Yoo *et al. Hepatoma Res* 2020;6:9
DOI: 10.20517/2394-5079.2019.49

Hepatoma Research

Review

Open Access

The interplay between direct-acting antivirals and hepatocellular carcinoma in chronic hepatitis C

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How to cite this article: Yoo SH, Kwon JH. The interplay between direct-acting antivirals and hepatocellular carcinoma in chronic hepatitis C. *Hepatoma Res* 2020;6:9. http://dx.doi.org/10.20517/2394-5079.2019.49

Received: 15 Dec 2019 **First Decision:** 3 Feb 2020 **Revised:** 17 Feb 2020 **Accepted:** 26 Feb 2020 **Published:** 6 Mar 2020

Science Editor: Ming-Lung Yu **Copy Editor:** Jing-Wen Zhang **Production Editor:** Tian Zhang

Abstract

Direct-acting antivirals (DAAs) have been introduced for the treatment of hepatitis C virus, and the sustained virological response rate after DAAs was reported to be over 95%. Because of the high sustained virological response rate, the risk of hepatocellular carcinoma (HCC) was expected to be reduced. However, an unexpected high risk of HCC recurrence after DAA treatment was reported, and thus the dispute about the association of DAA and HCC arose. The present article reviews the interplay between DAAs and HCC.

Keywords: Chronic hepatitis C, hepatocellular carcinoma, direct-acting antivirals

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and the most common primary liver cancer. The major causes of HCC are cirrhosis of any cause, chronic hepatitis B, chronic hepatitis C (CHC), alcohol, and nonalcoholic fatty liver disease. Among the causes, the incidence of chronic viral hepatitis-related HCC is 3%-5% per year in patients with cirrhosis and < 1.5% per year in patients with both hepatitis C and stage 3 fibrosis[1]. The sustained virological response (SVR) rate for pegylated interferon (IFN)-based therapy has been reported to be 42%-65% for genotype 1 and 74%-93% for genotype 2 virus[2-4]. Despite the low SVR, several previous retrospective studies suggest that achieving SVR after pegylated IFN plus ribavirin therapy reduces the risk of hepatic decompensation, liver related mortality, liver transplantation, and HCC[5-7].

Recently, an IFN-free regimen as a treatment for CHC including NS3/4A protease inhibitor, NS5A inhibitor, and NS5B polymerase inhibitor was introduced. There have been several reports indicating that the SVR rate is up to 97.8% and the adverse event rate at all stages of CHC is lower in patients treated with direct-acting antivirals than IFN-based therapy[8-12]. Despite expectations of a decrease in the incidence of HCC because of the high rate of SVR, Reig *et al.*[13] reported an unexpected high rate of HCC recurrence after treating with direct-acting antivirals (DAA) in patients who experience previous HCC. Conti *et al.*[14] also reported a high rate of HCC recurrence (28.81%) 24 weeks after DAAs. Since the two aforementioned reports were published, much debate has been raised about the recurrence and occurrence of HCC after treating DAAs.

In this article, we review the pros and cons of the effects of the DAAs on occurrence/recurrence of HCC.

THE INTERPLAY BETWEEN DIRECT-ACTING ANTIVIRALS AND OCCURRENCE OF HEPATOCELLULAR CARCINOMA

CHC is the most common cause of HCC worldwide. The incidence of HCC is below 1% per year in CHC patients without liver cirrhosis[15]. However, the risk of HCC increases by 2%-8% in CHC with liver cirrhosis[16].

The papers on HCC occurrence related to DAAs are listed in Table 1. A negative paper was first published on the occurrence of the HCC after the treatment of DAAs. In 2016, Conti *et al.*[14] published the first report about early occurrence of HCC in hepatitis C virus-related cirrhosis treated with DAAs. They retrospectively analyzed 285 consecutive cirrhotic patients who completed antiviral therapy with DAA regimens and HCC developed in 9 of 285 patients (3.16%, 95%CI: 1.45-5.90) during the 24-week post-treatment evaluation. The report concluded that DAA-induced resolution of HCV infection does not seem to reduce occurrence of HCC.

