Received: 9 June 2023 | Accepted: 16 October 2023

DOI: 10.1097/HEP.0000000000000687

ORIGINAL ARTICLE

OPEN

Prevalence and characteristics of hepatitis delta virus infection in patients with hepatitis B in the United States: An analysis of the All-Payer Claims Database

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Abstract

Background and Aims: HDV leads to the most severe form of viral hepatitis; however, the prevalence of HDV is not well understood. Using real-world data from the All-Payer Claims Database, this study estimates the prevalence of HBV/HDV infection among the chronic HBV population and describes patient/clinical characteristics for adults with HBV/HDV infection in the United States.

Approach and Results: Adults ($\geq$18 years) with $\geq$1 inpatient claim or $\geq$2 outpatient claims for HDV infection or HBV in the All-Payer Claims Database from January 1, 2014, to December 31, 2020, were identified. HDV prevalence was calculated as the proportion of patients with HBV/HDV infection among total patients with HBV infection. Patient characteristics, socio-economic status, advanced liver complications (eg, cirrhosis, HCC), and

Abbreviations: AASLD, American Association for the Study of Liver Disease; APASL, Asian-Pacific Association for Study of the Liver; APCD, All-Payer Claims Database; CC, compensated cirrhosis; CHB, chronic hepatitis B; DCC, decompensated cirrhosis; EASL, European Association for the Study of the Liver; FDA, Federal Drug Administration; FIPS, Federal Information Processing Standards; HIPAA, Health Insurance Portability and Accountability Act; ICD, International Classification of Diseases; USDA, US Department of Agriculture.

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.hepjournal.com.

comorbidities were assessed. A total of 6719 patients were diagnosed with HBV/HDV among 144,975 with HBV and 12 months of continuous data, for a prevalence of 4.6%. At diagnosis, 31.7% of patients with HBV/HDV had advanced liver complications, including compensated cirrhosis (16.3%) and decompensated cirrhosis (10.4%). Diabetes (50.5%), hypertension (49.8%), and HIV infection (30.9%) were the top 3 comorbidities.

Conclusions: In a large database capturing approximately 80% of the US-insured population, HBV/HDV infection prevalence was 4.6% among adults infected with HBV. Patients infected with HDV had high rates of baseline liver complications and other comorbidities at the time of diagnosis, suggesting potentially delayed diagnosis and/or treatment. Earlier identification of HBV/HDV infection among the population with HBV may provide opportunities to improve linkage to care and treatment, thereby reducing the risk of liver-related morbidity and mortality.

INTRODUCTION

The HDV is a defective RNA virus that requires concomitant HBV infection in order for HDV to propagate, invade hepatocytes, transmit infection, and cause pathogenesis through either simultaneous acute infection with both viruses or superinfection (asynchronous infection in which HDV infection occurs in the setting of pre-existing HBV infection).[1,2] HBV/HDV infection is recognized as the most severe form of viral hepatitis and is associated with a high risk of progression to compensated cirrhosis, decompensated cirrhosis (DCC), HCC, and/or end-stage liver disease. Recent data suggest that people with HBV/HDV infection are nearly 4 times more likely to develop cirrhosis compared to patients with HBV monoinfection.[3] Patients with combined HBV/HDV infection progress to cirrhosis within 5 years and to HCC within 10 years, on average.[3]

According to Center for Disease Analysis Foundation's Polaris Observatory 2021 (dashboard reporting global epidemiological data for HBV and hepatitis C), an estimated 272 million people are living with chronic HBV infection worldwide, with an incidence of 1.9 million new infections each year despite the existence of an effective vaccine that confers high levels of long-lasting protection.[4–6] The prevalence of HDV is poorly understood. Recent studies report a wide estimated range of global (12–74 million people) and regional prevalence rates that are confounded by several factors (eg, human migratory patterns, insufficient screening, lack of surveillance).[3,7–9] Within the United States, the prevalence of chronic hepatitis B (CHB) is estimated to be 1.59 million (1.25–2.49 million) people.[10] However, prevalence estimates for HBV/HDV infection in the United States vary considerably and are often derived and extrapolated from special populations (eg, immigrants, patients from Veterans Affairs hospitals, injection drug users), are regional or obtained by means of cross-sectional surveys.[11–15] Most recently, the prevalence of HBV/HDV infection, as reflected by the presence of anti-HDV (total antibody to HDV) among people with HBV was estimated to be 5.9% or approximately 59 positive cases per 1000 people with CHB.[8] There is a critical need to improve screening and monitoring for HBV/HDV given the increased risk of morbidity and mortality in this population.

Consistent guidance on the effective screening and diagnosis of HDV is lacking, which may contribute to delayed diagnosis of HBV/HDV infection when patients are already experiencing advanced liver disease. The American Association for the Study of Liver Diseases (AASLD) recommends a risk-based approach to screening patients with CHB who are at high risk for HBV/HDV infection (eg, immigrants, persons who have injected drugs). In contrast, the European Association for the Study of the Liver (EASL) and the Asian-Pacific Association for the Study of the Liver (APASL) Clinical Practice Guidelines recommend universal screening of all patients with CHB.[16–18]

Harmonizing best practices for screening will be important to the timely identification of patients for treatment, with the goal being sustained HDV virological response and, ultimately, clearance of the HBsAg post-treatment completion.[19] Current HBV/HDV treatment options include Peg-IFN-α and concurrent nucleos(t)ide analog treatment to suppress underlying HBV infection; however, limited efficacy is available for these HDV therapies, with nucleos(t)ide analog agents conferring no suppression of HDV RNA, and none are

approved by the US Federal Drug Administration (FDA) for HBV/HDV.[16,17]

Understanding the prevalence of HBV/HDV infection and key patient characteristics at diagnosis are critical elements to transitioning from unsuccessful risk-based screening programs to universal screening programs for early HDV diagnosis and effective treatment strategies. The aim of this study was to use real-world claims data from the All-Payer Claims Database (APCD) in the United States to evaluate (1) the most recent estimates of HBV/HDV prevalence and (2) patient characteristics for patients with chronic HBV/HDV and HBV infection between 2014 and 2020.

