Surveillance for Hepatocellular Carcinoma in Patients with Successfully Treated Viral Disease of the Liver: A Systematic Review

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Abstract

Background: Surveillance for hepatocellular carcinoma (HCC) has been proven to increase the proportion of tumors detected at early stages and the chance of receiving curative therapies, reducing mortality by about 30%. ***Summary:*** Current recommendations consist of a semi-annual abdominal ultrasound with or without serum alpha-fetoprotein measurement in patients with cirrhosis and specific subgroups of populations with chronic viral hepatitis. Antiviral therapies, such as nucleot(s)ide analogs that efficiently suppress the replication of hepatitis B virus (HBV) and direct-acting antiviral drugs able to eliminate the hepatitis C virus (HCV) in >90% of patients, have radically changed the outcomes of viral liver disease and decreased, but not eliminated, the risk of HCC in both cirrhotic and non-cirrhotic patients. HCC risk is a key starting point for implementing a cost-effective surveillance and should also guide the decision-making process concerning its modality. As the global number of effectively treated viral patients continues to rise, there is a pressing need to identify those for whom the benefit-to-harm ratio of surveillance is favorable and to determine how to conduct cost-effective screening on such patients. ***Key Messages:*** This article addresses this topic and attempts to determine which patients should continue HCC surveillance after HBV suppression or HCV eradication, based on cost-effectiveness principles and the fact that HCC risk declines over time. We also formulate a proposal for a surveillance algorithm that switches the use of surveillance for HCC from the "one-size-fits-all" approach to individualized programs based on oncologic risk (*precision surveillance*).

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Introduction

Hepatocellular carcinoma (HCC) is the third cause of cancer-related deaths worldwide, with estimated 800,000 deaths per year, and the leading cause of mortality in patients with compensated cirrhosis [1, 2]. Although randomized controlled trials on HCC surveillance in patients with liver cirrhosis or advanced fibrosis are unavailable or not feasible [3], there is general consensus that these patients should be enrolled in surveillance programs based on the repetition of liver ultrasound (US) ± measurement of plasma alpha-fetoprotein (AFP). This position is robustly supported by the results of a recent meta-analysis of 59 studies involving >140,000 patients [4], demonstrating

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that surveillance increases the proportion of early-stage tumor detection and amenability to curative therapies, thus reducing mortality by 33% (pooled hazard ratio 0.67, 95% confidence interval [CI] 0.61–0.72).

However, US-based surveillance is burdened by some disadvantages, such as the risk of overdiagnosis and, in approximately 20% of patients, false positive or indeterminate results triggering potentially harmful downstream investigations, such as exposure to radiation and contrast agents or liver biopsy [5]. Surveillance-induced physical harm is observed in at least 9% of patients, with an increasing proportion as the number of US performed increases [6]. A modeling study has revealed a great disproportion between the number needed to screen to prevent 1 HCC-related death and the number needed to harm (77 vs. 7) [7]. Moreover, one cannot disregard patient stress and anxiety caused by the suspicion of having cancer. In semi-structured interviews, patients reported anxiety, emotional distress, and coping strategies in relation to surveillance tests for HCC [8]. Lastly, unnecessary downstream investigations increase surveillance costs for both the patient and the healthcare system.

From a cost-effective perspective, US-based surveillance is conventionally recommended for patients with cirrhosis or advanced fibrosis who have a risk of developing HCC >1.5% per year [9]. However, even in these patients, the cost-effectiveness of the procedure is determined by the individual risk and the survival benefit obtainable with HCC treatment [10]. Moreover, if a patient is considered suitable for surveillance for HCC, its recommended modality (semi-annual US ± AFP) is always the same, regardless of the individual risk of HCC, in accordance with the policy of "one-size-fits-all" [11, 12].

Another problem with this recommendation lies in the suboptimal sensitivity and specificity of conventional surveillance tests. The diagnostic accuracy of US is indeed highly operator dependent and influenced by a number of patient-specific factors [13]. In a cirrhotic liver, the overall sensitivity of US for HCC is >80% but falls under 50% for lesions <2 cm, which represents the target for an early diagnosis [14]. Adding AFP to US enhances sensitivity to as high as 63%, decreasing the rate of missed diagnosis of these tiny lesions from about half to approximately one-third of cases [15].

The availability of effective antiviral therapies has introduced another conceptual problem. Nucleot(s)ide analogs (NUCs), that efficiently suppress the replication of hepatitis B virus (HBV), and direct-acting antiviral drugs (DAA), that produce a sustained virological response (SVR) in >90% of patients infected by hepatitis C virus (HCV), have radically changed the outcome of viral liver disease. Large prospective cohort studies have proved that NUCs remarkably decrease the risk of developing HCC in both cirrhotic and non-cirrhotic patients [16]. Similarly, SVR reduces the risk of HCC by up to 70% compared to treatment failure, regardless of whether SVR was achieved with DAA or interferon-based regimens [17]. However, virologic HBV suppression and HCV eradication do not eliminate the risk of HCC. According to a recent decision-analytical model, by 2030 the worldwide prevalence of HCC in HCV-eradicated patients will be seven times higher than it was in 2012 (7,000 patients vs. 1,000 confirmed cases) [18]. Moreover, both HBV suppression and HCV eradication blunt the competing mortality risk of cirrhosis and the risk that a progression of liver dysfunction will impede the feasibility of effective treatments once HCC is detected. With this in mind, and considering the growing proportion of HBV-suppressed and HCV-cured patients worldwide, how to properly survey this population represents a hitherto unresolved mounting problem in hepatology. To date, there are no detailed indications on how and for how long surveillance should be continued in this setting, considering the cost-effectiveness of this procedure. Current guidelines lack granular recommendations for patients who achieve SVR. Although there is general agreement that semi-annual US must be continued in cirrhotic patients after the cure of infection, there are discordant indications for patients with advanced fibrosis (F3). European guidelines recommend continuing surveillance in non-cirrhotic F3 patients [11], whereas American guidelines restrict continuation to cirrhotic patients [12]. Moreover, the utilization of serum biomarkers such as AFP is still debated.

