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Background: Changing US demographics and evolving chronic hepatitis B (CHB) treatments may affect longitudinal trends in CHB-related complications. We studied trends in the prevalence of cirrhosis (past or present) and incidence of all-cause mortality, stratified by patient age, sex, race, and antiviral treatment status, in a sample from US health care systems.

Methods: Joinpoint and Poisson regression (univariate and multivariable) were used to estimate the annual percent change in each outcome from 2006 to 2016.

Results: Among 5528 CHB patients, cirrhosis prevalence (including decompensated cirrhosis) rose from 6.7% in 2006 to 13.7% in 2016; overall mortality was unchanged. Overall rates of cirrhosis and mortality were higher among treated patients, but adjusted annual percent changes (aAPC) were significantly lower among treated than untreated patients (cirrhosis: aAPC +2.4% vs. +6.2%, mortality: aAPC −3.9% vs. +4.0%). Likewise, among treated patients, the aAPC for mortality declined −3.9% per year whereas among untreated patients, mortality increased +4.0% per year.

Conclusions: From 2006 to 2016, the prevalence of cirrhosis among CHB patients doubled. Notably, all-cause mortality increased among untreated patients but decreased among treated patients. These results suggest that antiviral treatment attenuates the progression of cirrhosis and the risk of death among patients with CHB.

Key Words: cirrhosis prevalence, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, joinpoint modeling, HCC

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Patients with chronic hepatitis B (CHB) infection are at risk of a number of serious long-term outcomes—including cirrhosis and liver-related mortality.[1] Although these outcomes are well-described by natural history studies[2,3] and point-prevalence studies within defined cohorts,[4,5] there are remarkably few longitudinal analyses of trends in CHB-related cirrhosis and mortality—and none in the United States.

CHB prevention and treatment strategies have changed dramatically in the past several decades, with universal hepatitis B vaccination campaigns preventing new infections and the emergence of highly effective antiviral treatment regimens reducing sequelae from chronic infections. At the same time, some of the well-known drivers of CHB epidemiology in the United States—including an aging US population, migration from regions where CHB is endemic, and continued challenges in widespread screening and access to treatment—likely attenuate some of those positive gains. Antiviral treatment is not recommended for all CHB patients; indications vary by viral load, host immune status, and severity of the liver disease. Emerging evidence, however, suggests that liver fibrosis may progress even among patients with low-level viremia who may not meet thresholds for treatment[6]; even among these patients, however, antiviral treatment can reduce risks of complications, such as hepatocellular carcinoma.[7]

Changing US demographics may affect longitudinal trends in CHB-related complications. The Chronic Hepatitis Cohort Study (CHeCS) includes over 5000 CHB patients receiving care

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at one of 4 large health systems with a combined population of over 2 million adult patients. Because CHeCS comprises a geographically and racially diverse sample of "real world" patients receiving routine clinical care, it is broadly generalizable to CHB patients throughout the US.[8] We used comprehensive medical record data and our validated serum and clinical markers for cirrhosis identification to investigate the impact of age, race, sex, and treatment status on trends in prevalence of cirrhosis and incidence of mortality among CHB patients from 2006 to 2016.

METHODS

CHeCS includes patients aged 18 years and above who received health care services on or after January 1, 2006 at one of 4 health care systems—Henry Ford Health System (HFHS), Detroit, MI; Geisinger Health System (GHS), Danville, PA; Kaiser Permanente Northwest (KPNW), Portland, OR; and Kaiser Permanente Hawai'i (KPHI), Honolulu, HI. The study follows all guidelines of the US Department of Health and Human Services (HHS) regarding the protection of human subjects; the CHeCS protocol was approved and is renewed annually by the institutional review board at each of the 4 sites. Due to the deidentified nature of this observational study, requirements for written informed consent were waived.

CHeCS methods have been described elsewhere.[8,9] Briefly, CHeCS has a comprehensive data collection system based on electronic health records. Patients are identified electronically using a combination of laboratory and International Classification of Disease (ICD) 9 and 10–based criteria; CHB is subsequently confirmed through chart abstraction.[8] CHeCS uses a "dynamic" sampling design; for each data collection cycle, a random sample of new patients is added to the cohort, while existing patients continue to be followed, this method allows us to generalize our findings to other populations. Retrospective patient data are captured through the early 1990s (when available), and data have been collected prospectively through December 31, 2016.

