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MINIREVIEWS

Surveillance for hepatocellular carcinoma in chronic viral hepatitis: Is it time to personalize it?

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Abstract

Surveillance with abdominal ultrasound with or without alpha-fetoprotein is recommended by clinical practice guidelines for patients who are considered to be at risk of developing hepatocellular carcinoma (HCC), including those with cirrhosis, advanced fibrosis and special subgroups of chronic hepatitis B (CHB). Application of the standard surveillance strategy to all patients with chronic liver disease (CLD) with or without cirrhosis imposes major sustainability and economic burdens on healthcare systems. Thus, a number of HCC risk scores were constructed, mainly from Asian cohorts, to stratify the HCC prediction in patients with CHB. Similarly, even if less than for CHB, a few scoring systems were developed for chronic hepatitis C patients or cirrhotic patients with CLD of different etiologies. Recently, a few newsworthy HCC-risk algorithms were developed for patients with cirrhosis using the combination of serologic HCC markers and clinical parameters. Overall, the HCC risk stratification appears at hand by several validated multiple score systems, but their optimal performance is obtained only in populations who show highly homogenous clinic-pathologic, epidemiologic, etiologic and therapeutic characteristics and this limitation poses a major drawback to their sustainable use in clinical practice. A better understanding of the dynamic process driving the progression from CLD to HCC derived from studies based on molecular approaches and genetics, epigenetics and liquid biopsy will enable the identification of new biomarkers to define the individual risk of HCC in the near future, with the possibility to achieve a real and cost/effective personalization of surveillance.

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Core Tip: The risk of hepatocellular carcinoma (HCC) is not uniform and may increase due to underlying parameters in chronic viral hepatitis. Several clinical HCC risk scores and biomarker integrated algorithms have been proposed to stratify patients according to their HCC risk level. In the present review, we summarize the efforts for personalized HCC surveillance in the literature and discuss their applicability to clinical practice.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second leading cause of cancer-related deaths globally[1]. The majority of HCC cases (> 90%), at least in the Western countries, occur in the setting of cirrhosis, as approximately one-third of patients with cirrhosis eventually develop HCC in the long term, with an annual risk of 1%-8%, varying upon several risk factors[2,3]. Globally, approximately 80% of HCC are associated with hepatitis B virus (HBV) or hepatitis C virus (HCV) infection and their geographical distribution depends on the epidemiology of the two viral infections. Most HCCs are associated with chronic hepatitis B (CHB) virus infection (> 60%) in Asian countries, whereas chronic hepatitis C (CHC) appears to be the most commonly established etiology for HCC in western countries[4]. However, in recent years, a progressive increase of HCC in patients with non-viral (mainly metabolic) liver disease has been reported[5].

CHB has carcinogenetic potential itself by several insertional mutagenetic routes, and up to 30% of CHB-related HCCs arise in non-cirrhotic liver, mainly in Asian patients[6]. Current management of CHB with long-term nucleotide analogues treatment by inhibiting HBV replication had been shown to decrease HCC incidence. Nevertheless, despite on-therapy virological remission, the annual incidence of HCC ranges from 0.01% to 5.4% in CHB[7]. In the last decade, wondrous new achievements occurred in the treatment of CHC, and sustained virological response (SVR) rates exceeded 95% with direct-acting antiviral (DAA) therapies[8]. Successful DAA treatment has resulted in a 71% reduction in HCC risk[9]. The HCC incidence fell from 3.6% to 1.8% per year with the DAA therapies[10]. However, many patients, after the clearance of HCV infection, maintain additional co-factors of liver disease (*i.e.* metabolic or alcohol-induced liver damage) that may contribute to the persistence of a significant HCC risk. Accordingly, a recent long-term study conducted in the Veterans cohort showed that HCC incidence remained stable at 1.5 to 2.3/100 person years, even up to 3.6 years, after DAA-induced SVR[11]. Cirrhosis is the primary risk factor for HCC regardless of liver disease etiology, with an annual HCC incidence greater than 1%[12]. CHC patients with cirrhosis and advanced fibrosis (F3) continue to have a significantly elevated risk of HCC despite achieving SVR and have stayed the target of surveillance programs. According to the general principles of surveillance, the definition of the target population must consider the incidence of HCC in a specific set of patients and the probability that effective therapies, particularly the curative ones, can be applied to these patients. Decision analysis and cost-effectiveness models suggest that an intervention is considered cost-effective if it provides life expectancy increases of at least 3 mo with a cost below the threshold of ultrasonography (US) of $50000 per year of lives saved[13]. Based on these premises, there is currently a general consensus on using abdominal US with or without alpha-fetoprotein (AFP) as a diagnostic tool to perform HCC surveillance.

Beyond the fact that several host-related (cirrhosis, chronic hepatic necroinflammation, older age, male sex, African origin, alcohol abuse, chronic co-infections with other hepatitis viruses or human immunodeficiency virus, diabetes or metabolic syndrome, active smoking, positive family history) and virus-related (high HBV-DNA and/or hepatitis B surface antigen [HBsAg] levels, HBV genotype C > B, specific mutations) factors influence the risk of HCC development[14], in the setting of CHB, HCC surveillance is recommended by American Association for the Study of Liver Diseases (AASLD), Asia-Pacific Association for the Study of Liver Diseases and European Association for the Study of Liver Diseases (EASL) for all patients with cirrhosis, hepatitis B carriers with a family history of HCC, Asian males older than 40 years, Asian females older than 50 years, and African males older than 20 years[15-18]. Additionally, all patients with chronic liver disease (CLD) and advanced fibrosis (F3) are also recommended to undergo HCC surveillance by EASL[18] (Table 1). In general, a cut-off for HCC incidence of 0.2%/year for hepatitis B, 1.5%/year for hepatitis C and all cirrhotics regardless of etiology is considered cost-effective for HCC surveillance, since it was first described in AASLD guidelines in 2005[19]. However, an area of uncertainty exists for CHC patients with viral clearance but F3 fibrosis. On one hand, the AASLD HCV guidance statement recommends HCC surveillance for this group, but on the other, the AASLD HCC guidance statement recommends surveillance only in presence of cirrhosis[16,20]. A recent study, using the Markov model, found out that HCC surveillance is cost-effective among CHC patients with cirrhosis but not for those with F3 fibrosis[21]. However, in clinical practice, the differentiation between advanced fibrosis (F3) and cirrhosis is not always straightforward. For this reason, EASL recommends HCC surveillance to patients with F3 fibrosis regardless of etiology, with a more clinically oriented approach. Given the limitations of the current surveillance protocols, several HCC risk scores have been developed mainly from Asian cohorts for patients with CHB. Even if in limited number, a few risk scores are also available for CHC or all-cirrhotic patients.

