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Hepatocellular Carcinoma (HCC) Surveillance Beyond the Guidelines:
Surveillance in Non-Cirrhotic Viral Hepatitis and Metabolic Dysfunction-Associated Steatohepatitis, and the Role of HCC Biomarkers

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Introduction

Hepatocellular carcinoma (HCC) remains a leading cause of morbidity and mortality in the United States (US) and worldwide.[1,2] In 2023, the American Cancer Society estimated that over 40,000 new individuals were diagnosed with liver cancer, and nearly 30,000 people died from it.[3] While cirrhosis is the primary risk factor for HCC development, it can also develop in patients with chronic liver disease without cirrhosis, particularly those with chronic hepatitis B (CHB). There is also increasing concern about noncirrhotic HCC (NCHCC) in patients with metabolic dysfunction-associated steatotic liver disease/metabolic dysfunction-associated steatohepatitis (MASLD/MASH).[4] HCC surveillance leads to diagnosing tumors at earlier stages, which translates into more options for potentially curative treatments and improved overall survival.[5–8] However, effective implementation of HCC surveillance remains a challenge. Additionally, there remains confusion and conflicting approaches to HCC surveillance in certain high-risk groups of individuals with non-cirrhotic chronic liver disease. In this review, we examine the existing literature and provide consensus expert guidance on practical approaches to implementing HCC surveillance in non-cirrhotic individuals with CHB, chronic hepatitis C (CHC), and MASLD/MASH.

The recently updated practice guidance from the American Association for the Study of Liver Diseases (AASLD) recommends HCC surveillance for individuals with cirrhosis of any etiology, except for those with Child-Pugh-Turcotte (CPT) class C cirrhosis who are ineligible for liver transplantation or those with life-limiting conditions or co-morbidities that cannot be improved with liver transplantation or targeted therapies.[2] The guidance also recommends HCC surveillance in non-cirrhotic chronic hepatitis B (CHB) patients who meet the following criteria: men over 40 years and women over 50 years from regions with high CHB endemicity (i.e., regions with an HBsAg seroprevalence > 8%),[9] individuals from Africa in their third decade of life, those with a family history of HCC, and people with a PAGE-B score > 10.[10] However, little guidance is provided regarding individuals with non-cirrhotic CHB outside of the aforementioned criteria. The AASLD guidelines specifically recommend against routine HCC surveillance for individuals with non-cirrhotic CHC or MASH with F3 fibrosis. However, the European Association for the Study of the Liver (EASL) guidelines recommend surveillance for HCV patients with F3 and F4 fibrosis, including after a sustained virologic response (SVR).[11] Individuals in these categories, for whom AASLD guidelines do not recommend HCC surveillance, can still develop HCC. Additionally, significant heterogeneity exists in real-world surveillance practices. In the following sections, we will address each of these challenging scenarios.

Surveillance for HCC among patients at risk remains suboptimal. A recent meta-analysis of 29 studies involving 118,799 patients with cirrhosis reported a pooled estimate of 24.0% for HCC surveillance utilization.[12] Another recent analysis in a cohort of over 2,000 cirrhosis patients found that the proportion of time covered by surveillance was 24.9%, with only 16% of patients having semi-annual surveillance in the year prior to HCC diagnosis.[13] Low utilization of HCC surveillance in patients with cirrhosis, coupled with data from the National Cancer Institute's Surveillance Epidemiology and End Results database showing overall five-year survival in patients with HCC less

than 30% highlights an urgent need for improvement in surveillance. The reasons for low HCC surveillance utilization are complex and multifactorial, reflecting patient, provider, and system-level factors.[14–16] While HCC surveillance is alarmingly underutilized, equally concerning are disparities observed in effective surveillance. These disparities are particularly notable among ethnic minority, low socioeconomic, and safety-net populations, who face disproportionate impacts of HCC and increased HCC mortality rates.[17–19] HCC surveillance is lower in these groups, contributing to worse outcomes.[20–25]

Current AASLD guidelines recommend HCC surveillance using abdominal ultrasound with alpha-fetoprotein (AFP) at six-month intervals.[2] However, effective implementation of HCC surveillance using these modalities remains suboptimal, with many studies reporting that less than a third of high-risk patients with cirrhosis receiving timely surveillance.[12] Emerging data on the role of serologic biomarkers for HCC surveillance are promising and may help narrow the gap in patients receiving appropriate surveillance given that blood-based testing can be completed together with routine laboratory monitoring and preventative care testing. However, for advances in serological biomarkers for HCC to potentially replace currently recommended modalities for surveillance, one must keep in mind the World Health Organization's Wilson and Jungner's principles, namely that these principles outline 10 key criteria for an ideal screening test (Table 1).[26] A review of current HCC biomarkers and a practical approach to their implementation in clinical practice will be discussed below.

