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VIRAL HEPATITIS

Advancing Age and Comorbidity in a US Insured Population-Based Cohort of Patients With Chronic Hepatitis B

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Chronic hepatitis B (CHB) comorbidity data are limited. Using insurance claims databases, our aims were to determine the prevalence and incidence of nonliver comorbidities in CHB patients over time and the predictors of select comorbidities in CHB patients. Patients were adults with continuous coverage (commercial/Medicare or Medicaid) 6 months prior to and after the first CHB diagnosis and matched non-CHB patients. Deyo-Charlson Comorbidity Index (DCCI) and comorbidities were analyzed (cardiovascular disease [CVD], carcinoma, diabetes mellitus [DM], obesity, hypertension [HTN], hyperlipidemia, alcohol use, renal impairment, chronic kidney disease [CKD], and osteoporosis/fracture [OF]). The study population included 44,026 CHB cases and 121,568 matched controls. CHB patient mean age increased from 48.1 ± 11.9 years in 2006 to 51.8 ± 12.4 years in 2015 for commercial/Medicare and from 44.1 ± 11.1 years to 50.2 ± 10.2 years for Medicaid ($P < 0.001$ for both). The Medicaid CHB cohort was the sickest (DCCI, 2.6, $P < 0.001$). The commercial/Medicare 2006 CKD prevalence rate was 36.1/1,000 in CHB patients and 10.2/1,000 in controls, increasing to 97.6 and 38.8 in 2015, respectively. The 2006 CKD incidence (per 1,000 person-years) was 10.3 and 4.8 and 15.2 and 11.3 by 2015, respectively ($P < 0.05$ for all). The strongest predictors for CKD were DM (hazard ratio [HR], 2.48), HTN (HR, 3.29), and CVD (HR, 2.61) (all $P < 0.0001$). Similar prevalence and incidence changes were observed for OF. The strongest predictors for OF were female gender (HR, 2.22), alcohol use (HR, 2.02), and viral coinfection (HR, 1.37) (all $P < 0.0001$). *Conclusion:* Insured CHB patients were older, had more comorbidities, and experienced higher incidence and prevalence of CKD and OF than controls. (Hepatology 2019;69:959-973).

Hepatitis B virus (HBV) affects an estimated 257 million people worldwide.[1] In 2015, chronic hepatitis B (CHB) resulted in 884,000 deaths, mostly from complications of cirrhosis and hepatocellular carcinoma (HCC).[1] In the United States, recent population-based data showed that the economic burden for hospital care of CHB patients is considerable and higher in patients with CHB compared to those with chronic hepatitis C.[2,3]

Currently, there are effective and well-tolerated oral anti-HBV drugs for long-term or lifelong suppressive treatment with little or no risk of antiviral resistance.

Abbreviations: CHB, chronic hepatitis B; CKD, chronic kidney disease; CVD, cardiovascular disease; DCCI, Deyo-Charlson Comorbidity Index; DM, diabetes mellitus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; HTN, hypertension; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; NAFLD, nonalcoholic liver disease; OF, osteoporosis/fractures.

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Among the first-line therapies, entecavir (ETV) was introduced in 2006, followed by tenofovir disoproxil fumarate (TDF) in 2008. Tenofovir alafenamide was also introduced in 2016. However, despite the continual evolution of medications for CHB, there is still no cure.[4,5] Therefore, attention has been drawn to the long-term management and safety of anti-HBV therapies, especially in more clinically complex patients.[6,7]

Understanding the care of clinically complex CHB patients is especially relevant because the rate of screening, diagnosis, and linkage to care for CHB patients is poor.[7,8] Current estimates suggest that only one third of CHB-affected patients in the United States are aware of their diagnosis and that only a small fraction of diagnosed patients are linked to care and/or treated at an early stage in their disease.[8-10] Due to this often-delayed diagnosis and treatment, CHB patients are now presenting at an older age and with more liver and nonliver comorbidities that can further complicate their management, as shown by a recent study of a large multicenter cohort of CHB patients including community primary care patients in the United States.[11] Recent population-based data from Taiwan have also suggested that CHB patients have more nonliver comorbidities than non-CHB subjects. In addition, these studies have found evidence of an association between CHB and renal function impairment as well as an increased risk of osteoporosis relative to non-CHB controls.[12-15] Furthermore, updated treatment guidelines for the management of CHB noted that patients may experience renal function decline and decreased bone mineral density due to long-term treatment with certain anti-HBV medications.[16]

However, data on nonliver comorbidities in CHB patients are still limited, especially in a more nationally representative sample of the United States; therefore, the purpose of this study was to characterize the demographics and presence of renal, bone, and other non-liver-related comorbidities in a large, diverse population with CHB compared to non-CHB controls in the United States. The second purpose was to ascertain the longitudinal trend of specific comorbidities over the past 10 years.

Materials and Methods

STUDY DESIGN AND DATA SOURCES

This was a retrospective, observational study where case matching was used for comparison. Data were obtained from a large deidentified US administrative health care claims database, Truven Health MarketScan® Commercial, Medicare Supplemental and Coordination of Benefits, and Multi-State Medicaid Databases. Data were extracted from the years 2004-2015. The commercial database contained the pooled health care experience of over 41 million commercial enrollees (general population). The Medicare database contained the pooled health care experience of approximately 4 million patients (age 65 and older) with employer-sponsored Medicare supplemental insurance. The Medicaid database contained the pooled health care experience of approximately 8 million low-income enrollees each year in 10-12 geographically dispersed states. The databases contained medical and pharmacy claims for health care services performed in both inpatient and outpatient settings plus enrollment and demographic data for covered enrollees. The study was considered exempt by the institutional review board at Stanford University, Stanford, California. All coauthors had access to the study data and reviewed and approved the final manuscript.

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PATIENT SELECTION

Patients aged 18 or greater with at least one inpatient or two outpatient claims for a known diagnosis of CHB were selected using *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM), diagnosis code 070.22, 070.32, or 070.30 in any diagnostic position between July 1, 2004, and June 30, 2015. However, due to lack of data among Medicaid CHB patients for the years 2004 and 2005, patients included in the study analysis were drawn from July 1, 2006, to June 30, 2015. The index date was the date of first CHB claim.

Patients were excluded for not having at least 6 months of continuous medical and prescription coverage before and after their index date, not having continuous enrollment for at least one full calendar year during the study period as described above, or having claims for hepatitis delta coinfection (ICD-9-CM diagnosis code 070.23, 070.33, or 070.31).

Non-CHB controls were selected from the same databases and requirements for continuous medical and prescription coverage as CHB patients. Non-CHB controls were then matched to CHB patients by CHB index year, age at index date, gender, geographic region, and race (available for Medicaid only). Index dates for non-CHB controls were randomly assigned. Given the known differences in the prevalence of CHB between the general population (27-38 cases per 10,000 persons) and the Medicaid population (15.6 per 10,000, obtained from five states),[17,18] analysis was carried out for the commercial/Medicare insurance group and the Medicaid group separately.

STUDY PERIOD

The study observation period spanned calendar years July 1, 2006, through June 30, 2015. The enrollment period for the study, as detailed above, started as early as January 1, 2006.

