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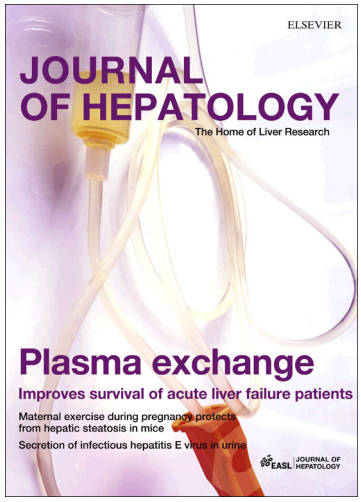

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Effectiveness of hepatitis c antiviral treatment in a USA cohort of veteran patients with hepatocellular carcinoma

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Author contributions:

All authors approved the final version of the manuscript

Lauren Beste: Study concept and design, interpretation of data, drafting of the manuscript, critical revision of the manuscript

Pamela Green: Analysis of data

Kristin Berry: Study design and analysis of data

Matthew J. Kogut: Interpretation of data, critical revision of the manuscript

Stephen K. Allison: Interpretation of data, critical revision of the manuscript

George Ioannou: Study concept and design, acquisition of data, statistical analysis and interpretation of data, critical revision of the manuscript, obtained funding

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Abstract

Background & Aims: Hepatitis C virus (HCV) treatment for patients with hepatocellular carcinoma (HCC) was uncommon before direct acting antiviral (DAA) medications. Real-world effectiveness of DAAs for HCV in patients with HCC is unclear. We describe rates of sustained virologic response (SVR) with DAA regimens by HCV genotype in patients with history of HCC.

Methods: We identified patients who initiated antiviral treatment between January 1, 2014 and June 30, 2015 in the national Veterans Affairs health care system. Regimens included sofosobuvir, ledipasvir/ sofosbuvir, and paritaprevir/ ritonavir/ ombitasvir and dasabuvir with or without ribavirin. HCC patients were divided into those who were treated with liver transplantation after HCC diagnosis ("HCC/LT" group) and those treated with other modalities prior to antiviral therapy ("HCC" group).

Results: Of 17,487 HCV treatment recipients, 624 (3.6%) had prior HCC, including 142 with HCC/LT and 482 with HCC. Overall SVR was 91.9% in non- HCC, 74.5% in HCC, and 93.4% in HCC/LT. Among HCC patients, genotype 1 had the highest SVR overall (79.0% in HCC and 96.0% in HCC/LT), and genotype 3 the lowest (47.0% in HCC and 88.9% in HCC/LT). After adjustment for confounders, the presence of HCC was associated with lower likelihood of SVR overall (AOR 0.38 [95%CI 0.29, 0.48], p<.001).

Conclusion: HCV can be cured with DAAs in the majority of patients with prior HCC, and in virtually all HCC patients post-liver transplant. Deferral of HCV treatment until the post-transplant setting may be considered among HCC patients listed for transplantation.

Lay Summary: Over three quarters of patients with hepatocellular carcinoma who have hepatitis C can achieve viral cure with direct acting antiviral drugs. Among patients with hepatocellular carcinoma who subsequently received liver transplantation, over 90% of patients can achieve viral cure.

Hepatocellular carcinoma (HCC) mortality increased 72% in the United States (US) between 2003-2012, making it the fastest-growing cause of cancer-related mortality.[1] HCC incidence also rose during this time, with a delay-adjusted average annual percentage change of 3.7%, second only to thyroid cancer nationally.[1] HCV is implicated in the majority of HCC cases in the US.[2-4] Until the widespread use of direct acting antivirals (DAAs), antiviral treatment for patients with HCC and HCV was hampered by the poor efficacy and tolerability of interferon. Very few HCC patients were eligible for treatment due to interferon contraindications, such as advanced cirrhosis. HCV is now largely curable using DAAs, even in populations once considered difficult to treat.[5-7] However, only one clinical trial for a DAA-based regimen has specifically targeted patients with HCC (n=61), and this trial involved patients already listed for liver transplantation.[8]

The role of DAAs in patients with a history of HCC remains uncertain. Patients with advanced HCC may not be offered antiviral treatment due to high cancer-related mortality. Those with severely decompensated cirrhosis may not be offered antiviral treatment due to high cirrhosis-related mortality, particularly if they are not candidates for transplantation. Finally, HCC patients tend to be older than other patients with HCV, which is associated with extra-hepatic comorbidities that might limit possible benefits from antiviral treatment.

There are also many reasons for considering HCV treatment in selected patients with a history of HCC. First, HCV treatment in liver transplant recipients is considered a cornerstone of care, including in those with prior HCC.[9] Patients with decompensated cirrhosis may benefit from regression or stabilization of their cirrhosis and improvement in liver function as a result of HCV eradication, even allowing for transplant delisting in some cases.[10, 11] Finally, in the interferon era, HCV treatment was suggested to reduce the future risk of HCC recurrence [12-16], though conflicting reports have arisen surrounding risk of HCC recurrence after DAA therapy.[11, 17-20]

The real-world effectiveness of DAA treatment in patients with a history of HCC is unknown. The Department of Veterans Affairs (VA) healthcare system encompasses the largest cohorts of HCV patients and HCC patients in the US. The objective of this study was to describe the characteristics of HCC patients who receive DAA-based antiviral treatment and to report the rates and predictors of SVR.

