Research Paper

What is killing people with hepatitis C virus infection? Analysis of a population-based cohort in Canada

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ABSTRACT

Background: Persons with hepatitis C virus (HCV) infection are at risk of mortality from both chronic liver disease and HCV acquisition risk activities. We compared causes of death among HCV positive and negative individuals to characterize contributions of acquisition risks and viral sequelae.
Methods: The British Columbia (BC) Hepatitis Testers Cohort (BC-HTC) includes all individuals tested for HCV or reported as a HCV case since 1992, linked to health administrative data. ICD-10 codes were used to classify deaths as: 1) liver-related (LR); 2) HCV acquisition risk-related (AR); and 3) other causes. Mortality proportions and trends were assessed among HCV positive and negative individuals overall and by birth cohort (born < 1945, 1945–64 and ≥1965).
Results: As of December 31, 2018, of 1,300,204 HCV-tested individuals, 20,049 (27.5%) HCV positive and 132,999 (10.2%) HCV negative individuals had died (median age at death: 56.4 vs. 74.5 years, respectively). HCV positive individuals were more likely than negatives to die from both AR (24.7%/4.2%) and LR (23.4%/6.2%) causes. Deaths among older HCV positive individuals were more likely to be LR while younger individuals were more likely AR: 1) birth cohort < 1945 (25.3%/2.7%); 2) 1945–64 (26.5%/23.7%) and ≥1965 (7.7%/59.9%). Among HCV positives, LR mortality increased from 1992 to 2014, then declined sharply, coinciding with the introduction and uptake of direct-acting antiviral drugs. AR mortality increased from 1992 to 2000, declined slowly until 2013, then rapidly increased, coinciding with the recent surge in opioid overdose deaths.
Conclusions: Curative HCV treatments reduce LR mortality, but typically will not impact AR mortality. This will need to be addressed if the World Health Organization 2030 HCV mortality reduction goals are to be achieved.

Introduction

Hepatitis C virus (HCV) infection is a major cause of morbidity and mortality. Worldwide, in 2015, an estimated 71 million people were chronically HCV infected (The Polaris Observatory, 2017). Without treatment, 399,000–490,000 are estimated to die annually, most from decompensated cirrhosis and liver cancer (Naghavi, Abajobir, & Abbafati, 2017; World Health Organization, 2017). In Canada in 2011, an estimated 230,000 to 450,000 individuals (0.66%–1.3%) had chronic HCV infection (Trubnikov, Yan, & Archibald, 2014), and British Columbia (BC) has a ˜50% higher HCV prevalence than the rest of Canada (BC Centre for Disease Control, 2017). About 25% of infected individuals clear HCV spontaneously (Alter, Kruszon-Moran, & Nainan, 1999; Islam, Krajden, & Gilbert, 2017) and these individuals are not at

risk of HCV-related chronic liver disease (Hajarizadeh, Grebely, & Dore, 2013). Of those who develop chronic infection, over decades approximately 20% will develop cirrhosis, end-stage liver disease, and hepatocellular carcinoma (Thein, Yi, & Dore, 2008).

Most new HCV infections in developed countries occur among people who inject drugs (PWID), whose HCV acquisition risk activities may result in mortality unrelated to HCV (Alavi, Grebely, & Hajarizadeh, 2018; Innes, McAuley, & Alavi, 2017; Janjua, Yu, & Kuo, 2016; Yu, Spinelli, & Cook, 2013). There is also a high HCV disease burden among "baby boomers", i.e., those born 1945–1964, many of whom acquired infection decades ago from injection drug use, contaminated blood products or iatrogenic transmission (Janjua, Yu et al., 2016; Joy, McCloskey, & Nguyen, 2016; Remis, 2007). Most baby boomers no longer engage in transmission risk activities, but if

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untreated, are at risk of dying prematurely from HCV-related liver disease (Backus, Belperio, Shahoumian, & Mole, 2017; Backus, Belperio, Shahoumian, & Mole, 2018; Janjua, Wong, & Rossi, 2018; Krajden, Cook, & Rossi, 2018).

Achieving a treatment-induced sustained virological response (SVR) reduces morbidity and mortality and improves quality of life (Backus et al., 2018, 2019; Janjua, Chong, & Kuo, 2017). Highly tolerated and effective direct acting antiviral (DAA) medications with SVR rates exceeding 95% (Hézode, 2018) prompted the World Health Organization (WHO) to issue its 2030 global viral hepatitis elimination strategy (World Health Organization, 2016), which aims to reduce HCV incidence by 90% and HCV-related mortality by 65%. DAA treatment is also expected to reduce HCV transmissions by reducing the pool of chronically infected individuals (Harris, Martin, & Rand, 2016; Hellard, Doyle, & Sacks-Davis, 2014). While SVR reduces mortality from HCV-related sequelae, importantly, curative treatment does not address acquisition risk-related mortality, such as drug overdoses and other related harms. Approximately 50% of the HCV-related mortality among PWID was estimated to be health behaviour risk- and not viral-related (Innes et al., 2017). The recent opioid overdose crises in Canada (Public Health Agency of Canada, 2018) and the United States (US) (Gomes, Tadrous, & Mamdani, 2018; Vivolo-Kantor, Seth, & Gladden, 2018) have dramatically increased the risk of premature death among PWID. Therefore, while the WHO HCV liver-related mortality goals may be achieved by curing HCV infections, this will not address acquisition-risk related mortality.

We previously reported high liver-related mortality among those with chronic HCV infection, while acquisition risk-related mortality mainly occurred among those acquiring new HCV infections (Yu et al., 2013). In this study, we compare mortality causes among HCV negative and positive individuals, and describe trends in liver- and acquisition risk-related mortality.

