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CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on Screening and Surveillance for Hepatocellular Carcinoma in Patients With Nonalcoholic Fatty Liver Disease: Expert Review

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Nonalcoholic fatty liver disease (NAFLD) is a leading etiology for chronic liver disease with an immense public health impact and affects >25% of the US and global population. Up to 1 in 4 NAFLD patients may have nonalcoholic steatohepatitis (NASH). NASH is associated with significant morbidity and mortality due to complications of liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC). Recent data confirm that HCC represents the fifth most common cancer and is the second leading cause of cancer-related death worldwide, and NAFLD has been identified as a rapidly emerging risk factor for this malignancy. NAFLD-associated liver complications are projected to become the leading indication for liver transplantation in the next decade. Despite evidence that NAFLD-associated HCC may arise in the absence of cirrhosis, is often diagnosed at advanced stages, and is associated with lower receipt of curative therapy and with poorer survival, current society guidelines provide limited guidance/recommendations addressing HCC surveillance in patients with NAFLD outside the context of established cirrhosis. Limited data are presently available to guide clinicians with respect to which patients with NAFLD should undergo HCC surveillance, optimal screening tools, frequency of monitoring, and the influence of coexisting host- and disease-related risk factors. Herein we present an evidence-based review addressing HCC risk in patients with NAFLD and provide Best Practice Advice statements to address key issues in clinical management.

Keywords: HCC; NASH; Fibrosis; Cirrhosis.

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the world, including the United States. It is estimated that 80–100 million Americans may have NAFLD. NAFLD is strongly associated with obesity, diabetes, and metabolic syndrome.[1–3] NAFLD is broadly classified into 2 subtypes: NAFL, a mostly nonprogressive subtype, and nonalcoholic steatohepatitis (NASH), the progressive subtype of NAFLD. NASH may incite liver injury that can result in progressive hepatic fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). The advancement of NAFLD-related liver disease to cirrhosis and HCC is associated with a significant increase in liver-related morbidity and mortality.[4,5] NASH has become the second leading indication for liver transplantation in the United States, and is expected to become the leading indication in the next decade.[6]

The incidence of NAFLD-related HCC is increasing in the United States.[7] Despite this rise in the incidence, screening and surveillance for HCC among patients at risk of developing HCC is suboptimal in general, and is disproportionately lower in patients with NAFLD-related HCC.[8–10] Therefore, there is a major unmet need to provide clear Best Practice Advice to clinicians regarding risk assessment of HCC among patients with NAFLD and appropriate screening and surveillance strategies. Additionally, in the face of increasing incidence of NAFLD-related HCC, there is a pressing need to identify interventions to mitigate risk for HCC. Screening is defined as the index assessment for the identification of HCC in those at risk, while surveillance is defined as ongoing periodic, systematic assessment for the identification of HCC in those at risk. For simplicity, we will use screening throughout this article for both index and follow-up assessment for HCC in the population at risk.

This review is designed to provide recommendations and guidance on several key clinical issues pertaining to HCC risk, screening, and interventions in patients with NAFLD. We have developed Best Practice Advice statements to address 8 key clinical issues. This expert review was commissioned and approved by the American Gastroenterological Association (AGA) Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer

Abbreviations used in this paper: **AGA, American Gastroenterological Association; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; HR, hazard ratio; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OR, odds ratio; PAF, population attributable fraction; T2DM, type 2 diabetes mellitus; VCTE, virtual contrast transient elastography.**

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review by the Clinical Practice Updates Committee and external peer review through standard procedures of the Journal.

Best Practice Advice 1: Screening for Hepatocellular Carcinoma Should Be Considered in All Patients With Cirrhosis Due to Nonalcoholic Fatty Liver Disease

The association between NAFLD cirrhosis and HCC is well-established, and most experts believe that screening should be recommended in this setting. The decision to enter a patient into a screening program for HCC is determined by the level of risk for HCC, while also taking into account the patient's age, overall health, functional status, and willingness and ability to comply with screening assessment and, if found, to have an HCC, whether this individual would be an appropriate candidate for treatment. Understanding the aforementioned caveats, HCC screening should be offered for patients with cirrhosis of varying etiologies when the risk of HCC is approximately $\geq$1.5% per year, as has been noted with NAFLD cirrhosis. It is now well-established from several observational cohort and case–control studies that cirrhosis due to NAFLD is associated with an increased risk of HCC, and emerging data suggests that the incidence of NAFLD-related HCC is rising in the United States, thereby, necessitating the importance of screening for HCC in this patient population.[11]

Both NAFLD cirrhosis and HCC share common risk factors, including obesity, metabolic syndrome, and diabetes.[4] This becomes particularly relevant as approximately 80% of patients with NAFLD cirrhosis have co-existing diabetes or obesity.

