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Risk of Hepatocellular Cancer in HCV Patients Treated With Direct-Acting Antiviral Agents

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e21. Learning Objective: Upon completion of this CME activity, successful learners will be able to (1) discuss the absolute risk and risk factors for hepatocellular cancer (HCC) in hepatitis C virus (HCV) -infected patients after successful treatment with direct-acting antiviral (DAAs), (2) recognize the impact of DAAs on HCC risk in virologically cured patients, and (3) identify when a successfully treated patient should undergo screening for HCC.

See Covering the Cover synopsis on page 875; see editorial on page 890.

BACKGROUND AND AIMS: The risk of hepatocellular cancer (HCC) after sustained virological response (SVR) with direct-acting antivirals (DAA) is unclear. Our aim was to examine the risk and determinants of HCC in patients cured with DAA. **METHODS:** We conducted a retrospective cohort study of hepatitis C virus patients who were treated with DAA in any of the 129 Veterans Health Administration hospitals between January 1, 2015 and December 31, 2015. We calculated the annual incidence rates of HCC by SVR. We used Cox regression models to compare the risk of HCC in patients with vs those without SVR and to identify factors associated with incident HCC among patients with SVR. We reviewed a sample of HCC patients for tumor size and stage at diagnosis. **RESULTS:** Among 22,500 patients treated with DAA (19,518 with SVR; 2982 without SVR), the mean (standard deviation) age was 61.6 (6.1) years, and 39.0% had cirrhosis. There were 271 new cases of HCC, including 183 in patients with SVR. Compared with patients without SVR, those with SVR had a significantly reduced risk of HCC (0.90 vs 3.45 HCC/100 person-years; adjusted hazard ratio, 0.28, 95% CI=0.22–0.36). Patients with cirrhosis had the highest annual incidence of HCC after SVR (1.82 vs 0.34/100 person-years in patients without cirrhosis; adjusted hazard ratio, 4.73. 95% CI, 3.34-6.68). Most (>44.8%) HCC were classified as stage I. Maximum size of the largest lesion was ≤5 cm in over 75% of cases. **CONCLUSIONS:** Among patients treated with DAA, SVR was associated with a considerable reduction in the risk of HCC. We did not find any evidence to suggest that DAAs promote HCC. However, in patients with SVR, the absolute risk of HCC remained high in patients with established cirrhosis. These patients should be considered for ongoing HCC surveillance.

Keywords: Liver Cancer; Outcome; Viral Hepatitis; Therapy.

Background

In the US, hepatocellular cancer (HCC) is the fastest growing cause of cancer-related deaths.[1] Chronic infection with hepatitis C virus (HCV) is the leading risk factor for HCC[2]; the annual risk of HCC is as high as 3% in patients with cirrhosis and untreated or uncured HCV.[2] However, with the advent of highly effective and well-tolerated direct-acting antiviral agents (DAA),[3,4] HCV treatment rates and number of patients cured of HCV have increased dramatically. Within the next decade, most HCV patients seen in clinical practice in the US will likely be in sustained virological response (SVR).[5]

Subsequent risk of HCC may persist in some patients even after achieving SVR. We recently reported that the risk of HCC in patients successfully treated to SVR with the previous interferon-based treatment remained high in several groups, including patients cured after age 65 and those with advanced liver fibrosis or cirrhosis.[6]

However, data on HCC risk following DAA-induced SVR are still sparse and conflicting. Recent studies reported that HCV-infected patients with HCC who had an initial complete response to hepatic resection or local ablation and subsequently had DAA-related SVR experienced an increased risk of HCC recurrence.[7,8] In a single center study in Italy, 9 out of 285 (3.2%) patients without previous HCC developed de novo HCC within 15 months of DAA-induced SVR.[8] Similarly, in a recent series of 66

Abbreviations used in this paper: **AUDIT-C, Alcohol Use Disorders Identification Test; CCR, Central Cancer Registry; CDW, Corporate Data Warehouse; CI, confidence interval; DAA, direct acting antivirals; HCC, hepatocellular cancer; HCV, hepatitis C virus; HR, hazard ratio; PY, person-years; SVR, sustained virological response; VHA, Veterans Health Administration.**

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EDITOR'S NOTES

BACKGROUND AND CONTEXT

Direct acting antivirals (DAAs) are an effective treatment for hepatitis C virus (HCV), but the risk of developing hepatocellular carcinoma (HCC) after sustained virologic response (SVR) with DAAs is unclear.

NEW FINDINGS

Among HCV-infected patients treated with DAAs, SVR is associated with a considerable reduction in the risk of HCC; however, the risk for HCC remained high in patients with cirrhosis at the time of SVR.

LIMITATIONS

This study included only veterans, potentially limiting generalizability of results.

IMPACT

Even though successful treatment of HCV reduced the risk for HCC, patients with underlying cirrhosis should still be screened for HCC after SVR.

patients treated in a single tertiary care center in the US, 6 patients (9.1%) developed HCC either during or within 6 months of DAA treatment, suggesting an unusually high rate of HCC after DAA.[9]

In contrast, in a French prospective cohort study, SVR was associated with decreased HCC incidence in patients with cirrhosis compared with patients without SVR.[10] Incident HCC occurred in 0.93% of patients treated with DAAs in a multicenter study in Spain.[11] However, these studies were limited by relatively small numbers of patients treated with new DAAs and HCC cases that developed in these patients. There have been no studies that followed a sufficient number of DAA-treated patients to examine the risk and risk factors of HCC in this new generation of virologically cured patients.

We conducted a large cohort study to examine the risk of HCC following SVR among 22,500 HCV patients who received DAAs in the national Veterans Health Administration (VHA) system.

