HEPATOLOGY

HEPATOLOGY, VOL. 71, NO. 6, 2020

Cure With Interferon-Free Direct-Acting Antiviral Is Associated With Increased Survival in Patients With Hepatitis C Virus-Related Hepatocellular Carcinoma From Both East and West

Hansen Dang,[1,2*] Yee Hui Yeo,[1*] Satoshi Yasuda,[3] Chung-Feng Huang,[4] Etsuko Iio,[5] Charles Landis,[6] Dae Won Jun,[7] Masaru Enomoto,[8] Eiichi Ogawa,[9] Pei-Chien Tsai,[4] An Le,[1] Matthew Liu,[6] Mayumi Maeda,[1] Brian Nguyen,[1] Nathan Ramrakhiani,[1] Linda Henry,[1] Ramsey Cheung,[1,10] Akihiro Tamori,[8] Takashi Kumada,[3] Yasuhito Tanaka,[5] Ming-Lung Yu,[4] Hidenori Toyoda,[3] and Mindie H. Nguyen[1]

BACKGROUND AND AIMS: Survival data among patients with hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC) after achieving sustained virologic response (SVR) with interferon-free direct-acting antivirals (DAAs) in both Asian and western countries are limited. Survival rates were compared between patients with HCV-related HCC who were untreated for HCV and those who achieved SVR.

APPROACH AND RESULTS: Using data from two U.S. and six Asian centers from 2005 to 2017, we categorized 1,676 patients who were mono-infected with HCV-related HCC into patients untreated for HCV (untreated group) and DAA-treated patients with SVR (SVR group) and matched by propensity score matching (PSM); multivariable Cox regression with HCV treatment status as a time-varying covariate was used to determine mortality risk and landmark analysis to avoid immortal time bias. There were 1,239 untreated patients and 437 patients with SVR. After PSM, background risks of the 321 pairs of matched patients were balanced (all $P > 0.05$). After time-varying adjustment for HCV treatment initiation compared with untreated patients, patients with SVR had significantly higher 5-year overall survival (87.78% vs. 66.05%, $P < 0.001$). Multivariable Cox regression showed that SVR was independently associated with a 63% lower risk of 5-year all-cause mortality (hazard ratio [HR], 0.37; 95% confidence interval [CI], 0.16-0.83; $P = 0.016$) and 66% lower risk of 5-year liver-related mortality (HR, 0.34; 95% CI, 0.13-0.88; $P = 0.026$) with similar trends after removing patients with liver transplants. Landmark analysis at 90, 180, and 360 days showed consistent results (HRs ranged 0.22 to 0.44, all $P < 0.05$).

CONCLUSION: In this multinational consortium, patients with HCV-related HCC who obtained SVR achieved a 60%-70% improvement in 5-year survival (both all-cause and liver related) compared with patients untreated for HCV. Patients eligible for HCC therapy should also be considered for DAA therapy. (Hepatology 2020;71:1910-1922).

Hepatitis C virus (HCV) affects 71.1 million patients worldwide, including 3.2 million infected persons in the United States and 10.5 million infected persons in East Asia.[1,2] HCV is also a leading cause of chronic liver disease and hepatocellular carcinoma (HCC) in the United States and globally.[3,4] In 2015, there were 854,000 incident

Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CTP, Child-Turcotte-Pugh; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; IFN, interferon; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; OS, overall survival; PSM, propensity score matching; SVR, sustained virological response.

Received August 6, 2019; accepted September 27, 2019.

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.30988/suppinfo.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the appropriate institutional review committee, which also included patients' consent waivers at each participating study center.

**These authors contributed equally to this work.*

HCC cases worldwide.[5] In the United States, the HCV-related HCC burden has also increased between 1990 and 2015.[6]

Unfortunately, despite technological and therapeutic advances, HCC is one of the few cancers with an increasing incidence and a dismal 5-year survival rate of only 18.1%, according to a 2017 report.[7] Indeed, recent advances in systemic palliative therapies for HCC reported only a modest survival advantage from palliative treatment, with a median overall survival (OS) of about 10-13 months in treated patients compared with 7-8 months in placebo groups.[8]

As a result, efforts geared toward prevention have been identified as the most effective method to reverse this increasing trend. The Global Burden of Disease Liver Cancer Collaboration stated that most cases of liver cancer can be prevented through various therapies, including antiviral treatment for HCC associated with viral diseases.[6] For HCV, the recent advent of interferon (IFN)-free direct-acting antivirals (DAAs) has introduced highly effective (>80%-90% cure rate) and well-tolerated treatment, even for patients with advanced liver disease, including HCC.[9-14] It has been shown to reduce HCC risk and does not increase the risk of HCC recurrence.[11,15-17] Furthermore, HCV cure with DAA therapies is associated with improved survival to include those with advanced disease, such as cirrhosis.[18,19] Recently, investigators reported that patients with HCV-induced cirrhosis who had been successfully treated for HCC in its early stages obtained a significant improvement in their OS following treatment with the new DAA treatment regimens.[20] However, with a cohort of 163 patients who achieved sustained virological response (SVR) that only included those with early stages of HCC, the question remains how treatment with DAAs affects survival in a multinational group of patients with HCV at all different stages of HCC who received either curative or palliative treatment for their HCC. Therefore, the purpose of this study was to determine the effect of DAA treatment on overall and liver-related mortality among persons with HCV and HCC who received either palliative or curative HCC treatment using data from Asia and North America.

View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep.30988

Potential conflict of interest: Dr. Landis has received research support from Pfizer, Gilead Sciences, AbbVie, Bristol-Myers Squibb, and Intercept. Dr. Cheung has received research support from Gilead Sciences. Dr. Kumada has received lecturer fees from Gilead Sciences and Bristol-Meyers Squibb. Dr. Tanaka has received research support from Bristol-Myers Squibb and Chugai Pharmaceutical Ci., Ltd, and has served as an advisory board member as well as a speaker for Gilead. Dr. Yu has received research support from Bristol-Myers Squibb, Gilead Sciences, and Merck Sharp & Dohme, has served as an advisory board member or consultant for AbbVie, Bristol-Myers Squibb, Gilead Sciences, and Merck Sharp & Dohme, and has served as a speaker for AbbVie, Bristol-Myers Squibb, Gilead Sciences, and Merck Sharp & Dohme. Dr. Toyoda has served as a speaker for Merck Sharp & Dohme and Abbvie; Dr. M. H. Nguyen has received research support from Pfizer, Gilead Sciences, Janssen Pharmaceutical, B. K. Kee Foundation, and the National Cancer Institute and has served as an advisory board member or consultant for Dynavax, Gilead, Intercept, Alnylam, Bristol-Myers Squibb, Novartis, Eisai, Bayer, Exact Science, Laboratory of Advanced Medicine, Spring Bank, and Janssen.

