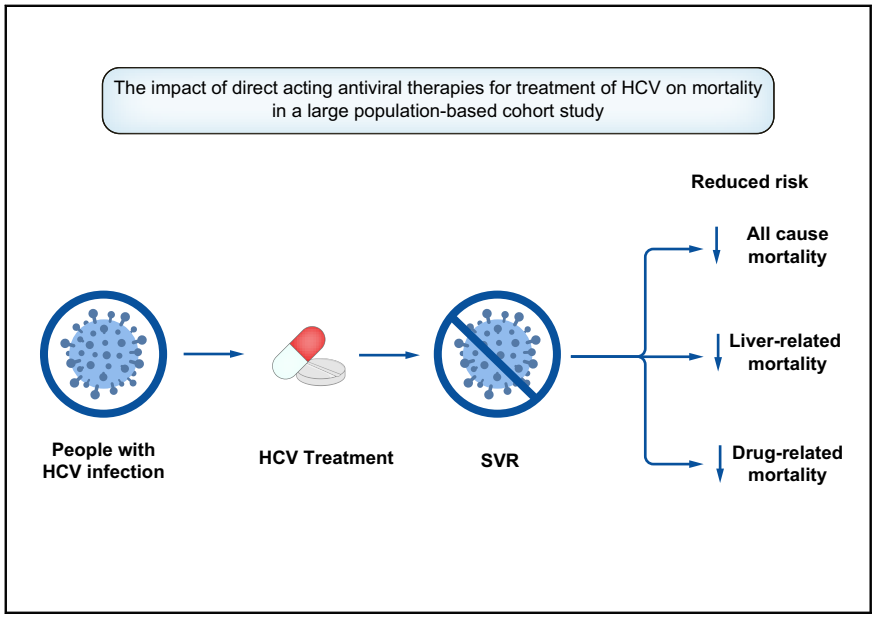
Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Impact of direct-acting antivirals for HCV on mortality in a large population-based cohort study

Graphical abstract



Highlights

- Chronic HCV is associated with a higher risk of mortality.
- SVR from DAAs was associated with a significant reduction in the risk of all-cause, liver- and drug-related mortality.
- Older age and cirrhosis were associated with higher risk of liver-related mortality.
- Younger age, injection drug use, and problematic alcohol use were associated with higher risk of drug-related mortality.

Authors

Naveed Z. Janjua, Stanley Wong, Younathan Abdia, …, Sofia Bartlett, Maria Alvarez, Mel Krajden

Correspondence

naveed.janjua@bccdc.ca
(N.Z. Janjua).

Lay summary

We assessed the effect of treatment of hepatitis C virus infection with direct-acting antiviral drugs on deaths from all causes, liver disease and drug use. We found that treatment with direct-acting antiviral drugs is associated with substantial lowering in risk of death from all causes, liver disease and drug use among people with hepatitis C virus infection.

https://doi.org/10.1016/j.jhep.2021.05.028

Research Article
Viral Hepatitis

JOURNAL OF HEPATOLOGY

Impact of direct-acting antivirals for HCV on mortality in a large population-based cohort study

Naveed Z. Janjua[1,2,*], Stanley Wong[1], Younathan Abdia[1,2], Dahn Jeong[2], Terri Buller-Taylor[1], Prince A. Adu[1,2], Hasina Samji[1,3], James Wilton[1], Margo Pearce[1,2], Zahid A. Butt[4], Amanda Yu[1], Mawuena Binka[1], Sofia Bartlett[1,5], Maria Alvarez[1], Mel Krajden[1,5]

[1]*British Columbia Centre for Disease Control, Vancouver, BC, Canada;* [2]*School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada;* [3]*Health Sciences, Simon Fraser University, Vancouver, BC, Canada;* [4]*School of Public Health and Health System, University of Waterloo, Waterloo, ON, Canada;* [5]*Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada*

Background & Aims: We evaluated the effect of direct-acting antiviral (DAA)-induced sustained virologic response (SVR) on all-cause, liver- and drug-related mortality in a population-based cohort in British Columbia, Canada.

Methods: We used data from the British Columbia Hepatitis Testers Cohort, which includes people tested for HCV since 1990, linked with data on medical visits, hospitalizations, prescription drugs and mortality. We followed people who received DAAs and people who did not receive any HCV treatment to death or December 31, 2019. We used inverse probability of treatment weighting to balance the baseline profile of treated and untreated individuals and performed multivariable proportional hazard modelling to assess the effect of DAAs on mortality.

Results: Our cohort comprised 10,851 people treated with DAAs (SVR 10,426 [96%], no-SVR: 425) and 10,851 matched untreated individuals. Median follow-up time was 2.2 years (IQR 1.3–3.6; maximum 6.2). The all-cause mortality rate was 19.5/1,000 person-years (PY) among the SVR group (deaths = 552), 86.5/1,000 PY among the no-SVR group (deaths = 96), and 99.2/1,000 PY among the untreated group (deaths = 2,133). In the multivariable model, SVR was associated with significant reduction in all-cause (adjusted hazard ratio [aHR] 0.19; 95% CI 0.17–0.21), liver- (adjusted subdistribution HR [asHR] 0.22, 95% CI 0.18–0.27) and drug-related mortality (asHR 0.26, 95% CI 0.21–0.32) compared to no-treatment. Older age and cirrhosis were associated with higher risk of liver-related mortality while younger age, injection drug use (IDU), problematic alcohol use and HIV/HBV co-infections were associated with a higher risk of drug-related mortality.

Conclusions: DAA treatment is associated with a substantial reduction in all-cause, liver- and drug-related mortality. The association of IDU and related syndemic factors with a higher risk of drug-related mortality calls for an integrated social support, addiction, and HCV care approach among people who inject drugs.

Lay summary: We assessed the effect of treatment of hepatitis C virus infection with direct-acting antiviral drugs on deaths from all causes, liver disease and drug use. We found that treatment with direct-acting antiviral drugs is associated with substantial lowering in risk of death from all causes, liver disease and drug use among people with hepatitis C virus infection.

Introduction

HCV infection is a major global health concern with about 71 million people living with the virus world-wide.[1] In North America, about two-thirds of chronic HCV infections are among people born between 1945–1965 who, having acquired the virus decades ago, are now increasingly being diagnosed with serious liver-related illnesses including decompensated cirrhosis and hepatocellular carcinoma (HCC).[2–4] In contrast, most (>80%) new HCV infections occur in people who inject drugs (PWID), many of whom also live with concurrent problematic alcohol use, mental illnesses, or HIV coinfection.[2,5,6] PWID with HCV infections are more likely to die from drug-related causes than liver-related causes.[7,8] We have recently reported that liver-related deaths among people with HCV infections have started to decline while drug-related deaths are increasing.[9] In recent years, the increase in drug-related deaths is related to the opioid overdose epidemic that is gripping North America, and many parts of Europe and Australia.[10–12]

Highly effective (~95% cured) and well-tolerated interferon-free direct-acting antiviral (DAA) agents represent a major breakthrough in the management of HCV.[13] DAAs are expected to reduce the high rate of end-stage liver disease and mortality. Data on the early effects of DAAs on all-cause mortality and HCC have started to emerge, with evidence of a significant reduction in these outcomes.[14–19] Available data are mainly derived from US veterans, who are 95% male and their risk profile may be different. Thus, these findings may not be generalizable to the general population.[15–17] In addition, the effect of DAAs on cause-specific mortality is not well known and not quantified. It is expected, as shown in recent studies from France and the US, that DAAs will prevent liver-related deaths. However, as

Keywords: Treatment effectiveness; Real-world; Population-based cohort; SVR; Hepatitis C; DAA.
Received 27 January 2021; received in revised form 11 May 2021; accepted 17 May 2021; available online 25 June 2021
* Corresponding author. Address: British Columbia Centre for Disease Control, 655 West 12th Avenue, Vancouver, BC V5Z 4R4, Canada; Tel.: 604-707-2514, fax: 604-707-2401.
E-mail address: naveed.janjua@bccdc.ca (N.Z. Janjua).
https://doi.org/10.1016/j.jhep.2021.05.028

highlighted above, a large number of deaths among young people with HCV are occurring due to drug overdoses. Engagement with HCV care and treatment may reduce drug-related harms among PWID living with HCV. However, the impact of HCV treatment on drug-related mortality is not known.