Table 1. WHO Wilson and Junger's Principles of an Ideal Screening Test[26]

- Condition being screened for is an important health problem.
- Accepted treatments should be available for individuals diagnosed with the condition.
- Facilities for diagnosis and treatment should be readily available.
- Condition is in a recognizable early or latent phase during which to implement screening should be easily identifiable.
- Test should be suitable and perform accurately.
- Test should be acceptable to the population.
- The natural history of the condition, including disease progression from early/latent phase to disease state, should be adequately understood.
- There should be agreed policy or practice guidance on who should be treated.
- The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
- Case-finding should be a continuous process and not a "once and for all" project (i.e., surveillance)

HCC and Hepatitis B and C Virus Infections

Globally, 292 million people are infected with CHB, with 2.2 million cases reported in the US.[27–30] CHC affects 50 million people worldwide,[31] with an estimated 2.7 to 3.9 million people in the US.[32] CHB and CHC account for an estimated 75% to 80% and 10% to 20%, respectively, of cases of virus-associated HCC.[33] In general, chronic hepatitis B virus (HBV) infection and chronic hepatitis C virus (HCV) infection lead to repeated cycles of cellular inflammation-necrosis-fibrosis, and potential clonal expansion of dysregulated hepatocytes, that culminate in malignancy.[34–36] According to an authoritative review, 70%–90% of patients with CHB-associated HCC have cirrhosis.[37,38] A study within the US Veterans Administration system found that 9.5% of patients with HBV-associated HCC did not have cirrhosis, with African-Americans and Asians at higher risk than other groups.[39] The role of demographic factors in determining the frequency of HCC in non-cirrhotic CHB patients was underscored in a study conducted in China that highlighted the association of HBV with NCHCC.[40]

Extensive research is ongoing into the mechanisms underlying neoplastic transformation caused by the integration of viral DNA into human chromosomes, with resultant genetic dysregulation that can culminate in HCC.[41] The hepatitis B x protein has also been implicated in predisposing to HCC through various proposed pathways.[42] These features of CHB infection are biologically distinct from HCV, and, while certainly contribute to HCC risk in cirrhosis, are also presumed to largely explain the higher risk of NCHCC in CHB-infected patients. Furthermore, they contribute to differences in guidelines for HCC screening and surveillance between these two viral infections.

Several factors that increase the risk of HCC development in HBV and HCV-infected patients have been identified. A classic study conducted by Chen and colleagues in Taiwan followed over 3,600 HBsAg-positive individuals for a mean of 13 years. The study concluded that elevated serum HBV DNA levels (> or =10,000 copies/mL) were a strong predictor of HCC risk, independent of HBeAg status, serum ALT levels, and liver cirrhosis.[43] Men and individuals with a family history of first-degree relatives with HBV-associated HCC are at higher risk of HBV-associated HCC. In a controversial area, several studies and meta-analyses suggest that antiviral therapy with tenofovir for HBV reduces the risk of HCC compared to entecavir treatment, but a similar number of studies report no difference when demographic and other factors are incorporated into the analyses considered. However, no study has suggested the opposite, i.e., that entecavir is associated with lower risk.[44] Notably, coinfection with HBV and hepatitis D virus infection (HDV) increases the risk of HCC three- to six-fold compared with HBV mono-infection.[45]

Based on the considerations discussed above, the AASLD Practice Guidance on HCC recommends that the following CHB patient populations undergo regular surveillance: (1) All persons with cirrhosis; (2) Men from endemic countries older than 40 years of age; (3) Women from endemic countries older than 50 years of age; (4) Africans at an earlier age (can be initiated as early as the third decade of life); (5) Persons with a first-degree family member with a history of HCC; and (6) Persons with a PAGE-B score greater than 10 (requires use of the PAGE-B calculator).[2] Although patients under 40 years old do not meet the threshold warranting surveillance of an annual HCC incidence over 0.2%, many clinicians have encountered such patients. Consequently, some clinicians prefer to discuss surveillance with all their adult CHB patients, regardless of age, and make individualized decisions.[47]

