

Review

Open Access



Challenges and barriers in hepatocellular carcinoma (HCC) surveillance for patients with non-alcoholic fatty liver disease (NAFLD)

Kara Wegermann¹, Anna Mae Diehl¹, Cynthia A. Moylan^{1,2}

¹Division of Gastroenterology, Department of Medicine, Duke University Health System, Durham, NC 27710, USA.

²Department of Medicine, Durham Veterans Affairs Medical Center, Durham, NC 27710, USA.

Correspondence to: Cynthia A. Moylan, MD, MHS, Division of Gastroenterology, Department of Medicine, Duke University Health System, DUMC 3256 Snyderman Building/GSRB1, 905 South LaSalle Street, Durham, NC 27710, USA. E-mail: cynthia.moylan@duke.edu

How to cite this article: Wegermann K, Diehl AM, Moylan CA. Challenges and barriers in hepatocellular carcinoma (HCC) surveillance for patients with non-alcoholic fatty liver disease (NAFLD). *Hepatoma Res* 2023;9:11. <https://dx.doi.org/10.20517/2394-5079.2022.92>

Received: 30 Nov 2022 **First Decision:** 28 Feb 2023 **Revised:** 21 Mar 2023 **Accepted:** 28 Mar 2023 **Published:** 31 Mar 2023

Academic Editor: Giuliano Ramadori **Copy Editor:** Yanbing Bai **Production Editor:** Yanbing Bai

Abstract

The proportion of hepatocellular carcinoma (HCC) cases due to NAFLD is expected to increase, paralleling the rise in NAFLD due to the obesity epidemic. Early detection is critical, as it potentially enables curative treatment. Current guidelines recommend ultrasound imaging with or without serum AFP measurement in patients with cirrhosis. Unfortunately, several challenges and barriers impede the effective surveillance of HCC in patients with NAFLD. In this review, we focus on four main challenges and barriers: the scale of the NAFLD epidemic, the lack of accurate risk stratification tools, the limitations of available surveillance tools themselves, and the existing disparities in access to care for chronic liver disease. We describe potential solutions, including public health approaches to obesity, improving clinical risk scores using genomic and metabolomic data, improved imaging techniques and blood-based biomarkers, and focusing on underserved groups with liver disease.

Keywords: NAFLD, HCC, non-invasive biomarker, radiomics

INTRODUCTION

Numerous challenges and barriers impede effective surveillance for hepatocellular carcinoma (HCC) in



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, sharing, adaptation, distribution and reproduction in any medium or format, for any purpose, even commercially, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.



patients with non-alcoholic fatty liver disease (NAFLD). In this review, we focus on four main challenges and barriers: the scale of the NAFLD epidemic, the lack of accurate risk stratification tools, the limitations of available surveillance tools themselves, and the existing disparities in access to care for chronic liver disease. We also provide initial suggestions for potential solutions to address these barriers [Figure 1].

THE SCALE OF THE PROBLEM

The scale of the NAFLD epidemic makes HCC surveillance difficult and expensive. It is estimated that NAFLD affects one-quarter of the world population and about one-third of the US population^[1]. Regrettably, the incidence and prevalence of NAFLD are projected to increase, paralleling increases in diabetes and other features of the metabolic syndrome. One recent study projected a 21% increase in NAFLD prevalence in the United States from 2018 to 2030. This translates into a NAFLD prevalence of 33.5% (or more than 117 million adults) in the US by 2030^[2]. Of equal concern is the increase in pediatric obesity and features of the metabolic syndrome in children, which will increase the frequency and severity of adult NAFLD and resultant cirrhosis in the coming years. Multiple large studies have associated weight gain in childhood and adolescence with severe liver damage and liver-related mortality in adulthood^[3,4].

Although HCC related to viral hepatitis is declining due to improved interventions to prevent and treat hepatitis B and C^[5], the rise in NAFLD will neutralize this benefit by promoting cirrhosis, HCC, and liver-related mortality. The risk of HCC in NAFLD cirrhosis is about 1.5% per year^[6], with estimates ranging from 0.5%-2.6%^[7]. Although NAFLD patients without cirrhosis have a lower risk, their risk remains substantially higher than those with some other etiologies of chronic liver disease.

