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Cross-sectional retrospective analysis of clinical characteristics of chronic hepatitis B patients with oral antiviral treatment in eastern China

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Abstract

Background: In China, more than 20 million patients with chronic hepatitis B need antiviral treatment. Side effects of antiviral treatment such as renal complications can be problematic, particularly in an aging population.

Methods: The data were retrospectively extracted from the hospital medical charts of five centers in eastern China from January 1 to December 31, 2018.

Results: A total of 8309 patients with CHB was enrolled in this study. The median age of the patients was 46 years. The prevalence of diabetes mellitus, hypertension, and hepatic cirrhosis was respectively 3.49%, 4.42%, and 23.72%. The prevalence of these comorbidities increased with age ($P < 0.001$). Of the patients with CHB, 5332 had complete renal function results. Among them, patients with an estimated glomerular filtration rate of < 60 mL/min/1.73m^2 accounted for 4.14%, and those with proteinuria for 8.33%. According to the definition of chronic kidney disease, the proportion of patients with chronic kidney disease was 11.37%. The prevalence of chronic kidney disease increased with age ($P < 0.001$). In a multivariate analysis, age group [odds ratio (OR) = 2.387], diabetes mellitus (OR = 1.486), hypertension (OR = 2.557), hepatic cirrhosis (OR = 1.295), and a history of exposure to adefovir dipivoxil (OR = 1.644) were significantly associated with CKD ($P < 0.05$). Among patients with CKD, 17.66% (107/606) had a history of lamivudine exposure, and 34.65% (210/606) had a history of nucleotide analogue exposure

Conclusion: The management of Chinese patients with CHB should take into consideration age, previous medication history, and renal impairment.

Keywords: Chronic hepatitis B, Antiviral treatment, Comorbidity, Aging

Introduction

Hepatitis B virus (HBV) infection is a major public-health challenge worldwide. In particular, China has a high rate of morbidity due to HBV infection. The rate of positivity for the HBV surface antigen (HBsAg) was approximately 6.1% in the general population of China in 2016, but only 19% of these patients were diagnosed [1]. More than 80 million patients are infected with the hepatitis B virus,

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and 20 million patients with chronic hepatitis B (CHB) are in need of antiviral treatment, but only a small proportion of patients with CHB receive treatment [1–3].

In 1992, the rate of HBsAg carriage in China was 9.75% [4]. To control the spread of HBV, the government carried out a series of national immunization programs. Due to hepatitis B vaccination, the incidence of HBV infection in children and young people has declined significantly [2, 5]. In an observational study of HBV infection in China from 2004 to 2014, the rate of infection was significantly lower in people less than 24 years of age but significantly higher in those more than 55 years of age [6]. Carriers of hepatitis B virus are aging, particularly those infected before the introduction of hepatitis B vaccination. A recent multi-center cohort study of patients with CHB in the United States showed that elderly patients had a higher incidence of liver and non-liver complications [7]. However, to our knowledge, the data on this phenomenon in China are sparse.

CKD should be monitored because it stems from long-term renal function damage, which is both painful for the patient and imposes a considerable burden on society. At present, whether HBV infection increases the risk of chronic kidney disease is still controversial [8–10]. A single-center Chinese study reported that only 7.9% of patients with CHB had CKD, less than the prevalence in the adult Chinese population in a national cross-sectional survey [11]. Therefore, the incidence of CKD in patients with CHB warrants further investigation. And because hepatitis B cannot be cured, long-term or even lifelong treatment is required. Therefore, the common side effects of long-term treatment, such as kidney complications, need to be evaluated [12]. In some patients with CHB, prolonged use of nucleotide antivirals, including adefovir dipivoxil (ADV) and tenofovir diester fumarate (TDF), leads to renal dysfunction [13–15]. In a retrospective study of 687 patients with CHB treated with ADV, 10.5% exhibited a 20% decrease in the estimated glomerular filtration rate (eGFR) relative to the baseline [16]. A large-scale real-world cohort study also showed that patients with CHB treated with TDF had a slightly increased risk of CKD [17]. However, the data on the prevalence of early renal injury in patients with CHB treated with antiviral agents are sparse.

The study sites were in Zhejiang Province, eastern China. The overall prevalence of chronic HBV carriage in Zhejiang Province was 11.61% in 1992 and 8.79% in 2006, both higher than the national average [18]. Regarding ethnicity, the Han predominates both in Zhejiang Province and nationwide. HBV genotypes B and C are prevalent in China, whereas genotypes A and D are rare [19]. Therefore, data from Zhejiang Province could reflect the HBV infection status nationwide. The economic development and healthcare system of Zhejiang Province are relatively advanced, and the provincial reimbursement program covers the cost of antiviral treatment for hepatitis B. Also, physicians and patients are aware of the importance of HBV suppression. The majority of patients with CHB eligible for antiviral treatment according to the China HBV guidelines begin treatment at the time of diagnosis. We gathered the information of these patients and determined the optimal treatment strategy.

Methods

Study population

This was a cross-sectional, multi-center study at five centers in eastern China—the First Affiliated Hospital of Zhejiang University; Ningbo No. 2 Hospital; Huzhou Central Hospital; Shaoxing Municipal Hospital; and Taizhou Hospital Affiliated to Wenzhou Medical College. The study protocol was approved by the Ethics Committee of The First Affiliated Hospital, College of Medicine, Zhejiang University.

