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Association of reduced renal function with different phase of chronic hepatitis B virus infection

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ABSTRACT

Background: The association between chronic hepatitis B virus (HBV) infection and the development of chronic kidney disease (CKD) remains controversial, and whether the cause is related to the different phases of chronic HBV infection remains unclear. **Methods:** A large cross-sectional study was performed to show the prevalence of reduced renal function during chronic HBV infection in adults from 7 multi-centers of Shenzhen City in China. Estimated glomerular filtration rate (eGFR) was used to evaluate the effect of HBV infection on the risk of renal impairment. **Results:** 33.04% HBsAg (+) patients had eGFR < 90, while patients without HBV exposure, 32.73% had eGFR < 90, showing no significant difference. There was no significant difference between those with elevated and normal alanine aminotransferase (ALT) in chronic hepatitis B (CHB) groups. Moreover, according to stratified statistics of different phases of the disease, liver cirrhosis, especially decompensated liver cirrhosis, hepatocellular carcinoma (HCC) showed a significant decrease in renal function compared with CBH (P = 0). Multivariate logistic regression analysis showed that liver disease different phases independently associated with reduced renal function. **Conclusion**: During the early CHB phase of chronic HBV infection (either elevated ALT or normal) did not increase the risk of renal dysfunction compares no exposure to HBV. However, when CHB progress to end-stage liver disease were associated with reduced kidney function. Additionally, Hoek formula should be recommended for patients with end-stage liver disease.

Key words: chronic hepatitis B, estimated glomerular filtration rate (eGFR), reduced renal function; nucleos(t)ide analogues (NAs) antiviral therapy

INTRODUCTION

Chronic kidney disease (CKD) has become an important public health problem in China. In Chinese adults, the incidence of CKD is rising throughout the country, with a prevalence of 10.8%.[1] CKD increases the risks for cardiovascular diseases and death.[2] A Chinese cross-

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sectional survey revealed that 33% and 1.6% of 4,7204 members of the general population had an eGFR of 60–89 mL/min/1.73 m^2 and 30–59 mL/min/1.73 m^2, respectively.[1] Given that CKD imposes a socioeconomic burden on the country's public health[3], identifying its associated risk factors is of great importance.[4]

Date from the first Shanghai community-based Chinese epidemiological other study on CKD patients, and the prevalence of CKD in the community population in Shanghai is 11.8%. All the factors including age, central obesity, hypertension, diabetes, anaemia, hyperuricaemia and nephrolithiasis are positively correlated with the development of CKD in this subject.[5] As we all know, Hepatitis B virus (HBV) infection is also a major public health issue that affects approximately 240 million people worldwide.[6] In China the prevalence of chronic HBV infection is 7.18%.[7] Some investigation has reported that renal function, assessed by the estimated glomerular filtration rate (eGFR), is frequently impaired in chronic HBV infection.[8] Over the past few decades, a strong association between HBV infection and renal disease has been discovered. The pathogenetic role of HBV infection in renal disease has been documented primarily by the demonstration of hepatitis B antigen-antibody complexes in renal lesions *via* immunofluorescence microscopy, including the deposition of HBV e Antigen (HBeAg) in membranous nephropathy.[9–11] HBV DNA and RNA have been localized to glomerular and tubular cells in infected patients.[12,13] However, whether HBV infection on kidney damage causes reduced renal function, different studies have different results. In the study of the relationship between HBV infection and CKD, Two cross-sectional studies[14,15] demonstrated a positive association of HBV with CKD. And a 13-year Taiwan, China cohort study reported that untreated chronic HBV infection was also associated with an increased risk of CKD.[16] However, another mainland China study found no association between HBV exposure and progression to CKD.[17] In the Japanese study, HCV infection was positively associated with low eGFR and with albuminuria, whereas prevalence of neither low eGFR nor albuminuria was greater in individuals with HBV infection than in hepatitis-negative subjects.[18] Another cross-sectional study in Taiwan, China found that hepatitis C virus (HCV) infection was significantly associated with the prevalence and severity of chronic kidney disease (CKD), but not with HBV infection.[19] A meta-study of Asian populations also showed that there was no association between exposure to HBV and the risk of developing CKD in Asian populations.[20]

Generally believe that chronic hepatitis B, especially closely related to decompensated cirrhosis and chronic kidney disease (CKD). The cross-sectional study in Beijing, China, HBV infection with elevated alanine aminotransferase (ALT), rather than HBV infection alone, was associated with reduced renal function.[21] This result demonstrated above indicates that elevated ALT probably related to eGFR in CHB patients. Besides, among decompensated patients, creatinine clearance < 70 mL/min was observed in 33% of patients with end-stage liver disease (ESLD).[22–25] In a clinical analysis of patients with liver cirrhosis, 62 of 298 subjects suffered renal dysfunction (eGFR of 60–89 mL/min/1.73 m^2), however, this renal dysfunction did not show that development of renal dysfunction in patients with liver cirrhosis was associated with cirrhosis stage by using simplified MDRD equation.[26]

Currently, five oral nucleos(t)ide analogues (NAs) antiviral treatments for chronic HBV infected patients are currently available. Some drugs have been confirmed to be nephrotoxic. Some study confirmed that renal impairment is frequently observed after long-term treatment with adefovir (ADV) or tenofovir (TDF).[27–30] These data demonstrated that eGFR of CHB patients could be declined due to long-term NAs usage. Therefore, the use of these drugs before to assess renal function is very important. However, there are many inconsistencies in the assessment results of renal function in the current studies on HBV-related liver diseases. These studies only investigate exposure to HBV and do not stratify the different stages of chronic HBV infection, such as chronic hepatitis, cirrhosis and liver cancer. It is still unclear whether the different stages of liver disease affect the assessment results of renal function. In China, the overall incidence of renal function decline in chronic HBV infection is not unsure, nor is it clear whether renal function is overestimated in end-stage liver disease using creatinine-based assessment formulas.

Therefore, in this large cross-sectional study, we enrolled patients with HBV infection from department of infection or liver diseases (both outpatient and hospitalization) at seven major hospitals in Shenzhen, southern China. The purpose of the present study is to investigate whether there is a difference in reduced renal function between patients with chronic HBV infection and the general population, as well, whether different stages of disease, including chronic hepatitis (normal and abnormal liver function), liver cirrhosis, liver cancer could affect renal function, providing clinical instructive significance of medical treatment.

