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

Cristina Maria Muzica, Carol Stanciu, Laura Huiban, Ana-Maria Singeap, Catalin Sfarti, Sebastian Zenovia, Camelia Cojocariu, Anca Trifan

Abstract

Direct acting antivirals (DAAs) have revolutionized the treatment of hepatitis C virus (HCV) infection, achieving high rates (≥ 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

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.
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[16]. 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[14]. 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-cell checkpoints[8]. 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\(^{[29-33]}\). 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\(^{[34]}\). HCC development due to HCV is a gradual process spanning two to four decades\(^{[35]}\). 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\(^{[36]}\). 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\(^{[37]}\).

### 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\(^{[38-40]}\). 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\(^{[41,42]}\). 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\(^{[43,44]}\). 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\(^{[45,46]}\). 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)\(^{[47]}\). Similarly, Ioannou et al\(^{[48]}\) 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\(^{[49]}\) 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\(^{[50]}\) 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\(^{[51]}\) 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       | De novo HCC incidence |
|--------------------|--------------------|-------------------------------------------------|----------------------|------------------------|
| Conti et al\(^{[4]}\) | Retrospective study | Cirrhotic patients treated with DAAs (n = 285)   | Mean FU: 5.6 mo      | 3.16%                  |
| Ravi et al\(^{[5]}\)  | Retrospective study | Cirrhotic patients treated with DAAs (n = 66)    | From SOT to 6 mo after EOT | 9.1%                  |
| Singer et al\(^{[6]}\) | Retrospective study | DAA-treated (n = 30183), IFN-treated (n = 12948), untreated (n = 137502) | Mean FU: 1.05 yr | 1.18 per 100 PY        |
| Nahon et al\(^{[7]}\)  | 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 et al\(^{[8]}\) | 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 et al\(^{[9]}\) | Retrospective study | DAA-treated (n = 22500)                          | Mean FU: 1.02 yr     | 1.18 per 100 PY        |
| Cheung et al\(^{[10]}\) | Prospective study  | DAA-treated (n = 406), untreated (n = 261)      | Median FU: 18 mo     | 4%                     |
| Calleja et al\(^{[11]}\) | Retrospective study | DAA-treated (n = 3325)                          | Mean FU: 18 mo      | 11.3%                  |
| Mettke et al\(^{[12]}\) | Prospective study  | DAA-treated (n = 158), untreated (n = 184)      | Median FU: 440 d     | 2.90 per 100 PY        |
| Carrat et al\(^{[13]}\) | Prospective study  | DAA-treated (n = 7344), untreated (n = 2551)    | Median FU: 33.4 mo (IQR: 24.0-40.7) | 1.40 per 100 PY        |
| Janjua et al\(^{[14]}\) | Retrospective study | IFN-treated (n = 8871), DAA-treated (n = 3905) | Median FU: 1.0 yr | 6.9 per 1000 PY        |
| Pourdad et al\(^{[15]}\) | Prospective study  | DAA-treated (n = 2211)                          | Mean FU: 17 mo     | 3.1 per 100 PY         |
| Sangiovanni et al\(^{[16]}\) | Prospective study  | DAA-treated (n = 1285)                          | 156 wk from EOT | 1.4%                   |
| Kanwal et al\(^{[17]}\) | Retrospective study | DAA-treated (n = 18076)                         | Mean FU: 2.9 yr     | 3%                     |
| Romano et al\(^{[18]}\) | Prospective study  | DAA-treated (n = 3917)                          | Median FU: 523 d, (IQR: 381-699 d) | 0.97 per 100 PY        |
| Tani et al\(^{[19]}\)  | Retrospective study | DAA-treated (n = 1088)                          | Median FU: 13.8 mo  | 2.38%                  |
| Watanabe et al\(^{[20]}\) | 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\(^{[21]}\), 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\(^{[22]}\). 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\(^{[23]}\). In a retrospective study, Tani et al\(^{[24]}\) demonstrated that the 12- and 36-mo cumulative incidences of HCC were 1.88 and 6.00%, respectively. Similarly, Watanabe et al\(^{[25]}\) 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\(^{[26]}\) 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\textsuperscript{(40).} A large prospective study by Mettke \textit{et al}\textsuperscript{(41)} 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 \textit{et al}\textsuperscript{(42)} 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\textsuperscript{(43)}. Another recent prospective study by Sangiovanni \textit{et al}\textsuperscript{(44)}, including 1285 consecutive patients with HCV-related cirrhosis without any history of HCC (group 1), and 124 cirrhotics with previous HCC and compete response to treatment (group 2) found an yearly incidence of 3.1/100 PY-recent data from a prospective study by Romano \textit{et al}\textsuperscript{(45)} 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 patients with HCV-related cirrhosis treated with DAAs.

