Impact of Sustained Virologic Response with Direct-Acting Antiviral Treatment on Mortality in Patients with Advanced Liver Disease

Lisa I. Backus MD PhD, Pamela S. Belperio PharmD, Troy A. Shahoumian PhD and Larry A. Mole PharmD

Department of Veterans Affairs, Population Health Services, Palo Alto Health Care System, Palo Alto, CA, USA

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Corresponding Author:

Lisa I. Backus, MD PhD, Patient Care Services/Population Health Services, Veterans Affairs Palo Alto Health Care System, 3801 Miranda Avenue (132), Palo Alto, CA 94304, Phone: 650-849-0365, Fax: 650-849-0266, Email: Lisa.Backus@va.gov

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List of Abbreviations

HCV – hepatitis C virus

SVR – sustained virologic response

DAA – direct acting antiviral

HCC – hepatocellular carcinoma

VA – Department of Veterans Affairs

EOT – end of treatment

BMI – body mass index

eGFR – estimated glomerular filtration rate

HR – hazard ratio

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Abstract

The impact of sustained virologic response (SVR) on mortality after direct-acting antiviral (DAA) treatment is not well documented. This study evaluated the impact of DAA-induced SVR on all-cause mortality and on incident hepatocellular carcinoma (HCC) in 15,059 HCV-infected patients with advanced liver disease defined by a FIB-4 >3.25. Overall, 1,067 patients did not achieve SVR (No SVR) and 13,992 patients achieved SVR. In a mean follow-up period of approximately 1.6 years, 195 No SVR patients and 598 SVR patients died. Mortality rates were 12.3 deaths/100 patient years of follow-up for No SVR patients and 2.6 deaths/100 patient years for SVR patients, a 78.9% reduction (p<0.001). Among patients without a prior diagnosis of HCC, 140 No SVR patients and 397 SVR patients were diagnosed with incident HCC. HCC rates were 11.5 HCC/100 patient years for No SVR patients and 1.9 HCC/100 patient years for SVR patients, an 83.5% reduction (p<0.001). In multivariable Cox proportional hazard models controlling for baseline demographics, clinical characteristics and comorbidities, SVR was independently associated with reduced risk of death compared to No SVR (hazard ratio (HR) 0.26, 95% confidence interval (CI) 0.22-0.31, p<0.001). A history of decompensated liver disease (HR 1.57, 95%CI 1.34-1.83, p<0.001) and decreased albumin (HR 2.70 per 1 g/dL decrease 95%CI 2.38-3.12, p<0.001) were independently associated with increased risk of death. ***Conclusion***: Those achieving SVR after DAA treatment had significantly lower all-cause mortality and lower incident HCC rates than those who did not achieve SVR.

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Hepatitis C virus (HCV) antiviral treatment effectiveness is assessed by the surrogate end point of sustained virologic response (SVR), however, reduced all-cause mortality remains the ideal marker of treatment benefit and the ultimate goal. The prior research on the effects of SVR on mortality was conducted after treatment with interferon-based regimens and before the introduction of more selective direct acting antivirals (DAAs).(1-6) The oral DAAs have led to markedly increased SVR rates in the majority of patients treated, including those with comorbidities and cirrhosis. It is widely assumed that the mortality benefits realized from SVR with the previous interferon-based therapies will also occur from SVR with oral DAA therapies. However, the broader population receiving DAAs, the shorter durations of treatment, and the differing mechanism of action compared to interferon-based treatment may alter the impact of DAA-induced SVR on mortality.(7) An assessment of the impact of DAA-induced SVR on mortality is needed rather than continued reliance on data concerning mechanistically different therapy, particularly to help value the use of costlier DAAs.

Data on the impact of SVR in patients with advanced liver disease is particularly important as there are data demonstrating continued disease progression after achieving SVR, evidenced by decompensation or development of hepatocellular carcinoma (HCC), which may, in turn, diminish survival benefits.(5,8-12) Thus, there remains the need for definitive evidence of the mortality benefits of achieving SVR in a range of populations and most certainly in patients with advanced liver disease where lower rates of SVR are generally observed and life-threatening complications are more likely.

Understanding the effectiveness of HCV antiviral regimens is a priority for the Department of Veterans Affairs (VA), the largest U.S. provider of healthcare to HCV-infected individuals in which over 80,000 veterans have already been treated with DAAs.(13) Given the rapid uptake of DAAs within VA, this work sought to evaluate the impact of DAA-induced SVR on all-cause mortality in veterans with advanced liver disease.

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MATERIALS AND METHODS

This observational cohort analysis used data from the VA's Clinical Case Registry for HCV, an extract of the VA's electronic medical record for all HCV-infected veterans receiving care at VA medical facilities.(14) Eligible subjects included all HCV-infected veterans with advanced liver disease, defined by a FIB-4>3.25, at the start of DAA treatment who stopped a VA-prescribed DAA (daclatasvir, elbasvir/grazoprevir, ledipasvir/sofosbuvir, ombitasivir/parataprevir/ritonavir/dasabuvir, simeprevir, or sofosbuvir) by September 30, 2016 who had laboratory testing after the end of treatment (EOT) that allowed for categorization of the virologic response as SVR or No SVR. For patients who received multiple courses of therapy, only the most recent course of therapy and follow-up thereafter was considered. The decision to treat, regimen choice and subsequent clinical care was at the discretion of the provider. Patients were excluded if they had undergone liver transplantation prior to DAA treatment (n=242).

Treatment Outcomes

SVR was defined as HCV RNA results below the lower limit of quantification at least 12 weeks or more after the EOT. Patients were categorized as No SVR if they had a HCV RNA above the limit of quantification 12 weeks or more after EOT, or at any time after the EOT and no subsequent test ≥12 weeks after EOT. Patients who lacked definitive laboratory information, for example patients with HCV RNA below the limit of quantification on their last HCV viral load test but no tests ≥12 weeks after the EOT were excluded from the analysis. Given that SVR patients must live at least 12 weeks to have the laboratory testing that qualifies them as SVR but No SVR patients do not have this same definitional survival requirement, we also excluded 8 patients who had laboratory testing after EOT that qualified as No SVR but who died before 12 weeks of follow-up.