In this paper, we present data from a large population-based cohort in Canada to evaluate the effect of treatment with DAAs on all- cause, liver-and drug-related mortality risk.

Patients and methods

The cohort

The British Columbia (BC) Hepatitis Testers Cohort (BC-HTC) includes all individuals (~1.7 million) tested for HCV or HIV at the BC Centre for Disease Control Public Health Laboratory (BCCDC-PHL), or any individual reported to public health as a confirmed case of HCV, HBV, HIV/AIDS, since 1990. These data are integrated with data on medical visits, hospitalizations, prescription drugs, cancers and deaths (Table S1). More than 95% of HCV serology and all HCV RNA testing in BC are performed at the BCCDC-PHL. All dispensed prescriptions in BC including HCV treatments are recorded in a central system called PharmaNet and all deaths in BC are registered in the death registry. Details of the cohort creation and epidemiological characteristics have been reported previously.[2,20]

Study population, design and exposure

In this analysis, we included individuals who had a chronic HCV infection, defined as being tested positive for HCV RNA before treatment initiation or on their last available RNA measurement for untreated individuals. Individuals who filled at least 1 prescription of DAAs were considered to have received HCV treatment with DAAs. Physicians providing care made treatment decisions based on Canadian and American Association for the Study of Liver Disease (AASLD) Guidelines and drug coverage by PharmaCare. Untreated individuals never received any HCV treatment. People treated with only interferon-based treatments were excluded. The primary exposure of interest was treatment with DAAs compared to no-treatment. Treated individuals were further classified as people who achieved sustained virologic response (SVR) and people who did not. We defined SVR as undetectable serum HCV RNA at ≥10 weeks post treatment, with most people receiving SVR assessment ≥12 weeks after treatment.[21]

Outcome assessment

The main outcomes of interest were all-cause mortality, liver-related deaths and drug-related deaths. Assessments of deaths and cause of death were based on the BC Vital Statistics Registry, including data up to December 31, 2019 (Table S2).

Assessment of potential risk factors

We assessed potential risk factors for mortality including age, birth cohort, sex, HCV genotype, previous treatment, cirrhosis, coinfection with HIV, HBV, diabetes, heart failure, hypertension, chronic kidney disease, problematic alcohol use, injection drug use (IDU), major mental illness and material and social deprivation. We assessed multiple comorbidities through a composite comorbidity index, the Elixhauser index. [22] HIV and HBV diagnoses were based on laboratory confirmation or being reported as a confirmed case in the public health reportable disease database. IDU, mental illness, problematic alcohol use, diabetes, and cirrhosis were assessed using validated algorithms based on diagnostic codes and/or prescription drug records in administrative health datasets (Table S2).[23]

Statistical analysis

To avoid immortal time bias and ensure comparability between treated and untreated individuals, we used incidence density sampling to select the untreated group.[24] Specifically, we matched each treated individual with an untreated individual based on their first positive RNA test date. Person-time at risk started at the last treatment dispensation date (index date) for treated and matched untreated pairs and ended at death or end of follow-up (December 31, 2019), whichever occurred earlier. An inverse probability of treatment weighting (IPTW) approach was used to make the baseline profiles of treated and untreated groups comparable (confounding by indication).[25] Weights were calculated using a propensity score computed through a logistic regression model for HCV treatment receipt which included age, sex, year of HCV diagnosis, cirrhosis, diabetes, HIV, HBV, material derivation, IDU, and problematic alcohol use. The adequacy of weighting was assessed using standardized mean differences (Table S3), with a value <0.1 considered evidence of a balanced distribution.[25] We computed the mortality rate among people who achieved SVR, people who did not and untreated individuals and constructed survival curves comparing survival probability among the 3 groups. For liver- and drug-related mortality we computed cumulative incidence curves while accounting for competing mortality risk using the Fine & Grey approach.[26]

We used a Cox proportional hazards model to assess the effect of SVR compared to no-SVR on all-cause mortality. To assess the effect of SVR on liver- and drug-related mortality, we performed subdistribution proportional hazards modelling using the competing risk regression approach while accounting for other important covariates of interest.[26]

For evaluation of treatment impact on mortality in comparison to no-treatment, we performed proportional hazards modelling on the IPTW-weighted cohort, adjusting for important covariates to further account for any residual confounding.[25,27] Where proportionality assumptions were violated, we interpreted hazards ratios as an average effect over time and 95% CIs were computed through 10,000 bootstrap resamples.[28] The sensitivity analysis was restricted to people who had at least 1 year of post-treatment follow-up. Analyses were performed using SAS 9.4 and R.

Data Linkage to establish the BC-HTC was performed under the BCCDC's public health mandate. This study was reviewed and approved by the Behavioral Research Ethics Board at the University of British Columbia (H14-01649).

Results

Study cohort

During the study period, 74,095 people were diagnosed with HCV, of whom 40,419 were RNA positive. Overall, 20,712 received treatment and 12,311 were treated with DAAs. Of those who received DAA treatment, 10,851 were eligible for analysis after excluding 1,460 individuals with missing SVR, or inadequate follow-up. Of these 10,426 (96%) achieved SVR and 425 did not. This group was matched with 10,851 untreated individuals based on diagnosis date (Fig. S1).

Table 1. Participant of profile: individuals treated with DAAs by SVR status, untreated individuals and all.

