

Editorial

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Hepatocellular carcinoma surveillance in non-alcoholic fatty liver disease patients

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease worldwide and is an umbrella term for liver disease encompassing non-alcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis, and/or hepatocellular carcinoma (HCC)^[1]. The burden of NAFLD is rapidly mounting alongside rising rates of metabolic syndrome and obesity, and NAFLD is projected to become the leading cause of HCC in the United States^[2]. Among the NAFLD's global burden, HCC surveillance in patients with NAFLD is challenging given the drawbacks of specific screening modalities and the well-recognized potential for HCC development in those without cirrhosis and even in those with lean NAFLD^[3].

THE PREVALENCE OF HCC IN NAFLD

Using the National Veterans Affairs system, a retrospective cohort study of 296,707 NAFLD patients found that the overall mean risk of HCC in NAFLD was 1.06% annually in the United States^[4]. More specifically, HCC incidence in NAFLD was 0.03 and 3.78 per 100 person-years, respectively, for those without and with cirrhosis, according to a meta-analysis that included 470,404 patients from 18 studies^[5]. According to the United Network for Organ Sharing registry, NAFLD is the most rapidly growing etiology of HCC-related liver transplant, and the number of NAFLD patients undergoing liver transplantation for HCC nearly quadrupled from 2002 to 2012 based on a study of 61,868 liver transplant patients, including 10,061 patients



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with HCC, in the United States^[6-8].

The incidence of HCC in NAFLD patients with cirrhosis is ~1 per 100 person-years^[9,10]. Although HCC incidence in NAFLD cirrhosis is lower or comparable compared to that of hepatitis C virus (HCV) or alcoholic cirrhosis, respectively, NAFLD and its high prevalence contribute to a greater global burden of HCC compared to other chronic liver disease etiologies^[10].

Up to 40% of HCC cases can develop in NAFLD patients without cirrhosis, and NAFLD represents the most common cause of HCC in those without cirrhosis, accounting for 26.3% of 605 HCC cases without cirrhosis compared to 13.4% of 4539 of HCC cases with cirrhosis^[11-13]. In the NAFLD spectrum, HCC incidence in patients with uncomplicated steatosis is estimated to be approximately 0.8-6.2 per 100 person-years, but is poorly reported in NASH due to its invasive histological nature^[14-16]. However, it is reasonable to approximate the incidence of HCC in NASH to the median prevalence of simple steatosis and cirrhosis^[13]. The pathophysiology of NAFLD may therefore independently contribute to the development of HCC regardless of fibrosis stage and brings up key challenges regarding screening for HCC^[17].

Furthermore, NAFLD has been shown to develop in approximately 10%-20% of non-obese [body mass index (BMI) < 30 kg/m²] or lean (BMI < 25 kg/m²) Americans, for whom clinical suspicion for and timely diagnosis of HCC may remain low^[18]. However, prevalence rates of HCC in lean NAFLD have yet to be investigated.

HCC SURVEILLANCE IN PATIENTS WITH NAFLD

Targeted Patient Populations for HCC Surveillance

Surveillance for HCC remains suboptimal in NAFLD, as 51.5% of NASH cirrhotic fail to undergo any screening before the diagnosis of HCC, compared with 25.9% of HCV cirrhotics^[19]. This may be due in part to the fact that NAFLD and HCC can often be clinically silent, especially in the early stages, and patients may therefore never consult the doctor. NASH cirrhotics with complete HCC screening had smaller tumors ($P = 0.006$) at diagnosis but no differences in treatment outcomes ($P = 0.281$) or mortality ($P = 0.468$) in comparison with NASH cirrhotics with incomplete or no screening^[19]. Similarly, compared with 13.3% of HCV-associated HCC cases ($P < 0.01$) and 40.2% of alcohol-associated HCC cases ($P < 0.01$), 56.7% of NAFLD-associated HCC cases did not follow recommended surveillance for HCC in the 3 years before diagnosis based on a United States national cohort of 1500 veterans who developed HCC from 2005-2010^[20].

Currently, the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) recommend surveillance for HCC for NAFLD patients with cirrhosis regardless of compensation or decompensation, which is cost-effective given that the predicted HCC incidence remains $\geq 1.5\%$ annually^[21,22].

Recommendations for HCC surveillance in those without cirrhosis remain controversial. Both EASL guidelines and the American Gastroenterological Association (AGA) Clinical Practice Update recommend surveilling for HCC in those with advanced fibrosis, defined as fibrosis stage 3 or higher ($F \geq 3$)^[22,23]. Additionally, AASLD guidance advises against screening for HCC in those with advanced fibrosis, considering the need for additional cost-effectiveness studies^[21,24]. In the absence of advanced fibrosis, AASLD and AGA clinical practice guidance recommend against routine HCC screening, whereas EASL states that this remains unclear given the known possibility of HCC occurrence in NAFLD patients without advanced fibrosis^[21-23].

