Current Challenges and Future Direction in Surveillance for Hepatocellular Carcinoma in Patients with Nonalcoholic Fatty Liver Disease

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Semin Liver Dis 2023;43:89–99.

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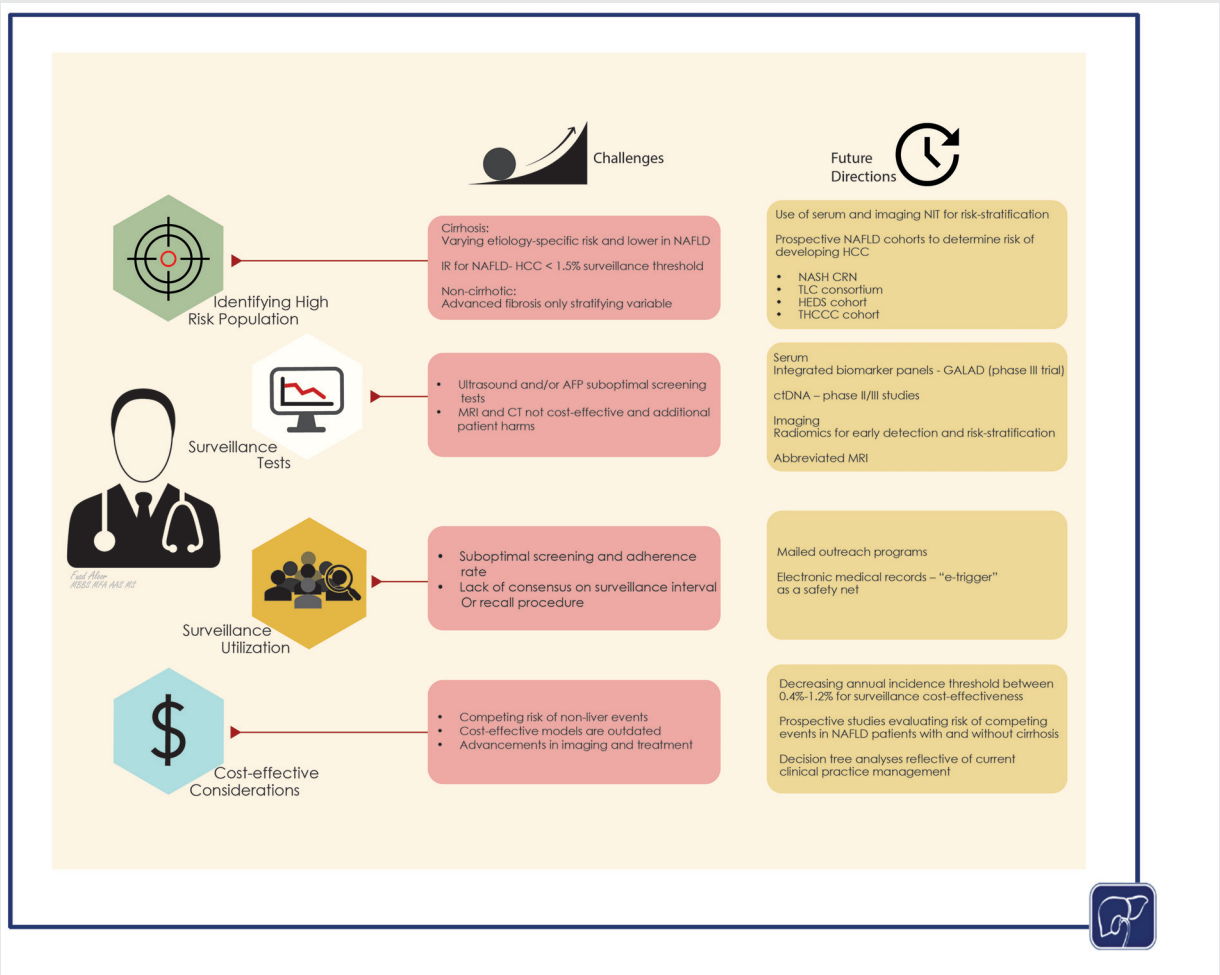
Graphical Abstract



accepted manuscript online
October 10, 2022
article published online
December 26, 2022

Thieme Medical Publishers, Inc.,
333 Seventh Avenue, 18th Floor,
New York, NY 10001, USA

DOI https://doi.org/10.1055/a-1957-8540.
ISSN 0272-8087.

Abstract

The burden for hepatocellular carcinoma (HCC) attributed to nonalcoholic fatty liver disease (NAFLD) continues to grow in parallel with rising global trends in obesity. The risk of HCC is elevated among patients with NAFLD-related cirrhosis to a level that justifies surveillance based on cost-effectiveness argument. The quality of current evidence for HCC surveillance in all patients with chronic liver disease is poor, and even lower in those with NAFLD. For a lack of more precise risk-stratification tools, current approaches to defining a target population in noncirrhotic NAFLD are limited to noninvasive tests for liver fibrosis, as a proxy for liver-related morbidity and mortality. Beyond etiology and severity of liver disease, traditional and metabolic risk factors, such as diabetes mellitus, older age, male gender and tobacco smoking, are not enough for HCC risk stratification for surveillance efficacy and effectiveness in NAFLD. There is an association between molecular and genetic factors and HCC risk in NAFLD, and risk models integrating both clinical and genetic factors will be key to personalizing HCC risk. In this review, we discuss concerns regarding defining a target population, surveillance test accuracy, surveillance underuse, and other cost-effective considerations for HCC surveillance in individuals with NAFLD.