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Survival time was calculated from the EOT. Mortality data were available through May 31, 2017, from the VA Medical Record and from the VA Vital Status File, which draws from the Medicare Vital Status Files, Social Security Administration Death Master Files, VA Beneficiary Identification Records Locator Subsystem Death File, and VA Medical Records, and compares favorably with the National Death Index. Because the mortality data are national and drawn from non-VA as well as VA sources, it is reasonable to assume that no patients are lost to follow-up evaluation with respect to measurement of survival. Overall mortality rates were calculated as deaths per 100 years of patient follow-up. In addition, since follow-up is relatively limited given the recent introduction of DAAs and it is possible that the mortality rate changes over time, one-year mortality rates were also determined. The one-year mortality rates were calculated as the number of deaths within one year of the EOT among those people who stopped treatment by May 31, 2016 so there was at least one year of follow-up on all included patients.

As a secondary outcome, rates of incident HCC were calculated similarly to mortality rates. Patients with a history of HCC at the time of DAA initiation or within 12 weeks of DAA completion were excluded from the HCC analysis to account for patients who likely already had HCC while receiving DAA treatment. HCC rates were then calculated as incident HCC diagnosis per 100 years of patient follow-up. One-year HCC rates were also calculated as the number of patients with an incident diagnosis of HCC within one year of the EOT among those people who stopped treatment by January 31, 2016.

Control Variables

Demographic and other baseline variables were determined at the time of treatment initiation and included age, sex, race/ethnicity, body mass index (BMI), history of decompensated liver disease (defined by ICD-9/10 codes for esophageal variceal hemorrhage, hepatic coma, hepatorenal syndrome or spontaneous bacterial peritonitis),

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history of HCC (defined by ICD-9/10 codes), HIV coinfection, alanine aminotransferase, albumin, aspartate aminotransferase, creatinine, platelets, FIB-4 score, baseline HCV RNA, HCV genotype, and DAA treatment. Baseline values for height and weight used to calculate BMI and the laboratory tests for alanine aminotransferase, albumin, aspartate aminotransferase, creatinine, platelets, and baseline HCV RNA were defined as the value within one year before and closest to the treatment start date. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation.(15) Genotype subtype 1a included patients with results of 1a, mixed 1a/1b or 1 with subtype unspecified. Using ICD-9/10 codes and requiring a code within one year of the DAA treatment start date to identify recent or active comorbidities that may affect HCV treatment response and survival, we also determined the presence of alcohol abuse, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, cerebrovascular disease, diabetes, hard drug use (amphetamines, cocaine or opiates), and hypertension.

Statistical Analysis

Univariate comparisons used the Pearson Chi-square test with Yates' continuity correction for categorical variables and *t* tests for continuous variables. Kaplan-Meier curves of survival and of HCC-free survival by SVR were compared with log-rank tests. Mortality and incident HCC rates per 100 patient years of follow-up were compared with the Exact Poisson test. One-year mortality and HCC rates were compared with proportion tests. Multivariable Cox proportional hazard models were constructed to identify predictors of mortality and the impact of SVR. Models included variables selected *a priori* of age, sex, race/ethnicity, BMI, history of decompensated liver disease, HIV, other baseline comorbidities, albumin, eGFR, and SVR status. Additional multivariable sensitivity models were constructed: using age, albumin and eGFR as categorical variables, including a variable for genotype for the four most common genotypes, separately for patients with each of the four most common genotypes, separately for patients with and without a history of decompensated liver disease,

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limited to patients who achieved SVR, and limited to those with No SVR. A final multivariable Cox model considered a composite outcome of death or liver transplant in follow-up.

For all comparisons, a p value <0.05 was considered statistically significant. All analyses were performed using R version 3.2 (R Foundation for Statistical Computing, Vienna, Austria).

The protocol was approved by the Stanford University Institutional Review Board and the VA Palo Alto Health Care System Research and Development Committee.

RESULTS

There were 15,059 HCV-infected patients with advanced liver disease from 128 VA facilities who stopped DAA treatment by 30 September 2016 for whom SVR data were available; 1,067 (7.1%) were No SVR and 13,992 (92.9%) were SVR. Among the No SVR patients, 355 (33.3%) were virologic failure defined by not achieving an undetectable HCV RNA while on treatment and 712 (66.7%) were relapses. Baseline patient and treatment characteristics appear in Table 1. The cohort was overwhelmingly male (97.2%) with a mean age of 63.1 years. Although all patients had advanced liver disease based on FIB-4>3.25, the No SVR group had indications of more severe liver disease compared to the SVR group. Specifically, a history of decompensated liver disease was more common in the No SVR group compared to the SVR group (35.0% vs. 25.4% respectively p<0.001) as was a prior diagnosis of HCC (13.7% vs. 4.8%, p<0.001). Mean albumin was lower in the No SVR group compared to the SVR group (3.4±0.6 vs 3.6±0.5, p<0.001) and mean FIB-4 score was also higher in the No SVR group compared to the SVR group (7.5±4.7 vs 6.5±4.0, p<0.001). The No SVR group also had higher rates of recent diagnoses of alcohol abuse and hard drug use compared to the SVR group. Ledipasvir/sofosbuvir±ribavirin was the most commonly prescribed DAA for both groups.

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Among No SVR patients, 195 died during a mean follow-up period of 1.5 years after EOT. Among SVR patients, 598 died during a mean follow-up period of 1.6 years after the EOT. In unadjusted analysis, SVR was associated with statistically significantly reduced all-cause mortality compared to No SVR ($p<0.001$)(Figure 1). The cumulative mortality curves for No SVR and SVR diverged early in the follow-up period and the reductions in all-cause mortality among SVR patients appear clinically significant.