Covariates	SVR n (%)	No-SVR n (%)	All treated n (%)	p value[a]	Untreated n (%)	All n (%)	p value[b]
N	10,426 (96)	425 (4)	10,851 (50)		10,851 (50)	21,702	
Previous treatment							
No	8,547 (82)	329 (77.4)	8,876 (81.8)	0.0168	10,851 (100)	19,727 (90.9)	<0.0001
Yes	1,879 (18)	96 (22.6)	1,975 (18.2)			1,975 (9.1)	
Birth year							
<1945	373 (3.6)	17 (4)	390 (3.6)	<0.0001	632 (5.8)	1,022 (4.7)	<0.0001
1945-1964	7,291 (69.9)	256 (60.2)	7,547 (69.6)		5,578 (51.4)	13,125 (60.5)	
1965-1974	1,723 (16.5)	84 (19.8)	1,807 (16.7)		2,558 (23.6)	4,365 (20.1)	
≥1975	1,039 (10)	68 (16)	1,107 (10.2)		2,083 (19.2)	3,190 (14.7)	
Age							
≤29	178 (1.7)	15 (3.5)	193 (1.7)	0.0007	476 (4.4)	669 (3.1)	<0.0001
30-39	609 (5.8)	38 (8.9)	647 (6)		1,213 (11.2)	1,830 (8.6)	
40-59	5,110 (49)	211 (49.6)	5,321 (49)		5,662 (52.2)	10,983 (50.6)	
≥60	4,529 (43.4)	161 (37.9)	4,690 (43.2)		3,500 (32.3)	8,190 (37.7)	
Median[IQR]	58[51-63]	56[47-62]	58[51-63]		54[45-62]	56[48-63]	
Sex							
Female	3,673 (35.2)	120 (28.2)	3,793 (34.9)	0.003	3,579 (33)	7,372 (34)	0.0022
Male	6,753 (64.8)	305 (71.8)	7,058 (65)		7,272 (67)	14,330 (66)	
Genotype							
1	6,933 (66.5)	250 (58.8)	7,183 (66.2)	<0.0001	4,608 (42.5)	11,791 (54.3)	<0.0001
2	1,078 (10.3)	33 (7.8)	1,111 (10.2)		873 (8)	1,984 (9.1)	
3	2,031 (19.5)	132 (31.1)	2,163 (19.9)		1,937 (17.9)	4,400 (18.9)	
Other/unknown	384 (3.7)	10 (2.4)	394 (3.6)		3,433 (31.6)	3,827 (17.6)	
Material deprivation							
Q1 (most privileged)	1,630 (15.6)	69 (16.2)	1,699 (15.6)	0.3468	1,496 (13.8)	3,195 (14.7)	<0.0001
Q2	1,745 (16.7)	63 (14.8)	1,808 (16.7)		1,439 (13.3)	3,247 (14.9)	
Q3	2,025 (19.4)	75 (17.6)	2,100 (19.4)		1,817 (16.7)	3,917 (18.1)	
Q4	2,318 (22.2)	88 (20.7)	2,406 (22.2)		2,359 (21.7)	4,765 (22)	
Q5 (most deprived)	2,583 (24.8)	123 (28.9)	2,706 (24.9)		3,392 (31.3)	6,098 (28.1)	
Unknown	125 (1.2)	7 (1.6)	132 (1.3)		348 (3.2)	480 (2.2)	
Social deprivation							
Q1 (most privileged)	1,082 (10.4)	39 (9.2)	1,121 (10.4)	0.0557	1,050 (9.7)	2,171 (10)	<0.0001
Q2	1,281 (12.3)	43 (10.1)	1,324 (12.2)		1,110 (10.2)	2,434 (11.2)	
Q3	1,740 (16.7)	65 (15.3)	1,805 (16.6)		1,430 (13.2)	3,235 (14.9)	
Q4	2,348 (22.5)	83 (19.5)	2,431 (22.4)		2,193 (20.2)	4,624 (21.3)	
Q5 (most deprived)	3,850 (36.9)	188 (44.2)	4,038 (37.2)		4,720 (43.5)	8,758 (40.3)	
Unknown	125 (1.2)	7 (1.6)	132 (1.3)		348 (3.2)	480 (2.2)	
Chronic kidney disease							
No	9,967 (95.6)	406 (95.5)	10,373 (95.6)	0.9465	10,409 (95.9)	20,782 (95.8)	0.2252
Yes	459 (4.4)	19 (4.5)	478 (4.4)		442 (4.1)	920 (4.2)	
Congestive heart failure							
No	10,096 (96.8)	407 (95.8)	10,503 (96.8)	0.2197	10,416 (96)	20,919 (96.4)	0.0015
Yes	330 (3.2)	18 (4.2)	348 (3.2)		435 (4)	783 (3.6)	
Coronary heart disease							
No	9,918 (95.1)	411 (96.7)	10,329 (95.2)	0.1361	10,421 (96)	20,750 (95.6)	0.0023
Yes	508 (4.9)	14 (3.3)	522 (4.8)		430 (4)	952 (4.4)	
Hypertension							
No	7,454 (71.5)	321 (75.5)	7,775 (71.7)	0.0704	8,686 (80)	16,461 (75.8)	<0.0001
Yes	2,972 (28.5)	104 (24.5)	3,076 (28.4)		2,165 (20)	5,241 (24.2)	
Cirrhosis							
No	9,538 (91.5)	366 (86.1)	9,904 (91.3)	0.0001	10,272 (94.7)	20,176 (92.9)	<0.0001
Yes	888 (8.5)	59 (13.9)	947 (8.7)		579 (5.3)	1,526 (7.1)	
Decompensated cirrhosis							
No	10,021 (96.1)	396 (93.2)	10,417 (96)	0.0024	10,460 (96.4)	20,877 (96.2)	0.1269
Yes	405 (3.9)	29 (6.8)	434 (4)		391 (3.6)	825 (3.8)	
HBV							
No	9,778 (93.8)	405 (95.3)	10,183 (93.8)	0.2045	10,294 (94.9)	20,477 (94.3)	0.0011
Yes	648 (6.2)	20 (4.7)	668 (6.2)		557 (5.1)	1,225 (5.7)	
HIV							
No	9,593 (92)	376 (88.5)	9,969 (91.9)	0.0089	10,341 (95.3)	20,310 (93.5)	<0.0001
Yes	833 (8)	49 (11.5)	882 (8.2)		510 (4.7)	1,392 (6.5)	
TB							
No	10,379 (99.5)	424 (99.8)	10,803 (99.6)	0.5117	10,772 (99.3)	21,575 (99.4)	0.0058
Yes	47 (0.5)	1 (0.2)	48 (0.4)		79 (0.7)	127 (0.6)	
Diabetes							
No	8,890 (85.3)	357 (84)	9,247 (85.2)	0.4705	9,682 (89.2)	18,929 (87.2)	<0.0001

(*continued on next page*)

Table 1. (*continued*)

Covariates	SVR n (%)	No-SVR n (%)	All treated n (%)	*p* value[a]	Untreated n (%)	All n (%)	*p* value[b]
Yes	1,536 (14.7)	68 (16)	1,604 (14.8)		1,169 (10.8)	2,773 (12.8)	
Injection drug use							
No	6,994 (67.1)	219 (51.5)	7,213 (66.5)	<0.0001	6,028 (55.6)	13,241 (61)	<0.0001
Yes	3,432 (32.9)	206 (48.5)	3,638 (33.5)		4,823 (44.4)	8,461 (39)	
Problematic alcohol use							
No	7,517 (72.1)	275 (64.7)	7,792 (71.8)	0.0009	7,246 (66.8)	15,038 (69.3)	<0.0001
Yes	2,909 (27.9)	150 (35.3)	3,059 (28.2)		3,605 (33.2)	6,664 (30.7)	
Mental illness							
No	6,934 (66.5)	248 (58.4)	7,182 (66.2)	0.0005	6,902 (63.6)	14,084 (64.9)	<0.0001
Yes	3,492 (33.5)	177 (41.6)	3,669 (33.8)		3,949 (36.4)	7,618 (35.1)	
Statins							
No	9,096 (87.2)	383 (90.1)	9,479 (87.3)	0.0805	9,795 (90.3)	19,274 (88.8)	<0.0001
Yes	1,330 (12.8)	42 (9.9)	1,372 (12.7)		1,056 (9.7)	2,428 (11.2)	
Elixhauser index							
No	4,221 (40.5)	115 (27.1)	4,360 (40)	<0.0001	4,381 (40.4)	8,717 (40.2)	0.5332
Yes	6,205 (59.5)	310 (72.9)	6,515 (60.1)		6,470 (59.6)	12,985 (59.8)	

DAA, direct-acting antiviral; SVR, sustained virologic response; TB, tuberculosis.
[a]Chi-square test for comparison between SVR and no-SVR group.
[b]Chi-square test for comparison between treated and untreated groups.