METHODS

Data source

The APCD real-world data consist of medical and pharmacy claims that capture health care data and resource utilization on over 80% of the US health care system. APCD real-world data are comparable with other all-payer claims repositories. Data are sourced daily directly from claims clearinghouses that are responsible for managing claims transactions between payers and providers.

Confidentiality and institutional review board requirements

No identifiable information or medical records were disclosed for this study, and there was no collection, use, or transmittal of individually identifiable data. Patient data that are deidentified *a priori* are exempt from the Federal Policy for the Protection of Human Subjects (1991) and do not meet the identification criteria necessary to be privileged under the Health Insurance Portability and Accountability Act (HIPAA); therefore, this study was exempt from Institutional Review Board approval.

Study design

A retrospective cohort study design was used to identify adult patients (18+ years) who were diagnosed with HBV monoinfection and those diagnosed with HBV/HDV infection using the APCD database between January 1, 2014, and December 31, 2020. Patients were identified using continuous capture, which requires patients to have at least 1 claim in both the baseline period (ie, 12-month pre-index) and the follow-up period (ie, 12-month postindex) over the study period (January 1, 2014, to December 31, 2020) (Figure 1). The index date was defined as either the first date of an HBV diagnosis (with no subsequent HDV diagnosis) or the date in which an individual with HBV received a subsequent HDV diagnosis (HBV/HDV) during the identification period. Patients with index dates within the identification period were captured, and data from 12 months before (baseline period) and 12 months after (follow-up period) were collected. Patients who did not have a claim related to either HBV or HDV prior to the baseline period (12-month preindex) were considered "newly diagnosed" patients.

Adult patients (on the index date) were included in the study if they had at least one inpatient or 2 outpatient claims $\geq$30 days apart with an International Classification of Diseases, 9th/10th Revisions, Clinical Modifications (ICD-9/10-CM) for HBV (ICD-9: 70.20, 70.22, 70.30, 70.32; ICD-10: B18.1, B19.10, B19.11, B16.9, B16.2), or HBV/HDV (ICD-9: 70.21, 70.23, 70.31, 70.33, 70.42, 70.52; ICD-10: B16.0, B17.0, B16.1, B18.0) infections.[20–22] Patients with HBV diagnosis were considered to have an HBV monoinfection if there was no other evidence of an HBV/HDV infection diagnosis during the study period. Please see the Supplemental Digital Content, http://links.lww.com/HEP/I120 for the detailed list of diagnostic codes used.

Patient demographics and clinical characteristics, including age, sex, comorbidities, primary insurance status, treatment for both HBV/HDV and HBV during the baseline period, and geographic region at index date,

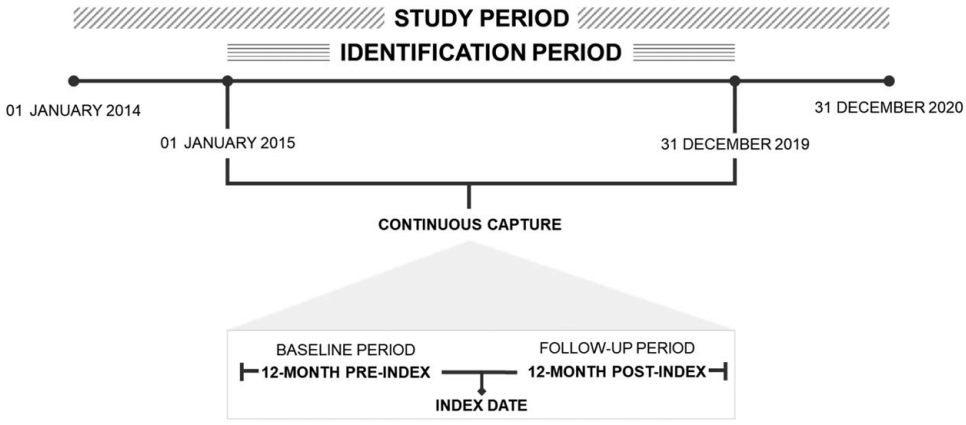

FIGURE 1 Diagram representing the study design used.

were captured. Age at index date was retained in the dataset as a continuous variable and stratified into the following age groups: 18–34, 35–44, 45–54, 55–64, 65–74, and 75 years of age or above. Primary insurance payers at index date were categorized as commercial, Medicare, Medicaid, and others. Medications were defined as HBV (ie, PegIFN, interferon-alfa 2b, interferon-alpha N3, adefovir, telbivudine, lamivudine, tenofovir disoproxil, tenofovir alafenamide, entecavir), or HBV/HDV-related medications (eg, PegIFN alfa-2a) in combination with an HBV/HDV diagnosis (see Supplemental Table S1 in the Supplemental Digital Content, http://links.lww.com/HEP/I119). The geographic region at index date was determined by the 3-digit ZIP code of the indexing provider, and states were categorized into 5 health plan regions (see Supplemental Table S2 in the Supplemental Digital Content, http://links.lww.com/HEP/I119). ZIP codes were converted to Federal Information Processing Standards (FIPS) codes identifying the county of the indexing provider. FIPS codes were matched to US Department of Agriculture (USDA) rural-urban codes to determine which areas were classified as rural and urban.

Liver-related complications (eg, DCC, compensated cirrhosis, HCC, and liver transplant) and other patient comorbidities (eg, sexually transmitted infections, obesity, history of smoking) at baseline were captured using ICD-9/10-CM codes (Supplemental Digital Content, http://links.lww.com/HEP/I120). Additionally, the Quan-Charlson Comorbidity Index Score was used to assign a weighted score from 1 to 6 to evaluate patients' comorbidity during the baseline period (12 months prior to the index date).

