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The Impact of Direct-acting Antiviral Therapy on End Stage Liver Disease Among Individuals with Chronic Hepatitis C and Substance Use Disorders

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Abbreviations:

AASLD/IDSA- American Association for the Study of Liver Disease/Infectious Diseases Society of America

ALD- alcohol liver disease

CI- confidence interval

CDC- Centers for Disease Control and Prevention

COMP- comprehensive insurances

CPT- current procedural terminology

DAA- direct acting antiviral

DCC- decompensated cirrhosis

HCC- hepatocellular carcinoma

HCV- hepatitis C virus

HIV- human immunodeficiency virus

HMO- health maintenance organization

HR- hazard ratio

ICD- CM- International Classification of Diseases, Clinical Modification

IPTW- inverse probability of treatment weighting

NDC- National Drug Code

PPO- preferred provider organization

RBV- ribavirin

SUD- substance abuse disorder

SVR- sustained virologic response

U.S.- United States

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Abstract (273 words)

To evaluate the impact of direct-acting antivirals (DAAs) on decompensated cirrhosis (DCC) and hepatocellular carcinoma (HCC) in patients with chronic hepatitis C virus (HCV) and substance use disorder (SUD) compared to those without an SUD. This retrospective cohort study used the MarketScan database (2013–2018) to identify 29 228 patients with chronic HCV, where 22% (n=6385) had ≥1 SUD diagnosis. The inverse probability of treatment weighted (IPTW) multivariable Cox proportional hazard models were used to compare the risk of developing DCC and HCC. Among the non-cirrhotics, treatment reduced the DCC risk among SUD (aHR 0.13; 95% CI, 0.06-0.30) and non-SUD (aHR 0.11; 95% CI, 0.07-0.18) while the risk for HCC was not reduced for the SUD group (aHR 0.91; 95% CI, 0.33-2.48). For those with cirrhosis, compared to untreated patients, treatment reduced the HCC risk among SUD (aHR, 0.33; 95% CI, 0.13–0.88) and non-SUD (aHR, 0.40; 95% CI, 0.25–0.65) while the risk for DCC was not reduced for the SUD group (aHR, 0.64; 95% CI, 0.37–1.13). Among untreated patients with cirrhosis, the SUD group had a higher risk of DCC (aHR, 1.52; 95% CI, 1.03-2.24) and HCC (aHR, 1.69; 95% CI, 1.05-2.72) compared to non-SUD group.

Conclusions: Among the HCV SUD group, DAA treatment reduced the risk of DCC but not HCC for the non-cirrhotics while DAA treatment reduced the risk of HCC but not DCC for those with cirrhosis. Among the non-treated, patients with an SUD had a significantly higher risk of DCC and HCC compared to those without an SUD. Thus, DAA treatment should be considered for all HCV patients with an SUD while also addressing the SUD.

Hepatitis C virus (HCV) infection is the most common chronic blood-borne infection in the United States (U.S.) and is a substantial cause of morbidity and mortality. In the U.S., individuals with a substance use disorder (SUD) are disproportionately affected by HCV. In fact, injection drug use, which is the most common risk factor for contracting HCV, accounts for ~75% of newly acquired cases of HCV and ~50% of cases of chronic HCV infection. (1, 2) In addition, the majority of HCV-infected patients also have an alcohol use disorder, which is highly associated with concomitant use of illegal substances leading to an increased risk for HCV. (3, 4)

In light of the opioid crisis among young persons, the U.S. Centers for Disease Control and Prevention (CDC) reported that the number of cases of acute HCV more than tripled between 2010 and 2016. (5, 6) As a result, the CDC and the US Preventive Services Task Force have now changed their HCV testing recommendations to test all those over the age of 18 once and those with high-risk factors such as an SUD annually. (7, 8)

Despite the burgeoning impact the opioid crisis is having on the incidence of new HCV infections, the possibility of a cure for chronic HCV is now feasible. HCV treatment took a major step forward in 2013 with the introduction of highly efficacious all-oral direct-acting antiviral (DAA) interferon-free treatments. Treatment with DAAs has a therapeutic efficacy in more than 95% of patients across the four major HCV genotypes and can be administered to groups of patients for whom interferon is contraindicated (e.g., those with SUD and pre-existing medical conditions). (9)

In several clinical trials and observational studies, patients with an SUD enrolled in an opioid treatment program who were treated with DAAs achieved equally high sustained virologic response (SVR) rates as treated patients without an SUD. (10-16) Such results now provide the opportunity for the U.S. to work towards the HCV elimination goals established in the 2017–2020 National Viral Hepatitis Action Plan. Nevertheless, patients with HCV and an SUD continue to be under treated. (17-19) As a result, patients with chronic HCV and an SUD may be at higher risk for developing end stage liver disease specifically, decompensated cirrhosis (DCC) and hepatocellular carcinoma (HCC) compared to those without an SUD. However, little is known about the effects of DAAs on clinical outcome data (DCC and HCC) among this cohort of patients. Therefore, using a large national insurance database, we evaluated the effects of DAA therapy on the incidence of DCC and HCC in chronically HCV-infected patients with an SUD compared to those without an SUD.

METHODS

Data Source

We conducted a retrospective cohort study using the Truven Health Analytic MarketScan Commercial database (>80 million unique beneficiaries) and Medicare Supplemental (>6 million unique beneficiaries) databases from 2012 to 2018. Each database contains person-level data for diagnoses, procedures, and dispensed medications across all settings, including physician outpatient office visits, hospital stays, and pharmacy claims. The University of Florida Institutional Review Board approved this study.

Study Population

Identification of Newly Diagnosed HCV Patients

We used 2013–2018 data to establish the new chronic HCV cohort while the 2012 data were used to ensure at least one year of claims prior to chronic HCV diagnosis and to ensure that patients did not have HCV in the previous 12 months. We identified patients aged ≥18 years with a chronic HCV diagnosis using International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 070.44, 070.54, 070.70, 070.71 or V02.62 and the International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM] codes: B18.2, B19.20, B19.21, and Z22.52). A patient was determined to have chronic HCV if they had met the criteria of one inpatient or two outpatient chronic HCV diagnoses on separate days within one year, which is a previously validated identification method. (20) Patients were included if they were 18 years old or older and continuously enrolled in their health plan for one year before and 6 months after their initial chronic HCV diagnosis. Patients were excluded if during the one-year period prior to the index date (baseline) they: 1) had a DCC or HCC diagnosis, 2) received any DAA treatment, or 3) underwent liver transplantation.

Based on the treatment received, we classified patients into two exposure statuses: patients who were treated with all-oral DAA therapy (DAA group), or patients who did not receive any HCV treatment (untreated group). We excluded any patients who received interferon-based therapy during the follow-up period. The following available all-oral DAA therapies approved by the U.S. Food and Drug Administration (FDA) or recommended by the American Association for the Study of Liver Disease/Infectious Diseases Society of America (AASLD/IDSA) for treatment-naïve patients included: [sofosbuvir, sofosbuvir + daclatasvir, sofosbuvir + simeprevir, sofosbuvir/ledipasvir, paritaprevir/ritonavir/ombitasvir ± dasabuvir, elbasvir/grazoprevir, sofosbuvir/velpatasvir,

sofosbuvir/velpatasvir/voxilaprevir, and glecaprevir/pibrentasvir] ± ribavirin (RBV). For patients who received treatment, the first DAA prescription date was assigned as the index date.

To avoid survival bias, we assigned the index date for untreated patients using prescription time-distribution matching using the number of days from the first HCV diagnosis to the dispensing time of the first DAA prescription for treated patients. (21) For each untreated patient, a hypothetical index date was selected at random based on the distribution for treated patients. Thus, the overall distribution of the index date of the untreated patients was matched to that of the treated patients' index date. We further stratified patients by cirrhosis status prior to their index date as advanced fibrosis is one of the strongest predictors of DCC and HCC.(22-24) We determined the presence of cirrhosis prior to their index date based on one inpatient or outpatient ICD-9-CM or ICD-10-CM diagnosis.