The risk of incident HCC in NAFLD cirrhosis is estimated in the literature to range between 1% and 3% per year.[12] Ascha et al[13] conducted a retrospective study including 195 patients with NASH cirrhosis who were followed for a median duration of 3.2 years, and 25 of them developed incident HCC at a cumulative incidence rate of 2.6% per year.[13] On multivariable analyses, older age and consumption of alcohol were the only independent predictors of incident HCC in NAFLD cirrhosis. In a Japanese study including 69 patients with NASH cirrhosis who were followed for a median duration of 5 years, 11 developed HCC at an annual incidence rate of 2.3%.[14] A recent large retrospective cohort study from the national Veterans Affairs system in the United States estimated HCC risk in 296,707 NAFLD patients and 296,707 matched controls without known liver disease and found the risk of HCC to be several fold higher than controls. Among patients with NAFLD, those with cirrhosis had the highest overall annual incidence of HCC (1.06% annual risk), but it ranged from 0.2% in women to 2.4% in older Hispanics with cirrhosis. Most estimates of HCC in subgroups of age, sex, and race were close to or exceeded 1% per year and, therefore, although these differences are possibly informative to disease pathophysiology, we do not recommend using (age, sex, and ethnicity-specific) them yet in the clinical decision making of whether to screen or not for HCC in NAFLD-related cirrhosis.

In general, the incidence rate of HCC in NAFLD cirrhosis is estimated to be >1.5% per year and, therefore, screening for HCC in this group is justifiable, based on cost-effectiveness considerations. Therefore, we recommend that best practice guidance is to consider and offer HCC screening to all patients with NAFLD cirrhosis. At this point, we believe that HCC screening benefit is restricted to patients with compensated cirrhosis or those with decompensated cirrhosis listed for liver transplantation.

Best Practice Advice 2: Patients With Nonalcoholic Fatty Liver Disease With Noninvasive Markers Showing Evidence of Advanced Liver Fibrosis or Cirrhosis Should Be Considered for Hepatocellular Carcinoma Screening

Staging of liver fibrosis in NAFLD is a clinical priority, given that the risk of liver-related mortality, including HCC, is increased in those with advanced fibrosis.[5] Liver biopsy may provide clinically helpful information in NAFLD, including features and severity of NASH and staging of fibrosis.[15] However, due to the large burden of NAFLD, with the majority of cases having mild and nonprogressive phenotype (NAFL), liver biopsy is not tenable as a primary staging method in routine clinical practice.[16] Liver imaging is useful for ruling in cirrhosis, but has low negative predictive value in that the absence of overt imaging features of cirrhosis do not exclude the presence of advanced fibrosis. In cases where advanced fibrosis or cirrhosis has not been established via histology or imaging, noninvasive testing offers the opportunity to identify patients with fibrosis severity that places them at sufficiently high HCC risk to justify HCC surveillance.

The advent and availability of noninvasive methods to estimate the presence and degree of liver fibrosis has led to increasing utilization of this approach in clinical practice to risk stratify NAFLD patients.[17] There are 3 groups of noninvasive tests for fibrosis: point-of-care tests, specialized blood tests, and imaging-based tests. Point-of-care tests use a combination of demographic and clinical laboratory tests requiring no or little cost; these tests include the aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio; AST to platelet ratio index; body mass index (BMI), AST, ALT, and diabetes; NAFLD fibrosis score (age, BMI, AST, ALT, platelets, albumin, and diabetes/impaired fasting glucose), and FIB-4 (age, AST, ALT, and platelets). For example, an FIB-4 score >2.67 has been associated with higher odds of having cirrhosis or bridging fibrosis. Using a large Veterans Affairs database, Kanwal et al.[18] showed that FIB-4 >2.67 is associated with increased risk of HCC not only in those with known cirrhosis but also in those without prior diagnosis of cirrhosis. Specialized serum-/plasma-based tests include Enhanced Liver Fibrosis panel (contains hyaluronic acid, PIIINP, and TIMP-1), Fibrospect 2 (contains hyaluronic acid, α-2 macroglobulin, and TIMP-1), FibroMeter, and

