



Hepatocellular carcinoma after direct-acting antiviral hepatitis C virus therapy: A debate near the end

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Abstract

Direct acting antivirals (DAAs) have revolutionized the treatment of hepatitis C virus (HCV) infection, achieving high rates ($\geq 95\%$) of sustained virological response, with a good safety profile and high compliance rates. Consequently, it had been expected that viral clearance will reduce morbidity and mortality rates, as well as the risk of hepatocellular carcinoma (HCC). However, since 2016, concerns have been raised over an unexpected high rate of HCC occurrence and recurrence after DAA therapy, which led to an avalanche of studies with contradictory results. We aimed to review the most recent and relevant articles regarding the risk of HCC after DAA treatment and identify the associated risk factors.

Key Words: Hepatocellular carcinoma; Direct acting antivirals therapy; Hepatitis C virus infection; Sustained virological response; Risk factors of hepatocellular carcinoma; Review

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Core Tip: The risk of hepatocellular carcinoma (HCC) occurrence or recurrence in patients with chronic hepatitis C virus (HCV) infection receiving direct acting antivirals (DAAs) has been debated through the last 4 years. Data provided by current literature indicate a decreasing incidence rate of HCC (both *de novo* and recurrent) in patients with chronic hepatitis C, HCV-related cirrhosis, and HCV-related HCC after achieving sustained virological response with DAAs.

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INTRODUCTION

Hepatocellular carcinoma (HCC) represents the most frequent histologic type among primary liver neoplasia, and is the fifth most common cancer globally comprising 5.6% of all cancers and the second most common cause of cancer death^[1]. The leading risk factor for HCC is chronic hepatitis C virus (HCV) infection with a 3% annual risk in patients with HCV liver cirrhosis^[2]. Data from WHO's global hepatitis report shows that 1% of the world population is infected with HCV^[3]. Beside inducing liver injury and fibrosis which subsequently will lead to liver cirrhosis, HCV has a direct carcinogenic potential with pro-oncogenic effects upon the infected cell through oxidative stress, DNA damage and deregulation of host cell checkpoints^[4].

Most studies regarding the risk of HCC in patients with HCV chronic infection treated with interferon (IFN)-based therapy reported that achieving sustained viral response (SVR) reduced the risk to 0.5%-1% per year^[5,6]. However, IFN-based therapy was limited by a low SVR rate (approximately 40%-50%) and a poor tolerance among patients with cirrhosis due to multiple adverse events^[7].

The therapy of HCV infection was revolutionized by the introduction of the currently approved IFN-free regimens containing all-oral direct-acting antivirals (DAAs) which target viral proteins such as NS3/4A protease, NS5B polymerase and the NS5A replication complex, achieving SVR rates in over 95% of patients, with good safety profile and excellent tolerance^[8-10]. Thus, it was expected that viral clearance will reduce morbidity and mortality rates implying a decreased risk of HCC. Several studies which assessed the risk of HCC occurrence and recurrence in patients treated with IFN-based therapy, have shown that the risk is significantly lower in those who achieved a SVR than in those who did not^[11]. In addition, SVR-achieving patients benefit from long-term preserved liver function and consequently a longer survival^[12]. However, data provided by 2 studies published in 2016 were a matter of concern regarding the high risk of HCC occurrence and recurrence after DAA therapies^[13,14]. The debate was continued by several studies reporting conflicting data and thus casting a shadow over the relation between DAA therapy and HCC. Although it is commonly known that the risk of HCC remains even after HCV clearance, it is important to clarify whether DAAs have a role in suppressing the development of HCC.

We carried out a review of the most recent and relevant articles regarding the risk of HCC after DAA therapy and identify the associated risk factors.

