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Hepatocellular carcinoma risk after viral response in hepatitis C virus-advanced fibrosis: Who to screen and for how long?

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Abstract

Hepatitis C virus (HCV) chronic infection is associated with fibrosis progression, end-stage liver complications and HCC. Not surprisingly, HCV infection is a leading cause of liver-related morbidity and mortality worldwide. After sustained virological response (SVR), the risk of developing hepatocellular carcinoma is not completely eliminated in patients with established cirrhosis or with advanced fibrosis. Therefore, lifelong surveillance is currently recommended. This strategy is likely not universally cost-effective and harmless, considering that not all patients with advanced fibrosis have the same risk of developing HCC. Factors related to the severity of liver disease and its potential to improve after SVR, the molecular and epigenetic changes that occur during infection and other associated comorbidities might account for different risk levels and are likely essential for identifying patients who would benefit from screening programs after SVR. Efforts to develop predictive models and risk calculators, biomarkers and genetic panels and even deep learning models to estimate the individual risk of HCC have been made in the direct-acting antiviral agents era, when thousands of patients with advanced fibrosis and cirrhosis have reached SVR. These tools could help to identify patients with very low HCC risk in whom surveillance might not be justified. In this review, factors affecting the probability of HCC development after SVR, the benefits and risks of surveillance, suggested strategies to estimate individualized HCC risk and the current evidence to recommend lifelong surveillance are discussed.

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Core Tip: Hepatocellular carcinoma (HCC) risk is reduced after sustained viral response, but a substantial threat persists over time. Understanding the natural history of hepatitis C virus infection and the variable influence of viral eradication in the molecular and epigenetic changes that occur during infection are essential to explain the different risk of developing HCC in patients with advanced fibrosis. The definition of the appropriate tools to estimate the individual risk of HCC after antiviral treatment providing reliable recommendations about HCC surveillance is probably the most important challenge to be clarified in this field.

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INTRODUCTION

Hepatitis C virus (HCV) chronic infection is a major cause of liver-related morbidity and mortality worldwide. Direct-acting antiviral agents (DAAs) have definitely changed the natural history of the disease by reducing liver-related complications in patients with advanced liver fibrosis (including those with cirrhosis) and improving the survival rate. Nonetheless, the risk of developing hepatocellular carcinoma is not completely eliminated with viral clearance. Not surprisingly, clinical guidelines still recommend life-long ultrasound surveillance in all patients with advanced fibrosis (F3) and cirrhosis (F4)[1,2].

However, the risk of HCC occurrence is not homogenous within the spectrum of compensated advanced chronic liver disease (c-ACLD). Therefore, surveillance strategies might not be cost-effective or harmless in all patients. Thus, the identification of patients who truly benefit from screening programs and for how long is a matter of debate.

HCC risk factors are associated with the severity of liver disease and the degree of improvement after sustained virological response but also with the presence of other comorbidities and preneoplastic changes induced by HCV. All of them are discussed in this review, as well as their predictive capacity to estimate individualized HCC risk. We also discuss the current evidence to recommend surveillance.

FACTORS AFFECTING HCC OCCURRENCE IN HCV PATIENTS

A combination of different factors, occurring either before or after SVR, is involved in the risk of HCC associated with HCV chronic infection (Figure 1).

Development of fibrosis during HCV infection

Chronic HCV infection typically causes damage and inflammation in the liver parenchyma, which can be followed by fibrosis deposition of different severities. Fibrogenesis is a dynamic process characterized by the synthesis of extracellular matrix (ECM), composed of a mixed complex of glycoproteins (collagen, elastin, fibronectin, laminin) and proteoglycans organized in a three-dimensional network[3]. Therefore, fibrosis is a physiological mechanism that can become pathological when viral infection and chronic hepatocellular injury persist[4].

