Treatment Status of Hepatocellular Carcinoma Does Not Influence Rates of Sustained Virologic Response: An HCV-TARGET Analysis

Kavita Radhakrishnan,[1] Adrian M. Di Bisceglie,[2] K. Rajender Reddy ,[3] Joseph K. Lim,[4] Josh Levitsky,[5] Mohamed A. Hassan,[6] Jama M. Darling,[7] Jordan J. Feld,[8] Lucy Akushevich,[7] Monika Vainorius,[7] David R. Nelson,[9] Michael W. Fried,[7] Robert S. Brown Jr.,[10] and Norah A. Terrault [11]

Recent studies have suggested a negative impact of hepatocellular carcinoma (HCC) on sustained virologic response (SVR) to hepatitis C virus (HCV) direct acting antivirals (DAAs). We compared the effectiveness of DAAs in patients with cirrhosis, with and without HCC, and in those with HCC partially treated or untreated (PT/UT-HCC) versus completely treated (CT-HCC). HCC status was based on imaging 6 months before or 2 months after start of DAA therapy. Absence and presence of enhancing lesions after HCC treatment defined CT-HCC and PT/UT-HCC, respectively. Using minimally adjusted logistic regression, the association between the presence of HCC and SVR rates was estimated. Among the 1,457 patients with cirrhosis from HCV-TARGET with complete virologic data (per-protocol population) who did not undergo liver transplantation during treatment and followup, 1,300 were without HCC, 91 with CT-HCC, and 66 with PT/UT-HCC. Most patients were genotype 1 (81%) and treatment-experienced (56%), 41% had history of prior decompensation, and the median pretreatment Model for End-Stage Liver Disease was 9 (range 6-39). The SVR rates were 91% for patients without HCC, 84% for CT-HCC, and 80% for PT/UT-HCC. The presence of HCC (versus not having HCC) was associated with significantly lower odds of achieving SVR (odds ratio [OR] = 0.51, 95% confidence interval [CI]: 0.33-0.81; P = 0.003). However, among those with HCC, HCC treatment status (PT/UT-HCC versus CT-HCC) did not show association with SVR (OR = 0.79, 95% CI: 0.35-1.79, P = 0.569). *Conclusions:* The presence of HCC reduces the likelihood of SVR by 50%, but with no evident difference in those with completely treated HCC versus partially treated/untreated HCC. (*Hepatology Communications* 2019;3:1388-1399).

Direct-acting antiviral agents (DAAs) have dramatically improved the outcomes of patients with chronic hepatitis C virus (HCV) with overall sustained virologic response (SVR) rates of about 95%, including those with compensated cirrhosis.[1-5] Additional benefits of

Abbreviations: AE, adverse event; BMI, body mass index; CI, confidence interval; CT, completely treated; DAAs, direct acting antivirals; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, Model for End-stage Liver Disease; OR, odds ratio; PPI, proton-pump inhibitor; PT, partially treated; RBV, ribavirin; SVR, sustained virologic response; UT, untreated.

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achieving HCV eradication among patients with advanced liver disease include reversal of symptoms of decompensation, improvement in Model for End-Stage Liver Disease (MELD) and Child-Pugh scores, and reduced liver-related and all-cause mortality.[4,6] Thus, HCV-infected patients with complications of cirrhosis are a high priority for HCV treatment.

However, there has been controversy regarding DAA therapy in patients with cirrhosis and hepatocellular carcinoma (HCC). Initial, uncontrolled studies suggested a higher rate of HCC recurrence after curative therapy among patients treated with DAAs,[7] but subsequent retrospective and prospective controlled studies have refuted this.[8,9] Adding further to the complexity of the decisions in patients with HCC is the concern that DAA efficacy may be reduced in patients with HCC, as reported in a large VA study of DAA-treated patients.[10] Finally, a single-center study suggested that presence of active versus treated HCC was the relevant predictor for treatment failure, with SVR rates of 52% in those with untreated or partially treated HCC at time of DAA therapy as compared with 100% in those with HCC that was treated completely.[11] The timing of DAA therapy has important ramifications, as delays in DAA therapy in patients with cirrhosis may result in worsening decompensation, which in turn affects the ability to provide curative HCC options.

With the goal of bringing greater clarity to the decisions surrounding use of DAAs in patients with cirrhosis and HCC, we used the HCV-TARGET consortium to study SVR rates with DAA therapy in HCV-infected patients with cirrhosis with and without HCC, and to specifically address whether the treatment status of HCC influenced SVR rates.

Methods

STUDY POPULATION AND DESIGN

HCV-TARGET is a longitudinal, observational study of chronic hepatitis C patients that began in December 2011 and is ongoing. This consortium includes academic (n = 46) and community (n = 16) centers from North America (n = 58) and Europe (n = 4), collecting data on DAA regimens and outcomes in this rapidly changing therapeutic area. Prospective data are captured from enrolled patients using a common database that uses novel, standardized source data abstraction as described previously.[12,13] All captured data are managed using Research Electronic Data Capture, with electronic data capture tools hosted at the University of North

Potential conflict of interest: Dr. Fried consults and received grants from AbbVie, Merck, and Bristol-Myers Squibb; he consults and owns stock in TARGET PharmaSolutions; he received grants from Gilead. Dr. Feld consults and received grants from AbbVie and Gilead; he consults for Enanta and Roche; he received grants from Janssen and Wako. Dr. Brown consults and received grants from Gilead and AbbVie. Dr. Di Bisceglie consults for AbbVie, Gilead, and Bristol-Myers Squibb. Dr. Nelson received grants from AbbVie, Gilead, and Merck. Dr. Levitsky consults and owns stock in Transplant Genomics; he is on the speakers' bureau and received grants from Novartis. Dr. Lim consults and received grants from Gilead. Dr. Reddy advises and received grants from Merck; he advises Shionogi, Dova, and Spark; he received grants from Intercept, Mallinckrodt, Gilead, Conatus, Exact Sciences, and Bristol-Myers Squibb. Dr. Terrault received grants from Gilead.

