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Association of Direct-Acting Antiviral Treatment with Mortality Among Medicare Beneficiaries with Hepatitis C

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Abstract

Importance: Direct-acting antivirals (DAAs) are highly effective in treating hepatitis C virus (HCV). Prior simulations used extended lives as a key health benefit of DAAs. However, real-world evidence on whether DAA treatment reduces mortality is limited.

Objectives: To examine the association of DAA treatment with mortality among Medicare patients with HCV.

Design, Setting, and Participants: This retrospective cohort study used data from Medicare patients seeking HCV care between January 1, 2014, and December 31, 2016 after at least a one-year wash-out period. We used Cox proportional hazard regression models with time-varying exposure to compare mortality rates between propensity score-matched cohorts of DAA-treated and untreated patients. Matching and model estimation were done separately for patients with and without cirrhosis. We examined heterogeneity in the association between DAA treatment and mortality by gender and dual eligibility for Medicare and Medicaid. Data were analyzed between September 2019 and March 2020.

Exposure: Completion of DAA treatment.

Main Outcomes and Measures: Time to death from the date of newly seeking HCV care after at least a one-year wash-out period.

Results: Propensity score-matched cohorts of 8,240 patients (36.6% female; mean [SD] age, 62.3 [9.7] years) with cirrhosis and 43,238 patients (41.6% female; mean [SD] age, 58.8 [11.3]

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Access to Data: Yamini Kalidindi and Dr. Jeah Jung had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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years) without cirrhosis were included in the analysis. The adjusted hazard ratio [HR] of dying between DAA-treated and untreated patients with cirrhosis was 0.51 (95% CI, 0.46–0.57). The association of DAA treatment with mortality did not differ by gender (p=0.27) or dual-eligibility status (p=0.80) among cirrhosis patients. The adjusted HR of dying between DAA-treated and untreated patients without cirrhosis was 0.54 (95% CI, 0.50–0.58). The association of DAA treatment with mortality did not differ by gender (p=0.66) among non-cirrhosis patients. However, the survival benefit of DAAs for non-dual eligibles (HR, 0.47; 95% CI, 0.41–0.55) was higher than for dual eligibles (HR, 0.56; 95% CI, 0.52–0.62) among the non-cirrhosis patients, and this difference was significant (p=0.02).

Conclusions and Relevance: DAA treatment was associated with a decreased mortality in Medicare patients with and without cirrhosis. Increasing access to DAAs for all HCV-infected patients, regardless of disease progression, could improve population health.

Hepatitis C virus infection (HCV) is the most common blood-borne illness in the US.[1] About 2.4 million people in the US were estimated to have HCV infection between 2013 and 2016.[2] If chronic HCV infection is untreated, serious health problems, such as hepatocellular cancer, cirrhosis, and liver damage, can occur.[3] HCV-infected people also experience increased mortality compared with the general population,[4–6] and nearly 20,000 Americans die each year from hepatitis C-related causes.[7]

The availability of second-generation direct-acting antivirals (DAAs) has provided an unprecedented opportunity to address HCV infection and thereby improve population health.[8,9] DAAs are highly effective – with cure rates of 90%,[10–13] which is much higher than 50% for the earlier interferon-based HCV therapy.[14] In addition, DAAs have few adverse effects and improved tolerability, which lead patients to complete the therapy.[10–13] Literature on interferon-based therapy indicated that curing HCV was associated with improved clinical outcomes, such as a decrease in the incidence of hepatocellular cancer and decreased mortality rates.[15–20] More patients with HCV are expected to have these benefits when treated with DAAs, given the higher cure and completion rates of DAAs.

Several studies of clinical outcomes reported that DAA-treated patients with cirrhosis were less likely to develop hepatocellular cancer than DAA-untreated patients.[21,22] Prior simulations used extended lives as a key outcome to indicate that the benefits from DAA treatment can exceed DAA treatment costs.[23–25] However, real-world evidence is limited on whether DAA treatment reduces mortality, which is crucial to assess the value of costly DAAs.

Recently, a few studies examined the association of DAA treatment with mortality.[26–28] One study focused on patients with a history of hepatocellular carcinoma from 31 health systems across the US and Canada.[28] It reported that DAA therapy was associated with a 71% reduction in mortality compared with untreated patients.[28] However, the study sample is not representative of the HCV-infected population because only 1%−5% of HCV patients suffer from hepatocellular carcinoma.[2] The other two studies used a sample of HCV patients in the Veteran Affairs (VA) health system and reported that DAA treatment was associated with a decrease in mortality.[26, 27] However, 97% of the patients in these VA studies were males.

