Review

Nonalcoholic Fatty Liver Disease
A Systematic Review

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IMPORTANCE Nonalcoholic fatty liver disease and its subtype nonalcoholic steatohepatitis affect approximately 30% and 5%, respectively, of the US population. In patients with nonalcoholic steatohepatitis, half of deaths are due to cardiovascular disease and malignancy, yet awareness of this remains low. Cirrhosis, the third leading cause of death in patients with nonalcoholic fatty liver disease, is predicted to become the most common indication for liver transplantation.

OBJECTIVES To illustrate how to identify patients with nonalcoholic fatty liver disease at greatest risk of nonalcoholic steatohepatitis and cirrhosis; to discuss the role and limitations of current diagnostics and liver biopsy to diagnose nonalcoholic steatohepatitis; and to provide an outline for the management of patients across the spectrum of nonalcoholic fatty liver disease.

EVIDENCE REVIEW PubMed was queried for published articles through February 28, 2015, using the search terms *NAFLD and cirrhosis, mortality, biomarkers,* and *treatment*. A total of 88 references were selected, including 16 randomized clinical trials, 44 cohort or case-control studies, 6 population-based studies, and 7 meta-analyses.

FINDINGS Sixty-six percent of patients older than 50 years with diabetes or obesity are thought to have nonalcoholic steatohepatitis with advanced fibrosis. Even though the ability to identify the nonalcoholic steatohepatitis subtype within those with nonalcoholic fatty liver disease still requires liver biopsy, biomarkers to detect advanced fibrosis are increasingly reliable. Lifestyle modification is the foundation of treatment for patients with nonalcoholic steatosis. Available treatments with proven benefit include vitamin E, pioglitazone, and obeticholic acid; however, the effect size is modest (<50%) and none is approved by the US Food and Drug Administration. The association between nonalcoholic steatohepatitis and cardiovascular disease is clear, though causality remains to be proven in well-controlled prospective studies. The incidence of nonalcoholic fatty liver disease–related hepatocellular carcinoma is increasing and up to 50% of cases may occur in the absence of cirrhosis.

CONCLUSIONS AND RELEVANCE Between 75 million and 100 million individuals in the United States are estimated to have nonalcoholic fatty liver disease and its potential morbidity extends beyond the liver. It is important that primary care physicians, endocrinologists, and other specialists be aware of the scope and long-term effects of the disease. Early identification of patients with nonalcoholic steatohepatitis may help improve patient outcomes through treatment intervention, including transplantation for those with decompensated cirrhosis.

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Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease worldwide with prevalence estimates ranging from 25% to 45% in most studies, increasing in parallel with that of obesity and diabetes.[1,2] Most current estimates suggest that 68% of US adults are overweight or obese; given this estimated prevalence, between 75 million and 100 million individuals in the United States likely have NAFLD.[3] Because of the burden of disease, it is important to identify which patients are most likely to have increased morbidity and mortality related to NAFLD. It is neither practical nor feasible to perform liver biopsies on such a large number of patients.

Nonalcoholic fatty liver disease was first described in 1980 and is divided into the histological categories of (1) nonalcoholic fatty liver, which includes patients with isolated hepatic steatosis and patients with steatosis and mild nonspecific inflammation, and (2) nonalcoholic steatohepatitis, which is distinguished from the former by the additional presence of features of hepatocellular injury with or without fibrosis[4,5] (**Figure 1**). Nonalcoholic steatohepatitis is considered to be the progressive subtype of NAFLD; however, data suggest that hepatic steatosis with inflammation has a distinct and more progressive natural history than isolated hepatic steatosis.[5-7]

The presence of hepatic fibrosis is the most important determinant of outcome and, using the Metavir scoring system, it ranges from absent (stage 0) to cirrhosis (stage 4). Because most patients who progress to advanced stages of fibrosis originally had nonalcoholic steatohepatitis, hepatic morbidity is largely attributable to those with this subtype who have an estimated risk of progression to cirrhosis of approximately 20%.[8] In contrast, nonalcoholic fatty liver is believed to have a much more benign course with an estimated risk of progression to cirrhosis of less than 4% with the caveat that a less well-defined subgroup of patients within the diagnosis of nonalcoholic fatty liver (ie, those with inflammation who do not meet histological criteria for nonalcoholic steatohepatitis) may be at increased risk.[6-8]

Clinical risk factors, such as the presence of the metabolic syndrome and its features, as well as emerging biomarkers can help select patients for liver biopsy and identify those at highest risk of nonalcoholic steatohepatitis and advanced liver disease. Patients with NAFLD overall, and those with nonalcoholic steatohepatitis in particular, are at increased risk of mortality from liver disease (13%), and more commonly from cardiovascular disease (25%) and malignancy (28%).[9]

At a Glance

- Current estimates suggest that nonalcoholic fatty liver disease (NAFLD) and its progressive subtype nonalcoholic steatohepatitis affect 30% and 5%, respectively, of the current US population.
- The most common causes of death in patients with nonalcoholic steatohepatitis are cardiovascular disease and malignancy and it is the most rapidly increasing indication for liver transplantation.
- Lifestyle intervention with weight loss is important for all patients with NAFLD. Existing treatments should be reserved for those with biopsy-proven nonalcoholic steatohepatitis.

Literature Search

A literature review was conducted in PubMed to identify relevant articles published through February 28, 2015. The search terms *NAFLD and cirrhosis, mortality, biomarkers,* and *treatment* were used to identify articles for consideration and were divided into those identified, the number of published clinical trials, and the number referenced. For *NAFLD and cirrhosis*, there were 3396 identified, 163 clinical trials reviewed, and 31 referenced; *mortality*, 537 identified, 163 clinical trials reviewed, and 11 referenced; *biomarkers*, 1117 identified, 73 clinical trials reviewed, and 28 referenced; and *treatment*, 3107 identified, 223 clinical trials reviewed, and 37 referenced.

