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## Hepatitis C eradication with direct-acting antivirals reduces the risk of variceal bleeding

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### Summary

**Background:** The real-world, long-term benefits of sustained virologic response (SVR) on the risk of variceal bleeding remain unclear.

**Aim:** We aimed to assess the association between DAA-induced SVR and post-treatment variceal bleeding.

**Methods:** We identified patients who initiated DAA-only antiviral treatments in the Veterans Affairs healthcare system from 2013–2015. We followed patients until 01/01/2019 for the development of gastroesophageal variceal bleeding defined by diagnostic codes. We used multivariable Cox proportional hazards regression to assess the association between SVR and development of variceal bleeding, adjusting for potential confounders.

**Results:** Among 33,582 DAA-treated patients, 549 (1.6%) developed variceal bleeding after treatment (mean follow-up 3.1 years). Compared to no-SVR, SVR was associated with a significantly lower incidence of variceal bleeding among all patients (0.46 vs. 1.26 per 100-patient years, adjusted hazard ratio [AHR] 0.66, 95% CI 0.52–0.83), among patients with pre-treatment cirrhosis (1.55 vs 2.96 per 100 patient-years, AHR 0.73, 95% CI 0.57–0.93) and among patients without pre-treatment cirrhosis (0.07 vs. 0.29 per 100 patient-years, AHR 0.33, 95% CI 0.17–

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Authors' Contributions and Authorship Statement

George Ioannou is the guarantor of this paper. All authors approved the final version of the manuscript.

Moon: Analysis of data, critical revision of manuscript.

Green: Acquisition of data, study design, analysis of data.

Berry: Study design, analysis of data, critical revision of manuscript.

Rockey: Analysis of data, critical revision of manuscript

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

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0.65). The risk of variceal bleeding after treatment was lower in those who achieved SVR versus no SVR among patients who had non-bleeding varices (3.5 vs 4.9 per 100 patient-years) or bleeding varices (12.9 vs 16.4 per 100 patient-years) diagnosed before treatment, but these differences were not statistically significant in adjusted analyses.

**Conclusion:** DAA-induced SVR is independently associated with lower risk of variceal bleeding during long-term follow-up in patients with and without pre-treatment cirrhosis. These findings demonstrate an important real-world benefit of DAA treatment.

### Keywords

cirrhosis; haemorrhage; portal hypertension; liver disease

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### Introduction

Gastroesophageal varices are a common complication of cirrhosis that can lead to substantial morbidity and mortality<sup>1-3</sup>. Hepatitis C virus (HCV) infection is a leading cause of cirrhosis in the US<sup>4</sup>. With the advent of direct-acting antiviral agents (DAA), HCV cure rates have increased dramatically and the majority of patients with HCV are now expected to achieve sustained virologic response (SVR)<sup>5</sup>. Furthermore, SVR can now be achieved in the majority of patients with established cirrhosis, including patients with advanced or decompensated cirrhosis, such as those with a history of ascites, encephalopathy, varices and variceal bleeding.

Since all available randomized, placebo-controlled trials of antiviral treatment have very short follow-up, some have argued that the long-term clinical benefits of antiviral treatment and sustained virologic response (SVR) have not yet been demonstrated<sup>6</sup>. As such, some insurance providers and states require that significant fibrosis be present before covering HCV antiviral treatment<sup>7</sup>. It is therefore imperative to evaluate the long-term benefits of DAA-induced SVR in adequately powered and designed observational studies. DAAs have now led to eradication of HCV in unprecedented numbers of patients with cirrhosis and decompensated cirrhosis and we now have long-term follow up data, enabling us to address these questions<sup>8</sup>.

We hypothesized that HCV eradication may lead to a reduced risk of variceal bleeding both in patients with and those without pre-treatment cirrhosis during long-term follow-up. In patients without pre-treatment cirrhosis, HCV eradication may reduce the risk of progressing to cirrhosis thereby reducing the risk of developing varices and variceal bleeding. HCV eradication in patients with cirrhosis may stop fibrosis progression or even cause fibrosis regression, leading to improved portal hypertension and reduced risk of variceal bleeding<sup>9</sup>. Finally, HCV eradication might reduce the risk of variceal bleeding even in the highest risk patients, i.e. those who with known varices or variceal bleeding prior to SVR.

In this study, we used Veterans Affairs Healthcare System (VAHS) data to examine associations between DAA-induced HCV eradication and the risk of variceal bleeding, in clinically relevant subgroups such as the ones outlined above. Furthermore, we aimed to

investigate other characteristics that are associated with variceal bleeding in patients who received antiviral treatment and achieved SVR.

## Methods

### Data Source

The VAHS is the largest integrated healthcare provider of HCV antiviral treatment in the United States<sup>8</sup>. Nationwide, the VA uses a single comprehensive electronic healthcare information network which integrates all care applications into a single, common database. We obtained data on all patients who initiated antiviral therapy for chronic HCV in the VA system using the VA Corporate Data Warehouse (CDW), a national, continually updated repository of healthcare data including all patient pharmacy prescriptions, demographics, inpatient and outpatient visits, problem lists, procedures, vital signs, diagnostic tests, and laboratory tests<sup>10</sup>. The study was approved by the Institutional Review Board of the Veterans Affairs Puget Sound Healthcare System.