In chronic hepatitis, including hepatitis C, active fibrosis begins around the portal areas (periportal or zone 1 fibrosis) and gradually extends out into the lobules toward the central veins (zone 3), with septum formation and then bridging fibrosis[5]. The

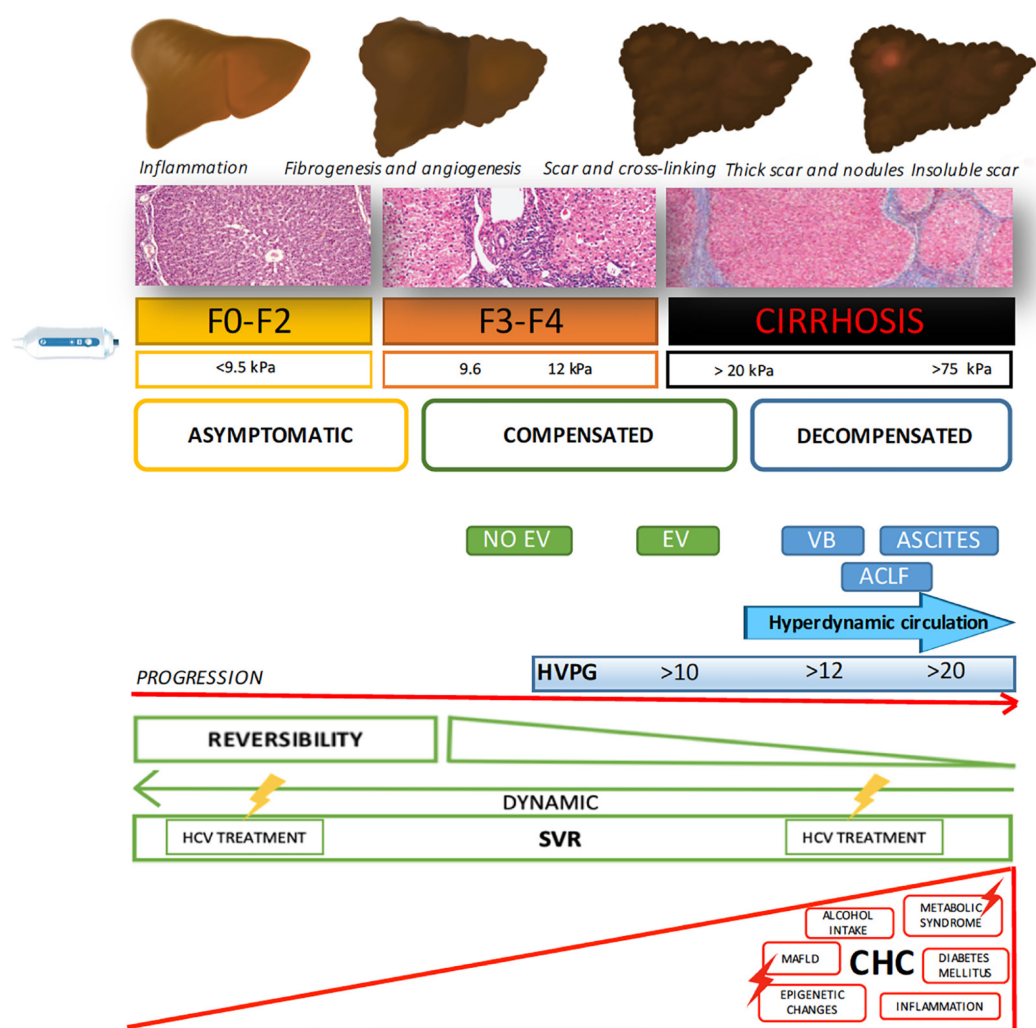


Figure 1 Factors involved in increasing or decreasing hepatocellular carcinoma risk, either before or after sustained virologic response. EV: Esophageal varices; VB: Variceal bleeding; ACLF: Acute on chronic liver failure; PH: Portal hypertension; SVR: Sustained virologic response; HCC: Hepatocellular carcinoma; MAFLD: Metabolic associated fatty liver disease.

final stage of this process constitutes cirrhosis, in which extensive fibrosis linking portal and central areas and nodular regeneration of the liver parenchyma appear. Collagen and matrix proteins are largely produced by activated hepatic stellate cells (HSCs). In contrast, activated liver sinusoidal endothelial cells (LSECs) contribute to ECM production, including the synthesis of basement membrane components, leading to perisinusoidal fibrosis. They also produce cytokines that activate HSCs and secrete factors that contribute to intrahepatic vasoconstriction and to portal hypertension in cirrhosis[6]. It has been widely demonstrated that the severity of liver fibrosis and the development of cirrhosis are the most important risk factors for HCC[7-9]. Therefore, the earlier that this process is discontinued by means of SVR, the lower that the likelihood is of HCC occurrence.