Priority was given to well-powered randomized clinical trials, prospective cohort studies, and longitudinal observational studies. Articles were excluded if similar findings were illustrated by other larger studies or those that were better controlled. Retrospective or smaller studies were excluded if controlled prospective data were available. Overall, 16 randomized clinical trials, 44 cohort or case-control studies, 6 population-based studies, 7 meta-analyses, 2 practice guidelines, and 23 classified as other were used for this analysis (additional details appear in the Supplement).

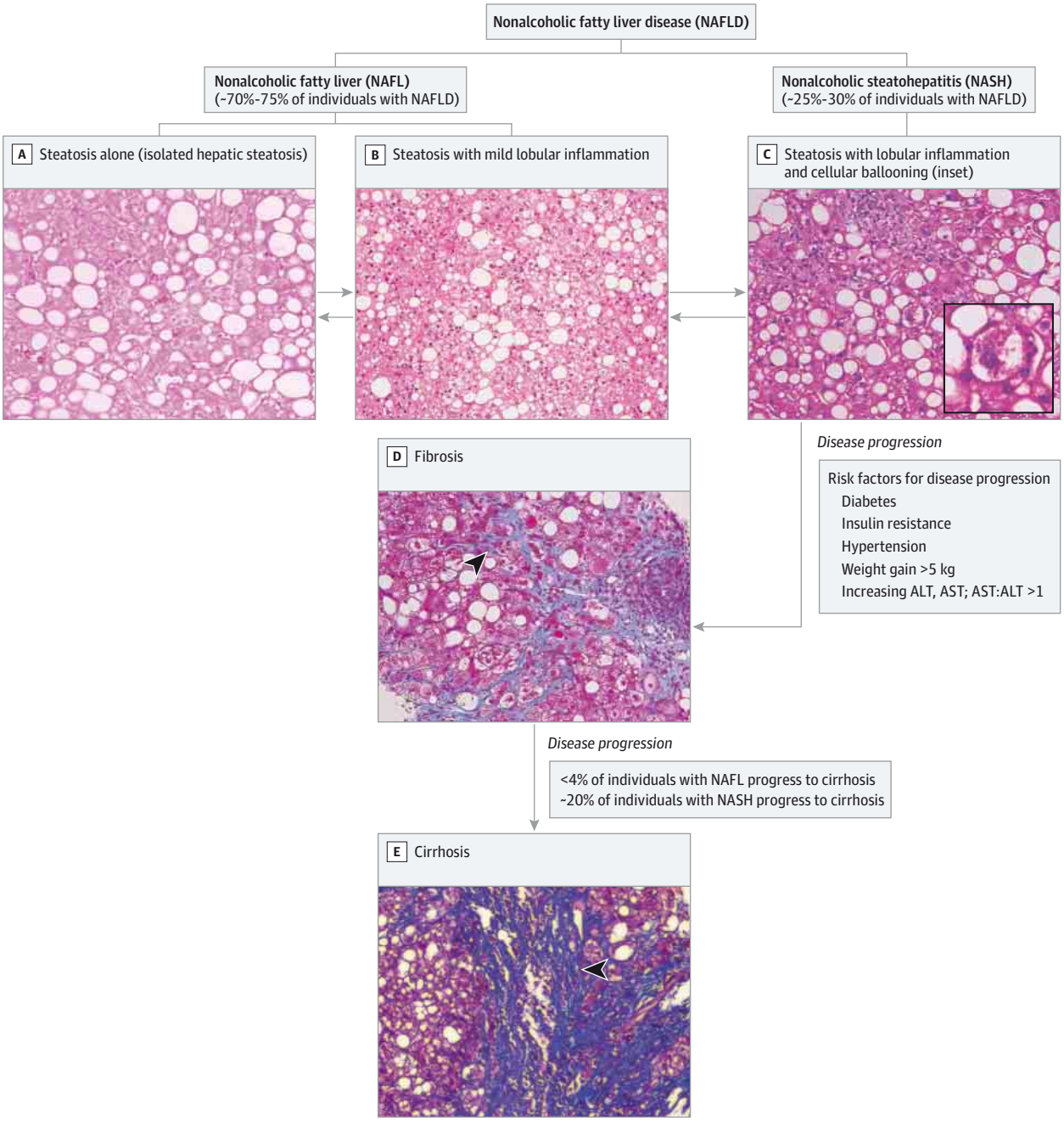
Pathophysiology of Nonalcoholic Steatohepatitis

Nonalcoholic steatohepatitis is a complex disease that is modulated by numerous mechanisms including metabolic, genetic, environmental, and gut microbial factors.[10] Although the presence of steatosis is requisite for nonalcoholic steatohepatitis, the specific mechanisms that lead one patient to develop nonalcoholic steatohepatitis and another to only have isolated steatosis are not well delineated. Visceral adipose tissue generates multiple signals that alter lipid and glucose metabolism, which lead to hepatic fat accumulation, and creates a proinflammatory milieu that triggers cellular injury in the liver and other tissues. The inability to quell injurious processes, such as oxidative stress, dysregulation of the unfolded protein response (leading to endoplasmic reticulum stress), lipotoxicity, and apoptotic pathways, contribute to liver damage, progressive fibrosis that can lead to cirrhosis, and the development of hepatocellular cancer in some patients (**Figure 2**).