Methods

The BC hepatitis Testers Cohort (BC-HTC)

As of December 2015, the BC-HTC included ˜1.7 million individuals tested for HCV or HIV since 1992, or reported to the provincial communicable disease registry as a case of HCV, hepatitis B (HBV), HIV or active tuberculosis. The BC Public Health Laboratory performs > 95% of all HCV testing in BC and these tests become part of the cohort. This includes those tested because of HCV risks, investigation of liver disease, routine screening of those undergoing procedures such as renal dialysis, and individuals tested during blood system lookbacks in the mid-1990s. The population-level cohort is deterministically linked, using each individual's unique personal health number, with health administrative data on medical visits, hospitalizations, cancers, prescription drugs, and deaths (Supplementary Table 1). A personal health number is issued to all BC residents and indicates coverage by the universal provincial health insurance plan. Details of the cohort design and characteristics of linked and unlinked participants have been described in detail previously (Janjua, Kuo, & Chong, 2016). For the present analysis, linked mortality data were available to December 31, 2018.

Study population

Eligible individuals had at least one HCV test (i.e., anti-HCV or HCV RNA) performed or were a reported HCV case from April 1992 to December 2015, with mortality follow-up until December 31, 2018. HCV status was classified as two mutually exclusive categories: 1) *HCV negative*: anti-HCV negative at the most recent test; or 2) *HCV positive*: anti-HCV positive and/or HCV RNA positive at the most recent test, or reported as a case of HCV. For some analyses, the HCV positive group was sub-stratified: 1) *HCV RNA positive*: anti-HCV and HCV RNA

positive; 2) *spontaneous clearance*: anti-HCV positive and HCV RNA negative at the time of diagnosis; 3) *Treated*: HCV RNA positive with at least one filled prescription for interferon- or DAA-based medications; 4) *SVR (subset of category 3)*: treated individuals with an end-of-treatment SVR assessment and an undetectable plasma HCV RNA ≥ 12 weeks (range 10 weeks or greater) post-treatment; 5) *No SVR (subset of category 3)*: treated individuals assessed for SVR with a positive plasma HCV RNA ≥ 12 weeks post treatment (i.e., treatment failure or re-infection). For individuals treated more than once, the most recent treatment was used. An individual was classified as having incident HCV infection if they had tested anti-HCV negative one or more times and subsequently tested anti-HCV positive, i.e., seroconverted, during the study period. An individual with prevalent HCV infection was defined as HCV positive at their first test during the study period, i.e., no record of a prior negative test. It is recognized that a small proportion of prevalent cases may in fact be incident, but there is no record of prior testing.

Causes of death

Underlying causes of death (UCOD), cancer diagnoses and other diseases were coded according to ICD-10 (World Health Organization, 2007). The UCOD ICD-10 code was used to classify deaths as 1) liver-related, including decompensated liver disease, liver cancer, HCV, other types of viral hepatitis, and alcoholic or non-alcoholic liver disease; 2) acquisition risk-related, including injection drug- and HIV-related causes; and 3) all other causes of death (Supplementary Table 2). UCOD R99 (other ill-defined and unspecified causes) was re-categorized as drug-related if the deaths were attributed to a person aged 20–64 years who also injects drugs, as these deaths are likely drug-related, based on validation studies in the US (Centers for Disease Control & Prevention, 2018). Subject characteristics such as injection drug use and problematic alcohol use were based on having at least two medical visits, one hospitalization or emergency room visit, or a death with an ICD-10 coded diagnosis for these conditions. Liver cancer diagnosis was obtained from the provincial cancer registry. Age was defined as age at death. Co-morbidities were based on the Elixhauser method; results are expressed as the number of co-morbidities present for a given individual, based on ICD-10 diagnosis codes found in administrative data (Elixhauser, Steiner, Harris, & Coffey, 1998). Material and social deprivation scores were calculated by the method of Pampalon, Gamache, and Hamel (2009), which is comprised of six indicators derived from Canadian census data, including employment status, education level, average income, living alone, and the proportion of single-parent families. Deprivation is expressed in quintiles ranging from least to most deprived.

Statistical methods

We described characteristics of HCV positive and negative individuals, as well as sub-groups of HCV positives, who died from any cause during the study period. We also compared characteristics, including UCOD, of individuals with incident and prevalent HCV infections to assess differences in liver- and acquisition risk-related mortality between the two groups. We then presented mortality causes among HCV positive, including sub-groups, and HCV negative individuals. Age-adjusted liver- and acquisition risk-related mortality rates and trends were calculated for HCV positive individuals. Kaplan-Meier survival curves were constructed to compare the survival time from latest HCV status to event among the groups. Cox proportional-hazard model was used to assess the effect of HCV status on mortality, while adjusting for birth year, sex, injection drug use, opioid substitution therapy, problematic alcohol use, mental illness, HIV status, material and social deprivation, Elixhauser co-morbidities, cirrhosis, diabetes, statin use, heart failure, and hypertension. P values were calculated by chi-square test, except for median age comparisons which used the

Table 1

Profile of people who died within the BC Hepatitis Testers Cohort, 1992 to 2018.