MATERIALS AND METHODS

Study Population

A total of 7531 patients who met included criteria were recruited from January 2016 to December 2016 at 7 different hospitals (Shenzhen Traditional Chinese

Medicine Hospital, Shenzhen People's Hospital, the Third People's Hospital of Shenzhen, Peking University Shenzhen Hospital, Shenzhen Sixth People's Hospital, Baoan People's Hospital of Shenzhen, and Longgang District People's Hospital of Shenzhen) for this study. The baseline demographic and laboratory characteristics are listed in Table 1. Routine laboratory examination was conducted in all subjects.

The recruitment criteria were as follows: (1) hepatitis B surface antigen (HBsAg) negative; (2) HBsAg positive for more than 6 months, including chronic hepatitis B, HBV-related compensated/decompensated cirrhosis and hepatocellular carcinoma (HCC); (3) more than 16 years old and (4) signed informed consent to voluntarily participate in this clinical trial.

Patients with the following conditions were excluded: (1) under 18 years old; (2) coinfection with Human Immunodeficiency Virus (HIV), hepatitis A, C, D, E or G virus; (3) autoimmune hepatitis and alcoholic hepatitis; (4) treated with NAs antiviral drugs for more than 6 months; (5) pregnancy or lactation; (6) diagnosed with hypertension, diabetes, proteinuria, urinary calculi, active glomerulonephritis or other serious kidney diseases; and (7) serious mental diseases.

Of these patients, 5149 were HBsAg positive with antiviral naïve or have never received antiviral therapies and 2382 were HBsAg negative. A total of 6407 subjects were eligible, excluding hypertension, diabetes mellitus and proteinuria, among whom 4488 had HBsAg positive with no antiviral or prior antiviral therapy and 1919 had HBsAg negative.

Data Collection and Measurements

Data were collected at 7 local hospitals once the patients were enrolled into this study. Each patient's age, gender, cardiovascular diseases (myocardial infarction or stroke), history of hypertension, diabetes, kidney disease, nephrolithiasis, and nephrotoxic medications, including nonsteroidal anti-inflammatory drugs and herbs containing aristolochic acid were documented. BP was measured according to standard protocols. Blood samples from vein were collected after an overnight fast of 8–12 hours. Moreover, the early morning urine was measured for urinary albumin, creatinine and Cystatin C (Cys C). All blood and urine samples were analyzed at the central laboratory of each hospital. All the study laboratories successfully underwent a standardization and certification program. HBsAg and hepatitis C virus (HCV) antibodies were detected by chemiluminescence (Abbott Architecti2000SR), respectively. Serum HBsAg positivity was considered to be HBV infection. Fasting blood glucose, serum lipids, and ALT levels were measured using an OlympusAU5400 autoanalyzer (Olympus, Japan). Considering the gender disparity of the upper limit of normal (ULN) ALT, gender-specific ALT cutoffs were adopted in our study (ALT- was defined as < 30 U/L for female and < 40 U/L for male, ALT+ was defined as > 30 U/L for female and > 40 U/L for male). Similarly, gender-specific HLD-C cutoffs were performed as well (1.29 mmol/L for female and 1.03 mmol/L for male). Serum creatinine was determined using the Dimension TM clinical chemistry system (Dade Behring) with a commercial assay based on the Jaffe method. Cys C was analyzed with a fully automated latex-enhanced immunonephelometric method covering the range from 0.3–8 mg/L (N Latex Cystatin C Nephelometer II, Dade-Behring). To measure eGFR, blood was collected by venipuncture after an overnight fast of at least 10 hours. eGFR was calculated based on the equation developed by adaptation of the Modification of Diet in Renal Disease (MDRD) or Hoek formula, respectively. Reduced renal function was defined as an eGFR less than 90 mL/min/1.73 m^2. eGFR was calculated according to the following formulae:

MDRD = 175 × Scr - 1.234 × age - 0.179 (if female, × 0.79) where Scr is serum creatinine concentration (in mg/dL) and age in years.[31,32]

Hoek formulae: eGFR = -4.32 + 80.35 × 1/Cys C.[33]

Albuminuria was measured by immunoturbidimetric tests. Urinary creatinine was measured using an enzymatic method. The urinary albumin to creatinine ratio (ACR; mg/g) was calculated. ACR greater than 30 mg/g was defined as albuminuria. Proteinuria was defined as the concentration of urinary albumin more than 20 mg/L. Diabetes was defined as the fasting serum glucose concentration greater than 7.0 mmol/L or a previous diagnosis of diabetes. Hypertension was defined as the systolic blood pressure (BP) > 140 mm Hg or diastolic BP > 90 mm Hg or by the use of antihypertensive medications in the previous 2 weeks. Serum total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG), and uric acid were measured with commercially available reagents. LDL-C and HDL-C were detected by a timed-endpoint colorimetric method.

Statistical Analyses

Population characteristics are expressed as the mean and standard deviation (mean ± SD) or median (interquartile range) for continuous variables and as frequencies or percentages for categorical variables. Qualitative and quantitative differences between two subgroups were analyzed by the chi-square test for categorical parameters and Student's *t*-test or Mann-Whitney's test for continuous parameters.