Methods

Data Sources

We used national data in the VHA Corporate Data Warehouse (CDW) and Central Cancer Registry (CCR). The CDW includes all laboratory test results, pharmacy, as well as diagnosis (ICD-9 and 10) codes for all outpatient and inpatient encounters nationwide. The CDW also contains information from annual Alcohol Use Disorders Identification Test (AUDIT-C) screen and Vital Status files.[12] The CCR is a centralized repository for over 750,000 VHA patients with cancer and includes information on date of diagnosis, primary site, and histology. HCC is identified with primary site code C220 with histology codes 817XX through 818XX.

Study Cohort

We included patients 18 years or older who received DAA treatment in any of the 129 VHA hospitals. We defined DAA treatment as $\geq$1 filled prescription of sofosbuvir, simeprevir, ledipasvir, combination of paritaprevir/ritonavir, ombitasvir and dasabuvir, and daclatasvir between January 1, 2015 and December 31, 2015. This timeframe allowed $\geq$6 months for treatment completion and SVR testing by September 30, 2016 (end of study follow-up) for all patients. We used the date of first filled prescription as treatment initiation and the last date covered by the final prescription as treatment completion date. For patients with multiple DAA courses, we used the first course and censored their follow-up at the time of subsequent course.

Because our objective was to examine the risk of incident HCC, we excluded patients with evidence of HCC before or during DAA initiation from the primary analysis. However, in a secondary analysis, we examined all patients who initiated DAA treatment (including those who developed HCC during treatment) given studies suggesting that DAA may promote HCC in the short term.

Outcome

The study outcome was new cases of HCC after completing DAA. HCC was defined based on 2 or more instances of ICD-9 (155.0) or ICD-10 codes (C22.0, C22.8, C22.9, D01.5) in CDW or any instance of HCC recorded in the CCR. We reviewed electronic medical records of a random sample of 50 cases that had ICD codes but not included in CCR; all had evidence of HCC in the medical records.

Predictor Variables

We classified patients as having achieved SVR if all HCV RNA tests were negative after end of DAA treatment, with 1 test recorded at least 12 weeks after treatment completion. Other predictors were age, gender, race/ethnicity, cirrhosis, HCV genotype, previous HCV treatment status, HIV, diabetes, alcohol use, drug abuse, other medical comorbidity, and health care utilization. We defined cirrhosis based on ICD-9 or 10 codes for cirrhosis or its complications recorded any time prior to DAA treatment.[13] For each patient, we also calculated a biomarker of liver fibrosis, FIB-4,[14] using the values of aspartate aminotransferase, alanine aminotransferase, and platelet tests performed within the year before and nearest to treatment initiation. We categorized FIB-4 as $<$1.45, 1.45 to 3.25, and $>$3.25.[14] We defined HIV, diabetes, drug abuse, depression, and Deyo index by presence of ICD-9/10 codes before DAA initiation. We defined alcohol use based on at least 1 ICD-9/10 code or an AUDIT-C $\geq$4 ($\geq$3 for women). We defined prior HCV treatment based on filled prescriptions for interferon, boceprevir, or telaprevir. We used the number of outpatient visits in the year prior to index as a surrogate for health care utilization.

Statistical Analysis

For the primary analysis, we calculated the annual incidence rates for HCC in the cohort of patients who completed DAA with or without SVR. We used the date of DAA completion as the index and followed patients to the development of HCC, death, or September 30, 2016, whichever was earlier. We calculated the incidence rate with 95% confidence interval (CI) as the number of HCC events divided by total person-years (PY) of follow-up. We generated Kaplan–Meier curves to illustrate and compare the cumulative incidence rates of HCC by SVR and used the log-rank test to evaluate the differences between these

curves. We also compared the time to HCC in patients with vs those without SVR using a non-parametric Kruskal–Wallis test.

We used a multivariable Cox proportional hazard model to compare the risk of HCC in patients with SVR vs those without SVR (model 1). Independent variables were SVR, age, gender, race/ethnicity, cirrhosis, HCV genotype, previous HCV treatment status, HIV, diabetes, alcohol use, drug abuse, other medical comorbidity, and health care utilization. We included cirrhosis diagnosis in the primary analysis but repeated the analyses using FIB-4 based definition of liver fibrosis. We estimated hazard ratio (HR) and 95% CI.

To examine the factors associated with HCC in patients who have achieved SVR, we calculated the annual incidence rates for HCC in different subgroups of SVR patients. We then used Cox proportional hazard model to isolate the factors independently associated with increased risk of HCC after SVR (model 2). Independent variables were as described above.

Secondary analyses. Because FIB-4 might provide more granular risk stratification for HCC, we repeated the models using the 3-level FIB-4 variable instead of the indicator variable for cirrhosis diagnosis. We classified any HCC that developed after index as incident HCC in the primary analysis, which this might have inflated our risk estimates. Therefore, we excluded patients who developed HCC in the first 3 months after index as part of a sensitivity analysis. We also developed separate models for patients with and without cirrhosis diagnosis to determine if the effect of SVR on HCC (model 1) or factors associated with HCC (model 2) were different in the 2 subgroups. Last, given data that DAAs might promote HCC in some patients,[7–9] we compared the demographic and clinical characteristics of patients with HCC that developed during DAA treatment (early cases) with those who developed HCC following end of treatment using χ^2 and Fisher exact tests. We also reviewed a convenience sample of 108 HCC patients (29 HCC that developed during and 79 that developed after treatment) included in the VHA CCR for tumor size and stage at diagnosis defined based on the American Joint Committee on Cancer tumor/node/metastasis system.

Results

Patient Characteristics

We identified 25,232 patients who received DAA treatment. We excluded 1948 (7.7%) in whom SVR status could not be determined and 705 who had evidence of HCC before initiation of DAA. We further excluded 79 patients from the primary analysis because they developed HCC during the course of DAA treatment but examined them in the secondary analysis.