For chronic HCV infection, male sex, advanced age (> 60 years), genotype 3 infection, viral coinfection (HBV, HIV), F3 fibrosis, steatosis (especially in genotype 3 patients), metabolic syndrome, elevated ALT at the end of treatment, and history of alcohol and/or tobacco abuse have all been reported to potentially contribute to HCC risk.[34,48] One study found that HCV-infected Black/African American patients develop HCC at earlier stages of liver disease compared to other racial groups; further data are needed to elucidate the contributory biological mechanisms.[49]

In patients infected with HBV or HCV, antiviral therapy is imperative. However, it is important to note that these treatments will reduce but not completely eliminate the risk of developing HCC.[50–52] This is likely due to risk factors not influenced by treatment, including decades of cellular damage that occurred prior to treatment.[50] The goal of HCV treatment is to achieve SVR, which is defined as undetectable HCV RNA at 12 weeks after the end of treatment. This is now considered tantamount to virologic “cure,” making HCV treatment very different from HBV treatment, which aims for chronic suppression rather than cure. Data indicate that achieving SVR in HCV-infected patients is associated with a reduced risk of HCC development, among other liver-related outcomes.[53,54]

Per the AASLD guidance, HCC surveillance is recommended for patients with cirrhosis of any etiology, including HCV, even after SVR is achieved with antiviral therapy.[2] However, there is no recommendation for surveillance in patients with F3 fibrosis. In contrast, EASL recommends HCC surveillance for patients with HCV and F3 fibrosis, citing the risk of these patients being understaged and further noting that “the transition from advanced fibrosis and cirrhosis cannot be accurately defined.” EASL further recommends that surveillance should continue after SVR has been attained.[11,55]

Our literature search on HCC surveillance in CHC F3 patients post-SVR provided mixed results (Table 2), but, as one study concluded, "more cost-effective models that could better identify at-risk individuals, especially among patients with F3 fibrosis are warranted."[56] It is also important to point out that, following the approval of direct-acting antiviral (DAA) treatment for HCV infection, one controversial study suggested a time-related association between DAA treatment and HCC recurrence.[57] However, a recent meta-analysis demonstrated no such association. The study did demonstrate that patients treated with DAAs remain at risk of developing HCC and that DAAs do not necessarily improve survival rates when administered in patients already treated for HCC;[58–61] however, recent studies focusing on patients treated for HCC with curative intent demonstrated improved survival if treated with antiviral therapy for HBV or HCV infection.[62]

Table 2. Highlights of a Literature Search on HCC Surveillance in CHC Patients Post-SVR with F3[56,63–67]

Study Design	Results
A Markov model evaluated the cost-effectiveness of biannual or annual HCC ultrasound surveillance vs. no surveillance in 50-year-old patients with advanced fibrosis after achieving SVR with anti-HCV therapy.[63]	HCC surveillance after achieving SVR to HCV treatment was found to be cost-effective for patients with cirrhosis. However, it was not cost-effective for F3 patients.
A study prospectively followed 491 patients with HCV and F3 fibrosis or higher after achieving SVR with interferon-free therapies. Clinical-biological parameters and LSM were performed before starting treatment and at SVR, and HCC surveillance was conducted. Two predictive models based on LSM (Model-A) or FIB-4 score (Model-B) were proposed.[64]	During a median follow-up of 49.8 months, 29 patients developed HCC (incidence 1.6 per 100 person-years). The study suggested that incorporating multiple factors, including age, serum albumin, FIB-4 score, and transient elastography measurements, could better risk stratify and identify patients with a low risk of HCC (<1%/year). For these patients, HCC surveillance could be discontinued.
A total of 8,796 patients with advanced fibrosis (F3/F4) who developed incident post-SVR HCC between March 2015 and October 2021 were identified from 30 sites in Europe, North America, South America, the Middle East, South Asia, East Asia, and Southeast Asia.[65]	After adjusting for geographic region, HCC surveillance was associated with early-stage detection (Barcelona Clinic Liver Cancer stage 0/A, 71.0% vs. 21.3%; P < .0001) and lower mortality rates (adjusted hazard ratio, 0.29; 95% CI, 0.18–0.46). The authors concluded that the clinical characteristics, including early-stage detection and prognosis of post-SVR HCC, differed significantly across geographic regions. Surveillance utilization appears to be a high-yield intervention target to improve prognosis among patients with post-SVR HCC globally.
31 studies, from January 1, 2014 to December 31, 2020, assessing HCC incidence or outcomes by cirrhosis status in adults with HCV who achieved SVR after DAAs were identified and analyzed.[66]	In patients without cirrhosis, including F3 fibrosis, HCC incidence was lower than the thresholds associated with cost-effective HCC screening. In patients with F3 fibrosis, the lack of between-study heterogeneity provides strong evidence that HCC screening may not be warranted.
A multicenter, observational, and retrospective study was conducted to describe the post-SVR follow-up in clinical practice for patients with F3 fibrosis (n=219) and determine the predictive factors for the development of HCC.[67]	The analysis adjusted for sex, age, presence of diabetes and alcohol consumption and found that a post-SVR FIB-4 ≥ 3.25 was associated with a 12-fold increase in HCC risk (p < 0.001).
A systematic review and meta-analysis identified 44 studies (107,548 person-years of follow-up) assessing the incidence of HCC after HCV cure among patients with F3 fibrosis or cirrhosis.[56]	The incidence of HCC was 0.5 per 100 person-years (95% CI, 0.3–0.7) among patients with F3 fibrosis, which is below the recommended threshold for cost-effective screening.

