Published in final edited form as:

Annu Rev Med. 2022 January 27; 73: 529–544. doi:10.1146/annurev-med-042220-020407.

Fatty Liver Disease: Diagnosis and Stratification

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is a major public health crisis affecting approximately 25% of the world's population. The spectrum of NAFLD ranges from bland steatosis to steatohepatitis with fibrosis; eventual development of cirrhosis in a subgroup of patients now represents the leading indication for liver transplant in women and in individuals older than 65. The development of noninvasive liver disease assessment tools has led to substantial progress in the diagnosis of NAFLD. Patients with NAFLD are at increased risk of cardiometabolic disease, which should therefore be an important part of the therapeutic approach. This review focuses on diagnosis and risk stratification of NAFLD across the full spectrum of disease, including important considerations in the approach to patients with cirrhosis.

Keywords

fatty liver; nonalcoholic fatty liver disease; NAFLD; nonalcoholic steatohepatitis; NASH; cirrhosis; noninvasive liver disease assessment; NILDA

GENERAL OVERVIEW AND DIAGNOSIS OF NONALCOHOLIC FATTY LIVER DISEASE AND NONALCOHOLIC STEATOHEPATITIS

Nonalcoholic fatty liver disease (NAFLD) is a major public health crisis in the United States and many other areas of the world. Nearly 30% of the US population, or 100 million persons, are predicted to have steatosis; the prevalence approaches 75% in patients with associated risk factors of obesity and diabetes (1–3).The diagnosis of NAFLD remains one of exclusion, requiring evidence of hepatic steatosis by either imaging or histology as well

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DISCLOSURE STATEMENT

M.E.R. has had consulting contracts (canceled as of 2021) with 3vBio (Sagimet), 89Bio, Alnylam, Amgen,AMRA,BMS,BoehringerIngelheim,Centara,Coherus,Enanta,Fractyl,Galecto,Gelesis, Intercept Pharmaceuticals, Madrigal, NGM Biopharmaceuticals, Novartis, Novo Nordisk, Pfizer, Rivus, Siemens, Thetis, and Terns. A.D.R. has consulted for Axcella Health, Inc.

as a lack of alternate etiologies including alcohol consumption, although in many patients both metabolic and alcohol components contribute to liver injury. Additional factors can also promote the accumulation of fat in the liver (4) (Table 1). Nonalcoholic steatohepatitis (NASH), which is the presence of hepatic steatosis with concomitant hepatocellular injury and inflammation, remains a histological diagnosis.

NAFLD is not a single disease but rather a spectrum ranging from bland steatosis to NASH, with concomitant fibrosis and eventual cirrhosis in some patients. Thus, understanding the progression of disease and the specific hepatic and extrahepatic morbidities associated with each stage is crucial for optimal patient management. While it was previously thought that 20–30% of patients with steatosis or nonalcoholic fatty liver (NAFL) would progress to NASH and only 2–5% would develop cirrhosis and end-stage liver disease (ESLD), we now know that the disease progresses and regresses in a nonlinear fashion, even in the case of fibrosis (Figure 1). It is critical to identify patients with NAFLD and advancing stages of fibrosis, as the presence and extent of fibrosis drive both liver-related outcomes (e.g., progression to cirrhosis, hepatic decompensation) and mortality. Patients with NAFLD and, to some extent, NASH are at greater risk of developing cardiovascular disease, cancer [apart from hepatocellular carcinoma (HCC)], and infectious diseases (5). While fibrosis has the clearest direct association with adverse outcomes, its collinearity with NASH in the setting of advanced fibrosis makes it difficult to identify an important contribution from NASH activity (6–8). Nonetheless, even the presence of NAFL alone (simple steatosis) imparts a twofold-increased risk of developing diabetes and hypertension. Therefore, NAFL and metabolic syndrome compound the risk of cardiovascular disease and require accurate and timely diagnosis (9–11).

ECONOMIC BURDEN OF NONALCOHOLIC FATTY LIVER DISEASE AND RATIONALE FOR SCREENING

The annual economic burden of NAFLD in the United States has been estimated at $103 billion in indirect costs, with an additional $188 billion in societal costs (12). Despite this enormous economic burden, early studies suggested that population-wide screening is neither feasible nor cost-effective (1). The lack of enthusiasm for NAFLD screening derives from (*a*) the absence of an accurate biomarker with cost-effective scalability for population-wide screening, (*b*) a lack of effective treatments, and (*c*) unclear long-term benefits of early diagnosis. Nonetheless, a high degree of suspicion is necessary in patients with components of metabolic syndrome, including diabetes, obesity, dyslipidemia, and/or hypertension, because the progression of NAFLD from simple steatosis to cirrhosis and HCC increases exponentially in these patients (4, 13). The 2018 practice guidance of the American Association for the Study of Liver Diseases did not recommend targeted screening in high-risk populations such as patients with diabetes (4), in contrast to European societies' recommendation to screen subjects with features of metabolic syndrome, particularly those at high risk (i.e., patients with diabetes and age >50 years) (2, 14, 15). More recently, the American Diabetes Association recommended screening and risk stratification for NAFLD in patients with diabetes mellitus (16, 17).