A total of 22,500 patients were included in the primary analysis. Of these, 19,518 patients had SVR and 2982 did not achieve SVR (Table 1). Mean age at the time of DAA initiation was 61.6 years (standard deviation, 6.1 year), 96.7% were men, 49.3% were white, and 36.5% were African American. A total of 39.0% of patients had a diagnosis of cirrhosis; 29.7% had a FIB-4 value >3.25 indicating advanced fibrosis, and 22.5% were previously treated for HCV. The cohort had a high burden of comorbidity; 43.6% had diabetes, 61.4% had alcohol use, and 54.2% had history of drug use. Patients were treated with sofosbuvir (75.2%; 51.1% in combination with ledipasvir), simeprevir (0.7%), combination of paritaprevir/ritonavir (23.3%), and daclatasvir-based (0.8%) treatments.

Compared with patients with SVR, those who did not achieve SVR were more likely to be Hispanic, have cirrhosis diagnosis, HCV genotype 3, and history of alcohol or drug use (Table 1).

Table 1. Demographic and Clinical Characteristics of HCV Treated With DAA Agents Overall and by SVR

Characteristics	Overall (N=22,500) N (%)	SVR (N=19,518) N (%)	No SVR (N=2982) N (%)	*P* value
Age, *y*, mean (*SD*)	61.6 (6.1)	61.6 (6.1)	61.2 (5.8)	.003
Gender				.004
Female	739 (3.3)	667 (3.4)	72 (2.4)	
Male	21,761 (96.7)	18851 (96.6)	2910 (97.6)	
Race				<.0001
White	11,099 (49.3)	9674 (49.5)	1425 (47.8)	
African American	8214 (36.5)	7114 (36.5)	1100 (36.9)	
Hispanic	850 (3.8)	691 (3.5)	159 (5.3)	
Other racial groups	433 (1.9)	368 (1.9)	65 (2.2)	
Missing	1904 (8.5)	1671 (8.6)	233 (7.8)	
Cirrhosis diagnosis				<.0001
Yes	8766 (39.0)	7495 (38.4)	1271 (42.6)	
No	13,734 (61.0)	12,023 (61.6)	1711 (57.4)	
FIB-4				<.0001
<1.45	4562 (20.3)	4015 (20.6)	547 (18.3)	
1.45–3.25	10,199 (45.3)	9001 (46.1)	1198 (40.2)	
>3.25	6690 (29.7)	5614 (28.8)	1076 (36.1)	
Missing	1049 (4.7)	888 (4.6)	161 (5.4)	
HCV genotype				<.0001
1	19,531 (86.8)	17164 (87.9)	2367 (79.4)	
2	1422 (6.3)	1140 (5.8)	282 (9.4)	
3	940 (4.2)	678 (3.5)	262 (8.8)	
4–6	217 (1.0)	188 (1.0)	29 (1.0)	
Missing	390 (1.7)	348 (1.8)	42 (1.4)	
Previous HCV antiviral treatment				.04
Yes	5066 (22.5)	4438 (22.7)	628 (21.1)	
No	17,434 (77.5)	15,080 (77.3)	2354 (78.9)	
HIV co-infection				.37
Yes	1311 (5.8)	1148 (5.9)	163 (5.5)	
No	21,189 (94.2)	18370 (94.1)	2819 (94.5)	
Diabetes				.26
Yes	9807 (43.6)	8479 (43.4)	1328 (44.5)	
No	12,693 (56.4)	11,039 (56.6)	1654 (55.5)	
Alcohol abuse				<.0001
Yes	13,814 (61.4)	11826 (60.6)	1988 (66.7)	
No	8686 (38.6)	7692 (39.4)	994 (33.3)	
Drug use				<.0001
Yes	12,182 (54.1)	10,426 (53.4)	1756 (58.9)	
No	10,318 (45.9)	9092 (46.6)	1226 (41.1)	
Deyo score				.12
0	9519 (42.3)	8299 (42.5)	1220 (40.9)	
1–2	8400 (37.3)	7282 (37.3)	1118 (37.5)	
≥3	4581 (20.4)	3937 (20.2)	644 (21.6)	

DAA, direct acting antiviral; HCV, hepatitis C virus; PY, person-years; SD, standard deviation; SVR, sustained virological response.

Table 2. Association Between SVR and Incident HCC in Patients Treated With DAA Agents

SVR	PY of follow-up	HCC N	Incidence rate (per 100 PY, 95% CI)	Adjusted hazard ratio[a] (95% CI)	*P* value
No	2547.34	88	3.45 (2.73–4.18)	1	
Yes	20,415.3	183	0.90 (0.77–1.03)	0.28[b] (0.22–0.36)	<.0001

CI, confidence interval; DAA, direct acting antiviral; HCC, hepatocellular cancer; HCV, hepatitis C virus; PY, person-years; SVR, sustained virological response.
[a]Multivariable model adjusted for age, gender, race, cirrhosis diagnosis, HCV genotype, diabetes, HIV, alcohol use, drug use, Deyo index, and number of outpatient visits in the year prior to DAA treatment (full model is presented in Supplementary Appendix Table 1).
[b]The magnitude and direction of SVR did not change in the multivariable model that used FIB-4 in lieu of cirrhosis diagnosis.

Risk of HCC following DAA treatment. There were 271 cases of HCC after treatment completion diagnosed during 22963 PY of follow-up; with an annual HCC incidence rate of 1.18 per 100 PY (or 1.18%, 95% CI, 1.04–1.32%). HCC developed in 183 patients with SVR during 20,415 PY follow-up at an annual incidence of 0.90 per 100 PY (or 0.90%, 95% CI, 0.77–1.03%). This rate was considerably lower than the 3.45 per 100 PY incidence rate in patients without SVR (88 HCC cases during 2547 PY follow-up or 3.45%, 95% CI, 2.73–4.18) (Table 2). Median (interquartile) time to HCC diagnosis was 5.2 (8.6 to 15.6) months in patients with vs 6.1 (9.1 to 15.8) months in patients without SVR (P=.06). Excluding HCCs that developed in the first 3 months after index resulted in an annual incidence of 0.63 and 2.91 per 100 PY for patients with and without SVR, respectively.