STUDY VARIABLES AND OUTCOMES

The primary patient comorbidities were captured using ICD-9 codes for both inpatient and outpatient visits from each calendar year beginning July 1, 2006 (study start), and ending June 30, 2015 (study end). Comorbidities included common chronic medical conditions, such as alcohol use, chronic hepatitis C, human immunodeficiency virus (HIV) infection, smoking, overweight/obesity/morbid obesity, malignancy (any), osteoporosis and/or pathological/nontraumatic bone fractures (OF), cardiovascular disease (CVD), diabetes mellitus (DM; includes controlled and uncontrolled diabetes, diabetes with and without complications, diabetic ketoacidosis, diabetic neuropathy, and diabetic retinopathy), hyperlipidemia, hypertension (HTN), renal impairment (includes end-stage renal disease, dialysis, glomerulonephritis, nephropathy, and renal insufficiency) and chronic kidney disease (CKD; defined as stages I-IV, unspecified CKD, end-stage renal disease, hypertensive CKD stages I-IV, hypertensive heart and chronic kidney disease stages I-IV, or dialysis) (Supporting Information). The average Deyo-Charlson Comorbidity Index (DCCI) was also calculated.[19]

Concomitant medication use was captured for the following major classes of medications: corticosteroids (excluding topical and inhaled corticosteroids and triamcinolone), osteoporosis medications, hormone suppression therapy, biologics/targeted/immunotherapies (abatacept, adalimumab, ado-trastuzumab emtansine, anakinra, bevacizumab, certolizumab, cetuximab, erlotinib hydrochloride, etanercept, golimumab, lapatinib ditosylate, palivizumab, pertuzumab, infliximab, rituximab, secukinumab, sunitinib malate, tocilizumab, trastuzumab and ustekinumab, other tumor necrosis factor–inhibiting agents), and cardiovascular medications (including beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, atrial fibrillation/flutter medications, statins, anticoagulants, and aspirin). The anti-HBV medications captured included lamivudine, adefovir, telbivudine, ETV, TDF, interferon-α, and pegylated interferon-α.

Other study outcomes investigated were the prevalence (per 1,000 persons) and incidence (per 1,000 person-years) of CKD and/or OF in CHB and non-CHB controls for 2006, 2010, and 2015.

STATISTICAL ANALYSES

Descriptive statistics included means and standard deviations or median (range) reported for continuous measures and counts and percentages reported for categorical variables. Continuous variables of two independent study groups were compared by student *t* tests if data followed a normal distribution; otherwise, nonparametric methods were used. Comparisons of categorical variables from 2006 to 2015, such as proportions of

patients with different age groups or comorbidities, were performed using the asymptotic Pearson chi-squared and Fisher's exact tests. Known risk factors for CKD and/or OF from the literature were used to create stepwise forward multivariate models to identify significant variables for incidence of CKD and OF. Our approach was confirmed with both univariate and multivariate models. Significant *P* values were <0.05 (two-tailed).

Both cross-sectional (between CHB and non-CHB patients and at specific time points such as 2006, 2010, and/or 2015) and longitudinal (from CHB index date to date of occurrence of event of interest such as CKD or OF or end of study follow-up) analyses were performed. For longitudinal analysis, individual patients were followed for at least 1 year and up to 10 years (2006-2015).

Cox's proportional hazards regression models were constructed to estimate hazard ratios (HRs) relating baseline characteristics to development of CKD or OF. Testing of model assumptions was performed using methods described by Lin et al.[20] The outcome modeled was time from CHB index diagnosis to first event, where the event was the occurrence of CKD or OF. Univariate and multivariate HRs were calculated for the following potential risk factors: chronic hepatitis C infection or HIV, DM/diabetes medication, HTN, CVD for the CKD model, and the addition of smoking and alcoholism to the OF model. All HRs were reported with 95% confidence intervals. Also, in our model analyses, patients were excluded for having CKD or OF before CHB index date. All statistical tests were performed using the program SAS (version 9.4; SAS Institute Inc., Cary, NC).

Results

STUDY PATIENTS

Supporting Fig. S1 shows the study's recruitment schema. Table 1 displays the characteristics of patients with CHB in the commercial/Medicare and the Medicaid groups reported in the years 2006 and 2015. The average age in 2006 for the commercial/Medicare patients (n = 32,523) was 48.1 years (median, 48.0) compared to 51.8 years (median, 52) in 2015, with male patients making up the majority. The average age of Medicaid patients (n = 11,503) was 44.1 years (median, 45) in 2006 and rose to 50.2 years (median, 50.2) in 2015. Unlike the commercial/Medicare cohort, female patients comprised the majority of this group in both 2006 (54.6%) and 2015 (54.3%).

The commercial/Medicare control group was comprised of 91,132 patients without CHB, with a median age of 49 years in 2006 and 53 years in 2015. The Medicaid group was comprised of 30,436 non-CHB patients, with a median age of 46 years in 2006 and 53 years in 2015 (Supporting Fig. S1 and Table S1A). Supporting Table S1B compares age and sex distribution in CHB patients and non-CHB controls for 2015. CHB patients in the commercial/Medicare Group were slightly younger (median age, 52 years versus 53 years in controls; $P < 0.001$), with the same trend noted for the Medicaid group. Male patients were the majority for all groups across all payers (Supporting Table S1B).

TABLE 1. Demographic Characteristics of CHB Patients Over Time: 2006 Versus 2015, by Insurance Type

	Commercial and Medicare			Medicaid		
Demographic Characteristics	CHB (2006) (n = 3,819)	CHB (2015) (n = 9,094)	*P*	CHB (2006) (n = 1,425)	CHB (2015) (n = 2,278)	*P*
Age (years), mean (SD)	48.1 (11.9)	51.8 (12.4)	<0.001	44.1 (11.1)	50.2 (10.2)	<0.001
Median	48.0	52.0		45.0	52.0	
Age group (n, %)						
18-34	531 (13.9%)	764 (8.4%)	<0.001	310 (21.8%)	235 (10.3%)	<0.001
35-44	975 (25.5%)	1,922 (21.1%)		364 (25.5%)	342 (15.0%)	
45-54	1,147 (30.0%)	2,541 (27.9%)		491 (34.5%)	774 (34.0%)	
55-64	893 (23.4%)	2,775 (30.5%)		247 (17.3%)	883 (38.8%)	
65+	273 (7.2%)	1,092 (12.0%)		13 (0.9%)	44 (1.9%)	
Gender (n, %)						
Male	2,296 (60.1%)	5,091 (56.0%)	<0.001	647 (45.4%)	1,040 (45.7%)	0.88
Female	1,523 (39.9%)	4,003 (44.0%)		778 (54.6%)	1,238 (54.3%)	

TABLE 2. Clinical Characteristics of CHB Patients in 2015 Compared With Non-CHB Controls in 2015, by Insurance Type