ARTICLE INFORMATION:

From the [1]Division of Gastroenterology and Hepatology, Department of Medicine, Stanford University Medical Center, Palo Alto, CA; [2]University of California, Davis, Davis, CA; [3]Department of Gastroenterology, Ogaki Municipal Hospital, Ogaki, Japan; [4]Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [5]Department of Virology and Liver Unit, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; [6]Department of Gastroenterology, University of Washington Medical Center, Seattle, WA; [7]Department of Gastroenterology, Hanyang University, Seoul, South Korea; [8]Department of Hepatology, Osaka City University Graduate School of Medicine, Osaka, Japan; [9]Department of General Internal Medicine, Kyushu University Hospital, Fukuoka, Japan; [10]Division of Gastroenterology and Hepatology, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS:

Mindie H. Nguyen
Division of GI, Hepatology, & Liver Transplant
Stanford University Medical Center
780 Welch Rd., CJ250K
Palo Alto, CA, 94304
E-mail: mindiehn@stanford.edu
Tel.: +1 650 498-6094

or
Hidenori Toyoda
Department of Gastroenterology, Ogaki Municipal Hospital
4-86 Minaminokawa
Ogaki, Gifu 503-8502, Japan
E-mail: hmtoyoda@spice.ocn.ne.jp
Tel.: +81 584 81 3341

Patients and Methods

STUDY DESIGN AND PATIENT POPULATION

This was a retrospective cohort study of patients with HCV-related HCC seen at eight medical centers in the United States, Japan, South Korea, and Taiwan between 2005 and 2017 (Supporting Appendix S1). The study protocol was approved by the Institutional Review Board at each site.

Patients were identified through institutional databases with subsequent individual chart review for relevant clinical, laboratory, pathology, pharmacy, and imaging data. We included patients who were confirmed to have HCV infection and HCC. Patients were excluded if they were under 18 years of age, were coinfected with human immunodeficiency or hepatitis B virus, achieved HCV cure through SVR more than 6 months before HCC diagnosis, did not receive treatment for HCC, or had non-HCC cancers.

Patients were categorized into two groups: (1) the untreated for HCV group, who were patients with HCC who had never received antiviral therapy for HCV, and (2) the SVR group, who were patients with HCC who achieved SVR with IFN-free DAAs after HCC diagnosis. All mortality-related data were obtained from medical record review and were supplemented by a National Death Index query for U.S. patients.

To balance the two study groups (patients untreated for HCV and patients with SVR), propensity score matching (PSM), including age, sex, study country/region (United States vs. Asia), cirrhosis status, alpha-fetoprotein (AFP), albumin-bilirubin (ALBI) score, HCV treatment status, Milan criteria eligibility, and HCC treatment, was performed. It is important to note that we chose to use Milan criteria for PSM as it is a clinically meaningful indicator for tumor burden and allows for better matching than size or number of tumors alone because of arbitrary set points.[21] We also matched on the ALBI score rather than Child-Turcotte-Pugh (CTP) score, as it is now recognized as providing better prognostic performance in survival analysis.[22]

DEFINITIONS

HCV diagnoses were determined by positive HCV RNA PCR or HCV antibody tests, a history of anti-HCV therapy, or a documented history of HCV from physicians' notes. Cirrhosis diagnoses were determined by the presence of fibrosis stage 4, nodular contour, ascites, encephalopathy, splenomegaly, esophageal varices, other varices, or platelets <120,000/mL in either physician notes, laboratory records, radiology reports, endoscopy, or pathology reports. HCC diagnoses were confirmed through radiology or pathology reports based on the American Association for the Study of Liver Diseases diagnosis guidelines.[23] SVR was determined by the confirmation of undetectable HCV RNA (limit of detection of 25 IU/mL) 12 weeks after the treatment end date. HCC treatment groups included the curative group (liver transplant, surgical resection, or radiofrequency ablation with curative intent) and palliative group (transarterial chemoembolization or sorafenib).

STATISTICAL ANALYSIS

Descriptive statistics were reported as proportions (%) for categorical variables and mean ± SD or median (interquartile ranges [IQRs]) for continuous variables. Analyses of normally distributed continuous variables were performed using Student *t* tests. Analyses of non-normally distributed continuous variables were performed using the Kruskal-Wallis test. The chi-squared test was performed for the comparison of normally distributed categorical variables, whereas Fischer's exact test was used for non-normally distributed categorical variables.

In PSM analysis, we used logistic regression to estimate the probability of a patient to be in the SVR group and generated a propensity score for each patient. Caliper matching on the propensity score was performed, and pairs were matched to within a range of 0.25 of the standard deviation of the logit of the propensity score. To avoid bias because of no HCC treatment, patients who did not receive treatment for HCC were not included before PSM.

We assigned DAA treatment as a time-varying covariate by setting the period between the HCC diagnosis date and DAA treatment initiation date as the unexposed period and the period after DAA treatment initiation date as the exposed period. Follow-up periods were defined by the date of HCC diagnosis until the date of death, date of last follow-up, or study end date of each study site, whichever came first (Fig. 1B). Person-years of follow-up were calculated by