In this review, we summarize the characteristics and discuss the applicability of HCC-risk scores in clinical practice, with a special focus on chronic viral hepatitis. Several reviews investigated the impact of HCC risk scores on clinical practice in recent years, but newer scores and comparison studies have emerged since then[22-25]. Furthermore, new serologic biomarkers have been introduced for early detection of HCC with promising results, and some of them got involved in algorithms in combination with clinical and laboratory parameters.

HCC RISK SCORES FOR CHB PATIENTS

Risk scores for untreated CHB patients

The guide with age, gender, HBV-DNA, core promoter mutations, and cirrhosis (GAG-HCC) risk score was the first attempt to stratify HCC risk among CHB patients, which was published in 2009[26]. The study was conducted with 820 untreated CHB subjects (15% with cirrhosis) from Hong-Kong, and all patients were followed up for a median period of 77 mo. They showed that cirrhosis, age, gender, viral load, and precore mutation were independent predictors of HCC and used them all in the risk score. However, due to the unavailability of pre-core mutation assays in the routine clinical practice, they repeated the analysis without this variable and showed no loss of performance in the risk score. The area under the receiver-operating characteristics curve (AUROC) for GAG-HCC to predict HCC in 5 and 10 years was 0.87 and 0.88, respectively. The determined optimal cut-off value of 101 showed high sensitivity (88%) and specificity (78.7%) for the prediction of HCC at 10 years. Chinese University-HCC risk score (CU-HCC) was the second attempt for HCC risk stratification in CHB patients, which was published in 2010[27]. Using the same methodology, the investigators confirmed age, viral load, and cirrhosis as independent predictors of HCC during a median follow-up period of 10 years, with the addition of two markers of liver function (bilirubin and albumin). They proposed a three category risk score to distinguish low (< 5), intermediate (5-20), and high risk (> 20) CHB patients for HCC development. The model showed a good general performance in predicting 5- and 10-year HCC risk by showing AUROC values of 0.76 and 0.78, respectively. The 5-year HCC-free survival rates were 98.3%, 90.5%, and 78.9% in the low-, medium-, and high-risk groups, respectively. The determined cut-off value of 5 ruled out the risk of HCC development with high accuracy (negative predictive value [NPV] of 97.8% and 97.3 in training and validation cohorts, respectively), suggesting that HCC surveillance in low-risk group may not be cost-effective. Interestingly, the

Table 1 Patients for whom surveillance of hepatocellular carcinoma is recommended according to society guidelines

Cirrhotic patients regardless of etiology, Child-Pugh stage A-B[12-14]
Cirrhotic patients regardless of etiology, Child-Pugh stage C awaiting liver transplantation[12-14]
Asian male hepatitis B carriers over the age of 40 yr[12-14]
Asian female hepatitis B carriers over the age of 50 yr[12-14]
Hepatitis B carriers with a family history of HCC[12-14]
Non-cirrhotic F3 patients, regardless of etiology, may be considered for surveillance based on an individual risk assessment[14]

HCC: Hepatocellular carcinoma.

authors of GAG-HCC and CU-HCC, despite proposing their risk scores as tools to identify CHB patients at high risk for HCC development, never suggested their applicability in selecting candidates for HCC surveillance.

After two relatively small-sized studies, another HCC-risk score for untreated CHB patients without cirrhosis was proposed from Taiwan in 2010[28]. The risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B) score was developed in 3584 CHB Taiwanese patients without cirrhosis and validated in 1505 patients (18% of whom with cirrhosis) from Hong Kong and Korea[29]. The REACH-B score included male sex, age, alanine aminotransferase (ALT), hepatitis B e antigen (HBeAg), and HBV-DNA as parameters, but not cirrhosis, as the training cohort only consisted of patients without cirrhosis. Instead of using cut-off values, the score was proposed as a range from 0 to 17 points, with a progressively increasing risk of HCC development. The REACH-B score had a 5 and 10-year AUROC of 0.796 and 0.769 in the validation cohort. The 5 and 10-year AUROC values decreased to 0.698 and 0.647 in the analysis of the cirrhotic group only. This finding confirms that the presence of cirrhosis per se is a major determinant for HCC development. These findings suggest that the training cohort should reflect the overall population at HCC risk more balanced to produce a reliable score for use in clinical practice.

In the upcoming years, the score was revised (REACH-BII) with the inclusion of quantitative HBsAg, which proved to be an additional independent predictor for the development of HCC[30]. In 2014, REACH-B risk score went through a final modification in a South Korean cohort where liver stiffness measurement (LSM) by transient elastography substituted HBV-DNA level: The better performance of the modified score (AUROC values; mREACH-B: 0.814 *vs* REACH-B: 0.629) was consistent with the fact that the CHB patients included in the Korean study were under entecavir treatment[31]. Similar findings were reported by the investigators of the original REACH-B risk score study when they applied the old and modified score to CHB patients treated with nucleotide analogue[32].

Liver stiffness values, in addition to age, albumin and HBV-DNA were used by the group of investigators of the CU-HCC score in 2014, to develop a new score for untreated CHB patients, namely LSM-HCC[33]. The new scoring system ranged from 0 to 30, with an optimal cut-off value of 11 to identify patients at HCC risk. Patients with a LSM-HCC score lower than 11 had a very low 5-year risk for HCC, with 92% sensitivity, 71% specificity, and 100% NPV. In 2016, another HCC risk score was developed based on real-world data of 538 untreated CHB patients from Singapore, namely the real-world score-HCC (RWS-HCC)[34]. The RWS-HCC score included gender, age, cirrhosis, and AFP as independent predictors. Upon validation in 3353 patients from REACH-B, GAG-HCC and CU-HCC cohorts, RWS-HCC score had AUROC values of 0.767, 0.830, and 0.902 and NPV of 97.0%, 97.9%, and 93.0% respectively. In 2018, a novel score (HCC-ESC) was developed for 723 CHB patients who achieved HBeAg seroclearance; age, gender, cirrhosis, albumin, HBV-DNA, and ALT serum levels were the parameters of the risk score to identify the long-term risk. The HCC-ESC score showed an AUROC value of 0.92 in the validation cohort[35]. Finally, in 2019, another HCC risk score (AGED score) was proposed from a longer term (21-year follow-up period) cohort study[36]. The AGED score included age, gender, HBeAg status, and HBV-DNA as independent parameters. The AGED score categorized patients into three groups according to their HCC risk as low (0-4), intermediate (5-9), and high (10-12) risk using a 12-point score. A total of 1663 HBsAg-positive participants were recruited as the validation cohort, and the AGED score had AUROC values of 0.73 and 0.74.