PRACTICAL APPROACH TO NONALCOHOLIC FATTY LIVER DISEASE IN PRIMARY CARE

The presence of NAFLD and the risk of NASH and fibrosis should be considered in three populations: (*a*) patients with persistently elevated liver chemistries, (*b*) patients with multiple NAFLD-associated metabolic risk factors (e.g., medically complicated obesity), and (*c*) patients with evidence of steatosis on imaging (Table 2). Novel evidence suggests that screening high-risk populations, including patients with type 2 diabetes, with noninvasive liver disease assessment (NILDA) tools (formerly known as noninvasive testing) might prove to be a cost-effective way to facilitate early diagnosis and therapeutic intervention (17). Such a strategy involves an initial screening with a liver chemistry panel and an abdominal ultrasound, followed by liver stiffness measurements (LSMs) (17). Evaluation of elevated liver chemistries requires a detailed analysis of additional etiologies of liver disease, with special attention to alcohol and medication use. Blood workup can also be coupled with readily available NILDAs such as the fibrosis-4 (FIB-4) index for liver fibrosis or the NAFLD fibrosis score to investigate advanced fibrosis. Finally, hepatic steatosis that is incidentally diagnosed on abdominal imaging is a frequent occurrence in the primary care setting. In these patients, careful metabolic risk profiling and detailed alcohol use screening should guide the necessity for subspecialization referral.

Figure 2 describes three scenarios a primary care physician will frequently encounter in clinical practice and how to approach them. We propose using a FIB-4 score of 1.3 to rule out significant disease that would mandate referral to a liver specialist. Although this cutoff has been validated as the most sensitive way to rule out advanced fibrosis or cirrhosis (i.e., fibrosis stage 3 or 4) with a negative predictive value of 90% (18), it fails to identify patients with significant fibrosis (i.e., fibrosis stage 2) for whom there is no current screening strategy. Importantly, since FIB-4 incorporates age as one of its components, it might overestimate fibrosis in older subjects (19), and although a cutoff value of 2.0 has been suggested for patients 65 years and older in order to decrease unnecessary referrals, an age-adjusted FIB-4 strategy requires further validation (20, 21). Thus, patients with a FIB-4 score below 1.3 should remain within their primary care physician practice and have their NAFL risk factors (e.g., alcohol, tamoxifen use) assessed and addressed whenever liver steatosis is observed on imaging. For these patients, strategies for a healthy lifestyle prioritizing weight loss would be beneficial, along with treatment optimization of all applicable components of metabolic syndrome. Patients with diabetes and steatosis might benefit from glucose-lowering agents that target NAFLD/NASH (e.g., glucagon-like peptide 1 receptor agonists and sodium-glucose cotransporter 2 inhibitors) as well as from statins, and their use is guided by standard practice guidelines. Patients with a FIB-4 score of 1.3 or higher can be referred directly to a liver specialist or sent for further testing with a second blood-based (20) or imaging-based NILDA. LSMs from either transient elastography or shear-wave elastography can be used as a second test to classify patients with a FIB-4 score between 1.3 and 3.25 (the cutoff value with a high predictive value for advanced fibrosis). An LSM below 8 kPa is sufficient to ruleout advanced fibrosis and avoid a referral to hepatology (19). A recent study (22) evaluated the utility of transient elastography for the identification of advanced fibrosis and cirrhosis in 5,648 patients with staging liver biopsy.

Using cutoff values with >90% sensitivity to rule out the condition and >90% specificity to rule it in, the authors validated LSMs of <8 kPa and ≥12 kPa for advanced fibrosis and <10 kPa and >15 kPa for cirrhosis, respectively (22). Values between 8 and 11 kPa are indeterminate for advanced fibrosis and warrant hepatology.

ALCOHOL USE IN NONALCOHOLIC FATTY LIVER DISEASE

Alcohol use disorder (AUD) is the leading cause of advanced liver disease in the United States and, together with NAFLD, accounts for ~65% of cases of advanced liver disease. Pathogenesis shared between alcohol-associated liver disease (ALD) and NAFLD includes activation of hepatic inflammatory cascades, altered lipid metabolism, and development of endoplasmic reticulum stress causing hepatocyte toxicity (23). This shared pathophysiology is further evidenced by an association of variants in *PNPLA3*, which are strongly associated with both NAFLD and ALD (24). In light of this significant overlap, patients with NAFLD can have subsequent alcohol-related injury that cannot be distinguished. The concurrence of NAFLD and ALD can lead to additive or even synergistic effects on the progression of liver disease, with more rapid progression of fibrosis and development of ESLD (25, 26). This is particularly common in patients who have undergone bariatric surgery (27).