Epigenetic changes involved in hepatitis C infection

Cirrhosis of all causes can be complicated by the appearance of liver tumors, but the risk is higher in patients with chronic liver disease of a viral etiology[7]. In 2018, a large cohort study aimed to compare HCC risk according to the etiology of liver disease and showed that patients with HCV-related cirrhosis had a 3-fold increased HCC risk compared to ALD or NAFLD-related cirrhosis, suggesting that hepatitis C virus itself might have a direct carcinogenic effect[10].

HCV is an RNA virus with limited potential for integration into the host genome and therefore requires continuous replication to maintain chronic infection. HCV directly contributes to hepatocarcinogenesis, interrupting the signal transduction pathways that affect cell survival, proliferation, and transformation *via* HCV protein or RNA and indirectly by inducing chronic inflammation[8,11].

Epigenetic regulation is an indispensable process for the normal development and preservation of tissue-specific gene expression profiles. Thus, any perturbation of the epigenetic landscape can lead to shifted gene function and malignant cellular transformation. The changed epigenome of HCC is characterized by gene-specific hypermethylation or hypomethylation, global genomic hypomethylation, abnormal expression of DNA methyltransferases and histone modifying enzymes, altered histone modification patterns, and aberrant expression of microRNAs, which can affect the expression of oncogenes, tumor suppressor genes and other tumor-related genes altering the cancer development pathways over time[12]. In fact, a recent study showed a clear, positive correlation between epigenetic changes and fibrosis stages in HCV chronic infection[13], which persist after SVR.

Reversibility of liver fibrosis

Effective antiviral treatment has proved to change the natural history of HCV-related liver disease, reducing the risk of liver events and HCC, even in patients with advanced liver disease and cirrhosis. A recent meta-analysis[14] showed a significant absolute risk reduction in HCC after SVR, which was even greater in patients with cirrhosis (22%; 95%CI: 13-31) than in patients with any stage of fibrosis (6.7%; 95%CI: 5-8). It has been suggested that regression of fibrosis is one of the key mechanisms. In contrast to what was previously believed, there is currently substantial evidence indicating that the removal of fibrosis, hepatocyte repopulation and microvasculature remodeling occur after SVR following several cellular processes[15,16]. Mechanisms of the resolution of liver fibrosis involve senescence and apoptosis of activated HSCs/myofibroblasts caused by deprivation of fibrogenic cytokines. Reversal of these cells to an inactive phenotype during liver fibrosis regression[6,15] has also been described. However, regression of liver disease depends on the severity of fibrosis before antiviral therapy, with total regression being more likely in patients with mild/moderate fibrosis than in those with established cirrhosis due to the presence of a stronger cross-linking matrix, which is more difficult to remove by methalloproteases. Furthermore, the presence of architectural distortion with vascular shunts also contributes to the persistence of architectural changes[17-21]. However, the “point of no return” is controversial. A Canadian study[16] examined explants of patients with cirrhosis or precirrhosis who underwent transplantation, in which the causative agent of the liver disease was controlled or had been removed. The authors found that regression involves two main processes: removal of fibrosis and repopulation of scarred regions with hepatocytes, concluding that reversibility is possible in all stages of fibrosis, including precirrhotic stages and even macronodular cirrhosis. Interestingly, “sinusoidal capillarization” was considered the “point of no return”. Moreover, advanced stages of cirrhosis with thicker septa and smaller micronodules are associated with the presence of clinically significant portal hypertension and therefore with a lower likelihood of reversibility[20].

An Italian study including patients with cirrhosis with paired biopsies after achieving SVR with PEGINF/RBV showed that, in more than half of the patients, regression of cirrhosis was observed during follow-up. Patients who did not change their METAVIR scores after SVR also presented a decrease in the amount of collagen fibers, coinciding with the transformation of micronodular cirrhosis into a macronodular form or incomplete septal cirrhosis[21]. Finally, a Spanish study published in 2018 evaluated the regression of fibrosis using paired biopsies in 112 patients with posttransplant recurrence of HCV infection after treatment with DAAs [22]. Fibrosis regression occurred in 72-85% of the patients without liver cirrhosis (F1-F3) and in 43% of the patients with cirrhosis. Interestingly, in this study, more than 50% of the cirrhotic patients had a history of decompensation, suggesting that patients with liver cirrhosis without clinically significant portal hypertension are more likely to have improved liver injury, likely decreasing the risk of developing HCC after SVR.

Therefore, among patients with advanced fibrosis and cirrhosis, the risk of HCC seems to be lower in patients with less severe disease, who are in fact those who benefit the most after SVR.