	All (n; column %)	HCV Positive (n; column %)	HCV Negative (n; column %)
Cohort (row %)	1,373,214	72,825 (5.3)	1,300,389 (94.7)
Deaths	153,048 (11.1)	20,049 (27.5)	132,999 (10.2)
Median age at death (IQR)	72.1 (71.9, 72.2)	56.4 (56.3, 56.7)	74.5 (74.4, 74.6)
Birth cohort			
< 1945	93,724 (61.2)	4,326 (21.6)	89,398 (67.2)
1945–1964	45,174 (29.5)	12,685 (63.3)	32,489 (24.4)
≥1965	14,150 (9.2)	3,038 (15.2)	11,112 (8.4)
Sex			
Male	88,677 (57.9)	14,025 (70)	74,652 (56.1)
Female	64,250 (42)	6,021 (30)	58,229 (43.8)
Unknown	121 (0.1)	3 (0)	118 (0.1)
Illicit drug use (ever)	22,305 (14.6)	10,648 (53.1)	11,657 (8.8)
Injection drug use (ever)	20,266 (13.2)	10,385 (51.4)	9,881 (7.4)
Opioid substitution therapy (ever)	7,764 (5.1)	4,739 (23.6)	3,025 (2.3)
Problematic alcohol use (ever)	28,916 (18.9)	8,697 (43.4)	20,219 (15.2)
Major mental illness (ever)	41,749 (27.3)	7,483 (37.3)	34,266 (25.8)
HIV co-infection	3,312 (2.2)	2,210 (11)	1,102 (0.8)
HBV co-infection	4,999 (3.3)	2,318 (11.6)	2,681 (2)
Material deprivation quintile			
Q1	18,712 (12.2)	2,144 (10.7)	16,568 (12.5)
Q2	21,361 (14)	2,512 (12.5)	18,849 (14.2)
Q3	25,501 (16.7)	2,916 (14.5)	22,585 (17)
Q4	30,123 (19.7)	3,897 (19.4)	26,226 (19.7)
Q5 (most deprived)	32,629 (21.3)	5,626 (28.1)	27,003 (20.3)
Unknown	24,722 (16.2)	2,954 (14.7)	21,768 (16.4)
Social deprivation quintile			
Q1	14,889 (9.7)	1,369 (6.8)	13,520 (10.2)
Q2	16,148 (10.6)	1,684 (8.4)	14,464 (10.9)
Q3	19,653 (12.8)	2,324 (11.6)	17,329 (13)
Q4	28,597 (18.7)	3,687 (18.4)	24,910 (18.7)
Q5 (most deprived)	49,039 (32)	8,031 (40.1)	41,008 (30.8)
Unknown	24,722 (16.2)	2,954 (14.7)	21,768 (16.4)
Elixhauser co-morbidities			
0	74,397 (48.6)	9,880 (49.3)	64,517 (48.5)
1	4,914 (3.2)	613 (3.1)	4,301 (3.2)
2	11,249 (7.3)	1,423 (7.1)	9,826 (7.4)
≥3 (most co-morbidities)	62,488 (40.8)	8,133 (40.6)	54,355 (40.9)
Year of HCV diagnosis or last negative test			
< 1997	35,305 (23.1)	8,295 (41.4)	27,010 (20.3)
1998–2002	32,376 (21.2)	6,162 (30.7)	26,214 (19.7)
2003–2007	30,550 (20)	3,098 (15.5)	27,452 (20.6)
2008–2012	28,362 (18.5)	1,737 (8.7)	26,625 (20)
≥2013	26,455 (17.3)	757 (3.8)	25,698 (19.3)

Abbreviations: HCV: hepatitis C virus; IQR: interquartile range; HIV: human immunodeficiency virus; HBV: hepatitis B virus.

Wilcoxon Rank Sum test. All analyses were performed using SAS v.9.4 (SAS Institute, Cary NC, USA); Kaplan-Meier survival curves were constructed using R version 3.5.0.

Ethics

The study was approved by the University of British Columbia Clinical Research Ethics Board (H14-01649).

Results

Participant profile and characteristics of those who died

Of the ˜1.7 million individuals in the BC-HTC as of December 31, 2015, 1,373,124 had been HCV tested or reported as a HCV case; 72,825 (5.3%) were HCV positive and 1,300,389 (94.7%) were negative (Table 1). As of December 31, 2018, 27.5% of HCV positive vs. 10.2% of negative individuals had died, a 2.7-fold difference. Median age at death (interquartile range [IQR]) was 56.4 (56.3–56.7) vs. 74.5 (74.4–74.6) years respectively, a difference of 18.1 years. HCV positive individuals who died were more likely to be male (70.0% vs. 56.1%), and to have a history of injection drug use (53.1% vs. 8.8%), problematic alcohol use (43.4% vs. 15.2%), HIV co-infection (11.0% vs. 0.8%) and HBV co-infection (11.6% vs. 2.0%) compared to those HCV negative. Co-morbidities were similar, but HCV positive vs. negative individuals who died were more likely to fall within higher (i.e., Q4/5) material (47.5% vs. 40.0%) and social (58.5% vs. 49.5%) deprivation quintiles. For those with incident HCV infection, the lower median age at death was even more striking at 44.8 years [IQR: 44.1–45.7], a 29.7 year difference vs. HCV negatives (Table 2). Incident HCV cases who died had higher rates of ever injection drug use (81.3% vs. 49.0%), problematic alcohol use (56.3% vs. 42.1%), major mental illness (58.1% vs. 35.3%) and HIV co-infection (15.5% vs. 10.6%) than individuals with prevalent infection. As expected, incident cases had a higher spontaneous clearance rate (30.4% vs. 24.9%) than individuals with prevalent infection.

Of note, the median age at death was similar for HCV positive individuals with spontaneous clearance (56.6 years); those HCV RNA positive, untreated (57.5); and those treated, regardless of whether they achieved SVR (SVR: 61.6 vs. no SVR: 59.9) (Table 3). A similar pattern was observed for those with incident infection (spontaneous clearance: 45.5 years; untreated: 45.5; SVR: 52.2; no SVR: 51.5; data not shown). Of treated individuals who achieved SVR, among those born ≥1965, 40.0% (88/220) died, compared to 31.9% (741/2,230) for those born < 1945, which likely reflects greater ongoing acquisition risks in younger individuals.

Causes of mortality

Overall, 24.7% (4,949/20,049) vs. 23.4% (4,683/20,049) of HCV positive individuals died of acquisition risk- and liver-related causes (Table 4) respectively; and for HCV negatives, 4.2% (5,582/132,999) vs. 6.2% (8,264/132,989). Corresponding values for those with incident HCV infection were 53.4% (911/1,763) and 8.3% (147/1,763; Table 2). HCV negative individuals were more likely to die of age-related causes, e.g., non-liver cancer and cardiovascular diseases, compared to HCV positives (Supplementary Fig. S1), many of whom died prematurely prior to developing age-related conditions. HCV positive individuals who spontaneously cleared infection had a significantly lower proportion of liver-related deaths compared to those with untreated chronic infection (14.3% vs. 26.7%, respectively; p < 0.001), while acquisition risk-related deaths were similar (26.6% vs. 23.8%, respectively) (Table 4). When stratified by birth cohort, HCV positive individuals born < 1945 had the lowest acquisition risk-related death rate (2.7%), which may reflect a survival bias, while the 1945-64 (23.7%) and ≥1965 (59.9%) cohorts had higher rates (Table 5; Supplementary Fig. S2). Liver-related deaths among HCV positives were similar for both the < 1945 and 1945–1964 birth cohorts (25.3% vs. 26.5% respectively) and lowest for those born ≥1965 (7.7%). Among HCV negative individuals, a similar pattern of acquisition risk-related deaths was observed but the magnitude was lower for all birth cohorts. The HCV negative < 1945 and ≥1965 birth cohorts had similar rates of liver-related death (5.0% and 5.2% respectively), while the 1945–1964 cohort had the highest rate (9.8%).