Given the benefit of HCC surveillance for early liver cancer detection and survival suggested by a recent meta-analysis^[9], the scale of the NAFLD epidemic per se should not prevent its adoption. In fact, HCC surveillance in patients with cirrhosis displays similar cost-effectiveness to colonoscopy^[10], and the latter is recommended for all average-risk adults ages 45 and older. As with improving non-invasive methods for colon cancer screening, such as stool-based tests, it is imperative to find inexpensive and rapid HCC surveillance tools.

LACK OF RISK STRATIFICATION TOOLS

AASLD guidelines recommend twice-yearly HCC surveillance for all patients with NAFLD cirrhosis^[11]. A recent meta-analysis estimated the incidence of HCC in non-cirrhotic NAFLD patients at 0.03 per 100 person-years^[12], and an AGA 2020 clinical practice update recommends that patients with advanced fibrosis (F3) on liver biopsy or two distinct non-invasive measures undergo HCC surveillance^[13], but this has not been widely adopted. Two important questions therefore remain unanswered: (1) Do some patients with NAFLD cirrhosis need more intensive HCC surveillance than guidelines recommend? (2) Which patients, if any, with NAFLD and F0-F3 fibrosis warrant HCC surveillance? Below, we discuss clinical, tumor marker, genetic and metabolomic strategies for risk stratification, which could collectively help answer these questions.

Clinical risk factors provide a rudimentary risk stratification system. The strongest predictor of liver-related events including HCC in NAFLD is the advanced fibrosis stage^[14]. Although liver biopsy remains the gold standard for assessing fibrosis, non-invasive methods are gaining popularity. Scoring systems such as the Fibrosis-4 (FIB-4) score, AST to platelet ratio index (APRI), and NAFLD fibrosis score (NFS) are based on readily available laboratory results and clinical data and have excellent performance characteristics. In one European cohort of 1,173 NAFLD patients, NFS had the best performance for predicting the development of HCC, and both NFS and FIB-4 predicted liver-related events^[15]. A retrospective study of almost 30,000

Challenges and barriers in HCC surveillance for patients with NAFLD

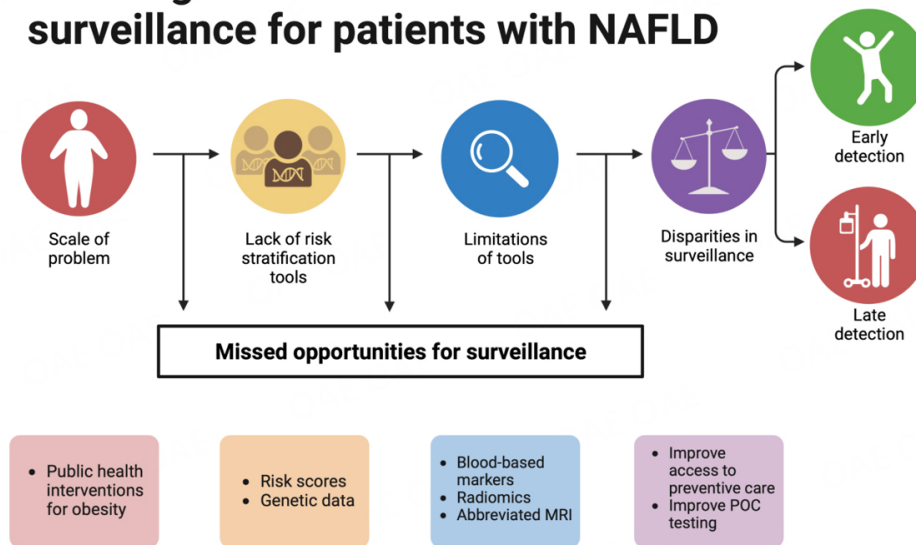


Figure 1. Barriers to effective HCC surveillance in NAFLD and potential solutions. Created with BioRender.

patients in Germany found that a FIB-4 score greater than or equal to 1.3 was a strong predictor of HCC over 10 years^[16]. More recently, a cohort of 81,108 patients was assessed over a mean-follow up of 34 months, and FIB-4 independently predicted overall mortality and liver-related adverse outcomes^[17]. For this reason, recent AASLD practice guidance recommends risk stratification with FIB-4 followed by transient elastography for patients with scores indicative of advanced fibrosis^[18].