One important issue is how to assess fibrosis regression since liver biopsy is an invasive procedure, does not distinguish early from advanced stages of cirrhosis and cannot be performed repeatedly after SVR. Not surprisingly, noninvasive elastographic and direct or indirect serological markers have been widely used to assess fibrosis regression[23]. However, in regressed cirrhosis, macronodules and aberrant vasculature with capillarization of the sinusoids can persist despite a decrease in liver stiffness assessed by TE. The study from D’ Ambrosio *et al*[24] revealed that, after 61 mo of follow-up, 38% of patients with biopsy-proven F4 had liver stiffness < 12 kPa, resulting in low predictive power of TE to diagnose cirrhosis after viral

eradication. Thus, a combination of TE and serological noninvasive markers might improve the capacity to assess fibrosis regression.

Inflammation and liver cancer

Another factor specifically affecting HCC risk during HCV chronic infection is the presence of inflammation. Various types of cancer arise in the setting of chronic inflammation, indicating a strong link between inflammation and cancer. It has been estimated that approximately 15% of all human cancers are associated with inflammation and chronic infections[25]. During chronic viral hepatitis, host immune responses to HBV or HCV are often not sufficiently strong to completely eradicate the infection, inducing persistent stimulation of antigen-specific immune responses. Host immune cells are known to destroy virus-infected liver cells, resulting in the production of different cytokines and growth factors, consequently inducing compensatory regeneration of hepatocytes. The persistent cycle of hepatocyte necroinflammation and regeneration has a synergistic effect with the severity of liver fibrosis and cirrhosis, promoting architectural distortion and portal hypertension with reduced sinusoidal perfusion favoring hypoxia, which is the substrate for the formation of hypervascular tumors. These factors increase the risk of genetic changes in hepatocytes, promoting the survival and expansion of the initiated cells and leading to dysregulated hepatocyte proliferation, which contributes to the development and progression of liver cancer. Furthermore, oxidative stress accelerates hepatocarcinogenesis through several mechanisms, including transcription and activation of cytokines and growth factors, oxidative DNA damage, DNA methylation, and hepatocyte injury[26-30]. Therefore, HCC risk is expected to decrease after eradicating infection and the subsequent decrease in inflammation mechanisms.

HCC RISK CAN PERSIST AFTER SUSTAINED VIROLOGICAL RESPONSE

Although SVR is associated with a reduction in some of the HCC pathogenetic factors mentioned above, there are many other contributors to HCC occurrence that can persist after viral eradication, related either to the stage of liver disease (*e.g.*, Child B, portal hypertension, low platelet count) or to the presence of comorbidities, such as diabetes, alcohol consumption, smoking and older age[31-34].

A recent publication suggested that regression of liver damage after SVR can last for years, with HCC risk persisting during this period; in other patients, liver injury is not reversed due to advanced cirrhosis stage, or it progresses because of the coexistence of other factors, such as obesity, diabetes, and alcohol intake[35]. In addition, older age contributes, even years after SVR, to the progression of liver fibrosis and to an increased risk of HCC.

Epigenetic memory is another of the possible mechanisms involved in HCC risk persistence after SVR. As mentioned above, HCV infection induces epigenetic alterations. DAA treatment eliminates the virus inside cells, but it is not able to restore the concomitant epigenetic signatures already produced and associated with the risk of HCC. Available data suggest that, when infection has already induced epigenetic changes, gene expression is conserved in cells; therefore, the presence of the virus is no longer necessary to exert oncogenic effects on host cells, producing what is known as epigenetic memory or persistent epigenetic changes[13,36].

HCC SURVEILLANCE AFTER SVR: CURRENT RECOMMENDATIONS

Current guidelines from EASL[1] and AASLD[37] agree regarding the recommendation of hepatocellular carcinoma surveillance after SVR in all patients with cirrhosis. However, EASL recommends indefinite HCC screening in patients with advanced fibrosis (F3) by ultrasound every six months, whereas AASLD does not. These differences are likely related to controversy regarding the risk of developing HCC in F3 patients due to the heterogeneity of this population, which could include misclassified patients (over- or underestimating the severity of fibrosis).