Participant profile

Compared to the SVR group, the no-SVR group were slightly younger (median age 56 *vs.* 58 years) and included a higher proportion who had: previously been treated (22.5% *vs.* 18.0%), cirrhosis (13.8% *vs.* 8.5%), a history of IDU (48.4% *vs.* 32.9%), problematic alcohol use (35.2% *vs.* 27.9%) and a higher frequency of comorbidities included in the Elixhauser index (72.8% *vs.* 59.5%) (Table 1).

Mortality rate by SVR

Overall, 96 deaths occurred during 924.7 PY of follow-up among people who did not achieve SVR, resulting in a mortality rate of 103.8/1,000 PY (95% CI 85.0–126.8). The mortality rate was substantially lower in the SVR group, in which 552 deaths occurred during 27,752.7 PY of follow-up, yielding a mortality rate of 19.9/1,000 PY (95% CI 18.3–21.6; Table 2). The mortality rate among people with cirrhosis was higher in both the no-SVR group and the SVR group (211.6/1,000 PY *vs.* 45.9/1,000 PY) compared to people with no cirrhosis (82.0/1,000 PY *vs.* 16.7/1,000 PY). Similar trends in mortality rates for liver- and drug-related mortality were observed, with significantly lower rates among people with SVR compared to no-SVR. However, in people without cirrhosis, drug-related mortality was slightly higher than liver-related mortality among people who achieved SVR, while much lower in people who did not achieve SVR. In people with cirrhosis, liver-related mortality was higher. Drug-related mortality rates were substantiality higher among people with a history of IDU compared to people with no IDU both in SVR (11.7/1,000PY *vs.* 1.5/1,000PY) and no-SVR (30.7/1,000PY *vs.* 7.4/1,000PY) groups.

Effect of SVR on mortality risk and impact of cirrhosis

In the multivariable model, the all-cause mortality risk was significantly lower among people with SVR compared to people with no-SVR (adjusted hazard ratio [aHR] 0.19; 95% CI 0.15–0.24). Results did not differ by cirrhosis status (Table 3). SVR was associated with an 87% reduction in liver-related mortality (adjusted subdistribution hazard ratio [asHR] 0.13; 95% CI 0.09–0.17), with a slightly lower reduction in those with cirrhosis compared to those without cirrhosis. SVR was also associated with a reduction in drug-related mortality (asHR 0.36; 95% CI 0.21–0.62).

Effect of SVR/treatment on mortality risk compared to no-treatment

The IPTW analysis included 10,851 treated individuals and 10,851 untreated individuals. Untreated individuals were younger (median age: 54 years *vs.* 58 years), were more materially deprived (5th quintile: 31.3% *vs.* 24.9%), had higher rates of IDU (44.4% *vs.* 33.5%) and problematic alcohol use (33.2% *vs.* 28.2%), but lower rates of cirrhosis (5.3% *vs.* 8.7%), HIV coinfection (8.2% *vs.* 4.7%), diabetes (10.8% *vs.* 14.8%) and other comorbidities. IPTW reduced the differences in characteristics between treated and untreated individuals as shown by standardized mean differences (Table S3). Median (IQR) duration of follow-up for people with SVR was 2.5 years (1.5–3.9; maximum 6.2), for the no-SVR group 1.8 years (1.0–3.2; maximum 5.6) and for the untreated group 1.9 years (1.1–3.3; maximum 5.9).

Mortality rates

Untreated individuals had higher all-cause (99.2/1,000PY *vs.* 19.5/1,000PY), liver- (25.0/1,000PY *vs.* 5.7/1,000PY) and drug-related (23.0/1,000PY *vs.* 5.0/1,000PY) mortality rates compared to people who achieved SVR. Among people without cirrhosis, drug-related mortality rates were higher compared to liver-related mortality among those with SVR (5.1/1,000PY *vs.* 3.4/1,000PY) and those untreated (22.0 *vs.* 15.2). However, among people with no-SVR and those with cirrhosis, liver-related mortality was higher than drug-related mortality (Table 2).

Kaplan Meier survival curves for all-cause mortality showed significantly higher survival and cumulative incidence curves for liver-related mortality showed lower mortality among people with SVR compared to people with no-SVR and people who had not yet received treatment (Fig 1A). As expected, there was a steeper decline in survival among people with cirrhosis, and the decline was steeper among people with no-SVR and no-treatment (Fig 1B). Similarly, there was steeper increase in cumulative incidence of liver-related mortality for the no-SVR and no-treatment group in people with cirrhosis (Fig. 1C,D). There was an increase in drug-related mortality among all groups over

Table 2. Mortality rate among treated individuals by SVR status and those among IPTW matched treatment and untreated individuals by SVR status.

	SVR		No-SVR		Untreated	
	n/PY	MR (95%CI)	n/PY	MR (95%CI)	n/PY	MR (95%CI)
SVR *vs.* no-SVR						
All-cause mortality	552/27752.7	19.9 (18.3–21.6)	96/924.7	103.8 (85–126.8)		
Liver-related mortality	163/27752.7	5.9 (5–6.8)	54/924.7	58.4 (44.7–76.2)		
Drug-related mortality	125/27752.7	4.5 (3.8–5.4)	16/924.7	17.3 (10.6–28.2)		
Without cirrhosis						
All-cause mortality	412/24704	16.7 (15.1–18.4)	63/768.7	82 (64–104.9)		
Liver-related mortality	84/24704	3.4 (2.7–4.2)	27/768.7	35.1 (24.1–51.2)		
Drug-related mortality	114/24704	4.6 (3.8–5.5)	15/768.7	19.5 (11.8–32.4)		
With cirrhosis						
All-cause mortality	140/3048.7	45.9 (38.9–54.2)	33/156	211.6 (150.4–297.6)		
Liver-related mortality	79/3048.7	25.9 (20.8–32.3)	27/156	173.1 (118.7–252.5)		
Drug-related mortality	11/3048.7	3.6 (2–6.5)	1/156	6.4 (0.9–45.5)		
Treated *vs.* untreated IPTW[a]						
All-cause mortality	552/27752.7	19.5 (17.9–21.3)	96/924.7	86.5 (69.6–107.7)	2133/23625.1	99.2 (95.2–103.3)
Liver-related mortality	163/27752.7	5.7 (4.8–6.6)	54/924.7	45.7 (33.8–61.7)	505/23625.1	25.0 (23.1–27.1)
Drug-related mortality	125/27752.7	5.0 (4.2–5.9)	16/924.7	15.7 (9.4–26.2)	583/23625.1	23.0 (21.1–25.0)
Without cirrhosis						
All-cause mortality	412/24704	16.7 (15.1–17.3)	63/768.7	77.6 (60.9–98.8)	1799/22768.3	84.6 (80.8–88.5)
Liver-related mortality	84/24704	3.4 (2.8–4.2)	27/768.7	35.6 (24.9–51.0)	319/22768.3	15.2 (13.7–16.9)
Drug-related mortality	114/24704	5.1 (4.2–6.0)	15/768.7	16.7 (9.9–28.2)	541/22768.3	22.0 (20.2–24.1)
With cirrhosis						
All-cause mortality	140/3048.7	48.1 (40.2–57.6)	33/156	172.6 (104.3–285.5)	334/856.8	387.7 (353.0–425.8)
Liver-related mortality	79/3048.7	27.8 (22.0–35.2)	27/156	142.2 (81.7–247.5)	186/856.8	218.4 (192.8–247.5)
Drug-related mortality	11/3048.7	4.1 (2.2–7.6)	1/156	5.5 (0.3–91.9)	42/856.8	41.8 (31.4–55.6)

IPTW, inverse probability of treatment weighting; MR, mortality rate; PY, person-years; SVR, sustained virologic response.
[a]Rates are based on IPTW cohort while deaths and person time is based unweighted sample.

time, but the increase was steeper among the no-SVR and no-treatment groups (Fig. 1E). Similarly, drug-related mortality was higher among PWID and the increase was steeper (Fig. 1F).

