

# Surveillance for hepatocellular carcinoma in patients with advanced liver fibrosis

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## Abstract

Surveillance is the only pragmatic approach to improve treatment of hepatocellular carcinoma (HCC) owing to the fact that it allows detection of the tumor at an early and better curable stage. International liver societies recommend surveillance with biannual abdominal ultrasound (US) for patients with cirrhosis of any etiology because of their high risk of developing HCC. This strategy is considered cost-effective, as surveillance requires an articulated and costly set of interventions, including linkage to care of patients with an early detected tumor. However, as transition to HCC is increasingly being observed in noncirrhotic patients, the majority of which does not reach the threshold of cost effectiveness for screening. The European and Japanese liver societies elected to confine recommendations for HCC screening to noncirrhotic patients with advanced fibrosis due to hepatitis C or hepatitis B only. These latter recommendations, however, are challenged by the increasing number of patients with viral hepatitis in whom HCC risk has been attenuated but not eradicated by successful antiviral therapy. In this set of patients, entry criteria of surveillance need to be refined in the light of the suboptimal diagnostic accuracy of non invasive tests that are employed to identify the ideal candidates for surveillance.

**Keywords:** HCC, hepatitis B, hepatitis C, liver fibrosis, NAFLD, surveillance

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality worldwide.<sup>[1]</sup> The incidence of this tumor is rising globally due to ageing and increasing exposure of the world population to environmental risk factors, such as hepatitis B, hepatitis C, alcohol and metabolic syndrome.<sup>[2]</sup> In the Kingdom of Saudi Arabia (KSA), the overall age adjusted incidence rate of this cancer is 4.5 per 100 thousand persons, with chronic viral hepatitis and metabolic liver diseases standing as the leading etiological risk factors.<sup>[3]</sup> Owing

to this epidemiological scenario, mortality of HCC can reasonably be counteracted with both measures of primary and secondary prevention, the latter ones implying identification and surveillance of the population at risk. Indeed, international liver societies recommend surveillance for patients with cirrhosis of any etiology because of their high risk of developing HCC, an approach that requires an articulated set of interventions that need to be delivered, including those who experience successful viral hepatitis suppression or eradication.<sup>[4-6]</sup> In short, bi-annual examination with abdominal ultrasounds (US),

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with or without serum alfa-fetoprotein (AFP) level, is widely recognized to confer measurable survival benefits to cirrhotic patients, provided that linkage to effective care is granted.<sup>[7]</sup> The recent demonstration that a correlation exists between cirrhosis and the risk of intrahepatic cholangiocarcinoma, and that surveillance allows detection of this lethal cancer at an early and better treatable stage, has further corroborated our perception of the clinical utility of surveillance in cirrhosis.<sup>[8]</sup> While abdominal US stands as the pillar of surveillance practice worldwide, international liver societies substantially differ with respect to the utilization of AFP. This test, in fact, is mandatory in the surveillance programme of the Asian Pacific Association for the Study of the Liver (APASL) and Japanese Society of Hepatology (JSH), and it is recommended by the Latin American Association for the Study of the Liver (LAASL) whenever US is not available.<sup>[6,9,10]</sup> The AFP test is optional in the guidelines of the American Association for the Study of Liver Diseases (AASLD), and not recommended by the European Association for the Study of the Liver (EASL).<sup>[4,5]</sup> This happens because AFP has been shown to improve sensitivity and specificity of ultrasound alone in a recent study from Asia, while addition of AFP is not perceived by EASL as cost effective in routine surveillance.<sup>[4,7]</sup>

Intriguingly, EASL and APASL recommendations extend surveillance to well-defined, noncirrhotic, high-risk groups including patients with advanced fibrosis, while AASLD does not recommend surveillance for HCC in non hepatitis B, non-cirrhotic patients. On top of these discrepancies, it is widely recognized how difficult it is to

obtain a trustable staging of liver fibrosis with both invasive and non-invasive methods, and running a cost effective surveillance in noncirrhotic patients in the presence of non liver-related competing risks of mortality.<sup>[5]</sup> These latter constraints are most impactful on cost effectiveness of surveillance programs in patients with non alcoholic fatty liver disease (NAFLD) who are at risk of HCC.

