# Nonalcoholic Fatty Liver Disease: Identification and Management of High-Risk Patients

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**Nonalcoholic fatty liver disease (NAFLD) is an increasingly dominant cause of liver disease worldwide. The progressive subtype, nonalcoholic steatohepatitis, is a leading indication for liver transplantation and a noteworthy cause of hepatocellular carcinoma. The overall prevalence of NAFLD is on the rise, and even more concerning data modeling predicts that an increasing percentage of those with NAFLD will develop advanced disease. This increased volume of patients with advanced liver disease will impose a significant health care burden in terms of resources and cost. Thus, the identification of patients with established fibrosis or at high risk of developing advanced liver disease is critical to effectively intervene and prevent overall and liver-related morbidity and mortality. Herein, we provide a framework to consider for the identification of patients with NAFLD at high risk of nonalcoholic steatohepatitis with advanced fibrosis and provide a critical assessment of currently accessible diagnostic and treatment modalities.**

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## INTRODUCTION

The global burden of nonalcoholic fatty liver disease (NAFLD) is high, with an estimated 1 in 4 adults affected worldwide. The true prevalence of nonalcoholic steatohepatitis (NASH) is difficult to quantify, given the need for invasive testing to make the diagnosis, but currently available data suggest that nearly 1 in 3 patients with NAFLD have NASH (1). Because of the aging population and increasing rates of obesity and diabetes, the prevalence of NAFLD, NASH, and cirrhosis is expected to increase concomitantly. Using a Markov model for prediction, an estimated 33.5% of adults will have NAFLD, 27% of patients with NAFLD will have NASH, and 29% of patients with NASH will have advanced fibrosis by 2030 (2). In other words, approximately 1 in 40 adults will have advanced fibrosis secondary to NASH. Patients with NAFLD currently have a significant impact on health care utilization with an annual economic burden of $292 billion in the United States alone (3).

There is an urgent need to identify patients at high risk of progression or those who have already developed advanced disease from NASH. However, the process of identifying the high-risk patient can be arduous since patients with advanced disease are often asymptomatic and may have normal liver chemistries. An effective and inexpensive noninvasive biomarker does not currently exist, and it would be inappropriate to perform a liver biopsy on all patients as a screening tool for NASH.

## DRIVERS OF DISEASE PROGRESSION

The leading cause of death in patients with NAFLD is cardiovascular disease, followed by malignancy and liver-related disease (4). The increased risk of cardiovascular disease is largely attributed to common comorbidities including diabetes mellitus and hypertension (HTN), and NAFLD behaves in large part as a risk marker (5). However, mounting data suggest that NAFLD may contribute to cardiovascular disease independently because of proatherogenic dyslipidemia, changes in arterial stiffness, myocardial remodeling, and heart failure (6–9).

In addition to the cardiovascular disease burden, patients with NAFLD also have diminished quality of life and increased rates of malignancy and overall mortality (1,10–12). This is likely largely attributable to the subset of patients with NASH and primarily driven by the presence and extent of fibrosis. In fact, patients with NASH and advanced fibrosis have significantly higher rates of liver-related mortality compared with those without fibrosis (13–17). Disease progression in NAFLD is influenced by additional factors including metabolic comorbidities and genetic predisposition.

### Metabolic comorbidities

Metabolic comorbidities in patients with NAFLD are important drivers of cardiovascular events and liver-related and overall mortality (18–20). The metabolic syndrome is characterized by central obesity (waist circumference ≥102 cm in men and ≥88 cm in women), HTN (blood pressure >130/85 mm Hg), elevated fasting glucose level (>110 mg/dL), and dyslipidemia, particularly elevated triglyceride levels (≥150 mg/dL) and reduced HDL levels (<40 mg/dL in men and <50 mg/dL in women) (21–23). The presence of diabetes, HTN, dyslipidemia, and the metabolic syndrome occurs at significantly higher rates in patients with NAFLD (6,24–28). Moreover, the pooled prevalence of these comorbidities is even greater in patients with NASH, both with and without advanced fibrosis (1,29–32). Conversely, patients with features of the metabolic syndrome are at a greater risk of NAFLD including NASH and subsequent advanced fibrosis (18,29,31–38). The association between NAFLD and the metabolic comorbidities seems to be bidirectional, although definitive

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causation has not been proven (39). Furthermore, the presence of metabolic comorbidities alongside NAFLD increases morbidity and mortality risk, particularly cardiovascular events (9,10).

### Role of genetics and ethnicity

Genetic predisposition influences the development of NASH and disease progression as demonstrated by genome-wide association studies in addition to familial aggregation and twin studies (40–42). Large ultrasound (US)-based population studies have identified the highest prevalence of NAFLD in Hispanics, followed by non-Hispanic whites, and lowest prevalence in African Americans (24,43,44). The difference in prevalence rates among ethnic groups may be explained by genetic variants.

Multiple alleles of the patatin-like phospholipase domain-containing 3 gene are associated with NAFLD. More specifically, the I148M allele is associated with increased hepatic fat content and is found more commonly in Hispanics; on the other hand, the S453I allele is associated with decreased hepatic fat content and is found more commonly in African Americans (40). The I148M genetic variant is also associated with a greater risk of steatohepatitis, cirrhosis, and hepatocellular carcinoma (45–47).