Table 1: Demographic and clinical characteristics of subjects

Variable		Total *N* = 7531 (%)	HBsAg (+) (*n* = 5149) (%)	HBsAg (-) (*n* = 2382) (%)	*P*
Gender	Male	4610 (61.21)	3191 (61.97)	1419 (59.57)	0.047
	Female	2921 (38.79)	1958 (38.03)	963 (40.43)	
Age	Total	42.58 ± 13.04	40.65 ± 12.68	43.98 ± 12.63	0
	<30	1227 (16.29)	1032 (20.04)	195 (8.19)	0
	30–39	2298 (30.51)	1712 (33.25)	586 (24.60)	0
	40–49	1801 (23.91)	1089 (21.15)	712 (29.89)	0
	≥50	2205 (29.29)	1316 (25.56)	889 (37.32)	0
ALT	M > 40 U/L F > 30 U/L	3500 (46.47)	2746 (53.33)	754 (31.65)	0
Lipidemia	TG (≥ 1.7mmol/L)	1591(21.13)	1086 (21.09)	505 (21.20)	0.914
	HDL cholesterol M ≥ 1.03 mmol/L F ≥ 1.29 mmol/L	4145 (55.04)	2836 (55.08)	1309 (54.95)	0.919
	Blood glucose (>5.6 μmol/L)	1122 (14.90)	677 (13.15)	445 (18.68)	0
	Uric acid (μmol/L)	324.97 ± 96.66	322.37 ± 97.26	326.58 ± 97.22	0.081
	Cystatin C (mg/L)	1.04 ± 0.43	1.09 ± 0.53	0.96 ± 0.20	0.295
Uric examination	Proteinuria (+)	171 (2.27)	139 (2.70)	32 (1.34)	0
	Hematuria (+)	660 (8.76)	429 (8.33)	231 (9.70)	0.051
Complication	Hypertension	432 (5.74)	261 (5.07)	171 (7.18)	0
	Diabetes	432 (5.74)	222 (4.31)	210 (8.82)	0
	Hypertension and diabetes	16 (0.21)	9 (0.17)	7 (0.36)	0.225
	Hypertension or diabetes with proteinuria	73 (0.97)	30 (0.58)	43 (2.24)	0
	CHB	4355 (57.83)	4355 (84.58)	0 (0)	/
	Compensation	344 (4.57)	344 (6.68)	0 (0)	/
	Decompensation	173 (2.30)	173 (3.36)	0 (0)	/
	HCC	277 (3.68)	277 (5.38)	0 (0)	/
	eGFR (mL/min/1.73 m^2)	101.51 ± 31.33	101.16 ± 31.73	101.74 ± 30.44	0.455

Categorical data were presented as number (%), continuous data were expressed as median and interquartile range. The Mann-Whitney test and chi-square test were used. ALT, alanine amino transferase; TG, triglyceride; HDL, high density lipoprotein; CHB, chronic hepatitis B; HCC, hepatocellular carcinoma. /: n of HBsAg(-) patients is 0, no comparisons.

We used the matching method to reduce significant differences in age and sex between the HBsAg (+) and HBsAg (-) groups. Using multiple logistic regression analysis, a matching was estimated for all patients. Multivariable odds ratios (ORs) with 95% CIs were reported as well. Covariates included in the multivariable logistic regression models were age, gender, history of hematuria, course of disease, levels of ALT, TG, HDL-C, BG and UA. Traditionally, these factors will affect the changes in eGFR. Factors affecting eGFR were assigned as follows: gender (female, male); age (< 40 year, ≥ 40 year); ALT (female < 30 U/L, ≥ 30 U/L; male < 40 U/L, ≥ 40 U/L); TG (< 1.7 mmol/L; ≥ 1.7 mmol/L); HDL-C (male < 1.03 mmol/L, ≥ 1.03 mmol/L; female < 1.29 mmol/L, ≥ 1.29 mmol/L); BG (< 5.6 μmol/L, ≥ 5.6 μmol/L); UA (< 420 μmol/, ≥ 420 μmol/L); hematuria (negative; positive); CHB (negative means cirrhosis or HCC; positive); among others. Whether there was a renal impairment remained to be an observation target, regarded as a binary dependent variable. All the independent variables were firstly analyzed by univariate logistic regression, and sequentially performed by multivariate logistic regression analysis according to statistical results and clinical experience.

P-values of less than 0.05 were regarded as statistically significant. All data analyses were performed using SPSS 22.0 software (SPSS Inc, Chicago, IL, USA).

RESULTS

Demographic and clinical characteristics of the study population

There were 1,0251 people recruited, of whom 2720 HBsAg positive with antiviral therapy for 6 months, and 7531 eligible the enrollment criteria. Of these populations, 5149 had HBsAg positive with never

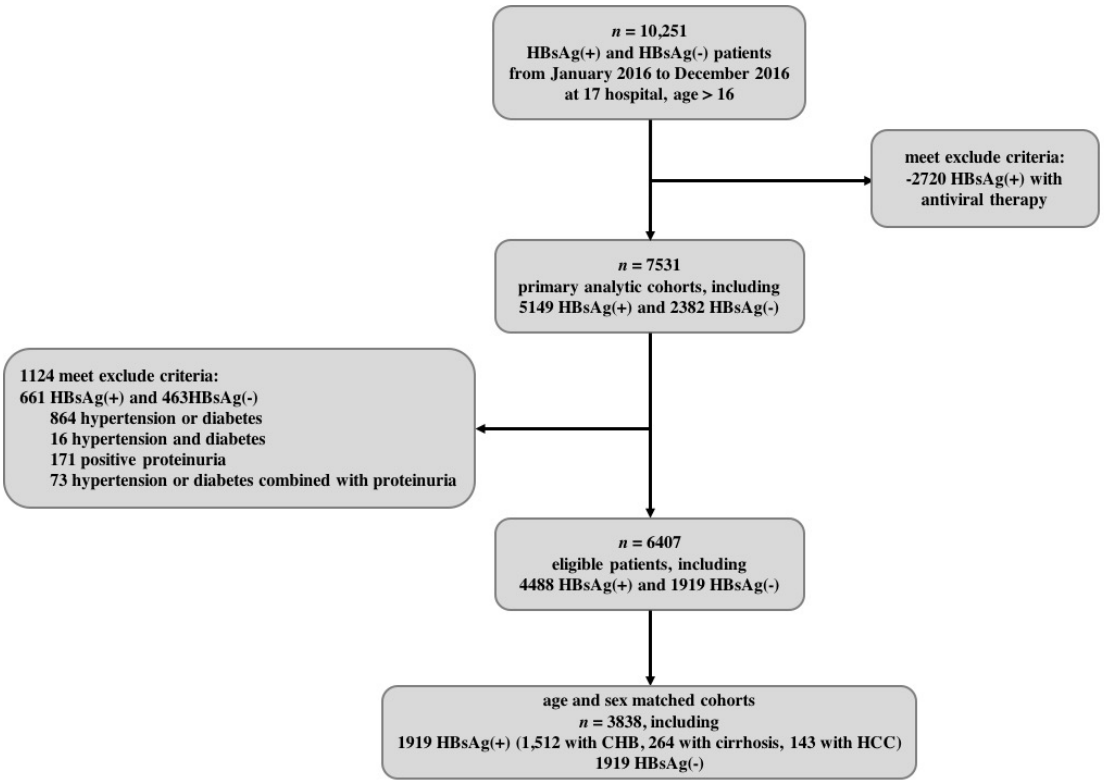

Figure 1. Flowchart of selection of study population.

received any antiviral treatment and 2382 had HBsAg negative. Antiviral treatment was defined as the use of a NAs, including five oral antiviral drugs.

