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Original Article

Risk Factors of Chronic Kidney Disease in Chronic Hepatitis B: A Hospital-based Case-control Study from China

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Abstract

Background and Aims: Chronic kidney disease (CKD) usually occurs during the chronic infection of hepatitis B virus (HBV). However, the risk factors of CKD in an HBV population have not been completely demonstrated. Our present study aimed to investigate the risk factors of CKD in chronic HBV infection using a hospital based cross-sectional study in the northern area of China. ***Methods:*** During January 2013 to December 2017, a total of 94 patients with CKD complicated by chronic HBV infection were consecutively enrolled in the study, as well as 548 age- and sex-matched hepatitis B patients without CKD who were enrolled as controls. Univariate and multivariate regression analyses were used to determine the effects of each variable after adjusting for cofounding factors. ***Results:*** Multivariate analysis showed that HBeAg-positive status (odds ratio [OR]=2.099, 95% CI 1.128–3.907), dyslipidemia (OR: 3.025, 95% CI 1.747–5.239), and hypertension (OR: 12.523, 95% CI 6.283–24.958) were independently associated with the incidence of CKD, while duration of HBV infection (≥240 months) (OR: 0.401, 95% CI 0.179–0.894), Log_{10} HBsAg (OR: 0.514, 95% CI 0.336–0.786), and coronary heart disease (OR: 0.078, 95% CI 0.008–0.768) were protective factors for the incidence of CKD. Duration of HBV infection, Log_{10} HBsAg, HBeAg-positive status and dyslipidemia remained the risk factors for CKD after adjusting for diabetes mellitus, hypertension, and coronary heart disease. ***Conclusions:*** Duration of HBV infection, Log_{10} HBsAg, HBeAg-positive status and dyslipidemia contributed to the incidence of CKD during chronic HBV infection in a Chinese population.

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Introduction

Hepatitis B virus (HBV) is still a serious public health problem and there are an estimated 257 million people suffering from HBV infection around the world.[1] In China, 5.49% of the adult population are infected,[2] while the prevalence of HBV might reach as high as 12.17% among the population aged 20 to 49 years-old.[3] During the long history of chronic HBV infection, there are about 3% to 5% of patients who might develop into chronic kidney diseases (CKDs).[4,5] The risk factors for the incidence of CKD usually contain demographical variables (including age and sex), comorbidities (including diabetes mellitus, hypertension, and overweight), and living habits (including smoking, alcohol intake, and physical exercise).[6,7] In addition, HBV infection has also been reported to increase risk for the incidence of CKD, such as membranous glomerulonephritis.[8,9] However, the risk factors of CKD in patients with chronic HBV infection, especially in China, have not yet been demonstrated completely.

As is known, the incidence of CKD during chronic HBV infection might be attributed to the kidney injury induced by HBV itself and/or the renal side effects of anti-HBV drugs.[10] The pathogenetic effects of HBV on the kidney function has been approved by the local staining of hepatitis B antigen-antibody complexes.[11] The low molecular weight of HBV e antigen (HBeAg) has been reported to traverse into the glo-

Keywords: Chronic kidney disease; Hepatitis B virus; Risk factors; Cross-sectional study; Case-control study.

Abbreviations: ADV, adefovir dipivoxil; BP, blood pressure; CHB, chronic hepatitis B; CI, confidence interval; CHD, Coronary heart disease; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ESRD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBV DNA, hepatitis B virus DNA; HBV-GN, Hepatitis B virus-associated glomerulonephritis; KDIGO, Kidney Disease: Improving Global Outcomes; LDL, low density lipoprotein; MCD, minimal change disease; MN, membranous nephropathy; MPGN, mesangial capillary glomerulonephritis; NAs, nucleos(t)ide analogues; OR, odds ratio; TAF, tenofovir alafenamide; TC, total cholesterol; TDF, tenofovir disoproxil fumarate.