Polymorphisms of transmembrane 6 superfamily member 2 are found more commonly in Europeans and have been linked to favorable lipid profiles with an associated protective effect from cardiovascular disease but increased hepatic fat content with a greater risk of NAFLD (48). The significance of this variant, among others, remains unclear because an association with clinically meaningful disease or progression to hard end points has not yet been demonstrated (49,50).

### Alcohol use

Alcohol use is pervasive, and alcohol-related liver disease is an extremely important contributor to morbidity and mortality. Without additional chronic liver diseases present, women and men who consume greater than two or three drinks daily, respectively, or binge drink are at an increased risk of alcohol-related liver disease (51). Further acceleration of liver injury occurs in patients with underlying chronic liver disease, such as hepatitis C and hemochromatosis (51–53). The extent to which mild or moderate alcohol use impacts disease progression in NAFLD is not completely clear, but heavy drinking and binge drinking have been shown to independently accelerate disease progression (54,55). Although many studies have shown that moderate alcohol use favorably impacts cardiovascular risk in the general population, it remains unclear whether this is true in the NAFLD population (56). Moderate alcohol use may be protective in the setting of NAFLD because of improved insulin sensitivity and decreased triglyceride and fasting insulin concentrations seen in this patient population (57), but proving causation or even strong association between any degree of alcohol use and NASH is difficult because of the numerous possibilities of bias and error (58). A recent analysis of modest drinkers from the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) database not on pharmacotherapy and patients on placebo from the Pioglitazone vs Vitamin E vs Placebo for the Treatment of Non-Diabetic Patients with Nonalcoholic Steatohepatitis (PIVENS) and farnesoidXnuclear receptor ligand obeticholic acid for noncirrhotic, non-alcoholic steatohepatitis (FLINT) trials showed less improvement in steatosis or resolution of NASH and no beneficial effects on biochemical or other histologic parameters (59). The role of alcohol in altering the course of disease in NAFLD still requires further clarification. However, it seems wise to recommend minimal alcohol consumption in the setting of NASH until the interaction between alcohol intake and NASH progression is better delineated.

## IMPORTANCE OF DIAGNOSING NASH AND QUANTIFYING FIBROSIS

In addition to the increased risk of cardiovascular disease and malignancy, patients with NASH are at an increased risk of liver disease progression and should be targeted for intervention (36,60). The presence and extent of fibrosis in NASH is the only histologic feature proven to be clearly associated with adverse outcomes (14–17). However, it is important to note the co-linearity between the presence of NASH and increasing degrees of fibrosis makes it very difficult to measure the impact of NASH on outcomes independently. Nonalcoholic steatohepatitis is the engine that drives the development of fibrosis, and its resolution is a key treatment goal, which should secondarily result in fibrosis improvement. Nonetheless, quantifying hepatic fibrosis remains an important factor for patient care and allows more accurate prognostication (16).

### Noninvasive tools for the diagnosis of NAFLD

***Steatosis.*** Ultrasound, controlled attenuation parameter (CAP) with vibration-controlled transient elastography (VCTE), computed tomography (CT), and magnetic resonance imaging (MRI) can be used to measure steatosis. Of these imaging modalities, US is the most readily available and affordable, but does not reliably quantify the degree of steatosis or detect less than 30% steatosis (61). Computed tomography has similar performance characteristics to US with a modest ability to quantify steatosis. Although CAP with VCTE is able to detect the presence of steatosis reliably, MRI-derived proton density fat fraction is superior for quantification of steatosis when compared with histological steatosis grade (62,63) (Table 1) Furthermore, MRI-derived proton density fat fraction is able to detect dynamic changes in response to treatment interventions and correlates with improvement in histologic disease activity. (64–67).

***Steatohepatitis.*** An accurate biomarker for the identification of steatohepatitis remains elusive. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are often used clinically, but they have poor sensitivity and are often normal even in advanced disease (68). The most extensively studied biomarker for NASH is plasma cytokeratin-18 fragment concentration, a marker of hepatocyte caspase-mediated apoptosis (69). However, the routine use of cytokeratin-18 fragment levels has been limited by its poor sensitivity and negative predictive value and failure to show diagnostic superiority compared with aminotransferase levels in its ability to identify NASH or correlate with treatment response (70).

Biomarker panels include proposed markers for NASH and components of the extracellular fibrosis matrix. Early results from lipidomic, metabolomic, and proteomic studies suggest that distinct signatures derived from lipid oxidation, *de novo* lipogenesis, peroxismal dysfunction, and other relevant pathways may identify NAFL and NASH (7,71–73). Emerging technologies such as multiparametric MRI or Liver Multiscan may identify those likely to have NASH with reasonable accuracy, although this requires further study and validation (74). Until validated biomarkers are available, liver biopsy remains necessary to identify patients with NASH across the disease spectrum. Biomarker development is one of the field's highest priorities, and

