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ABOUT COVER

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MINIREVIEWS

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 (≥ 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	*De novo* HCC incidence
Conti *et al*[14]	Retrospective study	Cirrhotic patients treated with DAAs (*n* = 285)	Mean FU: 5.6 mo	3.16%
Ravi *et al*[33]	Retrospective study	Cirrhotic patients treated with DAAs (*n* = 66)	From SOT to 6 mo after EOT	9.1%
Singer *et al*[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 *et al*[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 *et al*[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 *et al*[37]	Retrospective study	DAA-treated (*n* = 22500)	Mean FU: 1.02 yr	1.18 per 100 PY
Cheung *et al*[42]	Prospectivestudy	DAA-treated (*n* = 406), untreated (*n* = 261)	Median FU: 18 mo	4%
Calleja *et al*[38]	Retrospectivestudy	DAA-treated (*n* = 3325)	Mean FU: 18 mo	11.3%
Mettke *et al*[44]	Prospective study	DAA-treated (*n* = 158), untreated (*n* = 184)	Median FU: 440 d	2.90 per 100 PY
Carrat *et al*[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 *et al*[36]	Retrospective study	IFN-treated (*n* = 8871), DAA-treated (*n* = 3905)	Median FU: 1.0 yr	6.9 per 1000 PY
Poordad *et al*[46]	Prospective study	DAA-treated (*n* = 2211)	156 wk from EOT	1.4%
Sangiovanni *et al*[47]	Prospective study	DAA-treated (*n* = 1285)	Mean FU: 17 mo	3.1 per 100 PY
Kanwal *et al*[39]	Retrospective study	DAA-treated (*n* = 18076)	Mean FU: 2.9 yr	3%
Romano *et al*[48]	Prospective study	DAA-treated (*n* = 3917)	Median FU: 523 d, (IQR: 381-699 d)	0.97 per 100 PY
Tani *et al*[40]	Retrospective study	DAA-treated (*n* = 1088)	Median FU: 13.8 mo	2.38%
Watanabe *et al*[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 compete 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 microenviroment[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/metachronic 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 *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[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 *et al*[65]	Prospective study	DAA-treated (*n* = 143)	Mean FU: 8.7 mo	20.3%
Lin *et al*[59]	Retrospective study	DAA-treated (*n* = 60), untreated (*n* = 47)	Median FU: 20 mo	37.1%
Singal *et al*[60]	Retrospectivestudy	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 *et al*[62]	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*[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 × 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[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 Egipt, 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 *et al*[14]	Retrospective study	Cirrhotic patients treated with DAAs (*n* = 285)	No associated factor for *de novo* HCC, older age, liver stiffness for HCC recurrence
Singer *et al*[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 *et al*[35]	Retrospective study	DAA-treated (*n* = 21948), IFN-treated (*n* = 35871), DAA + IFN treated (*n* = 4535)	Non-SVR, cirrhosis
Kanwal *et al*[37]	Retrospective study	DAA-treated (*n* = 22500)	Non-SVR, alcohol use, non-African Americans, cirrhosis
Hanafy *et al*[71]	Prospectivestudy	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 *et al*[39]	Retrospective study	DAA-treated (*n* = 18076)	High FIB-4/APRI, alcohol use, older age, genotype 3
Watanabe *et al*[41]	Retrospective study	DAA-treated (*n* = 1438)	High FIB-4 index, AFP
Nagata *et al*[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 *et al*[68]	Prospectivestudy	CHC DAA-treated (*n* = 2552)	Age ≥ 62 yr, male gender, FIB-4 index ≥ 4.6, GGTP level ≥ 44 IU/L
Calvaruso *et al*[69]	Prospective study	HCV cirrhosis DAA-treated (*n* = 2249)	Albumin < 3.5 g/dL, platelets < 120 × 10^9/L, absence of SVR
Romano *et al*[48]	Prospective study	CHC > F3 DAA-treated (*n* = 3917)	HBsAg+, APRI ≥ 2.5, CPT B, treatment failure
Sangiovanni *et al*[47]	Retrospective study	1161 HCC-free HCV cirrhotics, DAA treated, 124 HCV cirrhotics who had received a curative treatment for an HCC DAA treated	*De novo* 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.

REFERENCES

1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

2 **El-Serag HB**. Hepatocellular carcinoma. *N Engl J Med* 2011; **365**: 1118-1127 [PMID: 21992124 DOI: 10.1056/NEJMra1001683]

3 **World Health Organization**. Global hepatitis report, 2017. April 2017 [cited 9 January 2020]. Available from: https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/

4 **Lemon SM**, McGivern DR. Is hepatitis C virus carcinogenic? *Gastroenterology* 2012; **142**: 1274-1278 [PMID: 22537433 DOI: 10.1053/j.gastro.2012.01.045]

5 **Janjua NZ**, Chong M, Kuo M, Woods R, Wong J, Yoshida EM, Sherman M, Butt ZA, Samji H, Cook D, Yu A, Alvarez M, Tyndall M, Krajden M. Long-term effect of sustained virological response on hepatocellular carcinoma in patients with hepatitis C in Canada. *J Hepatol* 2017; **66**: 504-513 [PMID: 27818234 DOI: 10.1016/j.jhep.2016.10.028]

6 **Brown JL**. Interferon therapy reduces the risk for hepatocellular carcinoma. *Gut* 2000; **47**: 610-611 [PMID: 11034573 DOI: 10.1136/gut.47.5.610]

7 **Ikeda M**, Fujiyama S, Tanaka M, Sata M, Ide T, Yatsuhashi H, Watanabe H. Risk factors for development of hepatocellular carcinoma in patients with chronic hepatitis C after sustained response to interferon. *J Gastroenterol* 2005; **40**: 148-156 [PMID: 15770398 DOI: 10.1007/s00535-004-1519-2]

8 **Bourlière M**, Bronowicki JP, de Ledinghen V, Hézode C, Zoulim F, Mathurin P, Tran A, Larrey DG, Ratziu V, Alric L, Hyland RH, Jiang D, Doehle B, Pang PS, Symonds WT, Subramanian GM, McHutchison JG, Marcellin P, Habersetzer F, Guyader D, Grangé JD, Loustaud-Ratti V, Serfaty L, Metivier S, Leroy V, Abergel A, Pol S. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). *Lancet Infect Dis* 2015; **15**: 397-404 [PMID: 25773757 DOI: 10.1016/S1473-3099(15)70050-2]

9 **Charlton M**, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS Jr, Fried MW, Terrault NA, O'Leary JG, Vargas HE, Kuo A, Schiff E, Sulkowski MS, Gilroy R, Watt KD, Brown K, Kwo P, Pungpapong S, Korenblat KM, Muir AJ, Teperman L, Fontana RJ, Denning J, Arterburn S, Dvory-Sobol H, Brandt-Sarif T, Pang PS, McHutchison JG, Reddy KR, Afdhal N; SOLAR-1 Investigators. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. *Gastroenterology* 2015; **149**: 649-659 [PMID: 25985734 DOI: 10.1053/j.gastro.2015.05.010]

10 **Leroy V**, Angus P, Bronowicki JP, Dore GJ, Hezode C, Pianko S, Pol S, Stuart K, Tse E, McPhee F, Bhore R, Jimenez-Exposito MJ, Thompson AJ. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: A randomized phase III study (ALLY-3+). *Hepatology* 2016; **63**: 1430-1441 [PMID: 26822022 DOI: 10.1002/hep.28473]

11 **Morgan RL**, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. *Ann Intern Med* 2013; **158**: 329-337 [PMID: 23460056 DOI: 10.7326/0003-4819-158-5-201303050-00005]

12 **Cabibbo G**, Celsa C, Calvaruso V, Petta S, Cacciola I, Cannavò MR, Madonia S, Rossi M, Magro B, Rini F, Distefano M, Larocca L, Prestileo T, Malizia G, Bertino G, Benanti F, Licata A, Scalisi I, Mazzola G, Di Rosolini MA, Alaimo G, Averna A, Cartabellotta F, Alessi N, Guastella S, Russello M, Scifo G, Squadrito G, Raimondo G, Trevisani F, Craxì A, Di Marco V, Cammà C; Rete Sicilia Selezione Terapia – HCV (RESIST-HCV) and Italian Liver Cancer (ITA. LI.CA.) Group. Direct-acting antivirals after successful treatment of early hepatocellular carcinoma improve survival in HCV-cirrhotic patients. *J Hepatol* 2019; **71**: 265-273 [PMID: 30959157 DOI: 10.1016/j.jhep.2019.03.027]

13 **Reig M**, Mariño Z, Perelló C, Iñarrairaegui M, Ribeiro A, Lens S, Díaz A, Vilana R, Darnell A, Varela M, Sangro B, Calleja JL, Forns X, Bruix J. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. *J Hepatol* 2016; **65**: 719-726 [PMID: 27084592 DOI: 10.1016/j.jhep.2016.04.008]

14 **Conti F**, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, Caraceni P, Foschi FG, Lenzi M, Mazzella G, Verucchi G, Andreone P, Brillanti S. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. *J Hepatol* 2016; **65**: 727-733 [PMID: 27349488 DOI: 10.1016/j.jhep.2016.06.015]

15 **Moradpour D**, Penin F. Hepatitis C virus proteins: from structure to function. *Curr Top Microbiol Immunol* 2013; **369**: 113-142 [PMID: 23463199 DOI: 10.1007/978-3-642-27340-7_5]

16 **Preda CM**, Popescu CP, Baicus C, Voiosu TA, Manuc M, Pop CS, Gheorghe L, Sporea I, Trifan A, Tantau M, Tantau A, Ceausu E, Proca D, Constantinescu I, Ruta SM, Diculescu MM, Oproiu A. Real-world efficacy and safety of ombitasvir, paritaprevir/r+dasabuvir+ribavirin in genotype 1b patients with hepatitis C virus cirrhosis. *Liver Int* 2018; **38**: 602-610 [PMID: 28816020 DOI: 10.1111/liv.13550]

17 **Bartenschlager R**, Penin F, Lohmann V, André P. Assembly of infectious hepatitis C virus particles. *Trends Microbiol* 2011; **19**: 95-103 [PMID: 21146993 DOI: 10.1016/j.tim.2010.11.005]

18 **Raimondi S**, Bruno S, Mondelli MU, Maisonneuve P. Hepatitis C virus genotype 1b as a risk factor for hepatocellular carcinoma development: a meta-analysis. *J Hepatol* 2009; **50**: 1142-1154 [PMID: 19395111 DOI: 10.1016/j.jhep.2009.01.019]

19 **Kanwal F**, Kramer JR, Ilyas J, Duan Z, El-Serag HB. HCV genotype 3 is associated with an increased risk of cirrhosis and hepatocellular cancer in a national sample of U.S. Veterans with HCV. *Hepatology* 2014; **60**: 98-105 [PMID: 24615981 DOI: 10.1002/hep.27095]

20 **Lee MH**, Hsiao TI, Subramaniam SR, Le AK, Vu VD, Trinh HN, Zhang J, Jin M, Wong VW, Wong GL, Nguyen MH. HCV Genotype 6 Increased the Risk for Hepatocellular Carcinoma Among Asian Patients With Liver Cirrhosis. *Am J Gastroenterol* 2017; **112**: 1111-1119 [PMID: 28440303 DOI: 10.1038/ajg.2017.123]

21 **Bartosch B**, Thimme R, Blum HE, Zoulim F. Hepatitis C virus-induced hepatocarcinogenesis. *J Hepatol* 2009; **51**: 810-820 [PMID: 19545926 DOI: 10.1016/j.jhep.2009.05.008]

22 **Vescovo T**, Refolo G, Vitagliano G, Fimia GM, Piacentini M. Molecular mechanisms of hepatitis C virus-induced hepatocellular carcinoma. *Clin Microbiol Infect* 2016; **22**: 853-861 [PMID: 27476823 DOI: 10.1016/j.cmi.2016.07.019]

23 **Yu GY**, He G, Li CY, Tang M, Grivennikov S, Tsai WT, Wu MS, Hsu CW, Tsai Y, Wang LH, Karin M. Hepatic expression of HCV RNA-dependent RNA polymerase triggers innate immune signaling and cytokine production. *Mol Cell* 2012; **48**: 313-321 [PMID: 22959272 DOI: 10.1016/j.molcel.2012.07.032]

24 **Tomasetti C**, Li L, Vogelstein B. Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. *Science* 2017; **355**: 1330-1334 [PMID: 28336671 DOI: 10.1126/science.aaf9011]

25 **Tada T**, Kumada T, Toyoda H, Kiriyama S, Tanikawa M, Hisanaga Y, Kanamori A, Kitabatake S, Yama T, Tanaka J. Viral eradication reduces all-cause mortality in patients with chronic hepatitis C virus infection: a propensity score analysis. *Liver Int* 2016; **36**: 817-826 [PMID: 26787002 DOI: 10.1111/liv.13071]

26 **Innes HA**, McDonald SA, Dillon JF, Allen S, Hayes PC, Goldberg D, Mills PR, Barclay ST, Wilks D, Valerio H, Fox R, Bhattacharyya D, Kennedy N, Morris J, Fraser A, Stanley AJ, Bramley P, Hutchinson SJ. Toward a more complete understanding of the association between a hepatitis C sustained viral response and

cause-specific outcomes. *Hepatology* 2015; **62**: 355-364 [PMID: 25716707 DOI: 10.1002/hep.27766]

27 **Bruno S**, Di Marco V, Iavarone M, Roffi L, Crosignani A, Calvaruso V, Aghemo A, Cabibbo G, Viganò M, Boccaccio V, Craxí A, Colombo M, Maisonneuve P. Survival of patients with HCV cirrhosis and sustained virologic response is similar to the general population. *J Hepatol* 2016; **64**: 1217-1223 [PMID: 27059129 DOI: 10.1016/j.jhep.2016.01.034]

28 **El-Serag HB**, Kanwal F, Richardson P, Kramer J. Risk of hepatocellular carcinoma after sustained virological response in Veterans with hepatitis C virus infection. *Hepatology* 2016; **64**: 130-137 [PMID: 26946190 DOI: 10.1002/hep.28535]

29 **Asahina Y**, Tsuchiya K, Nishimura T, Muraoka M, Suzuki Y, Tamaki N, Yasui Y, Hosokawa T, Ueda K, Nakanishi H, Itakura J, Takahashi Y, Kurosaki M, Enomoto N, Nakagawa M, Kakinuma S, Watanabe M, Izumi N. α-fetoprotein levels after interferon therapy and risk of hepatocarcinogenesis in chronic hepatitis C. *Hepatology* 2013; **58**: 1253-1262 [PMID: 23564522 DOI: 10.1002/hep.26442]

30 **Oze T**, Hiramatsu N, Yakushijin T, Miyazaki M, Yamada A, Oshita M, Hagiwara H, Mita E, Ito T, Fukui H, Inui Y, Hijioka T, Inada M, Katayama K, Tamura S, Yoshihara H, Inoue A, Imai Y, Hayashi E, Kato M, Miyagi T, Yoshida Y, Tatsumi T, Kasahara A, Hamasaki T, Hayashi N, Takehara T; Osaka Liver Forum. Post-treatment levels of α-fetoprotein predict incidence of hepatocellular carcinoma after interferon therapy. *Clin Gastroenterol Hepatol* 2014; **12**: 1186-1195 [PMID: 24321207 DOI: 10.1016/j.cgh.2013.11.033]

31 **van der Meer AJ**, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, Heathcote EJ, Manns MP, Kuske L, Zeuzem S, Hofmann WP, de Knegt RJ, Hansen BE, Janssen HL. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012; **308**: 2584-2593 [PMID: 23268517 DOI: 10.1001/jama.2012.144878]

32 **D'Ambrosio R**, Della Corte C, Colombo M. Hepatocellular Carcinoma in Patients with a Sustained Response to Anti-Hepatitis C Therapy. *Int J Mol Sci* 2015; **16**: 19698-19712 [PMID: 26295392 DOI: 10.3390/ijms160819698]

33 **Ravi S**, Axley P, Jones D, Kodali S, Simpson H, McGuire BM, Singal AK. Unusually High Rates of Hepatocellular Carcinoma After Treatment With Direct-Acting Antiviral Therapy for Hepatitis C Related Cirrhosis. *Gastroenterology* 2017; **152**: 911-912 [PMID: 28161225 DOI: 10.1053/j.gastro.2016.12.021]

34 **Singer AW**, Reddy KR, Telep LE, Osinusi AO, Brainard DM, Buti M, Chokkalingam AP. Direct-acting antiviral treatment for hepatitis C virus infection and risk of incident liver cancer: a retrospective cohort study. *Aliment Pharmacol Ther* 2018; **47**: 1278-1287 [PMID: 29516535 DOI: 10.1111/apt.14593]

35 **Ioannou GN**, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. *J Hepatol* 2017; S0168-8278(17)32273-0 [PMID: 28887168 DOI: 10.1016/j.jhep.2017.08.030]

36 **Janjua NZ**, Wong S, Darvishian M, Butt ZA, Yu A, Binka M, Alvarez M, Woods R, Yoshida EM, Ramji A, Feld J, Krajden M. The impact of SVR from direct-acting antiviral- and interferon-based treatments for HCV on hepatocellular carcinoma risk. *J Viral Hepat* 2020; **27**: 781-793 [PMID: 32187430 DOI: 10.1111/jvh.13295]

37 **Kanwal F**, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of Hepatocellular Cancer in HCV Patients Treated With Direct-Acting Antiviral Agents. *Gastroenterology* 2017; **153**: 996-1005. e1 [PMID: 28642197 DOI: 10.1053/j.gastro.2017.06.012]

38 **Calleja JL**, Crespo J, Rincón D, Ruiz-Antorán B, Fernandez I, Perelló C, Gea F, Lens S, García-Samaniego J, Sacristán B, García-Eliz M, Llerena S, Pascasio JM, Turnes J, Torras X, Morillas RM, Llaneras J, Serra MA, Diago M, Rodriguez CF, Ampuero J, Jorquera F, Simon MA, Arenas J, Navascues CA, Bañares R, Muñoz R, Albillos A, Mariño Z; Spanish Group for the Study of the Use of Direct-acting Drugs Hepatitis C Collaborating Group. Effectiveness, safety and clinical outcomes of direct-acting antiviral therapy in HCV genotype 1 infection: Results from a Spanish real-world cohort. *J Hepatol* 2017; **66**: 1138-1148 [PMID: 28189751 DOI: 10.1016/j.jhep.2017.01.028]

39 **Kanwal F**, Kramer JR, Asch SM, Cao Y, Li L, El-Serag HB. Long-Term Risk of Hepatocellular Carcinoma in HCV Patients Treated With Direct Acting Antiviral Agents. *Hepatology* 2020; **71**: 44-55 [PMID: 31222774 DOI: 10.1002/hep.30823]

40 **Tani J**, Morishita A, Sakamoto T, Takuma K, Nakahara M, Fujita K, Oura K, Tadokoro T, Mimura S, Nomura T, Yoneyama H, Kobara H, Himoto T, Tsutsui A, Senoh T, Nagano T, Ogawa C, Moriya A, Deguchi A, Takaguchi K, Masaki T. Simple scoring system for prediction of hepatocellular carcinoma occurrence after hepatitis C virus eradication by direct-acting antiviral treatment: All Kagawa Liver Disease Group Study. *Oncol Lett* 2020; **19**: 2205-2212 [PMID: 32194718 DOI: 10.3892/ol.2020.11341]

41 **Watanabe T**, Tokumoto Y, Joko K, Michitaka K, Horiike N, Tanaka Y, Tada F, Kisaka Y, Nakanishi S, Yamauchi K, Yukimoto A, Nakamura Y, Hirooka M, Abe M, Hiasa Y. Sex difference in the development of hepatocellular carcinoma after direct-acting antiviral therapy in patients with HCV infection. *J Med Virol* 2020 [PMID: 32374470 DOI: 10.1002/jmv.25984]

42 **Cheung MCM**, Walker AJ, Hudson BE, Verma S, McLauchlan J, Mutimer DJ, Brown A, Gelson WTH, MacDonald DC, Agarwal K, Foster GR, Irving WL; HCV Research UK. Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol* 2016; **65**: 741-747 [PMID: 27388925 DOI: 10.1016/j.jhep.2016.06.019]

43 **Nahon P**, Layese R, Bourcier V, Cagnot C, Marcellin P, Guyader D, Pol S, Larrey D, De Lédinghen V, Ouzan D, Zoulim F, Roulot D, Tran A, Bronowicki JP, Zarski JP, Riachi G, Calès P, Péron JM, Alric L, Bourlière M, Mathurin P, Blanc JF, Abergel A, Serfaty L, Mallat A, Grangé JD, Attali P, Bacq Y, Wartelle C, Dao T, Thabut D, Pilette C, Silvain C, Christidis C, Nguyen-Khac E, Bernard-Chabert B, Zucman D, Di Martino V, Sutton A, Roudot-Thoraval F, Audureau E; ANRS CO12 CirVir Group. Incidence of Hepatocellular Carcinoma After Direct Antiviral Therapy for HCV in Patients With Cirrhosis Included in Surveillance Programs. *Gastroenterology* 2018; **155**: 1436-1450. e6 [PMID: 30031138 DOI: 10.1053/j.gastro.2018.07.015]

44 **Mettke F**, Schlevogt B, Deterding K, Wranke A, Smith A, Port K, Manns MP, Vogel A, Cornberg M, Wedemeyer H. Interferon-free therapy of chronic hepatitis C with direct-acting antivirals does not change the

short-term risk for de novo hepatocellular carcinoma in patients with liver cirrhosis. *Aliment Pharmacol Ther* 2018; **47**: 516-525 [PMID: 29205405 DOI: 10.1111/apt.14427]

45 **Carrat F**, Fontaine H, Dorival C, Simony M, Diallo A, Hezode C, De Ledinghen V, Larrey D, Haour G, Bronowicki JP, Zoulim F, Asselah T, Marcellin P, Thabut D, Leroy V, Tran A, Habersetzer F, Samuel D, Guyader D, Chazouilleres O, Mathurin P, Metivier S, Alric L, Riachi G, Gournay J, Abergel A, Cales P, Ganne N, Loustaud-Ratti V, D'Alteroche L, Causse X, Geist C, Minello A, Rosa I, Gelu-Simeon M, Portal I, Raffi F, Bourliere M, Pol S; French ANRS CO22 Hepather cohort. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. *Lancet* 2019; **393**: 1453-1464 [PMID: 30765123 DOI: 10.1016/S0140-6736(18)32111-1]

46 **Poordad F**, Castro RE, Asatryan A, Aguilar H, Cacoub P, Dieterich D, Marinho RT, Carvalho A, Siddique A, Hu YB, Charafeddine M, Bondin M, Khan N, Cohen DE, Felizarta F. Long-term safety and efficacy results in hepatitis C virus genotype 1-infected patients receiving ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin in the TOPAZ-I and TOPAZ-II trials. *J Viral Hepat* 2020; **27**: 497-504 [PMID: 31954087 DOI: 10.1111/jvh.13261]

47 **Sangiovanni A**, Alimenti E, Gattai R, Filomia R, Parente E, Valenti L, Marzi L, Pellegatta G, Borgia G, Gambato M, Terreni N, Serio I, Belli L, Oliveri F, Maimone S, Brunacci M, D'Ambrosio R, Forzenigo LV, Russo FP, Rumi M, Barone M, Fracanzani AL, Raimondo G, Giannini EG, Brunetto MR, Villa E, Biganzoli E, Colombo M, Lampertico P. Undefined/non-malignant hepatic nodules are associated with early occurrence of HCC in DAA-treated patients with HCV-related cirrhosis. *J Hepatol* 2020; **73**: 593-602 [PMID: 32243959 DOI: 10.1016/j.jhep.2020.03.030]

48 **Romano A**, Angeli P, Piovesan S, Noventa F, Anastassopoulos G, Chemello L, Cavalletto L, Gambato M, Russo FP, Burra P, Vincenzi V, Scotton PG, Panese S, Tempesta D, Bertin T, Carrara M, Carlotto A, Capra F, Carolo G, Scroccaro G, Alberti A. Newly diagnosed hepatocellular carcinoma in patients with advanced hepatitis C treated with DAAs: A prospective population study. *J Hepatol* 2018; **69**: 345-352 [PMID: 29551707 DOI: 10.1016/j.jhep.2018.03.009]

49 **Ma L**, Liu J, Wang W, Yang F, Li P, Cai S, Zhou X, Chen X, Zhuang X, Zhang H, Cao G. Direct-acting antivirals and interferon-based therapy on hepatocellular carcinoma risk in chronic hepatitis-C patients. *Future Oncol* 2020; **16**: 675-686 [PMID: 32223423 DOI: 10.2217/fon-2019-0845]

50 **Bruix J**, Gores GJ, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. *Gut* 2014; **63**: 844-855 [PMID: 24531850 DOI: 10.1136/gutjnl-2013-306627]

51 **Bruix J**, Reig M, Sherman M. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. *Gastroenterology* 2016; **150**: 835-853 [PMID: 26795574 DOI: 10.1053/j.gastro.2015.12.041]

52 **Ferrer-Fàbrega J**, Forner A, Liccioni A, Miquel R, Molina V, Navasa M, Fondevila C, García-Valdecasas JC, Bruix J, Fuster J. Prospective validation of ab initio liver transplantation in hepatocellular carcinoma upon detection of risk factors for recurrence after resection. *Hepatology* 2016; **63**: 839-849 [PMID: 26567038 DOI: 10.1002/hep.28339]

53 **Malladi S**, Macalinao DG, Jin X, He L, Basnet H, Zou Y, de Stanchina E, Massagué J. Metastatic Latency and Immune Evasion through Autocrine Inhibition of WNT. *Cell* 2016; **165**: 45-60 [PMID: 27015306 DOI: 10.1016/j.cell.2016.02.025]

54 **Singal AK**, Freeman DH Jr, Anand BS. Meta-analysis: interferon improves outcomes following ablation or resection of hepatocellular carcinoma. *Aliment Pharmacol Ther* 2010; **32**: 851-858 [PMID: 20659285 DOI: 10.1111/j.1365-2036.2010.04414.x]

55 **Miao RY**, Zhao HT, Yang HY, Mao YL, Lu X, Zhao Y, Liu CN, Zhong SX, Sang XT, Huang JF. Postoperative adjuvant antiviral therapy for hepatitis B/C virus-related hepatocellular carcinoma: a meta-analysis. *World J Gastroenterol* 2010; **16**: 2931-2942 [PMID: 20556841 DOI: 10.3748/wjg.v16.i23.2931]

56 **Zhuang L**, Zeng X, Yang Z, Meng Z. Effect and safety of interferon for hepatocellular carcinoma: a systematic review and meta-analysis. *PLoS One* 2013; **8**: e61361 [PMID: 24069133 DOI: 10.1371/journal.pone.0061361]

57 **Zhang W**, Song TQ, Zhang T, Wu Q, Kong DL, Li Q, Sun HC. Adjuvant interferon for early or late recurrence of hepatocellular carcinoma and mortality from hepatocellular carcinoma following curative treatment: A meta-analysis with comparison of different types of hepatitis. *Mol Clin Oncol* 2014; **2**: 1125-1134 [PMID: 25279210 DOI: 10.3892/mco.2014.386]

58 **Ioannou GN**, Feld JJ. What Are the Benefits of a Sustained Virologic Response to Direct-Acting Antiviral Therapy for Hepatitis C Virus Infection? *Gastroenterology* 2019; **156**: 446-460.e2 [PMID: 30367836 DOI: 10.1053/j.gastro.2018.10.033]

59 **Lin WC**, Lin YS, Chang CW, Chang CW, Wang TE, Wang HY, Chen MJ. Impact of direct-acting antiviral therapy for hepatitis C-related hepatocellular carcinoma. *PLoS One* 2020; **15**: e0233212 [PMID: 32442193 DOI: 10.1371/journal.pone.0233212]

60 **Singal AG**, Rich NE, Mehta N, Branch A, Pillai A, Hoteit M, Volk M, Odewole M, Scaglione S, Guy J, Said A, Feld JJ, John BV, Frenette C, Mantry P, Rangnekar AS, Oloruntoba O, Leise M, Jou JH, Bhamidimarri KR, Kulik L, Tran T, Samant H, Dhanasekaran R, Duarte-Rojo A, Salgia R, Eswaran S, Jalal P, Flores A, Satapathy SK, Wong R, Huang A, Misra S, Schwartz M, Mitrani R, Nakka S, Noureddine W, Ho C, Konjeti VR, Dao A, Nelson K, Delarosa K, Rahim U, Mavuram M, Xie JJ, Murphy CC, Parikh ND. Direct-Acting Antiviral Therapy Not Associated With Recurrence of Hepatocellular Carcinoma in a Multicenter North American Cohort Study. *Gastroenterology* 2019; **156**: 1683-1692. e1 [PMID: 30660729 DOI: 10.1053/j.gastro.2019.01.027]

61 **Lui FH**, Moosvi Z, Patel A, Hussain S, Duong A, Duong J, Nguyen DL. Decreased risk of hepatocellular carcinoma recurrence with direct-acting antivirals compared with no treatment for hepatitis C: a meta-analysis. *Ann Gastroenterol* 2020; **33**: 293-298 [PMID: 32382233 DOI: 10.20524/aog.2020.0470]

62 **Nagata H**, Nakagawa M, Asahina Y, Sato A, Asano Y, Tsunoda T, Miyoshi M, Kaneko S, Otani S, Kawai-Kitahata F, Murakawa M, Nitta S, Itsui Y, Azuma S, Kakinuma S, Nouchi T, Sakai H, Tomita M, Watanabe M; Ochanomizu Liver Conference Study Group. Effect of interferon-based and -free therapy on early occurrence and recurrence of hepatocellular carcinoma in chronic hepatitis C. *J Hepatol* 2017; **67**: 933-939

[PMID: 28627363 DOI: 10.1016/j.jhep.2017.05.028]

63 **Imai K**, Takai K, Hanai T, Suetsugu A, Shiraki M, Shimizu M. Sustained virological response by direct-acting antivirals reduces the recurrence risk of hepatitis C-related hepatocellular carcinoma after curative treatment. *Mol Clin Oncol* 2020; **12**: 111-116 [PMID: 31929880 DOI: 10.3892/mco.2019.1956]

64 **ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CirVir and CO23 CUPILT cohorts)**. Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: Data from three ANRS cohorts. *J Hepatol* 2016; **65**: 734-740 [PMID: 27288051 DOI: 10.1016/j.jhep.2016.05.045]

65 **Cabibbo G**, Petta S, Calvaruso V, Cacciola I, Cannavò MR, Madonia S, Distefano M, Larocca L, Prestileo T, Tinè F, Bertino G, Giannitrapani L, Benanti F, Licata A, Scalisi I, Mazzola G, Cartabellotta F, Alessi N, Barbàra M, Russello M, Scifo G, Squadrito G, Raimondo G, Craxì A, Di Marco V, Cammà C; Rete Sicilia Selezione Terapia - HCV (RESIST-HCV). Is early recurrence of hepatocellular carcinoma in HCV cirrhotic patients affected by treatment with direct-acting antivirals? *Aliment Pharmacol Ther* 2017; **46**: 688-695 [PMID: 28791711 DOI: 10.1111/apt.14256]

66 **El-Serag HB**. Hepatocellular carcinoma and hepatitis C in the United States. *Hepatology* 2002; **36**: S74-S83 [PMID: 12407579 DOI: 10.1053/jhep.2002.36807]

67 **Kim HS**, El-Serag HB. The Epidemiology of Hepatocellular Carcinoma in the USA. *Curr Gastroenterol Rep* 2019; **21**: 17 [PMID: 30976932 DOI: 10.1007/s11894-019-0681-x]

68 **Ide T**, Koga H, Nakano M, Hashimoto S, Yatsuhashi H, Higuchi N, Nakamuta M, Oeda S, Eguchi Y, Shakado S, Sakisaka S, Yoshimaru Y, Sasaki Y, Honma Y, Harada M, Seike M, Maeshiro T, Miuma S, Nakao K, Mawatari S, Ido A, Nagata K, Matsumoto S, Takami Y, Sohda T, Kakuma T, Torimura T. Direct-acting antiviral agents do not increase the incidence of hepatocellular carcinoma development: a prospective, multicenter study. *Hepatol Int* 2019; **13**: 293-301 [PMID: 30820753 DOI: 10.1007/s12072-019-09939-2]

69 **Calvaruso V**, Cabibbo G, Cacciola I, Petta S, Madonia S, Bellia A, Tinè F, Distefano M, Licata A, Giannitrapani L, Prestileo T, Mazzola G, Di Rosolini MA, Larocca L, Bertino G, Digiacomo A, Benanti F, Guarneri L, Averna A, Iacobello C, Magro A, Scalisi I, Cartabellotta F, Savalli F, Barbara M, Davì A, Russello M, Scifo G, Squadrito G, Cammà C, Raimondo G, Craxì A, Di Marco V; Rete Sicilia Selezione Terapia–HCV (RESIST-HCV). Incidence of Hepatocellular Carcinoma in Patients With HCV-Associated Cirrhosis Treated With Direct-Acting Antiviral Agents. *Gastroenterology* 2018; **155**: 411-421. e4 [PMID: 29655836 DOI: 10.1053/j.gastro.2018.04.008]

70 **Nishibatake Kinoshita M**, Minami T, Tateishi R, Wake T, Nakagomi R, Fujiwara N, Sato M, Uchino K, Enooku K, Nakagawa H, Asaoka Y, Shiina S, Koike K. Impact of direct-acting antivirals on early recurrence of HCV-related HCC: Comparison with interferon-based therapy. *J Hepatol* 2019; **70**: 78-86 [PMID: 30336183 DOI: 10.1016/j.jhep.2018.09.029]

71 **Hanafy AS**, Bassiony MA, Basha MAA. Management of HCV-related decompensated cirrhosis with direct-acting antiviral agents: who should be treated? *Hepatol Int* 2019; **13**: 165-172 [PMID: 30758786 DOI: 10.1007/s12072-019-09933-8]

72 **Yamada R**, Hiramatsu N, Oze T, Urabe A, Tahata Y, Morishita N, Kodama T, Hikita H, Sakamori R, Yakushijin T, Yamada A, Hagiwara H, Mita E, Oshita M, Itoh T, Fukui H, Inui Y, Hijioka T, Inada M, Katayama K, Tamura S, Inoue A, Imai Y, Tatsumi T, Hamasaki T, Hayashi N, Takehara T. Incidence and risk factors of hepatocellular carcinoma change over time in patients with hepatitis C virus infection who achieved sustained virologic response. *Hepatol Res* 2019; **49**: 570-578 [PMID: 30623521 DOI: 10.1111/hepr.13310]

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