With regard to HBV patients on NUC, there is general consensus on the importance of surveillance in Hepatitis B surface Antigen (HBsAg) positive patients with cirrhosis, while a disagreement surrounds non-cirrhotic patients. European guidelines propose "personalized" surveillance tailored to the individual risk of HCC calculated with the PAGE-B (Platelet Age GEnder-HBV) score [11, 19]. American and Asian guidelines recommend implementing surveillance in specific subgroups, mostly depending on the presence of a family history of HCC, age, and ethnicity [12, 20].

This review provides information that can be used to determine *which patients* may benefit from surveillance, how to properly perform a cost-effective procedure, and *for how long*, given that non-viremic patients tend to reduce their HCC risk over time [21, 22]. We addressed this topic by answering five key questions using evidence

found in the literature reported by PubMed from January 2013 to April 2023. To explore the literature, we used the following search terms: "hepatocellular carcinoma," "HCC," "hepatoma," "surveillance," "screening," "sustained virologic response," "SVR," "antivirals," "direct-acting antivirals," "DAA," "nucleoside analogs," "NA," "NUC," and "score," followed by a manual review of the literature.

Is the Risk of HCC a Key Determinant of the Cost-Effectiveness of Surveillance?

A Markov model has demonstrated that in compensated cirrhosis semi-annual surveillance is more cost-effective than the annual program if the yearly HCC incidence is ≥3.2% and the survival gain provided by HCC treatment is at least 20% higher than that achievable with annual surveillance [10]. Using a Markov model, Farhang et al. [23] analyzed this topic in patients with pre-treatment cirrhosis or advanced fibrosis who had achieved SVR with interferon or DAA. They confirmed that cost-effectiveness strictly depends on HCC incidence, showing that the incremental cost-effectiveness ratio (ICER) of surveillance hyperbolically increases as the risk falls. The annual incidence of HCC generating a cost-effective semi-annual surveillance (attested by an ICER < USD 50,000 per quality-adjusted life year as willingness-to-pay threshold) is >1.32%, a threshold typically met by patients with cirrhosis but not with F3 fibrosis. Considering annual surveillance, the ICER remains approximately USD 50,000/quality-adjusted life year if the yearly incidence of HCC is >0.82%.

These findings clearly indicate that the individual risk for HCC is a key determinant of the cost-effectiveness of surveillance. Hence, the use of a semi-annual program would be inappropriate for low-risk patients, such as those without cirrhosis who have achieved SVR.

In Patients with Cirrhosis, Is the Residual Risk Higher Than in Those with F3 Fibrosis following SVR or Viral Suppression?

In HCV-infected patients, HCC risk decreases following SVR because of reduced inflammation in the liver and the elimination of the direct pro-oncogenic mechanisms of HCV. However, a residual risk persists due to two mechanisms: first, although cirrhosis and fibrosis may regress, this process requires years during which concomitant hepatotoxic injuries can progress the natural

history of liver disease; second, HCV is thought to induce genetic and epigenetic changes that may indefinitely promote the carcinogenic process [24].

In a French prospective study involving 7,344 patients with chronic hepatitis C, SVR obtained with DAA reduced both liver- and non-liver-related mortality and the risk of HCC (hazard ratio 0.66, 95% CI, 46–93%) in both cirrhotic (representing approximately 40% of the sample size) and non-cirrhotic patients [22]. This benefit was confirmed after adjustment for several potential confounders.

A systematic review and meta-analysis of 44 studies evaluated the incidence of HCC following SVR in patients with cirrhosis or F3 fibrosis [25]. In cirrhotic patients, the annual incidence of HCC was 2.1% (95% CI, 1.9–2.4), with moderate heterogeneity between studies (I^2 = 69.3%). Older age and prior decompensation were associated with an increased incidence of HCC, whereas HCV genotype, HCV treatment type (interferon or DAA), and geographical data did not influence cancer risk. In patients with F3 fibrosis, the annual incidence of HCC was 0.5% (95% CI, 0.3–0.7), with lower heterogeneity when compared to cirrhotic patients.

Another meta-analysis of 31 studies with a total of 27,711 patients with DAA-cured infection confirmed a higher yearly incidence of HCC in patients with cirrhosis (2.99%) than in patients with F3 fibrosis (0.63%) or no documented cirrhosis (0.47%) [26]. In these 2 last patient groups, HCC incidence was far below the threshold (>1.32%) needed to implement cost-effective semi-annual surveillance [23].

With regard to HBV chronic infection (chronic hepatitis B [CHB]), NUCs such as entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide fumarate have high antiviral power and a high-resistance barrier. Almost all compliant patients treated with NUCs achieve viral suppression, which is one of the main treatment goals, preventing the progression to liver decompensation and ameliorating liver histology and patient survival [27–29].

