

Review

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Impact of direct-acting antivirals on *de novo* occurrence of hepatocellular carcinoma in hepatitis C virus patients

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Abstract

Hepatitis C Virus (HCV) infection constitutes a significant burden to world health, leading to liver cirrhosis and hepatocellular carcinoma (HCC). In the past decades, pegylated interferon combined with ribavirin has been used extensively for HCV treatment, and interferon (IFN) is thought to have antitumor property. Direct-acting antivirals (DAAs) have fundamentally changed HCV therapy, due to their high efficacy and tolerability. However, recent studies have reported relatively high rates of HCC occurrence, and recurrence, following successful HCV treatment using DAAs. These studies were grossly underpowered due to their retrospective design, lack of untreated or IFN controls, small sample size, and limited patient follow-up time. From then, many retrospective and prospective cohort studies with larger size and longer follow-up duration after DAAs therapy have been published. These studies showed that treatment with DAAs can reduce the risk of HCC compared to no treatment, didn't increase the risk of HCC compared to IFN-based therapy after adjusting for the potential confounders of these two groups, and DAAs-induced sustained virological response decreased the risk of HCC compared to DAAs treatment failure. In conclusion, DAAs treatment doesn't appear to increase the development of HCC, even in cirrhotic patients. However, cirrhotic patients should be monitored for the development of HCC during and after DAAs treatment.

Keywords: Sustained virological response, hepatocellular carcinoma, liver cirrhosis



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INTRODUCTION

It is estimated that 71 million people have chronic hepatitis C virus (HCV) infection, which can lead to liver cirrhosis and hepatocellular carcinoma (HCC)^[1]. It seems reasonable that HCV eradication would reduce the risk of HCV-related complications including HCC. Cirrhosis is the major risk factor of HCC and about 3% patients with HCV related cirrhosis develop HCC annually^[2]. In the past decades, pegylated interferon combined with ribavirin (PR) has been widely used for the treatment of HCV. Despite the sustained virological response (SVR) rates associated with PR therapy not being high enough, and relatively more adverse events^[3] reported, studies have demonstrated that interferon (IFN)-induced SVR could reduce HCC incidence^[4]. The annual incidence of HCC is mostly less than 2% in cirrhotic patients achieving SVR after IFN-based regimens^[5,6].

Direct-acting antivirals (DAAs) have fundamentally changed HCV therapy because of their high efficacy and tolerability, even in the patients with cirrhosis^[7-9]. In these studies, patients with SVR showed improvements in disease severity and mortality. In 2016, relatively high rates of HCC occurrence and recurrence were reported after the success treatment of HCV using DAAs^[10,11]. Since then, this has been a highly controversial topic.

This review article summarizes the relevant articles focusing on the impact of DAAs on *de novo* occurrence of HCC in HCV patients. We searched the MEDLINE electronic database using the search terms ["hepatitis C" (MeSH)], ("direct-acting antivirals"), and ["hepatocellular carcinoma" (MeSH)] from the start of the database (1996 year) until April 19, 2020. Searches were limited to human studies written in English. Eligible study designs included retrospective or prospective observational cohort studies, randomized controlled trials and interventional studies. [Figure 1](#) shows the study flow chart.

STUDIES SUPPORTING HIGH RATES OF HCC OCCURRENCE AFTER DAAS TREATMENT

[Table 1](#) summarizes the studies supporting high rates of HCC occurrence after DAAs treatment^[11-14]. [Conti *et al.*^{\[11\]}](#) from Italy reported that HCC was detected in 3.2 % (9/285) cirrhotic patients at 24-week follow-up after DAAs therapy. [Ravi *et al.*^{\[14\]}](#) from the United States (US) reported that 9.1% (6/66 patients) of cirrhotic patients developed HCC within six months of DAAs treatment. Studies from Portugal^[12] and Austria^[13] also reported high rates of HCC occurrence after DAAs treatment. This data raised concerns that DAAs may promote the development of HCC. However, these studies were underpowered because of their retrospective design, lack of untreated or IFN controls, small sample size, and limited follow-up time.