THE RELATION BETWEEN HCC AND CHRONIC HCV INFECTION

Commonly, HCC develops in a liver with histologic abnormalities, the presence of chronic liver disease representing a potential risk for tumour initiation and progression. In about 90% of the cases, HCC is associated with a known risk factor^[2]. The most important risk factor for the development of HCC is liver cirrhosis of whatever etiology, which is considered a premalignant lesion and is present in over 70% of cases^[15]. Liver cirrhosis marks the final stage of all chronic hepatopathies and the most common causes are chronic infection with HBV or HCV, alcohol consumption, hereditary metabolic diseases such as hemochromatosis or alpha-1-antitrypsin deficiency and non-alcoholic steatohepatitis^[16]. All etiologic forms of cirrhosis may be complicated by the development of HCC, but patients with chronic HBV and HCV infection are under a higher risk.

HCV is an RNA virus that belongs to the *Flaviviridae* family, consisting of single-stranded RNA whose genome encodes a protein comprising 3000 amino acids from which, *via* proteolysis, result structural and nonstructural proteins. Structural proteins (core, envelope E1 and E2) play an important role in determining the morphological viral characteristics and in the invasion process of host-cells^[15]. Nonstructural proteins (P1, NS2, NS3, NS4A, NS4B, NS5A and NS5B) are involved in viral replication and the pathogenesis of secondary liver injury^[17]. The HCV genome is very heterogeneous

with at least seven genotypes and several subtypes reported so far. HCV genotype 1, 3 and 6 have been incriminated in a poor clinical outcome as compared to the other genotypes, with a higher prevalence of cirrhosis or HCC^[18-20]. The hepatocarcinogenesis induced by chronic HCV infection is a multistage and multifactorial process, in which direct and indirect mechanisms interact leading to the creation of a pro-carcinogenic microenvironment represented by liver cirrhosis, in which viral protein structures act as promoters of malignant degeneration^[21]. HCC development due to HCV is a gradual process spanning two to four decades^[22]. HCV carcinogenesis is mediated by viral-induced factors and host immunologic response which is mediated by tumoral necrosis factor, IFNs and chronic inflammation secondary to HCV^[23]. Cell cycles are associated with mutations that can transform hepatocytes to malignant cells. Telomerase reverse transcriptase, tumour protein 53, β catenin are the most frequent genes mutated in HCC^[24].

HCC OCCURRENCE AFTER DAA THERAPY

IFN-based therapy provided undisputed clinical benefit in pre-cirrhotic and cirrhotic SVR-achieving patients, with a significant reduction in disease progression and complications, including HCC when compared to those without SVR or untreated^[11,25-27]. The risk factors associated with HCC development in IFN-treated patients achieving SVR are older age, male gender, advanced liver fibrosis, fatty liver, and a high posttreatment serum alpha-fetoprotein (AFP) level^[28-30]. However, due to restrictive inclusion criteria, low SVR rates and high treatment-related toxicity, IFN-based therapy was not an ideal treatment in patients with chronic HCV infection.

The IFN-free regimens using new DAAs represent a turning point in the treatment of patients with chronic HCV infection, providing high SVR rates and fair tolerance, which raised the expectations of preventing complications of advanced liver disease in HCV patients, including HCC. These prospects are based on data provided by previous studies carried out in the IFN era, demonstrating a decline in HCC incidence in SVR-achieving patients^[31,32]. Nonetheless, despite evidences that achieving SVR provide protection against HCC development, several articles published in 2016 and 2017 reported an unexpected increased occurrence, recurrence and a more aggressive pattern of HCC after DAA therapy in cirrhotic HCV patients^[13,14,33]. The results of these studies were countered by many because of the small cohort size, the absence of control groups, and short follow-up periods (Table 1).