The question of whether a patient with NAFLD may consume alcohol is common. Moderate alcohol consumption in the general population (≤1 standard drinks/day in females and ≤2 drinks/day in males) is associated with an improvement in cardiometabolic risk (28). Similarly, early studies demonstrated a potential protective effect of modest alcohol consumption in patients with NAFLD, though these conclusions were later challenged (29, 30). No prospective studies have evaluated the effect of alcohol consumption on the natural history of NAFLD. Excessive alcohol consumption in the setting of NAFLD is deleterious, and retrospective analyses suggest that no amount of alcohol is safe in patients with NAFLD (26). In a cohort of patients enrolled in the NASH Clinical Research Network study, after 4 years of follow-up, patients reporting no alcohol consumption had a greater reduction in steatosis grade (0.49 versus 0.30; $p = 0.04$) and aspartate aminotransferase levels (7 U/L versus 2 U/L; $p = 0.04$) and an increased adjusted odds ratio (OR) of NASH resolution (0.32; $p = 0.04$) compared with patients consuming ≤2 drinks/day (31). Similarly, in a Finnish study of more than 6,000 patients, moderate alcohol consumption was a significant risk factor for development of liver disease, along with other metabolic risk factors, suggesting that any alcohol consumption in patients with NAFLD presents a risk (32).

Furthermore, alcohol may precipitate hepatic decompensations in patients with NAFLD-associated cirrhosis and increase the risk of extrahepatic complications of NAFLD. Therefore, it is imperative to screen for alcohol use in patients at risk and reinforce absolute abstinence at each visit. The National Institute of Alcohol Abuse and Alcoholism endorses a single-question assessment for binge drinking that, if positive, should trigger evaluation with AUDIT (Alcohol Use Disorders Inventory Test) (33, 34). Furthermore, clinicians can use phosphatidylethanol, a blood test that can identify moderate to heavy drinking up to 2–4 weeks after alcohol cessation, to monitor patients' abstinence and to identify patients requiring referral to an addiction specialist (35).

STANDARD CIRRHOSIS STRATIFICATION

Cirrhosis has traditionally been classified as either compensated or decompensated. More recently, advanced fibrosis and cirrhosis have been combined into what is known as advanced chronic liver disease (36–39) (Figure 3), as this is the stage at which liver-related adverse outcomes can first occur (40). Advanced chronic liver disease is the earliest stage at which clinically significant portal hypertension can present (defined as a hepatic venous pressure gradient ≥10 mm Hg), thus heralding decompensated cirrhosis. Nonetheless, patients with compensated cirrhosis require routine HCC screening as well as monitoring of their underlying liver disease to prevent or timely treat decompensations. Despite the occasional presentation of HCC in patients with NASH and advanced fibrosis (i.e., fibrosis stage 3 but no cirrhosis), to date there is insufficient evidence to screen for HCC in this subgroup of patients (41, 42). Referral for liver transplantation (LT) is advised for any patient in whom HCC or any form of decompensation is identified.

Most patients with advanced chronic liver disease have no features of decompensation (i.e., prior bleeding varices, ascites, or hepatic encephalopathy). Decompensation typically occurs at a rate of 4–7% per year (43, 44), although prospective data show rates as high as 20% per year in patients with NASH (45–48). In compensated cirrhosis, development of clinically significant portal hypertension and nonbleeding varices (which herald hepatic decompensation) confers a low mortality of no more than 10% at 5 years. With increasing portal hypertension, decompensations ensue through multiple mechanisms, including a hyperdynamic circulation, gut bacterial translocation, activation of systemic inflammatory cascades, and hepatocyte dysfunction (49, 50). However, not all forms of decompensation confer the same mortality risk, and the accrual of multiple decompensations has a synergistic effect on mortality. For example, ascites, hepatic encephalopathy, or jaundice carries a higher risk of mortality than bleeding varices (30% versus20%), but the combination of bleeding varices and a second, nonbleeding decompensation results in a 5-year mortality approaching 90%. Severe insults, such as an infection or an adverse drug event, can rapidly push patients with NASH into a highly lethal clinical condition known as acute-on-chronic liver failure, which carries the highest short-term mortality (51).

Accurate staging assignment traditionally required invasive measurement of the hepatic venous pressure gradient, which is not routinely performed. Nonetheless, any LSM method can be used to diagnose advanced chronic liver disease and cirrhosis (discussed above) (22, 52, 53) and to predict the presence of esophageal varices at high risk of bleeding. Baveno VI guidelines recommend avoiding endoscopic variceal screening in patients with a platelet count above 150,000 per cubic millimeter and an LSM below 20 kPa, given their low risk of clinically significant portal hypertension (40). This recommendation was later validated in a cohort of patients with compensated viral cirrhosis; none of the 80 patients meeting Baveno VI criteria exhibited varices requiring intervention. Furthermore, all patients who eventually developed clinical evidence of portal hypertension showed worsening of their platelet count and LSM, suggesting that the Baveno VI criteria can be used to monitor progression of portal hypertension (54).