Fibrosure.[19] Noninvasive imaging methods include vibration-controlled transient elastography (VCTE), shear-wave elastography, acoustic radiation force impulse imaging, and magnetic resonance elastography (MRE). Based on published data and guidelines, we believe that it is reasonable to consider HCC screening in patients who have NAFLD with noninvasive markers suggestive of cirrhosis in the absence of biopsy-confirmed cirrhosis or overt cirrhosis on imaging.

We recommend combining at least 2 noninvasive testing modalities,[16,20,21] each coming from 1 of the main 3 groups of tests (such as FIB-4 [point of care] or Enhanced Liver Fibrosis Panel [serum-based specialized test]; Enhanced Liver Fibrosis cut-point $\geq$11.3 associated with cirrhosis] with elastography examination). Individuals in whom both tests are concordant for advanced fibrosis or cirrhosis should be considered for HCC screening. These tests should also be interpreted in context of full clinical information, including physical examination, laboratory profile, and imaging findings.[22–24]

When utilizing noninvasive tests to risk stratify patients for HCC screening, a higher cut-point threshold is desirable to maximize specificity (90%). The following cut points for VCTE and MRE may be considered for noninvasive detection of cirrhosis for purposes of HCC screening: VCTE 16.1 kPa and MRE of 5 kPa.[25] The threshold for detection of cirrhosis are different between VCTE and MRE because different formulas are used to calculate the liver stiffness value in kPa units; for example, Young's modulus is used for VCTE and Shear modulus is used for MRE, resulting in different thresholds.[16]

Best Practice Advice 3: Patients With Nonalcoholic Fatty Liver Disease in the Absence of Advanced Liver Fibrosis Should Not Be Routinely Considered for Hepatocellular Carcinoma Screening

Several studies have shown that patients with NAFLD without cirrhosis may, albeit rarely, develop HCC.[26] White et al[27] conducted a systematic review and a meta-analysis to determine the point estimate of the risk of incident HCC in noncirrhotic NAFLD, and concluded that the risk estimate is likely to be too low to justify routine screening in those who have early NAFLD with no evidence of advanced fibrosis. These data were recently updated by Reig and colleagues,[28] who also reached a similar conclusion. In the previously mentioned national Veterans Affairs study, HCC incidence rates were 0.21/1000 person-years (0.02% annual risk) in NAFLD and 0.02/1000 person-years (0.002% annual) in controls with adjusted hazard ratio (HR) of 7.62 (95% confidence interval [CI], 5.76–10.09). We believe that, based on current evidence, the incidence of HCC in those with NAFLD and earlier stages of fibrosis (stage 0–2) is extremely low and not precisely defined. Therefore, systematic HCC screening may not be prudent at this time.[18]

The role of genetic risk factors in identifying those at higher risk at earlier stages is an area of active research. However, there are no clear data to justify routine genetic risk–based HCC screening in NAFLD at this time, although the presence of the PNPLA3 risk allele is increased in those with NAFLD-related HCC and those with NAFLD-related cirrhosis. Due to the limited ability to obtain this test in clinical practice and the absence of relevant data to justify using PNPLA3 status for identifying those at higher risk of HCC, independent of the presence of cirrhosis, the clinical utility of a genetic risk–based approach is currently not supported.[29,30] Recent studies have shown a possible protective effect for HSD17B13 genotype in the risk of progression to cirrhosis due to NAFLD.[31] However, it is unknown whether harboring this SNP or a group of SNPs may alter the risk of HCC in NAFLD patients, especially those without cirrhosis. Future studies are needed to assess whether there may be specific genetic risk scores that can be utilized to identify a population with elevated HCC risk that is high enough to justify routine screening of HCC in early stages of NAFLD fibrosis.