EXPERIMENTAL PROCEDURES

Data Source

All data were obtained from the VA Corporate Data Warehouse, a comprehensive repository of data from the VA's universal electronic medical record system.[21] Data extracted included all patient pharmacy prescriptions, demographics, inpatient and outpatient visits, problem lists, procedures, vital signs, diagnostic tests, and laboratory tests.

Human Subjects

All study procedures were approved by the VA Puget Sound Institutional Review Board. All procedures conform to the ethical guidelines of the 1975 Declaration of Helsinki. A waiver of informed patient consent was obtained prior to project initiation.

Study Population

The national VA system includes 167 medical centers and 875 ambulatory clinics, and served a total of 174,889 patients with chronic HCV diagnosis in 2014.[22] We identified 24,089 HCV regimens initiated between 1/1/2014-6/30/2015 and completed before 10/1/2015. We identified patients who initiated antiviral treatment including sofosbuvir (SOF), ledipasvir/sofosbuvir (LDV/SOF) and paritaprevir/ritonavir/ombitasvir and dasabuvir (PrOD) during the 18-month period from 1/1/2014 (when SOF was approved by the US Food and Drug Administration) to 6/30/2015 (n=24,089). We excluded 6,193 regimens that were no longer recommended in the VA by the time we conducted this study, such as SOF+simeprevir±ribavirin (n=3,669), SOF +pegylated-interferon (PEG)±ribavirin for genotype 1 HCV (n=1,766), SOF+ribavirin for genotype 1 HCV (n=418) or other regimens (n=340). We also excluded 409 duplicate regimens that were very short in duration ($\leq$14 days) and were therefore considered erroneous or postponed prescriptions, leaving 17,487 patients in the current analysis.

Data extended forward until 4/10/2016 to allow completion of treatment and ascertainment of SVR. Duration of antiviral therapy was calculated using the total duration of the DAA prescriptions filled. A course was considered terminated if medications were not refilled within 45 days after the final prescription was exhausted. Data extended backwards to 10/1/1999 in order to allow determination of previous antiviral treatments and past medical history. Diagnosis of HCC was ascertained using previously validated methods requiring at least 2 instances of International Classification of Diseases, 9th Revision (ICD-9) codes for HCC (155.0) on separate days.[23-28] We identified 624 cases with a diagnosis of HCC prior to first DAA prescription, including 142 with HCC/LT prior to antiviral treatment. HCC patients who received liver transplantation (HCC/LT) before HCV treatment were analyzed separately, as we expected this group to have very different SVR rates. HCC patients who received liver transplant after HCV treatment (n=8) were included in the HCC group.

Treatments for HCC were classified as local ablation (radiofrequency ablation, cryotherapy, ethanol injection, or unspecified ablation), surgical resection, trans-arterial chemoembolization (TACE), Yttrium-90, or sorafenib. ICD-9 and Current Procedural Terminology codes for HCC-related procedures were identified by 2 board-certified interventional radiologists (MJK, SKA) and through review of previously published work (Supplemental Table 1).[29] VA facilities that do not offer certain HCC treatments may outsource them to non-VA facilities through the "fee services" mechanism. Therefore, in addition to searching for HCC treatments provided at VA facilities, we also searched "fee services" data.

Baseline Characteristics

We ascertained age, race, ethnicity, gender, and prior antiviral treatment since 1999 ("treatment experienced"). We used ICD-9 codes to define diagnosis of cirrhosis, diabetes, liver transplantation, depression, post-traumatic stress disorder, anxiety or panic disorder, schizophrenia , alcohol use disorders, and substance use disorders (SUD) (Supplemental Table 2). ICD-9 codes used in defining comorbidities have been widely used and validated in VA medical records.[26, 30-34] All comorbid diagnosis variables were ascertained using ICD-9 codes recorded at least twice, on separate days, before the initiation of antiviral treatment. All patients with HCC/LT were considered to be non-cirrhotic,

given that it would be impossible to determine whether the diagnoses for cirrhosis reflected their current condition as opposed to their pre-transplant condition.

We extracted all laboratory tests shown in Table 1 and recorded the value of each test closest to the treatment start date within the preceding 6 months. We calculated the FIB-4 score [35] (FIB-4= [age x AST]/ [platelets x $ALT^{1/2}$]), which is associated with advanced fibrosis and cirrhosis. Of 17,487 regimens, 678 had missing genotype. These patients were treated either with PrOD±ribavirin(n=130) or with LDV/SOF monotherapy(n=548) and were assigned genotype 1 since these regimens are used almost exclusively for genotype 1 HCV infection. Among patients with known genotype treated with these regimens 11,761 out of 11,871(99%) had genotype 1 HCV infection.

Sustained Virologic Response

SVR was defined by a viral load below the limit of quantification performed >12 weeks after the end of treatment.[36] Prior work has demonstrated that SVR ascertained based on viral load 4 weeks after the end of treatment has 98% concordance with SVR based on viral load >12 weeks after the end of treatment in SOF-treated patients.[36] Therefore, if no viral load test was available >12 weeks after the end of treatment, then we defined SVR by a viral load performed 4-12 weeks post-treatment(n=996).