A total of 1124 patients was excluded. Among them, 864 cases were diagnosed with hypertension or diabetes, 16 cases with hypertension and diabetes were treated with antihypertensive or hypoglycemic therapy, 171 cases with positive proteinuria, and 73 cases with hypertension or diabetes combined with proteinuria (Figure 1).

The reduced eGFR had no association between HBsAg (+) and HBsAg (-)

There were 6407 patients who were eligible with excluded hypertension, diabetes mellitus and proteinuria, among whom 4488 with HBsAg (+) and 1919 had HBsAg (-) (Table 2). The eGFR for HBsAg (+) and HBsAg (-) was 101.36 ± 30.23 mL/min/1.73 m^2 and 102.24 ± 30.16 mL/min/1.73 m^2, respectively. There is no significant difference between them (P = 0.286; Table 2). The matching process resulted in a matched sample size that consisted of 1919 patients in each group (Table 2). In the matched cohort study, 33.04% (634/1919; 95% CI: 0.312–0.349) HBsAg (+) patients had eGFR < 90, while patients without HBV exposure, 32.73% (628/1919; 95% CI: 0.309–0.319) had eGFR < 90, which showed no significant difference. (P > 0.05; Table 2).

Elevated ALT did not show significant difference in eGFR in CHB patients

Total of matching 1919 chronic HBV infection, patients without antiviral treatment or prior antiviral, among 1512 patients were CHB (normal ALT and abnormal ALT). Age and gender were no different in the normal and abnormal ALT groups (P = 0.078). 59.52% (95% CI: 0.576–0.614) of 1919 CHB patients had elevated ALT and 30.77% (95% CI: 0.284–0.331) had an eGFR < 90 mL/min/1.73 m^2. There were 40.50% patients with normal ALT (95% CI: 0.386–0.425) and 34.44% with eGFR < 90 mL/min/1.73 m^2 (95% CI: 0.315–0.374). This difference was not significant (P = 0.057; Figure 2).

Association of eGFR with different phases of chronic HBV Infection

Chronic HBV infection is a dynamic process reflecting the interaction between HBV replication and the host immune response. Usually, the progression of chronic HBV infection has been schematically divided into 4 stages, including CHB, compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma (HCC). Of 1512 patients, 78.79% had CHB, cirrhotic patients' liver function of 175(9.12%) were compensated, 89(4.64%) were decompensated. Moreover, 143(7.4%) had HCC. CHB patients with eGFR < 90 mL/min/1.73 m^2 accounted for 34.33% (95% CI: 0.330–0.363), compensation for 37.14% (95% CI: 0.338–0.416), decompensation for 33.71% (95% CI:

Table 2: The eGFR of HBsAg (+) patients and HBsAg (-) population in different subgroups

Characteristics	Pooled cohort			Matched cohort		
	HBsAg (+) (*n* = 4488)	HBsAg (-) (*n* = 1919)	*P*	HBsAg (+) (*n* = 1919)	HBsAg (-) (*n* = 1919)	*P*
Age (years)	40 ± 12	42 ± 13	0.029	42 ± 13	42 ± 13	0.870
Male N (%)	2852 (63.54)	1171 (61.02)	0.055	1171 (61.02)	1171 (61.02)	0.450
Female N (%)	1636 (36.46)	748 (38.98)	0.055	748 (38.98)	748 (38.98)	0.670
eGFR (mL/min/1.73 m^2)	101.36 ± 30.23	102.24 ± 30.16	0.286	101.96 ± 20.12	102.11 ± 19.68	0.815
≥90	2930 (65.29)	1273 (66.34)	0.417	1285 (66.96)	1291 (67.27)	0.837
60–89	1451 (32.33)	603 (31.42)	0.476	595 (31.01)	590 (30.75)	0.861
30–59	88 (1.96)	36 (1.88)	0.821	33 (1.72)	31 (1.62)	0.801
15–29	11 (0.25)	7 (0.36)	0.407	6 (0.31)	7 (0.36)	0.781
<15	0 (0)	0 (0)	1.000	0	0	1.000

Table 3: Prevalence of renal function in patients with different stages

Stage	CHB *N* (%)	Prevalence	Compensation *N* (%)	Prevalence	Decompensation *N* (%)	Prevalence	HCC *N* (%)	Prevalence	Total
	1512 (78.79)	(95% CI)	175 (9.12%)	(95% CI)	89 (4.64)	(95% CI)	143 (7.45)	(95% CI)	1919 (100)
CKD Stage 1 (≥90)	993 (65.67)	0.640–0.673	110 (62.86)	0.593–0.670	59 (66.29)	0.594–0.702	85 (59.44)	0.544–0.644	1247 (64.98)
CKD Stage 2 (60–89)	503 (33.27)	0.316–0.349	62 (35.43)	0.314–0.390	27 (30.34)	0.249–0.355	44 (30.77)	0.262–0.356	636 (33.14)
CKD Stage 3 (30–59)	16 (1.06)	0.007–0.014	3 (1.71)	0.006–0.026	3 (3.37)	0.009–0.046	8 (5.59)	0.035–0.083	30 (1.56)
CKD Stage 4 15–29	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (2.80)	0.01–0.043	4 (0.21)
CKD Stage 5 <15	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.40)	0–0.021	2 (0.11)
P			0.604		0.135		0		

CI, confidence interval. *P* values were compared with total eGFR < 90 mL/min/1.73 m^2 in every subgroup (chi-square test). eGFR was calculated according to MDRD formula. Data are given as Mean ± standard deviation. $^*P$: compared with the compensated subgroup by Hoek formula. CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; CKD, chronic kidney disease; MDRD, modification of diet in renal disease.

0.292–0.402), and HCC for 40.56% (95% CI: 0.544–0.644). There were no significant differences between the CHB patients and compensated/decompensated cirrhotic patients ($P = 0.604$, $P = 0.135$; Table 3).

