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Mortality Among Patients With Chronic Hepatitis B Infection: The Chronic Hepatitis Cohort Study (CHeCS)

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Abstract

Background.—According to death certificates, approximately 1800 persons die from hepatitis B annually in the United States; however, this figure may underestimate true mortality from chronic hepatitis B (CHB).

Methods.—We analyzed data from CHB patients seen in the Chronic Hepatitis Cohort Study (CHeCS) between 1 January 2006 and 31 December 2013. We compared overall and cause-specific death rates and mean ages at death between CHeCS CHB decedents and U.S. decedents from the Multiple Cause of Death (MCOD) file.

Results.—Of 4389 CHB patients followed for a mean of 5.38 years, 492 (11%) CHB patients died after a mean follow-up of 3.00 years. Compared to survivors, decedents were older, more likely to be White (40.6%), African-American (27.1%), or male (74.2%); and more likely to have had cirrhosis (59.8%), diabetes (27.2%), alcohol abuse (17.7%), hepatocellular carcinoma (17.5%), or a liver transplant (5.7%); whereas survivors were more likely to be Asian (48.8%; all $P < .001$). CHB patients died at an average age of 59.8 years—14 years younger than the general U.S. population—and at higher rates for all causes (relative risk [RR] = 1.85, 95% confidence interval [CI], 1.851–1.857) and liver-related causes (RR = 15.91, 95% CI, 15.81–16.01). Only 19% of CHB decedents and 40% of those dying of liver disease had hepatitis B reported on their death certificates.

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Disclaimer.

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Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Conclusions.—Compared to the general population, CHB patients die at younger ages and higher rates from all causes and liver-related causes. Death certificates underrepresent the true mortality from CHB.

Keywords

chronic hepatitis B; mortality; liver disease; risk factors; cause of death

Chronic hepatitis B (CHB), an indolent viral infection, progresses over decades to cirrhosis, liver failure, hepatocellular carcinoma, and premature death [1–3] in some patients. In the United States, about 1800 death certificates annually list hepatitis B virus (HBV) as an underlying or contributing cause of death [4]. However, accurately quantifying mortality related to hepatitis is difficult because of the prolonged period between infection and death and because death is not always linked to the underlying infection [5]. Manos et al. [6] found that only 48% of the deaths that were identified as HBV-associated in the medical records of patients with chronic liver disease were also captured as HBV-associated on their death certificates.

Underestimating the true prognosis of CHB infections may have real consequences for patients. Adults known to have high prevalences of CHB infections—including foreign-born Asian-Pacific Islanders [7], racial and ethnic minorities [8], and adults diagnosed with sexually transmitted infections [9]—are often not screened for HBV as recommended. Many high-risk adults are also not vaccinated against hepatitis B [9–11]. Even patients diagnosed with CHB receive less than the recommended monitoring to document changes in the disease activity or any development of hepatocellular carcinoma [12–14], which would allow them to receive timely and effective treatment.

The National Academies of Sciences, Engineering, and Medicine recently determined that hepatitis B elimination is feasible through vaccinations at birth, to infants, and to high-risk adults, and through screening and treatment of HBV-infected adults [15]; they recommended enhanced estimates of morbidity and mortality to guide elimination efforts [16]. Therefore, using data from the Chronic Hepatitis Cohort Study (CHeCS), we sought to (1) describe baseline demographic and clinical characteristics of CHB decedents and survivors, and (2) compare mean ages at death and all-cause and cause-specific mortality rates between CHB decedents and other U.S. decedents through the Multiple Cause of Death (MCOD) file.

