Association of hepatitis B virus treatment with all-cause and liver-related mortality among individuals with HBV and cirrhosis: a population-based cohort study

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Summary

Background We evaluated the association of hepatitis B virus (HBV) treatment with all-cause, and liver-related mortality among individuals with HBV and cirrhosis in British Columbia (BC), Canada.

Methods This analysis included people diagnosed with HBV and had cirrhosis in the BC Hepatitis Testers Cohort, including data on all individuals diagnosed with HBV from 1990 to 2015 in BC and integrated with healthcare administrative data. We followed people with cirrhosis from the first cirrhosis diagnosis date until death or December 31, 2020. We compared all-cause and liver related mortality between those who received treatment and those who did not. HBV treatment was considered a time-varying variable. We performed multivariable Cox proportional hazards model and competing risk regression models to assess the association of HBV treatment with all causes, and liver-related mortality respectively using inverse probability of treatment weighted population.

Findings Among 4962 individuals with HBV and cirrhosis, 48.1% received HBV treatment. Treated individuals had a median follow-up of 2.97 years, compared to 2.87 years for untreated individuals. The treated group was older (median age 57 vs 54 years), had higher proportion of treated of males [1802 (75.50%) vs 1766 (68.8%)], from urban area [2318 (97.2%) vs 2355 (91.8%)], and from East and South Asian ethnicity [1506 (63.1%) vs 709 (27.5%)] compared to untreated group. Untreated people experienced higher all-cause mortality (115.47 vs. 35.72 per 1000 person-years) and liver-related mortality (49.86 vs. 11.39 per 1000 person-years). Multivariable models showed that HBV treatment significantly lowered the risk of all-cause mortality (adjusted hazard ratio (aHR) 0.74; 95% CI: 0.65, 0.84) and liver-related mortality (adjusted subdistribution hazard ratio (asHR) 0.72; 95% CI: 0.58, 0.89) compared to untreated individuals. Among untreated individuals with HBV, those with HCV coinfection had a higher risk of both all-cause and liver-related mortality (aHR 1.57; 95% CI: 1.22, 2.04, and asHR 1.60; 95% CI: 1.25, 2.05, respectively).

Interpretation HBV treatment was associated with a significant reduction in all-cause and liver-related mortality among individuals with cirrhosis. The findings highlight the need for treatment among individuals with HBV related cirrhosis especially those with coinfection with hepatitis C virus.

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Research in context

Evidence before this study

Hepatitis B virus (HBV) is a significant contributor to the liver disease burden in United States (US) and Canada. However, the data on HBV treatment outcomes in US and Canada are scarce. Population living with HBV in North America is more diverse with respect to sociodemographic characteristics, comorbidity, and co-infection profile.

We searched PubMed, Google Scholar, medRxiv, and the hepatitis B and liver related complications Database via Ovid in August 2022 for synonyms of "HBV liver-related mortality among individuals with cirrhosis", "all causes of mortality among individuals with HBV and cirrhosis", and "HBV treatment outcomes among people with cirrhosis". These were supplemented with internet searches (Google), searching of references in identified papers, and the authors' own knowledge. Studies were restricted to those conducted in Northern America and other developed countries. Data in US and Canada showed that liver-related mortality was higher among those with HBV infection compared to those without infection. Previous studies in Asia have shown that long-term HBV treatment with antiviral therapy among patients with cirrhosis showed the reduction of liver fibrosis, decreased the number of people needing transplantations, and increased the survival rate. The international guidelines recommend treatment for HBV among people with cirrhosis to control HBV viremia, prevent disease complications, and increase survival. However, few population level studies have explored the effect of HBV treatment on all-cause and liver-related mortality especially in Canada and USA.

Added value of this study

This study included a large population-based sample of individuals with HBV and cirrhosis, including those who received HBV treatment and those who were never treated to assess the effect of HBV treatment on reducing all causes and liver-related mortality. The study included relatively large sample size (approximately 5000 participants) and data spanning the years 1992–2015, with a follow-up that extends to December 2020. In addition to overall treatment effect, we conducted an analysis on the effects of high-potent antivirals (TDF and Entecavir). We showed that HBV treatment is effective in reducing all cause and liver related mortality among people with HBV and cirrhosis. Additionally, this study shows that HBV/HCV coinfection is associated with a higher risk of death from all causes and liver-related causes among untreated individuals. Study results come to complement existing evidence that HBV treatment is essential in prevention of deaths among individuals with HBV and cirrhosis especially in Northern America where data on HBV treatment outcome is limited.

Implications of all the available evidence

HBV treatment was associated with a significant reduction in all-cause and liver-related mortality in individuals with cirrhosis. Thus, treatment could improve survival among people with HBV infection. Higher risk of mortality among people with HBV/HCV co-infection could be mitigated with treatment for HBV as well as highly effective direct acting antivirals for HCV treatment. Efforts are needed to expand treatment initiation to reduce overall burden of poor health outcomes related to HBV.

Introduction

Cirrhosis is a significant cause of morbidity and mortality worldwide. It is the 11th leading cause of death, accounting for 2.2% of deaths worldwide in 2016[1] and 2.4% in 2017.[2] The burden of cirrhosis in North America has increased substantially in recent years.[3] In the United States, annual deaths from cirrhosis increased by 65% from 1996 to 2016.[4] Over half of all cases of cirrhosis are attributable to the hepatitis B virus (HBV) or hepatitis C virus (HCV) in North America.[2] HBV is estimated to cause around a quarter of all liver cancers in developed countries.[5] In 2021, World Health Organization (WHO) estimated that about one in ten of the 257 million people with HBV infection may be in urgent need of treatment because of cirrhosis.[6]

Although not all HBV patients are recommended to receive treatment, the international guidelines recommend treatment for HBV among people with cirrhosis to control HBV viremia, prevent disease complications, and increase survival.[5] Studies in Korea and Taiwan have shown that long-term HBV treatment with antiviral therapy among patients with cirrhosis showed the reduction of liver fibrosis, decreased the number of people needing transplantations, and increased the survival rate.[7] The European Association for Study of Liver (EASL) Clinical Practice Guidelines recommend treating HBV cirrhosis that exhibits any level of HBV-DNA, either compensated or decompensated, with potent antivirals that have a low risk of resistance (i.e. tenofovir and entecavir).[8] However, few population level studies have explored the effect of HBV treatment on all-cause and liver-related mortality. A retrospective cohort study in Hong Kong has shown that entecavir reduced both all-cause and liver-related mortality.[9] Another study conducted in China showed that the coverage of antiviral therapy by basic medical insurance reduced the risk of liver-related death for patients with compensated cirrhotic chronic HBV.[10]

Data in US and Canada showed that liver-related mortality was higher among those with HBV infection compared to those without infection.[11–14] However, the data on HBV treatment outcomes in US and Canada are scarce. Population living with HBV in North America is more diverse with respect to sociodemographic characteristics, comorbidity and co-infection profile. Therefore, we aimed to evaluate the association of HBV treatment with all-cause, and liver-related mortality among individuals who have tested positive for HBV and diagnosed with cirrhosis in British Columbia (BC), Canada.

