

# Perspectives on the Underlying Etiology of HCC and Its Effects on Treatment Outcomes

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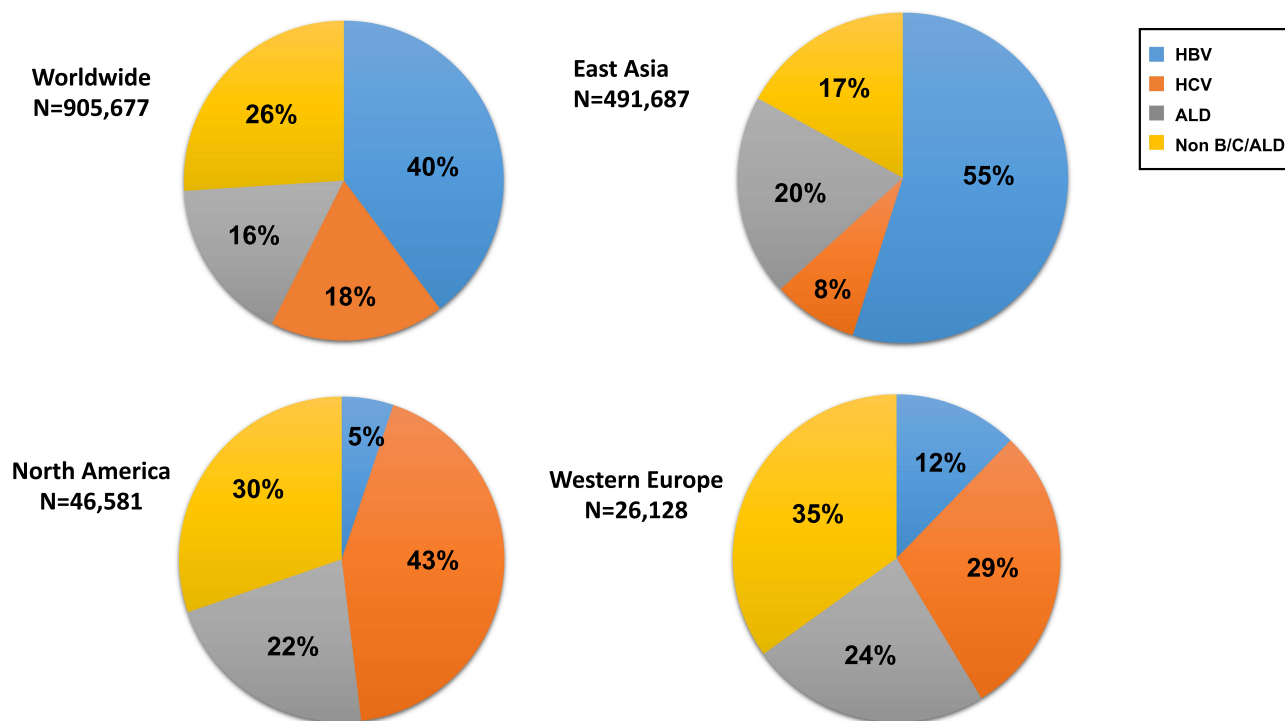
**Abstract:** Hepatocellular carcinoma (HCC) continues to be a serious medical problem with poor prognosis worldwide. The distribution of the major etiologies of HCC is changing due to the progress of anti-viral treatments, including hepatitis B virus (HBV) suppression by nucleoside/nucleotide analogues (NAs) and increased sustained virologic response (SVR) rates by direct-acting antivirals (DAAs) for hepatitis C virus (HCV), as well as the rising trend of nonviral liver disease. Although viral hepatitis remains the most common cause of HCC, non-alcoholic liver disease (NAFLD) with metabolic syndrome and alcohol-associated liver disease (ALD) are increasing. Effective and well-tolerated NAs treatment can slow the disease progression of chronic HBV infection to cirrhosis, end-stage liver disease, and reduce HCC risk. Treatment with NAs is also associated with significant improvement in the long-term survival of patients with HBV infection who already have HCC. DAAs have achieved viral elimination in almost all patients with HCV without significant adverse events, even in patients with decompensated liver cirrhosis and HCC. Similarly, DAA therapy can reduce disease progression, liver and non-liver complications, and improve the long-term survival of patients with chronic HCV infection with or without HCC. Meanwhile, NAFLD is a rapidly increasing cause of HCC along with the epidemics of obesity and type 2 diabetes globally. NAFLD-related HCC can occur in patients without cirrhosis and is known to have a lower survival rate than viral hepatitis-related HCC. Since there is currently no specific pharmacotherapy effective for NAFLD, lifestyle modification and prevention of complications are important to improve prognosis. Additionally, ALD is the second fastest-growing cause of HCC-related deaths, especially with an accelerated trend since the COVID-19 pandemic. This review provides an overview of the epidemiologic trends in the etiologies of HCC, and the progress of treatments for each etiology and the impact on outcome in the patients with HCC.

**Keywords:** hepatocellular carcinoma, etiology, hepatitis B, hepatitis C, non-alcoholic fatty liver disease, alcohol-associated liver disease

## Introduction

Liver cancer is the sixth most common malignant tumor ( $n = 905,677$ ; 4.7%) and is the third leading cause of cancer-related death ( $n = 830,180$ ; 8.3%) in 2020 based on GLOBOCAN database.<sup>1</sup> Among liver cancers, hepatocellular carcinoma (HCC) accounts for around 90% of primary malignant liver tumors.<sup>2,3</sup> Thus, HCC is one of the most common cancers worldwide and represents a major global health challenge.<sup>4-6</sup> Additionally, the incidence rate of HCC has been increasing for the last 3 decades in the United States and is projected to continue to rise through 2030.<sup>7,8</sup>