### Study Population

Using VA pharmacy prescription data, we identified all DAA-only HCV antiviral regimens initiated in the VA from 2013 to 2015 (Figure 1). We defined sustained virologic response (SVR) as a serum HCV RNA viral load test below the lower limit of detection performed at least 12 weeks after the end of antiviral treatment<sup>11</sup>. We excluded patients with missing SVR data or prior liver transplant. Patients were excluded if variceal bleed, death or last follow-up visit occurred within the first 90 days after the start of DAA treatment. For patients who received multiple DAA regimens, we analyzed only the results of the first one and censored them at the point of a subsequent regimen that resulted in SVR, if one existed. The most common DAA regimen was sofosbuvir/ledipasvir (58.1%) followed by Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir (19.1%), Sofosbuvir ( $\pm$ daclatasvir) (13.1%), and Sofosbuvir +Simeprevir (9.6%).

### Gastroesophageal Varices

Gastroesophageal varices without bleeding were defined by the presence of appropriate diagnostic codes (ICD-9 codes 456.1, 456.21 or ICD-10 codes I85.00, I86.4 or I85.10) recorded at least twice. These diagnostic codes have been validated within the VA and have a positive predictive value of approximately 90% for identifying oesophageal varices compared to chart review<sup>12,13</sup>. Gastroesophageal varices with bleeding were defined by the presence of appropriate diagnostic codes (ICD-9 codes 456.0, 456.20 or ICD-10 codes I85.10, I85.01, I86.41, or I85.11) recorded at least once. A single recording was required for bleeding varices (rather than two or more) because many patients may only have a single bleeding episode.

Nonselective beta blockers (NSBBs), frequently used to prevent variceal bleeding, were not included in the diagnostic criteria for gastroesophageal varices because they have many other indications (hypertension, angina prophylaxis, essential tremor, migraine prophylaxis, post-traumatic stress disorder) and therefore were not considered specific enough. However,

we did evaluate NSBB as a potential confounder of the association between SVR and variceal bleeding.

### Baseline Patient Characteristics and Potential Confounders

We collected baseline data including age, sex, race/ethnicity, diabetes, body mass index (BMI), HCV genotype, HCV viral load, and receipt of prior antiviral treatment. We extracted all clinical factors and laboratory tests [including components of the model for end-stage liver disease (MELD) score<sup>14</sup>] prior to treatment and recorded the value of each test closest to the treatment starting date within the preceding 6 months. We defined hepatitis B virus (HBV) coinfection by positive HBV surface antigen or viral load. We also determined the presence of cirrhosis, or complications of cirrhosis (ascites, spontaneous bacterial peritonitis, encephalopathy, gastroesophageal varices and hepatorenal syndrome), type 2 diabetes mellitus, alcohol use disorders, substance use disorders, based on appropriate ICD-9 or ICD-10 codes recorded at least twice *prior to* treatment initiation in any inpatient or outpatient encounter. These ICD-based definitions of cirrhosis and other comorbidities have been widely used and validated in studies using VA medical records<sup>15–20</sup>. We assessed treatment with NSBBs (i.e. nadolol, propranolol or carvedilol) at the time of DAA initiation, since NSBBs may reduce the risk of variceal bleeding or may be associated with the presence of large gastroesophageal varices or prior variceal bleeding requiring prophylaxis<sup>21–23</sup>.

In addition to determining the history of alcohol use disorders by ICD-9/10 codes, we used the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) score to estimate the severity of alcohol use at baseline. AUDIT-C is a validated screening tool for assessing alcohol misuse and scores range from 0–12, with higher scores reflecting higher amounts of alcohol consumption<sup>24,25</sup>. Since 2004, AUDIT-C has been used to screen all veterans for unhealthy alcohol use annually in the outpatient setting<sup>26</sup>. Baseline alcohol use was defined by the AUDIT-C score reported within 1 year before initiation of antiviral treatment and categorized into abstinent (score of 0), low-level drinking (score of 1–3 in men, 1–2 in women), and unhealthy drinking (score of 4–12 in men, 3–12 in women)<sup>27,28</sup>.

### Statistical Analysis

We used Cox proportional hazards regression to compare patients who achieved SVR to those who did not achieve SVR with respect to the risk of developing gastroesophageal variceal bleeding after antiviral treatment (or, more accurately 90 days after the initiation of antiviral treatment). Our comparison group was DAA-treated patients who did not achieve SVR, rather than patients who were never treated with DAAs, to avoid the risk of health initiator bias (selective provision of treatments to healthy and health-conscious patients and avoidance of treatment of frail individuals<sup>29,30</sup>) and immortal time bias (treated patients experience “immortal time” prior to treatment during which outcomes cannot occur). Any episodes of variceal bleeding that occurred within 90 days of initiation of treatment were excluded because they occurred during the DAA treatment and might have caused failure of treatment, thus resulting in a spurious association between failure of treatment and variceal haemorrhage. Analyses were adjusted for the following potential confounders that may be associated with both SVR and the risk of progressive liver disease and variceal bleeding:

cirrhosis, prior history of varices, variceal bleeding, ascites, bacterial peritonitis or encephalopathy, age, sex, race/ethnicity, body mass index, HBV co-infection, type 2 diabetes mellitus, hepatocellular carcinoma, alcohol use disorders, substance use disorder, baseline alcohol use, NSBB use, platelet count, serum bilirubin, serum creatinine, serum albumin, INR, and hemoglobin levels. Continuous variables were categorized and modeled as dummy categorical variables.