Assessment, Diagnosis, and Identification of Patients With Advanced Disease

Nonalcoholic fatty liver disease is the most prevalent form of liver disease in the United States and is the most common cause of elevated liver chemistry test results. The majority of individuals are asymptomatic or have nonspecific symptoms such as fatigue; however, some report pain in the right upper quadrant. Therefore, the diagnosis of NAFLD is often made incidentally on imaging when a patient undergoes testing for an unrelated symptom or condition. There are no characteristic physical examination findings, but central obesity and hepatomegaly are common. Acanthosis nigricans correlates with insulin resistance, which is more pronounced with more advanced disease, and the presence of a dorsocervical hump

Figure 1. Histological Subtypes of NAFLD and Their Implications for Disease Progression

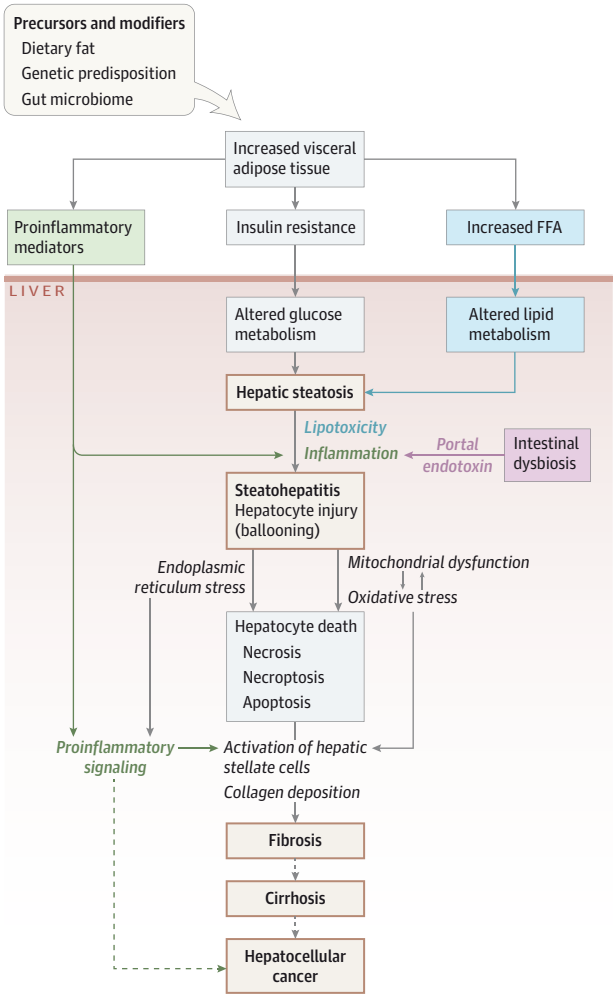


Nonalcoholic fatty liver disease is broadly divided into those with NAFL (isolated steatosis with or without nonspecific inflammation) and NASH, with varying degrees of hepatic fibrosis. A, Isolated steatosis characterized by macrovesicular fatty change in the absence of cellular injury (ballooning) (hematoxylin-eosin, original magnification × 10). B, Steatosis with nonspecific inflammation (hematoxylin-eosin, original magnification × 20). C, NASH characterized by the additional presence of cellular ballooning (inset) (hematoxylin-eosin, original magnification × 20). D, NASH with early fibrosis in a typical pericellular pattern (arrowhead) (Trichrome, original magnification × 20). E, NASH cirrhosis characterized by the development of broad collagen bands that form nodules (arrowhead) (Trichrome, original magnification × 10). Other characteristic features of NASH may or may not be present once cirrhosis has developed. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; AST:ALT, ratio of AST to ALT.

has been associated with the presence of nonalcoholic steatohepatitis specifically.[11]

Once cirrhosis develops, other findings such as palmar erythema, spider angiomata, gynecomastia, or prominent upper abdominal veins may appear. In patients with decompensated cirrhosis, these findings become more pronounced and additional features may be present, such as ascites, icterus, nail changes (Terry or Lindsay nails), splenomegaly, or asterixis. Low awareness of patients at risk for progression, coupled with the lack of a reliable diagnostic test or screening modality, explains why the

Figure 2. Mechanisms Involved in the Pathophysiology of Nonalcoholic Fatty Liver Disease



Dashed lines indicate emerging data. FFA indicates free fatty acids.

development of progressive nonalcoholic steatohepatitis goes unnoticed in many until cirrhosis is established.[12] Until such tests are available, general practitioners as well as specialists, who are likely to see a patient population with a high prevalence of nonalcoholic steatohepatitis (ie, endocrinologists, cardiologists), need to be aware of risk factors for disease progression to allow for early intervention.

Among patients with NAFLD, those with nonalcoholic steatohepatitis are much more likely to progress to cirrhosis than those with only hepatic steatosis.[8] The presence of features of the metabolic syndrome (characterized primarily by central obesity, hypertension, insulin resistance, high level of triglycerides, and low level of high-density lipoprotein cholesterol) is associated with higher risk of nonalcoholic steatohepatitis and more progressive disease (**Box 1**). Two large cohort studies demonstrated that 66% of patients older than 50 years with diabetes or obesity had nonalcoholic steatohepatitis with advanced fibrosis on index liver biopsy.[14,15] Although metabolic risk factors are associated with more advanced disease, progression rates differ substantially even among patients with nonalcoholic steatohepatitis, with some experiencing minimal progression over a decade and others progressing to advanced fibrosis or cirrhosis in 5 years or less.