Identification of HCV Patients with an SUD

HCV patients were further categorized based on a diagnosis of SUDs recorded between one year before and six months after their first HCV diagnosis [SUD group vs. non-SUD group]. By using a recently validated algorithm with a sensitivity of 0.85 and a specificity of 0.80 for identifying people with SUD using claims data, (25) patients were considered to have an SUD if they met one of two criteria: they (1) had at least one inpatient or outpatient claim of a drug or an alcohol use disorder using ICD-9/ICD-10 codes (**Supplemental Table 1**); or (2) had a record of methadone, buprenorphine, acamprosate, or naltrexone (oral and injectable) for either opioid use disorder or alcohol use disorder. (26, 27) Patients who had methadone dispensed for opioid use disorder were identified using Current Procedural Terminology (CPT) codes H0020, J1230, while the CPT code J2315 or the National Drug Codes (NDC) in pharmacy claims were used to capture injectable naltrexone dispensed. We used NDCs to capture oral naltrexone, acamprosate, and buprenorphine. The following SUD diagnoses were examined: opioid use disorder, other drug-related (cocaine, heroin, sedatives, stimulants, other (un) specified drug dependence, cannabis, and hallucinogens), and alcohol use disorder.

Incidence Rate of DCC and HCC

The clinical outcomes were incidence rates of DCC and HCC in DAA treated and untreated patients with HCV, stratified by the presence of an SUD. HCC was defined as the presence of at least one inpatient or two outpatient ICD-9-CM or ICD-10-CM diagnoses of HCC (28, 29). DCC was defined as the presence of at least one inpatient or two outpatient ICD-9-CM or ICD-10-CM diagnoses of

ascites, paracentesis, or esophageal varices complication (bleeding) or one ICD diagnosis with one procedure code. (28) Based on the results of a previous validation study, we did not include the diagnosis for hepatic encephalopathy as this diagnosis has been frequently linked to unrelated conditions. (30) The earliest date for a diagnosis of DCC or HCC after the index date was considered as the incident date of DCC or HCC. Follow-up started from the index date of DAA treatment and continued until the incidence of DCC or HCC, end of enrollment, or the end of the study (31 December 2018), whichever came first. In a sensitivity analysis, we defined HCC as the presence of at least 1 inpatient or 2 outpatient ICD-9-CM or ICD-10-CM codes for HCC and DCC made ≥ 3 months after the index date of DAA treatment. Additionally, we used cause-specific hazard modeling to adjust for the competing risk for death based on inpatient death information, available for included patients from 2012 through 2016. In a subgroup analysis, we excluded patients with early discontinuation of DAA treatment. A subgroup analysis was conducted for the SUD group categorized by the presence or absence of alcohol use disorder.

Statistical Analysis

Baseline characteristics were compared between the DAA and untreated HCV patients categorized by the presence of an SUD using the standardized difference to check the balance between the two groups; 0.1 was defined as the threshold to determine statistically significant differences. The stabilized inverse probability of treatment weighting (IPTW) was used to balance the baseline characteristics between the DAA and untreated groups, categorized by the presence of an SUD and cirrhosis. We calculated the IPTW using the propensity score estimated using logistic regression, based on patients' baseline demographic characteristics and comorbidities, which were identified by one inpatient or outpatient ICD-9-CM or ICD-10-CM diagnosis during the one-year period prior to the index date. The covariates used to create IPTW included the following: age, gender, region, type of benefit plan, diagnosed HCV disease duration, diabetes, hypertension, dyslipidemia, cardiovascular disease (CVD), chronic kidney disease (CKD), chronic obstructive pulmonary disease, human immunodeficiency virus (HIV) infection, schizophrenia/bipolar disorder, depression, pregnancy, and other liver diseases (i.e., alcoholic liver disease [ALD], nonalcoholic fatty liver disease, hepatitis B infection, hepatitis A infection and cirrhosis).

The number of HCC and DCC events and the person-time of observation were determined for each group and used to calculate the incidence rates of HCC and DCC (number of events/1000 person-years). We performed the weighted multivariable Cox proportional hazards regression modeling

using IPTW with robust standard errors to compare the risk of developing HCC or DCC between the DAA-treated and untreated HCV groups, stratified by the presence of an SUD and cirrhosis. We adjusted for all covariates used to calculate the IPTW in the regression models. The proportional hazard assumption was tested using Schoenfeld residuals. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

Of 29 228 patients newly diagnosed with HCV, 22% (n = 6385) had an SUD while 78% (n = 22 843) did not (**Figure 1**). HCV patients with an SUD were more likely to be younger (40% vs. 6% aged 18–35 years) at the time of the HCV diagnosis, male (63% vs. 58%), and to have ALD (4.6% vs. 0.7%) compared to HCV patients in the non-SUD group (P-values <0.001) (**Supplemental Table 2**). Among the HCV patients with an SUD, 24% initiated DAA therapy, which is significantly lower compared to the initiation rate of 34% of HCV patients without an SUD (**Table 1**). **Table 1** summarizes the patient characteristics between the treated and untreated groups, categorized by the presence of an SUD prior to the index date. Of the HCV patients with an SUD, 57% had a diagnosis of opioid use disorder, 61% had a diagnosis of other drug-related disorders (22% with cocaine and heroin, 15% with sedatives, 11% with stimulants, 21% with cannabis), and 48% had a diagnosis of alcohol use disorder. Approximately one-third of the individuals with an SUD received some form of medication for opioid use disorder or alcohol use disorder during the one year before and six months after their first HCV diagnosis. After we applied IPTW weighting, in the SUD and non-SUD cohort patients in the DAA and non-DAA groups achieved an acceptable balance (with standardized difference of each covariate <0.1).

Incidence Rate of Decompensated Cirrhosis among HCV Patients without Cirrhosis

Among patients without cirrhosis (n=26 312), there were 108 DCC events (1.9%) in the SUD group (n=5767) and 240 DCC events (1.2%) in the non-SUD group (n=20 545) **(Table 2).** In the SUD group, the majority of DCC events (87%) occurred in patients who received no treatment, providing an incidence rate of 17 per 1000 person-years compared to the DCC incidence rate in the DAA-treated patients of 8 per 1000 person-years (P<0.05). For the non-SUD group, the incidence rate was 11 per 1000 person-years for the untreated patients and 4 per 1000 person-years for the DAA treated patients (P<0.05). After adjusting for covariates in the IPTW weighted Cox regression model, in the SUD group, the treated patients had an 87% decrease in risk of developing DCC compared to

those who received no treatment (aHR, 0.13; 95% CI, 0.06–0.30), while in the non-SUD group, treated patients had an 89% decrease in risk (aHR, 0.11; 95% CI, 0.07–0.18). Among untreated patients, we observed a two-fold increased risk of DCC in the SUD group compared to those in the non-SUD group (aHR, 2.31; 95% CI, 1.85–2.88).

Incidence Rate of Hepatocellular Carcinoma among HCV Patients without Cirrhosis

There were 26 new HCC events (0.5%) in the SUD group and 122 HCC events (0.6%) in the non-SUD group (**Table 2)**. In the SUD group, the crude incidence rate of HCC was 3 per 1000 person-years for the untreated patients and 4 per 1000 person-years for the treated patients (P>0.05). In the non-SUD group, the crude incidence rate of HCC was 5 per 1000 person-years in the untreated patients and 2 per 1000 person-years in the treated patients (P<0.05). After adjusting for covariates in the IPTW weighted Cox regression model, treated patients in the SUD group did not experience a risk reduction (aHR, 0.91; 95% CI, 0.33–2.48) for developing HCC compared to non-treated patients. Among the non-SUD group, there was a 69% decreased risk of developing HCC compared to those who received no treatment (aHR, 0.31; 95% CI, 0.18–0.53).