Keywords

- liver cancer
- cirrhosis
- surveillance
- guidelines
- biomarkers
- fatty liver

Epidemiology for NAFLD and HCC and Rationale for HCC Surveillance

Hepatocellular carcinoma (HCC) is a major contributor to the global cancer burden, with rising global frequency of cases, and in some regions of the United States and several parts of the Western world also rising incidence and mortality rates over the past decade shown in ►**Fig. 1** (2010–2019).[1] Most patients with HCC are diagnosed at a late stage, for which the prognosis is typically dismal. In few patients who are diagnosed at an early stage, receipt of curative treatment (i.e., liver transplantation, resection, or ablation) and long-term survival may be possible.[2–4] Therefore, knowledge of the epidemiology and risk factors of HCC is essential for the primary and secondary prevention efforts in the form of screening and treatment of HCC risk factors. Such knowledge is also crucial for tertiary prevention in the form of identifying high-risk populations followed by surveillance for early-stage HCC detection, so that intervention can be applied to improve overall prognosis.

Most HCCs develop in the setting of cirrhosis from chronic liver disease, with hepatitis B virus (HBV) and hepatitis C virus (HCV) as the predominant risk factors worldwide. Due to effective vaccination programs for HBV and treatment for HBV and HCV, the population attributable factor (PAF) for HCC from chronic viral hepatitis has started and is expected to continue to decline over the coming years.[2,5,6] In parallel with the rising prevalence of obesity and metabolic syndrome, nonalcoholic fatty liver disease (NAFLD) has emerged as the leading cause of HCC and is anticipated to result in up to 135,000 HCC cases in the United States between 2015 and 2030.[7] Between 2010 and 2019, NAFLD was the fastest growing etiology of liver cancer deaths (+38%), worldwide (►**Fig. 2**).[1] Despite the growing concern for HCC attributed to

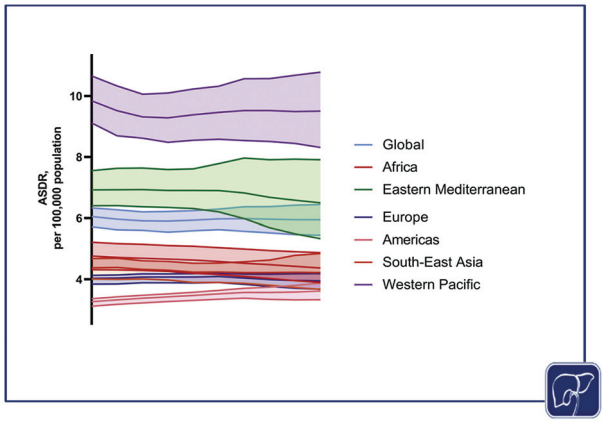


Fig. 1 Age-standardized death rates of liver cancer by World Health Organization region from 2010 to 2019. (Reprinted with permission from Huang DQ, Singal AG, Kono Y, et al. Changing global epidemiology of liver cancer from 2010 to 2019: NASH is the fastest growing cause of liver cancer. Cell Metab 2022;34:969–977, e962).[1]

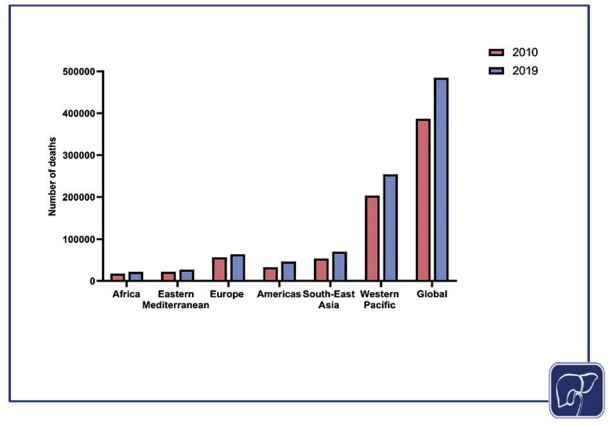


Fig. 2 Frequency of liver cancer deaths in 2010 versus 2019 by etiology by World Health Organization region. (Reprinted with permission from Huang DQ, Singal AG, Kono Y, et al. Changing global epidemiology of liver cancer from 2010 to 2019: NASH is the fastest growing cause of liver cancer. Cell Metab 2022;34:969–977, e962).[1]

NAFLD, the HCC risk according to the presence and severity of NAFLD is not well established.

NAFLD is the most common cause of chronic liver disease, affecting 20 to 30% people worldwide.[8–10] The spectrum of NAFLD is diverse, ranging from steatosis to a more progressive form, nonalcoholic steatohepatitis (NASH), all of which carry a variable risk for HCC which is largely driven by progression in fibrosis and cirrhosis. Up to one-third of HCCs from NAFLD develop in the absence of cirrhosis.[11–13] Due to cost and capacity concerns, winnowing down this large group to target individuals at higher risk for developing HCC has been a challenge. In this review, we discuss the evidence and rationale supporting current approaches and future direction in HCC surveillance for NAFLD patients.

Overall, the HCC risk in patients with NAFLD is higher than in controls without NAFLD, but is quite low (e.g., 0.21 per 1,000 person-years [PY] in one U.S. cohort study).[14] The main risk factor for NAFLD HCC is cirrhosis where the incidence rates of HCC is around 2% per year (range: 0.3–4.7% per year).[3,15,16] Other risk factors for HCC in NAFLD include older age, Hispanic ethnicity in the United States, the presence of features of metabolic dysfunction especially diabetes, and possibly high body mass index, dyslipidemia, and hypertension, as well as genetic factors. There is weak evidence that alcohol drinking in low to moderate amounts significantly increases HCC risk in the presence of NAFLD-related advanced fibrosis and cirrhosis.[13,14,17–21]

Evidence for Current HCC Surveillance Practice and Strategies in NAFLD

Current societal guidelines recommend HCC surveillance in individuals at high risk, which is largely restricted to those with cirrhosis.[2,22–24] In patients with chronic liver disease in the absence of cirrhosis, surveillance recommendations are limited to a subgroup of individuals with chronic HBV or chronic HCV and advanced fibrosis.[25] However, there is insufficient high-level evidence from randomized control trials (RCTs) for HCC surveillance in those with chronic liver disease, with only level I data stemming from one RCT conducted in China during the 1990s in a cohort exclusively with chronic HBV infection,[26] thereby limiting its generalizability to the contemporary landscape for chronic liver disease.

