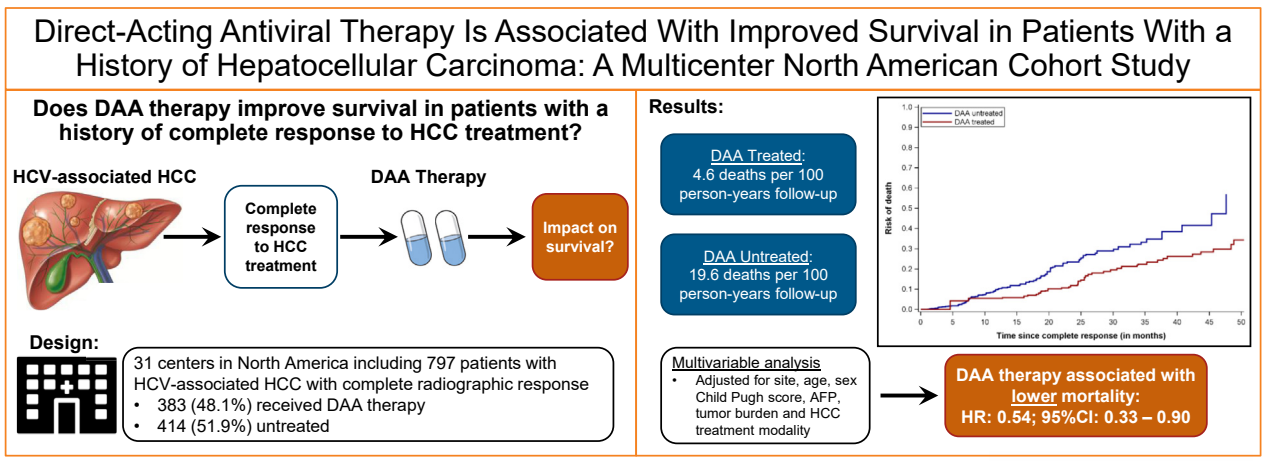
Gastroenterology 2019;157:1253–1263

Direct-Acting Antiviral Therapy for Hepatitis C Virus Infection Is Associated With Increased Survival in Patients With a History of Hepatocellular Carcinoma

Amit G. Singal,[1] Nicole E. Rich,[1] Neil Mehta,[2] Andrea D. Branch,[3] Anjana Pillai,[4] Maarouf Hoteit,[5] Michael Volk,[6] Mobolaji Odewole,[1] Steven Scaglione,[7] Jennifer Guy,[8] Adnan Said,[9] Jordan J. Feld,[10] Binu V. John,[11] Catherine Frenette,[12] Parvez Mantry,[13] Amol S. Rangnekar,[14] Omobonike Oloruntoba,[15] Michael Leise,[16] Janice H. Jou,[17] Kalyan Ram Bhamidimarri,[18] Laura Kulik,[19] George N. Ioannou,[20] Annsa Huang,[2] Tram Tran,[21] Hrishikesh Samant,[22] Renumathy Dhanasekaran,[23] Andres Duarte-Rojo,[24] Reena Salgia,[25] Sheila Eswaran,[26] Prasun Jalal,[27] Avegail Flores,[28] Sanjaya K. Satapathy,[29] Sofia Kagan,[1] Purva Gopal,[30] Robert Wong,[31] Neehar D. Parikh,[32,§] and Caitlin C. Murphy[1,§]

[1]Division of Digestive and Liver Disease, UT Southwestern Medical Center, Dallas, Texas; [2]Division of Gastroenterology, University of California San Francisco, San Francisco, California; [3]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York; [4]Division of Gastroenterology, Hepatology and Nutrition, University of Chicago, Chicago, Illinois; [5]Division of Gastroenterology and Hepatology, University of Pennsylvania, Philadelphia, Pennsylvania; [6]Transplantation Institute and Division of Gastroenterology, Loma Linda University Health, Loma Linda, California; [7]Division of Hepatology, Loyola University Medical Center and Edward Hines Veterans Affairs, Hines, Illinois; [8]Department of Transplantation, California Pacific Medical Center, San Francisco, California; [9]Division of Gastroenterology and Hepatology, University of Wisconsin School of Medicine, Madison, Wisconsin; [10]Toronto Center for Liver Disease, Toronto General Hospital, Toronto, Ontario, Canada; [11]Division of Gastroenterology and Hepatology, McGuire VA Medical Center, Richmond, Virginia; [12]Division of Organ Transplantation, Scripps Green Hospital, San Diego, California; [13]Liver Institute at Methodist Dallas, Dallas, Texas; [14]Division of Gastroenterology, Georgetown University Hospital, Washington, District of Columbia; [15]Division of Gastroenterology and Hepatology, Duke University Health Center, Durham, North Carolina; [16]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; [17]Division of Gastroenterology and Hepatology, Oregon Health and Science University, Portland, Oregon; [18]Division of Hepatology, University of Miami Miller School or Medicine, Miami, Florida; [19]Division of Hepatology, Northwestern University, Chicago, Illinois; [20]Division of Gastroenterology and Research and Development, Veterans Affairs Puget Sound Healthcare System and University of Washington, Seattle, Washington; [21]Liver Disease and Transplant Center, Cedars-Sinai Medical Center, Los Angeles, California; [22]Division of Gastroenterology and Hepatology, Louisiana State University Health Sciences Center, New Orleans, Louisiana; [23]Division of Gastroenterology and Hepatology, Stanford University, Stanford, California; [24]Division of Gastroenterology and Hepatology, University of Arkansas for Medical Sciences, Little Rock, Arkansas; [25]Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan; [26]Division of Gastroenterology, Rush Medical College, Chicago, Illinois; [27]Division of Abdominal Transplantation, Baylor College of Medicine, Houston, Texas; [28]Division of Gastroenterology, Washington University School of Medicine, St Louis, Missouri; [29]Division of Hepatology, Donald and Barbara Zucker School of Medicine, Northshore University Hospital, Northwell Health, Manhasset, New York; [30]Department of Pathology, UT Southwestern Medical Center, Dallas, Texas; [31]Division of Gastroenterology and Hepatology, Alameda Health System, Oakland, California; and [32]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, Michigan