However, the ratio of eGFR in CHB and cirrhotic patients differs by MDRD and Hoek assessments. Among a total of 1512 patients with CHB and 264 patients with cirrhosis (175 compensation and 89 decompensation), the eGFR of CHB patients was 101.99 ± 28.86 and 90.98 ± 8.98 mL/min/1.73 m^2, the eGFR of compensated cirrhosis was 101.83 ± 25.17 and 80.03 ± 1.35 mL/min/1.73 m^2, and the eGFR of decompensated cirrhosis was 100.67 ± 32.65 and 77.86 ± 11.15 mL/min/1.73 m^2, according to the MDRD formula and Hoek formula, respectively. Tables 4 and 5 show that there were no significant differences in eGFR between CHB patients and compensated/decompensated patients using the MDRD formula. However, when the Hoek formula was applied to calculate the eGFR, compared with patients with CHB, patients with compensated/decompensated cirrhosis had reduced renal function ($P = 0$). Furthermore, by Hoek formula, compensated compared with decompensated and HCC subgroup, the eGFR of the decompensated was significantly decreased ($P = 0.012$), while there was no difference compared with HCC ($P = 0.113$). However, the eGFR of compensated and HCC subjects remained comparable ($P = 0.795$). There was a significant difference between CHB and HCC assessed by MDRD or Hoek formula ($P = 0.005$, $P = 0$).

We used the matching method to reduce significant

Table 4: The eGFR of HBsAg (+) patients and HBsAg (-) population (Pooled cohort)

Characteristics	CHB (1512)	Compensation (175)	*P*	Decompensation (89)	*P*	HCC (143)	*P*
Male N (%)	909 (60.12)	114 (65.14)	0.198	60 (67.42)	0.171	102 (71.33)	0.009
Age (years)	38 ± 13	50 ± 16	0	51 ± 18	0	53 ± 15	
eGFR (mL/min/1.73 m^2)	101.99 ± 28.86	101.33 ± 25.17	0.772	100.67 ± 32.65	0.677	94.91 ± 30.32	0.005
Hoek formula	90.98 ± 8.98	80.03 ± 1.35	0	77.86 ± 11.15	0/0.012*	78.32 ± 14.16	0/0.013*

P-values were compared with CHB group in every subgroup. *P: compared with compensated cirrhosis in decompensated and HCC (chi-square test or *t*-test). eGFR was calculated according to MDRD formula. CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; MDRD, modification of diet in renal disease.

Table 5: The eGFR of HBsAg (+) patients and HBsAg (-) population (Matched cohort)

Characteristics	CHB (175)	Compensation (175)	*P*	CHB(89)	Decompensation (89)	*P*	CHB (143)	HCC (143)	*P*
Male N (%)	114 (65.14)	114 (65.14)	1	60 (67.42)	60 (67.42)	1	10 2 (71.33)	102 (71.33)	1
Age (years)	50 ± 16	50 ± 16	1	51 ± 18	51 ± 18	1	53 ± 15	53 ± 15	1
eGFR (mL/min/1.73 m^2)	101.56 ± 33.12	101.33 ±25.17	0.942	100.97 ± 22.5	100.67 ± 32.65	0.943	99.17 ± 28.15	94.91 ± 30.32	0.219
Hoek formula	88.37 ± 1.86	80.03 ± 1.35	0	87.18 ± 10.51	77.86 ± 11.15	0	88.87 ± 12.13	78.32 ± 14.16	0

P-values were compared with CHB group in every subgroup. *P: compared with compensated cirrhosis in decompensated and HCC (chi-square test or *t*-test). eGFR was calculated according to MDRD formula. CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; MDRD, modification of diet in renal disease.

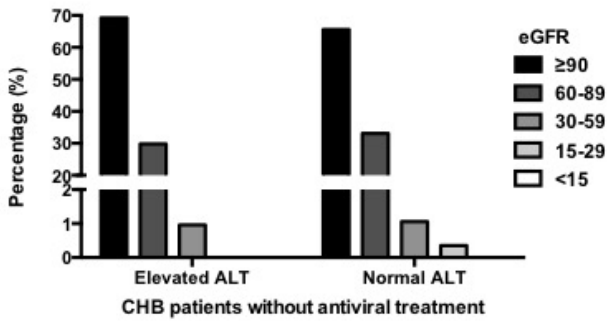

Figure 2. Impact of ALT level on renal function of CHB patients without antiviral treatment. Columns represent percentage of patients in different eGFR level (mL/min/1.73 m^2). Compared with normal ALT groups, *P*-value of elevated ALT groups was 0.057 by Chi-square test. ALT, alanine aminotransferase; CHB, chronic hepatitis B.

differences in age and sex, and matched CHB with cirrhosis, decompensated cirrhosis and HCC one by one, showing that eGFR decreased with age, but the results of matched cohort were consistent with Pooled cohort.

The univariate and multivariate logistic regression models in the presence of reduced renal function

To allow a common ground for comparison between the two cohorts, we used matching with selected key characteristics in age and sex. And exclude factors that hypertension, diabetes, Proteinuria positively correlated with the development of CKD. The matching process resulted in a matched sample size that consisted of 1919 patients in each group (Table 2). Table 6 shows the univariate and multivariate logistic regression models for factors associated with reduced renal function. Age, metabolic syndrome (HDL-C male ≥ 1.03 mmol/L, female ≥ 1.29 mmol/L), BG (> 5.6 μmol/L), UA (> 420 μmol/L) and Hematuria (+) were independently associated with reduced renal function. However, elevated serum ALT did not show any risk in CHB patients. Decompensated cirrhosis was an independent risk factor for reduced renal function in different stages of chronic hepatitis B.

DISCUSSION

eGFR plays a major role as an indicator of kidney function, allowing the assessment and management of CKD. In a real world study, it is reported that renal function impairment, identified as eGRF < 90 mL/min/1.73 m^2, is a common complication in patients with chronic HBV infection.[27,34] A study reported by Zhang *et al.* showed that in an epidemiological survey of CKD in China, 34.8 % of the total population had an eGFR < 90 mL/min/1.73 m^2.[1] However, in China, what is the rate of reduced renal function in patients with chronic HBV infection? Is HBV exposure related to renal function decline? Different studies have obtained different results, and what are the reasons?