Methods

Data source, study design and study population

This analysis used data from the BC Hepatitis Testers Cohort, which includes more than 45,000 people who tested positive for HBV from 1990 to 2015 and treated for HBV from January 3rd, 1992 to December 31st, 2020.[13] In BC Hepatitis Testers Cohort, an individual was confirmed as a case of HBV infection with a positive HBV surface antigen (HBsAg), HBV DNA or HBV e antigen (HBeAg) test result, or those who had a record of receiving HBV treatment.[15] These data were integrated with different administrative healthcare datasets and provincial registries, including vital statistics, cancer registry, medical visits, hospital discharge data, emergency visits, and drug dispensations through a personal health number[16](Supplementary Table S1). Individuals with chronic HBV according to BC Viral hepatitis testing guidelines[17] diagnosed with cirrhosis during the specified period above were included in the analysis. A more detailed description of this cohort has been reported in previously published papers.[15,18] For this analysis, people with missing data on sex, and people who started treatment before diagnosis of cirrhosis were excluded (Fig. 1). The University of British Columbia Behavioural Research Ethics Board approved this study (H23-02171). The analysis was conducted using de-identified data collected as part of routine healthcare. Hence, written informed consent was not needed.

Outcome and exposure

The outcomes of interest are all-cause and liver-related death, which were ascertained to December 31, 2020. Assessment of all-cause and liver-related deaths was

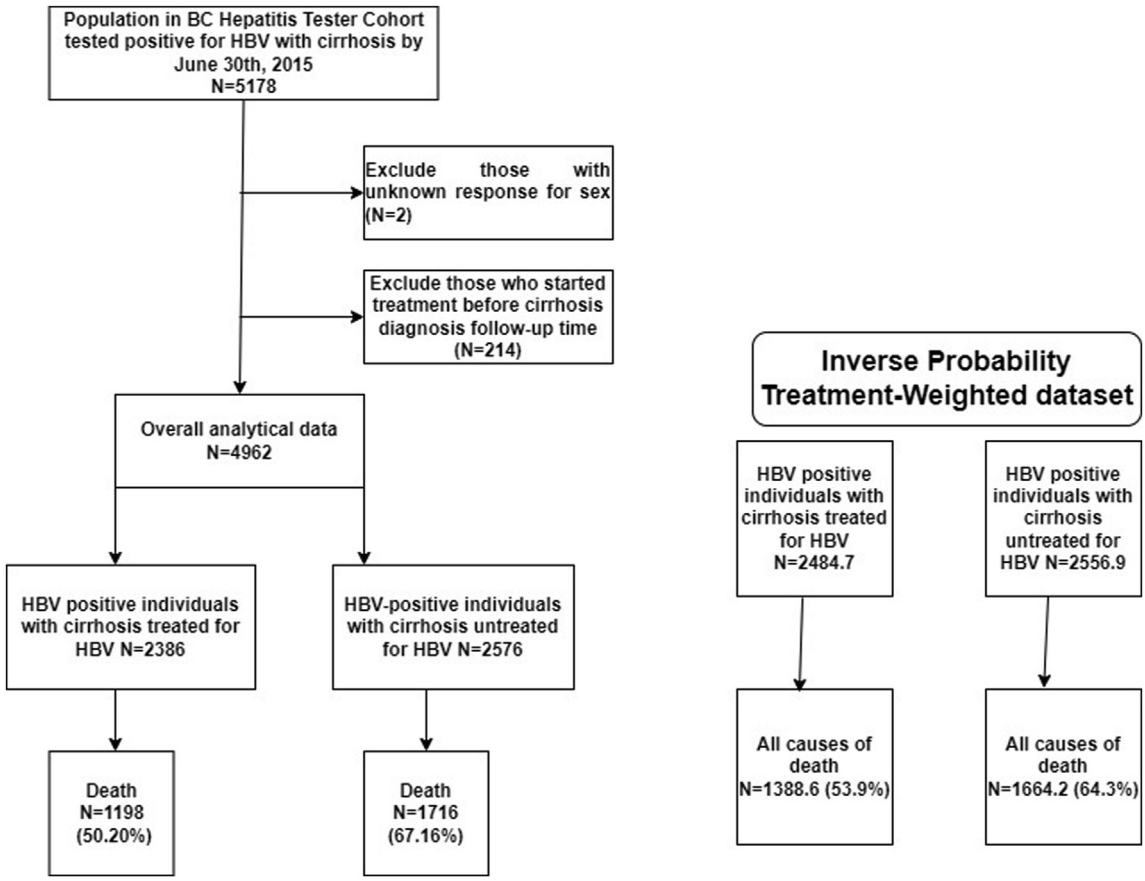

Fig. 1: Study population flowchart for all-cause of mortality among BC population cohort living with HBV infection with cirrhosis from 1990 to 2015. BC, British Columbia; HBV, hepatitis B virus.

based on data from the BC Vital Statistics Registry.[19] In BC, all conditions, diseases and events noted on the certificates are coded and tabulated according to the latest revision of the International Classification of Diseases, which was adopted by the World Health Assembly in 1975.[20] Liver-related death was defined according to the International Classification of Diseases, ninth (ICD-9) and 10th (ICD-10) editions.[21,22] People whose death certificate had an ICD-9 code 571 (for the period 1990–2007) or an ICD-10 codes (for the period 2008–2020) of viral hepatitis (B15-19), sequelae of viral hepatitis (B942), liver cancer (C22), alcoholic liver disease (K70) or non-alcoholic liver disease (K71-77) were considered to have liver-related cause of deaths. Cirrhosis was identified at the first occurrence of either of one physician visit or one hospitalization code relevant to cirrhosis (definition Supplementary Table S2). We considered HBV treatment as a time-varying exposure. Individuals who received one of the following antivirals: tenofovir, entecavir, adefovir, lamivudine, interferon-alpha, and peg-interferon were considered as treated for HBV. With the goal of prevention of liver cirrhosis and its consequences such as liver failure and hepatocellular carcinoma, Canadian guidelines for management of HBV of 2018 consider several criteria to be eligible for HBV treatment including cirrhosis, HBV DNA level of >2,000UI/mL and elevated ALT.[23] Individuals were considered to have received HBV treatment if they had at least one prescription dispensed in the BC PharmaNet database (Supplementary Table S3).

Potential predictors

We considered demographic variables at an individual's first cirrhosis diagnosis date (Supplementary Table S2), including age (categorized as <45, 45–54, and 55 and above according to clinical reasoning for people at risk of getting HBV and HCV: baby boomers, generation following baby boomers, and young people with low risk of getting viral hepatitis), sex (male or female), and ethnicity (East Asian, South Asian and Other) as predictors for HBV treatment.[24,25] Ethnicity was determined using a validated algorithm, Onomap[26,27] and classified into three categories (South Asian and East Asian, and Other: White, Black, Central Asian, Latin American, Pacific Islander, and West Asian individuals). Due to small sample size for liver -related and all cause of mortality in South and East Asian population groups, these were combined and presented as Asian ethnicity. We assessed socioeconomic status using the Québec Index of Material and Social Deprivation defined in five quintiles from Q1 (less deprived) to Q5 (most deprived).[28] Guided by the literature, we also considered other predictors related to all-cause and liver-related deaths or living with hepatitis B infection, including injection drug use, problematic alcohol use, and non-alcoholic fatty liver diseases.[29,30] We assessed other comorbidities such as diabetes, chronic kidney disease, hypertension, hepatic complications (varices, hepatic encephalopathy, etc.), decompensated cirrhosis, liver cancer using validated algorithms based on diagnostic codes and prescription drug records in administrative health datasets.[31] HIV and HCV infections were diagnosed based on laboratory confirmation according to BC provincial guidelines for HIV and HCV testing, HCV infection status was defined by a confirmed case of HCV or has a positive lab test (HCV-antibody, HCV RNA positive result or genotype) or by one or more HCV treatment dispensation in PharmaNet.[17,32] We also assessed categorization of the year of cirrhosis diagnosis before and after 2010 based on the availability of potent antivirals (tenofovir and entecavir) in Canada.[33]