	Commercial and Medicare			Medicaid		
Clinical Characteristics	CHB (n = 9,094)	No CHB (n = 26,337)	*P*	CHB (n = 2,278)	No CHB (n = 5,773)	*P*
Mean DCCI (SD)	1.1 (2.2)	0.5 (1.2)	<0.001	2.6 (3.0)	1.2 (1.8)	<0.001
Mean DCCI without liver disease (SD)	1.0 (2.1)	0.5 (1.2)	<0.001	2.4 (2.9)	1.2 (1.8)	<0.001
Comorbidities (n, %)						
Alcoholism	154 (1.7%)	236 (0.9%)	<0.001	426 (18.7%)	422 (7.3%)	<0.001
Carcinoma, malignancy (any)	569 (7.3%)	1,592 (6.0)%	<0.001	153 (6.7%)	254 (4.4%)	<0.001
CVD	1,076 (11.8)%	2,506 (9.5%)	<0.001	564 (24.8%)	1,135 (19.7%)	<0.001
Diabetes	1,392 (15.3%)	3,257 (12.4%)	<0.001	620 (27.2%)	1,604 (27.8%)	0.608
HCV	395 (4.3%)	49 (0.2%)	<0.001	589 (25.9)%	188 (3.3%)	<0.001
HIV	371 (4.1%)	46 (0.2%)	<0.001	369 (16.2)%	109 (1.9%)	<0.001
Hyperlipidemia	2,103 (23.1%)	6,528 (24.8%)	0.001	629 (27.6%)	1,955 (33.9%)	0.002
HTN	2,910 (32.0%)	8,326 (31.6%)	0.495	1,337 (58.7%)	3,167 (54.9%)	<0.001
Osteoporosis	197 (2.2%)	410 (0.9%)	<0.001	43 (1.9%)	91 (1.6%)	0.325
Overweight, obesity, morbid obesity	982 (10.8%)	3,271 (12.4%)	<0.001	451 (19.8%)	1,125 (19.5%)	0.752
Renal impairment*	1,091 (12.0%)	1,307 (5.0%)	<0.001	556 (24.4%)	707 (12.3%)	<0.001
Smoking	584 (8.4%)	1,318 (5.0%)	<0.001	1,192 (52.3%)	1,818 (31.5%)	<0.001
Concomitant medication use (n, %)						
Corticosteroids	1,224 (13.5%)	3,759 (14.3%)	0.054	610 (26.8%)	1,307 (22.6%)	<0.001
Osteoporosis medications	233 (2.6%)	432 (1.6%)	<0.001	44 (1.9%)	112 (1.9%)	0.980
Hormone suppression therapy	137 (1.5%)	235 (0.9%)	<0.001	35 (1.5%)	90 (1.6%)	0.941
Biologics/targeted/immunotherapies	221 (2.4%)	450 (1.7%)	<0.001	247 (10.8%)	383 (6.6%)	<0.001
Cardiovascular medications	3,076 (33.8%)	9,964 (37.8%)	<0.001	1,149 (50.4%)	2,974 (51.5%)	0.384
Antidiabetes medications	1,060 (11.7%)	2,728 (10.4%)	0.001	446 (19.6%)	1,292 (22.4%)	0.006

*Renal impairment includes CKD, end-stage renal disease, dialysis, glomerulonephritis, nephropathy, and renal insufficiency.

PATIENT CHARACTERISTICS AND COMORBIDITIES (EXCLUDING CKD, OSTEOPOROSIS, AND FRACTURES)

Table 2 presents the clinical characteristics in 2015 for the commercial/Medicare group compared to the matched non-CHB group. The average DCCI score was low for both groups but higher in the CHB group (1.1 versus 0.5, respectively, $P < 0.001$). The most prevalent comorbidity for both groups was HTN (32% versus 31.6%, respectively, $P = 0.495$), followed by hyperlipidemia (23.1% versus 24.8%, respectively, $P < 0.001$) and then DM (15.3% versus 12.4%, $P < 0.001$, respectively). The CHB group also had more advanced liver disease than the non-CHB group (15.4% versus 4.8%, $P < 0.001$), particularly for DCCI score (11.5% versus 4.7%, $P < 0.001$, respectively).

The Medicaid group had a higher DCCI score than the commercial/Medicare group, with a DCCI score of 2.6 for CHB patients and 1.2 for controls ($P < 0.001$). The three most prevalent comorbidities for this group were HTN, hyperlipidemia, and DM (CHB patients versus non-CHB controls, 58.7% versus 54.9%, 27.6% versus 33.9%, 27.2% versus 27.8%; $P < 0.001$, $P = 0.002$, $P = 0.608$) (Table 2). The CHB group also had more advanced liver disease than the non-CHB group (26.4% versus 9.5%, $P < 0.001$), particularly for DCCI score (24.6% versus 9.1%, $P < 0.001$).

The prevalence of comorbidities among CHB patients in the commercial/Medicare group as well as the Medicaid group significantly increased from 2006 to 2015 ($P < 0.01$ for both groups) (Fig. 1A,B). By 2015, approximately 1 in 3 CHB patients presented with HTN, 1 in 7 with DM, and 1 in 8 with renal impairment among commercial/Medicare patients. Medicaid CHB patients in 2015 experienced higher rates of comorbidities, with 1 in 2 having HTN and 1 in 4 having DM, hyperlipidemia, or renal impairment. Similar increases in comorbidities were noted for the non-CHB cohort in the commercial and

