Direct-Acting Antiviral Sustained Virologic Response: Impact on Mortality in Patients without Advanced Liver Disease

Short Title: SVR and Death post DAA in non-ALD

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Abbreviations: BMI, body mass index; DAA, direct-acting antiviral; eGFR. Estimated glomerular filtration rate; EOT, end of treatment; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; SVR, sustained virologic response; VA, Department of Veteran's Affairs

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3 HEP-17-2052

Abstract

The impact of sustained virologic response (SVR) on mortality after direct-acting antiviral (DAA) treatment is not well documented in patients without advanced liver disease and affects access to treatment. This study evaluated the impact of SVR achieved with interferon-free DAA treatment on all-cause mortality in hepatitis C (HCV) infected patients without advanced liver disease. This observational cohort analysis was comprised of 103,346 genotype 1, 2 and 3, HCV-monoinfected patients without advanced liver disease, defined by FIB-4 ≤3.25 and no diagnosis of cirrhosis, hepatic decompensation, hepatocellular carcinoma or history of liver transplantation, identified from the Veterans Affairs Hepatitis C Clinical Case Registry. Among 40,664 patients treated with interferon-free DAA regimens, 39,374 (96.8%) achieved SVR and 1,290 (3.2%) patients were No SVR; 62,682 patients constituted the untreated cohort. The mortality rate for SVR patients of 1.18 deaths/100 patient years was significantly lower than both the rate for No SVR patients (2.84 deaths/100 patient years)($p<0.001$) and untreated patients (3.84 deaths/100 patient years)($p<0.001$). SVR patients with FIB-4 <1.45 and 1.45-3.25 had a 46.0% ($p=0.036$) and 63.2% ($p<0.001$) reduction in mortality rates, respectively, compared to No SVR patients and a 66.7% ($p<0.001$) and 70.6% ($p<0.001$) reduction in mortality rates, respectively, compared to untreated patients. In multivariate 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) 0.44, 95% confidence interval (CI) 0.32-0.59, $p<0.001$) and compared to untreated patients (HR 0.32, 95%CI 0.29-0.36, $p<0.001$). **Conclusion*:*** Successfully treating HCV with DAAs in patients without clinically apparent advanced liver disease translates into a significant mortality benefit.

Reduced all-cause mortality remains the ultimate goal of hepatitis C virus (HCV) antiviral treatment.[1,2] Oral DAA therapy has led to markedly increased sustained virologic response (SVR) rates in the majority of patients treated.[3-11] While expected to lead to all-cause mortality benefits, as seen with peginterferon-based regimens,[12-15] evidence of reduction in mortality with DAAs, particularly in those without advanced disease, is lacking.[16-19] Data on the impact of SVR in patients without advanced liver disease is especially important because many public and private insurers incorporate prioritization or eligibility criteria to limit coverage to only those with advanced liver disease, despite national guideline recommendations to treat all patients regardless of stage of disease.[11,20-22] Thus, there remains a need for definitive evidence of the mortality impact of achieving SVR in patients without advanced liver disease to better understand the potential benefits of treating these patients and to mitigate existing restrictions based on the stage of liver disease.

Understanding the effectiveness and outcomes of HCV antiviral regimens continues to be a priority for the Department of Veterans Affairs (VA), the largest U.S. provider of healthcare to HCV-infected individuals in which over 90,000 veterans have already received DAA therapy.[23-24] VA's decision to treat all patients with HCV, regardless of the stage of liver disease, and the rapid uptake of DAAs within VA provide a robust population to assess critical clinical questions. This work sought to evaluate the impact of SVR achieved with oral DAAs on all-cause mortality in veterans without clinically apparent advanced liver disease.

METHODS

For this observational cohort analysis we used the VA's Clinical Case Registry for HCV, an extract of the VA's electronic medical record, including VA pharmacy records, outpatient visits and laboratory data, for all HCV-infected veterans receiving care at VA medical facilities.[25] Eligible subjects included all HCV genotype 1, 2 or

3 monoinfected veterans without clinically apparent advanced liver disease who received a VA-prescribed all-oral DAA regimen containing daclatasvir, elbasvir/grazoprevir, ledipasvir/sofosbuvir, ombitasvir/paratаprevir/ritonavir/dasabuvir, simeprevir, or sofosbuvir after December 31, 2013 and stopped treatment by March 31, 2017, and 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 DAA therapy, only the most recent course and follow-up thereafter was considered. A comparison group of untreated HCV monoinfected patients in care in the DAA era was composed of patients who were in VA care in 2015, who were without clinically apparent advanced liver disease as of December 31, 2015 and who had not been treated with a DAA by December 31, 2015. To qualify as without advanced liver disease, patients had to have a FIB-4 ≤3.25, no diagnosis of cirrhosis (defined by ICD-9/10 codes), no history of decompensated liver disease (defined by ICD-9/10 codes for ascites, esophageal varices, hepatic coma, hepatic encephalopathy, hepatorenal syndrome, or spontaneous bacterial peritonitis), no history of hepatocellular carcinoma (HCC), and no history of liver transplantation at the start of DAA treatment. The decision to treat, regimen choice and subsequent clinical care was at the discretion of the provider. Within VA, all patients were eligible for HCV treatment.[26] Figure 1 depicts the treated patients meeting inclusion and exclusion criteria.

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. On-treatment HCV RNA was used as a surrogate marker for adherence and No SVR patients were characterized as having a result either below the lower limit of quantification (LLOQ), a ≥2-log decrease from

baseline, or a <2-log decrease from baseline at least 4 weeks after treatment start. VA guidance recommends that providers obtain a 4 week on treatment HCV RNA for all patients receiving DAA therapy.[26] In patients treated in routine medical practice, however, providers may not order labs as recommended, patients may not obtain the laboratories even if ordered, and laboratories may not be able to obtain useable results.

Survival time for SVR and No SVR patients was calculated from the EOT. Survival time for untreated patients was calculated from December 31, 2015. Untreated patients were censored if they started DAA therapy. Given that SVR patients must live at least 12 weeks to have the laboratory testing that qualifies them as SVR but No SVR patients and untreated patients do not have this same definitional survival requirement, we also excluded 3 patients who had laboratory testing after EOT that qualified as No SVR but died before 12 weeks of follow-up and 503 untreated patients who died within 12 weeks of December 31, 2015. Mortality data were available through August 15, 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. One-year mortality rates were calculated as the number of deaths within one year of the EOT among those people who stopped treatment by August 15, 2016 and within one year of December 31, 2015 among the untreated so there was at least one year of follow-up on all included patients.