Factors such as genetics may play a role in the pathophysiology of HCC in NAFLD without advanced fibrosis or cirrhosis. Impacting 40% of the European population, the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) rs738409 [G] risk allele is a genetic polymorphism that is independently linked to a 3- to 12-fold HCC risk^[25-28]. To better stratify risk in NAFLD without advanced fibrosis or cirrhosis, *PNPLA3* has been incorporated into several polygenic risk scores to predict the risk of HCC, yet these risk scores possess a low area under the receiver operating characteristic curve (AUROC) of 0.65 and sensitivity of 43%^[29]. In addition, routine genetic screening for *PNPLA3* is not currently justified or recommended given the lack of data, restricted access to genetic testing, and high cost^[22]. Other genetic polymorphisms including *MBOAT7* and *TM6SF2* may contribute to the pathophysiology of NAFLD-associated HCC, but additional studies are needed for clarification.

Staging for NAFLD

Staging fibrosis is a priority in NAFLD not only because HCC surveillance is based on fibrosis stage, but also because Angulo *et al.* have shown that fibrosis stage is independently associated with long-term overall mortality, liver transplantation, and major adverse liver events^[30]. Liver biopsy is the gold standard but is unsuitable as the initial staging method due to its invasive nature, risk of complications, high expense, and potential for sampling error^[31-33].

Aside from liver biopsy, other modalities for staging include non-invasive serum biomarkers, imaging [i.e., vibration-controlled transient elastography (VCTE, cirrhosis cutoff 16.1 kPa) and magnetic resonance elastography (MRE, cirrhosis cutoff 5 kPa)], and/or risk stratifying algorithms^[33-36]. However, compared to the gold standard, imaging modalities are often limited by the inability to definitively exclude advanced fibrosis given their low negative predictive values.

Non-invasive algorithms that offer risk stratification for HCC development include the Agile 3+ and 4 scores, Aspartate Aminotransferase-to-Platelet Ratio Index (APRI), Fibrosis-4 score (FIB-4), NAFLD fibrosis score (NFS), Metabolomics-Advanced Steatohepatitis Fibrosis (MASEF), MAST score and MR elastography combined with fibrosis-4 (MEFIB) score^[35,37-44]. In NAFLD, a FIB-4 score of ≥ 2.67 is associated with a higher HCC risk of 13.5/1000 person-years in those with cirrhosis and 0.39/1000 person-years in those without cirrhosis, both of which are higher than the HCC risk of 0.04/1000 person-years in those without cirrhosis with a low FIB-4 score^[4]. With a median follow-up of 7 years, HFS and NFS have similar performances compared to that of FIB-4 in predicting the development of HCC^[45].

Given the drawbacks of percutaneous liver biopsy and the vast array of available non-invasive testing, advanced fibrosis for which HCC surveillance can be considered in NAFLD may be determined via concordance from 2 non-invasive tests (1 serum-based, 1 imaging-based), based on the AGA Clinical Practice Update^[23]. However, this guidance is limited in that these NAFLD patients with advanced fibrosis may have a HCC risk that is less than the proposed 1.5% deemed optimal for cost-effectiveness. As such, utilizing higher thresholds with 90% specificity for HCC surveillance is recommended by the AGA^[23].

HCC Surveillance

Both EASL and AASLD recommend biannual ultrasonography (US) with or without serum α -fetoprotein (AFP) levels for NAFLD patients meeting the aforementioned recommended eligibility criteria for HCC screening^[21,22]. AFP testing alongside US remains much debated. EASL recommends using abdominal US alone, but AASLD supports US with or without AFP, whose combination with US increases HCC detection sensitivity from 45% (only US) to 63% (US + AFP)^[21,22,46].

Other biomarkers have been investigated for HCC surveillance. Some promising, risk-stratifying HCC biomarkers include lens culinaris agglutinin-reactive AFP (AFP-L3), des-gamma-carboxyprothrombin (DCP), methylated DNA markers, circulating tumor DNA (ctDNA), and circulating tumor cells (CTCs). However, robust phase 3 clinical trials are necessary before clinical use, and several phase 2 clinical trials have proven the insufficiency of sole DCP or AFP-L3 use^[47-49]. In light of these findings, biomarker-based algorithms such as the GALAD score have been developed to predict the development of HCC^[47,50]. Utilizing gender, age, DCP, AFP, and AFP-L3, the GALAD score is more accurate in detecting HCC than US (GALAD: AUROC 0.95, 95%CI: 0.93-0.97, US: AUROC 0.82, $P < 0.01$)^[50]. In addition, GALAD used in conjunction with US (GALADUS) has AUROC of 0.98 (95%CI: 0.96-0.99), specificity of 91%, and sensitivity of 95%^[50].

