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Review Article

Beyond the Cure: Navigating Hepatocellular Risk and Surveillance after Hepatitis C Eradication in the Direct-acting Antiviral Era

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Abstract

Direct-acting antivirals (DAAs) have dramatically changed the landscape of chronic hepatitis C virus (HCV) treatment and significantly reduced the risk of HCV-related hepatocellular carcinoma (HCC) after achieving sustained virologic response. However, the risk of HCC persists, particularly in patients with pre-treatment cirrhosis or fibrosis stage 3 (F3), even after DAA-induced viral eradication. While professional guidelines agree on the need for surveillance in cirrhotic patients, there is no consensus regarding surveillance for the pre-treatment F3 population following HCV eradication. The risk of HCC in the F3 population falls below the threshold for cost-effective surveillance. However, co-existing risk factors—such as diabetes, hepatic steatosis, alcohol use, advanced age, and elevated alpha-fetoprotein levels—may warrant reconsideration of HCC surveillance in this group. This underscores the need for an individualized, risk-based approach to HCC surveillance. This review provided a simplified algorithm to assist clinicians in managing patients with HCV after DAA-induced sustained virologic response.

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Introduction

The World Health Organization declared that chronic hepatitis C virus (HCV) infection affected an estimated 58 million individuals globally in 2022. Each year, approximately 1.5 million new cases and 300,000 deaths are attributed to the disease. Alarmingly, only 21% of those infected have been diagnosed, and just 13% have received treatment, highlighting the urgent need for effective HCV elimination strategies.[1]

Keywords: Hepatocellular carcinoma; Direct-acting antivirals; Hepatitis C virus; Sustained virologic response; Cirrhosis; Hepatic fibrosis.

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In June 2016, the World Health Organization introduced its inaugural global health sector strategy, which outlines objectives for HCV, including a 90% reduction in both incidence and prevalence, treatment of 80% of individuals eligible for chronic infection therapy, a 65% reduction in deaths caused by HCV, and ensuring universal access to essential prevention and treatment services by 2030.[2,3]

Chronic infection with HCV often results in necro-inflammation and fibrosis. Around 65–85% of individuals acutely infected with HCV develop chronic hepatitis.[2] Initial clinic-based estimates overstated the prevalence of cirrhosis, while community studies show it affects 5–10% of individuals after 20 years of HCV infection.[2]

The Global Burden of Disease estimated 534,000 new cases of primary liver cancer in 2019 and determined that 28.5% of liver cancer incidence is attributable to HCV.[1,4] Primary liver cancer ranks as the third leading cause of cancer-related mortality worldwide. New cases are projected to increase from 0.9 million in 2020 to 1.4 million by 2040. Hepatocellular carcinoma (HCC) constitutes approximately 80% of all primary liver cancers, with HCV serving as a major driver of HCC globally.[5] The yearly occurrence of HCC in individuals with HCV-related chronic hepatitis is approximately 1–4%, rising to 3–8% in patients with cirrhosis caused by HCV.[6,7]

The introduction of direct-acting antiviral (DAA) therapy has transformed HCV management and advanced progress toward its elimination. DAA therapy achieves sustained virologic response (SVR) in over 95% of treated individuals.[3] Studies have demonstrated that achieving SVR through DAA therapy can lead to a roughly 70% reduction in the risk of HCC in individuals with chronic HCV infection, regardless of cirrhosis status.[8,9] This protective effect becomes apparent within three to six months following viral eradication and continues to increase over time.[5,9]

Despite the reduction in HCC risk after HCV eradication, the risk persists in the pre-treatment bridging fibrosis or cirrhosis population.[10] This review provides an updated perspective on HCC after HCV eradication, focusing on risk factors, pathogenesis, and surveillance approaches in the DAA era.