DAAs, direct-acting antivirals; F3, stage 3 fibrosis; F4, stage 4 fibrosis; FIB-4, Fibrosis 4 Index; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LSM, liver stiffness measurement; SVR, sustained virologic response.

HCC and Steatotic Liver Disease

In recent years, MASLD/MASH has emerged as the most significant risk factor for HCC due to its large disease burden. Over the last decade, SLD has been rapidly growing as one of the leading etiologies for chronic liver disease progressing to HCC.[68,69] The evolution to the present disease state of MASLD, which is associated with an estimated worldwide prevalence of 25.24%,[70] is mainly linked to the global increase in obesity-related disease burden.[71,72] Data indicates that MASLD accounts for about 13% of HCC cases. Wong et al. have reported that MASLD (previously referred to as nonalcoholic fatty liver disease [NAFLD]) is the fastest-growing etiology of HCC among adults awaiting liver transplantation in the US.[73] HCC incidence parallels the severity of MASLD, reaching 5.29 per 1000 person-years in MASH patients, and up to 0.5% to 2.6% in patients with MASH-cirrhosis.[74] Interestingly, approximately 20%–50% of MASLD-related HCC develops in non-cirrhotic livers.[4,75–78] Despite these supporting data, the implementation of HCC surveillance in this patient population may be challenging due to the large prevalence of MASLD in the underserved communities, including the Hispanic population that has a higher prevalence of MASLD; technical difficulties in performing ultrasound in individuals with obesity; and the occurrence of NCHCC in MASLD patients.[75]

The mechanisms in MASLD that promote the progression to HCC are multifaceted and still under investigation.[79] Factors such as altered immune cell function and accumulation of free fatty acids in hepatocytes are thought to lead to cell damage and oncogenic transformation.[75,79] Certain risk factors may contribute to the pathophysiological processes. For example, chronic inflammation associated with type 2 diabetes mellitus and obesity is linked to the overproduction of reactive oxygen species, insulin resistance, hepatocyte death, activation of hepatic stellate cells, and release of inflammatory cytokines. This exacerbates the development of MASH and fibrosis, ultimately initiating and expanding HCC.[75] Other data indicate that a high-calorie diet and ethanol act synergistically at multiple levels, potentiating hepatocarcinogenesis.[69,80] MASLD/MASH and associated risk factors for HCC have been extensively studied, and further details are explored in Table 3.