METHODS

Study Population and Follow-up

Based on a study of hepatitis C mortality [17], we hypothesized that reported deaths underrepresent the true mortality from hepatitis B. Methods for CHeCS data collection and inclusion criteria for patients with chronic hepatitis B (CHB) have been described [18–20]. Briefly, the cohort is based on electronic health records (EHR) for patients aged ≥18 years who received outpatient, inpatient, emergency department, or laboratory services on or after 1 January 2006 at 1 of 4 large health systems: Geisinger Health System in Danville, Pennsylvania, serving approximately 2.6 million Pennsylvania residents in 44 counties;

Henry Ford Health System in Detroit, Michigan, serving over 1 million southeast Michigan residents; Kaiser Permanente–Northwest in Portland, Oregon, serving approximately 500 000 members; and Kaiser Permanente–Honolulu in Honolulu, Hawaii, serving about 220 000 patients, or approximately one-sixth of the Hawaiian population. Patients were classified as having CHB primarily by laboratory results and secondarily based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes [18–21]. Electronically-available data were supplemented with reviews of EHR text fields to collect additional information on demographics, hepatitis treatments, non-electronic laboratory results from other medical facilities, and liver biopsy results. Following standard procedures, trained personnel performed medical record abstraction for all patients in the original 2006–2008 cohort. Due to capacity and funding constraints, patients meeting electronic cohort criteria after 2008 were selected by simple random sampling for chart abstraction as funding allowed [19]; a final total of 69% of all patients meeting HBV cohort eligibility criteria had data abstraction. After data abstractors confirmed CHB infection from medical records or an electronically-available test that detects viral hepatitis nucleic acid, all available retrospective data back to the first health system visit was included for enrolled patients.

Each study site compares cohort patient records with the National Death Index, Social Security Death Index, or electronic state death registries annually [17] for those patients known to have died or for those not seen in the health system for 2 years. Deaths are also ascertained from hospitals and clinics reporting through the EHR. EHR-reported deaths without a matching death certificate do not have MCOD data.

Follow-up was defined to begin on 1 January 2006, regardless of the date of first visit, and age was calculated from date of birth as of that date. The study population included patients receiving their first clinical services through 31 December 2013. Follow-up was truncated on 31 December 2014 or the date of death, whichever came first.

Demographic and Clinical Data

Baseline demographic data and mean follow-up time in years were analyzed for CHB decedents and survivors based on data extracted from the EHR. Geocoded addresses obtained at the time of entry into the cohort were matched to U.S. census data in order to estimate each household's income. Insurance status was defined as of the most recent visit. Positive hepatitis B e antigen (HBeAg) was defined as any positive laboratory value reported during follow-up. HBV deoxyribonucleic acid levels were defined as the first available level. Baseline FIB-4 (fibrosis) score was calculated as the average of [Age(years)*aspartate transaminase (AST) (U/L)]/{Platelet count(10^9/L)*[alanine transaminase (ALT) (U/L)]$^{1/2}$} from clinical laboratory values measured within 1 week of each other during the first 2 years of observation, beginning on or after 1 January 2004 and excluding values generated during hospitalizations. If no FIB-4 value could be calculated in the first 2 years of observation, the first available value was used. FIB-4 values greater than 5.17 predict cirrhosis with a high degree of accuracy in the CHeCS CHB population; patients with FIB-4 less than or equal to 1.58 are unlikely to have cirrhosis [22, 23]. We defined cirrhosis as (1) a FIB-4 value greater than 5.17; (2) cirrhosis noted at any time during follow-up by liver biopsy;

(3) ICD-9-CM codes 571.2 and 571.5, for uncomplicated cirrhosis, documented in the EHR; or (4) ICD-9-CM and CPT codes for 1 or more of the following documented in the EHR: decompensated cirrhosis, including liver failure with hepatorenal syndrome (572.4), hepatic encephalopathy (572.2), portal hypertension/portal decompression procedures (572.3, 37 140, 37 160, 37 180, 37 181, 37 182, 37 183), esophageal varices complications with bleeding (456.0, 456.20, 42.91, 44.91, 96.06, 43 204, 43 205, 43 243, 43 244, 43 400 and 43 401), and ascites/paracentesis procedures (789.5, 789.59, 54.91, 49 080, 49 081) [24].