When considering deaths per 100 patient years of follow-up, SVR was associated with a 78.9% reduction in mortality (Table 2). The percentage reductions across genotypes 1a, 1b, 2 and 3, where there were a material number of deaths, were similar and ranged from a 72.7% reduction for genotype 2 to a 79.7% reduction for genotype 1a.

A similar pattern of significantly reduced mortality associated with SVR was evident when considering one-year mortality rates. SVR was associated with a 79.6% reduction in one-year mortality for all genotypes combined and among the most common genotypes ranged from 73.9% reduction for genotype 1b to an 81.7% reduction for genotype 3.

For the secondary endpoint of incident HCC diagnosis, 818 patients in the cohort (147 No SVR and 671 SVR) had a history of HCC prior to DAA treatment and an additional 217 patients (49 No SVR and 168 SVR) had a first diagnosis of HCC while on DAA treatment or within 84 days after EOT and were not included in the incident HCC outcome. During follow-up, 140 of 871 No SVR patients and 397 of 13,153 SVR patients had a first diagnosis of HCC. SVR was strongly associated with delayed time until development of HCC ($p<0.001$)(Figure 2). When considering HCC per 100 patient years of follow-up, SVR was associated with an 83.5% reduction in incident HCC (Table 2). A similar reduction associated with SVR was evident when considering one-year HCC rates.

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There were 732 patients who had HCC first diagnosed within five years before the start of DAA; 135 were No SVR of whom 39 died in follow-up and 597 were SVR of whom 72 died in follow-up. The death rate for those with prior HCC and No SVR was 21.0 deaths/100 patient years (95%CI 14.9-28.7) compared to 7.5 deaths/100 patient years (95%CI 5.9-9.5) for those with prior HCC and SVR – a 64.3% reduction in the death rate ($p<0.001$). For those without a diagnosis of HCC prior to DAA, 871 were No SVR of whom 133 died in follow-up and 13,153 were SVR of whom 497 died in follow-up. Deaths rates for those without prior HCC and No SVR were 10.1 deaths/100 patient years (95%CI 8.4-11.9) compared to 2.3 deaths/100 patient years (95%CI 2.1-2.5) for those without prior HCC and SVR – a 77.2% reduction in the death rate ($p<0.001$).

Table 3 presents the hazard ratios (HR) for death from multivariable Cox proportional hazard models for patients with advanced liver disease treated with DAAs. Reduced risk of all-cause mortality occurred with achievement of SVR compared to No SVR (HR 0.26, 95% confidence intervals (CI) 0.22-0.31, $p<0.001$) while controlling for numerous baseline demographic and clinical characteristics. Patients with a history of decompensated liver disease had an increased risk of death. Each 1 g/dL decrease in albumin was also independently associated with increased risk of death. When included in the multivariable model as categorical variables, albumin 3.0-3.4 g/dL (HR 2.01, 95%CI 1.69-2.40, $p<0.001$) and albumin <3.0 g/dL (HR 3.86, 95%CI 3.21-4.65) $p<0.001$) were independently associated with significantly increased risk of death compared to albumin ≥3.5 g/dL. Similarly, decreasing categories of eGFR were also associated with increased risk of death compared to eGFR ≥ 90 ml/min/1.73m^2 (eGFR 60-89, HR 1.05, 95%CI 0.90-1.23, $p=0.55$; eGFR 30-59, HR 1.44, 95%CI 1.14-1.81, $p=0.002$; eGFR <30, HR 1.58, 95%CI 0.90-2.78, $p=0.11$).

In sensitivity analysis, SVR was associated with a nearly identical reduced risk of death compared to No SVR when limiting the multivariable model to patients with the four most common genotypes and controlling for

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genotype (HR 0.27, 95%CI 0.23-0.32, p<0.001). In this model, genotype 3 was associated with increased risk of death compared to genotype 1a. When multivariable models were constructed separately for each common genotype, the impact of achieving SVR on risk of death was similar (genotype 1a HR 0.26, 95%CI 0.21-0.33, p<0.001; genotype 1b HR 0.24, 95%CI 0.15-0.39, p<0.001; genotype 2 HR 0.30, 95%CI 0.17-0.54, p<0.001; genotype 3 HR 0.28, 95%CI 0.17-0.44, p<0.001). Excluding patients with a history of hepatic decompensation, SVR was associated with a slightly larger reduction in the risk of death than when considering the entire cohort of advanced liver disease patients (HR 0.20, 95%CI 0.16-0.25, p<0.001). Considering only patients with a history of hepatic decompensation, SVR was still associated with a substantially reduced risk of death (HR 0.33, 95%CI 0.26-0.42, p<0.001).

In a multivariable model including only those who achieved SVR, the significant predictors were similar to those in the main model; females and African Americans had decreased risk of death while older age, low BMI, history of decompensated liver disease, decreasing albumin, decreasing eGFR, congestive heart failure, chronic obstructive pulmonary disease, and hypertension predicted increased risk of death (data not shown). When the model was limited to only those with No SVR, significant predictors associated with increased risk of death were decreasing albumin (HR 2.17, 95%CI 1.67-2.78, p<0.001) and diabetes (HR 1.48, 95%CI 1.10-2.00, p=0.009).

In follow-up, 8 No SVR (0.75%) and 53 SVR (0.38%)(p=0.11) patients underwent liver transplant. In additional sensitivity analysis, in a multivariable Cox model with the composite outcome of death or liver transplant, the pattern of significant predictors was unchanged from the main mortality model. Specifically, SVR was associated with a significant reduction in the risk of the composite outcome virtually identical to the main mortality model (HR 0.27, 95%CI 0.23-0.32, p<0.001).