[26,27] In addition, these VA studies did not match DAA-treated and untreated patients, despite different distributions of health risk in the treated and untreated groups.[26,27]

We examined whether DAA treatment reduced mortality among Medicare patients with HCV. It is important to assess this issue in Medicare for the following reasons. First, Medicare covers many baby boomers – the group with highest prevalence of HCV.[29,30] As this population ages, they experience more HCV complications, which can increase mortality. Medicare is thus expected to play a large role in HCV care. In fact, Medicare paid for half of DAA pills in 2015, making it the largest payer of DAAs in that year.[31,32]

Second, the Medicare population is 54 percent female,[33] and 42 percent of the Medicare patients with HCV in our study are women. HCV progression differs between men and women.[34] Women are more likely than men to clear the virus spontaneously after initial HCV infection and have slower rates of liver disease progression after becoming chronically infected.[34] Yet, little is known about survival benefits of DAAs among female patients.

Third, Medicare covers non-elderly people who are disabled and have low incomes – demographics that are associated with a higher prevalence of HCV than the general population.[35] Most of these patients are dually eligible for both Medicare and Medicaid due to their low-income status, which is associated with poor health outcomes.[36] But potential differences in health benefits of DAAs by dual eligibility have not been explored in prior work.

We examined the association between DAA treatment and mortality in a national cohort of Medicare beneficiaries with HCV. We also assessed whether that association varied by patient gender and by dual-eligibility.

METHODS

Data

We used 2013–2016 Medicare claims for inpatient, skilled nursing facility, outpatient, and physician services to identify HCV patients and the presence of cirrhosis. The 2013 files were used only to ensure that patients did not seek HCV care during that year. We used 2014–2017 Medicare Part D files to identify DAA initiation and completion. We required patients to be enrolled in Part D during the entire study period to identify DAA initiation.

Information on death dates was available through December 31, 2017, for all Medicare-enrolled patients from Master Beneficiary Summary Files (MBSF). We also obtained demographic information and indicators of health risks from MBSF.

This study was approved by the Pennsylvania State University's institutional review board and received a waiver of informed consent. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies. Data were analyzed between September 2019 and March 2020.

Sample selection

The study population was Medicare Fee-For-Service beneficiaries who newly sought HCV care between January 1, 2014, and December 31, 2016, after at least a one-year wash-out period. We then considered the date of the first HCV claim after the wash-out period as the index date. eAppendix 1 describes details of wash-out periods, index date, and sensitivity checks. We identified patients with HCV following the standard algorithm used by the Centers for Medicare and Medicaid Services (eAppendix 1).[37]

We excluded patients who died within six months after the index date. DAAs were unlikely to be given to those patients because the course of DAA treatment usually ranges between three and six months.

DAA treated group

DAA initiators were identified as those who were treated with one of the following DAAs: elbasvir/grazoprevir, ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir plus dasabuvir, sofosbuvir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, or glecaprevir/pibrentasvir. We defined DAA-treated patients as DAA initiators who completed treatment before December 30, 2017. The completion of a DAA was defined as filling prescriptions for the expected duration of the DAA identified from package inserts or randomized trials. eAppendix A1 describes details of the definition of completion.

DAA untreated group

Patients who did not initiate DAA therapy during the study period were considered DAA-untreated patients. We selected the DAA-untreated group based on one-to-one propensity score matching (within 10% of the standard deviation of propensity scores). Patients were matched on demographics and health risks at the index date. eTable 1 describes the definitions and data sources of all covariates used in matching.

We performed matching separately for patients with and without cirrhosis at the index date. We required patients without cirrhosis at the index date in the DAA-treated group to remain without cirrhosis until treatment. Figure 1 presents a diagram of the study sample selection.

Outcome and exposure

We followed up all patients from the index date until they died or reached the end of study period [December 31, 2017]. The outcome of analysis was time to death from the index date.

The completion of DAA treatment was examined as a time-varying exposure measure. DAA-treated patients contributed to unexposed person-time until they completed treatment. Following completion of the treatment, they contributed toward exposed person-time. Untreated patients contributed only toward unexposed person-time. Examining DAA treatment as time-varying exposure addresses “immortal bias” – which favors the treatment group because treated individuals survive at least until exposure.[38–40]

Analysis

We conducted all analyses separately for the cirrhosis and non-cirrhosis cohorts. We first described the patient characteristics at the index date in the full unmatched sample. We then compared patient characteristics at the index date between DAA-treated and untreated patients in the propensity-score matched samples, separately for those with and without cirrhosis. We assessed that the characteristics were "balanced" after matching between the groups when standardized differences were less than 10%.[41]

We calculated mortality rates as deaths per 100 person-years in the DAA-treated and untreated groups and obtained the crude mortality rate ratios. Kaplan-Meier (KM) survival curves were plotted for DAA-treated and untreated groups. We also estimated crude mortality rate ratios and plotted KM curves separately for females, males, non-dual eligible, and dual eligible patients.