Follow-up for development of variceal bleeding extended until 01/01/2019 so that even the patients treated in late 2015 (i.e. the most recent in our cohort) had adequate follow-up. Patients without incident variceal bleeding were censored at the time of death or last follow-up in the VA. We presented subgroup analyses according to prior history of varices or variceal bleeding, cirrhosis, MELD score, FIB-4 score, and alcohol use disorders (suggesting comorbid alcohol-related liver disease).

Survival analyses were stratified by the Veterans Affairs facility at which the antiviral treatment was administered. We analyzed only the first antiviral regimen administered between 2013–2015. Patients who did not achieve SVR with this regimen and were subsequently treated again at any point up to 01/01/2019 and achieved SVR, were censored at the time of initiation of the regimen that led to SVR.

## Results

### Characteristics of study population

Patients with (n=29,998) and without SVR (n=3,584) were of similar age (61.1 vs. 60.6 years), sex (96.6% vs. 98.1% male), and race/ethnicity (52.4% vs. 52.7% white/non-Hispanic) (Table 1). Patients without SVR were more likely to have cirrhosis (41.1% vs. 26.4%), non-bleeding varices (11.6% vs. 5.0%), and bleeding varices (2.9% vs. 1.4%).

There were 9,399 patients with cirrhosis, including 7,927 (84.3%) who achieved SVR and 1,472 (15.7%) who did not achieve SVR (Table 2). Baseline demographic characteristics and MELD scores were similar among cirrhotic patients who did and did not achieve SVR. Patients without SVR had a higher proportion of complications of cirrhosis, including varices without bleeding (27.5% vs. 18.2%), varices with bleeding (7.1% vs. 5.1%), encephalopathy (28.2% vs 18.3%), and hepatocellular carcinoma (13.5% vs. 6.1%).

### Association between SVR and variceal bleeding

**All patients**—During a mean follow-up time of 3.1 years, 549 patients developed variceal bleeding (incidence 0.53 per 100 patient-years) (Table 3). Among patients with SVR (n=29,998), 434 developed variceal bleeding (incidence 0.46 per 100 patient-years) compared to 115 of 3,584 patients without SVR (1.26 per 100 patient-years) and this difference was statistically significantly different after adjustment for baseline characteristics (adjusted hazards ratio [AHR] 0.66, 95% CI 0.52–0.83). SVR was also associated with a reduced risk of variceal bleeding in many clinically relevant sub-groups that we evaluated, such as patients with cirrhosis (AHR 0.73, 95% CI 0.57–0.93), without cirrhosis (AHR 0.33, 95% CI 0.17–0.65), MELD <9 (AHR 0.41, 95% CI 0.28–0.61), alcohol use disorder (AHR 0.65, 95% CI 0.48–0.88), and no alcohol use disorder (AHR 0.67, 95% CI 0.45–0.99).

**Patients with cirrhosis**—Among 9,399 patients with cirrhosis, 480 (5.1%) developed variceal bleeding during 3.07 years of mean follow-up (incidence 1.66 per 100 patient years). The incidence of variceal bleeding was lower among those with SVR (1.55 per 100 patient-years) compared to those without SVR (2.96 per 100 patient-years) and this difference remained statistically significantly after multivariable adjustment in Cox proportional hazards models (AHR 0.73, 95% CI 0.57–0.93) (Table 3/Figure 2).

**Patients with a prior history of varices or variceal bleeding**—The absolute incidence of variceal bleeding after antiviral treatment was much greater in patients who had a prior history of variceal bleeding (13.38 per 100 patient-years) or varices without bleeding (3.71 per 100 patient-years) than in patients who had no prior history of varices (0.20 per 100 patient-years). Patients with SVR had a lower incidence of variceal bleeding than patients without SVR among those without prior varices (0.17 vs 0.56 per 100 patient-years), with prior non-bleeding varices (3.48 vs 4.87 per 100 patient-years), and with prior bleeding varices (12.86 vs 16.38 per 100 patient-years) (Table 3/Figure 2). In the Cox proportional hazards models, the difference in variceal bleeding rate by SVR was statistically significant among patients without prior varices (AHR 0.52, 95% CI 0.35–0.76) but not among those with non-bleeding varices (AHR 0.77, 95% CI 0.52–1.15) or bleeding varices (AHR 0.60, 95% CI 0.33–1.09).