Importantly, liver disease progression is neither linear nor predictable, and patients can present with any form of decompensation and can skip stages. Also, these clinically defined states can resolve with improvement in the underlying hepatic injury (i.e., successful treatment of comorbidities and lifestyle modification) (44), and reversal of fibrosis and cirrhosis in some patients is possible (Figures 1 and 3). Proper stage determination and risk stratification in patients with NAFLD are critical to permit clinicians to make fine therapeutic adjustments in the setting of advanced chronic liver disease.

Adequate glucose control is crucial for treatment of NAFLD, though the decreased capacity of a cirrhotic liver to store glycogen increases the risk of hypoglycemia (55). Furthermore, HbA1c (glycosylated hemoglobin) measurements become less reliable in cirrhosis, particularly once decompensation occurs. Thus, cirrhosis and decompensation should mark a transition toward reliance on pre- and postprandial glycemia and a discontinuation of oral medications conferring risk of hypoglycemia. Similarly, patients with ascites should avoid the use of all medications with the potential to decrease renal perfusion (nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers) in order to prevent acute kidney injury (56, 57). The preventive role of β-blockers for primary and secondary variceal prophylaxis after occurrence of advanced decompensation episodes (i.e., stage 5 or acute-on-chronic liver failure in Figure 3) (58–63), when a mean arterial pressure of ≥65 mm Hg is key to maintain adequate renal perfusion (64), continues to be debated.

FUNCTIONAL STATUS IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE

The importance of physical function and frailty in cirrhosis management has become increasingly clear over the last decade. Frailty is a decrease in physiologic reserve and resistance to stress, leading to poor health outcomes (65). In patients awaiting LT, frailty and poor physical function are associated with increased wait-list mortality and post-LT morbidity and mortality (66,67). Factors contributing to frailty in patients with liver disease include a decline in physiological systems, poor cognition associated with hepatic encephalopathy, and frequent hospitalizations (68). Frailty is highly prevalent in patients with NAFLD (69) and is linked to poor nutritional status, comorbid cardiometabolic conditions, and sedentary lifestyle common in patients with metabolic syndrome (70). Physical activity can be further compromised by the presence of osteoarthritis, weakness, and social anxiety associated with exercise in patients with obesity.

While the severity of liver disease and of frailty progress together, interventions such as aerobic and anaerobic exercise are expected to slow the progression of hepatic decompensation and improve patient outcomes (71). Every patient with advanced chronic liver disease should undergo concurrent assessment for frailty and mobility, followed by exercise education and prescription, which are crucial for NAFLD patients (72,73).Multiple tools have been developed to assess frailty in elderly patients (reviewed in 74) and combine subjective and objective measures of physical ability. Many of these tools have been adopted for use in patients with liver disease, including the Fried Frailty Index, the Clinical Frailty

Scale, and the six-minute walk test (6MWT). The 6MWT is an independent predictor of patient survival in patients with cirrhosis, and each 100-m improvement is associated with improved survival (75).

The Liver Frailty Index was developed specifically for patients with ESLD. It combines grip strength, chair stands, and balance as independent predictors of wait-list mortality and a complicated post-LT course (76). Significantly, patients who experienced an improvement in their Liver Frailty Index scores had a lower risk of death on the LT wait-list, demonstrating the importance of mitigating or improving frailty (77). To date, most studies assessing frailty have focused on LT candidates, and there are few data on the role of frailty in predicting progression or regression of liver disease. Despite the need for frailty studies and exercise interventions specifically targeting the NAFLD population, ongoing assessment of frailty should be performed for all patients with advanced chronic liver disease. Concern regarding the development of frailty or loss of baseline function should trigger referral for specific counseling on interventions to slow or reduce development of frailty. Technology-based programs, which leverage home-based exercise and the use of motivational strategies, are promising for NAFLD (78).

SARCOPENIA IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE

Sarcopenia, or loss of muscle mass, is a marker of disease and confers a poor prognosis. Sarcopenia results from changes in the metabolic and endocrine function of muscle that in turn cause changes in physical conditioning, and it may be an independent driver of the development and progression of NAFLD. While sarcopenia is an important component of frailty, these two conditions are independently associated with patient outcomes (72). Multiple meta-analyses and population-based studies have demonstrated an association between sarcopenia and NAFLD, specifically, a 1.3–1.5-fold-increased risk of incidental NAFLD in patients with sarcopenia (79,80).In a Korean population-based study, the OR of developing NAFLD was 5.16 (95% CI, 1.63–16.33) between the lowest and highest quartiles of skeletal muscle mass (81). Additionally, the presence of sarcopenia in NAFLD was associated with a >2.5-fold increase in NASH and advanced fibrosis (81).