We estimated adjusted hazard ratios of death between DAA-treated and untreated patients using the Cox proportional hazards model with time-varying exposure. We examined heterogeneity in the relation between DAA treatment and mortality rates across different patient groups by estimating separate Cox regression models for the following sub-groups: females, males, non-dual eligibles, and dual eligibles. These separate analyses allow the associations of DAA treatment and all other covariates with mortality to vary in each group. We assessed whether the survival effect of DAAs was significantly different between groups by including interaction terms between DAA treatment and group indicators in a Cox model with all patients.[42]

We considered $p < 0.05$ as statistically significant for all comparisons. We used SAS 9.4 (SAS Institute) and Stata15 (StataCorp LLC) for the analyses.

Sensitivity Analysis:

We estimated the model limiting the sample to patients who were alive for at least one year after the index date. This analysis was to consider a recommendation that DAA therapy be given to those with a life expectancy greater than one year.[43] We used a propensity-score matched cohort for this analysis.

RESULTS

Patient characteristics

The analysis included a propensity score matched sample of 51,478 beneficiaries (40.8% female; mean [SD] age, 59.4 [11.1] years), consisting of 8,240 patients with cirrhosis (36.6% female; mean [SD] age, 62.3 [9.7] years) and 43,238 patients without cirrhosis (41.6% female; mean [SD] age, 58.8 [11.3] years).

Patient characteristics in the unmatched sample are reported in eTable 2. Compared with DAA-treated patients, untreated patients were likely to be older and have other conditions such as anemia, lung disease, cardiac disease, dementia, diabetes, kidney disorders, and drug and alcohol related disorders.

Table 1 presents the patient characteristics in the matched sample. Baseline patient characteristics after matching were balanced – the estimates of standardized difference scores after matching were all less than 10%. Among patients with cirrhosis, the median time from Hepatitis C index date to treatment completion was 9.1 months (interquartile range {IQR}, 5.8 – 15.5 months), with 28% treated within six months. Among patients without cirrhosis, the median time from Hepatitis C index date to treatment completion was 8.6 months (IQR, 5,2 – 15.7 months), with 33% treated within six months.

Descriptive results

In the cirrhosis group, 480 deaths occurred during 10,531.2 person-years of follow-up among DAA-treated beneficiaries (4.76 deaths/100 person-years; 95% confidence interval [CI], 4.15–4.97). In comparison, 1,310 deaths occurred during 9,234.8 person-years of follow-up (14.19 deaths/100 person-years; 95% CI, 13.42–14.95) in untreated beneficiaries (Table 2). The crude mortality rate ratio between the two groups was 0.32 (95% CI, 0.29–0.35). The 1-year risk of mortality for DAA-treated patients was 2.2%, compared with 10.4% among untreated patients (data not shown). The crude mortality rate ratio between treated and untreated patients did not differ by gender: 0.31 (95% CI, 0.25–0.37) in females versus 0.33 (95% CI, 0.28–0.37) in males. Similarly, no difference was observed by dual-eligibility status: 0.33 (95% CI, 0.27–0.40) in non-duals versus 0.32 (95% CI, 0.28–0.37) in dual eligibles.

In the non-cirrhosis group, 912 deaths occurred during 55,794.9 person-years of follow-up among DAA-treated patients (1.63 deaths/100 person-years; 95% CI, 1.53–1.74). In contrast, 2,955 deaths occurred during 61,587.8 person-years of follow-up (4.80 deaths/100 person-years; 95% CI, 4.63–4.97) among the untreated patients (Table 2). The crude mortality rate ratio between the two groups was 0.34 (95% CI, 0.32–0.37). The 1-year risk of mortality for DAA-treated patients was 0.6%, compared with 2.9% among untreated patients (data not shown). We observed little difference in the crude mortality rate ratio by gender: 0.33 (95% CI, 0.29–0.38) in females versus 0.34 (95% CI, 0.31–0.37) in males. No difference in the crude mortality rate ratio was observed by dual eligibility status: 0.31 (95% CI, 0.27–0.36) in non-duals versus 0.35 (95% CI, 0.32–0.38) in dual eligibles.

Figure 2 depicts the Kaplan-Meier (KM) survival curves. DAA treatment was associated with a statistically significant reduction in mortality in both cirrhosis and non-cirrhosis groups. The KM curves for each sub-group – males, females, non-dual eligible, and dual eligible – are provided in the Appendix (eFigure1 and eFigure2). They indicated survival benefits of DAAs in all of those groups, irrespective of cirrhosis at the index date.