Effect of SVR on mortality risk compared to no-treatment

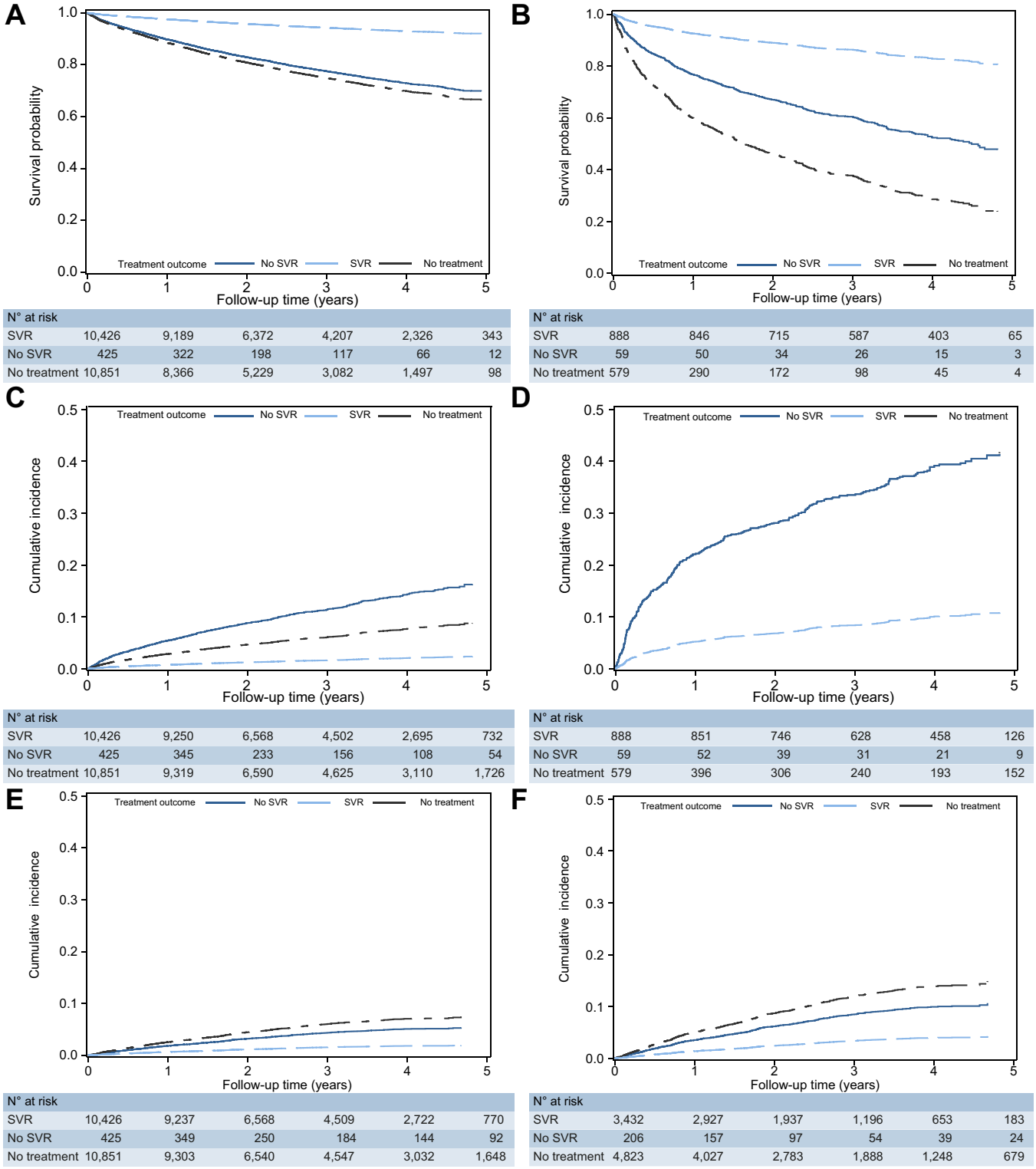
Compared to untreated individuals in multivariable hazards model, SVR was associated with significant reductions in all-cause (aHR 0.19; 95% CI 0.17–0.21), liver-related (asHR 0.22; 95% CI 0.18–0.27) and drug-related mortality risk (asHR 0.26; 95% CI 0.21–0.32). Compared to no-treatment, no-SVR was associated with significantly higher liver-related mortality risk (asHR 1.53; 95% CI 1.08–2.17), while the relationship with all-cause and drug-related mortality was not significant. The effect of SVR was similar in people with and without cirrhosis (Table 3 and Table S3).

Other factors associated with increased all-cause mortality risk were cirrhosis at treatment initiation (aHR 2.18; 95% CI 1.99–2.65), older age (40-59 years aHR 1.42; 95% CI 1.08–1.93; ≥60 years aHR 2.21; 95% CI 1.68–3.03 compared to ≤29 years), being male (aHR 1.35; 95% CI 1.23–1.48), HIV coinfection (aHR 1.58; 95% CI 1.35–1.85), and problematic alcohol use (aHR 1.34; 95% CI 1.22–1.48). There were some notable differences in factors associated with liver-related and drug-related mortality. Cirrhosis was associated with a higher risk of liver-related mortality (asHR 6.79; 95% CI 5.71–8.07) while IDU was associated with a significantly higher risk of drug-related mortality (asHR

Table 3. Multivariable models for effect of SVR on all-cause, liver- and drug-related mortality by treatment and cirrhosis status.[a]

	All	Without cirrhosis	With cirrhosis
	Adjusted (s)HR (95%CI)	Adjusted (s)HR (95%CI)	Adjusted (s)HR (95%CI)
Treated individuals: SVR *vs.* no-SVR			
All-cause mortality	0.19 (0.15–0.24)	0.19 (0.14–0.25)	0.19 (0.13–0.29)
Liver-related mortality	0.13 (0.09–0.17)	0.08 (0.05–0.13)	0.16 (0.10–0.25)
Drug-related mortality	0.36 (0.20–0.62)	0.34 (0.19–0.60)	NE
Treated (SVR and no-SVR) *vs.* untreated IPTW-weighted			
SVR			
All-cause mortality	0.19 (0.17–0.21)	0.19 (0.16–0.21)	0.17 (0.13–0.21)
Liver-related mortality	0.22 (0.18–0.27)	0.21 (0.16–0.28)	0.22 (0.16–0.30)
Drug-related mortality	0.26 (0.21–0.32)	0.26 (0.21–0.32)	0.29 (0.14–0.57)
No-SVR			
All-cause mortality	0.86 (0.68–1.07)	0.92 (0.69–1.18)	0.63 (0.39–0.92)
Liver-related mortality	1.53 (1.08–2.17)	2.22 (1.48–3.32)	0.92 (0.53–1.60)
Drug-related mortality	0.75 (0.44–1.27)	0.76 (0.44–1.30)	0.91 (0.04–20.17)

Adjusted (s)HR, adjusted hazard ratio computed for all-cause mortality and subdistribution hazard ratio computed for liver- and drug-related mortality through Fine & Grey competing risk models; IPTW, inverse probability of treatment weighting; NE, not estimated due to small sample size; SVR, sustained virologic response.
[a]Adjusted for: age, sex, genotype, previous treatment, cirrhosis status (except for stratified models), material deprivation, HBV, HIV, diabetes, problematic alcohol use, injection drug use, mental illness, statin, chronic kidney disease, hypertension, health failure, and Exlihauser comorbidity index.



