Enferm Infecc Microbiol Clin. 2021;39(1):14–21

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Original article

Associations between hepatitis B infection and chronic kidney disease: 10-Year results from the U.S. National Inpatient Sample

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ARTICLE INFO

Article history:
Received 18 December 2019
Accepted 27 February 2020
Available online 22 April 2020

Keywords:
Chronic kidney disease (CKD)
End-stage renal disease (ESRD)
Hepatitis B
U.S. Nationwide Inpatient Sample (NIS)

ABSTRACT

Introduction: Viral hepatitis infection is associated with negative impacts on renal function that may lead to nephropathy. We investigated associations between chronic hepatitis B virus (HBV) infection and chronic kidney disease (CKD) and/or end-stage renal disease (ESRD) in a large, representative sample from a nationwide U.S. database.
Methods: This population-based, retrospective observational study extracted data from the U.S. Nationwide Inpatient Sample (NIS) database, including adults ≥18 years old admitted to U.S. hospitals between 2005 and 2014 with records of chronic HBV infection in medical history. The final analytic sample included 70,674 HBV-infected patients and 282,696 matched non-HBV controls. Study endpoints were prevalent CKD and ESRD. Associations between CKD/ESRD and HBV and patients' clinical characteristics were determined by logistic regression analysis.
Results: HBV infection was associated with slightly increased risk of prevalent CKD (OR: 1.06, 95% CI: 1.004–1.119) and an approximate 2-times risk of prevalent ESRD (OR: 1.98, 95% CI: 1.880–2.086). HBV infection in both genders was associated with slightly increased risk of CKD (males, OR: 1.09, 95% CI: 1.02–1.16; females, OR: 1.07, 95% CI: 0.98,1.17), and significantly associated with increased risk for CKD among non-diabetic patients (OR: 1.23, 95% CI: 1.15–1.32), white patients (OR: 1.14, 95% CI: 1.06–1.23) and Asian/Pacific Islanders (OR: 1.13, 95% CI: 0.98–1.30).
Conclusions: Chronic HBV infection is associated with slightly increased risk for CKD and greater risk for ESRD in males and females, Whites and Asian/Pacific Islanders and non-diabetic patients.

Relaciones entre la infección por hepatitis B y la enfermedad renal crónica: resultados de 10 años de la muestra nacional de pacientes hospitalizados de EE. UU

Palabras clave:
Enfermedad renal crónica (ERC)
Enfermedad renal terminal (ERT)
Hepatitis B
Muestra nacional de pacientes hospitalizados (NIS)

RESUMEN

Introducción: La infección por el virus de la hepatitis se asocia a impactos negativos en la función renal que pueden derivar en nefropatía. Investigamos las asociaciones entre la infección crónica por el virus de la hepatitis B (VHB) y la enfermedad renal crónica (ERC) y/o la enfermedad renal terminal (ERT) en una muestra de grandes dimensiones y representativa procedente de una base de datos nacional de los Estados Unidos.
Métodos: Este estudio observacional retrospectivo y poblacional extrajo datos de la base de datos de la muestra nacional de pacientes hospitalizados (*Nationwide Inpatient Sample*, NIS) de los EE. UU., que incluye adultos ≥18 años ingresados en hospitales de los EE. UU. entre 2005 y 2014 con registros de infección crónica por VHB en su historia médica. La muestra analítica final incluyó a 70.674 pacientes infectados por el VHB y a 282.696 controles emparejados no infectados por el VHB. Los criterios de valoración del estudio fueron la enfermedad renal crónica y la enfermedad renal terminal prevalentes. Las asociaciones entre la ERC o la ERT y el VHB y las características clínicas de los pacientes se determinaron mediante un análisis de regresión logística.

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https://doi.org/10.1016/j.eimc.2020.02.029

Resultados: La infección por VHB se asoció a un riesgo ligeramente mayor de prevalencia de enfermedad renal crónica (OR: 1,06; IC del 95%: 1,004–1,119) y un riesgo aproximadamente dos veces mayor de enfermedad renal terminal (OR: 1,98; IC del 95%: 1,880-2,086). La infección por VHB se asoció en ambos sexo a un riesgo ligeramente mayor de enfermedad renal crónica (hombres, OR: 1,09, IC del 95%: 1,02-1,16; mujeres, OR: 1,07, IC del 95%: 0,98-1,17), y se asoció significativamente a un mayor riesgo de enfermedad renal crónica entre los pacientes no diabéticos (OR: 1,23, IC del 95%: 1,15-1,32), pacientes blancos (OR: 1,14, IC del 95%: 1,06-1,23) y asiáticos o de las islas del Pacífico (OR: 1,13, IC del 95%: 0,98-1,30).
Conclusiones: La infección crónica por VHB se asocia a un riesgo ligeramente mayor de enfermedad renal crónica y a un mayor riesgo de enfermedad renal terminal en hombres y mujeres, blancos y asiáticos o de las islas del Pacífico y pacientes no diabéticos.