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DISCUSSION

In this evaluation, the high SVR rates attained with oral DAAs translated into an all-cause mortality benefit after adjusting for numerous baseline patient characteristics and comorbidities. In this large cohort of patients with advanced liver disease, achievement of SVR conferred a significantly reduced risk of death regardless of genotype for the entire cohort, for the subset of patients with prior HCC and for the subset of patients with prior hepatic decompensation. Furthermore, attainment of SVR reduced the risk of developing a first episode of HCC after DAA treatment by 84%.

The magnitude of risk reduction observed soon after achieving SVR underscores the importance of timely treatment in HCV-infected patients with advanced liver disease. The risk of mortality was 79% lower in those achieving SVR. From a population health perspective, as more patients are treated with potent all-oral DAA regimens and consequently more patients achieve SVR, more deaths will be averted than had been previously averted with older, less effective therapies. While the risk of all-cause mortality with peginterferon-based treatment was similarly reduced on the magnitude of 50%-75% in patients with SVR, overall fewer patients achieved SVR thus the population impact was less.(1,2)

The mechanism of the observed reduction in all-cause mortality associated with SVR cannot be elucidated with the present research but is undoubtedly multifactorial. We did not have information about reported cause of death so we cannot address what proportion of the reduction in mortality was potentially related to reduction in liver-related mortality. Beyond direct liver-related mechanisms, however, increasing evidence links chronic inflammatory states with all-cause mortality.(16-19) Thus, it is conceivable that SVR eliminates chronic inflammation from HCV which then substantially contributes to reduced all-cause mortality through mechanisms that are still being defined. From a patient and family perspective, all-cause mortality may be a more meaningful outcome of concern rather than disease-specific mortality.

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It is evident from this evaluation that a history of hepatic decompensation and albumin levels strongly influence mortality. In patients without a history of decompensation, SVR was associated with an 80% reduction in risk of death compared to a 67% reduction in risk of death for patients with a history of decompensation. In addition, decreasing albumin independently predicted increased mortality regardless of if the patient did or did not achieve SVR. Both findings may serve as additional support for treating patients earlier in their HCV infection, prior to a decompensation or prior to substantial impairment in liver synthetic function. As previously shown in peginterferon-based studies, we confirmed that genotype 3 negatively impacted mortality and may provide additional impetus to treat genotype 3 patients.(1,2) Our findings also serve as a reminder that patients with HCV may have other comorbidities associated with increased mortality, such as congestive heart failure, that may be amenable to intervention regardless of HCV treatment status.

In contrast to studies with peginterferon-based treatment where the risk of HCC was reduced among patients with SVR, existing reports on the risk of HCC occurrence or recurrence after DAA treatment are discordant.(20-27) Some data suggest a higher incidence of HCC occurrence or recurrence and a more aggressive course following successful DAA therapy.(20-23) Others have observed similar HCC rates in treated and untreated patients.(24-27) The disparate data is theorized to reflect differences in patient populations treated with peginterferon therapy versus DAA therapy, the latter being older and having more advanced liver disease which may inherently increase risk of HCC. Many of these studies, however, are limited by the fact that they did not concomitantly report on the occurrence or recurrence in patients who did not achieve SVR. In this study, patients with SVR after treatment with DAAs had a significantly reduced rate of HCC occurrence compared to patients without SVR after DAAs. The rate of incident HCC observed post-DAA treatment in those achieving SVR was low at 1.9 cases/100 patient years and represented an 84% reduction in HCC cases compared to patients with no SVR. Some reports suggest a time association between DAA initiation and HCC development

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such that HCC may occur sooner in those treated with DAAs.(20,23) Our data indicated that the time to development of HCC was delayed in those who achieved SVR compared to those without SVR. Moreover, the risk of all-cause mortality was reduced in patients with a history of HCC who achieved SVR after DAA treatment. While the reduction in death rate was less pronounced in those with a history of HCC within 5 years of DAA initiation compared to those with no HCC history, achievement of SVR was still associated with a 64% reduction in death rate compared to those patients with no SVR, highly suggesting that successful treatment with DAAs in the setting of prior HCC was beneficial. This magnitude of reduction was similar to that observed in other smaller trials.(24,25,27)

This study has several limitations. Because the determination of SVR requires laboratory testing 12 weeks or more after EOT, which is an inherent survival advantage for SVR patients, we excluded patients who died before 12 weeks of follow up which may underestimate the death rate for both the No SVR and SVR groups. Because many of our measures of comorbidities rely on ICD-9/10 coding and required a code within 1 year of DAA treatment, it is likely that some diagnoses of interest are underreported, although it is reasonable to assume that the rate of underreporting is similar between SVR and No SVR patients. As previously noted, we did not have complete information about reported cause of death so we cannot address what proportion of the reduction in mortality was related to reduction in liver-related mortality. We did not assess the impact of SVR on HCC recurrence, only incident HCC and death in patients with a recent history of HCC. In patients that developed HCC after DAA treatment we were unable to assess the stage, size or clinical presentation of HCC at diagnosis due to limitations of the administrative database. Given the relatively recent widespread use of interferon-free DAA regimens, our study is limited by the short available follow-up time. The observed differences in risk of death and risk of HCC may change over time as more time from treatment elapses. It is possible that providers more aggressively screen for HCC in No SVR patients compared to SVR patients and consequently more HCC may be diagnosed in No SVR patients. Nonetheless, it is reassuring that all-cause

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mortality was markedly reduced with SVR such that even if HCC was present but had not been diagnosed, fewer SVR patients apparently died from it. Finally, despite controlling for numerous factors, it is possible that No SVR and SVR patients differ on unmeasured, and possibly nonmeasurable, factors that might account for the observed differences in mortality. However, it is difficult to envision that residual confounding could account for the quite substantial difference in all-cause mortality we observed associated with SVR.

In conclusion, DAA-induced SVR was associated with reduced all-cause mortality among patients with advanced liver disease and HCV genotypes 1, 2, and 3 treated in routine medical practice. These findings strongly support a clinically significant benefit of DAA treatment in patients with advanced liver disease irrespective of HCV genotype. As more people are treated for HCV infection with DAAs, fewer deaths should result in this population.