CLINICAL LIVER



BACKGROUND & AIMS: There is controversy regarding the benefits of direct-acting antiviral (DAA) therapy for hepatitis C virus (HCV) infection for patients with a history of hepatocellular carcinoma (HCC). We performed a multicenter cohort study to compare overall survival between patients with HCV infection treated with DAAs and patients who did not receive DAA treatment for their HCV infection after complete response to prior HCC therapy. **METHODS:** We conducted a retrospective cohort study of patients with HCV-related HCC who achieved a complete response to resection, local ablation, transarterial chemo- or radioembolization, or radiation therapy, from January 2013 through December 2017 at 31 health care systems throughout the United States and Canada. We used Cox proportional hazards regression to determine the association between receipt of DAA therapy, modeled as a time-varying covariate, and all-cause mortality, accounting for informative censoring and confounding using inverse probability weighting. **RESULTS:** Of 797 patients with HCV-related HCC, 383 (48.1%) received DAA therapy and 414 (51.9%) did not receive treatment for their HCV infection after complete response to prior HCC therapy. Among DAA-treated patients, 43 deaths occurred during 941 person-years of follow-up, compared with 103 deaths during 526.6 person-years of follow-up among patients who did not receive DAA therapy (crude rate ratio, 0.23; 95% confidence interval [CI], 0.16–0.33). In inverse probability-weighted analyses, DAA therapy was associated with a significant reduction in risk of death (hazard ratio, 0.54; 95% CI, 0.33–0.90). This association differed by sustained virologic response to DAA therapy; risk of death was reduced in patients with sustained virologic response to DAA therapy (hazard ratio, 0.29; 95% CI, 0.18–0.47), but not in patients without a sustained virologic response (hazard ratio, 1.13; 95% CI, 0.55–2.33). **CONCLUSIONS:** In an analysis of nearly 800 patients with complete response to HCC treatment, DAA therapy was associated with a significant reduction in risk of death.

Keywords: Liver Cancer; HCC; Hepatitis C; Survival.

CLINICAL LIVER

WHAT YOU NEED TO KNOW

BACKGROUND & CONTEXT

Direct acting antiviral (DAA) treatment is associated with increased survival in patients with cirrhosis, but little is known about its effect in patients with a history of hepatocellular carcinoma (HCC).

NEW FINDINGS

DAA therapy for patients who had a complete response to HCC therapy is associated with increased overall survival, as long as the patients had a sustained virologic response to DAA treatment, which reduces liver-related mortality.

LIMITATIONS

This was a retrospective cohort study with possible selection bias and residual confounding.

IMPACT

Patients with HCV-related HCC who have a confirmed complete response should be considered for DAA treatment, which can increase survival.

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide, and a leading cause of death in patients with compensated cirrhosis.[1] Given the majority of HCC cases occur in the setting of chronic liver disease, prognosis depends on both tumor burden and degree of liver dysfunction. Most patients with HCC are diagnosed at late stages, with limited treatment options and a median survival of approximately 1 year.[2] Those diagnosed with HCC at an early stage are eligible for curative treatments, resulting in 5-year survival rate approaching 70%; however, outside of liver transplantation, these therapies are limited by a high risk of recurrence and a continued risk of hepatic decompensation.[3–6]

Chronic hepatitis C virus (HCV) infection remains the most common cause of HCC in North America and Europe.[6] Several studies have reported a benefit of direct-acting antiviral (DAA) therapy in reducing incident HCC and mortality among HCV-infected individuals,[7–9] but the impact of these therapies on prognosis in patients who have had a complete response to HCC treatment is less clear. Interferon-based therapy was associated with reduced risk of recurrence and mortality in patients with a history of HCC; however, there is uncertainty whether this was mediated by a direct interferon-mediated effect that would not translate to DAA-based therapy.[10] In fact, some early observational studies suggested a higher than expected risk of HCC recurrence after DAA therapy.[11] Subsequent studies have produced conflicting data, with most reporting no significant difference in recurrence between DAA-treated and untreated patients, including our multi-center North American study, in which we found no significant difference in overall recurrence, early recurrence, or recurrence aggressiveness.[9,12–16]

To date, most studies have focused on the association between DAA therapy and HCC recurrence, with fewer examining the association between DAA therapy and overall survival in patients with a history of HCC. Notably, data from the ITA.LI.CA group demonstrated that hepatic decompensation might influence mortality more strongly in HCV-infected patients with a history of complete response to prior HCC therapy than HCC recurrence.[17] Therefore, DAA therapy can improve overall survival in patients with a history of HCC, independent of recurrence risk. The aim of this multicenter study was to compare overall survival between DAA-treated and untreated patients in a large cohort of North American patients with complete response to prior HCC-directed therapy.

[§] Authors share co-senior authorship.

Abbreviations used in this paper: CI, confidence interval; DAA, direct acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; IP, inverse probability; IQR, interquartile range; SVR, sustained virologic response; TACE, transarterial chemoembolization.

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0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2019.07.040

Methods

Study Population

As described previously,[15] we conducted a multicenter retrospective cohort study of adult patients with HCV-related HCC who achieved HCC complete response between January 2013 and December 2017. In brief, patients were identified from 31 health systems throughout the United States and Canada. HCC diagnosis was based on characteristic radiologic appearance or histology per American Association for the Study of Liver Diseases criteria.[18] Patients were required to have liver-localized tumor burden at presentation, and those with extrahepatic disease were excluded. We included patients who achieved complete HCC response by surgical resection, local ablative therapies, transarterial chemoembolization (TACE) or bland embolization, transarterial radioembolization, or stereotactic body radiation therapy. Complete response to HCC treatment was defined by modified Response Evaluation Criteria in Solid Tumors criteria, that is, disappearance of arterial enhancement from all HCC lesions on contrast-enhanced cross-sectional imaging. Patients with complete response after liver transplantation or systemic therapy were excluded.

We excluded patients who received interferon-based therapy or initiated DAA therapy before HCC complete response. We also excluded patients with unknown HCC response, for example, lack of contrast-enhanced imaging after HCC treatment, and patients who died within 30 days of complete response. The study was approved by Institutional Review Boards at each study site.