**Table 1. Performance characteristics for imaging modalities to characterize steatosis in nonalcoholic fatty liver disease**

| Predictive tools | Steatosis assessment | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | AUROC |
|---|---|---|---|---|---|---|
| VCTE CAP (68)[a] | CAP threshold | | | | | |
| | S1 263\|353 (285) | 90\|29 (80) | 35\|90 (77) | 96\|98 (99) | 15\|6 (16) | 0.76 |
| | S2 280\|367 (311) | 90\|20 (77) | 35\|90 (57) | 64\|70 (70) | 72\|46 (66) | 0.70 |
| | S3 274\|380 (306) | 90\|3 (80) | 20\|90 (40) | 29\|10 (32) | 84\|72 (85) | 0.58 |
| MRI-PDFF (63) | PDFF threshold | | | | | |
| | S1 5.2 | 90.0 | 93.3 | 89.2 | 51.9 | 0.96 |
| | S2 11.3 | 78.9 | 84.1 | 84.5 | 78.4 | 0.90 |
| | S3 17.1 | 73.7 | 81.0 | 63.2 | 95.3 | 0.79 |

AUROC, area under the receiver operating characteristic curve; CAP, controlled attenuation parameter; MRE, magnetic resonance elastography; NPV, negative predictive value; PDFF, proton density fat fraction; PPV, positive predictive value; VCTE, vibration-controlled transient elastography.
[a]Values for the VCTE study shown are "fixed 90% sensitivity"|"fixed 90% specificity" ("optimized sensitivity and specificity").

several promising platforms are likely to begin filling this gap in the near future.

***Fibrosis.*** *Serum-based methods.* Many noninvasive scoring systems to estimate fibrosis in patients with NAFLD have been developed based on routine clinical and laboratory values or direct markers of inflammation and fibrogenesis (Table 2). Of these clinical prediction models (CPMs), the FIB-4 and NAFLD fibrosis scores (NFS) are the best validated in NAFLD (75–78). The enhanced liver fibrosis (ELF) panel is a well-studied proprietary test in NAFLD using three markers of matrix turnover (79, 80). Although these CPMs and serum-based markers are reasonably accurate to identify those with significant fibrosis, their greatest strength and clinical utility is the ability to exclude advanced fibrosis. Importantly, the NFS, FIB-4 score, and ELF panel have reasonable predictive ability to identify patients at greatest risk of liver-related events and overall mortality (81–83). However, many patients fall into the intermediate range, which has lesser correlation with intermediate stages of fibrosis histologically.

A peptide released during type III collagen maturation, N-terminal type III collagen propeptide (pro-C3), is emerging as a biomarker that may differentiate between simple steatosis, steatohepatitis, and advanced fibrosis (84). Combining FIB-4 with pro-C3 has enhanced diagnostic accuracy compared with either test alone in a UK biobank cohort (85). The extent to which any of these noninvasive markers of fibrosis can distinguish necroinflammation from fibrosis remains unclear and thus are best considered to be reflective of the overall fibroinflammatory process (86).

**Table 2. Performance characteristics of noninvasive serum markers to characterize stiffness in NAFLD**

| Predictive tools | Cutoff | Sensitivity (%) | Specificity (%) | NPV (%) | PPV (%) |
|---|---|---|---|---|---|
| Clinical prediction models | | | | | |
| FIB-4 score (84): Age, ALT, AST, and platelets | Low < 1.3<br>High > 2.67 | 74<br>34 | 71<br>98 | 73<br>59 | 72<br>93 |
| NAFLD fibrosis score (85): Age, BMI, platelets, albumin, AST, ALT, and IFG/diabetes | Low < −1.455<br>High > 0.676 | 77<br>43 | 71<br>96 | 88<br>80 | 52<br>82 |
| BARD (86): BMI, AST, ALT, and diabetes | 2 | | | 96 | 43 |
| BAAT (34): Age, BMI, ALT, and triglycerides | 2 | 71 | 80 | 86 | 61 |
| Serum-based proprietary tests | | | | | |
| Enhanced liver fibrosis (ELF) panel (80)[a]: P3NP, hyaluronate, and TIMP-1 | Low −1.03\|0.21<br>High −0.11\|0.36 | 90\|45<br>90\|75 | 45\|90<br>80\|90 | 66\|53<br>96\|94 | 64\|86<br>52\|71 |
| NASH FibroTest/FibroSURE (87): Alpha-2 macroglobulin, apolipoprotein A1, haptoglobin, bilirubin, and GGT | 0.30<br>0.70 | 92<br>25 | 71<br>97 | 98<br>89 | 33<br>60 |
| Fibrometer (88): Age, weight, glucose, AST, ALT, platelets, and ferritin | 0.49 | 78.5 | 95.9 | 87.9 | 92.1 |

Calculators are available online for the NFS (http://gihep.com/calculators/hepatology/nafld-fibrosis-score) and FIB-4 score (http://gihep.com/calculators/hepatology/fibrosis-4-score).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; IFG, impaired fasting glucose; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score; NPV, negative predictive value; PPV, positive predictive value.
[a]Values for ELF shown are "fixed 90% sensitivity"|"fixed 90% specificity" ("optimized sensitivity and specificity").

*Imaging methods.* Standard imaging with US, CT, or MRI may identify advanced cirrhosis based on liver nodularity or signs of portal hypertension, including ascites, intra-abdominal varices, or portosystemic shunts. However, early cirrhosis and lesser degrees of fibrosis cannot be accurately detected or quantified with standard imaging. Elastographic modalities measure liver stiffness as a surrogate for fibrosis and have become invaluable tools in the identification of patients with advanced disease. Table 3 provides the performance characteristics at various cutoffs for elastographic assessment in the setting of NAFLD.