DAA impact on HCC: Turning the tide on risk reduction

Multiple studies have approved that interferon (IFN)-based

therapy-induced SVR can significantly reduce the risk of HCC occurrence compared with non-SVR patients.[11,12] However, two small-scale cohorts conducted during the early DAA era in 2016 observed an unusually high incidence of *de novo* HCC after DAA-induced viral eradication (3.16% among cirrhosis patients without prior HCC during 24 weeks of follow-up) and a high recurrence rate of HCC (27.6% among cirrhosis patients with a prior history of HCC). These studies raised concerns about whether DAA treatment might contribute to HCC development or at least be less effective than IFN-based therapy in reducing HCC risk after achieving SVR.[13,14] Later, multiple large-scale cohorts with extended follow-up periods after SVR confirmed that early HCC recurrence rates do not differ significantly between patients treated with IFN therapy and those who received DAA therapy. Ioannou *et al*. conducted a cohort study that included 62,354 Veterans Affairs (VA) patients. The patients were divided into those receiving IFN-only (35,871 patients), DAA + IFN (4,535 patients), and DAA-only regimens (21,948 patients). Over an average follow-up of 6.1 years, the study suggested that achieving SVR significantly reduced HCC risk, regardless of the treatment regimen. Patients who attained SVR experienced a 71% reduction in HCC risk compared to those with treatment failure. Notably, the risk reduction was consistent across treatment types, with an adjusted hazard ratio (HR) of 0.29 (95% CI 0.23–0.37) for DAA-only regimens, 0.48 (95% CI 0.32–0.73) for DAA + IFN, and 0.32 (95% CI 0.28–0.37) for IFN-only regimens. SVR is the key determinant of reducing HCC risk, rather than the type of antiviral therapy used. There was no evidence that DAA therapy increased the risk of HCC compared to IFN-based therapy.[15] Li *et al*. used data from 17,836 HCV-infected VA patients and demonstrated no significant difference in HCC risk between DAA- and IFN-treated patients, with an HR of 1.07 (95% CI, 0.55–2.08). In cirrhotic patients who achieved SVR, the HCC incidence rate was comparable between the DAA and IFN groups (2.12 vs. 2.28 per 100 person-years), and there was no significant difference in HCC-free survival. However, untreated cirrhotic patients had a much higher HCC incidence rate (4.53 per 100 person-years) than those treated with either DAAs or IFN. Previously reported higher HCC rates with DAAs may have been influenced by selection bias, as DAAs were often used in patients with greater baseline risk factors for HCC.[16] A similar conclusion was reached by Lee *et al*. In their retrospective cohort study, they included 603 patients treated with PegIFN and 479 patients treated with DAAs. The DAA group consisted of older patients with a higher proportion of individuals with cirrhosis. Initial observations showed a higher incidence of HCC in the DAA group compared to the PegIFN group. However, after adjusting for baseline differences through multivariate analysis, there was no significant association between treatment regimen and HCC risk. These findings were further supported by propensity score matching, which confirmed similar HCC risks between the PegIFN and DAA groups.[17]

Multiple meta-analyses also support that DAA therapy has a comparable effect to IFN in reducing HCC risk. Huang *et al*. included 20 cohorts encompassing 61,334 chronic HCV patients and found no significant difference in HCC risk between DAA- and IFN-treated patients. Both treatments effectively reduced HCC occurrence and recurrence rates, provided SVR was achieved. The analysis concluded that achieving SVR, regardless of treatment regimen, is key to reducing HCC risk, and there is no evidence to support the hypothesis that DAA therapy increases the risk of HCC compared to IFN therapy.[18] Saraiya *et al*. reached a similar conclusion in populations with a history of HCC. Their meta-analysis included 24 studies with a total of 1,820 chronic HCV patients with a history of HCC. Nine of the 24 studies compared DAA-treated and IFN-treated or untreated patients. They suggested that HCC recurrence rates after DAA therapy were comparable to IFN, especially if DAA treatment was delayed for at least six months following a complete response to HCC.[19]

Furthermore, Signer *et al*. conducted a large population-based analysis including 30,183 adult HCV patients who received DAAs and concluded that, compared to IFN-based treatment, DAA therapy demonstrated an even greater reduction in liver cancer risk, with a 31% lower risk (HR: 0.69, 95% CI: 0.59–0.81).[20] Whether DAA therapy offers superior efficacy over IFN in reducing HCC risk remains controversial. However, current high-quality evidence indicates that DAA therapy is not inferior to IFN in suppressing HCC risk among HCV patients. As additional studies are conducted, the long-term benefits of DAA treatment are expected to become increasingly evident.