Statistical Analysis

Descriptive statistics were used to characterize study participants overall and by HCC status. We determined unadjusted SVR and 95% confidence intervals by HCC status, regimen, genotype and clinically significant subgroups. We developed a multivariable logistic regression model to identify predictors of SVR. Covariates were selected *a priori* based on putative relationships between SVR and HCC. These included age, gender, race/ethnicity, genotype, subgenotype, baseline viral load, prior antiviral treatment, diabetes, alcohol use disorder, cirrhosis, platelets<100,000, serum bilirubin>1.1 g/dL, serum albumin<3.6 g/dL, and FIB-4 score>3.25.

Some patients had no post-treatment viral load data >4 weeks after the conclusion of DAA therapy, precluding ascertainment of SVR. Missing SVR occurred more frequently in HCC(11.6%) compared to HCC/LT(6.3%) or no HCC(9.1%). To evaluate the impact of missing data, we compared patients with and without SVR data with respect to baseline characteristics and treatment duration. We multiply imputed missing SVR using a logistic regression model with the 23 baseline patient characteristics shown in Table 1, along with duration of treatment. The number of imputations varied from 10 to 200 resulting in identical estimates up to four significant digits. The model was determined stable and m=20 imputations were used. The assumption of randomly missing data was found to be reasonable using the observed data.

Analyses were performed using STATA MP v14 (StataCorp, College Station, TX).

RESULTS

Population characteristics

Patients with HCC(n=482) or HCC/LT(n=142) tended to be older, white, and treatment-experienced compared to non-HCC(n=16,863, Table 1). The majority(85.1%) of non-transplanted HCC patients had documented cirrhosis; 31.5% had decompensated cirrhosis. Diabetes and depression were more common in HCC/LT compared to HCC(61.3% v. 36.9%, and 59.2% v. 47.9%).

Genotype 3 HCV was more common in HCC(11.6%) and HCC/LT(13.4%) compared to non-HCC(6.9%). Patients with HCC/LT tended to have higher rates of elevated creatinine and anemia compared to others, consistent with use of anti-rejection drugs. HCC patients without transplant tended to have higher rates of thrombocytopenia, elevated bilirubin, and low albumin, consistent with the higher prevalence of cirrhosis in this group.

Prior HCC treatments in patients without LT

Of 482 non-transplanted HCC patients, we identified 368(76.4%) who received HCC treatment through the VA. Of these, 50.6% received at least one instance of TACE, 37.3% local ablation, 17.0% surgical resection, and 14.3% sorafenib. HCC patients were included in multiple treatment categories if they received >1 modality.

Antiviral Treatment Regimens By Genotype and HCC status

Distribution of antiviral treatment regimens by genotype and HCC status is shown in Table 2. More genotype 1-infected patients with HCC and HCC/LT(88.1% and 99.1%) received a LDV/SOF-based regimen compared to 77.2% in the non-HCC group. Compared to patients who received LDV/SOF regimens, those receiving PrOD regimens were less likely to have elevated FIB-4 score(47.7% v. 73.1%), thrombocytopenia(23.1% v. 40.2%), or elevated bilirubin(21.6% v. 35.9%).

All genotype 2-infected patients received a combination of SOF and ribavirin. The majority of genotype 3-infected patients with HCC and HCC/LT received SOF+ribavirin(52.3% and 61.1%). A significant portion of HCC and HCC/LT patients received LDV/SOF plus ribavirin(35.3% and 38.9%) with the remainder of HCC patients(25.8%) receiving

SOF/PEG+ribavirin. Among genotype 3-infected patients without HCC, 57.1% received SOF plus ribavirin, 30.8% received LDV/SOF, and 12.1% received PEG/SOF+ribavirin.

Observed SVR Results

SVR outcomes were available for 15,884 patients who received HCV antiviral treatment (90.8% of those who initiated treatment)(Table 2). Overall SVR rates were substantially higher in the non-HCC group (91.9%[95%CI 90.6, 91.5]) and the HCC/LT group (94.0%[95%CI 88.3, 97.0]) than in the HCC group, (74.4%[95%CI 70.0, 78.3]) (Figure 1). A pattern of higher SVR rates in the non-HCC and HCC/LT groups compared to the HCC group persisted across all genotypes and DAA regimens, and across subgroups defined by cirrhosis status or prior antiviral treatment (Table 2). Patients infected with genotypes 1 and 4 HCV had the highest rates of SVR within each HCC category and genotype 3 the lowest. Those with HCC/LT tended to have the highest SVR rates for each genotype. Among patients with HCC, those with cirrhosis had substantially lower SVR rates than those without (73.0%[95%CI 68.2, 77.3] v. 82.5%[95%CI 70.8, 90.2]). Non-HCC patients with cirrhosis had lower SVR rates compared to the non-cirrhotic group (87.9%[95%CI 86.1, 88.8] v. 92.4%[95%CI 91.8, 92.8]).

