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Association between hepatitis B virus infection and chronic kidney disease

A cross-sectional study from 3 million population aged 20 to 49 years in rural China

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Abstract

Hepatitis B virus (HBV) infection can lead to different types of chronic kidney diseases (CKD) in clinical practice. However, HBV infection has been observed to have no significant association with CKD indicators in some epidemiological surveys. This research aims to estimate CKD prevalence in HBV infection population and clarify the relationship between HBV infection status and CKD.

The participants aged 20 to 49 years were selected by multistage random sampling from January 1, 2010 to December 31, 2012 across 31 provinces and regions in rural China. The data was collected by standard questionnaire and physical check-up. Status of HBV infection was diagnosed as immune tolerant phase, hepatitis B envelope antigen -positive chronic HBV infection, inactive HBV carrier, hepatitis B envelope antigen -negative chronic HBV infection and resolved HBV infection based on serological markers, and the level of hepatic function, respectively.

In total, 2,969,502 subjects were included in the study. In population aged 20 to 49 years in rural China, prevalence of HBV infection was 12.17%. Prevalence of proteinuria, hematuria, estimated glomerular filtration rate less than 60 mL/min/1.73m^2 and CKD was 0.94%(95% CI = 0.91–0.97%) vs. 0.65%(95% CI = 0.64–0.66%), 1.92%(95% CI = 1.87–1.96%) vs. 1.19% (95% CI = 1.18–1.21%), 1.02%(95% CI = 0.99–1.06%) vs. 0.77% (95% CI = 0.76–0.78%), and 3.85%(95% CI = 3.78–3.91%) vs. 2.60%(95% CI = 2.58–2.62%) in population with HBV infection and without infection, respectively. Prevalence of CKD and indicators was higher in population in every status of HBV infection than in population without infection, respectively (all $P < 0{\cdot}0001$). Every HBV infection status was a risk factor for CKD.

CKD prevalence was higher in population in every status of HBV infection than without infection. HBV infection was a risk factor for CKD in population aged 20 to 49 years in rural China.

Abbreviations: ALT = alanine aminotransferase, Anti-HBc: antibodies against hepatitis B core antigen, Anti-HBe = antibody against HBeAg, Anti-HBs = antibody against HBsAg, CI = confidence interval, CKD = chronic kidney diseases, , eGFR = estimated glomerular filtration rate, GFR = glomerular filtration rate HBeAg = hepatitis B envelope antigen, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, MN = membranous nephropathy, NFPHEP = National Free Pre-conception Health Examination Project.

Keywords: chronic kidney diseases, cross-sectional studies, epidemiology, hepatitis B virus infection

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1. Introduction

Hepatitis B virus (HBV) infection is one of the serious public health problems in the world. The research has estimated that 3.61% of the general population is chronically infected with HBV in 2010 worldwide.[1] About 30% of the population is confirmed with current or past HBV infection by serological evidence globally.[2] The association between HBV infection and kidney injury was reported first in 1971.[3] It has been known that HBV infection can lead to different types of chronic kidney diseases (CKD) in clinical practice for the past few decades.[4] However, HBV infection has been observed to have no significant association with CKD indicators in some epidemiological surveys completed in the areas with high prevalence of HBV infection.[5–7] There is still insufficient data on the prevalence of CKD indicators in population with HBV infection. It is essential to make a thorough understanding of the relationship between HBV infection and CKD.

China is one of the highly endemic areas in terms of the prevalence of hepatitis B surface antigen (HBsAg) in population.[8] Since hepatitis B vaccination program for infants was implemented and integrated into national immunization programs

in1992, China had made great achievement in hepatitis B prevention and control. HBsAg prevalence decreased to 5.49% in China in 2010.[1] HBsAg prevalence among people aged 1 to 12 years had been reduced to less than 1% in China in 2014.[9] With the effective control of hepatitis B infection among children, the adults become the main population for HBV infection.[10] The adults receive hepatitis B vaccination voluntarily and at their own expense in China. In rural areas, the vaccination coverage ratio was still 20% lower than in the urban areas.[11] HBV infection in the population with reproductive age result to the high risk of intrafamilial horizontal and vertical transmission. It is urgent to evaluate HBV infection prevalence in the population with reproductive age and explore association between HBV infection and CKD for reducing the burden of adverse outcomes association with HBV infection in China. This research aims to assess HBV infection prevalence and CKD prevalence in the HBV infection subjects among population with reproductive age in rural China.