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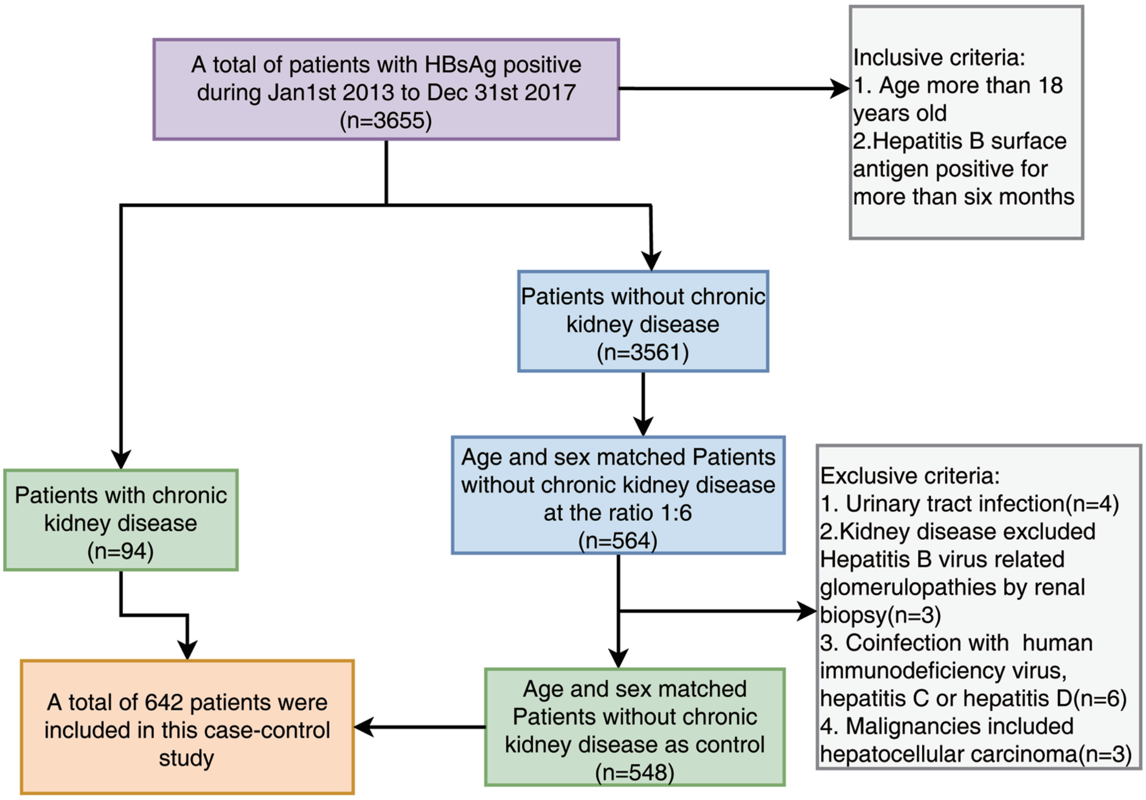

Fig. 1. Flowchart for the inclusion and exclusion of patients for study analysis.

merular basement membrane and eventually lead to the deposition of HBV immune complex in the formation of subepithelial membrane.[10] Meanwhile, there are six oral agents of nucleos(t)ide analogues (NAs) which have been widely used for anti-HBV treatment, namely lamivudine, telbivudine and entecavir as nucleoside; adefovir dipivoxil (ADV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) as nucleotide analogues. During long-term NAs therapy, a minimal decline of creatinine clearance rate has been reported.[11] Extrahepatic adverse effects of NAs may result from the mitochondrial toxic effect of NAs, including kidney injury and the elevation of creatine kinase.[12] In addition, NAs are cleared in the kidneys and therefore the dosage of NAs has to be ascribed according to the renal function in clinic.[13]

Epidemiological characteristics of CKD in the HBV-infected population usually vary among the different countries and areas.[14] The frequency of CKD is rather low in the USA and Western European countries, in which low prevalence rates of HBV have been reported.[4,15] In China, genotype C is the predominant HBV genotype in the northeastern region, while genotype B is in the central southern region, genotypes B and C in the southwestern region, and the recombinant genotype C/D in the northwestern region.[16] Therefore, the exact data for the risk factors of CKD in China are needed for the precise management of HBV infection.

In China, Hou *et al*.[14] demonstrated that hypertension, diabetes mellitus and cirrhosis were independent factors for the incidence of CKD, as determined through their single-center, cross-sectional study in which all patients received anti-HBV therapy. However, there are still few reports on the prevalence of CKD in patients with chronic HBV infection in the north area of China. Therefore, this present study aimed to investigate the risk factors for the incidence of CKD in chronic HBV infection using a hospital based cross-sectional case-control study in Northern China.

Methods

Study design

During January 1st 2013 to December 31st 2017, a total of 94 CKD patients with chronic HBV infection treated at the Qilu Hospital of Shandong University were consecutively enrolled in our study, as well as 548 age- and sex-matched hepatitis B patients without CKD who were enrolled as controls. The inclusive criteria of chronic HBV infection were the following: age ≥18 years; and hepatitis B surface antigen (HBsAg)-positive for more than 6 months.[17,18] The exclusion criteria for HBV patients without CKD were the following: urinary tract infection; kidney diseases, excluding HBV-related glomerulopathies; co-infection with human immunodeficiency virus, hepatitis C or hepatitis D; or malignancies, including hepatocellular carcinoma. The flowchart of the inclusion and exclusion criteria of the studied patients is shown in Figure 1. In detail, a total of consecutive 3,655 patients with HBsAg positivity were collected from January 2013 to December 2017 in our hospital, including 94 patients with CKD and 3,561 patients without CKD. Among the patients without CKD, 564 age- and sex-matched patients were selected at the ratio of 1:6 regarding the 94 patients with CKD. After the exclusion procession, a total of 548 patients without CKD were included as controls in this case-control study. This study protocol conformed to the Helsinki Declaration and was approved by the Institutional Review Board of Qilu Hospital of Shandong University (Approval Ethical Committee Number: 2019058).[19] The records and information of each patient were anonymized and de-identified prior to analysis, and the requirement for written informed consent was waived by the local Institutional Review Board.