N° at risk						
SVR	10,426	9,189	6,372	4,207	2,326	343
No SVR	425	322	198	117	66	12
No treatment	10,851	8,366	5,229	3,082	1,497	98

N° at risk						
SVR	888	846	715	587	403	65
No SVR	59	50	34	26	15	3
No treatment	579	290	172	98	45	4

N° at risk						
SVR	10,426	9,250	6,568	4,502	2,695	732
No SVR	425	345	233	156	108	54
No treatment	10,851	9,319	6,590	4,625	3,110	1,726

N° at risk						
SVR	888	851	746	628	458	126
No SVR	59	52	39	31	21	9
No treatment	579	396	306	240	193	152

N° at risk						
SVR	10,426	9,237	6,568	4,509	2,722	770
No SVR	425	349	250	184	144	92
No treatment	10,851	9,303	6,540	4,547	3,032	1,648

N° at risk						
SVR	3,432	2,927	1,937	1,196	653	183
No SVR	206	157	97	54	39	24
No treatment	4,823	4,027	2,783	1,888	1,248	679

Fig. 1. The survival curves by treatment status. All-cause mortality (A) overall and (B) for those with cirrhosis; cumulative incidence of liver-related mortality (C) overall and (D) for those with cirrhosis; and drug-related mortality (E) overall and (F) for people who inject drugs. SVR, sustained virologic response.

3.35; 95% CI 2.68–4.19). In addition, older age was associated with higher liver-related mortality while younger age was associated with higher drug-related mortality (Table 4).

In the analysis restricted to people with at least 1 year of follow-up post-treatment, the effect of SVR compared to no-treatment was smaller for all-cause (aHR 0.37; 95% CI

Table 4. Factors associated with all-cause, liver- and drug-related mortality among people treated with DAAs compared to untreated individuals, weighted by inverse probability of treatment.

	All-cause mortality	Liver-related mortality	Drug-related mortality
Covariate	**aHR (95%CI)**	**asHR (95%CI)**	**asHR (95%CI)**
Treatment	n = 21,702	n = 21,702	n = 21,702
Not treated	Ref.	Ref.	Ref.
Treated without SVR	0.86 (0.68–1.07)	1.53 (1.08–2.17)	0.75 (0.44–1.27)
Treated with SVR	0.19 (0.17–0.21)	0.22 (0.18–0.27)	0.26 (0.0.21–0.32)
Previous treatment	0.93 (0.77–1.11)	0.95 (0.69–1.30)	0.60 (0.36–1.00)
Age (years)[a]			
≤29	Ref.		1.76 (1.15–2.70)
30-39	0.77 (0.55–1.09)	Ref.	Ref.
40-59	1.42 (1.08–1.93)	14.63 (4.66–45.91)	1.34 (1.03–1.76)
≥60	2.21 (1.68–3.03)	26.19 (8.31–82.59)	0.46 (0.32–0.65)
Sex, male	1.35 (1.23–1.48)	1.34 (1.13–1.58)	1.75 (1.47–2.09)
Genotype			
GT1	Ref.	Ref.	Ref.
GT2	0.92 (0.79–1.06)	0.89 (0.68–1.16)	0.87 (0.63–1.21)
GT3	1.02 (0.91–1.14)	1.21 (1.00–1.47)	0.98 (0.81–1.19)
Unknown/others	0.96 (0.86–1.06)	0.87 (0.71–1.06)	0.78 (0.64–0.96)
Material deprivation			
Q1 (most privileged)	Ref.	Ref.	Ref.
Q2	0.99 (0.86–1.16)	1.31 (0.99–1.75)	0.84 (0.63–1.12)
Q3	0.94 (0.81–1.09)	1.23 (0.93–1.62)	0.72 (0.54–0.95)
Q4	0.99 (0.86–1.13)	1.26 (0.96–1.65)	0.87 (0.67–1.11)
Q5 (most deprived)	1.01 (0.88–1.15)	1.43 (1.11–1.86)	0.96 (0.77–1.20)
Unknown	0.68 (0.47–0.95)	0.47 (0.21–1.04)	1.18 (0.71–1.95)
Cirrhosis	2.18 (1.99–2.65)	6.79 (5.71–8.07)	1.19 (0.89–1.60)
HBV	1.18 (1.00–1.38)	0.67 (0.48–0.95)	1.27 (0.99–1.62)
HIV	1.58 (1.35–1.85)	1.04 (0.74–1.44)	1.62 (1.31–2.00)
Diabetes	1.12 (1.00–1.26)	1.13 (0.94–1.37)	0.96 (0.73–1.26)
Injection drug use	1.12 (1.01–1.24)	0.76 (0.63–0.92)	3.35 (2.68–4.19)
Problematic alcohol use	1.34 (1.22–1.48)	1.28 (1.08–1.53)	1.32 (1.11–1.57)
Mental illness	1.05 (0.96–1.15)	0.76 (0.64–0.91)	1.15 (0.97–1.36)
Statins	1.06 (0.93–1.21)	1.04 (0.84–1.29)	0.81 (0.58–1.13)
Elixhauser comorbidity index	1.95 (1.73–2.20)	1.74 (1.41–2.15)	1.03 (0.82–1.29)
Chronic kidney disease	1.38 (1.18–1.63)	0.82 (0.62–1.09)	1.31 (0.94–1.84)
Heart failure	1.87 (1.60–2.18)	0.99 (0.76–1.30)	1.22 (0.82–1.81)
Hypertension	1.34 (1.20–1.48)	1.13 (0.95–1.34)	1.19 (0.95–1.49)

Model: Weighted using stabilized IPTW. aHR, adjusted hazard ratio; asHR, adjusted subdistribution hazard ratio based on Fine & Grey competing risk model; IPTW, inverse probability of treatment weighting; SVR, sustained virologic response.
[a]Reference for liver-related mortality <40 years.

0.31–0.41), liver-related (asHR 0.47; 95% CI 0.37–0.60), and drug-related (asHR 0.45; 95% CI 0.35–0.58) mortality.