The diagnosis of sarcopenia is challenging, particularly in NAFLD patients in whom obesity may mask the clinical findings until the muscle loss becomes advanced (82). The reference standard of sarcopenia diagnosis is direct imaging-based measurements of the skeletal muscle mass area at the third lumbar (L3) vertebra by either computed tomography (CT) or magnetic resonance imaging (MRI). Sarcopenia defined by L3-skeletal muscle mass has demonstrated an association with pre- and post-LT morbidity and mortality (83, 84). While most studies on sarcopenia have focused on LT candidates, more recent research demonstrated an independent association between sarcopenia and NAFLD, and sarcopenia was associated with NAFLD (OR, 1.24; 95% CI, 1.03–1.48) and advanced fibrosis (OR,1.79; 95% CI,1.18–2.72) after adjustment of NAFLD-associated comorbidities (85, 86). Although obtaining such muscle area metrics is time consuming, artificial intelligence can do such calculations with high reliability (D.H. Hao, manuscript submitted), thus allowing future generalizability. Additionally, phase-angle bioelectrical impedance analysis

can accurately measure muscle mass and can be performed in the office setting, allowing for longitudinal data acquisition (87, 88).

These data suggest that sarcopenia has a direct effect on development of NAFLD and that management of sarcopenia may be important in slowing the progression of NASH. Patients with sarcopenia should be referred to a nutrition specialist for dietary recommendations to simultaneously treat sarcopenia and obesity, given that the caloric restriction required for weight loss needs to be counterbalanced by increased protein intake to help preserve muscle mass (68, 89). Dietary interventions, including increased lean protein consumption, late-night snacks, and branched-chain amino acid supplementation, should be encouraged, given their role in mitigating accelerated starvation and improving clinical and patient-reported outcomes (90).

CARDIOVASCULAR RISK STRATIFICATION

Cardiovascular disease, particularly coronary artery disease (CAD), is a leading cause of mortality in patients with NAFLD (91, 92). These patients have a greater risk of CAD compared with the general population [risk ratio (RR), 2.26; 95% CI, 1.04–4.92], even when adjusting for cardiovascular risk factors such as obesity and metabolic syndrome (6, 93, 94). In a cohort of 2,103 patients with diabetes followed for 6.5 years, those with NAFLD had a higher frequency of nonfatal CAD and cardiovascular death [hazard ratio (HR), 1.96; 95% CI, 1.4–2.7], again after adjustment for associated risk factors (91). A recent meta-analysis of more than 34,000 patients concluded that NAFLD confers a risk of fatal and nonfatal cardiovascular events (random effect OR, 1.64; 95% CI, 1.26–2.13) (95). Specifically, the presence of fibrosis and not just steatosis was independently associated with adverse cardiovascular outcomes (96). The use of NILDA for hepatic steatosis and fibrosis showed that LSM but not steatosis was associated with multiple cardiometabolic risk factors, including obesity, metabolic syndrome, and diabetes, providing further evidence of the association between NASH fibrosis and cardiovascular disease (97).

The atherosclerotic cardiovascular disease (ASCVD) risk estimator is used to classify patients as high risk for cardiovascular complications and initiation of statin therapy. A caveat of the ASCVD equation for patients with NAFLD is that systemic vasodilation might have overcome preexisting hypertension and synthetic dysfunction might have overshadowed prior dyslipidemia (98), thus rendering the equation inappropriate once disease is advanced. By applying the ASCVD risk estimator to patients with NAFLD, Lee et al. (99) demonstrated that high-risk patients with ultrasound evidence of steatosis had nearly twice the risk of cardiovascular mortality after a median follow-up of 17.7 years (adjusted HR, 2.02; 95% CI, 1.12–3.65). CT coronary artery calcification (CAC) can, however, predict the risk of CAD in the presence of advanced chronic liver disease. In a large study of healthy patients, Kim et al. (11) demonstrated that CAC is a similarly strong predictor of NAFLD (OR, 1.28; 95% CI, 1.04–1.59), even when controlling for traditional CAD risk factors including visceral adiposity. This finding suggests that NAFLD may be an independent risk factor for CAD. Therefore, these patients merit special consideration and aggressive risk modification. In particular, the use of statins is critical, though frequently underutilized due to unfounded concerns of hepatotoxicity. This underuse is evidenced

by a study in which fewer than 10% of patients undergoing a liver biopsy for NASH were prescribed a statin (100). Multiple studies have demonstrated that the rates of true statin-induced hepatotoxicity are exceedingly low and self-limited and that statin-associated hepatotoxicity is likely confounded by liver chemistry abnormalities related to undiagnosed NAFLD and not statins directly (101, 102). Statins are therefore considered safe in patients with Child–Pugh A and B cirrhosis, and each year of statin use is associated within an 8% decrease in mortality (HR, 0.920; 95% CI, 0.897–0.943) (103). In addition to protecting against cardiovascular risk, statin use has a favorable impact on portal hypertension (104, 105). Novel methods guiding ASCVD risk stratification in NAFLD, however, need to be explored.