Covariates

Demographic and clinical characteristics. We used a standardized data collection form to collect patients' demographic and clinical characteristics from electronic medical records at time of HCC diagnosis, including age, sex, race/ethnicity, presence of hepatitis B virus and human immunodeficiency virus co-infection, platelet count, aspartate aminotransferase, alanine aminotransferase, HCV viral load, HCV genotype, Eastern Cooperative Oncology Group performance status, and α-fetoprotein. Degree of liver dysfunction was assessed by Child–Pugh and Model for End-Stage Liver Disease scores. Tumor burden, as determined by radiologists' interpretation of imaging at each site, was categorized as very early stage (single tumor $<$2 cm), early stage (single tumor $<$5 cm or 2–3 tumors with each $<$3 cm in maximum diameter), or intermediate stage (beyond early stage but without extrahepatic spread). We also collected the type of treatment leading to complete response (ie, surgical resection, ablation, TACE, or other).

Direct-acting antiviral treatment. We considered DAA treatment to be time-varying, allowing patients to switch between unexposed and exposed status. Specifically, we assigned follow-up time for patients before DAA initiation as unexposed time and time after DAA initiation as exposed time. Patients who initiated DAA therapy after liver transplantation only contributed unexposed time. For DAA-treated patients, we extracted information on treatment regimen, time from HCC complete response to DAA initiation, and outcome (ie, sustained virologic response [SVR]).

Statistical Analyses

Primary analysis. We used χ^2 and Student t tests to characterize the study population by DAA treatment (DAA-treated vs untreated). Because we allowed treatment to be time-varying, for this purpose, we defined DAA-treated patients as patients who initiated DAA at any time during follow-up, regardless of SVR.

For both DAA-treated and untreated patients, we defined the index date as the date of complete response to HCC treatment. We followed each patient from complete response to date of death, liver transplantation, or last clinic visit. We classified causes of death into 4 mutually exclusive categories: liver-related (eg, acute on chronic liver failure, hepatorenal syndrome, and spontaneous bacterial peritonitis); HCC-related (eg, recurrent advanced stage HCC); non-liver/non-HCC related; and unknown (eg, died elsewhere). The primary outcome was death from all causes, and we estimated the rate of all-cause mortality as the number of deaths divided by person-years of follow-up. We also calculated the crude mortality rate ratio as the ratio between the mortality rate among DAA-treated patients and that among untreated patients.

We then used a Cox proportional hazards regression model with inverse probability (IP) weights to examine overall survival between DAA-treated and untreated patients. Using this approach, each patient is weighted to create a pseudo-population in which DAA therapy is not associated with baseline covariates, such that confounding is eliminated; and censoring by liver transplantation is not associated with DAA therapy or covariates, such that selection bias due to censoring is eliminated.[19,20] We used separate logistic regression models to estimate the probability of treatment (ie, initiating DAA therapy) and for the probability of not being censored (ie, not receiving liver transplant), including the following covariates: age, sex, Child–Pugh class, tumor burden, α-fetoprotein level, treatment leading to complete response, and time since complete response (censoring weight only). The resulting IP weight is the product of an estimated time-fixed IP treatment weight and an estimated time-varying IP censoring weight.

Sensitivity analysis. To assess the robustness of DAA treatment as a time-varying exposure, we performed a sensitivity analysis using a 180-day landmark. In this restricted subgroup, patients who initiated DAA within 180 days of complete response were categorized as DAA-treated, and those who did not initiate before 180 days were categorized as untreated. Patients who died, had HCC recurrence, received liver transplantation, or had their last clinic visit before the landmark were excluded. These restrictions avoid immortal time bias by synchronizing the start of follow-up for treated and untreated patients.[21,22] Survival by treatment group was then compared using Cox proportional hazards models with IP weights.

Secondary analyses. We hypothesized the association between DAA treatment and all-cause mortality differed among patients who achieved and did not achieve SVR. Therefore, we compared overall survival of DAA-treated patients with and without SVR to untreated patients. We also conducted secondary analyses stratified by tumor burden (within vs beyond Milan criteria), treatment leading to HCC complete response (resection vs ablation vs TACE/stereotactic body radiation therapy), and HCC recurrence.

All tests were 2-sided and performed at the 5% significance level. Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC).

Results

Patient Characteristics

Selection of the study population is illustrated in Figure 1. Of 852 eligible HCV-infected HCC patients who achieved complete response to HCC-directed therapy between January 2013 and December 2017, we excluded 47 patients who initiated DAA therapy and 8 patients who died within 30 days of HCC complete response. There were 797 remaining patients included in the final analysis, of whom 383 initiated DAA therapy and 414 were untreated.

Patient demographics are described in Table 1. Median age of patients was 61.5 years. Nearly three-fourths of patients were male and the cohort was racially diverse. At HCC diagnosis, nearly three-fourths of patients had a unifocal HCC and >80% were within Milan Criteria. One-third of patients achieved HCC complete response from local ablation and 14% from surgical resection, while approximately half achieved complete response from locoregional therapies. A higher proportion of DAA-treated patients were older, non-Hispanic white, had compensated cirrhosis with less portal hypertension, and achieved HCC complete response by resection than untreated patients; however, the 2 groups had similar tumor burden at diagnosis, including a similar proportion of patients presenting within Milan Criteria.

Median time from HCC diagnosis to HCC treatment was 2.7 months (interquartile range [IQR], 1.4–5.6 months), and median time from HCC treatment to complete response was 1.6 months (IQR, 1.1–3.2 months). Median time from HCC complete response to DAA initiation was 7.7 months (IQR, 3.6–14.1 months), with 20.2% treated within 3 months, 21.5% between 3 and 6 months, 25.5% between 6 and 12 months, and 32.9% more than 12 months after HCC complete response. SVR was documented in 79.4% of DAA-treated patients, while 11.5% had treatment failure and 9.1% did not have documented assessment of SVR.