Identification of Cirrhosis

CHeCS has previously validated the use of the Fibrosis-4 (FIB4) serum-based biomarker in CHB patients; we found that a FIB4 score >5.17, calculated from routine laboratory results, accurately classifies cirrhosis (Metavir fibrosis stage F4; area under the receiver operator characteristic curve = 88%; and positive predictive value = 82%) in patients with CHB.[10] We have also developed an electronic diagnosis code-based Classification and Regression Tree model to identify decompensated cirrhosis. An algorithm using 5 liver-related clusters yielded an area under the receiver operator characteristic curve of 92% and positive predictive value of 85%.[11] Due to the observational nature of this study, availability of cirrhosis data varied. Among all confirmed CHB patients, fewer than 10% had liver biopsy data; laboratory data for calculation of FIB4 were available for roughly 60% of patients. To overcome this variation, we implemented a hierarchical classification algorithm to identify presence of cirrhosis during a given year: (1) classification of decompensated cirrhosis using the Classification and Regression Tree model; (2) "F4" liver biopsy determination, or transient elastography >11.0[12]; (3) FIB4 $>$ 5.17; (4) presence of ICD-9/10 diagnosis codes for cirrhosis in the medical record. Cirrhosis was assumed to persist in following years unless records indicated receipt of a liver transplant. This algorithm was used consistently for determination of cirrhosis across the study period.

Incidence of All-cause Mortality

We used all-cause mortality rather than liver-related mortality because our previous work has shown that liver-related mortality is underreported in real world settings, particularly among patients with CHB.[13]

Statistical Analysis

We examined the prevalence of past or present cirrhosis (including decompensated cirrhosis) and incidence of all-cause mortality, among CHeCS CHB patients for each successive year during the 2006-2016 period. For the purpose of computing prevalence and incidence rates for each year, patients were included in the CHB population for any given year if they had been diagnosed with CHB before or during the given year and their last encounter was during or after the given year. CHB/hepatitis C coinfected patients were excluded; CHB/human immunodeficiency virus coinfected patients were included in analyses.

Outcomes of interest included prevalence of past or present cirrhosis, and incidence of all-cause mortality. Covariates of interest included: age during the given year (categorized as below 30, 30 to below 40, 40 to below 50, 50 to below 60, and 60 and above); sex; and race [categorized as black/African American, Asian American/American Indian/Pacific Islander (AAPI), white, and other/unknown]. A categorical age variable was used to assess the effect of aging within the cohort. Antiviral treatment status (ever treated vs. never treated) was included as a covariate due to its recognized impact on risk of progression of liver disease.[14] We note, however, that interpretation of this variable with regard to trends in cirrhosis prevalence should be undertaken with caution; antiviral treatment is not universally recommended for CHB patients and presence of cirrhosis may itself be an indication for treatment. We performed a propensity score–adjusted sensitivity analysis to further test the effect of antiviral treatment on mortality, which may be impacted by the presence of cirrhosis.

We adapted and extended a 2-step joinpoint Poisson regression modeling approach[15] to study change in prevalence in cirrhosis and incidence of all-cause mortality over time. Joinpoint regression analysis involves fitting a series of joined straight lines on a log scale to the trend; each joinpoint represents a statistically significant ($P<0.05$) change in trend (ie, the slope of the line segment). In the first step, we identified the optimal joinpoint(s) using a nonlinear modeling approach. For example, a single joinpoint splits the trend line into 2 segments, whereas a lack of joinpoints indicates that the best fit to the trend consists of only a single line segment. The unadjusted annual percent change (APC) [(rate of current year−rate of previous year)/rate of previous year] was estimated for each segment line and tested compared with no change (APC = 0).