Retrospective studies comparing outcomes after DAAs vs IFN-based therapy

A large cohort study which compared 30183 DAA-treated patients to 137502 patients without evidence of HCV treatment and 12948 IFN-treated patients, identified a more advanced age, predominance of male sex and cirrhosis at baseline in DAA-treated patients compared to those untreated. After adjustments for variables, the authors reported a significantly reduced risk of HCC relative to no treatment (adjusted HR = 0.84, 95%CI: 0.73-0.96), and relative to IFN-based treatment (HR = 0.69, 95%CI: 0.59-0.81)^[34]. Similarly, Ioannou *et al*^[35] conducted a study in which 60000 patients with antiviral treatment were enrolled between 1999 and 2015. The antiviral regimens were divided into 3 groups: 35871 IFN-only, 4535 DAA and IFN, and 21948 DAA-only with a mean follow-up time of 6.1 years for all patients and 1.53 years for the DAA-only group. The study found a significant reduction in HCC occurrence risk of 71% (adjusted HR = 0.29; 95%CI: 0.23-0.37) in patients with DAA-induced SVR. Janjua *et al*^[36] recently published a study which evaluated a large cohort treated with DAAs compared with a retrospective cohort treated with IFN. The authors found a similar rate reduction in HCC risk in patients who achieved SVR obtained either with DAAs or with IFN-based regimens (70% reduction for DAAs and 79% for IFN-based therapy).

Retrospective studies assessing outcomes after DAAs

Kanwal *et al*^[37] conducted a cohort study which evaluated the risk of HCC in 22500 DAA-treated patients with a mean follow-up period of 1.02 years. The study demonstrated that the risk of HCC in patients with SVR is significantly reduced as compared with non-SVR patients [0.90 vs 3.45 HCC/100 person year (PY); adjusted HR = 0.28, 95%CI: 0.22-0.36]. Similarly, in a study including almost 4000 DAA-treated HCV patients from several centers across Spain, Calleja *et al*^[38] aimed to evaluate the effectiveness, safety and clinical outcomes of DAA-based therapy in HCV genotype 1 infection, reported a HCC incidence of 0.93% within 18 mo of starting DAAs treatment

Table 1 *De novo* hepatocellular carcinoma incidence after direct-acting antiviral treatment

| Ref. | Type of study | Patient (n) and characteristics | Follow-up time | <i>De novo</i> HCC incidence |
|--|---------------------|---|-------------------------------------|------------------------------|
| Conti <i>et al</i> ^[14] | Retrospective study | Cirrhotic patients treated with DAAs (n = 285) | Mean FU: 5.6 mo | 3.16% |
| Ravi <i>et al</i> ^[33] | Retrospective study | Cirrhotic patients treated with DAAs (n = 66) | From SOT to 6 mo after EOT | 9.1% |
| Singer <i>et al</i> ^[34] | Retrospective study | DAA-treated (n = 30183), IFN-treated (n = 12948), untreated (n = 137502) | Mean FU: 1.05 yr | 1.18 per 100 PY |
| Nahon <i>et al</i> ^[43] | Retrospective study | All compensated cirrhotic patients DAA-treated (n = 336), IFN-treated with SVR (n = 495), IFN-treated without SVR (n = 439) | Median FU: 21.2 mo (IQR: 13.5-26.9) | 2.6 per 100 PY |
| Ioannou <i>et al</i> ^[35] | Retrospective study | DAA-treated (n = 21948), IFN-treated (n = 35871), DAA + IFN treated (n = 4535) | Mean FU: 6.1 yr | 1.32 per 100 PY |
| Kanwal <i>et al</i> ^[37] | Retrospective study | DAA-treated (n = 22500) | Mean FU: 1.02 yr | 1.18 per 100 PY |
| Cheung <i>et al</i> ^[42] | Prospectivestudy | DAA-treated (n = 406), untreated (n = 261) | Median FU: 18 mo | 4% |
| Calleja <i>et al</i> ^[38] | Retrospectivestudy | DAA-treated (n = 3325) | Mean FU: 18 mo | 11.3% |
| Mettke <i>et al</i> ^[44] | Prospective study | DAA-treated (n = 158), untreated (n = 184) | Median FU: 440 d | 2.90 per 100 PY |
| Carrat <i>et al</i> ^[45] | Prospectivestudy | DAA-treated (n = 7344), untreated (n = 2551) | Median FU: 33.4 mo (IQR: 24.0-40.7) | 1.40 per 100 PY |
| Janjua <i>et al</i> ^[36] | Retrospective study | IFN-treated (n = 8871), DAA-treated (n = 3905) | Median FU: 1.0 yr | 6.9 per 1000 PY |
| Poordad <i>et al</i> ^[46] | Prospective study | DAA-treated (n = 2211) | 156 wk from EOT | 1.4% |
| Sangiovanni <i>et al</i> ^[47] | Prospective study | DAA-treated (n = 1285) | Mean FU: 17 mo | 3.1 per 100 PY |
| Kanwal <i>et al</i> ^[39] | Retrospective study | DAA-treated (n = 18076) | Mean FU: 2.9 yr | 3% |
| Romano <i>et al</i> ^[48] | Prospective study | DAA-treated (n = 3917) | Median FU: 523 d, (IQR: 381-699 d) | 0.97 per 100 PY |
| Tani <i>et al</i> ^[40] | Retrospective study | DAA-treated (n = 1088) | Median FU: 13.8 mo | 2.38% |
| Watanabe <i>et al</i> ^[41] | Retrospective study | DAA-treated (n = 1438) | Median FU: 803 d | 3.82% |