Association Between Direct-Acting Antiviral Therapy and Overall Survival

Among DAA-treated patients, 43 deaths occurred during 941.0 person-years of follow-up compared to 103 deaths during 526.6 person-years of follow-up among untreated patients, yielding a crude rate ratio of 0.23 (95% confidence interval [CI], 0.16–0.33). The 1- and 2-year risk of mortality for DAA-treated patients was 5.5% and 11.8%, compared to 10.0% and 23.5% among untreated patients. Median time from HCC complete response to death among DAA-treated patients was 25.7 months (IQR, 19.4–33.9 months) compared to 11.5 months (IQR, 7.1–20.2 months) for untreated patients. The proportion of deaths that were liver-related was significantly lower in DAA-treated than untreated patients (16.3% vs 34.0%; $P = .03$), whereas the proportion of HCC-related deaths was similar between the 2 groups (30.2% vs 29.1%; $P = .89$).

In the primary analysis, DAA therapy was associated with reduced mortality in crude (hazard ratio [HR], 0.37; 95% CI, 0.26–0.54) and weighted (HR, 0.54; 95% CI, 0.33–0.90) models (Table 2, Figure 2). In the sensitivity analysis using a 180-day landmark, DAA therapy was associated with reduced mortality (weighted HR, 0.57; 95% CI, 0.30–1.09); however, few patients were classified as DAA-treated (n = 133), and the effect estimate did not reach statistical significance.

Subgroup analyses are detailed in Table 2. DAA therapy was associated with improved survival among patients with Child–Pugh A or B cirrhosis; assessing mortality benefit in those with Child C cirrhosis was limited by small sample size. We also observed a consistent benefit of DAA therapy among patients who initially had tumor burden within and beyond Milan Criteria. The reduction in mortality with DAA therapy was greater in patients who received resection or ablation than in those who received TACE, (interaction $P = .03$). Results were consistent in the subgroup of patients without history of HCC recurrence. However, as expected, there was a significantly greater benefit of DAA therapy in patients who remained recurrence-free during the study period (HR, 0.09; 95% CI, 0.02–0.29) compared to those who experienced HCC recurrence (HR, 0.86; 95% CI, 0.49–1.52) (interaction $P < .001$).

Association Between Direct-Acting Antiviral Therapy and Overall Survival, Stratified by Sustained Virologic Response Status

We expected the association between DAA therapy and mortality to differ by SVR and examined DAA-treated patients with and without SVR in greater detail. Characteristics of DAA-treated patients, stratified by SVR status, are detailed in Supplementary Table 1. Patients with SVR were more likely to be female and non-Hispanic white, but they had similar numbers of HCC nodules, maximum tumor diameter, proportion within Milan Criteria at diagnosis, as well as type and number of treatments leading to HCC complete response. We also found no significant difference in the degree of liver dysfunction at complete response, HCV genotype, type and duration of DAA regimen, and timing of treatment from HCC complete response. Although a higher proportion of patients with SVR subsequently underwent liver transplantation, this difference did not reach statistical significance (22.7% vs 13.6%; $P = .17$).

Among DAA-treated patients, patients with SVR had significantly reduced mortality from time of DAA initiation compared to non-SVR patients (HR, 0.27; 95% CI, 0.13–0.57). In a sensitivity analysis in which patients with missing SVR status were assumed to be non-SVR, SVR continued to be associated with reduced mortality (HR, 0.47; 95% CI, 0.35–0.64). We next compared both groups of DAA-treated patients (with and without SVR) to untreated patients. DAA-treated patients who achieved SVR had significantly reduced mortality compared to untreated patients (HR, 0.29; 95% CI, 0.18–0.47); however, a mortality benefit was not observed among DAA-treated patients who did not achieve SVR compared to untreated patients (HR, 1.13; 95% CI, 0.55–2.33).

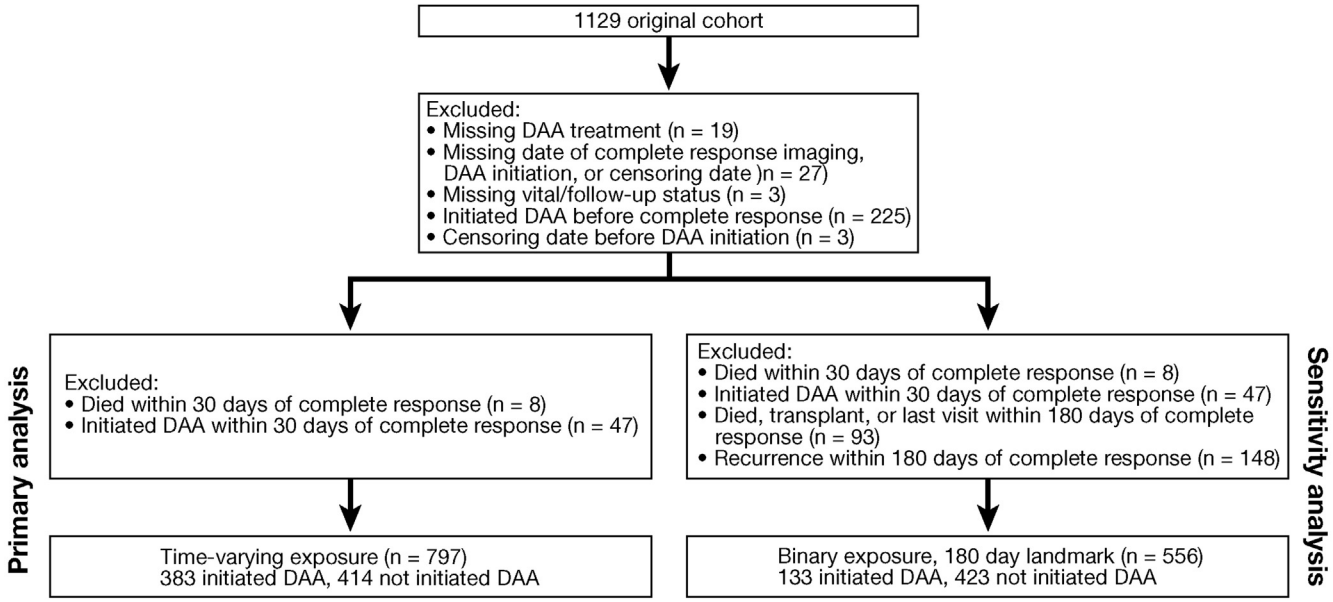

Figure 1. Study cohort inclusion and exclusion diagram.