In this key study, which enrolled 18,816 patients with history of chronic HBV infection, Zhang et al demonstrated that biannual surveillance with ultrasound and α-feta protein (AFP) improved rates for early HCC detection and receipt of curative treatment, leading to a 37% reduction in HCC-related mortality.[26] However, these findings from this RCT have since come into question, due to issues with poor study adherence (58%) and analytic principles, which could overestimate the survival benefit.[27] Another RCT conducted in China during 1989–1995 investigated the effectiveness of ultrasound and AFP for surveillance in 5,581 men with chronic HBV infection randomized to surveillance or non-surveillance.[28] Over a median follow-up of 5 years, semiannual surveillance was associated with a higher rate of early-stage HCC detection (29.6%) than the control group (6.0%). The study also had limitation including possible survivorship bias in the control group where most HCC cases were identified through a population-based cancer death registry. There are only few, otherwise small and underpowered, RCTs because of ethical concerns with randomizing at-risk individuals to a no surveillance arm. In one surveillance RCT which enrolled 205 patients, nearly all patients (99.5%) declined randomization to a no surveillance arm, providing further evidence that RCTs for surveillance may not be feasible when informed consent is conveyed.[29]

With regard to surveilling patients with cirrhosis for HCC, the evidence is largely observational, most of which are retrospective studies, and virtually none that is exclusive to patients with NAFLD. A systematic review of 59 studies from 2014 to 2020 demonstrated that HCC surveillance was associated with increased early-stage HCC detection rates (pooled risk ratio [RR]: 1.86, 95% confidence interval [CI]: 1.73–1.98) leading to higher receipt of curative treatment receipt (RR: 1.83, 95% CI: 1.69–1.97) and overall survival (RR for mortality: 0.67, 95% CI: 0.61–0.72).[30] The survival benefit associated with HCC surveillance was still seen when accounting for lead time and length biases seen with observational studies. A Markov model using U.S. population-level data demonstrated patients with compensated cirrhosis who received surveillance with ultrasound and AFP every 6 months had a 35.1 and 6.9% reduction in all cause and liver-related mortality, respectively, at 5 years.[31] While these data are suggestive of surveillance-related benefit, there are several patient, health care, and treatment level factors that cannot be accounted for in retrospective studies, thereby leading to level II evidence for surveillance in patients with cirrhosis. Furthermore, most of these studies did not include NAFLD as an etiology of HCC, and retrospective studies that did include NAFLD as an etiology suffer from methodological drawbacks.

Patients with NAFLD-related HCC are typically diagnosed at a more advanced stage than other etiologies. In a multicenter study conducted in Italy, patients with NAFLD-related HCC had a higher proportion diagnosed with Barcelona Clinic Liver Cancer C lesions compared with patients with HCV-related HCC (21 vs. 4%, $p < 0.001$).[11] A VA observational study which included 1,419 HCC patients also found similar more advanced stage HCC and large tumor size (> 5 cm).[32] In addition, a higher percentage of patients with NAFLD-related HCC did not receive HCC surveillance in the 3 years before their HCC diagnosis compared with other etiologies (NAFLD, 43% vs. alcohol-related liver disease [ALD], 60% vs. HCV 87%). A meta-analysis demonstrated, after adjusting for tumor characteristics and other confounding factors, that patients with NAFLD-related HCC had similar odds of receiving curative treatment and survival than others.[33] While no prospective studies have supported these findings, these data highlight the potential utility of surveillance to improving prognostic outcomes in individuals with NAFLD.

Issues with Study Design in HCC Surveillance in NAFLD

To date, there are no RCTs or prospective studies demonstrating the efficacy of surveillance in NAFLD patients.[15] Aside from lead and length time biases, relying on observational data from administrative datasets for surveillance is more problematic for NAFLD than other etiologies.[34] Due to limitations in blood- and imaging-based diagnostic markers, along with the risk and invasiveness of liver biopsy, most patients with NAFLD in retrospective studies are identified using imperfect inclusion and exclusion criteria. For example, large-sampled sized studies from Surveillance Epidemiology End Results (SEER) and Veterans Affairs (VA) registries use International Classification of Diseases (ICD)-9/10 codes and/or the presence of metabolic risk factors to define the NAFLD cohort; neither approach has been validated in comparison to liver biopsy.[2,35] In contrast to other etiologies of liver disease, ICD-9 did not include a diagnosis for NAFLD.[36] These diagnostic gaps for inclusion criteria to define individuals with NAFLD can lead to significant differential misclassification, which can reduce the internal validity of these studies. Cirrhosis and HCC attributed to NAFLD are also more likely to suffer from misclassification than other etiologies. Prospective studies with stricter inclusion criteria with liver biopsy for NAFLD/NASH are largely single-center or small studies that are underpowered.[37] Noninvasive tests (NITs) including imaging (ultrasound, computed tomography [CT], or standard magnetic resonance imaging [MRI]) or serum-based markers for NAFLD do not distinguish histologic subtypes such as NASH.