Statistical analysis

We estimated the follow-up time for each study participant in persons years starting on the first cirrhosis diagnosis date until death or December 31, 2020. HBV treatment was considered as time-dependent variable, where time period before treatment start date was considered untreated.[34] We computed the crude mortality rate by 1000 persons-years in general and by HBV treatment status. We constructed cumulative incidence curves using the one minus Kaplan–Meier test[35] for non-competing risk and the Aalen–Johansen test in case of competing risk,[36] comparing cumulative incidence probabilities between the two groups. We used the Pearson Chi-square test of independence to examine the association between categorical variables.[37] We performed Cox proportional hazards regression with inverse probability treatment weighting to assess the association of HBV treatment time-varying status with all-cause mortality and estimated adjusted hazard ratios (aHRs) adjusting for sociodemographic, clinical, and behavioural variables to account for confounding. For liver related mortality as outcome, we computed adjusted subdistribution hazard ratios (asHRs) through multivariable competing risk regression model using Fine Gray model to account for competing risk for liver-related mortality weighted with inverse probability treatment weighting.[38] We constructed the final model with variables identified in the minimum adjustment set from the direct acyclic graph (Supplementary Fig. S1A and B). We did not include decompensated cirrhosis and hepatocellular carcinoma as predictors in the model because they were considered as mediators.[39,40] We also conducted additional analyses to assess the effect of mediation of hepatocellular carcinoma by replicating exposure in current exposure and exposure counterfactual after running mediator model, then we run the outcome models using the 2 exposures.

In this study, we compared the distribution of characteristics of individuals treated for HBV vs non-treated individuals with standardized mean differences.[41] We estimated the propensity scores for treatment status

through logistic regression models with the estimand average treatment effect for treated and used to produce stabilized IPTW to account for differences between individuals who received treatment and those who did not receive treatment. The model included sex, ethnicity, social deprivation quintiles, HCV infection, HIV infection, diabetes, chronic kidney disease, injection drug use, alcohol use disorder, and non-alcoholic fatty liver disease. We selected the covariates for the PS model if the covariates were determined as a confounder in the relationship between HBV treatment and all-cause or liver-related mortality, or were risk factors for all-cause or liver-related mortality.[42] Finally, we calculated inverse probability treatment weighting for estimating average treatment effect for treated based on propensity score (inverse probability treatment weighting = 1 for treated individuals, and inverse probability treatment weighting = 1/(1-Prppensity Score) for untreated). We assumed the distribution of characteristics between those who were treated and untreated were balanced after weighting based on the standardized mean difference <0.2.[43]

In addition, as HCV infection is also an important risk factor of all-cause or liver-related death, the effect of HBV treatment may be modified by HCV infection status. To consider the effect modification of HBV treatment on all-cause and liver-related death by HCV infection, we calculated cumulative incidence curves and incidence mortality rates per 1000 person-years of follow-up in the overall study population by HBV treatment status for those who had HCV coinfection and those without HCV infection separately. First, we created a four-level variable that combines HBV treatment status and HCV infection status to assess and compare the incidence rate for all-cause and liver-related mortality across the four subgroups (HBV treated without HCV; HBV treated with HCV; HBV untreated without HCV; HBV untreated with HCV). Then, we used a multivariable Fine–Gray proportional hazards model[44] to compute asHR for liver-related mortality in each subgroup. Moreover, we conducted a stratified analysis to compute aHR for the association of HBV treatment with all-cause mortality by HCV status. We employed a double-robust approach to adjust for residual confounding by adjusting for covariates again in the Fine–Gray models after inverse probability treatment weighting.[45] To assess the effect modification of HBV treatment by HCV status, we included the interaction terms in the multivariable model and performed a likelihood ratio test based on the analysis of deviance.[46] Finally, we conducted a stratified analysis to compute aHR for the association of HBV treatment with all-cause mortality by high potent vs low potent HBV-antivirals (tenofovir or Entecavir vs other antivirals) as sensitivity analysis. We fitted the Fine–Gray models in the overall dataset with the inverse probability treatment weighting for average treatment effect for treated. The multivariable Fine–Gray model with inverse probability treatment weighting also assessed the interaction term. The dataset was created in Statistical Analysis System (SAS) version 9.4,[47] and was imported into R version 4.03[48] for analyses. This study followed the STROBE guidelines.

Role of the funding source

This study was supported by the BC Centre for Disease Control and the Canadian Institutes of Health Research (CIHR) [Grant # NHC-142832, PJT-156066, and SC1 -178736]. This funder had no role in the study design, in the collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

Results

Study participants characteristics

In this study, we identified 5178 HBV-positive individuals with cirrhosis. After excluding people with missing data on sex, and those who started treatment before their cirrhosis diagnosis we included 4962 HBV-positive individuals with cirrhosis. Among the 4962 HBV-positive individuals with cirrhosis, 2386 (48.08%) had a record of receiving HBV treatment; among those treated, 454 (19.20%) received tenofovir or entecavir, and the remaining received diverse treatments, including adefovir, lamivudine, peginterferon-alfa, and interferon-alpha. At cirrhosis diagnosis, the untreated group tended to be slightly younger compared to the treated group (median age 54 vs 57 years). A higher proportion of treated compared to untreated were males [1802 (75.50%) vs 1766 (68.8%)], from urban area [2318 (97.2%) vs 2355 (91.8%)], from East and South Asian ethnicity [1506 (63.1%) vs 709 (27.5%)] and diagnosed with liver cancer [606 (18.6%) vs 420 (14.3%)]. There was a smaller proportion of individuals with HCV co-infection among those who were treated for HBV compared to those who were not treated for HBV [294 (12.3%) vs 1101 (42.7%)] (Table 1). The inverse probability treatment weighting reduced the differences in majority of characteristics between cirrhotic individuals with HBV infection treated for HBV and those untreated (Table 1).

In total, 2914 individuals (58.73%) died during the study period; 932 (31.98%) from liver-related causes. Among the 2386 treated HBV individuals, 1198 (50.20%) and 191 (8.0%) died from all causes and liver-related causes, respectively. Among the 2576 individuals who did not receive treatment for HBV, 1716 (67.14%) and 741 (28.99%) died from all causes and liver-related causes, respectively. The median follow-up periods for treated individuals were 2.97 (Interquartile range: 6.70) years after the beginning of HBV treatment, and 2.87 (Interquartile range: 5.48) years for untreated individuals.