As for HCV, antiviral therapy reduces but does not remove the risk of HCC, probably because HBV promotes carcinogenesis through multiple mechanisms capable of generating the tumor even before cirrhosis [30]. These include chronic inflammation, mutagenesis, and genomic instability caused by HBV-DNA integration in the DNA of hepatocytes and aberrant epigenetic modifications induced by viral proteins [31].

HBsAg seroclearance is regarded as the "functional cure" for CHB [19, 32] because it further decreases the risk of cancer with regard to viral suppression. A systematic

review and meta-analysis of 26 studies demonstrated that HBsAg clearance is associated with a remarkable reduction in the risk of developing HCC (relative risk 0.30 [0.20–0.43], $p < 0.001$) [33]. Unfortunately, this event is uncommon, especially with NUCs. Continuous treatment with second-generation NUCs for up to 10 years resulted in an overall HBsAg seroclearance rate of 0–5%, with higher rates in hepatitis B e antigen (HBeAg)-positive patients [34]. HCC incidence equally decreases after NUC-induced or spontaneous HBsAg loss, demonstrating that *how* HBsAg loss is achieved has no bearing on its beneficial effect on HCC risk [35]. In light of the rarity of the functional cure, HBV-DNA suppression is accepted as the reference goal of NUC treatment.

In patients on NUCs, the annual incidence of HCC ranges from 0.01% to 1.4% in non-cirrhotic patients and from 0.9% to 5.4% in cirrhotic subjects. A meta-analysis of Asian studies comparing NUC-treated patients versus matched untreated controls showed that the treatment decreased HCC risk by approximately 30% in cirrhotic patients and by approximately 80% in non-cirrhotic subjects [16]. Instead, the benefit of virologic suppression in Caucasian patients remained controversial due to the lack of studies with matched untreated controls.

Can We Confidently Estimate the Residual Risk of HCC after the Eradication or Suppression of the Viral Infection?

Several predictive scores and systems have been developed to assess the risk of HCC in patients with eradicated or suppressed viral infections. This review addresses those that can confidently identify patients with a particularly *low* HCC incidence for whom surveillance would be *inappropriate* and those with the *highest* risk for whom a *reinforced* surveillance program may be warranted.

Nahon et al. [36] reviewed several large multicentric studies designed to validate the available HCC risk scores. They include variables associated with demographic characteristics, virologic factors, liver function tests, liver stiffness measurement (LSM), fibrosis scores, and signs of portal hypertension that may persist after infection control (Table 1). These scores enable the allocation of patients to a low-, moderate-, or high-HCC risk class.

Several scores are available to estimate the risk of HCC following SVR. Pons et al. [43] described HCC as the most frequent liver-related event following SVR, showing that the risk of developing HCC persists for at least 10 years following viral eradication. They identified two risk levels using albumin levels and LSM at follow-up:

- Patients with LSM ≥20 kPa and those with LSM 10–20 kPa and albumin <4.4 g/dL at 1-year follow-up were at higher risk (HCC incidence ≥1.9/100 patient-year).
- Patients with LSM <10 kPa at follow-up and those with LSM between 10 and 20 kPa and high albumin (≥4.4 g/dL at baseline) had an incidence <1/100 patient-year.

These authors have proposed a nomogram that predicts each individual's HCC risk using LSM and albumin measurements taken at 1 year of follow-up. More recently, another nomogram score capable of predicting HCC occurrence at 1, 3, and 5 years following SVR has been created from a cohort of 2,064 cirrhotic patients, based on three easy-to-obtain variables: age (continuous values), post-treatment platelet count (cut-off value of 120,000/mL), and albumin level (cut-off value of 3.5 g/dL) [48].

One of the easiest methods to measure HCC risk in HCV patients relies on the use of the fibrosis-4 (FIB-4) score, which is calculated with a formula that includes age, aminotransferases, and platelet count [49]. Ioannou et al. [50], following 48,135 patients for more than 5 years following SVR, found 1,509 incident HCCs and showed that both the pre-treatment FIB-4 score (≥3.25 vs. <3.25) and its change following SVR were able to predict HCC occurrence. In cirrhotic patients, a pre-treatment value of FIB-4 ≥3.25 predicted a yearly HCC incidence of 3.66%, which fell to 1.16% when the FIB-4 score was below this cut-off. Moreover, a post-SVR decrease in FIB-4 from a baseline value of ≥3.25 to <3.25 was associated with a 50% decrease in HCC risk, although the absolute annual risk in these patients remained above 2%. In contrast, the annual incidence of HCC in cirrhotic patients with a FIB-4 <3.25 both before and after SVR was <1%, which is below the threshold needed for implementing cost-effective surveillance. Patients without cirrhosis had a low risk of HCC, with the exception of those with a baseline FIB-4 ≥3.25 (1.22% per year) or a post-SVR FIB-4 ≥3.25 (2.39% per year). Therefore, the continuation of HCC surveillance in these subgroups is warranted, especially if the post-SVR FIB-4 remains ≥3.25.

In the case of a "poorly informative" FIB-4 value (i.e., 1.45–3.25), the combination with APRI (aspartate aminotransferase to platelet ratio index) would accurately predict cancer risk, regardless of the presence of cirrhosis. In a retrospective study on 18,076 patients, this risk was the highest in those with persistently elevated FIB-4/APRI scores following SVR, while it fell in those showing a decreasing score [51].