Screening protocol and data collection

The obtained data included demographic characteristics (age, sex) and personal history information (history of kidney disease, hypertension, coronary heart disease, diabetes mellitus, and so on). The history of antiviral treatment and blood pressure were extracted from the electronical medical database. The venous blood and urinary samples were collected after an overnight fast of 10–12 h. The laboratory assessments included liver function, renal function, virologic or serological tests for HBV, serum lipids, hemoglobin, prothrombin activity, and alpha-fetoprotein, as well as urine analysis. The serum HBV DNA level (with lower limit of detection of 100 IU/mL) and HBV markers were measured using the COBAS *Taq*Man platform and Elecsys (Roche, Basel, Switzerland). Urine protein and albuminuria levels were measured using an immediate semi-quantitative urine protein dipstick test. Urine protein was graded as absent, trace, 1+, 2+, 3+, or 4+. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was calculated to the estimated glomerular filtration rate (eGFR) as recommended by the Kidney Disease: Improving Global Outcomes Guideline (KDIGO) in 2012:[20,21] $eGFR = 141 \times \min(Scr/b,1)^{a} \times \max(Scr/b,1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black], in which b = 0.9 if male, b = 0.7 if female; a = −0.411 if male, a = −0.329 if female. Additionally, min (Scr/b, 1) = the minimum of Scr/b or 1, whereas max (Scr/b,1) = the maximum of Scr/b or 1.

Definition for observation variables

Albuminuria was defined as positive when >150 mg/L and the presence of proteinuria was defined as at least grade 1+ in the urine protein dipstick test. CKD was defined as abnormalities in kidney structure or function and as eGFR if <60 mL/min/1.73 m^2 or proteinuria at least grade 1+.[22] The stages of CKD were classified into the following six categories: stage 1, eGFR ≥90 mL/min/1.73 m^2 with kidney damage (proteinuria); stage 2, eGFR of 60–89 mL/min/1.73 m^2 with proteinuria; stage 3a, eGFR of 45–59 mL/min/1.73 m^2; stage 3b, eGFR of 30–44 mL/min/1.73 m^2; stage 4, eGFR of 15–29 mL/min/1.73 m^2; and stage 5, eGFR <15 mL/min /1.73 m^2.[23] The decreased GFR was defined as eGFR <60 mL/min/1.73 m^2 (GFR categories G3a–G5). Dyslipidemia was defined according to the guideline of the US National Cholesterol Education Program Adult Treatment Panel III.[24] High serum total cholesterol (TC) was defined as TC ≥ 240 mg/dL (6.2 mmol/L). High serum low density lipoprotein (LDL) was defined as LDL ≥ 160 mg/dL (4.13 mmol/L). High serum triglycerides was defined as triglycerides ≥150 mg/dL (1.7 mmol/L). Diabetes was defined as a fasting serum glucose concentration >7.0 mmol/L or history of diabetes.[25] Hypertension was defined with systolic blood pressure (BP) ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg.[26]

Statistical analysis

Data are presented as medians [interquartile range (IQR)] for continuous variables and dichotomous variables are presented as frequency and percentage. Variance analyses were used to compare the differences of dichotomous variables and the non-parametric Mann-Whitney *U*-test were used to compare the differences of variables if not normally distributed. The Fisher's exact test was used when dichotomous variables had a theoretical number <5. Univariable correlations of proteinuria and laboratory variables were determined using Pearson's test. Covariates analyzed by the univariate analysis with *p* value <0.20 were included in the multivariate analysis. The association of exposure covariates with the indicators of CKD was determined using multivariable logistic regression models. We reported the effect of the variables as odds ratios (ORs) with 95% confidence intervals (CIs). All the analyses were performed using Empower(R) (www.empowerstats.com; X&Y solutions, Inc, Boston, MA, USA) and R (http://www.R-project.org). The statistical significance was defined as *p* <0.05 two-sided.