Control Variables

Demographic and other baseline variables were determined at the time of treatment initiation for treated patients and as of December 31, 2015 for untreated patients. Baseline variables included age, sex, race/ethnicity, body mass index (BMI), diabetes, alanine aminotransferase (ALT), albumin, aspartate aminotransferase (AST), 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 albumin, alanine aminotransferase, aspartate aminotransferase, creatinine, platelets and baseline HCV RNA were defined as the value within one year before and closest to the treatment start date for treated patients and closest to December 31, 2015 for untreated patients. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation.[27] 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 for SVR and No SVR patients and during 2015 for untreated patients to identify recent or active comorbidities that may affect survival and HCV treatment response, we also determined the presence of alcohol abuse, cerebrovascular disease, chronic obstructive pulmonary disease, congestive heart failure, coronary artery 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 ANOVA for continuous variables. Kaplan-Meier curves of survival by SVR were compared with log-rank tests. Mortality rates per 100 patient years of follow-up were compared with the Exact Poisson test. One-year mortality rates were compared with proportion tests. Multivariate Cox proportional hazard models were constructed to identify predictors of mortality and the impact of DAA treatment and of SVR. Models included variables selected *a priori* of age, sex, race/ethnicity, BMI, the baseline comorbidities listed above, albumin, eGFR, genotype and treatment status. Additional sensitivity models were constructed: separately for

each genotype, limited to patients with FIB-4 <1.45, limited to patients with FIB-4 1.45-3.25, and, as an indicator of DAA adherence, limiting the No SVR patients to those patients who had at least a 2 log decrease in HCV RNA while on treatment and limiting the No SVR patients to those who had HCV RNA below the limit of quantification while on treatment.

For all comparisons, a p value <0.05 was considered statistically significant. All analyses were performed using R version 3.4.1 (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 40,664 HCV monoinfected patients without clinically apparent advanced liver disease from 129 VA facilities who stopped DAA treatment by 31 March 2017 for whom SVR data were available; 39,374 (96.8%) were SVR and 1,290 (3.2%) were No SVR. The earliest treatment start date was 22 January 2014. An additional 62,682 patients without clinically apparent advanced liver disease and not treated with DAAs by December 31, 2015 comprised the Untreated. Baseline patient and treatment characteristics appear in Table 1. Given the large sample size, the three groups differed statistically for the baseline measures although many of these differences would not be clinically meaningful. In general, the Untreated appeared slightly healthier than the treated group with lower BMI, lower ALT, lower AST, higher albumin, higher platelets, higher eGFR, and fewer comorbidities. For the treated, mean ALT, AST, platelets and FIB-4 scores did not differ between those with and without SVR (p values not shown). Ledipasvir/sofosbuvir was the most commonly prescribed DAA (65.5%).

In follow-up, 636 of 39,374 SVR patients died (1.6%), 46 of 1,290 No SVR patients died (3.6%), and 3,112 of 62,682 Untreated patients died (5.0%). In unadjusted analysis displayed in the Kaplan Meier survival curves, SVR was associated with statistically significantly reduced all-cause mortality compared to No SVR and compared to Untreated (Figure 2A). When examined separately for patients with FIB-4 <1.45 and 1.45-3.25, SVR was also associated with reduced all-cause mortality compared to Untreated and compared to No SVR although the statistical significance of the difference between SVR and No SVR was reduced for those with FIB-4<1.45 (Figure 2B and 2C). When considering deaths per 100 patient years of follow-up, SVR was associated with a 58.5% reduction in mortality when compared to No SVR ($p<0.001$) and a 69.3% reduction in mortality when compared to Untreated ($p<0.001$)(Table 2). For patients with FIB-4 <1.45 and 1.45-3.25, SVR compared to No SVR was associated with a significant 46.0% and 63.2% reduction in mortality, respectively ($p=0.036$ and $p<0.001$, respectively) and compared to Untreated was associated with a significant 66.7% and 70.6% reduction in mortality, respectively ($p<0.001$ and $p<0.001$). The percentage reductions across genotypes 1a, 1b, 2 and 3, ranged from a 48.4% reduction for genotype 1a to a 79.5% reduction for genotype 2 when comparing SVR to No SVR and ranged from a 69.3% reduction for genotype 1a to a 76.5% reduction for genotype 3 when comparing SVR to Untreated. When considering one-year mortality rates, SVR was still associated with a 40.6% reduction in mortality compared to No SVR ($p<0.001$) and a 31.0% reduction in mortality when compared to Untreated ($p<0.001$).

In the base case multivariate Cox proportion hazard model for 103,346 patients without clinically apparent advanced liver disease, SVR compared to Untreated was independently associated with a substantial reduced risk of all-cause mortality (HR 0.32, 95%CI 0.29-0.36, $p<0.001$) while controlling for numerous baseline demographic and clinical characteristics (Figure 3A). Multivariate models for subgroups, including models limited to patients with FIB-4 <1.45 and FIB-4 1.45-3.25, were consistently associated with a significant

reduced risk of all-cause mortality for SVR compared to Untreated with hazard ratios ranging from 0.25 to 0.39. In a model including albumin as a categorical variable, albumin <3.0 g/dL and albumin between 3.0-3.49 g/dL were each associated with increased risk of all-cause mortality compared to albumin of ≥3.5 g/dL (HR 3.31, 95%CI 2.81-3.91, p<0.001, HR 1.97, 95%CI 1.77-2.19, p<0.001, respectively). Notably in the base case, No SVR compared to Untreated was also independently associated with a reduced risk of all-cause mortality (HR 0.74, 95%CI 0.55-0.99, p<0.049) (Figure 3B).

In a separate multivariate model limited to the 40,644 patients who were treated with DAA regimens, SVR compared to No SVR was also independently associated with a substantial reduced risk of all-cause mortality (HR 0.44, 95%CI 0.32-0.59, p<0.001) (Figure 3C). Additional multivariate models limited to subgroups of these treated patients were again generally associated with a substantial reduced risk of all-cause mortality for SVR compared to No SVR. In the subgroup of patients treated with FIB-4 <1.45 (n=14,727), SVR was associated with a smaller reduction in the risk of death (HR 0.57, 95%CI 0.33-1.00, p=0.051). Supplemental Table 1 contains hazard ratios for all variables included in multivariable models of all-cause mortality in HCV-infected patients for the overall population and only in those who received treatment.