Meanwhile, the distribution of the major etiologies of HCC which include hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol, and metabolic disease (Figure 1) in contemporary clinical practice are changing along with increasing numbers of patients with sustained virological response (SVR) after HCV eradication by direct-acting antivirals (DAAs), of patients with suppressed HBV during nucleoside/nucleotide analogues (NAs) treatment, and of patients with non-alcoholic fatty liver disease (NAFLD) while alcohol-associated liver disease (ALD) remains a major contributor of HCC.<sup>9-11</sup> Prior studies have also reported differential disease presentation and natural history of nonviral HCC as



**Figure 1** The etiology of Liver cancer diagnosed as new cases based on GLOBOCAN 2020. Reproduced from GLOBOCAN 2020. Available from: <https://gco.iarc.fr/>.<sup>1</sup> East Asia includes China, Japan, Republic of Korea, Democratic People's Republic of Korea, and Mongolia. North America includes USA and Canada. Western Europe includes Austria, Belgium, France, Germany, Luxembourg, Switzerland, and Netherlands.

**Abbreviations:** HBV, hepatitis B virus; HCV, hepatitis C virus; ALD, alcohol-related liver disease.

compared to those of viral HCC.<sup>12</sup> Most recently, the COVID-19 pandemic has brought further changes with great impact on the changing epidemiology of chronic liver disease, particularly that of ALD as a result of increasing social isolation, increasing alcohol dependence, and poor access to mental health care.<sup>13</sup>

In this review, we discuss the epidemiologic trends in the etiologies of HCC, and the progress and impact of the treatment on the incidence and outcome of patients with HCC, with a focus on viral hepatitis, NAFLD, and ALD.

## Hepatitis B

HBV infection is a major global public health problem and is responsible for about 40% of the global HCC burden as of 2020 (Figure 1). The World Health Organization (WHO) estimates that worldwide, over 296 million people are positive for hepatitis B surface antigen (HBsAg) in 2019.<sup>14</sup> Chronic HBV infection progresses from an asymptomatic, persistently infected state to chronic hepatitis, cirrhosis, or HCC. Although there are no curative treatments for HBV currently, there are effective and well-tolerated suppressive anti-viral medications, which can slow the disease progression of chronic HBV infection to cirrhosis, end-stage liver disease (ESLD) and HCC.<sup>15</sup>

The two main classes of antiviral treatments for HBV are pegylated interferon- $\alpha$  (Peg-IFN $\alpha$ ) and nucleos(t)ide analogs (NAs).<sup>16,17</sup> However, the relatively high variability of response and unfavorable safety profile limit the Peg-IFN $\alpha$  use.<sup>16</sup> Due to its excellent safety and tolerability profile coupled with excellent effectiveness in suppressing viral replication, NAs may be the preferred option to Peg-IFN $\alpha$  for the vast majority of patients and has been the most commonly used antiviral agents for chronic HBV infection worldwide. Since 2005 and 2008, entecavir (ETV) and tenofovir disoproxil fumarate (TDF), respectively, have been the mainstay of treatment for chronic HBV infection because of their high genetic barrier against HBV resistance.<sup>17–19</sup> More recently, tenofovir alafenamide (TAF), a prodrug of tenofovir modified to be more quickly and thoroughly absorbed into the cells and thus reducing potential risks of renal impairment and bone loss, is another first-line treatment for chronic HBV infection.<sup>20</sup>

Though the use of NAs does not eliminate the risk of HCC in treated patients, it has been shown to significantly reduce the risk of HCC while also reducing the risk of progression to cirrhosis and ESLD or even reversing ESLD.<sup>15</sup> Several studies have reported that suppression of viruses using NAs by keeping a low or undetectable HBV DNA leads to a reduction of hepatocarcinogenesis.<sup>17,19,21</sup> An early study demonstrated reduced HCC incidence with long-term treatment with ETV in HBV patients with cirrhosis but not in non-cirrhosis.<sup>22</sup> Since then, additional studies have confirmed the benefit of HCC prevention with other antiviral agents for a wider range of patients with chronic HBV infection to include those without cirrhosis.<sup>23</sup> There have also been conflicting reports on the effectiveness of ETV and TDF in HCC prevention with some finding TDF to be superior while some found no significant differences between the two.<sup>24–26</sup> However, it appears that the source of heterogeneity and inconsistencies lies in the differences of not only the baseline characteristics but also the length of follow-up observation between the ETV vs TDF study populations among these various studies. Though TDF was approved only 3 years after ETV, reimbursement for TDF came many years after ETV, the higher HCC occurrence rates observed among ETV-treated patients may have been due to the fact that they were just observed for a longer time. Additionally, due to the “warehousing” effect for ETV as the first “good” antiviral agent, ETV-treated patients tended to have more advanced liver disease and thus higher risk for HCC and background risks between ETV-treated and TDF-treated patients may not have been adequately balanced by some studies, especially those relying on administrative claims database which usually lack detailed clinical and/or laboratory data. Indeed, in a recent meta-analysis involving 24,269 patients (tenofovir, n = 10,534 and entecavir n = 13,735) from 14 studies, no significant difference in the risk of HCC between patients who received ETV and patients who received TDF was found.<sup>27</sup> In the same meta-analysis, between study heterogeneity was resolved once studies based on administrative database and studies with significant differences in the follow-up time between the study groups were excluded. Currently, there are no long-term data regarding HCC risk for the newer first-line HBV medication TAF, though some studies have demonstrated that switching from ETV or TDF to TAF can lead to further increase in virologic response, while preserving renal function.<sup>28–35</sup>