### THE DISCREPANCIES BETWEEN SURVEILLANCE PROGRAMMES AROUND THE WORLD

Apart from serum AFP, other nuances have emerged between the recommendations of professional societies, that mostly relate to the selection of the target population, intervals of screening and the use of imaging modalities. Such discrepancies, however, do not substantially affect the ultimate goal of surveillance which is detection of small tumors at a stage that allows delivery of potentially curative therapies.

Both EASL and APASL identify patients with Child Pugh A and B cirrhosis as ideal candidates for screening, while restricting surveillance in Child Pugh C patients who await liver transplantation [Table 1]. In the APASL guidelines, patients selection to surveillance is not guided by the stage of cirrhosis, whereas in the LAASL guidelines the ideal target population is stratified into two subgroups: very high risk patients with hepatitis B and C cirrhosis, and high risk patients with non viral cirrhosis.

The definition of target population is even more articulated for patients without cirrhosis, where the NAFLD population

**Table 1 Comparison of the current international recommendations on surveillance for HCC**

Recommendation	EASL	AASLD	APASL
Target population Child-Pugh A or B	Any etiology Child-Pugh A or B Cirrhosis Child-Pugh C awaiting LT Any chronic HBV with $\geq 10$ PAGE-B score Chronic HCV with bridging fibrosis	Any etiology Child-Pugh A or B cirrhosis Any Child-Pugh cirrhosis awaiting LT Chronic HBV with active hepatitis or family history of HCC, Africans, African- Americans, Asian males > 40 yr and Asian females > 50 yr	Any etiology cirrhosis Asian males > 40 yr Asian females > 50 yr Africans > 20 yr Family history of HCC
Screening interval	Every 6 months	Every 6 (4-8) months	Every 6 months
Imaging	US	US	US
Biomarkers	None	At discretion	AFP
Confirmation	CT/MRI/CEUS for $\geq 1$ cm nodule	CT/MRI/CEUS for $\geq 1$ cm nodule	CT/MRI/CEUS
Liver biopsy	Mandatory in noncirrhotics	Not recommended as a routine	Unsolved $\geq 1$ cm size
Unsolved nodule	Different imaging or liver biopsy	Alternative imaging/contrast medium	Further imaging
< 1 cm nodule	US every 4 months in the 1 <sup>st</sup> yr. If size unchanged return to 6 months	Same as unsolved nodules	CT/MRI every 3-6 mo

LT = liver transplantation, PAGE-B score = patient, age & gender (range 0-18 points), US = ultrasound, AFP = alpha fetoprotein, CT = multiphasic computed tomography, MRI = magnetic resonance imaging, CEUS = contrast enhanced US.

with bridging fibrosis is excluded from surveillance since screening does not match the criteria of cost effectiveness. Instead, in hepatitis B patients, EASL recommends screening of patients with intermediate or high risk of HCC as those with a PAGE score  $\geq 10$ . AASLD recommends screening for HBV carriers with active hepatitis (elevated serum transaminases and/or high viral load), family history of HCC, Africans or African Americans, Asian males over 40 year of age and Asian females over 50 years of age. JSH recommends surveillance for patients with chronic hepatitis B or C as a whole, whereas APASL echoes AASLD guidelines by recommending screening of hepatitis B carriers with a family history of HCC, or who are Africans or African Americans, Asian males over 40 years of age, and Asian females over 50 years of age.

In the hepatitis C realm, AASLD and APASL provide no specific recommendations for non-cirrhotic patients, whereas a 6 monthly screening is recommended for patients with bridging fibrosis (Metavir F3) by EASL and for patients with any degree of liver fibrosis by JSH.

Along these lines, the above mentioned professional societies are not perfectly aligned with respect to screening intervals. The canonical 6-month interval of screening is recommended by EASL and APASL irrespective of the degree of liver disease in the target population. AASLD does recommend abdominal US examination every 6 months, but states that the optimal range for screening is between 4 and 8 months. The JSH guidelines recommend 6-month intervals of screening in high risk populations compared to 3 to 4 months in extremely high risk groups. In this latter group of patients, additional investigations every 6 to 12 months with contrast enhanced magnetic resonance imaging (MRI) or computed tomography (CT) scan are considered optional.

