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Association between liver cirrhosis and estimated glomerular filtration rates in patients with chronic HBV infection

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Abstract

To investigate the estimated glomerular filtration rates of chronic hepatitis B (CHB) patients with or without liver cirrhosis, and to explore the related risk factors.

A total of 559 CHB patients were enrolled. Liver cirrhosis was diagnosed with ultrasound. The Child-Pugh scoring system was used to stage patients with liver cirrhosis. The Modification of Diet in Renal Disease (MDRD) formula was used to calculate the estimated glomerular filtration rate (eGFR).

A total of 296 patients were involved. The results showed that the incidence of renal impairment in patients with liver cirrhosis was 8.45% (25/296). The incidence of renal impairment in Child-Pugh C patients was significantly higher than that in Child-Pugh B and Child-Pugh Grade A patients (i.e., 17.2% [17/99] vs 6.67% [7/105] vs 1.09% [1/92], respectively, $P < .001$); age, hyperuricemia, and Child-Pugh score are all risk factors for impaired renal function.

With the deterioration of liver function in patients with cirrhosis, the incidence of impaired renal function has increased significantly, and renal function should be closely monitored to guide patients in clinical medication.

Abbreviations: ADV = adefovir dipivoxil, CHB = chronic hepatitis B, CKD = chronic kidney disease, Cr = creatinine, eGFR = estimated glomerular filtration rate, ETV = entecavir, HBsAg = HBV surface antigen, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, LAM = lamivudine, LDT = telbivudine, MDR = modification of diet in renal disease, T2DM = type 2 diabetes, TDF = tenofovir disoproxil.

Keywords: Child-Pugh score, cirrhosis, estimated glomerular filtration rate, hepatitis B virus, renal function impairment

1. Introduction

Chronic hepatitis B (CHB) remains a global health burden.[1] It is reported that an estimated 240 million persons worldwide are chronically infected with hepatitis B virus (HBV), placing them at increased risk of developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC).[1,2] The Asia-Pacific region, including China, is a high-risk area for HBV infection.[3] Studies showed that the HBV surface antigen (HBsAg) carrier rate in the general population in China was 7.18%. There are ~93 million people with chronic HBV infection in China currently.[4]

In addition to causing liver damage such as chronic hepatitis and cirrhosis, HBV can also affect renal function through immune-mediated mechanisms.[5] HBV-related glomerular diseases occurring in patients with CHB are important causes of end-stage renal disease and renal replacement therapy.[6–8] Renal insufficiency is common in patients with HBV-related liver cirrhosis, and renal function impairment accompanied by hemodynamic changes will further exacerbate the decline in glomerular filtration rate, form hepatorenal syndrome, and increase patient mortality.[5,9–11] Studies found that among patients with CHB, the estimated glomerular filtration rates (eGFR) are significantly decreased.[12–14] However, until now, the difference in eGFR between CHB patients and CHB patients with cirrhosis is still unknown. There is also no study report on eGFR distribution in adult newly treated CHB patients with liver cirrhosis and the related risk factors.

Therefore, this study retrospectively analyzed the clinical data of CHB patients and CHB-related cirrhosis patients. The study aimed to evaluate the difference between CHB patients and CHB-cirrhosis patients, and to analyze the risk factors affecting renal function.

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Compliance with Ethical standards.

Ethical approval: The Institutional Review Board of Sixth People's Hospital had approved this study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent: Informed consent was obtained from all patients for inclusion in the study.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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2. Subjects and methods

2.1. Subjects

This study included CHB patients and HBV-related cirrhosis patients from January 1, 2015 to December 31, 2018. The enrollment criteria included: Subjects must

1. be aged over 18 years,
2. have hepatitis B surface antigen (HBsAg) positive for more than 6 months,[15,16]
3. not have received any anti-HBV treatment before.

Diagnosed with CHB related cirrhosis based on medical history and abdominal ultrasound. Conversely, patients were excluded when they met the following criteria:

1. evidence of co-infection with hepatitis C, hepatitis D, or human immunodeficiency virus,
2. have autoimmune liver disease, and
3. heavy alcohol consumption or alcohol abuse, defined as alcohol consumption of >10 g/day.[17]

The Institutional Review Board approved the study. Each enrolled patient provided written informed consent.