POSSIBLE MECHANISMS OF HCC OCCURRENCE AFTER DAAS TREATMENT

There is a complex equilibrium between pro tumor factors such as HCV and inflammation and anti-tumor factors such as the immune system. A rapid reduction in the HCV viral load by DAAs treatment might impair immune surveillance, resulting in the development of HCC. [Serti *et al.*^{\[15\]}](#) reported DAAs treatment was associated with a rapid decreased activation of natural killer cells. [Meissner *et al.*^{\[16\]}](#) reported that HCV clearance by DAAs treatment was accompanied by down regulation of IFN-stimulated genes and the levels of type II and III IFNs. The serum level of microRNA-122, a regulator of HCV replication and tumor suppressor against HCC^[17], decreased in patients with IFN-free therapy induced SVR^[18]. [Debes *et al.*^{\[19\]}](#) reported a panel of cytokines, apoptosis markers, and growth factors with higher levels before DAAs therapy in patients with new HCC compared with controls. Interestingly, their results suggested that the immune background rather than DAAs mediated immune modulation would lead to HCC development.

STUDIES AGAINST HIGH RATES OF HCC DEVELOPMENT AFTER DAAS TREATMENT

From 2016, many retrospective and prospective cohort studies with larger sizes and greater follow-up duration after DAAs therapy were published. [Table 2](#) summarizes the studies not supporting high rates

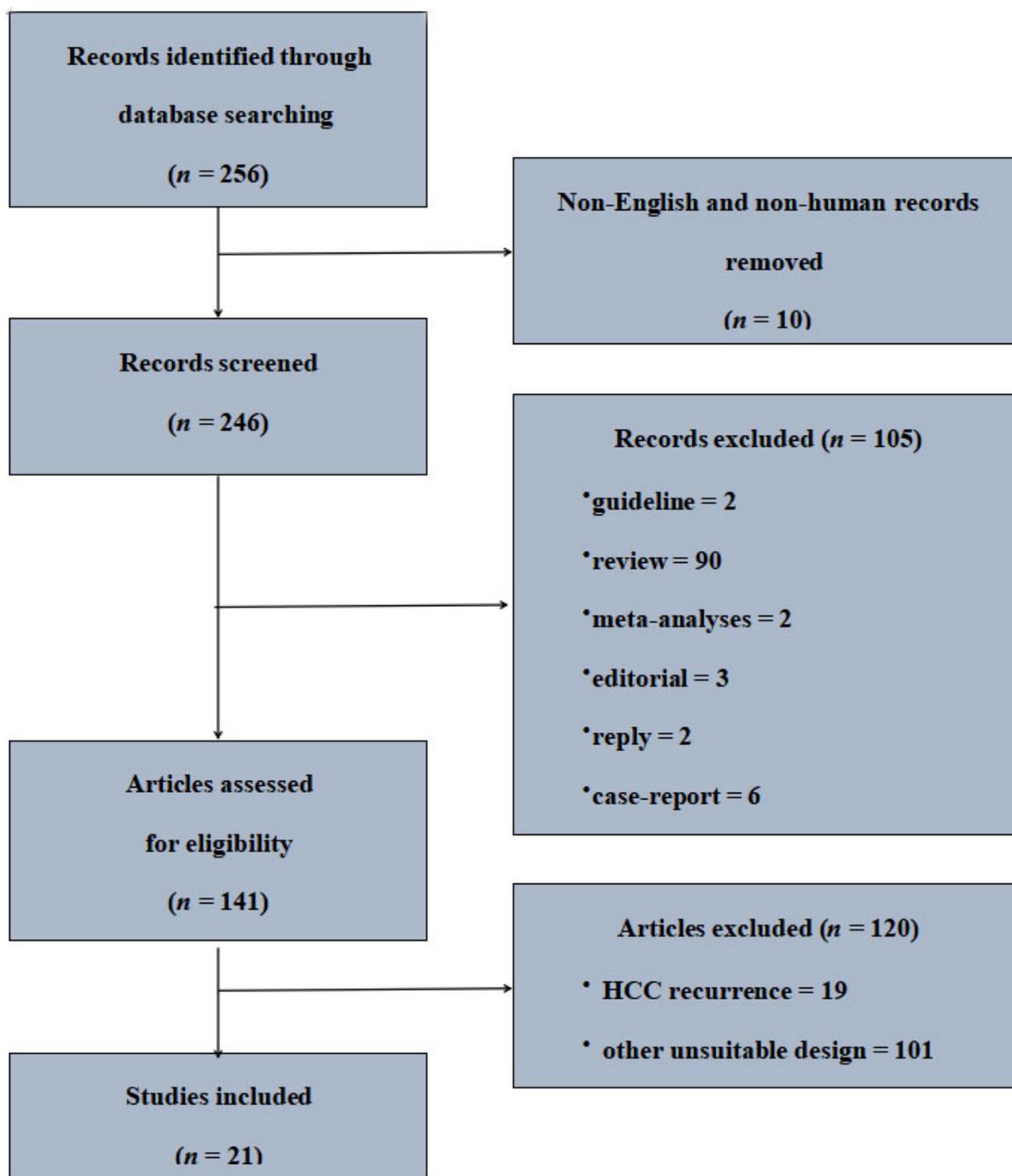


Figure 1. Study flow chart. HCC: hepatocellular carcinoma

Table 1. Studies in support of high rates of HCC odevelopment after DAAs treatment