Introduction

Chronic hepatitis B virus (HBV) infection continues to be a major public health issue worldwide. Even though a vaccine and potent antiviral treatments are available, the need for prevention and control of HBV infection is largely unmet, especially in countries with high endemicity.[1] Recent estimates from the Global Burden of Disease project indicate that morbidity and mortality associated with chronic HBV are high, although decreases in the incidence of HBV infection have been noted over the last twenty years[2]. Regarding the global burden of kidney disease,the prevalence of both HBV and HCV infectionsrepresents about 2–4% of the global population, and both infections are associated with kidney lesions and development of CKD.[3] Despite these decreases, the presence of viral hepatitis infection is associated with negative impacts on renal function that may lead to nephropathy,[4] which further complicates the global challenge. However, while HCV infection and kidney disease are shown to be linked in several important ways,[5] the mechanism underlying the link between HBV and chronic kidney disease (CKD) is not entirely understood. Prior meta-analysis and population-based studies have shown mixed results regarding the association between HBV infection and CKD,[6–8] but a recent systematic review highlighted two studies that linked HBV infection to an increased risk for CKD and end-stage renal disease (ESRD).[9] Results of a large prospective study showed that HBV infection was associated with CKD risk and also had synergistic effects with smoking, lack of physical activity and diabetes; however, when these risk factors were modified, the HBV/CKD link was negligible.[6] A recent cohort study demonstrated an association between HBsAg positive serology and a higher incidence of CKD, and the authors suggested that the association was due to a higher incidence of proteinuria in HBV-positive subjects.[10] Other forms of kidney injury also have been attributed to HBV infection, including membranous nephropathy, membranoproliferative glomerulonephritis and polyarteritis nodosa, which are suggested to arise from virus-induced immunologic response.[11]

Together, the increased incidence in CKD/ESRD along with the high costs of treatment and poor outcomes, have led to epidemic proportions of progressive kidney disease in some geographic areas, with only a few developed countries able to meet the economic challenge.[12] In nationwide surveys conducted in the United States, Australia, Japan and Europe, the prevalence of CKD was reported to range from 6% to 11% in the mid-2000s.[13] More recently, a cross-sectional survey in China found that CKD prevalence was 10.8% among adults in the general population (about 119.5 million).[14] Annual incidence of ESRD in the UK is about 100 new patients per million population, which is less than the reported incidence in Europe (about 135 per million) and the U.S. (about 336 per million), with even higher rates in less developed countries.[12]

Although many studies have focused on associations between exposure to or infection with hepatitis B and CKD/ESRD,[7–9] particularly in China,[10,15,16] the debate on the potential link between HBV infection and CKD/ESRD continues because the existing evidence remains inconclusive and few studies have examined this potential link at the population level. Since the link between HBV infection and CKD has not been explained sufficiently or established, it is of clinical importance to clarify the potential correlation and ultimately to focus on diminishing the critical impact of HBV-associated progressive kidney disease on public health. Therefore, we hypothesized that chronic hepatitis B infection is associated with increased risk of the development of CKD and/or ESRD. Moreover, we expected that this relationship may vary according to differences in patients' individual characteristics. Accordingly, the present study aimed to investigate associations between chronic HBV infection and the occurrence of CKD and/or ESRD in a large, representative sample from a nationwide U.S. database.

Patients and methods

Study design and data source

This population-based, retrospective observational study extracted data from the U.S. Nationwide Inpatient Sample (NIS) database, the largest all-payer, continuous inpatient care database, including about 8 million hospital stays each year.[17] Patient data include primary and secondary diagnoses, primary and secondary procedures, admission and discharge status, patient demographics, expected payment source, duration of hospital stay, and hospital characteristics (i.e., bed size/location/teaching status/hospital region). All patients are initially considered for inclusion. The most recent NIS database includes patient data derived from about 1050 hospitals from 44 States in the US, representing a 20% stratified sample of US community hospitals as defined by the American Hospital Association.

Ethical considerations

All data were obtained through request to the Online Healthcare Cost and Utilization Project (HCUP) Central Distributor (available at: https://www.distributor.hcup-us.ahrq.gov/), which administrates the database.[17] This study was given the certificate number HCUP-6DUX68H62 and conform to the data-use agreement of the NIS from HCUP. The study protocol was submitted to the Institutional Review Board (IRB) of Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital which exempted the study from IRB approval. Since all data in the NIS database are deidentified, the requirement for informed consent was also waived. As this study was a secondary analysis of the NIS database, patients and the public were not involved directly.

