Truong *et al. Hepatoma Res* 2022;8:40
DOI: 10.20517/2394-5079.2022.63

Hepatoma Research

Editorial

Open Access

Check for updates

Hepatocellular carcinoma surveillance in non-alcoholic fatty liver disease patients

Emily Truong[1], Mazen Noureddin[2,3]

[1]Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, California, CA 90048, USA.
[2]Houston Liver Institute, Houston, Texas, TX 77079, USA.
[3]Houston Research Institute, Houston, Texas, TX 77079, USA.

Correspondence to: Dr. Mazen Noureddin, M.D., M.H.Sc, Houston Liver Institute, 1155 Dairy Ashford Suite 200 Houston, Texas, TX 77079, USA. E-mail: noureddinmd@houtonresearchinstitute.com

How to cite this article: Truong E, Noureddin M. Hepatocellular carcinoma surveillance in non-alcoholic fatty liver disease patients. *Hepatoma Res* 2022;8:40. https://dx.doi.org/10.20517/2394-5079.2022.63

Received: 26 Aug 2022 **Accepted:** 3 Nov 2022 **Published:** 17 Nov 2022

Academic Editors: Guang-Wen Cao, Giuliano Ramadori, Chun-Hong Ma **Copy Editor:** Ying Han **Production Editor:** Ying Han

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

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/m^2] or lean (BMI < 25 kg/m^2) 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 ≥ 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/m^2[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.

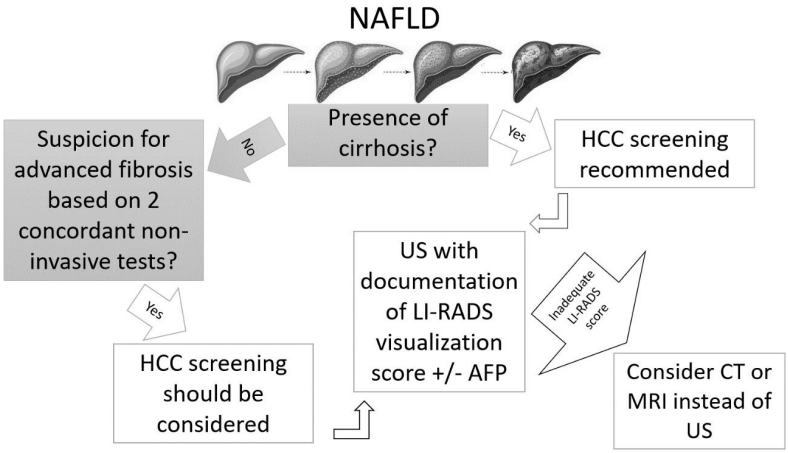

Figure 1. Recommendations for HCC Surveillance in NAFLD. AFP: α-fetoprotein; CT: computed tomography; HCC: hepatocellular carcinoma; LI-RADS: liver imaging reporting and data system; MRI: magnetic resonance imaging; NAFLD: non-alcoholic fatty liver disease; US: ultrasonography.

DECLARATIONS

Authors' contributions

Interpreted the data and drafted the manuscript: Truong E
Critically revised the manuscript for important intellectual content: Noureddin M

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Noureddin 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; Noureddin M has received research support from Allergan, BMS, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Madrigal, Novartis, Pfizer, Shire, Viking and Zydus; Noureddin 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.

REFERENCES

1. Vuppalanchi R, Noureddin M, Alkhouri N, Sanyal AJ. Therapeutic pipeline in nonalcoholic steatohepatitis. *Nat Rev Gastroenterol Hepatol* 2021;18:373-92. DOI PubMed