Next, multivariable analyses were performed based on the selected joinpoint(s) as well as the possible stratification variables, considering possible variable-by-trend (time) interactions. Variables were retained in the final model if they were significant or there were significant variable-by-time interactions at the level of 0.05. The adjusted annual percent changes (aAPCs) and 95% confidence intervals (CIs) for segment lines were also calculated using multivariable modeling; analyses were adjusted for all covariates/variable-by-time interactions retained in the model. A significant variable-by-time interaction indicated that APCs differed by variable category. From the same multivariable model, rate

ratios (RRs) were estimated to compare differences in rates between variable categories (eg, race). We did not use age-standardized rates in the model for aAPC estimation; this is consistent with the approach used in a recent study of trends of cirrhosis prevalence in specific subpopulations among US veterans with CHB.[16] However, age at a given year was included as a stratification variable in the model. Analyses were performed for each outcome of interest using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Across the entire 2006–2016 study period, we identified a total of 5528 confirmed CHB patients, with 952 cases of any cirrhosis [17%; including 401 cases of decompensated cirrhosis (7%)] and 628 deaths (11%). Cohort size increased across time—from 2564 in 2006 to 3411 in 2016. The yearly distribution of select patient demographics are presented in Table 1; a summary for the entire study period is presented in Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/JCG/A674). The proportion of female patients remained roughly the same across the study period (45% to 48%). Consistent with our previous report,[17] the rate of antiviral treatment for CHB rose from 20% in 2006 to 35% in 2016.

Prevalence of Cirrhosis (Past or Present)

Overall, the prevalence of cirrhosis (including decompensated cirrhosis) doubled over the study period, from 6.7% in 2006 to 13.8% in 2016. No joinpoint was identified; the multivariable model showed a single segment from 2006 to 2016, with unadjusted APC of +5.9% per year ($P < 0.01$; Table 2). The multivariable model showed that sex, race, and antiviral treatment status were associated with cirrhosis prevalence (Fig. 1). There was a treatment-by-time interaction—indicating that aAPC depended on treatment status. Although overall cirrhosis prevalence was higher among treated patients, aAPC was significantly lower, indicating that rates of cirrhosis increased more slowly among treated than untreated patients (+2.4% vs. +6.2% per year, respectively).

Table 3 displays RR comparisons within sex, race, age, and treatment status strata. Female patients had lower rates of cirrhosis than male patients (RR = 0.59; 95% CI: 0.55-0.64; $P < 0.01$) across the study period. Prevalence of any cirrhosis was lower among African American patients than white patients (RR = 0.87; 95% CI: 0.80-0.95; $P < 0.01$); rates among AAPI patients were even lower, roughly half that of white patients (RR = 0.54; 95% CI: 0.50-0.58; $P < 0.01$). There was a quantitative treatment status-by-time interaction. In 2006, prevalence of cirrhosis among treated patients was >4 times that of untreated patients; by 2016, that ratio had decreased to roughly 3-fold (2006: RR = 4.55, 95% CI: 3.23-6.25; 2016: RR = 3.13, 95% CI: 2.56-3.70).

Incidence of All-cause Mortality

Overall all-cause mortality did not change significantly across the study period, with rates of 1.4% in 2006 to 1.7% in 2016 (Table 1); no joinpoint was identified. Sex, race, age, and antiviral treatment status were retained in the final multivariable model (Fig. 2). As with cirrhosis, lower rates of mortality were observed among female (Table 3, RR = 0.68, 95% CI: 0.57-0.82, vs. male) and younger patients (RRs were 43% to 93% lower among patients younger than 60 y compared with those 60 y or older). African Americans had the highest rates of mortality, roughly 26% higher than white patients (RR = 1.26, 95% CI: 1.04-1.53), whereas