For genotype 1-infected patients, SVR rates were 79.1%(95%CI 74.4, 83.1) for patients with HCC, 96.4%(95%CI 90.1, 98.7) for HCC/LT, and 93.1%(95%CI 92.6, 93.5) for non-HCC. PrOD regimens(n=41) had the highest SVR in genotype 1-infected patients with HCC. Among patients who received PrOD with ribavirin(n=39), SVR was 97.4% (95% CI 82.6, 99.7) versus 76.3 (95% CI 68.8, 82.5) for LDV/ SOF(n=152) and 76.8% (95% CI 69.3, 82.9) for LDV/ SOF with ribavirin (n=151). Only 1 patient with HCC/LT received a PrOD regimen. SVR in genotype 1-infected patients with HCC/LT was 97.2% (95% CI.81, 99.6) for LDV/SOF and 96.0% (95% CI 87.9, 98.7) for LDV/SOF with ribavirin.

For genotype 2-infected patients, the rate of SVR was 68.9%(95%CI 49.0, 83.7) for HCC, and 86.5%(95%CI 84.9, 88.0) for patients without HCC. A very small number of genotype 2-infected patients with HCC/LT were identified(n=4), with an SVR rate of 50.0%(95%CI 2.5, 97.5). Among genotype 3-infected patients, the rate of SVR was 47.0%(95%CI 33.5, 61.1) for HCC, 88.9%(95%CI 61.0, 97.6) for HCC/LT and 75.9%(95%CI 73.3, 78.5) for patients without HCC. In HCC

genotype 3-infected patients, treatment success was highest among those receiving LDV/SOF+ribavirin(100%) compared with other regimens, though the sample size was small(n=7).

We examined SVR rates by type of HCC treatment modality (Supplemental Table 3). Patients with surgical resection had the highest SVR rate (78.9%[95%CI 68.1,86.8]), followed by local ablation (70.1% [95%CI 62.6,76.6]), TACE (70.0%[95%CI 63.6,75.7]), and sorafenib (59.0% 995%CI 46.0,70.9]). The SVR rate for patients without documented HCC treatment data was 78.0% (95%CI 68.2-85.4), similar to the rate of 73.4% (95%CI 68.4-77.9) for patients with HCC treatment documented within VA.

Early Treatment Discontinuation, Treatment Duration and HCC Status

Among all patients(n=17,487), early discontinuation of treatment before 8 weeks was slightly more common in patients without HCC(6.3%) compared to HCC(4.6%) or HCC/LT (4.9%) (Supplemental Table 4). Mean duration of treatment was shorter in non-HCC patients (84.9 days[SD 32.3]) than in HCC(102.2 [SD 42.4]) or HCC/LT patients(102.3[SD 40.4]). This was driven by two factors. First, non-HCC patients more commonly completed 8-week regimens(14.4%) than HCC or HCC/LT patients(4.6% and 1.4%), as expected since patients with cirrhosis or LT are ineligible for 8-week LED/SOF regimens. Second, patients with HCC or HCC/LT more commonly completed 24 week regimens(18.7% and 22.5%, respectively) than patients without HCC(8.0%).

Impact of Missing SVR Data and Imputation for Missing SVR

SVR data was missing in 1,603(9%) of 17,487 patients who initiated DAAs. We compared patients with and without missing SVR and found no clinically meaningful differences in HCC status, age, genotype, cirrhosis, and most other baseline characteristics (Supplemental Table 5). However, patients with missing SVR were more likely to be Hispanic, treatment naïve, and to have prior depression, or alcohol or substance use disorders. Duration of treatment was 71 days(SD 38) among patients with available SVR data and 87 days(SD 31) among patients with missing data. Among patients without SVR data, 25% discontinued therapy between week 0-8 compared with 4.4% with available SVR,

suggesting a possible relationship between early discontinuation and missing SVR. We performed several analyses to impute missing SVR using a logistic regression model including duration of treatment together with baseline patient characteristics shown in Table 1. After including imputed results, SVR rates were slightly lower compared to observed SVR results (1-2% difference across HCC subgroups) (Supplemental Table 6).

Predictors of antiviral treatment outcome

In multivariable analyses in all genotypes combined, HCC patients were less likely to achieve SVR than non-HCC patients (AOR .38[95%CI .26,.45], p<.001) after adjusting for genotype, cirrhosis, and other characteristics (Table 3). HCC negatively predicted SVR in patients infected with genotypes 1 (AOR .34[95%CI .26,.45], p<.001) and 3 (AOR .41[95%CI .22,.76], p=.005), with a nonsignificant trend observed in genotype 2 (AOR .59[95%CI .25,1.38], p=.22). A non-significant trend towards higher SVR was observed in patients with HCC/LT overall, and within genotypes 1, 2, and 3.

In multivariate analysis of non-transplanted HCC patients, genotype 3 was the only independent predictor of failure to achieve SVR (AOR .19[95%CI .10,.41], p<.001) (Table 4). Among HCC patients with genotype 1 HCV, multivariate analysis including drug regimen revealed that black race was associated with failure to achieve SVR (AOR .49[95%CI .24,.97], p=.04) while receipt of PrOD+ribavirin was associated with SVR relative to LDV/SOF (AOR 10.07[95%CI 1.28,79.3], p=.028). Hispanic race closely approached statistical significance as a negative predictor of SVR (AOR .30[95%CI .09,1.00], p=.05) (Table 4).