2. Methods

2.1. Study design and participants

Data were obtained from the National Free Pre-conception Health Examination Project (NFPHEP) in rural China. The participants were selected by multi-stage random sampling from January 1, 2010 to December 31, 2012. In total, 220 counties were sampled randomly across 31 provinces and regions in China. All couples in the selected counties with a plan to get pregnant within the next 6 months registered in the project.

Informed consent was required from every participant before enrollment. The basic information of the participants was collected by a standard questionnaire, including age, sex, hepatitis B vaccination history and the histories of HBV infection and hypertension. Measurement of weight and height was completed using standard methods, respectively. Age distribution of the study population was from 20 to 49 years.

2.2. Screening protocol and evaluation criteria

2.2.1. Diagnosis of HBV infection. Serological markers for HBV infection included HBsAg, antibody against HBsAg (anti-HBs), hepatitis B envelope antigen (HBeAg), antibody against HBeAg (anti-HBe), antibodies against hepatitis B core antigen (anti-HBc).[2]

Blood samples were collected after an overnight fast of at least 10 h by means of venipuncture. Serum was then tested for HBsAg, anti-HBs, HBeAg, anti-HB, and anti-HBc using enzyme-linked immunosorbent assay. The local laboratories choose reagent kits approved by China Food and Drug Administration on their preference, and National Center of Clinical Laboratories for Quality Inspection and Detection tested the reagent kits with reagents produced by Abbott (Abbott Park, IL) as the reference standard. Alanine aminotransferase (ALT) was tested by rate assay. Normal hepatic function was defined as ALT no more than 50 IU/mL for men and no more than 40 IU/mL for women, respectively.

The status of HBV infection was defined as followed.[12]

1. Immune tolerant phase: HBsAg positive, HBeAg positive, and normal aminotransferase concentrations.
2. HBeAg-positive chronic HBV infection: HBsAg positive, and HBeAg positive, increased aminotransferase concentrations.
3. Inactive HBV carrier: HBsAg positive, HBeAg negative, anti-HBe positive, and normal aminotransferase concentrations.
4. HBeAg-negative chronic HBV infection: HBsAg positive, HBeAg negative, and increased aminotransferase concentrations.
5. Resolved HBV infection: Previous known history of HBV infection, HBsAg negative, normal aminotransferase concentrations, and with anti-HBc positive or anti-HBs positive.

The participant in every status of HBV infection was classified as HBV infection group. The participant without evidence of HBV infection was classified as Non-HBV infection group.

2.2.2. Definition of CKD indicators. CKD indicators included proteinuria, or hematuria, or estimated glomerular filtration rate (eGFR) $< 60\,mL/min/1.73\,m^2$.[13]

The morning spot urine samples were collected to identify proteinuria and hematuria by means of automated urine dry chemical analysis. Samples with positive hematuria were reexamined through microscopic analysis within 2 h. Presence of 3 or more red blood cells per high-power field was considered abnormal. The subjects who were during menstruation did not be required for urinalysis. The samples with hematuria and leukocyturia were diagnosed as urinary tract infection and be excluded from analysis.

Serum creatinine was measured by enzymic method with Enzymatic Creatinine-2 Reagents (Siemens Healthcare Diagnostics Inc, Erlangen, Germany) and isotope dilution mass spectrometry method as the reference standard. eGFR was calculated by Asian-modified chronic kidney disease epidemiology collaboration equation.

2.2.3. Diagnosis of hypertension. We measured blood pressure three times at 5 min intervals by sphygmomanometer and calculated the mean of the three readings. If the difference between the readings was higher than 10 mm Hg, we would use the mean of the two closest measurements. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or by any self-reported history of hypertension.