Currently, professional society guidelines recommend antiviral treatment for patients without cirrhosis with elevated HBV DNA ( $\geq 2000$ – $20,000$  IU/mL) and elevated alanine aminotransferase (ALT) levels or fibrosis stage 2 or higher (Table 1)<sup>16,17,36–38</sup>. For patients with cirrhosis especially those with decompensated cirrhosis, antiviral therapy is generally recommended for patients with any level of detectable HBV DNA and irrespective of ALT levels.<sup>39–41</sup> However, viral suppression could reduce liver-related mortality, the effect of NAs on hepatocarcinogenesis in decompensated HBV cirrhosis may be limited as HCC incidence and non-liver mortality were not found to improve with NA therapy in a prior study.<sup>42</sup> On the other hand, among patients with existing HCC, antiviral therapy has been shown to associate with significant improvement in overall survival even in patients with decompensated cirrhosis, patients with advanced HCC stage, and in patients with supportive care only.<sup>43,44</sup>

**Table I** Summary of Latest Society Guidelines for Treatment of Chronic Hepatitis B

Guidelines	APASL 2015 <sup>38</sup>	EASL 2017 <sup>17</sup>	AASLD 2018 <sup>16,36</sup>	US Panel Algorithm 2021 <sup>37</sup>
<b>When to start treatment</b>	<ul style="list-style-type: none"> <li>• ALT level <math>&gt; 2 \times</math>ULN and HBV DNA level of <math>&gt;2000</math> IU/mL (HBeAg negative) or <math>&gt;20,000</math> IU/mL (HBeAg-positive) and/or moderate to severe inflammation or significant fibrosis</li> <li>• Compensated cirrhosis with HBV DNA level of <math>&gt;2000</math> IU/mL or with HBV DNA detectable if elevated ALT</li> <li>• Decompensated cirrhosis with detectable HBV DNA</li> </ul>	<ul style="list-style-type: none"> <li>• HBV DNA level of <math>&gt;2000</math> IU/mL, ALT level <math>&gt; \text{ULN}^a</math>, and/or at least moderate liver necroinflammation or fibrosis</li> <li>• HBV DNA level of <math>&gt;20,000</math> IU/mL and ALT level <math>&gt; 2 \times</math>ULN</li> <li>• Compensated or decompensated cirrhosis with detectable HBV DNA</li> <li>• HBeAg positive, high HBV DNA level, and age <math>&gt;30</math> yr</li> <li>• Family history of HCC or cirrhosis and extrahepatic manifestations</li> </ul>	<ul style="list-style-type: none"> <li>• ALT level <math>&gt; 2 \times</math>ULN<sup>b</sup> and HBV DNA level of <math>&gt;2000</math> IU/mL (HBeAg negative) or <math>&gt;20,000</math> IU/mL (HBeAg positive)</li> <li>• Compensated or decompensated cirrhosis with detectable HBV DNA</li> <li>• Other factors include age <math>&gt;40</math> yr, family history of HCC, previous treatment, and presence of extrahepatic manifestations</li> </ul>	<ul style="list-style-type: none"> <li>• ALT level <math>&gt; \text{ULN}^c</math>, HBV DNA level of <math>&gt;2000</math> IU/mL</li> <li>• Normal ALT with significant fibrosis and detectable HBV DNA</li> <li>• Compensated or decompensated cirrhosis with detectable HBV DNA</li> </ul>

**Notes:** <sup>a</sup>The ULN for ALT is 40 U/liter. <sup>b</sup>The ULN for ALT in healthy adults is 35 U/liter for males and 25 U/liter for women. <sup>c</sup>The ULN for ALT in healthy adults is 30 U/liter for males and 19 U/liter for females.

**Abbreviations:** ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

Unfortunately, it is estimated that only about 15% of patients with HBV infection in the US have been diagnosed, only about 70% of diagnosed patients who were linked to care undergo adequate evaluation for treatment, and only about 70% of those evaluated and met treatment criteria would receive treatment.<sup>44–47</sup> Most disturbingly, less than half of patients with chronic HBV infection and advanced disease such as cirrhosis or HCC received antiviral therapy.

Mother-to-child transmission (MTCT) is a major route for transmitting HBV. In order to prevent MTCT, all pregnant women should first be screened for HBsAg. Additionally, the combination of HBV vaccination and hepatitis B immune globulin (HBIG) is the most effective way to reduce the risk of MTCT.<sup>17</sup> On the other hand, infants born to women with high HBV viral load ( $>2 \times 10^5$  IU/mL) and with HBeAg positive are at high risk of MTCT, even if HBIG and HBV vaccine administration is completed immediately after birth. For these pregnant women with high HBV loads, NA therapy can reduce the incidence of MTCT of HBV without increasing adverse events related to pregnancy outcomes of the fetus.<sup>16,17,38,48</sup> As for the type of NA used, WHO recommends that pregnant women with high HBV viral load take TDF from the 28th week of pregnancy until at least delivery.<sup>49</sup> Thus, HBV-related HCC is a vaccine-preventable cancer.

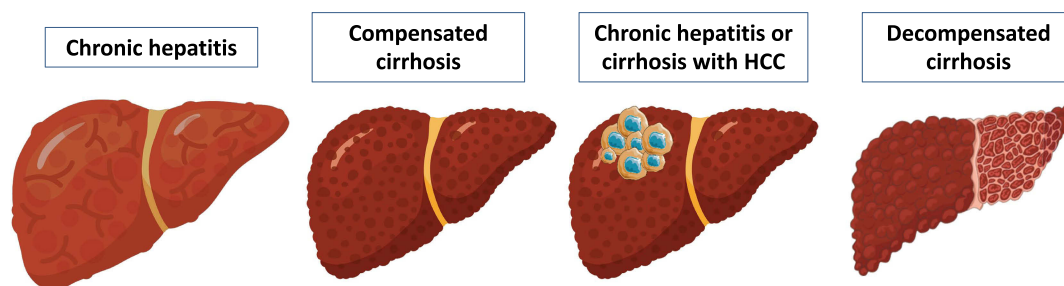
In summary, HBV contributes to almost half of the global HCC burden. While HBV-related HCC can be prevented by effective and well-tolerated NAs and the overall mortality in patients with HBV-related HCC can be reduced by NA treatment, HBV diagnosis and treatment rates are suboptimal, even for patients with severe complications such as HCC. Further education and public health efforts are needed to improve the currently poor linkage to care for patients with HBV infection.<sup>44</sup>