We performed an exploratory multivariable analysis of the impact of ribavirin in genotype 1 patients with HCC, limited to LDV/SOF since virtually all HCC patients receiving PrOD patients also received ribavirin. The adjusted odds ratio for LDV/SOF compared to LDV/SOF+ribavirin was 1.09 (95% CI 0.60,2.0), indicating no statistically significant effect of adding ribavirin.

DISCUSSION

DAAs have increased the efficacy of HCV therapy for many patients once considered difficult to treat, including those with prior HCC, with or without liver transplantation. Among non-transplanted HCC patients from the VA who received DAA therapy between 1/1/2014 and 6/30/2015 (n=426), SVR was achieved in 74.4% (95%CI 70.0,78.3). Among 133 additional HCC patients who underwent liver transplantation following HCC diagnosis, the SVR rate was much higher (94.0% [95%CI 88.3,97.0]) and similar to that of the general HCV population (91.1% [95%CI 90.6,91.5]). While the odds of SVR in non-transplanted HCC patients was significantly lower compared to non-HCC (AOR .34 [95%CI .26,.45], p<.001), treatment success remains within reach for most HCC patients.

As in the non-HCC population, SVR results vary by genotype in patients with HCC. HCC patients with genotype 1 infection achieved an SVR rate of 79.1% [95%CI 74.4, 83.1], while those with HCC/LT achieved an SVR rate of 96.4% [95%CI 90.1, 98.7%] which compares favorably to the general HCV population (93.1% [95%CI 92.6,93.5]). The overall rate of SVR in HCC genotype 2 and 3-infected patients was lower than for genotype 1 at 68.9% (95%CI 49.0,83.7) and 47.0% (95%CI 33.5,61.1), though findings are limited by small sample sizes. We did not detect an independent relationship between prior treatment and SVR.

It is unclear why patients with HCC had such lower SVR rates compared to patients without HCC. The association between HCC and treatment failure persisted after adjustment for cirrhosis, markers of liver dysfunction, and genotype (Table 3). Therefore, these factors cannot explain the lower SVR in patients with HCC, and lead us to suspect that HCC, itself, could be causally linked to antiviral treatment failure– for example, if HCV within tumor cells is relatively inaccessible to DAAs due to differences in blood supply or other reasons. Additionally, HCC arises in the setting of chronic inflammation, distorted liver architecture, and alterations in the cytokine and chemokine environment.[37, 38] We speculate that altered hepatic immune processes may predispose both to HCC and to poorer antiviral treatment outcomes. Finally, it is possible that viral factors such as resistance associated substitutions and quasispecies may differ in patients with HCC and contribute to treatment failure.

When limiting to genotype 1 patients, black race was an independent predictor of SVR (AOR .49 [95%CI .24,.97], p=.04) (Table 5). A recent pooled analysis showed similar rates of SVR12 in black (95%) v. non-black patients (97%) after 12 weeks of LDV/SOF±ribavirin.[39] While DAA regimens may have greatly mitigated the association between black race and treatment failure seen in the interferon era, additional study is warranted to explore the finding of lower SVR outcomes in black patients with HCC.

Among genotype 1-infected HCV patients with HCC, only a minority (15.3%, n=52) were initiated on PrOD compared to LDF/SOF regimens (84.6%, n=338). The rate of SVR was 97.4% (95%CI 82.6,99.7) for PrOD+ribavirin compared to 76.8% (95%CI (69.3,82.9) for LDV/SOF +ribavirin. We investigated whether genotype 1-infected patients who received LDV/SOF were more likely to have selected adverse factors related to poor liver function, given contraindications to PrOD in decompensated cirrhosis.[40] Compared to patients who received LDV/SOF regimens, those receiving PrOD regimens were less likely to have markers of cirrhosis such as elevated FIB-4 (47.7% v. 73.1%), thrombocytopenia (23.1% v. 40.2%), or elevated bilirubin (21.6% v. 35.9%). However, after adjustment for race, bilirubin, platelet count, albumin, FIB-4, viral load, alcohol use, diabetes, and treatment experience, we continued to find an association between PrOD regimens and SVR compared to LDV/SOF (AOR 10.07 [95%CI 1.28,79.3], p=.028). In the general HCV population, PrOD regimens were previously reported to have similar SVR compared to LDV/SOF in genotype 1-infected patients.[41] Given our small population of genotype 1-infected HCC patients who received PrOD, our finding requires confirmation in other populations with HCC.

Patients with a history of HCC and subsequent liver transplant had superior SVR (94.0% [95%CI 88.3,97.0]) compared to non-transplanted patients with HCC (74.4% [95% CI 70.0,78.3]). High rates of SVR in HCC/LT likely result from correction of liver dysfunction and removal of the underlying HCC. In addition, transplant patients typically receive expert follow-up care, usually from subspecialists at tertiary centers. Finally, transplant patients are selected for high levels of motivation and medical adherence, which likely predicts compliance with antiviral regimens. The high rates of SVR we observed in post-transplant patients echo multiple HCV clinical trials performed in the post-transplant setting, though no published trials have focused solely on transplant patients with a history of HCC.[6, 8, 42-44]