Decoding the pathogenesis of HCC after HCV eradication: Genetic and epigenetic alterations

As discussed previously, HCV eradication reduces but does not eliminate the risk of HCC. Virus eradication may abort or mitigate some pro-carcinogenesis processes, including: (1) Immune-mediated production of reactive oxygen species and pro-inflammatory cytokines, leading to genomic instability and oncogenic transformations. (2) HCV proteins, including core and NS5A, disrupting hepatocyte proliferation, differentiation, apoptosis, and neovascularization (3) Endoplasmic reticulum stress caused by HCV replication.[5,21–24] However, tumorigenesis persists after virus eradication, likely due to the latent accumulation of genetic mutations.[25] The genetic and epigenetic modifications accumulated during chronic HCV infection underscore the mechanisms driving hepatocarcinogenesis after HCV eradication.[6]

One prominent genetic alteration observed in HCC is associated with the telomerase reverse transcriptase gene, including promoter mutations and chromosomal rearrangements. Additionally, mutations are frequently identified in genes linked to oxidative stress responses, cell cycle regulation, chromatin remodeling, and liver differentiation processes. These alterations involve critical molecular pathways, including Wnt/beta-catenin, p53, PI3K/Akt/mTOR, RAS/RAF/MAPK signaling cascades, and TGF signaling pathways.[6,26,27]

HCV infection also induces epigenetic changes in hepatocytes, which can contribute to the development of HCC even after achieving SVR. A study by Hamdane *et al*. revealed that histone modifications induced by HCV, particularly changes in H3K27ac, persist in the human liver following viral eradication with DAAs. Using genome-wide ChIP-seq and RNA-seq analyses of liver tissues, they identified the upregulation of SPHK1 as a critical alteration linked to an elevated risk of HCC post-SVR.[28] A comprehensive transcriptomic analysis of post-SVR liver tissues showed that certain pro-carcinogenesis pathways, involving cell proliferation, adhesion, cycle regulation, and inflammation, remain upregulated despite viral eradication and fail to return to baseline.[29]

Chronic HCV infection and its associated inflammation led to a gradual, multi-step accumulation of genetic and epigenetic alterations, contributing to hepatocarcinogenesis. While achieving SVR through DAA therapy halts inflammation and fibrosis progression and reduces carcinogenic risk, accumulated genetic and epigenetic changes prior to viral eradication may remain imprinted in the liver. These alterations can drive abnormal cell proliferation, impaired apoptosis, and disrupted intracellular signaling, forming the