Incidence Rate of Decompensated Cirrhosis among HCV Patients with Cirrhosis

Among patients with cirrhosis (n=2916), the crude incidence rate of DCC in the SUD group was 100 per 1000 person-years for the untreated patients and 41 per 1000 person-years for the DAA-treated patients (P<0.05) (**Table 3**). Among the non-SUD group, the incidence rate was 75 per 1000 person-years for the untreated patients and 23 per 1000 person-years for the DAA-treated patients (P<0.05). After adjusting for covariates, treated patients with cirrhosis and an SUD had a decreased risk of developing DCC compared to those who did not receive treatment although this was not statistically significant (aHR, 0.64; 95% CI, 0.37–1.13). Among the non-SUD group with cirrhosis, there was a 73% reduced risk (aHR, 0.27; 95% CI, 0.18–0.41) for developing DCC when compared to those who were not treated. Among untreated patients, we observed a 52% increased risk of DCC in the SUD group compared to those in the non-SUD group (aHR, 1.52; 95% CI, 1.03–2.24).

Incidence Rate of Hepatocellular Carcinoma among HCV Patients with Cirrhosis

The crude incidence rate of HCC was 41 per 1000 person-years for the untreated patients and 21 per 1000 person-years for the DAA-treated patients with cirrhosis (P>0.05) (**Table 3**). For the non-SUD group, the incidence rate was 43 per 1000 person-years for the untreated patients and 19 per

1000 person-years for the DAA-treated patients (P<0.05). After adjusting for covariates in the regression model, patients with an SUD and cirrhosis who were treated had a decreased risk of developing HCC compared to those who received no treatment (aHR, 0.33; 95% CI, 0.13–0.88). Among the non-SUD group with cirrhosis who were treated, there was a 60% decrease in risk of developing HCC (aHR, 0.40; 95% CI, 0.25–0.65) compared to those who did not receive treatment. Among the untreated patients with cirrhosis, an increased risk of developing HCC (aHR, 1.69; 95% CI, 1.05–2.72) was observed with the SUD group compared to the non-SUD group.

Sensitivity and Subgroup Analyses

In the sensitivity analysis for patients with an HCC (**Table 4)** or a DCC (**Table 5**) diagnosis ≥ 3 months after the index date of DAA treatment, a subgroup analysis of patients who received DAAs for at least 8–12 weeks of treatment and in patients with and without alcohol use disorders among the SUD group (**Supplemental Table 3**), the study results remained consistent with the primary analysis. The study results also remained consistent in the regression analysis that included inpatient death as a competing risk (**Supplemental Table 4**).

Factors Associated with Increased Risk of Decompensated Cirrhosis and/or Hepatocellular Carcinoma

Supplemental Table 5 displays the risk of developing DCC and/or HCC among the patients with HCV, stratified by SUD status and receipt of DAA treatment. Among HCV patients in the SUD group (n=6385), factors associated with an increased risk of developing DCC or HCC included having cirrhosis (aHR, 2.89; 95% CI, 2.05–4.06), ALD (aHR, 2.02; 95% CI, 1.35–3.02), hepatitis A virus (aHR, 5.26; 95% CI, 2.05–13.50), CKD (aHR, 2.21; 95% CI, 1.37–3.58), and having an SUD with an alcohol use disorder (vs. SUD without alcohol use disorder: aHR, 1.61; 95% CI, 1.15–2.25). However, DAA treatment (aHR, 0.45; 95% CI, 0.29–0.68) and being of younger age (18-35 years vs. 51-64 years: aHR, 0.18; 95% CI, 0.09-0.34) were associated with a decrease in the risk of DCC and/or HCC**.** Among HCV patients without an SUD diagnosis, being male (aHR, 1.55; 95% CI, 1.28–1.88), having cirrhosis (aHR, 5.37; 95% CI, 4.48–6.44), diabetes (aHR, 1.51; 95% CI, 1.25–1.83), or CKD (aHR, 2.03; 95% CI, 1.54–2.68) were associated with an increased risk of DCC or HCC; while DAA treatment (aHR, 0.27; 95% CI, 0.21–0.35) and being of younger age (18-35 years vs. 51-64 years: aHR, 0.14; 95% CI, 0.04-0.49; 36-50 years vs. 51-64 years: aHR, 0.60; 95% CI, 0.42-0.85) were associated with a decrease in the risk of developing DCC and/or HCC.

DISCUSSION

This retrospective cohort study provides U.S. population-based evidence for the effects of all-oral DAA therapy on the incidence of DCC and HCC among a specific but growing population of HCV-infected patients—those with an SUD. Despite the National Viral Hepatitis Action Plan that prioritizes efforts to focus on improving access to care and treatment among HCV patients with an SUD, (31) less than one-fourth of HCV patients with an SUD initiated DAA therapy.

For both groups of patients, those with and without an SUD, treatment with DAAs resulted in a lower incidence of DCC and HCC when compared to no treatment; this finding further confirms the recommendations of the current treatment guidelines which suggest that HCV antiviral therapy is feasible in patients with an SUD and should be provided as indicated to avoid the development of liver complications. (32) These results continue to be very encouraging because they help confirm prior studies which showed that SUD patients treated for HCV can achieve similar adherence and SVR rates (10–14) as non-SUD patients, countering arguments that have been commonly used to limit treatment access in the SUD patient population. (33, 34)

In fact, we found that those with an SUD who were not treated had a significantly higher risk of developing DCC while those with an SUD and cirrhosis had a significantly higher risk for developing both DCC and HCC compared to those untreated without an SUD. Such a finding suggests that having an SUD may confer a more rapid progression to end stage liver disease especially if one has been diagnosed with ALD or uses alcohol with opioids or other drugs (polysubstance use disorder), most likely due to the synergic hepatotoxic effect of HCV and alcohol. (35) This suggestion becomes more apparent when we see that the DAA-treated non-SUD group received benefits against DCC and HCC regardless of their cirrhosis status. Therefore, we suggest that patients with HCV who also have ALD or use alcohol with other drugs are a group of patients at a particularly high risk for liver related adverse outcomes even with DAA treatment, a finding that was recently reported from a large Australian study. (36) As such, strategies must be developed that combine DAA therapy with the management of alcohol use disorder especially as some studies have suggested that patients with an alcohol use disorder and HCV are more likely to participate in risky drinking behaviors since to them severe liver-related outcomes appear to be inevitable. (37, 38)

Another factor associated with the development of DCC or HCC among those with HCV and an SUD was the presence of CKD in which one was over two times more likely to be diagnosed. This finding

is most likely due to the known association of renal failure in patients with advanced liver disease and HCV. (39, 40) However, the presence of CKD does highlight the need to find, diagnose, and treat HCV before liver disease progresses to a point where other organ failure occurs. (39)

The reasons chronic HCV patients with SUD did not receive treatment may include insurance company restrictions (19), provider bias or lack of knowledge that new HCV medications do not have a negative impact on SUD, or a failure to follow up by the patients for HCV evaluation visits. Therefore, we think addressing the above barriers to treatment outside of health insurance is going to be key to meeting the U.S. Action Plan for Viral Hepatitis (31) as well as the World Health Organization's goal of elimination of HCV by 2030, (41) especially for those with SUD–a group whose incidence of HCV is growing.