Discussion

There has been extensive debate about the potential benefit of DAA therapy in patients with a history of HCC, primarily related to concerns about the risk of HCC recurrence. While recent data have suggested that DAA therapy after complete HCC response does not appear to increase recurrence, to the best of our knowledge our study represents the first to demonstrate a survival benefit of DAA therapy in this patient population.

Although HCC treatments, such as surgical resection and local ablative therapies, are potentially curative, they are limited by high risk of recurrence, and 5-year mortality rate approaches 50%. Prior attempts to identify adjuvant therapies to reduce HCC recurrence, such as the STORM (Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma) trial evaluating sorafenib after resection or ablation, largely failed.[23] Cabibbo and colleagues[17] recently demonstrated that hepatic decompensation was a stronger driver of mortality than HCC recurrence in patients with complete response to HCC therapy, suggesting interventions that reduce portal hypertension and other manifestations of advanced liver disease could improve survival. Albeit of limited sample size, results from the ANRS (Agence Nationale de Recherche sur le SIDA et les Hépatites virales) CirVir prospective cohort study suggested a potential benefit of DAA-associated SVR to reduce hepatic decompensation in patients with HCC.[24] Hepatic decompensation was one of the most common causes of death in patients without SVR, but was not observed in any of the 4 patients with SVR. Similarly, Bruno and colleagues[25] found that more than one-third of HCC patients with untreated HCV infection died of hepatic decompensation, compared to 0 of 19 patients who had achieved SVR before HCC diagnosis. However, these studies both evaluated the benefit of SVR before HCC diagnosis, where there may be a longer time frame to experience fibrosis regression and improvement in portal hypertension.[26,27] Our study adds to this literature and reinforces that DAA therapy may also reduce mortality in patients with a history of HCC.

Although DAA therapy was associated with a consistent survival benefit across most patient subgroups, this association was mitigated in those who were treated with TACE, as well as those with HCC recurrence, likely due to a higher risk of HCC mortality. Although DAA therapy can help improve or stabilize liver function in these patients, the high risk of recurrence and persistent HCC-related mortality highlights a continued need for adjuvant therapy after HCC complete response. In the absence of proven adjuvant agents, close surveillance after complete response may increase early tumor detection and minimize HCC-related mortality.[28,29] As reported previously, more than two-thirds of patients with recurrence in our study were detected at an early stage (Barcelona Clinic Liver Cancer stage 0/A), and >50% of those with known treatment response had an objective response.[15] It is important to note that although the association between DAA therapy and survival was not statistically significant in these subgroups, the samples sizes were too small to make definitive conclusions, and the point estimates still suggested a potential benefit. Further studies are needed in these patients to determine whether DAA therapy may be of potential benefit.

Although we observed a benefit of DAA therapy in patients with a history of HCC, the optimal timing of DAA therapy in relation to HCC treatment remains unclear. Should patients initiate DAA therapy concurrent with HCC treatment, immediately thereafter, or is it best to wait for documented complete response? Although some studies suggest a lower proportion of patients with active HCC achieve SVR, it is unclear if this concern should drive decisions of timing.[9,30–32] If the potential benefit of DAA

therapy is truly related to preventing liver dysfunction, earlier treatment may be better. Extending this further is the question of whether DAA therapy would have similar benefits among patients with active intermediate-stage, or even advanced-stage, HCC.[33] Further studies in these patient populations to address these important clinical dilemmas are clearly needed.

It is possible that the association between DAA therapy and reduced mortality may be driven by confounding, with DAA therapy being used selectively in patients with better prognosis. We attempted to adjust for measured confounders and selection bias with IP weighting, and we mitigated the effect of immortal time bias by using time-varying and landmark analyses. Further, we observed no

Table 1. Patient Characteristics, Stratified by Direct-Acting Antiviral Treatment Status

Variable[a]	DAA-treated (n = 383)	DAA-untreated (n = 414)	*P* value
Age at time of complete response, *y*	62.1 (58.6–66.1)	61.2 (57.0–65.0)	.01
Sex, *male*, n (%)	276 (72.1)	320 (77.3)	.09
Race/ethnicity, n (%)			.02
Non-Hispanic white	187 (48.8)	159 (38.4)	
Hispanic white	58 (15.1)	66 (15.9)	
Black	75 (19.6)	92 (22.2)	
Other	18 (4.7)	22 (5.3)	
Missing	45 (11.8)	75 (18.1)	
No. of HCC nodules at diagnosis, n (%)			.01
1	291 (77.2)	270 (67.8)	
2	65 (17.2)	88 (22.1)	
3	17 (4.5)	25 (6.3)	
4	4 (1.1)	15 (3.7)	
Maximum HCC diameter at diagnosis, *cm*	2.4 (1.7–3.3)	2.6 (2.0–3.7)	.42
HCC within Milan Criteria at diagnosis, n (%)	313 (82.6)	332 (80.8)	.51
AFP at time of HCC diagnosis, *ng/mL*	18.5 (7.3–67)	18.3 (7.9–68)	.29
Treatment leading to complete response, n (%)			<.001
Resection	81 (21.2)	33 (8.0)	
Local ablation	138 (36.0)	130 (31.4)	
TACE	136 (35.5)	222 (53.8)	
TARE/SBRT/other	28 (7.3)	28 (6.8)	
No. of HCC therapies required to achieve complete response, n (%)			.13
1	220 (60.8)	205 (55.3)	
2	92 (25.4)	95 (25.6)	
3 or more	50 (13.8)	71 (19.1)	
Child–Pugh class at complete response, n (%)			<.001
A	235 (61.4)	199 (48.1)	
B	127 (33.2)	160 (38.7)	
C	21 (5.5)	55 (13.3)	
Presence of ascites, n (%)	98 (26.0)	151 (37.8)	<.001
Presence of hepatic encephalopathy, n (%)	56 (14.9)	89 (22.3)	.008
Platelet count at complete response	109 (75–158)	87 (60–133)	<.001
Bilirubin at complete response, *mg/dL*	1.0 (0.6–1.6)	1.3 (0.7–2.1)	.18
HCV genotype, n (%)			<.001
1	293 (77.9)	331 (69.6)	
2	27 (7.2)	17 (3.9)	
3	43 (11.4)	70 (14.9)	
4–6	11 (2.9)	17 (2.9)	
Viral co-infection, n (%)			.38
Hepatitis B	8 (2.2)	5 (1.3)	
Human immunodeficiency virus	9 (2.5)	6 (1.6)	
DAA regimen,[b] n (%)		NA	
Sofosbuvir/ledipasvir	237 (63.0)		
Sofosbuvir	56 (14.9)		
Simeprevir/sofosbuvir	32 (8.5)		
Sofosbuvir/velpatasvir	18 (4.8)		
Daclatasvir/sofosbuvir	16 (4.3)		
Ombitasvir/partiprevir/ritonavir/dasabuvir	7 (1.9)		
Elbasavir/grazoprevir	3 (0.8)		
Other	7 (1.9)		