Whether to offer HCV treatment pre-transplant versus deferring to the post-transplant setting remains an area of clinical uncertainty. Our findings suggest that HCC patients currently listed for transplantation, or those with a high probability of getting transplanted quickly, might benefit from postponing antiviral treatment until after transplant in order to maximize the chances of SVR. However, our findings also show that non-transplanted HCC patients, representing the majority of the HCC population, can still achieve SVR in most cases (74.4% [95% CI 70.0,78.3]). A small (n=58), retrospective, non-randomized study recently reported an "unexpected high rate" of early tumor recurrence in patients with HCV-related HCC after DAA therapy.[17] The investigators speculated that HCV eradication may facilitate HCC recurrence by altering host immune status. A second single-center observational report from a US center (n=112) similarly reported a trend towards higher risk of post-transplant HCC recurrence in patients who received DAAs pre-transplant compared to untreated patients who received transplant (27.8% v. 9.5%, p=.06), though these results were not adjusted for length of follow-up time nor for predictors of HCC recurrence.[20] On the converse, the largest retrospective cohort study to date (n=314 HCC patients with transplant; n=202 HCC patients without) did not find an increased risk of HCC recurrence after DAA therapy.[19] These early findings needs to be confirmed by larger, prospective, controlled studies before they can be used to guide practice.

Our study benefited from a large cohort of HCC patients in a single-payer national system with near-complete capture of laboratory and pharmacy data obtained within VA. Our findings should be interpreted with several caveats. SVR outcome was missing in 11.6% of HCC patients and 6.3% of HCC patients treated with transplant. Most baseline patient characteristics were similar for those with and without known SVR status, but patients with missing SVR data appeared more likely to discontinue treatment before 8 weeks. Of note, patients with HCC and HCC/LT were less likely to discontinue therapy early (before 8 weeks) compared to those without HCC, suggesting that the lower SVR noted in the HCC population is unlikely due to premature discontinuation of therapy. After careful imputation of missing SVR results, including duration of therapy as a predictor, imputed SVR appeared negligibly lower than observed values (1-2% difference across HCC subgroups). A second limitation concerns the availability of HCC treatment data, which was missing in 23.6% of non-transplanted cases, even after we searched for HCC interventions outsourced to non-VA

settings. Patients with a history of HCC are extremely likely to have received some form of HCC-specific treatment as a prerequisite before antiviral therapy, as it would be difficult to rationalize antiviral therapy in a patient with untreated liver cancer. It is possible that some HCC treatments were provided through non-VA health insurance, and therefore not captured by our methodology, or that the coding of HCC-related interventions is incomplete. It is also possible that some patients who were listed for LT received antiviral therapy pre-emptively, in the absence of HCC treatment. Further validation work is needed to clarify the specific types of HCC treatments received, responses to HCC therapy, and the time elapsed between HCC treatment and antiviral therapy. A third limitation concerns the ascertainment of HCC itself. Although we used well-validated ICD-9 codes to identify cases of HCC, misclassification of patients with HCC is always a risk. Finally, though HCC generally tends to be a male-predominant condition, results from our overwhelmingly male study population may have limited generalizability to women.

Future study is needed to determine if overall and cancer-specific mortality is improved in HCC patients who achieve SVR as a result of HCV antiviral therapy relative to those who do not achieve SVR or relative to those who remain untreated. Our observational results suggest that HCV can be cured in the majority of patients with HCC, and in virtually all with a prior history of HCC and subsequent liver transplantation.

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Table 1. Baseline characteristics of patients with HCC who initiated HCV antiviral treatment in the national VA healthcare system from January 2014 to June 2015 (N=17,487)

	No HCC (n=16,863)	HCC (n=482)	HCC/LT (n=142)
Age, years(mean, SD)	60.7 (6.6)	63.0 (4.9)	62.7 (4.7)
Male(%)	96.8	98.1	97.2
Race/Ethnicity(%)			
White, non-Hispanic	52.1	52.5	66.9
Black, non-Hispanic	29.0	28.4	16.9
Hispanic	5.2	6.0	7.8
Asian, Pacific Islander, American Indian	1.6	2.3	2.1
Missing	12.2	10.8	6.3
HCV Treatment Experienced(%)	28.7	43.9	40.1
HCV RNA Viral load >6 million IU/mL(%)	19.7	12.2	22.1
HIV co-infection(%)	4.2	2.1	1.4
Cirrhosis(%)	28.7	85.1	n/a
Decompensated Cirrhosis(%)	7.7	31.5	n/a
Diabetes(%)	28.7	36.9	61.3
Alcohol Use Disorder(%)	43.8	53.7	56.3
Substance Use Disorder(%)	37.1	35.5	33.8
Depression(%)	47.3	47.9	59.2
PTSD(%)	26.8	29.3	23.9
Anxiety/ Panic(%)	34.1	32.6	35.2
Schizophrenia(%)	5.5	3.3	1.4
Genotype(%)			
1	79.9	80.9	83.8
2	12.4	6.9	2.8
3	7.0	11.6	13.4
4	0.8	0.6	0.0
Laboratory Results(%)			
Anemia§	13.9	30.3	34.5
Platelet Count<100 k/μL	12.8	39.4	16.2
Creatinine > 1.1 mg/dL	19.6	16.1	53.6
Bilirubin > 1.1 g/dL	13.4	33.1	21.8
Albumin < 3.6 g/dL	19.4	51.2	26.8
INR > 1.1	21.1	47.9	21.4
FIB-4 score > 3.25	34.7	71.4	45.0