The goals of HCV treatment are to not only prevent the complications of liver disease, but also to prevent transmission of HCV. (42) Thus, DAA treatment is a key component in preventing HCV transmission especially among intravenous SUD patients. (43) It is noteworthy to mention that among newly diagnosed HCV patients aged 18–35 years, almost 66% of patients had at least one SUD diagnosis, which is significantly higher when compared to all other age groups. The substantially high proportion of SUD in young HCV patients is reflective of the recent changes in the demographics of HCV patients as a result of the opioid epidemic and the increase in injectable drug use. (4) Although those who were younger (18 to 35 years old) were less likely to develop DCC or HCC, this result highlights the need to follow the new CDC and the United States Preventive Services Task Force recommendation to screen for HCV more frequently among those with high-risk behaviors so that treatment with DAAs, if indicated, can be initiated before further liver damage is incurred. (7, 8)

Our study has several strengths. This retrospective, IPTW weighted cohort analysis is, to the best of our knowledge, one of the first population-based studies to report a reduced risk of developing DCC and HCC associated with DAA therapy among HCV patients with SUD compared to those without. This study has a large sample size and our cohort was representative of the general, insured population in the U.S. This study also has methodological strengths as it employed a prescription time-distribution matching to adjust time to initiate HCV treatment after diagnosis and the use of IPTW propensity scores to balance the characteristics of the treated and untreated groups. There are also limitations to this study as this was an analysis of administrative claims data using ICD-9-CM and ICD-10-CM codes, which lacks laboratory results, so we were unable to report SVR

and viral load to assess for reinfection, which could potentially have affected our outcomes of DCC or HCC. In addition, although a prior study has validated the use of billing ICD-9-CM and ICD-10-CM codes for the diagnosis of SUD definition (23) and this approach is commonly used in retrospective claims data analyses, some individuals with SUD remain unrecognized and underdiagnosed in routine practice. Thus, we may have underestimated the risk of DCC or HCC in the untreated patients with SUD. Although the methods we used to identify patients with cirrhosis and outcomes (DCC and HCC) have been validated and are highly accurate, (25, 28, 44) it is possible that incomplete, missing, or miscoded claims may impact the study findings; however, coding errors are likely distributed evenly between the treated and untreated patients. This study is also limited by its design as a retrospective cohort study; however, prospective studies comparing the effects of DAA therapy with no treatment would be unethical as DAAs have been shown to be highly efficacious. Another limitation is that we were only able to identify individuals who engaged the system, so our findings cannot be generalized to HCV patients with an SUD who do not have health insurance or Medicaid. As many state Medicaid programs still restrict access to DAA therapies for illicit drug or alcohol users, it is important to evaluate the risk of end-stage liver disease among Medicaid HCV patients with an SUD. In addition, patient mortality status is not fully captured in the claims database. A potential bias due to the competing risk of death may exist. We also were not able to differentiate between individuals with former and current SUDs as well as those who lived in rural versus urban areas. Finally, although we used the first five years of data after the approval of all-oral DAAs, we have a relatively short follow-up, which did not allow us to explore the long-term effect of all-oral DAAs.

In conclusion, despite the availability of effective all-oral DAA therapies, the rate of DAA prescribed treatment is much lower among HCV patients with an SUD compared to HCV patients without an SUD. The incidence rates for DCC and HCC were higher for those with an SUD compared to those without an SUD, but treatment with DAA therapy was significantly associated with a decreased risk for DCC and HCC. Our findings suggest that all those with HCV and an SUD should receive DAA treatment, and it is important to develop strategies that complement the initiation of DAA treatment and treatment of SUD, especially for those with an alcohol use disorder.

References

1. Hagan H. Hepatitis C virus transmission dynamics in injection drug users. Subst Use Misuse 1998;33:1197-1212.
2. Jordan AE, Des Jarlais DC, Arasteh K, McKnight C, Nash D, Perlman DC. Incidence and prevalence of hepatitis c virus infection among persons who inject drugs in New York City: 2006-2013. Drug Alcohol Depend 2015;152:194-200.
3. Campbell JV, Hagan H, Latka MH, Garfein RS, Golub ET, Coady MH, Thomas DL, et al. High prevalence of alcohol use among hepatitis C virus antibody positive injection drug users in three US cities. Drug Alcohol Depend 2006;81:259-265.
4. Russell M, Pauly MP, Moore CD, Chia C, Dorrell J, Cunanan RJ, Witt G, et al. The impact of lifetime alcohol use on hepatitis C treatment outcomes in privately insured members of an integrated health care plan. Hepatology 2012;56:1223-1230.
5. The Centers for Disease Control and Prevention (CDC). Surveillence for Viral Hepatitis - United States, 2016. 2016. https://www.cdc.gov/hepatitis/statistics/2016surveillance/commentary.htm.
6. Zibbell JE, Asher AK, Patel RC, Kupronis B, Iqbal K, Ward JW, Holtzman D. Increases in Acute Hepatitis C Virus Infection Related to a Growing Opioid Epidemic and Associated Injection Drug Use, United States, 2004 to 2014. Am J Public Health 2018;108:175-181.
7. Schillie S, Wester C, Osborne M, Wesolowski L, Ryerson AB. CDC Recommendations for Hepatitis C Screening Among Adults - United States, 2020. MMWR Recomm Rep 2020;69:1-17.
8. U. S. Preventive Services Task Force, Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, Caughey AB, et al. Screening for Hepatitis C Virus Infection in Adolescents and Adults: US Preventive Services Task Force Recommendation Statement. JAMA 2020;323:970-975.
9. Falade-Nwulia O, Suarez-Cuervo C, Nelson DR, Fried MW, Segal JB, Sulkowski MS. Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection: A Systematic Review. Ann Intern Med 2017;166:637-648.
10. Grebely J, Bruggmann P, Treloar C, Byrne J, Rhodes T, Dore GJ, International Network for Hepatitis in Substance U. Expanding access to prevention, care and treatment for hepatitis C virus infection among people who inject drugs. Int J Drug Policy 2015;26:893-898.

11. Dore GJ, Altice F, Litwin AH, Dalgard O, Gane EJ, Shibolet O, Luetkemeyer A, et al. Elbasvir-Grazoprevir to Treat Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy: A Randomized Trial. Ann Intern Med 2016;165:625-634.

12. Lalezari J, Sullivan JG, Varunok P, Galen E, Kowdley KV, Rustgi V, Aguilar H, et al. Ombitasvir/paritaprevir/r and dasabuvir plus ribavirin in HCV genotype 1-infected patients on methadone or buprenorphine. J Hepatol 2015;63:364-369.

13. Grebely J, Feld JJ, Wyles D, Sulkowski M, Ni L, Llewellyn J, Mir HM, et al. Sofosbuvir-Based Direct-Acting Antiviral Therapies for HCV in People Receiving Opioid Substitution Therapy: An Analysis of Phase 3 Studies. Open Forum Infect Dis 2018;5:ofy001.

14. Butner JL, Gupta N, Fabian C, Henry S, Shi JM, Tetrault JM. Onsite treatment of HCV infection with direct acting antivirals within an opioid treatment program. J Subst Abuse Treat 2017;75:49-53.

15. Christensen S, Buggisch P, Mauss S, Boker KHW, Schott E, Klinker H, Zimmermann T, et al. Direct-acting antiviral treatment of chronic HCV-infected patients on opioid substitution therapy: Still a concern in clinical practice? Addiction 2018;113:868-882.

16. Ottman AA, Townsend ML, Hashem MG, Britt RB. Impact of Substance Use Disorder on the Rate of Sustained Virological Response in Veterans With Chronic Hepatitis C Treated With Direct-Acting Antivirals. Ann Pharmacother 2019:1060028018824988.

17. Do A, Mittal Y, Liapakis A, Cohen E, Chau H, Bertuccio C, Sapir D, et al. Drug Authorization for Sofosbuvir/Ledipasvir (Harvoni) for Chronic HCV Infection in a Real-World Cohort: A New Barrier in the HCV Care Cascade. PLoS One 2015;10:e0135645.