Covariates	Overall study population by treatment status				Inverse probability of treatment weighted (IPTW) dataset[a]		
	Total study participants (N = 4962)	Cirrhotic HBV + treated (n = 2386)	Cirrhotic HBV + untreated (n = 2576)	SMD	Cirrhotic HBV + treated (n = 2484.7)	Cirrhotic HBV + untreated (n = 2556.9)	SMD
Sex (%)				0.156			0.006
Female	1394 (28.1)	584 (24.5)	810 (32.4)		697 (28.0)	723 (28.3)	
Male	3568 (71.9)	1802 (75.5)	1766 (68.6)		1788 (72.0)	1834 (71.7)	
Age group (%)				0.220			0.077
<45 years old	1133 (22.8)	458 (19.2)	675 (26.2)		641 (25.8)	575 (22.5)	
45–54 years old	1381 (27.8)	622 (26.1)	759 (29.5)		667 (26.9)	714 (27.9)	
55 years old and above	2448 (49.3)	1306 (54.7)	1142 (44.3)		1177 (47.4)	1268 (49.6)	
Ethnicity (%)				0.766			0.032
Other[b]	2747 (55.4)	880 (36.9)	1867 (72.5)		1424 (57.3)	1424 (55.7)	
East and South Asian	2215 (44.6)	1506 (63.1)	709 (27.5)		1061 (42.7)	1133 (44.3)	
Material deprivation (%)				0.229			0.085
Less deprived (Q1)	751 (15.1)	344 (14.4)	407 (15.8)		354 (14.2)	394 (15.4)	
Q2	816 (16.4)	398 (16.7)	427 (16.6)		407 (16.4)	428 (16.7)	
Q3	858 (17.3)	442 (18.5)	416 (16.1)		450 (18.1)	450 (17.6)	
Q4	951 (19.2)	458 (19.2)	493 (19.1)		443 (17.8)	480 (18.8)	
Most deprived (Q5)	1384 (27.9)	702 (29.4)	682 (26.5)		691 (27.8)	703 (27.5)	
Area of residence				0.237			0.237
Rural	251 (5.1)	60 (2.5)	191 (7.4)		29 (2.5)	99 (7.4)	
Urban	4673 (94.2)	2318 (97.2)	2355 (91.8)		1115 (97.2)	1223 (91.8)	
Unknown	28 (0.6)	8 (0.3)	20 (0.8)		4 (0.3)	10 (0.8)	
Hepatitis C virus (%)				0.724			0.069
Negative or Unknown	3567 (71.9)	2092 (87.7)	1475 (57.3)		1698 (68.4)	1829 (71.5)	
Positive	1395 (28.1)	294 (12.3)	1101 (42.7)		786 (31.6)	728 (28.5)	
HIV (%)				0.44			0.158
Negative or Unknown	4584 (92.4)	2316 (97.1)	2268 (88.0)		2170 (87.3)	2355 (92.1)	
Positive	378 (7.6)	70 (2.9)	308 (12.0)		315 (12.7)	202 (7.9)	
Diabetes (%)				0.031	143.6		0.036
No	3814 (76.9)	1806 (75.7)	2008 (78.0)		1946 (69.8)	1964 (76.8)	
Yes	1148 (23.1)	580 (24.3)	568 (22.0)		539 (21.7)	593 (23.2)	
Chronic Kidney Disease (%)				0.161			0.085
No	4725 (95.2)	2304 (96.6)	2421 (94.0)		2308 (92.9)	2427 (94.9)	
Yes	237 (4.8)	82 (3.4)	155 (6.0)		177 (7.1)	130 (5.1)	
Hypertension (%)				0.104			0.039
No	3418 (68.9)	1562 (65.5)	1856 (72.0)		1699 (68.4)	1795 (70.2)	
Yes	1544 (31.1)	824 (34.5)	720 (28.0)		786 (31.6)	762 (29.8)	
History of injection drug use (%)				0.46			0.106
No	4027 (81.2)	2264 (94.9)	1763 (75.8)		2006 (83.3)	2167 (84.8)	
Yes	745 (15.0)	122 (5.1)	623 (24.2)		478 (15.2)	390 (15.2)	
Alcohol use disorder (%)				0.421			0.089
No	4167 (84.0)	2252 (94.4)	1915 (74.3)		1991 (80.1)	2136 (83.5)	
Yes	795 (16.0)	134 (5.6)	661 (25.7)		494 (19.9)	421 (16.5)	
Non-alcoholic fatty liver disease (%)				0.043			0.120
No	4915 (99.1)	2372 (99.4)	2543 (98.7)		2424 (97.6)	2534 (99.1)	
Yes	47 (0.9)	14 (0.6)	33 (1.3)		60 (2.4)	23 (0.9)	
Liver cancer				<0.001			<0.001
No	3057 (61.6)	1780 (74.6)	2156 (83.7)		1926.8 (77.5)	2061 (83.0)	
Yes	1026 (20.7)	606 (18.6)	420 (16.3)		558 (22.5)	496. (27.0)	
Type of drugs received							
Tenofovir or Entecavir	454 (9.1)	454 (19.2)	NA		227 (9.1)	NA	
Other antiviral[c]	1908 (38.5)	1908 (80.8)	NA		2259 (90.9)	NA	
Type of physician							
Specialist	1914 (38.6)	1914 (80.2)	NA		920 (80.2)	NA	
General practitioner	472 (9.5)	472 (19.8)	NA		1574 (19.8)	NA	

(Table 1 continues on next page)

Covariates	Overall study population by treatment status				Inverse probability of treatment weighted (IPTW) dataset[a]		
	Total study participants (N = 4962)	Cirrhotic HBV + treated (n = 2386)	Cirrhotic HBV + untreated (n = 2576)	SMD	Cirrhotic HBV + treated (n = 2484.7)	Cirrhotic HBV + untreated (n = 2556.9)	SMD
(Continued from previous page)							
Year of cirrhosis diagnosis				0.244			0.021
Before 2010	3025 (61.0)	1527 (66.7)	1498 (54.8)		1484 (60.6)	1556 (59.5)	
2010 and after	1937 (39.0)	859 (33.3)	1078 (45.2)		1010 (39.4)	1000 (40.5)	

HBV, hepatitis B virus; HCV, hepatitis C virus; NA, Non applicable; Q, quintile; SMD, standardized mean difference. [a]The propensity scores (PS)-weighted dataset used inverse probability weights (IPW) to estimate the average treatment effect (ATE). The IPTW were computed based on age at 1st HBV testing, sex, ethnicity, social deprivation quintiles, HCV infection, diabetes, chronic kidney disease, history of injection drug use, alcohol use disorder, and non-alcoholic fatty liver disease. The IPW analysis includes 2386 cirrhotic individuals treated for HBV infection and 2576 cirrhotic individuals not treated for HBV infection. [b]Other: White, Black, Central Asian, Latin American, Pacific Islander, and West Asian individuals. [c]Other antiviral: adefovir, lamivudine, interferon-alpha, and peg-interferon.

Table 1: **Baseline study participants' characteristics by HBV treatment status dataset from the British Columbia Hepatitis Testers Cohort 1990–2015.**

All-cause and liver-related mortality rates among participants

In the overall study sample, crude all-cause and liver-related mortality rates were higher among people who were not treated compared to those who received treatment (all-cause mortality: 115.47; 95% CI: 110.14, 121.07 vs 35.72; 95% CI: 32.97, 38.70 per 1000 person-years; liver-related mortality: 49.86; 95% CI: 46.40, 53.59 vs 11.39; 95% CI: 9.88, 13.13 per 1000 person-years, respectively) (Table 2). Among people with HCV coinfection who were treated for HBV infection, the rate of all-cause mortality and liver-related mortality was 56.90/1000 person-years and 27.24/1000 person-years, respectively. Among people with HCV coinfection not treated for HBV, the rate of all-cause mortality and liver-related mortality were 147.89/1000 person-years and 68.15/1000 person-years, respectively (Table 2). The unadjusted and adjusted cumulative incidence curves showed significantly higher probabilities of all-cause and liver-related deaths with increase over time among individuals with cirrhosis non-treated for HBV infection (vs those treated for HBV infection) (Fig. 2A–D, Fig. 3A–D).