Body mass index (BMI) was defined as the first value recorded in the EHR. We defined other diagnoses as present if they were recorded in the EHR at any time during observation, including alcohol abuse (ICD-9-CM 291.0, 291.1, 291.2, 291.3, 291.4, 291.5, 291.8, 291.81, 291.82, 291.89, 291.9, 303.00, 303.01, 303.02, 303.90, 303.91, 303.92, 305.00, 305.01, 305.02, 980.0) [25]; diabetes (ICD-9-CM 250.Xx), if recorded in the EHR twice at 30 or more days apart; hepatitis C [18]; human immunodeficiency virus (HIV; any positive laboratory test, including third-generation enzyme-linked immunosorbent assay antibody test, fourth-generation combined antigen/antibody test, quantitative or qualitative viral load, and/or Western blot test); or liver transplantation (ICD-9-CM and CPT 996.82, 50.5, 50.51, 50.59, 47 135, 47 136, V42.7). Hepatocellular carcinoma was ascertained through validated tumor registry data. We defined “ever treated for CHB” as any prescription for medication licensed for treatment of hepatitis B.

Comparisons With Multiple Cause of Death Data

We calculated all-cause and cause-specific death rates for CHeCS CHB patients by dividing the number of deaths from 2006 through 2014 among CHB patients by the total person-years among CHeCS CHB population seen between 2006 and 2013. We used groupings of International Classification of Diseases, Tenth Revision (ICD-10) codes to classify causes of death as hepatitis B (B16, B16.x, B17.0, and B18.0, B18.1); hepatitis C (B 17.1, B18.2); liver-related, non-alcohol (K71-K77); liver-related, alcohol (K70); liver cancer (C22, D37.6); other hepatitis-related (B15, B15.x, B17.2, B17.8, B17.9, B18.8, B18.9, B 19, B94.2); HIV (B20-B24); cancer, except liver cancer (C00–C97 [except C22] and D37–48 [except D37.6]); circulatory (I00–I99); respiratory (J00–J99); diabetes (E10–E14); genitourinary (N00–N99); injuries and trauma (S00–S99, T00–T98, V01-V99, W00–W99, X00–X99 and Y00–Y36); mental and behavioral disorders (F00–F99); digestive, extra-hepatic (K00–K67 and K80–K93); and other (ICD-10 codes not specifically listed in any of our other classifications) [17]. Deaths were classified as belonging to a group if the underlying cause of death or MCOD fell into that category; decedents could be classified in more than one category if they had more than one cause of death. All-cause and cause-specific death rates were calculated per 100 000 person-years among CHeCS CHB patients and adjusted to the age distribution of the 2010 U.S. census population. For comparison, we calculated all-cause and cause-specific death rates from the U.S. MCOD database using data from 2006–2014 and the same ICD-10 grouping and age criteria, per 100 000 US population age-adjusted to the U.S. 2010 Census.

We calculated mean age at death for CHeCS CHB decedents for all-cause and cause-specific deaths, and compared that number with the mean age at death for adults aged ≥18 years from the 2006–2014 MCOD file.

Death Certificate Reporting of Hepatitis B Virus Infection

For all-cause and cause-specific deaths of CHeCS CHB decedents, we calculated the proportion of deaths for which hepatitis B was listed as underlying cause or contributing cause of death, defined as ICD-10 codes B16, B17.0, B18.0, and B18.1.

We also compared coding on the EHR for cirrhosis, hepatocellular carcinoma, or liver transplantation versus coding on the death certificate for hepatitis B or any liver disease. Liver disease included ICD-10 codes for liver-related conditions (K70–77), hepatocellular carcinoma (C22, D37.6), and hepatitis (B15-B19).

Statistical Analysis

SAS version 9.4 (SAS Institute Inc., Cary, NC) was used to prepare data for analysis, calculate unadjusted descriptive statistics on baseline characteristics and age-adjusted mortality rates, and compare the mortality rates and mean ages at death between CHeCS and MCOD data. All-cause and cause-specific mortality rates were calculated per 100000 person-years within the follow-up period. We used the Pearson Chi-square test for testing differences in percentages and t-tests for testing differences in mean ages and follow-up years. All tests were 2 sided. A P value < .05 was considered statistically significant.