Beyond the fibrosis stage, male sex, older age, smoking, diabetes, and obesity are known to increase the risk for HCC^[6]. In a large retrospective analysis of European patients ($n = 136,703$) with NAFLD, diabetes was the strongest predictor of cirrhosis and HCC^[19]. Hypertension, hyperlipidemia, and alcohol intake have also been associated with increased HCC risk in NAFLD^[20,21]. Although race and ethnicity may affect susceptibility to, and progression of NAFLD, our understanding of this relationship remains underdeveloped. Available data suggest that within commonly described racial and ethnic groups such as “Hispanic”, the prevalence of NAFLD may differ significantly. For example, one study found that the prevalence of NAFLD was 33% in patients of Mexican heritage, but only 16% in patients whose heritage was from the Dominican Republic^[22]. This may be due to genetic, epigenetic, or environmental factors, or a combination thereof. Considering more specific ancestry in statistical analyses of NAFLD patients may allow for improved phenotyping and risk stratification for HCC.

Non-invasive biomarkers including genetic, proteomic and metabolomic data may aid in risk stratification for HCC surveillance for both patients with and without NAFLD cirrhosis. One example of the use of genetic markers was recently published using individuals from the UK Biobank and Denmark. Authors combined single nucleotide polymorphisms (SNPs) on *PNPLA3*, *TM6SF2*, and *HSD17B13* into a risk score and found that the number of risk alleles was associated with the risk for HCC, with 6 risk alleles corresponding to an odds ratio of 29 compared to those with 0 risk alleles^[23]. A SNP on *MBOAT7* has also been associated with HCC risk in non-cirrhotic NAFLD specifically^[24]. Transcriptomic data may also aid in risk stratification of patients with NAFLD. A 32-gene expression signature previously developed in patients with cirrhosis due to HCV was associated with an annual incidence of HCC in patients with cirrhosis of any

etiology, and the association remained significant in the subgroup with NAFLD^[25]. More recently, the same group found that a 133-gene liver tissue-based expression signature predicted the longitudinal development of HCC in a cohort of NAFLD patients. This was translated into a 4-component serum panel, which was associated with HCC development independent of clinical risk factors^[26]. Additional gene expression-based risk stratification biomarkers have been developed in patients with other etiologies of cirrhosis (largely viral hepatitis) and should be validated in patients with NAFLD to determine their utility. These include fatty acids^[27], osteopontin^[28], serum glycome (Cirrhosis Risk Score), and IGF1^[29]. Gene expression may fluctuate over time, which is an advantage compared to static data such as SNP genotypes (because changes in gene expression may capture disease progression) but introduces complications for clinical applicability, including how and when to capture this data.

Presumably, the most useful tools for patients and clinicians would be risk stratification scores that incorporate clinical and biomarker data. For example, clinical factors with strong predictive value such as age and diabetes status could be combined with gene expression or SNP data to sort patients into low, intermediate, and high-risk groups. Such classification could aid in prioritizing patients for new and improved surveillance strategies when these are developed.