2.2. Patient information collection

Patient information was extracted from medical records, including demographic data, diagnosis of type 2 diabetes (T2DM), hyperuricemia, and kidney stones, which may be related to eGFR decline.[18–20] Data on liver function, HBV DNA quantification, and HBV serological marker were also collected. The unit of serum creatine is umoI/L, and the unit of ALT is U/L. Patients were classified according to the Child-Pugh score classification criteria: A score of 5 to 6 points was classified as A, 7 to 9 points was classified as B, and a score ≥10 points was classified as C.[21] HBV DNA was quantified using fluorescent quantitative PCR detection, HBV serological markers were applied using ELISA.

2.3. Renal function assessment

The GFR was estimated according to the MDRD formula recommended by the American Kidney Foundation, which is listed below: eGFR (mL/min/1.73 m^2) = 175*(serum creatinine)$^{-1.154}$*(age)$^{-0.203}$*(0.742 if female).

2.4. Statistical methods

The data were analyzed using the SPSS software (version 19; SPSS Inc, Chicago, IL). The comparison of variables was performed using the chi-square test or Student's *t* test when appropriate. Multivariate logistic regression analysis was used to analyze the risk factors of renal impairment. Values of $P < .05$ (two-sides) indicates statistical difference.

3. Results

3.1. Patient demographics

A total of 559 patients were involved. Among them, 212 were CHB patients without cirrhosis and 347 of them were CHB-related cirrhosis patients. The sex, age, ALT level, HBV DNA level, HBeAg status, proportion of nephrolith, T2DM, and hyperuricemia were similar for the two groups. Serum creatinine (Cr) was significantly higher in CHB-related cirrhosis patients ($P = .008$), as shown in Table 1.

Table 1

Baseline demographic and clinical characteristics by groups.

Variables	Chronic hepatitis B		*P*
	Without cirrhosis	With cirrhosis	
Sample size	212	347	
Sex, M/F	163/49	282/65	.212
Age, years	44.28 ± 10.38	45.93 ± 11.47	.087
ALT, U/L	105.42 ± 113.18	91.05 ± 102.68	.123
Serum Cr, umol/L	65.32 ± 63.18	81.18 ± 72.12	.008
HBV DNA log IU/mL	5.24 ± 1.18	5.31 ± 1.22	.505
HBeAg, positive/negative	58/154	75/272	.122
Nephrolith, Y/N	71/141	108/239	.561
T2DM, Y/N	31/181	42/305	.391
Hyperuricemia, Y/N	73/139	93/254	.056

3.2. Renal function impairment among CHB patients

Among the 559 patients involved, we analyzed the eGFR level between these two groups. The results are shown in Table 2. A total of 33 (15.6%) CHB patients had eGFR of 60–90 mL/min while 11(5.2%) patients had eGFR < 60 mL/min. In CHB-related cirrhosis patients, 85 (24.5%) patients had eGFR of 60 to 90 mL/min and 40 (11.5%) had eGFR < 60 mL/min. CHB-related cirrhosis patients showed a more severe renal function impairment ($P = .001$).

3.3. Risk factors related to impaired renal function in all patients involved

Univariate and multivariate analyses were conducted to explore the independent factors that affected decreased eGFR. The univariate analysis results showed that serum Cr, T2DM, hyperuricemia, and liver cirrhosis were the factors associated with the decrease in eGFR in CHB patients. However, multivariate analysis suggested that serum Cr ($P < .001$), T2DM ($P = .023$), and liver cirrhsosis ($P = .036$) were the independent factors that affected the decreased eGFR in CHB patients (Table 3).

3.4. Patient demographics among CHB-related cirrhosis patients

To further evaluate the association between liver cirrhosis and renal function in CHB patients, we compared the differences in patients' demographics in CHB-related cirrhosis patients. Among the 347 patients with cirrhosis, 192 staged with Child-Pugh A

Table 2

Proportion of renal function by groups.

Variables	Chronic hepatitis B		*P*
	Without cirrhosis	With cirrhosis	
Sample size	212	347	
e-GFR score			.001
≥90 mL/min	168	222	
60–90 mL/min	33	85	
<60 mL/min	11	40	

Table 3

Risk factors associated with impaired renal function in CHB.