Discussion

In this large general population Canadian cohort, we assessed the effect of DAA-induced SVR on mortality risk. This is the first study to evaluate the effectiveness of DAAs on liver- and drug-related mortality from a population-based cohort with more than 5 years of follow-up. We found that SVR from DAAs compared to no-treatment is associated with an 81% reduction in all-cause mortality, a 78% reduction in liver-related, and a 74% reduction in drug-related mortality risk. Within the treated group, SVR compared to no-SVR was associated with slightly higher reduction in all-cause (81%), and liver-related mortality (87%), but a lower reduction in drug-related (64%) mortality risk. The reduction in mortality risk was lower among people with cirrhosis. Cirrhosis and older age (≥40 years) was associated with higher liver-related mortality risk while IDU, younger age, problematic alcohol use, and HIV/HBV co-infections were associated with higher drug-related mortality risk. These findings indicate that DAAs will have a major impact on reducing mortality risk among people living with HCV; however, people with substance use disorder and HCV will need further integrated support services to reduce drug-related harms to maintain the benefits achieved through curative DAAs.

Few studies have assessed the effect of DAAs compared to no-treatment and SVR compared to no-SVR on all-cause and liver-related mortality.[17,18,29–31] Design and comparison groups differ across studies. Our findings on the impact of SVR from DAAs on all-cause and liver-related mortality are consistent with some studies, while a relatively lower reduction was reported in other studies. Our study had the longest follow-up time among studies published so far and is a population-based cohort, while most other studies were based on specific populations or cohorts. In a study among US veterans, treatment (DAA and interferon) compared to no-treatment was associated with a 75% reduction in mortality while SVR (DAA and interferon) *vs.* no-SVR was associated with 90% reduction in mortality.[30] In an earlier study among US veterans, SVR compared to no-treatment was associated with a 68% reduction in all-cause mortality (aHR 0.32; 95% CI 0.29–0.36), while SVR compared to no-SVR was associated with a lower reduction than in our study (aHR 0.44; 95% CI 0.32–0.59).[29] In Scotland, SVR compared to no-SVR was associated with a 87% reduction in liver-related death (aHR 0.13; 95% CI

0.05–0.34), and a 70% reduction in all-cause mortality (aHR 0.30; 95% CI 0.12–0.76) among those with cirrhosis.[32]

However, DAA treatment compared to no-treatment in a French cohort was associated with a lower reduction in all-cause (aHR 0.48; 95% CI 0.33–0.70) and liver-related (aHR 0.39; 95% CI 0.21–0.71) mortality.[18] Similar findings of lower all-cause mortality reduction have been reported from Medicare beneficiaries from the US (without cirrhosis aHR 0.51; 95% CI 0.46–0.57).[31] None of these studies assessed the impact of treatment and SVR on drug-related mortality, which is a critical issue among people with HCV in Canada, the US and many other countries.[10–12] Overall, our findings indicate a significant impact of DAAs on mortality.

SVR compared to no-treatment was associated with reduced drug-related mortality. The impact of HCV treatment on drug-related mortality has not been evaluated before. IDU was the strongest factor associated with drug-related mortality, in addition to younger age, problematic alcohol use, HIV and HBV co-infection. This highlights the presence of a syndemic of substance use and bloodborne infections associated with high drug-related mortality.[33] It is postulated that engagement in HCV care and treatment is expected to provide more stability to people who use substances and could have resulted in reduced drug-related mortality. Previous studies have shown a reduction or stability in drug and alcohol use behaviour following HCV treatment.[34] Some of the impact of HCV treatment could be related to HCV care that is accompanied by social support, mental health support and care targeted at substance use disorders. In BC, many care providers who provide HCV treatment to PWID incorporate a more comprehensive model including social support and addiction care.[35,36] On the other hand, engagement in HCV care and treatment could also be related to overall life stability and readiness for treatment, which may be contributing to decreased drug-related mortality.[37] Further studies are needed to understand the role of specific behavioural, pharmacological and care related factors associated with reduce drug-related mortality.

Our results indicate that cirrhosis at treatment initiation, older age and problematic alcohol use are significantly associated with a higher risk of liver-related mortality. Treatment of HCV before the development of cirrhosis will be necessary to substantially reduce the future risk of liver-related mortality. Canada and many developed countries have recently removed fibrosis-based restrictions on treatment coverage, however, treatment uptake needs to be scaled up quickly to realize the full benefits of DAAs in reducing mortality.[38]

The assessment of risk factors such as cirrhosis, problematic alcohol consumption and diabetes was based on diagnostic codes, as in other similar studies, which could lead to misclassification of these conditions. [15,16] To make these definitions more specific and reduce misclassification, we required at least 1 hospitalization or 2 medical visits and/or prescription drugs specific to the condition such as anti-diabetic medications to define these conditions.

In conclusion, in this large population-based cohort of HCV treated and untreated individuals, we showed that SVR from DAAs is associated with substantial reduction in the risk of all-cause and liver- and drug-related mortality. The reduction of liver-related mortality risk post-treatment was lower among people with cirrhosis, indicating an urgent need for early treatment and scaling-up of treatment programmes to fully realize the benefits of DAAs. IDU, problematic alcohol use, and co-infection with HIV or HBV were associated with a higher risk of drug-related mortality, highlighting the need for service integration to improve the overall well-being and survival of people with substance use disorder.

Abbreviations

aHR, adjusted hazard ratio; asHR, adjusted subdistribution hazard ratio; BC, British Columbia; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; IDU, injection drug use; IPTW, inverse probability of treatment weighting; PWID, people who inject drugs; PY, person-years; SVR, sustained virologic response.

Financial support

This work was supported by BC Centre for Disease Control and the Canadian Institutes of Health Research [Grant # NHC-348216, PHE-337680, and PJT-156066].

Conflict of interest

MK has received grant funding via his institution from Roche Molecular Systems, Boehringer Ingelheim, Merck, Siemens Healthcare Diagnostics and Hologic Inc. SB has advised and spoken for Gilead Sciences (all personal payments given as unrestricted donations to BC Centre for Disease Control Foundation for Public Health).

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

NJ conceived the analysis presented in this paper. NJ, SW, YA, MK participated in the study design. NJ guided the statistical analysis performed by SW and YA. NJ wrote the first draft and incorporated revisions. All authors contributed in the interpretation of results, manuscript preparation and revisions. All authors read and approved the final manuscript.

Data availability statement

The study is based on data contained in various provincial registries and databases. Access to data could be requested through the BC Centre for Disease Control Institutional Data Access for researchers who meet the criteria for access to confidential data. Requests for the data may be sent to datarequest@bccdc.ca.

Acknowledgements

We acknowledge the assistance of BCCDC, PHSA Data Analytics Reporting & Evaluation (DARE), Information Analysts, Ministry of Health Data Access, Research and Stewardship, & MSP, DAD and Medical Beneficiary and Pharmaceutical Services programme areas, BC Ministry of Health, and BC Cancer and their staff involved in data access and procurement, and data management. All inferences, opinions, and conclusions drawn in this publication are those of the author (s), and do not necessarily reflect the opinions or policies of the [British Columbia] Ministry of Health.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.05.028.

References

[1] Blach S, Zeuzem S, Manns M, Altraif I, Duberg A-S, Muljono DH, et al. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol 2017;2:161–176.

[2] Janjua NZ, Yu A, Kuo M, Alvarez M, Cook D, Wong J, et al. Twin epidemics of new and prevalent hepatitis C infections in Canada: BC Hepatitis Testers Cohort. BMC Infect Dis 2016;16:334.

[3] Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Ward JW. Hepatitis C virus testing of persons born during 1945-1965: recommendations from the Centers for Disease Control and Prevention. Ann Intern Med 2012;157:817–822.

[4] Beste LA, Leipertz SL, Green PK, Dominitz JA, Ross D, Ioannou GN. Trends in burden of cirrhosis and hepatocellular carcinoma by underlying liver disease in US veterans, 2001-2013. Gastroenterology 2015;149. 1471-1482.e1475; quiz e1417-1478.