Vibration-controlled transient elastography is a US-based tool originally developed to assess the ripeness of cheese that is currently used extensively to measure liver stiffness. Most of the available data were obtained from studies on viral hepatitis, and the majority of the VCTE data in NAFLD are from non-US cohorts, which is important to note because cutoff values differ across populations (87–91). A recent study from the NASH CRN used a VCTE cutoff >5.6 kPa to identify patients with stage 2–4 fibrosis with 90% sensitivity and exclude stage 0 or 1 fibrosis with a negative predictive value of 0.81; meanwhile, VCTE cutoff >12.1 kPa identified cirrhosis with 90% sensitivity and stage 3 or 4 fibrosis with a positive predictive value of 0.71 (90). Although these cutoffs require further validation, they may be used to guide clinicians in determining patients who can be monitored without further intervention and patients who need close monitoring for complications of advanced liver disease such as hepatocellular carcinoma (HCC) screening.

Vibration-controlled transient elastography has several limitations worth noting. Obesity can affect the accuracy of liver stiffness measurements; thus, it is important to use the extra large (XL) probe in patients with a body mass index greater than 30 kg/m$^2$ (91,92). Some studies have not used the XL probe when appropriate, which potentially alters the validity of their findings in obese patients. Because VCTE measures liver stiffness, not fibrosis directly, it can be elevated in postprandial state, hepatic congestion, cholestasis, or inflammation (93–95). In a European cohort, supersonic shear imaging and acoustic radiation force impulse imaging performed similarly to VCTE for diagnosing stage of fibrosis (96).

Magnetic resonance elastography (MRE) evaluates the entire liver and thus circumvents the problem of heterogeneity of steatosis, inflammation, and fibrosis throughout the liver. Of all

**Table 3. Performance characteristics for imaging modalities to characterize stiffness in nonalcoholic fatty liver disease**

| Predictive tools | Stiffness | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | AUROC |
|---|---|---|---|---|---|---|
| VCTE LSM (87),[a] | kPa cutoff | | | | | |
| | F1 4.9\|9.4 (8.6) | 90\|46 (53) | 31\|90 (87) | 80\|93 (93) | 48\|34 (37) | 0.74 |
| | F2 5.6\|11.9 (8.6) | 90\|40 (66) | 44\|90 (80) | 62\|80 (78) | 81\|59 (70) | 0.79 |
| | F3 6.5\|12.1 (8.6) | 90\|52 (80) | 47\|90 (74) | 45\|71 (59) | 91\|80 (89) | 0.83 |
| | F4 12.1\|14.9 (13.1) | 90\|69 (69) | 82\|90 (86) | 34\|41 (39) | 99\|97 (99) | 0.93 |
| US ARFI (88) | m/s cutoff | | | | | |
| | F2 1.32–1.34 | 56–82 | 78–91 | 57 | 92 | 0.77–0.85 |
| | F3 1.19–1.77 | 59–100 | 74–91 | 43–71 | 99–100 | 0.84–0.97 |
| | F4 1.9–2.48 | 44–100 | 90–96 | 47–75 | 98–100 | 0.84–0.98 |
| MRE (2D 60Hz) (62, 63, 89–91) | kPa cutoff | | | | | |
| | F1 2.5–3.02 | 55.4–76.5 | 77–90.7 | 81.3–99 | 61.5–86.2 | 0.8–0.86 |
| | F2 2.86–3.4 | 79.3–87.3 | 81.8–85 | 65.7–88.4 | 83.6–89.8 | 0.78–0.89 |
| | F3 2.99–4.8 | 74.5–77.8 | 80.3–86.9 | 48.3–74.5 | 81–93.8 | 0.87–0.89 |
| | F4 3.35–6.7 | 75–90.9 | 81.4–94.5 | 27.3–58.8 | 97.2–99.2 | 0.87–0.97 |
| MRE (3D 40 Hz) (92) | kPa cutoff | | | | | |
| | F1 1.77 | | | | | 0.85 |
| | F2 2.38 | | | | | 0.86 |
| | F3 2.43 | 92.3 | 93.7 | 70.6 | 98.7 | 0.98 |
| | F4 3.21 | | | | | 0.99 |
| SSI (88, 93) | kPa cutoff | | | | | |
| | F2 6.3–8.7 | 71–90 | 50–90 | 64.2 | 70 | 0.86 |
| | F3 8.3–10.7 | 71–91 | 61.2–90 | 48.6 | 93.8 | 0.89 |
| | F4 10.5–15.1 | 58–90 | 72–90 | 40.9 | 97.9 | 0.88 |

AUROC, area under the receiver operating characteristic curve; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; NPV, negative predictive value; PPV, positive predictive value; SSI, supersonic shear imaging; US ARFI, ultrasound acoustic radiation force impulse; VCTE, vibration-controlled transient elastography.
[a]Values for VCTE shown are "fixed 90% sensitivity" | "fixed 90% specificity" ("optimized sensitivity and specificity").

the available methods to measure liver stiffness, MRE is currently the most accurate imaging modality for detection of fibrosis in patients with NAFLD, particularly in the setting of obesity (62,97). Moreover, MRE is superior to VCTE for determining the degree of liver fibrosis when compared with histological stage (62,63,98). Magnetic resonance elastography should be considered the reference standard in clinical trials, but high cost and lack of availability at point of care make it less practical for routine clinical use.