18. Barua S, Greenwald R, Grebely J, Dore GJ, Swan T, Taylor LE. Restrictions for Medicaid Reimbursement of Sofosbuvir for the Treatment of Hepatitis C Virus Infection in the United States. Ann Intern Med 2015;163:215-223.

19. Jain MK, Thamer M, Therapondos G, Shiffman ML, Kshirsagar O, Clark C, Wong RJ. Has Access to Hepatitis C Virus Therapy Changed for Patients With Mental Health or Substance Use Disorders in the Direct-Acting-Antiviral Period? Hepatology 2019;69:51-63.

20. Niu B, Forde KA, Goldberg DS. Coding algorithms for identifying patients with cirrhosis and hepatitis B or C virus using administrative data. Pharmacoepidemiol Drug Saf 2015;24:107-111.

21. Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. Am J Epidemiol 2005;162:1016-1023.

22. Li DK, Ren Y, Fierer DS, Rutledge S, Shaikh OS, Lo Re V, 3rd, Simon T, et al. The short-term incidence of hepatocellular carcinoma is not increased after hepatitis C treatment with direct-acting antivirals: An ERCHIVES study. Hepatology 2018;67:2244-2253.

23. Park H, Wang W, Henry L, Nelson DR. Impact of All-Oral Direct-Acting Antivirals on Clinical and Economic Outcomes in Patients With Chronic Hepatitis C in the United States. Hepatology 2019;69:1032-1045.

24. Kanwal F, Kramer JR, Asch SM, Cao Y, Li L, El-Serag HB. Long-Term Risk of Hepatocellular Carcinoma in HCV Patients Treated With Direct Acting Antiviral Agents. Hepatology 2020;71:44-55.

25. Janjua NZ, Islam N, Kuo M, Yu A, Wong S, Butt ZA, Gilbert M, et al. Identifying injection drug use and estimating population size of people who inject drugs using healthcare administrative datasets. International Journal of Drug Policy 2018;55:31-39.

26. Lo‐Ciganic WH, Gellad WF, Gordon AJ, Cochran G, Zemaitis MA, Cathers T, Kelley D, et al. Association between trajectories of buprenorphine treatment and emergency department and in‐patient utilization. Addiction 2016;111:892-902.

27. Reus VI, Fochtmann LJ, Bukstein O, Eyler AE, Hilty DM, Horvitz-Lennon M, Mahoney J, et al. The American Psychiatric Association Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder. FOCUS, A Journal of the American Psychiatric Association 2019;17:158-162.

28. Lu M, Chacra W, Rabin D, Rupp LB, Trudeau S, Li J, Gordon SC. Validity of an automated algorithm using diagnosis and procedure codes to identify decompensated cirrhosis using electronic health records. Clin Epidemiol. 2017;9:369-376.:10.2147/CLEP.S136134. eCollection 132017.

29. Goldberg DS, Lewis JD, Halpern SD, Weiner MG, Lo Re V, 3rd. Validation of a coding algorithm to identify patients with hepatocellular carcinoma in an administrative database. Pharmacoepidemiol Drug Saf. 2013;22:103-107. doi: 110.1002/pds.3367. Epub 2012 Nov 1004.

30. Lo Re V, 3rd, Lim JK, Goetz MB, Tate J, Bathulapalli H, Klein MB, Rimland D, et al. Validity of diagnostic codes and liver-related laboratory abnormalities to identify hepatic decompensation events in the Veterans Aging Cohort Study. Pharmacoepidemiol Drug Saf 2011;20:689-699.

31. US Department of Health & Human Services. National Viral Hepatitis Action Plan. 2018. https://www.hhs.gov/hepatitis/viral-hepatitis-action-plan/index.html.

32. AASLD/IDSA/IAS-USA. HCV Guidance: Recommnedations for testing, managing, and treating Hepatitis C, Key populations: identification and management of HCV in pepole who inject drugs. 2018. https://www.hcvguidelines.org/unique-populations/pwid.

33. Hellard M, Doyle JS, Sacks-Davis R, Thompson AJ, McBryde E. Eradication of hepatitis C infection: the importance of targeting people who inject drugs. Hepatology 2014;59:366-369.

34. Grebely J, Matthews GV, Hellard M, Shaw D, van Beek I, Petoumenos K, Alavi M, et al. Adherence to treatment for recently acquired hepatitis C virus (HCV) infection among injecting drug users. J Hepatol 2011;55:76-85.

35. Novo-Veleiro I, Alvela-Suarez L, Chamorro AJ, Gonzalez-Sarmiento R, Laso FJ, Marcos M. Alcoholic liver disease and hepatitis C virus infection. World J Gastroenterol 2016;22:1411-1420.

36. Alavi M, Law MG, Valerio H, Grebely J, Amin J, Hajarizadeh B, Selvey C, et al. Declining hepatitis C virus-related liver disease burden in the direct-acting antiviral therapy era in New South Wales, Australia. J Hepatol 2019;71:281-288.

37. Elliott JC, Hasin DS, Des Jarlais DC. Perceived risk for severe outcomes and drinking status among drug users with HIV and Hepatitis C Virus (HCV). Addict Behav 2016;63:57-62.

38. Schiff ER, Ozden N. Hepatitis C and alcohol. Alcohol Res Health 2003;27:232-239.

39. Park H, Chen C, Wang W, Henry L, Cook RL, Nelson DR. Chronic hepatitis C virus (HCV) increases the risk of chronic kidney disease (CKD) while effective HCV treatment decreases the incidence of CKD. Hepatology 2018;67:492-504.

40. Park H, Adeyemi A, Henry L, Stepanova M, Younossi Z. A meta-analytic assessment of the risk of chronic kidney disease in patients with chronic hepatitis C virus infection. J Viral Hepat 2015.

41. World Health Organization. Global Health Sector Strategy on Viral Hepatitis 2016-2021 towards ending viral hepatitis; 2016.

42. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol 2018;69:461-511.

43. Martin NK, Vickerman P, Grebely J, Hellard M, Hutchinson SJ, Lima VD, Foster GR, et al. Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. Hepatology 2013;58:1598-1609.

44. Goldberg DS, Lewis JD, Halpern SD, Weiner MG, Lo Re V, 3rd. Validation of a coding algorithm to identify patients with hepatocellular carcinoma in an administrative database. Pharmacoepidemiol Drug Saf 2013;22:103-107.

Figure Legend

Figure 1. Flow chart of the cohort creation

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Table 1. Baseline characteristics for chronic hepatitis C virus-infected patients with SUD status after propensity score weighting*

	HCV patients with SUD			HCV patients without SUD		
Characteristics (n)	**DAA treatment (n=1529)**	**No treatment (n=4856)**	**Standardized difference**	**DAA treatment (n=7825)**	**No treatment (n=15018)**	**Standardized difference**
Weighted No.	1640 (100%)	4800 (100%)		8461(100%)	14517 (100%)	
Age			-0.030			0.005
18-35	695 (42.4%)	1927 (40.1%)		386 (4.6%)	860 (5.9%)	
36-50	182 (11.1%)	659 (13.7%)		1068 (12.6%)	2146 (14.8%)	
51-64	675 (41.2%)	1905 (39.7%)		5999 (70.9%)	9124 (62.9%)	
≥65	88 (5.4%)	396 (8.3%)		1007 (11.9%)	2388 (16.4%)	
Gender (male)	1025 (62.5%)	3015 (62.8%)	0.006	4835 (57.1%)	8336 (57.4%)	0.006
Region			-0.011			-0.010
Northeast	346 (21.1%)	1003 (20.9%)		1618 (19.1%)	2990 (20.6%)	
North central	362 (22.1%)	1227 (25.6%)		1374 (16.2%)	2622 (18.1%)	
South	752 (45.9%)	1868 (38.9%)		4148 (49.0%)	5920 (40.8%)	
West	173 (10.5%)	653 (13.6%)		1277 (15.1%)	2792 (19.2%)	
Unknown	7 (0.4%)	47 (1.0%)		44 (0.5%)	194 (1.3%)	
Type of insurance			-0.012			-0.004
PPO	898 (54.8%)	2588 (53.9%)		4659 (55.1%)	7895 (54.4%)	
HMO	168 (10.2%)	656 (13.7%)		1030 (12.2%)	2147 (14.8%)	
COMP	166 (10.1%)	539 (11.2%)		644 (7.6%)	1486 (10.2%)	
POS	136 (8.3%)	339 (7.1%)		687 (8.1%)	951 (6.6%)	
Others †	273 (16.6%)	677 (14.1%)		1442 (17.0%)	2039 (14.0%)	