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Figure 1. Survival Curves for Patients with and without Sustained Virologic Response

The number of patients at risk is shown below at each time point.

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Figure 2. HCC Disease Free Survival for Patients with and without Sustained Virologic Response.

The number of patients at risk is shown below at each time point.

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Authorship Statement

1. Guarantor of the Article: Lisa I. Backus, MD, PhD
2. Specific Author Contributions: Study concept and design: Drs. Backus, Belperio and Mole; analysis and interpretation of data: Drs. Backus, Belperio, Shahoumian and Mole; drafting of the manuscript: Drs. Backus, Belperio, critical revision of the manuscript for important intellectual content: Drs. Backus, Belperio and Mole; statistical analysis: Dr. Shahoumian.
3. This statement acknowledges that all authors approved the final version of the article, including the authorship list.

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STROBE Statement

	Item No	Recommendation
Title and abstract	√	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	√	Explain the scientific background and rationale for the investigation being reported
Objectives	√	State specific objectives, including any prespecified hypotheses
Methods		
Study design	√	Present key elements of study design early in the paper
Setting	√	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	√	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	√	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	√	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	√	Describe any efforts to address potential sources of bias
Study size	√	Explain how the study size was arrived at
Quantitative variables	√	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	√	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	√	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage

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		(c) Consider use of a flow diagram
Descriptive data	√	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	√	Report numbers of outcome events or summary measures over time
Main results	√	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	√	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	√	Summarise key results with reference to study objectives
Limitations	√	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	√	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	√	Discuss the generalisability (external validity) of the study results
Other information		
Funding	√	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

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Table 1. Baseline Characteristics of Patients with Advanced Liver Disease who Received Direct-Acting Antivirals

	All Patients N=15,059	No SVR N=1,067	SVR N=13,992	P
Age (years)	63.1±5.5 (30.2-90.5)	62.1±5.6 (30.2-85.2)	63.2±5.5 (31.4-90.5)	<0.001
Age categories				<0.001
< 55	888 (5.9%)	88 (8.2%)	800 (5.7%)	
55-64	8,849 (58.8%)	652 (61.1%)	8,197 (58.6%)	
≥ 65	5,322 (35.3%)	327 (30.6%)	4,995 (35.7%)	
Sex Male	14,642 (97.2%)	1,047 (98.1%)	13,595 (97.2%)	0.08
Race/ethnicity				0.15
African-American	4,651 (30.9%)	301 (28.2%)	4,350 (31.1%)	
Caucasian	8,253 (54.8%)	602 (56.4%)	7,651 (54.7%)	
Hispanic	1,125 (7.5%)	92 (8.6%)	1,033 (7.4%)	
Other/multiple	1,030 (6.8%)	72 (6.7%)	958 (6.8%)	
BMI (kg/m^2)	28.6±5.5 (11.0-74.1)	29.1±5.8 (15.1-55.1)	28.6±5.5 (11.0-74.1)	0.005
BMI categories				0.02
<25	3,964 (26.3%)	275 (25.5%)	3,692 (26.4%)	
25-29	5,901 (39.2%)	385 (36.1%)	5,516 (39.4%)	
≥30	5,194 (34.5%)	410 (38.4%)	4,784 (34.2%)	
History of Decompensated liver disease	3,931 (26.1%)	373 (35.0%)	3,558 (25.4%)	<0.001
History of HCC	818 (5.4%)	147 (13.7%)	671 (4.8%)	<0.001
HIV coinfected	614 (4.1%)	49 (4.6%)	565 (4.0%)	0.42
Recent diagnosis				
Alcohol abuse	3,197 (21.2%)	319 (29.9%)	2,878 (20.6%)	<0.001
Cerebrovascular disease	402 (2.7%)	23 (2.2%)	379 (2.7%)	0.33
Chronic obstructive pulmonary disease	2,213 (14.7%)	194 (18.2%)	2,019 (14.4%)	<0.001
Congestive heart failure	551 (3.7%)	35 (3.3%)	516 (3.7%)	0.55
Coronary artery disease	1,593 (10.6%)	90 (8.4%)	1,503 (10.7%)	0.02
Diabetes	5,400 (35.9%)	362 (33.9%)	5,038 (36.0%)	0.18
Hard drug use	1,709 (11.3%)	169 (15.8%)	1,540 (11.0%)	<0.001
Hypertension	8,356 (55.5%)	565 (53.0%)	7,791 (55.7%)	0.09
Albumin (g/dL)	3.6±0.5 (1.2-5.2)	3.4±0.6 (1.6-4.9)	3.6±0.5 (1.2-5.2)	<0.001
Albumin categories				<0.001
≥3.5	9,893 (65.7%)	555 (52.0%)	9,338 (66.7%)	
3.0-3.4	3,461 (23.0%)	297 (27.8%)	3,164 (22.6%)	
<3.0	1,705 (11.3%)	215 (20.1%)	1,490 (10.6%)	
ALT (U/L)	98.6±73.8 (2-1958)	92.7±58.3 (5-467)	99±74.8 (2-1958)	0.007
AST (U/L)	101.7±62.8 (16-2467)	104.8±56.3 (21-459)	101.5±63.3 (16-2467)	0.09
Creatinine (mg/dL)	1.0±0.6 (0.4-16.8)	0.9±0.4 (0.4-8.1)	1.0±0.6 (0.4-16.8)	0.02
eGFR (mL/min/1.73m^2)	87.3±19.0 (3.1-150.1)	89.6±18.9 (7.3-138.9)	87.1±19.0 (3.1-150.1)	<0.001
eGFR categories				#
≥90	8,137 (54.0%)	654 (61.3%)	7,483 (53.5%)	
60-89	5,551 (36.9%)	326 (30.6%)	5,225 (37.3%)	
30-59	1,238 (8.2%)	78 (7.3%)	1,160 (8.3%)	
15-29	75 (0.5%)	6 (0.6%)	69 (0.5%)	
<15	58 (0.4%)	3 (0.3%)	55 (0.4%)	
Platelets (K/μL)	115.6±42.3 (10-451)	105.2±39.6 (15-260)	116.4±42.4 (10-451)	<0.001
FIB-4	6.5±4.0 (3.3-62.2)	7.5±4.7 (3.3-62.2)	6.5±4.0 (3.3-61.6)	<0.001