### Risk-stratifying patients: who needs a liver biopsy?

Although liver biopsy is considered the reference standard for diagnosing NASH, it does have limitations. Interobserver and intraobserver variability has been shown with moderate concordance in the assessment of hepatocyte ballooning, lobular inflammation, and NAFLD activity score (99,100). Sampling variability is well described and not surprising, considering that the average liver biopsy provides a sample that is 1/50,000th of the liver (101). These limitations are minimized by using a 16-gauge cutting needle to obtain a core biopsy at least 2-3 cm in length (102). The increasing use of smaller 18- or 19-gauge needles, particularly with specimens obtained *via* transjugular and transgastric routes, provides smaller and fragmented specimens with lower rates of diagnosis in patients with diffuse parenchymal disease like NAFLD but no difference in complication rates (103–106). Obtaining adequate specimens is essential for histopathologic disease classification and potential enrollment in clinical trials (107,108).

Liver biopsy is still essential because current serum- and imaging-based modalities only identify patients with either minimal or advanced disease but are unable to reliably diagnose steatohepatitis or provide more granular detail at intermediate stages of fibrosis (Tables 2 and 3). This is an important unmet need because patients with NASH and established fibrosis often have no signs or symptoms of advanced disease until they have progressed to cirrhosis or develop complications including hepatocellular carcinoma (109,110). Figure 1 provides an algorithm to prioritize patients needing a liver biopsy based on the likelihood of more advanced disease.

The first step in the assessment of patients with NAFLD is determining the likelihood of NASH because most patients with non-NASH NAFLD will not have increased liver-related events. Although causality is difficult to prove, there is a clear association between patients with metabolic comorbidities (i.e., obesity, diabetes, dyslipidemia, and HTN) and development of NASH with advanced fibrosis (1,29–33,35,37,38). Similarly, genetic variations also increase susceptibility (41,42,45–47,49,50). Because genetic testing is not routinely performed in the clinical setting, the presence of family members with NAFLD should be considered an additional risk factor. Advancing age has been associated with increasing presence of NASH and advanced fibrosis (30,73,111–114). Although patients with NASH may have normal aminotransferase levels and patients without NASH may have abnormal aminotransferase levels, persistent elevation in aminotransferase levels is associated with disease progression. In the absence of a validated clinical prediction tool, the likelihood of NASH is determined by the presence of these risk factors, although the number of risk factors needed to be classified as high risk is unclear at this time. Previous work suggests that the presence of metabolic features, particularly diabetes and HTN, has the greatest impact and biologically plausible connection with the pathophysiology of NASH (6,115).

The NAFLD fibrosis (age, body mass index, AST, ALT, platelets, albumin, and presence of impaired fasting glucose or diabetes) and FIB-4 (age, AST, ALT, and platelets) scores are calculated with readily available parameters and may predict the likelihood of fibrosis (112,116). These CPMs have the most utility in excluding advanced fibrosis, given their excellent negative predictive values (75). Of note, the ELF panel performs similarly well but requires serum-based testing that is not routinely available (80). Patients with NFS $< -1.455$ or FIB-4 $<1.3$ along with normal liver stiffness values have low likelihood of advanced disease, and these patients may be monitored without further invasive testing.

On the other end of the spectrum, there are laboratory parameters and radiologic findings that are highly suggestive of advanced fibrosis, and these patients can be managed as cirrhosis without a diagnostic liver biopsy. In patients with NASH, an AST to ALT ratio greater than 0.8 to 1 is a strong predictor of advanced fibrosis (113,117). This alteration of the AST:ALT ratio is believed to result from decreased ALT production and AST clearance by the impaired liver and is often the first sign of advanced liver disease (118). Thrombocytopenia occurs because of splenic sequestration in the setting of portal HTN, decreased thrombopoietin production by the liver, or myelosuppression, and it is the first hematological abnormality to occur as liver disease progress (119). International normalized ratio or prothrombin time increase with worsening liver function because of decreased synthesis of coagulation factors, vitamin K deficiency, and reduced clearance of fibrinolytic factors. Radiologic features suggestive of cirrhosis, other than a nodular-appearing liver, are a manifestation of portal HTN that develops as liver disease progresses. These signs may include splenomegaly, ascites, intra-abdominal varices, and portosystemic shunts.

Patients with NAFLD in the intermediate-risk category who cannot be ruled out definitively as minimal fibrosis or cirrhosis based on available laboratory or radiologic findings require further investigation. Normal liver stiffness measurements have excellent ability to rule out advanced fibrosis. Patients with normal levels are unlikely to have clinically significant NASH, and these patients may be monitored without further invasive testing. However, patients with abnormal liver stiffness or discordant liver stiffness results compared with CPMs require a liver biopsy for further assessment and prognostication. It is important to identify patients at risk. Among patients with NAFLD, only those with NASH have demonstrably inferior outcomes, and this becomes accentuated at higher fibrosis stages (13–17). The necroinflammatory activity in NASH is the driving force of fibrogenesis and progression to cirrhosis (120). The average fibrosis progression rate of patients with NASH is 1 stage every 7 years compared with 1 stage every 14 years in those with NAFL (32). However, approximately 20% of patients are "fast progressors," and *a priori* identification of such patients is not currently possible, although techniques that estimate collagen turnover may further elucidate this in the future (121).

