Current Hepatology Reports (2023) 22:1–8
https://doi.org/10.1007/s11901-023-00595-7

HEPATIC CANCER (N PARIKH, SECTION EDITOR)

Risk Stratification for Hepatocellular Carcinoma in Patients with Non-alcoholic Fatty Liver Disease

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Accepted: 22 November 2022 / Published online: 1 March 2023

Abstract

Purposeof Review This review aims to supply up-to-date recommendations on risk stratification for hepatocellular carcinoma (HCC) in patients with non-alcoholic fatty liver disease (NAFLD).

Recent Findings NAFLD is the most rapidly growing cause of HCC in the USA. HCC surveillance in patients with NAFLD remains a clinical challenge due to the large global burden of NAFLD, limitations in surveillance modalities, and the widely recognized possibility of HCC development in NAFLD in the absence of cirrhosis.

Summary Based on fibrosis staging, HCC screening in NAFLD is recommended in cirrhosis, considered in advanced fibrosis, and not recommended in the absence of advanced fibrosis. Though liver biopsy is the gold standard for staging, evidence of advanced fibrosis warranting HCC surveillance in NAFLD can be based on 2 concordant noninvasive tests. Those meeting recommended criteria for HCC surveillance should undergo imaging with or without serum α-fetoprotein levels every 6 months at minimum.

Keywords Fatty liver · NAFLD · Hepatocellular carcinoma · HCC screening · HCC surveillance (up to 6)

Introduction

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver disease ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) to advanced fibrosis to cirrhosis and/or hepatocellular carcinoma (HCC) [1]. With the rising global burden of obesity and metabolic syndrome, NAFLD is the most rapidly growing cause of HCC in the USA [2] However, screening for HCC in NAFLD currently remains a clinical challenge due to the large prevalence of NAFLD, limitations in screening modalities, and the well-known possibility of NAFLD-related HCC even in the absence of cirrhosis [3]. A recent meta-analysis on NAFLD-HCC estimates that up to 40% of NAFLD-HCC exist in the absence of cirrhosis [4]. This review aims to supply up-to-date recommendations on risk stratification for HCC in patients with NAFLD.

The Prevalence of HCC in NAFLD

In the USA, the average annual risk of HCC in 296,707 patients with NAFLD was 1.06% based on a retrospective cohort study from the national Veterans Affairs system [5]. Orci et al.'s recent meta-analysis of 18 studies including 470,404 patients found that the incidence rate of HCC was 0.03 per 100 person-years in NAFLD patients without cirrhosis and 3.78 per 100 person-years in NAFLD patients with cirrhosis [6•]. NAFLD has become the most rapidly growing cause of HCC-related liver transplantation according to the United Network for Organ Sharing registry [7, 8]. In a study of 61,868 adults who underwent liver transplant in the USA, including 10,061 patients with HCC, the number

This article is part of the Topical Collection on *Hepatic Cancer*

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of patients who underwent liver transplant for NAFLD-related HCC increased by almost 4-fold between 2002 and 2012 [9]. Notably, HCC can develop in NAFLD regardless of the absence or presence of cirrhosis.

Among those with NAFLD cirrhosis, HCC incidence has been estimated to be approximately 1 per 100 person-years, and the 1-, 5-, and 10-year cumulative incidence of HCC remains about 2.5%, 11%, and 30%, respectively [10, 11]. The incidence of HCC in NAFLD cirrhosis is similar to that of alcoholic cirrhosis but lower than that of hepatitis C virus (HCV) cirrhosis [11]. However, the global burden of HCC due to NAFLD compared to other causes of chronic liver disease remains much larger given the high prevalence of NAFLD and its comorbid cardiometabolic risk factors.