Risk scores for treated CHB patients

At present, most CHB patients are under antiviral treatment, as it has a significant positive impact on the course of liver disease, reducing the progression to cirrhosis and its complications, including HCC[37,38]. Therefore, scores developed in cohorts of untreated CHB patients could not be adequate for treated patients because they include parameters that are not any more relevant in patients with sustained suppression of viral replication. PAGE-B is the first risk score developed in 1815 Caucasian CHB patients including those under nucleos(t)ide analogue (entecavir/tenofovir) treatment for at least 1 year[39]. This was a multicenter study where 1325 patients were set in derivation and 490 enrolled as validation cohort. The regression analysis identified age, gender, and platelet count as independent predictors of HCC. Cirrhosis was not included in the model, but the platelet count can be considered the surrogate marker for the cirrhotic (portal hypertension) stage. The c-statistic of PAGE-B score was found 0.82 in both the derivation and validation cohorts. Having a PAGE-B score < 9 (low risk), 10-17 (intermediate risk), > 18 (high risk) resulted in 5-year cumulative HCC incidences of 0%, 3%-4% and 16%-17%, respectively. The PAGE-B score shows a higher discriminatory ability in the identification of high-risk HBV patients from those with low-risk (100% NPV), contributing to define different surveillance strategies according to the individual risk. By contrast, the intermediate-risk group has to be considered as a borderline group, where the definition of individualized surveillance algorithm is more difficult. The original findings of the PAGE-B score were confirmed and validated in Spanish and South Korean cohorts[40,41]. In 2018, Kim *et al*[42] revised the PAGE-B risk score in 3001 Asian CHB patients receiving entecavir/tenofovir therapy by adding albumin to the PAGE-B risk score. They showed a significant improvement of prediction as compared to previous models, including CU-HCC, GAG-HCC, REACH-B, and PAGE-B, with an AUROC value of 0.82 at 5-year in HCC prediction and 100% NPV. Low- and intermediate-risk patients had an annual HCC development risk of approximately 0.2%-1%, which turned to be higher than 3% in the high-risk group. In an independent Asian HBV cohort, the mPAGE-B score showed similar accuracy with PAGE-B and GAG-HCC scores, but its discrimination ability was better than the REACH-B and CU-HCC scores[43]. PAGE-B and mPAGE-B risk scores showed promising results for adoption to HCC surveillance algorithm, particularly because of the very high NPV.

In 2017, the HCC-Risk Estimating Score in CHB patients under Entecavir (HCC-RESCUE) score based on age, gender, and cirrhosis was proposed for South Korean treated CHB patients[44]. The AUROC at 1, 3, and 5-year was 0.82, 0.81, and 0.81, respectively, in the validation cohort. In the same year, the age, platelet, AFP (APA)-B score was proposed from Taiwan[45]. It ranged from 0 to 15, with the optimal cut-off for low risk set at 6. The AUROCs for 2-, 3-, and 5-year HCC prediction was 0.939, 0.892, and 0.862, and the NPV for the low-risk group was 99.1% in the validation cohort.

In 2018, the cirrhosis, age, male gender, diabetes (CAMD) score, which aimed to predict HCC during antiviral treatment, was proposed by the analysis of population-wide data from the healthcare systems in Taiwan (training cohort of 23851 CHB patients) and Hong Kong (validation cohort of 19321 patients)[46]. The CAMD score was the first to integrate diabetes mellitus as a risk factor for HCC, extracted from the multivariable Cox proportional hazards model. These four parameters were weighed to develop the CAMD score ranging from 0 to 19 points, with the categorization of CHB patients in three groups as low (< 8), intermediate (9-12), and high (> 13) risk. Low-risk patients had an annual HCC incidence of 0.3%. The c-indices were higher than 0.75 within the first 5 years in the training and validation cohorts. The CAMD score can be easily computed with simple information at the baseline of treatment initiation.

In 2019, a multicenter study from Korea proposed the Age-Albumin-Sex-Liver cirrhosis (AASL-HCC) score[47]. Age, albumin, male gender, and cirrhosis were extracted as independent predictors of HCC development while under entecavir or tenofovir treatment in a cohort of 1242 consecutive treatment-naive HBV patients, who were followed from 2007 to 2017. Low (< 5), intermediate (6-19), and high (> 20) risk groups showed HCC incidence rates of 0%, 3.7%-7.4%, and 17.6%-30.9%, respectively. The AUROC value for HCC prediction in 3-year, 5-year and total follow-up period was 0.850, 0.805, and 0.797, respectively, in the validation cohort.

In 2020, a multicenter study, enrolling 8048 Asian CHB patients under antiviral treatment from 25 centers in the United States and Asian-Pacific region, developed the REAL-B score[48]. It includes seven variables (male gender, age, alcohol use, diabetes, baseline cirrhosis, platelet count, and AFP) to categorize patients into the following three groups: Those at low (0-3), moderate (7), and high (8-13) risk. All AUROCs for

HCC prediction were higher than 0.8 at 3, 5, and 10 years, with a better predictive performance than PAGE-B in the same cohort (AUROC values at same time points; 0.73-0.74). The previously described HCC-ESC score was revised in 2020 in a Korean cohort of CHB patients under antiviral treatment and called HCC-ESC$_{AVT}$[49]. The risk score targeted CHB patients with HBeAg seroclearance like the original version and used the following three parameters: Male gender, cirrhosis, and fibrosis-4 index. The AUROC values for 5-year HCC prediction were 0.770 and 0.774 in the training and validation cohorts, respectively.