Study population

Adults ≥18 years old admitted to U.S. hospitals between 2005 and 2014 with a diagnosis of chronic HBV infection were identified in the NIS database. International Classification of Diseases, Ninth Revision (ICD-9) diagnostic codes and procedure codes and Clinical Classifications Software (CCS) codes were used to identify the discharge diagnoses, procedures received during hospitalization, and comorbidities CCS, developed by the Agency for Healthcare Research and Quality (AHRQ)[18] is a tool for clustering patient diagnoses and procedures into clinically meaningful categories. Participants with acute kidney injury (584.x), history of renal transplant (V42.0, 996.81), malignant neoplasm of kidney (189), kidney surgeries (procedure code 55), and congenital anomalies of the renal system (753) were excluded. Patients with malignant neoplasm of the liver (155.0), acute liver injury (570, 572.2, 573.31), diagnoses of liver cirrhosis or any symptoms of liver decompensation (571.2; 571.5, 571.6; 572.3, 572.4, 456.0–456.2, 567.23) were also excluded, As well as those with evidence of liver cirrhosis who are more susceptible to developing CKD.[19] To allow primary focus on HBV, patients with diagnoses of HCV (070.41; 070.44; 070.51; 070.54; 070.70; 070.71; V02.62) and HIV infection (042, 079.53, V08) were also excluded from the primary cohort.

Study variables and outcome measures

HBV infection

Data of patients with a diagnosis of chronic HBV infection (070.20–23; 070.30–33; V02.6) in their medical history were extracted from the NIS database, as previously described.[20] An age- and gender-matched (1:4) control group was obtained from non-HBV patients in the primary cohort.

CKD and ESRD

Study endpoints were prevalent (non-dialysis) CKD (585.3–585.5; 585.9) and ESRD (585.6, V56.x, 792.5; procedure code of dialysis: 39.95, 39.27, 39.42, 39.43, 39.93, 54.98). These codes have been used by previously published NIS database studies to accurately identify patients with CKD or ESRD.[21]

Covariates

Patients' characteristics included age (grouped by decades), gender, race/ethnicity, income level, insurance status (primary payer), and admission type (elective or emergent). Comorbidities were identified from AHRQ comorbidity measures in the database and determined with ICD-9 diagnostic codes using algorithms validated by Elixhauser.[22] Hospital-related characteristics (bed size/location/teaching status/hospital region) were also extracted from the NIS database as part of the comprehensive data available for all participants.

Statistical analysis

All categorical variables are expressed as counts (percentages). Comparisons of proportions between groups for categorical variables were performed using Fisher's exact test or Chi-Square test. Variables that were significant in baseline characteristics were entered into multivariate logistic regression after adjustments. Additional stratified analyses were conducted for gender, diabetes status and race/ethnicity. All statistical analyses were performed using SAS statistical software version 9.4 (SAS, Cary, NC, USA). Two-sided *p*-values below 0.05 were considered statistically significant.

Results

After screening the 2005–2014 NIS database sample for inclusion and exclusion criteria, a total of 56,744,647 patients remained, of whom 353,370 were determined to be eligible for inclusion. After 1:4 age- and gender-matching, 70,674 patients with HBV infection (HBV infection group) and 282,696 non-HBV controls (non-HBV control group) were included as the analytic sample. Patients' baseline demographic and hospital characteristics are summarized in Table 1.

The distribution of race/ethnicity, income by ZIP code, insurance status, admission type, most comorbidities and hospital characteristics differed significantly between the HBV infection group and non-HBV controls (all $p < 0.001$). The most common comorbidity was hypertension, which was found in 37.26% and 36.27% of the non-HBV control group and HBV infection group, respectively. Frequencies of depression, diabetes, metastatic cancer, paralysis, peripheral vascular disorders and peptic ulcer were not significantly different between the two groups (Table 1).

Associations between patients' characteristics and CKD/ESRD

The results of univariate and multivariate regression analysis on the associations between patients' characteristics and CKD/ESRD are summarized in Table 2. After adjusting for all relevant confounders, HBV infection was associated with slightly increased risk of prevalent CKD (OR: 1.06, 95% CI: 1.004–1.119) and about a 2-times risk of prevalent ESRD (OR: 1.98, 95% CI: 1.880–2.086) (Table 2).

Associations between HBV infection and Chronic Kidney Disease

The results of additional stratified analyses are shown in Table 3. After adjusting for variables that were significant in baseline characteristics, multivariable regression analysis revealed that HBV infection in both males and females was associated with slightly increased risk of CKD (males, OR: 1.09, 95% CI: 1.02–1.16; females, OR: 1.07, 95% CI: 0.98,1.17). HBV infection was also significantly associated with increased risk for CKD among patients who did not have diabetes (OR: 1.23, 95% CI: 1.15–1.32), but no association was found among those with diabetes (OR: 0.96, 95% CI: 0.89–1.04). HBV infection was associated with slightly increased risk for prevalent CKD among only white patients (OR: 1.14, 95% CI: 1.06–1.23) and Asian/Pacific Islanders (OR: 1.13, 95% CI: 0.98–1.30) (Table 3).