Though HCC primarily occurs in the setting of cirrhosis, HCC development in the absence of cirrhosis remains well-recognized, embodying approximately 11.7% of 5144 HCC cases between 2000 and 2014 in the USA [12]. Indeed, NAFLD comprises the largest proportion of non-cirrhotic HCC cases, accounting for 26.3% (159/605) of non-cirrhotic HCC cases compared to 13.4% (608/4539) of cirrhotic HCC cases [12, 13]. In those with NAFLD with simple steatosis, the incidence of HCC ranges from 0.8 to 6.2 per 100 person-years [14, 15]. HCC incidence in NASH remains poorly described as NASH is a histological diagnosis that requires invasive liver biopsy [16]. However, HCC incidence in NASH can be reasonably assumed to be in-between that of simple steatosis and cirrhosis [4]. Given these findings, NAFLD pathophysiology may thus play roles in the pathophysiology of HCC development independent of liver disease progression to advanced fibrosis or cirrhosis, posing clinical practice challenges in terms of recommendations for HCC surveillance [17].

Surveillance for HCC in NAFLD

Who Should Get Screened for HCC?

Although prior studies have substantiated the development of NAFLD-related HCC with and without the presence of co-existing cirrhosis, HCC screening remains underutilized in NAFLD. A retrospective analysis from a tertiary care center found that 51.5% of adults with NASH cirrhosis have no screening before HCC diagnosis, compared to 25.9% of adults with HCV cirrhosis [18]. Compared to those with incomplete or lack of screening, those with NASH cirrhosis who underwent complete screening developed smaller HCC tumors ($p = 0.006$) [18]. In a US Veterans Administration national cohort of 1500 patients with HCC development from 2005 to 2010, 56.7% of patients with NAFLD-related HCC failed to undergo HCC surveillance in the 3 years leading up to HCC diagnosis compared with 40.2% of patients with alcohol abuse–related HCC ($p < 0.01$) and 13.3% of patients with HCV-related HCC ($p < 0.01$) [19].

Presently, there is a dearth of highly powered studies to adequately inform societal guidelines with respect to which patients warrant HCC screening in NAFLD, the best modality or combination of modalities for monitoring, or the ideal frequency of surveillance. Based on consideration of cost-effectiveness, the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) recommend HCC screening for cirrhotic patients if the expected incidence of HCC is $\geq 1.5\%$ per year, which includes those with compensated and decompensated cirrhosis in NAFLD [20••, 21••].

Societal guidelines provide limited guidance on monitoring for HCC development in the absence of cirrhosis. EASL guidelines recommend considering HCC surveillance in those with fibrosis stage 3 (F3), including F3 diagnosed by either liver biopsy or vibration-controlled transient elastography [21••]. Agreeing with EASL guidelines, the American Gastroenterological Association (AGA) Clinical Practice Update states that NAFLD patients with evidence of advanced fibrosis should be considered for HCC surveillance [22••]. However, AASLD guidelines recommend against HCC screening in F3 [20••]. Cost-effective studies similar to those done to assess screening in high-risk populations for NAFLD are urgently needed to assess if screening for HCC in NAFLD patients with stage 3 fibrosis meets cost-effectiveness [23].

Finally, NAFLD patients without evidence of advanced fibrosis should not be routinely considered for HCC screening according to AASLD and AGA clinical practice guidance [20••, 22••]. On the other hand, EASL guidelines state that the role for HCC surveillance in NAFLD patients remains unclear and needs to be addressed by future research, as a significant proportion of HCCs occur in patients with NAFLD without advanced fibrosis (fibrosis stages 0 to 2) [21••]. Given that fibrosis stage is not the sole determinant of HCC risk in NAFLD patients, future studies should investigate the most accurate combination of predictors and risk factors (including older age, higher BMI, and higher prevalence of metabolic comorbidities such as diabetes, hypertension, hyperlipidemia, and cardiovascular disease) that could improve risk stratification for HCC in patients with NAFLD [4].

A genetic polymorphism that affects 40% of the European population, the patatin-like phospholipase domain-containing protein 3 (PNPLA3) rs738409 [G] risk allele has been independently associated with a three- to 12-fold increased risk of HCC and has been combined into polygenic risk scores in hopes of better risk-stratifying patients with NAFLD without advanced fibrosis [24–27]. However, such polygenic risk scores for HCC prediction have been shown to have low area under the receiver operating characteristic curve (AUROC) (0.65) and sensitivity (43%) [28].