Table 3. MASLD/MASH and Risk Factors for HCC

Risk Factor	Details
Older Age	• MASLD-associated HCC is more prevalent in older individuals due to the increase in metabolic and cardiovascular comorbidities.[81]
Alcohol Consumption	• Alcohol-associated cirrhosis is a known risk factor for HCC; however, as a cofactor with other etiologies, it increases HCC risk as much as five-fold.[82] • Alcohol- and MASLD-related HCC have increased in both incidence and mortality.[83] • Heavy alcohol use (> four drinks/day) is associated with an almost four-fold increased risk among women, but only a 59% increased risk among men.[84] • The risk of HCC with moderate drinking has conflicting evidence; a meta-analysis demonstrated that lower levels of consumption (< three drinks/day) showed no association,[85] but another study showed that moderate drinking appeared to be a risk factor for HCC in patients with MASLD, particularly those with advanced fibrosis.[86]
Diabetes	• A US study (n=271,906 individuals with MASLD) with a mean nine-year follow-up reported that diabetes contributed independently to the risk of HCC and had the strongest association with incident HCC (HR, 2.8). The duration of diabetes was also found to correlate with the development of HCC.[87] • Studies in diverse populations have reported that diabetes is associated with a two- to three-fold increased risk of HCC, with a significantly greater relative risk among men than women.[88] • Another study found that those who had diabetes for 10 years had a two-fold increased HCC risk compared to those with the disease for five years (OR, 2.2; 95% CI, 1.2–4.8).[89]
Dyslipidemia	• *De novo* cholesterol synthesis and uptake of excess cholesterol in the circulation occur in the liver. When cholesterol is elevated, this process can lead to the accumulation of oxidized LDL, causing lipotoxicity and inflammation, which promotes HCC.[90] • The aforementioned US study (n=271,906 individuals with MASLD) with a mean nine-year follow-up reported that dyslipidemia was a metabolic trait that independently contributed to the risk of HCC.[87]
Elevated ALT and Markers of Liver Inflammation	• Elevated ALT and markers of liver inflammation are independently associated with an increased risk of HCC (HR 6.80, 95% CI: 3.00–15.42; $p < 0.001$) in patients with non-cirrhotic MASLD, according to the role of a proliferative environment and inflammation on tumorigenesis[91]
Metabolic Syndrome	• Studies have confirmed that metabolic syndrome components have an additive impact on HCC risk.[86,92] • A 2014 meta-analysis estimated that metabolic syndrome was associated with an 81% increased risk of HCC. [93] • The aforementioned US study (n=271,906 individuals with MASLD) with a mean nine-year follow-up reported that metabolic syndrome was a metabolic trait that independently contributed to the risk of HCC.[87]
Obesity	• Liver damage caused by obesity and chronic liver disease itself may synergistically interact together and further facilitate the progression and/or development of HCC in patients with CLD.[94] • Obesity is the primary driver of MASLD[95], with approximately 50%, 80%, and 43% of patients with MASLD, MASH, and MASH-related cirrhosis, respectively, presenting with obesity.[70] • Meta-analyses in general, mostly Western, populations have shown that obesity increased the risk of HCC (or primary liver cancer) by approximately two times.[96,97] • A Danish study reported that a one-unit increase in BMI z-score at ages 7 or 13 was associated with a 20%–30% increased risk of liver cancer later in life.[98] • Other studies have found that obesity is an independent risk factor for HCC.[87,99] • However, it should be noted that there is limited and conflicting evidence of the association between obesity and HCC, even in cases of MASLD.[94] ◊ Nasereldin et al. assessed the association of HCC risk and obesity based on individuals' underlying metabolic dysfunction (i.e., dyslipidemia, hypertension, and diabetes). They did not find any association between HCC risk and being overweight or obese in participants without any metabolic abnormalities. However, among participants with metabolic dysfunction, being overweight (OR, 1.89; 95% CI, 1.31–2.72) or obese (OR, 1.50; 95% CI, 1.07–2.09) was associated with a higher HCC risk.[100] ◊ Some studies conducted among MASLD patients of Western populations, including those without cirrhosis or fibrosis, found that BMI or obesity was not statistically significantly associated with HCC.[87, 101, 102]

ALT, alanine aminotransferase; BMI, body mass index; CLD, chronic liver disease; HR, hazard ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; OR, odds ratio.

Despite many studies indicating that risk factors linked to MASLD/MASH are also linked to HCC, uncertainties remain. For instance, although obesity is considered the primary cause of MASLD, there are conflicting evidence implicating obesity as an independent risk factor for HCC (as indicated by the data in Table 3). Similarly, while excessive alcohol consumption is clearly linked to HCC, the effects of mild-to-moderate alcohol consumption are uncertain.[103] Currently, no liver-safe limit of alcohol consumption has been firmly established.[104] Reinforcing a healthy lifestyle may help control risk factors and reduce HCC risk. For instance, data indicates that better glycemic control has been shown to decrease the risk of developing HCC.[105] Therefore, the AASLD recommends that "patients with CLD should be counseled to maintain a healthy weight, have a balanced diet, avoid tobacco and alcohol, and achieve adequate control of comorbid conditions including components of the metabolic syndrome. A healthy lifestyle has many benefits and may decrease HCC risk."[2] To effectively implement these interventions, it is crucial to identify MASLD in patients exhibiting these modifiable high-risk features.[106]