Results

Baseline characteristics of enrolled patients

A total of 642 patients with chronic HBV infection were enrolled into this case-control study, including 94 (14.64%) CKD patients and 548 (84.36%) non-CKD patients, and all the basic characteristics of the patients with or without CKD are shown in Table 1. There were a total of 530 (82.55%) patients without albuminuria and 112 (17.45%) with albuminuria; the mean age was 44.00 (35.25–54.00) years-old. There were 498 (77.57%) male patients, and 41.43% of the patients (*n*=266) had a history of NAs treatments. The prevalence of hypertension, diabetes mellitus, coronary heart disease and dyslipidemia was 10.44% (67/642), 9.50% (61/642), 2.18% (14/642) and 19.94% (128/642), respectively, in this population.

The characteristics of patients stratified by cirrhosis and non-cirrhosis have been summarized in Table 2. We demonstrated that 232 (36.10%) patients with cirrhosis were older (49.00 vs. 40.00, *p*<0.001), had a higher prevalence of diabetes mellitus (12.93% vs. 7.56%, *p*=0.026), and had significant higher levels of serum total bilirubin (27.20 vs. 17.75, *p*<0.001), Cyc-s (1.15 vs. 0.98, *p*<0.001), Log_{10} HBsAg level (3.80 vs. 3.61, *p*<0.001) compared with that in patients with non-cirrhosis. In contrast, compared with patients with cirrhosis, patients without cirrhosis had a higher prevalence of dyslipidemia (24.88% vs. 11.21%, *P*<0.001), and had significant in the laboratory indicators including alanine aminotransferase, aspartate aminotransferase, albumin, HBeAg levels, HBV DNA levels, creatinine, uric acid, hemoglobin, prothrombin activity, TC, triglycerides, LDL (all *p*<0.05, respectively). By adopting the CKD-EPI equation for eGFR, the prevalence of renal dysfunction were significantly different between cirrhosis and non-cirrhosis patients (*p*=0.004). However, we did not find the significant difference of incidence of CKD in patients with and without liver cirrhosis (*p*=0.647), suggesting that liver cirrhosis might not be the main risk factor for the incidence of CKD in chronic HBV infection.

Prevalence of albuminuria, proteinuria and CKD among all the HBV patients

Table 3 showed that the overall prevalence of albuminuria (≥150 mg/L), proteinuria (at least grade 1+), a decreased eGFR and the prevalence of CKD were detected in 17.45% (112/642), 14.02% (90/642), 3.42% (22/642) and 14.64% (94/642), respectively. In the patients with proteinuria (at least grade 1+), the prevalence rates of dyslipidemia and hypertension were 32.03% and 50.78%, respectively. The

Table 1. Basic characteristics of HBV patients with and without CKD

	Total, *n*=642	**CKD, *n*=94**	**Non-CKD, *n*=548**	***p*-value**
Female	144 (22.43%)	19 (20.21%)	125 (22.81%)	0.577
Age, years	44.00 (35.25–54.00)	46.00 (37.25–54.75)	44.00 (35.00–53.00)	0.239
Log_{10} HBsAg	3.70 (3.43–3.81)	3.63 (3.28–3.79)	3.71 (3.45–3.82)	0.008
Log_{10} HBV DNA	5.37 (3.38–6.77)	5.16 (2.99–7.20)	5.37 (3.51–6.68)	0.976
HBeAg-positive	403 (62.77%)	65 (69.15%)	338 (61.68%)	0.166
HBV DNA positive	571 (88.94%)	78 (82.98%)	493 (89.96%)	0.046
Creatinine, µmol/L	64.00 (56.00–73.00)	78.00 (61.50–103.25)	64.00 (55.00–70.25)	<0.001
Uric acid, µmol/L	263.50 (207.00–319.00)	348.00 (290.00–435.00)	255.00 (200.75–302.25)	<0.001
Cystatin C, mg/mL	1.04 (0.89–1.27)	1.25 (0.96–1.82)	1.02 (0.88–1.21)	<0.001
Hemoglobin, g/L	138.15 (125.00–152.75)	130.00 (109.25–143.00)	140.00 (127.00–153.00)	<0.001
Prothrombin activity, %	76.00 (63.00–89.00)	91.00 (77.00–98.75)	75.00 (62.00–86.00)	<0.001
Total cholesterol, mmol/L	3.92 (3.27–4.55)	5.12 (4.04–6.34)	3.81 (3.20–4.36)	<0.001
Triglycerides, mmol/L	1.08 (0.75–1.44)	1.40 (1.08–1.93)	1.00 (0.74–1.36)	<0.001
Low-density lipoprotein cholesterol, mmol/L	1.83 (1.36–2.33)	2.79 (2.02–3.75)	1.73 (1.32–2.21)	<0.001
eGFR, mL/ min/1.73 m^2				<0.001
>90	577 (89.88%)	57 (60.64%)	520 (94.89%)	
60–89	43 (6.70%)	15 (15.96%)	28 (5.11%)	
45–59	9 (1.40%)	9 (9.57%)	0 (0.00%)	
30–44	4 (0.62%)	4 (4.26%)	0 (0.00%)	
16–29	3 (0.47%)	3 (3.19%)	0 (0.00%)	
<15	6 (0.93%)	6 (6.38%)	0 (0.00%)	
Dyslipidemia	128 (19.94%)	41 (43.62%)	87 (15.88%)	<0.001
Diabetes mellitus	61 (9.50%)	16 (17.02%)	45 (8.21%)	0.007
Hypertension	67 (10.44%)	33 (6.02%)	34 (36.17%)	<0.001
Disease course, months				0.003
0–60	236 (36.76%)	186 (33.94%)	50 (53.19%)	
60–120	102 (15.89%)	88 (16.06%)	14 (14.89%)	
120–240	190 (29.60%)	171 (31.20%)	19 (20.21%)	
≥240	114 (17.76%)	103 (18.80%)	11 (11.70%)	
Antiviral drugs	266(41.43%)			0.45
Adefovir	66 (24.81%)	7 (18.42%)	59 (25.88%)	
Entecavir	111 (41.73%)	20 (52.63%)	91 (39.91%)	
Lamivudine	27 (10.15%)	3 (7.89%)	24 (10.53%)	
Telbivudine	6 (2.26%)	2 (5.26%)	4 (1.75%)	
Interferon	10 (3.76%)	0 (0.00%)	10 (4.39%)	
Use two or more antiviral drugs	46 (17.29%)	6 (15.79%)	40 (17.54%)	