2.2.4. Definition of obesity. The BMI was calculated as weight in kilograms divided by height in meters squared. Obesity was defined as BMI$\geq 28.0\,kg/m^2$ according to Chinese criteria of weight for adults.[14]

2.2.5. Statistical analysis. Continuous variables were analyzed by means of *t* test and one-way analysis of variance. Differences were analyzed by means of χ^2 test for categorical data. To investigate the risk factors for CKD, the logistic regression models were applied. The crude and multivariable-adjusted odds ratios were reported. Covariates included in the multivariable logistic regression models were gender, age (every one year), hypertension (yes *vs.* no), obesity (yes *vs.* no), status of HBV infection (immune tolerant phase, HBeAg-positive chronic HBV infection, inactive HBV carrier, HBeAg-negative chronic HBV infection, and resolved HBV infection). All statistical data were handled by removing the missing items. All *P* values were two-sided, and *P* less than 0.05 was considered significant.

Statistical analyses were performed with SPSS version 21.0, IBM.

3. Results

In total, 3,091,379 participants registered in NFPHEP from January 1, 2010 to December 31, 2012. In total, 121,877 participants did not complete blood test or urinalysis. Rate of loss of participants was 3.94%. A total of 2,969,502 eligible subjects

Table 1

Prevalence of HBV infection according to serological markers and infectious status in general population aged 20 to 49 years in rural China.

Classification	Participants	Prevalence
Serological markers for HBV infection		
HBsAg positive	165,482	5.57%
anti-HBs positive	894,854	30.13%
HBeAg positive	54,311	1.83%
anti-HBe positive	116,295	3.92%
anti-HBc positive	270,795	9.12%
Status of HBV infection		
Immune tolerant phase	35,034	1.18%
HBeAg-positive chronic HBV infection	19,277	0.65%
Inactive HBV carrier	245,206	8.26%
HBeAg-negative chronic HBV infection	58,578	1.97%
Resolved HBV infection	3236	0.11%

Anti-HBc = antibodies against hepatitis B core antigen, Anti-HBe = antibody against HBeAg, Anti-HBs = antibody against HBsAg, HBeAg = hepatitis B envelope antigen, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus.

were included in the study; 49.9% of the subjects were males. Average age of the population was 26.99 ± 7.16 years. 797,789 subjects (26.87%) reported to be vaccinated with hepatitis B vaccine, and 19,874 subjects (0.67%) reported the history of HBV infection. 2,608,171 subjects (87.83%) had been verified by blood test to be without current or past HBV infection. Classification of 361,331 subjects (12.17%) with HBV infection according to distinct status of infection was shown in Table 1. Inactive HBV carriers constituted the dominant portion in the subjects with HBV infection.

As shown in Table 2, in the population with HBV infection and without infection, prevalence of proteinuria, hematuria, eGFR less than 60 mL/min/1.73m^2 and CKD was 0.94%(95% CI=0.91–0.97%) vs. 0.65%(95% CI=0.64–0.66%), 1.92% (95% CI=1.87–1.96%) vs. 1.19% (95% CI=1.18–1.21%), 1.02% (95% CI=0.99–1.06%) vs. 0.77% (95% CI=0.76–0.78%), and 3.85% (95% CI=3.78–3.91%) vs. 2.60% (95% CI=2.58–2.62%), respectively.

Table 2

Clinical characteristics and prevalence of CKD indicators between the population with and without HBV infection aged 20 to 49 years in rural China.

	Non-HBV infection	HBV infection	*P*
Participants n/(%)	2,608,171 (87.83%)	361,331 (12.17%)	
Female (%)	48.54	56.22	
Age (years)	27.01 ± 7.40	26.86 ± 5.11	<.001
Scr (μmol/l)	77.13 ± 20.12	78.26 ± 21.85	<.001
ALT (U/L)	26.46 ± 20.83	34.66 ± 39.36	<.001
BMI (kg/cm^2)	21.95 ± 3.70	21.66 ± 4.42	<.001
Hypertension (%)	4.08 (4.06–4.10)	3.92 (3.86–3.99)	<.001
Obesity (%)	3.47 (3.44–3.49)	3.42 (3.36–3.48)	<.001
Hematuria (%)	1.19 (1.18–1.21)	1.92 (1.87–1.96)	<.001
Proteinuria (%)	0.65 (0.64–0.66)	0.94 (0.91–0.97)	<.001
EGFR<60 mmol/l) (%)	0.77 (0.76–0.78)	1.02 (0.99–1.06)	<.001
CKD (%)	2.60 (2.58–2.62)	3.85 (3.78–3.91)	<.001

ALT = alanine transaminase; BMI = body mass index; CKD = chronic kidney diseases; EGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; Scr = serum creatinine.
Data are represented as n (%), mean ± SD, or % (95% CI). CI = confidence interval, SD = standard deviation.