DAA: Direct-acting antivirals; SOT: Start of treatment; FU: Follow-up; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; IFN: Interferon; IQR: Interquartile range; PY: Person-year; EOT: End of treatment; SVR: Sustained viral response.

with ombitasvir/paritaprevir/ritonavir plus dasabuvir (OMV/PTV/r+DSV) and ledipasvir/sofosbuvir (LDV/SOF). It should be mentioned that measuring the incidence of HCC was not an objective of this study. In contrast to these results, the same team that had previously reported a reduced risk of HCC in patients with chronic HCV infection treated with DAAs^[37], recently published another retrospective cohort study in which evaluated the long-term risk of HCC in patients with SVR to DAAs, followed up for over 3.5 years after SVR^[39]. From 18076 patients who achieved SVR with DAAs, they found 544 patients with *de novo* HCC, with 1-, 2-, and 3-year cumulative risks of HCC of 1.1%, 1.9% and 2.8%, respectively. Results from another two recently published studies are consistent with those reported by this second study by Kanwal *et al*^[39]. In a retrospective study, Tani *et al*^[40] demonstrated that the 12- and 36-mo cumulative incidences of HCC were 1.88 and 6.00%, respectively. Similarly, Watanabe *et al*^[41] reported 1- and 2-year cumulative incidences of HCC of 1.9 and 4.1%, respectively.

Prospective studies

A prospective study by Cheung *et al*^[42] which included 406 patients with decompensated cirrhosis found no evidence of an increased risk for HCC during DAA therapy or during the 12-mo follow-up. The authors found a 4.2% HCC incidence in the first six months from the start of DAA treatment, the equivalent to the occurrence seen in a matched control group containing untreated patients. Furthermore, the authors suggested the possibility of pre-existing undiagnosed cancer in patients which developed HCC during DAA treatment. Another large prospective study from ANRS CO12 CirVir cohort including 1270 HCV patients with compensated biopsy-proven

cirrhosis reported that after Cox analysis there was no statistically significant increase in the risk of HCC development associated with DAAs use^[43]. A large prospective study by Mettke *et al*^[44] containing 158 HCV-related cirrhotic patients treated with DAAs and 184 HCV-related cirrhotic patients without treatment, demonstrated a similar HCC incidence over a short period of time in the two groups (HCC developed in 6 DAA-treated patients and 14 untreated patients, yielding HCC incidence rates of 2.90 and 4.48 per 100 person-years, respectively). A multi-center prospective cohort study published by Carrat *et al*^[45] in France also found that treatment with DAAs was associated with a reduced risk for mortality and HCC. The study included 7344 patients with DAA treatment and 2551 patients without treatment, with a mean follow-up period of 33.4 mo. 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). Also, recent results from the ongoing phase 3b trials TOPAZ-I and TOPAZ-II demonstrated a low incidence rate of HCC in DAA-treated HCV patients. The combined interim results from both the TOPAZ-I and TOPAZ-II studies performed up to 156 wk posttreatment showed that the rates of liver transplantation, liver decompensation, HCC and liver-related death were 0.6%, 2.0%, 1.4%, and 0.3%, respectively^[46]. Another recent prospective study by Sangiovanni *et al*^[47], including 1285 consecutive patients with HCV-related cirrhosis without any history of HCC (group 1), and 124 cirrhotics with previous HCC and complete response to treatment (group 2) found an yearly incidence of 3.1/100 PY-recent data from a prospective study by Romano *et al*^[48] showed a HCC incidence rate of 0.97 per 100 PY (95%CI: 0.73-1.26) and a sharp decline in HCC risk in the 2nd year of follow-up in patients with HCV-related cirrhosis treated with DAAs.