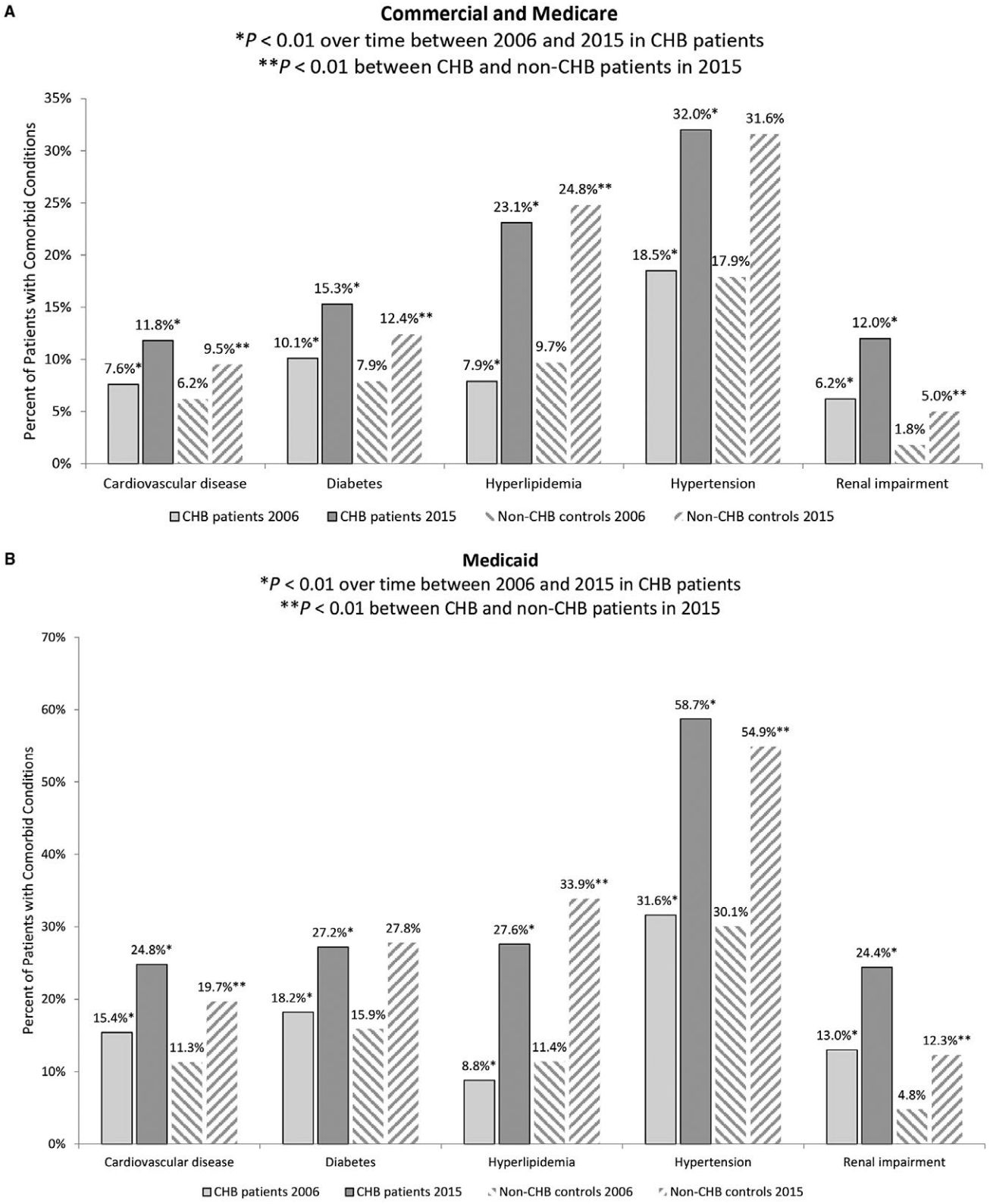


FIG. 1. (A) Comorbidities over time (2006 versus 2015) in commercial and Medicare CHB patients (2006 n = 3,819, 2015 n = 9,094) and non-CHB controls (2006 n = 9,546, 2015 n = 26,337) (renal impairment includes CKD, end-stage renal disease, dialysis, glomerulonephritis, nephropathy, and renal insufficiency). (B) Comorbidities over time (2006 versus 2015) in Medicaid CHB patients (2006 n = 1,425, 2015 n = 2,278) and non-CHB controls (2006 n = 3,141, 2015 n = 5,773).

Medicare cohort; however, the prevalence rates of the comorbidities were significantly higher in the CHB group compared to the non-CHB group across both time points except for HTN (Fig. 1A). Within the Medicaid cohort, the same trend was noted for all comorbidities in the non-CHB group as the CHB cohort, though the CHB group also had a significantly higher increase in prevalence across all comorbidities in 2006 except for DM and HTN and for 2015 only DM was not significantly different at the $P < 0.01$ level (Fig. 1B).

Corresponding to the increase in comorbidity over time, the use of associated concomitant medications also increased (Table 2). The use of cardiovascular medications and antidiabetic medications increased significantly between 2006 and 2015, including over one third of commercial/Medicare CHB patients and one half of Medicaid CHB patients in 2015 (all $P < 0.01$) (Supporting Table S2A). In fact, across both payers, more than 1 in 10 CHB patients used antidiabetic medications in 2015. However, the proportion of patients using osteoporosis medications did not change over time in the Medicaid group and decreased in the commercial/Medicare group ($P < 0.01$), despite a significantly higher proportion of patients having a diagnosis of osteoporosis in 2015 compared to 2006 in both payer groups (Supporting Table S2A).

Changes in concomitant medication use for non-CHB controls over time are described in Supporting Table S2B with a similar increase in most comorbidities.

ANTIVIRAL THERAPY AND PREVALENCE OF COMORBIDITIES IN 2015

Overall, the number of patients who received treatment was low, with only 23% (n = 10,206) receiving treatment (commercial/Medicare = 25% treated; Medicaid = 14% treated).

In the commercial/Medicare cohort, CHB patients who were treated compared to those not treated were younger (51.5 versus 52.3 years, $P = 0.010$) and more likely to be male (65.7%). There was no differences in the groups by DCCI score ($P = 1.000$); however, the treated group was less likely to have CVD, HTN, or hyperlipidemia; to be obese; to have CKD; and to smoke but had significantly more advanced liver disease (16.4% versus 11.2%, $P < 0.001$) (Supporting Table S3A,B).

In the Medicaid group, the CHB patients who received treatment were the same age (50.9 versus 50.4, $P = 0.454$) as those not treated but were more likely to be male (55.6%). The treated patients were sicker, as noted by a significantly higher DCCI score (3.4 versus 2.4, $P < 0.001$) as a result of those treated being more likely to be coinfected with hepatitis C virus (HCV; 33.6% versus 23.9%, $P < 0.001$) and or HIV (30.2% versus 14.2%, $P < 0.0001$) compared to those not treated as there were no significant differences in other comorbidities except for CKD, which was higher in those treated (15.3% versus 10.2%, $P = 0.13$). There was no difference in the number with advanced liver disease. However, those treated were more likely to receive a liver transplant (3.4% versus 0.5%, $P < 0.001$) (Supporting Table S3A,B).

CHB PATIENTS COINFECTED WITH HCV AND/OR HIV

In the commercial/Medicare cohort, 15% of the group was coinfected with HCV and/or HIV. The majority (53.7%) of the coinfected was 55 years or older compared to 40.6% in CHB patients not coinfected ($P < 0.001$; Supporting Table S4A). Furthermore, in comparison to the noncoinfected CHB patients, the CHB coinfected had an increased DCCI score (3.0 versus 0.8, $P < 0.001$), more comorbidities, more alcohol abuse (3.5% versus 1.4%, $P < 0.001$), more smoking (12.3% versus 5.4%, $P < 0.001$), and more advanced liver disease (22.8% versus 11.2%, $P < 0.001$), respectively (Supporting Table S4B).

In the Medicaid cohort, 54% of the group was coinfected with HCV and/or HIV. The coinfected patients were also older, with 45.8% older than 55 years compared to 34.6% in the noncoinfected CHB group ($P < 0.001$) (Supporting Table S4A). In comparison to the noncoinfected CHB patients, the coinfected CHB patients had a higher DCCI score (3.5 versus 1.5, $P < 0.001$), more alcohol abuse (22.6% versus 14.0%, $P < 0.001$), smoking (58.5% versus 45%, $P < 0.001$), and advanced liver disease (31.6% versus 20.3%, $P < 0.001$), respectively. However, those coinfected with HCV or HIV had fewer comorbidities than those without coinfection except for HTN (61.3% versus 55.6%, $P = 0.006$), renal impairment (27.1% versus 21.2%, $P = 0.001$), and any cancer