Association of HBV treatment with all-cause and liver-related mortality

In the IPTW analysis, after adjusting for potential confounders and competing mortality risk (for liver-related mortality), the aHR and asHR for the association of HBV treatment with all-cause and liver-related mortality were 0.74 (95% CI: 0.65, 0.84) and 0.72 (95% CI: 0.58,0.89), respectively (Table 3). Other risk factors associated with both all-cause and liver-related mortality included advanced age, HCV infection, chronic kidney disease, injection drug use, high blood pressure, and alcohol use disorder (Table 3). In sensitivity analysis, compared to non-treated individuals, the aHR and asHR for the association of HBV treatment stratified by Tenofovir and entecavir vs other antivirals (adefovir, lamivudine, interferon-alpha, and peg-interferon) status with all-cause and liver-related mortality were 0.62 (95% CI: 0.50, 0.77) vs 0.72 (95% CI: 0.65; 0.80) and 0.40 (95% CI: 0.26, 0.63) vs 0.69 (95% CI: 0.58,0.83), respectively (Table 4). While in the mediation analysis considering HCC as mediator, the aHR and asHR for the association of HBV treatment with all-cause and liver-related mortality were 0.98 (95% CI: 0.92, 1.04) and 0.70 (95% CI: 0.63, 0.76), respectively (Supplementary Table S4).

The effect of HCV infection in the association of HBV treatment and all-cause and liver-related mortality

After adjustment for potential confounders and other competing mortality risks for liver-related mortality, we computed the aHR or asHR for each subgroup of the composite variable combining HBV treatment with HCV infection. Compared to individuals with cirrhosis without

	n/person years	MR (per 1000 PY)	95% CI
Liver-related mortality			
Total study population	932/31, 628.89	29.47	(27.63, 31.42)
HBV + treated	191/16, 768.31	11.39	(9.88, 13.13)
HBV + untreated	741/14, 860.58	49.86	(46.40, 53.59)
HBV + treated without HCV	146/15116.36	9.66	(8.21, 11.35)
HBV + treated with HCV	45/1651.95	27.24	(20.34, 36.48)
HBV + untreated with HCV	359/5267.49	68.15	(61.45, 75.58)
HBV + untreated without HCV	382/9593.092	39.82	(36.02, 44.02)
All-cause mortality			
Total study population	2914/31,628.89	92.13	(88.85, 95.54)
HBV + treated	599/16,768.308	35.72	(32.97, 38.70)
HBV + untreated	1716/14,860.58	115.47	(110.14, 121.07)
HBV + treated without HCV	505/15116.36	33.41	(30.62, 36.45)
HBV + treated with HCV	94/1651.948	56.90	(46.49, 69.65)
HBV + untreated with HCV	779/5267.49	147.89	(137.86, 158.65)
HBV + untreated without HCV	937/9593.09	97.67	(91.62, 104.13)

PY, person-years; n, number of deaths; MR, Mortality rate; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus. Rates, deaths, and person time are based on the total population sample.

Table 2: **Liver-related and all-cause mortality rates among HBV + individuals with cirrhosis by treatment and co-infection HBV/HCV status based on the total population.**

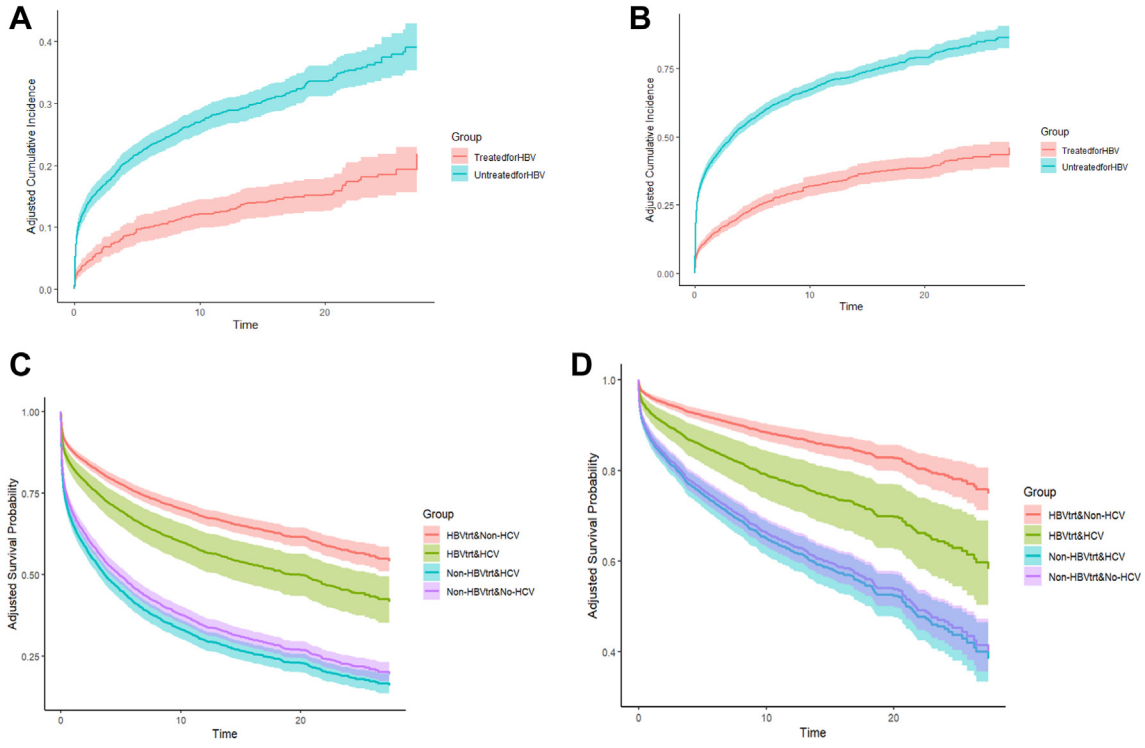

Fig. 2: **A**. The adjusted cumulative incidence rate of all-cause of mortality for individuals with cirrhosis and HBV treated for HBV vs those not treated in BC from 1990 to 2015. CI, Confidence interval; HBV, hepatitis B virus; UntreatedforHBV, individuals not treated for HBV; treatedforHBV, individuals treated for HBV. **B.** The adjusted cumulative incidence of liver-related mortality for individuals with HBV and cirrhosis treated for HBV vs those not treated in BC from 1990 to 2015. CI, Confidence interval; HBV, hepatitis B virus; UntreatedforHBV, individuals not treated for HBV; treatedforHBV, individuals treated for HBV. **C.** Adjusted survival probability of all causes of mortality for individuals with HBV and cirrhosis treated for HBV vs those not treated with interaction with HCV infection in BC from 1990 to 2015. HCV, hepatitis C virus; HBV, hepatitis B virus. HBVtrt & HCV, co-infected HBV and HCV and treated for HBV; HBVtrt&Non-HCV, HBV infection without coinfection with HCV and treated for HBV; Non-HBVtrt & HCV, co-infection HBV and HCV and non-treated for HBV; Non-HBVtrt&No-HCV, HBV infection non-co-infected with HCV and non-treated for HBV. **D.** Adjusted Survival probability of liver-related mortality for individuals with HBV and cirrhosis treated for HBV vs those not treated with interaction with HCV infection in BC from 1990 to 2015. HCV, hepatitis C virus; HBV, hepatitis B virus. HBVtrt & HCV, co-infected HBV and HCV and treated for HBV; HBVtrt&Non-HCV, HBV infection without coinfection with HCV and treated for HBV; Non-HBVtrt & HCV, co-infection HBV and HCV and non-treated for HBV; Non-HBVtrt&No-HCV, HBV infection non-co-infected with HCV and non-treated for HBV.