Interpretation and comparison of CHB-specific HCC risk scores

CHB specific HCC risk scores are summarized in Table 2. Most of them had been developed in Asian CHB patients, resulting from the urgency to have an accurate, precise, simple-to-use HCC risk score to be used in routine clinical activity, particularly in geographical areas where the burden of HBV infection is higher. The majority were developed in Asian patients and were also validated in Caucasians with acceptable performance. Nevertheless, most validation performances were lower than in the training cohort. Accordingly, the validation studies with Caucasian CHB patients showed AUROC values ranging from 0.74 to 0.86 for GAG-HCC, 0.62 to 0.91 for CU-HCC, 0.54 to 0.77 for REACH-B, and 0.85 for RWS-HCC risk scores[41,50-54]. These findings indicate that specific features of the population significantly influence the risk of HCC development. On the other hand, it is well known that the duration of HBV infection and florid viral replication, HBV genotype, exposure to other oncogenic factors (such as aflatoxins), and co-morbidities play a relevant role in HCC development[14]. As a consequence, a universal and highly accurate HCC score is unrealistic. Conversely, a predictive model based on data reflecting the virologic and clinical features of a given geographical area will provide a reliable tool for the same specific population. Nevertheless, such a model will require continuous adjustments reflecting the dynamic variations of the population based on the changing patterns of both HBV epidemiology and cirrhosis prevalence, HBV population aging, the variable impact of antiviral treatment according to its timing during the CHB course, and the variations of all the other co-factors of liver disease. Accordingly, the GAG-HCC, CU-HCC, REACH-B, LSM-HCC, and RWS-HCC scores, all derived from untreated CHB cohorts, as they were developed from patients followed in the 1990s or early 2000s, are not any more of interest because at present most of HBsAg carriers with evidence of CHB are under antiviral therapy. Another vital issue is the prevalence of cirrhosis in the studied cohorts, which may modify and alter the power of other parameters significantly involved in the scoring systems. The best example for this issue is that the REACH-B score, derived from a cohort of purely non-cirrhotic patients, has degraded performance in validation studies involving cirrhotic patients. In general, all the validated risk scores showed high NPV (95% to 100%) in both the original and external validation cohorts, suggesting redundancy of standard surveillance strategy to low-risk groups. The high-risk groups showed a wide range of annual HCC incidence, ranging from 2.3% to 9.2%, in CHB specific risk scores. By contrast, it indicates that we require additional studies to stratify the individual risk and define new surveillance strategies with more sensitive imaging or serologic tools.

In conclusion, risk stratification is attainable by validated HCC risk scores, but the optimal performance is obtained only in populations with similar characteristics to those where the score was developed. Besides, continuous validation of the predictive models is required to adjust them according to the dynamic variation of all factors influencing the individual HCC risk.

HCC RISK SCORES FOR CHC PATIENTS

As compared to CHB, there are a few proposed modeling studies in CHC patients to predict their HCC risk (Table 3), and their major limitation is the lack of external validation cohorts for most. The latter drawback for their use in clinical practice is the heterogeneity of CHC patients. It may be due to different co-factors affecting the disease progression of HCV and different prevalence across the world. Furthermore, the availability of DAAs in clinical practice acted as a watershed in the clinical needs to optimize the management of CHC patients with advanced fibrosis or cirrhosis; the current unmet need is an algorithm to guide the clinician to personalize the surveillance according to the residual HCC risk. The antiviral treatment proved useful to improve the outcome of CHC and reduce the HCC incidence since the introduction of interferon and ribavirin[55]. However, patients with advanced liver disease had a

Table 2 Hepatocellular carcinoma prediction risk scores for chronic hepatitis B patients

Risk scores	Cohort: Patients/ratio of cirrhosis	Study population	Antiviral treatment	Variables	External validation
GAG-HCC (Yuen *et al* [26], 2009)	Training: 820/15%; Validation: -	Asian (Hong Kong)	No	Age; Gender; HBV-DNA; Cirrhosis	Asian, Caucasian
CU-HCC (Wong *et al*[27], 2010)	Training: 1055/38%; Validation: 428/16%	Asian (Hong Kong)	No	Age; Albumin; Bilirubin; HBV-DNA; Radiologic cirrhosis	Asian, Caucasian
REACH-B (Yang *et al* [29], 2011)	Training: 3584/0; Validation: 1505/18%	Asian (Taiwan)	No	Age; Gender; ALT; HBeAg status; HBV-DNA concentration	Asian, Caucasian
REACH-BII(Lee *et al*[30], 2013)	Training: 2227/0; Validation: 1113/0	Asian (Taiwan)	No	Age; Gender; ALT; HBeAg/HBV-DNA/HBsAg/Genotype status	- (Internal only)
mREACH-B (Lee *et al* [31], 2014)	Training: 192/46.9%; Validation: -	Asian (South Korea)	ETV	Gender; ALT; HBeAg status; LSM value	Asian
LSM-HCC (Wong *et al* [33], 2014)	Training: 1035/32%; Validation: 520/31%	Asian (Hong Kong)	No	Age; Albumin; HBV-DNA concentration; LSM value	Asian
RWS-HCC (Poh *et al*[34], 2016)	Training: 583/13.7%; Validation: 3353/NA	Asian (Singapore)	No	Age; Sex; Cirrhosis; AFP	Asian, Caucasian
PAGE-B (Papatheodoridis *et al* [39], 2016)	Training: 1325/20%; Validation: 490/48%	Caucasians (Europe)	ETV/TDF	Age; Gender; Platelet count	Asian, Caucasian
mPAGE-B (Kim *et al*[42], 2018)	Training: 2001/19%; Validation: 1000/20%	Asian (South Korea)	ETV/TDF	Age; Gender; Platelet count; Albumin	Asian
HCC-RESCUE (Sohn *et al* [44], 2017)	Training: 990/39%; Validation: 1071/35%	Asian (South Korea)	ETV	Age; Gender; Cirrhosis	Asian
APA-B (Chen *et al*[45], 2017)	Training: 883/36%; Validation: 442/236%	Asian (Taiwan)	ETV	Age; Platelet; AFP	Asian
HCC-ESC (Fung *et al*[35], 2018)	Training: 723/NA; Validation: -	Asian (Hong Kong)	No	Age; Gender; Cirrhosis; Hypoalbuminemia; HBV-DNA; ALT	-
CAMD (Hsu *et al*[46], 2018)	Training: 23851/26.4%; Validation: 19321/7.1%	Asian (Taiwan)	ETV/TDF	Age; Gender; Diabetes; Cirrhosis	Asian
AGED (Fan *et al*[36], 2019)	Training: 628/0%; Validation: 1663/0%	Asian (China)	No	Age; Gender; HBeAg status; HBV-DNA	- (Internal only)
AASL-HCC (Yu *et al*[47], 2019)	Training: 944/39%; Validation: 298/39%	Asian (South Korea)	ETV/TDF	Age; Gender; Albumin; Cirrhosis	Asian
REAL-B (Yang *et al*[48], 2020)	Training: 5365/20.2%; Validation: 2683/22.1%	Asian (Multiethnicity)	Yes (not specified)	Age; Gender; Alcohol use; Diabetes; Platelet count; Cirrhosis; AFP	- (Internal only)
HCC-ESC$_{AVT}$ (Lim *et al* [49], 2020)	Training: 769/41.5%; Validation: 1061/26.1%	Asian (South Korea)	ETV/TDF	Gender; Cirrhosis; Fibrosis-4 index	- (Internal only)