## Hepatitis C

HCV affects approximately 58 million people and contributes to 18% of the HCC burden worldwide (Figure 1).<sup>50</sup> The chronic infection of HCV is one of the leading causes of liver cirrhosis and HCC, but the progression to cirrhosis is often clinically silent as well as HBV infection, and some patients are unaware of the HCV infection.<sup>51–53</sup> Among patients with cirrhosis and HCV infection, HCC develops at an average rate of 3% to 7% per year based on the data before interferon (IFN) free direct-acting antivirals era (DAAs).<sup>54,55</sup> The achievement of a sustained virologic response (SVR) to antiviral treatment for HCV has been shown to prevent liver-related complications in patients with HCV-related cirrhosis.<sup>56–58</sup>

Although IFN had been used for anti-HCV therapy for decades, peg-IFN-based therapy was contraindicated in some patients due to its adverse event (AE) and serious adverse event (SAE) profiles.<sup>59</sup> Since 2013, highly efficacious and well-tolerated IFN-free-DAA regimens have revolutionized HCV treatment with cure rate of over 90% including most historically difficult-to-treat patient groups such as those with decompensated cirrhosis and HCC<sup>60–69</sup> (Figure 2).

For patients with chronic HCV infection who have not yet developed HCC, the first reports regarding the preventive effect of DAA on HCC development in patients with chronic hepatitis C (CHC) indicated conflicting results. Early small case series reported a higher de novo HCC incidence and higher rates of HCC recurrence following HCV cure by IFN-free DAA



### ● DAA for Hepatitis C

SVR rate (SVR12)	> 99 % <sup>63–65</sup>	97–99 % <sup>66, 67</sup>	93–94% (inactive HCC) 73–85 % (active HCC) <sup>62, 68</sup>	83.3 % <sup>69</sup>
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**Figure 2** Sustained virologic response (SVR) rate with interferon-free direct-acting antivirals (DAAs) in hepatitis C patients with or without cirrhosis / HCC. **Abbreviations:** SVR, Sustained virologic response; DAA, direct-acting antivirals; HCC, hepatocellular carcinoma; SVR, sustained viral response.<sup>62–69</sup>

therapy,<sup>70,71</sup> while some other studies showed that an SVR was associated with reduced risk of HCC development.<sup>72–74</sup> A landmark meta-analysis of 41 studies on HCC occurrence and recurrence in both IFN- and DAA-treated HCV patients found that DAA-treated patients were much older biasing towards higher HCC rate in such patients, and that most HCC occurrences in DAA-treated patients occurred within 6–12 months of DAA therapy, suggesting those HCC cases were probably prevalent HCC rather than new HCC development.<sup>75</sup> In fact, following meta-regression analysis adjusting for relevant confounders, there was no significant difference in HCC risk among patients treated with IFN versus those treated with DAA in this meta-analysis. The findings of this meta-analysis of early studies have been confirmed by large cohort studies of patients for both HCC recurrence and HCC occurrence and in both Western and Eastern patients.<sup>61,76</sup> As a result, professional society guidelines have recommended IFN free-DAA treatment to reduce the risk of HCC.<sup>60,77</sup> Taken together, it has been shown that DAAs treatment reduces HCC risk and does not increase the risk of HCC incidence/recurrence. In the case of patients with HCV infection and decompensated, cirrhosis, DAA therapy has also shown a high rate of viral clearance (SVR rate >90%),<sup>60</sup> improved hepatic function,<sup>78</sup> reduced liver transplantation due to hepatic decompensation,<sup>79</sup> as well as reduced new HCC development (HCC developed 6 months after DAA treatment).<sup>80</sup>

As in the case with HBV, antiviral treatment reduces HCC risk but does not eliminate the risk though in the case of HCV, the risk mainly persists in patients who already developed advanced fibrosis or cirrhosis prior to HCV treatment and cure.<sup>81</sup> Reported risk factors of de-novo HCC after SVR include older age, male sex, the presence of diabetes, alcohol consumption, and viral co-infections.<sup>82</sup> Although no established therapy exists for preventing hepatocarcinogenesis after the achievement of SVR, there are several reports on medications showing efficacy in preventing the development of HCC in CHC patients with diabetes and dyslipidemia. Very recently, Tsai et al showed that the use of metformin reduced the HCC risk after SVR by IFN-based antiviral therapy in diabetic patients with CHC. A simple risk stratification composed of cirrhosis and DM non-metformin use could predict the long-term outcomes of CHC patients who achieved SVR.<sup>83</sup> Statin use has been reported to be associated with the reduction of HCC and cirrhosis risk in a dose-dependent manner in CHC patients or those without antiviral therapy.<sup>84,85</sup> Nevertheless, since HCC risk persists after HCV cure, higher risk patients should continue to undergo regular HCC surveillance with tumor markers (eg,  $\alpha$ -fetoprotein) and imaging every 6 months.<sup>86–88</sup>

For patients with HCV infection who have already developed HCC, early reports also suggested concerns for lower SVR with DAA though DAAs were shown to be safe and well tolerated.<sup>81,89,90</sup> However, the number of patients included in these early studies was relatively small and there was heterogeneity of clinical characteristics. A large systematic review and meta-analysis showed significantly lower SVR rate in active HCC (HCC that have not been treated or treated adequately) but not in inactive/ablated HCC (HCC that have been treated and without evidence of residual viable HCC on imaging) (Figure 2, Table 2).<sup>68</sup> Another study with individual data of 6081 patients (HCC, n = 465; non-HCC, n = 5616) treated by interferon-free DAAs from a multi-center international cohort indicated a similar result with inactive HCC having a similar SVR rate as non-HCC patients and active HCC having lower SVR compared with inactive HCC or non-HCC patients, though the cure rate was still relatively high (85%) in active HCC patients (Table 2).<sup>62,68,91</sup> Therefore, to achieve optimal cure rate with DAA, DAA therapy should be delayed in patients with HCV-related HCC until HCC treatment has been completed, except in cases where early DAA treatment may help improve liver function to allow for HCC treatment that would otherwise not be an option due to impaired hepatic function.