Opportunities Ahead

Prospective studies, with clear inclusion and exclusion diagnostic criteria, can help reduce the high degree of ascertainment biases and misclassification of exposures and outcomes seen from previous observational data. Most prospective clinical trials for NAFLD/NASH require more stringent diagnostic entry criteria with liver biopsy, which contribute to the lack of study participation. However, NITs for steatosis and fibrosis have been adopted in clinical practice. In lieu of liver biopsy, MRI with proton-density fat fraction and elastography has been utilized in early, phase 1 and 2a trials for screening and therapeutic response as a primary endpoint in patients with NAFLD.[38]

Several active prospective consortia are investigating the progression of NAFLD to HCC beyond known traditional risk factors. The maturation of large collaborative efforts from the NASH CRN, National Cancer Institute's U01 Translational Liver Cancer (TLC) consortium, the Hepatocellular carcinoma Early Detection Strategy (HEDS) cohort, and the Texas Hepatocellular Carcinoma Consortium (THCCC) cohort can help answer key knowledge gaps in our understanding of the biomarkers and risk factors associated with NAFLD-related HCC.[3,39] These cohorts leverage longitudinal, blood- and imaging-based biorepository to facilitate in biomarker evaluation and future risk-stratification efforts. However, enrollment in these prospective studies is largely limited to individuals with cirrhosis and the large population of NAFLD-related HCC without cirrhosis will be missed.

Efficacy and Effectiveness of Surveillance in Patients with NAFLD

Surveillance aims are centered on the efficacy and effectiveness of an intervention in high-risk individuals, for which there is a lack of evidence for HCC surveillance in NAFLD patients including any subgroups.[40,41] Efficacy studies evaluate the potential benefits and harms of an intervention (surveillance) and it will work in a highly controlled study protocol, ideally a RCT, and suggest high internal validity. In contrast, effectiveness studies evaluate the external validity or real-world practice of an intervention in a more heterogenous population seen in clinical practice. In the context of NAFLD, evidence for effectiveness of HCC surveillance in NAFLD is limited by the (1) inability to identify high-risk individuals, (2) concerns regarding surveillance test accuracy, (3) surveillance utilization, and (4) cost-effectiveness.

1. Identifying a High-Risk (for HCC) Target Population within Patients with NAFLD

Varying Risk of HCC in Cirrhosis

Several professional societies have defined individuals who have 1.5% or greater annual risk for developing HCC as a high-risk target population for which surveillance should be offered.[2,23,24] Even when held to this cutoff, there is disagreement whether all patients with cirrhosis, with respect to etiology, meet this suggested threshold for surveillance. The annual risk of HCC with cirrhosis varies within different etiologies ranging from 0.5 to 5%,[16,23,42] with a lower reported annual incidence rate falling in between 0.5 and 2.6% in individuals with NAFLD cirrhosis.[14] This wide variation may be explained by length and lead time biases from observational data, differences in liver disease activity and severity, and burden of other comorbidities in these study populations. For example, Ascha et al reported an annual incidence rate for HCC of 2.6% in individuals with NAFLD cirrhosis, but the study population had a higher percentage of with diabetes and alcohol use, both risk factors shown to potentiate risk of HCC.[17,43] A large retrospective VA cohort study, which included 1,084 patients with NAFLD cirrhosis, reported a lower annual incidence rate of 1.1% (95% CI: 1.0–1.2) and ranged between 0.2 and 2.4% in demographic subgroups with the highest rate seen in Hispanics.[14]

Furthermore, current surveillance recommendations for those with cirrhosis are based on historical cohorts with untreated HCV and HBV infection, with an annual incidence rate between 2 and 8%, with active HCV conferring the highest risk.[16,44] Due to widespread availability of safe and effective direct acting antiviral (DAA) therapy for HCV, most patients with compensated cirrhosis from HCV managed in clinical practice meet criteria for DAA therapy and achieve cure rates above 95%.[45] Similarly, patients with HBV who are treated with nucleotide analogs and achieve sustained

virologic suppression have over a 50 to 70% reduction for developing HCC than those who remain untreated.[46,47] In a prospective, multicenter consortium in Texas, 2,733 patients with cirrhosis were enrolled from 2016 to 2020 and followed up until HCC diagnosis, with 80% receiving at least one HCC surveillance imaging.[48] At enrollment, 19.0% had active HCV, 23.3% had cured HCV, 30.1% had NAFLD, and 16.1% had ALD. As expected, patients with active HCV infection had the highest annual incidence rate of 3.4%. But the annual HCC incidence rate was 1.7% in patients with cured HCV, 1.3% in patients with ALD, and 1.2% in patients with NAFLD. While the disparity in HCC risk among etiologies has narrowed down considerably, more heterogenous, contemporary data in patients with cirrhosis are needed to guide cost-effective decision models.

Risk of HCC in NAFLD Patients without Cirrhosis

The risk for developing HCC according to the presence and severity of NAFLD is not well established. While cirrhosis is a risk factor for HCC, up to one-third of HCC in patients with NAFLD occurs in the absence of cirrhosis.[37] Only 5 to 10% of NAFLD patients have underlying cirrhosis.[2] Given the large population size of patients with NAFLD and the high PAF from noncirrhotic NAFLD, surveilling all patients with NAFLD is not feasible or cost-effective.

The natural progression of NAFLD to HCC is poorly understood, but there is evidence showing a strong stepwise association between worsening histological severity and incidence for HCC. The histological spectrum of NAFLD ranges from simple steatosis, NASH with and without advanced fibrosis, to cirrhosis. A population-based retrospective study of 8,892 Swedish adults with biopsy-proven NAFLD/NASH assessed the risk of developing HCC with histological severity. Over a median of 13.8 years, HCC developed at the rate of 0.8 per 1,000 PY with simple steatosis, 1.2 per 1,000 PY with NASH without advanced fibrosis, 2.3 per 1,000 PY in NASH with advanced fibrosis, and 6.2 per 1,000 PY with NAFLD cirrhosis.[49] Similar association between histological severity and HCC risk was reported from the NASH Clinical Research Network (CRN), which leveraged biopsy-proven patients with NAFLD/NASH prospectively, but over a shorter median follow-up of 4 years.[50] Although HCC risk is lower in NAFLD patients without cirrhosis, this risk is higher than the general population.[49] There also remains significant gaps in knowledge for other key subgroups of individuals with NAFLD without cirrhosis, including those with lean NAFLD and noncirrhotic portal hypertension.