Comorbidity						
Diabetes	224 (13.7%)	676 (14.1%)	0.013	1876 (22.2%)	3185 (21.9%)	-0.006
Hypertension	613 (37.4%)	1862 (38.8%)	0.029	4300 (50.8%)	7349 (50.6%)	-0.004
Dyslipidemia	371 (22.6%)	1111 (23.1%)	0.012	3142 (37.1%)	5349 (36.8%)	-0.006
CVD‡	273 (16.6%)	805 (16.8%)	0.003	1658 (19.6%)	2721 (18.7%)	-0.022
Chronic kidney disease	59 (3.6%)	160 (3.3%)	-0.014	463 (5.5%)	773 (5.3%)	-0.007
COPD	257 (15.7%)	798 (16.6%)	0.025	1035 (12.2%)	1786 (12.3%)	0.002
HIV	33 (2.0%)	100 (2.1%)	0.005	266 (3.1%)	426 (2.9%)	-0.013
Schizophrenia/bipolar	138 (8.4%)	447 (9.3%)	0.032	93 (1.1%)	186 (1.3%)	0.016
Depression	711 (43.4%)	2084 (43.4%)	0.002	1094 (12.9%)	1858 (12.8%)	-0.004
Epilepsy	57 (3.5%)	184 (3.8%)	0.020	88 (1.0%)	154 (1.1%)	0.003
Pregnancy	76 (4.6%)	181 (3.8%)	-0.050	90 (1.1%)	157 (1.1%)	0.003
Alcoholic liver disease	82 (5.0%)	223 (4.6%)	0.013	63 (0.7%)	102 (0.7%)	-0.005
Non-alcoholic liver disease	113 (6.9%)	339 (7.1%)	0.006	668 (7.9%)	1138 (7.8%)	-0.002
Hepatitis A virus	9 (0.5%)	33 (0.7%)	0.017	41 (0.5%)	68 (0.5%)	-0.002
Hepatitis B virus	36 (2.2%)	109 (2.3%)	0.004	265 (3.1%)	485 (3.3%)	0.012
Liver severity						
Cirrhosis	148 (9.0%)	448 (9.3%)	0.009	791 (9.3%)	1363 (9.4%)	0.001
Substance use disorder						
Opioid	950 (57.9%)	2698 (56.2%)	-0.035	N/A	N/A	N/A
Other drug-related	1015 (61.9%)	2896 (60.3%)	-0.032	N/A	N/A	N/A
Opioid + other drugs	394 (24.0%)	1091 (22.7%)	-0.032	N/A	N/A	N/A
Alcohol	788 (48.0%)	2302 (48.0%)	-0.002	N/A	N/A	N/A
Alcohol + opioid or other drugs	131 (8.0%)	389 (8.1%)	0.004	N/A	N/A	N/A

Alcohol + opioid + other drugs	309 (18.8%)	854 (17.8%)	-0.029	N/A	N/A	N/A
Medication for opioid or alcohol use disorder	535 (32.6%)	1562 (32.5%)	0.002	N/A	N/A	N/A
Methadone	59 (3.6%)	165 (3.4%)	-0.007	N/A	N/A	N/A
Buprenorphine	417 (25.4%)	1244 (25.9%)	0.011	N/A	N/A	N/A
Naltrexone	131 (8.0%)	364 (7.6%)	-0.016	N/A	N/A	N/A
Acamprosate	16 (1.0%)	48 (1.0%)	0.001	N/A	N/A	N/A

HCV = hepatitis C virus; SUD = substance use disorders; DAA = direct acting antiviral; PPO = Preferred Provider Organization; HMO = Health Maintenance Organization; COMP = comprehensive insurance; POS = non-Capitated Point-of-Service; CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus; N/A = not available

* Data are reported as numbers (percentages).

† Others included basic/major medical, capitated or partially capitated Point-of-Service, Exclusive Provider Organization (EPO), Consumer-Driven Health Plan (CDHP), and High Deductible Health Plan (HDHP).

‡ CVD includes cerebrovascular disease, coronary artery disease, and peripheral vascular disease.

Table 2. Incidence rate of complications of decompensated cirrhosis and hepatocellular carcinoma after DAA treatment in HCV patients without cirrhosis weighted by stabilized inverse probability of treatment weighting (IPTW), stratified by presence of SUD

Patients without cirrhosis (n=26312)	**No. of events**	**Person-years**	**Crude Incidence/ 1000 person-years**	**DAA vs. no treatment, unadjusted HR (95% CI)**	**DAA vs. no treatment, adjusted HR (95% CI) ***	**SUD vs. non-SUD among no treatment, adjusted HR (95% CI) †**
Decompensated cirrhosis						
SUD group (n=5767)						
DAA treatment (n=1231)	14	1581	8**	0.23 (0.11-0.48)	0.13 (0.06-0.30)	2.31 (1.85-2.88)
No treatment (n=4536)	94	4766	17	reference	reference	
Non-SUD group (n=20 545)						
DAA treatment (n=6517)	43	10 027	4**	0.22 (0.14-0.33)	0.11 (0.07-0.18)	
No treatment (n=14028)	197	15 629	11	reference	reference	reference
Hepatocellular carcinoma						
SUD group (n=5767)						
DAA treatment (n=1231)	7	1577	4	1.05 (0.40-2.74)	0.91 (0.33-2.48)	1.35 (0.88-2.08)
No treatment (n=4536)	19	4775	3	reference	reference	
Non-SUD group (n=20545)						
DAA treatment (n=6517)	32	10 027	2**	0.40 (0.24-0.66)	0.31(0.18-0.53)	
No treatment (n=14028)	90	15 647	5	reference	reference	reference

DAA = direct acting antiviral; HCV = hepatitis C virus; SUD = substance use disorders; HR = hazard ratio; CI = confidence interval; IPTW = inverse probability of treatment weighting

* The risk of decompensated cirrhosis (DCC) and hepatocellular carcinoma (HCC) was compared between DAA treated and untreated patients using Cox proportional hazards modeling with stabilized IPTW to adjust for age, gender, region, health plan, diabetes, cardiovascular disease (cerebrovascular disease, coronary artery disease, and peripheral vascular disease), chronic kidney disease, mental disorder (schizophrenia/bipolar, depression, epilepsy), diabetes, pregnancy, alcoholic liver disease, non-alcoholic liver disease, hepatitis A virus, hepatitis B virus, and human immunodeficiency virus. Stabilized IPTW was generated for SUD and non-SUD separately.

† The risk of DCC and HCC was compared between the SUD and non-SUD groups among untreated HCV patients using Cox proportional hazards modeling with stabilized IPTW to adjust for age, gender, region, health plan, diabetes, cardiovascular disease (cerebrovascular disease, coronary artery disease, and peripheral vascular disease), chronic kidney disease, mental disorder (schizophrenia/bipolar, depression, epilepsy), diabetes, pregnancy, alcoholic liver disease, non-alcoholic liver disease, hepatitis A virus, hepatitis B virus, and human immunodeficiency virus.