The prevalence of both HBV monoinfection and HBV/HDV infection was identified by screening for patients with at least one inpatient or at least 2 outpatient claims that were $\geq$30 days apart. Patients without at least 1 inpatient claim or 2 outpatient claims were excluded from the analysis. The sum of patients with HBV monoinfection and patients with HBV/HDV infections (HBV + HBV/HDV) was used as the denominator to determine the prevalence of HBV/HDV infection among the total HBV population. A secondary outcome variable of interest was capturing physician specialty for the index date of diagnosis by means of national provider identifiers. National provider identifiers are numeric identifiers used by HIPAA providers that are used to identify specific health care practitioners for claims transactions.

Statistical analysis

The mean (SD), median (interquartile range), minimum, and maximum values are reported for all continuous variables. Descriptive statistics such as counts (frequencies) and percentages are reported for categorical values. Demographics and patient comorbidities were summarized and reported at baseline. Wilcoxon signed-rank tests were used to compare all continuous measures, and McNemar tests were used to compare dichotomous variables. All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC), and two-tailed statistical significance was determined *a priori* at $p < 0.05$. This study was reported per the STOBE statement (see the STROBE checklist in the Supplemental Digital Content, http://links.lww.com/HEP/I215).

RESULTS

Study population

A total of 195,894 patients with a diagnosis of HBV or HBV/HDV between January 1, 2014, and December 31, 2020, were identified in the APCD claims database. Of those, 194,573 met the criteria for age (18 years of age or above), with 184,837 patients with an HBV monoinfection diagnosis and 9376 patients determined to have an HBV/HDV diagnosis. A total of 138,256 patients with HBV and 6719 patients with HBV/HDV met the criteria for continuous data across the 12-month baseline (12-month preindex) and follow-up periods (12-month postindex) to be included for analysis (Figure 2).

Patient and clinical characteristics

Descriptive analyses of patient and clinical characteristics for individuals diagnosed with either HBV monoinfection or HBV/HDV infection from the APCD during the study period are reported in Table 1. Overall, the mean age was similar for patients with HBV monoinfection (53 years of age) and HBV/HDV infection (52 years of age). A slightly higher proportion of patients aged 18–34 was observed in the HBV/HDV infection cohort. Nearly equal proportion of males and females were captured across the cohorts, with a slightly higher proportion of males in the HBV monoinfection group (males: HBV/HDV: 49.5%; HBV: 53.9%). The majority of the patients captured in the claims database were White, of non-Hispanic ethnicity, and most likely to be high school educated. Patients diagnosed with HBV/HDV had a slightly lower mean income relative to patients diagnosed with HBV [HBV/HDV: $41,515 (SD $44,697); HBV: $49,590 (SD $51,135)]. Overall, most of the patients in both cohorts were covered by commercial insurance (HBV/HDV: 42.7%; HBV: 53.3%). A higher proportion of patients with HBV/HDV infection (34%) had Medicaid coverage relative to patients with HBV monoinfection (19%).

The proportion of Black patients with HBV/HDV was more than double that in the cohort with HBV monoinfection (HBV/HDV: 36.6%; HBV: 17.3%) (Table 1).

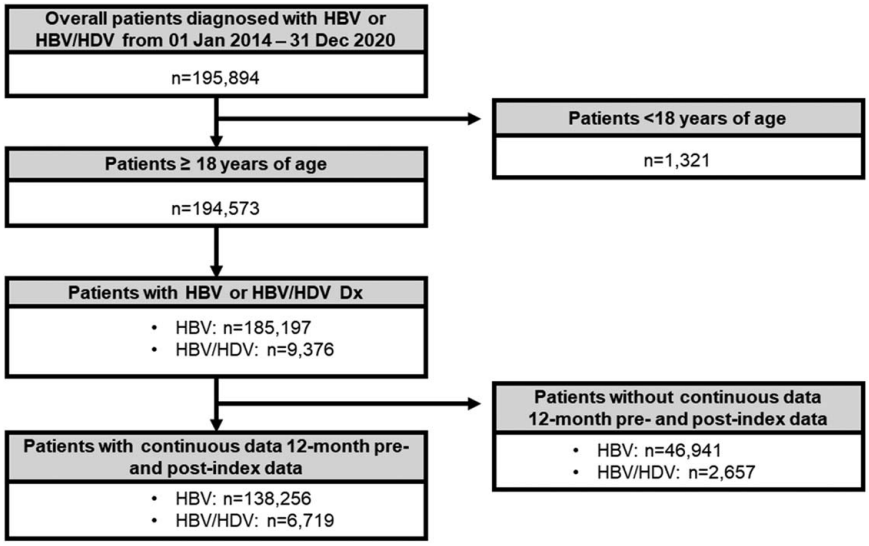

FIGURE 2 Flow diagram depicting patient selection from the All-Payer Claims Database between 2014 and 2020. Abbreviation: Dx, diagnosis.

Conversely, more than double the proportion of Asian patients were diagnosed with HBV in relation to the proportion of Asian patients diagnosed with HBV/HDV over the same time period (HBV/HDV: 13.7%; HBV: 32.8%).

Patients diagnosed with HBV/HDV had a significantly higher mean Charlson Comorbidity Index score compared to patients diagnosed with HBV monoinfection [1.7 (SD 2.3) vs.1.2 (SD 1.9), $p < 0.0001$], suggesting a greater prevalence of comorbidities associated with a higher risk of mortality and healthcare resource utilization. Patients diagnosed with HBV/HDV infection experienced a significantly higher frequency of every comorbidity of interest (with the exception of NASH) than patients with HBV monoinfection (Table 1). Comorbid conditions associated with potentially modifiable behaviors were significantly higher in frequency for patients with HBV/HDV infection. Compared to patients with HBV monoinfection, patients with HBV/HDV infection had significantly greater proportion of sexually transmitted infections (18.7% vs. 2.2%, $p < 0.0001$), HIV diagnosis (30.9% vs. 8.1%, $p < 0.0001$), and substance abuse (28.7% vs. 13.2%, $p < 0.0001$), hypertension (49.8% vs. 39.7%, $p < 0.0001$), diabetes (50.5% vs. 26.2%, <0.0001), and obesity (15.1% vs. 10.8%, <0.0001) (Table 1).