Current (and Future Direction) Approach to HCC Risk Stratification in NAFLD

In the absence of cirrhosis, there are no validated effective risk stratification tools or biomarkers for the development of HCC in patients with NAFLD who progress to HCC. Similarly, within the large group of patients with cirrhosis, there are no validated effective risk stratifiers to further guide resource-intense HCC prevention and early detection. Ideally, a multi-tiered program where NAFLD patients without cirrhosis are first risk stratified by a risk prediction tool, followed by offering HCC screening to individuals with "high-risk" while eliminating those with "low-risk" would likely improve the eventual effectiveness of HCC screening in this group. However, to get there, we will need a series of carefully designed, multicenter studies that examine existing as well as novel biomarkers of risk to stratify NAFLD patients. HCC risk calculators including VA score and NAFLD fibrosis score have incorporated some of these clinical risk factors, with only modest performance for HCC risk stratification in NAFLD.

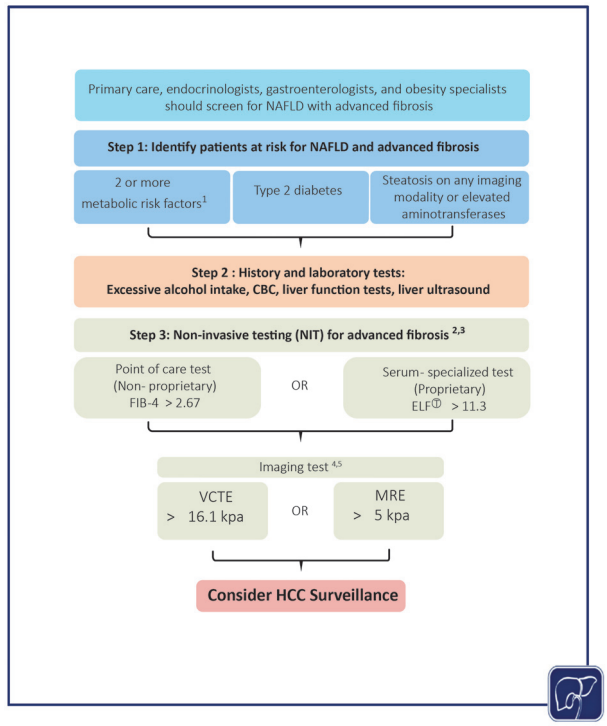


Fig. 3 Proposed algorithm for HCC screening in patients with NAFLD in the absence of clinically obvious cirrhosis.

Current approaches to managing noncirrhotic NAFLD are limited to monitoring for progression in liver fibrosis, for which individuals with advanced fibrosis (stages F3–F4) are at greatest risk for developing HCC. Because of the large PAF for HCC from noncirrhotic NAFLD, offering HCC surveillance to individuals with advanced fibrosis may be justified. Therefore, the American Gastroenterology Association (AGA) has recommended that NAFLD patients with cirrhosis or advanced fibrosis should be considered for HCC surveillance.[51] With the use of NITs for liver fibrosis, the AGA has proposed a clinical care pathway to help clinicians identify NAFLD patients with advanced fibrosis that should be considered for HCC surveillance, which is shown in ►**Fig. 3**.

NIT for liver fibrosis can be categorized as (1) point-of-care blood tests (nonproprietary test using clinical and laboratory parameters, i.e., fibrosis-4 score [FIB-4]), (2) specialized blood tests (proprietary, Enhanced Liver Fibrosis [ELF] panel), and (3) imaging tests (i.e., vibration-controlled transient elastography [VCTE] and MRI elastography).[2,18] While these NIT modalities have adequate

sensitivity for ruling out advanced fibrosis (> 85%), they have suboptimal positive predictive value for detecting advanced fibrosis in NAFLD.[52] Sequential combination of two NITs has shown to improve the diagnostic accuracy for advanced fibrosis to greater than 90%. Thus, the recommendation is that individuals with two NITs concordant with advanced fibrosis or cirrhosis, each coming from one of the main three groups of tests (point-of-care, specialized, or imaging) should be considered for HCC surveillance.[2]

NITs for liver fibrosis have shown some promise for HCC risk stratification in NAFLD patients. Population-based, observational studies in Europe and Asia have shown that NAFLD patients with elevated FIB-4 (FIB-4 > 1.3) had a 12- to 15-fold increased risk for developing HCC with median follow-up ranging between 7 and 10 years.[12,27,53] Repeated measurements of NIT over time has also shown to be strongly associated with risk developing severe liver-related events such as HCC. Because 20% of NAFLD patients with advanced fibrosis rapidly progress to cirrhosis within 3 years,[54] capturing longitudinal changes in fibrosis with NIT allows clinicians to monitor and determine the risk of progressing to cirrhosis and/or HCC.[55] Incorporating longitudinal information on NIT in clinical practice may strengthen the predictive ability of risk models in stratifying HCC risk in NAFLD.

Beyond the extent of liver fibrosis and comorbid metabolic traits, HCC risk is higher in older patients, men, and with current alcohol and tobacco use.[16] There is also an association between molecular and genetic factors and HCC risk within NAFLD. Several recent large genome-wide association studies have identified SNPs such as *PNPLA3* and *TM6SF2* influencing the severity of NAFLD and development of HCC.[56] Two non-U.S. studies have demonstrated potential utility of a polygenic risk score derived from these NAFLD-related SNPs for predicting HCC in NAFLD patients without cirrhosis.[57,58] It will likely take a combination of highly precise genetic and molecular biomarkers along with NIT for fibrosis, to identify a high-risk, target population in NAFLD patients for HCC surveillance to be cost-effective.