As patients may have treatment failure for a variety of reasons including viral relapse as well as non-adherence, we addressed the potential impact of adherence by assessing on treatment HCV RNA. In a multivariate model of treated patients strictly limiting the No SVR patients to the 803 No SVR patients who achieved HCV RNA below LLOQ, SVR was still associated with a significantly reduced risk of all-cause mortality (HR 0.62, 95%CI 0.40-0.96, p=0.033). In multivariate models of the entire cohort, those No SVR patients with high levels of adherence as assessed by on treatment HCV RNA also had reduced risk of all-cause mortality when compared to Untreated patients.

11 HEP-17-2052

DISCUSSION

This study provides the strongest and most direct evidence yet that treatment of HCV infection in patients without advanced liver disease results in significant clinical benefit. Specifically, successful interferon-free DAA treatment was associated with an unadjusted 69% reduction in all-cause mortality compared to untreated patients and a 59% reduction in all-cause mortality compared to DAA-treated patients who did not achieve SVR in this large cohort of patients without clinically apparent advanced liver disease cared for in routine medical practice. In multivariate models controlling for numerous clinical characteristics and co-morbidities, SVR was associated with a 68% reduction in the risk of death compared to untreated patients and a 56% reduction in the risk of death compared to treated patients who did not achieve SVR. Even when limited to patients with the least evidence of liver disease - FIB-4 <1.45 - SVR was still associated with a 67% reduction in the risk of death compared to untreated patients and a 43% reduction in the risk of death compared to treated patients who did not achieve SVR. As such, this data provides strong support for initiation of DAA-based therapies in patients without advanced liver disease and helps to validate decisions to treat all patients with HCV regardless of the stage of liver disease, as has been done in VA. We provide impetus to lift existing restrictions imposed by private and other public payers that restrict treatment to those with more advanced liver disease.

All oral DAA regimens only became widely available after 2014 and there has been no long-term data on the benefit of achieving SVR with interferon-free DAA regimens in those with mild liver disease. While it is speculated that clinical benefits seen with HCV cures obtained with interferon-free DAAs would be similar to those observed with SVR after prior interferon-based regimens, we provide direct evidence to support this.[12,13] The considerable number of HCV patients that have received DAA treatment in VA provided the power necessary to assess mortality that is not possible in smaller healthcare systems or in smaller clinical trials with limited follow-up. The present work demonstrates a substantial all-cause mortality benefit in patients without

advanced liver disease – a population where demonstration of clinical benefit has been sparse, sparking controversy regarding the clinical urgency in treating this population.[2,11,16-17,20-22,28-29]

The observed 56% reduction in the risk of mortality in well-controlled multivariate models in patients without clinically apparent advanced liver disease when comparing SVR patients to treated patients who did not achieve SVR is less than the 80% reduction observed in similar analyses of DAA-treated patients with advanced liver disease, but remains clinically significant.[30] While the mortality benefit for those in the lowest FIB-4 strata (<1.45) is less than those with FIB-4 in a higher strata (1.45-3.25), indicating that risk of death indeed increases with worsening liver disease, substantial mortality benefit was observed even in those with milder disease. As identified in other studies, albumin level, even at near normal levels, influenced mortality in this evaluation independently of SVR status.[31] This suggests that the mortality benefits of SVR in patients with synthetic dysfunction may be slightly lessened and serves as additional leverage for treating patients earlier in their HCV infection, prior to development of more advanced liver disease. From a population standpoint, in addition to the reduction in mortality, treating all patients with HCV regardless of stage of disease would also further reduce HCV transmission.[18,20,22,28,32]

In this cohort, we compared patients who achieved SVR to both untreated patients and patients who were treated but did not achieve SVR, though the latter comparison between patients who achieved SVR and those who were treated and did not achieve SVR is the more relevant comparison to assess the mortality benefit of SVR with DAA treatment. Unlike many other healthcare providers and systems, in VA there were minimal treatment restrictions, all patients were considered for treatment, and extensive outreach occurred to bring patients in for treatment. Thus, those patients who did not receive treatment in this aggressive treatment environment likely represent a fundamentally different population than those who did receive HCV antiviral treatment. This may help explain why, in the multivariate models, the risk for death for the No SVR patients

was generally lower than the risk for death for untreated patients despite the finding that untreated patients appeared generally healthier at baseline. Perhaps a somewhat surprising finding in our analysis was that the number of primary care visits was the same for all three groups in the year prior to evaluation and the number of outpatient visits overall was similar between the untreated and those with SVR and higher in those treated with No SVR. This suggests that the observed difference in mortality did not arise from a difference in medical care. Some VA data suggest that compared with patients engaged in care, non-engaged patients were significantly more likely to have unstable housing or active substance use.[33] Considering the data we present, it is possible that the untreated patients have other social or behavioral priorities which are being addressed prior to receipt of HCV treatment, or are engaged in care but are uninterested or have made a personal decision not to receive HCV treatment. These scenarios cannot be identified from the electronic data. Regardless, outreach to HCV-infected individuals and, ideally, initiation of HCV treatment may provide a good opportunity for patients to engage in the health care system and improve overall outcomes. Nevertheless, for the purposes of assessing the impact of SVR on mortality, the most appropriate comparison is the comparison between SVR patients and No SVR patients as these patients are already engaged in HCV treatment.

Information about reported cause of death was unavailable, thus we were unable to determine liver-related mortality. As such, the mechanism of the observed reduction in all-cause mortality associated with SVR cannot be elucidated with the present research but is likely multifactorial. Chronic HCV infection is known to lead to a multifaceted systemic disease whereby some extrahepatic manifestations are immune mediated and others driven by chronic inflammation.[34] A growing body of evidence supports the essential role of chronic HCV-related inflammation in the pathogenesis of hepatic and extrahepatic HCV-related disease,[35] and increasing evidence links chronic inflammatory states with all-cause mortality.[36-39] The relatively early appearance of an effect on mortality which occurred in patients who were treated with DAA's compared to untreated patients, suggests that any exposure to DAAs may reduce chronic inflammation and SVR may eliminate chronic

inflammation from HCV contributing to reduced all-cause mortality through mechanisms still being defined. Patients and their families remain concerned with death from any cause, not necessarily disease-specific mortality, making all-cause mortality a relevant outcome and the observed effect meaningful.