Cox proportional hazards regression results

DAA treatment was associated with reduced mortality after controlling for patient characteristics (Figure 3). In the cirrhosis group, the adjusted hazard ratio (HR) of dying between DAA-treated and untreated patients was 0.51 (95% CI, 0.46–0.57). Being older, male, having decompensated cirrhosis, and having other health conditions were associated with increased mortality (full regression results are reported in eTable 3). Separate analyses by gender revealed consistent survival benefits of DAAs for both females (HR, 0.46; 95%

CI, 0.38–0.56) and males (HR, 0.53; 95% CI, 0.47–0.60). This difference in HR by gender was not statistically significant (p=0.27 on the interaction term, eTable 4). DAA treatment was associated with a slightly smaller reduction in mortality in non-dual eligibles (HR, 0.52; 95% CI, 0.43–0.63) than in dual eligibles (HR, 0.50; 95% CI, 0.44–0.57). This difference was not statistically significant (p=0.80 on the interaction term, eTable 4).

In the non-cirrhosis group, the adjusted HR of dying between DAA-treated and untreated patients was 0.54 (95% CI, 0.50–0.58). Being older, male, and having other health conditions were associated with increased mortality (eTable 3). Survival benefit of DAAs was observed for both females (HR, 0.53; 95% CI, 0.46–0.60) and males (HR, 0.55; 95% CI, 0.50–0.60). This difference in HR by gender was not statistically significant (p=0.66 on the interaction term, eTable 4). However, DAA treatment was associated with a larger reduction in mortality in non-dual eligibles (HR, 0.47; 95% CI, 0.41–0.55) than in dual eligibles (HR, 0.57; 95% CI, 0.52–0.62). This difference was statistically significant (p=0.02 on the interaction term, eTable 4).

Results from sensitivity analysis

The findings from the analysis with HCV patients who were alive for at least one year after the index date were very similar to those from the main analysis (eFigure 3). The adjusted hazard ratio (HR) of dying between DAA-treated and untreated patients was 0.47 (95% CI, 0.42–0.53) in the cirrhosis group and 0.54 (95% CI, 0.50–0.58) in the non-cirrhosis group.

DISCUSSION

DAA treatment was associated with lower mortality among Medicare patients with and without cirrhosis (adjusted mortality ratio reductions of 49% and 46%, respectively). This finding is important evidence that DAA treatment has a large health benefit, even among patients without advanced liver disease. Because of the high costs of DAAs, payers have restricted coverage for DAAs to patients with advanced fibrosis.[44–46] Some payers, such as the VA, have removed this restriction,[26] but it still remains in other programs.[44–46] Restrictive coverage for DAAs has been based partially on uncertainty about the immediate benefits of treatment in patients without serious HCV progression.[26] However, our analysis suggests that expanding coverage for DAAs to all HCV-infected patients regardless of disease progression can avert deaths. Our finding also supports the recent recommendation of HCV testing for all adults between 18–79 years because diagnosis is a precursor to treatment.[47]

The estimated survival benefit in non-cirrhosis patients (46% reduction in the mortality ratio) is smaller than prior work, which reported a 68% decrease in the mortality ratio.[26] This difference may be due to the following. First, it may partially stem from our analytic approach that addressed immortal bias by considering only time after treatment as exposed in the DAA-treated group. Second, we used propensity score matching to improve balance in patient risks between treated and untreated groups. Both of these approaches remove sources of selection bias that would favor the treatment group and thereby result in a smaller effect than otherwise.

The sub-group analyses indicated limited heterogeneity in the health benefit of DAAs across patient groups. First, the mortality ratio reduction after DAA treatment was similar between males and females. Being male is a predictor of HCV prevalence and fast disease progression.[34] However, it did not play a role in the association between DAA treatment and mortality, regardless of the presence of cirrhosis. This is an important extension of prior evidence on the survival benefits of DAAs in males or patients with a history of liver cancer.[26,27]

Second, the association of DAA treatment with mortality was similar for cirrhosis patients who were dually eligible for both Medicare and Medicaid and those who were eligible for Medicare only. However, among non-cirrhosis patients, we found a smaller association of treatment with mortality for dually eligible patients. Dual eligibles are sicker and have lower incomes than Medicare-only beneficiaries.[48] They may have encountered barriers to seeking health care and improvement in health outcomes, leading to a smaller association between DAA treatment and mortality. Identifying those barriers was beyond the scope of our study, but it could help explore ways to increase the survival benefit from DAA treatment in this group.