[5] Butt ZA, Shrestha N, Wong S, Kuo M, Gesink D, Gilbert M, et al. A syndemic approach to assess the effect of substance use and social disparities on the evolution of HIV/HCV infections in British Columbia. PLoS One 2017;12: e0183609.

[6] Kuo M, Janjua NZ, Burchell AN, Buxton JA, Krajden M, Gilbert M. Decreasing hepatitis C incidence among a population with repeated tests: British Columbia, Canada, 1993-2011. Am J Public Health 2015;105:1604–1610.

[7] Yu A, Spinelli JJ, Cook DA, Buxton JA, Krajden M. Mortality among British Columbians testing for heaptitis C antibody. BMC public health 2013;13.

[8] Samji H, Yu A, Wong S, Wilton J, Binka M, Alvarez M, et al. Drug-related deaths in a population-level cohort of people living with and without hepatitis C virus in British Columbia, Canada. Int J Drug Pol 2020;86:102989.

[9] Krajden M, Cook DA, Wong S, Yu A, Butt ZA, Rossi C, et al. What is killing people with hepatitis C virus infection? Analysis of a population-based cohort in Canada. Int J Drug Pol 2019;72:114–122.

[10] Ahmad FB, Rossen LM, Sutton P. Provisional Drug Overdose Death Counts. Atlanta, GA: National Centre for Health Statistics, Centres for Disease Control and Prevention; 2020.

[11] National Statistics. Drug-related deaths in Scotland in 2019. Scotland: National Records of Scotland; 2020.

[12] Special Advisory Committee on the Epidemic of Opioid Overdoses. Opioids and stimulant-related Harms in Canada. Ottawa: Public Health Agency of Canada; 2020.

[13] Janjua NZ, Darvishian M, Wong S, Yu A, Rossi C, Ramji A, et al. Effectiveness of ledipasvir/sofosbuvir and sofosbuvir/velpatasvir in people who inject drugs and/or those in opioid agonist therapy. Hepatol Commun 2019;3(4):478–492.

[14] Janjua NZ, Wong S, Darvishian M, Butt ZA, Yu A, Binka M, et al. The impact of SVR from direct-acting antiviral- and interferon-based treatments for HCV on hepatocellular carcinoma risk. J Viral Hepat 2020;27:781–793.

[15] Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. J Hepatol 2018;68(1):25–32.

[16] Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. Gastroenterology 2017;153:996–1005 e1001.

[17] Backus LI, Belperio PS, Shahoumian TA, Mole LA. Impact of sustained virologic response with direct-acting antiviral treatment on mortality in patients with advanced liver disease. Hepatology 2019;69:487–497.

[18] Carrat F, Fontaine H, Dorival C, Simony M, Diallo A, Hezode C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. Lancet 2019;393:1453–1464.

[19] Nahon P, Layese R, Bourcier V, Cagnot C, Marcellin P, Guyader D, et al. Incidence of hepatocellular carcinoma after direct antiviral therapy for HCV in patients with cirrhosis included in surveillance programs. Gastroenterology 2018;155:1436–1450 e1436.

[20] Janjua NZ, Kuo M, Chong M, Yu A, Alvarez M, Cook D, et al. Assessing hepatitis C burden and treatment effectiveness through the British Columbia hepatitis Testers cohort (BC-HTC): design and characteristics of linked and unlinked participants. PloS one 2016;11:e0150176.

[21] Myers RP, Ramji A, Bilodeau M, Wong S, Feld JJ. An update on the management of hepatitis C: consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol = J canadien de gastroenterologie 2012;26:359–375.

[22] Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130–1139.

[23] Janjua NZ, Islam N, Kuo M, Yu A, Wong S, Butt ZA, et al. Identifying injection drug use and estimating population size of people who inject drugs using healthcare administrative datasets. Int J Drug Pol 2018;55:31–39.

[24] Karim ME, Gustafson P, Petkau J, Tremlett H, et al. Long-Term Benefits and Adverse Effects of Beta-Interferon for Multiple Sclerosis (BeAMS) Study Group. Comparison of statistical approaches for dealing with immortal time bias in drug effectiveness studies. Am J Epidemiol 2016;184:325–335.

[25] Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015;34:3661–3679.

[26] Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.

[27] Nguyen TL, Collins GS, Spence J, Devereaux PJ, Daures JP, Landais P, et al. Comparison of the ability of double-robust estimators to correct bias in propensity score matching analysis. A Monte Carlo simulation study. Pharmacoepidemiol Drug Saf 2017;26:1513–1519.

[28] Stensrud MJ, Hernan MA. Why test for proportional hazards? JAMA : J Am Med Assoc 2020;323:1401–1402.

[29] Backus LI, Belperio PS, Shahoumian TA, Mole LA. Direct-acting antiviral sustained virologic response: impact on mortality in patients without advanced liver disease. Hepatology 2018;68:827–838.

[30] Butt AA, Yan P, Shaikh OS, Lo Re 3rd V, Abou-Samra AB, Sherman KE. Treatment of HCV reduces viral hepatitis-associated liver-related mortality in patients: an ERCHIVES study. J Hepatol 2020;73:277–284.

[31] Kalidindi Y, Jung J, Feldman R, Riley 3rd T. Association of direct-acting antiviral treatment with mortality among medicare beneficiaries with hepatitis C. JAMA Netw open 2020;3:e2011055.

[32] McDonald SA, Pollock KG, Barclay ST, Goldberg DJ, Bathgate A, Bramley P, et al. Real-world impact following initiation of interferon-free hepatitis C regimens on liver-related outcomes and all-cause mortality among patients with compensated cirrhosis. J viral Hepat 2020;27: 270–280.

[33] Butt ZA, Wong S, Rossi C, Binka M, Wong J, Yu A, et al. Concurrent hepatitis C and B virus and human immunodeficiency virus infections are associated with higher mortality risk illustrating the impact of syndemics on health outcomes. Open Forum Infect Dis 2020;7(9):ofaa347.

[34] Artenie AA, Cunningham EB, Dore GJ, Conway B, Dalgard O, Powis J, et al. Patterns of drug and alcohol use and injection equipment sharing among people with recent injecting drug use or receiving opioid agonist treatment during and following hepatitis C virus treatment with direct-acting antiviral therapies: an international study. Clin Infect Dis 2020;70:2369–2376.

[35] Holeksa J, Magel T, Alimohammadi A, Thiam A, Yung R, Chu L, et al. Low rate of reinfection among a cohort of people who use drugs successfully treated for hepatitis C virus infection in Vancouver, Canada. Int J Drug Pol 2019;72:177–180.

[36] Selfridge M, Cunningham EB, Milne R, Drost A, Barnett T, Lundgren K, et al. Direct-acting antiviral treatment for hepatitis C, reinfection and mortality among people attending an inner-city community health centre in Victoria, Canada. Int J Drug Pol 2019;72:106–113.

[37] Madden A, Hopwood M, Neale J, Treloar C. Beyond interferon side effects: what residual barriers exist to DAA hepatitis C treatment for people who inject drugs? PloS one 2018;13:e0207226.

[38] Binka M, Janjua NZ, Grebely J, Estes C, Schanzer D, Kwon JA, et al. Assessment of treatment strategies to achieve hepatitis C elimination in Canada using a validated model. JAMA Netw open 2020;3:e204192.