Despite the promise of improving HCC risk stratification in the absence of advanced fibrosis, there also remains a lack of clear data to justify routine genetic screening given the lack of cost-effectiveness and limited access to genetic testing in clinical practice [21••]. Additional studies are necessary to investigate whether polygenic risk scores can accurately identify patient populations with sufficiently high risk of HCC to warrant routine HCC screening in the absence of advanced fibrosis. Other genetic polymorphisms such as TM6sF2 and MBOAT7 are suspected to play a role in NAFLD-related HCC, but more data is necessary for elucidation.

How Should Staging Be Performed in NAFLD?

Given that guidance recommendations for HCC screening are based on staging, staging liver fibrosis in NAFLD is a predominant priority. Though percutaneous liver biopsy is the gold standard for staging, liver biopsy is invasive with limitations including high cost, possibility of sampling error, and associated risk of complications, making liver biopsy unsuitable as the initial staging modality in routine clinical practice [29–31].

Alternative staging methods include noninvasive risk stratification using imaging, serum biomarkers, and/or diagnostic algorithms [32–34]. Imaging methods include vibration-controlled transient elastography (VCTE) and magnetic resonance elastography (MRE) with respective cut-offs of 16.1 kPa and 5 kPa for ruling in cirrhosis [35]. However, such imaging modalities may possess low negative predictive values and do not excel in excluding advanced fibrosis in the absence of overt imaging findings.

On the other hand, noninvasive staging scores (Table 1) including the Aspartate Aminotransferase-to-Platelet Ratio Index (APRI), NAFLD Fibrosis Score (NFS), Fibrosis-4 Score (FIB-4), Hepamet Fibrosis Score (HFS), Agile 3 + and 4 Scores, MAST Score, MR Elastography combined with Fibrosis-4 (MEFIB) Score, and the Metabolomics-Advanced StEatohepatitis Fibrosis (MASEF) Score may offer stratification for NAFLD-HCC [34, 36–43]. For instance, a FIB-4 score of ≥ 2.67 has been shown to be associated with increased risk of HCC in those with NAFLD with or without cirrhosis [5]. Specifically, though high FIB-4 alongside cirrhosis is associated with the highest risk of HCC at 13.5 per 1000 person-years, HCC risk in non-cirrhotic patients with high FIB-4 remained high at 0.39 per 1000 person-years

Table 1 Novel noninvasive tests for fibrosis staging in NAFLD

	Name	Abbreviation	Demographic components	Comorbidity components	Serum components	Imaging components
Serum-based	NAFLD Fibrosis Score	NFS	Age, BMI	Diabetes or impaired fasting glucose	Platelets, ALT, AST, albumin	
	Fibrosis-4 Score	FIB-4	Age		Platelets, ALT, AST	
	Hepamet Fibrosis Score	HFS	Age, gender	Diabetes, HOMA	Platelets, AST, albumin, glucose, insulin	
	Metabolomics-Advanced StEatohepatitis Fibrosis Score	MASEF	BMI		ALT, AST, serum lipids	
	Aspartate Aminotransferase-to-Platelet Ratio Index	APRI			Platelets, AST	
	Enhanced Liver Fibrosis Score	ELF			Hyaluronic acid, tissue inhibitor of metalloproteinase 1, amino-terminal propeptide of type III procollagen	
Imaging-based	Vibration-controlled transient elastography	VCTE				
	Magnetic resonance elastography	MRE				
Both serum- and imaging-based	Agile 3 + and 4 Scores				Platelets, ALT, AST	Liver stiffness measurement by VCTE
	MR Elastography combined with Fibrosis-4	MEFIB	Age		Platelets, ALT, AST	MR elastography
	MRI-AST Score	MAST			AST	MRI

ALT, alanine aminotransferase; *AST*, aspartate aminotransferase; *BMI*, body mass index; *FIB-4*, Fibrosis-4 Score; *HFS*, Hepamet Fibrosis Score; *HOMA*, homeostatic model assessment; *MASEF*, Metabolomics-Advanced StEatohepatitis Fibrosis; *MAST*, MRI-AST Score; *MEFIB*, MR Elastography combined with Fibrosis-4; *MRE*, magnetic resonance elastography; *NAFLD*, non-alcoholic fatty liver disease; *NFS*, NAFLD Fibrosis Score; *VCTE*, vibration-controlled transient elastography

compared to HCC risk of 0.04 per 1000 person-years in non-cirrhotic patients with low FIB-4 [5]. Compared to FIB-4, NFS and HFS performed similarly well in predicting HCC after a median follow-up of about 7 years [44].

