropriately.
- ✓ Liver biopsy is the gold standard for diagnosing NASH and staging fibrosis.
- ✓ Liver biopsy is invasive and carries risks.
- ✓ Several noninvasive tests are useful for staging NASH; guidance on their use is not clearly delineated.

WHAT IS NEW HERE

- ✓ Straightforward practical diagnosis and staging decision tree/algorithm for gastroenterologists/hepatologists managing NAFLD/NASH.
- ✓ Insight into how this algorithm was developed.
- ✓ Recommendations for its use in clinical practice to risk stratify patients with NAFLD.

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