Box 1. Established Risk Factors Associated With Nonalcoholic Steatohepatitis and More Progressive Disease

Risk Factors
- Obesity (central)
- Hypertension
- Dyslipidemia
- Type 2 diabetes
- Metabolic syndrome

Adult Treatment Panel III Definition of the Metabolic Syndrome[13]

Patient must have 3 or more of the following:
- Waist circumference of greater than 102 cm in men and greater than 88 cm in women
- Level of triglycerides of 150 mg/dL or greater
- High-density lipoprotein cholesterol level of less than 40 mg/dL in men and less than 50 mg/dL in women
- Systolic blood pressure of 130 mm Hg or greater or diastolic blood pressure of 85 mm Hg
- Fasting plasma glucose level of 110 mg/dL or greater

Alanine Aminotransferase as a Biomarker for Nonalcoholic Steatohepatitis

Even though a persistently elevated level of alanine aminotransferase (ALT) can be associated with an increased risk of disease progression, patients with advanced disease often have normal liver enzyme levels, making the identification of at-risk patients more nuanced.[16,17] The sensitivity and specificity of an elevated level of ALT for the diagnosis of nonalcoholic steatohepatitis are 45% and 85%, respectively. Elevations in ALT level among patients with nonalcoholic steatohepatitis may correlate with insulin resistance and intrahepatic fat content; however, patients with a normal ALT level have comparable risk of disease progression.[18] Even patients with diabetes and normal ALT levels have a high prevalence of NAFLD and nonalcoholic steatohepatitis (76% and 56%, respectively).[19]

Based on currently accepted threshold values, approximately 30% to 60% of patients with biopsy-confirmed nonalcoholic steatohepatitis have a normal ALT level.[16-18] Historically, an ALT level of greater than 1.5 times the upper limit of normal has been considered for enrollment into randomized clinical trials; therefore, an ALT level of greater than 60 IU/L may help to identify those patients with a higher likelihood of nonalcoholic steatohepatitis (the specific threshold that constitutes an elevated ALT level has yet to be established).[20] The current normal values for ALT are likely too high given that when determined in the 1980s undiagnosed hepatitis C virus and NAFLD were in the population from which normal values were derived. Lower cutoff values have been proposed to be more reflective of a true normal across various populations, but these have yet to be adopted.[20,21]

Noninvasive Assessment of Hepatic Steatosis

The diagnosis and quantification of hepatic fat can be useful in that it can predict future development of diabetes and other car-

diovascular risk factors.[22,23] Ultrasound is an inexpensive diagnostic tool that has a sensitivity of 93% when steatosis is greater than 33%; however, sensitivity is poor when steatosis is less than 30%.[24,25] Newer ultrasound techniques that can more accurately quantify fat may be able to overcome this limitation.[26] An important caveat with ultrasound is that characteristic features of hepatic steatosis, such as increased brightness (echo texture) and vascular blurring, can also be observed in the setting of fibrosis and thus could represent fibrosis and even early cirrhosis in addition to or in lieu of steatosis.

The controlled attenuation parameter is a promising new technique that may be able to quantify steatosis at lesser degrees; however, this technique requires further validation.[27] Computed tomography does not substantially improve sensitivity if steatosis is mild and carries the disadvantages of increased cost and exposure to radiation. Magnetic resonance imaging (MRI), including magnetic resonance spectroscopy, is able to detect the presence of hepatic fat greater than 5.56% (the defining threshold) with an accuracy that is nearly 100%.[28] Both are expensive and magnetic resonance spectroscopy has limited availability (mainly academic medical centers).

Predictive assays that use readily available parameters, such as those used to calculate the fatty liver index (body mass index, waist circumference, level of triglycerides, and level of γ-glutamyltransferase), could be considered. Due to variable performance across ethnic groups, a US fatty liver index was developed using data from the National Health and Nutrition Examination Survey and performance characteristics were compared with ultrasound-detected hepatic steatosis diagnoses. Performance characteristics were the worst for non-Hispanic blacks. Overall, to rule in fatty liver, a cutoff of 30 or greater had a sensitivity of 62%, a specificity of 88%, a positive likelihood ratio of 5.2, and a negative likelihood ratio of 0.43. To exclude hepatic steatosis, a cutoff of less than 10 had a sensitivity of 86%, a specificity of 48%, a positive likelihood ratio of 1.7, and a negative likelihood ratio of 0.28.[29]

Noninvasive Assessment of Nonalcoholic Steatohepatitis

Current techniques can adequately measure hepatic steatosis; however, it is more clinically relevant and challenging to identify patients with nonalcoholic steatohepatitis. The main limitation of imaging studies remains in their inability to differentiate nonalcoholic steatohepatitis from isolated hepatic steatosis. Emerging MRI techniques may make this possible in the future.[30] Nonalcoholic steatohepatitis remains underdiagnosed due in part to an overreliance on elevated levels of ALT and aspartate aminotransferase (AST).[12,31] Even though elevated levels of ALT and AST have moderate specificity in the appropriate clinical setting, their sensitivity makes them unreliable to identify those with nonalcoholic steatohepatitis. In patients with the metabolic syndrome, those who have ultrasound findings of hepatic steatosis (irrespective of elevated levels of ALT and AST) are at risk for nonalcoholic steatohepatitis.[2]

Several individual and combinations of clinical and laboratory parameters have been studied in an attempt to noninvasively diagnose nonalcoholic steatohepatitis. However, the available data are largely limited to pilot analyses in heterogeneous groups of patients. Of the clinical and laboratory parameters, the best studied is cytokeratin 18, which is a breakdown product resulting from caspase 3–mediated apoptosis of hepatocytes.[32,33] Combination of cytokeratin 18 with other markers may further enhance its performance characteristics; however, reported improvements in diagnosis are modest and need to be validated in outside cohorts.[34,35] In a multiethnic cohort, the sensitivity and specificity of cytokeratin 18 to detect nonalcoholic steatohepatitis was 58% and 68%, respectively.[36]

The most promising biomarkers are limited to the clinical research setting and lack sufficient accuracy to replace or significantly limit liver biopsy to diagnose nonalcoholic steatohepatitis. New biomarkers will need to (1) be assessed in different populations, (2) be useful for longitudinal evaluation, and (3) accurately measure response to therapy. Because current biomarkers have limited utility, liver biopsy remains the most reliable method to identify patients with nonalcoholic steatohepatitis.