RESULTS

A total of 4389 patients with CHB, seen at 1 of 4 participating medical centers during 2006 through 2013, were followed for a mean of 5.38 years through 31 December 2014. During that timeframe, 492 (11%) CHB patients died, after a mean follow-up of 3.00 years.

Demographic and Clinical Descriptive Data

Demographic and clinical variables for CHeCS CHB decedents and survivors are shown in Table 1. Compared to survivors, decedents were older and twice as likely to be White or African-American. Survivors were more than twice as likely as decedents to be Asian (48.8% vs. 18.4%). Decedents were significantly more likely than survivors to have evidence of cirrhosis (59.8% vs. 12.0%, P < .001). Decedents were also more likely to have evidence of diabetes, a history of alcohol abuse, a hepatitis C or HIV coinfection, hepatocellular carcinoma, a liver transplantation, or a history of treatment for CHB (all P < .001, compared with survivors).

Mortality

Death certificates with MCOD data were available for 409 (83%) CHeCS CHB decedents. Cause-specific and all-cause age-adjusted mortality rates during 2006–2014 for CHeCS patients with CHB were compared with the general U.S. population through the MCOD file, and are shown as sorted by relative risk in Table 2. Patients with missing death certificates were included in all-cause deaths, but in no other category. Risk of death from all causes

(relative risk [RR] = 1.854, 95% confidence interval [CI], 1.851–1.857) and all liver-related causes (RR = 15.91, 95% CI, 15.81–16.01) was elevated in CHeCS CHB patients compared to the general population. While death rates from non–liver-related causes were clustered in the lower range of the distribution, only 3 causes of death were significantly lower among CHB patients compared to the MCOD file: injuries/trauma, circulatory, and respiratory causes. (Note that patients may have more than 1 cause of death listed on a death certificate.)

Sorted in ascending order, mean ages at death were compared for CHeCS CHB patients and the U.S. general population (MCOD) in Table 3. On average, patients with CHB died significantly younger from all causes than persons in the general population (59.8 vs. 73.9 years, $P < .0001$). CHeCS CHB patients died, on average, before age 60 from HIV, alcohol-related liver disease, hepatitis C, other hepatitis causes, and non–alcohol-related liver disease. These differences were only significant for non–alcohol-related liver disease (59.3 years for CHeCS CHB patients versus 63 years for MCOD data, $P = .0013$) and other hepatitis causes (56.4 years for CHeCS CHB patients versus 62.6 years for MCOD data, $P = .0158$). For CHeCS CHB patients, the mean age at death for most non-hepatitis causes, such as respiratory illness, circulatory illness, and diabetes, was 60.5 to 63.5 years: for each cause, this mean was 10 to 16 years younger for those same causes in the U.S. population as a whole.

Death Certificate Reporting

Overall, 78 (19%) of 409 CHeCS CHB patients with matching death certificates had hepatitis B reported on the death certificate. In addition, only 40% of CHB patients with non-alcoholic liver disease, 13% of CHB patients with alcoholic liver disease, 29% of CHB patients with liver cancer, 50% of CHB patients with hepatitis C, and 33% of patients with another form of hepatitis had hepatitis B reported on the death certificate. For patients with any liver disease, including hepatitis B, reported on the death certificate, 40% had hepatitis B documented among the causes of death (Table 4).

We also evaluated the proportion of CHeCS CHB decedents who had liver disease coded in the EHR (Table 5). Of 249 CHeCS CHB decedents with cirrhosis by any criteria, 69 (27.7%) had hepatitis B and 159 (66.3%) had any liver disease reported on the death certificate. Hepatitis B was also less likely than any liver disease to be reported on the death certificate for patients with liver cancer (29.3% vs. 100%) or liver transplantation (12.0% vs. 80.8%).