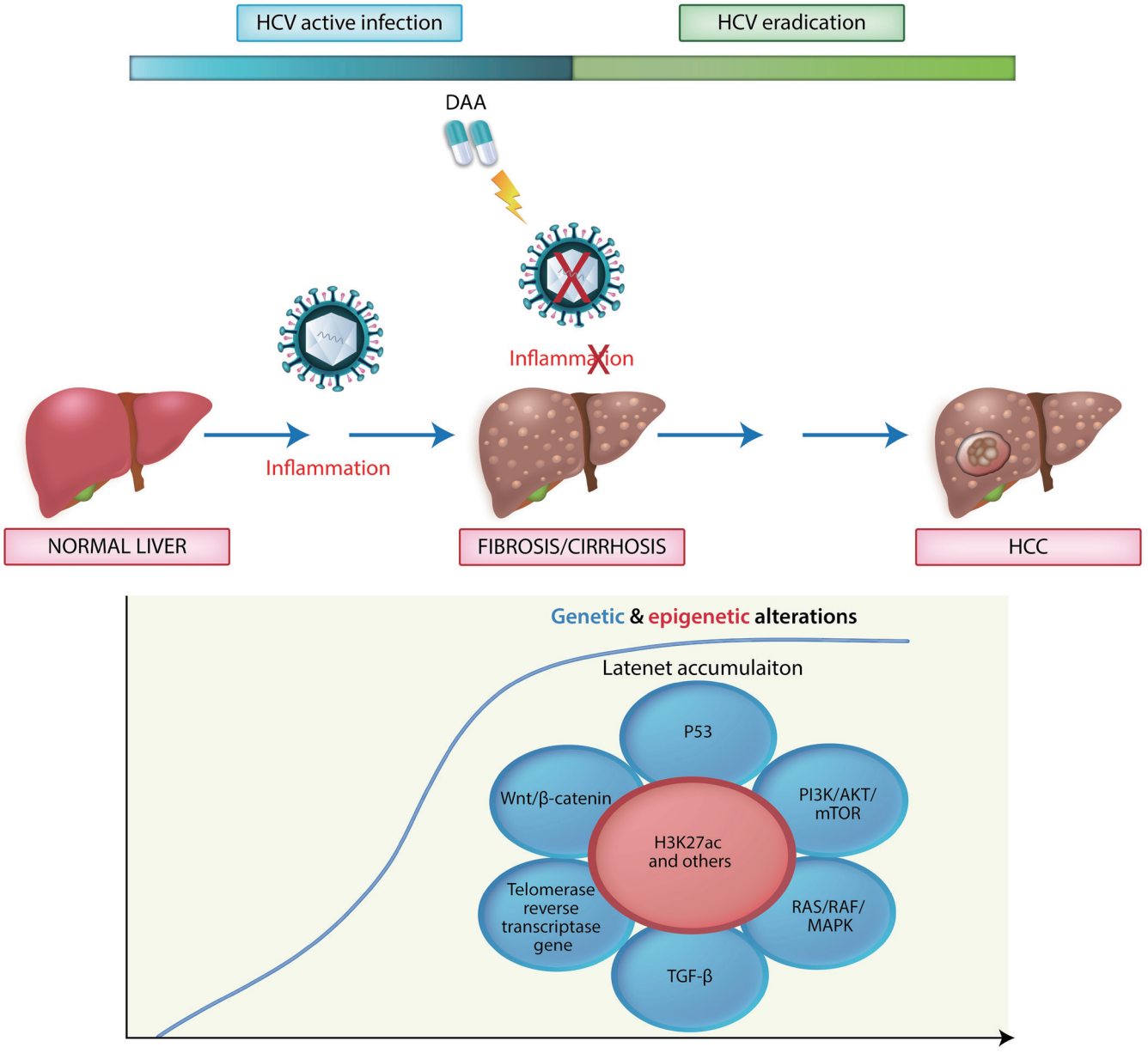

Fig. 1. Pathogenesis of HCC development in HCV patients who achieve SVR by DAA. DAA eradicates the HCV virus and the associated inflammatory process, halting further liver fibrosis progression or decompensation. However, the latent accumulation of genetic and epigenetic aberrations persists and eventually leads to HCC development, even after HCV eradication. HCC, hepatocellular carcinoma; SVR, sustained virologic response; DAA, direct-acting antiviral agent; HCV, hepatitis C virus.

molecular foundation for HCC development post-HCV eradication (Fig. 1).[6]

Risk factors for HCC after HCV eradication

Research indicates that DAA regimens improve fibrosis scores in 61.9% of patients within 12 weeks, regardless of clinical or virological factors.[30] However, the correlation between pre-treatment bridging fibrosis, liver cirrhosis, and an increased risk of HCC in HCV patients is well-established.[10] A cohort of 572 patients who achieved SVR with a median follow-up of 2.8 years identified key predictors of HCC risk, including albumin levels (<4.4 g/dL) and liver stiffness measurement (LSM) (≥10 kPa) at follow-up. Patients with LSM ≥20 kPa or LSM 10–20 kPa with low albumin levels were at the highest risk of HCC, with an HCC incidence of ≥1.9 per 100 patient-years.[31] Liver fibrosis serologic markers, such as the fibrosis-4 index (FIB-4), have proven valuable in predicting HCC occurrence following the achievement of SVR through DAA therapy. A cohort of 48,135 HCV patients suggested that pre-SVR FIB-4 scores ≥ 3.25 were significantly associated with a higher annual HCC incidence (3.66 per 100 patient-years) compared to those with FIB-4 scores <3.25 (1.16 per 100 patient-years) during an average follow-up of 5.4 years.[32]

Not only does the pre-treatment fibrosis stage matter, but a lack of fibrosis regression after viral eradication could also be a predictor of HCC risk. Ravaioli *et al*. investigated the role

of LSM changes as a predictor of HCC development among 139 HCV-related cirrhotic patients after HCV cure. During a median follow-up of 15 months, the significant reduction in LSM was lower in the patients who developed HCC than in those who did not (18.0% reduction vs. 28.9% reduction, $p = 0.005$). Further multivariate analysis indicated that (1) LSM reduction of less than 30%, (2) Child-Turcotte-Pugh-B, and (3) A prior history of HCC were independently associated with an increased risk of HCC.[33]