CANCER SCREENING

All patients with cirrhosis should undergo routine screening for HCC. The annual incidence of HCC ranges from 1% to 6%, depending on the etiology of cirrhosis and the presence of concomitant risk factors. The annual incidence of NASH cirrhosis is not clearly defined, though studies report high ranges between 2.6% and 12.8% that are likely influenced by NAFLD comorbidities functioning as independent risk factors for HCC (106). Individualized risk stratification that accounts for risk factors apart from cirrhosis, such as smoking, diabetes, or a family history of HCC (107), could help triage HCC screening across the whole spectrum of patients with advanced chronic liver disease.

Patients with NAFLD-associated cirrhosis should undergo screening for HCC every 6 months. Abdominal ultrasound is routinely used for HCC screening; however, in patients with obesity the sensitivity of ultrasound to detect HCC is only 20%, compared with 60% in nonobese patients. This is in contrast to a sensitivity of 98% with cross-sectional imaging (108,109); therefore, either CT or MRI is the preferred method of screening in the setting of obesity with a poor ultrasound window (110–112). Incorporation of a novel ultrasound visualization score into LI-RADS (Liver Imaging Reporting and Data System) represents a step toward proper selection of patients who will benefit from CT- or MRI-based screening (113). Even though up to 12% of HCC cases are diagnosed in the absence of cirrhosis and mostly in the setting of NAFLD, to date there is insufficient evidence to screen for HCC prior to establishing a diagnosis of cirrhosis (41, 112, 114). However, NILDA-based diagnosis of cirrhosis using two methods (e.g., FIB-4 ≥ 2.67 and LSM ≥ 16.2 kPa) justifies commencing HCC screening (42).

NAFLD is also independently associated with multiple extrahepatic malignances, including colon and breast cancer. These are especially important because they can be prevented by routine screening (115). While there is no evidence to suggest a more aggressive screening protocol, patients with NAFLD should adhere to timely, age-appropriate screening protocols.

CONCLUSION

Despite the enormous clinical and economic burden of NAFLD, clinicians still struggle to identify patients at risk of liver disease progression and those who have it, due to the largely silent nature of the disease. The identification of patients with more advanced disease would

be greatly facilitated by the incorporation of NILDA into routine clinical practice. In this rapidly evolving field, there is still much to be learned about the factors that drive disease progression and result in a more rapidly evolving phenotype in a subset of individuals Emerging insights into genetic and microbial factors, as well as multiplatform omics data, are likely to assist in this endeavor in the short term. Large ongoing prospective studies will continue to deepen our understanding of the disease's natural history, clinical outcomes, and interaction with cardiometabolic risk factors in patients across the disease spectrum. Moreover, improved treatment strategies to induce durable weight loss and to specifically target NASH disease activity and fibrosis will be critical in damping the sequelae of this disease.

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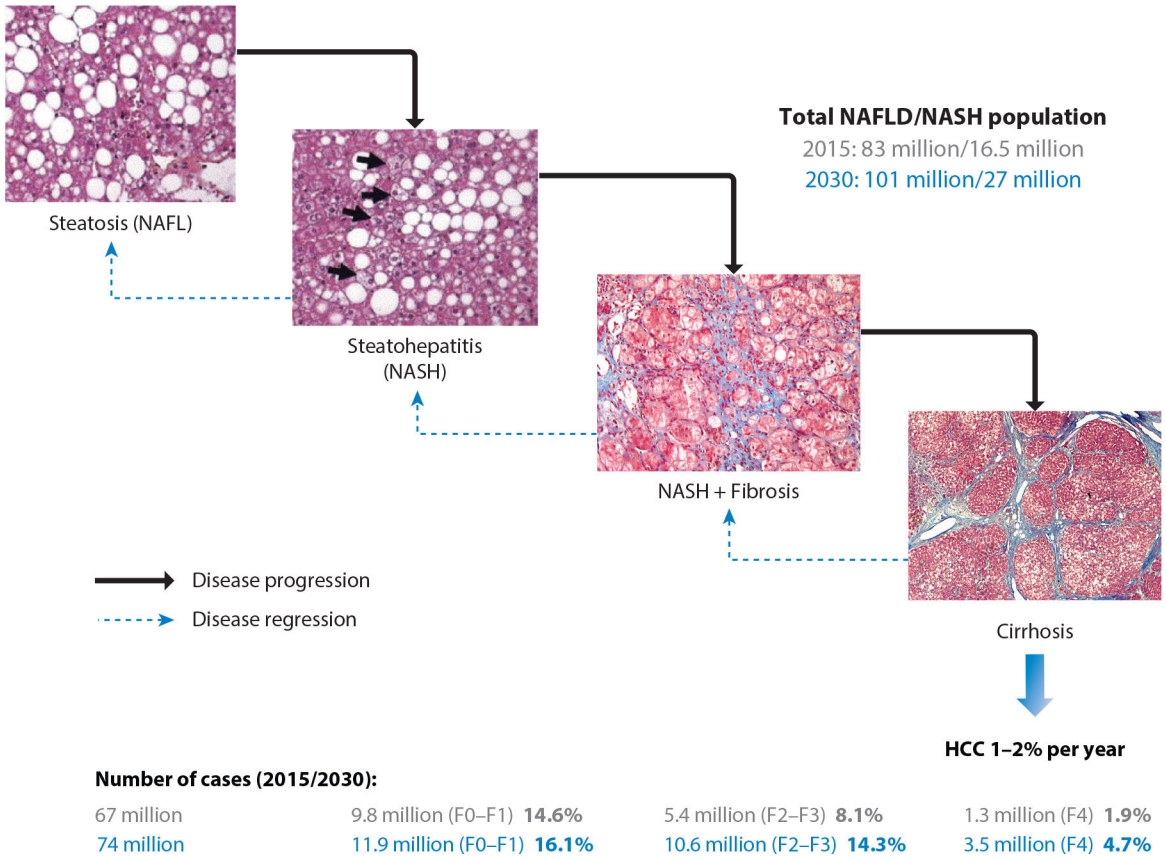