Our study is the largest to date investigation of eGFR in patients with HBV infection in China. This present study containing 7531 subjects, excluding the most important factors affecting renal function, 4488 cases of chronic HBV infection and 1919 HBsAg (-) were counted, and the results showed that the prevalence of

Table 6: Multivariable logistic regression models for the prevalence of renal function

Variable		Total (*N* =1919)		Total (*N* = 1919)	
		Univariate odds ratio (95% CI)	Multivariate odds ratio (95% CI)	Univariate odds ratio (95% CI)	Multivariate odds ratio (95% CI)
Sex		1.015 (0.888–1.161)		0.943 (0.815–1.091)	
Age		1.247 (1.149–1.353)*	1.013 (1.001–1.396)*	1.212 (1.073–1.369)*	
ALT (M > 40 U/L, F > 30 U/L)		0.935 (0.818–1.069)		1.154 (0.999–1.333)	
Lipidemia	TG (≥1.7mmol/L) (%)	0.844 (0.720–0.989)*		1.181 (0.992–1.406)	
	HDL cholesterol (%)	1.189 (0.059–1.335)	1.169 (1.047–1.306)*	1.311 (1.100–1.562)*	1.186 (1.052–1.339)*
	M ≥ 1.03 mmol/L				
	F ≥ 1.29 mmol/L)				
	Blood glucose	1.215 (1.013–1.425)*	1.292 (1.112–1.500)*	1.311 (1.100–1.562)*	1.336 (1.122–1.591)*
	(> 5.6 μmol/L) (%)				
	Uric acid (μmol/L)	2.025 (1.765–2.387)*	2.063 (1.776–2.397)*	1.972 (1.667–1.334)*	1.978 (1.673–2.339)*
	Hematuria (+) (%)	1.029 (1.014–1.482)*	1.098 (1.014–1.931)*	1.139 (1.049–1.642)*	1.181 (1.074–2.013)*
	Compensation (%)				
	MDRD formula	1.008 (0.806–1.261)			
	Hoek formula	1.913 (1.151–2.233)*			
	Decompensation (%)				
	MDRD formula	1.058 (0.873–1.282)			
	Hoek formula	2.136 (1.715–2.435)*			
	HCC (%)				
	MDRD formula	1.129 (0.670–1.901)			
	Hoek formula	2.313 (1.631–2.519)*			

*P-value < 0.05. ALT, alanine aminotransferase, M, male; F, female; TG, triglycerides; HDL, high density lipoprotein; CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; MDRD, modification of diet in renal disease.

CKD in chronic HBV infection was 33.04% with matched cohort. In 1919 patients without HBV exposure, 32.73% had eGFR < 90, and the difference was not statistically significant. Excluding age and sex, the two most important confounders, in the matched sample size of 1919 patients' results were the same as above.

In patients with chronic HBV infection, our study did not find an increased risk of renal impairment with chronic HBV infection compared with no exposure to HBV. As we know, chronic HBV infection also includes cirrhosis (both compensatory and decompensated), and HBV-related HCC. It need point out that in this study, 78.79% of patients were chronic hepatitis B (including ALT normal and abnormal). The uneven sample distribution may lead to the deviation of the study. Therefore, stratification analysis is necessary to the different stages of renal function reduction in patients with chronic HBV infection.

In a multivariate analysis, HBsAg positivity was an independent factor associated with GFR < 60 mL/min/1.73 m^2 along with age, blood levels of albumin, bilirubin, anemia.[35] However, there is still no reliable data demonstrating whether different stages of chronic HBV progression are associated with reduced eGFR so far. In CHB patients, ALT is usually an indicator of the natural history of chronic HBV infection.[9,36] Once patients are infected with HBV, the host immune response to HBV is activated which induces an elevation of ALT.[8,11,33,34] However, it remains unknown whether elevated ALT is in connection with reduced eGFR in hepatitis B phase. A previous study reported that renal dysfunction of CHB patients with elevated ALT is four times higher than those without HBV infection. However, there existed relatively large sampling error in this study due to a total of 300 HBV-infected subjects enrolled. Through analysis of our large scale (1512, elevated ALT had 900) of CHB patients with elevated ALT, compared with those with normal ALT, the results did not exhibit marked difference in renal function, which further confirmed that elevated ALT did not significantly affect eGFR during chronic hepatitis B phase.

It is generally considered that HBV can be mediated by immune mechanisms, subsequently affecting kidney

function. In addition, renal dysfunction is common in patients with HBV-related cirrhosis.[11,37] Axelsen *et al.* revealed that there existed glomerular damage, with minimal lesions and, most commonly, glomerular sclerosis in patients with cirrhosis by kidney biopsy.[38] Renal dysfunction can be caused by many factors, such as hypertension, diabetes, urinary calculi, drugs and the like. To obtain a more accurate understanding of HBV-related cirrhosis complicated by renal function impairment, we excluded people with CKD and those risk factors mentioned above. Our results discovered that in chronic HBV infected patients with compensated or decompensated cirrhosis, the ratios of damage eGFR were 37.14% and 33.71%, respectively by MDRD assessment. Compared with the chronic hepatitis B, eGFR (34.13%) of patients with cirrhosis and decompensated cirrhosis had no significant difference. By Hoek formulae, however, we found that there are significant differences between them, all *P*-value < 0.001 (Tables 4 and 5). Furthermore, distinct from previous studies, our study revealed that development of renal dysfunction (eGFR < 90 mL/min/1.73 m^2) was associated with hepatic cirrhosis stage.