Of 16,821 HCV RNA positive individuals who received treatment

Table 2

Selected characteristics of HCV positive individuals with incident and prevalent HCV infections, BC Hepatitis Testers Cohort, 1992-2018.

	All HCV Positive	Incident[a]	Prevalent[b]	p-value
Cohort n (% of cohort)	72,825	10,125 (13.9)	62,700 (86.1)	
n deaths (% of cohort)	20,049 (27.5)	1,763 (17.4)	18,286 (29.2)	< .0001
Median age at death (IQR)	56.4 (56.3, 56.7)	44.8 (44.1, 45.7)	57.4 (57.1, 57.6)	< .0001
Illicit drug use (ever); n deaths (%)	10,648 (53.1)	1,474 (83.6)	9,174 (50.2)	< .0001
Injection drug use (ever); n deaths (%)	10,385 (51.8)	1,433 (81.3)	8,952 (49)	< .0001
Opioid substitution therapy (ever); n deaths (%)	4,739 (23.6)	741 (42)	3,998 (21.9)	< .0001
Problematic alcohol use (ever); n deaths (%)	8,697 (43.4)	993 (56.3)	7,704 (42.1)	< .0001
Major mental illness (ever); n deaths (%)	7,483 (37.3)	1,025 (58.1)	6,458 (35.3)	< .0001
HIV co-infection; n deaths (%)	2,210 (11)	273 (15.5)	1,937 (10.6)	< .0001
Spontaneous clearance; n/n tested for HCV RNA (%)	14,365/55,828 (25.7)	2,662/8,765 (30.4)	11,703/47,063 (24.9)	< .0001
Liver-related death; n deaths (%)	4,683 (23.4)	147 (8.3)	4,536 (24.8)	< .0001
Acquisition risk-related death; n deaths (%)	4,949 (24.7)	941 (53.4)	4,008 (21.9)	< .0001
Treated with SVR; n deaths/n treated with SVR assessment (%)	799/1,681 (47.5)	57/86 (66.3)	742/1,595 (46.5)	
Treated with no SVR; n deaths/n treated with SVR assessment (%)	882/1,681 (52.5)	29/86 (33.7)	853/1,595 (53.5)	

Abbreviations: HCV: hepatitis C virus; HIV: human immunodeficiency virus; SVR: sustained virologic response.

[a] Incident cases tested anti-HCV negative one or more times and subsequently tested anti-HCV positive during the study period.

[b] Individuals with prevalent infection were HCV positive at their first test during the study period, i.e., no record of a prior negative test.

(both interferon- and DAA-based, as well as DAA re-treatment of interferon-based failures) and were subsequently assessed, 84.2% achieved SVR (Table 3). Of treated individuals who died, 47.5% (799/1,681) had achieved SVR vs. 52.5% (882/1,681) for no SVR. Those with SVR who died had a significantly lower liver-related death rate (26.4%; 211/799) vs. no SVR (55.8%; 492/882; p < 0.001; Table 4). However, treated individuals who achieved SVR and died still had a significantly higher liver-related death rate (26.4%; 211/799) than those who spontaneously cleared infection (14.3%; 323/2,260; p < 0.001), which may reflect that individuals treated with interferon-based treatments or having early access to DAAs already had advanced liver disease. Deaths from acquisition risks were similar for those with spontaneous clearance (26.6%; 601/2,260) and those HCV RNA positive, untreated (23.8%; 1,813/7,622), but were lower for those with SVR (20.5%; 164/799) and no SVR (9.9%; 87/882).

The Kaplan-Meier survival analysis (Fig. 1) demonstrated that those treated and who achieved SVR had only slightly reduced survival compared to HCV negatives, while those who did not achieve SVR had the poorest survival. This is likely because most of those who failed treatment had late stage liver disease, which was more difficult to cure, and other underlying co-morbidities associated with high mortality. Spontaneous clearance was associated with improved survival compared to those HCV RNA positive, but untreated. Compared to HCV negative individuals, the Cox proportional hazard model (Table 6) demonstrated higher adjusted hazard ratios (aHR) for those HCV RNA positive untreated (aHR = 2.56; 95%CI: 2.49–2.63), those treated with no SVR (aHR = 2.22; 95%CI: 2.09–2.38), and those with spontaneous clearance (aHR = 1.48; 95%CI:1.41–1.54), while treatment leading to SVR had a lower risk (aHR = 0.58; 95%CI: 0.54–0.62).

Mortality rate trends

Age-adjusted liver-related mortality rates among HCV positive individuals increased from 1992 to 2002, remained stable until 2009, and increased until 2014. This was followed by a sharp decline between 2014 and 2018 (Fig. 2), coinciding with the introduction and uptake of DAA treatment in BC. By 2014, liver-related mortality was approximately three times higher among males (Supplementary Fig. S3), but trends among males and females were similar. In contrast, age-adjusted injection drug-related mortality rates increased from 1992 to 2000, gradually declined until 2013, and increased dramatically from 2014 to 2018, coinciding with the increase in fentanyl and analogue-related overdose deaths. Of note, injection drug-related mortality also increased slowly over time among HCV negative individuals, with a similar dramatic increase starting in 2014 (data not shown).