SVR was strongly associated with time until development of HCC ($P < .0001$) (Figure 1). HCC rates were higher in the non-SVR group early on and became more evident with longer follow-up. In Cox analyses, SVR was associated with a 76% decrease in the risk of HCC (unadjusted HR=0.24, 95% CI=0.19–0.31). This inverse association did not change when we adjusted for demographic, clinical, and health utilization differences (adjusted HR=0.28, 95% CI=0.22–0.36) (Table 2). The full model is displayed in Supplementary Appendix Table 1.

The SVR effect did not change in the models that used FIB-4 in lieu of cirrhosis diagnosis (adjusted HR=0.29, 95% CI=0.23–0.38) or those that excluded HCC cases within 3 months after index (adjusted HR=0.22, 95% CI=0.17–0.30). The magnitude of SVR protective effect was also similar in patients with (adjusted HR=0.32, 95% CI=0.23–0.44) and without cirrhosis diagnosis (adjusted HR=0.18, 95% CI=0.11–0.30). See Supplementary Appendix Table 1.

Factors associated with risk of HCC in patients with DAA induced SVR. Patients with a diagnosis of cirrhosis had the highest annual incidence of HCC (1.82%, 95% CI, 1.52–2.12% vs 0.34%, 95% CI, 0.24–0.45% in patients without cirrhosis) (Table 3). The risk of HCC was 4.7-fold higher in patients with a diagnosis of cirrhosis than those without cirrhosis (adjusted HR=4.73, 95% CI, 3.34–6.68). HCC annual incidence was also higher among patients with alcohol use (1.01%, 95% CI, 0.83–1.19) compared with those without alcohol use (0.72%, 95% CI, 0.54–0.91%; adjusted HR=1.56, 95% CI, 1.11–2.18). African American patients had lower risk of HCC than patients from other racial groups (annual incidence=0.58%, 95% CI=0.41–0.75%, adjusted HR compared with whites=0.56, 95% CI=0.39–0.81) (Table 3).

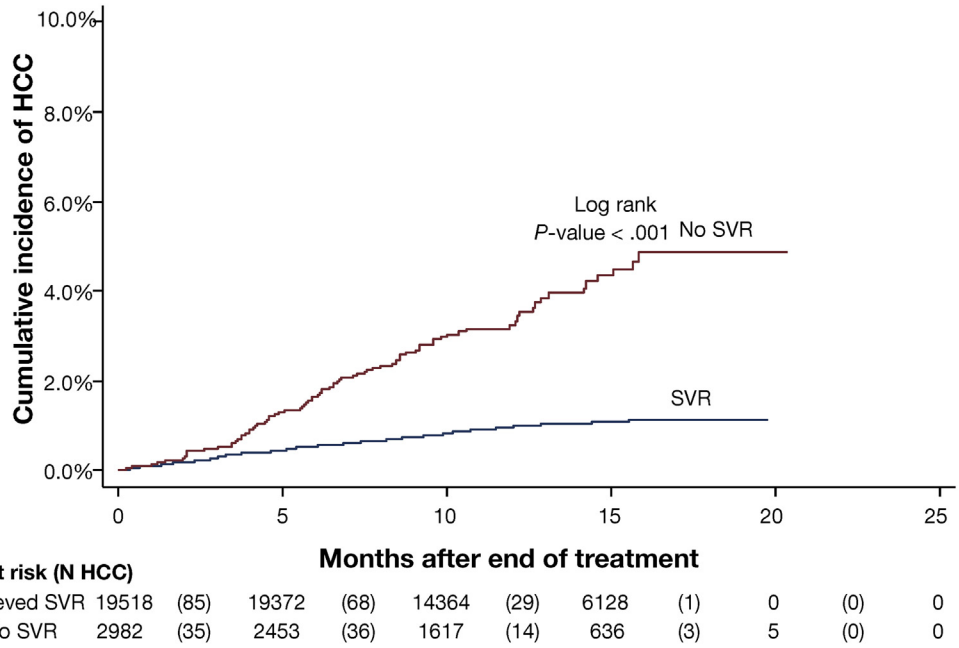

Figure 1. Cumulative incidence of hepatocellular cancer (HCC) among 22,500 patients treated with DAA agents. SVR, sustained virological response.