2. Surveillance Tests

Imaging Tests

Most societal guidelines recommend biannual liver ultrasound, with or without AFP, in all patients with compensated cirrhosis, including those with cirrhosis due to NAFLD. Ultrasound has several advantages as an initial screening modality; it is a widely available and inexpensive test with minimal patient risks. However, nearly 20% of all ultrasounds performed for surveillance in patients with cirrhosis are inadequate in quality to exclude liver lesions, with a higher proportion seen in NAFLD than other etiologies.[3] Increased liver nodularity and obesity and truncal adiposity are seen in higher proportion of patients with NAFLD, and lead to higher likelihood for impaired visualization and reduce the sensitivity of ultrasound-based surveillance in patients with NAFLD.[52] There is also a wide variation with operator expertise and dependency with ultrasound that the pooled sensitivity in a meta-analysis was only 45% with ultrasound-based surveillance for early HCC detection.[59]

The AGA Best Practice consensus for HCC surveillance in NAFLD has suggested that if the quality and visualization of the ultrasound is severely limited (category C, defined as the examination may miss focal liver lesion), other higher-level imaging modalities for surveillance should be considered.[2] While CT and MRI have higher sensitivity and specificity than ultrasound, they provide additional harms and risks with contrast and may not be a cost-effective strategy at this time. Aside from radiation exposure with CT, patients with NAFLD also have higher rates of chronic kidney disease, and may be more susceptible to contrast-induced complications with CT-based surveillance. A prospective cohort study compared HCC detection rates in 407 patients with cirrhosis who received one to three biannual surveillance with both MRI and ultrasound.[60] In this comparator study, MRI was found higher sensitivity and detection rates (85.7 vs. 26.2%) for early stage (< 2 cm) HCC, but this study did not capture patients with NAFLD and its generalizability and application in this population.

Serum Tests

Recommendations on using AFP in combination with ultrasound for surveillance strategies differ slightly among professional societies. The AGA and American Association for the Study of Liver Disease (AASLD) guidelines neither support nor discourage use of AFP as an add on to ultrasound-based surveillance.[2,23] Despite AFP being the only serum biomarker that has completed all five phases of biomarker research, this rationale is based on the lack of studies directly comparing AFP to ultrasound.[3] In a meta-analysis, the pooled sensitivity of surveillance for HCC modestly improved from 45% with ultrasound alone to 63% in combination with AFP.[30] Yet, these studies did not account for limitations with ultrasound and were underpowered; and no studies have shown an overall improvement in survival with ultrasound used in combination with AFP. Given the lower sensitivity of ultrasound for liver lesions due to obesity, AFP may have greater value in patients with NAFLD who undergo ultrasound-based surveillance. The interpretation of a single AFP measurement is problematic. For example, the lower threshold for acceptable sensitivity of AFP is unclear and the physical harms associated with false positive or indeterminate AFP values should be considered in clinical decision making.

There are no direct comparative data for AFP as a surveillance test in patients with NAFLD compared with other groups. However, AFP as a diagnostic marker for HCC may have higher accuracy in non-active HCV patients than those with HCV infection. Active HCV infection is associated with higher nontumoral secretion of AFP and HCV patients often have elevated AFP in the absence of HCC. Other clinical factors associated with reduced sensitivity with AFP include high serum aspartate transaminase levels, Black race, and HIV infection; all of these factors have lower prevalence in individuals with NAFLD than those with viral hepatitis.[61] In Asia, countries such as Japan and Taiwan have integrated AFP,

along with other biomarkers such as *Lens culinaris* agglutinin-reactive AFP (AFP-L3) and des-γ-carboxy prothrombin (DCP), in their national HCC surveillance algorithm.[22] AFP-L3 and DCP remain in phase II/III of biomarker discovery clinical trials.

Future Direction

Serum Biomarkers

The five clinical trial phases of biomarker research set forth by the National Cancer Institute for early cancer detection include early biomarker discovery (phase I), biomarker performance and accuracy (phase II/III), and validation in prospective cohorts (phase IV) and RCTs (phase V).[56] Aside from AFP, all other biomarkers for early HCC detection have yet to reach phase IV/V in clinical trials. There has been increased interest in integrating biomarker panels along with clinical risk factors, to enhance risk prediction models for HCC.[62] More recently, GALAD, a biomarker panel which incorporates gender, age, AFP, AFP-L3, and DCP, has a reported sensitivity of more than 70% for detecting early-stage HCC lesions in phase II/III studies including patients with NAFLD, but is also associated with a much higher false-positive results than using individual biomarkers.[63,64] Therefore, the overall accuracy and cost-effectiveness of GALAD remain unclear and need to be examined before advocating wider use. Other novel blood-based biomarker research still in the early phases (I/II) includes circulating tumor cells (CTCs), cell-tumor–derived DNA (ctDNA), and high-throughput "omics" (proteomics, lipidomics, and metabolomics) platforms. Of these, ctDNA biomarkers have shown the most promise thus far.[65] Characteristic methylation patterns and mutations found in ctDNA have been studied for early-stage HCC detection, and early phase I/II studies have shown ctDNA biomarkers to outperform AFP for small HCC lesions under 2 cm, but these studies were largely in patients with HBV-related HCC.[66] CTC biomarkers, along with characteristic metabolomics and lipidomics signatures, have also shown good discriminative ability for HCC. However, these biomarkers have shown conflicting data for NAFLD-related HCC and only few studies included patients with early-stage HCC.[65]

Imaging Biomarkers

Because imaging plays a crucial role in HCC diagnosis and surveillance, the application of radiomics to develop imaging biomarkers is well-suited for early-stage HCC detection. Radiomics quantifies textural information from high-level cross-sectional CT or MRI imaging to develop computer-assisted biomarker features which can reduce the subjectivity from radiologists with the widely used Liver Imaging Reporting and Data System (LIRADS) for HCC diagnosis. These high-dimensional biomarkers can be leveraged to characterize patient heterogeneity and build precision medicine algorithms for HCC diagnosis and predictive tasks for targeted surveillance. CT-based radiomics nomogram models have shown good discriminative ability for HCC compared with controls with normal liver and benign liver masses with more than 90% accuracy.[67] Variation in image quality and software, lack of transparency in model construction with artificial intelligence ("black box" warning), radiologist's operator dependency for image segmentation, and lack of large enough cohorts with early-stage HCC limit the application of radiomics for HCC detection and surveillance.[68,69] Aside from radiomics, there has been interest in developing a more cost-effective imaging techniques with less physical harms, such as an abbreviated MRI.[70] Different abbreviated MRI approaches with and without contrast are being investigated, all of which have the advantage of being simpler, less expensive to perform, and safer due to the use of noncontrast MRI than regular MRI.[71] However, this may come at the cost of reducing sensitivity for detecting early HCC lesions. In addition, recall CT and MRI are generally required for a positive abbreviated MRI examination.