Therefore, although there is a higher risk of developing HCC in those with earlier stages of NAFLD than people without NAFLD, the incidence rates and determinants of risk have not been well-quantified and are probably too low to justify routine screening at this point.

Best Practice Advice 4: Adequacy of Ultrasound in Assessing the Liver Parenchyma for Mass Lesions Should Be Documented When Used for Hepatocellular Carcinoma Screening in Patients With Cirrhosis Due to Nonalcoholic Fatty Liver Disease

Best Practice Advice 5: When the Quality of Ultrasonography Is Suboptimal for Screening of Hepatocellular Carcinoma (eg, Due to Obesity) Future Screening Should Be Performed by Either Computed Tomography or Magnetic Resonance Imaging Scan, With or Without α-Fetoprotein, Every 6 Months

In patients with cirrhosis who have a good acoustic window, ultrasound is highly accurate as well as cost-effective for detection of HCC. There is published evidence as well as anecdotal experience suggesting that liver ultrasound quality, as assessed by independent review from abdominal-trained radiologists, can be inadequate for HCC screening in approximately 20% of all patients. A few observational studies have reported that the likelihood of inadequate ultrasound quality is significantly higher in overweight or obese patients[32,33] who, in turn, are more likely to have a NASH etiology for cirrhosis.[32,33] Irrespective of cirrhosis etiology, ultrasound is also operator-dependent. The recommendation is for ultrasound to be performed by individuals with at least level 2 credentials according to the European Federation of Societies

for Ultrasound in Medicine and Biology and Societatea Română de Ultrasonografie în Medicină și Biologie Classification of Level of Practice for Ultrasound (www.efsumb.org or www.srumb.ro); this entails a combination of technical experience as measured by volume of procedures, supervision, knowledge of anatomy, and disease processes. The degree to which these requirements are followed in clinical practice is unclear. Therefore, we recommend to consistently record the adequacy of liver ultrasound, including parenchyma heterogeneity, visualization of entire liver, and beam attenuation. These criteria were recently compiled by 2017 Liver Imaging Reporting and Data System ultrasound quality criteria,[32,34] although there are no studies that systematically assess the utility of these criteria. The visualization score for ultrasound for HCC screening is graded into the following categories: A as no or minimal limitation; B as moderate limitation defined, as the examination may obscure small masses; and C as severe limitation, defined as the examination may miss focal liver lesions. Consequently, if ultrasound quality is inadequate (especially if category C or in some cases with category B), we recommend considering other imaging modalities (eg, computed tomography scan or magnetic resonance imaging [MRI]) for HCC screening. While the PRIUS study (A Prospective Intra-individual Cohort Study to Compare Gadoxetic Acid [Primovist®]-Enhanced Magnetic Resonance Image and Ultrasonography for the Surveillance of Early Stage Hepatocellular Carcinoma in Patients at High-Risk) suggested that MRI-based screening may be superior to ultrasound-based screening, this comparison was not specifically studied or reported in patients with poor ultrasound quality. The cost-effectiveness of HCC screening is not likely to be favorable if computed tomography or MRI replaces ultrasound among all comers[35] with NAFLD-related cirrhosis and, therefore, is best reserved for those in whom ultrasound quality is low.[35] In one cost-effectiveness analysis, based on the aforementioned PRIUS study,[36] the use of MRI incurred $5562 incremental costs, 0.384 incremental life-years, and 0.221 incremental quality life-years saved compared to ultrasound. However, the study was limited to patients with hepatitis B virus–related cirrhosis and the annual HCC incidence was the most influential factor on the cost-effectiveness as expressed by incremental cost-effectiveness ratio. When the annual HCC incidence rate was >1.81%, the incremental cost-effectiveness ratio was <$50,000/quality life-year. The annual risk of HCC in NAFLD-related cirrhosis may be slightly lower than these estimates (0.5%–1.4% per year).[18,27] Finally, the appropriate interval of follow-up imaging in the context of either CT or MRI and their use in combination with serum α-fetoprotein remains to be studied.[37]