Table 3. Incidence of HCC) in 19,518 Patients Who Achieved SVR With DAA Agents

Characteristic	PY of follow-up	HCC N	Incidence rate (per 100 PY, 95% CI)	Adjusted HR (95% CI)[a]	*P* value[a]
Age (*y*)					.08
<65	14,061.6	112	0.80 (0.65–0.94)	1	
≥65	6353.7	71	1.12 (0.86–1.38)	1.30 (0.96–1.76)	
Gender					.17
Male	19,708.8	181	0.92 (0.78–1.05)	1	
Female	706.5	2	0.28 (0–0.68)	0.38 (0.10–1.54)	
Race					.02
White	10,184.3	108	1.05 (0.86–1.26)	1	
African Americans	7397.9	43	0.58 (0.41–0.75)	0.56 (0.39–0.81)	
Hispanic	707.8	11	1.55 (0.64–2.47)	1.22 (0.65–2.27)	
Others	392.0	4	1.02 (0.02–2.02)	0.95 (0.35–2.58)	
Missing	1733.4	17	0.98 (0.51–1.45)	0.95 (0.57–1.58)	
Cirrhosis					<.0001
No	12,769.6	44	0.34 (0.24–0.45)	1	
Yes	7645.7	139	1.82 (1.52–2.12)	4.73 (3.34–6.68)	
HCV genotype					.45
1	18,013.2	163	0.90 (0.77–1.04)	1	
2	1176.8	8	0.68 (0.21-1.15)	0.70 (0.34–1.42)	
3	645.4	5	0.77 (0.10–1.45)	0.72 (0.29–1.75)	
4-6	199.4	1	0.50 (0–1.48)	0.56 (0.08–3.99)	
Previous HCV antiviral treatment					.44
No	15,696.8	128	0.82 (0.67–0.96)	1	
Yes	4718.5	55	1.17 (0.86–1.47)	1.13 (0.82–1.56)	
HIV coinfection					.89
No	19,241.8	176	0.91 (0.78–1.05)	1	
Yes	1173.5	7	0.60 (0.15–1.04)	0.95 (0.42–2.13)	
Diabetes					.13
No	11,661.0	87	0.75 (0.59–0.90)	1	
Yes	8754.3	96	1.10 (0.88–1.32)	1.28 (0.92–1.78)	
Alcohol abuse					.01
No	8156.7	59	0.72 (0.54–0.91)	1	
Yes	12,258.6	124	1.01 (0.83–1.19)	1.56 (1.11–2.18)	
Drug use					.15
No	9638.0	92	0.95 (0.76–1.15)	1	
Yes	10,777.3	91	0.84 (0.67–1.02)	0.79 (0.57–1.10)	

CI, confidence interval; DAA, direct acting antiviral; HCC, hepatocellular cancer; HCV, hepatitis C virus; HR, hazard ratio; PY, person-years; SVR, sustained virological response.
[a]HR (with 95% CI and *P* values) derived from multivariable model. In addition to the variables displayed, the model was also adjusted for Deyo index and number of outpatient visits in the year prior to DAA treatment.

Using FIB-4 in lieu of cirrhosis diagnosis did not change the magnitude or direction of other variables. Patients with FIB-4 >3.25 (indicating advanced fibrosis or cirrhosis) had an annual HCC incidence of 2.16% (95% CI, 1.78–2.54%) compared with 0.45% (95% CI, 0.32–0.59%) in patients with FIB-4 between 1.45 and 3.25, and 0.30% (95% CI, 0.14–0.46%) in patients with FIB-4 of 1.45 or lower. The adjusted risk for HCC was 6.0-fold higher in patients with FIB-4 >3.25 than those with values of 1.45 or lower (adjusted HR=6.23, 95% CI=3.50–11.08). There was no statistically significant difference in the risk of HCC among patients with low vs intermediate FIB-4 (Supplementary Appendix Table 2).

To determine if the risk factors (and risk groups) were different in patients with and without cirrhosis, based on a-priori consideration, we conducted stratified analyses based on cirrhosis diagnosis. We included FIB-4 in the analyses limited to patients without cirrhosis given data that cirrhosis may be under-diagnosed in some patients.[15] The annual HCC incidence rates were higher than 1.0% in all patients with cirrhosis (Figure 2). There were no statistically significant associations between demographic and clinical factors and risk of HCC in patients with baseline cirrhosis diagnosis, with the exception of race effect. The risk of HCC was significantly lower in African American patients compared with whites; the risk was higher in Hispanics, although this association did not reach statistical significance (Table 4). In contrast, in patients without cirrhosis diagnosis, patients with high FIB-4, diabetes, and alcohol use were associated with approximately 5-, 2-, and 3-fold higher risk of developing HCC, respectively, than their counterparts (Table 4). However, the annual incidence of HCC was low in all subgroups without cirrhosis, except in patients with baseline FIB-4 >3.25. The annual incidence of HCC approached 1.0% in this subgroup of patients (0.99/100 PY, 95% CI, 0.54–1.43 per 100 PY).