Table 1. Continued

Variable[a]	DAA-treated (n = 383)	DAA-untreated (n = 414)	*P* value
DAA regimen duration, n (%)		NA	
<12 wk	15 (4.0)		
12 wk	197 (53.1)		
>12 wk but <24 wk	26 (7.0)		
24 weeks	126 (34.0)		
>than 24 wk	7 (1.9)		
Time from HCC complete response to DAA, n (%)		NA	
<3 mo	76 (20.2)		
>3–6 mo	81 (21.5)		
>6–12 mo	96 (25.5)		
>12–24 mo	92 (24.4)		
>24 mo	32 (8.5)		

AFP, α-fetoprotein; SBRT, stereotactic body radiation therapy; TARE, transarterial radioembolization.
[a]Continuous data presented as median (IQR).
[b]All DAA regimens are with or without ribavirin.

association between DAA therapy and survival among those who were treated but did not achieve SVR. We still acknowledge the potential for residual confounding. For example, DAA-treated patients had less portal hypertension than untreated patients, which could partly explain results.

Results from our study must be interpreted in light of other potential limitations. First, we used imaging interpretation through routine clinical care instead of centralized imaging review, which could have affected classification of HCC complete response.[34] However, all included health systems were academic centers with gastrointestinal-trained radiologists, and most centers use multidisciplinary tumor boards.[35,36] Importantly, reductions in mortality were most evident in patients undergoing surgical resection or ablation, which would be less prone to misclassification of complete response. The weaker association between DAA therapy and reduced mortality in patients undergoing TACE may have been related in part to unrecognized microscopic residual disease. Second, approximately 9% of patients were lost to follow-up, with a higher proportion in the DAA-untreated group. Finally, we did not have data on incident development of hepatic decompensation during study follow-up and were unable to demonstrate whether the survival benefit we observed was definitively related to preservation of liver function. Ongoing multicenter prospective cohort studies with longer follow-up will hopefully address some of these limitations; however, these are years away from reporting. These limitations were believed to be outweighed by the study's notable strengths, including its multicenter design, large cohort of patients, rigorous

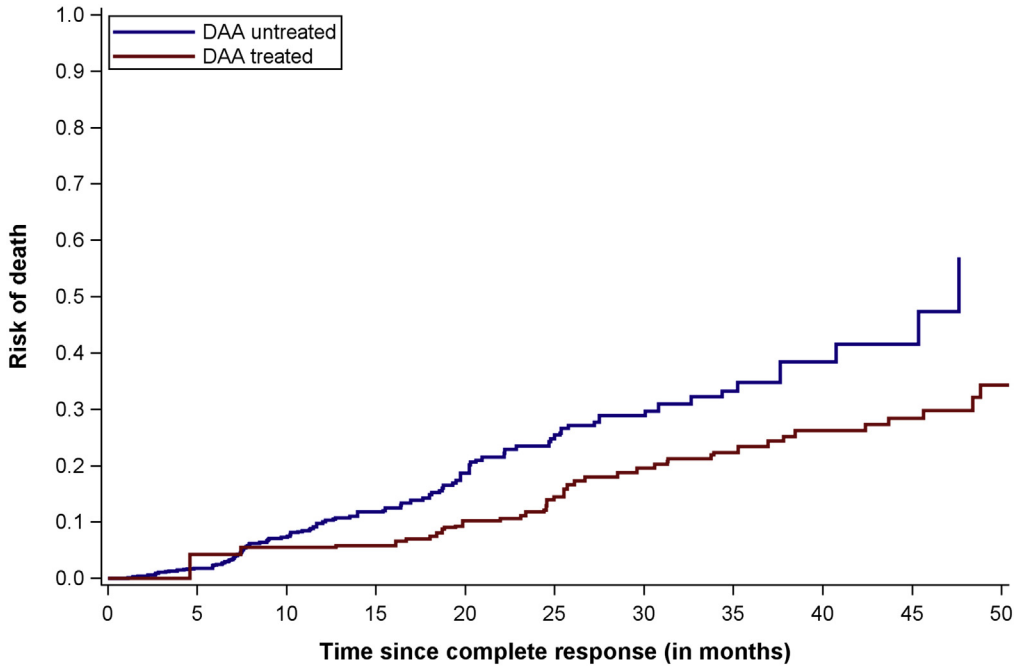

Figure 2. Overall survival, stratified by receipt of DAA hepatitis C therapy.