Noninvasive Assessment of Hepatic Fibrosis

The rate of liver disease progression in NAFLD is unlikely to be linear over time, but is rather a dynamic entity influenced by a multitude of factors.[10] The development of tools to predict progression of liver disease in patients with nonalcoholic steatohepatitis is a major research focus. Identification and quantification of fibrosis are clinically important because fibrosis correlates with clinical outcomes. As demonstrated by a prospective study of 619 patients who had liver biopsies with a mean (SD) follow-up of 152 (88) months, the presence and extent of fibrosis were the only histological features of NAFLD that predicted future decompensation and death during a mean (SD) follow-up period of 152 (88) months (range, 4-551 months).[37]

Several predictive models have been developed using clinical parameters and measures of byproducts of the fibrogenic process. Among these, the NAFLD fibrosis score (NFS) and the enhanced liver fibrosis panel are examples of clinical and laboratory parameters that allow the prediction of severe fibrosis in NAFLD with fairly high accuracy. Of these, the NFS is the best validated and can predict liver-related outcomes.[38] The NFS is calculated using readily available clinical data (age, body mass index, presence or absence of hyperglycemia, platelet count, albumin level, and ratio of AST to ALT) to help identify patients with more severe disease who may benefit most from liver biopsy and highlights the importance of metabolic risk factors in nonalcoholic steatohepatitis progression[39,40] (**Box 2**).

An NFS below the low cutoff score (−1.455) excludes advanced fibrosis with a sensitivity and specificity of 75% and 58%, respectively. An NFS above 0.676 identifies the presence of advanced fibrosis with a sensitivity and specificity of 33% and 98%, respectively, and an area under the receiver operating characteristic curve of 0.81 (95% CI, 0.71-0.91).[39,41,42] Current nonalcoholic steatohepatitis biomarkers and noninvasive tests for nonalcoholic steatohepatitis fibrosis have often not met the Standards for Reporting of Diagnostic Accuracy (STARD) quality metrics for diagnostic tests.[43] Therefore, a new extension of the STARD statement to assess the quality of diagnostic tests for liver fibrosis was proposed.[44]

During the past several years, advances in imaging technology have greatly enhanced the ability to noninvasively quantify hepatic fibrosis. The 2 best-studied imaging modalities are transient elastography and magnetic resonance elastography (MRE). Transient elastography can be performed in an office setting for the quantification of liver fibrosis in patients with NAFLD; however, further

Box 2. Nonalcoholic Fatty Liver Disease (NAFLD) Fibrosis Score Formula and Fibrosis Score Cutoff Categories

NAFLD Fibrosis Score Formula

−1.675 + 0.037 × age (units: years) + 0.094 × body mass index (units: kilograms/meters squared) + 1.13 × impaired fasting glucose level or diabetes (yes = 1, no = 0) + 0.99 × ratio of aspartate aminotransferase to alanine aminotransferase − 0.013 × platelet count (units: × 10^9/L) − albumin level (units: g/dL)[a]

NAFLD Fibrosis Score Cutoff Categories

- No fibrosis to fibrosis stage 2: score of less than −1.455
- Fibrosis indeterminate: score of −1.455 to 0.675
- Fibrosis stages 3 and 4: score of greater than 0.675

[a]Further information on this formula is available at http://nafldscore.com/, which is an online calculator.

studies are needed to address limitations of test performance related to obesity or higher degrees of hepatic steatosis.[45] Several different modalities, including vibration-controlled transient elastography (Fibroscan) and elastography with acoustic radiation force impulse, have been studied. Both vibration-controlled transient elastography and ultrasound with acoustic radiation force impulse are fairly accurate in the detection of hepatic fibrosis and are the most reliable modalities for the diagnosis of advanced fibrosis (cirrhosis or precirrhosis).

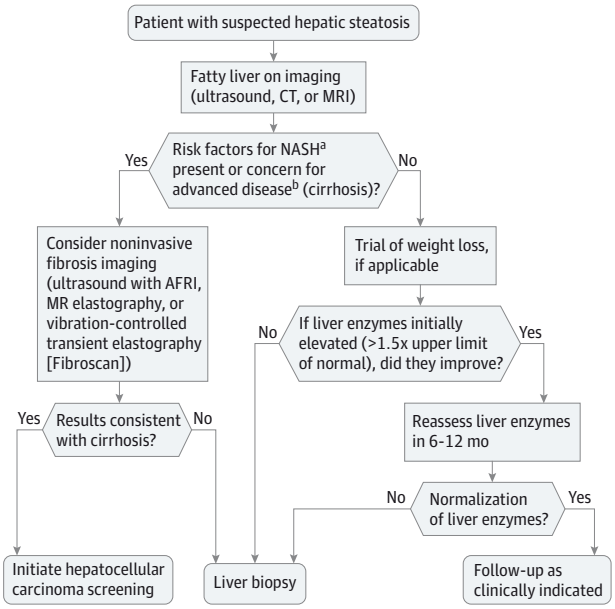
Magnetic resonance elastography may be more reliable than transient elastography; however, MRE is costly and not widely available. In a prospective study[46] examining the ability of 2-dimensional MRE to stage hepatic fibrosis and distinguish between advanced fibrosis and earlier stages of fibrosis, MRE had excellent predictive accuracy. Two-dimensional MRE had a sensitivity of 0.86 (95% CI, 0.65-0.97) and a specificity of 0.91 (95% CI, 0.83-0.96) to identify those with more advanced fibrosis.[46] The area under the receiver operating characteristic curve was 0.92 to discriminate between advanced and early stages of fibrosis (P<.001).[46] Even though these results are intriguing, they do require additional validation. Overall, current imaging technology is fairly reliable in distinguishing advanced from mild or no fibrosis but it remains inadequate to identify those with moderate fibrosis. When imaging yields uncertainty regarding the degree of fibrosis, liver biopsy is necessary.