There are several other study limitations. Since the determination of SVR requires testing at least 12 weeks after EOT, we excluded patients who died before 12 weeks of follow up which may underestimate the death rate. Our categorization of patients as without advanced liver disease relied on FIB-4 score ≤3.25, no clinical diagnosis of cirrhosis, decompensation or HCC and no history of liver transplant. Thus, it is important to note that our cohort may still include some patients who have occult advanced liver disease, although that diagnosis did not seem clinically apparent. Many of our measures of comorbidities rely on ICD-9/10 coding and required a code within 1 year of DAA treatment, thus some diagnoses may be underreported in both the treated and untreated groups though the rate of underreporting is likely similar. The follow-up time is limited given the relatively recent introduction of interferon-free DAA regimens. The observed differences in risk of death may change over time as more time from treatment elapses, however, longer term benefits in survival rate are likely to be realized given the substantial benefits already observed in the short term and as shown in the Kaplan-Meier survival curves. Despite controlling for multiple factors in multivariable analysis, it is possible that No SVR, SVR, and untreated patients differ on unmeasured or unmeasurable factors that might account for the observed differences in SVR benefit and mortality.

Successfully treating HCV before the development of clinically apparent advanced liver disease translates into a significant mortality benefit. These data strongly support a clinically significant benefit of DAA treatment in patients without clinically apparent advanced liver disease and establishes SVR as a pivotal outcome post DAA treatment specifically in relation to mortality. Increasing access to DAAs for all HCV-infected individuals should result in fewer deaths.

15 HEP-17-2052

Figure 1. Patient Selection Criteria

Abbreviations: DAA, direct-acting antiviral; EOT, end of treatment; SVR, sustained virologic response

Figure 2A. Survival Curves for Patients without Advanced Liver Disease

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

Figure 2B. Survival Curves for Patients without Advanced Liver Disease with FIB-4 1.45-3.25

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

Figure 2C. Survival Curves for Patients without Advanced Liver Disease with FIB-4 <1.45

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

16 HEP-17-2052

Figure 3A. Hazard Ratios for Mortality for Patients without Advanced Liver Disease Comparing SVR to Untreated

Figure 3B. Hazard Ratios for Mortality for Patients without Advanced Liver Disease Comparing No SVR to Untreated

Figure 3C. Hazard Ratios for Mortality for Patients without Advanced Liver Disease Treated with interferon-free Direct-Acting Antivirals Comparing SVR to No SVR

17 HEP-17-2052

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21 HEP-17-2052

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Table 1. Baseline Characteristics of Patients without Advanced Liver Disease Treated and Untreated with Interferon-free Direct-Acting Antivirals

	SVR N=39,374	No SVR N=1,290	Untreated N=62,682	P
Age (years)	61.2±7.4 (22.9-92.8)	60.3±8.5 (24.8-89.2)	61.0±7.9 (22.6-95.5)	<0.001
Sex Male	37,769 (95.9%)	1,253 (97.1%)	60,293 (96.2%)	0.02
Race/ethnicity				<0.001
African-American	14,793 (37.6%)	551 (42.7%)	25,139 (40.1%)	
Caucasian	20,321 (51.6%)	586 (45.4%)	30,334 (48.4%)	
Hispanic	1,815 (4.6%)	65 (5.0%)	3,043 (4.9%)	
Other/multiple	2,445 (6.2%)	88 (6.9%)	4,166 (6.6%)	
Body Mass Index (kg/m2)	28.2±5.3 (14.0-66.3)	28.6±5.9 (16.9-60.6)	27.1±5.3 (12.9-72.4)	<0.001
Body Mass Index categories				<0.001
<25	11,187 (28.4%)	374 (29.0%)	23,622 (37.7%)	
25-29	15,678 (39.9%)	467 (36.2%)	23,248 (37.2%)	
≥30	12,509 (31.8%)	449 (34.8%)	15,712 (25.1%)	
Recent diagnosis				
Alcohol abuse	7,754 (19.7%)	342 (26.5%)	8,481 (13.5%)	<0.001
Cerebrovascular disease	1,077 (2.7%)	38 (2.9%)	2,257 (3.6%)	<0.001
Chronic obstructive pulmonary disease	6,016 (15.3%)	216 (16.7%)	5,929 (9.3%)	<0.001
Congestive heart failure	1,148 (2.9%)	47 (3.6%)	1,570 (2.5%)	<0.001
Coronary artery disease	2,570 (6.5%)	79 (6.1%)	3,380 (5.4%)	<0.001
Diabetes	11,500 (29.2%)	412 (31.9%)	7,808 (12.5%)	<0.001
Hard drug use	5,325 (13.5%)	273 (21.2%)	7,531 (12.0%)	<0.001
Hypertension	17,528 (44.5%)	566 (43.1%)	18,053 (28.8%)	<0.001
Alanine aminotransferase (U/L)	59.2±47.6 (5-1784)	60.0±48.3 (6-424)	53.0±46.7 (3-2001)	<0.001
Albumin (g/dL)	4.0±0.4 (1.4-5.5)	3.9±0.4 (1.5-5.3)	4.1±0.4 (1.5-6.0)	<0.001
Aspartate aminotransferase (U/L)	45.1±25.6 (5-599)	46.3±26.5 (5-260)	42.7±25.8 (3-753)	<0.001
Creatinine (mg/dL)	1.1±0.8 (0.2-19.9)	1.1±0.8 (0.4-13.2)	1.0±0.9 (0.1-19.6)	<0.001
eGFR (mL/min/1.73m^2)	85.9±19.8 (2.6-196.7)	87.9±20.2 (4.0-138.9)	90.1±21.8 (2.6-234.8)	<0.001
Platelets (K/μL)	219.7±59.5 (66-1078)	220.4±57.3 (87-623)	226.4±66.2 (65-1378)	<0.001
FIB4	1.8±0.6 (0.1-3.2)	1.7±0.7 (0.2-3.2)	1.7±0.7 (0.2-3.2)	<0.001
FIB-4 categories				<0.001
<1.45	14,247 (36.2%)	480 (37.2%)	24,409 (38.9%)	
1.45-3.25	25,127 (63.8%)	810 (62.8%)	38,273 (63.7%)	
	N=38,970	N=1,290	N=59,073	
HCV RNA (log IU/mL)	6.2±0.8 (0.8-9.5)	6.4±0.7 (2.6-7.8)	6.2±0.9 (0.7-9.4)	<0.001
<6,000,000 IU/mL	30,706 (78.8%)	933 (72.3%)	46,503 (78.7%)	<0.001