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	N=14,858	N=1,055	N=13,803	
HCV RNA (log IU/mL)	6.1±0.8 (1.1-8.1)	6.1±0.7 (1.1-7.6)	6.1±0.8 (1.1-8.1)	0.44
<6,000,000 IU/mL	12,890 (86.8%)	924 (87.6%)	11,966 (86.7%)	0.44
HCV genotype*				#
1a	9,327 (61.9%)	614 (57.5%)	8,713 (62.3%)	
1b	3,477 (23.1%)	144 (13.6%)	3,332 (23.8%)	
2	1,104 (7.3%)	113 (10.6%)	991 (7.1%)	
3	995 (6.6%)	183 (17.2%)	812 (5.8%)	
4	103 (0.7%)	9 (0.8%)	94 (0.7%)	
6	8 (0.1%)	1 (0.1%)	7 (0.1%)	
Other	45 (0.3%)	2 (0.2%)	43 (0.3%)	
Direct-Acting Antiviral regimen				
Daclatasvir+sofosbuvir±ribavirin	354 (2.4%)	43 (4.0%)	311 (2.2%)	<0.001
Ledipasvir/sofosbuvir±ribavirin	8,947 (59.4%)	619 (58.0%)	8,328 (59.5%)	0.35
OPrD±ribavirin	1,959 (13.0%)	84 (7.9%)	1,875 (13.4%)	<0.001
Simeprevir+sofosbuvir±ribavirin	1,525 (10.1%)	70 (6.5%)	1,455 (10.4%)	<0.001
Sofosbuvir+ribavirin	1,911 (12.7%)	231 (21.6%)	1,680 (12.0%)	<0.001
Ribavirin containing DAA regimen	7,738 (51.4%)	642 (60.2%)	7,096 (50.7%)	<0.001
Mean follow-up (days)	591.3±217.4 (85-1,191)	541.5±224.2 (85-1,191)	595.1±216.5 (89-1,172)	<0.001

Continuous variables reported as mean±standard deviation (range). Categorical variables reported as n (%). # P values not reported when the minimum expected value in any cell is <5. *Genotype 1a includes 1a, 1 with subtype unspecified and mixed 1a/1b; Other includes people with indeterminate genotype or multiple genotypes e.g. 1a and 2b. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; HCC, hepatocellular carcinoma; OPrD, ombitasvir/paritaprevir/ritonavir+dasabuvir; SVR, sustained virologic response

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Table 2. Mortality Rates and Hepatocellular Carcinoma Rates after Direct-Acting Antivirals in Patients with Advanced Liver Disease

	No SVR		SVR			
Genotype	Deaths	Deaths/100py (95%CI)†	Deaths	Deaths/100py (95%CI)†	Reduction	P
1a*	112	12.8 (10.6-15.5)	364	2.6 (2.3-2.8)	79.7%	<0.001
1b	24	11.2 (7.2-16.7)	137	2.5 (2.1-3.0)	77.7%	<0.001
2	19	9.9 (6.0-15.5)	48	2.7 (2.0-3.6)	72.7%	<0.001
3	37	12.8 (9.0-17.7)	43	3.3 (2.4-4.4)	74.2%	<0.001
4	2	15.0 (1.8-54.2)	4	2.6 (0.7-6.7)	82.7%	0.08
6	0	0.0 (0.0-229.4)	0	0.0 (0.0-28.7)	--	NA
Other	1	38.8 (1.0-216.1)	2	3.0 (0.4-11.0)	92.3%	0.11
TOTAL	195	12.3 (10.6-14.2)	598	2.6 (2.4-2.8)	78.9%	<0.001
Genotype	One-year Deaths	One-year mortality rate (95%CI)‡	One-year Deaths	One-year mortality rate (95%CI)‡	Reduction	
1a*	60	12.2% (9.5%-15.5%)	174	2.4% (2.0%-2.8%)	80.3%	<0.001
1b	10	8.8% (4.5%-15.9%)	65	2.3% (1.8%-3.0%)	73.9%	<0.001
2	8	7.9% (3.7%-15.5%	13	1.6% (0.9%-2.8%)	79.7%	<0.001
3	18	11.5% (7.1%-17.8%)	14	2.1% (1.2%-3.6%)	81.7%	<0.001
4	2	22.2% (3.9%-59.8%)	3	3.8% (1.0%-11.3%)	82.9%	0.13
6	0	0.0% (0.0%-94.5%)	0	0.0% (0.0-43.9%)	--	NA
Other	1	50.0% (9.5%-90.5%)	1	2.8% (0.1%-16.2%)	94.4%	0.19
TOTAL	99	11.3% (9.3%-13.6%)	270	2.3% (2.0%-2.6%)	79.6%	<0.001
HCC						
Genotype	HCC	HCC/100py (95%CI)†	HCC	HCC/100py (95%CI)†	Reduction	P
1a*	74	11.0 (8.6-13.8)	214	1.6 (1.4-1.9)	85.5%	<0.001
1b	14	8.5 (4.7-14.3)	115	2.3 (1.9-2.8)	72.9%	<0.001
2	21	13.7 (8.5-21.0)	34	2.0 (1.4-2.8)	85.4%	<0.001
3	31	14.7 (10.0-20.9)	31	2.6 (1.8-3.6)	82.3%	<0.001
4	0	0.0 (0.0-41.1)	1	0.0 (0.0-3.7)	--	1.0
6	0	0.0 (0.0-229.4)	0	0.0 (0.0-33.6)	--	NA
Other	0	0.0 (0.0-143.1)	2	3.3 (0.4-12.0)	--	1.0
TOTAL	140	11.5 (9.7-13.6)	397	1.9 (1.7-2.1)	83.5%	<0.001
Genotype	One-year HCC	One-year HCC rate (95%CI)‡	One-year HCC	One-year HCC rate (95%CI)‡	Reduction	
1a*	37	9.3% (6.7%-12.7%)	118	1.7% (1.4%-2.1%)	81.7%	<0.001
1b	5	5.5% (2.0%-12.9%)	59	2.3% (1.8%-3.0%)	58.2%	0.11
2	13	14.3% (8.1%-23.6%)	14	1.8% (1.0%-3.0%)	87.4%	<0.001
3	12	9.8% (5.4%-16.9%)	17	2.7% (1.6%-4.4%)	72.4%	<0.001
4	0	0.0% (0.0%-48.3%)	0	0.0% (0.0%-5.7%)	--	NA
6	0	0.0% (0.0%-94.5%)	0	0.0% (0.0%-48.3%)	--	NA
Other	0	0.0% (0.0%-80.2%)	2	6.1% (1.1%-21.6%)	--	1.0
TOTAL	67	9.4% (7.4%-11.9%)	210	1.9% (1.7%-2.2%)	79.8%	<0.001