DISCUSSION

Compared to the general population, CHeCS CHB patients died at higher rates from all causes and from liver-related causes, including liver cancer. They also died, on average, 14 years younger than decedents in the general population. Almost half (48%) of CHB decedents died at an average age of <60 years, with liver disease listed as an underlying or contributing cause of death on the death certificate. Despite this, only 40% of CHB decedents dying with liver disease had hepatitis B reported as an underlying or contributing cause on the death certificate. Although the relative contribution of HBV to any individual death cannot always be determined with CHeCS data, our study suggests a meaningful effect of CHB on mortality for people living with this chronic infection.

Because risk-based screening is incompletely implemented in medical practices [7–9], only 26% of persons with CHB were aware of their infection in the 2011–2014 National Health and Nutrition Examination Survey [26]. In fact, 41% of CHeCS CHB patients reported that they were first diagnosed with hepatitis B because of clinical symptoms [27]. Among patients in ongoing medical care with clinical indications for testing (2 or more abnormal ALT levels), less than half were subsequently tested for hepatitis B and an estimated one-fifth of CHB patients in care went undiagnosed with hepatitis B infection [28]. Patients diagnosed with CHB are unlikely to be followed optimally to detect the development of cirrhosis and hepatocellular carcinoma [12–14]. Finally, our data demonstrate that even patients with documented complications of CHB, including cirrhosis, liver transplantation, or liver cancer, were unlikely to have the diagnosis of hepatitis B recorded on their death certificate. To summarize, many patients with CHB are unlikely to be diagnosed [7–9, 26–28]; their fibrosis or other hepatic complications may go undetected [12–14]; and their chronic infection with hepatitis B is unlikely to be recorded at the time of death.

Others have confirmed that hepatitis B is associated with premature death and with elevated rates of death from all causes and from liver-related causes, including hepatocellular carcinoma [29–31]. Similar to our findings, diabetes [32, 33] and alcohol abuse [33, 34] are associated with an increased risk of death in persons with CHB. HIV coinfection also confers an increased risk of death [30, 35], especially in cirrhotic patients [35]. Although some have postulated a protective effect of hepatitis C viral infection on mortality from hepatitis B [36], other data demonstrates worse outcomes from hepatitis B and C coinfection compared to mono-infection [37, 38]. We were unable to evaluate the contribution of tobacco use in our study; however, smoking has been identified as a risk factor for hepatocellular carcinoma among persons with CHB [39]. Strengths of the study include similarities in age at death between the CHeCS CHB population and hepatitis B decedents in the MCOD data, and similar demographic [6, 26, 29] and prognostic [29, 30, 32, 35, 38] factors as those identified in other U.S. studies, suggesting that the CHeCS CHB decedents are similar to CHB decedents in the U.S. general population.

Limitations to our analysis include missing death certificates for 83 (17%) CHB decedents. BMI was missing for 13% of the CHeCS population and 34% of decedents. Smoking data was available for only 10% of the study population and was omitted from this analysis. In addition, laboratory test results were unavailable for many patients [12], including hepatitis e antigen (29.9%), HBV deoxyribonucleic acid level (35.7%), and FIB-4 (22.5%) results. Also, hepatitis B screening tests may not be ordered for high-risk persons, leading to underreporting of chronic hepatitis B [28]. EHR coding underestimates alcohol abuse [25] and may underestimate other clinical parameters. Finally, the CHeCS cohort represents people who received documented medical care for hepatitis B on at least 2 occasions that were 6 or more months apart, and is thus lacking representation from incarcerated persons, uninsured persons, and persons with limited or sporadic access to health care [18].

In conclusion, we observed increased prevalences of cirrhosis and other liver-related complications among CHB decedents compared to survivors, and increased risks of death from all causes and from all liver-related causes among CHB patients compared to the U.S. population. CHB patients also died, of all causes, on average, 14 years younger than persons

in the general population. Almost half of these patients died at an average age of <60, with liver disease listed as an underlying or contributing cause. Despite this, only 40% of CHB decedents dying of liver disease had hepatitis B reported on their death certificates, implying that national vital statistics data substantially underestimate the mortality burden of HBV. These findings strongly support hepatitis B elimination as a national public health goal [15, 16]. Clinicians can contribute to elimination of hepatitis B by (1) vaccinating all unvaccinated high-risk adults for HBV; (2) appropriately screening all high-risk persons for HBV; and (3) assuring that persons with HBV receive posttest counseling and clinical care [40].