### Practical approach to therapy in patients with NASH with or without fibrosis

Appropriate management of NASH includes consideration of both hepatic and nonhepatic morbidity and mortality. A notable increase in adverse liver-related events is observed in patients with greater than stage 2 fibrosis (14–17). Although NASH does not seem to have additive impact in dual biopsy cohort studies, its colinearity with fibrosis makes it difficult to

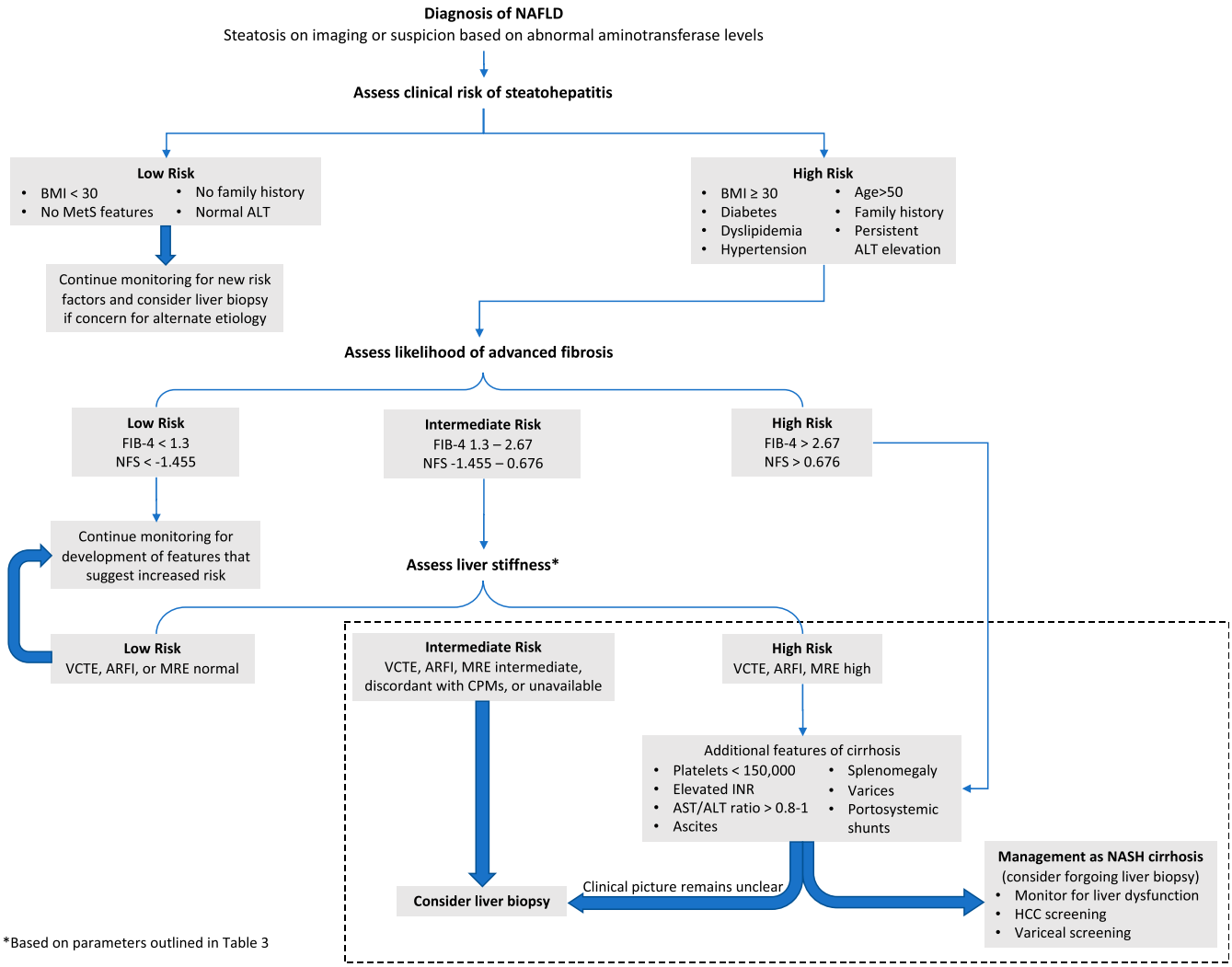


**Figure 1.** Algorithm for risk stratification of NAFLD. Liver biopsy is not needed for all patients with NAFLD. Initial characterization of liver related risk can be performed though a combination of clinical prediction rules and non-invasive measures of liver stiffness. Identifying those who may have NASH and/or fibrosis is important due to the increased risk for poor liver related outcomes. Clinical prediction models such as the FIB-4 and NFS can assist in the initial evaluation of patients with NAFLD as the calculations use readily available variables. Liver stiffness measurement is warranted in those falling into the intermediate or high risk group and this can further assist in the identification of patients who may have more advanced disease or select those who should be considered for liver biopsy. NFS: NAFLD fibrosis score; FIB-4: fibrosis-4 index; VCTE: vibration controlled transient elastography; MRE: magnetic resonance elastography; BMI: body mass index; MetS: Metabolic syndrome.

assess independently (17). Therefore, although we anticipate that treatment interventions that improve fibrosis will have a positive impact on hepatic outcomes, it seems a reasonable assumption that resolution of NASH will have a similar favorable outcome because it drives the development of fibrosis and disease progression.