* Genotype 1a includes 1a, 1 with subtype unspecified and mixed 1a/1b

†Deaths or incident HCC diagnosis in the entire cohort at any time 12 weeks after the end of treatment

‡Deaths or incident HCC diagnosis which occurred within one year of the end of treatment among patients who had at least one year of available follow-up

Abbreviations: CI, confidence interval; HCC, hepatocellular carcinoma; py patient years; SVR, sustained virologic response

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Table 3. Hazard Ratios from Multivariable Models of All-Cause Mortality after Treatment with Direct-Acting Antivirals in HCV-Infected Patients with Advanced Liver Disease

	HR (95%CI) N=15,059	P	HR (95%CI) N=14,903	P
SVR	**0.26 (0.22-0.31)**	**<0.001**	**0.27 (0.23-0.32)**	**<0.001**
Females (ref. Male)	**0.33 (0.16-0.70)**	**0.004**	**0.34 (0.16-0.71)**	**0.004**
Age (per 5 year increase)	1.07 (1.00-1.15)	0.07	**1.08 (1.00-1.16)**	**0.046**
African Americans (ref. Caucasians)	**0.74 (0.62-0.88)**	**<0.001**	**0.76 (0.63-0.91)**	**0.003**
Hispanic (ref. Caucasians)	0.97 (0.75-1.26)	0.83	1.00 (0.77-1.29)	0.99
Other/multiple (ref. Caucasians)	1.03 (0.78-1.36)	0.83	1.06 (0.80-1.39)	0.71
BMI <25 kg/m^2 (ref. BMI 25-29)	**1.21 (1.01-1.45)**	**0.04**	**1.21 (1.01-1.45)**	**0.04**
BMI ≥30 kg/m^2 (ref. BMI 25-29)	0.98 (0.83-1.16)	0.83	0.99 (0.84-1.17)	0.92
Decompensated liver disease (ref. no)	**1.57 (1.34-1.83)**	**<0.001**	**1.58 (1.35-1.84)**	**<0.001**
HIV (ref. no)	1.02 (0.72-1.46)	0.89	1.06 (0.75-1.51)	0.74
Albumin (per 1 g/dL decrease)	**2.70 (2.38-3.12)**	**<0.001**	**2.78 (2.44-2.13)**	**<0.001**
eGFR (per 10 mL/min/1.73m^2 decrease)	**1.04 (1.00-1.08)**	**0.04**	**1.04 (1.00-1.08)**	**0.046**
Alcohol abuse	1.17 (0.99-1.39)	0.07	1.16 (0.97-1.37)	0.10
Cerebrovascular disease	0.97 (0.63-1.49)	0.90	1.03 (0.67-1.59)	0.88
Chronic obstructive pulmonary disease	**1.33 (1.11-1.59)**	**0.002**	**1.31 (1.09-1.57)**	**0.003**
Congestive heart failure	**1.57 (1.18-2.09)**	**0.002**	**1.56 (1.18-2.08)**	**0.002**
Coronary artery disease	1.10 (0.89-1.37)	0.38	1.12 (0.90-1.39)	0.31
Diabetes	**1.24 (1.07-1.44)**	**0.005**	**1.26 (1.08-1.46)**	**0.002**
Hard drug use	0.85 (0.67-1.07)	0.17	0.85 (0.67-1.08)	0.19
Hypertension	**1.19 (1.02-1.39)**	**0.02**	**1.18 (1.02-1.38)**	**0.03**
Ribavirin-containing regimen	0.94 (0.81-1.08)	0.37	0.87 (0.74-1.01)	0.07
Genotype 1b (ref. 1a*)	--	--	1.00 (0.83-1.20)	0.98
Genotype 2 (ref. 1a*)	--	--	1.14 (0.87-1.50)	0.35
Genotype 3 (ref. 1a*)	--	--	**1.48 (1.15-1.92)**	**0.003**

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SVR, sustained virologic response.