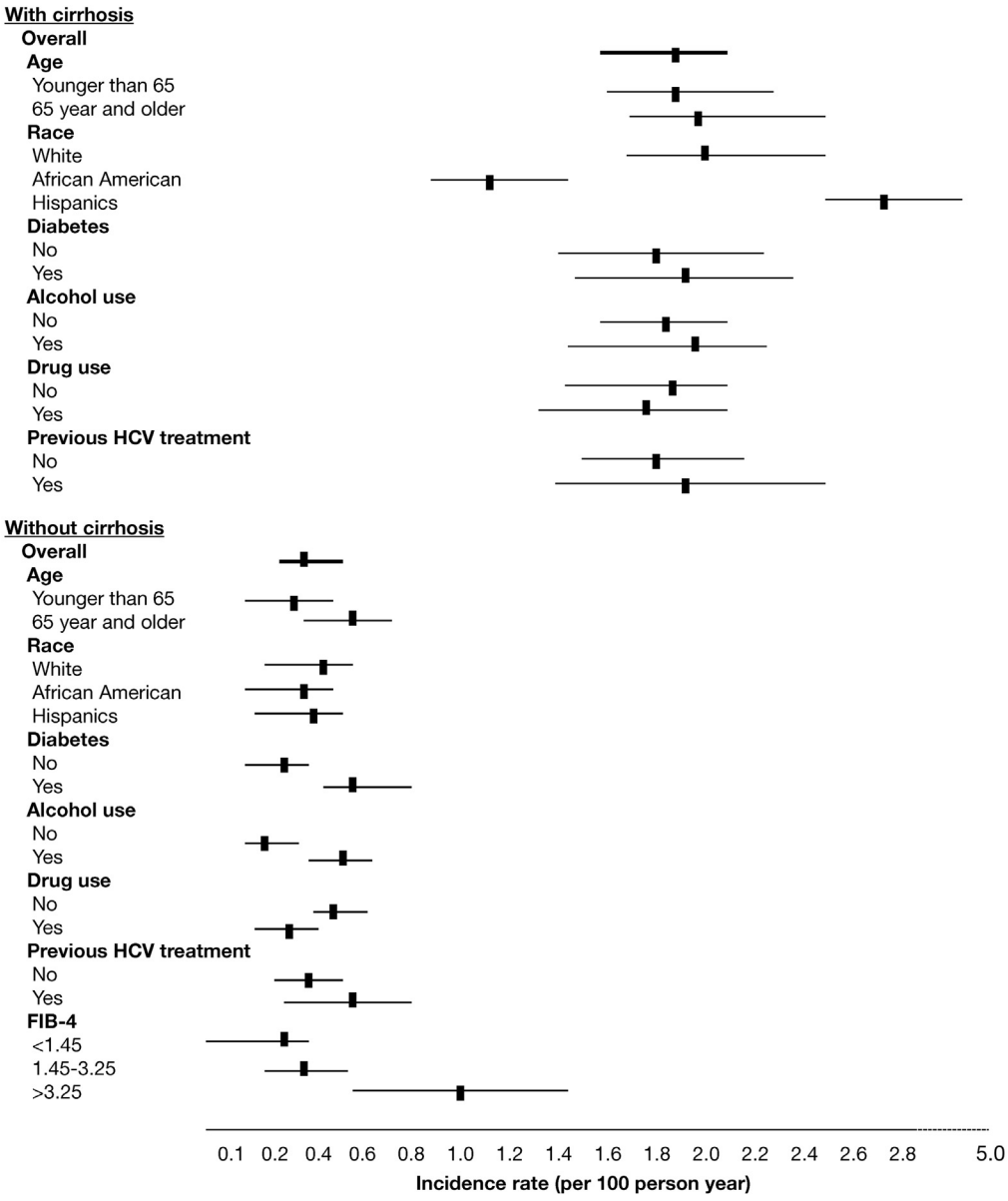

Figure 2. Annual incidence of hepatocellular cancer (HCC) among patients with SVR stratified by the presence or absence of cirrhosis at baseline. The *horizontal lines* represent the 95% CIs surrounding the annual incidence estimate. The *dashed vertical line* represents the 1.0 per 100 PY cut-off beyond which HCC surveillance may be cost-effective.

Risk of HCC during DAA treatment. Of the 22,579 patients who received DAAs, 79 (0.34%) developed HCC during treatment (vs 271 after end of DAA treatment). There were no statistically significant differences in demographic and clinical characteristics between patients with HCC in these 2 periods (Table 5). Most (>44.8%) HCC diagnosed during DAA treatment were classified as stage I; only 3 cases were stage III or IV at the time of diagnosis, and the maximum size of the largest tumor lesion was ≤5 cm in over 75% of cases. There were no statistically significant differences in the tumor stage or size between patients who developed HCC during or after DAA treatment.

Discussion

Our study has 3 key findings. First, we found that in patients treated with DAAs, SVR was associated with a 76% reduction in risk of HCC compared with those who did not achieve SVR. The HCC preventive effect of SVR was evident early on and increased over time (Figure 1). The relative benefit of SVR persisted after we accounted for demographic and clinical differences between patients, and was similar in those with and without cirrhosis. These data show that successful eradication of HCV confers a benefit in patients treated with DAA. Although few recent studies have raised concerns that DAA might accelerate the risk of HCC in some patients early in the course of treatment,[7–9] we did not find any factors that differentiated patients with HCC that developed during DAA treatment compared with HCC that developed later in follow-up. We also did not find any evidence that tumor biology, as indicated by stage and size, differed substantially between patients with early vs delayed HCC. Collectively, our findings do not support the notion that DAAs may promote hepatocarcinogenesis.

Table 4. Factors Associated With Incident HCC In Virologically Cured Patients With and Without Cirrhosis

Characteristics	With cirrhosis[b]		Without cirrhosis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, *y* (reference <65 year)		.21		.42
≥65 year	1.25 (0.88–1.77)		1.29 (0.69–2.40)	
Gender (reference male)		.18		.85
Female	0.26 (0.04–1.86)		0.83 (0.11–6.13)	
Race (reference white)		.02		.18
African American	0.52 (0.34–0.81)		0.59 (0.30–1.15)	
Hispanic	1.31 (0.68–2.55)		0.66 (0.09–4.89)	
Other	0.59 (0.14–2.44)		2.23 (0.53–9.46)	
Missing	1.20 (0.70–2.06)		0.23 (0.03–1.66)	
HCV genotype (reference 1)		.20		.52
2	0.98 (0.48–2.03)		–[a]	
3	0.76 (0.28–2.07)		0.52 (0.07–3.84)	
4–6	–*		2.55 (0.35–18.61)	
Missing	2.38 (1.04–5.43)		–[a]	
Previous antiviral treatment (reference no)		.70		.31
Yes	1.07 (0.75–1.54)		1.42 (0.72–2.82)	
HIV (reference no)		.43		
Yes	1.38 (0.60–3.18)		–[a]	
Diabetes (reference no)		.58		.02
Yes	1.11 (0.76–1.62)		2.14 (1.11–4.12)	
Alcohol abuse (reference no)		.18		.005
Yes	1.30 (0.88–1.90)		2.93 (1.38–6.21)	
Drug use (reference no)		.33		.22
Yes	0.83 (0.57–1.21)		0.67 (0.35–1.28)	
FIB-4 (reference <1.45)				.0005
1.45–3.25			1.44 (0.57–3.66)	
>3.25			4.58 (1.81–11.60)	

NOTE. Results from multivariable models. In addition to the variables displayed, the models were also adjusted for Deyo index and number of outpatient visits in the year prior to DAA treatment.
CI, confidence interval; HCC, hepatocellular cancer; HCV, hepatitis C virus; HR, hazard ratio.
[a]No HCC case in this category. The models were run removing the category with missing HCC cases.
[b]The model for cirrhosis did not include FIB-4.