† FIB-4 score[35] = [age x AST]/[platelets x $ALT^{1/2}$]

§ Defined as a hemoglobin concentration <13 g/dL in men or <12 g/dL in women

Table 2. SVR among clinically relevant subgroups by HCC treatment class and antiviral regimen*

	n	No HCC (% [95%CI])	n	HCC (% [95%CI])	n	HCC/LT (% [95%CI])
All Patients	15,325	91.1 (90.6, 91.5)	426	74.4 (70.0, 78.3)	133	94.0 (88.3, 97.0)
Genotype 1	12,289	93.1 (92.6, 93.5)	344	79.1 (74.4, 83.1)	111	96.4 (90.1, 98.7)
LDV/SOF	7,224	93.1 (92.5, 93.7)	152	76.3 (68.8, 82.5)	36	97.2 (81.2, 99.6)
LDV/SOF+Ribavirin	2,275	92.9 (91.8, 93.9)	151	76.8 (69.3, 82.9)	74	96.0 (87.9, 98.7)
PrOD	702	94.9 (93.0, 96.2)	2	100.0 -	0	-
PrOD+Ribavirin	2,088	92.3 (91.1, 93.4)	39	97.4 (82.6, 99.7)	1	100.0 -
Genotype 2 SOF+Ribavirin	1,877	86.5 (84.9, 88.0)	29	68.9 (49.0, 83.7)	4	50.0 (2.5, 97.5)
Genotype 3	1,036	75.9 (73.3,78.5)	51	47.0 (33.5, 61.1)	18	88.9 (61.0, 97.6)
LDV/SOF+Ribavirin	319	78.9 (74.1,83.1)	18	50.0 (26.4, 73.6)	7	100.0 -
SOF + PEG+Ribavirin	125	88.8 (81.9,93.3)	6	50.0 (9.1, 90.9)	0	-
SOF+Ribavirin	592	71.6 (67.8, 75.1)	27	44.4 (26.2, 64.3)	11	81.8 (42.0, 96.5)
Genotype 4 LDV/SOF±Ribavirin or PrOD±Ribavirin	123	90.2 (83.5, 94.4)	2	50.0 -	0	-
No Cirrhosis	10,915	92.4 (91.8, 92.8)	63	82.5 (70.8, 90.2)	133	94.0 (88.3, 97.0)
Cirrhosis	4,410	87.9 (86.1, 88.8)	363	73.0 (68.2, 77.3)	0	-
Treatment Naïve	10,840	91.4 (90.9, 91.9)	238	76.8 (71.1, 81.8)	81	92.6 (84.2, 96.7)
Treatment Experienced	4,485	90.3 (89.4, 91.1)	188	71.3 (64.3, 77.3)	52	96.1 (85.2, 99.1)

* N's differ from Table 1 because Table 2 is limited to patients with known SVR status.

Table 3. Association between HCC and SVR in multivariable logistic regression models

	All Patients (n=15,573)		Genotype 1 (n=12,493)		Genotype 2 (n=1,868)		Genotype 3 (n=1,084)	
	AOR (95%CI)†	p	AOR (95%CI)†	p	AOR (95%CI)†	p	AOR (95%CI)†	p
NO HCC	1	-	1	-	1	-	1	-
HCC	0.38 (.29, .48)	<.001	0.34 (.26,.45)	<.001	0.59 (.25,1.38)	.224	.41 (.22, .76)	.005
HCC/LT	1.57 (.75, 3.28)	0.23	1.89 (.68,5.20)	.21	.10 (.01, .82)	.03	2.7 (.58, 12.6)	.20

† AOR: Adjusted odds ratio, by multivariable logistic regression modeling including age, gender, race/ethnicity, alcohol use disorders, genotype, subgenotype, HCV regimen, baseline HCV viral load, diabetes, treatment naïve/experienced, cirrhosis, decompensated cirrhosis, platelet count, bilirubin, and albumin.

Table 4. Predictors of SVR among patients with history of HCC and without prior liver transplant