Our study provides real-world evidence that DAA treatment leads to fewer deaths in HCV-infected Medicare patients. This suggests that that improving access to DAAs – perhaps with particular attention to patient groups with low DAA uptake – could have a significant health benefit for the population.

LIMITATIONS

We note several limitations of the study. First, Medicare claims data do not have clinical information, such as genotype or sustained virologic response status. Some DAA treated patients in our analysis may not have cured HCV. However, not accounting for this factor leads to conservative estimates in our analysis. Second, selection bias may remain even after propensity score matching due to differences in unobservable characteristics. However, it is unlikely to change the study conclusions given the large estimates of DAA health impacts. Third, we measured only overall mortality rates – i.e. all-cause deaths. Some deaths in the study sample may not be related to HCV. But condition-specific deaths are not identifiable in claims data. Fourth, we lacked information on the date of initial HCV diagnosis in our five years of claims data. Finally, the study findings may not generalize to patients covered by Medicaid only, commercial insurers, or Medicare Advantage.

CONCLUSIONS

DAA treatment was associated with a decrease in mortality in Medicare patients with HCV regardless of the presence of cirrhosis. This is important real-world evidence on the survival benefit of DAAs and suggests that increasing access to DAAs regardless of disease progression could improve population health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS

Question:

Is direct-acting antiviral (DAA) therapy to treat hepatitis C virus (HCV) associated with a reduction in mortality among Medicare patients?

Findings:

In this retrospective cohort study of 51,478 propensity-score matched Medicare patients, DAA treatment was significantly associated with a decrease in mortality among patients with and without cirrhosis. The association of DAA treatment with mortality was similar for males and females regardless of the presence of cirrhosis, and it was slightly smaller among non-cirrhosis dual-eligible patients than among Medicare-only patients.

Meaning:

Increasing access to DAAs for all HCV-infected patients, regardless of disease progression, could improve population health.