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Table 1.

Baseline Demographic and Clinical Characteristics of CHeCS CHB Decedents and Survivors Aged ≥18 Years, 2006–2014

	Number (%)		
Baseline Characteristics	**CHeCS CHB Decedents, n = 492**	**Surviving CHeCS CHB Population, n = 3897**	***P* Value**
Age as of 1/1/2006, in years (86 missing)			
18–29	12 (2.4)	796 (20.9)	
30–44	91 (18.5)	1495 (39.2)	
45–59	223 (45.4)	1195 (31.4)	
60–74	129 (26.3)	298 (7.8)	
75+	36 (7.3)	28 (0.7)	<.001
Sex			
Male	365 (74.2)	2072 (53.2)	
Female	127 (25.8)	1825 (46.8)	<.001
Race (23 missing)			
White	199 (40.6)	788 (20.3)	
Black	133 (27.1)	519 (13.4)	
Hispanic	7 (1.4)	65 (1.7)	
Asian	90 (18.4)	1890 (48.8)	
Hawaiian/Pacific Islander	29 (5.9)	277 (7.2)	
American Indian/Alaskan Native	32 (6.5)	337 (8.7)	<.001
Site			
Kaiser Permanente–Northwest, Portland, Oregon	85 (17.3)	1277 (32.8)	
Kaiser Permanente–Honolulu, Hawaii	82 (16.7)	1063 (27.3)	
Henry Ford Health System, Detroit, Michigan	267 (54.3)	1260 (32.3)	
Geisinger Health System, Danville, Pennsylvania	58 (11.8)	297 (7.6)	<.001
Median household income			
<$15000	16 (3.4)	55 (1.5)	
>$15000–30 000	97 (20.4)	477 (12.9)	
>$30 000–<50 000	231 (48.5)	1502 (40.5)	
>$50 000–<75 000	93 (19.5)	1162 (31.3)	
>$75 000	39 (8.2)	513 (13.8)	<.001

	Number (%)		
Baseline Characteristics	**CHeCS CHB Decedents, n = 492**	**Surviving CHeCS CHB Population, n = 3897**	***P* Value**
Insurance status			
Medicaid	44 (9.4)	367 (9.6)	
Medicare only	94 (20.0)	337 (8.8)	
Medicare Plus	125 (26.6)	364 (9.5)	
Private	175 (37.2)	2649 (69.1)	
None	32 (6.8)	119 (3.1)	<.001
Baseline clinical characteristics			
HBeAg status			
Ever HBeAg(+)	127 (25.8)	701 (18.0)	
Always HBeAg(−)	169 (34.3)	2080 (53.4)	
HBeAg status missing	196 (39.8)	1116 (28.6)	<.001
Median HBV DNA level			
<2000 IU/mL	69 (14.0)	1046 (26.8)	
2000–20 000 IU/mL	36 (7.3)	510 (13.1)	
>20 000 IU/mL	144 (29.3)	878 (22.5)	
HBV DNA positive; level unknown	23 (4.7)	116 (3.0)	
HBV DNA missing	220 (44.7)	1347 (34.6)	<.001
Cirrhosis			
FIB-4 > 5.17	132 (26.8)	119 (3.1)	<.001
FIB-4 > 1.58 to ≤5.17	176 (35.8)	808 (20.7)	
FIB-4 ≤ 1.58	78 (15.9)	2086 (53.5)	
FIB-4 missing	106 (21.5)	884 (22.7)	
Liver biopsy evidence of cirrhosis	16 (3.2)	28 (0.7)	<.001
ICD-9-CM and CPT codes for cirrhosis	60 (12.2)	93 (2.4)	<.001
ICD-9-CM and CPT codes for hepatic decompensation	182 (37.0)	116 (3.0)	<.001
Cirrhosis by any criteria (above)	294 (59.8)	467 (12.0)	<.001
Selected risk factors and outcomes			
BMI < 25	115 (23.4)	1607 (41.2)	<.001
BMI 25 to < 30	106 (21.5)	1056 (27.1)	
BMI ≥ 30	102 (20.7)	814 (20.9)	