ARTICLE INFORMATION:

From the [1]University of California, San Francisco, San Francisco, CA; [2]St. Louis University School of Medicine, St. Louis, MO; [3]University of Pennsylvania, Philadelphia, PA; [4]Yale University School of Medicine, New Haven, CT; [5]Northwestern University, Evanston, IL; [6]University of Minnesota, Minneapolis, MN; [7]University of North Carolina at Chapel Hill, Chapel Hill, NC; [8]Toronto Western Hospital Liver Center, Toronto, Canada; [9]University of Florida, Gainesville, FL; [10]Weill Cornell Medical College, New York, NY; [11]Keck School of Medicine of the University of Southern California, Los Angeles, CA.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Norah Terrault, M.D., M.P.H.
Division of Gastroenterology and Liver Diseases
University of California of Southern California
1450 San Pablo Street, HC4 3000
Los Angeles, CA 90033
E-mail: terrault@usc.edu

Carolina at Chapel Hill. Research Electronic Data Capture is a secure, web-based application designed to support data capture for research studies.[14] A centralized team of trained coders reviews all redacted medical records obtained from participating sites for data entry and systematically monitors the data entries for completeness and accuracy. All records were screened for extreme or unlikely values and verified/resolved with additional queries. The study protocol did not define specific populations, regimens, dosing, and duration or safety management.

For this analysis, patients were eligible if they were 18 years or older, had cirrhosis with and without history of HCC, had not undergone liver transplantation, initiated HCV therapy with select (see subsequently) all-oral DAA regimens between February 2014 and February 2017, and had available virologic outcome as well as HCC information obtained from the enrolling sites.

The per protocol population consisted of patients who either completed the assigned HCV treatment or discontinued treatment early due to lack of efficacy and had virological outcome data available. A sensitivity analysis was performed that included patients who had undergone liver transplantation on treatment and those who discontinued treatment early due to adverse events (AEs).

Chronic HCV infection was defined as detectable HCV RNA by real-time polymerase chain reaction at time of treatment initiation. The presence of cirrhosis was defined at the time of enrollment by biopsy and/or a combination of clinical, laboratory, elastography, and imaging criteria established beforehand.[12] Patients were determined to have cirrhosis if they had evidence of stage 4 fibrosis by liver biopsy or hepatic elastography at any time before therapy, or evidence of stage 3 fibrosis by liver biopsy at any time before therapy with any of the following criteria: platelet count less than 140,000 per milliliter, presence of esophageal varices on esophagogastroduodenoscopy, evidence of cirrhosis and/or portal hypertension and/or ascites by imaging studies, Fibro-Sure or equivalent test, vibration-controlled transient elastography, or equivalent were deemed to be compatible with stage 4 fibrosis. In the absence of biopsy or if biopsy results showed stage 2 fibrosis or less, the presence of two or more of the these clinical/ laboratory criteria were deemed to be compatible with stage 4 fibrosis.

HCC status was based on local imaging obtained within 6 months before or 2 months after start of DAA therapy. Alpha-fetoprotein values were not available. Completely treated (CT-HCC) was defined as no enhancing lesions after HCC therapies. Partially treated or untreated (PT/UT-HCC) was defined as enhancing lesion present or persisting after HCC therapy.

DATA COLLECTION

Demographic, clinical, adverse event, and virologic data were collected at baseline and as available throughout the treatment period and the posttreatment follow-up. The collected demographic data included the patient's age, sex, race, body mass index (BMI), proton-pump inhibitor (PPI) use, calculated MELD score, and history of hepatic decompensation. History of hepatic decompensation was defined as evidence of prior or current diagnosis of ascites, hepatic encephalopathy, spontaneous bacterial peritonitis or variceal hemorrhage, or baseline concomitant medications with a specific use listed for these indications. HCV-specific data included baseline viral load, genotype, prior treatment history, and type and duration of DAA therapy. Laboratory data, collected per standard practice, included levels of serum creatinine, albumin, total bilirubin, alanine aminotransferase levels, hemoglobin, international normalized ratio platelet count, and HCV RNA.

Patients in the HCC group had additional cancer-specific data collected. These included stage at time of diagnosis and treatment history from time of diagnosis through 12 weeks after completion of DAA therapy. HCC treatment history was categorized as resection only, loco-regional therapy only, systemic therapy only, or more than one modality of therapy. The time period between diagnosis of HCC and initiation of HCV therapy was collected. Treatment status (CT-HCC versus PT/UT-HCC) was ascertained from radiology reports. The time period between imaging and initiation of DAA therapy was also collected.

AEs, defined as any new symptom or event recorded in the medical record that occurred during the HCV treatment period, were collected and reported regardless of the need or lack thereof for a prescription medication or a dose reduction or discontinuation of HCV

treatment. AEs recorded in the patient's clinical note were identified by HCV-TARGET data abstractors and then entered into the database as text and further coded by the clinically validated international medical terminology dictionary, MedDRA (the Medical Dictionary for Regulatory Activities). Serious AEs were defined as any AE that required hospitalization or met the criteria for expedited reporting per US Food and Drug Administration form MEDWATCH 3500.

TREATMENT REGIMENS

The choice of treatment regimen was at the discretion of the local treating physician, as was the use of ribavirin (RBV). Similarly, treatment duration was determined by the treating physician and, for the purposes of analysis, was defined as less than or equal to 12 weeks, 12 to 16 weeks, and greater than or equal to 16 weeks. For the purposes of this analysis, the combinations of sofosbuvir plus ribavirin and sofosbuvir plus peginterferon plus RBV were excluded due to the recognized lower rates of SVR compared with the next generation of DAA options.

PRIMARY ENDPOINT

The primary endpoint was SVR, defined by a plasma HCV RNA level below quantitation or undetectable at least 64 days after treatment completion (SVR12). The primary predictors were presence of HCC, and among those with HCC, whether the HCC was CT versus PT/UT.

ANALYTIC APPROACH

Demographic characteristics, laboratory values, AEs, and treatment response were analyzed by HCC status for the per protocol population, which consisted of patients who either completed the assigned HCV treatment or discontinued treatment early due to lack of efficacy and had virologic outcomes available. Sensitivity analyses were also performed, including the patients who discontinued treatment early due to AE as well as patients who underwent liver transplantation during DAA therapy or during the 12 weeks of follow-up.

The unadjusted rates of SVR and exact binomial confidence intervals (CIs) were calculated for the non-HCC as well as CT-HCC and PT/UT-HCC groups, in addition to the subgroups of interest, particularly based on genotype and treatment regimen, including use of RBV.

Minimally adjusted (for history of decompensation) Firth penalized logistic regression was used to assess the association between baseline covariate and SVR outcome.[15] The set of covariates was selected beforehand based on a consensus of clinical expertise and included the most well-established baseline covariates associated with SVR: sex, race, MELD (<10, ≥10), albumin (<3.5 g/dL, ≥3.5 g/dL), total bilirubin (≤1.2 mg/dL, >1.2 mg/dL), a history of antiviral treatment, use of RBV, HCV genotype, PPI use, platelet count, and BMI. The primary predictor variable of interest was HCC status (no-HCC, CT-HCC, PT/UT-HCC). All models were adjusted for history of decompensation. Select trivariate analyses were also performed.