Table 2. Associations Between Direct-Acting Viral Treatment and Mortality in Hepatitis C Virus–Infected Patients With Hepatocellular Carcinoma

Variable	Patients, n	Deaths, n	Person-years	Mortality rate per 100 person-years (95% CI)	Crude rate ratio (95% CI)	Adjusted HR[a] (95% CI)	Sample size in adjusted HR
DAA treatment as time-varying exposure[b]							
Overall							
Untreated	414	103	526.63	19.56 (16.05–23.62)	—	—	401
DAA-treated	383	43	941.01	4.57 (3.35–6.09)	0.23 (0.16–0.33)	0.54 (0.33–0.90)	339
Within Milan							
Untreated	332	83	427.95	19.35 (15.55–23.91)	—	—	323
DAA-treated	313	38	777.54	4.89 (3.51–6.63)	0.25 (0.17–0.37)	0.56 (0.32–0.98)	280
Beyond Milan							
Untreated	79	18	96.22	18.71 (11.48–28.93)	—	—	78
DAA-treated	66	5	155.00	3.23 (1.22–7.07)	0.17 (0.06–0.46)	0.53 (0.21–1.39)	59
Surgical resection							
Untreated	33	9	58.91	15.28 (7.55–27.89)	—	—	30
DAA-treated	81	5	235.89	2.12 (0.80–4.65)	0.14 (0.05–0.41)	0.21 (0.06–0.76)	73
Local ablation							
Untreated	130	42	174.59	24.06 (17.58–32.19)	—	—	123
DAA-treated	138	13	326.02	3.99 (2.23–6.63)	0.17 (0.09–0.31)	0.26 (0.13–0.51)	116
TACE							
Untreated	222	43	264.59	16.25 (11.92–21.67)	—	—	220
DAA-treated	136	23	312.42	7.36 (4.79–10.86)	0.45 (0.27–0.75)	0.99 (0.47–2.08)	129
Child–Pugh A							
Untreated	199	45	301.80	14.91 (11.02–19.76)	—	—	191
DAA-treated	235	17	600.47	2.83 (1.71–4.43)	0.19 (0.11–0.33)	0.25 (0.14–0.48)	206
Child–Pugh B							
Untreated	160	44	182.43	24.12 (17.76–32.07)	—	—	155
DAA-treated	127	18	303.71	5.93 (3.64–9.17)	0.25 (0.14–0.43)	0.43 (0.24–0.79)	116
Child–Pugh C							
Untreated	55	14	42.40	33.02 (18.91–53.92)	—	—	55
DAA-treated	44	11	36.83	3.62 (1.92–6.27)	0.90 (0.41–1.99)	1.92 (0.56–6.51)	17
Recurrence							
Untreated	205	62	326.40	19.00 (14.70–24.18)	—	—	196
DAA-treated	209	39	535.88	7.28 (5.25–9.84)	0.38 (0.26–0.57)	0.86 (0.49–1.52)	184

Table 2. Continued

Variable	Patients, n	Deaths, n	Person-years	Mortality rate per 100 person-years (95% CI)	Crude rate ratio (95% CI)	Adjusted HR[a] (95% CI)	Sample size in adjusted HR
No recurrence							
Untreated	199	40	197.62	20.24 (14.67–27.27)	—	—	195
DAA-treated	174	4	405.13	0.99 (0.33–2.35)	0.05 (0.02–0.14)	0.09 (0.02–0.29)	155
No prior recurrence							
Untreated	400	95	508.91	18.67 (15.19–22.71)	—	—	387
DAA-treated	372	43	917.13	4.69 (3.44–6.25)	0.25 (0.18–0.36)	0.57 (0.34–0.94)	329
Using 180-d landmark[c]							
Overall							
Untreated	423	73	714.16	10.22 (8.07–12.78)	—	—	394
DAA-treated	133	11	204.14	5.39 (2.86–9.33)	0.53 (0.28–0.99)	0.57 (0.30–1.09)	115

[a]Adjusted for age, sex, Child–Pugh class, HCC tumor stage, α-fetoprotein level, and type of HCC treatment.
[b]Exposure to DAAs modeled as a time-dependent covariate.
[c]DAA group includes patients who initiated DAA therapy within 180 d from HCC complete response. Patients who died, developed recurrence, received liver transplantation, or had their last clinic visit within 180 d were excluded.

statistical analysis plan, and inclusion of a contemporary untreated comparison group.

In summary, DAA therapy was associated with a significant reduction in mortality among HCV-infected patients with documented complete response to HCC therapy. Overall, our results suggest use of DAA therapies is likely beneficial in HCV-infected patients with a history of HCC.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dxdoi.org/10.1053/j.gastro.2019.07.040.

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Author names in bold designate shared co-first authorship.

Received March 24, 2019. Accepted July 22, 2019.

Reprint requests
Address requests for reprints to: Amit G. Singal, MD, MS, Division of Digestive and Liver Diseases, UT Southwestern Medical Center, 5959 Harry Hines Boulevard, PO Box 1, Suite 420, Dallas, Texas 75390-8887. e-mail: amit.singal@utsouthwestern.edu; fax: 214-645-6114.

Acknowledgments
Author contributions: Study concept and design: Amit G. Singal and Neehar D. Parikh. Acquisition of the data: all authors. Analysis and interpretation of the data: Amit G. Singal and Caitlin C. Murphy. Drafting of the manuscript: Amit G. Singal. Critical revision of the manuscript for important intellectual content: all authors. Obtained funding: Amit G. Singal. Administrative, technical, and material support: Amit G. Singal. Study supervision: Amit G. Singal. Amit G. Singal had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest
These authors disclose the following: Amit Singal was on speakers bureau for Gilead, Bayer, and Bristol Meyers Squibb. He has served on advisory boards