Last but not least, the JSH endorses the use of lens culinaris-agglutinin-reactive fraction of AFP (AFP-L3) and protein induced by vitamin K absence or antagonist-II (PIVKA) as additional biomarkers in the prediction of HCC in patients at risk. In the West, these markers are still under investigation for their clinical utility, with some evidence that they might be more useful as predictors of cancer aggressiveness rather than as markers of cancer risk during surveillance.

## THE CHALLENGES OF SURVEILLANCE IN NON CIRRHOTIC PATIENTS

### Hepatitis B

For the sake of cost effectiveness, surveillance of patients at

risk of HCC is guided by the level of risk and effectiveness of detection methods. In the first AASLD guidelines, surveillance with abdominal US was recommended for carriers of hepatitis B with at least a 0.2% annual risk of developing HCC and in cirrhotic patients of any etiology with an annual risk of 1.5%, in consideration of the higher rates of competing risk factors of mortality in cirrhotics compared to noncirrhotics.<sup>[5]</sup> Thus, personalized assessment of the individual risk of HCC is deemed necessary to identify those hepatitis B patients in whom surveillance is cost effective, and this is even more so for prioritization of patients for HCC screening at a time of limited resources, concern over potential nosocomial transmission and strict social distancing. Patient's stratification for HCC risk is usually achieved with the use of risk scores built on a varying combination of host and disease factors, given that the multistep nature of liver carcinogenesis prevents a robust predictive performance of a single parameter. A number of scores are available to stratify hepatitis B patients in subgroups of low, intermediate and high HCC risk, whose design has evolved in parallel with the development of effective antiviral treatments. In the pre nucleos(t)ide analogues (NA) era, the first scores were developed in Asia in untreated patients and incorporated serum HBV DNA as a predictor of HCC. The GAG-HCC score incorporated sex, age, cirrhosis, core promoter and HBV DNA compared to sex, age, HBeAg and HBV DNA in the Reach-B. The CU-HCC and LSM-HCC scores were developed in both treated and untreated Asian patients: the first score incorporated age, bilirubin, albumin, cirrhosis and HBV DNA, whereas the second one incorporated age, albumin, HBV DNA and liver stiffness by fibroscan as a surrogate of liver disease severity. All these scores had a robust negative predictive value equal or above 98% in the face of a modest (8-21%) positive predictive value, but differed in terms of applicability given the need in three out of four scores of obtaining a trustable diagnosis of cirrhosis.<sup>[11]</sup> Interestingly, in each of these scores an optimal cut-off value was identified that allowed recognition of low risk patients in whom surveillance could safely be deferred. This is also the case for two other scores that were developed for the stratification of patients with permanently NA suppressed HBV, thereby no longer incorporating HBV DNA. The modified REACH-B score was built on sex, age, transaminase, HBeAg and liver stiffness assessed with fibroscan, whereas PAGE B, which was developed in Western patients, was even more user friendly as it only included platelets, age and gender. Remarkably, after 5 years of NA suppression of HBV, a cut-off of 9 points, out of a range of 0-18, had 100% negative predictive value whereas in its modified version

developed in Asia a cut-off of 10 (range of 0-21) had a negative predictive value of 97.5%.<sup>[12]</sup> Although modified REACH-B score outperformed the other scores in Asian patients with suppressed hepatitis B,<sup>[13,14]</sup> uncertainties remain since the existing scores do not cover some ethnicities/races, African above all, who develop cancer early in life, and since these scores have not been validated in untreated Caucasians owing to the fact that in the West most treatment-eligible patients are actively recruited to NA therapy at the time of diagnosis. Further, these scores hardly apply to HBeAg immunotolerant populations and to patients with less active infection who may have a fluctuating liver disease requiring dynamic evaluation of HCC risk. In noncirrhotic patients with pharmacologically suppressed HBV, dynamic evaluation of risk scores may in fact provide more robust prediction of HCC risk than does spot analysis. This is the clear message of the PAGE B cohort of chronic hepatitis B Caucasian patients in whom the risk of developing HCC was 1.2% in the 7 years beyond 5 years of effective NA therapy and was accurately predicted by liver stiffness, with 0% risk of HCC development in those < 49 years and transient elastography readings < 12 kPa.<sup>[15]</sup>

