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AGA Clinical Practice Update on Risk Stratification and Emerging Surveillance Strategies for Hepatocellular Carcinoma: Expert Review

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Abstract

Description: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death in patients with cirrhosis. While advancements in surgical, locoregional, and systemic therapies have improved outcomes for patients with early-stage HCC, most cases are diagnosed at later stages due to both the limitations of currently recommended surveillance modalities and their underuse, with fewer than one in four patients with cirrhosis receiving surveillance for this tumor. Current guidelines recommend biannual surveillance with ultrasound and alpha-fetoprotein (AFP), but this strategy has suboptimal sensitivity, and alternative imaging techniques (e.g., CT and MRI) have their own risks and challenges with implementation. HCC surveillance has established benefits in certain at-risk populations, including patients with cirrhosis (of any etiology) and selected patients with chronic hepatitis B. The burden of HCC is rising most rapidly among patients with non-viral liver diseases including metabolic-dysfunction associated steatotic liver disease (MASLD) and alcohol related liver disease (ALD), among whom the annual incidence rate of HCC is significantly lower than was previously observed in patients with viral hepatitis. This underscores the need for better biomarker and risk stratification tools to detect HCC earlier and improve surveillance efficiency, though integrating them into routine clinical practice presents a significant challenge. This AGA Clinical Practice Update aims to provide best practice advice on emerging strategies for HCC risk stratification and surveillance.

Methods: This expert review was commissioned and approved by the American Gastroenterological Association (AGA) Institute Clinical Practice Updates Committee (CPUC) and the AGA Governing Board to provide timely guidance on this topic of high clinical

importance to the AGA membership and underwent internal peer review by the CPUC and external review procedures through the standard review process for *Gastroenterology*. These Best Practice Advice (BPA) statements were drawn from a review of the published literature and from expert opinion. Because a systematic review was not performed, these BPA statements do not carry formal ratings of the quality of available evidence or the strength of the presented advice.

Keywords

liver cancer; screening; surveillance; biomarkers; risk scores; prediction models

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide and a major cause of mortality among patients with cirrhosis. Historically associated with a poor prognosis, survival rates have improved due to recent advancements in surgical, locoregional and systemic therapies. As curative treatments are available for those diagnosed at an early stage, early detection is crucial for improving HCC survival.

Despite this, only 30–40% of HCC cases are diagnosed at an early stage, largely due to limitations and underutilization of HCC surveillance. Societal guidelines recommend semiannual surveillance with ultrasound and alpha-fetoprotein (AFP) for all patients at high risk for HCC; however, this strategy has suboptimal sensitivity in real-world practice. Uptake of HCC surveillance also remains far lower than for other cancers, with fewer than one in four patients with cirrhosis receiving consistent surveillance. At the same time, the epidemiology of cirrhosis and HCC in the U.S. is shifting from predominantly viral hepatitis C (HCV)-related disease toward non-viral liver diseases, particularly MASLD and alcohol-related liver disease.¹ Although these non-viral etiologies have lower annual HCC incidence rates, they represent rapidly growing populations, which increases the number needed to screen (NNS) and further complicates effective surveillance efforts.

Given these challenges, there is a critical need for improved biomarkers and more precise risk stratification tools to improve the efficiency of HCC early detection. Several promising blood- and imaging-based biomarkers are in various stages of clinical validation; however, integrating these tools into routine clinical practice remains a key challenge.

This review provides best practice guidance on risk stratification and surveillance strategies for HCC. We have developed Best Practice Advice statements developed to address 8 key clinical issues.

Best Practice Advice 1: The best strategy for reducing HCC morbidity and mortality is to prevent cirrhosis. These strategies include vaccination and treatment of viral hepatitis (e.g., HCV and HBV), recognizing and treating

alcohol use disorder, managing metabolic syndrome, and addressing liver diseases at early stages.