Since the publication of the previous paper, several papers have been published indicating that DAAs are not associated with occurrence of HCC. A thesis against the previous study was published by Kanwal *et al.*[17] in 2017. This retrospective cohort study included 22,500 patients who received DAA treatment; 39.0% of the patients had cirrhosis and 86.74% achieved SVR. The incidence rate of HCC was 0.90 per 100 person-year (95%CI: 0.77-1.03) in patients with SVR and 3.45 per 100 person-year (95%CI: 2.73-4.18) in patients without SVR.

A large prospective study of 2249 patients with HCV-associated cirrhosis was published in Italy by Calvaruso and his colleagues[18]. SVR after DAA treatment was achieved in 95.2% of patients and the overall rate of HCC occurrence was 3.4%. They analyzed the HCC incidence according to achieved SVR, and HCC occurrence was 3% in SVR group and 12.8% in non-SVR group ($P < 0.001$). Although this study did not contain the analysis of control group, they found the SVR to DAA treatment decreased the incidence of HCC. A similar study in the same country including 3917 patients with fibrosis stage ≥ F3 was published by Romano and colleagues[19]. This large, prospective cohort study showed that the incidence of HCC occurrence was 0.42% in F3, 1.88% in cirrhosis, and 0.97 per 100 person-year (95%CI: 0.73-1.26) in all patients.

Nagata *et al.*[20] compared data between IFN-based and IFN-free regimens for occurrence of HCC. This report included 1085 patients treated with IFN and 669 patients treated with DAAs. The cumulative incidence of HCC occurrence after SVR was 2.6% (five-year incidence) in IFN-based and 3.3% (three-year incidence) in IFN-free therapies. Although the incidence of HCC appears to be higher in IFN-free group than IFN-based group, there are no significant differences between the two groups after performing

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Table 1. Studies about de novo HCC occurrence after receiving DAAs in patients with hepatitis C virus infection

Author	Study design	Patient number	Median follow-up period (months)	SVR rate	Outcomes	Conclusion
Conti *et al.*[14]	Retrospective observational cohort study	HCV-associated cirrhosis with DAAs (*n* = 285)	5.6	91.00%	HCC occurrence rate (3.16%)	DAA-induced resolution of HCV infection does not seem to reduce occurrence of HCC
Kanwal *et al.*[17]	Retrospective observational cohort study	Chronic hepatitis C with DAAs (*n* = 22,500)	NA	86.74%	HCC occurrence rate (1.2%) - SVR (0.90/100 PY) - non-SVR (3.45/100 PY)	Among patients treated with DAA, SVR was associated with a considerable reduction in the risk of HCC
Calvaruso *et al.*[18]	Prospective observational cohort study	HCV-associated cirrhosis with DAAs (*n* = 2249)	14	95.20%	HCC occurrence rate - CPC A + SVR (2.1%) - CPC A + no SVR (6.6%) - CPC B + SVR (7.8%) - CPC B + no SVR (12.4%)	SVR to DAA treatment decreased the incidence of HCC over a mean follow-up of 14 months
Romano *et al.*[19]	Prospective observational cohort study	Fibrosis stage U F3 CHC with DAAs (*n* = 3917)	17.9	93.90%	HCC occurrence rate (1.4%)	In patients with advanced hepatitis C receiving DAAs, the risk of "de novo" HCC during the first year is not higher, and might be lower, than that of untreated patients
Nagata *et al.*[20]	Retrospective observational cohort study	Chronic hepatitis C -IFN (*n* = 1145) -DAAs (*n* = 752)	IFN 81.6 DAAs 21.6	96.00%	HCC occurrence rate after viral eradication - IFN (3.3%), DAAs (1.4%)	The risks of early HCC occurrence and recurrence after viral eradication were similar between IFN-based and IFN-free therapies
Nahon *et al.*[21]	Prospective observational cohort study	Biopsy-proven HCV-associated cirrhosis with DAAs (*n* = 1270) -DAAs (*n* = 336) -SVR-IFN (*n* = 495) -non-SVR (*n* = 439)	67.5		HCC occurrence rate (5 year-CumI 14.7%) - DAAs 3-year CumI: 5.9% - SVR-IFN 3-year CumI: 3.1% - non-SVR 3-year CumI: 12.7%	There is no statistically significant increase in risk of HCC was associated with DAA use
Ioannou *et al.*[42]	Retrospective observational cohort study	Chronic hepatitis C -IFN only (*n* = 35,871, 58%) -DAA + IFN (*n* = 4535, 7.2%) -DAA only (*n* = 21,948, 35%)	73.2	NA	HCC occurrence rate (5.2%)	DAA-induced SVR is associated with a 71% reduction in HCC risk. Treatment with DAAs is not associated with increased HCC risk compared with treatment with IFN
Yoo *et al.*[22]	Retrospective observational cohort study	Chronic hepatitis C -DAAs (*n* = 574) -IFN (*n* = 211)	IFN 43.6 DAAs 10.4	DAAs 95.1% IFN 75.4%	HCC occurrence rate (0.89%) - DAAs (1.05%) - IFN (0.47%)	The rate of early development of HCC did not differ between patients treated with IFN and those treated with DAAs
Singer *et al.*[23]	Retrospective observational cohort study	Chronic hepatitis C -DAAs (*n* = 30,183) -Untreated (*n* = 137,502) -IFN (*n* =1 2,948)	DAAs 1.05 PY Untreated 1.24 PY	NA	HCC occurrence rate - DAAs 0.64/100 PY - Untreated 1.18/100 PY	DAA-based treatment was associated with a reduced risk of incident liver cancer relative to both no HCV treatment and to IFN-based treatment in the pre-DAA era
Carrat *et al.*[24]	Prospective observational cohort study	Chronic hepatitis C -DAA (*n* = 7344) -Untreated (*n* = 2551)	33.4	94.00%	HCC occurrence rate of DAA treated group (2.54%)	Treatment with direct-acting antivirals is associated with reduced risk for mortality and hepatocellular carcinoma
Ide *et al.*[25]	Prospective observational cohort study	Chronic hepatitis C with DAAs (*n* = 2552)	NA	NA	HCC occurrence rate (2.7%)	Achieving SVR by DAA treatment reduces the incidence of HCC