A unique factor to consider in the MASLD/MASH patient population is that MASLD-associated HCC is five times more frequent in the precirrhotic phase of the disease compared to other etiologies of CLD.[4] Data indicate the NCHCC prevalence in patients with MASLD/MASH ranges between 38% and 43%.[77,107–112] MASLD-related NCHCC shows lower prevalence in mild steatosis and much higher incidence in patients with grade 3 steatosis.[113] Additional characteristics of NCHCC, when compared to HCC in cirrhotic patients in multiple studies, include older patient age at presentation,[77] larger tumor size at diagnosis,[76,77] poorer prognosis/survival,[76,114] and higher recurrence rates.[77] The serious consequences associated with NCHCC likely reflect the absence of HCC screening programs in this patient population.[75]

Biomarkers for HCC Surveillance and Early Detection

Improving survival in HCC relies on early diagnoses through effective surveillance, which necessitates proficient tests.[115,116] Ultrasound alone lacks the sensitivity to diagnose early-stage HCC,[117] shows significant variation across studies, and is not universally accessible.[118] It also exhibits limited quality in patients who are obese or have nonviral etiologies of liver diseases such as MASLD and Child-Pugh class B cirrhosis.[119–121] Data indicate that approximately one in five ultrasound exams may be of inadequate quality for analysis.[122] AFP is the most widely used biomarker for HCC testing and disease monitoring, but like ultrasound, cannot stand alone for adequate surveillance.[123] AFP levels are not elevated in all cases of HCC, demonstrating suboptimal sensitivity (32%–49%) in detecting early-stage disease.[124–126] Furthermore, AFP levels can be elevated in other conditions such as CHB and HCV.[127]

Despite its limitations for standalone use, accumulating evidence suggests that combining AFP with ultrasound-based surveillance significantly improves test performance.[128,129] A meta-analysis reported the sensitivity of that ultrasound for early-stage HCC detection is 45%, which increases to 63% with the addition of AFP.[118] Cross-sectional imaging using computed tomography (CT) or magnetic resonance imaging (MRI) is more sensitive than ultrasound, with MRI being preferred due to its avoidance of radiation exposure inherent in CT. In a study involving 407 patients, showing a highly disparate level of sensitivity for detection of HCC, most of them small, MRI was 86% sensitive vs. 27.9% for ultrasound ($p < 0.001$).[130] A recent modification of MRI, called abbreviated MRI (AMRI), which uses protocols comprised of a small number of select sequences tailored specifically for HCC detection, is being actively explored.[131] Despite the superior performance of MRI for HCC detection, its much greater expense and limited availability to many sectors of the population have resulted in ultrasound continuing to be the imaging modality of choice in published guidelines.

The AASLD guidance recommends HCC surveillance using abdominal ultrasound with AFP at six-month intervals (Table 4),[2] but it should be noted that this approach misses over one-third of early HCC cases due to its 63% sensitivity.[132] Several promising biomarkers and panels are currently under evaluation for HCC surveillance, with the most extensively studied

highlighted in the updated AASLD guidance and summarized in Table 4. These newer tests are expected to demonstrate performance characteristics at least comparable to the recommended ultrasound and AFP surveillance.[123] Similar to AFP, early data suggests that serum biomarkers AFP-L3% and DCP may not improve early-stage HCC detection when used alone. The AASLD notes that "these biomarkers may be complementary to AFP, underscoring the potential of biomarker panels to improve surveillance test performance."[2]

These aforementioned panel-based strategies highlighted by the AASLD (Table 4) include GALAD, Doylestown Plus, and the multitarget HCC blood test (m-HBT). Data indicate that these panels could significantly improve early detection and eligibility for curative treatment in patients at risk for HCC. In one study, GALAD was evaluated in a subgroup of patients with non-cirrhotic MASH (HCC, n = 30 vs. 182 controls) and achieved an AUROC of 0.98 for detecting HCC, with 93.3% sensitivity and 96.1% specificity.[133] Currently, a prospective trial is ongoing comparing the GALAD score with ultrasound plus AFP surveillance (NCT06084234).

As indicated in Table 4, surveillance using abdominal ultrasound with AFP has completed all five phases of validation, whereas the new tests still require validation through larger phase 3 and 4 studies.[2] The cost-effectiveness of these tests for early surveillance also warrants further investigation.