Discussion

In this large population-based analysis in BC, prevalent HCV positive individuals had approximately two, and those with incident HCV infection had about three, decades of potential life lost from all causes compared to HCV negatives. Among HCV positive individuals, similar numbers of premature deaths occurred from liver disease (23.6%) and the risks associated with injection drug use (24.5%). For HCV positive individuals born < 1945, liver-related deaths were approximately 10-fold higher than acquisition risk-related deaths, whereas the distribution was almost equal for baby boomers. In contrast, for those born ≥1965, acquisition risk-related deaths were approximately 8-fold higher than liver-related deaths. The observation that HCV positive individuals with both spontaneous clearance and treatment-induced SVR had a similar median age of death as individuals with untreated chronic infection suggests that ongoing acquisition risks are a major contributor to their premature mortality. This was also observed in the survival analysis, where individuals who spontaneously cleared had higher mortality compared to HCV negatives and those who achieved SVR. It is also consistent with the study by Innes et al. (2017) who reported that approximately half of all HCV-related premature deaths in the US National Health and Nutrition Examination Survey resulted from health risk behaviours. In addition, in the SIMPLIFY study, which achieved 94% DAA cure rates in individuals actively engaged in drug use, four drug-related deaths occurred during the study and short follow up period (Grebely, Dalgard, & Conway, 2018).

The HCV positive group is heterogeneous and includes individuals with both incident and prevalent HCV infection (Janjua, Yu et al., 2016). Incident cases (initially seronegative and subsequently seropositive) represent infections diagnosed after HCV testing became available in 1992. Many baby boomers acquired their infections decades ago and were diagnosed with prevalent HCV infections during the study period. Therefore, a bias exists as HCV positive individuals who died prior to 1992 are not captured in the BC-HTC. Thus, HCV positive baby boomers reflect individuals who survived their acquisition risks and are now dying from liver disease and age-related conditions. On the other hand, individuals with incident infection have ongoing injection drug use as a major acquisition risk, given that blood-borne and iatrogenic transmission had largely been eliminated by the time HCV tests became available (Stramer, Wend, & Candotti, 2011). Thus, the incident infection sub-population represents individuals who are at a high risk of acquisition risk-related death, but they may also die of liver disease if they survive long enough.

The liver-related mortality trend among individuals with chronic HCV infection increased from 1992 to 2002, remained stable until

Table 3
Profile of HCV positive people who died within the BC Hepatitis Testers Cohort, 1992 to 2018.

	HCV Positive (n)	Tested for HCV RNA (n; % of HCV pos)	HCV RNA Negative (spontaneous clearance) (n; % of RNA tested)	HCV RNA Positive (not treated) (n; % of RNA tested)	HCV RNA Positive (treated) (n; % of RNA tested)	Treatment outcome: n treated and assessed for SVR (% of treated)	SVR (n; % of those assessed)	No SVR (n; % of those assessed)
Cohort	72,825	55,828 (76.7)	14,365 (25.7)	24,642 (44.1)	16,821 (30.1)	13,338 (79.3)	11,226 (84.2)	2,112 (15.8)
Deaths	20,049	12,332 (61.5)	2,260 (18.3)	7,622 (61.8)	2,450 (19.9)	1,681 (68.6)	799 (47.5)	882 (52.5)
Median age at death (IQR)	56.4 (56.3, 56.7)	58.0 (57.8, 58.2)	56.6 (56.0, 57.2)	57.5 (57.2, 57.8)	60.2 (59.7, 60.5)	60.6 (60.3, 61.1)	61.6 (61.1, 62.1)	59.9 (59.2, 60.4)
Birth cohort								
< 1945	4,326	2,008 (46.4)	346 (17.2)	1,343 (66.9)	319 (15.9)	212 (66.5)	88 (41.5)	124 (58.5)
1945–1964	12,685	8,244 (65)	1,336 (16.2)	4,997 (60.6)	1,911 (23.2)	1,336 (69.9)	623 (46.6)	713 (53.4)
≥ 1965	3,038	2,080 (68.5)	578 (27.8)	1,282 (61.6)	220 (10.6)	133 (60.5)	88 (66.2)	45 (33.8)
Sex								
Male	14,025	8,585 (61.2)	1,343 (15.6)	5,415 (63.1)	1,827 (21.3)	1,255 (68.7)	607 (48.4)	648 (51.6)
Female	6,021	3,747 (62.2)	917 (24.5)	2,207 (58.9)	623 (16.6)	426 (68.4)	192 (45.1)	234 (54.9)
Unknown	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Illicit drug use (ever)	10,648	6,765 (63.5)	1,401 (20.7)	4,294 (63.5)	1,070 (15.8)	707 (66.1)	357 (50.5)	350 (49.5)
Injection drug use (ever)	10,385	6,462 (62.2)	1,283 (19.9)	4,171 (64.5)	1,008 (15.6)	655 (65)	328 (50.1)	327 (49.9)
Opioid substitution therapy (ever)	4,739	3,260 (68.8)	699 (21.4)	2,048 (62.8)	513 (15.7)	326 (63.5)	175 (53.7)	151 (46.3)
Problematic alcohol use (ever)	8,697	5,497 (63.2)	1,110 (20.2)	3,474 (63.2)	913 (16.6)	600 (65.7)	286 (47.7)	314 (52.3)
Major mental illness (ever)	7,483	4,986 (66.6)	1,024 (20.5)	3,065 (61.5)	897 (18)	593 (66.1)	290 (48.9)	303 (51.1)
HIV co-infection	2,210	1,277 (57.8)	237 (18.6)	873 (68.4)	167 (13.1)	120 (71.9)	74 (61.7)	46 (38.3)
HBV co-infection	2,318	1,429 (61.6)	368 (25.8)	827 (57.9)	234 (16.4)	162 (69.2)	79 (48.8)	83 (51.2)
Material deprivation quintile								
Q1	2,144	1,285 (59.9)	210 (16.3)	810 (63)	265 (20.6)	174 (65.7)	64 (36.8)	110 (63.2)
Q2	2,512	1,415 (56.3)	227 (16)	912 (64.5)	276 (19.5)	174 (63)	62 (35.6)	112 (64.4)
Q3	2,916	1,752 (60.1)	292 (16.7)	1,108 (63.2)	352 (20.1)	243 (69)	74 (30.5)	169 (69.5)
Q4	3,897	2,250 (57.7)	372 (16.5)	1,464 (65.1)	414 (18.4)	256 (61.8)	79 (30.9)	177 (69.1)
Q5 (most deprived)	5,626	3,147 (55.9)	598 (19)	2,065 (65.6)	484 (15.4)	314 (64.9)	103 (32.8)	211 (67.2)
Unknown	2,954	2,483 (84.1)	561 (22.6)	1,263 (50.9)	659 (26.5)	520 (78.9)	417 (80.2)	103 (19.8)
Social deprivation quintile								
Q1	1,369	801 (58.5)	129 (16.1)	493 (61.5)	179 (22.3)	101 (56.4)	31 (30.7)	70 (69.3)
Q2	1,684	966 (57.4)	141 (14.6)	604 (62.5)	221 (22.9)	150 (67.9)	52 (34.7)	98 (65.3)
Q3	2,324	1,333 (57.4)	234 (17.6)	813 (61)	286 (21.5)	191 (66.8)	63 (33)	128 (67)
Q4	3,687	2,188 (59.3)	376 (17.2)	1,416 (64.7)	396 (18.1)	275 (69.4)	80 (29.1)	195 (70.9)
Q5 (most deprived)	8,031	4,561 (56.8)	819 (18)	3,033 (66.5)	709 (15.5)	444 (62.6)	156 (35.1)	288 (64.9)
Unknown	2,954	2,483 (84.1)	561 (22.6)	1,263 (50.9)	659 (26.5)	520 (78.9)	417 (80.2)	103 (19.8)
Elixhauser co-morbidities								
0	9,880	6,505 (65.8)	1,342 (20.6)	3,808 (58.5)	1,355 (20.8)	949 (70)	627 (66.1)	322 (33.9)
1	613	287 (46.8)	33 (11.5)	195 (67.9)	59 (20.6)	40 (67.8)	10 (25)	30 (75)
2	1,423	756 (53.1)	104 (13.8)	511 (67.6)	141 (18.7)	98 (69.5)	26 (26.5)	72 (73.5)
≥3 (most co-morbidities)	8,133	4,784 (58.8)	781 (16.3)	3,108 (65)	895 (18.7)	594 (66.4)	136 (22.9)	458 (77.1)
Year of HCV diagnosis or last negative test								
< 1997	8,295	4,087 (49.3)	771 (18.9)	2,458 (60.1)	858 (21)	570 (66.4)	248 (43.5)	322 (56.5)
1998-2002	6,162	3,835 (62.2)	648 (16.9)	2,310 (60.2)	877 (22.9)	604 (68.9)	264 (43.7)	340 (56.3)
2003-2007	3,098	2,365 (76.3)	417 (17.6)	1,490 (63)	458 (19.4)	334 (72.9)	172 (51.5)	162 (48.5)
2008-2012	1,737	1,432 (82.4)	288 (20.1)	951 (66.4)	193 (13.5)	133 (68.9)	81 (60.9)	52 (39.1)
≥2013	757	613 (81)	136 (22.2)	413 (67.4)	64 (10.4)	40 (62.5)	34 (85)	6 (15)