Associations between HBV infection and ESRD

After adjusting for all variables that were significant in patients' baseline characteristics, multivariable analysis revealed that HBV infection was significantly associated with increased risk (about double in each subgroup) for ESRD (Table 3).

Discussion

Results of the present study show that patients with chronic HBV infection have an approximate two-times greater risk for prevalent ESRD, after adjusting for all relevant comorbidities and patients' characteristics. This association remains significant across different subgroups (gender, diabetes status, race/ethnicity). HBV infection is associated with a comparatively lower increase in risk forprevalent CKD in both males and females, White and Asian/Pacific Islanders and those without comorbid diabetes, but not in diabetic patients or other races/ethnicities.

Over several decades, longitudinal, cross-sectional, database studies, and meta-analyses have been conducted to investigate the issue of hepatitis B exposure or HBV infection and CKD or

Table 1
Baseline demographic and clinical characteristics of study population ($N = 353,370$).

	Non-HBV control $n = 282,696$	HBV infection $n = 70,674$	p-Value
Demographic			
Age (years)			
18–29	42,150 (14.91%)	10,490 (14.84%)	1.00
30–39	59,049 (20.89%)	14,759 (20.88%)	
40–49	48,039 (16.99%)	12,023 (17.01%)	
50–59	58,458 (20.68%)	14,615 (20.68%)	
60–69	41,499 (14.68%)	10,369 (14.67%)	
70–79	22,706 (8.03%)	5716 (8.09%)	
80–89	9662 (3.42%)	2420 (3.42%)	
90+	1133 (0.40%)	282 (0.40%)	
Gender			
Male	123,670 (43.75%)	30,999 (43.86%)	0.58
Female	159,026 (56.25%)	39,675 (56.14%)	
Race/ethnicity			
White	156,165 (65.64%)	24,296 (39.30%)	<0.001
Black	36,517 (15.35%)	14,586 (23.59%)	
Hispanic	29,351 (12.34%)	4716 (7.63%)	
Asian or Pacific Islander	6211 (2.61%)	14,754 (23.86%)	
Native American	1663 (0.70%)	373 (0.60%)	
Other	8011 (3.37%)	3101 (5.02%)	
Income by ZIP code			
Q1	80,605 (29.26%)	21,559 (31.73%)	<0.001
Q2	70,909 (25.74%)	15,629 (23.00%)	
Q3	65,669 (23.84%)	14,724 (21.67%)	
Q4	58,284 (21.16%)	16,033 (23.60%)	
Insurance status			
Medicare	77,262 (27.39%)	20,324 (28.81%)	<0.001
Medicaid	54,572 (19.35%)	19,408 (27.51%)	
Private insurance	115,863 (41.08%)	21,465 (30.43%)	
Self-pay	20,247 (7.18%)	5899 (8.36%)	
No charge	2106 (0.75%)	723 (1.02%)	
Other	11,995 (4.25%)	2721 (3.86%)	
Admission type			
Elective	85,642 (30.40%)	17,844 (25.30%)	<0.001
Non-elective	196,096 (69.60%)	52,677 (74.70%)	
Comorbidities			
NAFLD	1553 (0.55%)	714 (1.01%)	<0.001
Dislipidemia	57,626 (20.38%)	11,297 (15.98%)	<0.001
Smoking	63,819 (22.58%)	16,322 (23.09%)	0.003
Alcohol abuse	13,424 (4.75%)	4918 (6.96%)	<0.001
Anemia, chronic blood loss, deficiency	35,479 (12.55%)	12,525 (17.72%)	<0.001
Rheumatoid arthritis/collagenvascular diseases	5222 (1.85%)	1488 (2.11%)	<0.001
Congestive heart failure	11,695 (4.14%)	3575 (5.06%)	<0.001
Chronic pulmonary disease	40,249 (14.24%)	10,302 (14.58%)	0.021
Coagulopathy	6705 (2.37%)	4510 (6.38%)	<0.001
Depression	25,041 (8.86%)	6106 (8.64%)	0.067
Diabetes, uncomplicated, complicated	50,393 (17.83%)	12,647 (17.89%)	0.668
Drug abuse	13,096 (4.63%)	6561 (9.28%)	<0.001
Hypertension	105,321 (37.26%)	25,632 (36.27%)	<0.001
Hypothyroidism	19,328 (6.84%)	4335 (6.13%)	<0.001
Lymphoma	1448 (0.51%)	986 (1.40%)	<0.001
Fluid/electrolyte disorders	38,293 (13.55%)	11,712 (16.57%)	<0.001
Metastatic cancer	4783 (1.69%)	1232 (1.74%)	0.346
Other neurological disorders	14,493 (5.13%)	4407 (6.24%)	<0.001
Obesity	28,653 (10.14%)	4448 (6.29%)	<0.001
Paralysis	5654 (2.00%)	1469 (2.08%)	0.184
Peripheral vascular disorders	9739 (3.45%)	2395 (3.39%)	0.463
Psychoses	11,689 (4.13%)	4149 (5.87%)	<0.001
Pulmonary circulation disorders	2727 (0.96%)	909 (1.29%)	<0.001
Non-metastatic cancer	3635 (1.29%)	965 (1.37%)	0.095
Peptic ulcer	71 (0.03%)	26 (0.04%)	0.094
Valvular disease	5618 (1.99%)	1780 (2.52%)	<0.001
Weight loss	6448 (2.28%)	2724 (3.85%)	<0.001
Elixhauser comorbidity score			
0–2	178,931 (63.3%)	42,099 (59.6%)	<0.001
3+	103,765 (36.7%)	28,575 (40.4%)	