The proportion of patients with liver-related complications (ie, DCC, cirrhosis, HCC) was also significantly higher in patients with HBV/HDV infection compared to patients with HBV monoinfection (Table 1). Furthermore, the proportion of patients diagnosed with HBV/HDV having received a liver transplant was double that of patients with HBV monoinfection (2.2% vs. 0.8%, $p < 0.0001$).

Prevalence was calculated as the proportion of patients diagnosed with HBV/HDV infection identified in the claims data among the total number of patients diagnosed with HBV monoinfection (n = 138,256) and HBV/HDV infection (n = 6719). The estimated HBV/HDV infection prevalence among the HBV population above 18 years of age with continuous data over the study period in the United States, identified by means of the APCD claims database, is 4.6%. Of the 6719 patients diagnosed with HBV/HDV between 2015 and 2019, a total of 5962 (88.7%) were newly diagnosed patients.

Distribution of HBV/HDV and HBV by geographic area

Among patients with HBV/HDV infection, the greatest proportion of patients (44.9%) were located in the North Central region (Wisconsin, Michigan, Illinois, Indiana, Ohio, North Dakota, South Dakota, Nebraska, Kansas, Minnesota, Iowa, and Missouri), followed by 23.7% in the Northeast region, 16.7% in the South region, and 14.4% in the West region (Table 2).

The state of Illinois was the main driver of the high distribution of HBV/HDV captured in the North Central region. Approximately 38.1% of patients diagnosed with HBV/HDV infection in the United States between 2014 and 2020 were residing in the state of Illinois at baseline diagnosis, followed by New York (16.3%), California (10.5%), and Florida (5.8%) (Figure 3).

Urban versus rural distribution of patients diagnosed with HBV/HDV

The urban versus rural location of patients diagnosed with HBV/HDV were evaluated by the indexing provider's ZIP code, within each state, at baseline diagnosis. The majority of the patients diagnosed with

TABLE 1 Patient and clinical characteristics in the United States (2014–2020)

Patient characteristics	HBV/HDV (n = 6719)	HBV (n = 138,256)	*p*
Mean age, y (SD)	51.9 (15.0)	53.2 (14.2)	**< 0.0001**
18–34, n (%)	1019 (15.2)	16,200 (11.7)	**< 0.0001**
35–44, n (%)	1038 (15.4)	23,056 (16.7)	**0.0083**
45–54, n (%)	1504 (22.4)	31,824 (23.0)	0.2278
55–64, n (%)	1761 (26.2)	34, 527 (25.0)	**0.0224**
65–74, n (%)	971 (14.5)	23,933 (17.3)	**< 0.0001**
≥ 75, n (%)	426 (6.3)	8716 (6.3)	0.9057
Sex, n (%)	—	—	**< 0.0001**
Female	3391 (50.5%)	63,786 (46.1%)	—
Male	3328 (49.5%)	74,470 (53.9%)	—
Race, n (%)[a]			—
White	1500 (48.8)	27,568 (49.3)	—
Black	1127 (36.6)	9690 (17.3)	—
Asian	420 (13.7)	18,371 (32.8)	—
Other	29 (0.9)	328 (0.6)	—
Ethnicity, n (%)[a]	—	—	—
Hispanic	581 (21.4)	7471 (14.5)	—
Non-Hispanic	2140 (78.6)	44,124 (85.5)	—
Level of education, n (%)[a]	—	—	—
Some high school	60 (3.2)	675 (1.9)	—
High school	1219 (64.0)	19,731 (55.6)	—
College	400 (21.0)	9579 (27.0)	—
Postgraduate	225 (11.8)	5515 (15.5)	—
Mean income (SD)	$41,515 ($44,697)	$49,590 ($51,135)	—
Insurance, n (%)	—	—	—
Commercial	2871 (42.7)	73,729 (53.3)	—
Medicare	1338 (19.9)	32,623 (23.6)	—
Medicaid	2295 (34.2)	26,335 (19.1)	—
Other	215 (3.2)	5569 (4.0)	—
Clinical characteristics			
Mean Quan-Charlson Comorbidity Index (SD)	1.7 (2.3)	1.2 (1.9)	**< 0.0001**
Liver-related complications at the time of HBV or HBV/HDV diagnosis			
Compensated cirrhosis	1094 (16.3)	20,847 (15.1)	**0.0072**
Decompensated cirrhosis	698 (10.4)	10,212 (7.4)	**< 0.0001**
HCC	190 (2.8)	2554 (1.8)	**< 0.0001**
Liver transplant	147 (2.2)	1141 (0.8)	**< 0.0001**
Comorbidities of interest			
Sexually transmitted infections	1254 (18.7)	3082 (2.2)	**< 0.0001**
Hypertension	3346 (49.8)	54,885 (39.7)	**< 0.0001**
History of smoking	1889 (28.1)	28,585 (20.7)	**< 0.0001**
HCV infection	669 (10.0)	11,730 (8.5)	**< 0.0001**
HIV infection	2074 (30.9)	11,181 (8.1)	**< 0.0001**
Mental health disorder	1121 (16.7)	16,365 (11.8)	**< 0.0001**
Obesity	1014 (15.1)	14,966 (10.8)	**< 0.0001**
Substance abuse	1925 (28.7)	18,254 (13.2)	**< 0.0001**
Alcohol abuse or dependence/alcohol use disorder	662 (9.9)	8477 (6.1)	**< 0.0001**
NASH	329 (4.9)	7492 (5.4)	0.0642
Diabetes	3394 (50.5)	36,205 (26.2)	**< 0.0001**

Note: Bolded values highlight significance
Missing *p*-values indicate that the statistical comparison was not executed.
Table providing patient characteristic data for patients with HBV and HBV/HDV from the All-Payer Claims Database between 2014 and 2020.
[a]Race, ethnicity, and education were not available for all patients; therefore, the sum may not equal the total number of patients included in the analysis.
Abbreviation: n, sample size.