Ma \textit{et al}\textsuperscript{(46)} recently published a large meta-analysis in which 276,848 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\textsuperscript{(47)}. 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\textsuperscript{(48)}. 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\textsuperscript{(49)}. 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\textsuperscript{(50)}. Several studies from the IFN era highlighted the beneficial effect on HCC recurrence exerted by IFN-based therapy\textsuperscript{(45)-(47)}. 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\textsuperscript{(48)}.

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 et al[13]       | Retrospective study | DAA-treated (n = 103) | Mean FU: 5.7 mo | 27.6%                  |
| Conti et al[14]      | Retrospective study | DAA-treated (n = 59) | Mean FU: 5.6 mo | 28.8%                  |
| ANRS CO22 HEPATHER[6] | Prospective study | DAA-treated (n = 189), untreated (n = 78) | Mean FU: 20.2 mo | 0.73 per 100 person-months |
| ANRS CO12 CirVir[15] | 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[6]  | Prospective study | LT recipients for HCC, treated with DAA (n = 314) | Mean FU: 70 ± 64 mo after LT | 2.2%  |
| Cabibbo et al[16]    | Prospective study | DAA-treated (n = 143) | Mean FU: 8.7 mo | 20.3%                  |
| Lin et al[9]         | Retrospective study | DAA-treated (n = 60), untreated (n = 47) | Median FU: 20 mo | 37.1%                  |
| Singal et al[8]      | Retrospectivestudy | DAA-treated (n = 304), IFN-treated (n = 489) | Median FU: 10.4 mo (IQR: 5.3-20.8) | DAA treated 42.1%, untreated 52.9% |
| Nagata et al[12]     | Retrospectivestudy | 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 et al[10]       | 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 DAA of 28.81%. Contrasting results were reported by Lin et al[8] 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 DAA. 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)[8]. A meta-analysis published by Lui et al[11] 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; F = 88%).

A retrospective cohort study which compared outcomes of patients with prior HCV-related HCC treated with DAs 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)[12]. Consistent with these findings, results from a recent retrospective cohort from Japan showed that SVR by therapy with DAs exhibited an anti-liver tumorigenesis effect equal to that of IFN-based therapy and reduced the risk of HCC recurrence (P = 0.564)[13].

**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
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groups\(^6\). Cabibbo et al\(^6\) 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\(^6\). Also, tobacco smoking and exposure to aflatoxin are the most studied environmental risk factors involved in the development of HCC\(^6\). 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\(^6\) 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\(^6\) in a large cohort retrospective study, concluding that the incidence of HCC was highest in patients with cirrhosis and treatment failure. Singer et al\(^6\) 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\(^6\). A high FIB-4 index and posttreatment AFP were identified as independent factors that contributed to HCC occurrence in two recent studies\(^6\).

In the 2016 paper, Conti et al\(^6\) 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\(^6\).

In a recently published retrospective study, Sangiovanni et al\(^6\) 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\(^6\) 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\(^6\) found in their prospective study that albumin level (< 3.5 g/dL), platelets < 120 \(\times\) 10\(^9\)/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\(^6\). 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\(^6\). 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\(^6\).

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

# 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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