Ma *et al*^[49] recently published a large meta-analysis in which 276848 HCV-infected patients treated either with IFN-based therapy or with DAAs were included. The authors reported that DAA treatment is not better than IFN-based therapies in preventing the development of HCC, indicating that IFN-based therapy might currently be irreplaceable in the prophylaxis of HCC in patients with chronic hepatitis C.

HCC RECURRENCE AFTER DAA THERAPY

In patients with early disease stage HCC - Barcelona Clinic Liver Cancer Stage 0/A - BCLC 0/A, there are available potentially curative treatments such as surgical resection and local ablation, with high 5-year overall survival rate. However, tumour recurrence and decompensation of underlying cirrhosis contribute to long-term mortality even after curative treatment. As stated by previous research, HCC recurrence after an initial complete response may develop through either the dissemination of cells from the original tumor prior to curative therapy, or through de novo cancers arising in the cirrhotic genetically altered microenvironment^[50]. Thus, it seems appropriate to stratify the recurrence of HCC into: (1) Intra-hepatic metastasis of the original tumor; and (2) Multicentric carcinogenesis. The distinction between these models is mandatory and it could be made using the amount of time between curative therapy and recurrence. Thereby, an early recurrence within 1-2 years may be attributed to intrahepatic metastasis, whereas a recurrence > 2 years is supposedly due to metachronous HCC^[51]. Microscopic vascular invasion and/or satellites are high risk hallmarks for dissemination whilst sustained inflammation with persistent liver damage is predictive for multicentric carcinogenesis/metachronous tumors^[52]. The most important factor in predicting the growth of nested malignant cell from the primary tumor is the immune cancer surveillance which in a normal setting triggers the activation of stromal cells and lymphocyte recruitment, secondary leading to the suppression of cell clones^[53]. Several studies from the IFN era highlighted the beneficial effect on HCC recurrence exerted by IFN-based therapy^[54-57]. One of the major differences between IFN and DAA obtained SVR is the kinetics of viral suppression which may be the key in explaining the high recurrence rate of HCC. The mechanism proposed for HCC recurrence in patients with SVR obtained with DAAs in prior HCV-related HCC patients, consists of a disruption of the immune cancer surveillance due to an abrupt resolution of a chronic inflammatory state as the suppression of HCV replication occurs in the first days after therapy^[58].

However, available data regarding HCC recurrence in patients with initial complete response to hepatic resection or local ablation following DAA-induced SVR are scarce and conflicting (Table 2).

Table 2 Recurrent hepatocellular carcinoma incidence after direct-acting antiviral treatment