ACCURACY IN THE DIAGNOSIS OF ADVANCED FIBROSIS AND CIRRHOSIS

Considering that advanced fibrosis and especially cirrhosis are the main factors contributing to HCC risk, an accurate diagnosis prior to antiviral therapy is mandatory to predict individual risk after SVR. Liver biopsy remains the gold standard for the assessment of hepatic fibrosis, although noninvasive methods for estimating liver fibrosis are increasingly used. However, the accuracy of fibrosis staging in the noninvasive assessment era is imperfect -- even more so after sustained virological response. This fact is especially important in patients with advanced fibrosis but without cirrhosis, in which liver stiffness measurements (LSMs) can occasionally overestimate fibrosis, especially when marked inflammation is present[38]. Another problem is the definition of F3 stage by LSM, with cutoffs varying from 9.5 kPa to 14.5 kPa according to Castera's[39] study or up to 12.5 kPa as Ziol *et al*[40] suggested. Therefore, a substantial proportion of patients might be misclassified, overestimating or underestimating fibrosis and leading to an indefinite link to medical care or, alternatively, mistaken discharge. Thus, other clinical or serological markers should be available to accurately define the severity of compensated advanced liver disease and the remaining HCC risk after SVR.

COST-EFFECTIVENESS, BENEFITS AND RISKS OF HCC SURVEILLANCE

HCC surveillance aims to prolong patient survival and quality of life by improving early diagnosis and curative therapy. Based on estimated tumor doubling times, current guidelines recommend ultrasound every six months, and they establish an incidence of at least 1.5% per year to justify HCC surveillance. Although this threshold is likely too high due to the clinical benefits induced by DAA after SVR and the improvement in HCC therapies, it is not clear whether HCC surveillance remains cost effective in all patients with advanced fibrosis after SVR. Regarding this point, a study suggested that HCC surveillance is unlikely to be cost effective in patients with F3 fibrosis, whereas both annual and biannual modalities are likely to be cost effective for patients with cirrhosis compared with no surveillance[41]. The study suggested that an annual HCC incidence greater than 0.5% might be currently cost-effective, and it proved that both an APRI greater than 2 or an FIB-4 greater than 3.25 allow for the identification of patients for whom HCC surveillance becomes cost effective, suggesting that patients with values less than these thresholds should be discharged from follow-up evaluation. Another study evaluated the cost-effectiveness of risk-stratified HCC screening in cirrhosis based on a combination of biomarkers and clinical variables, including epidermal growth factor single-nucleotide polymorphism, age, sex, smoking status, alkaline phosphatase level, and platelet count. The study showed that HCC surveillance strategies targeting high- and intermediate-risk patients with cirrhosis are cost-effective. Finally, the authors suggested that omitting screening in the lowest-risk subjects was cost-effective compared with biannual screening, without sacrificing net survival benefit[42].

Moreover, in a recent opinion article, Jepsen *et al*[43] argued that randomized trials of HCC surveillance *vs* no surveillance are necessary to make formal recommendations involving thousands of patients. The authors made their arguments indicating that universal surveillance could negatively impact patients' quality of life by generating anxiety about the possibility of a cancer diagnosis. Furthermore, the problems associated with false positives in screening procedures and the need to be connected for life to hospital care in patients with negligible HCC risk are also matters of concern. Therefore, accurate models including predictive factors to identify different risk levels are likely the key to adequate follow-up of patients after SVR.

PREDICTIVE FACTORS OF HCC RISK

Multiple models including clinical, serological, molecular and elastographic variables have attempted to stratify HCC risk in patients with advanced fibrosis. Importantly, there are controversies about the markers that should be used and when they should be measured, considering the dynamic changes that occur after SVR. Table 1 summarizes some studies that have assessed the risk of HCC according to both baseline and dynamic risk factors.

Table 1 Studies assessing the risk of hepatocellular carcinoma according to baseline and dynamic risk factors