Another issue in patients with HCV infection who already developed HCC is whether treatment with DAA can improve overall survival. A large multicenter US study showed significant improvement in survival of DAA-treated patients with HCC, as well as a large multinational study inclusive of patients from the US and Asia Pacific region.<sup>61,92</sup> In the latter study, HCV-related HCC patients who achieved SVR had a 63% lower risk of 5-year all-cause and 66% lower risk of 5-year liver-related mortality compared with patients untreated for HCV after adjusting for relevant confounders.<sup>92</sup> Taken together, DAA therapy should be considered in all HCV-related HCC patients who are not yet moribund.<sup>61,92</sup>

In summary, DAA therapy is safe, efficacious with cure rate of >90%, and highly effective in the prevention of HCC in HCV-infected patients who have not developed HCC including those with decompensated cirrhosis and should be considered in all such patients. For patients with HCV infection who have developed HCC, DAA therapy is also safe, efficacious (>90% in well-treated HCC and 85% in active HCC), and can improve overall survival by over 60%.

**Table 2** Sustained Virologic Response (SVR) with Interferon-Free Direct-Acting Antivirals (DAAs) and Outcome in Patients with HCV-Related HCC Who Have Achieved SVR

Author/ Publication Year	Country/Region	DAA-Treated HCC Patients (n)	SVR in HCC Patients	SVR in Patients with Active HCC	SVR in Patients with Inactive HCC	SVR in HCC Patients with LC		SVR in HCC Patients Without LC		5-Year Overall Survival	
						Active HCC	Inactive HCC	Active HCC	Inactive HCC		
Beste et al 2017 <sup>81</sup>	USA	482	74.4% †91.1% in the non-HCC group †94.0% in the HCC/LT group			73.0% †87.9% in non-HCC patients with LC		82.5% †92.4% in non- HCC patients without LC			
Ji et al 2019 <sup>68</sup>	15 countries from USA, Japan, Italy, Egypt, France, China, Spain, United Kingdom, Germany, Switzerland, Romania, Belgium, Australia, Canada, and Poland	2581 *Including active HCC patients (n=277) and inactive HCC patients (n=2304)	89.6% †93.3% in the non-HCC group (P=0.0012)	73.1%	92.6%						
Ogawa et al 2020 <sup>62</sup>	Hong Kong, Japan, South Korea, and Taiwan	436 *Including active HCC patients (n=55), inactive HCC patients (n=366) and unknown (n=15)	92.7% †95.0% in the non-HCC group (P=0.16)	85.5%	93.7%						
Dang et al 2020 <sup>92</sup>	USA, Japan, South Korea, and Taiwan	321 *All achieved SVR *Propensity Score Matching patients								87.78% †66.05% in DAA- untreated HCC patients (P <0.001)	
He et al 2020 <sup>90</sup>	13 countries from France, Canada, US, Italy, UK, NZ, Spain, Egypt, Germany, Japan, Taiwan, Poland, and China	361	82.5% †90.4% in the curative HCC management group								
Chen et al 2021 <sup>91</sup>	Taiwan	1473 *Including active HCC patients (n=328) and inactive HCC patients (n=1145)	96.5% †98.5% in the non-HCC group (P <0.001)	93%	97.6%		Active HCC	Inactive HCC	Active HCC	Inactive HCC	
						Naïve LC	91.6%	97.7%	96.3%	96.3%	
						Prior treatment experience	92.2%	98.2%	98.1%	96.6%	

**Notes:** This table includes only studies with a number of DAA-treated HCC patients > 100. \*Comments on study population or/and method, †Analysis in subgroup.

**Abbreviations:** DAA, direct-acting antivirals; SVR, sustained virologic response; HCC, hepatocellular carcinoma; LC, liver cirrhosis; LT, liver transplantation; HR, hazard ratio; CI, confidence interval.

Therefore, DAA therapy should be considered in patients with HCV-related HCC whose HCC is not pre-terminal, though treatment should be delayed until after adequate HCC treatment in most cases.

## NAFLD

Another major and emerging cause of HCC globally is NAFLD (Figure 1). In both Asia and Western countries, NAFLD is increasing along with the epidemics of obesity and type 2 diabetes.<sup>93,94</sup> NAFLD is now a leading cause of cirrhosis, and is becoming the most common underlying chronic liver disease in patients with HCC awaiting orthotopic liver transplantation (OLT).<sup>95</sup> The prevalence of NAFLD is estimated to be 30% of the overall global population and this number is predicted to increase up to 55.7% by 2040.<sup>96</sup> Even in areas with historically lower NAFLD prevalence such as Japan, a recent systematic review and meta-analysis with forecasting found an overall NAFLD prevalence for Japan to be 25.5%, with an annual increase of 0.64% to reach 39.3% in 2030 and 44.8% in 2040.<sup>93</sup> NAFLD associated with metabolic syndrome has been considered a typical Western condition, but its prevalence has been increasing in Asia in recent years.<sup>94</sup> This is related to lifestyle changes associated with rapid economic growth in Asia (eg, westernized diets and physical activity).<sup>97</sup>

The percentage of cases with NAFLD/nonalcoholic steatohepatitis (NASH)-related HCC has also increased.<sup>10</sup> Compared with other etiologies, including viral hepatitis, NAFLD-related HCC was reported to be associated with lower surveillance receipt for HCC, and a lower rate of early-stage detection.<sup>98</sup> Due to a lack of awareness of NAFLD-related HCC in primary care and often delayed diagnosis, some patients with NAFLD-related HCC are diagnosed as advanced-stage with poor overall survival.<sup>99,100</sup> In addition, patients with NAFLD-related HCC are often older and with more comorbidities such as metabolic syndrome, cardiovascular diseases, and chronic kidney disease as compared to HCC patients due to the other etiologies.<sup>101,102</sup> For these reasons, curative treatment such as surgery may not be possible in many cases, and the prognosis for NAFLD-related HCC is poor.