HCV infection and treated for HBV infection as the reference, individuals with HCV infection, not treated for HBV infection had a higher hazard of both all-cause and liver-related mortality (aHR 1.57; 95% CI: 1.22, 2.04 and asHR 1.60; 95% CI 1.25, 2.05, respectively). Also, individuals without HCV infection and not treated for HBV infection had a higher risk of all-cause and liver-related mortality compared to the reference category (aHR 1.42; 95% CI: 1.12, 1.79 and asHR 1.45; 95% CI: 1.16, 1.81, respectively) (Table 5). Using the likelihood ratio test on the analysis of deviance to assess the effect modification, the model containing the interaction term was found to be superior to the one without it.

Discussion

In this population-based study, we found high all-cause and liver-related mortality rates in people with HBV and cirrhosis who were not treated. After adjusting for confounders and competing mortality for liver-related deaths, HBV treatment in people with HBV infection and cirrhosis reduced the risk of all-cause and liver-related mortality by approximately one-quarter, compared to individuals with HBV infection and cirrhosis who did not receive treatment. The risk of deaths was more pronounced in older individuals, and other ethnicities than East and South Asian. Furthermore, study participants with HCV coinfection who were not treated for their HBV had a higher risk of death from any cause and liver-related causes. These findings highlight the importance of HBV treatment in reducing of all-cause and liver related mortality among people with HBV infection and cirrhosis.

The findings from this study showed that among people diagnosed with HBV and cirrhosis, only a small number of people were on treatment. There are several

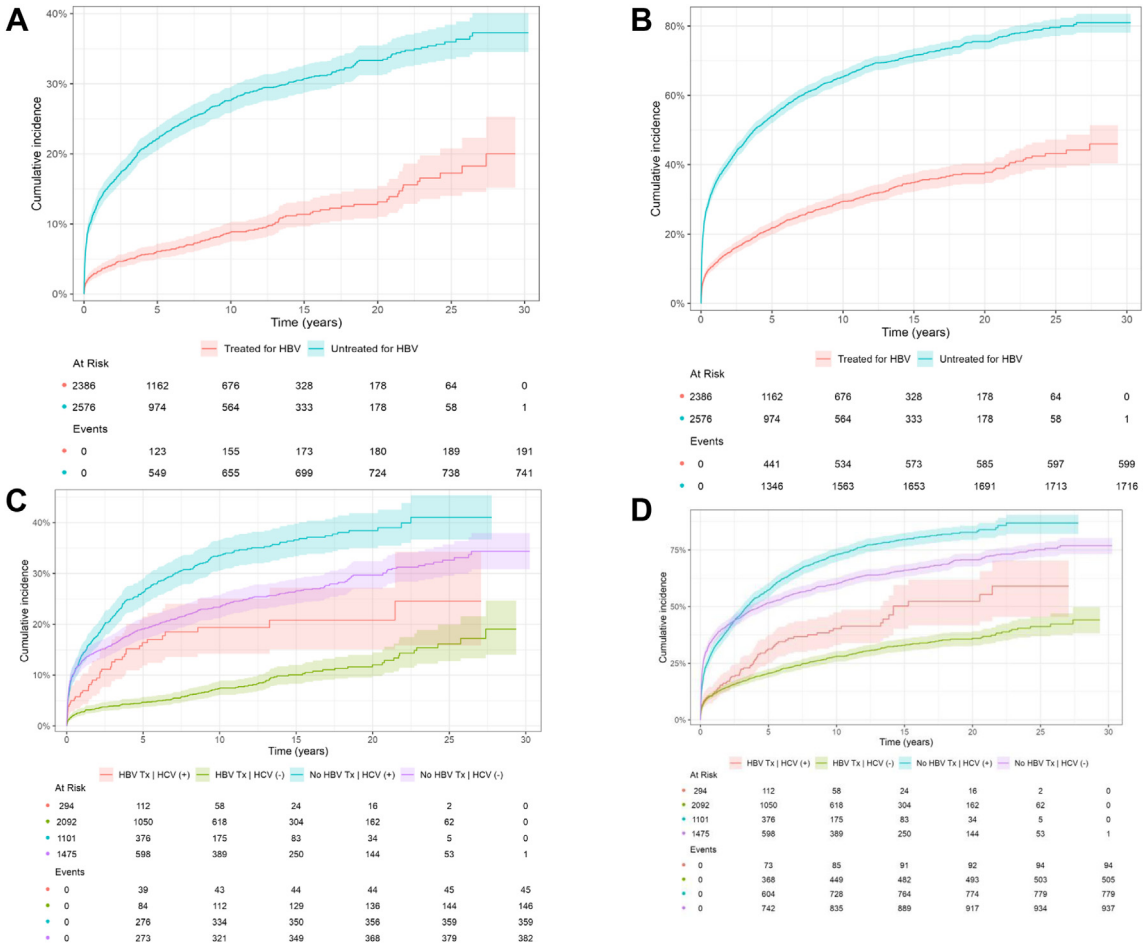

Fig. 3: **A.** The 30 years cumulative incidence rate of all causes of mortality for cirrhotic individuals living with HBV treated for HBV vs those not treated in BC from 1990 to 2015. Cumulative incidence of all causes of mortality in cirrhotic individuals treated and not treated for HBV infection, over 25 years of follow-up. Dash lines: cumulative incidence of all causes of mortality for cirrhotic individuals treated; continuous lines: cumulative incidence of all causes of mortality for cirrhotic individuals not treated for HBV. HBV, hepatitis B virus. **B.** The 30-year Cumulative incidence rate of liver-related mortality for cirrhotic individuals living with HBV treated for HBV vs those not treated in BC from 1990 to 2015. Cumulative incidence of liver-related mortality in cirrhotic individuals treated and not treated for HBV infection, over 20 years of follow-up. Dash lines: cumulative incidence of liver-related mortality for cirrhotic individuals treated; Continuous lines: cumulative incidence of liver-related mortality for cirrhotic individuals not treated for HBV. HBV, hepatitis B virus. **C.** The 30-years cumulative incidence rate of all causes of mortality for cirrhotic individuals living with HBV treated for HBV vs those not treated with interaction with HCV infection in BC from 1990 to 2015. Cumulative incidence of all causes of mortality in cirrhotic individuals treated and not treated for HBV infection with HCV interaction, over 30 years of follow-up. Blue lines: cumulative incidence of death for people treated for HBV without HCV; Red lines: cumulative incidence of death for people treated for HBV with HCV; violet lines: cumulative incidence of death for people non-treated for HBV without HCV; Green lines: cumulative incidence of death for people non-treated for HBV with HCV. HCV, hepatitis C virus; HBV, hepatitis B virus; HBV trt & HCV (+), co-infected HBV and HCV and treated for HBV; HBV trt & HCV (–), HBV infection without coinfection with HCV and treated for HBV; No HBV trt & HCV (+), co-infected HBV and HCV and non-treated for HBV; No HBV trt & HCV (–), HBV infection non-co-infected with HCV and non-treated for HBV. **D.** The 30-years Cumulative incidence rate of liver-related mortality for cirrhotic individuals living with HBV treated for HBV vs those not treated with interaction with HCV infection in BC from 1990 to 2015. Cumulative incidence of liver-related mortality in cirrhotic individuals treated and not treated for HBV infection with HCV interaction, over 30 years of follow-up. Blue lines: cumulative incidence of death for people treated for HBV without HCV; Red lines: cumulative incidence of death for people treated for HBV with HCV; violet lines: cumulative incidence of death for people non-treated for HBV without HCV; Green lines: cumulative incidence of death for people non-treated for HBV with HCV. HCV, hepatitis C virus; HBV, hepatitis B virus; HBV trt & HCV (+), co-infected HBV and HCV and treated for HBV; HBV trt & HCV (–), HBV infection without coinfection with HCV and treated for HBV; No HBV trt & HCV (+), co-infected HBV and HCV and non-treated for HBV; No HBV trt & HCV (–), HBV infection non-co-infected with HCV and non-treated for HBV.