Data are presented as *n* (%) or mean (range). CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

basic characteristics of the patients classified by the degree of proteinuria and the incidence of CKD are showed in Table 2. In detail, the prevalence of high BP and coronary heart diseases were significantly different, accompanied by the various degree of proteinuria (both $p<0.001$, respectively). In the patients with CKD, the prevalence rates of dyslipidemia and hypertension were 43.62% and 36.17%, respectively. Furthermore, the HBsAg level, diabetes mellitus, dyslipidemia, hypertension, and HBV DNA-positive status were significantly associated with the incidence of CKD in all the patients with chronic HBV infection (all $p<0.05$, respectively).

Table 4 shows the results of univariate analysis, in which duration of hepatitis B disease ≥120 months, HBsAg levels,

Table 2. Basic characteristics of HBV patients by cirrhosis and non-cirrhosis status

	Non-cirrhosis, n=410	Cirrhosis, n=232	*p*-value*
Age, years	40.00 (32.00–49.00)	49.00 (43.00–58.0)	<0.001
HBeAg-positive	285 (69.51%)	118 (50.86%)	<0.001
Log_{10} HBsAg	70.99 (0.20–852.7)	1.12 (0.10–26.54)	<0.001
Log_{10} HBV DNA	5.84 (4.00–7.22)	4.34 (2.95–5.89)	<0.001
Creatinine, μmol/L	65.50 (57.00–73.00)	62.50 (53.75–71.0)	0.030
Uric acid, μmol/L	266.00 (217.00–316.75)	257.00 (191.25–322.00)	0.035
Cystatin C, mg/mL	0.98 (0.87–1.19)	1.15 (1.01–1.42)	<0.001
Hemoglobin, g/L	146.00 (132.00–156.30)	128.00 (113.00–138.25)	<0.001
Prothrombin activity,%	83.00 (73.00–93.00)	63.00 (52.00–76.00)	<0.001
Total cholesterol, mmol/L	4.04 (3.42–4.64)	3.68 (3.05–4.33)	<0.001
Triglycerides, mmol/L	1.22 (0.87–1.63)	0.82 (0.62–1.10)	<0.001
Lipoprotein cholesterol, mmol/L	2.01 (1.50–2.50)	1.54 (1.22–1.98)	<0.001
eGFR, mL/ min/1.73 m^2			0.004
>90	373 (90.98%)	204 (87.93%)	
60–89	27 (6.59%)	16 (6.90%)	
45–59	1 (0.24%)	8 (3.45%)	
30–44	1 (0.24%)	3 (1.29%)	
16–29	2 (0.49%)	1 (0.43%)	
<15	6 (1.46%)	0 (0.00%)	
CKD	62 (15.12%)	32 (13.79%)	0.647
Dyslipidemia	102 (24.88%)	26 (11.21%)	<0.001
Diabetes mellitus	31 (7.56%)	30 (12.93%)	0.026

Data are presented as *n* (%) or mean (range). CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

HBV DNA level, dyslipidemia, hypertension, and diabetes mellitus were significantly associated with the presence of CKD (all $p<0.05$, respectively). Thereafter, the variables with $p<0.2$ in the univariate analysis were entered in the multivariate logistic regression model. The multivariate analysis demonstrated HBeAg-positive status (OR: 2.099, 95% CI: 1.128–3.907), dyslipidemia (OR: 3.025, 95% CI: 1.747–5.239), and hypertension (OR: 12.523, 95% CI: 6.283–24.958) were independently positively associated with the presence of CKD. However, duration of disease (≥240 months) (OR: 0.401, 95% CI: 0.179–0.894), HBsAg levels (OR: 0.514, 95% CI: 0.336–0.786), and coronary heart disease (OR: 0.078, 95% CI: 0.008–0.768) were independently negatively associated with the incidence of CKD. Age with per-10 years unit, sex, duration of disease (<120 months), antiviral therapy, and cirrhosis status were not significantly associated with the presence of CKD by multivariate analysis.