HCV: hepatitis C virus; DAAs: direct-acting antivirals; HCC: hepatocellular carcinoma; NA: not available; SVR: sustained virological response; PY: person-year; CPC: Child-Pugh Class; IFN: interferon; CumI: cumulative incidence

propensity score-matched analysis (three-year incidence: 3.3% in IFN-based therapy and 1.4% in IFN-free therapy; P = 0.49). In a study from France, Nahon *et al.*[21]. published a report about the incidence of HCC after DAA for HCV in patients with cirrhosis included in surveillance programs The retrospective cohort study included 1270 patients with biopsy-proven cirrhosis and classified into DAA group (n = 336), SVR-IFN group (n = 495), and non-SVR group (n = 439). The three-year cumulative incidences of HCC were 5.9% in the DAA group, 3.1% in the SVR-IFN group, and 12.7% in the non-SVR group (HR: 2.03, 95%CI: 1.07-3.84, P = 0.03 for the DAA group *vs.* the SVR-IFN group). However, under propensity score matched analysis, there was no significant increase in risk of HCC for DAA use (HR: 0.89, 95%CI: 0.46-1.73, P = 0.735). The DAA group was older, and had a higher rate of diabetes or portal hypertension than SVR-IFN group. These features suggested that a more advanced liver disease, older age, and higher rates of comorbidities favor liver carcinogenesis. Yoo *et al.*[22] published similar comparative data of *de novo* HCC occurrence in DAA group and IFN group. The cumulative incidence of HCC occurrence was not different between DAA group and IFN group (P = 0.827). In USA, Singer *et al.*[23] analyzed 30,138 patients receiving DAA treatment, 137,502 patients without any treatment, and 12,948 patients receiving IFN treatment. This study revealed that DAA treatment was associated with a reduced risk of HCC compared to IFN treatment after performing inverse probability of treatment weighting (adjusted HR: 0.69, 95%CI: 0.59-0.81).