Based on the AGA clinical practice update, evidence of advanced fibrosis warranting HCC surveillance in NAFLD can be based on 2 concordant noninvasive tests from separate categories, mainly serum-based and imaging-based [22••]. An inherent limitation to this recommendation, however, is that patients with advanced fibrosis determined via different noninvasive tests will likely have differing risk for HCC that is below the proposed societal guidelines for cost-effectiveness in HCC screening (HCC incidence ≥ 1.5% per year). Moreover, the AGA recommends utilizing higher cut-off thresholds maximizing specificity to 90% for the purpose of risk stratification for HCC screening [22••].

What Does HCC Screening Entail?

Those meeting recommended criteria for HCC surveillance should undergo ultrasonography (US) with or without measurement of serum α-fetoprotein (AFP) levels every 6 months, based on the AASLD and EASL clinical practice guidelines [20••, 21••]. Recommendations for utilizing inexpensive, widely available serum AFP testing in conjunction with US for HCC screening differ. AASLD practice guidelines recommend abdominal US with or without AFP, whereas EASL guidance supports the sole use of US [20••, 21••]. Combining AFP with US has been shown to increase the sensitivity for early HCC detection from 45% with sole US use to 63% for AFP with US [45].

Though AFP has been the most well-studied biomarker, other biomarkers have been evaluated. To begin, biomarkers such as des-gamma-carboxyprothrombin (DCP) and lens culinaris agglutinin-reactive AFP (AFP-L3), circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and methylated DNA markers possess vast potential and promise for empowering in-depth, individualized risk stratification for HCC, but need to be evaluated in robust phase 3 clinical trials [46–48]. As phase 2 clinical trials have shown that DCP and AFP-L3 are insufficient when used alone, serum biomarker-based models such as the GALAD score, which combines age, gender, AFP, AFP-L3, and DCP, have been developed with the goal of predicting HCC risk [46, 49]. A recent cohort study found that GALAD had higher accuracy (AUROC 0.95, 95% CI 0.93–0.97) for HCC detection compared to ultrasound (AUROC 0.82, $p < 0.01$) [49]. Furthermore, combining GALAD with ultrasound (GALADUS) achieved sensitivity of 95%, specificity of 91%, and AUROC of 0.98 (95% CI, 0.96–0.99) [49].

Prior research has shown that ultrasonographic quality may often be inadequate [50, 51]. A retrospective cohort study of 941 patients with cirrhosis previously found that 1 in 5 USs are inadequate for HCC exclusion and contribute to surveillance failure, and US inadequacy rose to over 1 in 3 in those with BMI > 35 kg/m^2 [51]. US may be suboptimal in overweight or obese patients due to focal fatty infiltration, parenchymal heterogeneity, and ultrasonographic attenuation through a hyperechoic liver leading to under-recognition of small HCC nodules [52]. In addition to its association with increased BMI (OR 1.67, 95% CI 1.45–1.93), inadequacy of US quality is associated with male gender (OR 1.68, 95% CI 1.14–2.48), Child–Pugh B or C cirrhosis (OR 1.93, 95% CI 1.32–2.81), or NAFLD cirrhosis (OR 2.87, 95% CI 1.71–4.80) [51]. Regardless of the etiology of cirrhosis, US also remains operator-dependent, relying on prior training and certification to maximize quality. Furthermore, limitations of US include high-performance variability among different centers, lowered sensitivity ranging between 32 and 89% for early HCC detection when used in isolation without serum AFP, and subsequent increased risk for indeterminate or false positive results, leading to further diagnostic procedures, expenses, and possible harm [45, 53, 54].