Table 1. Variables included in the main risk scores/indexes of HCC development

Predictive scores	Country or geographic area	Variables included	Follow-up duration (mean or median)	Cut-off value for HCC risk groups (points)	Proportion of cirrhosis/ advanced fibrosis
HBV scores					
CU-HCC [37]	Hong Kong, China	Age, albumin, bilirubin, HBV-DNA, US-diagnosed cirrhosis	9.94 years (median) (95% CI, 9.86–10.02)	Scoring range 0–44.5 Low risk 0–4 Medium risk 5–19 High risk 20–44.5	38.1% TC 16.3% VC
GAG-HCC [38]	Hong Kong	Age, gender, HBV-DNA, core promoter mutations, cirrhosis	67.4 months (median) (IQR 6.4–221.4)	High risk >101	15.1%
REACH-B [39]	Taiwan	Sex, age, AST, HBeAg, HBV-DNA level	12 years (median) (IQR 11.5–12.4) in TC 7 years (median) (IQR 5.0–10.3) in VC	Scoring ranging 0–17 with an increasing risk per each point: at 3 years (0–23.6%), at 5 years (0–47.4%), at 10 years (0–81.6%)	0% TC 19.4% VC
LSM-HCC [40]	Hong Kong, China	Age, albumin, bilirubin, HBV-DNA, LSM	69 months (mean) (95% CI ±8 months)	Scoring range 0–30 Low risk 0–10 High risk 11–30	32% TC 31% VC
CAMD score [41]	Taiwan, Hong Kong	Cirrhosis, age, male sex, diabetes mellitus	25.8 months (median) in TC, 33.3 months (median) in VC	Scoring range 0–19 Low risk <8 High risk >13	26.5% TC 7.1% VC
PAGE-B [21]	Greece, Italy, Spain, the Netherlands, Turkey	Platelets, age, gender	50 months (median) (range 31–62)	Scoring range 0–25 Low risk <9 Intermediate risk 10–17 High risk >18	64% TC 70% VC
mPAGE-B [42]	Korea	Platelets, age, gender, albumin	49 months (median) (IQR, 33–68)	Scoring range 0–21 Low risk <8 High risk >13	19.1% TC 20.1% VC
HCV scores					
Pons [43]	Spain	Albumin, LSM	2.9 years (median) (range 0.3–3.8)	Low risk: follow-up LSM <10 kPa or follow-up LSM 10–20 kPa + follow-up albumin ≥4.4 g/dL. High risk: follow-up LSM ≥20 kPa or follow-up LSM 10–20 kPa + follow-up albumin <4.4 g/dL	100%
Semmler [44]	Austria, Italy	AFP, age, liver stiffness, albumin, alcohol consumption	41 months (IQR±33)	Low risk 0–3 points High risk 4–9 points	100%
HEPATHER HCC [45]	France, Egypt	Gender, HCV genotype 3, esophageal varices, albumin <40 g/l, bilirubin >11 mmol/l, hypercholesterolemia, age >58, FIB-4 >3.25 at SVR	3.05 years (median) (IQR 1.94–3.88)	Low risk <7 points Medium risk 7–12 High risk ≥12	69% cirrhotic, 31% advanced fibrosis

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Table 1 (continued)

Predictive scores	Country or geographic area	Variables included	Follow-up duration (mean or median)	Cut-off value for HCC risk groups (points)	Proportion of cirrhosis/ advanced fibrosis
Universal scores					
Toronto HCC risk index [46]	Canada	Age, sex, etiology, platelet count	5.4 (median) (range 0.5–18.6) in TC 6.2 (median) (range 0.5–26.7) in VC	Low risk <120 Intermediate risk 120–240 High risk >240	100%
aMAP [47]	Asia, Europe	Age, sex, albumin-bilirubin, platelet count	Different from cohort to cohort (maximum 105.4 (median), range 100.8–108.4)	Scoring range 0–100 Low risk <50	Different among cohorts (range 12–100%)

AFP, alpha-fetoprotein; AST, aspartate aminotransferase; CI, confidence interval; FIB-4, fibrosis-4 score; HBeAg, hepatitis B e antigen; HCC, hepatocellular carcinoma; IQR, interquartile range; LSM, liver stiffness measurement; SVR, sustained virologic response; TC, training cohort; VC, validation cohort.

In a recent study, 1,000 patients with cured HCV infection were followed for 4 years with US-based semi-annual surveillance [52]. Patients were divided into four groups according to their baseline characteristics: LSM ≥9.5 ≤14.5 kPa, FIB-4 <3.25, and APRI <1.5 (*group 1*); LSM ≥9.5 ≤14.5 kPa, FIB-4 ≥3.25, and/or APRI ≥1.5 (*group 2*); LSM >14.5, FIB-4 <3.25, and APRI <1.5 (*group 3*); and LSM >14.5 kPa, FIB-4 ≥3.25, and/or APRI ≥1.5 (*group 4*). The annual incidence of HCC was 0.09% in group 1, 1.22% in group 2, 1.68% in group 3, and 4.01% in group 4. Therefore, group 1 patients, which accounted for one-third of the cases, had a negligible HCC risk that did not warrant surveillance.