	HCC, all genotypes (n=426)			HCC, genotype 1 HCV (n=344)		
	AOR†	**95%(CI)**	**p-value**	**AOR†**	**95%(CI)**	**p-value**
Age	.98	.92, 1.03	.42	.96	.90, 1.02	.24
Race/ Ethnicity						
White, non-Hispanic	1	1	1	1	1	1
Black, non-Hispanic	.66	.35, 1.23	.19	.49	.24, .97	.04
Hispanic	.51	.18, 1.43	.20	.30	.09, 1.00	.05
Asian, Pacific Islander, American Indian	.90	.17, 4.66	.90	.59	.11, 3.30	.55
Missing	1.41	.53, 3.78	.49	1.41	.42, 4.73	.57
Alcohol Use Disorder	.66	.39, 1.11	.12	.69	.38, 1.26	.23
Diabetes	.64	.38, 1.08	.09	.64	.35, 1.18	.16
Genotype						
1	1	1	1	n/a	n/a	n/a
2	.43	.16, 1.15	.09	n/a	n/a	n/a
3	.19	.10, .41	<.001	n/a	n/a	n/a
4	.26	.01, 5.01	.37	n/a	n/a	n/a
Antiviral Regimen						
LDV/SOF	n/a	n/a	n/a	1	1	1
LDV/SOF+Ribavirin	n/a	n/a	n/a	1.07	.58, 1.95	.83
PrOD	n/a	n/a	n/a	-	-	-
PrOD+Ribavirin	n/a	n/a	n/a	10.07	1.28, 79.3	.028
Baseline HCV RNA >6 million IU/mL	.55	.24, 1.24	.15	.55	.24, 1.24	.15
FIB-4 >3.25	.59	.30, 1.16	.12	.76	.34, 1.67	.49
Platelet < 100	.85	.47, 1.55	.60	.51	.24, .97	.07
Bilirubin > 1.1	.70	.39, 1.25	.23	.82	.42, 1.59	.56
Albumin <3.6	1.41	.80, 2.48	.23	1.62	.81, 3.23	.17
Cirrhosis	.68	.31, 1.48	.33	.84	.35, 2.07	.71
Treatment-Experienced	.79	.48, 1.31	.36	.81	.45, 1.47	.49

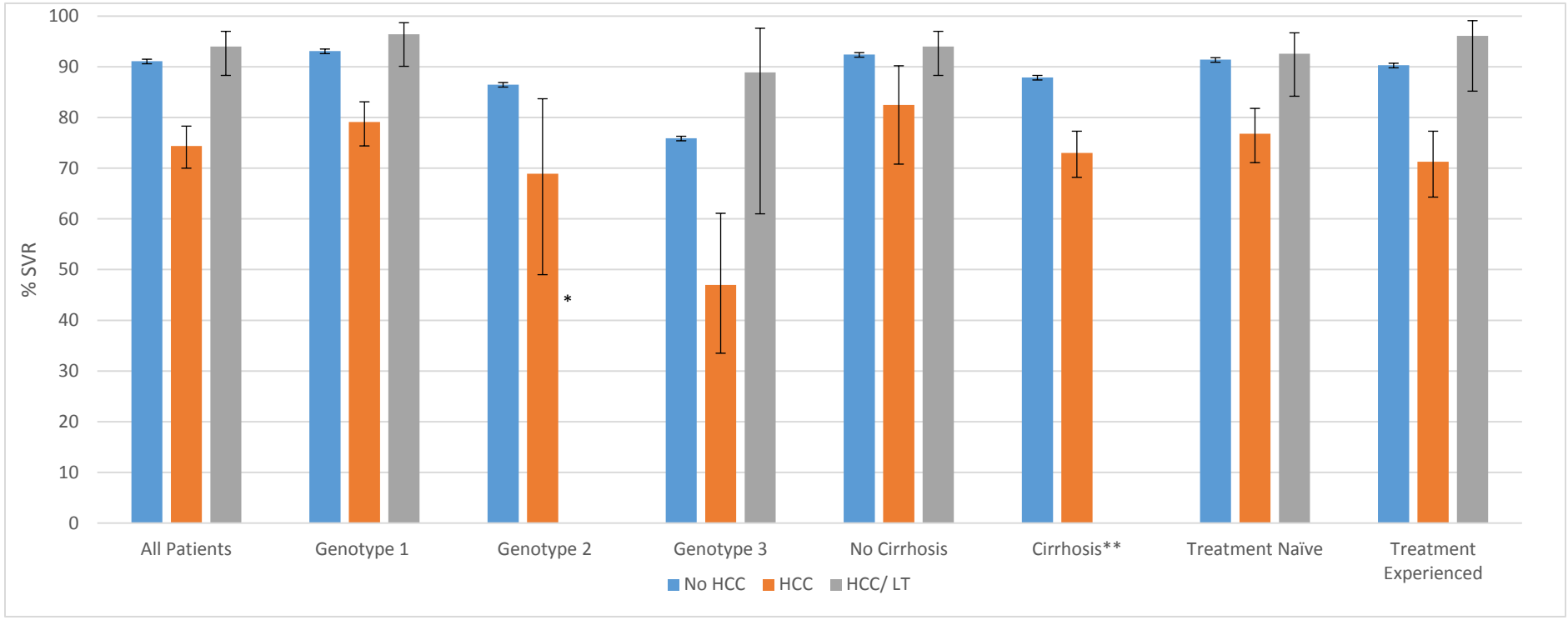
† AOR: Adjusted odds ratio, by multivariable logistic regression modeling including all variables shown in the Table.

Figure 1: SVR rates among patients with HCC, HCC/ OLT, and no HCC

Abbreviations: SVR (sustained virologic response), HCC (hepatocellular carcinoma), HCC/LT (HCC with previous liver transplantation)

* bars not included for subgroups containing <15 patients

** All patients with HCC/LT were considered to be non-cirrhotic


100
90
80
70
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50
40
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10
0
% SVR
*
All Patients
Genotype 1
Genotype 2
Genotype 3
No Cirrhosis
Cirrhosis**
Treatment Naïve
Treatment Experienced
No HCC
HCC
HCC/ LT

SVR among patients with HCC, HCC with subsequent liver transplantation, and no HCC