3. Surveillance Utilization

Adherence to screening and surveillance programs remains poor in clinical practice. Less than 20% of patients with cirrhosis undergo routine screening and surveillance. In those who do receive initial screening, compliance rates to surveillance programs at 5 years are dismal, as low as 12%, and largely inconsistent.[72] Although surveillance rates have shown to increase to rates as high as 52% in patients who receive regular care from a hepatology subspecialty clinic, only 33 to 45% of patients with cirrhosis in the United States are ever been evaluated by gastroenterologist or hepatologist.[73] Several factors can be attributed to surveillance underutilization including failure to identify those risk factors and who have or progress to cirrhosis and ordering surveillance.[73,74] Importantly, several non-gastrointestinal societies such the U.S. Preventive Services Task Force and American Cancer Society have not adopted a surveillance practice guideline for HCC due to lack of high-quality evidence for effectiveness.

The recommended surveillance interval is every 6 months in high-risk individuals.[73] An observational, multicenter Italian study demonstrated that patients who had surveillance every 6 months had higher early-stage HCC detection rates and improved survival than those who underwent annual surveillance.[75] A subsequent multicenter RCT in Italy suggested that reducing the surveillance interval from 6 months to every 3 months only modestly improved the proportion of HCC diagnosed at an early stage (79 vs. 71%; $p = 0.40$) but also led to higher false-positive rates and associated physical harms.[76] In addition, there is no consensus for recall procedure for LIRADS 3 and 4 indeterminate HCC lesions. The lack of clarity for surveillance interval and recall may reduce providers' willingness to commit patients to surveillance programs.

In the context of NAFLD, there are little to no reliable data for utilization and adherence rates for surveillance in individuals with NAFLD cirrhosis, but there are data to suggest it is lower in those with NAFLD than with other etiologies. In a meta-analysis comprising 61 studies in patients diagnosed with HCC, a lower proportion of patients with NAFLD underwent surveillance (32.8%) than did patients with HCC from other causes (55.7%).[33] In a SEER-Medicare study, HCC patients with

NAFLD had 78% lower odds for receipt of surveillance than HCC patients with HCV (adjusted odds ratio: 0.22, 95% CI: 0.17–0.28).[35] Patients with NAFLD seem to be further disadvantaged by the lack of provider awareness not only for recognizing cirrhosis but also for diagnosing NAFLD.

Opportunities Ahead

Few strategies have been proposed to improve surveillance utilization and adherence rates. An intention-to-screen RCT with 1,436 patients assigned to both a mailed HCC surveillance outreach arm and a visit-based surveillance arm over a 12-month period demonstrated that the mailed outreach arm had higher semiannual surveillance rates (35.1 vs. 21.9%) but clinical difference in proportion with early-stage HCC detection was seen in either arm.[77] Electronic medical record with clinical reminders (e-triggers) for HCC surveillance has also shown to improve surveillance underuse (18.2–27.6%) in VA cohort of patients with cirrhosis.[78] Although mailed outreach and e-triggers were associated with an increase in surveillance rates, the latter remained dismally low and further implementation strategies need to be developed and tested. Studies from the THCCC investigating the effects of HCC surveillance intervals and recall procedures in a contemporary clinical practice are underway.[79]

4. Cost-Effectiveness Considerations

Cost-effectiveness studies have suggested that individuals with an annual incidence of 1.5% or greater for developing HCC should enter surveillance programs, for which most societal guidelines include all patients with cirrhosis regardless of etiology as meeting this threshold.[23] This threshold was predicated on a decision tree analysis published in 1996 in patients with Child A cirrhosis who underwent ultrasound-based surveillance in combination with AFP.[80] These data reported that the target population for surveillance should meet an annual HCC incidence rate of 1.5% or higher to improve longevity and provide interventions that can be achieved at a cost of less than approximately 50,000 U.S. dollars per quality-adjusted life-year (QALY) for surveillance and be considered cost-effective in clinical practice. Yet, these decision analysis models are predicated on data from two decades prior and thus outdated.

For one, sensitivity for HCC detection with ultrasound has improved over the past two decades, and do not account for superior sensitivity seen with CT and MRI. In similar fashion, advancements in locoregional and systemic HCC therapy has increased life expectancy and should also factored in cost-effective studies. Recent Markov models incorporating current clinical practice with surveillance tests and treatment interventions have suggested that the HCC annual incidence rate for surveillance to be cost-effectiveness is lower, between 0.8 and 1.5%.[73] Parikh et al suggested an even lower threshold greater than 0.4% annual HCC rate for ultrasound-based surveillance when adjusting for inflation with a willingness to pay threshold of 100,000 U.S. dollars/QALY, as well as current performance of imaging-based surveillance.[81]