Ref.	Nature	Patients, <i>n</i>	Liver disease stage	Median follow-up duration	HCC, <i>n</i>	Incidence of HCC
Conti <i>et al.</i> ^[11]	Retrospective	285	cirrhosis	24 weeks	9	3.16% in first 6 months
Cardoso <i>et al.</i> ^[12]	Retrospective	54	cirrhosis	1 year	4	7.4% in the first year
Kozbial <i>et al.</i> ^[13]	Retrospective	195	all stages	48 weeks	13	6.60% in the first year
Ravi <i>et al.</i> ^[14]	Retrospective	66	cirrhosis	6 months	6	9.1% in first 6 months

HCC: hepatocellular carcinoma; DAAs: direct-acting antivirals

Table 2. Studies not supporting high rates of HCC occurrence after DAAs treatment

Ref.	Nature	Patients, n	Liver disease stage	Median follow-up duration	HCC, n	Incidence rate	P value
Cheung <i>et al.</i> ^[20]	Prospective + retrospective	DAAs, 406; Untreated, 261	Decompensated cirrhosis	DAAs, 15 months; Untreated, 6 months	DAAs, 27; Untreated, 11	6-month incidence: 4% for patients with DAAs vs. 4% for untreated patients	0.98
Nagata <i>et al.</i> ^[21]	Retrospective	IFN-free, 1145; IFN-based, 752	All stages	IFN-free, 1.8 years; IFN-based, 6.8 years	-	3-year incidence: 1.4% for IFN-free patients vs. 3.3% for IFN-based patients	0.49
Kanwal <i>et al.</i> ^[22]	Retrospective	DAAs, 22,500	All stages	NA	271	Annual incidence: 0.90% for patients with SVR vs. 3.45% for patients without SVR, AHR = 0.28	< 0.001
Ioannou <i>et al.</i> ^[23]	Retrospective	DAAs-only, 21948; DAAs + IFN, 4535; IFN-only, 35,871	All stages	DAAs-only, 1.53 years	DAAs-only, 2651; DAAs+IFN, 175; IFN-only, 445	Annual incidence: 1.32% for patients with DAAs-only vs. 1.06% for patients with DAAs + IFN vs. 0.81% for patients with IFN-only	> 0.05
Singer <i>et al.</i> ^[24]	Retrospective	DAAs, 30,183; IFN, 12,948; Untreated, 137,502	All stages	DAAs, 1.05 years; IFN, 2.93 years; Untreated, 1.24 years	DAAs, 433; IFN, 388; Untreated, 1232	Annual incidence: 1.18% for patients with DAAs vs. 0.64% for untreated patients, AHR = 0.84; 1.18% for patients with DAAs vs. 0.98% for patients with IFN, AHR = 0.69	< 0.05 < 0.05
Innes <i>et al.</i> ^[25]	Retrospective	IFN-Free, 272; IFN-containing, 585	Cirrhosis and with SVR	IFN-Free, 1.7 years; IFN-containing, 3.5 years	IFN-Free, 11; IFN-containing, 30	Annual incidence: 2.53% for IFN-Free patients vs. 1.26% for IFN-containing patients, AHR = 1.15	0.744
Li <i>et al.</i> ^[26]	Retrospective	DAAs, 5834; IFN, 3534; Untreated, 8468	All stages	DAAs, 396 days; IFN, 2719 days	DAAs, 50; IFN, 196; Untreated, 436	Annual incidence: 2.12% for cirrhotic patients with DAAs vs. 2.28% for cirrhotic patients with IFN; 4.53% for untreated patients	0.78 0.03
Romano <i>et al.</i> ^[27]	Prospective	DAAs, 3917	F3 or higher	536 days	55	Annual incidence: 0.95% for cirrhotic patients with SVR vs. 7.73% for cirrhotic patients without SVR	0.0001
Nahon <i>et al.</i> ^[28]	Prospective	DAAs, 336; SVR-IFN, 495; non-SVR, 439	Cirrhosis	DAAs, 21.2 months; SVR-IFN, 64.4 months; non-SVR-IFN, 47.4 months	DAAs, 15; SVR-IFN, 31; non-SVR, 154	3-year incidence: 5.9% for patients with DAAs vs. 3.1% for patients with SVR-IFN, AHR = 0.89	0.73
Calvaruso <i>et al.</i> ^[29]	Prospective	DAAs, 2249	Cirrhosis	14 months	78	1-year incidence: 2.6% for patients with SVR vs. 8% for patients without SVR	< 0.001
Lleo <i>et al.</i> ^[30]	Prospective	DAAs, 1766	Cirrhosis	NA	50	Annual incidence: 2.1% for patients with SVR vs. 11.3% for patients without SVR, AHR = 0.21	< 0.0001
Mettke <i>et al.</i> ^[31]	Prospective + retrospective	DAAs, 158; Untreated, 184	Cirrhosis	DAAs, 440 days; Untreated, 592 days	78	Annual incidence: 2.9% for patients with DAAs vs. 4.48% for untreated patients	0.39
Carrai <i>et al.</i> ^[32]	Prospective	DAAs, 7344; Untreated, 2551	All stages	DAAs, 34.5 months; Untreated, 32.3 months	DAAs, 187; Untreated, 71	Annual incidence: 1.4% for patients with DAAs vs. 0.56% for untreated patients, AHR = 0.66	0.018