Previous studies have shown that liver fibrosis is a well-known key driver of mortality in patients with NAFLD, and is strongly associated with the incidence of liver-related events, including hepatic carcinogenesis.<sup>103,104</sup> Meanwhile, it is also known that HCC can develop in non-cirrhotic patients with NAFLD. In a systematic review and meta-analysis based on the 19 studies with 168,571 participants, the prevalence of HCC in non-cirrhotic NASH is significantly higher than that in non-cirrhotic patients with chronic liver diseases of different etiologies, with a prevalence of 38% and 14%, respectively ( $P < 0.001$ ).<sup>105</sup> Currently, there is no established regular HCC surveillance system for patients with non-cirrhotic NAFLD.<sup>106</sup>

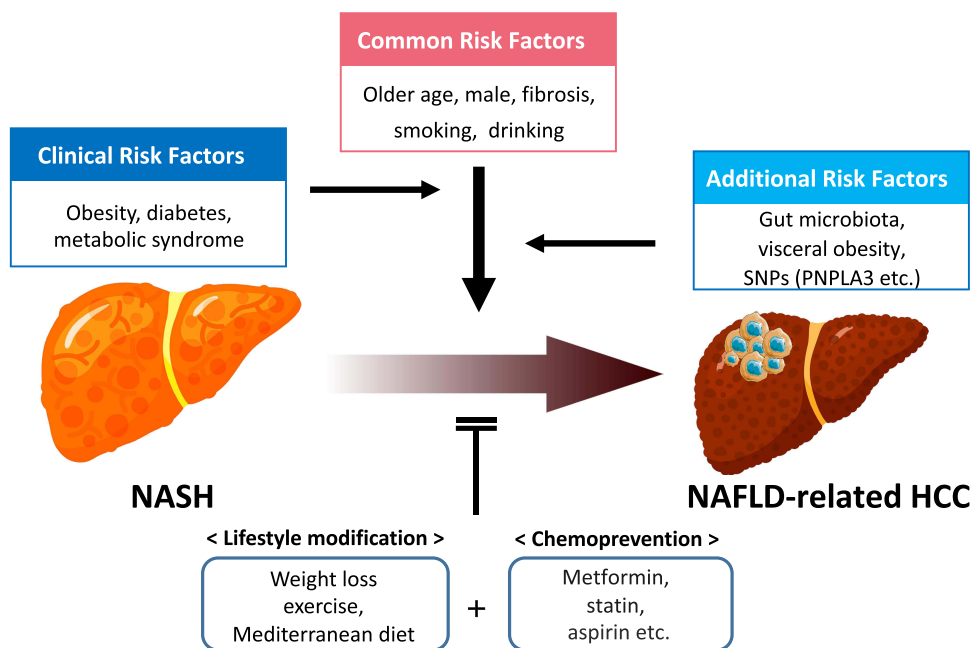
The mechanism of hepatocarcinogenesis in patients with NAFLD/NASH is complex and not fully understood. As with chronic liver disease of other etiologies, well-known common risk factors for HCC in patients with NAFLD also include older age, male sex, fibrosis stage, cigarette smoking, and alcohol consumption (Figure 3). Diabetes and obesity are also risk factors of HCC in NAFLD patients.<sup>107,108</sup> The presence of type 2 diabetes and metabolic syndrome along with diabetes increases the risk of HCC 2-fold and 5-fold, respectively, while obesity (body mass index [BMI]  $>30$  kg/m<sup>2</sup>) and severe obesity (BMI  $>35$  kg/m<sup>2</sup>) can increase the risk of HCC 2-fold and 4-fold, respectively.<sup>100</sup> Inflamed visceral adipose tissue induced by obesity secretes pro-inflammatory adipocytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- $\alpha$ ), thereby promoting systemic inflammation and insulin resistance, further exacerbating NAFLD.<sup>109,110</sup> Besides, the development of HCC in NAFLD is influenced by genetic variation. A single nucleotide polymorphism (SNP) of patatin-like phospholipase domain-containing 3 (*PNPLA3*) (rs738409) is among the most well-known risks associated with hepatic steatosis, steatohepatitis, cirrhosis, and risk of HCC and mortality in NAFLD patients.<sup>111–118</sup> Changes of gut microbiota are also thought to be a cause of HCC in NAFLD patients.<sup>119</sup> In patients with NAFLD, increased intestinal permeability associated with disruption of tight junctions deteriorates gastrointestinal leakage, allowing bacterial translocation or invasion of bacterial-derived products, such as lipopolysaccharide (LPS). Alterations in the gut microbiome that affect the gut–liver axis are common in individuals with obesity and are also associated with the progression of chronic liver disease and advanced fibrosis, such as NAFLD and cirrhosis.<sup>120–123</sup> Taken together, the causes of NAFLD progression and HCC are not simple and are intricately related to each other, which makes it more difficult for NAFLD-related HCC prevention.