Table 4. Early HCC Surveillance Tests Highlighted by the AASLD Guidance

Type of Biomarker	Name	Description	Performance Characteristics	Phase of Validation[2]	Commentary
Imaging/ Serum	**Ultrasound plus AFP**	Both or inadequate alone; synergistically improves early detection[128,129]	*Sensitivity:* 61%–63%[118] *Specificity:* 92%[134]	5	Recommended by the AASLD guidance for HCC surveillance at six-month intervals[2]
Serum	**AFP-L3%**	Also known as lens culinaris agglutinin-reactive AFP, a fucosylated glycoform of AFP[135]	*Sensitivity:* 62%[136] *Specificity:* 49%–60%, depending on cohort characteristics[123,136]	3	FDA approved for HCC risk stratification, not surveillance;[2] inadequate alone, but may play a role in a biomarker panel-based strategy for screening.[123]
	DCP	Des-gamma carboxyprothrombin, a prothrombin precursor	*Sensitivity:* 26%–40%[123,136] *Specificity:* 81%[136]	3	FDA approved for HCC risk stratification, not surveillance;[2] may not significantly increase the discriminatory power of the combination of AFP and AFP-L3 for early HCC detection[136]
Algorithms/ Scoring Systems	**GALAD**	A score based on Gender, Age, AFP-L3, AFP, and DCP[103]	*Sensitivity:* 54%–72%[137] *Specificity:* 90%[137]	2/3	May be useful for early HCC surveillance in non-cirrhotics and cirrhotics; performance warrants validation in further phase 3 studies[138,139]
	Doylestown Plus	A panel consisting of laboratory markers (log AFP, ALP, AST, fucosylated kininogen) and demographic factors (age and gender)[123]	*Sensitivity:* 90%[140] *Specificity:* 95%[140]	2/3	Early data indicate that this biomarker algorithm could significantly improve early HCC detection and curative treatment eligibility in patients with cirrhosis, especially AFP-negative HCCs;[140] testing of a modified version of the Doylestown Plus algorithm in larger phase 2 cohorts is underway[123]
	m-HBT	A blood test combining information from three methylation markers (HOXA1, TSPYL5, and reference marker B3GALT6), one protein marker (AFP), and patient sex[137]	*Sensitivity:* 82%[137] *Specificity:* 87%[137]	2	Initial results are promising; this panel is still undergoing larger prospective validation in direct comparison to ultrasound with or without AFP[123]

AASLD, American Association for the Study of Liver Diseases; AFP, alpha fetoprotein; ALP, alkaline phosphatase; AST, aspartate aminotransferase; DCP, des-gamma carboxyprothrombin; GALAD, Gender, Age, AFP-L3, AFP and Des-carboxy-prothrombin; HCC, hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis; m-HBT, multitarget HCC blood test; NCL, noncirrhotic liver.

Obtaining "liquid biopsies" via different mechanisms is also an area of interest for early HCC detection.[2,141] One approach is to detect tumor-specific genomic alterations in cell-free DNA (cfDNA). Several multi-analyte DNA tests are currently under investigation, including M-HBT, marketed as Oncoguard® Liver solution. This panel of biomarkers combines three methylated DNA biomarkers with AFP and patient sex. This test demonstrated 82% early-stage sensitivity and 94% later-stage sensitivity at 87% specificity in the clinical validation phase of development.[137] In a multicentered case-control study (n=135 with HCC; n=302 controls), Oncoguard® demonstrated a higher sensitivity (71%, 95% CI: 60%–81%) at 90% specificity for early-stage HCC compared to the GALAD score (41%, 95% CI: 30%–53%) or AFP ≥7.32 ng/mL (45%, 95% CI: 33%–57%). The AUC for the multi-target HCC panel for detecting any stage HCC was 0.92 compared with 0.87 for the GALAD score and 0.81 for AFP alone. Notably, this panel performed equally well in important subgroups based on liver disease etiology, presence of cirrhosis, or sex.[142] Currently, Oncoguard® is being prospectively tested against ultrasound (NCT05064553).

Another example is the HelioLiver Dx test, which demonstrated early-stage detection in 76% of cases with a specificity of 91% in a phase 2 study, including 122 individuals with HCC and 125 with chronic liver disease.[143] Initial findings from the CLiMB study were recently presented at the 2024 EASL annual meeting. CLiMB is a multi-site prospective study comparing the sensitivity and specificity of HelioLiver Dx to ultrasound for detection of HCC within a population (n=1268 in the validation cohort) at high risk of HCC due to liver cirrhosis. Investigators reported that the HelioLiver Dx test met the prespecified coprimary endpoints—overall superior sensitivity (>5%) and non-inferior specificity (>-10%) compared to ultrasound in detecting HCC lesions; met the prespecified secondary endpoint—possessed superior sensitivity compared to ultrasound for detecting HCC lesions ≤ 4 cm in diameter; and outperformed ultrasound for sensitivity to detect HCC lesions in cirrhotic patients. It should be noted that 82.6% of the patients enrolled in the study were from community centers versus 17.4% from academic centers. The sensitivity of the HelioLiver Dx test alone was 48% as compared to ultrasound alone, which was 28%.[144]