Risk factors for CKD in hepatitis B patients after adjusting for diabetes mellitus, hypertension or coronary heart disease

We further determined the risk factors of CKD in HBV patients without coronary heart disease, diabetes mellitus or hypertension. The univariate and multivariate analyses for the risk of CKD have been summarized in Table 5. The univariate analysis showed that duration of disease (≥120 months), HBsAg level and dyslipidemia were significantly associated with the presence of CKD. Multivariate analysis showed that dyslipidemia (OR: 2.999, 95% CI:1.498–6.004) was an independent positive risk factor for the incidence of CKD, as well as HBsAg levels (OR: 0.477, 95% CI: 0.299–0.761), duration of disease (120–240 months) (OR: 0.215, 95% CI: 0.086–0.536), and duration of disease (≥240 months) (OR: 0.357, 95% CI: 0.132–0.967) were independent protective factors against the presence of CKD in chronic HBV infection.

Discussion

CKD usually occurs in 3–13% of the HBV population in various countries and areas.[17,27] However, the risk factors of CKD in China have not been completely demonstrated. Our present study demonstrated that the presence of hypertension, dyslipidemia, and HBeAg-positive status were positively associated with the prevalence of CKD. Importantly, we have also reported that that HBsAg levels, duration of disease (≥120 months) of CHB patients might play protective role in the incidence of CKD among Chinese population with chronic HBV infection.

A recent national survey in China suggested that the prevalence rates of decreased eGFR, albuminuria and CKD were 1.7%, 9.4% and 10.8% in the general population.[14] The prevalence of proteinuria and CKD in our study was slightly higher than these rates, which suggested that HBV might increase the risk for the incidence of CKD. In a single-center cross-sectional survey without hypertension, dia-

Table 3. Basic characteristics of the patients classified by the degree of proteinuria and the incidence of CKD

	Proteinuria							CKD		
	−	±	+	2+	3+	4+	*p*-value	No, *n*=548	Yes, *n*=94	*p*-value
Female	120 (83.33%)	6 (4.17%)	4 (2.78%)	9 (6.25%)	5 (3.47%)	0 (0.00%)	0.735	125 (22.81%)	19 (20.21%)	0.577
Age, years							0.223			0.626
<30	74 (88.10%)	2 (2.38%)	2 (2.38%)	2 (2.38%)	4 (4.76%)	0 (0.00%)		76 (13.87%)	8 (8.51%)	
30–40	122 (84.14%)	4 (2.76%)	2 (1.38%)	7 (4.83%)	9 (6.21%)	1 (0.69%)		125 (22.81%)	20 (21.28%)	
40–50	169 (83.25%)	4 (1.97%)	8 (3.94%)	12 (5.91%)	10 (4.93%)	0 (0.00%)		172 (31.39%)	31 (32.98%)	
50–60	109 (81.95%)	3 (2.26%)	6 (4.51%)	6 (4.51%)	9 (6.77%)	0 (0.00%)		111 (20.26%)	22 (23.40%)	
≥60	57 (74.03%)	8 (10.39%)	2 (2.60%)	6 (7.79%)	4 (5.19%)	0 (0.00%)		64 (11.68%)	13 (13.83%)	
Cirrhosis	194 (83.62%)	10 (4.31%)	9 (3.88%)	9 (3.88%)	10 (4.31%)	0 (0.00%)	0.454	200 (36.50%)	32 (34.04%)	0.647
Diabetes mellitus	42 (68.85%)	4 (6.56%)	3 (4.92%)	6 (9.84%)	6 (9.84%)	0 (0.00%)	0.086	45 (8.21%)	16 (17.02%)	0.007
Dyslipidemia	83 (64.84%)	4 (3.12%)	4 (3.12%)	15 (11.72%)	21 (16.41%)	1 (0.78%)	<0.001	87 (15.88%)	41 (43.62%)	<0.001
Hypertension	30 (44.78%)	3 (4.48%)	3 (4.48%)	15 (22.39%)	16 (23.88%)	0 (0.00%)	<0.001	33 (6.02%)	34 (36.17%)	<0.001
CHD	13 (92.86%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	0.861	13 (2.37%)	1 (1.06%)	0.422
Log_{10} HBsAg	3.7 (3.5–3.8)	3.8 (3.4–3.9)	3.8 (3.4–3.8)	3.6 (3.3–3.7)	3.7 (3.3–3.8)	2.8 (2.8–2.8)	0.086	3.7 (3.5–3.8)	3.6 (3.3–3.8)	0.008
HBeAg-positive	328 (81.39%)	12 (2.98%)	18 (4.47%)	19 (4.71%)	25 (6.20%)	1 (0.25%)	0.13	338 (61.68%)	65 (69.15%)	0.166
HBV DNA positive	477 (83.54%)	20 (3.50%)	19 (3.33%)	26 (4.55%)	28 (4.90%)	1 (0.18%)	0.071	493 (89.96%)	78 (82.98%)	0.046