** P value < 0.05 for crude incidence rate of DAA treatment compared to no treatment based on 95% Poisson CI.

Table 3. Incidence rate of decompensated cirrhosis and hepatocellular carcinoma after DAA treatment in HCV patients with cirrhosis weighted by stabilized inverse probability of treatment weighting (IPTW), stratified by presence of SUD

Patients with cirrhosis (n=2916)	**No. of events**	**Person-years**	**Crude Incidence/ 1000 person-years**	**DAA vs. no treatment, unadjusted HR (95% CI)**	**DAA vs. no treatment, adjusted HR (95% CI) ***	**SUD vs. non-SUD among no treatment, adjusted HR (95% CI) †**
Decompensated cirrhosis						
SUD group (n=618)						
DAA treatment (n=298)	17	417	41**	0.84 (0.50-1.41)	0.64 (0.37-1.13)	1.52 (1.03-2.24)
No treatment (n=320)	35	351	100	reference	reference	
Non-SUD group (n=2298)						
DAA treatment (n=1308)	45	1999	23**	0.29 (0.20-0.43)	0.27 (0.18-0.41)	
No treatment (n=990)	86	1142	75	reference	reference	reference
Hepatocellular carcinoma						
SUD group (n=618)						
DAA treatment (n=298)	9	421	21	0.42 (0.17-1.03)	0.33 (0.13-0.88)	1.69 (1.05-2.72)
No treatment (n=320)	15	362	41	reference	reference	
Non-SUD group (n=2298)						
DAA treatment (n=1308)	37	1992	19**	0.42 (0.26-0.68)	0.40 (0.25-0.65)	
No treatment (n=990)	49	1136	43	reference	reference	reference

DAA = direct acting antiviral; HCV = hepatitis C virus; SUD = substance use disorders; HR = hazard ratio; CI = confidence interval; IPTW = inverse probability of treatment weighting

* The risk of decompensated cirrhosis (DCC) and hepatocellular carcinoma (HCC) was compared between DAA treated and untreated patients using Cox proportional hazards modeling with stabilized IPTW to adjust for age, gender, region, health plan, diabetes, cardiovascular disease (cerebrovascular disease, coronary artery disease, and peripheral vascular disease), chronic kidney disease, mental disorder (schizophrenia/bipolar, depression, epilepsy), diabetes, pregnancy, alcoholic liver disease, non-alcoholic liver disease, hepatitis A virus, hepatitis B virus, and human immunodeficiency virus. Stabilized IPTW was generated for SUD and non-SUD separately.

† The risk of DCC and HCC was compared between the SUD and non-SUD groups among untreated HCV patients using Cox proportional hazards modeling with stabilized IPTW to adjust for age, gender, region, health plan, diabetes, cardiovascular disease (cerebrovascular disease, coronary artery disease, and peripheral vascular disease), chronic kidney disease, mental disorder (schizophrenia/bipolar, depression, epilepsy), diabetes, pregnancy, alcoholic liver disease, non-alcoholic liver disease, hepatitis A virus, hepatitis B virus, and human immunodeficiency virus. Stabilized IPTW was generated among untreated HCV patients.

** P value < 0.05 for crude incidence rate of DAA treatment compared to no treatment based on 95% Poisson CI.

Table 4. Incidence rate of hepatocellular carcinoma after DAA treatment in HCV patients weighted by stabilized inverse probability of treatment weighting (IPTW), stratified by presence of SUD in sensitivity analyses

	No. of events	**Person-years**	**Crude Incidence/ 1000 person-years**	**DAA vs. no treatment, unadjusted HR (95% CI)**	**DAA vs. no treatment, adjusted HR (95% CI) ***	**SUD vs. non-SUD among no treatment, adjusted HR (95% CI) †**
Patients with HCC diagnosis ≥ 3 months after the index date						
Patients without cirrhosis (n=26 281)						
SUD group (n=5760)						
DAA treatment (n=1230)	6	1577	4	1.23 (0.43-3.52)	1.17 (0.38-3.58)	0.99 (0.58-1.70)
No treatment (n=4530)	13	4774	3	reference	reference	
Non-SUD group (n=20 521)						
DAA treatment (n=6509)	24	10 027	2**	0.26 (0.13-0.50)	0.18 (0.09-0.36)	

No treatment (n=14012)	74	15 646	5	reference	reference	reference
Patients with cirrhosis (n=2886)						
SUD group (n=613)						
DAA treatment (n=295)	6	420	14	0.33 (0.11-0.96)	0.27 (0.09-0.88)	2.20 (1.27-
No treatment (n=318)	13	362	36	reference	reference	3.83)
Non-SUD group (n=2273)						
DAA treatment (n=1298)	27	1991	14**	0.39 (0.22-0.70)	0.39 (0.22-0.71)	reference
No treatment (n=975)	34	1134	30	reference	reference	
Patients treated with DAAs at least 8~12 weeks						
Patients without cirrhosis (n=26 133)						
SUD group (n=5723)						
DAA treatment (n=1187)	7	1523	5	1.07 (0.41-2.81)	0.92 (0.34-2.54)	1.35 (0.88-
No treatment (n=4536)	19	4775	4	reference	reference	2.08)
Non-SUD group (n=20 410)						
DAA treatment (n=6382)	32	9826	3**	0.40 (0.24-0.67)	0.31 (0.19-0.53)	
No treatment (n=14 028)	90	15 647	6	reference	reference	reference
Patients with cirrhosis (n=2833)						
SUD group (n=601)						
DAA treatment (n=281)	8	410	21	0.38 (0.15-0.96)	0.31 (0.11-0.85)	1.69 (1.05-
No treatment (n=320)	15	362	41	reference	reference	2.72)
Non-SUD group (n=2232)						
DAA treatment (n=1242)	35	1907	18**	0.42 (0.26-0.67)	0.40 (0.24-0.64)	reference
No treatment (n=990)	49	1136	43	reference	reference	

DAA = direct acting antiviral; HCV = hepatitis C virus; SUD = substance use disorders; HR = hazard ratio; CI = confidence interval; IPTW = inverse probability of treatment weighting; HCC = hepatocellular carcinoma

* The risk of HCC was compared between DAA treated and untreated patients using Cox proportional hazards modeling with stabilized IPTW to adjust for age, gender, region, health plan, diabetes, cardiovascular disease (cerebrovascular disease, coronary artery disease, and peripheral vascular disease), chronic kidney disease, mental disorder (schizophrenia/bipolar, depression, epilepsy), diabetes, pregnancy, alcoholic liver disease, non-alcoholic liver disease, hepatitis A virus, hepatitis B virus, and human immunodeficiency virus. Stabilized IPTW was generated for SUD and non-SUD separately.

† The risk of HCC was compared between the SUD and non-SUD groups among untreated HCV patients using Cox proportional hazards modeling with stabilized IPTW to adjust for age, gender, region, health plan, diabetes, cardiovascular disease (cerebrovascular disease, coronary artery disease, and peripheral vascular disease), chronic kidney disease, mental disorder (schizophrenia/bipolar, depression, epilepsy), diabetes, pregnancy, alcoholic liver disease, non-alcoholic liver disease, hepatitis A virus, hepatitis B virus, and human immunodeficiency virus. Stabilized IPTW was generated among untreated HCV patients.