In another study involving 527 European patients with compensated advanced chronic liver disease and a validation cohort (VC) of 1,500 patients, Semmler et al. [44] developed an algorithm based on age, post-treatment AFP, LSM, albumin, and alcohol consumption that accurately predicted the risk of HCC. Data from the external VC confirmed the results derived from the training cohort. Notably, approximately 70% of cases had a calculated annual risk <1%, not fulfilling the pre-requisite for cost-effective surveillance.

A French study developed the HEPATHER HCC score, which includes male gender, HCV genotype 3, esophageal varices, albumin <40 g/L, bilirubin >1 mmol/L, and hypercholesterolemia as pre-DAA variables,

age >58, and FIB-4 >3.25 measured at the time of SVR. Its external validation showed good short-term predictive performance, identifying high-risk groups where surveillance following SVR is cost-effective [45].

Several scoring systems were set up to predict the risk of HCC among patients with CHB on NUCs, but many of them still lack external validation. CU-HCC, GAG-HCC, and REACH-B HCC are the most known scoring systems predicting HCC risk in patients treated with entecavir [37–39, 53]. In these models, advanced age, cirrhosis, and high viral load are the most important predictors, with a heavy weighting assigned to cirrhosis, traditionally diagnosed using B-mode US.

The CU-HCC score (composed of age, albumin, bilirubin, HBV-DNA, and US-diagnosed cirrhosis) can accurately predict HCC, but the suboptimal sensitivity of the US may produce an incorrect diagnosis of cirrhosis, leading to some errors in the prediction. The inclusion of LSM has been proposed in order to improve its performance: patients with an LSM-HCC score <11, representing around 70% of studied patients, would have a very low risk of developing HCC [40].

Hsu et al. [41] derived the CAMD score (cirrhosis, age, male sex, and diabetes mellitus as risk determinants) from Taiwan and Hong Kong healthcare databases of CHB patients on entecavir or tenofovir to predict the risk of HCC, especially during the first years of NUC treatment. This score was externally validated.

One of the limitations of the HCC risk scores for HBV patients is that they were mostly developed in Asian populations and provide poor-to-moderate predictability in Caucasian patients. To overcome this drawback, in 2016 Papatheodoridis [21] proposed the PAGE B risk score for Caucasian patients. This score, based on three easy-to-obtain variables (platelets, age, and gender), segregates patients on tenofovir and entecavir into three groups at different risks of developing HCC over 5 years: a score ⩽ 9 heralds a 0% 5-year risk, while the scores 10–17 and ⩾18 indicate a moderate (3–5%) and a high (16–17%) 5-year risk, respectively.

Unlike the scores that incorporate variables that are affected by treatment (such as HBV-DNA levels), the PAGE-B score offers good reproducibility over time. Moreover, the addition of cirrhosis did not substantially improve the discrimination of HCC risk.

In 2018, a modified PAGE-B score (mPAGE-B) that incorporates albumin was advised as more accurate than the original PAGE-B at predicting HCC risk in Asian patients on NUCs [42]. PAGE B and mPAGE-B can be confidently used to calculate HCC risk and to exclude low-risk patients from semi-annual US-based surveillance [35].

Etiology-independent prediction systems are also available. The Toronto HCC risk index (THRI) was developed using data from 2,079 cirrhotic patients, 19% of whom had a CHB and 42.5% had chronic hepatitis C 191 with SVR. THRI showed a Harrell's c statistic of 0.76 and was validated in an external cohort of 1,144 cirrhotic patients, where Harrell's c statistic was 0.77 [46]. Independent predictors of HCC were age, sex, etiology, and platelet count, from which a nomogram by point score was derived. Patients at low (score <120 points), intermediate (120–240), and high (>240) risk had a cumulative 10-year incidence of HCC of 2.7% (approximately 0.3%/year), 9.8%, and 32.1%, respectively. Interestingly, the cumulative 10-year incidence of HCC in HCV patients who had achieved SVR was 7.0%. THRI has been independently validated in European and Chinese patients with cirrhosis [54, 55].

The aMAP score was developed on 17,374 patients (including patients with HCV cirrhosis who achieved SVR), and it was validated on 13,686 patients from 9 VCs with different etiologies and ethnicities [47]. Particularly, it considers patients with chronic hepatitis regardless of etiology and ethnicity. Its variables are age, sex, albumin-bilirubin, and platelet data, and the score ranges from 0 to 100. Patients with aMAP score <50, accounting for 44% of the overall tested population, had an annual HCC incidence of <0.2%, a figure far below the threshold for cost-effective surveillance.

Despite the known impact of alcohol intake and metabolic disorders, such as obesity and diabetes, on the risk of HCC, which persists in patients after viral suppression or eradication [56], only two [41, 45] of the above-mentioned calculators included a metabolic parameter, one [44] included alcohol intake, and none included both variables. Therefore, the omission of these variables may have limited the potential accuracy of the available calculators, and, considering the growing prevalence of metabolic disorders and the frequent alcohol intake in viral patients, the improvement of current risk calculators can no longer neglect these aspects.

Contribution of Artificial Intelligence in Predicting HCC Risk

Artificial neural networks are increasingly being applied to healthcare to predict clinical events. In this context, machine-learning algorithms offer a great opportunity to improve HCC risk stratification and, therefore, to personalize surveillance programs.