NAFLD is generally associated with metabolic syndrome accompanied with obesity and insulin resistance, but it can develop in lean individuals, namely “lean NAFLD”. Of note, recent studies have shown that lean NAFLD, despite the absence of obesity, has a similar or poorer mortality risk as that of individuals with obesity and NAFLD.<sup>93,124,125</sup> However, whether the incidence of HCC in lean/non-obese NAFLD differs from those with obese/overweight NAFLD remains undetermined. It is possible that a subpopulation at high risk for HCC, such as “burned-out NASH” and sarcopenic obesity with metabolic syndrome, may be included in lean NAFLD.

The presence of hepatic steatosis also affects the risk of developing HCC in patients with viral hepatitis. Hepatic steatosis is among the factors associated with increased risk of HCC in HCV patients after DAA treatment.<sup>76</sup> The impact of hepatic steatosis on the natural history of chronic HBV infection is more controversial with studies showing conflicting results.<sup>126–128</sup> Recently, a panel of international experts from 22 countries proposed a new diagnostic entity called metabolic dysfunction-associated fatty liver disease (MAFLD), which can coexist with other liver diseases.<sup>129</sup> MAFLD would include patients with other causes of liver disease such as viral hepatitis, as opposed to NAFLD which requires exclusion of other liver disease.

For patients with NAFLD/NASH, the changes in lifestyle and management of metabolic risk factors may help prevent disease progression and consequently HCC (Figure 3). The primary treatment for overweight/obese patients with NAFLD is weight loss, which can improve liver steatosis and inflammation and suppress the progression of liver fibrosis.<sup>130</sup> However, its effect on decreasing HCC incidence has not yet been established. On the other hand, a recent study of 467,336 cases from a European cohort showed that physical activity is associated with a reduced risk of developing liver cancers over the next decade. For those reporting >2 hours/week compared to those with no vigorous activity, the hazard ratio (HR) for HCC was 0.50 (95% CI 0.33–0.76).<sup>131</sup> Turati et al reported that closer adherence to the Mediterranean diet can decrease HCC risk based on case-control studies undertaken in Italy and Greece that included 518 cases of HCC and 772 controls.<sup>132</sup> The Mediterranean diet is recommended by the European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO).<sup>133</sup>

There have also been several studies regarding medications with the effect of decreasing the risk of HCC in patients with fatty liver (Figure 3). Prior studies have demonstrated reduced HCC risk with long-term metformin use in diabetic



**Figure 3** Risk factors and prevention for HCC development in patients with NAFLD.

**Abbreviations:** HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; SNPs, Single Nucleotide Polymorphism; PNPLA3, patatin-like phospholipase domain-containing 3 gene; NASH, nonalcoholic steatohepatitis.



patients with NASH and advanced fibrosis,<sup>134</sup> with incremental decrease of HCC risk with each year of metformin use in diabetic patients.<sup>135</sup> Currently, there is insufficient evidence to support the regular use of metformin for preventing HCC in NAFLD patients without diabetes, but it should be considered in patients with NAFLD complicated by type 2 diabetes. Interestingly, in a large cohort study of 85,963 NAFLD patients with diabetes, while the use of metformin reduced 20% lower risk of HCC compared with no medication, the use of combination therapy with insulin and other oral medications was associated with increased risk, though adequate glycemic control overall was associated with a 31% lower risk of HCC.<sup>136</sup>

As seen with patients with HCV infection, statins have also been found to have a protective effect in reducing HCC risk in NAFLD patients. Statin use was significantly associated with 53% lower hazards of developing HCC in NAFLD in a nationwide cohort of 272,431 patients with NAFLD in the U.S., with consistent finding after adjusting for liver fibrosis.<sup>137</sup> A dose-dependent effect was also observed in this study.

Vitamin E use (800 IU/day) is another commonly recommended chemotherapy for patients with NAFLD and it has been shown to associate with significant reductions in overall mortality and hepatic decompensation failure in patients with bridging fibrosis and cirrhosis due to NAFLD, irrespective of the presence of diabetes, though it did not reduce the risks of HCC, vascular events, or extra-hepatic malignancies.<sup>138</sup>

Also, as observed with chronic viral hepatitis,<sup>139</sup> daily aspirin use was associated with less advanced histologic features of NAFLD and NASH, and lower risk for progression to advanced fibrosis with time.<sup>140</sup> Therefore, low-dose aspirin use has been advocated for patients with NAFLD to prevent HCC and progression of liver histology, as long as the risk of bleeding is acceptable.

In summary, NAFLD is a fast-emerging cause of HCC worldwide. NAFLD-related HCC often present in late-stage, can occur in patients without cirrhosis, and has poorer survival rates than viral-related HCC. Improved diagnosis and more accurate risk stratification for patients with NAFLD are needed, so appropriate patients can be identified to enter HCC surveillance as well as other therapeutic intervention.

## Alcohol-Associated Liver Disease

ALD refers to a wide spectrum of direct liver injuries ranging from steatosis, alcohol-associated hepatitis, cirrhosis, and HCC that are caused by excess alcohol consumption. As the International Agency for Research on Cancer (IARC) classifies alcohol as a group 1 human carcinogen,<sup>141</sup> alcohol consumption leads to approximately 5% of the global burden of cancer.<sup>142</sup> As mentioned above, alcohol is the second fastest-growing cause of liver cancer-related deaths from 2010 to 2019 after NAFLD,<sup>10</sup> and alcohol use disorder (AUD) has become an urgent global issue.