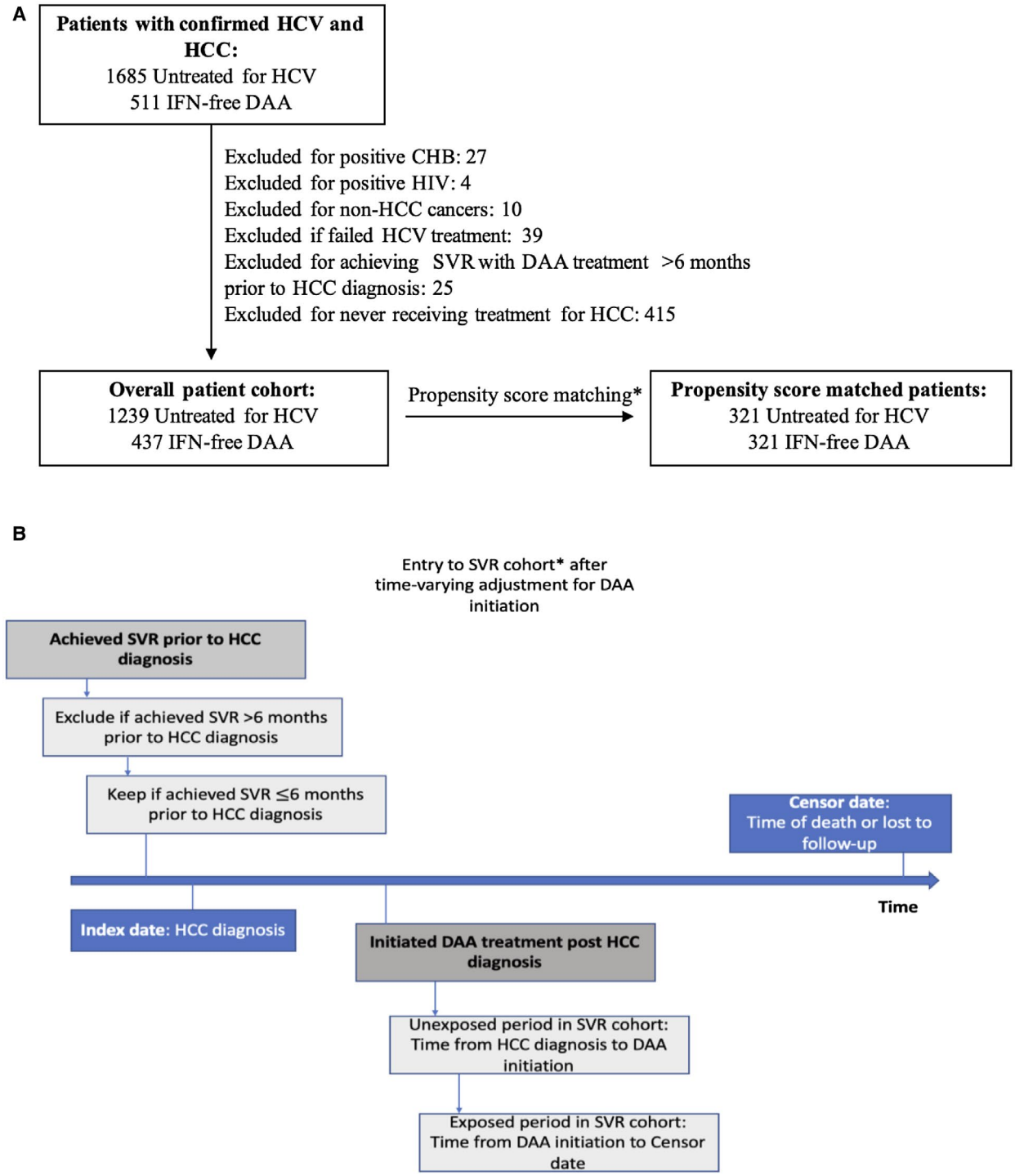

FIG. 1. (A) Flow chart of patient selection in study analysis; (B) SVR cohort entry of propensity score-matched patients with time-varying adjustment for HCV treatment status. *Propensity score matched on the following variables: age, sex, study country (United States vs. Asia), cirrhosis status, ALBI, HCV treatment status, Milan criteria eligibility, HCC treatment, and AFP. CHB, chronic hepatitis B; HIV, human immunodeficiency virus.

multiplying the number of patients by the mean follow-up period. Mortality rates were reported as rates per 1,000 person-years and annual incidence rates. We used Kaplan-Meier methods with time-varying adjustment to assess the 5-year cumulative survival and log-rank tests to compare between group survival

rates. Survival rates were further stratified by age, CTP class, Barcelona Clinic Liver Cancer (BCLC) stage, and type of HCC treatment.

We performed univariable and multivariable Cox proportional hazards regression to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs), relating background characteristics and HCV treatment status to survival outcomes. The selection of variables in the multivariable model was based on previous clinical and research experience. When checking for interactions, a significant interaction between BCLC stage and age was found. We incorporated the interaction term into the model. Cox-Snell residuals were plotted to examine the fitness of the model. The proportionality assumption was not violated. To address various potential biases inherent in observational study design, we performed several sensitivity analyses, including landmark analysis, exclusion of non-liver-related death, full cohort (before PSM) analysis, and estimation of E value. First, to mitigate the immortal and indication bias, we performed landmark analyses at 90, 120, 180, 250, and 360 days. Second, we excluded all patients with non-liver-related deaths, considering potential bias because of cause of death. Third, we evaluated the association between DAA-induced SVR in the overall cohort (1,239 patients untreated for HCV and 437 patients with SVR). Last, to determine the potential confounding from unmeasured factors, we estimated the E value, which represents the smallest effect between an unmeasured confounder and both exposure (SVR) and outcome (mortality) to explain away their observed association. The higher the E value, the lower the possibility of an unmeasured confounder. All data analyses were performed using Stata (V.14.2), and statistical significance was defined as a two-sided P value of <0.05.

Results

BASELINE, TUMOR, AND CANCER TREATMENT CHARACTERISTICS IN OVERALL COHORT

We included 2,196 adult patients with HCV and HCC diagnoses (untreated for HCV: 1,685; and IFN-free DAAs, both SVR and non-SVR: 511) in this study (Fig. 1A). After excluding patients who were ineligible, 1,676 patients (untreated: 1,239; SVR: 437) were analyzed for baseline and tumor characteristics.

The baseline demographic characteristics of the two study groups were similar, but several liver-related characteristics, including albumin, total bilirubin, CTP, Model for End-Stage Liver Disease (MELD), hepatic decompensation, and ALBI, were significantly different (Supporting Table S1). The median time to DAA treatment from HCC diagnosis was 18 months (range: 6-43 months).

Supporting Table S2 displays HCC tumor characteristics. Compared with patients with SVR, untreated patients had higher AFP levels, larger tumor sizes, a greater proportion with metastases or multiple tumors (four or more), and a lower proportion meeting Milan criteria for transplantation or receiving curative treatment.

BASELINE AND TUMOR CHARACTERISTICS OF PROPENSITY SCORE-MATCHED PATIENTS

After PSM, the baseline and tumor characteristics of the 321 pairs of matched patients from the two study groups (321 untreated for HCV and 321 SVR) were similar (Table 1). The average age was 66 years, and over 60% were male. The majority had cirrhosis (80%), were CTP class A (68%), and received curative treatment (70%).