*1a includes 1a, 1 with subtype unspecified and mixed 1a/1b

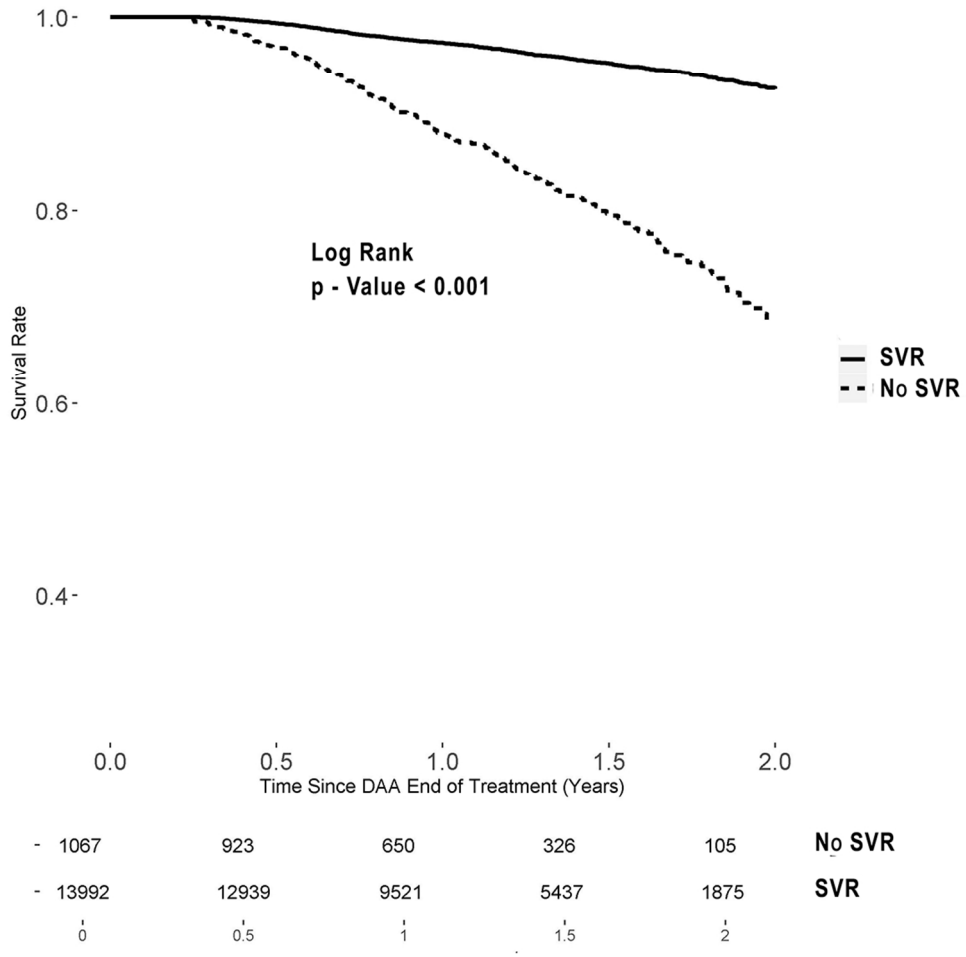

Figure 1. Survival Curves for Patients with and without Sustained Virologic Response. The number of patients at risk is shown below at each time point.

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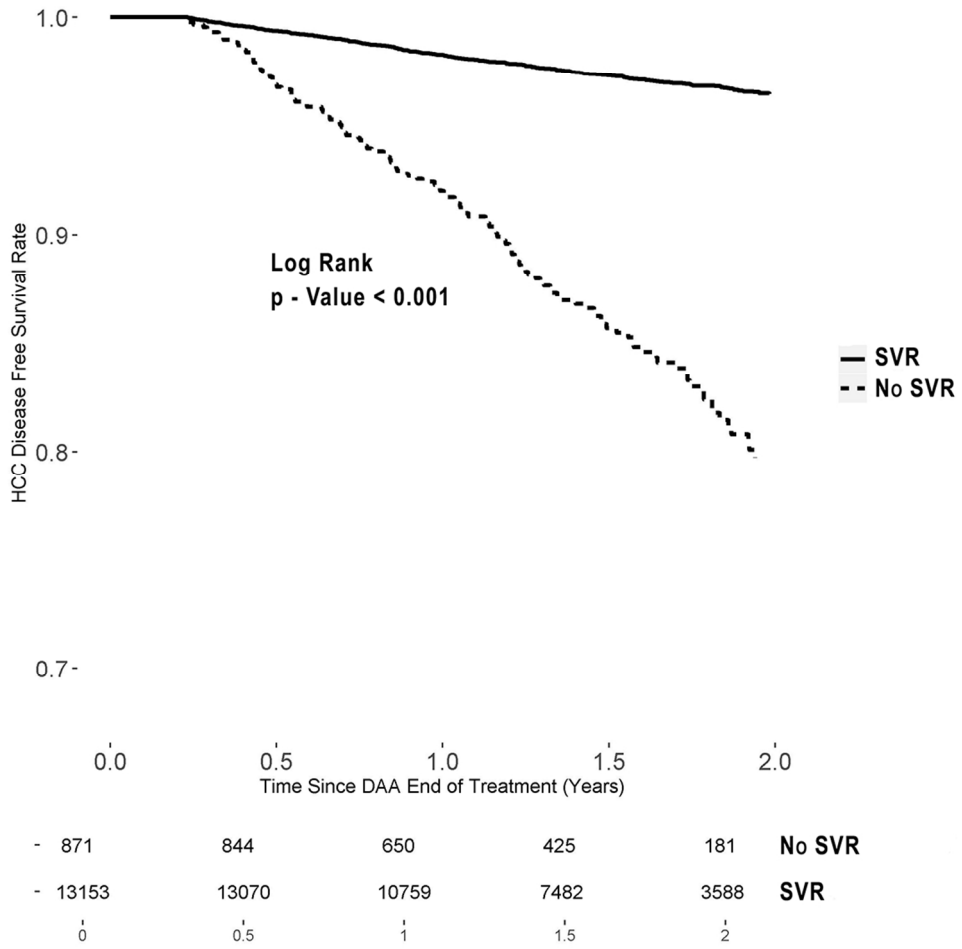

Figure 2. Hepatocellular Carcinoma Disease Free Survival for Patients with and without Sustained Virologic Response. The number of patients at risk is shown below at each time point.‼ ┼

101x101mm (300 x 300 DPI)