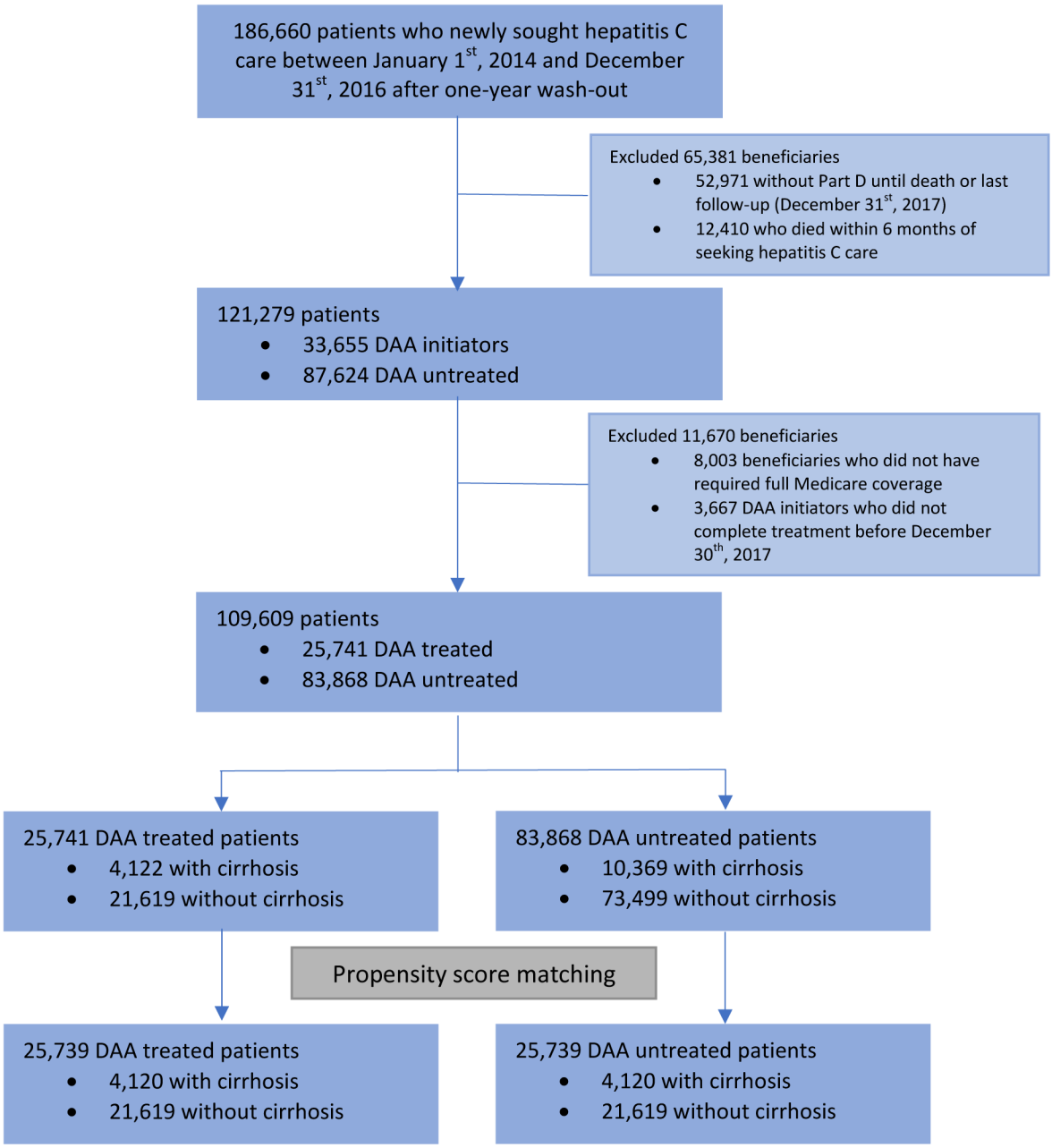


Figure 1:
Study sample selection
Abbreviations: DAA, Direct-acting antiviral agent

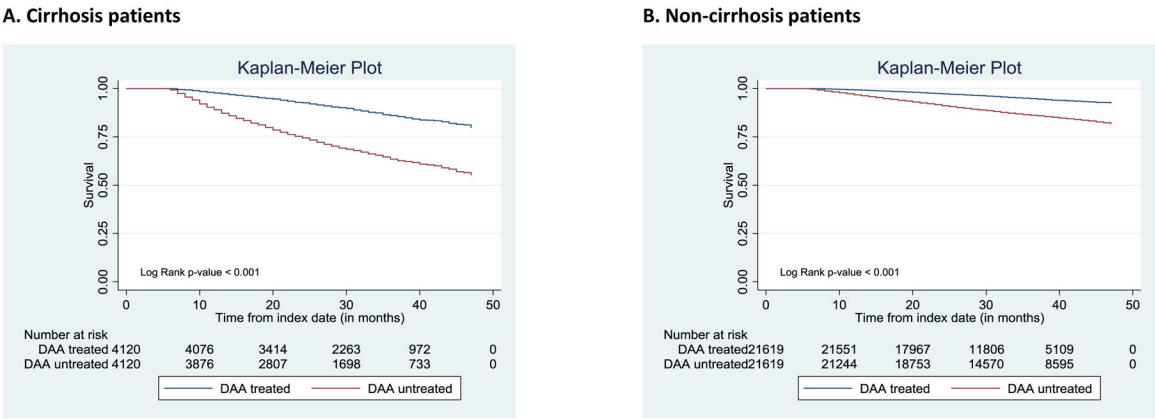


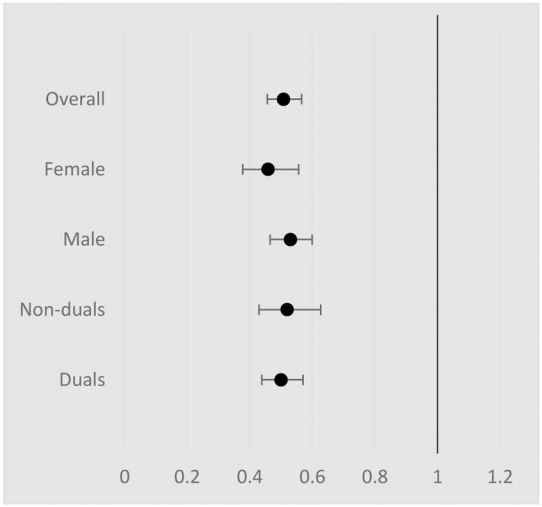
Figure 2:

Survival stratified by Direct-Acting Antiviral (DAA) treatment

Abbreviations: DAA, Direct-acting antiviral agent

A. Cirrhosis patients

	N	HR (95% CIs)	P value
Overall	8,240	0.51 (0.46-0.57)	<0.001
Female	3,016	0.46 (0.38-0.56)	<0.001
Male	5,224	0.53 (0.47-0.60)	<0.001
Non dual eligibles[b]	2,738	0.52 (0.43-0.63)	<0.001
Dual eligibles[c]	5,502	0.50 (0.44-0.57)	<0.001