LIMITATIONS OF AVAILABLE SURVEILLANCE TOOLS AND POTENTIAL SOLUTIONS

A third challenge remains the current suboptimal surveillance tools for identifying HCC at an early stage when curative treatments resulting in improved survival are available. Liver ultrasound is currently the standard of care, with a number of serum-based biomarkers in development to improve sensitivity or even replace imaging. One meta-analysis found that liver ultrasound was only 47% sensitive for the detection of early-stage HCC in patients with cirrhosis of any etiology. Detection sensitivity increased to 63% with the addition of alpha-fetoprotein (AFP) measurement^[30]. A more recent Cochrane review confirmed ultrasound sensitivity of 53% for resectable HCC, which increased to 79%-89% with the addition of AFP^[31]. Unfortunately, obesity further limits the accuracy of ultrasound as fat attenuates ultrasound beams directly^[32]. Additionally, ultrasound is operator-dependent and performance characteristics vary significantly. These challenges point to the importance of studying the sensitivity and specificity of this tool, particularly in obese NAFLD patients. Although contrast-enhanced CT and MRI have excellent sensitivity and specificity for detection of HCC, the time and cost of these technologies has prevented their adoption in place of ultrasound. Abbreviated MRI may provide a better option. Abbreviated MRI techniques utilize a limited number of sequences to detect HCC, and thus decrease time and costs while continuing to provide excellent sensitivity over ultrasound^[33]. Abbreviated MRI is currently being studied in the Veterans Affairs Health System (PREMIUM study, CSP #2023) and in a multi-center prospective study [FAST (Focused Abbreviated Screening Technique)-MRI Study, NCT04539717]. Such protocols would give a better definition and ability to apply radiomics compared to ultrasound and would limit time and cost.

Important additional considerations for optimal surveillance tools are tumor biology and tumor aggressiveness. While imaging may provide information about tumor size and macrovascular invasion into the portal vein or other surrounding structures, these key measures of cancer risk have not been well captured on imaging traditionally. That may change with the advent of radiomics which uses radiographic features to extrapolate biochemical or molecular characteristics of a lesion. Radiomics could offer several advantages, including the ability to account for heterogeneity within a lesion (which is not accurately captured by a random sample tumor biopsy)^[34]. Tumor grade, microvascular invasion, aggressiveness, and gene expression have been predicted with reasonable accuracy using cross-sectional imaging characteristics^[35-37]. Such technologies may contribute important information to the non-invasive characterization of HCC.

Tumor markers including alpha-fetoprotein have been used in combination with imaging for HCC surveillance. Attempts have been made to refine serum tumor marker-based panels to better risk stratify patients. The most notable example is the GALAD score, which was developed using European and Japanese cohorts and combines AFP-L3, AFP, and des-carboxy-prothrombin in addition to age and sex^[38].

Other non-invasive measures have been studied. Hypermethylation of certain genes can be detected in the blood prior to HCC diagnosis and could be used in combination with other modalities^[39]. Several studies have examined blood-based methylation profiles, in combination with gene expression or other data, to detect early-stage HCC. Such “liquid biopsies” may become standard of care in the future, given the cost and inconvenience associated with performing abdominal ultrasound as well as the limitations mentioned above. In one multi-center study, a panel using 3 methylated DNA markers as well as 2 protein markers including AFP was able to discriminate HCC cases from age-matched liver disease controls without HCC, with an area under the curve (AUC) of 0.92^[40]. A simplified blood-based panel from the same group using AFP and multiple DNA methylation markers revealed an AUC of 0.91 for any stage HCC and 0.86 for early-stage HCC. In a separate validation cohort, sensitivity for HCC detection was 88%^[41]. The funders have subsequently started a large, prospective clinical trial for this panel (Oncoguard®, Exact Sciences Inc, ALTUS Study, NCT05064553). Methylation profiles need further study and validation prior to use in general clinical practice, but methylation profiling is already in use in non-invasive colon cancer screening (Cologuard®) and holds great potential.

Extracellular vesicles (EVs) represent another type of “liquid biopsy” holding promise in HCC. As EVs contain DNA, RNA, proteins, metabolites and lipids from both normal and tumor cells and are present in circulation, several studies have investigated their role in detecting HCC among at-risk patients^[42-45]. A recently published phase 2 biomarker study revealed a 91% sensitivity and 90% specificity for distinguishing early-stage HCC from cirrhosis, of which NAFLD represented 20%^[46]. The HCC EV ECG score was calculated from three HCC EV subpopulations (EpCAM⁺ CD63⁺, CD147⁺ CD63⁺, and GPC3⁺CD63⁺) in a training cohort ($n = 106$) and independent validation cohort ($n = 72$). Further validation in larger multi-site trials is needed, but this promising method could augment current methods to detect HCC at earlier, more treatable stages.