Early identification and treatment of chronic liver disease is essential for reducing HCC risk. Viral hepatitis, particularly HBV and HCV, remains a leading cause of cirrhosis and HCC worldwide. The lifetime HCC risk for individuals with HBV is estimated to be 10–25%.² HBV-related HCC is relatively uncommon in the U.S., owing to the success of universal vaccination programs³ and effective antiviral therapies. Early identification and treatment of chronic HBV infection are crucial, as nucleos(t)ide analogs (e.g., tenofovir and entecavir) suppress viral replication, reduce liver inflammation, and prevent progression to cirrhosis. Patients should also be screened for coinfection with other viruses (HCV, Hepatitis D virus, HIV) which significantly increases HCC risk compared to HBV mono-infection.^{4, 5}

For decades, HCV has been the predominant etiology of HCC in the U.S. Direct-acting antivirals (DAAs) are effective, well-tolerated oral medications that have revolutionized the management of HCV. Achieving HCV cure not only halts further liver disease progression but can also reverse some of the damage caused by cirrhosis, lowering HCC risk.⁶ Expanding access to HCV testing and treatment, particularly in high-risk populations is essential to reducing the overall burden of HCC.⁷

MASLD, previously known as non-alcoholic fatty liver disease (NAFLD), is highly prevalent in the U.S. and, alarmingly, the most rapidly increasing etiology of HCC.⁸ It is closely linked to metabolic syndrome, obesity, and type 2 diabetes (all established, independent risk factors for HCC⁹). Lifestyle modifications, weight loss, a balanced diet, and regular exercise, provide the foundation for preventing and managing MASLD. New therapies such as resmetirom, an oral, liver-directed thyroid hormone receptor beta-agonist, and glucagon-like peptide 1 receptor agonists (and possibly the many other promising drugs in the MASLD pipeline with various mechanisms of action¹⁰) may reduce HCC risk by reducing fibrosis associated with MASH, but further studies with long-term follow-up are needed to confirm this effect.

ALD is emerging as an increasing cause of HCC.¹¹ Chronic heavy alcohol consumption induces liver inflammation, steatosis, and fibrosis, leading to cirrhosis and increased HCC risk. Prevention efforts include behavioral interventions, pharmacologic treatments for alcohol use disorder (e.g., naltrexone), and public health policies like alcohol taxes and awareness campaigns.

Best Practice Advice 2: The preferred current surveillance strategy for patients at risk of HCC is semiannual ultrasound (US) and alpha-fetoprotein (AFP) in combination. The benefits of surveillance include a higher

likelihood of detecting early-stage HCC, access to curative therapy, and improved survival.

HCC surveillance should be performed in at-risk individuals, particularly those with cirrhosis of any etiology and selected patients with chronic HBV infection, even in the absence of cirrhosis (Table 1).¹² Surveillance for patients with Child-Turcotte-Pugh (CTP) A or B cirrhosis is beneficial. In contrast, patients with CTP C cirrhosis who are not liver transplant candidates derive little benefit due to competing mortality risks. However, for patients with CTP C cirrhosis on transplant waitlists, surveillance remains important to identify early-stage tumors (which may increase transplant priority) and those with larger tumors that may preclude liver transplantation. Surveillance is not advised for patients with a life expectancy under 1–2 years due to other comorbidities that cannot be remedied by liver transplantation or HCC therapies.

The strongest evidence supporting HCC surveillance comes from a randomized trial in patients with chronic HBV infection, which showed that surveillance reduced HCC mortality (hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.41–0.98).¹³ While no similar trials exist for patients with cirrhosis, meta-analyses of observational studies suggest surveillance improves early detection, access to curative treatment, and survival.^{14, 15} While these studies have several potential limitations, the benefits of surveillance remained significant in studies that statistically adjusted for these biases.

Abdominal ultrasound (US) has been the cornerstone of surveillance, though it is limited by operator dependence and worse performance in patients with obesity, severe steatosis, or hepatic decompensation.¹⁶ The addition of AFP provides an incremental benefit in sensitivity (63% for US and AFP compared to 51% for US alone).¹⁷ Although this comes with a small decrease in specificity, the diagnostic odds ratio for the combination is higher than for US alone. Cost-effectiveness analyses also support the use of US and AFP in combination.¹⁸

While CT and MRI may offer higher sensitivity and specificity than ultrasound, they should not be considered for routine surveillance due to concerns related to radiation and contrast exposure, high cost, and low availability due to limited radiology capacity. Decision models suggest MRI-based surveillance may be cost-effective in select populations, but the incremental cost-effectiveness ratio varies widely based on HCC incidence, cirrhosis etiology, and test costs.¹⁹