Liver steatosis (LS) is a common histological presentation during chronic HCV, and the presence of LS is associated with fibrosis progression.[34] Furthermore, in a recent study, LS significantly increased the risk of HCC, independent of the fibrosis stage, in patients who achieved SVR with DAA. Peleg *et al*. conducted a cohort study that included 515 chronic HCV patients with a mean follow-up of 24 months. Those with LS had a 7.5-fold higher risk of combined mortality and HCC compared to those without LS, even after adjusting for metabolic syndrome components. There was no difference in the prevalence of advanced fibrosis or cirrhosis. This study highlighted LS as a critical predictor of HCC risk and suggested rigorous screening for patients with LS after SVR.[35]

Pre-existing diabetes mellitus (DM) is another risk factor for HCC after HCV cure. Hyperinsulinemia and insulin-dependent signaling pathways may play a role in the development and progression of HCC. Additionally, insulin resistance has been shown to accelerate fibrosis progression in patients with HCV infection.[36,37] Among patients without a cirrhosis diagnosis, those with DM were associated with an approximately twofold higher risk of developing HCC than counterparts without DM. However, the DM-associated HCC risk was not statistically significant among cirrhotic patients.[38] Degasperi *et al*. studied 565 patients with cirrhosis who received DAAs to achieve SVR. Among patients without a prior history of HCC, DM was independently associated with an increased risk of developing *de novo* HCC, with an HR of 2.52. Similarly, among patients with a prior history of HCC, DM was associated with a higher recurrence rate, with an HR of 4.12.[39] These findings suggest that DM is a key risk factor for HCC in the HCV-cured population and underscore the need for close monitoring of patients with DM following DAA therapy.

Alcohol consumption is an independent risk factor for HCC and can synergistically interact with other factors, such as viral hepatitis and diabetes, to further elevate HCC risk. Its carcinogenic effects may be mediated through several mechanisms, including acetaldehyde's mutagenic impact and reactive oxygen species generation due to excessive hepatic iron accumulation. Additionally, alcohol has been shown to enhance hepatitis C virus-related liver tumorigenesis via Toll-like receptor 4 signaling pathways.[40] Among patients with DAA-induced SVR, HCC annual incidence was significantly higher among patients with alcohol use (1.01 per 100 patient-years) compared with those without alcohol use (0.72 per 100 patient-years).[38] Another cohort study also reported that excessive drinking (≥60 g/day) after HCV cure is an independent risk factor for HCC development.[41]

Sangiovanni *et al*. conducted a large-scale multicenter prospective study that indicated cirrhosis patients with a previous history of HCC recurrence have a significantly higher rate of HCC incidence (HR 2.87; 95% CI 1.35–6.09; $p = 0.02$). This suggests that a history of HCC recurrence is also a predictor of HCC risk after HCV cure.[42]

A study conducted in Japan, including 1,088 HCV-infected patients, suggested that advanced age (greater than 75) and post-treatment alpha-fetoprotein (AFP) values (above 6 ng/mL) were two independent predictors associated with an increased risk of HCC after DAA-induced SVR.[43]

HCC surveillance after SVR

Despite the remarkable reduction in HCC risk following DAA-induced SVR, as mentioned above,[8] cirrhosis remains at high risk for HCC, with a yearly incidence as high as 2.12 per 100 person-years.[16] The role of AFP in HCC surveillance has been debated due to its low specificity, particularly in viremic patients, where active hepatitis can confound results at lower AFP thresholds (12–20 ng/mL). However, AFP's diagnostic accuracy improves significantly after achieving viral eradication, and higher AFP levels are associated with HCC risk at baseline and during follow-up in HCV-cured patients.[10] A recent cost-effectiveness study indicated that combining ultrasound (US) with AFP is the most cost-effective strategy for HCC surveillance, offering greater benefits compared to the US-alone strategy or no surveillance in patients with compensated cirrhosis.[44] However, the US has limited accuracy in some populations, such as obese patients. Thus, other enhanced detection modalities, such as CT and MRI, should be considered as alternatives. The availability of resources and costs require careful assessment, and CT or MRI should be prioritized for patients at relatively high risk of HCC incidence.[45–47]