Kim et al. [57] developed a prediction model using machine learning algorithms in 6,051 antiviral-treated patients with CHB, named PLAN B (Prediction of Liver cancer using Artificial intelligence-driven model for Network-hepatitis B), which comprises 10 baseline parameters: age, sex, cirrhosis, platelet count, entecavir/tenofovir treatment, serum ALT, HBV-DNA levels and HBeAg status, albumin, and bilirubin. Three different gradient-boosting machine models of HCC risk were developed, and their performances were compared. The best model was found by using a validation test. According to the risk probabilities calculated by the GBM model, patients were allocated to minimal-, low-, intermediate-, and high-risk groups. This model was validated in both Korean and Caucasian patients and showed a better discriminant function than PAGE-B, mPAGE-B, and CU-HCC.

Another artificial intelligence (AI) application in this setting was made by Audureau et al. [58] in 836 patients with compensated HCV-related cirrhosis undergoing semi-annual surveillance. HCC risk was stratified according to SVR status. Three models for HCC occurrence were implemented and compared for their predictive performance: (1) Fine-gray competing risk regression modeling was used to obtain a benchmark; (2) a single decision tree was built by recursive partitioning analysis using the conditional

inference tree methodology; and (3) a random survival forest for competing risk survival was derived. As expected, predictive factors differed according to the SVR status: in patients without SVR, excessive prior alcohol intake, HCV genotype 1, platelet count, gamma glutamyl-transferase, AFP, and albumin were the independent predictors of HCC; after SVR, elevated AST, low platelet count, and shorter (≤0.85 s) prothrombin time were associated with a high risk. Decision tree analysis revealed a complex interaction between risk factors, stratifying patients into eight different phenotypes with different risks. Low-risk patients (irrespective of their SVR status) represented 40–45% of the enrolled cases.

Deep learning machine algorithms were also applied to the Veteran Health Administration database, developing a recurrent neural network model that could improve surveillance strategies according to HCC incidence [59]. Three models predicting HCC over a 3-year period were developed and compared: (1) logistic regression (LR) with cross-sectional inputs (cross-sectional LR); (2) LR with longitudinal inputs (longitudinal LR); and (3) recurrent neural network with longitudinal inputs.

AI has also been applied to gene sequencing techniques to find genomic predictors of HCC. Next-generation sequencing can provide the genomic signatures of HCC, and machine-learning algorithms were implemented to extract genes associated with HCC in HCV-infected patients [60]. Pre-treatment PBMC DEFA1B, HBG2, ADCY4 genes and post-treatment TAS1R3, ABCA3, FOSL1 genes were found to be down-regulated in the group who developed HCC, while pre-treatment ANGPLT6 gene was up-regulated. A gene score was then created by means of decision tree analysis, and a nomogram, in which each parameter has a corresponding risk, was developed by combining the gene score with the FIB-4 index. The relative importance of the HCC predictors was evaluated using the random forest algorithm. Overall, 500 randomly and independently grown decision trees were used to determine the importance of the variables. The sum of points was converted to 5-year and 10-year survival probabilities. The accuracy of this nomogram in predicting HCC risk was excellent (AUC 0.95, 95 CI, 0.89–1.00). To conclude, although further validation of these AI-derived scores is necessary, it is worth mentioning that most of them would accurately differentiate low-risk patients (who represent the majority after the cure or suppression of viral infection) from intermediate- or high-risk subjects, thus offering the opportunity to adapt surveillance to the actual risk (precision surveillance).

Is There a Possibility of Improving the Performance of Surveillance Tests?

Advanced Imaging Techniques

Next-generation HCC surveillance will probably incorporate more sophisticated imaging techniques. Magnetic resonance imaging (MRI) has the greatest ability to detect very early-stage HCCs, and the use of *abbreviated* MRI (AMRI) may be cost-effective in surveying patients with the highest risk of developing HCC (>3% per year) [36].

AMRI protocols involve the acquisition of a limited number of sequences with or without contrast-enhanced phases. Compared to conventional MRI, AMRI markedly reduces acquisition and interpretation times and decreases costs. Although the sensitivity of AMRI for the detection of small (<2 cm) HCCs is lower than that for bigger lesions, it remains considerably higher than the sensitivity of US (82% vs. 53%) [61]. Therefore, AMRI may be a tool to be considered in planning precision surveillance.

Combination of Biomarkers

Due to tumor heterogeneity, single biomarkers show suboptimal performance for the early detection of HCC. Hence, the most recent models combine multiple biomarkers to improve sensitivity for early detection [62]. The GALAD score combines demographic factors (age and gender) with a panel of serum biomarkers (AFP, lectin-bound AFP, and des-carboxy-prothrombin) [63]. It was derived from a cohort of 670 patients from the UK and validated in 6,834 individuals from Japan, Germany, and Hong Kong. In phase II studies, the GALAD score showed good sensitivity (72–82%) and specificity (81–90%) in detecting early-stage HCC [64]. Skipping any instrumental test, the GALAD score could improve the patient's adherence to surveillance. Its performance, superior to US and AFP alone, may be further improved by combining it with US itself (GALADUS score) [65]. Nevertheless, validation in the different risk categories identified by the current article and the consequent calculation of cost-effectiveness are still necessary.

Can the Declining Risk of HCC following SVR or HBV Suppression Reach Negligible Figures to Avoid Surveillance?

The above-mentioned meta-analysis showed that in HCV patients with cirrhosis, the incidence of HCC was inversely related to the length of follow-up [25]. Indeed,

the pooled estimates of HCC annual incidence were 2.7% (95% CI, 2.4–3.1) in studies with a follow-up <2 years and 1.9% (95% CI, 1.6–2.2) when the follow-up was ≥2 years. Conversely, there was no significant variation over time in the number of patients with F3 fibrosis. The pooled incidence estimates were 0.6% (95% CI, 0.3–1.2) yearly in studies with a follow-up <2 years and 0.5% (95% CI, 0.3–0.8) when the follow-up was ≥2 years.

Kim et al. [66] followed a cohort of 29,033 patients treated with DAA for 7 years and stratified patients according to the pre-treatment presence of cirrhosis and a FIB-4 ≥3.25 or <3.25 in order to evaluate whether the annual risk of HCC had decreased to levels low enough to avoid surveillance. In cirrhotic patients with a pre-treatment FIB-4 score ≥3.25, the annual incidence of HCC decreased each year (from 3.8% at year 1 to 1.4% at year 7), thus remaining remarkable 7 years after SVR. Conversely, in cirrhotic patients with a pre-treatment FIB-4 score <3.25 the annual incidence of HCC ranged from 0.7% to 1.3% and did not change over time. In patients without cirrhosis and with a FIB-4 score ≥3.25, the annual incidence remained stable but substantial for up to 7 years following SVR (0.8–1.3%; $p = 0.06$). In those patients with a FIB-4 <3.25, the risk of HCC remained below the cost-effective threshold throughout the follow-up, suggesting that this is the only group for which long-term surveillance can be avoided.

In agreement with these results, Ioannou et al. [50] found that patients with established cirrhosis maintain a considerable residual risk of HCC for a long time following SVR achieved with interferon. Namely, the annual incidence steadily declined during the first 4 years following SVR (from 3.8% to 2.4%), but there was no further risk reduction in those who had a longer (>10 years) follow-up period.

In the aforementioned Kim et al. meta-analysis [66], the incidence of HCC in cirrhotic patients decreased as the length of follow-up increased. The annual risk of HCC was indeed the highest in studies with a follow-up <1 year (6.17%) and slowly declined as follow-up increased: 2.75% in studies with 1–2 years of follow-up, 2.90% in those with a follow-up of 2–3 years, and 1.83% when the follow-up was ≥3 years. In the meta-regression analysis, this result was not influenced by geographical region, publication year, presence of surveillance programs, study quality, study design (prospective vs. retrospective), and HBV or HIV co-infection.

This evidence would justify, as a general rule, continuing surveillance following SVR in patients with cirrhosis. However, even in these patients, the declining incidence of HCC and the heterogeneity of available results highlight the need to adopt individualized surveillance based on both the initial risk of HCC and its downstream modifications. Conversely, in the whole population of patients with F3 fibrosis the pooled incidence of HCC is much lower than in cirrhosis and below the threshold for cost-effective surveillance [23]. Therefore, we need predictive models capable of identifying individuals with a sufficiently elevated cancer risk in order to implement this procedure. Moreover, for F3 subjects on surveillance after SVR, a scheduled re-assessment (likely at 12-month interval) of the HCC risk should be adopted in order to remove from this procedure those who achieve a sufficiently low risk.

A large, multicenter cohort study, involving approximately 2,000 Caucasian patients with CHB, assessed the cumulative probability of HCC and the changes in risk over time [21]. It showed that the incidence rate in patients without cirrhosis did not differ within or after the first 5 years (0.49% vs. 0.47%), while it significantly declined in patients with compensated cirrhosis (from 3.22% to 1.57%, $p = 0.039$). Older age, low platelet counts (both at baseline and at year 5 of treatment), and liver stiffness ≥12 kPa at year 5 were independent predictors of HCC development.

Discordant results emerge from a Korean study in which the incidence of HCC did not change significantly before and after 5 years of entecavir therapy, regardless of the presence of cirrhosis [67]. One possible explanation for this disagreement is the higher frequency of genotype C and vertical transmission of HBV in Asian people, who are linked to an earlier and greater incidence of HCC. To partially reconcile the results of these two studies, it can be noted that the incidence of HCC significantly decreased even in the Korean cohort of cirrhotic patients when the temporal cut-off was extended to 7 years of therapy.

Proposal for Precision (Personalized) Surveillance Based on the Individual Risk of Developing HCC