Table 1 (*Continued*)

	Non-HBV control *n* = 282,696	HBV infection *n* = 70,674	*p*-Value
Hospital characteristics			
Bed size			
Small (<250)	36,876 (13.11%)	7621 (10.83%)	<0.001
Medium (250–450)	70,496 (25.06%)	17,381 (24.71%)	
Large (>450)	173,891 (61.83%)	45,341 (64.46%)	
Location/teaching status			
Rural	32,656 (11.61%)	3733 (5.31%)	<0.001
Urbannonteaching	112,443 (39.98%)	21,599 (30.71%)	
Urban teaching	136,164 (48.41%)	45,011 (63.99%)	
Region			
Northeast	54,214 (19.18%)	17,863 (25.28%)	<0.001
Midwest	64,103 (22.68%)	11,344 (16.05%)	
South	109,962 (38.90%)	24,046 (34.02%)	
West	54,417 (19.25%)	17,421 (24.65%)	

HBV: Hepatitis BVirus; Q1: 0–25th percentile; Q2: 26th to 50th percentile; Q3: 51st to 75th percentile; Q4: 76th to 100th percentile.

ESRD. Results have differed between prior longitudinal studies and cross-sectional studies, which implies that the study design is of importance, as well as how HBV infection and CKD are defined for the purpose of each study. Looking across recent studies, increased risk for CKD and ESRD was found in two studies of a systematic review,[9] and a recent cohort study also confirmed an association between HBsAg positive serology and higher incidence of CKD.[10] A nationwide cohort study by Chen et al. (2015)[16] found that chronic HBV infection in Taiwan was positively linked with risk of ESRD, a result compatible with our finding that risk was higher among patients with ESRD than among those with CKD. In another report from the same study,[23] the authors noted that untreated chronic HBV infection was associated with higher risk of ESRD, leading them to advise targeted monitoring of high-risk HBV-infected patients for ESRD. In a population-based study of a half-million Chinese adults, Si et al.,[6] found that CKD risk among HBsAg-positive participants with or without hepatitis or cirrhosis was higher in men than in women, and that smokers, those who were physically inactive and those with diabetes demonstrated the highest levels of CKD risk. In another Chinese cohort study, Kong et al.,[24] failed to show an association between occult HBV infection and CKD in patients followed for five years, suggesting once again that knowledge of the association between HBV infection and CVD is limited and controversial. Meanwhile, Lee et al.,[15] found that HCV infection but not HBV infection was significantly associated with both prevalence and severity of CKD in Taiwan, a country in which both hepatic viruses are endemic and CKD is highly prevalent. An earlier study in China had also found no association between exposure to HBV or HCV and development of CKD, albuminuria or low estimated glomerular filtration rate (eGFR), although the authors appeared to accept that a link exists between HBV infection and CKD.[14]

Mechanisms underlying the association of HBV infection and CKD/ESRD are complex and unclear. Several mechanisms that contribute to the deterioration in renal function have been proposed in previous studies. Extrahepatic manifestations of HBV infection have been shown to induce glomerular disease, and a direct pathogenic relationship is shown between virus replication and development of viral-associated glomerular nephritis.[25] Gupta and Quigg (2015)[26] have shown that chronic hepatitis B serum promotes apoptotic damage in human renal tubular cells, and HBV-related glomerulonephritis appears initially as membranous nephropathy (MN)with manifestations such as proteinuria and microscopic hematuria; as the most common histologic patterninHBV-related glomerular nephritis, MN (also designated as membranoproliferative glomerulonephritis or MPGN), occurs in a minority of patients, usually children, characterized bycirculating immune complexes containing anti-HBsAg. Both insulin resistance and oxidative stress also are associated with HBV infection and both conditions may contribute to renal injury.[27,28] While specific mechanisms underlying the link between HBV infection and CKD/ESRD need further investigation, the pathogenesis of HBV-associated nephropathy does seem dependent on interactions between the virus and host immune system function.[11]