TABLE 1. Characteristics of Patients With Chronic Hepatitis B, Stratified by Sex, Race Category, and Age Category, in Our Cohort, 2006-2016

	n (%)										
Covariates	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
	2564	2773	2935	3093	3293	3422	3467	3572	3663	3663	3411
Sex											
Female	1161 (45.3)	1259 (45.4)	1332 (45.4)	1421 (45.9)	1524 (46.3)	1589 (46.4)	1635 (47.2)	1690 (47.3)	1759 (48.0)	1811 (49.4)	1603 (47.0)
Male	1403 (54.7)	1514 (54.6)	1603 (54.6)	1672 (54.1)	1769 (53.7)	1833 (53.6)	1832 (52.8)	1882 (52.7)	1904 (52.0)	1852 (50.6)	1808 (53.0)
Race											
AAPI/other	1449 (56.5)	1560 (56.3)	1657 (56.5)	1733 (56.0)	1830 (55.6)	1918 (56.1)	1943 (56.0)	2039 (57.1)	2115 (57.7)	2146 (58.6)	1951 (57.2)
African American	369 (14.4)	410 (14.8)	424 (14.5)	461 (14.9)	477 (14.5)	499 (14.6)	512 (14.8)	504 (14.1)	508 (13.9)	508 (13.9)	490 (14.4)
White	601 (23.4)	636 (22.9)	656 (22.4)	674 (21.8)	726 (22.1)	756 (22.1)	769 (22.2)	781 (21.9)	774 (21.1)	753 (20.6)	733 (21.5)
Unknown	145 (5.7)	167 (6.0)	198 (6.8)	225 (7.3)	260 (7.9)	249 (7.3)	243 (7.0)	248 (6.9)	266 (7.3)	256 (7.0)	237 (7.0)
Age (y)											
< 30	820 (32.0)	860 (31.0)	885 (30.2)	918 (29.7)	951 (28.9)	972 (28.4)	938 (27.1)	930 (26.0)	937 (25.6)	910 (24.8)	792 (23.2)
30 to <40	644 (25.1)	699 (25.2)	744 (25.4)	780 (25.2)	844 (25.6)	884 (25.8)	904 (26.1)	935 (26.2)	949 (25.9)	963 (26.3)	880 (25.8)
40 to <50	574 (22.4)	625 (22.5)	657 (22.4)	694 (22.4)	741 (22.5)	771 (22.5)	781 (22.5)	817 (22.9)	848 (23.2)	848 (23.2)	806 (23.6)
50 to <60	353 (13.8)	391 (14.1)	421 (14.3)	457 (14.8)	495 (15.0)	507 (14.8)	537 (15.5)	562 (15.7)	568 (15.5)	580 (15.8)	554 (16.2)
≥ 60	173 (6.8)	198 (7.1)	228 (7.8)	244 (7.9)	262 (8.0)	288 (8.4)	307 (8.9)	328 (9.2)	361 (9.9)	362 (9.9)	379 (11.1)
Ever treated	522 (20.36)	654 (23.58)	757 (25.79)	857 (27.71)	934 (28.36)	981 (28.67)	1017 (29.33)	1075 (30.1)	1160 (31.67)	1208 (32.98)	1208 (35.41)
Outcomes											
Prevalent cirrhosis*	171 (6.7)	228 (8.2)	270 (9.2)	309 (10.0)	354 (10.8)	385 (11.3)	406 (11.7)	434 (12.2)	464 (12.7)	472 (12.9)	469 (13.8)
Deaths	36 (1.4)	40 (1.4)	56 (1.9)	54 (1.8)	64 (1.9)	55 (1.6)	55 (1.6)	60 (1.7)	83 (2.3)	70 (1.9)	58 (1.7)

*Includes compensated and decompensated cirrhosis.
AAPI indicates Asian American, American Indian/Pacific Islander.

TABLE 2. Multivariable Trend Model: Adjusted APC in Rates of Complications Among Patients With Chronic Hepatitis B in Our Cohort From 2006 Through 2016

	Any Cirrhosis		All-cause Mortality	
APC	**APC (95% CI)**	***P***	**APC (95% CI)**	***P***
Unadjusted APC	5.9% (4.8-7.0)	<0.01	2.0% (−0.6 to 4.6)	0.13
Adjusted* APC				
Ever treated	2.4% (1.1-3.7)	<0.01	−3.9% (−7.3 to −0.3)	0.03
No treatment	6.2% (4.5-8.1)	<0.01	4.0% (0.3-7.8)	0.035

*Adjusted analysis includes race, gender, and age-by-time interaction.
APC indicates annual percentage change; CI, confidence interval.