In 2019, the debate on the interplay between DAA and HCC continued, and Carrat *et al.*[24] and Ide *et al.*[25] published prospective cohort studies. In the former study in France, 7344 patients with DAA treatment, and 2551 patients without treatment were enrolled[24]. DAA treatment seems to increase the risk of HCC (HR: 2.77, 95%CI: 2.07-3.71). However, after adjustment for variables, DAA treatment was associated with a decrease in HCC (adjusted HR: 0.66, 95%CI: 0.46-0.91) and all-cause mortality (adjusted HR: 0.48, 95%CI: 0.33-0.70). A prospective study from Japan by Ide *et al.*[25] enrolled 2552 patients who were treated with DAAs and achieved a SVR. The three-year cumulative incidence of HCC was 4.9% in all patients, 10.0% in patients with cirrhosis, and 2.9% in patients without cirrhosis. They concluded that DAAs do not increase the risk of HCC occurrence after achieving SVR.

THE INTERPLAY BETWEEN DIRECT-ACTING ANTIVIRALS AND RECURRENCE OF HEPATOCELLULAR CARCINOMA

HCC is treated with curative treatment or non-curative interventions according to tumor stage, liver function, and performance status. After curative treatment such as surgical resection for HCC, the risk of recurrence is 60%-70% at five years[26,27]. Several studies have shown that adjuvant IFN therapy after curative treatment can reduce the recurrence rate of HCC[28-32].

The papers published on the HCC recurrence after DAA treatment are organized in Table 2. Despite expectations that achieving SVR after DAA treatment will reduce the recurrence of HCC, Reig *et al.*[13] reported an unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing DAA therapy in 2016. The study included 58 patients with prior history of treated HCC with complete response who lacked "non-characterized nodules". They reported unexpected high recurrence rate of 27.6% and median time from DAA start to recurrence was 3.5 months (range 1.1-8 months). Conti *et al.*[14] published another similar report about early recurrence of HCC. In this retrospective cohort study, the recurrence rate of HCC after completing DAA therapy was 28.81% (17 of 59 patients, 95%CI: 17.76-42.07) during the 24-week post-treatment evaluation. Fifty-nine patients with a history of previous HCC included 11 patients who received transarterial chemoembolization". This term has only been mentioned once for previous HCC. The study indicated that patients previously treated for HCC still have a high risk of tumor recurrence.

Opposite opinions to the previous paper were subsequently published. One prospective study used three French multicenter ANRS cohorts[33]. The DAA group and untreated group were analyzed and the rate

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Table 2. Studies about HCC recurrence after receiving DAAs in patients with hepatitis C virus infection