HCC surveillance should be performed semiannually. This frequency detects tumors at an earlier stage and improves survival compared to annual surveillance.²⁰ Despite this, surveillance remains significantly underutilized (estimated at around 24%) even among patients managed by subspecialists.²¹ Efforts to increase uptake include outreach (e.g., mailed invitations) and “in-reach” (e.g., electronic medical record reminders and provider education). These approaches have been shown to significantly increase participation in surveillance programs.^{22, 23}

Best Practice Advice 3: Among patients without cirrhosis, only a subset of those with chronic HBV should undergo HCC surveillance; surveillance is not advised for those without cirrhosis from other etiologies due to the low annual incidence rate.

Data are evolving regarding the value of surveillance in patients with HCV cirrhosis who have achieved cure (sustained virological response, SVR), patients with cured HCV who do not have cirrhosis, and patients with MASLD who do not have cirrhosis. Recent modeling studies suggest surveillance is cost-effective when annual HCC incidence is approximately 1.0% per year.¹⁸ Based on available data, patients with HCV cirrhosis remain at increased HCC risk for up to 10 years after achieving SVR²⁴, so surveillance should continue indefinitely. In contrast, in post-SVR patients who never had cirrhosis, HCC incidence is significantly lower than the cost-effectiveness threshold for surveillance.

Up to 20% of MASLD-HCC occurs in individuals without cirrhosis.²⁵ However, the overall HCC incidence in this group is low (~0.008 per 100 person-years).²⁶ More accurate tools are needed to risk-stratify patients with cured HCV and MASLD without cirrhosis and avoid unnecessary screening.

Best Practice Advice 4: While the benefits of HCC surveillance are well established, it is important for clinicians to consider the potential physical, psychological, and financial harms associated with the process.

While current surveillance modalities are non-invasive, they are not without risks. For example, false-positive results detected on ultrasound may lead to unnecessary contrast-enhanced imaging or biopsy. While serious complications are rare, physical harms of liver biopsy include bleeding, infection, and, rarely, tumor seeding. In one study of 614 patients enrolled in HCC surveillance, 19.2% (n=118) had abnormal screening results but only 26 developed HCC. Physical harms were observed in 10% of patients enrolled, but fortunately, most were mild or moderate in severity.²⁷

Potential psychological harms are often overlooked.²⁸ Uncertainty from indeterminate lesions or other incidental findings may cause anxiety, stress, and diminished quality of life. Even benign findings may prompt months of further testing and patient worry.

Financial harms are also an important concern. Though ultrasound is relatively low-cost, expenses related to repeat testing and follow-up diagnostic imaging can accumulate. In one trial of HCC screening outreach, 21.8% of patients reported moderate to severe financial burden from surveillance.²⁸ Missed work and travel costs add to the cost burden.

Given these potential harms, clinicians should individualize surveillance decisions. For patients with limited life expectancy and those who are not transplant candidates, surveillance offers little benefit and may only expose them to harm. Shared decision-making is key; patients should understand the limitations of surveillance, including the potential for false-positive and negative results, emotional distress, and financial implications.

Best Practice Advice 5: There are several promising novel blood-based biomarkers, such as GALAD, and radiological techniques currently undergoing clinical validation, but none are yet ready for widespread clinical use.

The limited sensitivity of ultrasound with AFP has prompted exploration of novel biomarkers.¹⁷ These biomarkers can be broadly classified in two main categories: blood-based and radiological.

The main advantage of blood-based biomarkers is their ease of use.²¹ A blood-based biomarker that only incrementally improves sensitivity may still significantly increase early detection rates by increasing surveillance utilization.²⁹

Currently, the most advanced blood-based biomarkers are lectin-reactive fraction of AFP (AFP-L3%) and des-gamma carboxyprothrombin (DCP). When used alone, these protein biomarkers do not outperform AFP, but their sensitivity for detecting small tumors (2–3 cm) increases to 70–80% when used in combination. This has prompted the development of combination strategies such as the GALAD and Hepatocellular Carcinoma Early Detection Screening (HES) score and the which combine multiple blood-based biomarkers with demographic and clinical variables.³⁰