The risk of death from competing non–liver-related events should also be taken into consideration for cost-effective decision analyses. Patients with NAFLD, including those with cirrhosis and HCC, have a high burden of chronic comorbidities and metabolic risk factors which contribute to higher all-cause mortality and competing risk for death from non–liver-related causes. Although cardiovascular disease is the leading cause of death in patients with NAFLD, accounting for 25 to 43% of deaths, liver-related mortality remains the leading cause in those with cirrhosis.[82,83] Even so, in a Swedish cohort study with 537 patients with biopsy-proven cirrhosis from NAFLD, Simon et al demonstrated that cirrhosis from NAFLD still carried an excess risk for mortality for extrahepatic cancer (adjusted hazard ratio [HR]: 2.12, 95% CI: 1.58–2.84) and cardiovascular disease (adjusted HR: 2.11, 95% CI: 1.63–2.73) than the general population.[84] To date, there are no prospective data on cause-specific mortality in patients with HCC from NAFLD. In a recent VA cohort study in 776 patients with incident HCC from NAFLD, most deaths (72.2% at 3 years) were attributable to HCC. Approximately 80% of patients presented with advanced HCC, but non-HCC mortality was a clinically meaningful competing event for patients undergoing curative treatment (30.2% of deaths) and early-stage HCC (41.7%).[82]

Current Recommendations for HCC Surveillance in NAFLD Patients

Surveillance Population

NAFLD with cirrhosis: Most professional societies strongly recommend HCC surveillance in patients with cirrhosis, regardless of etiology. In a small subset of decompensated patients with severe category of Child–Pugh class C cirrhosis who are not candidates for liver transplantation or have low anticipated survival, HCC surveillance is generally not recommended.[2,23]

Without cirrhosis: HCC surveillance in noncirrhotic NAFLD, if employed, should be restricted to patients with advanced fibrosis (i.e., F3/4). Multisocietal recommendations suggest screening for advanced fibrosis in key high-risk subgroups of NAFLD patients including those with (1) type 2 diabetes mellitus, (2) 2 or greater metabolic risk factors (central obesity, hypertension, dyslipidemia, or prediabetes), or (3) incidental hepatic steatosis on imaging or elevated alanine aminotransferase levels.[85,86] For example, several studies have demonstrated that the prevalence of advanced fibrosis in NAFLD patients with type 2 diabetes to be as high as 20%, and screening for advanced fibrosis in this subgroup is a cost-effective approach.

Following the proposed AGA pathway shown in ►**Fig. 3**, individuals with two NITs concordant with advanced fibrosis or cirrhosis, each coming from one of the main three groups of tests (point-of-care, specialized, or imaging NIT), should be considered for HCC surveillance.[2] In individuals who are at low or indeterminate risk, longitudinal assessment for advanced fibrosis with NIT every 2 to 3 years could be performed to identify individuals who eventually may meet the threshold for surveillance.[52] In areas with more limited radiologic capacity, where VCTE and MRI elastography may not be readily available, the use of point of care (i.e., FIB-4 or APRI), and/or specialized (ELF) blood tests, along

with histologic confirmation with liver biopsy can be used to identify those with advanced fibrosis.

Surveillance test: Ultrasound exam combined with AFP every 6 months is the initial recommended surveillance imaging test. In NAFLD patients with poor visualization on repeated ultrasound exam, cross-sectional imaging, such as CT or MRI for surveillance, can be considered.[2,23,24]

Surveillance interval: HCC surveillance should be performed in at-risk NAFLD patients at least every 6 months, like patients with cirrhosis from other causes. In a meta-analysis of prospective studies evaluating the efficacy of HCC surveillance tests, the pooled sensitivity for HCC detection with ultrasound surveillance at least every 6 months was significantly higher than performing surveillance on an annual basis (70.1 vs. 50.1%, $p < 0.001$).[3]

Conclusions

The PAF for HCC attributed to NAFLD continues to grow in parallel with rising global trends in obesity and metabolic syndrome. The risk of HCC is elevated among patients with NAFLD-related cirrhosis to a level that justifies surveillance based on cost-effectiveness argument. The quality of current evidence for HCC surveillance in all patients with chronic liver disease is poor, and even lower in those with NAFLD. For a lack of more precise risk stratification tools, current approaches to defining a target population are limited to NITs for liver fibrosis, as a proxy for liver-related morbidity and mortality. Beyond etiology and severity of liver disease, traditional and metabolic risk factors, such as diabetes mellitus, older age, male gender, and tobacco smoking, are not enough for HCC risk stratification for surveillance efficacy and effectiveness in individuals with NAFLD. There is an association between molecular and genetic factors and HCC risk in NAFLD, and risk models integrating both clinical and genetic factors will be key to personalizing HCC risk. However, concerns regarding surveillance test accuracy, surveillance underuse, and other cost-effective considerations also need to be addressed for HCC surveillance to achieve its intended goal of improving prognostic outcomes in individuals with NAFLD.

Summary

The risk of HCC is elevated among patients with NAFLD-related cirrhosis to a level that justifies surveillance based on cost-effectiveness argument, but the quality of current evidence for HCC surveillance in NAFLD is poor. For a lack of more precise risk-stratification tools, current approaches to defining a high-risk target population in noncirrhotic NAFLD are limited to NITs for liver fibrosis, as a proxy for liver-related morbidity and mortality. Risk models integrating both clinical and genetic factors will be key to personalizing HCC risk. Concerns regarding defining a target population, surveillance test accuracy, surveillance underuse, and other cost-effective considerations need to be addressed for HCC surveillance to be effective in individuals with NAFLD.

Authors' Contributions
Both the authors contributed equally in the conception, design, literature review, writing of first draft, and approval of the final draft.

Funding
This study was conducted with partial support from NIH U01 CA230997 (PI: Kanwal), CPRIT RP150587 and RP190641 (PI: El-Serag), and NIH P30DK056338 (PI: El-Serag). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or CPRIT. The funding agencies had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation of the manuscript.

Conflict of Interest
H.B.E-S. had grant funding from Gilead, Merck, Wako, and Glycotest. G.C. has no conflict of interests to report.

Acknowledgements
We would like to thank Fuad Aloor for his assistance with graphical illustrations for this article.

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