TABLE 2 Distribution of HBV/HDV and HBV by US Geographic Region (2014–2020)

US Geographic region	HBV/HDV, n (%)	HBV, n (%)
Northeast	1595 (23.7)	55,484 (40.1)
North Central	3018 (44.9)	16,373 (11.8)
South	1124 (16.7)	33,704 (24.4)
West	966 (14.4)	32,510 (23.5)
Other/unknown	16 (0.2)	185 (0.1)

Note: Geographic regions: Northeast region: Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, Pennsylvania, New Jersey. North Central region: Wisconsin, Michigan, Illinois, Indiana, Ohio, North Dakota, South Dakota, Nebraska, Kansas, Minnesota, Iowa, Missouri. South region: Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, Florida, Kentucky, Tennessee, Mississippi, Alabama, Oklahoma, Texas, Arkansas, Louisiana. West region: Montana, Wyoming, Nevada, Utah, Colorado, Arizona, New Mexico, Alaska, Washington, Oregon, California, Hawaii. Other: Puerto Rico, Virgin Islands.

Table presenting the distribution of patients with HBV and HBV/HDV across 5 regions in the United States from the All-Payer Claims Database between 2014 and 2020.

HBV/HDV (n = 6545/6719) were associated with provider ZIP codes located in urban areas across the United States, ranging from 75% to 100% in any given state. Approximately 38% of patients with urban providers diagnosed with HBV/HDV resided in the state of Illinois. Only n = 54 patients with HBV/HDV had index data reported by providers located in rural areas at baseline diagnosis. The state of New York had the highest proportion of patients diagnosed with HBV/HDV by providers located in rural areas at 14.8%, followed by Kentucky (11.1%), Tennessee, Texas (7.4%), West Virginia (7.4%), and Florida (5.6%).

Physician speciality in index diagnosis for patients with HBV and HBV/HDV

Most of the HBV (45.3%) and HBV/HDV (53.0%) diagnoses at index date in the United States between 2014 and 2020 were reported by primary care physicians, followed by gastroenterologists (HBV: 14.4%; HBV/HDV: 9.3%) (Figure 4).

DISCUSSION

This study presents novel data on the prevalence and key patient demographics for patients diagnosed with HBV/HDV infection in the United States. Currently, there are limited data regarding the prevalence of HDV in the United States. The results presented in this study provide an estimate of HBV/HDV infection prevalence of 4.6% among individuals with HBV within a large and generalizable population from the APCD (approximately 80% of the US-insured population).

The prevalence of HDV/HBV varies considerably across publications. Identifying HBV/HDV infection typically requires the identification of the antibody to HDAg, followed by testing for HDV RNA in the serum.[23,24] The anti-HDV IgM is detectable in the serum within 2 to 3 weeks of both acute coinfection with

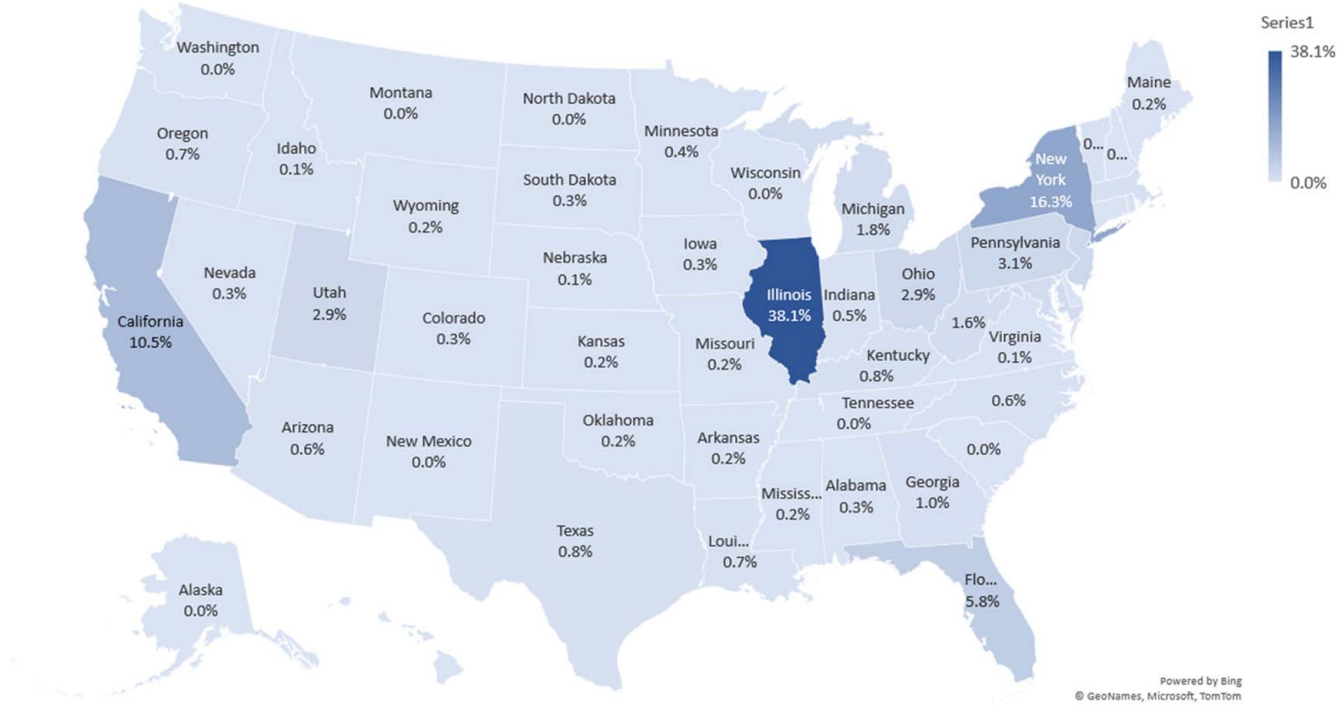

FIGURE 3 Map of the United States showing prevalence of HBV/HDV among the HBV population for each state from the All-Payer Claims Database between 2014 and 2020. Lighter colors represent a lower prevalence, whereas darker colors represent a higher prevalence.