GALAD score incorporates gender, age, AFP, AFP-L3%, and DCP to estimate HCC risk.³¹ While it has shown promise in case-control studies, with a sensitivity from 72% to 82% for early detection,³² GALAD's performance in longitudinal settings has been less robust. In a phase 3 validation study of 1558 patients with cirrhosis, GALAD (using a cutoff of -1.36 , 6 months prior to HCC diagnosis) had a sensitivity and specificity of 65% and 82%. Ongoing clinical trials, including the National Liver Cancer Screening Trial (TRACER) will provide more definitive answer regarding the role of GALAD for HCC surveillance.

The HES algorithm incorporates AFP trend, age, ALT, and platelet count. Its most recent iteration (HES v2.0) combines AFP (both current value and changes over last year) with AFP-L3%, DCP, ALT, platelet count, age, and cirrhosis etiology. In a phase 3 study, HES outperformed other scores (GALAD and ASAP), but its sensitivity was only 47% for detecting early-stage HCC. Further studies are needed to identify the optimal cutoff value for HES v2.0.

There is increasing interest in liquid biopsy for early HCC detection, which involves analyzing various tumor components released into the bloodstream, including cell-free DNA (cfDNA), circulating tumor cells (CTCs), and extracellular vesicles (EVs).³³ To date, most studies using liquid biopsy as a tool for early HCC detection have relied on phase 2 designs and focused on methylation changes in cell-free DNA and small RNA expression in EVs.^{34, 35} While some have sensitivities and specificities exceeding 80% for early detection, they remain in developmental stages, few have received FDA breakthrough device designation, and are not yet recommended for use in clinical practice.³⁶

There is also growing interest in novel radiological approaches for early detection.³⁷ Abbreviated MRI (aMRI), which reduces the number of sequences, exam time, and costs, has shown early promise.³⁸ In a prospective study of 208 patients, annual non-contrast aMRI had increased sensitivity for early-stage HCC compared to semiannual US (71% vs. 45%, respectively).³⁹ Small cohort studies also suggest comparable performance to conventional MRI.⁴⁰ PREventing Liver Cancer Mortality through Imaging with Ultrasound vs. MRI (PREMIUM) is evaluating aMRI in a large U.S based study and will provide definitive data on its utility for HCC surveillance.

Best Practice Advice 6: Multicancer blood-based biomarker detection panels should not be used in the screening or surveillance of patients at risk for HCC.

An early retrospective study found that 62% of localized tumors (e.g., colorectal, breast, lung, ovarian) were detected using targeted error-correction sequencing of cell-free DNA.⁴¹ Panels combining cfDNA mutations with protein biomarkers (e.g., CancerSEEK) have further improved sensitivity for detecting cancers such as ovary, liver, stomach, pancreas, and esophagus.⁴²

In a prospective case-control study of 2,800 participants with various tumor types and stages, whole-genome DNA methylation achieved 98% specificity and 34 – 39% sensitivity, showing promise for cancer detection. Despite these advances, multidetection panels have been studied in general populations with few patients with cirrhosis or HCC. Therefore, they should not be used as standard tools for HCC surveillance.

Best Practice Advice 7: Many HCC risk stratification scores exist for patients with cirrhosis. However, few scores have undergone sufficient validation to support their use in clinical practice.

HCC risk varies among patients with cirrhosis; with annual incidence rates ranging between 1–8%.⁴³ By improving risk stratification tools, surveillance intensity and test modality could be precisely tailored based on a patient's individual risk, enabling resource-intensive efforts to be directed toward those at highest risk and reducing screening intensity and related harms for lower-risk patients.⁴⁴

Current HCC risk stratification models offer some utility but face limitations and have been covered in recent reviews (selected subset in Table 2 published since the review by Singal *et al*).⁴⁵ Most were derived from cohorts of patients with viral etiologies and limited diversity, including few women and racial/ethnic minorities. A recent study conducted in a contemporary cohort of patients with cirrhosis with racial, ethnic, and etiological diversity, developed an HCC risk stratification index addressing some limitations of previous models.⁴⁶