INFORMED CONSENT

The protocol was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The independent ethics committee at each participating study center or a central institutional review board approved the protocol if a local institutional review board was not in place. All patients provided written informed consent for their participation. All authors had complete access to the study data and reviewed and approved the final manuscript.

Results

COHORT CHARACTERISTICS

During the study period, 1,618 patients with cirrhosis without history of liver transplantation and with liver imaging 6 months before or up to 2 months immediately following the initiation of DAA regimen for HCV were identified. Of those, 7 patients died, 20 discontinued treatment due to reasons other than AE or lack of efficacy, 16 were lost to follow-up, and 81 were lost in posttreatment follow-up (21 of whom died in posttreatment follow-up). For our main analyses we excluded those patients who discontinued treatment early due to AE (n = 16) or underwent transplant during treatment and up to 12 weeks of

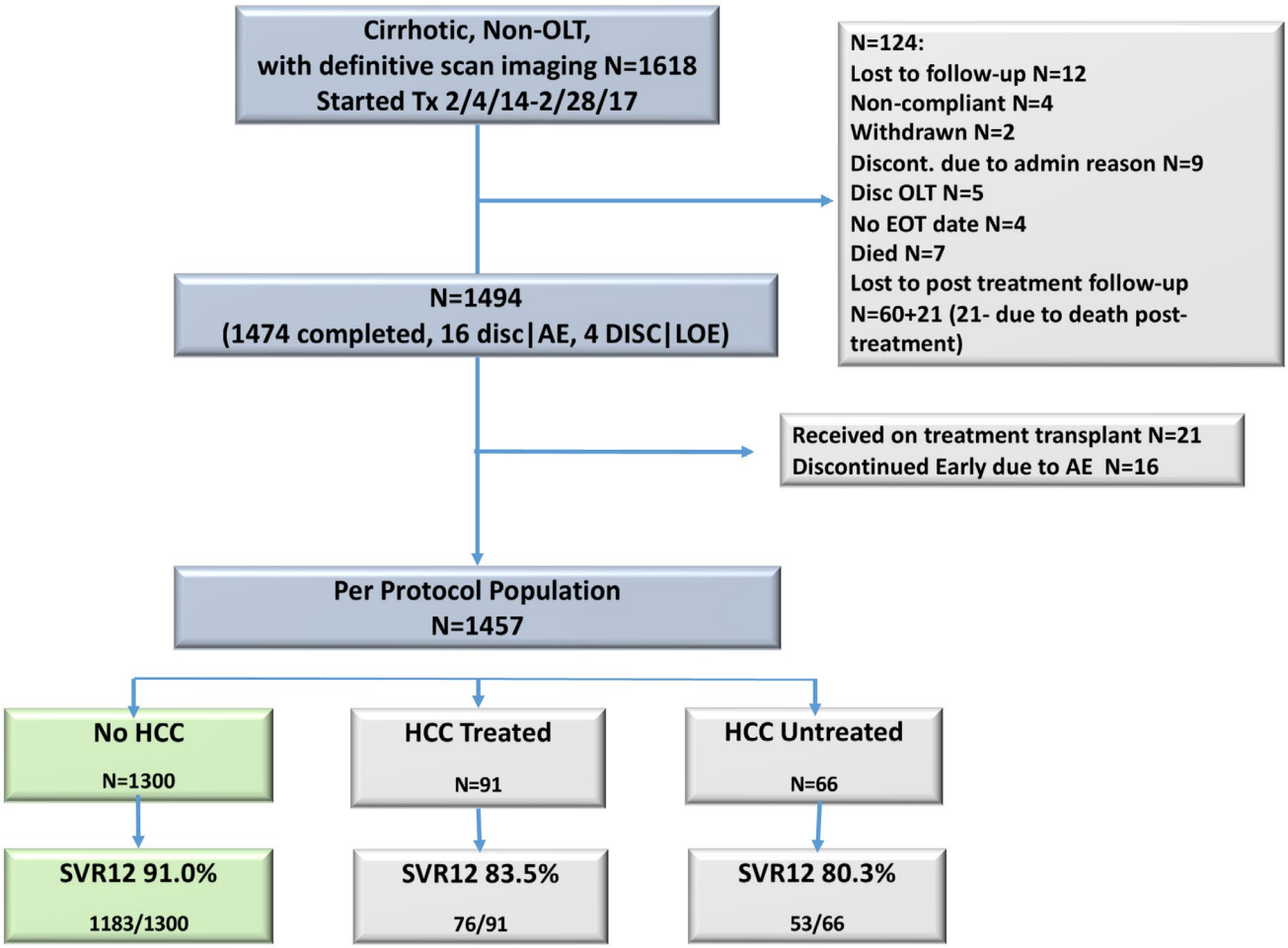

FIG. 1. Consort diagram. Abbreviations: Disc, discontinued; EOT, end of treatment; LOE, lack of efficacy; OLT, orthotopic liver transplantation; TX, treatment.

follow-up (n = 21), resulting in a per protocol population of 1,457: 1,300 without HCC and 157 with history of HCC. Among the HCC patients, 91 had CT-HCC and 66 had PT/UT-HCC at the time of DAA therapy (Fig. 1).

Baseline characteristics of the per protocol population, including demographics and laboratory data, are provided in Table 1. Overall, patients were predominantly white (74%), male (64%), with a median age of 60 years (range 19-90). Most patients were genotype 1 (81%) and treatment-experienced (56%). Forty-one percent had history of prior decompensation, and the median MELD pretreatment was 9 (range 6-39).