B. Non-cirrhosis patients

	N	HR (95% CIs)	P value
Overall	43,238	0.54 (0.50-0.58)	<0.001
Female	17,989	0.53 (0.46-0.60)	<0.001
Male	25,249	0.55 (0.50-0.60)	<0.001
Non dual eligibles[b]	12,755	0.47 (0.41-0.55)	<0.001
Dual eligibles[c]	30,483	0.57 (0.52-0.62)	<0.001

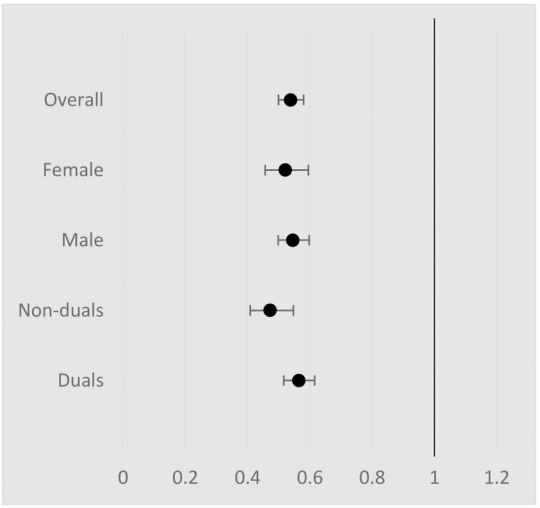


Figure 3:

Adjusted hazard ratios for mortality comparing direct-acting antiviral (DAA) treated and DAA untreated patients

Abbreviations: CIs, Confidence intervals; HR, Hazard ratios

[a] Adjusted for patient characteristics and risk factors summarized in eTable1

[b] Non dual eligibles are eligible for Medicare only

[c] Dual eligibles are eligible for Medicare and Medicaid

Table 1.

Patient characteristics in the propensity-score matched sample[a]

	Cirrhosis patients (N=8,240)			Non-cirrhosis patients (N=43,238)		
	DAA Treated (N=4,120)	DAA Untreated (N=4,120)	St.Diff,[b] %	DAA Treated (N=21,619)	DAA Untreated (N=21,619)	St.Diff,[b] %
Variable	**No. (%)**	**No. (%)**		**No. (%)**	**No. (%)**	
Age						
Age <65	2,355(57.2%)	2,480(60.2%)	−6.2	14,344(66.4%)	14,544(67.3%)	−2.0
Age 65–70	931(22.6%)	840(20.4%)	5.4	4,144(19.2%)	4,061(18.7%)	1.0
Age 70–75	458(11.1%)	421(10.2%)	2.9	1,941(9.0%)	1,855(8.6%)	1.4
Age >75	376(9.1%)	379(9.2%)	−0.3	1,190(5.5%)	1,159(5.4%)	0.6
Female Gender	1,515(36.8%)	1,501(36.4%)	0.7	8,994(41.6%)	8,995(41.6%)	0.0
Race						
White	2,917(70.8%)	3,030(73.5%)	−6.1	14,358(66.4%)	14,639(67.7%)	−2.8
African American	870(21.1%)	758(18.4%)	6.8	5,823(26.9%)	5,649(26.1%)	1.8
Hispanic	145(3.5%)	145(3.5%)	0.0	595(2.8%)	538(2.5%)	1.7
Other	188(4.6%)	187(4.5%)	0.1	843(3.9%)	793(3.7%)	1.2
Dual eligibility[c]	2,732(66.3%)	2,770(67.2%)	−2.0	15,182(70.2%)	15,301(70.8%)	−1.2
Conditions						
Decompensated cirrhosis	1,248(30.3%)	1,313(31.9%)	−3.4	-	-	-
HIV/AIDS	109(2.6%)	98(2.4%)	1.7	1,175(5.5%)	1,098(5.1%)	1.6
Hepatocellular cancer	239(5.8%)	264(6.4%)	−2.5	76(0.4%)	63(0.3%)	1.1
Anemia	1,808(43.9%)	1,863(45.2%)	−2.7	5,572(25.8%)	5,649(26.1%)	−0.8
Lung Disease	1,166(28.3%)	1,229(29.8%)	−3.4	5,364(24.8%)	5,368(24.8%)	0.0
Cancer	524(12.7%)	517(12.6%)	0.5	2,208(10.2%)	2,089(9.7%)	1.8
Cardiac disease	3,140(76.2%)	3,231(78.4%)	−5.3	14,742(68.2%)	14,975(69.3%)	−2.3
Dementia	254(6.2%)	226(5.5%)	2.9	895(4.1%)	826(3.8%)	1.6
Psychiatric conditions	1,810(43.4%)	1,925(46.7%)	−5.6	10,840(50.1%)	10,809(50.0%)	0.3
Diabetes	1,554(37.7%)	1,579(38.3%)	−1.2	6,123(28.3%)	6,083(28.1%)	0.4
Eye disease	673(16.3%)	630(15.3%)	2.9	3,403(15.7%)	3,324(15.4%)	1.0
Kidney disorders	1,150(27.9%)	1,206(29.3%)	−3.0	4,160(19.2%)	4,212(19.5%)	−0.6
Drug and alcohol related disorder	2,052(49.8%)	2,237(54.3%)	−9.0	10,123(46.8%)	10,061(46.5%)	0.6
Bone disease	1,520(36.9%)	1,570(38.1%)	−2.5	8,419(38.9%)	8,474(39.2%)	−0.5
ESRD	164(4.0%)	161(3.9%)	0.4	703(3.2%)	718(3.3%)	−0.4
Time from index date[d] **to DAA initiation**						
<6 months	1,150(27.9%)	NA		7,161(33.1%)	NA	
6–12 months	1,505(36.6%)			6,907(31.9%)		
12–24 months	1,086(26.4%)			5,195(24.0%)		
24–36 months	302(7.3%)			1,866(8.6%)		
>36 months	77(1.9%)			490(2.3%)		