US for HCC screening has previously been shown to be inadequate^[51,52]. According to a retrospective cohort study of 941 patients, 20% and over 33% of USs, respectively, are insufficient for excluding HCC in cirrhotic patients overall and with BMI > 35 kg/m²^[52]. Sonographic surveillance failure in overweight or obese patients results from heterogeneity in the parenchyma, focal fatty infiltration, and suboptimal sonographic attenuation, all of which prevent the identification of smaller cancerous nodules^[53]. Quantitatively, suboptimal sonographic quality has been associated with increased BMI [OR = 1.67, (95%CI: 1.45-1.93)], male gender [OR = 1.68, (95%CI: 1.14-2.48)], NAFLD cirrhosis [OR = 2.87, (95%CI: 1.71-4.80)], and Child-Pugh B or C cirrhosis [OR = 1.93, (95%CI: 1.32-2.81)]^[52]. Moreover, US is limited by its dependence on the operator with subsequent performance variability. Finally, US without AFP has been shown to have decreased sensitivity of 32%-89% for detecting HCC and therefore higher risk of false positives or indeterminacy^[46,54,55].

According to the AGA, the quality of US in detecting mass lesions in the liver parenchyma should be documented in order to identify those with suboptimal US screening who should instead undergo computed tomography (CT) or magnetic resonance imaging (MRI) in the future^[21,23,56]. Taking into account the extent to which the entire liver is visualized, beam attenuation, and echostructural heterogeneity, the 2017 Liver Imaging Reporting and Data System (LI-RADS) divides US quality into three categories: (1) no or negligible limitations that will not meaningfully impact sensitivity; (2) moderate limitations that may cause obscuration of smaller masses; or (3) severe limitations that significantly decrease the sensitivity for focal liver masses^[57]. Though the AGA states that CT or MRI should be utilized for patients with B or C visualization scores, additional guidance is necessary to determine the utility of concomitant AFP alongside CT or MRI and the appropriate intervals for surveillance^[23,46].

Figure 1 shows a summary of societal guidance recommendations for HCC surveillance in NAFLD.

CONCLUSION

As NAFLD remains the most rapidly growing cause of HCC in the United States, HCC surveillance in NAFLD is essential but plagued by questions surrounding the identification of those without advanced fibrosis or cirrhosis who may warrant HCC screening and the best screening modalities that balance cost-effectiveness and comprehensiveness in detecting HCC lesions. US remains the gold standard for screening for HCC but is often inadequate in NAFLD patients who are overweight or obese. Novel non-invasive tests are undergoing investigation for HCC risk stratification, but additional studies are needed for validation.

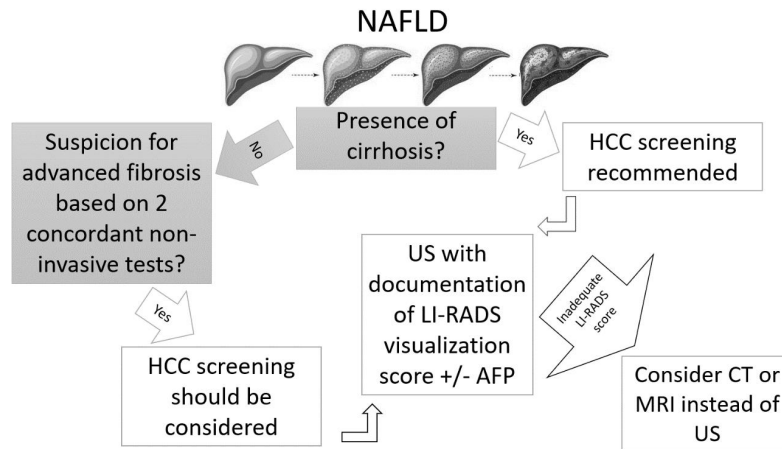


Figure 1. Recommendations for HCC Surveillance in NAFLD. AFP: α -fetoprotein; CT: computed tomography; HCC: hepatocellular carcinoma; LI-RADS: liver imaging reporting and data system; MRI: magnetic resonance imaging; NAFLD: non-alcoholic fatty liver disease; US: ultrasonography.

DECLARATIONS

Authors' contributions

Interpreted the data and drafted the manuscript: Truong E

Critically revised the manuscript for important intellectual content: Nouredin M

Availability of data and materials

Not applicable.

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Conflicts of interest

Nouredin M 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; Nouredin M has received research support from Allergan, BMS, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Madrigal, Novartis, Pfizer, Shire, Viking and Zydus; Nouredin M is a shareholder or has stocks in Anaetos, Chrownwell, Ciema, Rivus Pharma and Viking.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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