In the per protocol population of 157 patients with history of HCC, 91 patients (58%) had treated HCC without any evidence of active tumor present on imaging (CT-HCC), and 66 patients (42%) had PT/UT-HCC at the time of DAA treatment initiation. At the time of diagnosis, most patients with known tumor stage were within Milan criteria (75 of 87 [86%]) with similar proportions in the CT-HCC (49 of 55 [89%]) and PT/UT-HCC (26 of 32 [81%]) groups. The median time from HCC diagnosis to initiation of DAA therapy was 497 days in the CT-HCC group, whereas in the PT/UT-HCC group it was 377 days. The median time from HCC imaging to initiation of DAA therapy was 46 days in the CT-HCC group as compared with 52 days in the PT/UT-HCC group and 61 days in the no-HCC group. Loco-regional only therapies were the most frequently used HCC therapy: 59 of 78 (76%) in the CT-HCC group and 43

TABLE 1. BASELINE CHARACTERISTICS OF THE PER PROTOCOL COHORT

		With History of HCC			
	No HCC	CT-HCC	PT/UT-HCC	All HCC	Total
	n = 1,300 (%)	n = 91 (%)	n = 66 (%)	n = 157 (%)	n = 1,457 (%)
Male sex	817 (62.8%)	59 (64.8%)	54 (81.8%)	113 (72.0%)	930 (63.8%)
Age, median, years	60 (19-86)	63 (34-83)	63 (39-90)	63 (34-90)	60 (19-90)
Race					
White	955 (73.5%)	69 (75.8%)	49 (74.2%)	118 (75.2%)	1,073 (73.6%)
Black or African American	194 (15.4%)	10 (11.0%)	5 (7.6%)	15 (9.6%)	217 (14.9%)
Other or pending	143 (11.0%)	12 (13.2%)	12 (18.2%)	20 (14.4%)	24 (15.3%)
BMI (median)	27	27	26	27	28
HCV genotypes					
1	73 (80.2%)	73 (80.2%)	45 (68.2%)	118 (75.2%)	1,179 (80.9%)
2	53 (4.1%)	4 (4.4%)	0 (0.0%)	4 (2.5%)	57 (3.9%)
3	136 (10.5%)	12 (13.2%)	18 (27.3%)	30 (19.1%)	166 (11.4%)
4-6	47 (3.6%)	1 (1.1%)	2 (3.0%)	3 (1.9%)	50 (3.4%)
Not reported	3 (0.2%)	1 (1.1%)	1 (1.5%)	2 (1.3%)	5 (0.3%)
HCV treatment-experienced	729 (56.1%)	52 (57.1%)	36 (54.5%)	88 (56.1%)	817 (56.1%)
Prior decompensation	512 (39.4%)	53 (58.2%)	34 (51.5%)	87 (55.4%)	599 (41.1%)
HIV positive	31 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	31 (2.1%)
Diabetes	338 (26.0%)	19 (20.9%)	12 (18.2%)	31 (19.7%)	369 (25.3%)
PPI use	511 (39.3%)	38 (41.8%)	33 (50.0%)	71 (45.2%)	582 (39.9%)
Most-used treatment regimens*					
Sofosbuvir/simeprevir ± RBV	321 (24.7%)	26 (28.6%)	19 (28.8%)	45 (28.7%)	366 (25.1%)
Sofosbuvir/ledipasvir ± RBV	593 (45.6%)	34 (37.4%)	22 (33.3%)	56 (35.7%)	649 (44.5%)
Sofosbuvir/daclatasvir ± RBV	134 (10.3%)	12 (13.2%)	14 (21.2%)	26 (16.6%)	160 (11.0%)
Sofosbuvir/velpatasvir ± RBV	88 (6.8%)	10 (11.0%)	9 (13.6%)	19 (12.1%)	107 (7.3%)
Ribavirin added	389 (29.9%)	33 (36.2%)	34 (51.5%)	67 (42.7%)	456 (31.3%)
Treatment duration					
≤12 weeks	634 (48.8%)	53 (58.2%)	31 (47.0%)	84 (53.5%)	718 (49.3%)
ALT (IU/L) Median	68.0	66.0	64.5	66.0	68.0
Min-Max	9.0-813.0	15.0-398.0	14.0-316.0	14.0-398.0	9.0-813.0
Total bilirubin (mg/dL)†					
≤1.2	828 (63.7%)	58 (63.7%)	39 (59.1%)	97 (61.8%)	925 (63.5%)
>1.2	390 (30.0%)	31 (34.1%)	24 (36.4%)	55 (35.0%)	445 (30.5%)
Platelets ($\times 10^{-3}$/uL)†					
100,000+	696 (53.5%)	41 (45.1%)	24 (36.4%)	65 (41.4%)	761 (52.2%)
<100,000	559 (43.0%)	49 (53.8%)	41 (62.1%)	90 (57.3%)	649 (44.5%)
Albumin (g/dL)†					
3.5+	792 (60.9%)	45 (49.5%)	34 (51.5%)	79 (50.3%)	871 (59.8%)
<3.5	414 (31.8%)	44 (48.4%)	28 (42.4%)	72 (45.9%)	486 (33.4%)
eGFR‡					
30-59	140 (10.8%)	7 (7.7%)	6 (9.1%)	13 (8.3%)	153 (10.5%)
60-89	481 (37.0%)	43 (47.3%)	25 (37.9%)	68 (43.3%)	549 (37.7%)
≥90	554 (42.6%)	40 (44.0%)	30 (45.5%)	70 (44.6%)	624 (42.8%)
>30	34 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	37 (2.5%)
MELD Median	9.0	8.5	8.0	8.0	9 .0
Min-Max	6.0-39.0	6.0-19.0	6.0-28.0	6.0-28.0	6.0-39.0

*Other regimens used were ombitasvir-paritaprevir-ritonavir and dasabuvir with or without RBV, and elbasvir-grazoprevir with or without RBV.
†Totals do not add up to 100% due to patients' missing baseline values.
‡mL/min/1.73 m^2, as calculated by the modification of diet in renal disease study equation.
Abbreviations: ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; and HIV, human immunodeficiency virus.

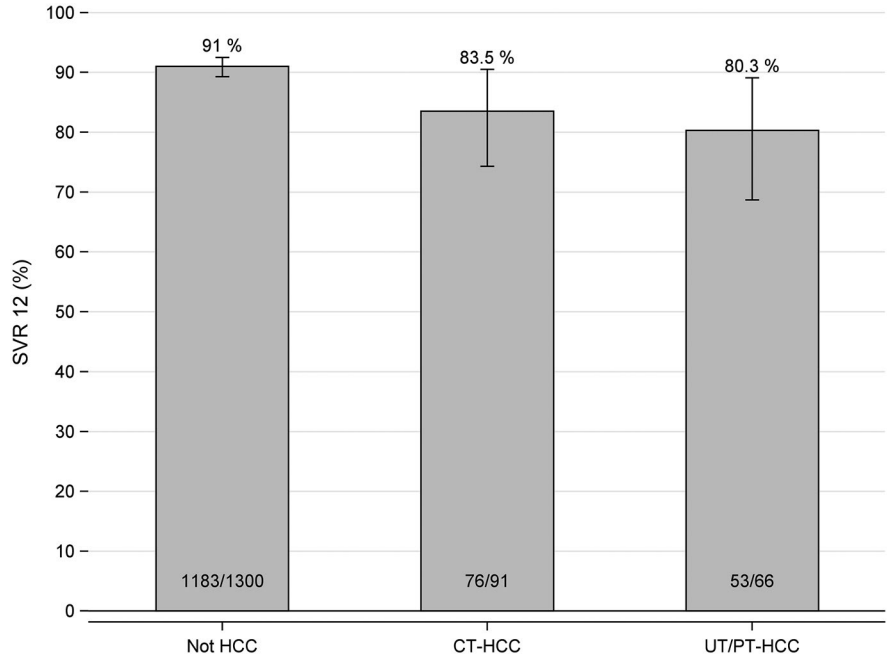

FIG. 2. SVR rates by HCC treatment status.