As shown in Figure 1, there were different effects in the prevalence of CKD and indicators according to status of HBV infection. Compared with the population without HBV infection, prevalence of CKD and indicators was higher in the population in every status of HBV infection, respectively. The highest prevalence of CKD occurred in the status of HBeAg-negative chronic HBV infection and resolved HBV infection.

Table 3 listed the crude and adjusted odds ratios for CKD. Age (per year), female, hypertension, obesity, and every status of HBV infection were identified as the independent risk factors for CKD in general population aged 20 to 49 years in rural China.

4. Discussion

Infectious disease can be one of important influence factors on development of CKD. It has been observed that there is a strong association between HBV infection and kidney disease over the recent decades. Renal injury is one of extrahepatic manifestations in chronic HBV infection.[15] Over 2 billion humans have been estimated to be with HBV infection worldwide.[8] The data on prevalence of CKD remain scanty in HBV-infected population. This study figured out a correlation between HBV infection and CKD based on population according to the international definition and stratification of HBV.

In this large-scale study, we investigated prevalence of CKD was 3.85% in HBV-infected population aged 20 to 49 years in rural China, which was higher than in population without HBV infection. Preliminary analyses have estimated significant differences in prevalence of CKD indicators according to different status of HBV infection. The results are an alert for clinicians and governments to pay close attention to CKD in population with HBV infection.

Prevalence of HBsAg was 7.2% in population aged 1 to 59 years in China.[16] In this study, prevalence of HBsAg was 5.57% in population aged 20 to 49 years in rural China. If HBV infection was defined as only presence of HBsAg in the epidemiological surveys, other status of HBV infection would be ignored and many HBV-infected people would not have been diagnosed. Prevalence of HBV infection including all status was 12.17% in the population with 20 to 49 years, and a high prevalence of inactive HBV carrier characterized HBV infection in rural China. This study suggested that the burdens of HBV infection and its related diseases remain heavy in rural China.

In this study, in the population with HBV infection, prevalence of CKD and indicators was markedly higher than that in the population without HBV infection, respectively. The findings were consistent with the other studies. In the multicentric cross-sectional Hepatitis and Renal Parameters Evaluation (HARPE) study, 64.6% of the active or inactive HBV-infected patients were diagnosed as CKD.[17] Prevalence of proteinuria, hematuria, and eGFR less than 90 mL/min/1.73m^2 was 38.1%, 20.6%, and 45.5%, respectively.[17] The risk of CKD was 2.58 times high in subjects with HBV infection contrast to controls in the large cohort study.[18] A prospective cohort study determined that prevalence of decreased eGFR and CKD in patients with positive anti-HBc was more than in subjects without exposure to HBV, respectively.[19] A meta-analysis suggested an association between HBV infection and reduced glomerular filtration rate (GFR) in cross-sectional surveys.[20] However, there are different conclusions in the other research. Both the prevalence of albuminuria and decreased eGFR were not higher in subjects with HBV infection than in hepatitis-negative subjects among Japanese.[21] There were no significant links between HBV