When performing US, the AGA recommends documenting the adequacy of US in assessing the liver parenchyma for mass lesions so that those with suboptimal ultrasonographic quality can undergo either computed tomography (CT) or magnetic resonance imaging (MRI) in lieu of abdominal US during future HCC screenings [20••, 22••, 55•]. According to the ultrasound quality criteria of the 2017 Liver Imaging Reporting and Data System (LI-RADS), documentation of US adequacy involves recording beam attenuation, degree of visualization of the entire liver, and echostructural heterogeneity (Table 2) [56•]. These 3 criteria contribute to an overall visualization score including (A) no or minimal limitations that are unlikely to meaningfully affect sensitivity, (B) moderate limitations that may obscure small masses, or (C) severe limitations that significantly lower sensitivity for focal liver lesions [56•]. The AGA recommends that those with visualization scores of B or C undergo CT or MRI instead of US for HCC surveillance [22••]. However, it remains unclear how either CT or MRI should be utilized in conjunction with serum AFP and in which proper screening intervals [45]. Figure 1 illustrates the recommended algorithm for HCC screening in those with NAFLD.

Due to the aforementioned limitations of ultrasound, alternative surveillance modalities with CT or MRI remain under evaluation. A prior randomized trial of 163 patients with compensated cirrhosis found that the sensitivity and specificity of CT (sensitivity 66.7%, specificity 94.4%) for HCC detection were lower than those of US (sensitivity 71.4%, specificity 97.5%) [57]. In addition, annual CT incurred overall costs compared to biannual US and was associated with harms of screening including possible injury from contrast and exposure to radiation [57–59]. On the other hand, a prospective surveillance

Table 2 LI-RADS visualization score

Score	Definition	Parenchymal heterogeneity	Bean attenuation	Visualization of the entire liver
A	Minimal limitations that are unlikely to meaningfully affect sensitivity	Homogeneous	Minimal	Near entire visualization
B	Moderate limitations that may obscure small masses	Moderately heterogeneous	Moderate	Some liver portions not visualized
C	Severe limitations that may significantly lower sensitivity for focal liver lesions	Severely heterogeneous	Severe (over 50% of the diaphragm not visualized)	Liver majority (over 50%) not visualized

LI-RADS, Liver Imaging Reporting and Data System

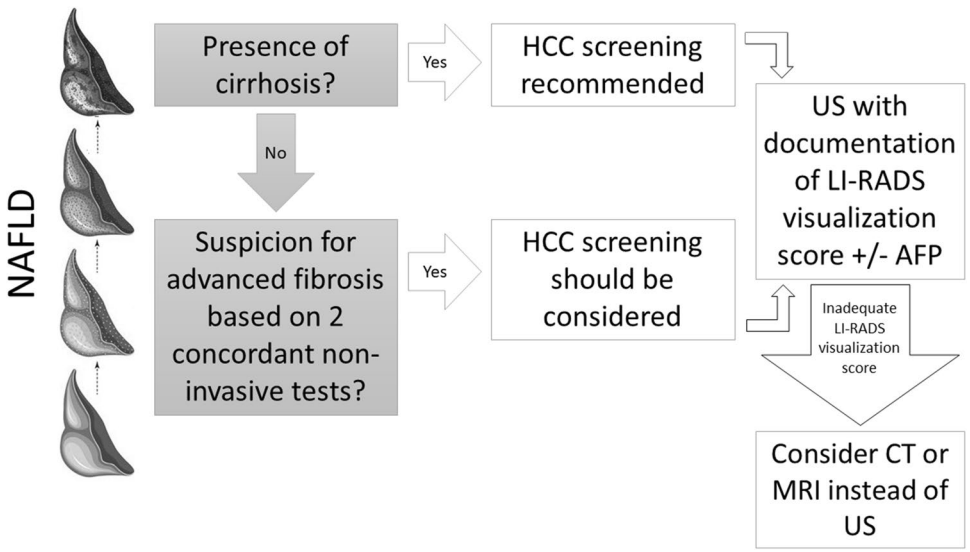

Fig. 1 Recommended algorithm for HCC screening in patients with NAFLD. AFP, α-fetoprotein; CT, computed tomography; HCC, hepatocellular carcinoma; LI-RADS, Liver Imaging Reporting and Data System; MRI, magnetic resonance imaging; NAFLD, non-alcoholic fatty liver disease; US, ultrasonography