Ref.	Country	n	Population at risk	Diagnosis of cirrhosis	Treatment regimens	Baseline risk factors	Dynamic risk factors
Lleo <i>et al</i> [33], 2019	Italy	1766	All cirrhosis 11.4% Child B/C	1 or more of the following: Stage 4 fibrosis by METAVIR score, esophageal and/or gastric varices at endoscopy, LSM > 12.5 kPa	All were treated with DAA	Age > 50 years old and presence of esophageal varices, platelets < 110000/L and LSM > 25 kPa	Lack of SVR
Ioannou <i>et al</i> [44], 2018	United States	45810	23% cirrhosis	Clinical, based on ICD-9 or 10 codes for cirrhosis or its complications	Either IFN or DAA	Cirrhosis, SVR, ALT, AST, platelets, albumin, age	
Ioannou <i>et al</i> [45], 2019	United States	48135	9784 with pretreatment cirrhosis	Clinical, based on ICD-9 or 10 codes for cirrhosis or its complications	Either IFN or DAA	Cirrhosis and FIB-4 ≥ 3.25 before treatment	FIB-4 ≥ 3.25 post-SVR
Ravaioli <i>et al</i> [47], 2018	Italy	139	All cirrhosis; Included previous HCC 11.5% Child B		All were treated with DAA	History of previous HCC	Child B and LSM reduction after DAA treatment < 30%
Pons <i>et al</i> [48], 2019	Spain	572	All LSM ≥ 10 kPa; All compensated	cACLD defined by LSM ≥ 10 kPa	All were treated with DAA	High risk: baseline albumin < 4 g/dL; Low risk: Baseline albumin ≥ 4 g/dL	High risk: LSM ≥ 20 kPa or LSM 10-20 kPa and albumin < 4.4 g/dL; Low risk: LSM < 10 kPa or LSM 10-20 kPa and albumin ≥ 4.4 g/dL
Fan <i>et al</i> [50], 2020	China	3566	75.3% cirrhosis compensated and decompensated	Histological and/or radiological	Either IFN or DAA	aMAP score; Low risk: 0-50; Intermediate risk: 50-60; High risk: 60-100	
Alonso <i>et al</i> [49], 2020	Spain	993	Advanced fibrosis or compensated cirrhosis	Clinical or histological; advanced fibrosis defined by a LSM by TE > 9.5 Kpa	All were treated with DAA	Albumin < 4.2 g/dL; LSM > 17,3 kPa FIB-4 > 3.7	Delta LSM < 25.5%; FIB-4 > 3.3; GGT > 42 IU
Ioannou <i>et al</i> [62], 2020	United States	48151	All cirrhosis compensated and decompensated	Clinical, based on ICD-9 or 10 codes for cirrhosis or its complications	Either IFN or DAA	Deep learning RNN model Cirrhosis diagnosis, sex, race and HCV genotype 3	Development of cirrhosis, SVR, BMI, AST, ALT, bilirubin, FIB-4, APRI, platelets

LSM: Liver stiffness measurement; TE: Transient elastography; INF: Interferon; DAA: Direct-acting antiviral agent; HCV: Hepatitis C virus; SVR: Sustained virologic response; FIB-4: Fibrosis 4; HCC: Hepatocellular carcinoma; c-ACLD: Compensated advanced chronic liver disease; CP: Child-Pugh; FU: Follow-up; amap: age, male, ALBI and platelets; GGT: Gamma-glutamyltransferase; RNN: Recurrent neural networks; APRI: AST to platelet ratio index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index.

The study by Ioannou *et al*[44] introduced the need for risk modeling, suggesting that screening strategies based on HCC risk models were superior to “screen-all” or “screen-none” strategies. The proposed HCC risk model, which included the presence of cirrhosis, SVR, baseline ALT, AST, platelets, albumin and age, allowed us to calculate the individual risk of HCC. However, the definition of cirrhosis was made based on the presence of portal hypertension signs and/or clinical complications, suggesting that perhaps patients with advanced fibrosis or with early stages of cirrhosis could be misclassified as not having cirrhosis.

In a further study, the authors used a different evaluation of liver disease severity, introducing not only baseline data but also changes in FIB-4 over time, to assess

different HCC risk levels. In this second study, the authors showed that patients in whom FIB-4 was less than 3.25 before treatment and after SVR had a lower risk of HCC[45].

Other predictive models have included different combinations of laboratory and elastographic parameters. A study from Italy[33] aimed to evaluate the risk of HCC occurrence and recurrence in cirrhotic patients after DAA therapy. The authors identified a subgroup of patients with SVR and the “Extended Baveno Criteria”[46] (> 110000 platelets and $LSM < 25$ kPa), with an HCC incidence of 0.5%/per year, suggesting that the Baveno Criteria could be an appropriate tool for stratification, advising less frequent follow-up in this population.

Models that include dynamic changes after SVR could be especially relevant since they can identify patients with less severe disease more likely to regress or improve after SVR. The dynamic change in LSM as an HCC risk factor was previously described in a study showing that a reduction in liver stiffness $> 30\%$ at the end of treatment was associated with a significantly lower risk of HCC at one year after EOT [47]. In this study, TE was likely performed too early to detect regression or improvement, although it could identify those patients with overestimated fibrosis at baseline, in whom the resolution of inflammatory activity accounts for the rapid decrease in liver stiffness.