of 54 (80%) in the PT/UT-HCC group. Available cancer and treatment information, including SVR rates, are found in Supporting Table S1.

DAA TREATMENT AND SVR RATES

Of the 1,618 patients who started HCV therapy, 1,457 (90%) were evaluable for SVR (Fig. 1). Treatment regimen and duration by HCC history in the per protocol population are given in Table 1. The combination of sofosbuvir/ledipasvir ± RBV (n = 649, 45%) and sofosbuvir plus simeprevir ± RBV (n = 366, 25%) were the most commonly used regimens, with sofosbuvir plus daclatasvir ± RBV being less used (n = 160, 11%). Thirty-one percent (n = 456) received RBV as a component of their treatment regimen. Overall, the median treatment duration was 86 days (range 50-219).

In the per protocol population, the crude rates of SVR among patients without HCC, CT-HCC, and PT/UT-HCC overall are shown in Fig. 2; the specific baseline factors are provided in Table 2.

Those treated with sofosbuvir plus simeprevir were primarily genotype 1 (98.1%), as were those treated with sofosbuvir/ledipasvir ± RBV (92.9%). The crude SVR rates for patients treated with sofosbuvir plus simeprevir ± RBV (82.8%, 95% CI 78.5-86.5) were lower than those treated with sofosbuvir/ledipasvir ± RBV (92.3%, CI: 90.0-94.2); $P < 0.0001$ (data not shown). The crude rates of SVR among patients without HCC, CT-HCC, and PT/UT-HCC treated with sofosbuvir plus simeprevir ± RBV were 83.8% (95% CI:79.3-87.7), 76.9% (95% CI:56.4-91.0) and 73.7% (95% CI:48.8-90.9), and treated with sofosbuvir/ledipasvir ± RBV were 93.1% (95% CI:90.7-95.0), 85.3% (95% CI:68.9-95.0), and 81.8% (95% CI:59.7-94.8) (Table 2).

The crude rates of SVR in genotype 3 patients treated with sofosbuvir/daclatasvir ± RBV (83.6%, 95% CI: 75.1-90.2) was lower than those treated with sofosbuvir/velpatasvir ± RBV (98.0%, 95% CI: 89.1-100.0); $P = 0.010$ (data not shown). The crude rates of SVR among genotype 3 patients without HCC, CT-HCC, and PT/UT-HCC were 88.2% (95% CI: 81.6-93.1), 91.7% (95% CI: 61.5-99.8) and 83.3% (95% CI: 58.6-96.4), respectively. Genotype 3 was more prevalent among patients with PT/UT-HCC (27.7%) as compared with CT-HCC (13.3%; $P = 0.026$) or no HCC (10.5%; $P < 0.0001$) (Table 2).

TABLE 2. SVR BY SUBPOPULATIONS

	HCC Category	Subgroup (n)	SVR	95% CI
All	CT-HCC	91	83.5%	74.2%-90.5%
	PT/UT-HCC	66	80.3%	68.7%-89.1%
	No HCC	1,300	91.0%	89.3%-92.5%
Female	CT-HCC	32	83.05%	67.2%-94.7%
	PT/UT-HCC	12	81.48%	42.8%-94.5%
	No HCC	483	88.98%	92.0%-96.3%
Male	CT-HCC	59	83.1%	71.0%-91.6%
	PT/UT-HCC	54	81.5%	68.6%-90.7%
	No HCC	817	89.0%	86.6%-91.0%
Genotype 1	CT-HCC	73	83.6%	73.0%-91.2%
	PT/UT-HCC	45	77.8%	62.9%-88.8%
	No HCC	1061	91.1%	89.3%-92.8%
Genotype 2	CT-HCC	4	75.0%	19.4%-99.4%
	No HCC	53	98.1%	89.9%-100.0%
Genotype 3	CT-HCC	12	91.7%	61.5%-99.8%
	PT/UT-HCC	18	83.3%	58.6%-96.4%
	No HCC	136	88.2%	81.6%-93.1%
Decomp	CT-HCC	53	84.9%	72.4%-93.3%
	PT/UT-HCC	34	73.5%	55.6%-87.1%
	No HCC	512	86.3%	83.0%-89.2%
Compensated	CT-HCC	38	81.6%	65.7%-92.3%
	PT/UT-HCC	32	87.5%	71.0%-96.5%
	No HCC	788	94.0%	92.1%-95.6%
Tx-experienced	CT-HCC	52	76.9%	63.2%-87.5%
	PT/UT-HCC	36	80.6%	64.0%-91.8%
	No HCC	729	90.3%	87.9%-92.3%
Tx-naïve	CT-HCC	39	92.3%	79.1%-98.4%
	PT/UT-HCC	30	80.0%	61.4%-92.3%
	No HCC	570	91.9%	89.4%-94.0%
SOF/SMV ± RBV	CT-HCC	26	76.9%	56.4%-91.0%
	PT/UT-HCC	19	73.7%	48.8%-90.9%
	No HCC	321	83.8%	79.3%-87.7%
SOF/DCV ± RBV	CT-HCC	12	100.0%	73.5%-100.0%
	PT/UT-HCC	14	78.6%	49.2%-95.3%
	No HCC	134	88.1%	81.3%-93.0%
LDV/SOF ± RBV	CT-HCC	34	85.3%	68.9%-95.0%
	PT/UT-HCC	22	81.8%	59.7%-94.8%
	No HCC	593	93.1%	90.7%-95.0%
Albumin < 3.5	CT-HCC	44	81.8%	67.3%-91.8%
	PT/UT-HCC	28	78.6%	59.0%-91.7%
	No HCC	414	83.6%	79.6%-87.0%
TBIL ≤ 1.2	CT-HCC	58	87.9%	76.7%-95.0%
	PT/UT-HCC	39	87.2%	72.6%-95.7%
	No HCC	828	94.0%	92.1%-95.5%
TBIL > 1.2	CT-HCC	31	74.2%	55.4%-88.1%
	PT/UT-HCC	24	70.8%	48.9%-87.4%
	No HCC	390	84.6%	80.6%-88.1%
MELD < 10	CT-HCC	49	91.8%	80.4%-97.7%
	PT/UT-HCC	33	78.8%	61.1%-91.0%
	No HCC	618	93.2%	90.9%-95.1%