study of 407 patients with cirrhosis found that liver-specific contrast-enhanced MRI had significantly higher sensitivity (83.7%) compared to ultrasound (25.6%) for early HCC identification [60]. However, as this study was performed in a population of patients with HBV, additional studies are needed to assess the surveillance accuracy of MRI in non-HBV patients [60]. Moreover, MRI remains more costly compared to ultrasound with limited routine use. Pending further investigation of alternative imaging modalities, US remains the gold standard surveillance strategy for HCC.

Conclusion

Given the rapid growth of NAFLD as a cause of HCC in the USA, risk stratification for HCC in patients with NAFLD remains a priority. Unique challenges to HCC surveillance among those with NAFLD include identifying individuals at the highest risk for HCC for screening given the possibility of carcinogenesis in those without cirrhosis, accurately staging fibrosis in NAFLD, and determining the most cost-effective but comprehensive HCC surveillance approach. As ultrasonographic screening is increasingly recognized as possessing suboptimal diagnostic performance, especially among those who are overweight or obese and at higher risk for NAFLD, novel noninvasive tests based on blood tests, imaging, and/or scoring algorithms are being investigated for risk stratification of HCC in NAFLD patients. However, future large epidemiological and longitudinal studies are necessary to better understand and validate where these novel noninvasive tests best fit into the HCC surveillance algorithm for those with NAFLD. In the interim, increasing public health awareness for the prevention of NAFLD development, deterrence of progression, and need for semi-annual HCC surveillance and follow-up in those with advanced fibrosis or cirrhosis remains of utmost importance.

Abbreviations *AASLD*: American Association for the Study of Liver Diseases; *AFP*: α-Fetoprotein; *AGA*: American Gastroenterological Association; *ALT*: Alanine aminotransferase; *APRI*: Aspartate aminotransferase-to-platelet ratio index; *AST*: Aspartate aminotransferase; *AUROC*: Area under the receiver operating curve; *BMI*: Body mass index; *CT*: Computed tomography; *EASL*: European Association for the Study of the Liver; *F3*: Fibrosis stage 3; *FIB-4*: Fibrosis-4 Score; *HCC*: Hepatocellular carcinoma; *HCV*: Hepatitis C virus; *HFS*: Hepamet Fibrosis Score; *HOMA*: Homeostatic model assessment; *LI-RADS*: Liver Imaging Reporting and Data System; *MASEF*: Metabolomics-Advanced StEatohepatitis Fibrosis; *MRE*: Magnetic resonance elastography; *MRI*: Magnetic resonance imaging; *NAFLD*: Non-alcoholic fatty liver disease; *NASH*: Non-alcoholic steatohepatitis; *NFS*: NAFLD Fibrosis Score; *US*: Ultrasonography; *VCTE*: Vibration-controlled transient elastography

Author Contribution ET interpreted the data and drafted the manuscript. CH, MM, and MN critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Declarations

Conflict of Interest Mazen Noureddin has been on the advisory board/consultant for 89BIO, Altimmune, Gilead, cohBar, CytoDyn, Intercept, Pfizer, Novo Nordisk, Blade, EchoSens, Fractyl, Madrgial, NorthSea, Prespecturm, Terns, Sami-Sabina group, Siemens and Roche diagnostic; MN has received research support from Allergan, BMS, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Madrigal, Novartis, Pfizer, Shire, Viking, and Zydus; MN is a shareholder or has stocks in Anaetos, Chrownwell, Ciema, Rivus Pharma, and Viking.
Emily Truong, Cheng Han, and Mark Muthiah declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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