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	Number (%)		
Baseline Characteristics	**CHeCS CHB Decedents, n = 492**	**Surviving CHeCS CHB Population, n = 3897**	***P* Value**
BMI missing	169 (34.3)	420 (10.8)	
History of alcohol abuse	87 (17.7)	235 (6.0)	<.001
History of diabetes	134 (27.2)	485(12.4)	<.001
Hepatitis C coinfection	52 (10.6)	118 (3.0)	<.001
HIV coinfection	67 (13.6)	214 (5.5)	<.001
Hepatocellular carcinoma	86 (17.5)	45 (1.2)	<.001
Liver transplantation	28 (5.7)	46 (1.2)	<.001
Ever treated for CHB	200 (40.7)	873 (22.4)	<.001
Mean (median) follow up (years) from 1 January 2006	3.0 (2.3)	5.68 (6.0)	<.001

Abbreviations: BMI, body mass index; CHB, chronic hepatitis B; CHeCS, Chronic Hepatitis Cohort Study; CPT, Current Procedural Terminology; DNA, deoxyribonucleic acid; FIB-4, fibrosis-4 score; HBeA, hepatitus B e antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

Table 2.

Age-adjusted Mortality Rates Among CHeCS CHB Patients Compared With the MCOD Data by Cause of Death, 2006–2014

	Annual Mortality Rate, per 100000 Person-Years			
Cause of Death	**CHeCS CHB (n = 492)[a]**	**MCOD (n = 2 464 447)[b]**	**Relative Risk**	**(95% CI)[*]**
Hepatitis B virus	299.105	0.761	392.7	(374.9–411.4)
Hepatitis-related (other)	17.901	0.102	173.3	(152.8–196.7)
HIV	193.617	4.518	42.96	(42.14–43.79)
Liver cancer	281.230	9.480	29.39	(29.00–29.78)
Any liver-related	716.571	44.876	15.91	(15.81–16.01)
Liver, non–alcohol-related	415.891	28.298	14.66	(14.55–14.78)
Hepatitis C virus	42.785	7.228	5.900	(5.805–5.997)
Liver, alcohol-related	24.719	8.994	2.746	(2.703–2.790)
Genitourinary	233.308	114.382	2.021	(2.011–2.030)
Overall	1948.137	1041.162	1.854	(1.851–1.857)
Other causes	639.560	374.191	1.689	(1.685–1.694)
Digestive, non-liver	80.506	49.860	1.601	(1.589–1.612)
Diabetes	159.329	100.396	1.575	(1.567–1.584)
Malignancy, non-liver	385.194	265.196	1.445	(1.441–1.450)
Mental and behavioral disorders	236.007	206.219	1.128	(1.124–1.132)
Circulatory	456.327	573.388	0.788	(0.786–0.790)
Injury/Trauma	75.569	95.927	0.784	(0.779–0.788)
Respiratory	198.685	269.264	0.730	(0.727–0.733)

Abbreviations: CHB, chronic hepatitis B; CHeCS, Chronic Hepatitis Cohort Study; CI, confidence interval; HIV, human immunodeficiency virus; MCOD, Multiple Cause of Death.

[a] Total number of deaths equals 492; total CHB deaths with a death certificate were 409. Cases could have >1 listed cause of death. A mean mortality rate from 2006–2014 was calculated for CHeCS and MCOD data. CHeCS data were age-standardized to the census population in 2010.

[b] Average deaths per year, 2006–2014, age-standardized to the 2010 U.S. census population.

[*] $P < .05$ for all variables.

Table 3.