**Characteristics associated with variceal bleeding**—In the multivariable Cox proportional hazards model among patients with cirrhosis (Table 4), characteristics associated with risk of variceal bleeding included prior varices without bleeding (AHR 3.09, 95% CI 2.39–4.00), prior varices with bleeding (AHR 9.39, 95% CI 7.08–12.46), non-selective beta-blocker use (AHR 1.37, 95% CI 1.08–1.72), ascites (AHR 1.71, 95% CI 1.02–2.87), spontaneous bacterial peritonitis (SBP) (AHR 2.15, 95% CI 1.31–3.52), PLT >100–150 (AHR 4.42, 95% CI 1.08–18.07) and PLT <100 (AHR 6.68, 95% CI 1.64–27.17) vs PLT >250, and hemoglobin <13.6 vs >15.6 (AHR 2.12, 95% CI 1.43–3.15). Increasing MELD scores were associated with increased risk of variceal bleed, although this did not meet statistical significance for MELD 16–19 (AHR 1.31, 95% CI 0.69–2.51) or MELD >19 (AHR 2.00, 95% CI 0.90–4.43) potentially due to fewer patients with advanced cirrhosis receiving DAAs. Variables associated with a decreased risk of variceal bleeding included SVR (AHR 0.68, 95% CI 0.53–0.86) and black/non-Hispanic race/ethnicity (AHR 0.74, 95% CI 0.56–0.99).

## Discussion

Variceal bleeding is a life-threatening complication of cirrhosis. In this large cohort of 33,582 US Veterans who underwent DAA treatment and were followed for a mean of 3.1 years after treatment, we extend our knowledge of the associations between SVR and variceal bleeding in several ways. First, we have shown that DAA-induced SVR was clearly associated with a reduced risk of variceal bleeding both among patients with established cirrhosis and among those without cirrhosis prior to antiviral treatment. Second, our results suggest that even among patients with a prior history of varices or variceal bleeding, which are the highest risk groups, DAA-induced SVR was associated with a lower risk of variceal bleeding (although this difference did not reach statistical significance in our multivariable

models). Finally, we found that although in cirrhotic patients SVR reduces the risk of variceal bleeding, a substantial residual risk remains and several important predictors of variceal bleeding are evident. Taken together, our results point to a beneficial effect of DAA-induced SVR with regard to the potentially deadly complication of variceal bleeding and add to the growing literature demonstrating the clinical benefits of HCV eradication with DAAs<sup>31–33</sup>.

Our results demonstrate that DAAs reduced the risk of variceal haemorrhage among patients without cirrhosis or pre-treatment varices, underscoring the importance of “early” HCV treatment. Given the nature of this study, although we do not know the histological stage of fibrosis of the cohort, natural history studies demonstrate that, among all-comers with untreated HCV, cirrhosis will develop in approximately 15% over 5 years<sup>34</sup> and, among patients with compensated cirrhosis, varices will occur in 7% annually<sup>35</sup>. Further, our data suggest the likelihood of variceal haemorrhage can be substantially reduced with early treatment of HCV – in our study, successful treatment of HCV prior to the development of cirrhosis nearly eliminated the risk of future variceal bleeding (incidence 0.07 per 100-person years). These findings provide further support for calls to expand of HCV screening<sup>36</sup> and for treatment of all patients with HCV regardless of fibrosis stage<sup>37</sup>.

We have also shown that SVR is associated with reduction in the risk of variceal bleeding among patients with cirrhosis, whether varices are present or not. This may be due to fibrosis reversion after successful DAA therapy, resulting in reduced portal pressures. Biologic plausibility for this is provided by studies showing that HCV treatment is associated with fibrosis reversion<sup>38–41</sup>, improvement in portal hypertension<sup>42–45</sup>, and decreased risk of oesophageal varices in compensated cirrhosis<sup>46</sup>. Not surprisingly, in our multivariable model low platelet count, an indirect measure of portal hypertension, and other sequelae of portal hypertension (e.g. ascites, SBP) were associated with an increased risk of variceal bleeding.

Despite SVR, certain patients developed variceal bleeding, including 4.8% of patients with pre-treatment cirrhosis. These data suggest that while some patients may have an improvement in portal hypertension (we speculate as a result of reduced fibrosis) with a concomitant reduction in the risk of variceal bleeding, this does not occur in all patients. This finding has several implications. First, the data suggest that there are likely highly specific biologic responses to SVR – leading to a reduction in portal pressure in some, but not all, patients. Further study to better understand these biologic responses, and the predictors of them, will be essential. Our multivariable model identified some known predictors of variceal bleeding including history of varices, other decompensation events, and low platelet count. NSBB use was also associated with an increased risk of variceal bleeding, as expected since these medications are preferentially used in patients with high-risk varices (e.g. large, red wale signs). Lastly, black race was associated with a lower risk of variceal bleeding, which has previously been reported and deserves more study<sup>47</sup>. Second, it suggests that it is important to continue endoscopic surveillance for varices and prophylaxis for variceal bleeding if indicated following SVR. This was particularly true among patients with pre-treatment varices. Conversely, it may be that cirrhosis patients without varices who achieve SVR may be able to safely receive screening endoscopies less frequently than every 2–3 years, as is currently recommended by the American Association for the Study of Liver

Diseases (AASLD)<sup>48</sup>. Future prospective and cost-effectiveness studies could help answer these questions.

This study is strengthened by its large, geographically distributed cohort of HCV patients with prolonged follow-up after treatment with DAAs. However, this study has some potential limitations. First, all patients were derived from a single, national healthcare system with fairly uniform antiviral treatment practices and guidelines across its facilities. Second, data were derived from the national VA healthcare system where male sex predominates. Third, since this is by necessity an observational study, we cannot exclude the possibility that residual confounding may have contributed to the associations we observed between SVR and variceal haemorrhage. However, the associations persisted after careful adjustment for >20 baseline characteristics known or suspected to be associated with SVR and variceal bleeding.