Author	Study design	Patient number	Median follow-up period (months)	SVR rate	Outcomes	Conclusion
Reig *et al.*[13]	Retrospective observational cohort study	Prior history of treated HCC with DAAs (*n* = 103)	5.7	97.50%	Tumor recurrence (27.6%)	The study showed an unexpected high rate and pattern of tumor recurrence coinciding with HCV clearance
Conti *et al.*[14]	Retrospective observational cohort study	Prior history of treated HCC in HCV-associated cirrhosis with DAAs (*n* = 59)	5.6	91.00%	HCC recurrence rate (28.81%)	DAA-induced resolution of HCV infection does not seem to reduce recurrence of HCC
ANRS[33]	Collaborative study Prospective observation cohort study	HEPATHER cohort Prior history of treated HCC - DAAs (*n* = 189) - Untreated (*n* = 78)	20.2	NA	HCC recurrence rate - DAA 0.73/100 person-month - Untreated 0.66/100 person-month	The study did not find an increase in HCC recurrence rate during the first 3 months of the treated period
		CirVir cohort Prior history of treated HCC in HCV-associated cirrhosis - DAAs (*n* = 13) - untreated (*n* = 66)	58.6	NA	HCC recurrence rate - DAA 1.11/100 person-month - Untreated 1.73/100 person-month	There was no evidence of an increased risk of HCC recurrence in treated compared with untreated patients
		CUPILT cohort Liver transplanted patients for HCC with DAA (*n* = 314)	70 months from LT	96.80%	HCC recurrence rate (2.2%)	The observed recurrence rate of 2.2% was lower than the expected rate according to previous studies with interferon regimen
Cabibbo *et al.*[34]	Prospective observational cohort study	Prior history of treated HCC with DAAs (*n* = 143)	9.1	96.50%	HCC recurrence rate (20.3%)	The risk of HCC early recurrence was comparable and not higher than that observed in DAA unexposed patients
Nagata *et al.*[20]	Retrospective observational cohort study	Chronic hepatitis C - IFN (*n* = 1145) - DAAs (*n* = 752)	IFN 81.6 DAAs 21.6	96.00%	HCC recurrence after viral eradication - IFN (54.2%) - DAAs DAAs (45.1%)	The risks of early HCC occurrence and recurrence after viral eradication were similar between IFN-based and IFN-free therapies
Nishibatake Kinoshita *et al.*[35]	Retrospective observational cohort study	RFA for HCV-related HCC - DAAs (*n* = 147) - IFN (*n* = 156)	IFN 86.4 DAAs 21.6	NA	HCC recurrence rate at 2years - DAAs (60%) - IFN (61%)	There is no significant difference in early HCC recurrence rates and patterns between patients who received interferon-based and direct-acting antiviral therapy after HCC treatment
Singal *et al.*[37]	Retrospective observational cohort study	Prior history of treated HCC (*n* = 793) - DAAs (*n* = 231) - Untreated (*n* = 562)	10.4	NA	HCC recurrence rate (52.5%) - DAAs (55.4%) - Untreated (51.2%)	DAA therapy was not significantly associated with increased or decreased risk of HCC recurrence

HCC: hepatocellular carcinoma; DAAs: direct-acting antivirals; NA: not available; HCV : hepatitis C virus; LT: liver transplantation; IFN: interferon

of HCC recurrence was not different between the two groups. This suggested that there was no evidence that DAA treatment increases the risk of HCC recurrence.

Cabibbo *et al.*[34] reported a prospective multicenter study in Italy. The study included 143 patients with complete response after curative treatment of HCC, and the incidences of HCC recurrence were 12%, 26.6%, and 29.1% at 6-, 12-, and 18-month follow-ups. Although risk of HCC recurrence remained high, the risk was comparable between DAA group and untreated group.

Table 3. Risk factors for occurrence/recurrence of HCC

Author/Study design	Occurrence/Recurrence	Risk factors for the development of HCC
Conti *et al.*[14]	Occurrence	No associate factor
	Recurrence	Age, liver stiffness
Kanwal *et al.*[17]	Occurrence	non-SVR, alcohol use, non-African Americans, cirrhosis
Calvaruso *et al.*[18]	Occurrence	Albumin < 3.5 g/dL, platelet count < 120 × 10^9/L, absence of SVR
Romano *et al.*[19]	Occurrence	Positive for HBsAg, APRI score ≥ 2.5, CPC B, treatment failure
Nagata *et al.*[20]	Occurrence	IL-28 genetic polymorphism, post-treatment WFA*M2BP
	Recurrence	IL-28 genetic polymorphism, post-treatment WFA*M2BP
Nahon *et al.*[21]	Occurrence	non-SVR, older age, excessive alcohol consumption, lower platelet count, high GGT levels, HCV genotype 1
Ioannou *et al.*[42]	Occurrence	non-SVR, cirrhosis
Yoo *et al.*[22]	Occurrence	Alpha-fetoprotein level > 9.5 ng/mL
Singer *et al.*[23]	Occurrence	Older age, male gender, cirrhosis, thrombocytopenia, portal hypertension, diabetes, tobacco use, alcoholic liver disease
Carrat *et al.*[24]	Occurrence	Untreated, non-SVR
Ide *et al.*[25]	Occurrence	Age ≥ 62 years old, male gender, FIB-4 index ≥ 4.6, and GGTP level ≥ 44 IU/L
Cabibbo *et al.*[34]	Recurrence	Main tumor size > 2.5 cm, history of prior recurrence
Nishibatake Kinoshita *et al.*[35]	Recurrence	Higher lens culinaris agglutinin-reactive fraction of alpha-fetoprotein level, a history of multiple HCC treatments, and a shorter interval between HCC treatment and initiation of antiviral therapy
Singal *et al.*[37]	Recurrence	No associate factor