A Spanish study developed a model to estimate HCC risk in patients with c-ACLD after SVR. This study revealed that the combination of follow-up LSM and serum albumin levels at one year after SVR was able to identify different HCC risk groups. The authors observed that patients with $LSM < 10$ kPa or with LSM between 10-20 kPa and high albumin levels at follow-up had an incidence rate of HCC of less than 1/100 patients per year; thus, the authors considered them a low-risk group[48].

Furthermore, a recent large, multicenter cohort study performed in our unit[49] confirmed the impact of both baseline and dynamic changes in noninvasive markers on the risk of HCC development. We constructed two simple models: the first one included baseline albumin (g/dL) and LSM (Kpa) and the percentage of LSM variation one year after EOT. Patients with baseline albumin > 4.2 g/dL, baseline $LSM \leq 17.3$ kPa, and 1-year $\Delta LSM > 25.5\%$ had the lowest HCC risk (cumulative incidence of HCC at 3 years of 0%). Considering that LSM might not be universally available, we also built a second model that exclusively included noninvasive serological markers. Similarly, the FIB-4-based model identified patients with baseline albumin > 4.2 g/dL, baseline $FIB-4 \leq 3.7$, 1-year $FIB-4$ score ≤ 3.3 , and 1-year $GGT \leq 42$ IU/mL as the group with the lowest HCC risk (cumulative incidence of 0.4% at 3 years). Notably, our results suggested that baseline and dynamic LSM (or FIB-4, when TE is not available) could identify patients with a lower incidence of HCC after SVR that does not justify continuous HCC screening. Approximately 20% of the patients were considered to have low or very low HCC risk, and according to our findings, they could be safely discharged from surveillance.

Another recently validated predictive model is the aMAP score[50], which includes laboratory and clinical parameters such as the albumin-bilirubin score (ALBI score) platelets, age and sex. The score identifies two different risk groups, suggesting that only patients belonging to the high-risk group (aMAP score > 60) should undergo intensive surveillance to detect early HCC. This prognostic tool was externally validated in patients with different cirrhosis etiologies from 11 global prospective studies; interestingly, the score properly discriminated 5-year HCC irrespective of etiology of liver disease and ethnicity.

Thus, predictive models and risk scores, preferably based on baseline data and dynamic changes, are likely the best approach for determining the individual risk of HCC after SVR.

LONG-TERM RISK OF HCC: DOES IT DECREASE OVER TIME?

Different long-term studies in HCV patients treated with IFN-based regimens have documented a reduction in the incidence of HCC by 75% in patients with SVR[51-53]. Currently, there is growing evidence that the same occurs after DAA therapy. Several data have shown that SVR after DAAs does not have a significant impact on the development of HCC in the short or medium term since many of the patients were treated with a more advanced disease, it but reduces the risk of HCC in the medium and long term, like what occurs in patients treated with IFN-based regimens[9].

Conversely, it has been suggested that HCC risk persists for up to 10 years after HCV eradication in patients with baseline cirrhosis or high FIB-4 scores[45]. In this

study, HCC incidence remained > 2% per year even 10 years after antiviral treatment in patients with a high baseline FIB-4 ≥ 3.25 , especially if it remained ≥ 3.25 after SVR. Conversely, patients with baseline FIB-4 < 3.25 had an HCC incidence < 1%.

Moreover, aging and comorbidities that can occur or progress over time could have an additive effect on HCC risk. Consequently, there is no strong evidence to support a dynamic assessment of HCC risk over time, and the best strategy is likely to continue screening patients with intermediate and high HCC risk until they reach an age when it is no longer cost effective.

HCC SCREENING: WHO DOES BENEFIT AND FOR HOW LONG?

It seems clear that the current recommendations regarding HCC screening after SVR in HCV patients with advanced fibrosis at baseline should be modified in the future. While changes become formal, we provide below a proposal based on the current data (Figure 2).

Cirrhotic patients with baseline decompensated or compensated advanced liver disease with significant portal hypertension. HCC risk in this population remains greater than the accepted threshold for surveillance; therefore, biannual US screening is recommended.

Patients with findings of advanced chronic liver disease without clear evidence of baseline portal hypertension. In our opinion, these patients should be screened for HCC at least 1 year after EOT to evaluate early dynamic changes and make more accurate estimations of the individual HCC risk.