DEATH INCIDENCE AND OS

Table 2A displays the all-cause mortality rates between the two PSM study groups after adjustment for the HCV treatment start date in the SVR group. The annual incidence of mortality for the untreated group was 7.70% (95% CI: 6.40-9.27) versus 2.38% (95% CI: 1.28-4.43) for the SVR group. The median survival (IQR) for the SVR group was 44.32 (26.43-71.18) months, about 18 months longer than the median of the untreated group (26.09 [15.29-50.60] months). Among those receiving only palliative treatment for HCC, the median survival (IQR) for the SVR group was approximately 8 months longer than those of untreated patients (27.39 [16.01-53.57] vs. 19.66 [11.51-36.10]). Table 2B displays the liver-related mortality rates. The annual incidence of liver-related mortality for the untreated group was 7.02% (95% CI: 5.76-8.57) compared with 1.46% (95% CI: 0.66-3.25) for the SVR group. As noted in Fig. 2A,

TABLE 1. Baseline and Tumor Characteristics of Propensity Score-Matched Patients

Characteristics	Untreated for HCV (n = 321)	SVR (n = 321)	*P* Value
Age	65.92 ± 9.13	66.39 ± 9.09	0.52
Male	194 (60.44)	197 (61.37)	0.81
Body mass index (kg/m^2) (n = 533)	24.59 ± 4.41	24.87 ± 5.06	0.50
Race/Ethnicity			
Non-Asian	108 (33.64)	100 (31.15)	0.50
Asian	213 (66.36)	221 (68.85)	
Country			
United States	139 (43.30)	130 (40.50)	0.47
Asia	182 (56.70)	191 (59.50)	
Median follow-up (months)	26.09 (15.29-50.60)	44.32 (26.43-71.18)	<0.001
Diabetes mellitus (n = 612)	80 (26.58)	98 (31.51)	0.18
AFP ($\log_{10}$ ng/mL)	1.35 ± 0.86	1.39 ± 0.74	0.61
CTP class (n = 494)			
A	167 (68.44)	168 (67.20)	0.79
B	66 (27.05)	73 (29.20)	
C	11 (4.51)	9 (3.60)	
Median MELD score (n = 491)	8.41 (6.87-10.64)	8.47 (7.34-10.71)	0.26
ALBI grade			
1	100 (31.15)	102 (31.78)	0.91
2	191 (59.50)	192 (59.81)	
3	30 (9.35)	27 (8.41)	
Cirrhosis	265 (82.55)	262 (81.62)	0.76
BCLC stage (n = 588)			
0/A	209 (72.57)	239 (79.67)	0.13
B	45 (15.62)	35 (11.67)	
C/D	34 (11.81)	26 (8.67)	
Milan	248 (77.26)	259 (80.69)	0.29
HCC treatment			
Palliative treatment*	97 (30.22)	92 (28.66)	0.67
Curative treatment†	224 (69.78)	229 (71.34)	
Time between HCC diagnosis and DAA treatment initiation (months)	—	18.90 (5.98-46.75)	

Note: Continuous variables are presented as mean ± SD or median (IQR) and categorical variables are presented as n (%). Patients were propensity score matched using the caliper method on the following variables: age, sex, study country (United States vs. Asia), cirrhosis status, ALBI, HCV treatment status, Milan criteria eligibility, HCC treatment, and AFP.
*Palliative treatment: transarterial chemoembolization or sorafenib.
†Curative treatment: liver transplant, surgical resection, or radiofrequency ablation with curative intent.

TABLE 2. Mortality Rates in Propensity Score-Matched Patients Who Were Untreated for HCV or Had SVR After IFN-Free DAA Treatment, With Time-Varying Adjustment for HCV Treatment Start Time

HCV Treatment Group	Person-Years	Death (n)	Rate per 1,000 Person-Years	Annual Incidence (%)
A. All-Cause Mortality				
Untreated for HCV	1,454.77	112	76.99	7.70 (6.40-9.27)
SVR	419.74	10	23.82	2.38 (1.28-4.43)
B. Liver-Related Mortality				
Untreated for HCV	1,381.30	97	70.22	7.02 (5.76-8.57)
SVR	410.33	6	14.62	1.46 (0.66-3.25)