Selection of Patients for Liver Biopsy

Liver biopsy is invasive, has the potential for resulting in severe complications, and is limited by sampling error.[47] Despite these potential negative outcomes, liver biopsy remains the best method for diagnosing and staging nonalcoholic steatohepatitis. The presence of nonalcoholic steatohepatitis on a patient's first liver biopsy is the main predictor for the development and progression of liver fibrosis.[6,33,34] In turn, progression of liver fibrosis is the main determinant of adverse liver–related clinical outcomes.[48] Therefore, diagnosing nonalcoholic steatohepatitis and cirrhosis have important prognostic and management implications.

Establishing a diagnosis of nonalcoholic steatohepatitis is needed prior to the initiation of treatment. Irrespective of the presence of aminotransferase elevation, any patient with suspected steatosis and the metabolic syndrome, or who has metabolic risk factors, particularly diabetes, has a high risk for nonalcoholic steatohepatitis and advanced fibrosis and should be considered for biopsy[14,15] (**Figure 3**).

Figure 3. Algorithm for the Decision to Perform Liver Biopsy in Patients With Presumed Nonalcoholic Fatty Liver Disease After Negative Serological Evaluation and Exclusion of Alcohol as a Contributing Factor



AFRI indicates acoustic radiation force impulse; CT, computed tomography; MR, magnetic resonance; MRI, magnetic resonance imaging; NASH, nonalcoholic steatohepatitis.

[a] Includes the metabolic syndrome (diabetes, hypertension, central obesity, high level of triglycerides or low level of high-density lipoprotein cholesterol), older than 60 years, and family history of diabetes.

[b] Higher level of aspartate aminotransferase than alanine aminotransferase, low platelet count, elevated international normalized ratio, and elevated bilirubin level without alternative explanation suggest the presence of cirrhosis.

In addition, patients with persistent elevation (>6 months) in levels of ALT and AST should undergo liver biopsy for further evaluation, particularly patients in whom concomitant disease (autoimmune, hemochromatosis) cannot otherwise be excluded.[2] There is no uniformly accepted threshold to define what is persistent elevation in liver enzyme levels to trigger a biopsy; however, 1.5 times the upper limit of normal has been used. Noninvasive prediction scores can also be used to select patients with a higher likelihood of nonalcoholic steatohepatitis and advanced fibrosis.[39] However, any evidence suggestive of progressive liver disease on laboratory testing (ratio of AST to ALT >1, hyperbilirubinemia, coagulopathy, thrombocytopenia) or physical examination evidence of advanced liver disease should prompt a liver biopsy to exclude cirrhosis.

If noninvasive imaging, such as transient elastography or MRE is inconclusive, then biopsy should be pursued to establish the degree of fibrosis or to determine the potential benefit of treatment or eligibility for a clinical trial (**Table 1** and **Box 3**). If there is clear evidence of cirrhosis by imaging and physical examination, biopsy is not needed. If cirrhosis is present, laboratory tests evaluating for liver

Table 1. Diagnosis, Monitoring, and Management Considerations for Nonalcoholic Fatty Liver Disease (NAFLD)

	NAFLD Disease Stage		
	Nonalcoholic Steatohepatitis With Fibrosis		
	Stages 0-1[a]	Stages 2-3[b]	Isolated Hepatic Steatosis
Evaluate clinical evidence	Development or worsening of metabolic diseases	For features of cirrhosis: development or worsening of metabolic diseases	Development or worsening of metabolic diseases
Monitor laboratory evidence of disease progression	Monitor liver chemistry test results Screen for dyslipidemia and diabetes	Monitor liver chemistry test results Screen for dyslipidemia and diabetes Laboratory features of advanced disease: Ratio of AST to ALT >1 Low platelet count Increased INR and bilirubin or lower albumin	Monitor liver chemistry test results Screen for dyslipidemia and diabetes
Management considerations			
Liver-directed therapy	Consider treatment with pioglitazone or vitamin E Consider eligibility for a clinical trial	Consider treatment with pioglitazone or vitamin E Consider eligibility for a clinical trial	No proven benefit
Other	Manage comorbidities, including behavioral and weight loss therapy Consider bariatric surgery if appropriate	Manage comorbidities, including behavioral and weight loss therapy Consider bariatric surgery if appropriate	Manage comorbidities, including behavioral and weight loss therapy Consider bariatric surgery if appropriate

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio.

[a] Indicates early or no fibrosis.

[b] Indicates moderate to severe fibrosis (precirrhosis).

failure should be obtained (eg, international normalized ratio, bilirubin level), the patient should be assessed for signs of hepatic decompensation (eg, ascites, hepatic encephalopathy, variceal bleeding), and the patient should be screened for hepatocellular cancer and esophageal varices (**Table 2**).

Treatment of NAFLD, Nonalcoholic Steatohepatitis, and Hepatic Fibrosis

Lifestyle Intervention

Diet and exercise are the mainstay treatment for the majority of patients with NAFLD. Weight loss is beneficial and the degree of liver histological improvement is directly proportional to the amount of weight lost.[49,50] In a prospective study of a dietary intervention in patients with biopsy-confirmed nonalcoholic steatohepatitis, a loss of 10% of body weight was associated with histological benefit.[51] The effect of weight loss also was demonstrated in a trial of 154 patients randomized to either a dietician-reinforced lifestyle intervention (included advice for diet and required participation in moderate intensity exercise 3 times per week) or general recommendations to lose weight for 12 months.[49] Resolution of NAFLD (as assessed by magnetic resonance spectroscopy) was observed in 64% of the intervention group compared with only 20% of the control group.[49] In another study,[52] lifestyle intervention was associated with histological benefit in patients with NAFLD, the majority of whom had nonalcoholic steatohepatitis at the outset.