Most existing models combine demographic and clinical factors. This approach has the practical advantage of relying on routinely collected data, resulting in relatively simple

tools that could be implemented in clinical practice. Although these basic models provide a good foundation for predicting HCC risk in cirrhosis, their performance is modest (model discrimination estimates from $\sim 0.70 - 0.80$) precluding widespread clinical use. Other lifestyle, genetic, and metabolic factors are associated with HCC risk.^{47–56}

Compared to simple models, multidimensional models incorporating factors from these domains (i.e., genetic, metabolic, and radiomic markers) may better distinguish low-risk from high-risk patients. In a study of patients in prospective cohorts, a seven-SNP genetic risk score, was associated with HCC risk. Adding this genetic score to a clinical model improved the clinical model's performance (C-indices of 0.786 and 0.783).⁵⁷ Similarly, El-Serag *et al.* derived and internally validated a 9-biomarker signature which predicted HCC risk in cirrhosis.⁵⁸ This biomarker panel resulted in a small but statistically significant improvement in predictive value for future HCC risk compared with a clinical model derived from demographic, clinical, and lifestyle variables.

Although building on simple clinical models by incorporating factors from multiple domains may improve their performance the added costs of additional testing must be weighed against potential incremental improvements in performance when considering the overall value of multidimensional model. Most models have not undergone extensive external validation to support their broad applicability. For a model to be relevant, clinicians should be able to use the predicted risk to guide decisions about surveillance or risk reduction. However, all current HCC risk stratification models produce false positives and false negatives. There is no consensus on acceptable levels of false negatives or false positives, and the widespread use of risk stratification models will remain limited until clinically relevant thresholds and corresponding decisions are agreed upon.

Finally, there is a lack of data on the impact of risk stratification models and decision rules on clinician behavior, patient behavior, and subsequent patient outcomes. A randomized controlled trial to examine the clinical utility of HCC risk stratification in patients with cirrhosis may not be forthcoming. A decision-analytical approach could help bridge this gap by simulating the clinical course of cirrhosis and quantifying how different risk stratification models may reduce HCC mortality through improved surveillance and early detection.

Best Practice Advice 8: Among patients with chronic hepatitis B virus infection without cirrhosis, PAGE-B and REAL-B scores can stratify patients based on their future risk of HCC.

Several risk prediction models have been developed to estimate future HCC risk in patients with HBV, enabling risk-stratified surveillance and individualized clinical decision-making. Examples include: REACH-B (includes age, sex, alanine aminotransferase [ALT], HBeAg, HBV DNA)⁵⁹; PAGE-B (age, sex, platelet)⁶⁰; mPAGE-B (age, sex, platelet, albumin)⁶¹; CU-HCC (age, cirrhosis, albumin, bilirubin, HBV DNA)⁶²; HCC-RESCUE (age, sex, cirrhosis)⁶³; CAMD (cirrhosis, age, sex, and diabetes mellitus)⁶⁴; APA-B (age, platelet, alpha-fetoprotein [AFP])⁶⁵; REAL-B (age, sex, alcohol use, cirrhosis, diabetes mellitus,

platelet, AFP)⁶⁶; AASL-HCC (age, albumin, sex, liver cirrhosis)⁶⁷; and RWS-HCC (age, sex, cirrhosis, AFP)⁶⁸ scores.

In a recent comparative study, most models showed good overall discrimination, with AUC values of 0.75 or greater for 7 of the 10 models (CAMD, APA-B, HCC-RESCUE, CU-HCC, AASL-HCC, RWS-HCC, REAL-B). AUC values for three models that incorporated AFP (APA-B, RWS-HCC, and REAL-B) were the highest (all >0.80). Three models identified low-risk groups with minimal misclassification. None of the patients in the low-risk groups defined by PAGE-B, mPAGE-B, AASL-HCC, or REAL-B developed HCC during the study period. However, REAL-B and AASL-HCC demonstrated better discrimination than PAGE-B in this cohort. Collectively, these data suggest that PAGE-B, AASL-HCC, and REAL-B can be used to risk stratify patients with HBV. Table 3 includes the components and cut-offs for these models, which can be applied to risk stratify patients with HBV. Other factors, including whether the patient is from an endemic region, age, or family history of HCC should also be considered in making surveillance decisions.