Although some of the past pathological studies have found that chronic HBV-infected patients with decompensated cirrhosis and HCC would develop kidney damage, even acute kidney injury (AKI) and hepatorenal syndrome (HRS), but some previous studies suggested that compensation and decompensation did not show different impact on eGFR.[25] This paradox is likely due to the MDRD or CKD-EPI assessment, based on creatinine as the main evaluation index, which is currently the most commonly used. Various factors, including diet, exercise, metabolism, could cause the reduction of serum creatinine to the level lower than expected based on a known GFR level. In addition to malnutrition and reduced muscle mass, it has been shown that creatinine synthesis itself may be reduced by 40%–50% in patients with cirrhosis.[38–40] Studies reveal that eGFR calculated by the CKD-EPI formula can better reflect the renal function of general people and mild renal impairment.[41] In our research, the results showed that the eGFR calculated by CKD-EPI was slightly lower than that by MDRD formula, but there was still no statistical difference in renal function at different stages of CHB. This further demonstrates that creatinine cannot respond to renal function in different stages of CHB[37], because they usually overestimate GFR. However, cystatin C, a cationic 13-kDa protein that is produced by nucleated cells and catabolized by renal tubular cells after traversing the glomerular filter, has recently been reported as a reliable endogenous marker of GFR in healthy adults and children as well as in patients with nephrologic, urologic, and rheumatologic disorders. Many studies have revealed that Hoek formula, based on Cys C, shows a significantly higher sensitivity for detecting reduced eGFR, in agreement with our study findings.[40] The bias of the Hoek formula is significantly smaller than that of the MDRD equation. Accuracy within 30% and 50% of the true GFR is best for the Hoek formula, especially in those patients with serious liver disesaes.[42–44] Decompensated cirrhosis was the independent factor of renal function decline by the univariate and multivariate logistic regression models. Owing to over-estimation of renal function in patients with cirrhosis assessed by MDRD formula, Hoek formula is more useful for doctors to estimate cirrhosis patients' renal function and to guide therapy.

This study demonstrated that the progression of chronic HBV infection is associated with an increased risk of CKD. In the other word, the progression of the disease leads to continuous damage to liver function, which in turn leads to decreased renal function. Therefore, to investigate the renal function in different stages of chronic HBV infection can the relationship between chronic HBV infection and function be more accurately answered. In addition, above study was no difference in eGFR at different stages of cirrhosis, the reason be used MDRD formula which overestimated renal function in decompensated cirrhosis phase.

Our study has some potential limitations. Its cross-sectional design makes it difficult to infer causality. Additionally, our results may have been derived from patients with an underlying condition. Since the subjects in our study was enrolled in the liver disease division of 7 hospitals, only represent the patient that examines during this period. Although HBsAg (-) is a patient of outpatient in physical examination, community population were not enrolled in this investigation, so it does not represent the general population.

In conclusion, the relationship between chronic HBV infection and renal function injury needs to be observed from the perspective of disease development, and the impact of different disease phase of the function is obviously different. There is no significant difference in the eGFR of chronic hepatitis B phase (including normal and abnormal ALT) and non-HBV infection. However, once the disease develops into liver cirrhosis, especially decompensated stage and HCC stage, with the aggravation of liver damage, kidney damage was deteriorating and renal function decreased significantly. In addition, Hoek assessment, more accurate than MDRD, should be recommended for patients with cirrhosis, especially with decompensated cirrhosis.

DECLARATION

Author contributions

Tong G and Zhong W acquired funding. Peng D, Jiang

X and Zhou T analyzed the results. Huang F, Tian C, Wei C, Xing Y, Yuan J, Yang J (jian Yang), Wu J, Yang J (Jiong Yang), Huang C and Qu Z conducted the experiment. Zhong W wrote the original draft. Tong G conceived supervised the study and revised the manuscript. All the authors approved the final version.

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Informed consent

The authors declare that they have obtained the patient's informed consent to publish in this article.

Ethics approval

This study was conducted in accordance with the Helsinki Declaration of 1975, approved by the ethics committees of Shenzhen Traditional Chinese Medical Hospital (CSTM-2015-07).

Conflict of interest

The author declares no conflict of interest.

Data sharing

The data presented in this study are available on request from the corresponding author.