	Univariate analysis			Multivariate analysis		
Variables	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Sex	0.842	0.413–1.648	.601			
Age	0.994	0.855–1.028	.855			
ALT	0.754	0.589–1.859	.169			
Serum Cr	1.852	1.690–3.156	<.001	1.147	1.239–2.847	<.001
HBV DNA log IU/mL	1.414	0.762–1.605	.467			
HBeAg, positive/negative	1.000	0.994–1.004	.928			
Nephrolith, Y/N	1.042	0.644–1.195	.547			
T2DM, Y/N	1.243	1.092–1.992	.012	1.122	1.087–1.796	.023
Hyperuricemia, Y/N	1.661	1.074–2.704	.009			
Cirrhosis, Y/N	1.188	1.016–1.997	.020	1.058	1.091–1.742	.036

and 155 staged with Child-Pugh B. Serum creatinine (Cr) was significantly higher in Child-Pugh B patients ($P = .047$) as shown in Table 4.

3.5. Renal function in patients with different Child-Pugh stage

The incidence of impaired renal function was different in patients with different Child-Pugh stage. In patients with Child-Pugh A, 42 had eGFR 60 to 90 mL/min and 15 had eGFR < 60 mL/min, while in Child-Pugh B, 43 patients who had eGFR 60 to 90 mL/min and 25 had eGFR < 60 mL/min ($P = .011$) as shown in Table 5.

3.6. Risk factors related to impaired renal function in liver cirrhosis patients

Univariate and multivariate analyses were conducted to explore the independent factors that affected decreased eGFR in CHB-related cirrhosis patients. The multivariate analysis suggested that serum Cr ($P < .001$), hyperuricemia ($P = .033$) and Child-Pugh score ($P = .030$) were the independent factors that affected the decreased eGFR in CHB-related cirrhosis patients (Table 6).

4. Discussion

In HBV infected patients, kidney damage can be caused by circulating immune complexes and in situ immune complexes.[22] Studies from Hong Kong found that 29% of HBV-associated nephritis developed into renal failure.[23,24] HBV-related liver cirrhosis is the end stage of liver disease.[25] Liver cirrhosis and the accompanying portal hypertension can lead to changes in systemic hemodynamics and damage to renal function.[25,26] Early renal damage is a functional change rather than an organic change, and timely treatment can reverse renal damage. Hence, the early identification of patients with renal impairment using risk factors could be an effective way for timely treatment. However, changes in renal function and the risk factors associated with decreased eGFR have not been reported yet. In our study, we found significantly more patients with impaired renal function in CHB-related cirrhosis compared with CHB patients. Moreover, among CHB-related cirrhosis patients, renal impairment was more severe in Child-Pugh B patients compared with Child-Pugh A patients. Multivariate analysis suggested that serum Cr, T2DM, and liver cirrhosis were the independent factors that affected decreased eGFR in CHB patients, while for patients with cirrhosis, serum Cr, hyperuricemia, and Child-Pugh score were the independent factors that affected decreased eGFR in cirrhosis patients.

An epidemiological survey showed that eGFR ≤60 mL/min accounted for 1.70% in Chinese population,[19] and there is no report on the decline of glomerular filtration rate in special populations (such as patients with HBV-related cirrhosis). Our study showed that among the 296 patients with newly diagnosed liver cirrhosis, the proportion of patients with impaired renal function was higher than that of the general population. The treatment guideline recommends that once a cirrhosis patient is diagnosed, the use of antiviral drugs should be determined.[27] However, oral anti-HBV drugs are excreted through the kidneys, so patients should be tested for eGFR before oral anti-HBV treatment.[5]

Currently, the antiviral drugs widely used in China's antiviral therapy include lamivudine (LAM), adefovir dipivoxil (ADV), telbivudine (LDT), entecavir (ETV), and tenofovir disoproxil

Table 4

Baseline demographic and clinical characteristics by groups.