In the future, we expect to see new (and iterative) models and approaches for HCC risk stratification in HBV. For example, a recent study incorporated HBV DNA viral load into the PAGE-B model, creating the PAGED-B model, which performed well in patients who underwent a phase change from chronic hepatitis B to HBeAg-positive HBV.⁶⁹ Artificial intelligence has emerged as a powerful tool to improve HCC risk prediction. For example, machine learning approach was used to derive the SMART-HCC score, which includes a liver stiffness measurement (LSM) and 8 other parameters including cirrhosis etiology, age, ALT, alkaline phosphatase, creatinine, platelet count, sex, and hypertension.⁷⁰ Although promising, these models will require further external validation before their widespread use can be recommended.

Conclusion

Although several novel biomarkers have shown potential in phase 2 and phase 3 validation studies, ultrasound combined with AFP remains the recommended HCC surveillance strategy in guidelines. Ongoing phase 4 and 5 biomarker clinical utility trials, such as TRACER and PREMIUM, will provide data to guide the integration of novel biomarkers into clinical practice. To optimize surveillance effectiveness and minimize harms, there is an unmet need for improved risk stratification –both to identify high-risk individuals more accurately as well as lower-risk individuals who may be monitored or surveilled with less intensity. This collaborative process will enable earlier adoption of precision screening strategies in clinical practice, ultimately improving HCC early detection and outcomes.

Conflicts of Interest:

Dr. Rich has served as consultant or on advisory boards for Genentech, Eisai, Exelixis and AstraZeneca.

Dr. Marrero is a consultant for Glycotest. He is also a member of the data safety monitoring board for 2 studies sponsored by AstraZeneca.

Dr. Villanueva has received consulting fees from FirstWorld, Pioneering Medicine and Genentech; advisory board fees from BMS, Roche, Astra Zeneca, Eisai, and NGM Pharmaceuticals; and research support from Eisai. He has stock options from Espervita and Atzeye. He is listed as an inventor on a patent related to early detection of HCC.

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The other authors have no relevant conflicts of interest.

Abbreviations:

AASLD	American Association for the Study of Liver Diseases
AFP	alpha-fetoprotein
AGA	American Gastroenterological Association
BPA	best practice alert
HCC	hepatocellular carcinoma
HBV	hepatitis B virus
HCV	hepatitis C virus

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Best Practice Advice Statements

Best Practice Advice 1:

The best strategy for reducing HCC morbidity and mortality is to prevent cirrhosis. These strategies include vaccination and treatment of viral hepatitis (e.g., Hepatitis C virus [HCV] and Hepatitis B virus [HBV]), recognizing and treating alcohol use disorder, managing metabolic syndrome, and addressing liver diseases at early stages.

Best Practice Advice 2:

The preferred current surveillance strategy for patients at risk of HCC is ultrasound (US) and alpha-fetoprotein (AFP) in combination. The benefits of surveillance include a higher likelihood of detecting early-stage HCC, access to curative therapy, and improved survival.

Best Practice Advice 3:

Among patients without cirrhosis, only a subset of those with chronic HBV should undergo HCC surveillance; surveillance is not advised for those without cirrhosis from other etiologies due to the low annual incidence rate.

Best Practice Advice 4:

While the benefits of HCC surveillance are well established, it is important for clinicians to consider the potential physical, psychological, and financial harms associated with the process.

Best Practice Advice 5:

Several novel blood-based biomarkers, such as GALAD, and radiological biomarkers are undergoing clinical validation. Some are already commercially available, but evidence is insufficient to support their use in routine HCC surveillance. These assays should not replace guideline-recommended tests, though their accessibility and potential cost-effectiveness may support broader use once sufficiently validated.

Best Practice Advice 6:

Multicancer blood-based biomarker detection panels should not be used in the screening or surveillance of patients at risk for HCC.

Best Practice Advice 7:

Many HCC risk stratification scores exist for patients with cirrhosis. However, few scores have undergone sufficient validation to support their use in clinical practice.

Best Practice Advice 8:

Among patients with chronic HBV infection without cirrhosis, PAGE-B and REAL-B scores can stratify patients based on their future risk of HCC.

Table 1.