AAPI/other patients had the lowest mortality (RR = 0.42, 95% CI: 0.34-0.51, compared with whites). A significant treatment status-by-time interaction was observed. In 2006, rates of mortality among treated patients were 3.5 times that of untreated patients; by 2016, that ratio had decreased by roughly half and was no longer significantly different (treated vs. untreated in 2006: RR = 3.57 95% CI: 1.82-7.14; in 2016, RR = 1.52 95% CI: 0.89-2.56). Treatment also impacted the APC in all-cause mortality—among treated patients, the aAPC for mortality declined −3.9% per year whereas among untreated patients, mortality increased +4.0% per year (Table 2).

In a sensitivity analysis evaluating whether cirrhosis influenced the effect of antiviral treatment on all-cause mortality, we used propensity scores to adjust for treatment selection bias; covariates included age, sex, race, hepatitis B e-antigen status, insurance, household income, and presence/absence of cirrhosis. We saw that the effect of treatment on mortality was influenced by presence of cirrhosis ($P < 0.001$ for treatment-by-cirrhosis interaction); among patients with cirrhosis, antiviral treatment was protective against risk of mortality (hazard ratio = 0.81; 95% CI: 0.67-0.99).

DISCUSSION

In a diverse "real world" cohort of over 5000 CHB patients, we observed that overall prevalence of cirrhosis doubled from 2006 to 2016, while incidence of all-cause mortality remained flat across the study period. The rate of treatment increased from 20.5% in 2006 to 35.4% in 2016; receipt of antiviral medication was more common among patients with cirrhosis, a finding that reflects current guidelines to initiate treatment for patients with advanced fibrosis. However, the relative increase in cirrhosis prevalence among treated patients was significantly lower than among untreated patients (aAPC = +2.4% vs. +6.2%,