Since patients under hemodialysis are vulnerable to HBV infection and are at increased risk for acquiring HBV, impaired immune system function will undoubtedly reduce the response of these patients to vaccination.[29,30] This inverse relationship may possibly exist in the present study but was not explored further since immunization data were not available for all patients on hemodialysis.

In the present study, after adjusting for covariates, multivariate regression analysis showed that the association between HBV infection and ESRD remained in all subgroups, although the relationship between HBV and CKD appeared to be modified by race/ethnicity and diabetes status. Although many previous studies did not evaluate associations between HBV infection and covariates, Chen et al.[23] determined overall risk and evaluated age- and gender-specific risks for ESRD in untreated HBV-infected patients, finding that risk was similar between men of any age and women younger than age 60 years, while the highest risk was in men younger than 60 years. The present study included adults over age 18 years but did not stratify the large patient sample by age. Further understanding of age and gender relationships requires more long-term multicenter prospective studies.

Strengths and limitations

The strength of the present study was the use of a large, representative sample from a nationwide U.S. database, allowing results to be generalized across the entire country. Also, unlike previous studies, comorbidities were considered and carefully adjusted in the analyses, adding credence to the results. Nevertheless, the present study has several limitations, including that it analyzed a secondary database retrospectively, which does not allow for inference of causation. In the NIS database, HBV infection was identified by the ICD-9 coding system documented by medical history but not through serologic screening, which may result in underestimation of HBV cases. We relied on administrative ICD-9 codes to identify patients with HBV infections in the database, and accuracy of the coding cannot be ascertained. It is possible that not all patients with HBV infections coded correctly, which may introduce bias. Even though we excluded patients with other factors that may be associated with CKD,it is still possible that patients who acquired HBV infection after the development of CKD, which limits the interpretation of results. Also, the disease activity in chronic

Table 2
Associations between HBV infection and CKD, ESRD.