At-risk populations for HCC in whom surveillance is recommended

	Patient Population	Annual Incidence
Sufficient risk; surveillance recommended	Child Pugh class A or B cirrhosis, any etiology - Hepatitis C (viremic and post-SVR) - Hepatitis B - Alcohol-associated liver disease - Metabolic-associated steatotic liver disease - Other etiologies (including primary biliary cholangitis, autoimmune liver disease, etc).	Varies, >1.0%
	Child Pugh class C cirrhosis, if transplant candidate*	Varies, >1.0%
	Chronic hepatitis B without cirrhosis - Men aged >40 years from endemic countries - Women aged >50 years from endemic countries - Patients from Africa at an earlier age - Family history of HCC - PAGE-B score ≥ 10	>0.2%
Insufficient risk to recommend routine surveillance in absence of new biomarkers and/or better risk stratification	Patients with stage 3 fibrosis or less including those with metabolic-associated liver disease and hepatitis C	<0.2%

Adapted from Singal et al. Hepatology 2023; AASLD Practice Guidance on prevention, diagnosis and treatment of hepatocellular carcinoma.

Table 2.

Select HCC risk stratification models in patients with cirrhosis published since recent reviews

Reference	Study design	Etiology	Cirrhosis	Variables	Output	HCC risk	Group with zero HCC risk	External validation
Johnson, Br J Cancer, 2022	Retrospective cohort	55% HCV (50% SVR at the end of follow up), 24% HBV, 21% other etiologies	25% cirrhosis	aMAP score, based on age, gender, platelet count and the ALBI score	C-index=0.78 (95% CI:0.76–0.80) overall.	Incidence rate was 0.98, 7.05 and 29.1 events per 1000-person years for individuals in the low, moderate and high risk aMAP groups, respectively	No	Yes
Ioannou, J Hep 2019	Retrospective cohort	Alcohol-related or MASLD-related cirrhosis	100% cirrhosis	age, gender, diabetes, body mass index, platelet count, serum albumin and aspartate aminotransferase to valanine aminotransferase ratio	Area under the receiver operating characteristic curve 0.75 for MASLD-cirrhosis and 0.76 for ALD-cirrhosis	3 groups with progressively higher annual HCC incidence: high risk >3%, medium risk 1–3%, low risk <1%	No	No
Nahon, J Hep 2023	Retrospective cohort	Alcohol-related and/or HCV-cured cirrhosis	100% cirrhosis	PNPLA3, TM6SF2, HSD17B13, APOE, MBOAT7, WNT3A-WNT9A rs708113 with and without clinical factors (age, sex, diabetes, platelet count, GGT, albumin)	C-Index of clinical model 0.769 for 5-year HCC risk. Addition of GRS increased to 0.786	3 groups with progressively increased 5-year HCC incidence (Group 1 [n = 627, 5.4%], Group 2 [n = 276, 10.7%], and Group 3 [n = 242, 15.3%])	No	
Kanwal, Clin Gastroenterol Hepatol 2023	Prospective cohort	Multi-etiology	100% cirrhosis	age, sex, smoking, alcohol use, body mass index, etiology, α -fetoprotein, albumin, alanine aminotransferase, and platelet levels	AUROC 0.77 (95% CI, 0.71–0.83) at 2 years	3-year HCC risk increased per decile, lowest decile 0.4% to highest decile at 18.7%	No	Yes
El-Serag, Gut 2024	Prospective cohort	Multi-etiology	100% cirrhosis	Model based on clinical factors (Kanwal CGH 2023) with a 9-marker panel	AUROC 0.78 (95% CI, 0.77–0.78) at 1 year and 0.748 (95% CI, 0.74–0.75)	NA	NA	No

Table 3.

Externally validated risk stratification models for patients with chronic HBV without cirrhosis

Model	Components	Risk groups and cutoffs
PAGE-B	Age, sex, platelet count	Low risk: <10 Intermediate risk: 10–17. High risk: >17
REAL-B	Age Male Alcohol use Cirrhosis Diabetes Platelet AFP	Low risk: <4 Intermediate risk: 4–7 High risk: 8–13
AASL-HCC	Age Male Albumin Cirrhosis	Low risk: ≤ 5 Intermediate risk: 6–19. High risk: