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ORIGINAL RESEARCH

Decreased Incidence of Hepatocellular Carcinoma after Directly Acting Antiviral Therapy in Patients with Hepatitis C–Related Advanced Fibrosis and Cirrhosis

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Background and Aim: Existing data are controversial regarding the incidence of hepatitis C (HCV)–related hepatocellular carcinoma (HCC) following directly acting antiviral (DAA) therapy. This prospective study aimed to assess incidence, and risk factorss of HCC following DAA therapy in patients with HCV-related advanced fibrosis (F3) and cirrhosis (F4).

Methods: Incidence of HCC was calculated in 1,630 patients with HCV-related F3 and F4 treated with DAA prospectively followed for up to 43 months in a single tertiary referral center and compared to historical controls. Risk factors of incident HCC were also determined.

Results: The crude outcome rate was 2.15/100 person-years, significantly lower than a similar historical cohort (5.57/100 person-years). Risk of developing HCC was higher with the presence of cirrhosis (F4 vs F3, AHR 3.59) and treatment failure (vs achieving SVR, AHR 3.37). Presence of decompensated cirrhosis, platelet count $<100\times10^3$/mL, and high AFP were independent risk factors of developing HCC.

Conclusion: Incidence of HCC was significantly lower in patients with HCV-related advanced fibrosis and cirrhosis treated with DAAs than in a historical cohort of untreated patients. Decompensated cirrhosis, baseline AFP ≥10 ng/mL, diabetes, and nonresponse to DAA were independent risk factors of incident HCC.

Keywords: HCC, DAA, HCC incidence, HCC predictors, HCC characteristics

Introduction

Chronic hepatitis C virus (HCV) infection has been identified as an independent risk factor of hepatocellular carcinoma (HCC) development, especially in patients with cirrhosis.[1] The risk of HCC development in HCV-related cirrhosis is estimated at 2%–8% per year,[2] which further increases with age, male sex, alcohol misuse, and coinfection with hepatitis B or HIV.[3,4]

Multiple studies have provided evidence that achieving sustained virological response (SVR) after IFN therapy is associated with a fourfold reduction in HCC risk.[5] Nevertheless, most patients with cirrhosis are not candidates for IFN therapy, and the risk of HCC persists in cirrhosis even after SVR, especially in elderly patients.[6,7] Since the introduction of directly acting antivirals (DAAs), tremendous advancement in the treatment of HCV patients has occurred, with SVR rates >90% in real-life settings[8–11] and excellent safety profiles, which has enabled their use

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even in patients with decompensated liver disease, who had not been eligible for IFN-based regimens.[12] Patients with cirrhosis who reach a DAA-induced SVR have shown lower rates of cirrhosis progression and downstream complications, especially decompensation, and all-cause mortality.[13]

Owing to the unprecedentedly high antiviral efficacy of DAAs, it was anticipated that the risk of HCC would be reduced. Several reports have suggested more frequent post-DAA HCC development and recurrence, and a DAA-induced HCC-preventive effect has been debated.[14–16] Other studies have not shown increased risk, with follow-up periods reaching 15 months.[17] As such, the impact of DAA therapy on HCC incidence remains controversial.

Data from Egypt have suggested an increase in recurrent HCC following DAA treatment,[18] but reports evaluating the incidence of de novo HCC after DAA treatment in HCV genotype 4 (HCV-G4) are limited.

In this study, we prospectively evaluated a cohort of patients with HCV G4–related cirrhosis or advanced fibrosis without previous diagnosis of HCC who had received DAA treatment, in order to assess HCC incidence, and identify predictive risk factors associated with HCC occurrence.

Methods

Study Cohort

This study included HCV-G4 patients 18 years or older with advanced fibrosis or cirrhosis who had received DAA treatment during 2016 at a single tertiary referral center in Egypt. They were prospectively followed every 3 months after treatment to assess incidence of HCC. Patients with hepatitis B coinfection or with HCC prior to starting DAA treatment were excluded.

The study was approved by the Ethics Committee of the National Liver Institute (IRB00003413) and performed in accordance with the 1975 Declaration of Helsinki. All authors had access to the study data and reviewed and approved the final manuscript.

Assessment of Patients' Baseline and Treatment-Related Parameters

Fibrosis was assessed by calculating Fibrosis4 (FIB-4) index scores (age [years] × AST [U/L]/platelet count [$\times 10^9$/L] × ALT [U/L])[19,20] and measuring liver stiffness by transient elastography using a FibroScan (Echosens, Paris, France) before DAA therapy. Advanced fibrosis was considered liver stiffness of >9.5–12.5 kPa, and cirrhosis was defined based on clinical features, ultrasonography, or liver stiffness >12.5 kPa.[21] All patients underwent abdominal ultrasound (and multislice triphasic CT scan if needed) to exclude presence of any focal lesion in the liver before the start of treatment.

Virological response to DAA therapy was assessed, and sustained virological response (SVR) was defined as having undetectable HCV RNA for 12 weeks or more following completion of treatment.

Outcome Events

The study outcome was first occurrence of HCC up to the end of June of 2019. Patients had liver ultrasound performed every 3 months or whenever new symptoms appeared. Although international guidelines recommend ultrasound screening for HCC every 6 months in follow-up of patients with cirrhosis, in this study the 3-month interval was due to the yet-unknown and possible increased risk of HCC after the use of DAAs. The low cost of ultrasound in our setting, added to the cost-effectiveness of screening for HCC based on our previously published results,[23] made screening using ultrasound every 3 months feasible and more reasonable for these patients. HCC was suspected based on ultrasound imaging and diagnosed according to current European Association for the Study of the Liver–European Organisation for Research and Treatment of Cancer guidelines by one dynamic imaging technique with triphasic CT scanning or dynamic contrast-enhanced MRI meeting the criteria typical of HCC (hypervascularity in the arterial phase with washout in the portal venous or delayed phases).[22] Duration of follow-up was calculated from the end of DAA therapy till diagnosis of HCC or end of follow-up. The date of HCC diagnosis was used as a surrogate for time of HCC occurrence.

The crude annual incidence of HCC development was calculated and categorized by fibrosis stage and SVR status. This was compared to the annual incidence of HCC in 1,254 patients with HCV cirrhosis followed before the era of DAA therapy who were not suitable for IFN therapy. These patients were prospectively followed up with liver ultrasound and AFP measurement every 6 months.[23]

Predictor Variables

The probability of HCC development was determined for baseline covariates. Cox's proportional- hazard model was used to identify risk factors associated with incident HCC.

Table 1 Baseline Demographic and Clinical Characteristics of HCV Patients Treated with Direct Acting Antiviral Agents (Overall and by Sustained Virological Response

Characteristics		Overall n=1,630	SVR n=1,531	No SVR[a] n=97	*P*[b]
Age	Mean ± SD Median	55.1±8.32 55.0	54.51±8.20 55.0	53.8±9.9 54.0	0.32
Sex, n (%)	Male Female	1,185 (72.7) 445 (27.3)	1,110 (93.8) 421 (94.8)	74 (6.2) 23 (5.2)	0.42
Diabetes, n (%)	No Yes	1,324 (81.2) 306 (18.8)	1,254 (94.8) 277 (90.8)	69 (5.2) 28 (9.2)	0.008
Ascites, n (%)	Yes No	112 (6.9) 1,518 (93.1)	106 (95.5) 1,425 (93.9)	5 (4.5) 92 (6.1)	0.50
Previous HCV antiviral treatment, n (%)	No Yes, with IFN Yes, with DAA	1,458 (89.4) 80 (4.9) 92 (5.6)	1,362 (93.5) 79 (98.8) 90 (97.8)	94 (6.5) 1 (1.2) 2 (2.2)	0.04*
ALT (IU/L)	Mean ± SD Median	62.1±40.4 52.0	61.7±40.2 51.0	67.1±42.3 59.0	0.10
AST (IU/L)	M± SD Median	63.3±38.3 55.0	63.2±38.9 55.0	64.3±28.4 59.0	0.13
AFP (IU/L)	Mean ± SD Median	15.6±22.9 8.0	15.5±22.8 8.0	17.3±25.2 8.9	0.59
Platelets, $\times 10^3/mm^3$	Mean ± SD Median	154.6±61.4 148.0	154.2±61.4 147.0	160.5±60.7 150.0	0.36**
Total bilirubin (mg/dL)	Mean ± SD Median	1.11±0.75 0.9	1.10±0.72 0.9	1.25±1.07 0.9	0.18
Albumin (g/dL)	Mean ± SD Median	3.81±0.49 3.8	3.82±0.49 3.8	3.77±0.47 3.8	0.32**
INR	Mean ± SD Median	1.13±0.28 1.1	1.13±0.28 1.1	1.14±0.21 1.1	0.23
Child–Turcotte–Pugh class,[c] n (%)	A B C	973 (81.2) 217 (18.1) 9 (0.8)	913 (93.8) 202 (93.5) 7 (77.8)	60 (6.2) 14 (6.5) 2 (22.2)	0.14*
Initial FIB-4 score, n (%)	<1.45 1.45–3.25 >3.25	205 (12.6) 697 (42.8) 728 (44.6)	187 (91.2) 661 (94.8) 683 (94.1)	18 (8.8) 36 (5.3) 43 (5.9)	0.16
DAA regimen[d]	Sof-Rbv Sof-PEG-Rbv Sof-Smv Sof-Smv-Rbv Sof-Dcv Sof-Dcv-Rbv Sof-Ldv Sof-Ldv-Rbv PRO-Rbv	158 (9.7) 82 (5) 116 (7.1) 518 (31.8) 185 (11.4) 329 (20.2) 89 (5.5) 120 (7.4) 21 (1.3)	126 (79.7) 70 (85.4) 113 (97.4) 497 (95.9) 176 (95.1) 319 (97) 86 (96.6) 114 (95) 20 (95.2)	32 (20.3) 12 (14.6) 3 (2.6) 21 (4.1) 9 (4.9) 10 (3) 3 (3.4) 6 (5) 1 (4.8)	<0.001

Notes: [a]Two patients died before SVR12; [b]comparison between patients with SVR and patients without; [c]data for 1,199 patients with cirrhosis; [d]DAA regimen was for 12 weeks, except Sof-Rbv (24 weeks). *P*-values from Chi-square test[2] and Mann–Whitney tests. *Fisher's exact test; **t-test.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAA, directly acting antiviral; Dcv, daclatasvir; FIB-4, Fibrosis 4 (index); HCV, hepatitis C virus; INR, international normalized ratio; Ldv, ledipasvir; PRO, paritaprevir–ritonavir–ombitasvir; Rbv, ribavirin; Sof, sofosbuvir; Smv, simeprevir; SVR, sustained virological response.

Covariates included in this analysis were baseline age, sex, diabetes, platelet count, AFP, ascites, Child–Turcotte–Pugh (CTP) score, FIB-4 score, and change in FIB-4 score following treatment.

Statistical Analysis

Annual incidence of HCC in the whole cohort of patients who had completed DAA treatment was calculated. We determined the date of DAA-treatment completion and followed patients to the development of HCC, death, or end of follow-up, whichever was earlier. We calculated incidence with 95% CIs as the number of HCC events divided by total person-years (PYs) of follow-up.

Incidence rate of HCC development in the subgroup of patients with F4 cirrhosis who did not respond to DAA therapy was compared to historical incidence rate of HCC development in patients with HCV-related cirrhosis without antiviral therapy before the era of DAAs in the same center.[22]

Cumulative probability of HCC occurrence was determined for each independent variable and compared using Kaplan–Meier curves, with differences between these curves evaluated using the log-rank tests. For Kaplan–Meier analysis with more than two factors, we used the Bonferroni method, and 0.016 was regarded as significant for this analysis.

We used the multivariate Cox proportional-hazard model to compare the risk factors of HCC in the whole cohort. Unadjusted and adjusted HRs with 95% CIs were calculated for each independent variable. Statistical analysis was performed using SPSS 20.0 and Stata 14.

Results

Patient Characteristics

A total of 1,630 patients with HCV-related advanced fibrosis or cirrhosis starting DAA therapy were prospectively included. Baseline characteristics, treatment regimen received, and virological outcomes of treatment are presented in Table 1. Mean age was 55.1±8.32 years, 72.7% were male, 18.8% had a history of diabetes, and 10.5% had previously been treated with antiviral therapy, of whom 92 had had exposure to DAAs. In sum, 1,202 (73.7%) patients had cirrhosis and 14.2% decompensated liver cirrhosis (Table 1).

Ribavirin was administered (600–1,000 mg total daily dose, depending on body weight) to 811 patients. Overall 1,531 patients (93.9%) achieved SVRs. Patients who did not achieve SVRs were more likely to be diabetic, have had previous antiviral therapy, and received Sof-Rbv for 24 weeks (Table 1).

A historical cohort of 1,254 patients with HCV-related cirrhosis was compared to this prospective cohort. Mean age was 51.5±8.7 years, 38.4% had CTP A, 61.6% had decompensated liver cirrhosis, and all had not previously been treated with antiviral therapy.

HCC Development after DAA Treatment

HCC developed in 66 patients over 22.4±11.7 months of follow-up. Cumulative probability of HCC occurrence at 6, 12, 18, 24, and 36 months was 1.8%, 2.4%, 4.3%, 4.8%, and 4.8%, respectively (Table 2, Figure 1A).

Patients with cirrhosis had significantly higher incidence of HCC than patients with advanced fibrosis (F3). A total of 63 patients with cirrhosis developed HCC over 2,192.2 PYs' follow-up (2.9 per 100 PYs, 95% CI 2.3–3.7), while three HCC cases developed in patients with F3 in 873.3 PYs' follow-up (0.33 per 100 PYs, 95% CI 0.11–1.01; Table 3, Figure 1B). The risk of HCC was 3.6-fold higher in patients with cirrhosis than those with advanced fibrosis (AHR 3.59, 95% CI 1.10–11.66).

HCC was diagnosed in 55 patients with SVR during 2,866.83 PYs' follow-up (1.91 per 100 PYs, 95% CI 1.47–2.49), while eleven patients who did not achieve SVR developed HCC over 196.5 PYs (5.59 per 100 PYs, 95% CI 3.1–10.1; Table 3, Figure 1C). Patients who failed to

Table 2 Follow-up Data and Outcome Events

		Prospective Cohort	Historical Cohort
Total persons		1,630	1,254
Total person-years follow-up		3,065.5	1,830.5
Number of outcome events (HCC occurrence)	Total ≤24 weeks follow-up >24 weeks follow-up	66 27 39	102 36 66
Follow-up duration (months)	Range Median	1–43 23	6–18 17.1
Crude outcome rate per 100-person years (95% CI)		2.15 (1.69–2.74)	5.57 (4.54–6.76)
Difference in outcome rate per 100-person years (95% CI)		3.42% (2.25%–4.59%)	

Abbreviations: DAA, directly acting antiviral; HCC, hepatocellular carcinoma.

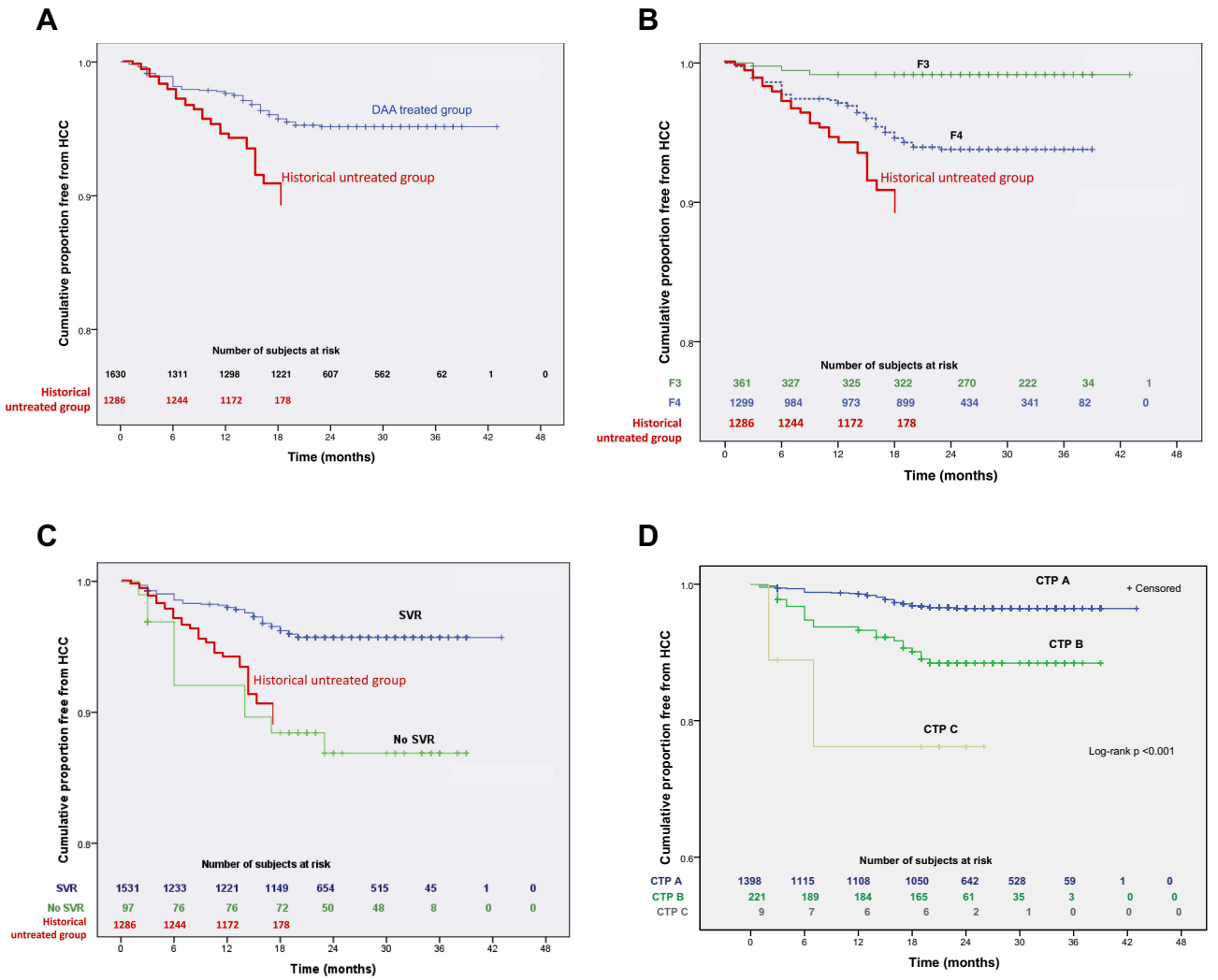

Figure 1 Continued.

respond to treatment had a 3.4% increased risk (AHR 3.37, 95% CI 1.75–6.52; P<0.001; Tables 4 and 5).

Compared to the historical cohort of untreated patients with HCV-related cirrhosis (Table 2), incidence in patients with cirrhosis treated with DAAs who achieved SVR was significantly lower (2.84 per 100 PYs, 95% CI 1.19–4.39 vs 5.57 per 100 PYs, 95% CI 4.54–6.76; difference 3.42 per 100 PYs, 95% CI 2.25–4.59), but not different in patients who did not achieve SVR (5.59 per 100 PYs, 95% CI 3.10–10.10 vs 5.57 per 100 PYs, 95% CI 4.54–6.76; difference −0.02 per 100 PYs, 95% CI −1.37 to 1.33).

Factors Associated with Risk of HCC in the Whole Cohort

The cumulative probability of developing HCC increased significantly with decompensated liver disease (Tables 4 and 5, Figure 1D), presence of ascites, low platelet count (<100×10^3/mL), high AFP (Figure 1E), and presence of DM (Figure 1F). Patients with high initial FIB-4 scores had significantly higher probability of HCC occurrence (Tables 4 and 5, Figure 1G). Patients with cirrhosis assessed by FIB-4 score ≥3.25 in whom FIB-4 score decreased posttreatment to <3.25 had significantly lower cumulative probability of developing HCC during follow-up than those for whom the FIB-4 scores did not improve posttreatment.

Discussion

HCV-induced liver fibrosis is a well-established risk factor of HCC development,[2] with cumulative HCC risk among patients with cirrhosis of 5%–30% within 5 years.[24] In Egypt, a systematic review of 13 studies that included

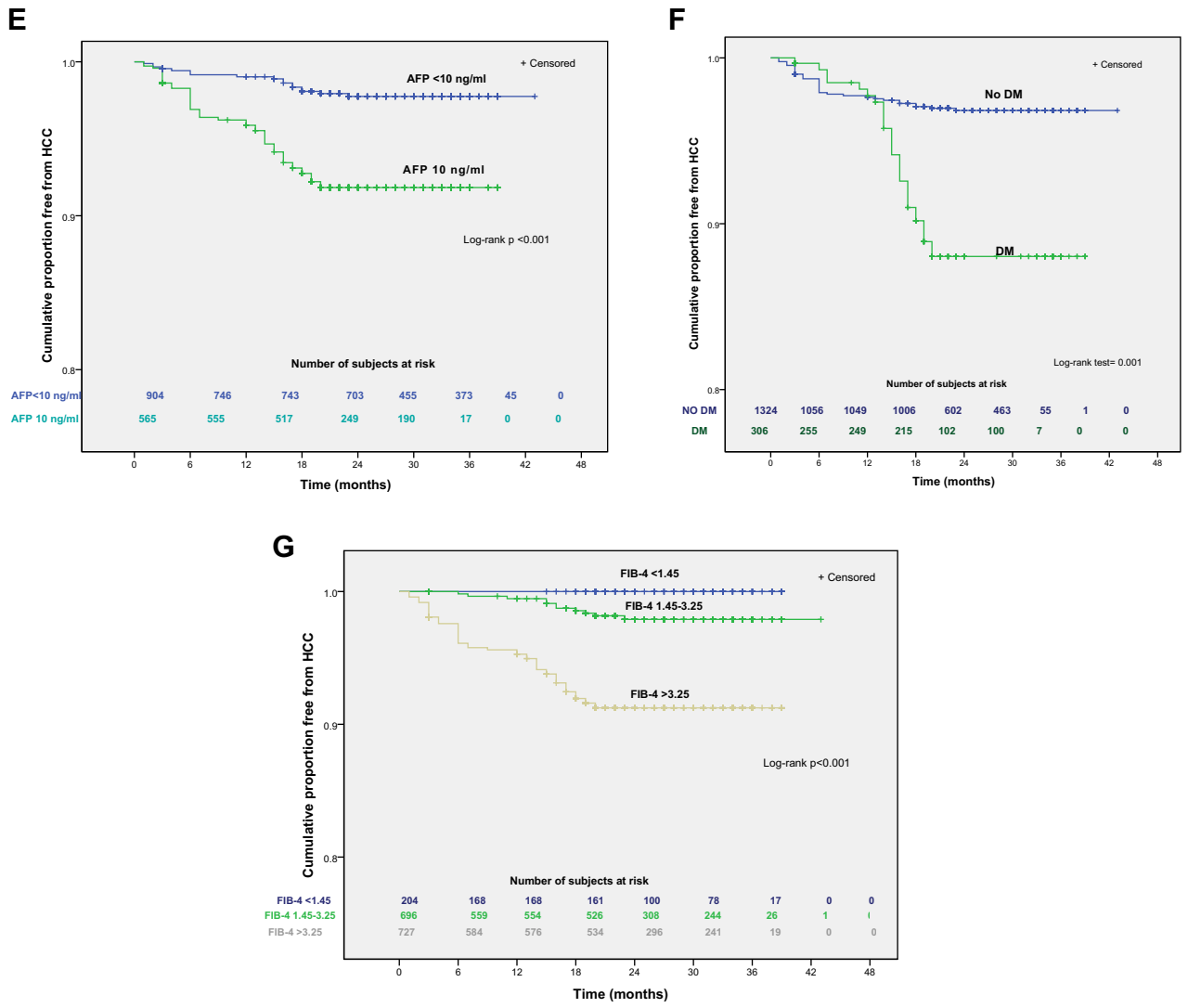

Figure 1 Curves of cumulative incidence of HCC among patients treated with DAAs and number of patients treated with DAA at risk at different times: overall (**A**); according to SVR (**B**); according to fibrosis stage (**C**); according to CTP (**D**); according to AFP level (**E**); according to DM (**F**); and according to initial FIB-4 score (**G**).

a total of 2,386 patients estimated the annual rates of decompensation and HCC development in patients with compensated HCV cirrhosis to be 6.37% and 3.36%, respectively.[25] A prospective study of 1,254 untreated Egyptian patients with HCV-related cirrhosis estimated annual incidence of HCC at 5.3%.[23]

With the availability of DAAs, the management of HCV was revolutionized, and treatment became effective, more tolerable, and safer, even in patients with decompensated cirrhosis.[17,26]

Several studies have recently addressed how DAA therapy alters the risk of HCC development.[7,14,15,27,28] Cardoso et al reported HCC occurrence of 7.4% in 54 patients after 12 months of follow-up after successful IFN-free antiviral therapy for HCV-associated cirrhosis,[16] and a report from Germany indicated that the short-term risk of HCC development is not reduced in patients with cirrhosis treated with DAAs vs those not treated.[29] On the other hand, a report from Spain that included data on about 4,000 patients treated with DAAs reported annual HCC incidence of 0.93% within 18 months of starting DAA therapy. They found higher HCC incidence among patients with cirrhosis, irrespective of response to DAAs.[30]

In this prospective study, 66 of 1,630 patients developed de novo HCC over a follow-up of 3,065.5 PYs, with overall crude incidence of 2.15 per 100 PYs (95% CI 1.69–2.74). Incidence in patients without cirrhosis (F3 fibrosis) was lower (0.35 per 100 PYs, 95% CI 0.11–

Table 3 Incidence of Hepatocellular Cancer in the Whole Cohort

Characteristics		Follow-Up (PYs)	Incidence Rate/100 PYs (95% CI)
Age, years	<50	773.2	1.81 (1.07–3.05)
	50-<60	1,340.9	2.08 (1.44–3.02)
	≥60	951.4	2.52 (1.69–3.67)
Sex	Male	2,231.9	2.32 (1.77–3.06)
	Female	833.6	1.68 (0.99–2.83)
Ascites	No	2,882.2	1.73 (1.31–2.28)
	Yes	183.3	8.73 (5.34–14.25)
Platelet count, $\times 10^3/mm^3$	≥150	1,555.0	0.83 (0.48–1.43)
	100 - <150	948.1	2.63 (1.78–3.90)
	<100	562.4	4.97 (3.43–7.21)
AFP, ng/mL	<10	1,809.9	0.93 (0.58–1.51)
	≥10	1,255.6	3.90 (2.94–5.16)
Diabetes mellitus	No	2,505.7	1.44 (1.44–1.99)
	Yes	559.8	5.35 (3.74–7.66)
Fibrosis stage	F3	873.3	0.33 (0.11–1.01)
	F4	2,192.2	2.90 (2.30–3.70)
CTP[a]	A	1,804.1	2.1 (1.5–2.9)
	B	375.9	6.1 (4.1–9.0)
	C	12.3	16.30 (4.6–44.1)
SVR[b]	Yes	2,866.8	1.91 (1.47–2.49)
	No	196.5	5.59 (3.10–10.10)
Initial FIB-4 score	<1.45	403.8	0.34 (0.03–1.76)
	1.45–3.25	1,308.3	1.22 (0.75–1.99)
	>3.25	1,353.4	3.62 (2.73–4.79)
FIB-4 score after EOT[c]	<1.45	856.3	0.35 (0.32–0.38)
	1.45–3.25	1,085.8	2.76 (1.86–3.94)
	>3.25	520.1	6.34 (4.37–8.91)
Change in FIB-4 (initial to posttreatment)	<3.25–<3.25	1,231.2	0.73 (0.33–1.39)
	<3.25–≥3.25	138.8	1.44 (0.17–5.20)
	≥3.25–<3.25	712.3	3.51 (2.27–5.18)
	≥3.25–≥3.25	454.8	7.89 (5.33–9.41)

Notes: [a]Patients with cirrhosis, not including those with advanced fibrosis; [b]data missing for two patients; [c]1,345 patients with available FIB-4 scores after EOT.
Abbreviations: CTP, Child–Turcotte–Pugh; DAA, directly acting antiviral; EOT, end of treatment; FIB-4, Fibrosis 4 (index); HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virological response; PYs, person-years.

1.07) than in patients with cirrhosis (2.88 per 100 PYs, 95% CI 2.25–3.69). El Tabbakh et al prospectively followed patients with HCV-related cirrhosis untreated in the same center through a screening program before the availability of DAAs. They found the crude incidence of HCC in untreated patients with HCV-related cirrhosis to be 5.57 per 100 PYs (95% CI 4.54–6.76). Our data showed a significant reduction in incidence in similar patients receiving DAA therapy (difference 2.69 per 100 PYs, 95% CI 1.43%–3.95%).

Several studies have found no evidence of increased rates of HCC in patients treated with DAAs compared to IFN-treated patients.[31,32] Innes et al documented the outcome of 857 patients with HCV who were treated with IFN-based or IFN-free regimens over 2.4 years' follow-up. HCC occurrence was doubled (2.53 vs 1.26 per 100 PYs) in patients who had been treated with DAAs. However, patients treated with DAAs were older and at higher Child–Pugh classes than patients treated with IFN-based regimens. With correction of the confounders, there was no difference between the two treatment regimens in terms of HCC occurrence (AHR 1.15, 95% CI 0.49–2.71).[31]

Our results indicate that the risk of developing HCC is higher during the first 18 months after antiviral therapy, suggesting that those patients might already have had microscopic HCC foci before the start of antiviral therapy. Mettke et al found that DAA therapy did not alter the short-term risk of HCC in DAA-treated vs untreated patients with HCV-related liver cirrhosis, although reduced HCC incidence may become evident after >15 months of DAA therapy.[29]

In the present study, several risk factors of HCC development after DAA treatment were identified. Patients with cirrhosis had significantly higher incidence of HCC than patients with advanced fibrosis, and risk increased with increased severity of cirrhosis assessed by CTP class. Also, we found that worsening of pretreatment FIB-4 scores after therapy was associated with increased risk, and improvement of pretreatment FIB-4 scores after the end of therapy was associated with a reduction in risk of HCC development. The risk factors identified are indicators of more advanced liver disease, which highlights the need for early treatment of HCV, preferably before cirrhosis is established.

Treatment failure was an important risk factor of HCC occurrence. The annual incidence of HCC in patients who achieved SVR was 1.91 per 100 PYs (95% CI 1.47–2.49), significantly lower than the 5.59 per 100 PYs (95% CI 3.1–10.1) incidence in patients without SVR. Incidence in patients who did not respond to therapy was similar to the historical incidence in patients with untreated cirrhosis.

Our data agree with the results of several large studies.[33–35] A study of 129 Veterans Administration hospitals in the United

Table 4 Factors Associated with Occurrence of HCC: Cumulative Probabilities of HCC Occurrence and Univariate Analysis

Variable Category		n	HCC Occurrence, n	Cumulative Probability of HCC Occurrence (%)	*P*	Univariate Hazard Ratio (95% CI)	*P*
Age, years	<50	410	14	4.5	0.43	1 (reference)	0.75
	50–<60	706	28	4.7		1.11 (0.59–2.11)	
	≥60	514	24	5.3		1.30 (0.67–2.50)	0.44
Sex	Male	1,185	52	5.2	0.25	1 (reference)	0.25
	Female	445	14	3.8		0.71 (0.39–1.27)	
CTP score[a]	A	973	38	4.7	<0.001	1 (reference)	<0.001
	B	217	23	11.9		2.69 (1.60–4.52)	
	C	9	2	23.8		6.45 (1.56–26.75)	0.003
Ascites	No	1,518	50	4.0	<0.001	1 (reference)	<0.001
	Yes	112	16	14.6		4.05 (2.31–7.12)	
Platelet count, $\times 10^3/mm^3$	≥150	808	13	1.9	<0.001	1 (reference)	0.001
	100–<150	503	25	6.0		3.08 (1.57–6.02)	
	<100	319	28	10.1		5.37 (2.78–10.38)	<0.001
AFP, ng/mL	<10	905	17	2.2	<0.001	1 (reference)	<0.001
	≥10	725	49	8.2		3.82 (2.20–6.63)	
Diabetes	No	1324	36	3.2	0.001	1 (reference)	<0.001
	Yes	306	30	12.0		3.62 (2.23–5.88)	
SVR[b]	Yes	1531	55	4.3	<0.001	1 (reference)	<0.001
	No	97	11	13.1		3.18 (1.67–6.08)	
Fibrosis stage	F3	431	3	0.8	<0.001	1 (reference)	0.001
	F4	1199	63	6.2		7.28 (2.29–23.19)	
Initial FIB-4 score	<1.45	205	1	0.5	<0.001	1 (reference)	0.13
	1.45–3.25	697	16	2.9		4.85 (0.64–36.56)	
	>3.25	728	49	7.9		14.23 (1.97–103.04)	0.009
Change in FIB-4 score >3.25 with treatment (n=609)	<3.25 after treatment	386	25	7.9	0.015	1 (reference)	0.017
	>3.25 after treatment	223	30	14.3		1.91 (1.12–3.25)	

Notes: [a]Patients with cirrhosis, not including those with advanced fibrosis; [b]two patients died before SVR12.

Abbreviations: CTP, Child–Turcotte–Pugh; EOT, end of treatment; FIB-4, Fibrosis 4 (index); HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virological response.

States, where 40% had cirrhosis before treatment, confirmed a considerable reduction in risk of HCC in patients with DAA-induced SVR compared to patients with treatment failure or no treatment (0.90 vs 3.45 HCC per 100 PYs, AHR 0.28, 95% CI 0.22–0.36).[33] Similarly, a prospective study on 2,249 patients with HCV-associated cirrhosis compared the risk of developing HCC based on liver reserve and SVR status after DAA therapy over 1 year's follow up. In patients with CTP class A, HCC developed in 2.1% of patients with SVR and 6.6% of patients without SVR, while in patients with decompensated cirrhosis, the risk was 7.8% in patients with SVR and 12.4% in patients with treatment failure.[34] Ioannou et al[28] reviewed data of 62,354 HCV patients and identified 3,271 incident HCC cases diagnosed after DAA therapy. The highest incidence was found in patients with cirrhosis and treatment failure (3.25 per 100 PYs), followed by patients with cirrhosis and SVR (1.97 per 100 PYs), absence of cirrhosis with treatment failure (0.87 per 100 PYs), and patients who achieved SVR in absence of cirrhosis (0.24 per 100 PYs). El-Serag et al reported that the risk of HCC after HCV cure, though considerably reduced, remained relatively high — 0.33% per year — and that older age and/or presence of cirrhosis at the time of SVR

Table 5 Multivariate Analysis of Factors Associated with Occurrence of HCC

	AHR (95% CI)[a]	P
CTP >A	2.77 (1.76–4.36)	<0.001
AFP >10	3.46 (1.96–6.11)	<0.001
No SVR	2.76 (1.39–5.48)	0.004
Diabetes	3.20 (1.94–5.28)	<0.001
FIB-4 score	3.59 (1.10–11.66)	0.03

Note: [a]Adjusted for age and sex.
Abbreviations: CTP, Child–Turcotte–Pugh; EOT, end of treatment; FIB-4, Fibrosis 4 (index); HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virological response.

were associated with a high-enough risk to warrant continued surveillance.[36] Similarly to our findings, Wu et al reported that risk factors of HCC in patients who achieved SVR were older age, presence of liver cirrhosis, higher pre- and posttreatment AFP, and high posttreatment AST:platelet ratio index, and that patients with persistently high AFP (≥15 ng/mL) and AST: platelet ratio index (≥0.7) before and after treatment had the highest incidence of HCC development.[37]

The main limitation of the study is that the untreated comparator cohort was a historical one of patients with HCV-related cirrhosis in the same location followed up and reported 5 years earlier. Also, the possibility of the presence of preexisting small HCCs at the beginning of DAA therapy cannot be excluded. Although all patients were examined by ultrasound before starting therapy and a small group by multidetector triphasic CT scans, even if all had been examined by CT or MRI, the possibility of the preexistence of small HCCs cannot be excluded. Had such lesions been present and detected, this would decrease even further the incidence of de novo HCC developing after DAA therapy.

Conclusion

Our data show that over a relatively long follow-up, the incidence of HCC following SVR induced by DAA therapy in patients with HCV-G4 was lowered in patients with advanced fibrosis and cirrhosis.

Although we found that the risk of HCC following DAA therapy was reduced in patients with cirrhosis who responded to treatment, our results showed much lower incidence in patients with advanced fibrosis and indicate the necessity of treating all patients with HCV infection, and preferably early treatment before the development of cirrhosis.

Also, our results indicate the necessity of following up patients with cirrhosis and SVR with close surveillance for the development of HCC, and more so for patients who do not achieve SVR (in whom incidence of HCC is not reduced and remains similar to untreated patients).

Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTP, Child–Turcotte–Pugh; DAA, directly acting antiviral; Dcv, daclatasvir; HCC, hepatocellular carcinoma; HCV-G4, HCV genotype 4; Ldv, ledipasvir; R, ritonavir; Rbv, ribavirin; Smv, simeprevir; Sof, sofosbuvir; SVR, sustained virological response.

Ethics

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

This trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of the National Liver Institute (IRB00003413), and informed consent was obtained from all participants.

Disclosure

Not related to this work, IW has served as a speaker for Hoffman La Roche, Merck, Gilead, and AbbVie, served on advisory boards for Astra-Zeneca, Lilly, Merck, and Eva Pharma, been principal investigator in clinical trials for AbbVie, Marcyrl, MenaPharm, Novartis, and Pharco, and has received nonfinancial support from Eva Pharma, and MenaPharma, MSD outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. Li DK, Chung RT. Impact of hepatitis C virus eradication on hepatocellular carcinogenesis. *Cancer*. 2015;121(17):2874–2882. doi:10.1002/cncr.29528
2. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53(3):1020–1022. doi:10.1002/hep.24199
3. D'amico G, Pasta L, Morabito A, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. *Aliment Pharmacol Ther*. 2014;39(10):1180–1193. doi:10.1111/apt.12721
4. Hassan MM, Hwang L-Y, Hatten CJ, et al. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. *Hepatology*. 2002;36(5):1206–1213. doi:10.1053/jhep.2002.36780
5. Baumert TF, Jühling F, Ono A, Hoshida Y. Hepatitis C-related hepatocellular carcinoma in the era of new generation antivirals. *BMC Med*. 2017;15(1):52. doi:10.1186/s12916-017-0815-7
6. Chang K-C, Hung C-H, Lu S-N, et al. A novel predictive score for hepatocellular carcinoma development in patients with chronic hepatitis C after sustained response to pegylated interferon and ribavirin combination therapy. *J Antimicrob Chemother*. 2012;67(11):2766–2772. doi:10.1093/jac/dks269

7. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA*. 2012;308(24):2584–2593. doi:10.1001/jama.2012.144878
8. Chung RT, Baumert TF. Curing chronic hepatitis C—the arc of a medical triumph. *N Engl J Med*. 2014;370(17):1576–1578. doi:10.1056/NEJMp1400986
9. Elsharkawy A, Fouad R, El Akel W, et al. Sofosbuvir-based treatment regimens: real life results of 14 409 chronic HCV genotype 4 patients in Egypt. *Aliment Pharmacol Ther*. 2017;45(5):681–687. doi:10.1111/apt.13923
10. Doss W, Esmat G, El-Serafy M, et al. Real-life results of sofosbuvir based therapy for Egyptian patients with hepatitis C and advanced fibrosis-cirrhosis. *J Hepatol*. 2016;64(2):S772. doi:10.1016/S0168-8278(16)01505-1
11. Elsharkawy A, El-Raziky M, El-Akel W, et al. Planning and prioritizing direct-acting antivirals treatment for HCV patients in countries with limited resources: lessons from the Egyptian experience. *J Hepatol*. 2018;68(4):691–698. doi:10.1016/j.jhep.2017.11.034
12. Pawlotsky J-M, Negro F, Aghemo A, et al. EASL recommendations on treatment of hepatitis C 2018. *J Hepatol*. 2018;69(2):461–511.
13. Backus LI, Belperio PS, Shahoumian TA, Mole LA. Impact of sustained virologic response with direct-acting antiviral treatment on mortality in patients with advanced liver disease. *Hepatology*. 2019;69(2):487–497. doi:10.1002/hep.29408
14. Conti F, Buonfiglioli F, Scuteri A, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. *J Hepatol*. 2016;65(4):727–733. doi:10.1016/j.jhep.2016.06.015
15. Kozbial K, Moser S, Schwarzer R, et al. Unexpected high incidence of hepatocellular carcinoma in cirrhotic patients with sustained virologic response following interferon-free direct-acting antiviral treatment. *J Hepatol*. 2016;65(4):856–858. doi:10.1016/j.jhep.2016.06.009
16. Cardoso H, Vale AM, Rodrigues S, et al. High incidence of hepatocellular carcinoma following successful interferon-free antiviral therapy for hepatitis C associated cirrhosis. *J Hepatol*. 2016;65(5):1070–1071. doi:10.1016/j.jhep.2016.07.027
17. Cheung MC, Walker AJ, Hudson BE, et al. Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol*. 2016;65(4):741–747. doi:10.1016/j.jhep.2016.06.019
18. El Kassas M, Funk A, Salaheldin M, et al. Increased recurrence rates of hepatocellular carcinoma after DAA therapy in a hepatitis C-infected Egyptian cohort: a comparative analysis. *J Viral Hepat*. 2018;25(6):623–630. doi:10.1111/jvh.12854
19. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology*. 2006;43(6):1317–1325. doi:10.1002/hep.21178
20. Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. *Hepatology*. 2007;46(1):32–36. doi:10.1002/hep.21669
21. Castera L, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. *J Hepatol*. 2008;48(5):835–847. doi:10.1016/j.jhep.2008.02.008
22. Llovet J, Ducreux M, Lencioni R, Di Bisceglie A, Galle P, Dufour J. European Association for the Study of the Liver European Organisation for Research and Treatment of Cancer: EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2012;56(4):908–943.
23. Eltabbakh M, Zaghla H, Abdel-Razek W, et al. Utility and cost-effectiveness of screening for hepatocellular carcinoma in a resource-limited setting. *Med Oncol*. 2015;32(1):432. doi:10.1007/s12032-014-0432-7
24. El-Serag HB. Hepatocellular carcinoma. *N Engl J Med*. 2011;365(12):1118–1127. doi:10.1056/NEJMra1001683
25. Alazawi W, Cunningham M, Dearden J, Foster GR. Systematic review: outcome of compensated cirrhosis due to chronic hepatitis C infection. *Aliment Pharmacol Ther*. 2010;32(3):344–355. doi:10.1111/j.1365-2036.2010.04370.x
26. Nahon P, Bourcier V, Layese R, et al. Eradication of hepatitis C virus infection in patients with cirrhosis reduces risk of liver and non-liver complications. *Gastroenterology*. 2017;152(1):142–156. e142. doi:10.1053/j.gastro.2016.09.009
27. Reig M, Mariño Z, Perelló C, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. *J Hepatol*. 2016;65(4):719–726. doi:10.1016/j.jhep.2016.04.008
28. Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. *J Hepatol*. 2018;68(1):25–32. doi:10.1016/j.jhep.2017.08.030
29. Mettke F, Schlevogt B, Deterding K, et al. 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(4):516–525. doi:10.1111/apt.14427
30. Calleja JL, Crespo J, Rincon D, et al. 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(6):1138–1148. doi:10.1016/j.jhep.2017.01.028
31. Innes H, Barclay ST, Hayes PC, et al. The risk of hepatocellular carcinoma in cirrhotic patients with hepatitis C and sustained viral response: role of the treatment regimen. *J Hepatol*. 2018;68(4):646–654. doi:10.1016/j.jhep.2017.10.033
32. Rutledge SM, Zheng H, Li DK, Chung RT. No evidence for higher rates of hepatocellular carcinoma after direct-acting antiviral treatment: a meta-analysis. *Hepatoma Res*. 2019;5. doi:10.20517/2394-5079.2019.19
33. 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(4):996–1005. e1001. doi:10.1053/j.gastro.2017.06.012
34. Calvaruso V, Cabibbo G, Cacciola I, et al. Incidence of hepatocellular carcinoma in patients with HCV-associated cirrhosis treated with direct-acting antiviral agents. *Gastroenterology*. 2018;155(2):411–421. e414. doi:10.1053/j.gastro.2018.04.008
35. Ogawa E, Furusyo N, Nomura H, et al. Short-term risk of hepatocellular carcinoma after hepatitis C virus eradication following direct-acting anti-viral treatment. *Aliment Pharmacol Ther*. 2018;47(1):104–113. doi:10.1111/apt.14380
36. 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(1):130–137. doi:10.1002/hep.28535
37. Wu CK, Chang KC, Hung CH, et al. Dynamic alpha-fetoprotein, platelets and AST-to-platelet ratio index predict hepatocellular carcinoma in chronic hepatitis C patients with sustained virological response after antiviral therapy. *J Antimicrob Chemother*. 2016;71(7):1943–1947. doi:10.1093/jac/dkw097