### Hepatitis C

Hepatitis C virus (HCV) is a leading cause of HCC in most industrialized regions of the West, in Japan, parts of Central Asia including Mongolia, Middle East and northern Africa where Egypt ranks first in terms of hepatitis C-related mortality.<sup>[16,17]</sup> While only recently elimination of hepatitis C has been promoted at a global level to counteract HCV related mortality, surveillance of patients with HCV related cirrhosis has long been recommended by all international scientific societies to prevent mortality from HCC.<sup>[4-6]</sup> However, the risk of hepatitis C transition to HCC does not appear to be confined to patients with cirrhosis only, yet the incidence of HCC in noncirrhotic patients with advanced liver fibrosis due to HCV is greater than the threshold of 1.5%, thus making HCC surveillance cost-effective. This explains why surveillance of noncirrhotic patients with advanced fibrosis (Metavir F3) is recommended by the European and Japanese liver societies.<sup>[4,9]</sup> Surveillance is not considered cost effective in patients with advanced liver impairment such as those with Child-Pugh class C or Child-Pugh class B when liver transplantation is not an option. A large grey area lies between these two wings of recommendations, represented by aged patients with comorbidities, where the lack of data prevents adoption of any specific recommendation and decisions are taken on individualized bases. In the last years, virologically cured hepatitis C has been emerging as a most important risk factor for HCC that partially obscures the growing

role of NAFLD in liver cancer. This results from the widespread access of patients with HCV to highly effective and well-tolerated direct-acting antiviral agents (DAAs), that caused the rates of both linkage-to-care and sustained virologic response (SVR) rates in patients with cirrhosis and advanced liver fibrosis to skyrocket. In a landmark study at the Veteran Administration hospitals, USA, the annual risk of HCC in more than 8700 patients with advanced hepatitis C who achieved a SVR with DAA was much lower than that in untreated or non responder patients (1.8% vs 2-8%).<sup>[18]</sup> In the same cohort of patients, the cumulative incidence of HCC at 1, 2, and 3-year post-SVR was 1.1%, 1.9% and 2.8%, respectively.<sup>[19]</sup> When Veterans were stratified by liver disease stage, it was confirmed that HCC risk was better attenuated in noncirrhotics than in cirrhotics. The HCC rate per 100 patients-year was 2.2 in cirrhotics as compared to 0.3 in noncirrhotics, while the corresponding feature in non SVR patients was 5.0 and 1.1, respectively.<sup>[20]</sup> Subsequently, in a retrospective analysis of 29,033 patients treated with DAA agents and 19,102 treated with interferon-based regimens, stratification of HCC risk according to pretreatment hepatitis severity was confirmed to stay for more than 10 years after SVR.<sup>[21]</sup> In cirrhotic patients with fibrosis-4 (FIB-4) scores  $\geq 3.25$  who achieved an SVR to DAAs, the HCC risk decreased from 3.8%/year in the first year after SVR to 2.4%/year by the fourth year ( $P = 0.01$ ). In patients with similar scores for disease severity who achieved an SVR to interferon, the annual HCC risk remained above 2%/year for as long as 10 years after SVR. However, it should be outlined that factors other than SVR can modulate the risk of HCC in HCV patients, including the metabolic phenotype defined by a body mass index of  $\geq 25$  kg/m<sup>2</sup>, diabetes, dyslipidemia or heavy alcohol consumption. In a retrospective scrutiny of a prospective multicenter study in France, the 5-year cumulative incidence of HCC in cirrhotics without metabolic features was 3.0% vs 8.8% ( $P = 0.042$ ) in those with metabolic phenotype.<sup>[22]</sup> Stressing the importance of clinical predictors of HCC risk is that weighting HCC risk in this patient population may be jeopardized by a faulty staging of hepatitis C as it may occur when a histological documentation is not available. As a matter of fact, a pretreatment liver biopsy is no longer required for linking to care HCV patients whereas surrogate markers of disease severity are widely employed for liver disease staging, such as liver stiffness assessment (LSM) with transient elastography or shear wave elastography. Likewise, compound surrogates for advanced fibrosis built on such serological assays as FibroTest and aspartate aminotransferase-to-platelet ratio (APRI) score, have proved to efficiently stratify viremic patients for severity of hepatitis C.<sup>[23]</sup> In DAA treated HCV patients, the predictive