In conclusion, these findings demonstrate that successful treatment of HCV with DAAs is associated with a reduced risk of subsequent variceal bleeding. This provides further evidence supporting the real-world benefits of DAAs in patients with and without cirrhosis and emphasizes the importance of early identification and treatment of HCV-infected patients.

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### Abbreviations:

<b>AASLD</b>	American Association for the Study of Liver Diseases
<b>AHR</b>	adjusted hazards ratio
<b>AUDIT-C</b>	Alcohol Use Disorders Identification Test-Consumption
<b>BMI</b>	body mass index
<b>CDW</b>	Corporate Data Warehouse
<b>DAA</b>	direct acting antiviral
<b>HBV</b>	hepatitis B virus
<b>HCV</b>	hepatitis C virus
<b>ICD</b>	International Classification of Diseases
<b>INR</b>	international normalized ratio
<b>MELD</b>	model for end-stage liver disease
<b>NSBBs</b>	nonselective beta blockers
<b>SBP</b>	spontaneous bacterial peritonitis



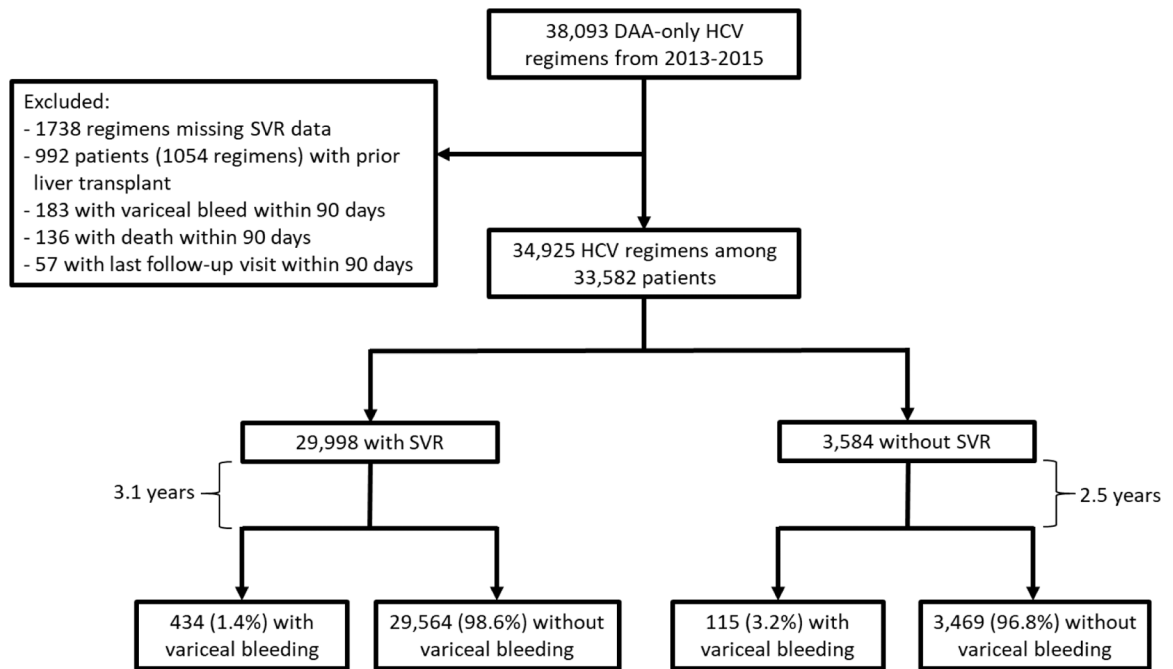
<b>SVR</b>	sustained virologic response
<b>VAHS</b>	Veterans Affairs Healthcare System