	CKD		ESRD	
	Univariate OR (95%CI)	Multivariate aOR (95%CI)	Univariate OR (95%CI)	Multivariate aOR (95%CI)
HBV infection				
No	Reference	Reference	Reference	Reference
Yes	**1.21 (1.157–1.265**	**1.06 (1.004–1.119)**	**2.73 (2.625–2.832)**	**1.98 (1.880–2.086)**
Race/ethnicity				
White	Reference	Reference	Reference	Reference
Black	**1.43 (1.362–1.501)**	**1.38 (1.306–1.462)**	**1.90 (4.679–5.136)**	**4.01 (3.782–4.250)**
Hispanic	**0.66 (0.614–0.716)**	**0.90 (0.828–0.979)**	**2.261 (2.121–2.409)**	**3.19 (2.952–3.440)**
Asian or Pacific Islander	**0.89 (0.818–0.968)**	**1.11 (1.010–1.229)**	**2.47 (2.296–2.663)**	**2.10 (1.906–2.313)**
Native American	0.83 (0.637–1.086)	0.96 (0.719–1.268)	**2.31 (1.857–2.883)**	**2.98 (2.284–3.894)**
Other	**0.70 (0.616–0.793)**	0.91 (0.794–1.044)	**1.57 (1.394–1.759)**	**1.96 (1.709–2.235)**
Income by ZIP code				
Q1	Reference	Reference	Reference	Reference
Q2	**0.90 (0.855–0.945)**	0.99 (0.933–1.046)	**0.69 (0.657–0.723)**	**0.93 (0.870–0.983)**
Q3	**0.83 (0.788–0.875)**	0.97 (0.912–1.030)	**0.60 (0.566–0.627)**	**0.86 (0.806–0.918)**
Q4	**0.78 (0.734–0.819)**	0.98 (0.918–1.046)	**0.50 (0.474–0.530)**	**0.79 (0.734–0.848)**
Insurance status				
Medicare	Reference	Reference	Reference	Reference
Medicaid	**0.24 (0.226–0.255)**	**0.45 (0.421–0.484)**	**0.22 (0.211–0.235)**	**0.26 (0.243–0.279)**
Private insurance	**0.21 (0.196–0.216)**	**0.41 (0.388–0.435)**	**0.10 (0.090–0.101)**	**0.19 (0.172–0.198)**
Self-pay	**0.20 (0.184–0.225)**	**0.41 (0.370–0.464)**	**0.07 (0.063–0.084)**	**0.10 (0.088–0.121)**
No charge	**0.18 (0.130–0.246)**	**0.35 (0.253–0.494)**	**0.10 (0.065–0.139)**	**0.09 (0.059–0.138)**
Other	**0.26 (0.227–0.288)**	**0.47 (0.406–0.533)**	**0.12 (0.103–0.140)**	**0.17 (0.145–0.208)**
Admission type				
Non-elective	Reference	Reference	Reference	Reference
Elective	**0.51 (0.485–0.535)**	**0.68 (0.642–0.718)**	**0.34 (0.321–0.357)**	**0.55 (0.514–0.586)**
Comorbidities				
NAFLD	1.22 (0.983–1.508)	0.89 (0.699–1.126)	**0.71 (0.542–0.932)**	**0.58 (0.418–0.800)**
Dislipidemia	**3.25 (3.124–3.372)**	**1.74 (1.663–1.821)**	**1.60 (1.538–1.672)**	**0.84 (0.795–0.885)**
Smoking	**1.10 (1.054–1.151)**	**0.92 (0.878–0.971)**	**0.70 (0.670–0.738)**	**0.69 (0.650–0.733)**
Alcohol abuse	**0.55 (0.492–0.612)**	**0.61 (0.536–0.688)**	**0.27 (0.236–0.317)**	**0.24 (0.197–0.282)**
Anemia, chronic blood loss, deficiency	**3.04 (2.918–3.167)**	**1.95 (1.859–2.046)**	**7.95 (7.653–8.251)**	**5.38 (5.130–5.636)**
Rheumatoid arthritis/collagen vascular diseases	**2.01 (1.818–2.227)**	**1.25 (1.114–1.400)**	**1.64 (1.469–1.832)**	**0.81 (0.709–0.933)**
Congestive heart failure	**5.42 (5.149–5.702)**	**2.21 (2.077–2.348)**	**7.97 (7.596–8.364)**	**3.31 (3.095–3.530)**
Chronic pulmonary disease	**2.01 (1.922–2.098)**	**1.20 (1.135–1.258)**	**1.28 (1.216–1.341)**	**0.72 (0.679–0.770)**
Coagulopathy	**1.94 (1.793–2.108)**	**1.26 (1.146–1.379)**	**2.75 (2.563–2.953)**	**1.23 (1.124–1.355)**
Drug abuse	**0.70 (0.633–0.766)**	1.00 (0.897–1.117)	**0.68 (0.621–0.749)**	0.91 (0.810–1.028)
Hypertension	**5.66 (5.416–5.909)**	**3.01 (2.856–3.172)**	**7.31 (6.990–7.649)**	**4.55 (4.295–4.81)**
Hypothyroidism	**2.16 (2.043–2.286)**	**1.29 (1.207–1.373)**	**1.34 (1.257–1.435)**	**0.87 (0.799–0.941)**
Lymphoma	**2.85 (2.467–3.286)**	**1.82 (1.538–2.144)**	**1.80 (1.511–2.147)**	**0.73 (0.583–0.903)**
Fluid/electrolyte disorders	**2.28 (2.186–2.381)**	**1.33 (1.269–1.402)**	**3.15 (3.022–3.273)**	**1.59 (1.512–1.678)**
Other neurological disorders	**1.55 (1.448–1.665)**	1.00 (0.923–1.081)	**1.69 (1.581–1.808)**	**0.91 (0.840–0.994)**
Obesity	**1.97 (1.868–2.068)**	**1.34 (1.268–1.425)**	1.02 (0.957–1.086)	**0.79 (0.727–0.848)**
Psychoses	1.03 (0.942–1.126)	**0.79 (0.718–0.879)**	**0.86 (0.778–0.941)**	**0.62 (0.556–0.701)**
Pulmonary circulation disorders	**2.87 (2.549–3.226)**	0.98 (0.857–1.128)	**4.11 (3.703–4.562)**	**1.21 (1.053–1.399)**
Valvular disease	**2.88 (2.649–3.135)**	**1.25 (1.132–1.376)**	**3.23 (2.974–3.502)**	**1.15 (1.031–1.285)**
Weight loss	**1.73 (1.577–1.900)**	1.00 (0.900–1.111)	**2.82 (2.611–3.043)**	**1.18 (1.066–1.302)**
Hospital characteristics				
Bed size				
Small (<250)	Reference	Reference	Reference	Reference
Medium (250–450)	0.98 (0.919–1.044)	1.00 (0.932–1.075)	**1.31 (1.222–1.413)**	**1.25 (1.146–1.365)**
Large (>450)	0.95 (0.897–1.005)	0.96 (0.904–1.028)	**1.59 (1.490–1.699)**	**1.50 (1.384–1.623)**
Location/teaching status				
Rural	Reference	Reference	Reference	Reference
Urban nonteaching	**0.85 (0.793–0.900)**	**0.83 (0.767–0.893)**	**1.74 (1.600–1.884)**	**1.74 (1.565–1.933)**
Urban teaching	**0.89 (0.833–0.941)**	**0.91 (0.847–0.984)**	**2.01 (1.855–2.175)**	**1.80 (1.626–2.002)**
Region				
Northeast	Reference	Reference	Reference	Reference
Midwest	**1.18 (1.109–1.245)**	1.06 (0.987–1.133)	1.01 (0.952–1.073)	1.01 (0.935–1.097)
South	**1.10 (1.040–1.155)**	0.96 (0.902–1.014)	**1.25 (1.185–1.313)**	**1.08 (1.016–1.152)**
West	**1.09 (1.025–1.156)**	**1.20 (1.121–1.283)**	**1.07 (1.008–1.136)**	1.07 (0.990–1.150)