Best Practice Advice 6: Patients With Cirrhosis Due to Nonalcoholic Fatty Liver Disease Should Be Counseled on Abstaining From Alcohol Drinking and Tobacco Smoking

Tobacco smoking has been associated with increased risk of NAFLD,[38,39] potentially mediated by insulin resistance and altered body fat distribution. Smoking has also been associated with advanced liver fibrosis in patients with NAFLD.[40] Several constituents of tobacco smoke have been identified as liver carcinogens, and tobacco use has generally been shown to be a modest-strength risk factor for HCC.[41,42] In a meta-analysis, compared with never smokers, the adjusted meta-relative risk for HCC was 1.51 (95% CI, 1.37–1.67) for current smokers and 1.12 (95% CI, 0.78–1.60) for former smokers.[42] Despite the modest risk estimates, the population attributable fraction (PAF) is relatively large due the high prevalence of smoking. Data from GLOBOCAN 2012 and the International Agency for Research on Cancer were utilized to determine global and regional PAFs for major HCC risk factors.[43] Smoking accounted for 13% and 9% of HCC globally and in North America, respectively. The Liver Cancer Pooling Project is a consortium of 14 US-based prospective cohort studies that includes data from 1,518,741 individuals and 1423 cases of HCC.[44] In an analysis of these pooled data, current smokers had increased risk of HCC (HR, 1.86; 95% CI 1.57–2.20), while individuals who quit more than 30 years ago had risk near equivalent to never smokers. Smoking is also associated with lower survival rates in HCC.[45,46] In summary, tobacco smoking may increase fibrosis progression, risk of developing HCC, and HCC-related mortality in patients with NAFLD. As such, we recommend that all patients with NAFLD should be counseled to abstain from tobacco smoking. Although specific data do not exist, we believe that e-cigarettes may turn out to be equally harmful and that patients should be counseled to abstain from those as well.

Data from GLOBOCAN 2012 and the International Agency for Research on Cancer found PAF for alcohol in HCC to be 26% and 32% globally and in North America, respectively.[43] Irrespective of NAFLD, the bulk of epidemiological data support alcohol drinking as a major risk for HCC (with PAF ranging from 13%–32%). A meta-analysis of prospective cohort and nested case–control studies found no significant increased risk for moderate alcohol use (<3 drinks/d) and relative risk (RR) 1.16 (95% CI, 1.01–1.34) for heavy drinking (≥3 drinks/d).[47] A second meta-analysis including data from both prospective and retrospective observational studies found only heavy drinking (>50 g/d) was associated with an increased risk of HCC (RR, 2.07 (95% CI, 1.66–2.58).[48] Similarly, Liver Cancer Pooling Project data found, compared to nondrinkers, only heavy alcohol consumption (≥7 drinks/d) was associated with an 87% increased HCC risk,[44] whereas light or moderate alcohol consumption (<3 drinks/d) was inversely associated with HCC risk. While alcohol use increases risk for death from HCC, this effect is attenuated after prolonged (>10 years) sobriety.[46] One single-center study evaluating risks for HCC among patients with cirrhosis due to NASH reported any alcohol use as an independent risk for cancer (HR, 3.8; 95% CI, 1.6–8.9; $P = .002$).[13] In summary, the evidence supports the association between heavy alcohol use and elevated HCC risk, but the precise threshold at which a higher risk of HCC becomes apparent varies across studies. Several population-based studies have also demonstrated the synergistic effect of alcohol and obesity in

increasing the risk of cirrhosis and HCC.[49,50] While data regarding HCC risk with lesser quantity of alcohol consumption are less well-defined, minimization of alcohol consumption with complete abstinence when feasible, is advised for patients with NAFLD and advanced liver fibrosis to reduce risk of developing HCC. We recommend that all patients with NAFLD cirrhosis should abstain from alcohol because alcohol increases HCC risk, as well as the risk of hepatic decompensation and death from liver disease.