Covariates	All causes of mortality aHR (95% CI)	Liver-related mortality asHR (95% CI)
HBV treatment status		
Untreated	Ref	Ref
Treated	0.74 (0.65, 0.84)	0.72 (0.58, 0.89)
Sex		
Female	Ref	Ref
Male	1.35 (1.21, 1.52)	1.00 (0.85, 1.19)
Age group		
<45 years old	Ref	Ref
45–54 years old	1.55 (1.32, 1.83)	1.39 (1.06, 1.83)
55 years old and above	2.35 (2.03, 2.71)	1.92 (1.43, 2.58)
Ethnicity		
East and South Asian	Ref	Ref
Other[c]	1.00 (0.90, 1.13)	1.31 (1.09, 1.57)
Material deprivation		
Less deprived (Q1)	Ref	Ref
Q2	0.87 (0.73, 1.04)	0.87 (0.67, 1.13)
Q3	1.05 (0.89, 1.25)	0.89 (0.68, 1.16)
Q4	0.97 (0.83, 1.15)	1.00 (0.78, 1.29)
Most deprived (Q5)	1.06 (0.91, 1.24)	0.97 (0.77, 1.23)
Year of cirrhosis diagnosis		
Before 2010	Ref	Ref
2010 and after	0.81 (0.72, 0.92)	1.24 (0.99, 1.55)
HCV status		
Negative	Ref	Ref
Positive	1.13 (1.00, 1.27)	1.20 (0.99, 1.46)
Diabetes		
No	Ref	Ref
Yes	0.95 (0.85, 1.08)	1.03 (0.85, 1.24)
Chronic kidney disease		
No	Ref	Ref
Yes	1.21 (1.00, 1.72)	2.07 (1.53, 2.81)
People who inject drugs		
No	Ref	Ref
Yes	1.27 (1.07, 1.50)	1.65 (1.26, 2.15)
Alcohol use disorder		
No	Ref	Ref
Yes	1.17 (0.99, 1.37)	1.31 (1.02, 1.68)
Hypertension		
No	Ref	Ref
Yes	1.22 (1.06, 1.48)	1.42 (1.17; 1.71)

aHR, adjusted hazard ratio; asHR, adjusted sub-distribution hazard ratio based on Fine & Grey competing risk model; IPTW, inverse probability of treatment weighting; CI, confidence interval; HBV, hepatitis B virus. [a]Model: Weighted using stabilized IPTW. [b]The PS-weighted dataset used inverse probability weights (IPW) estimating the average treatment effect for treated (ATT). IPW were estimated based on age at 1st HBV testing, sex, ethnicity, social deprivation quintiles, HCV infection, diabetes, chronic kidney disease, history of injection drug use, alcohol use disorder, year of cirrhosis diagnosis, and hypertension. [c]Other: White, Black, Central Asian, Latin American, Pacific Islander, and West Asian individuals.

Table 3: **Factors associated with all causes, and liver-related of mortality among cirrhotic people living with HBV treated for HBV compared to untreated in dataset weighted by inverse probability of treatment model.[a,b]**

factors associated with low treatment among individuals with HBV and cirrhosis including: people who are difficult to link with care such as people who inject drugs and those with alcohol use disorders, as well as patients' refusal for interferon-alfa-based therapy. In another study from Europe, a higher proportion of HBV treatment eligible individuals did not receive treatment (mean rate of non-treated equal to 46%). Factors influencing the non-treatment were similar as in our study.[49] There is a need for interventions to increase treatment uptake to realize the beneficial effect of treatment on health outcomes among people living with HBV.

To our knowledge, this is the first study in North America assessing the impact of HBV treatment on all-cause and liver-related mortality among individuals with HBV and cirrhosis. Previous research has shown that HBV infection was associated with increased all-cause and liver-related mortality in the USA and Canada,[12,50] however, none of these studies considered cirrhosis status in their analysis in this region. Results from our study are similar to those in other studies conducted among people with HBV infection and cirrhosis outside of North America. A retrospective cohort study conducted in Hong Kong has shown that, in a cohort of 482 individuals with cirrhosis who received treatment and 69 individuals with cirrhosis who did not receive treatment, the treated individuals had a lower risk of dying from both all-cause (aHR, 0.34; 95% CI, 0.18–0.62) and liver-related mortality (aHR, 0.26; 95% CI, 0.13–0.55).[9] However, the aHR for this study was lower than ours, possibly due to lower sample size, difference in population characteristics, exclusion of individuals with HCC, Child-Pugh C cirrhosis, and those with co-infection with HCV. Similar results were found in another multi-center, retrospective cohort study of 1088 chronic HBV patients with cirrhosis from Hong Kong, United States, and South Korea which assessed the impact of tenofovir on all-cause and liver-related mortality from January 2008 to 2016, showed that compared to untreated patients, tenofovir-treated patients experienced a 90% reduction in liver-related death and a 94% reduction in all-cause death.[51] In this study, the reduction of both all-cause and liver-related mortality were higher compared to our study results, probably because they only considered patients treated with tenofovir, while in our study, we considered all types of HBV treatment. In our study, tenofovir/entecavir group had better survival compared to non-tenofovir/entecavir group. In summary, our study along with previous studies show that treatment is associated with a significant improvement in survival among people with HBV and cirrhosis.