2. Kulik L, El-Serag HB. Epidemiology and management of hepatocellular carcinoma. *Gastroenterology* 2019;156:477-491.e1. DOI PubMed PMC
3. Ioannou GN. Epidemiology and risk-stratification of NAFLD-associated HCC. *J Hepatol* 2021;75:1476-84. DOI PubMed
4. Kanwal F, Kramer JR, Mapakshi S, et al. Risk of hepatocellular cancer in patients with non-alcoholic fatty liver disease. *Gastroenterology* 2018;155:1828-1837.e2. DOI PubMed PMC
5. 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
6. Younossi Z, Stepanova M, Ong JP, et al. Global nonalcoholic steatohepatitis council. Nonalcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. *Clin Gastroenterol Hepatol* 2019;17:748-755.e3. DOI PubMed
7. Noureddin M, Vipani A, Bresee C, et al. NASH leading cause of liver transplant in women: updated analysis of indications for liver transplant and ethnic and gender variances. *Am J Gastroenterol* 2018;113:1649-59. DOI PubMed PMC
8. Wong RJ, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. *Hepatology* 2014;59:2188-95. DOI PubMed
9. Yatsuji S, Hashimoto E, Tobari M, Taniai M, Tokushige K, Shiratori K. Clinical features and outcomes of cirrhosis due to non-alcoholic steatohepatitis compared with cirrhosis caused by chronic hepatitis C. *J Gastroenterol Hepatol* 2009;24:248-54. DOI PubMed
10. Ioannou GN, Green P, Lowy E, Mun EJ, Berry K. Differences in hepatocellular carcinoma risk, predictors and trends over time according to etiology of cirrhosis. *PLoS One* 2018;13:e0204412. DOI PubMed PMC
11. Gawrieh S, Dakhoul L, Miller E, et al. Characteristics, aetiologies and trends of hepatocellular carcinoma in patients without cirrhosis: a United States multicentre study. *Aliment Pharmacol Ther* 2019;50:809-21. DOI PubMed
12. Mittal S, El-Serag HB, Sada YH, et al. Hepatocellular carcinoma in the absence of cirrhosis in United States veterans is associated with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2016;14:124-31.e1. DOI PubMed PMC
13. Tan DJH, Ng CH, Lin SY, et al. Clinical characteristics, surveillance, treatment allocation, and outcomes of non-alcoholic fatty liver disease-related hepatocellular carcinoma: a systematic review and meta-analysis. *Lancet Oncol* 2022;23:521-30. DOI PubMed
14. Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005;129:113-21. DOI PubMed
15. White DL, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. *Clin Gastroenterol Hepatol* 2012;10:1342-1359.e2. DOI PubMed PMC
16. Noureddin M, Rinella ME. Nonalcoholic fatty liver disease, diabetes, obesity, and hepatocellular carcinoma. *Clin Liver Dis* 2015;19:361-79. DOI PubMed PMC
17. Zelber-Sagi S, Noureddin M, Shibolet O. Lifestyle and hepatocellular carcinoma what is the evidence and prevention recommendations. *Cancers (Basel)* 2021;14:103. DOI PubMed PMC
18. Younes R, Bugianesi E. NASH in lean individuals. *Semin Liver Dis* 2019;39:86-95. DOI PubMed
19. Aby E, Phan J, Truong E, Grotts J, Saab S. Inadequate hepatocellular carcinoma screening in patients with nonalcoholic steatohepatitis cirrhosis. *J Clin Gastroenterol* 2019;53:142-6. DOI PubMed
20. 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
21. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American association for the study of liver diseases. *Hepatology* 2018;68:723-50. DOI PubMed
22. Association for the Study of the Liver; Electronic address: easloffice@easloffice.eu.; European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018;69:182-236. DOI
23. 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
24. Noureddin M, Jones C, Alkhouri N, Gomez EV, Dieterich DT, Rinella ME; NASHNET. Screening for nonalcoholic fatty liver disease in persons with type 2 diabetes in the united states is cost-effective: a comprehensive cost-utility analysis. *Gastroenterology* 2020;159:1985-1987.e4. DOI PubMed
25. Lewis CM, Vassos E. Polygenic risk scores: from research tools to clinical instruments. *Genome Med* 2020;12:44. DOI PubMed PMC
26. Singal AG, Manjunath H, Yopp AC, et al. The effect of PNPLA3 on fibrosis progression and development of hepatocellular carcinoma: a meta-analysis. *Am J Gastroenterol* 2014;109:325-34. DOI PubMed PMC
27. Liu YL, Patman GL, Leathart JB, et al. Carriage of the PNPLA3 rs738409 C >G polymorphism confers an increased risk of non-alcoholic fatty liver disease associated hepatocellular carcinoma. *J Hepatol* 2014;61:75-81. DOI PubMed
28. Krawczyk M, Stokes CS, Romeo S, Lammert F. HCC and liver disease risks in homozygous PNPLA3 p.I148M carriers approach monogenic inheritance. *J Hepatol* 2015;62:980-1. DOI PubMed
29. Bianco C, Jamialahmadi O, Pelusi S, et al. Non-invasive stratification of hepatocellular carcinoma risk in non-alcoholic fatty liver using polygenic risk scores. *J Hepatol* 2021;74:775-82. DOI PubMed PMC
30. 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