Second, despite the relative reduction in risk of HCC, the absolute risk of HCC persisted in patients DAA-induced SVR. HCC developed in 183 patients during approximately 20,415 PY follow-up, at an annual incidence of 0.90%. Previous studies reported an overall annual incidence of approximately 0.3% in interferon-cured patients, including ours, which was conducted in a VA national cohort.[6,16,17] DAA offer a chance of cure for all patients with HCV, including patients with advanced cirrhosis, older patients, and those with alcohol use – all characteristics independently associated with risk of HCC in HCV.[6,18,19] These patients were typically either not treated or had poor response to interferon-based treatment. In this study, 39% of the DAA-cured patients had already progressed to cirrhosis, 30% were older than 65, and 61.4% has history of alcohol use vs 14.4%, 3.0%, and 44.7%, respectively, in our previous study of interferon-cured patients.[6] These data show the treated population has changed significantly in the DAA era to include many patients with other HCC risk factors; these differences likely explain why the newer cohorts of DAA-treated patients face higher absolute HCC risk than expected based on historic data.

Third, risk of HCC was the highest in all patients with a diagnosis of cirrhosis, ranging from 1.0% to 2.2% per year based on other demographic and clinical characteristics (Figure 2). These estimates reached or exceeded the cut-offs (0.8%–1.5% per year) beyond which HCC surveillance may become cost-effective.[20] In contrast, the risk of HCC was low in almost all patients without cirrhosis, with the exception of patients with a high baseline FIB-4 suggesting presence of advanced fibrosis. Based on these data, HCC surveillance or risk modification may be needed for all patients who have progressed to cirrhosis or advanced fibrosis (as indicated by high FIB-4) at the time of SVR.

Our data highlight the potential consequences of delaying treatment – either by lack of access or by patient/provider choice – on subsequent risk of HCC, and support treatment of all patients with HCV before their progression to advanced fibrosis and cirrhosis. Delaying treatment until patients progress to cirrhosis might be associated with substantial downstream costs incurred as part of life-long HCC surveillance and/or management of HCC. We also found a statistically significant race effect in our analyses. African American patients had a lower whereas Hispanics had a higher risk of developing HCC compared with whites,

Table 5. Demographic and Clinical Characteristics of HCV Patients Who Developed HCC During Antiviral Treatment vs Those Who Developed HCC After Treatment

Variable	HCC during treatment (early) N (%)	HCC after DAA treatment (delayed) N (%)	*P* value
Age (*y*), mean (*SD*)	63.3 (4.9)	63.2 (4.7)	.89
Gender			.53
Female	1 (1.3)	2 (0.7)	
Male	78 (98.7)	269 (99.3)	
Race			.95
African Americans	23 (29.1)	76 (28.0)	
White	45 (57.0)	152 (56.1)	
Hispanic	3 (3.8)	17 (6.3)	
Others	1 (1.3)	4 (1.5)	
Missing	7 (8.8)	22 (8.1)	
Cirrhosis			.46
No	24 (30.4)	71 (26.2)	
Yes	55 (69.6)	200 (73.8)	
FIB-4			.01
<1.45	1 (1.3)	19 (7.0)	
1.45–3.25	18 (22.8)	69 (25.5)	
>3.25	50 (63.3)	172 (63.5)	
Missing	10 (12.6)	11 (4.0)	
HCV genotype			.52
1	69 (87.3)	229 (84.5)	
2	3 (3.8)	16 (5.9)	
3	6 (7.6)	19 (7.0)	
4–6	1 (1.3)	1 (0.4)	
Missing	0 (0.0)	6 (2.2)	
Alcohol abuse			.44
No	29 (36.7)	87 (32.1)	
Yes	50 (63.3)	184 (67.9)	
Drug use			.64
No	37 (46.8)	135 (49.8)	
Yes	42 (53.2)	136 (50.2)	
Deyo score			.29
0	39 (49.4)	107 (39.5)	
1–2	27 (34.2)	111 (41.0)	
≥3	13 (16.4)	53 (19.5)	
Tumor characteristics[a]			
American Joint Committee on Cancer Stage			.81[b]
I	13 (44.8)	40 (50.6)	
II	9 (31.0)	19 (24.1)	
III/IV	3 (10.4)	6 (7.6)	
Missing	4 (13.8)	14 (17.7)	
Tumor size (largest tumor)			
≤2 cm	7 (24.1)	21 (26.6)	.27[b]
2–5 cm	15 (51.7)	40 (50.6)	
>5 cm	4 (13.8)	3 (3.8)	
Missing	3 (10.4)	15 (19.0)	

DAA, direct acting antiviral; HCC, hepatocellular cancer; HCV, hepatitis C virus; SD, standard deviation.
[a]Stage and size information available for only 108 patients.
[b]Fisher's exact.

although the latter effect did not reach statistical significance. These associations persisted even after adjusting for a range of factors including age, gender, HCV genotype, alcohol/drug use, diabetes, and health care utilization. As such, these data are consistent with previous studies of untreated patients with HCV and show that racial disparities in risk of HCC may persist after DAA-induced SVR.[21]

Our study was limited to Veterans with HCV. However, the VA HCV cohort represents the largest known such cohort in the world; one that had rapid and wide adoption of DAA, with almost complete capture of outcomes and patient characteristics. Furthermore, the biological process of hepatocarcinogenesis are likely similar in veterans and nonveterans, rendering our results generalizable to other patients. We considered but opted against including an untreated control group. Patients who received DAA in the earlier dissemination phase likely differed from those who did not. Some of these factors (such as noncompliance and

lack of interest in treatment) are unmeasurable in the database. Another possible control group could have been patients who achieved SVR with the previous interferon-based treatment. However, we did not use this group because of variable follow-up durations, as well as considerable differences in patients treated in the interferon vs current DAA era, as discussed earlier. Furthermore, we recently reported data on the risk of HCC after SVR in interferon-treated patients and use our previous work to draw comparisons with the results from the current study.[6] For this study, we chose patients who received but failed DAA as the control because they met the selection criteria for DAA in practice, thereby reducing the chance of confounding by indication. While control patients were more likely to have cirrhosis, HCV genotype 3, and history of alcohol and drug use than those with SVR, adjusting for these differences did not change the magnitude and direction of SVR effect. Our study is also limited by short average follow-up time. Risk of HCC might diminish as time from treatment elapses.