Best Practice Advice 7: Optimal Management of Diabetes and Dyslipidemia Through Lifestyle Modification and Pharmacotherapy Is Encouraged in Patients With Nonalcoholic Fatty Liver Disease and Advanced Liver Fibrosis Who Are at Risk for Hepatocellular Carcinoma

Type 2 diabetes mellitus (T2DM) is a common and well-established risk factor for NAFLD, advanced liver fibrosis, and HCC.[51] Multiple population-based case–control and cohort studies have confirmed a significant association between T2DM and incident HCC in patients with and without viral hepatitis.[51–54] In an analysis of 2 large observational cohorts (Nurses' Health Study and Health Professionals Follow-Up Study), which included 120,826 women and 50,284 men, with 32 years of follow-up (4,488,410 person-years), T2DM was associated with an increased HCC risk (HR, 4.59; 95% CI, 2.98–7.07), with the strongest association observed in patients with greater T2DM duration (HR, 7.52; 95% CI, 3.88–14.58 in patients with T2DM $\geq$10 years) and in those with increasing number of metabolic abnormalities (HR, 8.10; 95% CI, 2.48–26.70 if T2DM, obesity, hypertension, and dyslipidemia).[52] The association between T2DM and both HCC incidence and HCC mortality have been further confirmed in several meta-analyses.[54–57] Antidiabetic medications may potentially modify the risk of HCC in patients with T2DM. A meta-analysis by Singh et al[58] evaluating 10 studies with 22,650 HCC cases in 334,30 patients with T2DM revealed that while metformin use was associated with a reduction in HCC incidence (odds ratio [OR], 0.50; 95% CI 0.34–073). In contrast, sulfonylurea use (OR, 1.62; 95% CI, 1.16–2.24) and insulin use (OR, 2.61; 95% CI, 1.46–4.65) were associated with increased HCC incidence.[58] Other recent studies have further confirmed an association between metformin and decreased HCC incidence,[59,60] although uniform assessment of co-existing NASH was not performed in these studies. Metformin and other antidiabetic medications, such as sulfonylureas, insulin, sodium-glucose cotransporter-2 inhibitors, and dipeptidyl peptidase-4 inhibitors have not demonstrated meaningful improvement in liver histology end points among patients with NAFLD. In contrast, glucagon-like peptide-1 receptor agonists and thiazolidinediones with agonism for the nuclear transcription factor peroxisome proliferator–activated receptors α, γ, and/or δ have demonstrated potential activity for improvement in hepatic steatosis, inflammation, ballooning degeneration, and fibrosis. The peroxisome proliferator–activated receptor agonist pioglitazone and the glucagon-like peptide-1 receptor agonist liraglutide have demonstrated potential benefit in achieving NASH resolution in patients with biopsy-proven NASH in randomized placebo controlled trials,[61–64] although no association with change in HCC risk has been demonstrated. In summary, metformin is associated with a significant decrease in incident HCC among patients with T2DM who have cirrhosis and may be used in patients for whom treatment of T2DM is indicated, although further investigation in patients with coexisting NASH are needed.

Dyslipidemia (high serum triglyceride, decreased serum high-density lipoprotein levels, increased serum low-density lipoprotein) is also a well-established risk factor for NAFLD, which has an estimated overall prevalence of 53.8% of patients attending lipid clinics, and 78.0% among the subgroup with the highest total cholesterol to high-density lipoprotein cholesterol or triglyceride to high-density lipoprotein cholesterol ratios.[65] Among patients with NAFLD, dyslipidemia is associated with an increased risk of NASH and cardiovascular disease,[65–67] but has not been demonstrated to represent an independent risk factor for liver-related mortality.[66,67] Recent data suggest a possible association between hyperlipidemia and HCC incidence in non-cirrhotic patients with biopsy-proven NASH.[68] Dyslipidemia is routinely treated with antilipidemic agents, such as statins, although limited data are available to clarify the impact of statins on clinical outcomes in patients with NAFLD. Statins have not demonstrated evidence of histologic improvement in hepatic steatosis, steatohepatitis, or fibrosis among patients with biopsy-proven NASH and/or fibrosis, and mixed results have been observed in limited studies evaluating the impact of statins on cardiovascular outcomes in patients with NAFLD.[68–70] However, statins do not appear to be associated with higher risk for drug-induced liver injury in patients with NAFLD than patients without NAFLD and, therefore, can be used safely for the treatment of dyslipidemia.[4] Outside the context of NAFLD, statins have been demonstrated in multiple case–control and cohort studies to be associated with a decreased risk of HCC[71–73]; a recent meta-analysis of 10 studies involving 4298 HCC cases among 1,459,417 patients revealed a decreased risk for HCC in patients on statin (OR, 0.63; 95% CI, 0.52–0.76).[74] Overall dyslipidemia represents an independent risk factor for NAFLD, NASH, and cardiovascular disease, although there are inadequate data to confirm an association with HCC. Statin treatment can be used safely in patients with NAFLD, and has been consistently associated with a decreased risk of HCC, although further research is needed to clarify its effect on HCC in the context of NAFLD/NASH. This expert panel supports the notion that the benefits of statin therapy among patients with dyslipidemia and NAFLD significantly outweigh the risk and should be utilized routinely.