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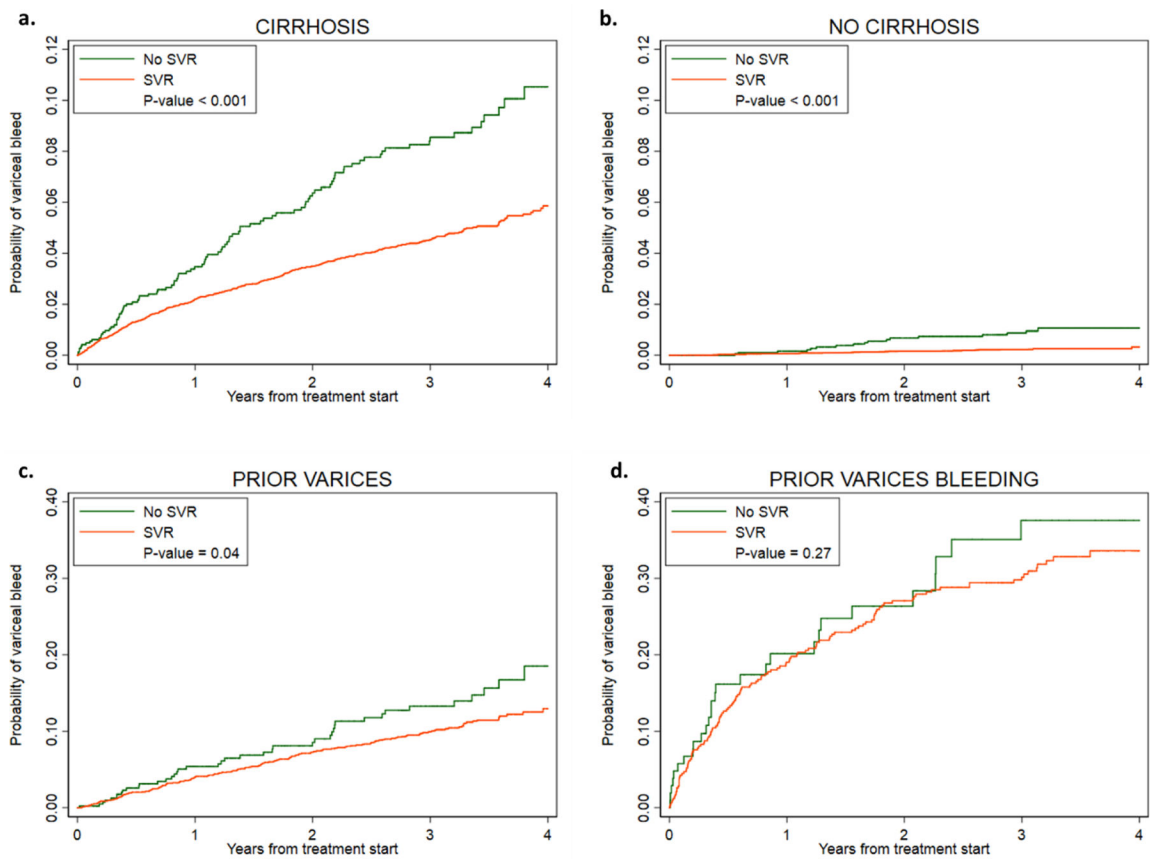
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**Figure 1. Flow diagram of HCV patients included in our analysis cohort**

Our cohort included all DAA-treated patients within the national VA from 2013–2015, excluding those with missing data, prior liver transplant, or variceal bleed, death or liver transplant within 90 days of DAA treatment. Of our resulting cohort of 33,582 patients, 29,998 (89.3%) had SVR and 3,584 (10.6%) had no SVR. Patients were followed for a mean of 3.1 years to assess for the development of variceal bleeding.



**Figure 2. Cumulative incidence curves among patients with SVR versus no SVR by presence of cirrhosis, varices and variceal bleeding**

The cumulative incidence of variceal haemorrhage among patients with and without sustained virologic response (SVR) after direct acting antiviral (DAA) treatment for hepatitis C virus (HCV) in (a) patients with cirrhosis, (b) patients without prior cirrhosis, (c) patients with prior varices, and (d) patients with prior variceal bleed.

**Table 1.**

Baseline characteristics of HCV-infected patients who received antiviral treatment with DAAs from 2013–2015, according to whether they achieved SVR

	No SVR (n=3,584)	SVR (n=29,998)	P-value
<b>Age, yrs (mean [SD])</b>	60.6 [6.6]	61.1 [6.5]	< 0.001
<b>BMI, (mean [SD])</b>	28.7 [5.8]	28.1 [5.4]	< 0.001
<b>Male (%)</b>	98.1	96.6	< 0.001
<b>Race/Ethnicity (%)</b>			< 0.001
White, non-Hispanic	52.7	52.4	
Black, non-Hispanic	30.6	33.1	
Hispanic	7.4	5.2	
Other	2	1.7	
Declined to answer/missing	7.3	7.8	
<b>Non-Genotype 1 (%)</b>	28.2	14.7	< 0.001
<b>HBV co-infection(%)</b>	0.8	1.3	0.01
<b>Cirrhosis (%)</b>	41.1	26.4	< 0.001
<b>Varices (%)</b>			< 0.001
No varices	85.5	93.6	
Varices, but no bleeding	11.6	5.0	
Varices with bleeding	2.9	1.4	
<b>Ascites (%)</b>	0.6	0.3	< 0.01
<b>Encephalopathy (%)</b>	13	6.3	< 0.001
<b>Hepatocellular Carcinoma (%)</b>	6.7	2	< 0.001
<b>Diabetes (%)</b>	32.9	29	< 0.001
<b>Non-selective beta blocker (%)</b>	10.6	7.9	< 0.001
<b>AUDIT-C scores* (%)</b>			0.09
Abstinent	67.2	66.2	
Low-level use	22.4	24	
Unhealthy use	10.4	9.8	
<b>Alcohol Use Disorder (%)</b>	50.3	44	< 0.001
<b>MELD score 9</b>	25.2	19.4	< 0.001
<b>Charlson Comorbidity Index (%)</b>			< 0.001
0	24.9	17.4	
1	26.6	33.7	
2	15	18.6	
> 2	33.5	30.3	
<b>Laboratory Results (mean [SD])</b>			
Alpha Fetoprotein, ng/mL	7.3 [4.7]	6.2 [4.3]	< 0.001
Hemoglobin, g/dL	14.3 [1.7]	14.5 [1.6]	< 0.001