Figure 1.

Clinical course of NAFLD and its estimated prevalence in the United States. NAFLD progresses from simple steatosis (NAFL) to steatosis with inflammation and hepatocyte damage (NASH), development of fibrosis (NASH + fibrosis), and eventual cirrhosis with an increased risk of HCC. As a result of the rise in obesity, 100 million people in the United States are expected to develop NAFLD by the year 2030. While most patients will not progress to cirrhosis, nearly 10.6 million patients will develop advanced-stage fibrosis (F2–F3). Eventual progression to cirrhosis is expected to affect ~3.5 million people in the United States with in the next decade. Disease progression is not linear but can progress, regress, or remain stable (4). Abbreviations: F, fibrosis stage; HCC, hepatocellular carcinoma; NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis. Images provided by Dr. Laura Lamps.

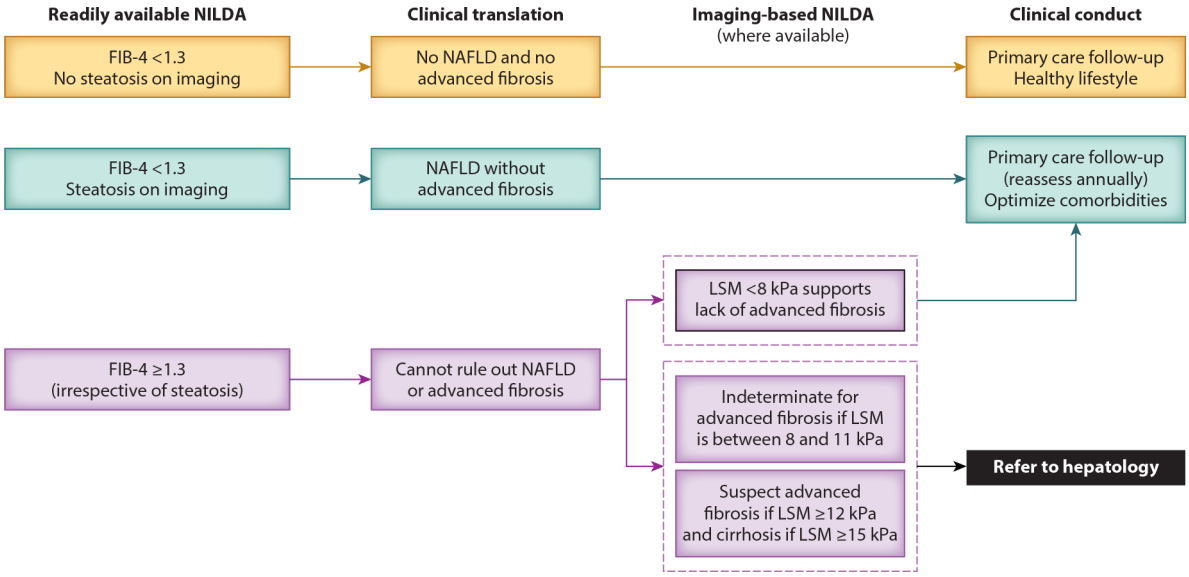

Figure 2.