GAG-HCC: The guide with age, gender, hepatitis B virus DNA, core promoter mutations, and cirrhosis risk score; CU-HCC: Chinese University-hepatocellular carcinoma risk score; REACH-B: The risk estimation for hepatocellular carcinoma in chronic hepatitis B score; RWS: Real-world score; APA-B: Age, platelet, alpha-fetoprotein-B score; CAMD: Cirrhosis, age, male gender, diabetes score; AFP: Alpha-fetoprotein, ALT: Alanine aminotransferase, HBeAg: Hepatitis B e Antigen, HBV: Hepatitis B virus, LSM: Liver stiffness measurement.

significantly lower SVR rate and reduced compliance to treatment. Thus, the availability of scoring systems to identify individuals at higher risk of HCC development among those with advanced liver disease was perceived as a major clinical interest.

The first HCC risk score attempt was derived from the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis cohort in 2009[56]. During a median follow-up of 4.6 years, 48 of 1005 (4.8%) patients developed HCC, with a 5-year HCC incidence comparable in peginterferon-treated or untreated patients (5.4% *vs* 5.0%). The presence of cirrhosis together with older age, Black race, lower platelet count, higher alkaline phosphatase, esophageal varices, and smoking status identified patients at higher risk. A few years later, another study conducted on 11721 HCV-related cirrhotic patients from the Veterans Administration Hepatitis C Virus Clinical Case Registry in the United States investigated the possibility to develop an AFP-based algorithm where biomarkers of disease activity (ALT) and disease stage (platelet count) were used to

Table 3 Hepatocellular carcinoma prediction risk scores for chronic hepatitis C patients

Ref.	Cohort: Patients/ratio of cirrhosis	Study population	Variables	External validation
Lok *et al*[56], 2009	Training: 1050/41%; Validation: -	North America (United States HALT-C cohort)	Age; Race (Black); ALP; Esophageal varices; Ever smoked; Platelet count	-
Masuzaki *et al*[58], 2009	Training: 866/22.6%; Validation: -	Asian (Japan)	LSM	-
Chang *et al*[59], 2012	Training: 871/27.9%; Validation: -	Asian (Taiwan)	Age; Platelet count; AFP; Fibrosis stage	-
El-Serag HB *et al*[57], 2014	Training: 11721/100%; Validation: 52135/0	North America (United States Veterans Administration)	Age; ALT; Platelet; AFP	-
Ganne-Carrié *et al*[60],2016	Training: 720/100%; Validation: 360/100%	Caucasian (France)	Age; Past excessive alcohol intake; Platelet count; GGT; SVR status	-
Shiha *et al*[63], 2020 (GES)	Training: 2372/73.1%; Validation 1: 687/61.5%; Validation 2: 1314/70.6%	Egypt	Age; Gender; Fibrosis stage; Albumin; Alpha-feto protein	Egypt

AFP: Alpha-fetoprotein, ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, LSM: Liver stiffness measurement, SVR: Sustained virologic response.

adjust the predictive accuracy of AFP[57]. At any given AFP value, low numbers of platelets and ALT and older age were associated with increased risk of HCC, and high levels of ALT and normal/high numbers of platelets were associated with low risk for HCC. The advantage of the model was its inclusion of routine laboratory tests and easy to manage parameters.

Two studies from Asia tackled the same issue with different approaches. Masuzaki *et al*[58] investigated the possibility to use LSM determined by FibroScan as a predictor of HCC in 866 HCV-infected patients. The cohort was prospectively followed for a mean period of 3 years after initial LSM determination. The odds ratio of HCC development was correlated with increasing LSM, and a LSM cut-off value of > 15 kPa had a greater association with HCC development. The other study from Taiwan enrolled 871 biopsy-proven CHC patients who achieved sustained response after peginterferon and ribavirin. They integrated the histologic fibrosis status with other parameters (age, AFP, low platelet counts) to define a HCC risk score[59]. Accordingly, low (< 10), intermediate (11-15), and high (> 16) risk groups had 1.37%, 9.14%, and 30.7% chances of HCC development, respectively. The authors proposed their novel risk score for HCC screening in CHC patients achieving SVR.

In 2016, a multicenter French cohort (ANRS CO12 CirVir) study with 1323 CHC-related cirrhosis patients was conducted to develop an individualized score for HCC prediction[60]. An 11-point risk score was established using the five variables independently associated with HCC (age > 50 years, past excessive alcohol intake, low platelet count, gamma-glutamyltransferase (GGT) > upper limit of normal, and absence of SVR). This new risk score was able to stratify the CHC-cirrhosis population into three groups according to HCC risk as low (< 3), intermediate (4-7), and high (> 8) risk. However, this score also lacked external validation.

In 2020, a different approach was used to refine HCC risk among patients with CHC-related cirrhosis from the same French cohort, by applying predictive machine learning approaches (Fine-Gray regression model) rather than traditional multivariate linear regression analysis[61]. The study was interesting in terms of bringing a new breath to risk-stratification models and personalized HCC-surveillance efforts. As expected, the authors showed that factors influencing the HCC risk varied after SVR. Only elevated AST, low platelet count, and shorter prothrombin time was independently associated with HCC risk after SVR, whereas there were six independent predictors (past excessive alcohol intake, genotype 1, elevated AFP, GGT, low platelet count, and albumin levels) before SVR. However, the interactions between the different parameters were quite complex, and eight different groups were identified with varying cancer risks and predictors depending on SVR achievement. The findings were interesting but not yet directly applicable in clinical practice. Nevertheless, the study showed that machine learning algorithms can refine the HCC risk assessment by revealing complex interactions between cancer predictors and eventually prompting more cost-effective tailored surveillance programs development.