Although the ideal diet for patients with NAFLD has yet to be determined, data suggest that dietary composition is important.[53] The Mediterranean diet was compared with an isocaloric low-fat, high-carbohydrate diet during a 6-week crossover study to determine its effect on liver fat. The Mediterranean diet was associated with reduced liver fat and improved insulin sensitivity without differences in weight loss.[54] A 2-week carbohydrate-restricted diet (<20 g/d of carbohydrates) compared with a reduced calorie diet (range, 1200-1500 kcal/d) resulted in similar weight loss between the groups; however, the carbohydrate-restricted group had a higher percentage reduction in hepatic fat (mean [SD] of 55% [14%]) compared with the reduced calorie diet group (mean [SD] of 28% [23%]) ($P < .001$).[55]

Box 3. Treatments for Nonalcoholic Fatty Liver Disease and the Target Population

Vitamin E
- Patients with nonalcoholic steatohepatitis
- Insufficient evidence to treat patients with diabetes or cirrhosis

Pioglitazone
- Patients with nonalcoholic steatohepatitis with or without diabetes
- Limited data in patients with cirrhosis

Pentoxifylline
- Patients with nonalcoholic steatohepatitis; however, further study is needed to determine the efficacy and ideal subpopulations

Data from current trials of these treatments have modest effect sizes and high placebo response rates, which are limitations to their use.

Exercise improves cardiovascular health and reduces peripheral, adipose, and hepatic insulin resistance independent of weight loss. It is not known conclusively if exercise exerts independent benefits on NAFLD. Limited data suggest that aerobic exercise results in greater reduction in hepatic fat than does resistance training and some data suggest that this effect of aerobic exercise on hepatic and visceral fat may be independent of weight loss.[56-58] The intensity and duration of exercise required to improve NAFLD are also poorly defined. A retrospective study[59] compared mild, moderate, and high intensity exercise regimens in 169 patients with detectable hepatic fat. Only participants in the highest intensity exercise group (>250 min/wk^{-1}) had improved metabolic parameters and significant hepatic fat reduction.[59]

Table 2. Diagnosis, Monitoring, and Management Considerations for Cirrhosis

	Type of Cirrhosis	
	Compensated	Decompensated
Evaluate clinical evidence	New or development of hepatic encephalopathy, gastrointestinal bleeding, or ascites[a] Development or worsening of metabolic diseases	New or worsening hepatic encephalopathy, gastrointestinal bleeding, ascites
Monitor laboratory evidence	Development or worsening of synthetic dysfunction assessed by abnormal international normalized ratio and levels bilirubin and albumin	Further deterioration of synthetic function
Screening		
Hepatocellular carcinoma	Every 6 mo	Every 6 mo
Varices	Upper endoscopy upon diagnosis and subsequently per variceal features	Upper endoscopy upon diagnosis and subsequently per variceal features
Management considerations	Management of comorbidities Consider treatment (eg, pioglitazone)	Consider liver transplant referral

[a] Presence of these features defines hepatic decompensation.

Bariatric surgery should be considered for those unable to lose weight. Many retrospective studies and 1 large prospective study with 5-year follow-up periods demonstrate that bariatric surgery can improve or even reverse NAFLD, nonalcoholic steatohepatitis, and fibrosis.[60,61]

Pharmacological Treatment of Nonalcoholic Steatohepatitis

Even though a drug has yet to be approved by the US Food and Drug Administration for the treatment of nonalcoholic steatohepatitis, some treatments have demonstrated efficacy in randomized clinical trials. The Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis (PIVENS) trial was the first to show a convincing histological benefit in patients with nonalcoholic steatohepatitis. Patients without diabetes with biopsy-confirmed nonalcoholic steatohepatitis (n = 247) were randomized to receive 30 mg of pioglitazone, 800 IU of vitamin E, or placebo for 96 weeks (primary comparisons were made only between pioglitazone and placebo or vitamin E and placebo, not between pioglitazone and vitamin E).[62]

The primary outcome in the PIVENS trial was an improvement in histological features of nonalcoholic steatohepatitis, which specifically required an improvement in hepatocellular ballooning. Patients treated with vitamin E met the primary end point. Even though the primary end point was not met in the pioglitazone group, pioglitazone was associated with significant improvements in hepatic steatosis, inflammation, insulin resistance, and liver enzyme levels. It is likely that the primary outcome was not met due to a disproportionate misclassification of the presence of ballooning in the pioglitazone group (noted on the central reading of the biopsies at study completion) relative to the other patients. Importantly, a greater proportion of participants receiving pioglitazone (47%) vs placebo (21%) had complete resolution of steatohepatitis on the biopsy performed at the end of treatment (P = .001).

Even though a meta-analysis suggested that pioglitazone improved fibrosis, the PIVENS trial did not demonstrate this. However, neither the PIVENS trial nor any of the preceding trials were designed to address fibrosis as a primary outcome.[63-65] Prior studies of pioglitazone included patients with cirrhosis and those with diabetes.[63,66] There is insufficient information to recommend vitamin E for patients with nonalcoholic steatohepatitis and concomitant diabetes or cirrhosis (Box 3).