	No SVR (n=3,584)	SVR (n=29,998)	P-value
Platelet Count, k/ $\mu$ L	155.8 [74.1]	178.6 [70.6]	< 0.001
Creatinine, mg/dL	1.0 [0.5]	1.0 [0.5]	< 0.01
Bilirubin, g/dL	0.8 [0.6]	0.7 [0.5]	< 0.001
Albumin g/dL	3.7 [0.6]	3.9 [0.5]	< 0.001
INR	1.2 [0.9]	1.2 [0.9]	0.42
FIB-4	5.3 [13.6]	3.9 [16.5]	< 0.001
MELD	8.6 [3.3]	8.3 [3.4]	< 0.001

DAA = direct acting antivirals, HBV = hepatitis B virus, IFN = interferon, INR = international normalized ratio, MELD = model for end-stage liver disease, SVR = sustained virologic response

\* Abstinent from alcohol: AUDIT-C score 0. Low-level alcohol use: AUDIT-C 1–3 in men, 1–2 in women. Unhealthy alcohol use: AUDIT-C 4–12 in men, 3–12 in women

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**Table 2.**

Baseline characteristics of HCV-infected patients with cirrhosis who received antiviral treatment with DAAs from 2013–2015, according to whether they achieved SVR or not

	No SVR (n=1,472)	SVR (n=7,927)	P-value
<b>Age, yrs (mean [SD])</b>	61.3 [5.4]	62.0 [5.3]	< 0.001
<b>BMI, (mean [SD])</b>	29.4 [5.9]	28.7 [5.5]	< 0.001
<b>Male (%)</b>	98.7	97	< 0.001
<b>Race/Ethnicity (%)</b>			< 0.001
White, non-Hispanic	55.9	53.8	
Black, non-Hispanic	24.5	29.2	
Hispanic	9.7	7.5	
Other	2.1	1.8	
Declined to answer/missing	7.8	7.7	
<b>Non-Genotype 1 (%)</b>	27.7	12.9	< 0.001
<b>HBV co-infection(%)</b>	0.7	1.8	< 0.01
<b>Varices (%)</b>			< 0.001
No varices	65.4	76.6	
Varices, but no bleeding	27.5	18.2	
Varices with bleeding	7.1	5.1	
<b>Ascites (%)</b>	1.4	1	0.2
<b>Encephalopathy (%)</b>	28.2	18.3	< 0.001
<b>Hepatocellular Carcinoma (%)</b>	13.5	6.1	< 0.001
<b>Diabetes (%)</b>	38.2	37.9	0.79
<b>Non-selective beta blocker (%)</b>	19.2	16.6	0.02
<b>AUDIT-C scores* (%)</b>			0.44
Abstinent	75.3	74.5	
Low-level use	17.1	18.3	
Unhealthy use	7.6	7.1	
<b>Alcohol Use Disorder (%)</b>	52.9	48	< 0.001
<b>MELD score 9</b>	39.5	31.5	< 0.001
<b>Charlson Comorbidity Index (%)</b>			< 0.001
0	25.5	14.1	
1	16.8	24.2	
2	10.7	16.1	
> 2	46.9	45.6	
<b>Laboratory Results (mean [SD])</b>			
Alpha Fetoprotein, ng/mL	8.5 [4.7]	7.7 [4.6]	< 0.001
Hemoglobin, g/dL	13.9 [1.7]	14.0 [1.7]	< 0.01
Platelet Count, k $\mu$ L	109.7 [56.7]	130.7 [63.9]	< 0.001



	No SVR (n=1,472)	SVR (n=7,927)	P-value
Creatinine, mg/dL	0.9 [0.5]	1.0 [0.5]	< 0.01
Bilirubin, g/dL	1.1 [0.8]	0.9 [0.7]	< 0.001
Albumin g/dL	3.4 [0.6]	3.6 [0.5]	< 0.001
INR	1.3 [1.0]	1.3 [1.2]	0.7
FIB-4	8.6 [20.5]	7.3 [29.9]	0.11
MELD	9.6 [3.6]	9.2 [3.8]	< 0.001

DAA = direct acting antivirals, HBV = hepatitis B virus, IFN = interferon, INR =international normalized ratio, MELD = model for end-stage liver disease, SVR = sustained virologic response

\* Abstinent from alcohol: AUDIT-C score 0. Low-level alcohol use: AUDIT-C 1–3 in men, 1–2 in women. Unhealthy alcohol use: AUDIT-C 4–12 in men, 3–12 in women

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**Table 3.**Association between DAA-induced SVR and the risk of developing variceal bleeding.