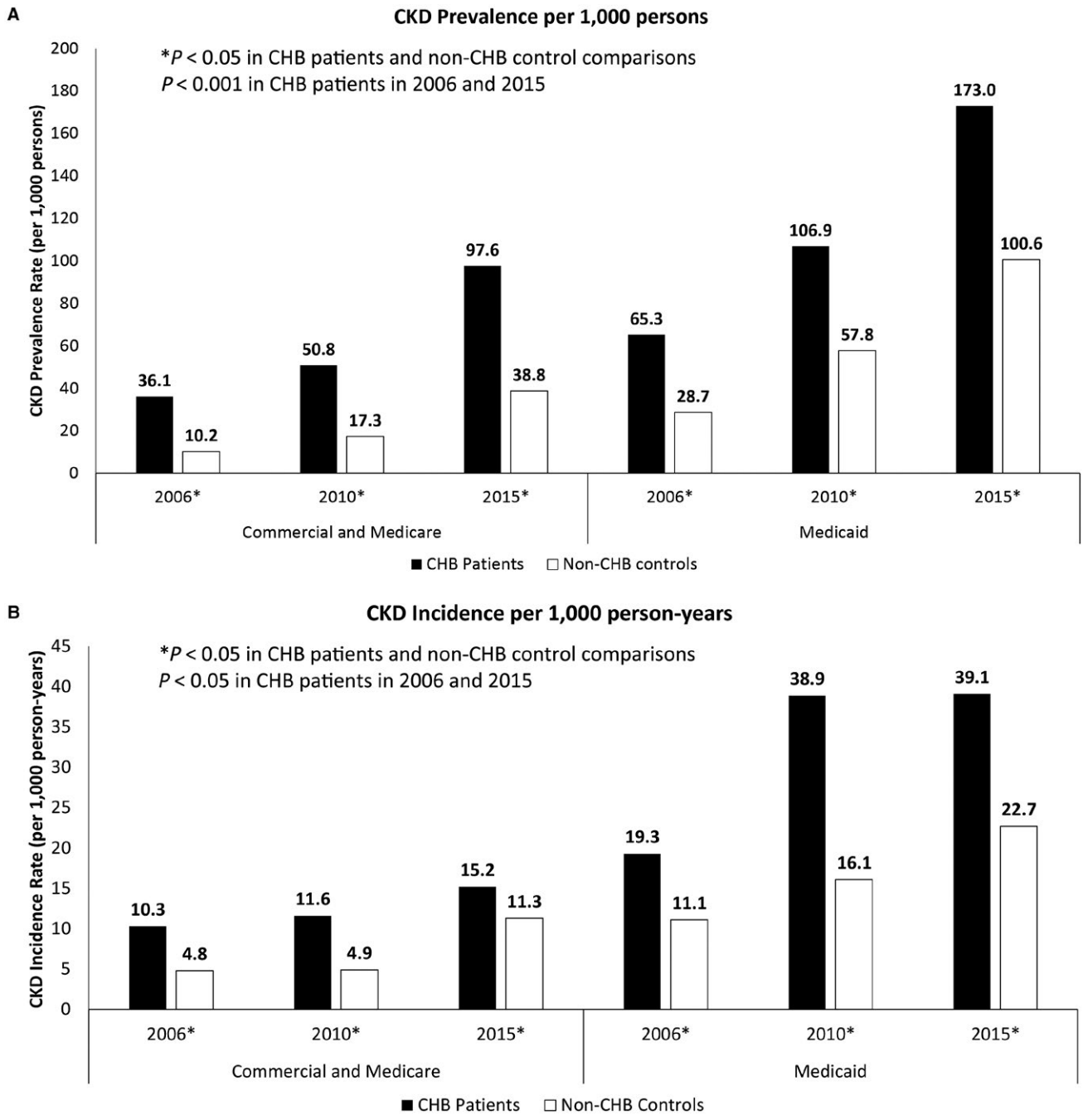


FIG. 2. (A) Prevalence of CKD in CHB patients compared to non-CHB controls over time: 2006, 2010, and 2015. Numbers are as follows: commercial and Medicare CHB patients, 2006 = 3,819, 2010 = 9,958, 2015 = 9,094; non-CHB controls, 2006 = 9,546, 2010 = 26,814, 2015 = 26,337; Medicaid CHB patients, 2006 = 1,425, 2010 = 2,067, 2015 = 2,278; non-CHB controls, 2006 = 3,141, 2010 = 4,582, 2015 = 5,773. (B) Incidence of CKD in CHB patients compared to non-CHB controls over time: 2006, 2010, and 2015. Numbers are as follows: commercial and Medicare CHB patients, 2006 = 3,819, 2010 = 9,958, 2015 = 9,094; non-CHB controls, 2006 = 9,546, 2010 = 26,814, 2015 = 26,337; Medicaid CHB patients, 2006 = 1,425, 2010 = 2,067, 2015 = 2,278; non-CHB controls, 2006 = 3,141, 2010 = 4,582, 2015 = 5,773.

(8.8% versus 4.2%, $P < 0.001$), respectively (Supporting Table S4b).

CKD PREVALENCE, INCIDENCE, AND RISK FACTORS

The prevalence of CKD among CHB patients increased over time and was higher than in non-CHB controls in each time period (2006, 2010, 2015). By 2015, the CKD prevalence was 97.6 per 1,000 persons in the CHB groups compared to 33.8 per 1,000 persons in the control group among commercial/Medicare patients and almost double in the Medicaid group (173.0 versus 100.6 per 1,000 persons; $P < 0.05$ for all CHB versus non-CHB control comparisons and $P < 0.001$ for all 2006 versus 2015 comparisons) (Fig. 2A).

CKD incidence among CHB patients also increased significantly over time and was higher than in non-CHB controls in each time period (2006, 2010, 2015) (Fig. 2B). In 2015, the CKD incidence for the commercial/Medicare CHB group was 15.2 per 1,000 person-years versus 11.3 per 1,000 person-years for the non-CHB control group ($P < 0.05$). Similar to prevalence, the incidence rates in the Medicaid group in both CHB patients and non-CHB controls were double the rates of the commercial/Medicare group (39.1 versus 22.7 per 1,000 person-years, respectively, $P < 0.05$).

In 2015, CKD prevalence in CHB patients with DM and HTN was more than 10-fold higher than in those without CHB among commercial/Medicare patients and more than 4-fold higher in Medicaid patients (Supporting Fig. S2). In commercial/Medicare CHB patients, CKD prevalence in patients 60 years of age or older was 4-fold higher than for patients aged 45-59 and nearly 10-fold higher than for patients aged 30-44.