Data are presented as *n* (%) or mean (range). CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; CHD, Coronary heart disease.

Table 4. Univariable and multivariable analyses for the risk factors associated with presence of CKD in HBV patients

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value value**
Disease course, months				
0–60	1		1	
60–120	0.592 (0.311, 1.128)	0.111	0.540(0.256, 1.140)	0.106
120–240	0.413 (0.234, 0.729)	0.002	0.460(0.241, 0.877)	0.018
≥240	0.397 (0.198, 0.797)	0.009	0.401(0.179, 0.894)	0.026
Age, years	1.112 (0.932, 1.328)	0.239		
Female	0.857 (0.499, 1.473)	0.577		
Log_{10} HBsAg	0.625 (0.435, 0.898)	0.011	0.514(0.336, 0.786)	0.002
Antiviral therapy	0.952 (0.610, 1.487)	0.830		
HBeAg-positive	1.393 (0.870, 2.229)	0.168	2.099(1.128, 3.907)	0.019
Log_{10} HBV DNA	0.544 (0.297, 0.997)	0.049	0.568(0.241, 1.341)	0.197
Dyslipidemia	4.099 (2.568, 6.543)	<0.001	3.025(1.747, 5.239)	<0.001
Hypertension	8.843 (5.110,15.305)	<0.001	12.523(6.283, 24.958)	<0.001
Diabetes mellitus	2.293 (1.235, 4.255)	0.009	1.664(0.750, 3.690)	0.210
CHD	0.443 (0.057, 3.423)	0.435		
Cirrhosis	0.898 (0.567, 1.424)	0.647		

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; CHD, Coronary heart disease.

betes mellitus or history of coronary heart disease, 7.9% of CHB patients with NAs therapy suffered from CKD, as well as 2.2% with decreased eGFR and 6.4% with albuminuria.[25] A 2-year multicenter cross-sectional, single-arm French study with the treatment of naïve CHB patients demonstrated that 64.6% (73/113) of patients presented with renal abnormalities, and 3.5% with decreased eGFR as well as 38.1% with proteinuria ≥1.[28] Our study demonstrated that the prevalence rates of a decreased GFR and proteinuria ≥1+ were 3.42% and 14.02%, respectively. Compared with the previous studies, the prevalence of proteinuria in our study was slightly lower. This discrepancy might be due to a difference of NAs treatment or selection bias, since antiviral drugs have adverse effects, including chronic renal impairment.[13,29]

The risk factors for the incidence of CKD in the present study included the presence of hypertension, dyslipidemia, and HBeAg-positive status. Previous studies have suggested that hypertension and diabetes mellitus were risk factors of CKD in patients with chronic hepatitis B,[11,14] but that diabetes mellitus was not a risk factor for CKD alone.[11] A recent study found that metabolic syndrome was an independent risk factor for the prevalence of CKD in HBV patients.[14] In particular, metabolic syndrome represents a

Table 5. Risk factors for CKD in hepatitis B patients after adjusting for diabetes mellitus, hypertension or coronary heart disease

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**
Disease course, months				
0–60	1		1	
60–120	0.574 (0.262, 1.256)	0.165	0.637 (0.277, 1.465)	0.288
120–240	0.176 (0.072, 0.429)	<0.001	0.215 (0.086, 0.536)	0.001
≥240	0.277 (0.105, 0.734)	0.010	0.357 (0.132, 0.967)	0.043
Age, years	1.082 (0.856, 1.367)	0.510		
Female	0.773 (0.377, 1.584)	0.481		
Log_{10} HBsAg	0.481 (0.323, 0.716)	<0.001	0.477 (0.299, 0.761)	0.002
Antiviral therapy	0.736 (0.410, 1.321)	0.305		
HBeAg-positive	1.827 (0.954, 3.497)	0.069	2.163 (0.993, 4.711)	0.052
Log_{10} HBV DNA	1.062 (0.403, 2.797)	0.903		
Dyslipidemia	3.127 (1.712, 5.714)	<0.001	2.999 (1.498, 6.004)	0.002
Cirrhosis	1.042 (0.579, 1.875)	0.890		