The pre-treatment fibrosis stage should favorably consider non-invasive tests (NITs) instead of liver biopsy, such as LSM by vibration-controlled transient elastography and blood-based scores like the FIB-4 and AST to platelet ratio index. A combination of NITs could improve the accuracy of fibrosis assessment. In cases of interpretation discrepancies between NITs, alternative assessment modalities such as US, upper endoscopy, or liver biopsy could be considered.[10] Professional guidelines agree that patients with pre-treatment cirrhosis should undergo regular HCC surveillance after achieving SVR, typically with ultrasound every six months, with or without AFP testing. This recommendation reflects the persistent and significant risk of HCC even after viral eradication. However, there is no consensus for patients with pre-treatment bridging fibrosis (F3) or earlier stages of fibrosis (F0–F2), as their risk of HCC is relatively lower, balancing the clinical benefit and cost-effectiveness.[10,48,49] The American Association for the Study of Liver Diseases (AASLD) has the most conservative recommendation regarding HCC surveillance. Lifelong routine semi-annual HCC surveillance is only recommended for HCV patients with cirrhosis, and routine surveillance is not recommended for HCV patients without cirrhosis, including F3.[49] The European Association for the Study of the Liver (EASL) offered relatively aggressive recommendations, suggesting lifelong routine semi-annual HCC surveillance for patients with pre-SVR fibrosis stage F3 and F4/cirrhosis who achieve SVR with DAA therapy.[10] The Asian Pacific Association for the Study of the Liver (APASL) offered the most aggressive recommendations on HCC surveillance. It concurred with EASL on lifelong routine semi-annual surveillance for F3/F4, but also suggested semi-annual surveillance in the first two years after achieving SVR for those with pre-SVR fibrosis F0-2, followed by annual screening thereafter. If SVR patients have other comorbidities, such as alcohol abuse and/or diabetes mellitus, regular HCC surveillance should be conducted.[48] Another hepatology organization, the International Liver Cancer Association, did not specify an HCC surveillance recommendation and suggested that surveillance policies should consider target populations and resource availability, tailored by each local health authority. Individuals with cirrhosis or stage 3 fibrosis should undergo

Table 1. Professional guidelines for HCC surveillance for HCV patients with SVR after DAA therapy[10,48,49]

Pre-treatment fibrosis stage	AASLD	EASL	APASL
F4/cirrhosis	Lifelong semi-annual screen*	Lifelong semi-annual screen ‡	Lifelong semi-annual screen ¥
F3	No recommended	Lifelong semi-annual screen ‡	Lifelong semi-annual screen ¥
F0-2	No recommended	No recommended	Semi-annual for the first two years and annual thereafter*. Regularly screen once other risk factors present, such as alcohol abuse and/or DM

*US±AFP, ‡ US, ¥ US with AFP, AFP-L3, and/or DCP. AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of Liver; APASL, Asian Pacific Association for the Study of Liver; HCC, hepatocellular carcinoma; SVR, sustained virologic response; DAA, direct-acting antiviral agent; HCV, hepatitis C virus; F0-F4, fibrosis stages 0 to 4; DM, diabetes mellitus; US, ultrasound; AFP, alpha-fetoprotein; AFP-L3, lens culinaris agglutinin-reactive alpha-fetoprotein isoform; DCP, des-γ-carboxy prothrombin.

HCC risk assessment, with surveillance methods adapted to local resources.[50]

Table 1 highlights the similarities and differences in professional guidelines for HCC surveillance following SVR. These guidelines aim to refine HCC risk prediction after DAA treatment, allowing for more tailored surveillance.[10,48,49] This likely reflects the challenges of varying NIT accuracy in staging fibrosis in active HCV infection patients with intrahepatic inflammation. Additionally, the cost-effectiveness of HCC screening in certain populations, particularly those with lower risk, remains controversial.[10]

There is a lack of consensus on surveillance recommendations for patients with F3 or those without cirrhosis, as well as debates about the optimal surveillance intervals and methods for HCC surveillance after HCV eradication. Achieving a balance between the benefits of routine screening and its potential costs and harms remains unclear after HCV eradication, and further studies are needed to refine surveillance strategies. [22,51]