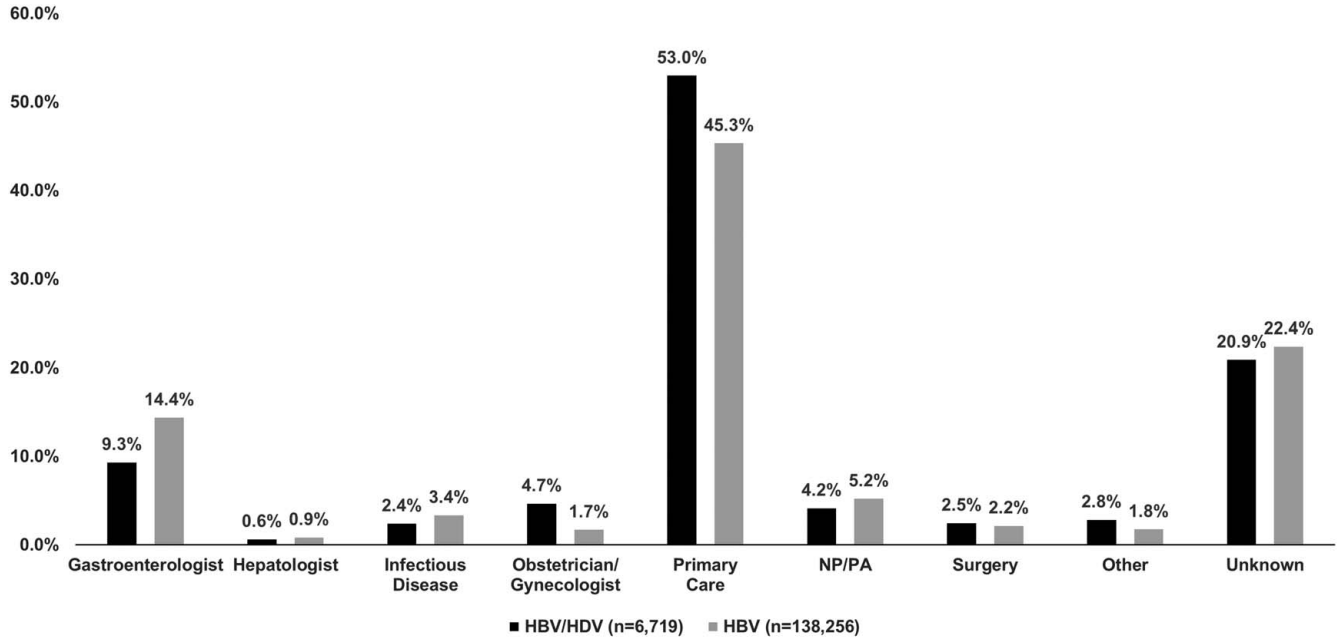

FIGURE 4 Graphical representation of the proportion of patients diagnosed with either HBV/HDV or HBV by physician specialty from the All-payer Claims Database between 2014 and 2020. Abbreviations: NP, nurse practitioner; PA, physician's assistant.

HBV and HDV or in acute HDV superinfection in patients with pre-existing CHB. Anti-HDV IgM decreases following acute infection within 2 months, and may appear during disease flares in patients with chronic disease.[24] Therefore, the sole use of anti-HDV IgM for diagnosis of HBV/HDV is not accurate and is likely a contributing factor to the heterogeneity of prevalence estimates across various studies. Other inherent issues to understanding true HBV/HDV infection prevalence are test sensitivity and access to testing, particularly over longer study periods. Variability exists across diagnostic assays, lending to a lack of test sensitivity which can result in misdiagnosis, the delay of appropriate treatment, and rapid disease progression.

A recent systematic review and meta-analysis by Stockdale et al[8] estimated a global prevalence of HBV/HDV infection among patients diagnosed with HBV (HBsAg) at 4.5% with a prevalence of 5.9% within the United States. The US prevalence was derived from literature indexed in electronic databases dating back to 1998, which may have included data collected as early as 1988.[8] A wide variety of gray literature sources, including national health surveillance programs, national health surveillance websites, surveys, census data, vital statistics, and other reports, were also included for analysis.[8] The final prevalence estimates of HBV/HDV infection among the HBV population were modeled using a binomial mixed model.[8] The prevalence estimate derived from our study was calculated directly from HDV diagnoses recorded in the APCD data using a 2-claim approach. Although the data from the APCD represent 80% of the insured population across the United States, national and regional surveys, gray literature, and data from hepatology clinics may better capture uninsured patient data. Similarly, the data from the APCD are only accessible from 2014 onward. Therefore, patients diagnosed prior to 2014 are not represented in the population identified for inclusion in this study but could be better represented in the Stockdale and colleagues estimate.

This study includes a large cross-section of the US-insured population, providing a greater understanding of national and regional patient characteristics of individuals diagnosed with HBV/HDV infection. The North Central region had the largest proportion of people diagnosed with HBV/HDV infection in the United States, with the largest concentration of patients residing in Illinois, followed by the Northeast region. As of 2023, Illinois is ranked as the sixth most populous state in the union, and according to the APCD, had the highest proportion of patients with HBV/HDV infection of any state, exceeding that of the nation's most populous states.

In 2017, Martins and colleagues estimated an 11.8% prevalence rate of HDV among patients with chronic HBV utilizing two large patient databases.[25] Geographical analysis showed that 25% of all patients diagnosed with HDV resided in Brooklyn, NY, Chicago, IL, the Bronx, NY, Corona, NY, and Huntington Station, NY.[25] The study also highlighted that the states of Illinois and Florida were emerging regions with a growing concentration of HDV infection during the 2008–2016 study period.[25] The data reported in our study support the geographic trends observed between 2008 and 2016 in the United States, particularly the climbing prevalence rates in the state of Illinois.