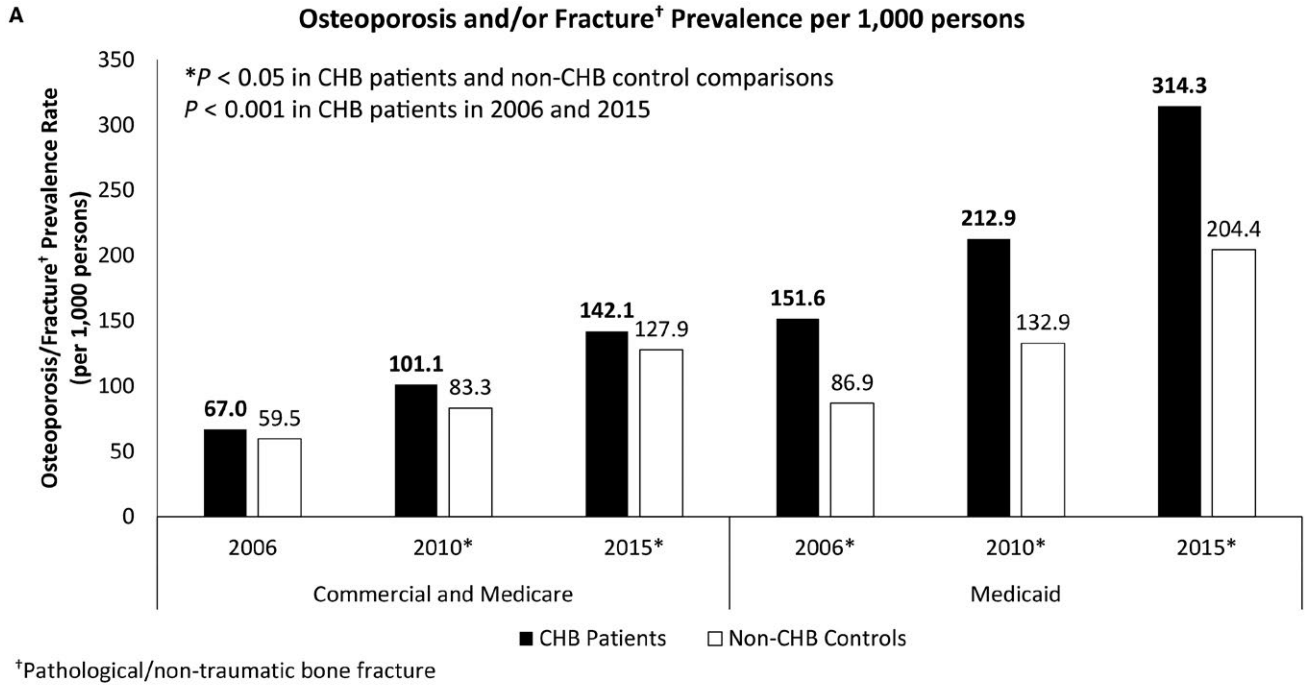
Table 3 describes the results of univariate and multivariate regression analyses to identify independent predictors for CKD among patients with CHB. Overall in multivariate analysis, older age (HR, 1.04), Medicaid coverage (HR, 1.71), years of follow-up (1 additional year; HR, 1.04), and comorbidities of HCV or HIV coinfection (HR, 1.80), DM (HR, 2.47), HTN (HR, 3.35), and CVD (HR, 2.61) were all associated with an increased risk of CKD. Notably, HTN, DM, and CVD were associated with at least a 2-fold increased risk of CKD. Only female gender was associated with a reduced risk (19% lower compared to men) of CKD. In addition, compared to non-CHB controls, CHB patients treated with anti-HBV therapies experienced an increased risk of CKD (HR, 1.79). Untreated CHB patients also experienced higher risk than non-CHB control patients (HR, 1.09).

OF PREVALENCE AND INCIDENCE

The prevalence of OF in CHB patients increased over time and was higher than in non-CHB controls in each time period (2006, 2010, 2015), such that by 2015 the OF prevalence among the commercial/Medicare CHB group was 142.1 versus 127.9 per 1,000 persons in the controls ($P < 0.05$) (Fig. 3A). The Medicaid group experienced the same findings, though the prevalence of OF was over double that of the commercial/Medicare group (CHB

TABLE 3. Risk Factors for CKD in Patients With CHB

		Univariate				Multivariate			
CKD Model	Risk Factors	HR	Lower CL	Upper CL	*P*	HR	Lower CL	Upper CL	*P*
Demographics	Baseline age	1.065	1.063	1.068	<0.0001	1.038	1.035	1.041	<0.0001
	Female versus male	0.69	0.65	0.73	<0.0001	0.81	0.76	0.86	<0.0001
	Medicaid versus commercial/Medicare	2.68	2.52	2.84	<0.0001	1.71	1.59	1.83	<0.0001
	Years of follow-up	1.07	1.06	1.09	<0.0001	1.04	1.02	1.05	<0.0001
Clinical characteristics	HCV or HIV	3.62	3.33	3.94	<0.0001	1.80	1.63	1.98	<0.0001
	Diabetes/diabetes medication	6.30	5.94	6.67	<0.0001	2.47	2.32	2.62	<0.0001
	HTN	9.05	8.42	9.74	<0.0001	3.35	3.09	3.63	<0.0001
	CVD	8.21	7.75	8.70	<0.0001	2.61	2.44	2.78	<0.0001
Treatments	CHB no treatment	1.50	1.40	1.60	<0.0001	1.09	1.02	1.17	0.0129
	CHB treatment	1.81	1.61	2.04	<0.0001	1.79	1.58	2.20	<0.0001
	Non-CHB matched control	1.00		Reference		1.00		Reference	