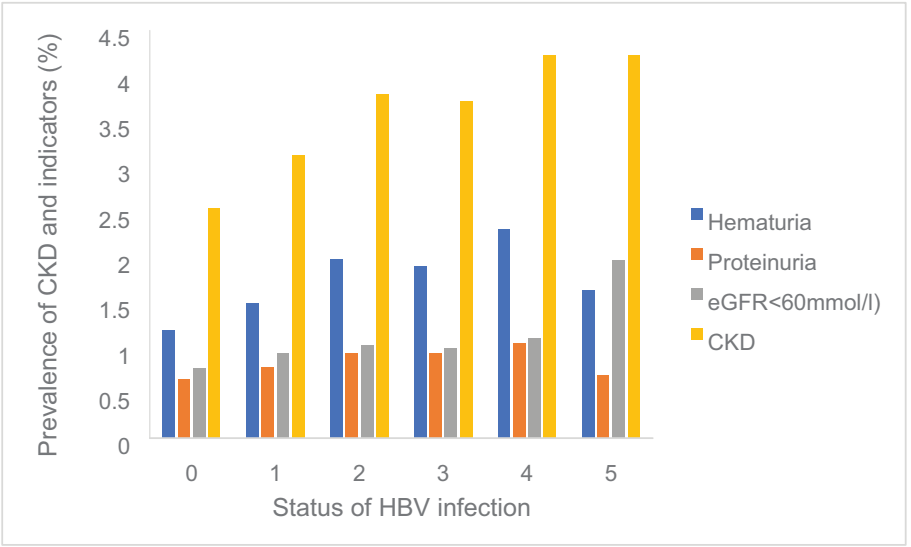

Figure 1. Comparison of prevalence of CKD and indicators according to status of HBV infection in the population aged 20 to 49 years in rural China.0. Non-HBV infection. 1. HBV infection Immune tolerant phase. 2. HBeAg-positive chronic HBV infection. 3. Inactive HBV carrier. 4. HBeAg-negative chronic HBV infection. 5. Resolved HBV infection. CKD = chronic kidney diseases, HBeAg = hepatitis B envelope antigen, HBV = hepatitis B virus.

infection and CKD, albuminuria or reduced eGFR in the hospital-based study.[22] No association between HBV sero-positive status and prevalence of proteinuria or CKD was observed in cross-sectional surveys.[7,20] The different results from the above studies might be attributed to several reasons. First lies in the variant definitions of HBV infection and CKD in different studies. HBV infection was defined as positive HBsAg and GFR was estimated using the Modification of Diet in Renal Disease (MDRD) Study equation in Taiwan and Tokyo study.[7,21] HBeAg and anti-HBe was not tested in the hospital-based study in China and hematuria was not defined as one of CKD markers.[22] This study analyzed the data according to the international definition and stratification of HBV and estimated GFR using chronic kidney disease epidemiology collaboration equation. Second, different demographic characteristics of the study population may cause various results. Gender distribution may play an important role. In most of the studies based on population, the percentage of HBsAg carrier was 1.5 to 2 times higher in men than in women.[23,24] HBV-related glomerular disease predominantly occurs in men.[25–27] The prevalence of HBeAg was significantly higher among women than among men.[28] From the above results, the diversity in male/female ratio may explain the different prevalence of CKD following HBV infection. Age difference can be another influence factor. The natural history of HBV-associated kidney disease improves gradually in younger patients, but continues to progress with a low remission rate in adults.[29] The prevalence of HBeAg reduced with age after adulthood in HBV carriers.[28] Average age of the population in this study was 26.99 ± 7.16 years, which was markedly lower than in the other studies. Third, some studies were based on the data from one hospital or local areas. The studies with small sample sizes may have the risk of bias.

Five major phases may appear in the natural history of HBV infection. These stages of infection may not arise sequentially in all patients. The transitions between the phases can be non-consecutive.[30] So it is necessary to clarify the association between every phase of HBV infection and CKD. In this study, CKD was highly prevalent in HBV-infected population, even in the status without elevated ALT, such as immune-tolerant phase, inactive HBV carrier, and resolved HBV infection. This study implied that HBV infection rather than hepatitis B alone was associated with CKD. The natural history of HBV infection is

Table 3

Risk factors for CKD in general population aged 20 to 49 years in rural China.

	OR (crude)			OR (adjusted)		
	Exp (B)	95% CI	*P*	Exp (B)	95% CI	*P*
Age (per year)	1.018	1.016–1.019	<.001	1.034	1.032–1.035	<.001
Female	2.043	2.013–2.073	<.001	2.259	2.224–2.294	<.001
Hypertension	1.616	1.570–1.664	<.001	1.652	1.603–1.702	<.001
Obesity	1.479	1.431–1.528	<.001	1.488	1.439–1.538	<.001
Status of HBV infection						
Non-HBV infection	1.000	Reference		1.000	Reference	
HBV immune tolerant phase	1.237	1.164–1.315	<.001	1.282	1.206–1.363	<.001
HBeAg-positive chronic HBV infection	1.514	1.406–1.631	<.001	1.551	1.439–1.671	<.001
Inactive HBV carrier	1.482	1.450–1.516	<.001	1.374	1.344–1.405	<.001
HBeAg-negative chronic HBV infection	1.696	1.628–1.767	<.001	1.591	1.527–1.658	<.001
Resolved HBV infection	1.698	1.431–2.016	<.001	1.629	1.372–1.935	<.001