Although some debate remains, it is generally accepted that an annual HCC risk exceeding 1.5% is the threshold for cost-effective surveillance.[10,49] A meta-analysis conducted by Lockart *et al*., including 44 studies and 107,548 person-years of follow-up, revealed that the incidence of HCC was significantly higher in patients with cirrhosis (2.1 per 100 person-years) compared to those with F3 (0.5 per 100 person-years) after SVR. This study justifies HCC surveillance for patients with cirrhosis despite the incidence decreasing over time, particularly in younger individuals with compensated cirrhosis. In contrast, the substantially lower risk observed in F3 patients falls below the threshold for cost-effective surveillance. Thus, the results of this study do not support routine HCC screening for F3 patients who achieve SVR. For patients with cirrhosis, older age and a history of prior liver decompensation were associated with an increased risk of HCC, while a longer duration of follow-up after HCV cure was linked to a lower incidence.[52] A similar conclusion was drawn in another meta-analysis conducted by Kim *et al*., which included data from 31 studies involving 27,711 patients with cirrhosis and 11 studies involving 32,123 patients without cirrhosis, including those with F3. The findings showed a significantly elevated HCC incidence in patients with cirrhosis (2.99 per 100 person-years), while the incidence was much lower in patients without cirrhosis (0.47 per 100 person-years) and those with F3 fibrosis (0.63 per 100 person-years). Notably, among patients with cirrhosis, HCC incidence was highest in studies with shorter follow-up periods (6.17 per 100 person-years for less than one year) and gradually declined with longer follow-up times, reaching 1.83 per 100 person-years after three or more years. The study concludes that while HCC risk appears to decline over time following HCV cure, it remains high in patients with cirrhosis and above the thresholds for cost-effective HCC surveillance.[53] This conclusion is consistent with a recent VA cohort, where individuals with pre-treatment cirrhosis or a pre-treatment FIB-4 score greater than 3.25 showed a gradual decline in yearly HCC incidence over time, but the rate consistently stayed above the threshold recommended for surveillance even after seven years of follow-up after viral eradication.[54] Similar to IFN-based therapy, patients with pre-treatment cirrhosis or an FIB-4 score greater than 3.25 remain at high risk of HCC even after 10 years of SVR.[32] In contrast, patients without cirrhosis, including those with F3 fibrosis, have significantly lower HCC incidence rates, falling below the thresholds for cost-effective HCC surveillance. The absence of study heterogeneity in the F3 fibrosis subgroup strengthens the evidence that routine HCC screening may not be necessary for this population.[53]

Based on the meta-analysis studies above, patients with F3 have an annual HCC incidence of about 0.5–0.63 per 100 person-years,[52,53] far below the recommended cost-effective surveillance threshold. However, if F3 fibrosis patients have additional risk factors, such as diabetes, hepatic steatosis, alcohol use, advanced age, or elevated AFP levels, they may face an increased risk of HCC even after achieving SVR. For these F3 fibrosis patients with relatively higher risk factors, annual HCC surveillance should be considered. A tailored approach, including ultrasound with or without AFP testing, should be considered to ensure timely detection based on individual risk profiles.[51] Duration of surveillance remains an ongoing debate, but there is limited data to make validated suggestions for the pre-treatment F3 fibrosis population with SVR. The authors propose a simplified algorithm for HCV patients who achieve SVR (Fig. 2) to guide clinicians in real-world practices, reflecting the balance of surveillance benefits with its potential costs and risks, while emphasizing a personalized, risk-based strategy. The authors suggest that based on the pre-treatment fibrosis stage, determined by NITs (preferred) or liver biopsy, universal HCC screening for F4 or cirrhosis patients with semi-annual US +/- AFP aligns with AASLD/EASL/APASL guidelines. The F3 population requires a personalized approach with a thorough discussion of the risks and benefits of HCC surveillance between providers and patients, especially for those with additional risk factors such as DM, LS, alcohol use, advanced age, and elevated AFP, who need to consider annual US+/- AFP. This approach balances current AASLD and EASL guidelines regarding HCC surveillance after HCV eradication. The authors do not recommend HCC