Comparison of Mean Age in Years Among CHeCS CHB Patients and the MCOD Data, by Cause of Death, 2006–2014

	Mean Age,[a] Years		
Cause of Death	**CHeCS CHB**	**MCOD**	***P* Value**
HIV	48.3	49.6	.4323
Injuries/trauma	51.4	56.7	.3592
Liver disease, alcohol-related	54.3	56.0	.6578
Hepatitis C virus	56.3	58.2	.4619
Hepatitis-related, other	56.4	62.6	.0158
Others	58.4	76.2	<.0001
Liver disease, non–alcohol-related	59.3	63.0	.0013
All liver-related	59.7	62.7	.0006
Overall	59.8	73.9	<.0001
Respiratory	60.5	76.5	<.0001
Genitourinary	60.6	77.2	<.0001
Digestive, non-liver	60.7	75.1	<.0001
Malignancy, non-liver	61.3	71.9	<.0001
Hepatitis B virus	61.6	59.2	.1150
Liver cancer	61.7	67.9	<.0001
Circulatory	62.3	77.0	<.0001
Diabetes	63.5	73.9	<.0001
Mental and behavioral disorders	63.5	75.8	<.0001

Abbreviations: CHB, chronic hepatitis B; CHeCS, Chronic Hepatitis Cohort Study; HIV, human immunodeficiency virus; MCOD, Multiple Cause of Death.

[a]Age-adjusted to U.S. 2010 census.

Table 4.

All Causes of Death With Hepatitis B Listed as an Underlying or Contributing Cause of Death for CHeCS CHB Patients, 2006–2014

Cause of Death (CHeCS CHB Patients)	Total Deaths[a]	HBV Listed on Death Certificate (%)
Liver disease, non-alcohol-related	111	44 (40)
Liver disease, alcohol-related	8	1 (13)
Liver cancer	75	22 (29)
Hepatitis C virus	14	7 (50)
Hepatitis-related, other	6	2 (33)
All liver-related causes	195	78 (40)
HIV	42	6 (14)
Cancer, except liver cancer	98	11 (11)
Circulatory	117	19 (16)
Respiratory	52	9 (17)
Diabetes	37	11 (30)
Genitourinary	61	8 (13)
Injuries/Trauma	16	3 (19)
Mental and behavioral disorders	52	8 (15)
Digestive (extra-hepatic)	25	7 (28)
Other	158	32 (20)
All causes	409	78 (19)

Abbreviations: CHB, chronic hepatitis B; CHeCS, Chronic Hepatitis Cohort Study; HBV, hepatitis B virus; HIV, human immunodeficiency virus.

[a]Total deaths with a death certificate were 409. More than 1 cause of death could be listed on death certificate, so individual causes will total more than 409.

Table 5.

Comparison of Liver Disease Diagnosis in EHR and Death Certificate Reporting Among CHeCS CHB Patients, by Liver-related Causes of Death, 2006–2014

		Death Certificate Reporting	
EHR Coding	**n**	**Hepatitis B Reported(%)**	**Liver Disease Reported (%)**
All CHB CHeCS decedents	409	78 (19.1)	195 (47.7)
No evidence of cirrhosis	160	9 (5.6)	30 (18.8)
Cirrhosis by any method of ascertainment	249	69 (27.7)	165 (66.3)
FIB-4 > 5.17	108	33 (30.6)	83 (76.9)
Liver biopsy evidence of cirrhosis	11	7 (63.6)	10 (90.9)
Diagnostic code for cirrhosis	48	17 (35.4)	42 (87.5)
Diagnostic / procedure code for decompensation	160	53 (33.1)	121 (75.6)
Liver cancer	75	22 (29.3)	75 (100.0)
Liver transplantation	25	3 (12.0)	20 (80.0)

Total number of deaths with a death certificate was 409. Patients could have more than 1 diagnosis or cause of death.

Abbreviations: CHB, chronic hepatitis B; CHeCS, Chronic Hepatitis Cohort Study; EHR, electronic health record; FIB-4, fibrosis-4 scores.