HCV genotype*				<0.001
1a	24,310 (61.7%)	842 (65.3%)	38,981 (62.2%)	
1b	9,209 (23.4%)	232 (18.0%)	13,697 (21.9%)	
2	4,000 (10.2%)	124 (9.6%)	6,482 (10.3%)	
3	1,855 (4.7%)	92 (7.1%)	3,522 (5.6%)	
Direct-Acting Antiviral regimen				
Daclatasvir+sofosbuvir ± ribavirin	493 (1.3%)	19 (1.5%)	--	0.57‡
Ledipasvir/sofosbuvir ± ribavirin	25,797 (65.5%)	824 (63.9%)	--	0.23‡
OPrD ± ribavirin	3,932 (10.0%)	119 (9.2%)	--	0.39‡
Simeprevir+sofosbuvir ± ribavirin	808 (2.1%)	18 (1.4%)	--	0.12‡
Sofosbuvir+ribavirin	3,453 (8.8%)	114 (8.8%)	--	0.97‡
Ribavirin containing DAA regimen	9,437 (24.0%)	340 (26.4%)	--	0.05‡
Median outpatient visits†	25 [13, 49]	32 [17, 64]	21 [9, 48]	
Median primary care visits †	3 [2,5]	3 [2,6]	3 [2, 5]	
Median follow-up (days)◊	434 [315, 658]	406 [287, 624]	468 [190, 592]	

Continuous variables reported as mean±standard deviation (range) except for outpatient visits and follow-up reported as median [25%, 75%]. Categorical variables reported as n (%). * Genotype 1a includes 1a, 1 with subtype unspecified and mixed 1a/1b. † Median number of visits in 365 days prior to DAA treatment start date for SVR and No SVR patients and in 365 days prior to 1/1/2016 for Untreated patients. ◊ Follow-up was from the end of treatment to 8/15/2017 for SVR and No SVR patients and from 12/31/2015 to 8/15/2017 for Untreated patients. ‡ Comparison between SVR and No SVR only. Abbreviations: eGFR, estimated glomerular filtration rate; OPrD, ombitasvir/paritaprevir/ritonavir+dasabuvir; SVR, sustained virologic response

Table 2. Mortality Rates among Patients without Advanced Liver Disease Treated with Interferon-Free Direct-Acting Antivirals and Untreated

	Treated				Untreated		SVR vs No SVR		SVR vs Untreated	
	SVR		No SVR							
	Deaths	Deaths/100py (95%CI)	Deaths	Deaths/100py (95%CI)	Deaths	Deaths/100py (95%CI)	SVR-Related Mortality Reduction	P	SVR-Related Mortality Reduction	P
Total	636	1.18 (1.09-1.28)	46	2.84 (2.08-3.79)	3112	3.84 (3.69-3.99)	58.5%	<0.001	69.3%	<0.001
FIB-4										
<1.45	218	1.14 (0.99-1.30)	13	2.11 (1.12-3.61)	1123	3.42 (3.21-3.65)	46.0%	0.036	66.7%	<0.001
1.45-3.25	418	1.21 (1.09-1.33)	33	3.29 (2.27-4.63)	1989	4.12 (3.92-4.32)	63.2%	<0.001	70.6%	<0.001
Genotype										
1a*	380	1.14 (1.03-1.27)	23	2.21 (1.40-3.31)	1832	3.71 (3.53-3.90)	48.4%	0.005	69.3%	<0.001
1b	161	1.27 (1.08-1.48)	8	2.90 (1.25-5.72)	697	4.01 (3.69-4.35)	56.2%	0.029	68.3%	<0.001
2	74	1.32 (1.03-1.65)	11	6.44 (3.21-11.52)	380	4.21 (3.76-4.70)	79.5%	<0.001	68.6%	<0.001
3	21	0.91 (0.56-1.39)	4	3.12 (0.85-7.98)	203	3.88 (3.31-4.52)	70.8%	0.040	76.5 %	<0.001
One-year mortality rate										
	One-year Deaths	One-year mortality rate (95% CI)	One-year Deaths	One-year mortality rate (95% CI)	One-year Deaths	One-year mortality rate (95% CI)	SVR-Related Mortality Reduction	P	SVR-Related Mortality Reduction	P
Total	348	1.3% (1.2-1.5)	25	3.2% (2.1-4.7)	1592	4.2% (4.0-4.5)	40.6%	<0.001	31.0%	<0.001
FIB-4										
<1.45	115	1.2% (1.0 - 1.5)	10	3.4% (1.7 - 6.4)	585	3.8% (3.5 - 4.2)	35.3%	0.003	31.6%	<0.001
1.45-3.25	233	1.4% (1.2 - 1.6)	15	3.0% (1.8 - 5.0)	1007	4.5% (4.2 - 4.8)	46.7%	0.005	31.1%	<0.001
Genotype										
1a*	209	1.3% (1.1 - 1.5)	13	2.5% (1.4 - 4.4)	945	4.1% (3.9 - 4.4)	52.0%	0.03	31.7%	<0.001
1b	93	1.5% (1.2 - 1.8)	5	3.6% (1.3 - 8.7)	360	4.6% (4.1 - 5.1)	41.7%	0.09	32.6%	<0.001
2	36	1.5% (1.0 - 2.0)	5	6.2% (2.3 - 14.6)	187	4.3% (3.7 - 5.0)	24.2%	0.004	34.9%	<0.001
3	10	1.0% (0.5 - 1.9)	2	3.5% (0.6 - 13.2)	100	4.1% (3.4 - 5.0)	28.6%	0.28	24.4%	<0.001

* Genotype 1a includes 1a, 1 with subtype unspecified, and mixed 1a/1b. Follow-up was from the end of treatment to 8/15/2017 for SVR and No SVR patients and from 12/31/2015 to 8/15/2017 for Untreated patients.