HCC: hepatocellular carcinoma; SVR: sustained virological response; CPC: Child-Pugh Class; HCV: hepatitis C virus; IFN: interferon

The retrospective cohort study from Japan by Nagata *et al.*[20] analyzed 60 patients in the IFN-based therapy group and 83 patients in the IFN-free therapy group. The incidence of HCC recurrence after locally curative treatment was not significantly different between IFN-based and IFN-free therapy groups by propensity score-matched analysis (five-year incidence: 54.2% in IFN-based and 45.1% in IFN-free therapy, $P = 0.54$). Nishibatake Kinoshita *et al.*[35] enrolled HCC patients previously treated with radiofrequency ablation (147 patients in DAA group and 156 patients in IFN group). The rate of HCC recurrence at one and two years was 39% and 61% in IFN group and 39% and 60% in DAA group, respectively ($P = 0.43$). There was also no significant difference between the two groups after performing matching analysis ($P = 0.68$). To compare the rate of HCC recurrence between the patients who received DAA and IFN-based therapies, Waziry *et al.*[36] published meta-analyses study containing 17 studies. The incidence of HCC recurrence after SVR was 9.21 per 100 person-year in DAA group and 12.16 per 100 person-year in IFN group. After adjusting analysis, DAA treatment was not associated with HCC recurrence (Relative risk: 0.62, 95%CI: 0.11-3.45, $P = 0.56$). To solve this debate firmly, a large study from USA and Canada was published by Singal *et al.*[37] in 2019. In total, 793 patients with HCV-associated HCC, including 304 patients who received DAA and 489 patients without treatment, were analyzed. HCC recurred in 42.1% patients in the DAA group and 58.9% in the untreated group. Although DAA treatment seems to decrease the risk of HCC recurrence (HR: 0.32, 95%CI: 025-0.41), after accounting for time-varying exposure, DAA treatment was not associated with increasing or decreasing the risk of HCC recurrence after complete response (HR: 0.90, 95%CI: 0.70-1.16).

RISK FACTORS FOR OCCURRENCE/RECURRENCE OF HEPATOCELLULAR CARCINOMA AFTER TREATING WITH DIRECT-ACTING ANTIVIRALS

In most of the studies on the interplay between DAA and HCC, non-SVR, advanced liver disease, and older age were associated with risk of HCC. Table 3 contains the risk factors for development of HCC.

In a report about the early occurrence and recurrence of HCC in HCV-related cirrhosis treated with DAA, Child-Pugh class (OR: 4.18, 95%CI: 1.17-14.8, $P = 0.03$) and history of HCC (OR: 12.0, 95%CI: 4.02-35.74, $P < 0.0001$) were associated with HCC development. There was no significant factor in patients without history of previous HCC, while age (OR: 0.82, 95%CI: 0.69-0.97, $P = 0.02$) and liver stiffness (OR: 1.19,

95%CI: 1.01-1.39, $P = 0.03$) were significant factors prone to experience HCC recurrence[14]. A study from Japan reported on the impact of DAA on early recurrence of HCC and higher alpha-fetoprotein (AFP)-L3 level (HR: 1.47, 95%CI: 1.02-2.11, $P = 0.04$), larger number of HCC treatments (HR: 1.65, 95%CI: 1.16-2.35, $P = 0.007$), and shorter interval between the last HCC treatment and initiation of antiviral therapy ($P = 0.007$) were associated with the risk of HCC recurrence[35]. In the comparative study for occurrence and recurrence of HCC in IFN-based and IFN-free therapies, AFP and WFA*M2BP levels were significantly associated with HCC occurrence after achieving an SVR[20]. This study suggested that AFP > 5.4 ng/mL and WFA*M2BP > 1.8 COI could be helpful markers of HCC occurrence. A prospective cohort study including 2249 patients with HCV-associated cirrhosis reported that albumin level < 3.5 g/dL (HR: 1.77, 95%CI: 1.12-2.82, $P = 0.01$), platelet count < 120 × 10^9/L (HR: 3.89, 95%CI: 2.11-7.15, $P < 0.001$), and absence of SVR (HR: 3.40, 95%CI: 1.89-6.12, $P < 0.001$) were associated with an increased risk of HCC occurrence[18].