series of dysfunctions, including central obesity, dyslipidemia, arterial hypertension, and elevated fasting glucose.[29] Accelerating reports have indicated that metabolic syndrome and its associated complications are significantly related to the development of CKD.[30] These results are in agreement with our present data that show dyslipidemia is an independent risk factor for the incidence of CKD in patients with chronic HBV infection. In our present study, we found that coronary heart disease was a protective factor for the incidence of CKD, by using multivariate logic regression analysis. However, this result does not mean that if one HBV patient suffers from heart disease, she/he will be at lower risk for CKD. The result was obtained from statistical analysis alone and the coronary heart disease might be a confounding factor in the multivariate analysis model. Therefore, we further adjusted for diabetes mellitus, hypertension or coronary heart disease and then analyzed the risk factors of CKD in a multivariate analysis model. Multivariate analysis showed that dyslipidemia, HBsAg levels, and duration of disease were independent factors associated with the presence of CKD in chronic HBV infection.

Interestingly, we have reported that the higher HBsAg level and duration of disease (≥120 months) were inversely correlated with CKD, making it seem that long duration of HBV replication might play protective roles in the incidence of CKD. However, these results might be attributed to the fact that CKD might occur at the early stage of 120 months after the onset of acute HBV infection. A population-based prospective cohort study indicated that HBsAg positivity had a positive effect on the incidence of CKD within 10 years after the onset of HBV infection.[11] In our manuscript, we reported that HBeAg-positive status was a risk factor, with OR 2.099, and Log_{10} HBsAg was a protective factor, with OR: 0.514, for the incidence of CKD in HBV infection. The data indicated that HBV patients with HBeAg-positive status might have 1.099-times the risk of those with HBeAg-negative status, while HBV patients with high HBsAg level might have 48.6% higher risk than those with low HBsAg level at the changes of 1 unit of Log_{10} HBsAg. The results are not contradictory and suggest that HBV replication increases the risk of CKD in HBV infection. Another large multicenter cross-sectional study also obtained the same conclusion that the presence of HBeAg was a strong risk factor of CKD at the early stage of HBV infection.[31] Furthermore, our data did not identify HBV DNA level as the risk factor for the incidence of CKD in HBV infection. In fact, these results could be mainly explained by the presence of HBV immune makers in kidney tissue, regardless of the status of HBV DNA level.[32] In addition, we did not find a difference in CKD incidence among the two populations: with/without cirrhosis. This find was in disagreement with the previous report by Hou *et al*.[14] and this disagreement might be attributed to the origin of patients in different areas of China.

After adjusting for diabetes mellitus, hypertension or coronary heart disease, HBsAg levels and duration of disease remained the independent protective factors for the presence of CKD in chronic HBV infection. These results strongly support the notion that the HBV itself might contribute to the kidney dysfunction. The serum level of HBsAg represents the complex equilibrium between the host immune system and the HBV itself, as well as the product of the transcription of specific HBV RNAs.[33] Median HBsAg level usually differs in the different phases of chronic HBV infection, and HBsAg level was highest in the immune tolerant phase.[34] Previous studies found that the HBV itself might contribute to dysfunction of the kidney and active immune response to the HBV.[35–37] Therefore, patients in the immune tolerance stages might be at lower risk for incidence of CKD.

There were several limitations inherent to this study. First, the definition of CKD status requires an at least 3-month observation of kidney function or decreased GFR, which was not documented in our study but rather was presumed. Second, our present study is a hospital-based, single-center cross-sectional and case-control study. Although the ratio of matched control to case reached as high as 6:1, the perspective cohort of natural HBV population in the real world is still needed in the future, which might provide more accurate and valuable information for clinical management of HBV.[38,39] Third, the method for measurement of GFR was not determined directly, and the eGFR might be an accurate indicator for renal function some serious liver diseases due to the decreased production of creatinine.

In conclusion, our present study demonstrated that dyslipidemia, HBeAg-positive status, hypertension, lower HBsAg levels, and duration of disease (<120 months) are independent risk factors for CKD in patients with chronic HBV infection. After adjusting for diabetes mellitus, hypertension, or coronary heart disease, HBsAg levels and duration of disease remained the independent protective factors for the presence of CKD in chronic HBV infection. However, the perspective study of a cohort of HBV patients with natural history is still needed in the future.

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Conflict of interest

YCF has been an associate editor of J*ournal of Clinical and Translational Hepatology* since 2013.The other authors have no conflicts of interest related to this publication.

Author contributions

Collecting the data (XW, HY, DL), statistical assistance (YL, FX), and design and oversight/guidance of the study (XY, YCF). All authors were involved in conceiving experiments, analyzing the data and writing the paper. All authors gave final approval of the submitted and published versions.

Data sharing statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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