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

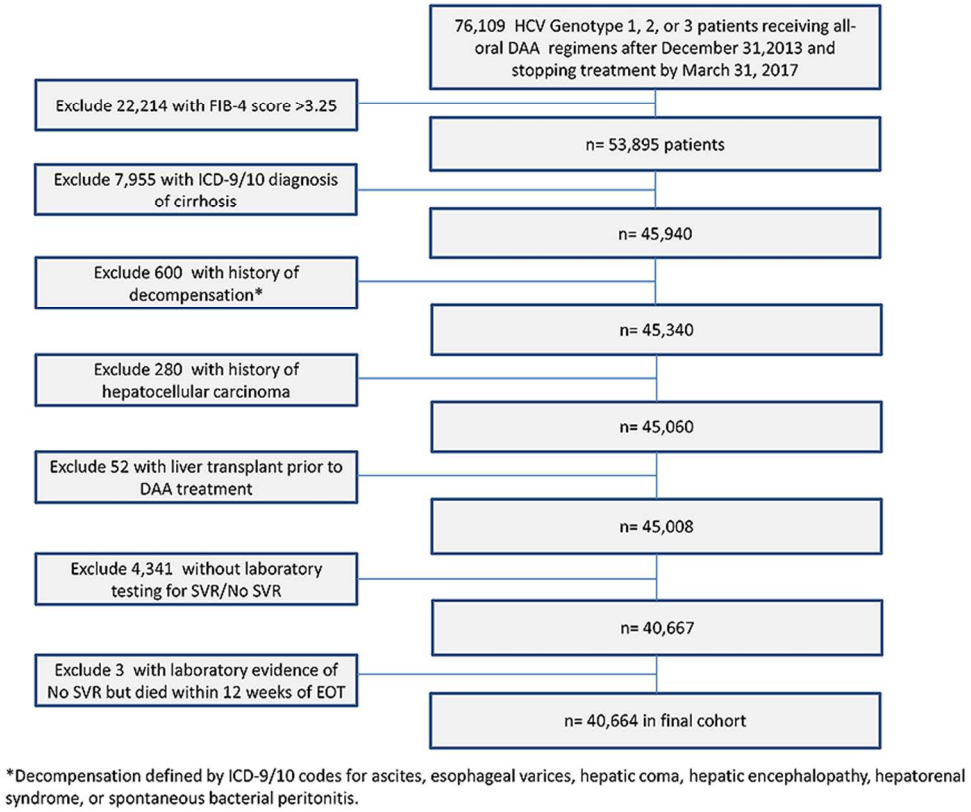

Figure 1. Patient Selection Criteria ‼ ┼ Abbreviations: DAA, direct-acting antiviral; EOT, end of treatment; SVR, sustained virologic response‼ ┼ ‼ ┼

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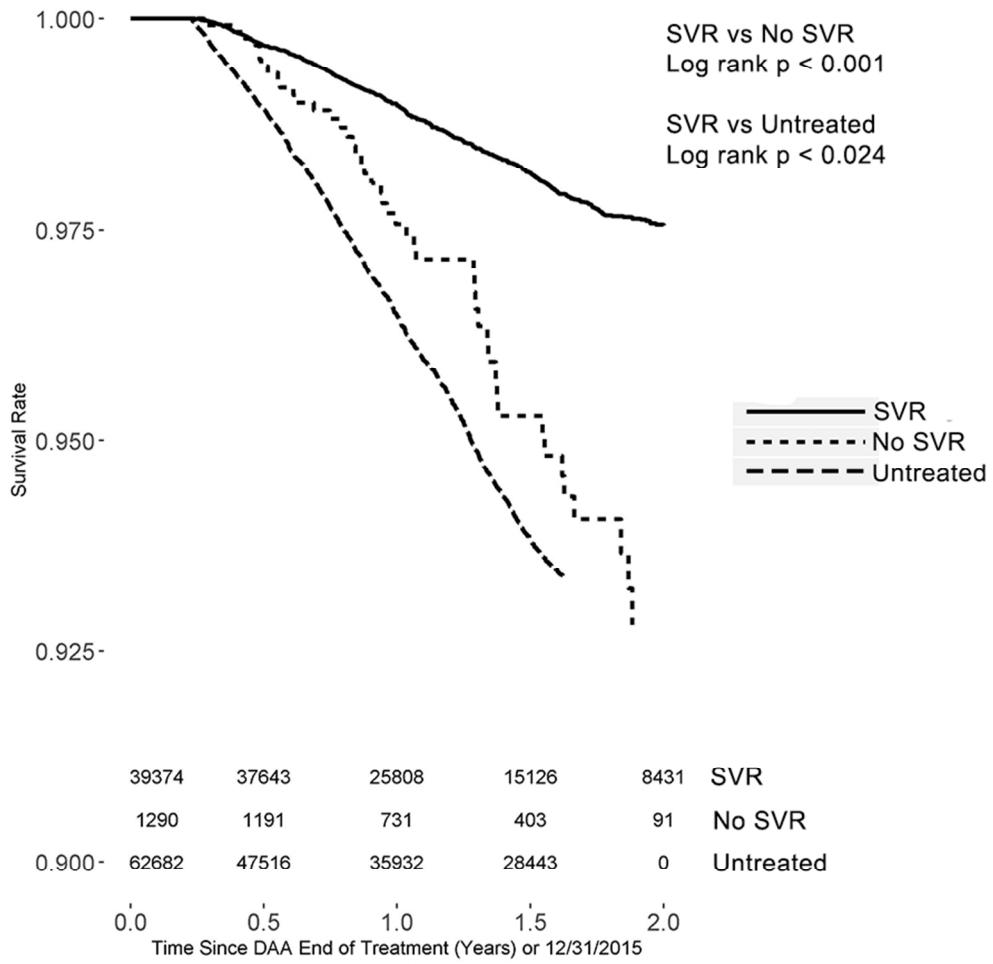

Figure 2A. Survival Curves for Patients without Advanced Liver Disease. The number of patients at risk is shown below at each time point.

76x76mm (300 x 300 DPI)

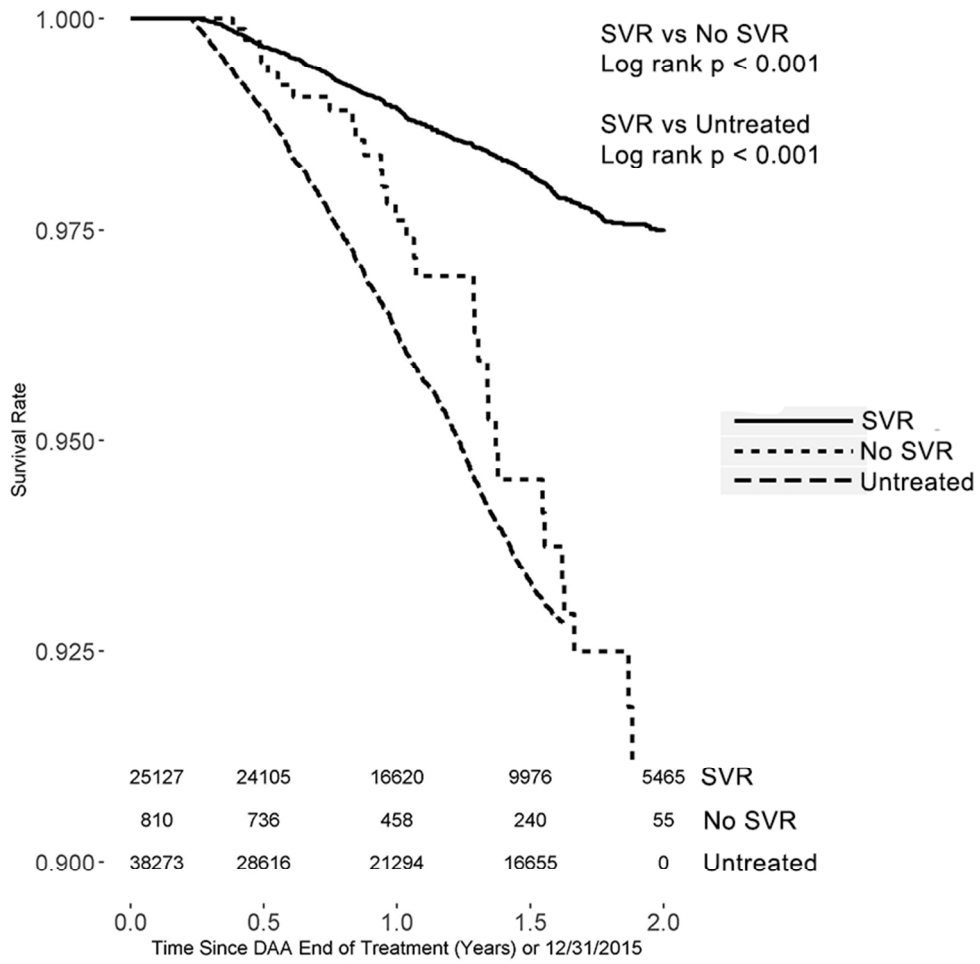

Figure 2B. Survival Curves for Patients without Advanced Liver Disease with FIB-4 1.45-3.25. The number of patients at risk is shown below at each time point.

76x76mm (300 x 300 DPI)

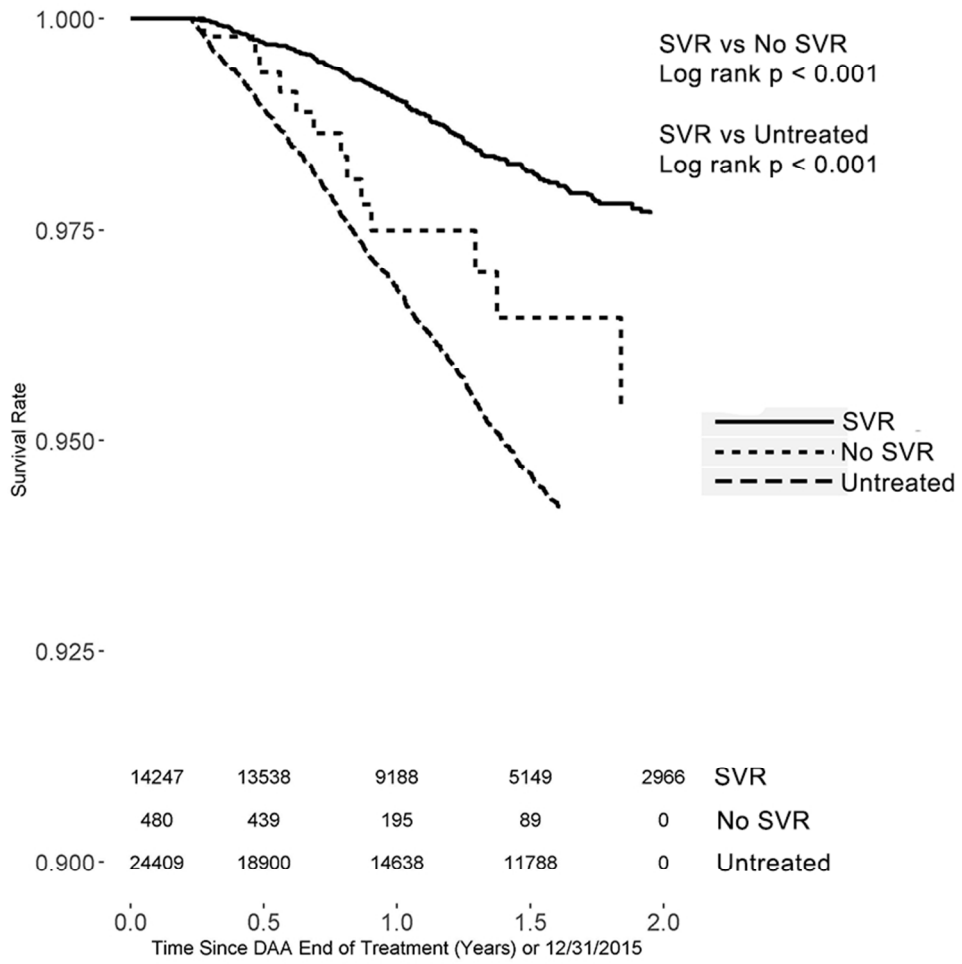

Figure 2C. Survival Curves for Patients without Advanced Liver Disease with FIB-4 <1.45. The number of patients at risk is shown below at each time point.

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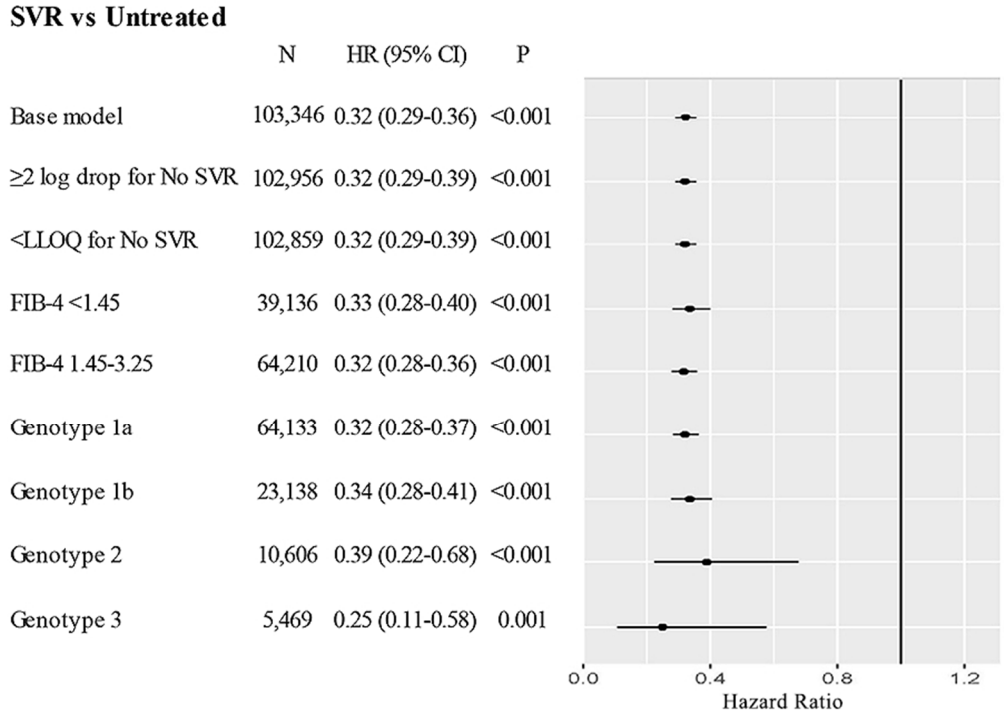
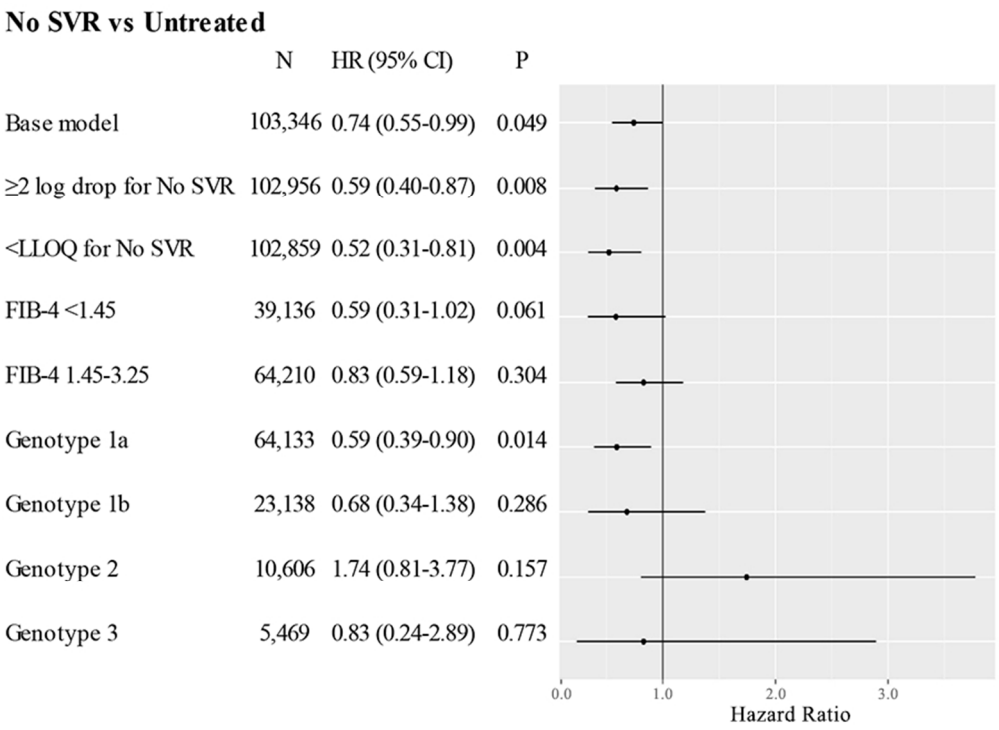


Model also adjusted for sex, age, race/ethnicity, BMI, albumin, eGFR, alcohol abuse, cerebrovascular disease, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, diabetes, hard drug use, hypertension, ribavirin-containing regimen, and genotype.

Figure 3A. Hazard Ratios for Mortality for Patients without Advanced Liver Disease Comparing SVR to Untreated

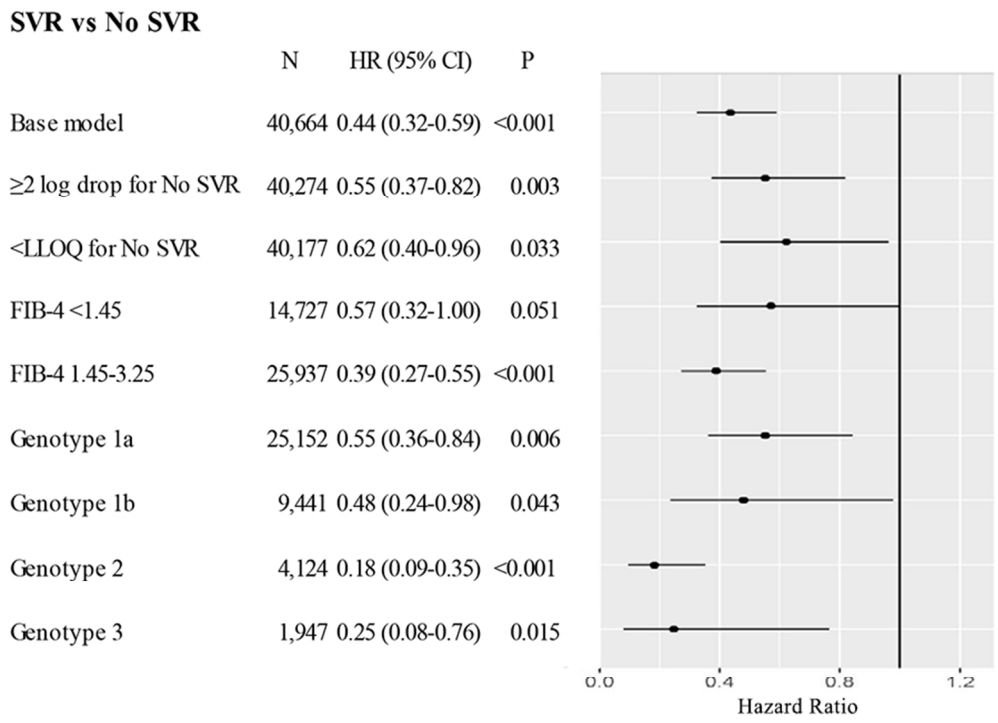
76x65mm (300 x 300 DPI)



Model also adjusted for sex, age, race/ethnicity, BMI, albumin, eGFR, alcohol abuse, cerebrovascular disease, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, diabetes, hard drug use, hypertension, ribavirin-containing regimen, and genotype.

Figure 3B. Hazard Ratios for Mortality for Patients without Advanced Liver Disease Comparing No SVR to Untreated

76x65mm (300 x 300 DPI)



Model also adjusted for sex, age, race/ethnicity, BMI, albumin, eGFR, alcohol abuse, cerebrovascular disease, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, diabetes, hard drug use, hypertension, ribavirin-containing regimen, and genotype.

Figure 3C. Hazard Ratios for Mortality for Patients without Advanced Liver Disease Treated with interferon-free Direct-Acting Antivirals Comparing SVR to No SVR

76x65mm (300 x 300 DPI)