for Gilead, AbbVie, Bayer, Eisai, Bristol Meyers Squibb, Wako Diagnostics, and Exact Sciences. He serves as a consultant to Bayer, Eisai, Exelixis, Roche, Exact Sciences, and Glycotest. He has received research funding from Gilead and AbbVie. Neil Mehta has received research funding from Wako Diagnostics. Anjana Pillai serves as a consultant and is on speakers bureau for Eisai and BTG. Jordan Feld has received research support from Gilead, AbbVie, Merck, and Janssen. Binu John has served on advisory boards for Eisai. Catherine Frenette is on speakers bureaus for Bayer, Bristol Meyers Squibb, Gilead, Merck, AbbVie, and Eisai. She served on advisory boards for Gilead, Eisai, and Wako. She served as a consultant for Bayer and Gilead. She received research funding from Bayer. Parvez Mantry is on speakers bureaus and served on advisory boards for Gilead, AbbVie, Bayer, BMS, Eisai, Merck, and BTG. He has received research funding from Gilead and Sirtex. Michael Leise has received research funding from AbbVie. Kalyan Ram Bhamidimarri serves as scientific advisory board member for Gilead, Merck, and AbbVie. He has received research funding from Gilead. Laura Kulik is on speakers bureau for Eisai, Gilead, and Dova. She serves as an advisory board member for BMS, Eisai, Bayer, and Exelixis. Reena Salgia is on speakers bureau for Bayer. She has served on advisory boards for Bayer, Eisai, and Exelixis. Sanjaya Satapathy has received grant/research support from Biotest, Conatus, Genfit, Gilead Sciences, Intercept, Dova, Bayer, Exact Sciences, and Shire; served on the advisory board or as consultant for AbbVie, Gilead Sciences, and Intercept; and on the speakers bureau for Intercept, Dova, and Alexion. Robert Wong is on the speakers bureau, served as consultant and on advisory boards, and has received research funding from Gilead. He has also received research funding from AbbVie. He was on the speakers bureau for Bayer. Neehar Parikh serves as a consultant to Exelexis and Bristol-Myers Squibb. He has served on advisory boards for Eisai and Bayer. Andrea Branch served as a consultant to Boehringer Ingelheim and has received research support from Gilead. The remaining authors disclose no conflicts.

Funding

This study was conducted with support National Cancer Institute R01 CA222900 and grant support from AbbVie. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or AbbVie. The funding agencies had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation of the manuscript.

Supplementary Table. Patient Characteristics of Direct-Acting Antiviral–Treated Patients, Stratified by Sustained Virologic Response Status

Variable[a]	SVR patients (n = 304)	Non-SVR patients (n = 44)	*P* value
Age at time of complete response, *y*	62.3 (58.6–66.5)	61.6 (59.9–64.0)	.19
Sex, male, n (%)	208 (68.4)	39 (86.6)	.001
Race/ethnicity, n (%)			.17
Non-Hispanic white	154 (50.7)	17 (38.6)	
Hispanic white	40 (13.2)	12 (27.3)	
Black	56 (18.4)	7 (15.9)	
Other	16 (5.3)	2 (4.6)	
Missing	38 (12.5)	6 (13.6)	
No. of HCC nodules at diagnosis, n (%)			.68
1	231 (76.7)	37 (84.1)	
2	54 (17.9)	6 (13.6)	
3	13 (4.3)	1 (2.3)	
4	3 (1.0)	0 (0)	
Maximum HCC diameter at diagnosis, *cm*	2.4 (1.7–3.3)	2.5 (1.7–3.8)	.11
HCC within Milan Criteria at diagnosis, n (%)	245 (81.7)	39 (88.6)	.26
AFP at time of HCC diagnosis, *ng/mL*	18.3 (7.2–68.9)	18.0 (7.1–47.6)	.87
Treatment leading to complete response, n (%)			.44
Resection	63 (20.7)	6 (13.6)	
Local ablation	109 (35.9)	21 (47.7)	
TACE	112 (36.8)	14 (31.8)	
TARE/SBRT/other	20 (6.6)	3 (6.8)	
No. of HCC therapies required to achieve complete response, n (%)			.95
1	174 (60.2)	25 (58.1)	
2	74 (25.6)	12 (27.9)	
3 or more	41 (14.2)	6 (14.0)	
Child–Pugh class at complete response, n (%)			.21
A	189 (62.2)	22 (50.0)	
B	101 (33.2)	18 (40.9)	
C	14 (4.6)	4 (9.1)	
Presence of ascites, n (%)	81 (26.9)	10 (22.7)	.56
Presence of hepatic encephalopathy, n (%)	43 (14.3)	9 (20.5)	.29
Platelet count at complete response	111 (76–158)	101 (62–134)	.12
Bilirubin at complete response, *mg/dL*	1.0 (0.6–1.6)	1.0 (0.7–2.2)	.46
HCV genotype, n (%)			.51
1	239 (79.7)	30 (68.2)	
2	20 (6.7)	5 (11.4)	
3	31 (10.3)	7 (15.9)	
4–6	10 (3.3)	2 (4.6)	
Viral co-infection, n (%)			.89
Hepatitis B	5 (1.7)	1 (2.3)	
Human immunodeficiency virus	7 (2.5)	2 (4.9)	
DAA regimen,[b] n (%)			.17
Sofosbuvir/ledipasvir	196 (65.1)	23 (54.7)	
Sofosbuvir	42 (14.0)	13 (18.7)	
Simeprevir/sofosbuvir	26 (8.6)	5 (8.0)	
Sofosbuvir/velpatasvir	11 (3.7)	0 (0)	
Daclatasvir/sofosbuvir	13 (4.3)	2 (4.6)	
Ombitasvir/partiprevir/ritonavir/dasabuvir	6 (2.0)	0 (0)	
Elbasavir/grazoprevir	3 (1.0)	0 (0.0)	
Other	4 (1.3)	1 (2.3)	
DAA regimen duration, n (%)			.46
<12 wk	13 (4.4)	1 (2.3)	
12 wk	156 (52.2)	23 (53.5)	
>12 wk but <24 wk	20 (6.7)	6 (14.0)	
24 wk	105 (35.1)	12 (27.9)	
>24 wk	5 (1.7)	1 (2.3)	

Supplementary Table. Continued

Variable[a]	SVR patients (n = 304)	Non-SVR patients (n = 44)	*P* value
Time from HCC complete response to DAA, n (%)			.22
<3 mo	65 (21.6)	8 (18.2)	
>3–6 m	65 (21.6)	11 (25.0)	
>6–12 mo	81 (26.9)	8 (18.2)	
>12–24 mo	70 (23.3)	10 (22.7)	
>24 mo	20 (6.6)	7 (15.9)	

AFP, α-fetoprotein; SBRT, stereotactic body radiation therapy; TARE, transarterial radioembolization.
[a]Continuous data presented as median (IQR).
[b]All DAA regimens are with or without ribavirin.