Backus <i>et al.</i> ^[33]	Retrospective	DAAs, 15,059	Advanced liver disease (FIB-4 > 3.25)	1.6 years	537	Annual incidence: 1.9% for patients with SVR vs. 11.5% for patients without SVR	< 0.001
Buonomo <i>et al.</i> ^[34]	Prospective	DAAs, 323	All stages	10 months	11	Per-month incidence: 0.2% for patients with SVR vs. 1.7% for patients without SVR	< 0.05
Colussi <i>et al.</i> ^[35]	Prospective	DAAs, 380	All stages	58 weeks	17	Annual incidence: 1.3% for patients with SVR vs. 59% for patients without SVR	< 0.001
Ebel <i>et al.</i> ^[36]	Prospective	DAAs, 158; Untreated, 184	Cirrhosis	DAAs, 1109 days; Untreated, NA	DAAs, 9; Untreated, 23	Annual incidence: 2.04% for patients with DAAs vs. 5.04% for untreated patients	0.008

HCC: hepatocellular carcinoma; DAAs: direct-acting antivirals; SVR: sustained virological response; IFN: interferon

of HCC development after DAAs treatment^[29-36]. We found that these studies could be divided into three categories: (1) DAAs-treated patients vs. untreated patients; (2) DAAs-treated patients vs. IFN-treated patients; and (3) patients with DAAs induced SVR vs. patients with DAAs failure.

A number of studies compared the risk of HCC in DAAs-treated patients with untreated patients^[20,24,26,31,32,36]. A study of decompensated cirrhotic patients from the United Kingdom reported the incidence of liver cancer was 4% at six months after DAAs treatment, comparable with untreated patients. The figures then dropped to 2.5% between month 6-15 after DAAs treatment^[20]. Similarly, a study of cirrhotic patients from Germany reported DAAs treatment did not change the short-term risk of HCC after 1.5 years of follow-up (2.9 per 100 person-years for patients with DAAs vs. 4.48 per 100 person-years for untreated patients, $P = 0.39$)^[31]. When the cohort was followed up for five years, a reduced HCC risk was confirmed (2.04 per 100 person-years for patients with DAAs vs. 5.04 per 100 person-years for untreated patients, $P = 0.008$)^[36]. Other studies showed DAAs treatment reduced *de novo* HCC directly^[54,26,32]. Singer *et al.*^[24] study from the US reported that DAAs therapy reduced risk of HCC compared to no treatment (AHR 0.84, 95%CI 0.73-0.96), and to IFN-based therapy (AHR 0.69, 95%CI: 0.59-0.81). Another large retrospective study from the US reported that among cirrhotic patients, the incidence of HCC was similar in the DAAs-induced SVR group compared to the IFN-induced SVR group (2.12 vs. 2.28 per 100 person-years, $P = 0.78$), but much higher in untreated group (4.53 per 100 person-years, $P = 0.03$)^[26]. A large prospective study from France, with a median follow-up of 33.4 months, reported that DAAs treatment was associated with a reduced risk of developing HCC, after adjusting for potential confounding factors (AHR 0.66, 95%CI 0.46-0.93)^[32].