In summary, we found that, among patients treated with DAA, virological cure of HCV resulted in a considerable reduction in the risk of HCC. We did not find any evidence to suggest that DAAs promote HCC either during or after treatment. However, the absolute risk of HCC was high in several patient groups who achieved cure, including approximately 40% of patients who had progressed to cirrhosis. Providers should take that risk into account in conducting HCC surveillance unless future studies find a diminution of risk of HCC as time-since-treatment elapses.[22]

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org/, and at http://dx.doi.org/10.1053/j.gastro.2017.06.012.

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The authors disclose no conflicts.

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Supplementary Appendix Table 1. Factors Associated With Incident HCC in Patients Treated With DAA Agents. Results from Multivariable Models

Characteristics	Overall cohort		Patients with cirrhosis		Patients without cirrhosis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
SVR (reference no)		<.0001		<.0001		<.0001
Yes	0.28 (0.22–0.36)		0.32 (0.23–0.44)		0.18 (0.11–0.30)	
Age, *y* (reference <65)		0.008		0.07		0.03
≥65	1.40 (1.09–1.79)		1.31 (0.98–1.74)		1.70 (1.05–2.75)	
Gender (reference male)		0.06		0.10		0.47
Female	0.27 (0.07–1.10)		0.19 (0.03–1.37)		0.49 (0.07–3.55)	
Race (reference white)		0.24		0.05		0.48
African American	0.74 (0.56–0.99)		0.64 (0.45–0.92)		0.95 (0.57–1.57)	
Hispanic	1.07 (0.65–1.78)		1.21 (0.71–2.05)		0.42 (0.06–3.05)	
Other	0.59 (0.22–1.59)		0.36 (0.09–1.46)		1.55 (0.37–6.45)	
Missing	0.85 (0.54–1.33)		1.01 (0.63–1.63)		0.33 (0.08–1.39)	
Cirrhosis (reference no)		<.0001		–		–
Yes	3.95 (2.99–5.22)		–		–	
HCV genotype (reference 1)		0.69		0.52		0.75
2	0.86 (0.52–1.44)		1.05 (0.59–1.86)		0.46 (0.14–1.47)	
3	1.22 (0.75–1.97)		1.37 (0.80–2.32)		0.86 (0.26–2.80)	
4–6	0.40 (0.05–2.89)		–		1.37 (0.19–9.91)	
Missing	1.28 (0.57–2.88)		1.82 (0.80–4.11)		–	
Previous antiviral treatment (reference no)		0.01		0.02		0.17
Yes	1.39 (1.08–1.80)		1.38 (1.04–1.85)		1.46 (0.84–2.52)	
HIV (reference no)		0.87		0.69		0.33
Yes	0.95 (0.48–1.86)		1.17 (0.55–2.49)		0.48 (0.11–2.11)	
Diabetes (reference no)		0.01		0.20		0.004
Yes	1.43 (1.09–1.88)		1.23 (0.90–1.69)		2.18 (1.28–3.71)	
Alcohol abuse (reference no)		0.001		0.05		0.053
Yes	1.45 (1.10–1.92)		1.38 (1.00–1.91)		1.72 (0.99–2.98)	
Drug use (reference no)		0.0365		0.0837		0.2349
Yes	0.75 (0.57–0.98)		0.76 (0.55–1.04)		0.73 (0.43–1.23)	
Deyo score (reference 0)		0.3114		0.3435		0.5862
1–2	0.90 (0.67–1.20)		0.97 (0.69–1.37)		0.74 (0.42–1.31)	
≥3	0.73 (0.49–1.09)		0.73 (0.45–1.16)		0.83 (0.39–1.76)	

NOTE. Multivariable model adjusted for number of outpatient visits in the year prior to DAA treatment.
DAA, direct acting antivirals; HCC, hepatocellular cancer; HCV, hepatitis C virus; HR, hazard ratio; SVR, sustained virological response.

Supplementary Appendix Table 2. Association Between FIB-4 and Risk of HCC in Patients With SVR With the DAA Agents

FIB-4	Total N (%)	PY of follow-up	HCC N	Incidence rate (per 100 PY, 95% CI)	Adjusted HR (95% CI)[a]	*P* value
<1.45	4015 (20.6)	4331.0	13	0.30 (0.14–0.46)	1	<.0001
1.45–3.25	9001 (46.1)	9473.1	43	0.45 (0.32–0.59)	1.43 (0.77–2.66)	
>3.25	5614 (28.8)	5652.7	122	2.16 (1.78–2.54)	6.23 (3.50–11.08)	
Missing	888 (4.5)	958.5	5	0.52 (0.06–0.98)	1.60 (0.57–4.49)	

CI, confidence interval; DAA, direct acting antivirals; HCC, hepatocellular cancer; HCV, hepatitis C virus; HR, hazard ratio; SVR, sustained virological response.
[a]Multivariable model adjusted for age, gender, race, HCV genotype, diabetes, HIV, alcohol use, drug use, Deyo index, and number of outpatient visits in the year prior to DAA treatment.