FUTURE STRATEGIES IN SURVEILLANCE

As previously stated, several questions remain concerning surveillance strategies. Most likely, the most important concern is that we do not have accurate information about whether HCC risk persists constantly over the long term and therefore for how long patients with medium or high risk should continue HCC surveillance.

It is possible that, in the near future, patients will benefit from a more specific biomarker panel, genetic and molecular profiles and even deep learning models to predict the risk of developing HCC.

Circulating biomarkers are promising tools for better stratification of patients[54-56]. Biomarker panels, such as the GALAD score, are excellent tools for the detection of early-stage HCC, including tumors with negative AFP (AUC of 0.96 for detection of early-stage HCC)[57,58]. As previously exposed, HCV induces epigenetic alterations persisting after DAA cure[13], so the opportunity to detect epigenetic changes of histones bound to circulating DNA in plasma represents a new opportunity to uncover biomarkers of HCC risk. These approaches could represent personalized, noninvasive and cost-effective alternatives based on clinical and biological findings for HCC screening.

The use of deep learning models, which have also been successfully applied in other settings to predict clinical events[59], could also be relevant. Various types of model architectures, such as recurrent neural networks, have been used to capture temporal dynamics and long-term information over time[60]. Recently, it was suggested that some machine-learning algorithms accurately stratify the risk of HCC in patients with cirrhosis, identifying those at high risk for developing HCC[61]. Additionally, it has been shown that, in terms of cost-effectiveness, deep learning and recurrent neural network models were able to improve HCC surveillance strategies in HCV patients, thereby identifying high-risk cases[62].

CONCLUSION

In conclusion, HCC surveillance in HCV patients should likely be based on an evaluation of individualized risk rather than exclusively based on baseline fibrosis stage. Currently available risk scores should be improved and validated, likely by including novel approaches, such as personalized biomarkers and deep learning methods.

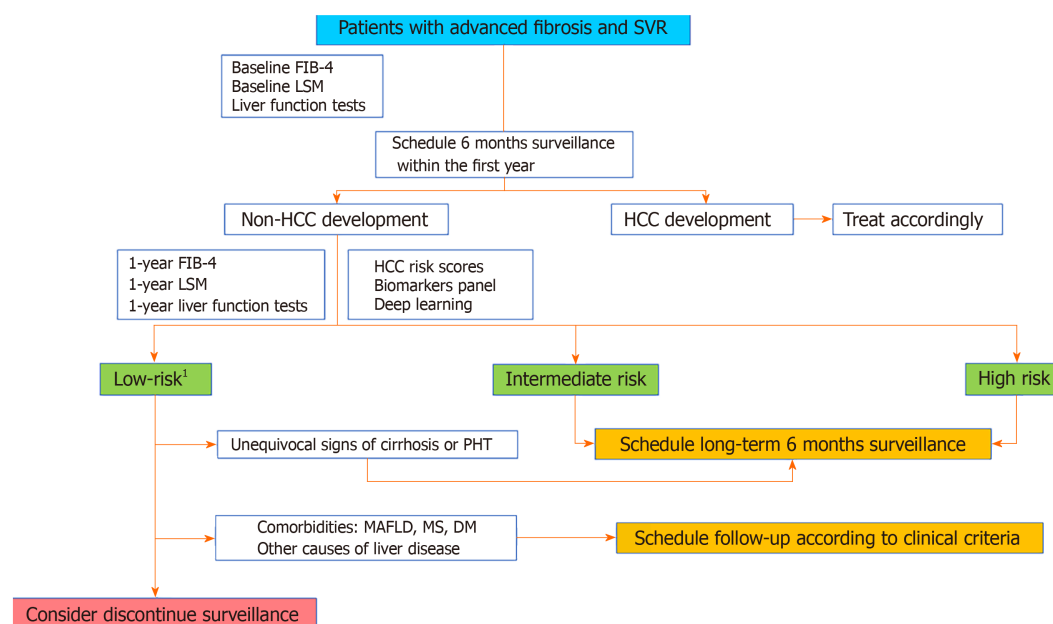


Figure 2 Surveillance hepatocellular carcinoma algorithm proposed. ¹Most likely, annual incidence < 0.5% per year. FIB-4: Fibrosis 4; LSM: Liver stiffness measurement; TE: Transient elastography; PHT: Portal hypertension; DM: Diabetes mellitus; MS: Metabolic syndrome; MAFLD: Metabolic associated fatty liver disease.

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