power of LSM assessment has been confirmed in a study in Italy where male gender, diabetes mellitus, and LSM ( $\geq 30$  kPa), were associated with an increased risk for HCC development in patients with cirrhosis.<sup>[24]</sup> This is also the message of a study from Japan describing higher pre-SVR values of LSM in patients who developed HCC compared to HCC-free patients suggesting that LSM values tended to increase significantly over time in those who eventually developed HCC.<sup>[25]</sup> In SVR patients, the dynamics of LSM have been reconstructed in a meta-analysis of 24 studies, where the post SVR decline of LSM was 2.4 kPa (95% CI, -1.7 to -3.0) at the end of antiviral therapy, 3.1 kPa (95% CI, -1.6 to -4.7) in the following 1-6 months, 3.2 kPa (90% CI, -2.6 to -3.9) in the following 6-12 months and 4.1 kPa (95% CI, -3.3 to -4.9) in the following 12 months or more. Conversely, liver stiffness values did not significantly change in patients who failed to achieve an SVR.<sup>[26]</sup> Interestingly, in 572 patients with LSM  $>10$  kPa prior to starting DAA, the HCC incidence rate/100 patient-years was 0.7 in patients with LSM  $<10$  kPa after one year of follow-up compared to 1.7 for those with LSM 10–19 kPa and 3.2 for those with LSM  $\geq 20$  kPa. However, mitigating the enthusiasm for LSM assessment to predict HCC in SVR patients were the 4 patients of the low risk group who developed HCC during a 3-year follow-up.

These findings add to the argument on the threshold of HCC incidence that makes surveillance cost-effective. In the US, where a \$ 50,000/quality-adjusted life-year (QALY) is accepted as a ceiling for the incremental cost-effectiveness ratio (ICER) for 12 month of surveillance, in SVR patients this ratio was \$ 31,096/QALY for cirrhosis, \$ 28,898/QALY for FIB-4  $>3.25$  and \$ 38,516/QALY for APRI score  $<2$ , calculated on an HCC mean incidence/yr of 1.39-1.82%, 2.16%, and 0.89%, respectively. While such thresholds shows a geographical variability depending on local resources, surveillance of HCV patients after SVR is recommended in those with cirrhosis and in those with a prognostic score suggesting a high risk of developing HCC.

### Non alcoholic fatty liver disease

Non alcoholic fatty liver disease (NAFLD) is a large spectrum of diseases resulting from hepatic fat deposition caused by overnutrition and sedentary lifestyle. This condition affects about a quarter of the world's adult population, thereby posing a major health and economic burden to all societies.<sup>[27]</sup> NAFLD patients, in fact, are facing an increased life-long risk of cardiovascular complications and, once the stage of non alcoholic steatohepatitis (NASH) is reached, of developing cirrhosis, liver failure and HCC.<sup>[28]</sup> As a matter of fact, NAFLD is a fast growing indication for liver transplantation in many high-resource countries such

as USA.<sup>[29]</sup> Intriguingly, liver complications of NAFLD tend to evolve silently in a majority of individuals, whereas liver disease may have an accelerated course in others, including genetically predisposed individuals and those exposed to environmental risk modifiers, such as heavy alcohol consumption.

The importance of genetic predisposition in the onset and progression of NAFLD is exemplified by the Patatin-like phospholipase domain containing 3 (PNPLA 3) I148M polymorphism, which, among others, is highly predictive of fatty liver development without any association with serum transaminase level.<sup>[30]</sup>