DISPARITIES IN HCC SURVEILLANCE

Disparities in access to HCC surveillance pose another major barrier to successful implementation. Overall surveillance rates for patients with cirrhosis are under 10% (ultrasound every 6-12 months) based on a recent analysis of a large US-based commercial database. During the study period from 2007-2016, 45% of patients had no HCC surveillance whatsoever^[47]. NAFLD patients may have even lower rates of surveillance; a multi-center study found that patients with NAFLD were less likely to undergo HCC surveillance compared to patients with chronic hepatitis C infection^[48]. Similar findings were discovered in a large cohort from the Department of Veterans Affairs, in which patients with NAFLD were less likely to have received HCC surveillance leading up to a diagnosis of HCC^[49]. It is possible that undiagnosed NAFLD contributed to this finding.

Although many patients report difficulty in presenting for HCC surveillance imaging due to time constraints, cost, and transportation^[50], disparities in HCC surveillance by race and socioeconomic status are well established. A single-center study from a large urban safety-net study found that Black patients were less likely to receive consistent HCC surveillance compared to White patients^[51]. Larger studies from the SEER-Medicare database and the Veterans Affairs population (specifically in patients with HCV) have also found lower rates of HCC surveillance among Black patients^[52,53]. The reasons for this are unclear.

Disparities in access to subspecialty hepatology care (which has been associated with higher HCC surveillance rates), socioeconomic disparities including transportation and financial resources for health care, could have contributed. In the abovementioned study, race was independently associated with lower HCC surveillance rates even after adjustment for insurance status and receipt of primary care services. Therefore, financial factors are unlikely to explain the difference. Provider bias may also contribute; in one study of 467 patients followed at a tertiary care center, more non-White patients reported that their doctors had never talked to them about HCC surveillance^[54].

Although telehealth technology may enable greater access to sub-specialty liver disease care, which is associated with better HCC surveillance rates, geographic areas with less access to specialty care also have lower rates of broadband internet coverage^[55]. In addition, it is unlikely that telehealth would fully address disparities in HCC surveillance, since barriers such as transportation and cost to obtain regular imaging and/or blood tests will persist. Engagement with primary care providers and community health centers may expand access to surveillance, and initiatives to educate patients and providers should continue.

CONCLUSIONS

Overall, the barriers to HCC surveillance are significant but surmountable. New technologies and better risk stratification will enable targeted interventions. At the same time, measures to increase surveillance rates in the cirrhosis population and in racial minorities are urgently needed.

DECLARATIONS

Authors' contributions

Conceptualization, investigation, writing original draft: Wegermann K

Conceptualization, supervision: Diehl AM

Conceptualization, supervision, writing review and editing: Moylan CA

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors have declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Copyright

© The Author(s) 2023.

REFERENCES

1. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol* 2018;15:11-20. DOI PubMed
2. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an