Another form of liquid biopsy is to analyze extracellular vesicles (EVs), which are enclosed structures produced by cancer cells that promote cell growth and survival, help shape the tumor microenvironment, and increase invasive and metastatic activity.[145] They may also contain various biochemical signals, including genetic material, that have the potential to serve as a biomarker for early HCC detection.[123] EV detection chips have been developed with immunoaffinity assays for efficient isolation. In a small study (n=36 with early-stage HCC vs. n=26 controls with cirrhosis), the EV chip demonstrated a sensitivity of 94.4% and specificity of 88.5%.[123,146] The aforementioned tests, and other similar tests, are currently undergoing larger-scale validation. The AASLD's current recommendation is that available data are too premature to recommend routine use of these tests in clinical practice.[2]

Summary

HCC remains a major clinical burden in the US and globally, leading to substantial morbidity and mortality. Effective implementation of HCC surveillance with the goal of early detection and linkage to potentially curative therapies is key to addressing these concerning epidemiological trends. However, as described in this review, major challenges remain in effective HCC surveillance. Even among patients with cirrhosis, which is a clear indication for HCC surveillance, major gaps and delays in timely surveillance persist, contributing to advanced stage HCC, limited curative options, and high mortality rates. Data suggest that decision-support tools for HCC can help standardize the diagnosis, staging, linkage-to-care, and treatment pathways, thereby improving overall patient care and outcomes. In 2022, the Chronic Liver Disease Foundation (CLDF) HCC working group launched a practical, interactive, web-based digital decision-support tool aimed at enhancing the HCC cascade of care. The surveillance component of this algorithm utilizes risk stratification to support appropriate screening and surveillance practices.[147] To access the algorithm, visit: https://www.chronicliverdisease.org/disease_focus/hcc.cfm?dstate=hcc&sec=Algorithm.

Beyond patients with cirrhosis, as discussed in our review, NCHCC can occur, including those with F3 fibrosis due to HCV or MASH. While it is evident that patients with HCV and MASH-related F3 fibrosis without cirrhosis have higher risk of HCC compared to those without any underlying liver disease, current data remains too limited and heterogenous to strongly advocate for routine HCC surveillance in these sub-populations. This limitation stems from inadequate data, but also reflects the limitations of the tools currently available for HCC surveillance, and underscores the shortcomings of existing surveillance tools, primarily ultrasound and AFP tests every six months. As noted above, the limited sensitivity, and specificity of this approach, along with issues of access and costs, contribute to the lack of cost-effectiveness in implementing this HCC surveillance modality in these sub-populations. However, several promising blood-based biomarkers in development offer encouraging results. An HCC biomarker that is highly sensitive and specific, easily accessible and economically balanced could potentially change the current paradigm of HCC surveillance, replacing ultrasound and AFP, and may lead to a more favorable cost-effectiveness assessment for expanding routine HCC surveillance to patients with HCV- and MASH-related advanced fibrosis.

Key Expert Consensus Guidance

1. While HCV patients with F3 fibrosis post-SVR have a non-negligible risk of HCC, the limitations of the current data do not support routine HCC surveillance with modalities currently available (ultrasound and AFP) in all patients. Implementation of HCC surveillance in these populations should be individualized and factor in other clinical characteristics that may increase HCC risk.

2. Similarly, while patients with MASH with F3 fibrosis also have a non-negligible risk of HCC, the limitations of the current data do not support routine HCC surveillance with the modalities currently available (ultrasound and AFP) in all patients with MASH and F3 fibrosis. Implementation of HCC surveillance in these populations should be individualized and factor in other clinical characteristics, co-morbidities (e.g., diabetes), and behavioral risks (e.g., excessive alcohol use) that may increase HCC risk.

3. Several blood-based biomarkers with promising performance data are currently available. However, limited data and validation preclude the ability to uniformly recommend utilizing these biomarkers in place of guideline-recommended HCC surveillance modalities with ultrasound and AFP. The utilization of currently available biomarkers in the current state should be complementary to imaging-based modalities, and can be helpful to improve risk stratification in situations where HCC risk remains unclear or where imaging findings are equivocal. The utilization of HCC biomarkers as a primary modality for HCC surveillance in situations or regions where access to imaging-based modalities is not feasible deserves greater consideration and research.

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