An absolute simplified model was derived and proposed from 1088 Japanese CHC patients who achieved SVR after DAA in the same year[62]. They revealed age and AFP as independent predictors of HCC after achieving SVR with DAAs. Using AFP and age only, they developed a scoring system (0-2 points) where the incidence of HCC at 2-years was 0.3% in the 0 points group, 6.27% in the 1-point group, and 18.37% in the 2-points group. This oversimplified approach is captivating; however, external validation in different populations is required, as specific features, such as HCV epidemiology in the geographical area, could significantly influence the findings. The General Evaluation Score (GES) was recently proposed by a study performed in Egypt on 4400 patients, with cirrhosis or advanced fibrosis who achieved a SVR[63]. Age, sex, serum albumin, AFP and, pretreatment fibrosis stage was identified as risk factors for HCC and used to construct the risk score, and categorized CHC patients into three groups. The 2-year cumulative HCC incidence was 1.2%, 3.3%, 7.1% for low-, medium-, and high-risk groups, respectively. The GES score had high predictive ability in internal and external validation cohorts from Egypt with c-statistics values of 0.80 and 0.81. Unfortunately, the findings of this interesting and promising study cannot be generalized because it included only HCV genotype 4-infected patients.

Overall, it appears that in the setting of CHC patients from one side, the proposed scoring systems are lacking adequate external validation, which is mandatory to warrant their use in clinical practice. Furthermore, the high variability of the epidemiology of HCV infection (different genotype distribution worldwide, distinct modalities of HCV spreading in the various geographical area and overtime) is even more complicated than in HBV, necessitating the implementation of a model in a different context. Nevertheless, the evidence that the risk of HCC significantly declines over time in patients who achieved SVR underlines the urgent need for new algorithms to personalize the HCC surveillance and optimize its cost/benefit.

PREDICTION OF HCC RISK FOR PATIENTS WITH CLD OR OTHER RISK FACTORS

HCC prediction risk scores, regardless of underlying liver disease etiology, are summarized in Table 4. Flemming *et al*[64] developed an HCC risk prediction model to estimate the 1-year probability of HCC to assist clinicians with patient counseling by studying a large cohort of patients (n = 34932) with cirrhosis from the United States liver transplantation waiting list database. Thus, the authors did not mean to create a score to modify the surveillance of cirrhotic patients but to provide an individualized approach to HCC counseling based on specific patient characteristics. They identified six baseline variables (age, diabetes, race, etiology of cirrhosis, sex, and severity [ADRESS] of liver dysfunction) independently associated with HCC and the c-indices of the ADRESS-HCC risk model were 0.704 and 0.691 in the derivation and internal validation cohorts, respectively. The major limitation of the study was the selection of patients with advanced liver disease, as they were cirrhotic already on the transplant waitlist. In 2017, the Toronto Hepatocellular carcinoma Risk Index (THRI) was developed to predict 10-year HCC risk, using simple clinical and laboratory parameters (age, gender, etiology, platelet)[65]. The THRI weighed etiologies, including the SVR status of HCV-related cirrhosis, and its performance had been studied in three external validation cohorts from different regions (Netherlands, China, Turkey) with similar accuracy in predicting HCC development[65-67]. All AUROC values ranged from 0.75 to 0.80, using the same cut-off value of 240 to identify the high-risk HCC group.

Diabetes is a risk factor for HCC in patients with CLD. Li *et al*[68] in 2018 approached the issue in the other way round, developing a risk score system to predict the HCC risk in patients with diabetes. They studied a cohort of 31723 Taiwanese patients with type 2 diabetes mellitus, followed-up for 8.3 years, and the final model (scores ranging from -6 to 40 points) included age, gender, smoking status, hemoglobin A1c, glutamic-pyruvic transaminase, cirrhosis, hepatitis B, hepatitis C, anti-diabetic and anti-hyperlipidemic medications, and total/high-density lipoprotein cholesterol ratio. The 3-, 5-, and 10-year AUROC values to predict HCC risk were 0.81, 0.80, and 0.77.

More recently, an ambitious study aimed to develop a global universal HCC risk score to predict the HCC development for patients with chronic hepatitis, published by an international study group. A total of 17374 patients (10578 Asian and 2510 Caucasian treated CHB patients, 3566 CHC; 2489 of whom with cirrhosis and SVR, and 720 patients with non-viral hepatitis) from 11 international prospective observational

Table 4 Hepatocellular carcinoma prediction risk scores regardless of etiology

Risk scores	Cohort: Patients	Study population	Variables	External validation
ADRESS-HCC, (Flemming *et al* [64], 2014)	Training: 17124/100%; Validation:17808/100%	North America (United States)	Age; Diabetes; Race; Etiology of liver disease; Gender; Child-Pugh Score	- (Internal only)
THRI, (Sharma *et al*[65], 2017)	Training: 2079/100%; Validation: 1144/100%	Caucasian (Canada)	Age; Gender; Etiology of liver disease; Platelet count	Asian, Caucasian
TDS, (Li *et al*[68], 2018)	Training: 21149/NA; Validation:10574/NA	Asian (Taiwan)	Age; Gender; Smoking status; HbA1c; Glutamic-pyruvic transaminase; Cirrhosis; Hepatitis B virus; Hepatitis C virus; Anti-diabetic medication; Anti-hyperlipidemic medicaiton; Total/HDL cholesterol ratio	- (Internal only)
aMAP, (Fan *et al* [69], 2020)	Training: 3688/19.3%; Validation cohorts: 13686/11.4%-100%	Multicenter (Asian + Caucasian)	Age; Gender; Albumin-bilirubin score; Platelet count	Asian, Caucasian

THRI: Toronto hepatocellular carcinoma risk index; ADRESS: Age, diabetes, race, etiology of cirrhosis, sex, and severity; HbA1c: Hemoglobin A1c; HDL: High-density lipoprotein.

cohorts or randomized controlled trials were analyzed[69]. This study is unique in terms of having a large validation cohort from several ethnicities and etiologies; however, the majority were still CHB patients. The aMAP score was obtained from a training cohort of 3688 Asian patients and validated in nine cohorts with different etiologies and ethnicities. The score ranges from 0 to 100 and involves age, male, albumin-bilirubin score, and platelet count; the value of 50 was identified as the optimal cut-off to predict HCC, with a sensitivity of 85.7%-100% and 99.3%-100% NPV. The authors proposed their risk score, based on five common parameters, showing high performance regardless of etiology and ethnicity, as a potential new tool to establish a risk score-guided HCC surveillance strategy worldwide.

TUMOR MARKERS AND HCC RISK SCORES

Several serologic biomarkers, other than AFP that have already been discussed and included in some scoring systems, such as osteopontin, alpha-fetoprotein-L3 (AFP-L3), des-gamma-carboxy prothrombin (DCP), also known as the protein induced by vitamin K absence or antagonist II (PIVKAII), glypican-3, alpha-1-fucosidase, midikine, dikkopf-1, Golgi protein-73, squamose cell carcinoma antigen, and fucosylated glycoprotein, have been investigated for their potential role in HCC screening. Ideally, blood-based biomarkers with adequate sensitivity or specificity could enable early detection of HCC, avoiding cumbersome ultrasound-based surveillance. However, at present, none of the biomarkers has been validated in phase III clinical trials and are used in clinical practice, with the exclusion of AFP and PIVKAII, recommended by Japanese HCC guidelines, particularly in Japan[70]. This can be explained by the high heterogeneity of HCC biology, where several pathway alterations are involved in the tumorigenesis process[71]. Therefore, the combination of different biomarkers and the available clinical and laboratory variables has been evaluated to develop predictive scores (Table 5).

The GALAD algorithm combining three biomarkers (AFP, AFP-L3, and DCP) with sex and age showed a remarkable overall performance (AUROC values of 0.95, 92% sensitivity, and 85% specificity) that remained high (AUROC: 0.92, sensitivity 92%, specificity 79%) for early HCC detection[72]. The model was validated in independent cohorts from Japan, Germany, and Hong Kong, with overall sensitivity ranging from 80%-91%, specificity from 81%-90%, and AUROC values from 0.85 to 0.95[73]. Both in the original and validation studies, the etiologies were mixed and dominantly consisted of alcohol-related liver disease and CHC patients. The homogeneity of the studied cohorts as far as the etiology of CLD is concerned is critical as the diagnostic performance of the most widely used standardized HCC biomarkers, namely AFP and PIVKAII is significantly influenced by the etiology and activity of CLD, and their combination provides a better diagnostic accuracy[74]. Interestingly, the GALAD score showed an AUC of 0.96 in the identification of HCC in a German cohort of patients with nonalcoholic steatohepatitis (NASH), with comparable performance in patients

Table 5 Algorithmic approaches using the combination of serologic and clinical parameters for hepatocellular carcinoma risk prediction

Risk scores	Cohort: Patients/ratio of cirrhosis	Study population	Variables	External validation
GALAD score (Johnson *et al*[72], 2014)	HCC case: 670/90%; CLD control: 339/97%	Caucasian (England)	AFP; AFP-L3; DCP	Asian, Caucasian
Doylestown algorithm (Wang *et al*[76], 2016)	Training HCC case: 165/100%; CLD control: 195/100%; Validation 1 HCC case: 432/100%; CLD control: 438/100%; Validation 2 HCC case: 113/100%; CLD control: 586/100%; Validation 3 HCC case: 425/100%; CLD control: 804/100%	North America (United States)	Age; Gender; ALT; ALP; AFP; Fucosylated kininogen	North America (United States)
GALADUS score (Yang *et al*[75], 2019)	Training HCC case: 111/98%; CLD control: 180/85%; Validation HCC case: 233/100%; CLD control: 412/100%	North America (United States)	AFP; AFP-L3; DCP; Ultrasonography	North America (United States)
HES algorithm (Tayob *et al*[78, 79], 2019)	HCC case: 4804/100%; CLD control: 33627/100%	North American (United States Veterans Administration)	Age; Rate of AFP change; ALT; Platelet count; Etiology of cirrhosis	-

AFP: Alpha-fetoprotein; AFP-L3: Alpha-fetoprotein-L3; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; DCP: Des-gamma-carboxy-prothrombin, HCC: Hepatocellular carcinoma; CLD: Chronic liver disease.

with or without cirrhosis. A cut-off value of -0.63 GALAD score identified patients with HCC within Milan Criteria with an AUC of 0.91 (68% sensitivity and 93% specificity). The same threshold had been proposed to identify NASH patients who will have imaging diagnosis 200 d later. The GALAD score performance for HCC detection was also compared with liver US and showed to be superior. The combination of GALAD and US score further improved the performance score in a single-center cohort, achieving an area under the curve of 0.98[75]. Overall, these findings indicate that the GALAD score can detect patients with early-stage HCC and might facilitate surveillance of patients, particularly those with NASH, who are often obese, which limits the sensitivity of detection of liver cancer by US. However, the optimal cut-off value has to be defined to develop a shared and standardized surveillance algorithm. Another risk score, namely the Doylestown algorithm, incorporates two biomarkers (AFP and fucosylated kininogen) with two clinical (age, gender) and two laboratory (ALT and alkaline phosphatase) variables[76]. The Doylestown algorithm had an 89% detection rate for early HCCs with an AUROC value of 0.97 in low-AFP patients. The promising results of the Doylestown algorithm require adequate validation in larger and adequate cohort series.

In 2015, White *et al*[77] published an adjusted AFP-based algorithm for HCC detection in patients with HCV-related cirrhosis. It was the implementation of a previously reported score where age, platelets, ALT values, and interaction terms (AFP and ALT, and AFP and platelets) were used. In the new model, serial AFP measurements were included, showing an improvement in the overall performance. More recently, the Hospital Episode Statistics (HES) algorithm was validated in a cohort, which included 33627 patients with cirrhosis of any etiology who did not develop HCC during follow-up (controls) and 4804 patients with incident HCC (cases)[78]. At 90% specificity, the HES algorithm identified HCC cases with 52.56% sensitivity, compared to 48.13% sensitivity for the AFP assay alone, within 6 mo before diagnosis, which was an absolute improvement of 4.43% ($P < 0.0005$). Overall, the algorithm offers a modest advantage over AFP alone in HCC surveillance. The findings were substantially confirmed in a subsequent study, where the etiology of cirrhosis was added to the model[79].

POTENTIAL MOLECULAR CANDIDATES FOR INTEGRATION TO HCC RISK SCORES

Several lines of research are aiming to identify new biomarkers for detection of HCC at a very early stage. CancerSEEK is a recently proposed platform assessing eight circulating proteins (CA125, CEA, CA19-9, prolactin, hepatocyte growth factor, osteopontin, myeloperoxidase, and tissue inhibitor of metalloproteinases 1) and mutations in cell-free DNA[80]. By a machine-learning approach, an algorithm was

developed with an overall sensitivity of 70% and a specificity of 99% in detecting eight cancers, including HCC. A major limitation is that the study enrolled known cancers, whereas the aim would be to identify HCC in asymptomatic patients. Furthermore, using cancer gene panels in cell-free DNA could give rise to a high number of false-positive in healthy individuals[81]. A large number of other biomarkers, such as circulating tumor cells, microRNAs, tumor cell-free DNAs, tumor-derived/associated extracellular vesicles, metabolites, and proteins, are under investigation to obtain a liquid biopsy for HCC[82]. Another interesting approach has been proposed recently by Liu *et al*[83], who showed that a viral exposure signature (VES) obtained by a synthetic viral scan technology of viral antibodies could discriminate HCC with high confidence from at-risk individuals (area under the curve of 0.91 at baseline and 0.98 at diagnosis) or healthy volunteers. The VES was validated in at-risk patients in a prospective HCC cohort; however, larger prospective studies are needed to evaluate its utility in HCC surveillance.

Finally, germ-line single gene polymorphisms have also been analyzed in genome-wide association studies as specific host factors that determine HCC susceptibility for chronic viral hepatitis patients. *EGF, IFNL3, MICA, TLL1, MERTK, K27 of histone H3-H3K27ac* for CHC[84-90], and *KIF1B, STAT4,* and *HLA-DQB1/HLA-DBA2* for CHB patients were the most promising ones[91,92]. It is not very likely that a single germ-line genetic variant may affect HCC development in chronic viral hepatitis, but future attempts may include integrating them into HCC-risk scales. The future efforts will be incorporating molecular profiling into HCC-surveillance algorithms that could also identify targets for potential chemo-preventive interventions.

CONCLUSION

The epidemiology of CLD is rapidly changing, with a progressive reduction of viral hepatitis burden and an increase of non-alcoholic fatty liver diseases (NAFLD). Considering the significant rise in NAFLD-related HCC cases globally, the ability to stratify the risk of HCC is becoming another urgent need. HCC does also occur in patients with non-cirrhotic NAFLD but surveillance is not recommended to this group as incidence rates are lower than 1% a year[93]. The HCC risk stratification tools in patients with NAFLD is not discussed here, as the aim of the present article is to focus on HCC surveillance of patients with chronic viral hepatitis. The incidence of HCC has become highly heterogeneous within patients with chronic viral hepatitis since it differs significantly according to the period of both viral infection, the beginning of treatment, and the rate of cirrhosis. As a consequence, the incidence of HCC differs according to the geographical distribution of risk factors. Thus, the identification of appropriate tools for tailoring the HCC screening decisions according to the different subgroups of patients based on the CLD etiology, relevant clinicopathologic and epidemiologic factors is a growing need in clinical practice. The individually tailored HCC surveillance would imply a cost-effective application of personalized protocols using highly sensitive imaging techniques[94]. However, such an important medical need remains currently unmet and it appears unlikely that it will be fulfilled by a universal generalized score. The HCC-risk stratification models appear helpful to generate reliable and personalized HCC predictive scores only if the scoring system is applied to cohorts whose clinic-pathologic characteristics are highly similar to those of the original discovery cohort for the particular model.

On the other hand, the more widespread use of current HCC biomarkers to increase the specificity for identifying patients with a more significant risk is controversial. All HCC markers so far identified have a highly dis-homogeneous prevalence in patients with different etiology of CLD that imposes their use in multiple markers panels. Furthermore, the serum levels of HCC biomarkers change over time, and the detection of this velocity might improve their specificity. Their analytical cut-off needs to be better standardized in this regard. For instance, the levels of AFP are influenced by liver regeneration prompted by flares of intrahepatic necroinflammation; thus, the range of AFP normality values vary consistently from patients with chronic viral hepatitis and sustained antiviral response to those with metabolic-associated fatty liver disease and ongoing steatohepatitis. Future studies should address these issues using, for instance, algorithms of the combined dynamics of ALT and AFP levels.

In conclusion, according to existing knowledge, there is a strong recommendation to perform surveillance in patients with cirrhosis regardless of their liver disease etiology, origin, age, and sex. The question remains as to whether the time intervals of US screening can be safely reduced in lower risk cirrhotic patients who recovered from

chronic viral hepatitis and maintain normal liver function tests after sustained response to antiviral therapy. The issue of HCC surveillance is much more complicated in patients without cirrhosis. An ideal risk score system should define optimal cut-off values to discriminate high-risk HCCs with high annual HCC incidence (> 3%-5%) and high PPV and low-risk HCCs with high NPV (> 99%). Most of the existing risk scores for CHB reached or were close to this performance, but they did not target the non-cirrhotic patients specifically and were highly dis-homogeneous for the cirrhosis rate. For HCC-risk scores specific for CHC patients without cirrhosis, there is a lack of validation in independent cohorts and proposed scores are not yet representative of CHC patients with complete SVR in the current era of DAAs. Currently proposed HCC-risk scores are not yet standardized to be incorporated into sustainable HCC-surveillance decision algorithms, and more efforts should be made to personalize HCC surveillance in CHB patients without cirrhosis and CHC patients with F3 fibrosis, at least in the near future. Patients with cirrhosis have to undergo HCC-surveillance regardless of liver disease etiology and prospective, large-scale multinational study with stratification on the basis of underlying CLD etiology, fibrosis status, ethnicity (including Africans and other parts of the world) are required. The potential of such a study must include a dynamic calculation of HCC-risk scores every 6 mo. Individual molecular profiling will provide a crucial integration of HCC-surveillance decision algorithms and help identify high-risk target populations in the future, but they are currently not widely available.

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