The pathogenesis of NAFLD related liver cancer is complex, being driven by the intense lipid accumulation leading to metabolic reprogramming and accumulation of potentially toxic metabolites that favor neoplastic transformation of liver cells. As for many other inflammatory tumors, liver cancer development in NAFLD is manipulated by genetic factors, particularly the PNPLA3 polymorphism that impairs mobilization of triglycerides from hepatic lipid droplets, and by TM6SF2 167 K variant that affects the metabolism of VLDL particles.<sup>[31]</sup> This latter marker offers the unique opportunity of disentangling the course of NAFLD in terms of evolution of liver complications and cardiovascular disease (CVD), towards which carriers of the TM6SF2 167 k variant are preferentially diverted.<sup>[32]</sup> This notwithstanding, we all acknowledge the existence of several obstacles to the prevention of the clinical consequences of NAFLD, which are not limited to the lack of effective medicines but extend to the difficulty of identifying those patients more exposed to HCC risk than others, and therefore might benefit from an early diagnosis through screening. This is even more compelling in patients with persistently normal transaminase levels, a confounder that often obscures the diagnosis of cirrhosis in patients with NAFLD, thus leading to delayed recognition and treatment of the lethal consequences of NAFLD.<sup>[33,34]</sup> On top of this, it should also be mentioned that serum levels of transaminases, a trustable predictor of mortality in the general population,<sup>[35]</sup> do not predict the stage of liver fibrosis which in turn is the strongest harbinger of all-cause mortality and HCC in NAFLD patients.<sup>[28,36]</sup>

Of note, liver fibrosis stage together with serum PNPLA 3, is also able to disentangle the incidence of CVD-related and liver-related outcomes in this patient population. In a multinational study of histologically classified patients with NAFLD, Metavir F3 patients were shown to preferentially evolve CVD complications compared to patients with cirrhosis (Metavir 4) in whom NAFLD more often led to

clinical decompensation or HCC.<sup>[36]</sup> Confirming previous seminal studies, HCC risk was also found to stratify according to the level of liver impairment as during an 8-year period of follow up, the annual incidence of HCC was 1.8% and 4.7% in patients with cirrhosis Child Pugh A5 and those with Child Pugh A6, respectively. The association of HCC risk with the degree of liver fibrosis emerged also from the scrutiny of a US database with more than 290 thousand patients classified with NAFLD.<sup>[34]</sup> In that survey, the risk of developing HCC in patients with cirrhosis was 13.5 and 4.8 per 1000 patients/year depending on whether FIB-4 score was more or less than 3.5 respectively, whereas the risk was much lower (0.39 per 1000 patients/year) for noncirrhotic patients with a FIB-4 score > 3.5. The study also provided the important information that in NAFLD noncirrhotic patients with lower indices of liver fibrosis, i.e., those with < 3.5 Fib-4 score accounting for three quarters of the entire cohort, HCC risk was 0.04 per 1000 patients/year only, i.e. 92 cases of HCC among 258,074 individuals over a follow up period of 8 years. Of note, a prospective study in United Kingdom (UK) with screening of NAFLD patients with FIB-4 in the community reported an optimal rate of referral and linkage-to-care, since it increased by 4.9 fold the diagnosis of advanced fibrosis and reduced by 81% unnecessary referrals from primary care.<sup>[37]</sup> In another study of community-based screening of Caucasian and Asian patients with metabolic risk factors, a liver stiffness value of 9.1 kPa allowed recognition of individuals with a significant liver fibrosis (METAVIR stages  $\geq$  F2).<sup>[38]</sup> Altogether, these and other studies support the widespread adoption of non invasive tests of fibrosis for staging NAFLD patients, in order to identify those patients who can be directed to liver specialists in a cost-effective continuum of care.<sup>[39]</sup> However, while it is crystal clear that the stage of liver fibrosis is the best independent predictor of NAFLD outcome, numerous histopathology studies have demonstrated that certain NAFLD patients may silently develop HCC in the absence of significant liver fibrosis.<sup>[40]</sup> While this challenges the crafting of cost-effective recommendations for community-based screening of HCC, it also generated uncertainties among hepatologists with respect to when, whom and how to screen patients with NAFLD for HCC risk. Although serum genetic markers are still to be validated as cost-effective predictors of NAFLD-related liver cancer, it is generally recognized that NAFLD patients with diabetes and, obesity carry an excess risk of developing HCC and therefore represent the ideal target for screening independently from their liver disease stage. This emerged also from the scrutiny of the Veterans Healthcare Administration repository of more than 750 thousand