This study has shown coinfection of HBV-HCV were associated with a higher risk of death from all causes and liver-related causes. Since direct acting antivirals as an effective HCV treatment has shown to be protective against all-cause and liver-related mortality, it can be hypothesized that having an untreated HCV infection may further exacerbate the risk of all-cause and liver-related mortality among people living with HBV. This is worse if HBV is also untreated as they are dealing

Covariates	aHR	95% CI	asHR	95% CI
	All causes of mortality		Liver-related mortality	
HBV treatment status				
HBV untreated	Ref		Ref	
HBV treated with tenofovir/Entecavir	0.62	(0.50, 0.77)	0.40	(0.26, 0.63)
HBV treated with other antivirals	0.72	(0.65; 0.80)	0.69	(0.58, 0.83)

Multivariable models were adjusted with sex, age at first HBV testing date, birth cohort, ethnicity, material deprivation quintiles, HCV infection, diabetes, chronic kidney diseases, alcohol use disorder, injection drug use, year of cirrhosis diagnosis, and other competing risks. aHR, adjusted hazard ratios; CI, confidence interval; HBV, hepatitis B virus. The PS-weighted dataset used inverse probability weights (IPW) estimating the average treatment effect (ATE). IPW were computed based on age at 1st HBV testing, sex, birth group, ethnicity, social deprivation quintiles, HCV infection, HIV infection, diabetes, chronic kidney disease, history of injection drug use, alcohol use disorder, and non-alcoholic fatty liver disease.

Table 4: **Association of HBV treatment with high potency vs low potency drugs with all-cause and liver-related mortality between 1990 and 2015 in the British Columbia Hepatitis Testers Cohort in a dataset weighted by inverse probability of treatment.**

with two untreated viral hepatitis infection.[19,52] The interaction with untreated HBV could enhance the risk of dying from all-cause causes, including liver-related causes. HCV treatment status was not assessed in our study population. We have shown that HCV treatment is effective in reducing all cause and liver related mortality.[19] Thus, we have effective interventions to reduce the effect of HBV and HCV on health of people living with co-infection. There is a need to treat people with co-infection for HBV as well as HCV.

This study has several strengths. First, this is the first study in North America to assess the impact of HBV treatment on all-cause and liver-related mortality among individuals diagnosed with HBV and cirrhosis. As an observational study, bias from unmeasured confounding cannot be completely eliminated. However, our use of IPTW minimized this limitation. Lastly, this study has a large sample size with over 5000 individuals with HBV and cirrhosis, increasing the study's statistical power and precision.

Limitations include the nature of administrative data, which did not include some variables such as education, smoking, dietary patterns, physical activity levels, the dosage of treatment regimen, HBV DNA levels, as well as clinical biomarkers, such as liver enzyme levels. It also did not include clinical aspect such as co-infection with hepatitis D virus, and the cirrhosis complications such as portal hypertension. These factors are among the risk factors for all-cause and liver-related mortality. The lack of these data may be the source of some level of unmeasured confounding. The unmeasured confounding could have overestimated or underestimated the association between HBV treatment and all cause and liver-related mortality.[53] However, by adjusting for several confounders that could be proxies to these unmeasured ones such as social deprivation, and diagnoses of liver-related comorbidities or other comorbidities, we try to mitigate unmeasured confounding. As noted above, we used methods to make treated and untreated group similar to their known confounding profiles there by reducing the residual confounding, however, in observational studies, confounding cannot be completely ruled out. Furthermore, we used a double-robust approach of adjusting for covariates in the inverse probability treatment weighting weighted regression models to reduce the residual confounding. In addition to that, we were not able to know the reasons why these individuals with HBV

Covariates	aHR	95% CI	asHR	95% CI
	All causes of mortality		Liver-related mortality	
HBV and HCV status				
HBV treated without HCV	Ref		Ref	
HBV untreated with HCV	1.57	(1.22, 2.04)	1.60	(1.25, 2.05)
HBV untreated without HCV	1.42	(1.12; 1.79)	1.45	(1.16, 1.81)
HBV treated with HCV	1.10	(0.74, 1.63)	1.13	(0.77, 1.67)

Multivariable models were adjusted with sex, age at first HBV testing date, birth cohort, ethnicity, material deprivation quintiles, HCV infection, diabetes, chronic kidney diseases, alcohol use disorder, injection drug use and other competing risks. aHR, adjusted hazard ratios; CI, confidence interval; HBV, hepatitis B virus. The PS-weighted dataset used inverse probability weights (IPW) estimating the average treatment effect (ATE). IPW were computed based on age at 1st HBV testing, sex, birth group, ethnicity, social deprivation quintiles, HCV infection, HIV infection, diabetes, chronic kidney disease, history of injection drug use, alcohol use disorder, year of cirrhosis diagnosis, and non-alcoholic fatty liver disease.

Table 5: **Association of HBV treatment and coinfection with HCV with all-cause and liver-related mortality between 1990 and 2015 in the British Columbia Hepatitis Testers Cohort in a dataset weighted by inverse probability of treatment.**

diagnosed with cirrhosis were not treated, further studies results bias assessing the causes of no treatment for these individuals are recommended. The majority of study participants (81%) who received HBV treatment were treated using older antiviral regimens, which are no longer used currently, as only 19% received entecavir or tenofovir. To mitigate this limitation, we conducted a sensitivity analysis evaluating the association of HBV treatment stratified by high potent (tenofovir or entecavir) vs low potent antivirals status with all-cause and liver-related mortality.

Conclusion

The findings from this study indicate that compared to individuals with cirrhosis who were untreated for HBV; treated individuals have a significantly reduced risk of all-cause and liver-related mortality. The effect of HBV treatment on both all-cause and liver-related mortality highlights the importance of early HBV treatment to individuals living with HBV and cirrhosis. Furthermore, early screening, diagnosis, and management of HCV in people with HBV could potentially reduce mortality.

Contributors

JDM and NZJ developed the study protocol. JDM, MB, AY, SW, and NZJ developed the study design. SW and AY created the dataset; JDM, SW, HAVG, and NZJ analyzed, produced data tables and figures, and interpreted the data. JDM wrote the paper with important contributions from DJ, PAA, and NZJ. All authors had full access to the data, participated in data interpretation, and provided critical feedback on the manuscript. JDM and NZJ had the final authority of the manuscript submission, and all authors accepted responsibility for submission for publication.

Data sharing statement

This study is based on data contained in various provincial registries and database. Access to the 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. Request for data may be sent to datarequest@bccdc.ca.

Declaration of interests

JDM and DJ are supported by the Canadian Network on Hepatitis C (CanHepC) Ph.D. fellowship, DJ is also supported by the CIHR Frederick Banting and Charles Best Doctoral Award. RLM received travel awards from the CIHR and the University of British Columbia but not related the current work. SB received grant/research support from Gilead Sciences and Abbvie. EY has received grant/research support from Paladin Laboratories, Pfizer Inc, Novodisc Inc, Genefit Inc, Intercept Inc, Madrigal Inc, Gilead Sciences, Merck Inc, Sonic Incytes. AR has received greant/research support from Abbvie, Assembly, Galmed, Gilead, Intercept, Janssen, Merck, Novartis, Novo-Nordisc, Pfizer. MK has received grant/research support from Roche, Merck, Siemens, Boehringer Ingelheim and Hologic. NZJ participated in advisory boards and has spoken for AbbVie, not related to current work. MB had no conflict of interest at the time of the study but is now an employee of AstraZeneca. SW, PAA, SB, GC, AY, MA, HS, HAVG, HHK, and YA have no conflicts of interest to declare.

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This study would not happen without contribution of British Columbia population who provided the data used in this study, the British Columbia Centre for Disease Control, Providence Health Services Authority, British Columbia Ministry of Health, British Columbia Cancer Agency, and their respective program staff involved in data access, procurement and data management for their assistance. We would like to thank them for their special contribution and support to this study. 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 Data Steward(s).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2024.100826.

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