TABLE 2. *Continued*

	HCC Category	Subgroup (n)	SVR	95% CI
MELD ≥ 10	CT-HCC	31	67.7%	48.6%-83.3%
	PT/UT-HCC	20	80.0%	56.3%-94.3%
	No HCC	399	86.2%	82.4%-86.2%
PLT < 100,000	CT-HCC	50	88.0%	75.7%-95.5%
	PT/UT-HCC	42	81.0%	65.9%-91.4%
	No HCC	604	87.4%	84.5%-90.0%
PLT ≥ 100,000	CT-HCC	41	78.1%	62.4%-89.4%
	PT/UT-HCC	24	79.2%	57.8%-92.9%
	No HCC	696	94.1%	92.1%-95.7%

Abbreviations: DCV, daclatasvir; Decomp, decompensation; LDV, ledipasvir; PLT, platelets; SMV, simeprevir; SOF, sofosbuvir; TBIL, total bilirubin; and Tx, treatment.

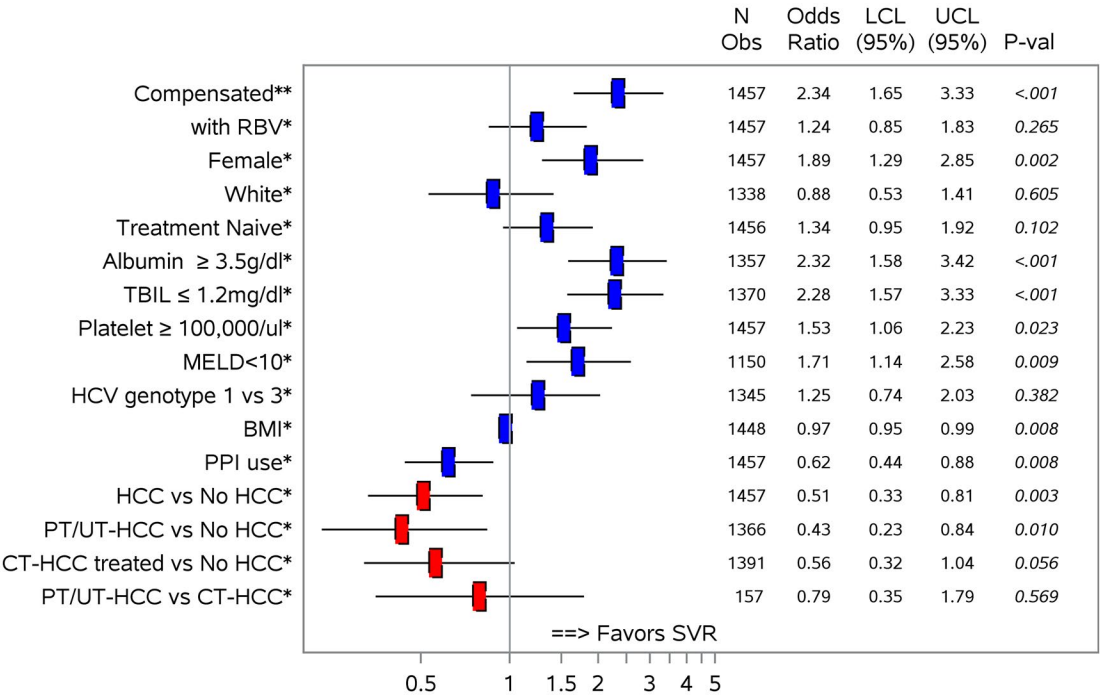

FIG. 3. Multivariable predictors of SVR. **Estimated with Firth's univariate logistic regression. *Estimated with Firth's logistic regression, adjusted for decompensation. Abbreviations: LCL, lower confidence level; N Obs, number of observations; TBIL, total bilirubin; UCL, upper confidence level.

An absence of either history of decompensated cirrhosis or low MELD score (<10) were associated with higher SVR rates. For patients with no HCC, CT-HCC and PT/UT-HCC, the rates of SVR were 86.3% (95% CI: 83.0-89.2), 84.9% (95% CI: 72.4-93.3), and 73.5% (95% CI: 55.6-87.1) for those with decompensated cirrhosis versus 94.0% (95% CI: 92.1-95.6), 81.6% (95% CI: 65.7-92.3), and 87.5% (95% CI: 71.0-96.5) for those with compensated cirrhosis and 86.2% (95% CI: 82.4-86.2), 67.7% (95% CI: 48.6-83.3), and 80.0% (95% CI: 56.3-94.3) for those with MELD ≥ 10 versus 93.2% (95% CI: 90.9-95.1), 91.8% (95%CI: 80.4-97.7) and 78.8% (95% CI: 61.1-91.0) for those with MELD < 10.

MINIMALLY ADJUSTED MODELS PREDICTING SVR

In logistic regression models that were adjusted for history of decompensation, the presence of HCC was associated with significantly lower odds of achieving SVR than not having HCC (OR = 0.51, 95% CI: 0.33-0.81; *P* = 0.003). PPI use (OR = 0.62, 95% CI: 0.44-0.88; *P* = 0.008), lower baseline MELD (<10) (OR = 1.71, 95% CI: 1.14-2.58; *P* = 0.009), lower baseline total bilirubin (OR = 2.28, 95% CI: 1.57-3.33; *P* < 0.001), higher baseline albumin (OR = 2.32, 95% CI: 1.58-3.42; *P* < 0.001), higher baseline platelet count (OR = 1.53, 95% CI: 1.06-2.23; *P* = 0.023), and female sex (OR = 1.89, 95% CI: 1.29-2.85; *P* = 0.002) were associated with SVR in the per protocol population. RBV was not associated with SVR (OR = 1.24, 95% CI: 0.85-1.83; *P* = 0.265) (Fig. 3). However, among those with HCC, HCC treatment status (PT/UT-HCC versus CT-HCC) did not show an association with SVR (OR = 0.79, 95% CI: 0.35-1.79; *P* = 0.569). Lower baseline MELD (<10) (OR = 2.57, 95% CI: 1.02-6.66; *P* = 0.048), lower baseline total bilirubin (OR = 2.76, 95% CI: 1.13-6.94; *P* = 0.028), and no PPI use (OR = 1.86, 95% CI: 1.32-2.63; *P* = 0.0004) were associated with SVR among those with HCC (data not shown).