The retrospective cohort study using national data of 22,500 patients revealed that the patients with SVR (HR: 0.24, 95%CI: 0.19-0.31, $P < 0.0001$) and African American patients (HR: 0.56, 95%CI: 0.39-0.81, $P = 0.02$) were associated with low risk of HCC[17]. Patients with cirrhosis (HR: 4.73, 95%CI: 3.34-6.68, $P < 0.0001$) and alcohol abuse (HR: 1.56, 95%CI: 1.11-2.18, $P = 0.01$) were associated with high incidence of HCC. A large, prospective, population-based study from Italy including 3917 patients with fibrosis stage ≥ F3 revealed that DAA treatment failure (HR: 9.09, 95%CI: 5.2-16.1, $P = 0.0001$), HBV coinfection (HR: 3.99, 95%CI: 1.24-12.91, $P = 0.021$), and APRI score > 2.5 (HR: 2.03, 95%CI: 1.14-3.61, $P = 0.016$) were significantly associated with HCC occurrence[19]. A comparative study including DAA group, SVR-IFN group, and non-SVR group suggested that increased age, alcohol consumption, HCV genotype 1, and impaired liver function were statistically significantly associated with risk of HCC[21]. There was no significant association between DAA use and risk of HCC. In our study, we compared the rates of HCC between DAA group and IFN group, and alpha-fetoprotein > 9.5 ng/mL at the time of end-of treatment response was the only significant risk factor for HCC occurrence[22]. Moreover, in a prospective study in France, exposure to DAA was strongly associated with a decrease in all-cause mortality (adjusted HR: 0.34, 95%CI: 0.22-0.55, $P < 0.0001$) and risk of HCC (adjusted HR: 0.57, 95%CI: 0.40-0.81 $P = 0.016$)[24]. A study including HCV patients with received DAAs and who achieved SVR showed that male gender (HR: 2.40, 95%CI: 1.46-3.96, $P = 0.0006$), older age (HR: 1.51, 95%CI: 1.20-1.91, $P = 0.0005$), higher FIB-4 index (HR: 1.12, 95%CI: 1.07-1.17, $P < 0.0001$), and higher GGTP level (HR: 1.04, 95%CI: 1.02-1.06, $P < 0.0001$) were independently associated with HCC occurrence[25].

CONCLUSION

Since the initial reports about the unexpected high rate of early recurrence of HCC were published, most recent reports showed favorable effects of DAA treatment in regard to HCC occurrence/recurrence. Several published studies have indicated that non-SVR, older age, advanced liver disease, combined liver disease (chronic hepatitis B and alcohol abuse), higher AFP, and history of previous HCC may play roles in increasing HCC risk. Accordingly, the Asian Pacific Association for the Study of the Liver guidelines suggest that surveillance be performed every six months for patients with SVR and liver cirrhosis and every four months for patients with SVR and previous history of HCC[38]. Achieving SVR in patients with HCV improved their outcomes in terms of deaths, Child-Pugh Class, and model for end-stage liver disease of advanced liver disease, as well as the incidence of HCC. In addition, patients with previous HCC after achieving SVR had significantly better survival than untreated patients, thus patients eligible for HCC therapy should be considered for DAA treatment[39]. However, the risk of HCC is not completely eliminated by achieving SVR after DAA treatment, and regular surveillance of HCC including biomarkers for tumor should be considered in patients with cirrhosis, combined liver disease, and previous history of HCC[40,41].

DECLARATIONS

Authors' contributions

Study concept and design: Yoo SH, Kwon JH
Acquisition of data: Yoo SH
Drafting of the manuscript: Yoo SH
Study supervision: Kwon JH

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

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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