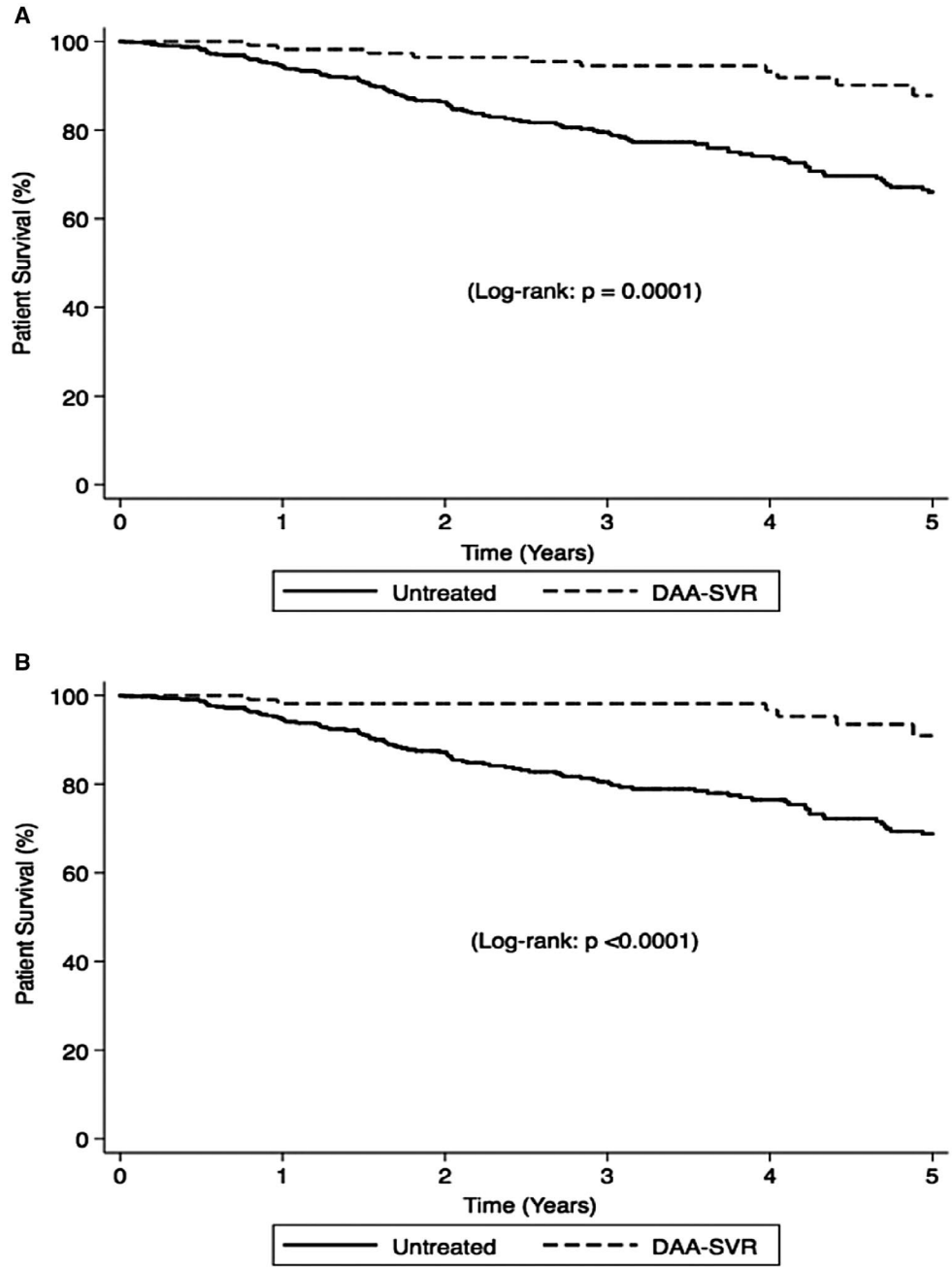

FIG. 2. Five-year survival in propensity score-matched patients who were untreated for HCV or had SVR after IFN-free DAA treatment, with time-varying adjustment for HCV treatment start time. (A) All-cause mortality; (B) liver-related mortality.

there was a significant difference in 5-year survival for all-cause mortality between the untreated and SVR groups ($P = 0.0001$). By year 5, 87.78% of the patients with SVR were still alive compared with only 66.05% of the untreated PSM group. Similar results were observed for the SVR and untreated groups when assessing liver-related mortality (90.90% vs. 68.76%, $P < 0.0001$; Fig. 2B). In liver-related mortality analysis (Supporting Table S3), untreated patients had significantly lower survival rates compared with patients with SVR in all age, cirrhosis/CTP, BCLC, and HCC treatment subgroups, except for the very young group (<50 years old), the noncirrhotic group (or CTP C), and the BCLC B and C/D groups. However, the

sample sizes in all these latter subgroups were very small (patient numbers ranged 9-59). Similar findings were noted in subgroup analyses for all-cause mortality (Supporting Table S3).

PREDICTORS FOR ALL-CAUSE AND LIVER-RELATED MORTALITY AMONG PSM GROUPS

All-Cause Mortality

As shown in Table 3, SVR was associated with a 71% reduction in all-cause mortality in unadjusted analysis (HR, 0.29; 95% CI: 0.15-0.55; $P < 0.001$). After adjusting for age, sex, race/ethnicity, study country/region, diabetes, cirrhosis, MELD scores, HCC diagnosis year, AFP, BCLC stage, and HCC treatment types in the multivariable Cox model, SVR remained significantly and strongly associated with decreased all-cause mortality (adjusted HR, 0.37; 95% CI, 0.16-0.83; $P = 0.016$). Other factors significantly associated with all-cause mortality in multivariable analysis were older age, male sex, Asian ethnicity, higher MELD score, higher AFP levels, higher BCLC stages, and curative HCC treatment (vs. palliative) but not study country/region (United States vs. Asia). The E value for SVR as a predictor of all-cause mortality was at 3.37 (lower 95% CI: 1.53), suggesting that the presence of unmeasured

TABLE 3. Multivariable Analysis for Predictors of All-Cause Mortality in Propensity Score-Matched Patients

Type of Mortality	Unadjusted HR (95% CI)	*P* Value	Adjusted HR* (95% CI)	*P* Value
HCV treatment status				
Untreated for HCV	Referent	Referent	Referent	Referent
SVR	0.29 (0.15-0.55)	**<0.001**	0.37 (0.16-0.83)	**0.016**
Age (per 5-year interval)	0.97 (0.88-1.06)	0.50	1.31 (1.14-1.51)	**<0.001**
Sex				
Female	Referent	Referent	Referent	Referent
Male	1.34 (0.92-1.95)	0.13	1.75 (1.11-2.76)	**0.016**
Race/ethnicity				
Non-Asian	Referent	Referent	Referent	Referent
Asian	0.41 (0.29-0.59)	**<0.001**	0.26 (0.12-0.57)	**0.001**
Diabetes mellitus	0.79 (0.52-1.22)	0.30	0.72 (0.45-1.14)	0.16
Cirrhosis	2.06 (1.11-3.83)	**0.022**	1.59 (0.74-3.41)	0.23
MELD score				
<10	Referent	Referent	Referent	Referent
10-15	0.96 (0.59-1.56)	0.88	0.78 (0.46-1.33)	0.36
≥15	2.52 (1.45-4.39)	**0.001**	2.72 (1.34-5.49)	**0.005**
HCC diagnosis year				
2005-2008	Referent	Referent	Referent	Referent
2009-2013	0.79 (0.54-1.15)	0.21	0.82 (0.53-1.28)	0.39
2014-2017	0.30 (0.16-0.58)	**<0.001**	0.51 (0.22-1.21)	0.13
AFP (log_{10} ng/mL)	1.39 (1.13-1.71)	**0.002**	1.49 (1.19-1.87)	**<0.001**
BCLC stage				
0/A	Referent	Referent	Referent	Referent
B	3.10 (1.98-4.85)	**<0.001**	2.45 (1.49-4.05)	**<0.001**
C/D	3.49 (2.12-5.73)	**<0.001**	2.20 (1.22-3.97)	**0.009**
HCC treatment type				
Palliative	Referent	Referent	Referent	Referent
Curative	0.47 (0.32-0.68)	**<0.001**	0.47 (0.30-0.73)	**0.001**
Country/region				
United States	Referent	Referent	Referent	Referent
Asia	0.44 (0.31-0.63)	**<0.001**	1.61 (0.75-3.48)	0.22

Notes: E value for SVR as a predictor for all-cause mortality: 3.366, (CI) 1.534. The values in bold-face represent significant predictors for all-cause mortality.
*Adjusted for age, sex, race/ethnicity, study country/region, diabetes, cirrhosis, MELD scores, HCC diagnosis year, AFP, BCLC stage, and HCC treatment types.

confounders in the above models was also very unlikely because the confounders would need to be significantly associated with both SVR and mortality with a high strength of association with HR of 3.4.

Liver-Related Mortality

Similar results were noted in the univariable and multivariable Cox proportional hazard model for liver-related mortality (Table 4). We found that there was an interaction between BCLC stage and age in this analysis, so this variation was subsequently adjusted for in the model as shown. The E value for SVR as a predictor of liver-related mortality was 3.60 (lower 95% CI: 1.41).