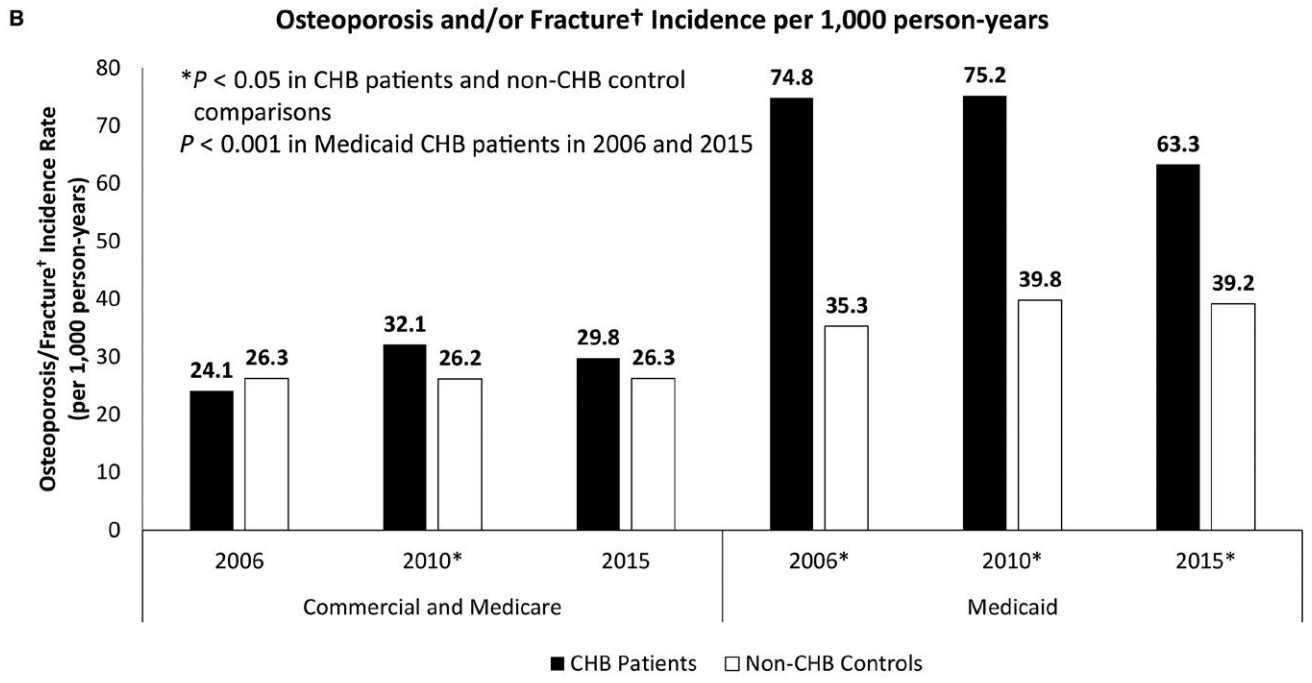


FIG. 3. (A) Prevalence of OF in CHB patients compared to non-CHB controls over time: 2006, 2010, and 2015. Numbers are as follows: commercial and Medicare CHB patients, 2006 = 3,819, 2010 = 9,958, 2015 = 9,094; non-CHB controls, 2006 = 9,546, 2010 = 26,814, 2015 = 26,337; Medicaid CHB patients, 2006 = 1,425, 2010 = 2,067, 2015 = 2,278; non-CHB controls, 2006 = 3,141, 2010 = 4,582, 2015 = 5,773. (B) Incidence of OF in CHB patients compared to non-CHB controls over time: 2006, 2010, and 2015. Numbers are as follows: commercial and Medicare CHB patients, 2006 = 3,819, 2010 = ; 2015 = 9,094; non-CHB controls, 2006 = 9,546, 2010 = 26,814, 2015 = 26,337; Medicaid CHB patients, 2006 = 1,425, 2010 = 2,067, 2015 = 2,278; non-CHB controls, 2006 = 3,141, 2010 = 4,582, 2015 = 5,773.

TABLE 4. Risk Factors for OF in Patients With CHB

		Univariate				Multivariate			
OF Model	Risk Factors	HR	Lower CL	Upper CL	*P*	HR	Lower CL	Upper CL	*P*
Demographics	Baseline age	1.039	1.038	1.041	<0.0001	1.04	1.039	1.042	<0.0001
	Female versus male	1.94	1.87	2.01	<0.0001	2.22	2.14	2.30	<0.0001
	Medicaid versus commercial/Medicare	1.73	1.66	1.80	<0.0001	1.31	1.25	1.38	<0.0001
	Years of follow-up	1.022	1.015	1.030	<0.0001	0.996	0.989	1.004	0.3124
Clinical characteristics	HCV or HIV	2.01	1.88	2.15	<0.0001	1.37	1.27	1.48	<0.0001
	Diabetes/diabetes medication	1.52	1.46	1.59	<0.0001	0.97	0.93	1.02	0.2269
	HTN	1.88	1.82	1.95	<0.0001	1.13	1.08	1.17	<0.0001
	CVD	2.23	2.13	2.33	<0.0001	1.28	1.22	1.35	<0.0001
	Smoking	2.58	2.45	2.71	<0.0001	1.76	1.66	1.87	<0.0001
	Alcohol use	3.25	3.02	3.49	<0.0001	2.02	1.87	2.19	<0.0001
Treatments	CHB no treatment	1.26	1.21	1.31	<0.0001	1.05	1.01	1.10	0.0221
	CHB treatment	0.97	0.88	1.06	0.4871	1.09	0.99	1.20	0.0748
	Non-CHB matched control	1.00		Reference		1.00		Reference	

versus controls, 314.3 versus 204.4 per 1,000 persons; $P < 0.05$).

The incidence of OF was significantly higher in Medicaid CHB patients (63.3-75.2 per 1,000 person-years) than in non-CHB controls (35.3-39.3 per 1,000 person-years) in each time period ($P < 0.001$) (Fig. 3B). However, the OF incidence in Medicaid CHB patients actually decreased from 2006 to 2015 ($P < 0.001$).

Table 4 describes results of univariate and multivariate regression analyses to identify independent predictors for OF. In multivariate analysis, compared to non-CHB controls, female gender (HR, 2.22), older age (HR, 1.04), Medicaid coverage (HR, 1.31), and comorbid conditions of HCV or HIV coinfection (HR, 1.37), HTN (HR, 1.13), CVD (HR, 1.28), smoking (HR, 1.76), and alcoholism (HR, 2.02) were more strongly associated with an increased risk of OF. In addition, both untreated CHB (HR, 1.05) and treated CHB (HR, 1.09, $P = 0.074$) patients trended toward a slightly increased risk of OF.

Discussion

This study characterized the longitudinal trends of comorbidities in a large, diverse US population of CHB patients derived from a unique insurance database. By analyzing specific comorbidities in CHB patients between 2006 and 2015 with commercial/Medicare Supplemental and Medicaid coverage and comparing them to a matched non-CHB control population, we found that CHB patients' DCCI scores and all evaluated comorbidities increased. Of special note was that Medicaid patients with and without CHB were more ill than patients with commercial/Medicare coverage as evidenced by their DCCI scores being 2-fold higher.

Another interesting finding was the aging of CHB patients over time, supporting findings that older age at presentation could reflect the continued underdiagnosis and poor linkage to care that has been well described for CHB in the United States.[7,21] The aging of the CHB population may also help to explain the age-associated increase in comorbidities such as DM, HTN, and renal and cardiovascular diseases.[22] However, the older age at presentation may also reflect an increasing uptake rate of HBV vaccination over time such that the incidence of CHB is falling, especially in children and younger individuals.[23]

Despite the aging trends, a striking finding was that patients with CHB had both a higher prevalence and a higher incidence of the selected comorbidities when compared to the matched non-CHB control group. This is especially noteworthy as the presence of various components of metabolic syndrome (obesity, hyperlipidemia, HTN, and DM) increased significantly during the study period. This incidental finding of increasing components of metabolic syndrome suggests the presence of another liver disease, nonalcoholic liver disease (NAFLD), and corraborates recent study findings of the increasing rate of NAFLD in the United States and globally, accounting

now for the second most common indication for liver transplant.[24,25] Health care providers should be cognizant of these comorbidities as NAFLD associated with HBV has been found to increase patient risk for end-stage liver disease and death.[25]

Questions often arise about the impact of antiviral therapy on the presence of comorbidities. When reviewing CHB patients who were treated or not treated in 2015, several things became apparent. First, <25% of patients received treatment for their CHB. Because we did not have laboratory values, we could not precisely determine the number and proportion of patients who were eligible for treatment; and this finding does require further investigation to discern the possible reasons to include insurance status as those on Medicaid were even less likely to receive treatment. Second, those who were treated were younger (<55 years), with a higher portion of male patients regardless of insurance status.

But for those in the commercial/Medicare group, patients treated were less sick and had fewer comorbidities but more advanced liver disease, probably because they were younger and male.[26] In the treated Medicaid cohort, patients coinfected with HCV and/or HIV were significantly more likely to have received treatment when compared to those not treated. A possible explanation for this finding is that CHB was found coincidentally prior to starting treatment for either HIV and/or HCV.[27,28]

It is important to keep in mind that one cannot determine whether treatment affected the prevalence of the extrahepatic comorbidities or whether there was selection bias on the part of the health care provider as to who received treatment. However, we did try to control for these concerns in our multivariate analysis for CKD and OF and found that the three major variables associated with increased risk for CKD were DM, HTN, and CVD. On the other hand, two of the three most predictive variables for OF were risky behaviors of alcohol abuse and smoking. Nonetheless, these findings do require further study using a matched sample to determine the drivers and impact of treatment.