Multivariate logistic regression was adjusted for significant variables in baseline characteristics.
Comorbidity reference group was non-comorbidity.
HBV: Hepatitis BVirus; CKD: Chronic Kidney Disease; ESRD: End Stage Renal Disease; OR: Odds Ratio; aOR: Adjusted OR; CI: Confidence Interval.
Numbers in bold indicate statistically significant ($p < 0.05$).

Table 3
Associations between HBV infection and CKD, ESRD stratified by gender, diabetes and race/ethnicity.

	CKD		ESRD	
	Univariate OR (95%CI)	Multivariate aOR (95%CI)	Univariate OR (95%CI)	Multivariate aOR (95%CI)
Male (*n* = 154,669)				
HBV infection				
No	1	1	1	1
Yes	**1.26 (1.19,1.33)**	**1.09 (1.02,1.16)**	**2.89 (2.76,3.04)**	**2.1 (1.98,2.23)**
Female (*n* = 198,701)				
HBV infection				
No	1	1	1	1
Yes	**1.13 (1.05,1.22)**	**1.07 (0.98,1.17)**	**2.54 (2.39,2.69)**	**1.99 (1.85,2.15)**
Non-diabetes (*n* = 290,330)				
HBV infection				
No	1	1	1	1
Yes	**1.37 (1.29,1.45)**	**1.23 (1.15,1.32)**	**3.01 (2.85,3.17)**	**2.19 (2.05,2.34)**
Diabetes (*n* = 63,040)				
HBV infection				
No	1	1	1	1
Yes	1.05 (0.98,1.12)	0.96 (0.89,1.04)	**2.65 (2.51,2.81)**	**2.08 (1.94,2.22)**
White (*n* = 180,461)				
HBV infection				
No	1	1	1	1
Yes	**1.32 (1.23,1.41)**	**1.14 (1.06,1.23)**	**2.45 (2.27,2.65)**	**2.01 (1.85,2.18)**
Black (*n* = 51,103)				
HBV infection				
No	1	1	1	1
Yes	1.06 (0.97,1.16)	1.02 (0.93,1.12)	**2.08 (1.95,2.22)**	**2.09 (1.94,2.25)**
Hispanic (*n* = 34,067)				
HBV infection				
No	1	1	1	1
Yes	1.13 (0.92,1.38)	0.95 (0.77,1.18)	**2.83 (2.51,3.19)**	**2.34 (2.05,2.68)**
Asian or Pacific Islander (*n* = 20,965)				
HBV infection				
No	1	1	1	1
Yes	**1.28 (1.12,1.46)**	**1.13 (0.98,1.30)**	**2.12 (1.88,2.39)**	**2.15 (1.88,2.47)**

HBV infection, as well as history of antiviral therapy, were not identified for all patients included in the database and therefore could not be accounted for in this study. Likewise, CKD was defined by the same billing code system while renal function represented by glomerular filtration rate (GFR) provides better information for disease status. Overall, due to the nature of the study design, the time frame of development and progression of CKD also could not be evaluated. Further prospective examination of HBV status and treatment history and patient follow-up are needed to help delineate the HBV/CKD association.

Conclusions

Chronic HBV infection is associated with slightly increased risk for CKD and greater risk for ESRD. Increased awareness and attention may be needed during follow-up of patients diagnosed with HBV infection in order to reduce risk of CKD/ESRD. More well-designed prospective, longitudinal studies are warranted in the future to confirm the findings of the present study and the underlying mechanisms suggested.

Funding

This study was supported by the Funding of Health Commission of Sichuan Province (No. 18PJ339).

Conflict of interest

The authors declare that they have no conflict of interest.

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