Sensitivity Analyses

To account for immortal and indication bias, we conducted landmark analyses examining the impact of SVR on mortality at 90, 120, 180, 250, and 360 days (Supporting Table S4). As shown, regardless of the length of time from the initiation of DAA therapy, multivariable Cox regression adjusting for the

TABLE 4. Multivariable Analysis for Predictors of Liver-Related Mortality in Propensity Score-Matched Patients

Type of Mortality	Unadjusted HR (95% CI)	*P* Value	Adjusted HR*,† (95% CI)	*P* Value
HCV treatment status				
Untreated for HCV	Referent	Referent	Referent	Referent
SVR	0.19 (0.08-0.44)	**<0.001**	0.34 (0.13-0.88)	**0.026**
Age (per 5-year interval)	0.96 (0.87-1.07)	0.47	1.25 (1.05-1.48)	**0.014**
Sex				
Female	Referent	Referent	Referent	Referent
Male	1.30 (0.86-1.95)	0.21	1.64 (0.99-2.71)	0.054
Race/ethnicity				
Non-Asian	Referent	Referent	Referent	Referent
Asian	0.36 (0.25-0.54)	**<0.001**	0.22 (0.10-0.51)	**<0.001**
Diabetes mellitus	0.87 (0.55-1.36)	0.54	0.84 (0.51-1.37)	0.48
Cirrhosis	2.79 (1.30-6.02)	**0.009**	1.65 (0.68-3.96)	0.27
MELD score				
<10	Referent	Referent	Referent	Referent
10-15	0.99 (0.59-1.67)	0.98	0.67 (0.38-1.21)	0.18
≥15	2.39 (1.26-4.53)	**0.008**	3.02 (1.39-6.56)	**0.005**
HCC diagnosis year				
2005-2008	Referent	Referent	Referent	Referent
2009-2013	0.82 (0.55-1.23)	0.34	0.75 (0.47-1.19)	0.22
2014-2017	0.18 (0.08-0.43)	**<0.001**	0.31 (0.11-0.87)	**0.026**
AFP (log_{10} ng/mL)	1.48 (1.19-1.84)	**<0.001**	1.54 (1.21-1.95)	**<0.001**
BCLC stage				
0/A	Referent	Referent	Referent	Referent
B	3.46 (2.15-5.58)	**<0.001**	2.74 (0.24-31.44)	0.42
C/D	3.10 (1.75-5.51)	**<0.001**	0.13 (0.01-1.96)	0.14
HCC treatment type				
Palliative	Referent	Referent	Referent	Referent
Curative	0.42 (0.28-0.63)	**<0.001**	0.44 (0.27-0.71)	**0.001**
Country				
United States	Referent	Referent	Referent	Referent
Asia	0.39 (0.26-0.58)	**<0.001**	1.63 (0.69-3.82)	0.26

Notes: E value for SVR treatment as a predictor for liver-related mortality: 3.603, (CI) 1.411. The values in bold-face represent significant predictors for liver-related mortality.
*Adjusted for age, sex, race/ethnicity, study country/region, diabetes, cirrhosis, MELD scores, HCC diagnosis year, AFP, BCLC stage, and HCC treatment types.
†Model for liver-related mortality also adjusted for with a significant interaction for BCLC stage and age (per 5-year interval).

same confounders in the main analysis (Tables 3 and 4) showed similar adjusted HRs, which ranged from 0.22 to 0.44 (all $P < 0.05$) for both all-cause and liver-related mortality. Because of the potential positive effects that liver transplantation can have on survival, we conducted a sensitivity analysis after removing patients who underwent a liver transplantation (n = 89) from the original cohort. After the exclusion, we used PSM to re-match the patients by the same variables and yielded 273 patients per group. As noted in Supporting Table S5, the protective effect of SVR was noted for all-cause mortality (adjusted HR, 0.40; 95% CI, 0.17-0.95; $P = 0.036$), and there was also a trend for a protective effect with liver-related mortality [adjusted HR, 0.43 (0.16-1.15); $P = 0.094$] after controlling for the same confounders in the main analysis. The E values for both models were 3.158 (lower 95% CI, 1.258) and 2.972 (lower 95% CI, 1.000), respectively.

Furthermore, as noted in Supporting Table S6, the protective effect of SVR was also significant and strong in the overall unmatched cohort (1,239 untreated patients and 437 patients with SVR) for both all-cause (adjusted HR, 0.29; 95% CI, 0.17-0.49; $P < 0.001$) and liver-related mortality (adjusted HR, 0.18; 95% CI, 0.08-0.37; $P < 0.001$) after controlling for the same confounders in the main analysis. The E values for both models were 4.08 (lower 95% CI, 2.65) and 5.77 (lower 95% CI, 3.37), respectively.

CAUSE OF DEATH IN PATIENTS WITH SVR AND PATIENTS WITH UNTREATED HCV

In the total cohort, among the 30 patients with SVR who died during follow-up, 18 (60.0%) were due to non-liver-related death. In contrast, the majority (86.4%) of the 559 patients who were untreated for HCV died of liver-related death. The median time of survival from HCC diagnosis was 44.88 months (IQR: 19.46-61.87) in those with SVR and 16.37 months (IQR: 7.59-31.36) in the untreated group.

Discussion

Ongoing controversy surrounding the risks of IFN-free DAAs in patients with HCC continues. Our study clearly provides evidence of the benefits of DAA treatment and the achievement of HCV cure through SVR for patients with HCV, even in those already burdened with HCC.

Using PSM, we demonstrated a superior 5-year survival rate of about 88% for patients with HCV cure compared with 66% in untreated patients. The annual death incidence for patients with SVR was also only about one third that of patients who were without HCV treatment (2.38% vs. 7.70%). Indeed, the difference in the median survival between patients with SVR and untreated patients in our study was about 18 months, a considerable survival difference for HCC, a cancer with an overall 5-year survival of only about 18%. In addition, new systemic therapies for palliative patients only provide a survival benefit for a few months.[5] We also demonstrated that SVR was independently associated with a 60%-70% risk reduction for both all-cause and liver-related death, following appropriate adjustment for various confounders. This survival benefit remained strong and significant through multiple sensitivity analyses. In the sensitivity analysis that removed patients who received liver transplantation, SVR was still significantly associated with about 60% improvement in OS. For liver-related survival, SVR was also associated with about 60% improvement, but this association did not reach a conventional level of statistical significance, likely because of a more limited sample size for this analysis.