Abbreviations: AIDS, Acquired immunodeficiency syndrome; DAA, Direct-acting antiviral drug; ESRD, End-stage renal disease; HIV, Human immunodeficiency virus; St.Diff, Standardized difference

[a] Patient characteristics are measured at index date

[b] A standardized difference less than 10% is considered to denote balanced patient characteristics

[c] Dual eligibility is an indicator of whether a person is eligible for both Medicare and Medicaid

[d] Index date is the date when the patient first sought HCV care after a one-year wash-out period

Table 2.

Comparison of mortality rates between direct-acting antiviral agent (DAA) treated patients and DAA untreated patients

DAA untreated versus treated	Patients, n	Deaths, n	Person-years	Mortality-rate per 100 person-years (95% CI)	Crude rate (95% CI)	P value
Cirrhosis patients						
Overall - DAA untreated	4,120	1,310	9,234.75	14.19 (13.42–14.95)	—	
Overall - DAA treated	4,120	480	10,531.15	4.56 (4.15–4.97)	0.32 (0.29–0.35)	<0.001
Female						
DAA untreated	1,501	420	3,431.03	12.24 (11.07–13.41)	—	
DAA treated	1,515	148	3,888.59	3.81 (3.19–4.42)	0.31 (0.25–0.37)	<0.001
Male						
DAA untreated	2,619	890	5,803.72	15.33 (14.33–16.34)	—	
DAA treated	2,605	332	6,642.55	5.00 (4.46–5.54)	0.33 (0.28–0.37)	<0.001
Non dual eligibles[a]						
DAA untreated	1,350	404	2,984.10	13.54 (12.22 – 14.86)	—	
DAA treated	1,388	159	3,517.55	4.52 (3.82–5.22)	0.33 (0.27–0.40)	<0.001
Dual eligibles[b]						
DAA untreated	2,770	906	6,250.65	14.49 (13.55–15.44)	—	
DAA treated	2,732	321	7,013.60	4.58 (4.08–5.08)	0.32 (0.28–0.36)	<0.001
Non-cirrhosis patients						
Overall - DAA untreated	21,619	2,955	61,587.84	4.80 (4.63–4.97)	—	
Overall - DAA treated	21,619	912	55,792.87	1.63 (1.53–1.74)	0.34 (0.32–0.37)	<0.001
Females						
DAA untreated	8,995	978	26,253.96	3.72 (3.49–3.96)	—	
DAA treated	8,994	291	23,322.38	1.25 (1.10–1.39)	0.33 (0.29–0.38)	<0.001
Males						
DAA untreated	12,624	1,977	35,333.88	5.59 (5.35–5.84)	—	
DAA treated	12,625	621	32,466.57	1.91 (1.76–2.06)	0.34 (0.31–0.37)	<0.001
Non dual eligibles[a]						
DAA untreated	6,318	787	17,082.09	4.61 (4.28–4.93)	—	
DAA treated	6,437	239	16,648.38	1.44 (1.25–1.62)	0.31 (0.27–0.36)	<0.001
Dual eligibles[b]						
DAA untreated	15,301	2,168	44,504.75	4.87 (4.67–5.08)	—	
DAA treated	15,182	673	39,140.58	1.72 (1.59–1.85)	0.35 (0.32–0.38)	<0.001

Abbreviations: CI, Confidence intervals; DAA, Direct-acting antiviral drug

[a]Non dual eligibles are eligible for Medicare only

[b]Dual eligibles are eligible for Medicare and Medicaid