Sensitivity analyses were also performed, including the patients who discontinued treatment early due to AE as well as patients who received liver transplant during DAA therapy or during the 12 weeks of follow-up (n = 1,430). The logistic regression models adjusted for decompensation showed that the presence of HCC was associated with significantly lower odds of achieving SVR than not having HCC (OR = 0.51, 95% CI: 0.34-0.81; *P* = 0.003) but HCC treatment status (PT/UT-HCC versus CT-HCC) was not associated with SVR (OR = 0.91, 95% CI: 0.42-1.99; *P* = 0.82) (Supporting Fig. S1).

Discussion

The treatment of patients with HCV and cirrhosis yields many benefits, but those patients who also have HCC present some complexities in terms of the decision to treat. While there has been controversy surrounding the effect of DAA therapy on HCC occurrence or recurrence, here we focus on the important issue of timing of HCV treatment in the presence of HCC. In a large real-world cohort, we have demonstrated that HCC is associated with a 50% lower likelihood of achieving SVR than in those patients with no HCC, but whether the HCC was "active" or treated did not influence SVR rates. The clinical implications of these results are 2-fold. First, patients and providers need to set expectations for SVR at a lower level in patients with HCC. Second, there is no need to delay HCV treatment until the HCC is treated, as the efficacy of DAA therapy is not affected by whether HCC has been treated.

We found an absolute difference in SVR rates of 9% among those with and without HCC. This differential is similar to the single-center report from Northwestern University[11] but substantially less than that reported by in the national Veterans Affairs study, in which the SVR rates for patients with HCC was 74% and for non-HCC patients was 91%.[10] The larger differential seen in the VA study may relate to their inclusion of patients receiving suboptimal regimens, namely, sofosbuvir and RBV for genotypes 2 and 3. In our study, such patients were excluded. Thus, when considering HCV treatment in patients with HCC, the modestly lower SVR rate is yet another factor that needs to be taken into consideration and may be especially relevant for transplant candidates who might benefit from deferral of therapy until after transplant, when higher SVR rates can be obtained.[16]

Why the presence or history of HCC influences the likelihood of achieving SVR is unknown. One proposed mechanism is that tumor cells serve as a sanctuary site for HCV. It has previously been demonstrated that HCV is able to replicate within tumor tissue in patients with HCC.[17-19] Because the uptake and intracellular effects of antiviral drugs by tumor cells is likely different from normal hepatocytes, it follows that HCV within tumor cells may evade the antiviral effects of DAA therapy. A second mechanism is related to the altered tumor microenvironment that may promote viral replication even outside of tumor cells. Specifically, HCV-infected HCC cells have been associated with alterations in signaling pathways, leading to increased tumor size, proliferation, and invasiveness.[20-22] The surrounding matrix changes, consisting of a myriad of cell types including immune and inflammatory cells,[23-25] and may alter the antiviral efficacy of DAA therapy. Furthermore, the underlying liver injury that predisposed the

patient to HCC may result in a relative deficiency in local immune function, which similarly may alter the efficacy of DAA therapy even after CT-HCC. Finally, the highly vascular nature of HCC may affect drug distribution within the liver. If drug concentrations are highly concentrated in the arterially supplied tumor, this could lead to reduced drug exposure and concentrations elsewhere in the liver.

Importantly, we found no difference in the likelihood of achieving SVR in patients with PT/UT-HCC (referred to as "active" in other studies) versus CT-HCC. These findings contrast with a previous single-center study from Prenner et al., in which the SVR rate was only 46% (27 of 59) in those with cirrhosis and active HCC versus 100% (18 of 18) in patients with inactive HCC.[11] The striking difference is possibly related to differences in baseline characteristics of the study populations, how HCC treatment response was ascertained, and the efficacy of the DAAs used. For example, we used radiologic criteria to define treatment response, typical of clinical practice, whereas explant pathology was used to define active tumor among those that went to liver transplant in the study from Prenner et al.[11] Additionally, we had a higher proportion of patients with decompensated cirrhosis in our study (41.1%), leading us to adjust for history of decompensation given the well-established relationship between decompensated cirrhosis and SVR rates. We also excluded patients treated with sofosbuvir and RBV, as SVR rates are clearly suboptimal with this combination. Thus, comparisons across studies are difficult. However, our larger, multicenter cohort should provide reassurance to clinicians that whether the HCC has been completely treated is not a major issue; rather, it is the presence of HCC *per se* that influences SVR rates. That said, because HCC treatment response often dictates the longer-term outcomes of patients with HCC, many clinicians prioritize HCC treatment and reserve HCV treatment until response to HCC treatment is known.

A history of decompensation as well as baseline features associated with current decompensation (low albumin, elevated bilirubin) were associated with lower SVR rates. PPI use was also associated with lower SVR rates, an effect independent of the type of DAA therapy. In patients with history of HCC, those not on PPI had a nearly 3-fold-higher odds of SVR than those who were on PPI. The importance of PPI use has been highlighted in previous studies.[26,27] With the goal of maximizing SVR rates in patients with HCV and liver cancer, providers should consider withdrawal of PPI in patients without clear indication for use.

Limitations are similar to those of any study with observational design, in that the treatment of HCV and HCC were not standardized and the assessments of HCC treatment response are based on information within imaging reports. However, the rigor of data collection is high with the use of a centralized team of trained coders that reviews all redacted medical records and systematically monitors for completeness and accuracy. Furthermore, some of the treatment regimens used during the study period are no longer commonly used. To minimize bias related to low-efficacy regimens while simultaneously maximizing the number of study participants, we chose to include all regimens that were associated with SVR rates of at least 80%. Using this criterion, patients receiving sofosbuvir and RBV therapy were excluded. Finally, as observational data, the ascertainment of HCC and response to HCC therapy may be influenced by imaging modality used for screening and site expertise with HCC management. However, only patients with imaging before DAA therapy were included, and we used a window of 6 months prior to 2 months after DAA to capture HCC status.