Higher prevalence rates could be indicative of increased screening for HDV both at a nationwide and local level. However, Martins et al[25] reported that higher rates of HDV infection were reported despite only a minimal increase in the testing rate. Approximately 4000 HDV antibody tests were ordered in 2016 (a 30% increase from 2012), only 4.7% were for patients who were newly diagnosed with chronic HBV compared to ~3.0% in 2012. However, the number of newly diagnosed HDV cases increased by 75% over the same period (5259 vs. 9079). Diagnostic data showed that roughly 35,000 physicians diagnosed a new HBV case, but only 2541 diagnosed a new HDV case in 2016. Together, these data signal that HDV may be underdiagnosed in patients with HBV due to a lack of testing.

All of the indexing physicians captured in the APCD who reported HDV diagnoses in the state of Illinois were associated with ZIP codes in urban areas. The city of Chicago has a population of over 2.7 million people; the metropolitan area surrounding Chicago is home to 9.7 million and the largest population of Mongolian-Americans.[26] The country of Mongolia is a highly endemic region for viral hepatitis with an HBV/HDV infection prevalence estimate of 36.9% among the population with HBV.[8,27] A recent study reported a high prevalence of chronic viral hepatitis among Mongols in southern California, home to the second largest population of Mongolian-Americans in the United States.[26,27] Among the 51 Mongols in the study who were HBsAg positive, 41.2% were anti-HDV positive and 33.3% were HDV RNA positive, suggesting that Mongolian-Americans are at a high risk for HBV/HDV infection.[27]

The United States has the largest immigrant population in the world. Data from the Migration Policy Institute in the United States reported that 31% of US immigrants in 2021 were from Asia.[28] Although Mongolian-Americans (or other immigrant populations) living in the Chicago metropolitan area may be contributing to the higher prevalence of HDV in Illinois, it is also likely that immigrant populations are not well represented in claims databases. Noncitizens and foreign-born individuals 19–64 years of age have the highest uninsured rates at 33.1% and 22.8%, respectively.[29] High uninsured rates suggest that many people in the United States may be unaware that they are infected if they have never sought care or been diagnosed. The most recent National Health and Nutrition Examination Survey (NHANES) reported that 50% of individuals who tested positive for HBsAg by means of blood test were unaware that they had HBV, 73% of which were born outside the United States.[30] These insights suggest that the prevalence of HBV in the United States may be substantially underestimated, further compounding issues surrounding the accuracy of HBV/HDV prevalence and potentially culminating in increased rates of advanced liver disease among the US population.

Similar findings of higher prevalence among immigrant groups have been reported. Every patient treated for HBV in a large tertiary center in the Netherlands is also screened for HDV. Between 2017 and 2019, the center reported a 2% prevalence rate of HDV among 925 patients.[31] Of those patients diagnosed with HDV, 94% were classified as “non-Dutch,” having migrated to the Netherlands from Eastern Europe, Africa, and the Middle East.[31]

Immigration status or country of origin was not collected as a part of this study. According to the APCD data in this study, White patients comprised the highest proportion of patients diagnosed with HBV/HDV during the study period, followed by Black, and lastly, Asian patients. We acknowledge that other patient demographics and risk factors are important to consider when evaluating the high rate of HBV/HDV infection in the North Central region and across the United States, particularly among White and Black patients with HBV/HDV observed in our study.

One of the more important results observed from the APCD was the clinical characteristics of patients with HBV/HDV infection compared to patients with HBV monoinfection. Patients diagnosed with HBV/HDV infection had a significantly higher mean Charlson Comorbidity Index score, indicating a greater risk of morbidity and mortality compared to patients with HBV monoinfection. Specifically, patients diagnosed with HBV/HDV infection during the study period had a significantly higher rate of advanced liver disease or liver disease–related complications at the time of diagnosis (ie, compensated cirrhosis, DCC, and HCC). The presence of severe liver-related complications at diagnosis supports recent findings in the literature that HBV/HDV infection is a more aggressive viral hepatitis infection that is strongly associated with worse liver outcomes.[3,32–34] The data captured in the APCD underscore the importance of improved HDV screening for early identification and linkage to care and treatment, thereby lower the risk of disease progression and liver-related morbidity and mortality.

A significantly larger proportion of patients diagnosed with HBV/HDV infection from the APCD had other comorbid conditions at diagnosis compared to patients with HBV monoinfection. The top 5 comorbid conditions for patients with HBV/HDV infection included diabetes, hypertension, HIV, substance abuse, and history of smoking. These observations may potentially help identify specific “high-risk” populations for HDV, and therefore, may benefit from targeted outreach programs to improve HDV screening. Caution is warranted when developing screening criteria based on risk alone. Previous attempts at risk-based testing for viral diseases such as HBV, HCV, and HIV have not been successful and can result in diagnosis gaps—even among high-risk populations.[35–37] For example, the failure of

physicians to properly identify patient risk factors has been identified as a contributing factor to the lack of effectiveness surrounding risk-based screening of HBV monoinfection.[37] Universal screening for HBV has been found to be cost-effective within a US adult population; therefore, it may be reasonable to hypothesize that universal screening for HDV among the HBV population may be a cost-effective approach as well.[38]

There remains a lack of consistent guidance on the effective screening and diagnosis of HDV in the United States. Current AASLD guidelines recommend a risk-based approach to screening targeting immigrants from regions with high HBV/HDV infection endemicity, persons who have injected drugs, men who have sex with men, individuals with HCV or HIV infections, persons with multiple sex partners or history of sexually transmitted infections, and individuals with elevated alanine aminotransferase or aspartate transaminase liver enzymes with low or undetectable HBV DNA.[16] Conversely, the EASL guidelines do not discriminate HDV testing based on risk factors, but rather suggest that all HBV patients should be considered for HDV screening to exclude other potential etiologies contributing to chronic liver disease.[17]

According to the data from the APCD, primary care physicians were responsible for the largest proportion of HBV/HDV infection diagnoses during the study period, followed by gastroenterologists. Unfortunately, data related to physician specialty were limited to provider National Provider Identifier numbers, preventing the synthesis of data into broader speciality groups. For example, providers who were captured as a subspeciality, such as "hepatologists," would not be captured under their primary speciality of gastroenterology. Similarly, this would apply to indexing practitioners who were captured as nurse practitioners or physician assistants, as opposed to the specialty of the supervising physician (eg,, primary care, gastroenterology). Nevertheless, continuing education for primary care physicians regarding the identification and screening of patients with HBV for HDV will be critical for the timely diagnosis of this aggressive viral infection.