- exponential increase in burden of disease. *Hepatology* 2018;67:123-33. DOI PubMed PMC
3. Hagström H, Stål P, Hultcrantz R, Hemmingsson T, Andreasson A. Overweight in late adolescence predicts development of severe liver disease later in life: a 39years follow-up study. *J Hepatol* 2016;65:363-8. DOI PubMed
 4. Zimmermann E, Gamborg M, Holst C, Baker JL, Sørensen TI, Berentzen TL. Body mass index in school-aged children and the risk of routinely diagnosed non-alcoholic fatty liver disease in adulthood: a prospective study based on the copenhagen school health records register. *BMJ Open* 2015;5:e006998. DOI PubMed PMC
 5. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of hepatocellular carcinoma. *Hepatology* 2021;73 Suppl 1:4-13. DOI PubMed PMC
 6. Ioannou GN. Epidemiology and risk-stratification of NAFLD-associated HCC. *J Hepatol* 2021;75:1476-84. DOI PubMed
 7. Huang DQ, El-Serag HB, Loomba R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol* 2021;18:223-38. DOI PubMed PMC
 8. Stine JG, Wentworth BJ, Zimmet A, et al. Systematic review with meta-analysis: risk of hepatocellular carcinoma in non-alcoholic steatohepatitis without cirrhosis compared to other liver diseases. *Aliment Pharmacol Ther* 2018;48:696-703. DOI PubMed PMC
 9. Singal AG, Zhang E, Narasimman M, et al. HCC surveillance improves early detection, curative treatment receipt, and survival in patients with cirrhosis: a meta-analysis. *J Hepatol* 2022;77:128-39. DOI PubMed PMC
 10. Lin OS, Keeffe EB, Sanders GD, Owens DK. Cost-effectiveness of screening for hepatocellular carcinoma in patients with cirrhosis due to chronic hepatitis C. *Aliment Pharmacol Ther* 2004;19:1159-72. DOI PubMed
 11. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American association for the study of liver diseases. *Hepatology* 2018;67:328-57. DOI
 12. Orci LA, Sanduzzi-Zamparelli M, Caballol B, et al. Incidence of hepatocellular carcinoma in patients with nonalcoholic fatty liver disease: a systematic review, meta-analysis, and meta-regression. *Clin Gastroenterol Hepatol* 2022;20:283-292.e10. DOI PubMed
 13. Loomba R, Lim JK, Patton H, El-Serag HB. AGA clinical practice update on screening and surveillance for hepatocellular carcinoma in patients with nonalcoholic fatty liver disease: expert review. *Gastroenterology* 2020;158:1822-30. DOI PubMed PMC
 14. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology* 2015;149:389-97.e10. DOI PubMed PMC
 15. Younes R, Caviglia GP, Govaere O, et al. Long-term outcomes and predictive ability of non-invasive scoring systems in patients with non-alcoholic fatty liver disease. *J Hepatol* 2021;75:786-94. DOI PubMed
 16. Loosen SH, Kostev K, Keitel V, Tacke F, Roderburg C, Luedde T. An elevated FIB-4 score predicts liver cancer development: a longitudinal analysis from 29,999 patients with NAFLD. *J Hepatol* 2022;76:247-8. DOI PubMed
 17. Vieira Barbosa J, Milligan S, Frick A, et al. Fibrosis-4 index as an independent predictor of mortality and liver-related outcomes in NAFLD. *Hepatol Commun* 2022;6:765-79. DOI PubMed PMC
 18. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology* 2023. DOI PubMed
 19. Alexander M, Loomis AK, van der Lei J, et al. Risks and clinical predictors of cirrhosis and hepatocellular carcinoma diagnoses in adults with diagnosed NAFLD: real-world study of 18 million patients in four European cohorts. *BMC Med* 2019;17:95. DOI PubMed PMC
 20. Jarvis H, Craig D, Barker R, et al. Metabolic risk factors and incident advanced liver disease in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of population-based observational studies. *PLoS Med* 2020;17:e1003100. DOI PubMed PMC
 21. Kimura T, Tanaka N, Fujimori N, et al. Mild drinking habit is a risk factor for hepatocarcinogenesis in non-alcoholic fatty liver disease with advanced fibrosis. *World J Gastroenterol* 2018;24:1440-50. DOI PubMed PMC
 22. Fleischman MW, Budoff M, Zeb I, Li D, Foster T. NAFLD prevalence differs among hispanic subgroups: the multi-ethnic study of atherosclerosis. *World J Gastroenterol* 2014;20:4987-93. DOI PubMed PMC
 23. Gellert-Kristensen H, Richardson TG, Davey Smith G, Nordestgaard BG, Tybjaerg-Hansen A, Stender S. Combined effect of PNPLA3, TM6SF2, and HSD17B13 variants on risk of cirrhosis and hepatocellular carcinoma in the general population. *Hepatology* 2020;72:845-56. DOI PubMed
 24. Donati B, Dongiovanni P, Romeo S, et al. MBOAT7 rs641738 variant and hepatocellular carcinoma in non-cirrhotic individuals. *Sci Rep* 2017;7:4492. DOI PubMed PMC
 25. Nakagawa S, Wei L, Song WM, et al; Precision liver cancer prevention consortium. molecular liver cancer prevention in cirrhosis by organ transcriptome analysis and lysophosphatidic acid pathway inhibition. *Cancer Cell* 2016;30:879-90. DOI PubMed PMC
 26. Fujiwara N, Kubota N, Crouchet E, et al. Molecular signatures of long-term hepatocellular carcinoma risk in nonalcoholic fatty liver disease. *Sci Transl Med* 2022;14:eabo4474. DOI PubMed PMC
 27. Khan IM, Gjukan D, Jiao J, et al. A novel biomarker panel for the early detection and risk assessment of hepatocellular carcinoma in patients with cirrhosis. *Cancer Prev Res* 2021;14:667-74. DOI PubMed PMC
 28. Duarte-Salles T, Misra S, Stepien M, et al. Circulating osteopontin and prediction of hepatocellular carcinoma development in a large european population. *Cancer Prev Res* 2016;9:758-65. DOI PubMed PMC
 29. Mazziotti G, Sorvillo F, Morisco F, et al. Serum insulin-like growth factor I evaluation as a useful tool for predicting the risk of developing hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis: a prospective study. *Cancer* 2002;95:2539-45. DOI PubMed