In conclusion, we have demonstrated that the presence of HCC reduces the likelihood of SVR by 50%, with no evident difference in those with CT-HCC versus PT/UT-HCC. This information will assist patients and providers in discussion on the risks, benefits, and optimal timing of treatment of HCV in this clinical setting.

REFERENCES

1) Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS Jr., et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology 2015;149:649-659.
2) Foster GR, Irving WL, Cheung MC, Walker AJ, Hudson BE, Verma S, et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016;64:1224-1231.
3) Lim JK, Liapakis AM, Shiffman ML, Lok AS, Zeuzem S, Terrault NA, et al. Safety and Effectiveness of ledipasvir and sofosbuvir, with or without ribavirin, in treatment-experienced patients with genotype 1 hepatitis C virus infection and cirrhosis. Clin Gastroenterol Hepatol 2018;16:1811-1819.
4) Manns M, Samuel D, Gane EJ, Mutimer D, McCaughan G, Buti M, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. Lancet Infect Dis 2016;16:685-697.

5) Reddy KR, Lim JK, Kuo A, Di Bisceglie AM, Galati JS, Morelli G, et al. All-oral direct-acting antiviral therapy in HCV-advanced liver disease is effective in real-world practice: observations through HCV-TARGET database. Aliment Pharmacol Ther 2017;45:115-126.
6) Welzel TM, Petersen J, Herzer K, Ferenci P, Gschwantler M, Wedemeyer H, et al. Daclatasvir plus sofosbuvir, with or without ribavirin, achieved high sustained virological response rates in patients with HCV infection and advanced liver disease in a real-world cohort. Gut 2016;65:1861-1870.
7) Reig M, Marino Z, Perello C, Inarrairaegui M, Ribeiro A, Lens S, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol 2016;65:719-726.
8) Cabibbo G, Petta S, Calvaruso V, Cacciola I, Cannavo MR, Madonia S, et al. Is early recurrence of hepatocellular carcinoma in HCV cirrhotic patients affected by treatment with direct-acting antivirals? A prospective multicentre study. Aliment Pharmacol Ther 2017;46:688-695.
9) Waziry R, Hajarizadeh B, Grebely J, Amin J, Law M, Danta M, et al. Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: a systematic review, meta-analyses, and meta-regression. J Hepatol 2017;67:1204-1212.
10) Beste LA, Green PK, Berry K, Kogut MJ, Allison SK, Ioannou GN. Effectiveness of hepatitis C antiviral treatment in a USA cohort of veteran patients with hepatocellular carcinoma. J Hepatol 2017;67:32-39.
11) Prenner SB, VanWagner LB, Flamm SL, Salem R, Lewandowski RJ, Kulik L. Hepatocellular carcinoma decreases the chance of successful hepatitis C virus therapy with direct-acting antivirals. J Hepatol 2017;66:1173-1181.
12) Gordon SC, Muir AJ, Lim JK, Pearlman B, Argo CK, Ramani A, et al. Safety profile of boceprevir and telaprevir in chronic hepatitis C: real world experience from HCV-TARGET. J Hepatol 2015;62:286-293.
13) Sulkowski MS, Vargas HE, Di Bisceglie AM, Kuo A, Reddy KR, Lim JK, et al. Effectiveness of simeprevir plus sofosbuvir, with or without ribavirin, in real-world patients with HCV genotype 1 infection. Gastroenterology 2016;150:419-429.
14) Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377-381.
15) Firth D. Bias reduction of maximum likelihood estimates. Biometrika 1993;80:27-38.
16) **Saxena V**, **Khungar V**, Verna EC, Levitsky J, Brown RS Jr., Hassan MA, et al. Safety and efficacy of current direct-acting antiviral regimens in kidney and liver transplant recipients with hepatitis C: results from the HCV-TARGET study. Hepatology 2017;66:1090-1101.
17) Chou WH, Yoneyama T, Takeuchi K, Harada H, Saito I, Miyamura T. Discrimination of hepatitis C virus in liver tissues from different patients with hepatocellular carcinomas by direct nucleotide sequencing of amplified cDNA of the viral genome. J Clin Microbiol 1991;29:2860-2864.
18) Gerber MA, Shieh YS, Shim KS, Thung SN, Demetris AJ, Schwartz M, et al. Detection of replicative hepatitis C virus sequences in hepatocellular carcinoma. Am J Pathol 1992;141: 1271-1277.
19) Niu J, Kumar U, Monjardino J, Goldin R, Rosin D, Thomas HC. Hepatitis C virus replication in hepatocellular carcinoma. J Clin Pathol 1995;48:880-882.
20) Chen JS, Wang Q, Fu XH, Huang XH, Chen XL, Cao LQ, et al. Involvement of PI3K/PTEN/AKT/mTOR pathway in invasion and metastasis in hepatocellular carcinoma: association with MMP-9. Hepatol Res 2009;39:177-186.
21) Schmitz KJ, Wohlschlaeger J, Lang H, Sotiropoulos GC, Malago M, Steveling K, et al. Activation of the ERK and AKT signalling pathway predicts poor prognosis in hepatocellular carcinoma and ERK activation in cancer tissue is associated with hepatitis C virus infection. J Hepatol 2008;48:83-90.
22) Tahmasebi Birgani M, Carloni V. Tumor microenvironment, a paradigm in hepatocellular carcinoma progression and therapy. Int J Mol Sci 2017;18:405.
23) Chen F, Zhuang X, Lin L, Yu P, Wang Y, Shi Y, et al. New horizons in tumor microenvironment biology: challenges and opportunities. BMC Med 2015;13:45.
24) Shimoda M, Mellody KT, Orimo A. Carcinoma-associated fibroblasts are a rate-limiting determinant for tumour progression. Semin Cell Dev Biol 2010;21:19-25.
25) Singh SR, Rameshwar P, Siegel P. Targeting tumor microenvironment in cancer therapy. Cancer Lett 2016;380:203-204.
26) Terrault NA, Zeuzem S, Di Bisceglie AM, Lim JK, Pockros PJ, Frazier LM, et al. Effectiveness of ledipasvir-sofosbuvir combination in patients with hepatitis C virus infection and factors associated with sustained virologic response. Gastroenterology 2016;151:1131-1140, e5.
27) Tapper EB, Bacon BR, Curry MP, Dieterich DT, Flamm SL, Guest LE, et al. Evaluation of proton pump inhibitor use on treatment outcomes with ledipasvir and sofosbuvir in a real-world cohort study. Hepatology 2016;64:1893-1899.

Author names in bold designate shared co-first authorship.

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