A limitation of this study is that the data captured from the APCD are limited to the insured population, which includes both private and government insurance programs (eg, Medicaid). Underserved populations without access to insurance would not be accurately represented in this study. This is important when considering that uninsured populations may have less access to adequate health care and a greater prevalence of high-risk behaviors that are associated with increased risk for HBV/HDV infection. Future studies should aim to capture immigration status and/or country of origin to better assess the prevalence of HBV/HDV among these populations. Recent discrepancies in pharmacy claims data have been noted when evaluating the APCD against local state-level databases.[39] The APCD captures prescription claims as opposed to prescription fills, which means out-of-pocket payments and/or claims from private insurers that are not required to report to the APCD are not represented.

Additionally, geographic location was determined by the indexing provider's ZIP code as opposed to the patient's ZIP code. Most patients diagnosed with HDV among the HBV population during the study period had providers located in urban areas. We are not able to verify whether patients were traveling to urban areas to seek medical attention without capturing the patient's current ZIP code at diagnosis. Therefore, it is possible that rural patients who were lacking in local healthcare practitioners traveled to urban areas and were misrepresented in the dataset. Conducting studies at a local level may provide better insight regarding patient proximity to treatment centers, in addition to valuable laboratory data, and the ability to assess changes in prevalence rates based on screening practices implemented by individual treatment centers or states.

The greatest strength of this study is the inclusion of a large, diverse population that captures 80% of the insured population using a 2-claim approach to better capture confirmed HDV diagnoses, thereby providing results that are generalizable to the broader population. Patient demographics, clinical characteristics, and prevalence by geographic location were captured specific to the US population, providing an evidence-based resource toward the improvement of screening in this high-risk population. This data can be used to support priority initiatives outlined by the American Liver and Hepatitis B Foundations that were recently published in HEPATOLOGY.[40]

This comprehensive database analysis estimates a 4.6% prevalence rate of HBV/HDV among patients with continuous data in the APCD diagnosed with HBV in the United States from 2015 to 2019. The largest concentration of patients with HBV/HDV reside in urban areas within the state of Illinois followed by New York, California, and Florida. Most of the HBV and HBV/HDV diagnoses captured in the APCD were reported by primary care physicians, followed by gastroenterologists. Patients with HBV/HDV infection have a significantly higher proportion of key comorbidities (ie, diabetes, hypertension) and conditions associated with modifiable behaviors (ie, sexually transmitted diseases, history of smoking, and substance abuse). Importantly, patients with HBV/HDV have a significantly higher rate of advanced liver disease at diagnosis, which may reflect a more aggressive disease progression and/or delays in diagnosis and treatment. These findings highlight the need for education to raise greater awareness of HDV among patients and providers, in addition to improved HDV screening that will include screening of all patients who are HBsAg positive. Reflex testing will enhance the detection of those patients who are viremic for HDV RNA for early diagnosis so that timely linkage to care and treatment can reduce long-term liver-

related morbidity and mortality. This is particularly important given clear and convincing data demonstrating the increased morbidity and mortality associated with HBV/HDV coinfection.

AUTHOR CONTRIBUTIONS

Robert G. Gish, Ira M. Jacobson, Joseph K. Lim, Ankita Kaushik, Robert J. Wong: study design, interpretation of data, review and revision of intellectual content, final approval. Christine Waters-Banker: interpretation of data, development, review, and revision of intellectual content/manuscript. Chong Kim: interpretation of data, review, and revision of intellectual content. Anissa Cyhaniuk: study design, analysis of data, and review of intellectual content.

FUNDING INFORMATION

This study was supported by Gilead Sciences Inc.

CONFLICTS OF INTEREST

Robert G. Gish consults, advises, and is on the speakers' bureau for AbbVie, Genentech, Gilead, and Intercept. He consults, advises, and owns stock in Genlantis. He consults and advises Arrowhead, Enyo, Helios, Janssen, Merck, and Pfizer. He consults, advises, and owns stock in HepaTX, HepQuant. He consults and advises Dynavax. He consults and is on the speakers' bureau for AstraZeneca and Eisai. He consults and owns stock in Abacus, Eiger, JBS Science, and Virion. He consults for Abbott, Albireo, Aligos, Altimmune, Antios, Audentes, Corcept, Effectus, Gerson Lehrman Group, GlaxoSmithKline, Kinnate Bio, Precision BioSciences, Seres, Topography Health, Tune, and Venatorx. He advises CymaBay, Durect, Fibronostics, Fujifilm/Wako, Kezar Life Sciences, Perspectum, Prodigy, Quest, Sagimet, Sonic Incytes, and Takeda. He is on the speakers' bureau for Bristol Myers Squibb, Diasorin, Mallinckrodt, and VBI Vaccines. He owns stock in AngioCrine, CoCrystal, and RiboSciences. Joseph K. Lim consults (without compensation) and received grants from Gilead. He received grants from Intercept, Inventiva, Novo Nordisk, Pfizer, and Viking. Christine Waters-Banker consults and is employed by Maple Health Group. She consults for Gilead. Ankita Kaushik is employed by and owns stock in Gilead. Chong Kim is employed by and owns stock in Gilead. Anissa Cyhaniuk is employed by STATinMED. Robert J. Wong consults and received grants from Gilead. He received grants from Exact and Thera. The remaining author has no conflicts to report.

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How to cite this article: Gish RG, Jacobson IM, Lim JK, Waters-Banker C, Kaushik A, Kim C, et al. Prevalence and characteristics of hepatitis delta virus infection in patients with hepatitis B in the United States: An analysis of the All-Payer Claims Database. Hepatology. 2024;79:1117–1128. https://doi.org/10.1097/HEP.0000000000000687