31. Tobkes AI, Nord HJ. Liver biopsy: review of methodology and complications. *Dig Dis* 1995;13:267-74. DOI PubMed
32. Saleh HA, Abu-Rashed AH. Liver biopsy remains the gold standard for evaluation of chronic hepatitis and fibrosis. *J Gastrointestin Liver Dis* 2007;16:425-6. PubMed
33. Guha IN, Parkes J, Roderick P, et al. Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: validating the European liver fibrosis panel and exploring simple markers. *Hepatology* 2008;47:455-60. DOI PubMed
34. Sanyal AJ; Friedman SL; McCullough AJ; Dimick-Santos L; American Association for the Study of Liver Diseases. Challenges and opportunities in drug and biomarker development for nonalcoholic steatohepatitis: findings and recommendations from an American association for the study of liver diseases-U.S. Food and Drug Administration joint workshop. *Hepatology* 2015;61:1392-405. DOI PubMed PMC
35. Angulo P, Hui JM, Marchesini G, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology* 2007;45:846-54. DOI PubMed
36. Hsu C, Caussy C, Imajo K, et al. Magnetic resonance vs transient elastography analysis of patients with nonalcoholic fatty liver disease: a systematic review and pooled analysis of individual participants. *Clin Gastroenterol Hepatol* 2019;17:630-637.e8. DOI PubMed PMC
37. Mayo R, Crespo J, Martínez-Arranz I, et al. Metabolomic-based noninvasive serum test to diagnose nonalcoholic steatohepatitis: results from discovery and validation cohorts. *Hepatol Commun* 2018;2:807-20. DOI PubMed PMC
38. Younossi ZM, Harrison SA, Newsome PN, et al. Agile 3+ development and validation: novel fibroscan based score to diagnose advanced fibrosis in non alcoholic fatty liver disease patients. Available from: https://www.postersessiononline.eu/173580348_eu/congresos/NAFLDsummit/aula/-PO_157_NAFLDsummit.pdf [Last accessed on 7 Nov 2022].
39. Younossi ZM, Harrison SA, Newsome PN, et al. LP12-improving diagnosis of cirrhosis in patients with NAFLD by combining liver stiffness measurement by vibration-controlled transient elastography and routine biomarkers: a global derivation and validation study. Available from: https://aasld.confex.com/aasld/2020/meetingapp.cgi/Paper/24427 [Last accessed on 7 Nov 2022].
40. Xiao G, Zhu S, Xiao X, Yan L, Yang J, Wu G. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: a meta-analysis. *Hepatology* 2017;66:1486-501. DOI PubMed
41. Ampuero J, Pais R, Aller R, et al. HEPAmet Registry. Development and validation of hepamet fibrosis scoring system-a simple, noninvasive test to identify patients with nonalcoholic fatty liver disease with advanced fibrosis. *Clin Gastroenterol Hepatol* 2020;18:216-225.e5. DOI PubMed
42. Jung J, Loomba RR, Imajo K, et al. MRE combined with FIB-4 (MEFIB) index in detection of candidates for pharmacological treatment of NASH-related fibrosis. *Gut* 2021;70:1946-53. DOI PubMed PMC
43. Noureddin M, Truong E, Gornbein JA, et al. MRI-based (MAST) score accurately identifies patients with NASH and significant fibrosis. *J Hepatol* 2022;76:781-7. DOI PubMed
44. Younossi ZM, Noureddin M, Bernstein D, et al. Role of noninvasive tests in clinical gastroenterology practices to identify patients with nonalcoholic steatohepatitis at high risk of adverse outcomes: expert panel recommendations. *Am J Gastroenterol* 2021;116:254-62. DOI PubMed
45. 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
46. 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
47. Rich N, Singal AG. Hepatocellular carcinoma tumour markers: current role and expectations. *Best Pract Res Clin Gastroenterol* 2014;28:843-53. DOI PubMed
48. Ye Q, Ling S, Zheng S, Xu X. Liquid biopsy in hepatocellular carcinoma: circulating tumor cells and circulating tumor DNA. *Mol Cancer* 2019;18:114. DOI PubMed PMC
49. Ahn JC, Teng PC, Chen PJ, et al. Detection of circulating tumor cells and their implications as a biomarker for diagnosis, prognostication, and therapeutic monitoring in hepatocellular carcinoma. *Hepatology* 2021;73:422-36. DOI PubMed PMC
50. Yang JD, Addissie BD, Mara KC, et al. GALAD Score for hepatocellular carcinoma detection in comparison with liver ultrasound and proposal of GALADUS score. *Cancer Epidemiol Biomarkers Prev* 2019;28:531-8. DOI PubMed PMC
51. Del Poggio P, Olmi S, Ciccarese F, et al. Italian Liver Cancer (ITA.LI.CA) Group. Factors that affect efficacy of ultrasound surveillance for early stage hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2014;12:1927-33.e2. DOI PubMed
52. Simmons O, Fetzer DT, Yokoo T, et al. Predictors of adequate ultrasound quality for hepatocellular carcinoma surveillance in patients with cirrhosis. *Aliment Pharmacol Ther* 2017;45:169-77. DOI PubMed PMC
53. Younes R, Bugianesi E. Should we undertake surveillance for HCC in patients with NAFLD? *J Hepatol* 2018;68:326-34. DOI PubMed
54. Schoenberger H, Chong N, Fetzer DT, et al. Dynamic changes in ultrasound quality for hepatocellular carcinoma screening in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2022;20:1561-1569.e4. DOI PubMed PMC
55. Atiq O, Tiro J, Yopp AC, et al. An assessment of benefits and harms of hepatocellular carcinoma surveillance in patients with cirrhosis. *Hepatology* 2017;65:1196-205. DOI PubMed PMC
56. Morgan TA, Maturen KE, Dahiya N, Sun MRM, Kamaya A, American College of Radiology Ultrasound Liver Imaging and Reporting

Data System (US LI-RADS) Working Group. US LI-RADS: ultrasound liver imaging reporting and data system for screening and surveillance of hepatocellular carcinoma. *Abdom Radiol (NY)* 2018;43:41-55. DOI PubMed

57. Chernyak V, Fowler KJ, Kamaya A, et al. Liver imaging reporting and data system (LI-RADS) version 2018: imaging of hepatocellular carcinoma in at-risk patients. *Radiology* 2018;289:816-30. DOI PubMed PMC