Some studies compared the risk of HCC in DAAs-treated patients with IFN-treated patients^[21,23,25,28]. All four studies showed HCC incidence was similar between DAAs-treated patients and IFN-treated patients after adjusting for the characteristics of these two groups. One important thing we should pay attention to is that candidates for DAAs are more prone to developing HCC because of advanced liver disease. Adjustment for confounders such as patient demographics, comorbidities, health behaviors, virology, and baseline liver disease stage adequately may go some way to help address potential bias. The prior screening for HCC in DAAs group was usually suboptimal and might fail to detect the HCC that are perhaps already present before DAAs therapy. It highlighted the importance of excluding the presence of HCC before initiation of DAAs treatment.

Other studies compared the risk of HCC in DAAs-cured patients with DAAs-failed patients^[22,27,29,30,33-35]. All of these studies showed that DAAs-induced SVR decreased the incidence of HCC. The HCC risk reduction by DAAs treatment was evident not only in patients without cirrhosis, but also in patients with cirrhosis. Romano *et al.*^[27] reported that the incidence of HCC was higher during the first year (0.46% in F3, 1.49% in CTP-A and 3.61% in CTP-B cirrhosis, respectively), and declined in the second year (0% in F3, 0.2% in CTP-A, and 0.69% in CTP-B cirrhosis, respectively). But some studies reported that in cirrhotic patients with DAAs-induced SVR, the incidence of HCC was usually still higher than 1.5% above which HCC surveillance is cost-effective. Kanwal *et al.*^[37] reported the quarterly incidence rate of HCC remained stable between 1.5 to 2.3 per 100 person-years in patients with cirrhosis, which indicated HCC risk of cirrhotic patients cured with DAAs did not progress or regress during follow-up. Ide *et al.*^[38] found the one, two, and three-year cumulative incidences of HCC in patients with cirrhosis were 2.5%, 5.2%, and 10.0% respectively. Recently, Ioannou *et al.*^[39] reported that in DAAs-treated patients with cirrhosis and a fibrosis index based on four factors (FIB-4) with scores ≥ 3.25 , the annual HCC incidence decreased from 3.8% in the first year after SVR to 2.4% by the fourth year, which was still at high risk of developing HCC. Although these studies with more than three years follow-up have confirmed HCC risk is not increased after SVR by DAAs^[37-39], the changes in HCC incidence over time deserve to be further clarified in longer-term studies.

Physicians are most interested in which patients should undergo HCC surveillance after achieving SVR by DAAs. Male gender, older age, alcohol abuse, diabetes mellitus, the existence of advanced fibrosis (F3) or cirrhosis, higher alpha-fetoprotein and no SVR are risk factors for HCC occurrence. The existence of cirrhosis is the most important risk factor for HCC development. Therefore, guidelines recommend patients with advanced liver fibrosis or cirrhosis at the time of DAAs treatment should stay in HCC surveillance even after DAA-induced SVR. FIB-4 and aspartate aminotransferase to platelet ratio index (APRI) are easily accessible non-invasive indicators which can be used as stratification risk factors for HCC development, alongside cirrhosis. Kanwal *et al.*^[37] divided cirrhotic patients who achieved SVR with DAAs into three groups: patients who had persistently high FIB-4/APRI over time, patients who experienced a decline in FIB-4/APRI, and patients who had persistently low FIB-4/APRI. Annual HCC incidence remained below 1.5% in the third subgroup, suggesting that it might be possible to exclude these cirrhotic patients from HCC surveillance programs. On the contrary, the annual HCC incidence was between 0.4% to 1.6% in non-cirrhotic patients but with high FIB-4/APRI subgroup (FIB-4 $>$ 3.25/APRI $>$ 1.5), which was high enough to recommend HCC surveillance in these patients.

Although the impact of DAAs treatment and HCC has been extensively published, our review has some strengths. Firstly, we divide the studies not supporting high rates of HCC occurrence after DAAs treatment into three categories, which facilitates easy comparison between studies. Secondly, we include the most recent published evidence on this topic up to April, 2020, with the majority of studies published in 2019 and 2020, with follow-up of three to five years. Thirdly, we discuss the changes in HCC incidence over time following DAAs-induced HCV eradication. Fourthly, we emphasize FIB-4/APRI as the stratification factors besides cirrhosis, which is more useful for the patients with F3 fibrosis.

CONCLUSION

DAAs treatment doesn't appear to increase the occurrence of HCC, even in the cirrhotic patients. DAAs treatment should be considered in all HCV patients. Cirrhotic patients should be monitored for development of HCC during and after DAAs treatment.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data acquisition and interpretation: Yang M, Ma R

Made manuscript revision: Wei L, Huang Y

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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