patients with cancer and clinical data, where the risk of developing HCC progressively increased with the presence of diabetes (from 5.5 to 8.6 fold) in association with one or more metabolic traits including hypertension, obesity and dyslipidemia. Of note, also noncirrhotic patients (without a history of excess alcohol intake) were found to be at increased risk of HCC, and the effects of obesity, diabetes, and dyslipidemia were stronger (adjusted HRs 1.19, 2.15, and 1.73, respectively) among these patients than the associations in the overall analysis (adjusted HRs 1.09, 1.31, and 1.23, respectively).<sup>[9]</sup> Altogether, these observations are consistent with the multiple pathobiological mechanisms leading to neoplastic transformation of the fatty livers, which involves insulin like growth factor signaling pathway modulation, activation of inflammatory cascades with production of proinflammatory cytokines, which cause genomic instability and inhibit apoptosis of hepatocytes, bacterial translocation and increased iron deposition.

### Alcoholic liver disease

EASL and AASLD recommend biannual screening with abdominal US of patients with alcoholic cirrhosis owing to the high risk of HCC this patient population faces. This happens despite the fact that the incidence of liver cancer in alcoholics with cirrhosis does not reach worldwide the 1.5% threshold of cost effectiveness across all studies. In a French cohort with Child-Pugh class A alcohol-related cirrhosis that recruited from 28 specialist centers, the HCC incidence rate was 29 per 1,000 person-years and the HCC risk was approximately 2.6% per year.<sup>[41]</sup> Conversely, in northern Europe, HCC incidence is definitively confined below 1%, often as a consequence of acute or chronic liver failure caused by acute binge pattern of alcohol abuse. In a large study of Danish outpatients with alcoholic cirrhosis, the annual risk of HCC was 0.7% only, whereas men aged 60 years or older could have a 1.5% risk per year, but with only 6.9% of deaths in this population attributable to HCC.<sup>[42]</sup> In a recent study in the US, male sex and older age, associated with severity of portal hypertension, were confirmed to identify those alcoholic patients with cirrhosis who were at higher risk of HCC.<sup>[43]</sup> In the same study, the potential benefit of widespread HCC surveillance was questioned by the finding that within 3 years one-third of patients decompensated, and 12.9% died without HCC, whereas the vast majority of patients with compensated cirrhosis had too advanced a cancer that prevented any linkage to curative treatments. Further, challenging the cost effectiveness of HCC screening in alcoholics, a study in the US reported alcohol abuse to be an independent predictor (OR, 0.14; 95% CI, 0.03–0.65) of low rates of uptake of surveillance in a series of 178 patients with cirrhosis.<sup>[44]</sup> This notwithstanding, HCC

surveillance is recommended by both EASL and AASLD in patients with alcohol-related cirrhosis, whereas it is not for noncirrhotic patients with advanced fibrosis.

### Other liver diseases

In patients with Hereditary Hemochromatosis, Alpha1 antitrypsin deficiency and primary biliary cholangitis surveillance is recommended for those with cirrhosis only, since in this strata HCC incidence rate is greater than 1.5% per year.<sup>[4]</sup>

### SHOULD SCREENING BE TAILORED BY THE LEVEL OF HCC RISK?

Screening intervals are not guided by the level of cancer risk, but only by the need of diagnosing a tumor as small as possible, in order to improve the outcome of treatment. This notwithstanding, relaxing surveillance intervals has repeatedly been suggested to optimize cost effectiveness of screening programmes in populations of individuals at low cancer risk. However, questioning the safety of this approach was the finding of 2 to 6% of patients with an optimal low risk cut-off across all risk stratification markers who were shown to develop a HCC during a 5-year surveillance period, likely a consequence of either false exclusion of cirrhosis or the co-occurrence of morbidities with an oncological potential.<sup>[45]</sup> Thus, relaxing surveillance of HCC in patients with an optimal low risk cut off may result in delayed diagnosis of the tumor in a small fraction of patients, leading to negative consequences in terms of efficacy of cancer treatment.