Liver cancer accounted for 830,180 deaths, and 150,000 cases of those were associated with alcohol drinking in 2020.<sup>1</sup> Although varied by region/country, an estimated 19% of deaths from liver cancer and 25% of cirrhosis deaths were associated with alcohol in 2019 (Figure 1).<sup>10,11,143</sup> The global estimated age-standardized death rate (ASDR) for alcohol-associated cirrhosis and liver cancer was 4.5 cases (95% confidence interval (CI) 3.8–5.3) and 1.1 deaths (95% CI 0.9–1.3) per 100,000 population in 2019, respectively.<sup>10,11,143,144</sup> The average level of alcohol consumption worldwide increased steadily from 5.5 liters in 2005 to 5.8 liters of pure alcohol per capita in 2019 and is predicted to increase to 7.6 liters in 2030.<sup>145</sup> In parallel with the increasing global per-capita alcohol consumption, ASDR for alcohol-associated HCC is increasing.<sup>144</sup>

The annual incidence of HCC among patients with alcohol-associated cirrhosis was reported at 0.9% to 5.6%,<sup>146,147</sup> and the cumulative incidence of HCC in alcohol-associated cirrhosis at 1, 5, and 10 years were reported 1%, 3%, and 9%, respectively.<sup>148</sup> Whereas alcohol consumption was found to have a strong association with increased risks of mortality and hepatic decompensation in a dose-dependent manner among patients with alcohol-associated cirrhosis, an association between alcohol use and the development of HCC was controversial<sup>149</sup>. Since women are more susceptible to alcohol-induced liver injury than men, women are at higher risk for developing cirrhosis than men with the same amount of alcohol consumption.<sup>150,151</sup> However, as alcohol consumption is substantially higher in men, ASDRs of alcohol-associated liver cancer are higher in men compared with women.<sup>152</sup>

The COVID-19 pandemic has inflicted a large impact on both the physical and mental well-being of people leading to increased alcohol consumption and dependence. There are diverse findings in trends of alcohol consumption during the

COVID-19 pandemic.<sup>153–155</sup> A nationwide USA survey demonstrated a 14% increase in alcohol consumption in 2020 compared with 2019<sup>156,157</sup> and predicted the increase of ALD over the next few years as a result.<sup>158</sup> Indeed, age-standardized mortality rates (ASMR) for ALD and NAFLD substantially increased during the COVID-19 pandemic with the largest disparities among the young, non-Hispanic White, and Alaska Indian/Native American populations.<sup>159</sup> The one-year increase in alcohol consumption during the COVID-19 pandemic was estimated to result in 8000 additional ALD-related deaths (95% uncertainty interval [UI], 7500–8600), 18,700 cases of decompensated cirrhosis (95% UI: 17,600–19,900), and 1000 cases of HCC (95% UI: 1000–1100) between 2020 and 2040.<sup>158</sup>

Since the proportion of HCCs diagnosed during the cirrhosis follow-up was lower in the non-abstinent cirrhosis patients compared to the abstinent patients (11.9% vs 28.4%;  $P < 0.0001$ ) while overall survival was also demonstrated to increase from 7.6 months in non-abstinent alcohol-related HCC patients to 11.7 months in abstinent alcohol-related HCC,<sup>160</sup> the importance of alcohol abstinence cannot be over-emphasized. However, it should also be noted that the association between alcohol abstinence and reduced HCC risk was only observed in patients with compensated alcohol-associated cirrhosis and not in decompensated patients<sup>161</sup>. Furthermore, while 27% of ALD patients can achieve histological normalization with abstinence, 18% would still progress to cirrhosis.<sup>162,163</sup> These findings indicated the need for an early diagnosis of ALD and early intervention for AUD including abstinence, treatment of withdrawal syndrome, relapse prevention medications and nutritional support.<sup>164,165</sup>

As with NAFLD-related HCC, ALD-related HCC also tend to present at later stage with poorer prognosis, and HCC surveillance in patients with alcohol-associated cirrhosis is also poorer than those of patients with viral-related cirrhosis.<sup>161</sup>

In summary, ALD is the second-fastest cause of HCC with an accelerated trend since the COVID-19 pandemic. Alcohol is a modifiable risk factor for HCC, but AUD is a disease and should be approached as such and without stigmatization. Disease control and prevention for AUD is urgently needed, and closer monitoring of patients with ALD is needed for intervention for AUD as well as HCC surveillance for those with cirrhosis.

## Conclusion

Viral hepatitis B and C remain the major cause of HCC globally but advances in antiviral treatment have helped to reduce HCC burden related to viral hepatitis and have helped improve the survival of viral-related HCC patients. However, viral hepatitis B and C remained underdiagnosed and undertreated, especially for patients with HCC, so further patient, provider education and public health intervention are needed to improve the linkage of care for patients with viral hepatitis. Alcohol and non-alcohol associated fatty liver diseases are two other major causes of HCC and are the two fastest rising contributors. Currently, there is no effective specific pharmacotherapy for either of these conditions, so disease control and prevention rely on behavioral modification which is complex and requires concerted effort and commitment from all stakeholders.

## Abbreviations

HCC, Hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; NAs, nucleoside/nucleotide analogues; DAAs; direct-acting antivirals; SVR, sustained virologic response; NAFLD, non-alcoholic liver disease; ALD, alcohol-associated liver disease; WHO, World Health Organization; HBsAg, hepatitis B surface antigen; ESLD, end-stage liver disease; Peg-IFN $\alpha$ , pegylated interferon- $\alpha$ ; ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; IFN, interferon; AE, adverse event; SAE, serious adverse event; MTCT, mother-to-child transmission; HBIG, hepatitis B immune globulin; CHC, chronic hepatitis C; OLT, orthotopic liver transplantation; NASH, nonalcoholic steatohepatitis; BMI, body mass index; IL-6, interleukin-6; TNF- $\alpha$ , tumor necrosis factor-alpha; SNP, single nucleotide polymorphism; PNPLA3, patatin-like phospholipase domain-containing 3; LPS, lipopolysaccharide; MAFLD, metabolic dysfunction-associated fatty liver disease; EASL, the European Association for the Study of the Liver; EASD, European Association for the Study of Diabetes; EASO, European Association for the Study of Obesity; IARC, the International Agency for Research on Cancer; AUD, alcohol use disorder; ASDR, age-standardized death rate; CI, confidence interval; ASMR, age-standardized mortality rates; UI, uncertainty interval.

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