		Number of patients (%)	Mean Follow-up (Years)	Number who developed variceal bleeding (%)	Variceal bleeding incidence per 100 patient-years	Crude hazard ratio (95% CI)	Adjusted* hazard ratio (95% CI)
All patients	No SVR	3,584(10.7)	2.5	115(3.2)	1.26	1	1
	SVR	29,998(89.3)	3.1	434(1.4)	0.46	0.38(0.31–0.47)	0.66(0.52–0.83)
No prior varices	No SVR	3,064(9.8)	2.6	45(1.5)	0.56	1	1
	SVR	28,070(90.2)	3.2	152(0.5)	0.17	0.31(0.22–0.43)	0.52(0.35–0.76)
Prior Varices without Bleeding	No SVR	416(21.7)	2.1	42(10.1)	4.87	1	1
	SVR	1,502(78.3)	3.0	155(10.3)	3.48	0.69(0.48–0.99)	0.77(0.52–1.15)
Prior variceal bleeding	No SVR	104(19.6)	1.6	28(26.9)	16.38	1	1
	SVR	426(80.4)	2.3	127(29.8)	12.86	0.76(0.47–1.23)	0.60(0.33–1.09)
Cirrhosis	No SVR	1,472(15.7)	2.2	98(6.7)	2.96	1	1
	SVR	7,927(84.3)	3.1	382(4.8)	1.55	0.55(0.44–0.69)	0.73(0.57–0.93)
No Cirrhosis	No SVR	2,112(8.7)	2.7	17(0.8)	0.29	1	1
	SVR	22,071(91.3)	3.1	52(0.2)	0.07	0.26(0.15–0.45)	0.33(0.17–0.65)
MELD < 9	No SVR	2,106(9.8)	2.7	43(2.0)	0.76	1	1
	SVR	19,487(90.2)	3.2	136(0.7)	0.22	0.28(0.20–0.40)	0.41(0.28–0.61)
MELD ≥ 9	No SVR	1,204(13.2)	2.3	67(5.6)	2.45	1	1
	SVR	7,889(86.8)	3.0	277(3.5)	1.15	0.50(0.38–0.66)	0.77(0.57–1.04)
Alcohol use disorder	No SVR	1,802(12.0)	2.5	70(3.9)	1.53	1	1
	SVR	13,187(88.0)	3.1	236(1.8)	0.57	0.38(0.29–0.50)	0.65(0.48–0.88)
No alcohol use disorder	No SVR	1,782(9.6)	2.5	45(2.5)	0.99	1	1
	SVR	16,811(90.4)	3.2	198(1.2)	0.37	0.38(0.28–0.53)	0.67(0.45–0.99)

\* Adjusted for cirrhosis, prior history of varices, variceal bleeding, ascites, bacterial peritonitis or encephalopathy, age, sex, race/ethnicity, body mass index, HBV co-infection, type 2 diabetes mellitus, hepatocellular carcinoma, alcohol use disorders, AUDIT-C score, non-selective beta blocker, substance use disorder, Charlson Comorbidity Index, platelet count, serum bilirubin, serum creatinine, serum albumin, INR and blood hemoglobin levels. The laboratory tests were categorized into quartiles and modeled as dummy categorical variables; MELD = model for end-stage liver disease, SVR = sustained virologic response

**Table 4.**

Characteristics associated with variceal bleeding in patients with cirrhosis following DAA-based antiviral treatment

	Variceal bleeding incidence per 100 patient-years	Adjusted* hazard ratio (95% CI)
<b>No SVR</b>	2.96	1
<b>SVR</b>	1.55	<b>0.68(0.53–0.86)</b>
<b>No Prior Varices</b>	0.64	1
<b>Prior Varices without bleeding</b>	3.66	<b>3.09(2.39–4.00)</b>
<b>Prior varices with bleeding</b>	13.92	<b>9.39(7.08–12.46)</b>
<b>Non-selective beta blocker use</b>		
No	1.21	1
Yes	4.47	<b>1.37(1.08–1.72)</b>
<b>Ascites</b>		
No	1.67	1
Yes	7.67	<b>1.71(1.02–2.87)</b>
<b>Bacterial peritonitis</b>		
No	1.65	1
Yes	13.14	<b>2.15(1.31–3.52)</b>
<b>MELD score</b>		
6	0.55	1
7–11	1.60	1.34(0.85–2.12)
12–15	4.03	<b>1.73(1.06–2.85)</b>
16–19	3.19	1.31(0.69–2.51)
>19	2.44	2.00(0.90–4.43)
<b>Platelet count</b>		
>250	0.17	1
>200–250	0.30	1.51(0.30–7.53)
>150–200	0.54	2.86(0.68–12.06)
>100–150	1.27	<b>4.42(1.08–18.07)</b>
100	3.30	<b>6.68(1.64–27.17)</b>
<b>Hemoglobin, g/dL</b>		
>15.6	0.69	1
>14.6–15.6	1.05	1.31(0.84–2.04)
>13.6–14.6	1.36	1.29(0.84–1.96)
13.6	2.91	<b>2.12(1.43–3.15)</b>
<b>Race/Ethnicity (%)</b>		
White, non-Hispanic	2.07	1
Black, non-Hispanic	1.01	<b>0.74(0.56–0.99)</b>
Hispanic	2.22	0.95(0.67–1.36)

	Variceal bleeding incidence per 100 patient-years	Adjusted* hazard ratio (95% CI)
Other	1.77	0.79(0.39–1.57)
Declined to answer/missing	1.46	0.86(0.58–1.28)
<b>BMI</b>		
<25	1.58	1
25-< 30	1.97	1.28(0.99–1.66)
30-< 35	1.52	1.08(0.81–1.45)
35	1.53	1.00(0.70–1.41)

\* Adjusted by Cox proportional hazards regression for all the characteristics shown in the Table

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