	Chronic hepatitis B-related cirrhosis		
Variables	**Child-Pugh A**	**Child-Pugh B**	***P***
Sample size	192	155	
Sex, M/F	157/35	125/30	.789
Age, years	45.17 ± 11.29	46.49 ± 12.53	.303
ALT, U/L	96.87 ± 102.21	87.94 ± 106.51	.428
Serum Cr, umol/L	70.29 ± 62.92	85.31 ± 77.45	.047
HBV DNA log IU/mL	2.28 ± 1.34	2.39 ± 1.87	.524
HBeAg, positive/negative	43/149	32/123	.694
Nephrolith, Y/N	67/125	41/114	.091
T2DM, Y/N	24/168	18/137	.801
Hyperuricemia, Y/N	51/141	42/113	.911

Table 5

Proportion of renal function by groups.

	Chronic hepatitis B-related cirrhosis		
Variables	**Child-Pugh A**	**Child-Pugh B**	***P***
Sample size	192	155	
e-GFR score			.011
≥90 mL/min	135	87	
60–90 mL/min	42	43	
<60 mL/min	15	25	

Table 6

Risk factors associated with impaired renal function in CHB-related cirrhosis.

	Univariate analysis			Multivariate analysis		
Variables	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Sex	0.551	0.184–1.514	.261			
Age	0.998	0.904–1.812	.481			
ALT	0.568	0.281–2.395	.411			
Serum Cr	1.919	1.379–5.743	<.001	1.733	1.035–3.181	<.001
HBV DNA log IU/mL	0.813	0.325–2.545	.873			
HBeAg, positive/negative	1.032	0.749–1.847	.680			
Nephrolith, Y/N	1.901	0.282–2.097	.163			
T2DM, Y/N	1.042	1.004–2.188	.032			
Hyperuricemia, Y/N	1.661	1.087–3.525	.024	1.740	1.128–3.061	.033
Child-Pugh score	1.976	1.588–2.765	.011	1.395	1.510–2.564	.030

(TDF). Previous study on the effects of long-term treatment with nucleoside drugs on renal function have shown differences between different drugs.[5] A cohort study reported a significantly more eGFR <50 mL/min in the ADV treatment group than in the non-ADV group.[26] Other reports on LDT showed that it was possible to improve renal function in patients, but the specific mechanism had not been elucidated.[5] Therefore, for patients with CHB-related cirrhosis, even those with asymptomatic compensatory cirrhosis, the renal safety of antiviral drugs should be considered when selecting antiviral drugs. CHB patients may develop renal impairment through three mechanisms. First, HBV infection may cause kidney function changes through the deposition of immune complexes, such as membranous nephropathy and vascular membrane capillary nephritis. Secondly, patients with end-stage CHB disease and liver cirrhosis often have renal impairment, which can be due to many reasons, including insufficient renal perfusion due to lack of effective circulating blood volume. Third, since all currently available nucleoside drugs are eliminated in an unaltered form mainly by renal, these drugs are believed to be related to dose-dependent nephrotoxicity, especially nucleotide analogs.

A number of studies analyzing chronic kidney disease (CKD)-related risk factors have suggested that age, gender, hypertension, diabetes, hyperuricemia, renal cysts, and kidney stones are CKD-related risk factors.[18,20] Our study suggested serum Cr, T2DM, and liver cirrhosis were the independent factors that affected decreased eGFR in CHB patients, while for patients with cirrhosis, serum Cr, hyperuricemia, and Child-Pugh score were the independent factors that affected the decreased eGFR in cirrhosis patients. Hyperuricemia was a risk factor for impaired renal function, which was consistent with previous reports. In addition, this study suggests that Child-Pugh classification is also a risk factor for impaired renal function in patients with liver cirrhosis, suggesting that as liver disease progresses, renal function damage also gradually increases.

This study had some limitations. All the patients were from one medical center, a prospective multicenter study is thus necessary. In our study, we failed to explore further the reasons why hyperuricemia and liver cirrhosis contributed to the decreased eGFR. We believe that a well-designed controlled study is needed to answer these questions. Another potential limitation is that only HBV-related patients were included in our study. The value of our work will be higher if included results from non-HBV related cirrhosis as well. In order to explore the effect of HBV on renal function, a study of cirrhosis with different etiology is needed.

In summary, this study evaluated the eGFR levels in CHB and CHB-related cirrhosis patients. Based on the results, it is recommended that renal function should be reviewed regularly in this group of people to avoid the use of drugs with potential nephrotoxicity, and to adjust antiviral drugs according to renal function in a timely manner. This is especially important for hyperuricemia patients and high Child-Pugh score patients.

Author contributions

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