Abbreviations: HCV: hepatitis C virus; RNA: ribonucleic acid; SVR: sustained virologic response; IQR: interquartile range; HIV: human immunodeficiency virus; HBV: hepatitis B virus.

Table 4
Mortality causes by HCV status, BC Hepatitis Testers Cohort, 1992 to 2018.

Cause of death	All n (col %)	HCV Negative n (col %)	HCV Positive n (col %)	HCV Positive Tested for HCV RNA			Treatment outcome		
				Spontaneous Clearance[a] n (col %)	HCV RNA Positive (not treated)[a] n (col %)	HCV RNA Positive (treated)[b] n (col %)	n treated and assessed for SVR (% of treated)	SVR (n; % of those assessed)	No SVR (n; % of those assessed)
All causes	153,048	132,999	20,049	2,260	7,622	2,450	1,681 (68.6)	799 (47.5)	882 (52.5)
Liver-related	12,947 (8.5)	8,264 (6.2)	4,683 (23.4)	323 (14.3)	2,037 (26.7)	982 (40.1)	703 (71.6)	211 (30.0)	492 (70.0)
Viral hepatitis	2,124 (1.4)	266 (0.2)	1,858 (9.3)	77 (3.4)	824 (10.8)	447 (18.2)	299 (66.9)	58 (19.4)	241 (80.1)
Viral hepatitis B	322 (0.2)	212 (0.2)	110 (0.5)	19 (0.8)	28 (0.4)	14 (0.6)	11 (78.6)	1 (9.0)	10 (90.9)
Viral hepatitis C	1,776 (1.2)	37 (0)	1,739 (8.7)	56 (2.5)	793 (10.4)	432 (17.6)	287 (66.4)	57 (19.9)	230 (80.1)
Viral hepatitis non-B/C	23 (0)	16 (0)	7 (0)	1 (0)	2 (0)	1 (0)	1 (100)	0 (0)	1 (100)
Sequelae of viral hepatitis	3 (0)	1 (0)	2 (0)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Liver cancer	4,116 (2.7)	2,617 (2)	1,499 (7.5)	76 (3.4)	705 (9.2)	392 (16)	311 (79.3)	123 (39.5)	188 (60.5)
Hepatocellular carcinoma	3,254 (2.1)	1,814 (1.4)	1,440 (7.2)	68 (3)	677 (8.9)	382 (15.6)	303 (79.3)	118 (38.9)	185 (61.1)
Intrahepatic cholangiocarcinoma	862 (0.6)	803 (0.6)	59 (0.3)	8 (0.4)	28 (0.4)	10 (0.4)	8 (80.0)	5 (62.5)	3 (37.5)
Liver disease	6,707 (4.4)	5,381 (4)	1,326 (6.6)	170 (7.5)	508 (6.7)	143 (5.8)	93 (65.0)	30 (32.3)	63 (67.7)
Alcoholic liver disease	4,084 (2.7)	3,168 (2.4)	916 (4.6)	147 (6.5)	379 (5)	101 (4.1)	69 (68.3)	20 (29.0)	49 (71.0)
Non-alcoholic liver disease	2,623 (1.7)	2,213 (1.7)	410 (2)	23 (1)	129 (1.7)	42 (1.7)	24 (57.1)	10 (41.7)	14 (58.3)
Acquisition risk-related	10,531 (6.9)	5,582 (4.2)	4,949 (24.7)	601 (26.6)	1,813 (23.8)	403 (16.4)	251 (62.3)	164 (65.3)	87 (34.7)
Injection Drug related	9,223 (6)	5,108 (3.8)	4,115 (20.5)	550 (24.3)	1,542 (20.2)	381 (15.6)	238 (62.5)	163 (68.5)	75 (31.5)
HIV	1,308 (0.9)	474 (0.4)	834 (4.2)	51 (2.3)	271 (3.6)	22 (0.9)	13 (59.1)	1 (7.7)	12 (92.3)
Other causes of death	129,570 (84.7)	119,153 (89.6)	10,417 (52)	1,336 (59.1)	3,772 (49.5)	1,065 (43.5)	727 (68.3)	424 (58.3)	303 (41.7)
Diabetes/Obesity	7,805 (5.1)	7,357 (5.5)	448 (2.2)	69 (3.1)	182 (2.4)	57 (2.3)	42 (73.6)	19 (45.2)	23 (54.8)
Non-liver cancer	40,439 (26.4)	37,673 (28.3)	2,766 (13.8)	330 (14.6)	1,049 (13.8)	360 (14.7)	256 (71.1)	158 (61.7)	98 (38.3)
Cardiovascular	35,543 (23.2)	33,076 (24.9)	2,467 (12.3)	313 (13.8)	841 (11)	241 (9.8)	171 (71.0)	101 (59.1)	70 (40.9)
Digestive (non-hepatic)	4,143 (2.7)	3,734 (2.8)	409 (2)	57 (2.5)	147 (1.9)	40 (1.6)	30 (75.0)	15 (50.0)	15 (50.0)
Genitourinary	3,884 (2.5)	3,638 (2.7)	246 (1.2)	31 (1.4)	97 (1.3)	25 (1)	16 (64.0)	5 (31.3)	11 (68.8)
Respiratory	13,022 (8.5)	11,677 (8.8)	1,345 (6.7)	210 (9.3)	499 (6.5)	109 (4.4)	70 (65.4)	44 (62.9)	26 (37.1)
All other ICD-10 codes	24,734 (16.2)	21,998 (16.5)	2,736 (13.6)	326 (14.4)	957 (12.6)	233 (9.5)	142 (60.9)	82 (57.7)	60 (42.3)