Equally challenging is to decide whether surveillance should be enhanced in patients at higher risk of HCC, owing to the fact that the positive predictive value of the optimal cut-offs of the various scores spans from 14% to 46%, only. In a meta-analysis of 20 studies of surveillance for HCC of different etiologies, the pooled tumor volume doubling time was 4.6 months with a 95% confidence interval of 3.9 to 5.3 months with one third of all cancers displaying rapid tumor growth. While this finding justifies the recommendation of semi-annual screening, the sensitivity analysis of studies from Asia reporting shorter tumor volume doubling time (4.1 vs 5.8 months) compared to the West, endorses the JSH recommendations of screening cirrhotics every three to four months. Along this line, it is worth mentioning that HBV-related tumors, the dominant etiologic group of HCC in the Asia Pacific region, have emerged as the faster growing tumors.<sup>[46]</sup> Of note, Western liver societies recommend accelerated surveillance of selected groups of patients like those in whom a firm diagnosis of HCC is not achieved with either radiology or echo-guided liver biopsy, and with a tumor that has recently been eradicated with either surgery or locoregional ablative procedures.

### SHOULD ALTERNATIVE IMAGING MODALITIES BE ADVOCATED?

Abdominal US is a reasonably cheap, user friendly and largely accessible screening modality for patients at risk of HCC.<sup>[4]</sup> However, in a pooled analysis of 32 studies performed between 1994 and 2016, the diagnostic performance of abdominal US for HCC surveillance was only 45% (95% CI: 30-60).<sup>[7]</sup> The wide ranges of confidence intervals in that study well match the notion that US is operator dependent and has poor performance in patient subgroups, such as those with obesity and NASH, a fact that led to increased interest in accompanying US screening with blood-based biomarkers and use of alternative imaging modalities. AFP is the only validated biomarker for HCC screening and in the previously commented meta-analysis, the diagnostic performance of abdominal US for HCC surveillance rose to 63% (95% CI: 48-75) when serum AFP was tested in combination. To enhance the rate of detection, CT alone and either standard or non-enhanced MRI have been investigated with promising results. CT scan outperformed US by 62.5% vs. 55.5% in a randomized study of 163 patients with cirrhosis.<sup>[47]</sup> In another study, CT showed a far higher sensitivity (83.3% vs. 29.2%,  $P < 0.001$ ) and specificity (95.6% vs. 87.7%,  $P = 0.03$ ) than US. A false-positive result was reported in 14 participants with US and 5 participants at two-phase LDCT, resulting in a significantly higher positive predictive value of CT (33.3% vs. 80%,  $P < 0.001$ ).<sup>[48]</sup> In a prospective cohort study of 407 patients with chronic hepatitis B, MRI led to HCC detection in 86% of cases compared to 28% of those who were investigated with US,<sup>[49]</sup> supporting that MRI might circumvent the loss of diagnostic accuracy of US in the surveillance of obese patients and those with massive steatosis.

### CONCLUSIONS

HCC surveillance of patients with cirrhosis of any etiology is recommended and generally considered to be cost-effective by all liver societies. In principle, HCC surveillance is not recommended for all noncirrhotic patients, yet there are exceptions reflecting significant nuances between societies with respect to etiology and fibrosis stage of the target population. In hepatitis B, all societies concur in recommending surveillance of noncirrhotic populations with any histological stage of chronic hepatitis B, and priority is given to certain subpopulations in relation with ethnicity, hepatitis activity and family history of HCC. In hepatitis C, surveillance of noncirrhotics is not universally endorsed, but is recommended only by EASL and JSH for patients with



bridging fibrosis and any fibrosis stage, respectively. In viral hepatitis, risk stratification with LSM seems to outperform serum markers of disease severity, though the latter approach has the advantage of overcoming several constitutional barriers that compromise the accuracy of transient elastography. On the other hand, a LSM cut-off as a watershed to define at-risk population is not universally recognised, whereas it needs to be prospectively validated after censoring for any possible confounder of LSM on an individual basis. While this is even more stringent for patients with chronically suppressed or eradicated viral hepatitis, dynamic evaluation of LSM in patients with cured hepatitis appears to be a more robust predictor of HCC risk than a single spotty examination with either mechanic or shear wave elastography.

Both Western and Eastern liver societies are still evolving their recommendations for surveillance of noncirrhotic patients with NAFLD, and this partially accounts for HCC surveillance being more often deferred in this patient population than in patients with viral liver disease worldwide. To circumvent this, studies are in progress testing whether screening and linkage to care of NAFLD patients may be better served by risk scores that combine serum genetic predictors with metabolic trait markers.

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### Conflicts of interest

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