These findings indicate that serious consideration should be given to providing IFN-free DAA treatment to all eligible patients, including those with HCC. In fact, our data could be further supported by findings that 60% of the patients with SVR who died in our study actually died of non-liver-related causes, which is also consistent with the fact that the majority of these patients had lower (<10) MELD scores, CTP class A, and small tumors without metastasis. IFN-free DAA treatment should not be withheld from patients with HCC who are eligible for HCC therapies because the improved survival benefit of HCV treatment may outweigh the cost of the care factor.[24,25]

Furthermore, the increased survival among those with SVRs was not limited to those who underwent HCC curative treatment but also included those who had only palliative treatment for HCC. This finding expands the results from a recent study that reported improved survival for those who were treated with DAAs for their HCV after being successfully treated for their early stage of HCC[20] by suggesting that

treatment should not be withheld from those who do not qualify for curative HCC treatment. On the other hand, it should be noted that further study is needed to determine the role of DAAs in patients with very advanced liver disease (CTP class C) or advanced cancer stage (BCLC stages B, C, and D) and in the very young (<50 years) group of patients with HCC because the sample sizes of these subgroups were small in our study.

A prior study from Europe studying patients with HCV-related HCC with compensated cirrhosis (19 with SVRs from IFN-based therapies and 156 patients who were viremic) also showed that patients with SVR had lower overall and liver-related mortality.[26] The 5-year OS rates were 65.9% and 31.9% in patients who achieved and did not achieve SVR after IFN-based antiviral therapy. However, IFN therapies are poorly tolerated, and only a few patients with HCC are treatment candidates. In 2017, another European multicenter study reported an HCC disease-free survival rate of 96% in 47 patients who were treated with DAAs after HCC diagnosis (82.6% BCLC stage A).[27] Despite a small sample size, the finding was consistent with our current study.

An interesting finding from our study was that those of Asian ethnicity were over 70% less likely to die than those of non-Asian ethnicity, although the country/region of residence was not significant. Although the reasons for this ethnic disparity remain unclear, it is a phenomenon that has long been described in several prior studies of the multiethnic U.S. population.[28-31] One recent study analyzed 1,284 Asian and 7,072 non-Hispanic white patients in a Surveillance, Epidemiology, and End Results Medicare-linked database, 1994-2011.[30] The study reported an absolute difference in 5-year survival rates of 5.8% (95% CI: 2.6%-9.3%) between Asians and non-Hispanic whites. This ethnic influence may also help explain the higher 5-year OS of about 88% for patients with SVR (from DAA) observed in our study compared with 65.9% for patients with SVR (from IFN) from the European study mentioned[26] because the majority of our patient cohort were Asian (68.85%). Furthermore, over half of our study population was also from Asia, and it is well known that Japan has a high HCC survival rate that is positively affected by treatment with DAAs for those who have suffered from HCV-related HCC.[32,33]

A major strength of our study is that we used a real-world multicenter, multinational cohort study that included patients from both the United States and East Asia to analyze the survival outcomes of patients with HCV-related HCC with SVR from DAA compared with untreated controls. Most importantly, we found that the study location, Asia versus non-Asia, was not a significant predictor that demonstrates the strong positive effect of DAA treatment on survival. We also employed several different statistical methods to balance the background risks of the two study groups to reduce biases that can occur in observational studies of survival outcomes.

On the other hand, we do recognize that there are several limitations to our study. First, this was a retrospective study, vulnerable to bias and confounding. But, as noted, we used PSM and multivariable adjustments to limit such issues. The high E values from our models also suggested that unmeasured confounders would be unlikely. Second, detailed recurrence data were lacking in our study, so we were not able to provide cancer progression-free survival (PFS) data. However, OS is the most important outcome in cancer research, and PFS is considered only a surrogate of survival.[34] In addition, we provided data for all-cause mortality and liver-related mortality. Third, some patients were censored out before their 5-year survival could be assessed because of IFN-free DAAs not being approved until late 2014, but the follow-up periods among the two groups were very comparable, and through the use of landmark analysis, the significant positive impact on survival for patients with SVR remained. Fourth, the rather recent arrival of IFN-free DAAs also limited the study from conducting longer-term survival analyses, but because the 5-year survival rate for those with HCC was low, we were able to demonstrate that SVRs achieved with IFN-free DAAs improved survival significantly, with annual mortality rates that were only about one third that of untreated patients. Fifth, the generalizability of our data for young patients with HCC (<50 years), patients with more advanced HCC stages (BCLC B, C, and D), and patients with very advanced liver disease (CTP class C) was limited because of small sample sizes. However, these subgroups may also stand to benefit more from SVRs, improving liver function sufficiently to tolerate needed HCC therapies. Further studies investigating these populations are urgently needed. We also did not include any patients who did not undergo therapy for HCC, so the impact of SVRs in this population is unknown. Lastly, the use

of and amount of alcohol consumed was lacking, so we were unable to account for the effect of alcohol on outcomes. However, because the E values were high, we feel the impact of alcohol would be small.

In conclusion, using data from both North America and East Asia, we demonstrate that, compared with patients without HCV therapy, SVR obtained following treatment with DAAs is strongly and significantly associated with improved OS in patients with HCV-related HCC who also received therapy (palliative or curative) for HCC (graphical summary as Supporting Fig. S1). Our findings advocate for the consideration of treatment with IFN-free DAAs for patients with HCV-related HCC who are also treatment candidates for HCC, whether curative or palliative. The impact of SVR in patients with HCV-related HCC who do not receive HCC treatment, have CTP class C or BCLC above stage A, and are younger than 50 years of age await additional investigation.

Author Contributions: M.H.N. was responsible for the study concept and supervision; H.D., Y.H.Y., H.T., and M.H.N. were responsible for the study design; all authors were responsible for data collection and/or interpretation; H.D., Y.H.Y., A.L., H.T., and M.H.N. were responsible for data analysis; H.D., Y.H.Y., L.H., and M.H.N. were responsible for manuscript drafting; all authors were responsible for manuscript edition and final approval.