Due to the aging of the CHB population, one must not overlook the impact of coinfection with HCV and/or HIV. Notably, in the commercial/Medicare insured group, those who were coinfected had a higher prevalence of comorbidities and advanced liver disease. This trend suggests that the presence of an additional infection may increase the risk for more comorbidities in addition to age. Another explanation may be that patients coinfected with HCV and/or HIV were found to be CHB-positive incidental to their other diagnoses such as that of advanced liver disease.[27-33] Therefore, appropriate and timely treatment is needed to reduce the burden associated with each disease separately and combined.[34]

In the Medicaid coinfected cohort, despite the significant increase in the prevalence of HCV and/or HIV from 2006 to 2015 and the increase in age, the only possible age-related comorbidities present at a significantly higher prevalence rate were HTN and renal impairment. A possible explanation for this finding is that those who were coinfected died at a faster rate before age-related comorbidities became apparent, especially if barriers were present precluding appropriate diagnosis and treatment.[29-32] Another possible explanation may be that patients were presenting with CHB at later ages, perhaps when they were diagnosed as being coinfected with HCV and/or HIV, and the diagnosis of CHB was incidental to other diagnoses, which may also explain the higher prevalence of advanced liver disease in the coinfected group.[28,33]

Between 2006 and 2015, along with the increase in metabolic morbidities, many of which are also known risk factors for renal disease, there was a notable increase in CKD prevalence among all insured patients. Specifically, CKD increased >1.5 times in the commercial/Medicare population and nearly 3 times in the Medicaid population. Although a significant increase in the presence of CKD was noted in both groups, Medicaid patients with and without CHB had significantly higher prevalence and incidence rates of CKD compared to commercial/Medicare patients. These findings further support the Institute of Medicine's findings that patients on Medicaid are more ill, experience more barriers to care, and have higher mortality.[21]

As a result of the significant increase in CKD, we performed a multivariate analysis to determine the highest risk factors for CKD development in CHB patients, especially considering significant increases in the prevalence of CVD, HTN, and DM and to determine the impact of anti-HBV therapy. Our results confirmed previous reports demonstrating that

an increased risk for CKD in patients with CHB is enhanced in the presence of comorbidities, particularly when both HTN and DM are present.[12-14,35] The higher CKD risk associated with CHB, especially treated CHB, compared to non-CHB controls can also be due to the fact that CHB patients receiving anti-HBV therapy most likely have more advanced liver disease, though a recent review also discusses potential nephrotoxicity risk with some of the older oral anti-HBV medications.[36] Furthermore, in line with the findings of recent treatment guidelines,[16] the receipt of anti-HBV therapy increased the risk of developing or having CKD, though a subanalysis of the impact of specific antiviral medications could not be conducted due to small sample sizes. On the other hand, female gender was protective for developing or having CKD.

The proportion of CHB patients with comorbidities that may influence bone mineralization and risk for OF (malignancy, smoking, and alcohol use) also increased significantly between 2006 and 2015 (all $P < 0.008$). However, in our multivariate analysis, female gender and alcohol use were associated with the highest risk for developing OF. In contrast, anti-HBV treatment was associated with only a small risk for developing OF, similar to recent literature confirming that bone events in patients with CHB may be largely attributable to comorbid risk factors independent of antiviral therapy.[15,36] Recent population-based data from Taiwan also reported similar findings of higher risk of CKD and osteoporosis in CHB patients compared to non-CHB controls.[15]

An interesting finding is the high percentage of patients with alcohol use in the HBV population, particularly those covered by Medicaid, though our findings are in line with the national estimates of alcohol use disorder (24.4%) or alcohol abuse (17.0%) among adult Medicaid recipients.[37] However, the elevated prevalence of HBV in patients with alcohol use disorder may be due to their potential for more risky behavior, including trauma, hospitalization, blood transfusions, and risky sexual activities. Therefore, addressing the use of alcohol in patients with HBV should be part of their care as alcohol use is known to increase the progression of HBV to HCC, cirrhosis, and end-stage liver disease.[38] Recently, Medicaid approved coverage for their recipients to receive substance abuse counseling and health care assistance, thus helping to diminish the barrier to care for these patients, which should encourage more practitioners to refer patients for specialty services.[39]

It is important to also note that smoking and the development of HCC among Chinese CHB patients is a significant association.[40-42] Smoking raises the risk of HCC and has been found to not only be additive but also multiplicative in those who ever smoked.

There are several limitations to this study. First, the study was conducted using a registry of administrative coding data. However, as noted, our population characteristics closely followed trends noted within the public records, especially for patients on Medicaid. Second, many comorbidities may be underrepresented due to coding issues, but as this is a large database maintained with rigorous methods, the misrepresentation of disease states is decreased. Similarly, surveillance bias in patients with one chronic disease such as CHB may also increase the reporting of comorbidities in CHB patients compared to controls. However, this should not affect the reporting of comorbidities among CHB patients over time. Third, because CHB was selected through the use of ICD-9 codes in any position, the incidence and prevalence rates of CHB may be either underestimated or overestimated. Comorbidities may also be undercoded or overrepresented as a result of a condition being ruled out or coded erroneously. However, this condition is no more likely to occur for cases or controls such that we do not believe the direction of our findings would change. In addition, data on the effect of anti-HBV on CKD or OF events and hormonal therapy and osteoporosis medications on OF are limited by lack of detailed data on treatment initiation and duration as well as patient adherence to the prescribed medication. In addition, only 1%-2% of patients were on osteoporosis treatment or hormone supplemental treatment, so their respective impact may be limited. Another potential limitation is that by limiting our outcomes of the incidence of chronic kidney disease and osteoporotic fractures to after the first hepatitis B diagnosis date, we may have entered a bias toward the null as HBV infection is chronic and most likely was preexisting prior to the initial diagnosis of HBV. Furthermore, the databases used in this study only included insured subjects, so the results may not apply to the uninsured population. Finally, we acknowledge that there is probably an underdiagnosis of well-compensated cirrhosis from the primary care and community settings due to the lack of liver biopsy data and

the subtle findings that patients with compensated cirrhosis may present with, which may be difficult for primary care and community physicians to recognize.

Over the past decade, CHB patients linked to insurance databases are aging (i.e., coded at an older age) and presenting with more comorbidities. In fact, when compared to matched controls without CHB, we found that the prevalence of comorbidities was significantly higher in CHB patients, particularly those on Medicaid. Our multivariate analysis determined that the presence of nonliver comorbidities such as HTN, CVD, and DM was among the primary risks for CKD development. As such, the management of CHB patients should take into account the safety profile of each anti-HBV medication and the impact of an aging CHB population with increasing nonliver comorbidities on clinical outcomes such as kidney disease and bone fractures. An interesting result from our study was that female gender appeared to be protective of CKD, a finding that certainly needs further study to determine the impact of gender and HBV on CKD. In addition, further effort is needed to identify and link CHB patients to care at a younger age when in a healthier state to avoid the complex management of the older patient with significant nonliver comorbidities.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.30246/suppinfo.