### Impact of lifestyle intervention on liver histology

Lifestyle modifications incorporating dietary change, exercise, and weight loss remain the cornerstone of NAFLD treatment. Slow and controlled weight loss can improve or resolve NASH and fibrosis to some extent (122). As little as 5% weight loss results in reduction of steatosis, whereas greater than 10% weight loss is needed to ameliorate portal inflammation and fibrosis (122,123). Independent of its histological benefits, weight loss also positively impacts metabolic comorbidities that are significant drivers of morbidity and mortality in this population (124). Although regular moderate to intense endurance exercise may decrease hepatic triglyceride content, it has limited effects on liver histology without concomitant weight loss (125). Furthermore, there is currently no randomized controlled trial (RCT) with long-term follow-up to determine whether histological improvement is sustained in patients with NASH who maintain the weight loss achieved with lifestyle interventions alone.

Lifestyle changes are difficult to achieve independently even with standard in-office counseling, and many patients require behavioral therapy alongside physical activity and dietary counseling (126). Patients who receive intense lifestyle intervention with weekly to biweekly small group sessions for nutrition counseling, physical activity, and behavior modification training achieve a significantly greater weight loss (127). Such resources

**Table 4. Rationale for the use of variables in the current algorithm described in Figure 1**

| | |
|---|---|
| Clinical features | |
| Metabolic syndrome, obesity, diabetes, dyslipidemia, HTN, age, family history of cirrhosis, or diabetes | Known risk factors for the presence of NASH and association with the development of advanced fibrosis |
| Laboratory values | |
| AST:ALT ratio, thrombocytopenia, and coagulopathy | Laboratory findings suggestive of advanced fibrosis and/or portal HTN |
| Radiologic features | |
| Splenomegaly, ascites, varices, and portosystemic shunts | Features associated with advanced fibrosis due to sequelae of portal HTN |
| Serum-based fibrosis scores | |
| FIB-4 and NFS | Composite scores using factors that correlate with advanced liver disease. They are most useful in their negative predictive value |
| Liver stiffness measurements | |
| VCTE, ARFI, and MRE | Fibrosis is an important contributor to liver stiffness. In the appropriate setting, such tests have good positive predictive value to detect advanced fibrosis, but have superior negative predictive value |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ARFI, acoustic radiation force impulse; HTN, hypertension; MRE, magnetic resonance elastography; NASH, nonalcoholic steatohepatitis; NFS, nonalcoholic fatty liver disease fibrosis score; VCTE, vibration-controlled transient elastography.

are not uniformly available, and weight loss can be difficult to maintain over time for the majority of patients even with support. Nonetheless, the importance of these changes must be emphasized, particularly in patients who additionally require weight loss to qualify for liver transplantation if their liver disease continues to progress.

***Dietary macronutrient content.*** Recommendations on the most effective diet are limited because of the paucity of controlled and long-term studies. Weight loss can be achieved with any calorie-restricted diet regardless of macronutrient composition. Low-carbohydrate diets have a greater effect on fasting glucose, whereas low-fat diets have a greater effect on low-density lipoprotein (123). The Mediterranean style diet is low in saturated fat and high in monounsaturated fat and dietary fiber with beneficial effects on dyslipidemia, diabetes, HTN, obesity, and cardiovascular disease (128,129). Even without exercise or significant weight loss, patients on a Mediterranean diet without total caloric restriction had decreased steatosis and improved insulin sensitivity (130,131). A recent study has shown that adherence to specific diets, such as the Mediterranean diet, decreases the risk of NAFLD even in those who are genetically predisposed (132). Regular coffee consumption, another practical recommendation if there are no contraindications, is associated with a reduced incidence of NAFLD, associated fibrosis, hepatocellular carcinoma, and improved overall, liver-related, and cardiovascular-related mortality (133–136).

### Identify and optimize comorbid disease

Nonalcoholic fatty liver disease is strongly associated with multiple diseases, including diabetes, dyslipidemia, HTN, obesity, renal disease, and obstructive sleep apnea, that increase the potential for cardiovascular disease (18–20). Identification of these comorbidities with a focus on cardiovascular risk reduction is imperative. Patients with NAFLD are insulin resistant and often have atherogenic lipid profiles characterized by elevated triglyceride levels, decreased high-density lipoprotein levels, and increased apolipoprotein B to apolipoprotein A1 ratio (137). Other than obesity in some cases, treatment of these comorbid diseases may not be sufficient to reverse NASH but may still have a favorable reduction on cardiovascular disease, the primary cause of death in patients with NAFLD.