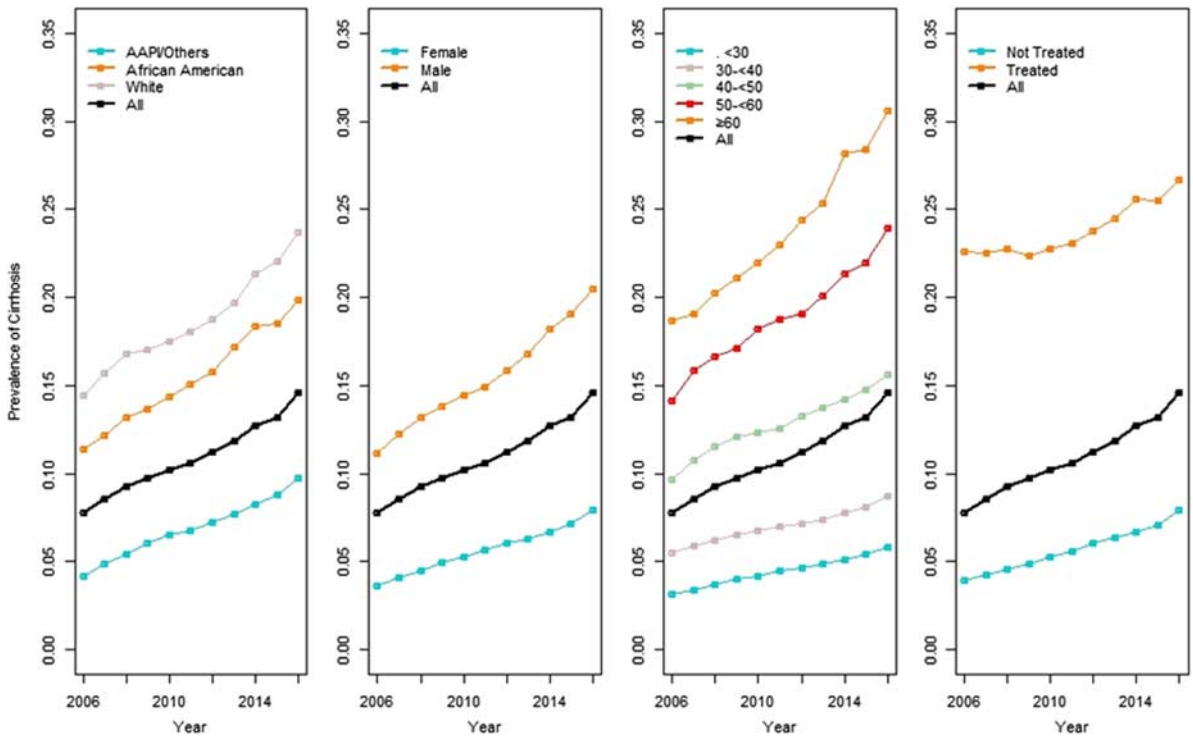

FIGURE 1. Prevalence of any cirrhosis by age, race, sex, and treatment status in patients with chronic hepatitis B in our cohort from 2006 to 2016. No joinpoint was identified. AAPI indicates Asian American/Pacific Islander.

TABLE 3. Multivariable Trend Model: Adjusted RRs for Comparisons by Sex, Race, and Age for Prevalence of Complications Among Patients With Chronic Hepatitis B in Our Cohort From 2006 Through 2016

		Cirrhosis*		All-cause Mortality	
Covariates	**Comparison**	**RR (95% CI)**	***P***	**RR (95% CI)**	***P***
Sex	Female vs. male	0.59 (0.55-0.64)	<0.01	0.68 (0.57-0.82)	<0.01
Race	AAPI/other vs. white	0.54 (0.50-0.58)	<0.01	0.42 (0.34-0.51)	<0.011
	African American vs. white	0.87 (0.80-0.95)	<0.01	1.26 (1.04-1.53)	0.02
	Unknown vs. white	0.71 (0.62-0.81)	<0.01	0.71 (0.51-1.00)	<0.05
Age	<30 vs. ≥60	0.26 (0.23-0.30)	<0.01	0.07 (0.04-0.10)	<0.01
	30 to <40 vs. ≥60	0.35 (0.31-0.38)	<0.01	0.13 (0.10-0.17)	<0.01
	40 to <50 vs. ≥60	0.57 (0.52-0.62)	<0.01	0.26 (0.21-0.33)	<0.01
	50 to <60 vs. ≥60	0.83 (0.76-0.91)	<0.01	0.57 (0.47-0.69)	<0.01
At 2006	Treated vs. untreated	4.55 (3.23-6.25)	<0.01	3.57 (1.82-7.14)	<0.01
At 2016	Treated vs. untreated	3.13 (2.56-3.70)	<0.01	1.52 (0.89-2.56)	0.12

*Includes compensated and decompensated cirrhosis.
AAPI indicates Asian American/Pacific Islander; CI, confidence interval; RR, rate ratio.

respectively). Furthermore, there was a significant treatment status-by-time interaction for all-cause mortality. In 2006, mortality was significantly higher among treated patients than untreated patients; by 2016, that difference had narrowed and became nonsignificant. This is reflected in aAPCs for mortality, which decreased roughly 4% per year among treated patients, but increased at a similar rate among untreated patients. We also observed treatment status-by-time interactions across the study period, with a slower increase in cirrhosis and a decline in mortality among treated patients, but the opposite among untreated patients. Given that cirrhosis is an indication for initiation of antiviral treatment, receipt of treatment is in some cases a rough proxy for disease severity. Our findings—slower increases in cirrhosis prevalence and reductions in mortality among treated patients—demonstrate the benefit of antiviral treatment, even among CHB patients with more severe liver disease.[18,19] A sensitivity analysis also demonstrated that antiviral treatment reduced mortality among patients who were cirrhotic at baseline.

The implications of our findings relative to untreated patients are rather complicated and less clear. Several studies have suggested the benefits of treatment even among patients with low-level viremia who do not necessarily meet the criteria for treatment initiation.[6] However, guidance regarding criteria for treatment initiation reflects the complex physiological

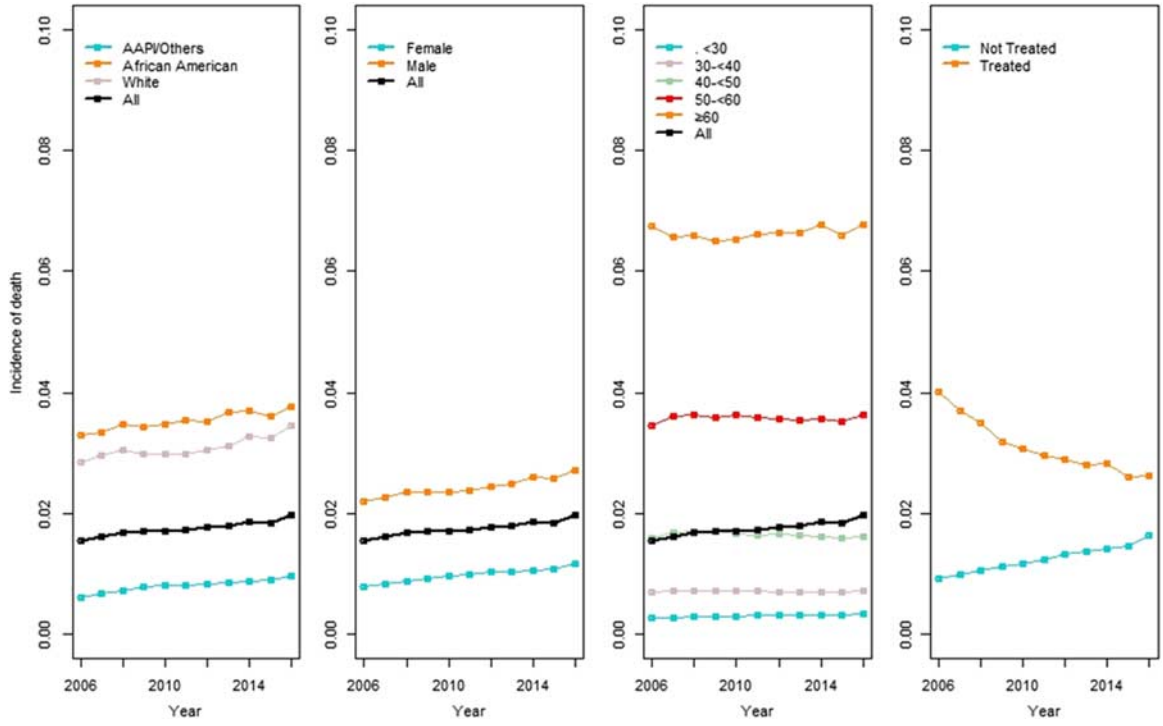

FIGURE 2. Incidence of all-cause mortality by age, race, sex, and treatment status with chronic hepatitis B in our cohort from 2006 to 2016. No joinpoint was identified. AAPI indicates Asian American/Pacific Islander.

interaction between viral load and immune response in CHB. Current recommendations prioritize patients with more severe liver disease or higher levels of viral replication. Importantly, there are many patients for whom treatment would be indicated, but who do not receive treatment due to lack of access to appropriate care.[14] As shown in Table 1, a large but decreasing proportion of our sample had never received antiviral treatment—roughly 80% in 2006, which fell to 65% in 2016. It is beyond the scope of the current analysis to differentiate between those patients for whom treatment was and was not indicated under guidelines current during each study year. Nonetheless, the significant increases in cirrhosis and mortality among untreated patients over the study period is of concern, and contrasts with the trends observed among treated patients; given suggestions that patients even with low-level viremia derive benefits from antiviral treatment, studies of additional indicators for treatment (eg, aminotransferase levels or new biomarkers such as quantitative hepatitis B surface antigen) may be warranted. In a previous study, we found that antiviral treatment can reduce risk for development of hepatocellular carcinoma by 83% among patients with baseline hepatitis B virus (HBV) DNA levels $>20{,}000$.[7] A planned analysis will focus on the impact of treatment indication status and access to care as risk factors for these outcomes among patients with CHB.

In addition, while mortality did not increase for AAPI/other or white patients, rates increased significantly for African American patients over time. This is despite lower rates of cirrhosis observed among African Americans versus whites. It is possible this is attributable to higher overall all-cause mortality among African Americans in general[20] or possible racial disparities in access to quality CHB care.[2] However, it is a limitation of our analysis that we were not able to assess this directly. Likewise, cirrhosis prevalence was low among AAPI patients, despite high rates of CHB in this community. It is possible that there are differences in social determinants of health or natural history of CHB that influence these observations, but because our study was not designed to investigate risk factors for cirrhosis development, we are limited in the interpretation of these findings.

Furthermore, independent of treatment status, we found significant differences in APCs for cirrhosis across age categories. CHB patients aged 60 years and above had the highest prevalence of cirrhosis and all-cause mortality; similar findings have been reported among US veterans.[21] Notably, although the oldest patients in our cohort (60 y and above) had the highest cirrhosis prevalence, the highest aAPC (indicating the largest proportional increases) occurred among patients aged 50 to less than 60 years, at least 2 times faster than other age groups; this suggests that CHB patients in this age group may benefit from close monitoring. Rates of complications were consistently higher in male patients than female. The 2:1 male: female ratio remained across time, even as rate of cirrhosis increased over the study period. Mortality was also higher among male patients. This is consistent with a number of studies of death among CHB patients.[22–24]

One of the strengths of this analysis was our use of validated methods for classifying patients with cirrhosis to ensure consistency across time. These methods, which encompass a variety of observational data sources (liver biopsy, transient elastography, FIB4 index, and ICD-9/10 diagnosis codes) address many of the limitations of relying solely on diagnosis code-based data in an observational cohort. Another strength of this analysis is the ongoing "dynamic" cohort accrual over 5000 CHB patients from 4 large health systems with a combined population of over 2 million adult patients. We are aware of at least one cross-sectional study that sought to estimate prevalence of cirrhosis among chronic HBV patients seen in a US health care system during a similar time period (2014-2016). They found an overall prevalence of 27.7%; rates differed by sex (lower among female than male patients) but not by race. The authors of this study noted a few limitations in their analysis, specifically that their sample included largely uninsured and underinsured patients drawn from a safety net health care system that were referred for specialty gastroenterology care. These differences likely underlie the higher rate of cirrhosis observed among their population compared with our own.[4] We note that the dynamic sampling design employed to generate our cohort is intended to increase the generalizability of our results by enrolling a random subset of CHB patients seen at our study sites.

Our study has several limitations. We used all-cause mortality instead of liver-related mortality because a previous CHeCS analysis demonstrated that liver-related mortality data is incomplete in routine-care settings.[13,25] Although our analysis is based on ongoing "dynamic" cohort accrual from health system populations, the cohort has aged significantly over time; patients 60 years and above made up only 7% of our 2006 cohort but 11% of the cohort in 2016. However, we did adjust for age in our analysis and found no indication of a qualitative interaction (change in direction of the effect) between age and time. Likewise, we were unable to confirm whether patients who did not receive antiviral treatment were eligible for such treatment, given the complexity of determining if and when treatment may be indicated. In a previous analysis of CHeCS data through 2013, approximately one-third of patients were "treatment eligible" (based on presence of immune-active disease and cirrhosis), of whom 60% had been treated.[26] Nevertheless, this analysis was designed to describe overall temporal changes in rates of CHB-related complications, rather than the effect of treatment on individual patients, a topic that has been previously covered. Finally, because our cohort consists of individuals with at least some contact with the health system, we are unable to estimate the prevalence of outcomes in CHB-positive individuals who remain undiagnosed or those without ongoing contact with a health care system. Such individuals are perhaps most at risk for poor outcomes. In addition, our study is based primarily upon health records data and may fail to capture factors that potentially affect clinical outcomes, such as disease duration or undiagnosed substance or alcohol misuse.

In conclusion, although the overall prevalence of cirrhosis doubled from 2006 through 2016 among CHB patients in the US-based CHeCS cohort, rates of all-cause mortality remained consistently low overall. Considering that cirrhosis is an indication for antiviral treatment, rates were higher but increased more slowly among patients who received antiviral treatment compared with untreated patients. Notably, all-cause mortality increased among untreated patients, but decreased among treated patients. These results suggest that antiviral treatment attenuates progression of cirrhosis and risk of death among patients with CHB.

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