REFERENCES

1. Zhang L, Wang F, Wang L, *et al.* Prevalence of chronic kidney disease in China: a cross-sectional survey. *Lancet.*. 2012;379(9818):815–822.
2. Wright J, Hutchison A. Cardiovascular disease in patients with chronic kidney disease. V. *asc Health Risk Manag.*. 2009; 5:713–722.
3. Foley RN. Temporal trends in the burden of chronic kidney disease in the United States. Curr Opin Nephrol Hypertens 2010;19:273–277.
4. Stengel B, Billon S, Van Dijk PC, *et al.* Trends in the incidence of renal replacement therapy for end-stage renal disease in Europe, 1990-1999. *Nephrol Dial Transplant.*. 2003;18(9):1824–1833.
5. Chen N, Wang W, Huang Y, *et al.* Community-based study on CKD subjects and the associated risk factors. *Nephrol Dial Transplant.*. 2009;24(7):2117–2123.
6. Li W. The hepatitis B virus receptor. *Annu Rev Cell Dev Biol.*. 2015;31:125–147.
7. Liang X, Bi S, Yang W, *et al.* Epidemiological serosurvey of hepatitis B in China--declining HBV prevalence due to hepatitis B vaccination. *Vaccine.* 2009;27(47):6550–6557.
8. Ganem D, Prince AM. Hepatitis B virus infection-natural history and clinical consequences. *N Engl J Med.*. 2004;350(11):1118–1129.
9. Johnson RJ, Couser WG. Hepatitis B infection and renal disease: clinical, immunopathogenetic and therapeutic considerations. *Kidney Int.*. 1990;37(2):663–676.
10. Takekoshi Y, Tochimaru H, Nagata Y, Itami N. Immunopathogenetic mechanisms of hepatitis B virus-related glomerulopathy. *Kidney Int Suppl.*. 1991;35:34–39.
11. Lai KN, Li PK, Lui SF, *et al.* Membranous nephropathy related to hepatitis B virus in adults. *N Engl J Med.* 1991;324(21):1457–1463.
12. Lai KN, Ho RT, Tam JS, Lai FM. Detection of hepatitis B virus DNA and RNA in kidneys of HBV related glomerulonephritis. *Kidney Int.*. 1996;50(6):1965–1977.
13. Fabrizi F, Donato FM, Messa P. Association between hepatitis B virus and chronic kidney disease: a systematic review and meta-analysis. *Ann Hepatol.*. 2017;16(1):21–47.
14. Lin MY, Chiu YW, Lee CH, *et al.* Factors associated with CKD in the elderly and nonelderly population. *Clin J Am Soc Nephrol.*. 2013;8(1):33–40.
15. Amet S, Bronowicki JP, Thabut D, *et al.* Prevalence of renal abnormalities in chronic HBV infection: the HARPE study. *Liver Int.*. 2015;35(1):148–155.
16. Chen YC, Su YC, Li CY, Hung SK. 13-year nationwide cohort study of chronic kidney disease risk among treatment-naive patients with chronic hepatitis B in Taiwan. *BMC Nephrol.*. 2015;16:110.
17. Zeng Q, Gong Y, Dong S, Xiang H, Wu Q. Association between exposure to hepatitis B virus and chronic kidney disease in China. *J Int Med Res.*. 2014;42(5):1178–1184.
18. Ishizaka N, Ishizaka Y, Seki G, Nagai R, Yamakado M, Koike K. Association between hepatitis B/C viral infection, chronic kidney disease and insulin resistance in individuals undergoing general health screening. *Hepatol Res.*. 2008;38(8):775–783.
19. Lee JJ, Lin MY, Yang YH, Lu SN, Chen HC, Hwang SJ. Association of hepatitis C and B virus infection with CKD in an endemic area in Taiwan: a cross-sectional study. *Am J Kidney Dis.*. 2010;56(1):23–31.
20. Cai QC, Zhao SQ, Shi TD, Ren H. Relationship between hepatitis B virus infection and chronic kidney disease in Asian populations: a meta-analysis. *Ren Fail.* 2016;38(10):1581–1588.
21. Cai J, Fan X, Mou L, *et al.* Association of reduced renal function with hepatitis B virus infection and elevated alanine aminotransferase. *Clin J Am Soc Nephrol.*. 2012;7:1561–1566.
22. Nair S, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. *Hepatology.*. 2002;35:1179–1185.
23. Amarapurkar DN, Dhawan P, Kalro RH. Role of routine estimation of creatinine clearance in patients with liver cirrhosis. *Indian J Gastroenterol.*. 1994;13(3):79–82.
24. Kim SU, Han KH, Nam CM, *et al.* Natural history of hepatitis B virus-related cirrhotic patients hospitalized to control ascites. *J Gastroenterol Hepatol.*. 2008;23(11):1722–1727.
25. Brown RS, Lombardero M, Lake JR. Outcome of patients with renal insufficiency undergoing liver or liver-kidney transplantation. *Transplantation.*. 1996;62(12):1788–1793.
26. Zuo L, Sun F, Wang X, *et al.* [Clinical analysis of 298 cases of liver cirrhosis and renal dysfunction]. *Zhonghua Gan Zang Bing Za Zhi.*. 2014;22(7):504–508.
27. Kim YJ, Cho HC, Sinn DH, *et al.* Frequency and risk factors of renal impairment during long-term adefovir dipivoxil treatment in chronic hepatitis B patients. *J Gastroenterol Hepatol.*. 2012;27(2):306–312.
28. Mederacke I, Yurdaydin C, Grosshennig A, *et al.* Renal function during treatment with adefovir plus peginterferon alfa-2a vs either drug alone in hepatitis B/D co-infection. *J Viral Hepat.* 2012;19:387–395.
29. Lampertico P, Vigano M, Yurdaydin C, *et al.* Effectiveness and Safety of Tenofovir Disoproxil Fumarate in Field Practice: A Multicenter European Cohort Study of 737 Patients with Chronic Hepatitis B. *Hepatology.*. 2010;52:503–503.
30. Gish RG, Clark MD, Kane SD, Shaw RE, Mangahas MF, Baqai S. Similar risk of renal events among patients treated with tenofovir or entecavir for chronic hepatitis B. *Clin Gastroenterol Hepatol.*. 2012;10(8):941–946.
31. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.*. 1976;16(1):31–41.
32. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med.*. 1999;130(6):461–470.
33. Levey AS, Stevens LA, Schmid CH, *et al.* A new equation to estimate

glomerular filtration rate. *Ann Intern Med.*. 2009;150(9):604–612.

34. Mauss S, Berger F, Filmann N, *et al*. Effect of HBV polymerase inhibitors on renal function in patients with chronic hepatitis B. *J Hepatol.*. 2011;55(6):1235–1240.
35. Kim SE, Jang ES, Ki M, *et al*. Chronic Hepatitis B Infection Is Significantly Associated with Chronic Kidney Disease: a Population-based, Matched Case-control Study. *J Korean Med Sci.*. 2018;33(42):264.
36. McMahon BJ. The natural history of chronic hepatitis B virus infection. *Hepatology.*. 2009;49:45–55.
37. Gluhovschi C, Velciov S, Buzas R, *et al*. Is There any Difference Between the Glomerular Filtration Rate of Patients With Chronic Hepatitis B and C and Patients With Cirrhosis? *Hepat Mon.*. 2013;13(4):6789.
38. Caregaro L, Menon F, Angeli P, *et al*. Limitations of serum creatinine level and creatinine clearance as filtration markers in cirrhosis. *Arch Intern Med.*. 1994;154(2):201–205.
39. Juutilainen A, Kastarinen H, Antikainen R, *et al*. Comparison of the MDRD Study and the CKD-EPI Study equations in evaluating trends of estimated kidney function at population level: findings from the National FINRISK Study. *Nephrol Dial Transplant.*. 2012;27(8):3210–3217.
40. Woitas RP, Stoffel-Wagner B, Flommersfeld S, *et al*. Correlation of serum concentrations of cystatin C and creatinine to inulin clearance in liver cirrhosis. *Clin Chem*. 2000;46:712–715.
41. Axelsen RA, Crawford DH, Endre ZH, *et al*. Renal glomerular lesions in unselected patients with cirrhosis undergoing orthotopic liver transplantation. *Pathology*. 1995;27(3):237–246.
42. Pöge U, Gerhardt T, Stoffel-Wagner B, *et al*. Cystatin C-based calculation of glomerular filtration rate in kidney transplant recipients. *Kidney Int.*. 2006;70(1):204–210.
43. Gerhardt T, Pöge U, Stoffel-Wagner B, *et al*. Estimation of glomerular filtration rates after orthotopic liver transplantation: Evaluation of cystatin C-based equations. *Liver Transpl.*. 2006;12(11):1667–1672.
44. Karetnikova VN, Osokina AV, Evseeva MV, *et al*. Renal function estimation formulas in predicting long-term cardiovascular outcomes in patients with myocardial infarction concurrent with diabetes mellitus. *Ter Arkh.*. 2016;88(4):35–40.