REFERENCES

1) Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 2006;144:705-714.
2) Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol 2017;2:161-176.
3) Schütte K, Bornschein J, Malfertheiner P. Hepatocellular carcinoma–epidemiological trends and risk factors. Dig Dis 2009;27:80-92.
4) Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. Lancet 2016;388:1081-1088.
5) Kudo M. Targeted and immune therapies for hepatocellular carcinoma: predictions for 2019 and beyond. World J Gastroenterol 2019;25:789-807.
6) Global Burden of Disease Liver Cancer Collaboration. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the Global Burden of Disease Study 2015. JAMA Oncol 2017;3:1683-1691.
7) Jemal A, Ward EM, Johnson CJ, Cronin KA, Ma J, Ryerson B, et al. Annual report to the nation on the status of cancer, 1975-2014, featuring survival. J Natl Cancer Inst 2017;109:djx030.
8) Medavaram S, Zhang Y. Emerging therapies in advanced hepatocellular carcinoma. Exp Hematol Oncol 2018;7:17.
9) 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.
10) **Falade-Nwulia O**, **Suarez-Cuervo C**, Nelson DR, Fried MW, Segal JB, Sulkowski MS. Oral direct-acting agent therapy for hepatitis C virus infection: a systematic review. Ann Intern Med 2017;166:637-648.
11) Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. J Hepatol 2017;68:25-32.
12) Liu PH, Hsu CY, Hsia CY, Lee YH, Su CW, Huang YH, et al. Prognosis of hepatocellular carcinoma: assessment of eleven staging systems. J Hepatol 2016;64:601-608.
13) Nordstrom EM, Keniston A, Baouchi F, Martinez-Camacho A. Interferon-based hepatitis C therapy in a safety net hospital: access, efficacy, and safety. Eur J Gastroenterol Hepatol 2017;29:10-16.
14) Persico M, Aglitti A, Aghemo A, Rendina M, Lleo A, Ciancio A, et al. High efficacy of direct-acting anti-viral agents in hepatitis C virus-infected cirrhotic patients with successfully treated hepatocellular carcinoma. Aliment Pharmacol Ther 2018;47:1705-1712.
15) Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. Gastroenterology 2017;153:996-1005.e1.
16) Singal AG, Rich NE, Mehta N, Branch A, Pillai A, Hoteit M, et al. Direct-acting antiviral therapy not associated with recurrence of hepatocellular carcinoma in a multicenter North American cohort study. Gastroenterology 2019;156:1683-1692.e1.
17) Zou WY, Choi K, Kramer JR, Yu X, Cao Y, El-Serag HB, et al. Risk of hepatocellular cancer recurrence in hepatitis C virus+ patients treated with direct-acting antiviral agents. Dig Dis Sci 2019. [Epub ahead of print.]
18) Backus LI, Belperio PS, Shahoumian TA, Mole LA. Direct-acting antiviral sustained virologic response: impact on mortality in patients without advanced liver disease. Hepatology 2018;68:827-838.
19) Calvaruso V, Cabibbo G, Cacciola I, Petta S, Madonia S, Bellia A, et al. Incidence of hepatocellular carcinoma in patients with HCV-associated cirrhosis treated with direct-acting antiviral agents. Gastroenterology 2018;155:411-421.e4.
20) **Cabibbo G**, **Celsa C**, Calvaruso V, Petta S, Cacciola I, Cannavò MR, et al. Direct-acting antivirals after successful treatment of early hepatocellular carcinoma improve survival in HCV-cirrhotic patients. J Hepatol 2019;71:265-273.
21) **Pavel MC**, **Fuster J**. Expansion of the hepatocellular carcinoma Milan criteria in liver transplantation: future directions. World J Gastroenterol 2018;24:3626-3636.
22) Na SK, Yim SY, Suh SJ, Jung YK, Kim JH, Seo YS, et al. ALBI versus Child-Pugh grading systems for liver function in patients with hepatocellular carcinoma. J Surg Oncol 2018;117:912-921.
23) Roberts LR, Sirlin CB, Zaiem F, Almasri J, Prokop LJ, Heimbach JK, et al. Imaging for the diagnosis of hepatocellular carcinoma: a systematic review and meta-analysis. Hepatology 2018;67:401-421.
24) Sorbo MC, Carioti L, Bellocchi MC, Antonucci F, Sforza D, Lenci I, et al. HCV resistance compartmentalization within tumoral and non-tumoral liver in transplanted patients with hepatocellular carcinoma. Liver Int 2019;39:1986-1998.

25) Younossi Z. What is the ethical responsibility of a provider when prescribing the new direct-acting antiviral agents to patients with hepatitis C infection? Clin Liver Dis (Hoboken) 2015;6:117-119.
26) Bruno S, Di Marco V, Iavarone M, Roffi L, Boccaccio V, Crosignani A, et al. Improved survival of patients with hepatocellular carcinoma and compensated hepatitis C virus-related cirrhosis who attained sustained virological response. Liver Int 2017;37:1526-1534.
27) Kolly P, Waidmann O, Vermehren J, Moreno C, Vögeli I, Berg T, et al. Hepatocellular carcinoma recurrence after direct antiviral agent treatment: a European multicentre study. J Hepatol 2017;67:876-878.
28) Devaki P, Wong RJ, Marupakula V, Nangia S, Nguyen L, Ditah IC, et al. Approximately one-half of patients with early-stage hepatocellular carcinoma meeting Milan criteria did not receive local tumor destructive or curative surgery in the post-MELD exception era. Cancer 2014;120:1725-1732.
29) Kim NG, Nguyen PP, Dang H, Kumari R, Garcia G, Esquivel CO, et al. Temporal trends in disease presentation and survival of patients with hepatocellular carcinoma: a real-world experience from 1998 to 2015. Cancer 2018;124:2588-2598.
30) Wang Z, Gu X, Thrift AP. Factors associated with favorable survival outcomes for Asians with hepatocellular carcinoma: a sequential matching cohort study. PLoS One 2019;14:e0214721.
31) Yip B, Wantuck JM, Kim LH, Wong RJ, Ahmed A, Garcia G, et al. Clinical presentation and survival of Asian and non-Asian patients with HCV-related hepatocellular carcinoma. Dig Dis Sci 2014;59:192-200.
32) **Nishibatake Kinoshita M**, **Minami T**, Tateishi R, Wake T, Nakagomi R, Fujiwara N, et al. Impact of direct-acting antivirals on early recurrence of HCV-related HCC: comparison with interferon-based therapy. J Hepatol 2019;70:78-86.
33) Toyoda H, Kumada T, Kiriyama S, Sone Y, Tanikawa M, Hisanaga Y, et al. Changes in the characteristics and survival rate of hepatocellular carcinoma from 1976 to 2000: analysis of 1365 patients in a single institution in Japan. Cancer 2004;100:2415-2421.
34) Llovet JM, Montal R, Villanueva A. Randomized trials and endpoints in advanced HCC: role of PFS as a surrogate of survival. J Hepatol 2019;70:1262-1277.

Author names in bold designate shared co-first authorship.

Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.30988/suppinfo.