CI = confidence interval, HBeAg = hepatitis B envelope antigen, HBV = hepatitis B virus, OR = odds ratio.

influenced by the complex interplay between host immune response and HBV replication.[2,8] The pathogenic mechanisms of HBV-related nephropathy have been uncertain. Serum of patients with chronic HBV infection was observed to induce renal tubular cells apoptosis.[4] HBV infection was also associated with oxidative stress and insulin resistance.[18] HBV antigens had been observed to express in kidney tissues, which may cause chronic immunologic injury and direct viral-induced pathological alterations.[23] The immunological deposits of HBV antigen and host antibody had been considered as the primary mechanism associated with kidney injury,[27] but the studies failed to reach agreement on which type of viral antigen would be the major etiological factor. HBeAg had been documented as the primary antigen in HBV-associated membranous nephropathy (MN).[23] Depositions of HBsAg, Hepatitis B Core Antigen (HBcAg), and HBeAg have been observed in HBV-associated MN.[23] HBsAg and HBcAg expressing in the renal tubular epithelial cells can upregulate complement-mediated inflammatory gene pathways that may contribute to the pathogenesis of kidney injury.[4] In every status of HBV infection, the pathogenic mechanisms of kidney injury need to be investigated further.

Antiviral therapy can relieve proteinuria effectively in the patients with HBV-MN.[5,31] The incidence of Hepatitis B virus associated glomerulonephritis in children has declined from 13.27% to 6.98% since putting HBV vaccination program into effect in Shanghai.[32] The association between HBV infection and CKD has been strengthened by above studies. This study confirmed that, in addition to the conventional risk factors for CKD, HBV infection was an additional risk factor in the population aged 20 to 49 years in rural China. The 13-year cohort study also verified that the risk of CKD was significantly more in the HBV-infected participants than in the non-HBV participants (6.2% vs. 2.7%).[18] The risk of end stage renal disease was significantly larger in the HBV-infected subjects than in the non-HBV subjects.[33] To sum up, on account of the result that HBV infection was a risk factor for CKD, the HBV-infected population should be targeted for monitoring for the occurrence and progress of CKD in rural China.

The study had the limitations as follows. First, HBV DNA is considered as a direct evidence of the viral load. HBV DNA testing faced great difficulty in the large investigation. This research used traditional HBeAg and anti-HBe as the marker of viral replication and infectivity. Diagnosis of HBV infection in this study was not fully complied with the definition that might result to the bias. Second, chronic HBV infection is defined as persistence of HBsAg beyond 6 months. In view of the negligible percentage of acute infection in adults with HBV infection, we did not confirm HBV sero-markers after 6 months which may lead to overrating prevalence of chronic HBV infection. Third, CKD should have indicators of kidney damage over three months according to Kidney Disease Improving Global Outcomes guideline. In this research, all the indicators of CKD were tested from single measurement, because repeated measures faced great difficulty in the large-scale investigation. No confirmation of dipstick urinalysis and serum creatinine would lead to overrating the CKD prevalence.

In population aged 20 to 49 years in rural China, prevalence of HBV infection including all status was tested to be 12.17%. A high prevalence of inactive HBV carrier characterized HBV infection. In the population with HBV infection, prevalence of proteinuria, hematuria, eGFR less than 60 L/min/1.73m^2, and CKD was 0.94%, 1.92%, 1.02%, and 3.85%, respectively, which was markedly higher than that in the population without HBV infection respectively. Compared with the population without HBV infection, prevalence of CKD and indicators was higher in the population in every status of HBV infection, respectively. Every status of HBV infection was identified as the independent risk factors for CKD in general population aged 20 to 49 years in rural China. HBV infection rather than Hepatitis B was associated with CKD. This study should have crucial influences on the government and clinicians to improve the surveillance and control strategy for HBV infection and CKD in rural China. The findings should alert clinicians to be aware that people with HBV infection might be at risk of CKD. The HBV-infected subjects in every status should complete urinalysis and renal function evaluation for monitoring the development of CKD. The patients with CKD in HBV highly endemic areas should be tested for HBV markers to identify risk factors.

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