Abbreviations: HCV: hepatitis C virus; RNA: ribonucleic acid; SVR: sustained virologic response; HIV: human immunodeficiency virus; ICD-10: International Classification of Diseases, version 10.
[a] HCV positive individuals who did not have a HCV RNA test are not included in these sub-groups.
[b] Treated individuals who did not have a SVR assessment are not included.

Table 5
Mortality causes by HCV status and birth cohort, BC Hepatitis Testers Cohort, 1992 to 2018.

	n deaths	Acquisition risk-related n (%)	Liver-related n (%)	Other n (%)
Anti-HCV Negative				
< 1945	89,398	276 (0.3)	4,511 (5)	84,611 (94.6)
1945–1964	32,489	1,979 (6.1)	3,176 (9.8)	27,334 (84.1)
≥1965	11,112	3,327 (29.9)	577 (5.2)	7,208 (64.9)
HCV Positive				
< 1945	4,326	116 (2.7)	1,093 (25.3)	3,117 (72.1)
1945–1964	12,685	3,012 (23.7)	3,356 (26.5)	6,317 (49.8)
≥1965	3,038	1,821 (59.9)	234 (7.7)	983 (32.4)
HCV RNA Negative (spontaneous clearance)				
< 1945	346	11 (3.2)	42 (12.1)	293 (84.7)
1945–1964	1,336	284 (21.3)	220 (16.5)	832 (62.3)
≥1965	578	306 (52.9)	61 (10.6)	211 (36.5)
HCV RNA Positive (untreated)				
< 1945	1,343	21 (1.6)	404 (30.1)	918 (68.4)
1945–1964	4,997	989 (19.8)	1,529 (30.6)	2,479 (49.6)
≥1965	1,282	803 (62.6)	104 (8.1)	375 (29.3)
HCV RNA Positive (treated)				
< 1945	319	4 (1.3)	147 (46.1)	168 (52.7)
1945–1964	1,911	284 (14.9)	801 (41.9)	826 (43.2)
≥1965	220	115 (52.3)	34 (15.5)	71 (32.3)
SVR				
< 1945	88	2 (2.3)	29 (33)	57 (64.8)
1945–1964	623	114 (18.3)	174 (27.9)	335 (53.8)
≥1965	88	48 (54.5)	8 (9.1)	32 (36.4)
No SVR				
< 1945	124	0 (0)	75 (60.5)	49 (39.5)
1945–1964	713	69 (9.7)	402 (56.4)	242 (33.9)
≥1965	45	18 (40)	15 (33.3)	12 (26.7)

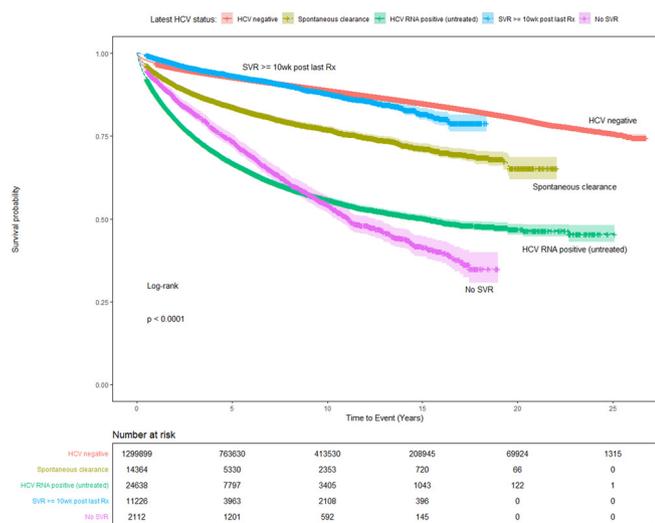Abbreviations: HCV: hepatitis C virus; RNA: ribonucleic acid; SVR: sustained virologic response.