| Ref. | Type of study | Patient (n) and characteristics | Follow-up time | Recurrent HCC incidence |
|--------------------------------------|---------------------|--|---|--------------------------------------|
| Reig <i>et al</i> ^[13] | Retrospective study | DAA-treated (n = 103) | Mean FU: 5.7 mo | 27.6% |
| Conti <i>et al</i> ^[14] | Retrospective study | DAA-treated (n = 59) | Mean FU: 5.6 mo | 28.8% |
| ANRS CO22 HEPATHER ^[64] | Prospective study | DAA-treated (n = 189), untreated (n = 78) | Mean FU: 20.2 mo | 0.73 per 100 person-months |
| ANRS CO12 CirVir ^[64] | Prospective study | All biopsy proven cirrhotic patients, DAA-treated (n = 13), untreated (n = 66) | Median FU: 21.3 mo (IQR: 13.0-33.5) | 1.11 per 100 person-months |
| ANRS CO23 CUPILT ^[64] | Prospective study | LT recipients for HCC, treated with DAA (n = 314) | Mean FU: 70 ± 64 mo after LT | 2.2% |
| Cabibbo <i>et al</i> ^[65] | Prospective study | DAA-treated (n = 143) | Mean FU: 8.7 mo | 20.3% |
| Lin <i>et al</i> ^[59] | Retrospective study | DAA-treated (n = 60), untreated (n = 47) | Median FU: 20 mo | 37.1% |
| Singal <i>et al</i> ^[60] | Retrospective study | DAA-treated (n = 304), IFN-treated (n = 489) | Median FU: 10.4 mo (IQR: 5.3-20.8) since complete remission | DAA treated 42.1%, untreated 52.9% |
| Nagata <i>et al</i> ^[62] | Retrospective study | DAA-treated (n = 83), IFN-treated (n = 60) | Mean FU: IFN 81.6 mo, DAA 21.6 mo | IFN-treated 54.2%, DAA-treated 45.1% |
| Imai <i>et al</i> ^[63] | Retrospective study | DAA-treated (n = 13), IFN-treated (n = 34), untreated (n = 70) | N/A | |

DAA: Direct-acting antivirals; FU: Follow-up; HCC: Hepatocellular carcinoma; IFN: Interferon; IQR: Interquartile range; LT: Liver transplant; N/A: Not available.

Retrospective studies

In 2016, Reig *et al*^[13] reported an unexpected high rate of 27.6% of early tumor recurrence in patients with HCV-related HCC undergoing DAA treatment. Similar results were found by Conti *et al*^[14] in a single-center retrospective cohort study, with a recurrence rate of HCC after DAAs of 28.81%. Contrasting results were reported by Lin *et al*^[59] in a recently published retrospective study which included 107 patients with HCV-related HCC, of whom 60 received DAA therapy after treatment for HCC. After a median follow-up of 20 mo, 37.1% patients had HCC recurrence after DAAs. The authors concluded that, compared to untreated patients, DAA therapy did not increase recurrent HCC after curative treatment and also improved the survival outcome of HCC patients. In line with these results, the largest retrospective cohort study ever reported was recently published, including untreated control arm, based on 31 health systems throughout the United States and Canada. The study included 793 HCV-related HCC patients of which 304 (38.3%) received DAA therapy and 489 (61.7%) were untreated. The rate of tumor recurrence was 42.1% in DAA-treated patients and 58.9% in the untreated group. After variable adjustments, the study reported that DAA exposure is not associated with an increased risk of HCC recurrence (HR = 0.90; 95%CI: 0.70-1.16)^[60]. A meta-analysis published by Lui *et al*^[61] also showed that the use of DAA therapy is associated with a significantly lower risk of HCC development compared to patients without DAA treatment. The authors found a > 60% lower risk of HCC recurrence in patients exposed to DAA compared to controls (OR = 0.36, 95%CI: 0.27-0.47; $P < 0.001$; $I^2 = 88\%$).

A retrospective cohort study which compared outcomes of patients with prior HCV-related HCC treated with DAAs *vs* IFN-based therapy found no significant difference between IFN-based and IFN-free therapy groups by propensity score-matched analysis (5-year incidence; 54.2% in IFN-based, 45.1% in IFN-free therapy; $P = 0.54$)^[62]. Consistent with these findings, results from a recent retrospective cohort from Japan showed that SVR by therapy with DAAs exhibited an anti-liver tumorigenesis effect equal to that of IFN-based therapy and reduced the risk of HCC recurrence ($P = 0.564$)^[63].

Prospective studies

A prospective multicenter French study that included ANRS cohorts concluded that the rate of HCC recurrence was not different between DAA-treated and untreated

groups^[64]. Cabibbo *et al*^[65] conducted a prospective multicenter study in Italy in which were included 143 patients with successfully treated BCLC 0/A HCC, and subsequently treated with DAAs. They found an HCC-recurrence incidence of 12%, 26.6%, and 29.1%, respectively in 6-, 12-, and 18-mo of follow-up, and concluded that although the risk of HCC recurrence remains high, it is comparable between the DAA group and the untreated group.