NAFLD decision-making tool for primary care physicians. It is important for physicians to consider the risk of liver disease in patients with metabolic syndrome. With the increased use and validation of noninvasive modalities to assess for NAFLD and advanced fibrosis, physicians can effectively screen high-risk patients. Patients with no evidence of steatosis and a low-risk FIB-4 score require no additional workup, and they should adopt a healthy lifestyle and general risk modification. Patients with steatosis on imaging and a low-risk FIB-4 score can be followed conservatively with lifestyle intervention. Finally, patients with a FIB-4 score of ≥1.3 are at higher risk and require additional workup irrespective of steatosis by imaging. Such patients should undergo noninvasive LSM to estimate their potential fibrosis burden. Patients who may have indeterminate or advanced fibrosis as suggested by LSM should be referred to hepatology for further workup and management of liver disease. Abbreviations: FIB-4, fibrosis-4 index for liver fibrosis; LSM, liver stiffness measurement; NAFLD, nonalcoholic fatty liver disease; NILDA, noninvasive liver disease assessment.

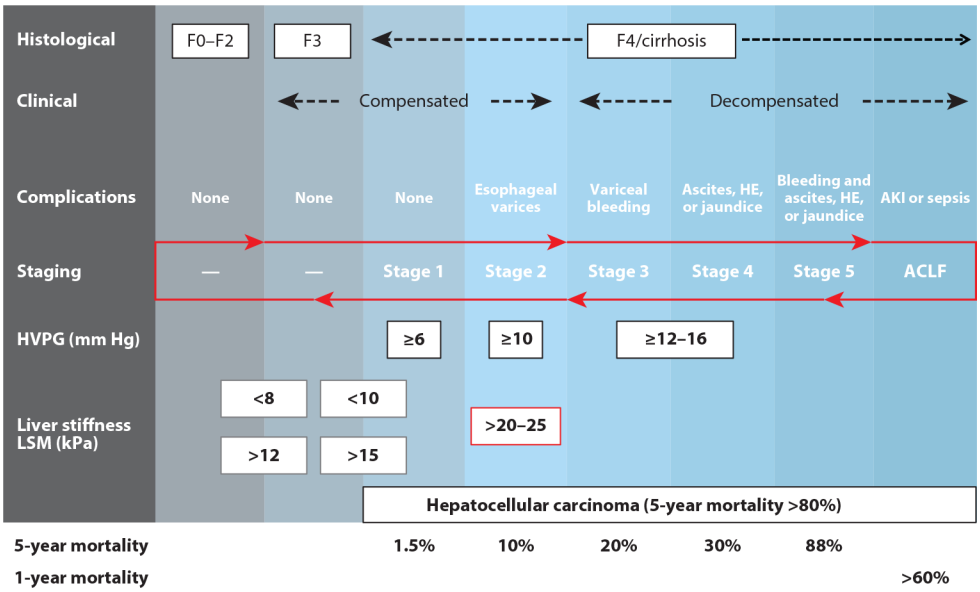

Figure 3.

Staging of chronic liver disease and associated mortality risk: a schematic representation of parameters associated with progression of liver disease. Compensated advanced chronic liver disease (stages 1–2) is characterized by the presence of cirrhosis, though with lower portal-hepatic pressure gradients and LSM and no clinical evidence of cirrhosis other than isolated nonbleeding esophageal varices. Disease progression is accompanied by an increase in LSM and portal pressure, resulting in progressive decompensating events including esophageal variceal bleeding, ascites, and encephalopathy. In the most severe cases, a secondary insult such as infection or kidney injury can precipitate ACLF, a highly lethal condition with poor overall survival. This is not a stepwise linear process, and patients can present at any stage of cirrhosis and undergo resolution of decompensating events with treatment of underlying hepatic injury. Abbreviations: ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; HE, hepatic encephalopathy; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement.

Table 1

Causes of hepatic steatosis

Macrovesicular	Microvesicular
Excessive alcohol	Acute fatty liver of pregnancy
Hepatitis C	HELLP syndrome[a]
Autoimmune hepatitis	Reye's syndrome
Parenteral nutrition	Inborn errors of metabolism
Starvation	Medications (valproate, antiretrovirals)
Wilson's disease	
Lipodystrophy	
Abetalipoproteinemia	
Medications (amiodarone, methotrexate, tamoxifen, corticosteroids, antiretrovirals)	

[a]Hemolysis, elevated liver enzymes, low platelet count.

Table 2

Clinical scenarios requiring workup of NAFLD

Abnormal liver chemistry	High-risk cardiometabolic features	Abnormal imaging
Persistent elevation (>6 months) Other causes of liver disease ruled out	Diabetes mellitus Age >50 years Obesity (race-adjusted body mass index) Hypertension Panhypopituitarism	Abdominal US with increased echogenicity Abdominal CT with evidence of steatosis Abdominal MR with evidence of steatosis

Abbreviations: CT, computed tomography; MR, magnetic resonance; NAFLD, nonalcoholic fatty liver disease; US, ultrasound.