** P value < 0.05 for crude incidence rate of DAA treatment compared to no treatment based on 95% Poisson CI.

Table 5. Incidence rate of decompensated cirrhosis after DAA treatment in HCV patients weighted by stabilized inverse probability of treatment weighting (IPTW), stratified by presence of SUD in sensitivity analyses

	No. of events	Person-years	Crude Incidence/ 1000 person-years	DAA vs. no treatment, unadjusted HR (95% CI)	DAA vs. no treatment, adjusted HR (95% CI) *	SUD vs. non-SUD among no treatment, adjusted HR (95% CI) †
Patients with DCC diagnosis ≥ 3 months after the index date						
Patients without cirrhosis (n=26 263)						
SUD group (n=5751)						
DAA treatment (n=1230)	13	1581	8**	0.22 (0.10-0.50)	0.11 (0.04-0.27)	2.22 (1.74-2.83)
No treatment (n=4521)	79	4764	16	reference	reference	
Non-SUD group (n=20 512)						
DAA treatment (n=6514)	40	10 026	4**	0.22 (0.14-0.35)	0.10 (0.06-0.18)	
No treatment (n=13998)	167	15 625	11	reference	reference	reference
Patients with cirrhosis (n=2876)						
SUD group (n=604)						
DAA treatment (n=293)	12	416	29**	0.87 (0.47-1.60)	0.82 (0.43-1.58)	1.30 (0.82-2.07)
No treatment (n=311)	26	350	74	reference	reference	
Non-SUD group (n=2272)						
DAA treatment (n=1297)	34	1998	17**	0.22 (0.14-0.36)	0.20 (0.12-0.33)	reference
No treatment (n=975)	71	1140	62	reference	reference	
Patients treated with DAAs at least 8~12 weeks						

Patients without cirrhosis (n=26 133)						
SUD group (n=5723)						
DAA treatment (n=1187)	14	1526	9**	0.24 (0.11-0.50)	0.13 (0.06-0.31)	2.31 (1.85-2.88)
No treatment (n=4536)	94	4766	20	reference	reference	
Non-SUD group (n=20 410)						
DAA treatment (n=6382)	42	9828	4**	0.21 (0.13-0.33)	0.11(0.07-0.18)	
No treatment (n=14 028)	197	15 629	13	reference	reference	reference
Patients with cirrhosis (n=2833)						
SUD group (n=601)						
DAA treatment (n=281)	17	401	42**	0.89 (0.53-1.49)	0.68 (0.39-1.20)	1.52 (1.03-2.24)
No treatment (n=320)	35	351	100	reference	reference	
Non-SUD group (n=2232)						
DAA treatment (n=1242)	43	1914	23**	0.29 (0.20-0.44)	0.27 (0.18-0.41)	reference
No treatment (n=990)	86	1142	75	reference	reference	

DAA = direct acting antiviral; HCV = hepatitis C virus; SUD = substance use disorders; HR = hazard ratio; CI = confidence interval; IPTW = inverse probability of treatment weighting; DCC= decompensated cirrhosis

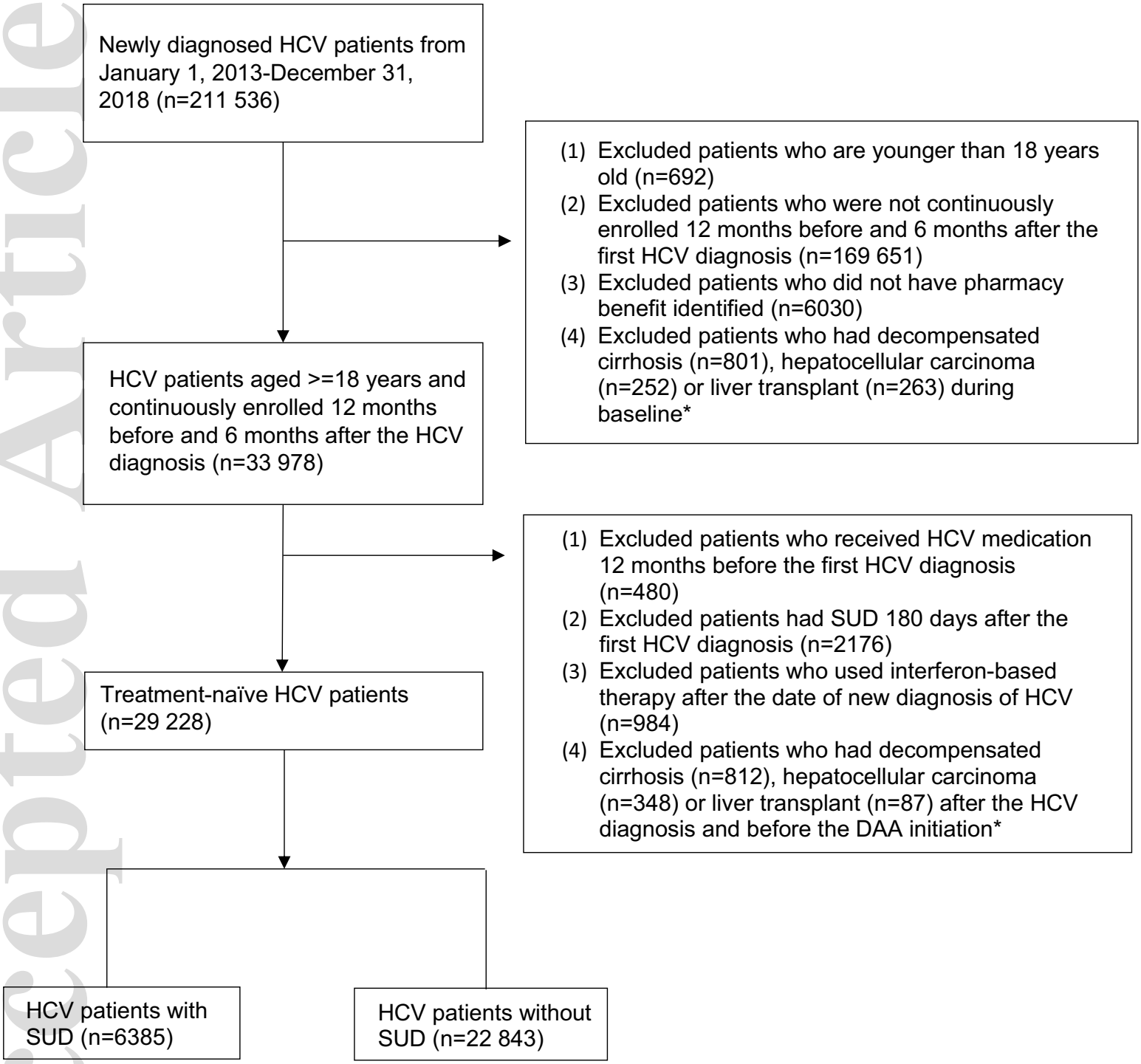
* The risk of DCC was compared between DAA treated and untreated patients using Cox proportional hazards modeling with stabilized IPTW to adjust for age, gender, region, health plan, diabetes, cardiovascular disease (cerebrovascular disease, coronary artery disease, and peripheral vascular disease), chronic kidney disease, mental disorder (schizophrenia/bipolar, depression, epilepsy), diabetes, pregnancy, alcoholic liver disease, non-alcoholic liver disease, hepatitis A virus, hepatitis B virus, and human immunodeficiency virus. Stabilized IPTW was generated for SUD and non-SUD separately.

† The risk of DCC was compared between the SUD and non-SUD groups among untreated HCV patients using Cox proportional hazards modeling with stabilized IPTW to adjust for age, gender, region, health plan, diabetes, cardiovascular disease (cerebrovascular disease, coronary artery disease, and peripheral vascular disease), chronic kidney disease, mental disorder (schizophrenia/bipolar, depression, epilepsy), diabetes,

pregnancy, alcoholic liver disease, non-alcoholic liver disease, hepatitis A virus, hepatitis B virus, and human immunodeficiency virus. Stabilized IPTW was generated among untreated HCV patients.

** P value < 0.05 for crude incidence rate of DAA treatment compared to no treatment based on 95% Poisson CI.

Figure 1. Flow chart of the cohort creation



*: Patients can at the same time have decompensated cirrhosis, and/or hepatocellular carcinoma and/or liver transplant.

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