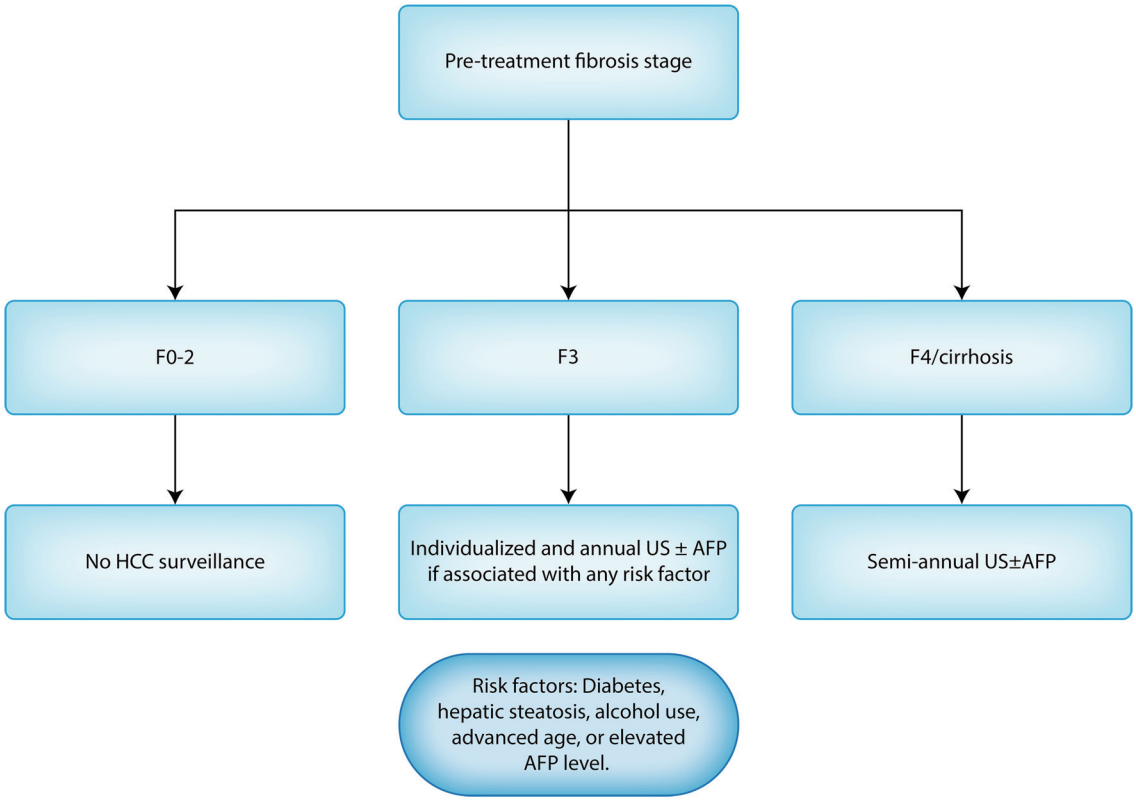

Fig. 2. A simplified algorithm for HCC surveillance in HCV patients who have achieved SVR by DAA. The algorithm provides recommendations for clinicians on HCC surveillance after HCV eradication. It is determined by the pre-treatment fibrosis stage, which is assessed by NITs (preferred) +/- liver biopsy. For F3 patients, clinicians need to apply individualized strategies and consider other associated risk factors for HCC. HCC, hepatocellular carcinoma; SVR, sustained virologic response; DAA, direct-acting antiviral agent; HCV: hepatitis C virus; F0-F4, fibrosis stages 0 to 4; DM, diabetes mellitus; US, ultrasound; AFP, alpha-fetoprotein.

surveillance for F0-2 patients, aligning with the AASLD and EASL guidelines, which differs from the APASL guideline. Further studies are needed to refine and justify this tentative strategy.

Conclusions

The advent of DAAs has dramatically impacted chronic HCV management, significantly reducing the risk of HCC development. However, in patients with cirrhosis who achieve HCV eradication, the risk of HCC remains high and exceeds the surveillance threshold, justifying lifetime HCC surveillance. For patients with pre-treatment stage 3 fibrosis, HCC surveillance after viral eradication remains a topic of debate. Tailored screening strategies that balance risk, cost, and benefit are essential for improving outcomes in this group. Further studies that carefully assess risk factors for HCC occurrence after HCV viral eradication are needed to optimize individualized surveillance approaches.

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Conflict of interest

AKS has been an Associate Editor of *Journal of Clinical and Translational Hepatology* since 2016. The other author has no conflict of interests related to this publication.

Author contributions

Writing of the manuscript (CX), and important intellectual input (AKS). All authors reviewed and approved the final version.

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