As already discussed, semi-annual US-based surveillance has several limitations, such as sub-optimal sensitivity for early-stage HCC, inter-operator variability, and false positive/indeterminate results. Moreover, it suffers from a relatively low rate of adherence to follow-up linked to the need to access qualified US services. This problem becomes particularly important following SVR, when patients are reassured by the improving prognosis of their liver disease, as evidenced by the annual decline in the percentage of patients who maintain regular hospital
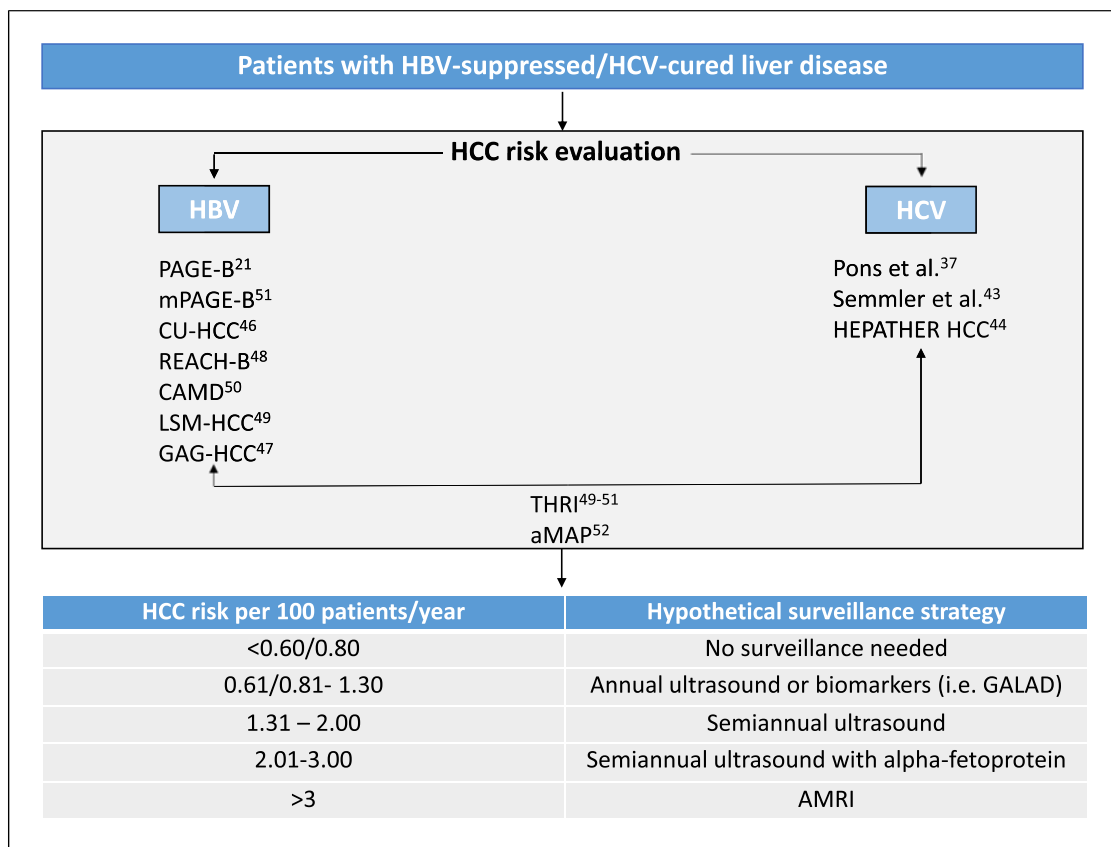
Fig. 1. Risk scores/indexes for calculating the risk of HCC in patients with hepatitis virus infections, as well as a hypothetical schematic flowchart of surveillance based on this risk. The proposed flowchart's granular subdivision is based on the opinion of the authors. AMRI, abbreviated magnetic resonance imaging; GALAD, gender, age, lectin-bound AFP, AFP, and des-carboxy-prothrombin.

visits following SVR [68]. Therefore, interventions to change the surveillance procedure at multiple levels are required to prevent this problem.

Moreover, semi-annual surveillance for HCC is not cost-effective in a large proportion of patients in whom the viral infection has been cured or suppressed. Therefore, the implementation of this procedure, regardless of the residual risk of HCC, inappropriately diverts economic resources from healthcare systems. Given that the low-risk population is rapidly expanding and that the performance and cost of screening tests vary considerably, a pragmatic approach to such a problem is to implement *personalized* surveillance tailored to the individual residual risk of HCC, also considering that an annual incidence <0.6–0.8 does not justify the procedure in terms of cost-effectiveness (Fig. 1). The rationale of this proposal considers the risk of developing HCC as well as the cost and performance (sensitivity, specificity, and false positive results) of each potential screening test (or

their combination). In general, both harms and increasing costs of surveillance become more and more justifiable as the oncologic risk increases. In particular, the negative impact on cost-effectiveness of a more stringent periodicity (semi-annual vs. annual US [10, 69]) or a more expensive surveillance tests (aMRI vs. US [9, 70, 71] or combinations with lower specificity (US + AFP vs. US alone [69, 72]) may result acceptable in high-risk patients since the *number needed to survey* to detect an early - and potentially curable - HCC decreases as the annual incidence of the tumor increases. Consequently, a differential use of surveillance modality based on HCC risk lessens the impact of screening harms and extra costs of expensive tests and/or false positive results, and drives the use of highly sensitive tests toward settings with a higher incidence of cancer. Nevertheless, our proposal needs to be re-modulated considering the local availability of resources, which greatly differs between countries.

Available evidence indicates that, adopting the proposed algorithm, up to 70% of patients with virologic suppression or SVR should not enter surveillance programs, thereby avoiding exposure to physical and psychological surveillance harms and freeing up more economic resources to optimize surveillance modalities for patients at higher risk. Moreover, since some HCC risk factors worsen (age) or improve (HBeAg/HBsAg status, liver fibrosis, and hepatic function) following prolonged viral suppression or SVR, monitoring cancer risk every 1–2 years for patients on surveillance can further improve their management and the allocation of economic resources [73].

With the widespread use of new potent antiviral drugs capable of modulating the risk of HCC, the shift from "one-size-fits-all" to precision surveillance has become a major priority in hepatology. As personalized screening relies on precise knowledge of the residual and potentially modifiable risk of HCC, validation of risk calculators and real-world studies to test the results of this innovative follow-up strategy are warranted.

Conflict of Interest Statement

Funding Sources

Author Contributions

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