Although there is insufficient evidence that statins improve NASH, they have clear cardiovascular benefit and should be used if indicated for treatment of dyslipidemia. In the *post hoc* analysis of the Greek Atorvastatin and Coronary-heart-disease Evaluation study, patients treated with statins had significant reduction of cardiovascular events alongside improvement in aminotransferases (138). A large systematic review and meta-analysis has shown lower mortality risk and rates of hepatic decompensation with statin therapy (139). In fact, statins may reduce portal HTN by enhancing nitric oxide production, thereby decreasing hepatic resistance (140). However, despite ample evidence that statins are safe in the setting of liver disease, including cirrhosis, the medical community remains reluctant to use statins in this setting. The extent of statin underutilization is significant, with a recent study showing that patients with NAFLD and concomitant dyslipidemia were 55% less likely than those without NAFLD to receive appropriate statin care (141).

### Currently available drugs that may improve NASH

The field is still a few years away from an FDA-approved drug for NASH. However, several currently available drugs studied in phase 2 trials have shown efficacy and could be considered in patients with biopsy confirmed NASH (Table 5). Vitamin E and pioglitazone, a peroxisome proliferator-activated receptor gamma agonist, are the best studied and compared with placebo in the PIVENS trial (142). Only vitamin E met the primary end point in the trial, but the results may have been skewed by a disproportionate allocation of patients to the pioglitazone arm who were later found on central review to have misclassification of ballooning presence at enrollment (143). The most appropriate and clinically significant primary outcome in clinical trials for NASH treatment remains to be determined (144). For instance, if the primary outcome in the PIVENS trial had been the absence of definite NASH on histology, pioglitazone does show a significant benefit over vitamin E (143). Additional studies have subsequently demonstrated that pioglitazone improves NASH in both patients with and without diabetes (145–147). Although effective at improving NASH, enthusiasm for its use is dampened by undesirable side effects including weight gain, decreased bone density, and cardiac dysfunction (142,145,148,149).

Vitamin E improves steatosis and NASH in patients without diabetes but should be avoided in those with cirrhosis, given the potential for increased bleeding risk. Safety concerns regarding the use of vitamin E include a possible increased risk of prostate cancer, hemorrhagic stroke, and all-cause mortality, although these concerns have later been challenged (150–156). Both vitamin E and pioglitazone improved inflammatory features of

**Table 5. Results of currently available pharmacotherapies from phase 2 trials**

| Drug | Mechanism | Histology | | | | | |
|---|---|---|---|---|---|---|---|
| | | Steatosis | Ballooning | Inflammation | NAS | NASH resolution | Fibrosis |
| Pioglitazone (142) | PPAR-γ agonist | ⇓ | ⇓ | ⇓ | ⇓ | + | – |
| Liraglutide (158) | GLP-1 agonist | ⇓ | ⇓ | – | – | + | – |
| Vitamin E (142) | Antioxidant | ⇓ | ⇓ | ⇓ | ⇓ | – | – |
| Pentoxifylline (159,160) | TNF-α inhibitor | ⇓ | ⇓/– | ⇓/– | ⇓/– | – | ⇓/– |

⇓Indicates a statistically significant decrease compared with placebo.
–Indicates no statistically significant difference compared with placebo.
+Sign for NASH resolution indicates a statistically significant improvement compared with placebo, although NASH resolution has been variably defined in the trials mentioned earlier.
NASH, nonalcoholic steatohepatitis.

NASH, but neither significantly reduced fibrosis in the PIVENS trial. A smaller study using a higher dose of pioglitazone demonstrated a difference in the mean change of fibrosis stage compared with placebo but only a trend for improvement in one or more fibrosis stages compared with placebo. Mean changes in fibrosis are less impactful because changes, particularly small ones, are dynamic, and the placebo response for improvement in one or more fibrosis stages ranges from 14% to 31% in published phase 2 trials (142,157,158).

Other available drugs studied in similar context include pentoxifylline and liraglutide, which were both evaluated in the context of small RCTs (158–161). Their true impact requires further validation, but use could be considered in the appropriate clinical context. The role of available compounds in the treatment of NASH was recently reviewed in the updated NAFLD guidance document (162).

### Drugs in development

The landscape of NASH therapeutic agents in development has been reviewed recently (39,163). Multiple phase 2 trials have demonstrated modest benefit in achieving NASH resolution or reducing NASH disease activity (67,157,164,165). Primary end points previously focused on improvement in the NAFLD activity score (NAS), but the field has moved to a more definitive end point of NASH resolution (whose definition has also evolved) and/or improvement in fibrosis. Although statistically favorable effects on fibrosis would potentially have an impact on liver-related outcomes, the results of current trials have not been overwhelming thus far (157). Muted response rates may be attributed to the significant impact of environmental and lifestyle factors on treatment and placebo arms as well as significant disease heterogeneity among those with histologically defined NASH, a complex and diverse pathophysiology.

## SUMMARY

Identification of patients with NAFLD at highest risk of progression is critical to provide early intervention and ideally prevent liver-related complications. Currently, the most critical need is a reliable, inexpensive, and widely accessible biomarker to identify NASH, risk stratify patients, and assess response to treatment. Although all patients with NAFLD benefit from lifestyle modifications including diet and exercise, currently only those with biopsy-proven NASH or evidence of associated fibrosis should be considered for pharmacotherapy. This is an exciting era for the field of NASH with extraordinary activity, rapidly evolving diagnostic technologies, and promising drugs in development that we hope have a positive impact on the millions affected with NASH in the near future.

## CONFLICTS OF INTEREST

**Guarantor of the article:** Mary E. Rinella, MD.
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