30. Tzartzeva K, Obi J, Rich NE, et al. Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: a meta-analysis. *Gastroenterology* 2018;154:1706-1718.e1. [DOI](#) [PubMed](#) [PMC](#)
31. Colli A, Nadarevic T, Miletic D, et al. Abdominal ultrasound and alpha-foetoprotein for the diagnosis of hepatocellular carcinoma in adults with chronic liver disease. *Cochrane Database Syst Rev* 2021;4:CD013346. [DOI](#) [PubMed](#) [PMC](#)
32. Uppot RN. Technical challenges of imaging & image-guided interventions in obese patients. *Br J Radiol* 2018;91:20170931. [DOI](#) [PubMed](#) [PMC](#)
33. Marks RM, Ryan A, Heba ER, et al. Diagnostic per-patient accuracy of an abbreviated hepatobiliary phase gadoxetic acid-enhanced MRI for hepatocellular carcinoma surveillance. *AJR Am J Roentgenol* 2015;204:527-35. [DOI](#) [PubMed](#)
34. Vietti Violi N, Lewis S, Hectors S, Taouli B, et al. Radiological diagnosis and characterization of HCC. In: Hoshida Y, editor. *Hepatocellular Carcinoma*. Cham: Springer International Publishing; 2019. pp. 71-92. [DOI](#)
35. Zhou W, Zhang L, Wang K, et al. Malignancy characterization of hepatocellular carcinomas based on texture analysis of contrast-enhanced MR images. *J Magn Reson Imaging* 2017;45:1476-84. [DOI](#) [PubMed](#)
36. Peng J, Zhang J, Zhang Q, Xu Y, Zhou J, Liu L. A radiomics nomogram for preoperative prediction of microvascular invasion risk in hepatitis B virus-related hepatocellular carcinoma. *Diagn Interv Radiol* 2018;24:121-7. [DOI](#) [PubMed](#) [PMC](#)
37. Segal E, Sirlin CB, Ooi C, et al. Decoding global gene expression programs in liver cancer by noninvasive imaging. *Nat Biotechnol* 2007;25:675-80. [DOI](#) [PubMed](#)
38. Johnson PJ, Pirrie SJ, Cox TF, et al. The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. *Cancer Epidemiol Biomarkers Prev* 2014;23:144-53. [DOI](#) [PubMed](#)
39. Shen J, Wang S, Zhang YJ, et al. Genome-wide DNA methylation profiles in hepatocellular carcinoma. *Hepatology* 2012;55:1799-808. [DOI](#)
40. Chalasani NP, Ramasubramanian TS, Bhattacharya A, et al. A novel blood-based panel of methylated DNA and protein markers for detection of early-stage hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2021;19:2597-2605.e4. [DOI](#) [PubMed](#)
41. Chalasani NP, Porter K, Bhattacharya A, et al. Validation of a novel multitarget blood test shows high sensitivity to detect early stage hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2022;20:173-182.e7. [DOI](#) [PubMed](#)
42. Lee YT, Tran BV, Wang JJ, et al. The role of extracellular vesicles in disease progression and detection of hepatocellular carcinoma. *Cancers* 2021;13:3076. [DOI](#) [PubMed](#) [PMC](#)
43. Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. *Nat Rev Mol Cell Biol* 2018;19:213-28. [DOI](#) [PubMed](#)
44. von Felden J, Garcia-Lezana T, Dogra N, et al. Unannotated small RNA clusters associated with circulating extracellular vesicles detect early stage liver cancer. *Gut* ;2021:2069-80. [DOI](#) [PubMed](#) [PMC](#)
45. Sun N, Lee YT, Zhang RY, et al. Purification of HCC-specific extracellular vesicles on nanosubstrates for early HCC detection by digital scoring. *Nat Commun* 2020;11:4489. [DOI](#) [PubMed](#) [PMC](#)
46. Sun N, Zhang C, Lee YT, et al. HCC EV ECG score: an extracellular vesicle-based protein assay for detection of early-stage hepatocellular carcinoma. *Hepatology* 2023;77:774-88. [DOI](#) [PubMed](#) [PMC](#)
47. Yeo YH, Hwang J, Jeong D, et al. Surveillance of patients with cirrhosis remains suboptimal in the United States. *J Hepatol* 2021;75:856-64. [DOI](#) [PubMed](#)
48. Tavakoli H, Robinson A, Liu B, et al. Cirrhosis patients with nonalcoholic steatohepatitis are significantly less likely to receive surveillance for hepatocellular carcinoma. *Dig Dis Sci* 2017;62:2174-81. [DOI](#) [PubMed](#)
49. Mittal S, Sada YH, El-Serag HB, et al. Temporal trends of nonalcoholic fatty liver disease-related hepatocellular carcinoma in the veteran affairs population. *Clin Gastroenterol Hepatol* 2015;13:594-601.e1. [DOI](#) [PubMed](#) [PMC](#)
50. Farvardin S, Patel J, Khambaty M, et al. Patient-reported barriers are associated with lower hepatocellular carcinoma surveillance rates in patients with cirrhosis. *Hepatology* 2017;65:875-84. [DOI](#) [PubMed](#) [PMC](#)
51. Singal AG, Li X, Tiro J, et al. Racial, social, and clinical determinants of hepatocellular carcinoma surveillance. *Am J Med* 2015;128:90.e1-7. [DOI](#) [PubMed](#) [PMC](#)
52. Davila JA, Morgan RO, Richardson PA, Du XL, McGlynn KA, El-Serag HB. Use of surveillance for hepatocellular carcinoma among patients with cirrhosis in the United States. *Hepatology* 2010;52:132-41. [DOI](#) [PubMed](#) [PMC](#)
53. Davila JA, Henderson L, Kramer JR, et al. Utilization of surveillance for hepatocellular carcinoma among hepatitis C virus-infected veterans in the United States. *Ann Intern Med* 2011;154:85-93. [DOI](#) [PubMed](#)
54. Li DJ, Park Y, Vachharajani N, Aung WY, Garonzik-Wang J, Chapman WC. Physician-patient communication is associated with hepatocellular carcinoma screening in chronic liver disease patients. *J Clin Gastroenterol* 2017;51:454-60. [DOI](#) [PubMed](#)
55. Henson JB, Wegermann K, Patel YA, Wilder JM, Muir AJ. Access to technology to support telehealth in areas without specialty care for liver disease. *Hepatology* 2023;77:176-85. [DOI](#) [PubMed](#)