Optimal management of diabetes and dyslipidemia is recommended for the established diabetic and cardiovascular benefits and as it may also mitigate incident risk of HCC. However, large randomized controlled trials are

needed to examine the role of specific antidiabetic and lipid-lowering therapies and their role as chemopreventive agents for reducing HCC risk in NAFLD cirrhosis.

Best Practice Advice 8: Optimal Management of Obesity Through Lifestyle Modification, Pharmacotherapy or Endoscopic or Surgical Bariatric Procedures Is Encouraged in Patients With Nonalcoholic Fatty Liver Disease and Advanced Liver Fibrosis Who Are at Risk for Hepatocellular Carcinoma

Obesity is the most common and well-described risk factor for NAFLD. This association is observed across the entire spectrum of obesity, including overweight (BMI 25.0–29.9 kg/m^2), obesity (BMI 30.0–39.9 kg/m^2), and morbid obesity (BMI $\geq$40.0 kg/m^2). Among individuals with morbid obesity undergoing bariatric surgery, >95% of patients have histologic evidence of NAFLD.[75] Furthermore, severity of obesity is associated with increased risk of advanced liver fibrosis and HCC in NAFLD.[76] Available data from randomized trials support a direct role for weight loss in reducing hepatic steatosis through hypocaloric diet (reduction of daily caloric intake of 500–1000 kcal) with or without associated moderate-intensity exercise, both of which can be generally recommended for patients with NAFLD and/or biopsy-proven NASH.[4] However, neither medical weight loss nor moderate-intensity exercise have been associated with a decreased risk of incident HCC.[77] Surgical weight loss through bariatric surgery has been associated with NASH resolution and fibrosis improvement in up to 85% and 33% of patients, respectively[78]; however, inadequate data are available to confirm the impact of bariatric surgery on HCC incidence and outcomes.[79] The impact of other weight-loss strategies (eg, pharmacotherapy, meal replacement, and bariatric endoscopy) on HCC risk has not been studied and requires further investigation. Overall, obesity remains an important risk factor for NAFLD and NAFLD-associated HCC. Weight-loss interventions are strongly recommended to improve NAFLD-related outcomes,[4] although additional investigation is needed to further examine the effect of weight loss on HCC risk in patients with NAFLD.

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Conflicts of interest

These authors disclose the following: Dr Loomba serves on the steering committee of the REGENERATE Trial funded by Intercept Pharmaceuticals. Dr Loomba serves as a consultant or advisory board member for Bird Rock Bio, Celgene, Enanta, GRI Bio, Madrigal, Metacrine, NGM, Receptos, Sanofi, Arrowhead Research, Galmed, NGM, GIR, and Metacrine. In addition, his institution has received grant support from Allergan, BMS, BI, Daiichi-Sankyo, Eli-Lilly, Galectin, Galmed, GE, Genfit, Intercept, Janssen, Madrigal, Merck, NGM, Pfizer, Prometheus, Siemens, and Sirius. He is also co-founder of Liponexus. Dr Lim has received research contracts (to Yale University) from Allergan, AbbVie, Conatus, Genfit, Gilead, and Intercept, and has received consulting honoraria from Gilead. Dr Patton has received funding for research (indirect, paid to institution) from Gilead Sciences. The remaining authors disclose no conflicts.

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