Fig. 1. Survival probability for HCV positive vs. negative individuals, BC Hepatitis Testers Cohort, 1992 to 2018.

Table 6
Cox proportional hazards model[a] for risk of death from any cause, BC Hepatitis Testers Cohort, 1992 to 2018.

	Adjusted Hazard Ratio[1] (95%CI)	P value
HCV negative	Ref	
HCV RNA positive	2.561 (2.493–2.630)	< 0.0001
Spontaneous clearance	1.475 (1.410–1.543)	< 0.0001
SVR ≥10 wk post treatment	0.577 (0.535–0.621)	< 0.0001
No SVR	2.222 (2.076–2.379)	< 0.0001

Abbreviations: HCV: hepatitis C virus; RNA: ribonucleic acid; SVR: sustained virological response; CI: confidence interval.

[a] Model adjusted for birth year, sex, injection drug use, opioid substitution therapy, problematic alcohol use, mental illness, HIV, material and social deprivation, Elixhauser co-morbidities, cirrhosis, diabetes, statin use, heart failure and hypertension.

2009, increased steadily until 2014, and thereafter declined sharply. Fibrosis-dependent interferon-based therapies were made available in BC in 2000 and were largely discontinued by 2014. Based on the observed trends, these therapies had little population impact in reducing liver-related mortality, similar to the observations of others (Alavi et al., 2018). The rapid decline from 2014 to 2018 coincides with the initial BC roll-out of DAA therapies for patients with ≥F2 fibrosis and those who had previously failed treatment, and likely reflects the early impact of DAAs in reducing late-stage liver-related mortality. With the approval of fibrosis-independent DAA therapy in 2018, it is expected that treatment-based cures will continue to reduce liver-related mortality, recognizing that problematic alcohol use contributes to liver progression risk. For example, a US analysis demonstrated that individuals 25–34 years experienced the highest increase in cirrhosis-related mortality from 1999 to 2016, which was driven entirely by alcohol use (Tapper & Parikh, 2018). As there has only been short-term follow-up to date (> =3 years), assessing the longer term impact of DAA-based cures on liver-related mortality will be important.

Acquisition risk-related mortality initially increased and then declined slightly, followed by a precipitous increase since 2014, coinciding with Canada's opioid overdose crisis (Public Health Agency of Canada, 2018) which disproportionately affects BC. At least 80% of BC fentanyl-related overdoses from 2014 to 2017 occurred in males (BC Coroners Service, 2018), which is reflected in the higher death rates observed among males in this study. In 2017, there were approximately two drug- for every liver-related death among both HCV positive (405 vs. 226 respectively) and HCV negative individuals (799 vs. 451), compared to 1,992 vs. 1,127 respectively for the general BC population. Similar recent increases in opioid-related deaths have occurred in other
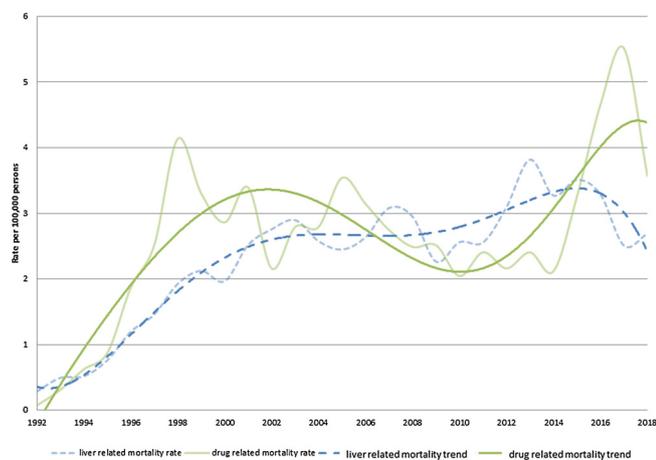
Fig. 2. Annual age-adjusted liver- and drug-related mortality rates and trends among HCV positive individuals, BC Hepatitis Testers Cohort, 1992 to 2018.

countries, including the US, Europe, Australia and Japan (Jalal, Buchanich, & Roberts, 2018; Pichini, Solimini, & Berretta, 2018; Vivolo-Kantor et al., 2018).

This study has some strengths and limitations. The BC-HTC is one of the world's largest cohorts linked to health administrative data to enable population level outcome analyses. Stratification of the HCV positive population enables tracking of acquisition risks and estimation of infection timing for those with incident infection, which is not possible for prevalent cases, many of whom are baby boomers who were only diagnosed once testing became available in 1992. The use of administrative data likely under-estimates co-morbid conditions such as problematic alcohol use, and it is possible that attribution of deaths to liver- or acquisition-related causes was also underestimated. For example, Moorman, Rupp, and Gordon (2018) found that only 30% of deaths from liver disease in the US CHeCS cohort had HCV on the death certificate even though most had evidence of advanced liver disease. For some deaths occurring close to the study end, the final UCOD is not available pending coroner's investigation and the deaths remain classified as undetermined (ICD10 code R99). R99-coded deaths among PWID aged 20–64 were classified as injection drug-related based on US validation (Centers for Disease Control & Prevention, 2018), but as some may ultimately not be related to drug use, there is potential for mis-classification of some of these recent deaths.

In conclusion, understanding mortality impacts among the HCV-infected population or those at risk for HCV provides critical information to enable policy makers to frame interventions to address both liver- and acquisition risk-related mortality across the prevention, care and treatment continuum. Liver-related deaths were more common among older individuals and are declining following DAA introduction. In contrast, acquisition risk-related deaths were more common among younger people engaged in injection drug use. These deaths are increasing and will require strategies beyond HCV treatment to achieve the WHO 2030 HCV elimination targets.

Authors' contributions

MK, NZJ: study concept and design. SW, AY: data assembly and analysis. MK, DAC, NZJ: writing of article. ZAB, CR, MD, MA, JAB, MT: review of manuscript and providing input for important intellectual content. All authors: reviewed the manuscript and agreed with the decision to submit for publication.

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Conflict of interest

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugpo.2019.06.003.

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