Weight gain of about 3 to 5 kg is the most common adverse effect of pioglitazone and occurs in about 60% to 70% of patients in clinical nonalcoholic steatohepatitis trials.[67] It should not be given to patients with clinically evident heart failure. Pioglitizone is also associated with postmenopausal bone loss and it may predispose patients to an increased risk of bladder cancer, although this is debatable.[68-71]

Vitamin E is considered to be relatively benign, but safety concerns have been raised. Claims that vitamin E is associated with increased mortality are unconvincing because the quality of evidence supporting this contention is poor.[72] Vitamin E use may be associated with increased risks of prostate cancer and hemorrhagic stroke; however, it also may be associated with a reduction in thrombotic stroke.[73-76]

Pentoxifylline has been studied in 2 small randomized clinical trials[77,78] (n = 85) that suggest histological benefit, including reducing hepatic fibrosis; however, these findings require confirmation in a larger trial. A phase 2b randomized clinical trial[79] (n = 283) showed that obeticholic acid was associated with liver histological benefit (including fibrosis) compared with placebo in patients with nonalcoholic steatohepatitis. Although these results are encouraging, the effect size was similar to that for vitamin E in the PIVENS trial. Importantly, concerns were raised about safety due to obeticholic acid's adverse effect of pruritus and unfavorable effects on the lipid profile. Further studies are needed to determine if lipid changes are clinically important.

Although there are now promising therapeutic options for patients with nonalcoholic steatohepatitis, none has been approved by the US Food and Drug Administration. Furthermore, no treatment has demonstrated efficacy in more than 50% of patients; thus, there continues to be an unmet need for therapeutics in patients with nonalcoholic steatohepatitis. Current clinical practice guidelines recommend that only patients with biopsy-confirmed nonalcoholic steatohepatitis, those with any degree of fibrosis, or those with both should be considered for liver-directed therapy.[2]

Cardiovascular disease is the most common cause of death in patients with NAFLD; both cardiovascular morbidity and nonalcoholic steatohepatitis, in particular, may persist even after liver transplantation in patients with nonalcoholic steatohepatitis.[80] At present, there is insufficient evidence to change cardiovascular risk stratification in patients with NAFLD because it remains unknown to what extent NAFLD or nonalcoholic steatohepatitis may provide additive risk beyond established risk factors. Lifestyle modification and optimization of comorbid factors that confer increased cardiovascular risk should be emphasized; importantly, patients with nonalcoholic steatohepatitis, including those

with cirrhosis, should be treated appropriately with statins based on established guidelines because they are safe in patients with liver disease.[81]

Management of Nonalcoholic Steatohepatitis Cirrhosis

Twenty percent or more of patients with nonalcoholic steatohepatitis will develop cirrhosis during their lifetime.[82] Decompensated cirrhosis occurs in approximately 45% of patients with nonalcoholic steatohepatitis cirrhosis during a 10-year period.[83] Although decompensated cirrhosis can occur in the form of variceal bleeding or the development of hepatic encephalopathy, the most common presentation is the development of ascites.

The most important predictor of death is the development of renal failure.[83] Patients with cirrhosis from any cause should be screened for hepatocellular cancer with imaging (ultrasound, computed tomography, or MRI) on a biannual basis. Screening recommendations have not yet accounted for the increasing numbers of patients developing hepatocellular cancer even though up to 50% of cases may occur in the absence of cirrhosis.[84,85]

Screening for varices should be initiated when cirrhosis is first diagnosed. The need for subsequent endoscopy is dictated by variceal size (large varices require closer follow-up) and the presence of high-risk signs such as red wales. Patients with large varices may benefit from primary prophylaxis with either variceal band ligation or a nonselective β-blocker to prevent bleeding. Patients with compensated cirrhosis should be monitored biannually for signs of decompensation or worsening hepatic synthetic function (international normalized ratio, levels of bilirubin and albumin). Patients with decompensated cirrhosis should be referred for liver transplantation evaluation (Table 2).

Prognosis

Compared with the general population, patients with NAFLD, particularly nonalcoholic steatohepatitis, have reduced survival that is primarily attributable to cardiovascular disease and malignancy.[9,48] Cardiovascular-related deaths predominate, accounting for twice as many deaths as those that occur due to liver-related causes.[9,86] The prognosis of NAFLD is directly dependent on liver histological features, isolated hepatic steatosis, and nonalcoholic steatohepatitis with or without fibrosis or cirrhosis. A pooled analysis[38] of several studies illustrated that approximately 1% of those with isolated steatosis died of liver-related causes compared with those with nonalcoholic steatohepatitis who developed cirrhosis (11%) or died of liver disease (7%) during a 15-year follow-up period.

The ability to predict the liver-related outcomes becomes more reliable as NAFLD advances to cirrhosis. Once cirrhosis is established, several parameters, including serum albumin level, model for end-stage liver disease score, and the hepatic venous pressure gradient, can predict the likelihood of hepatic decompensation or the development of hepatocellular cancer.[87,88]

Nonalcoholic fatty liver disease is a complex and heterogeneous disease that is widely prevalent in the general population and represents a major cause of hepatic morbidity and mortality that continues to increase in scale. Cardiovascular disease and malignancy are the 2 most common causes of death in this population and multiple mechanisms provide biological plausibility for these associations. While the current understanding of these complex associations continues to evolve, internists and medical subspecialists alike should be aware of clinical risk factors and tools to identify those likely to have advanced disease. Identifying patients at greatest risk for progression, who may benefit from a more aggressive treatment approach or even referral for liver transplantation, should ultimately translate into improved patient outcomes.

Conclusions

Between 75 million and 100 million individuals in the United States have NAFLD and its potential morbidity extends beyond the liver. It is important that primary care physicians, endocrinologists, and other specialists be aware of the scope and long-term effect of the disease. Early identification of patients with nonalcoholic steatohepatitis may help improve patient outcomes through treatment intervention, including transplantation for those with decompensated cirrhosis.

ARTICLE INFORMATION

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