RISK FACTORS FOR *DE NOVO* AND RECURRENT HCC

The increasing number of patients who will obtain HCV clearance with DAAs and the continued risk of hepatocarcinogenesis even after SVR require the identification of patients at highest risk of developing HCC. Regarding the host risk factors such as older age, male gender and family history, HBV or HIV co-infection, alcohol consumption, steatohepatitis and advanced liver disease are well known as associated risk factors^[66]. Also, tobacco smoking and exposure to aflatoxin are the most studied environmental risk factors involved in the development of HCC^[67]. The risk factors incriminated in HCC occurrence and recurrence, in patients treated with DAAs, are mainly older age, non-SVR and advanced liver disease (Table 3).

Retrospective studies

A study conducted by Kanwal *et al*^[37] which included DAA treated patients, reported a 4.7-fold higher HCC risk in cirrhotic patients than in those without cirrhosis (adjusted HR = 4.73; 95%CI: 3.34-6.68). Similar findings were disclosed by Ioannou *et al*^[35] in a large cohort retrospective study, concluding that the incidence of HCC was highest in patients with cirrhosis and treatment failure. Singer *et al*^[34] demonstrated that older age, male gender, liver cirrhosis, thrombocytopenia, portal hypertension, diabetes, tobacco use, alcoholic liver disease, and use of betablockers and anti-hypertensives were associated with an increased risk of HCC in multivariable adjusted models. Despite using different inclusion criteria and study methods, these three cohort studies demonstrated that the presence of cirrhosis and the absence of SVR were the major risk factors of HCC occurrence in HCV patients^[34,35,37]. A high FIB-4 index and posttreatment AFP were identified as independent factors that contributed to HCC occurrence in two recent studies^[39,41].

In the 2016 paper, Conti *et al*^[14] reported that decompensated cirrhosis characterized by a high Child-Pugh-Turcotte score (OR = 4.18, 95%CI: 1.17-14.8, $P = 0.03$) and a history of HCC (OR = 12.0, 95%CI: 4.02-35.74, $P < 0.0001$) were associated with HCC. In addition, a large comparative study from Japan revealed that posttreatment Wisteria floribunda agglutinin positive Mac-2 binding protein (WFA⁺M2BP) was significantly associated with HCC recurrence in patients with HCV without advanced liver fibrosis. In addition, the comparative study for occurrence and recurrence of HCC in IFN-based *vs* DAAs, showed that AFP (> 5.4 ng/mL) and WFA⁺M2BP levels (> 1.8 COI) were strongly associated with *de novo* HCC in those with DAA therapy^[61]. In a recently published retrospective study, Sangiovanni *et al*^[47] found at multivariable Cox regression models that ascites and AFP log-value were independently associated with HCC occurrence, while a history of alcohol abuse and HCC recurrence was associated with HCC recurrence.

Prospective studies

In addition to these findings from retrospective studies, Ide *et al*^[68] found that besides male gender and an older age, higher FIB-4 index and GGTP levels, were independently associated with HCC occurrence. Also, Calvaruso *et al*^[69] found in their prospective study that albumin level (< 3.5 g/dL), platelets < 120 × 10⁹/L and failure to achieve SVR were associated with an increased risk of HCC development. The failure in achieving SVR was also incriminated as a risk factor for HCC occurrence along with HBV coinfection and APRI > 2.5, in another study from Italy^[48]. Another study which enrolled patients with a history of successful radiofrequency ablation treatment for HCV-related HCC who had received antiviral therapy with DAAs (147 patients) or IFN (156 patients) reported that a higher AFP-L3 level, larger number of HCC treatments, and a shorter interval between the last HCC treatment and the initiation of antiviral therapy were associated with the risk of HCC recurrence^[70]. A recent study from Egypt, which enrolled 160 DAA-treated and 80 untreated HCV patients, showed that an ultrasound measured adequate liver volume (at a cutoff of 495 mL) predicted HCC occurrence after DAAs^[71].

Most of the studies we reviewed indicated that the major risk factors for HCC

Table 3 Risk factors for de novo and recurrent hepatocellular carcinoma after direct-acting antiviral therapy

| Ref. | Type of study | Patient (n) and characteristics | Risk factors |
|--|---------------------|--|---|
| Conti <i>et al</i> ^[14] | Retrospective study | Cirrhotic patients treated with DAAs (n = 285) | No associated factor for <i>de novo</i> HCC, older age, liver stiffness for HCC recurrence |
| Singer <i>et al</i> ^[34] | Retrospective study | DAA-treated (n = 30183), IFN-treated (n = 12948), untreated (n = 137502) | Older age, male gender, cirrhosis, thrombocytopenia, portal hypertension, diabetes, tobacco use, alcoholic liver disease |
| Ioannou <i>et al</i> ^[35] | Retrospective study | DAA-treated (n = 21948), IFN-treated (n = 35871), DAA + IFN treated (n = 4535) | Non-SVR, cirrhosis |
| Kanwal <i>et al</i> ^[37] | Retrospective study | DAA-treated (n = 22500) | Non-SVR, alcohol use, non-African Americans, cirrhosis |
| Hanafy <i>et al</i> ^[71] | Prospective study | All decompensated cirrhotic patients, DAA-treated (n = 160), untreated (n = 80) | An adequate baseline liver volume measured by ultrasound was associated with less HCC occurrence and better short-term survival |
| Kanwal <i>et al</i> ^[39] | Retrospective study | DAA-treated (n = 18076) | High FIB-4/APRI, alcohol use, older age, genotype 3 |
| Watanabe <i>et al</i> ^[41] | Retrospective study | DAA-treated (n = 1438) | High FIB-4 index, AFP |
| Nagata <i>et al</i> ^[62] | Retrospective study | DAA-treated (n = 83), IFN-treated (n = 60) | IL-28 genetic polymorphism, post-treatment WFA ⁺ M2BP, AFP (> 5.4 ng/mL) |
| Ide <i>et al</i> ^[68] | Prospective study | CHC DAA-treated (n = 2552) | Age ≥ 62 yr, male gender, FIB-4 index ≥ 4.6, GGTP level ≥ 44 IU/L |
| Calvaruso <i>et al</i> ^[69] | Prospective study | HCV cirrhosis DAA-treated (n = 2249) | Albumin < 3.5 g/dL, platelets < 120 × 10 ⁹ /L, absence of SVR |
| Romano <i>et al</i> ^[48] | Prospective study | CHC > F3 DAA-treated (n = 3917) | HBsAg+, APRI ≥ 2.5, CPT B, treatment failure |
| Sangiovanni <i>et al</i> ^[47] | Retrospective study | 1161 HCC-free HCV cirrhotics, DAA treated, 124 HCV cirrhotics who had received a curative treatment for an HCC DAA treated | <i>De novo</i> HCC: Ascites, AFP, recurrent HCC; History of alcohol abuse, history of HCC recurrence |

DAA: Direct-acting antivirals; FU: Follow-up; HCC: Hepatocellular carcinoma; SVR: Sustained virological response; IFN: Interferon; IQR: Interquartile range; LT: Liver transplant; CHC: Chronic hepatitis C; APRI: Aspartate aminotransferase to platelet ratio index; CPT: Child-Pugh-Turcotte; SVR: Sustained viral response; AFP: Alpha-fetoprotein; WFA⁺M2BP: Wisteria floribunda agglutinin positive Mac-2 binding protein; HCV: Chronic hepatitis C; GGTP: Gamma-glutamyl transpeptidase.

occurrence and recurrence are male gender, older age, non-SVR, advanced liver fibrosis and higher post-treatment AFP levels, in agreement with those identified by prior studies of the IFN era^[25,72].

CONCLUSION

Data provided by the most recent and relevant articles sustain a reduced incidence rate of both *de novo* and recurrent HCC after achieving SVR with DAA therapy, therefore we consider that the debate regarding the impact of DAAs on HCC risk is drawing to an end.

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