After reviewing patient medical charts, patients with CHB who met the following criteria were enrolled in the study: age $\geq$ 18 years; HBsAg positive for > 6 months; eligible for antiviral treatment according to the 2015 China HBV Guidelines; visited one of study hospitals from January 1 to December 30, 2018 and on nucleotide/nucleoside antivirals; no co-infection with hepatitis A virus, hepatitis C virus, hepatitis D virus, hepatitis E virus, or human immunodeficiency virus; no liver dysfunction of other causes; no concomitant liver or non-liver malignancy; and no pregnancy or lactation.

Data collection and definitions

The following data were extracted from electronic medical charts: demographics (age and sex); medical history [diabetes mellitus (DM) and hypertension identified by International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) code]; antiviral treatment (current nucleotide/nucleoside regimen, oral antiviral treatment duration and prior exposure); liver-related complications (identified by ICD-10 code); and liver cirrhosis (determined by liver histology or clinical, radiologic, or endoscopic evidence of portal hypertension [nodular contour on imaging, thrombocytopenia, splenomegaly, presence of varices, or clinical hepatic decompensation], or in the notes of the responsible physician).

Laboratory parameters were collected from the digital medical charts, if available. The most recent result was selected if multiple tests had been conducted during the study period. The laboratory parameters evaluated were as follows: HBV virological or serological markers [HBsAg, hepatitis B e antigen (HBeAg), anti-HBV core

(anti-HBc), and HBV DNA level]; hematological indicators [white blood cell (WBC) count, platelet (PLT) count; serum aminotransferase (ALT) level, and serum creatinine (Scr) level]; eGFR [estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation as recommended by the 2012 KDIGO guidelines]; and urinary tests [dipstick urinalysis and quantitative markers of proteinuria (uric micro-albumin)].

Data analysis

Descriptive statistics were reported as proportions (%) for categorical variables and as means ± standard deviations or medians with interquartile ranges in parentheses for continuous variables. Categorical variables were evaluated using the χ^2-test or Mantel–Haenszel χ^2-test. For continuous variables, one-way analysis of variance (ANOVA) was applied if a normal distribution was observed; otherwise, the Kruskal–Wallis H-test was used. A multivariate logistic regression analysis was conducted to identify predictors of CKD. All statistical tests were two-sided and a value of $P < 0.05$ was taken to indicate statistical significance. All analyses were performed using Statistical Package for the Social Sciences (SPSS) software, version 22.0 (IBM Corporation, Armonk, NY, USA).

Results

Patient characteristics

Basic information and laboratory parameters

From January to December 2018, a total of 8320 patients with CHB was consecutively enrolled in this study. After excluding 11 patients less than 18 years of age, the records of 8309 patients were analyzed. The median age of the patients with CHB was 46.00 (37.00–55.00) years, and the male-to-female ratio was 2.08:1. Regarding laboratory parameters, 76.96% of the patients with CHB had HBsAg levels of > 250 IU/mL (because a highly sensitive quantitative assay of HBsAg is not available at some hospitals, only the proportion of patients with HBsAg levels > 250 IU/mL was calculated). A total of 3326 (40.03%) patients tested positive for HBeAg. In 6334 (76.23%) of the patients with CHB, serum HBV DNA levels were < 30 IU/mL—i.e., undetectable, and the median HBV DNA level of the remaining patients was 3.12 (2.28–4.78) log10 IU/mL. In addition, the median ALT level, WBC count, and PLT count were 24.00 (17.00–35.00) U/L, 5.30 (4.30–6.40) 10E9/L, and 168 (122–214) 10E9/L, respectively (Table 1).

Table 1 Characteristics of the CHB patients

Chataceristics	Total
Number	8309
Age (years)	46.00 (37.00–55.00)
≥ 60 years old, n(%)	1293 (15.56)
Male, n(%)	5609 (67.51)
HBsAg > 250 IU/mL, n(%)	6395 (76.96)
HBeAg positive, n(%)	3326 (40.03)
HBV DNA undetectable, n(%)	6334 (76.23)
ALT (U/L)	24.00 (17.00–35.00)
WBC (10E9/L)	5.30 (4.30–6.40)
PLT (10E9/L)	168 (122–214)

Categorical variables were presented as count (percentage) and continuous variables were presented as median (interquartile range, IQR) or mean ± standard deviation (SD)

HBsAg hepatitis B virus surface antigen, *HBeAg* hepatitis B e antigen, *HBV* hepatitis B virus, *ALT* alanine transaminase, *WBC* white blood cell, *PLT* platelet

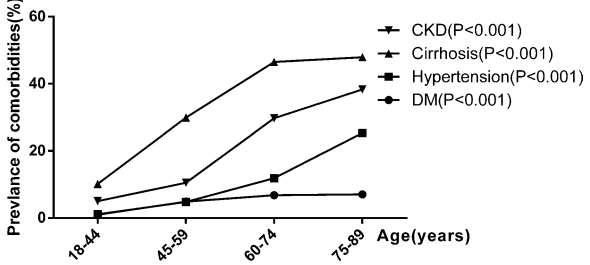

Fig. 1 Comorbidities of patients with chronic hepatitis B. *CKD* chronic kidney disease, *DM* diabetes mellitus

Age and comorbidities

Based on the categories defined by the World Health Organization, we divided the patients into the following four groups according to their age: 18–44, 45–59, 60–74, and 75–89 years [20]. The majority of the patients with CHB were young or middle-aged, whereas 15.56% (n = 1293) were more than 60 years of age.

The prevalence of diabetes mellitus, hypertension, and hepatic cirrhosis was respectively 3.49% (290/8309), 4.42% (367/8309), and 23.72% (1971/8309). The incidences of diabetes, hypertension, and cirrhosis in patients with CHB according to age group are shown in Fig. 1. The prevalence of diabetes (R = 0.123), hypertension (R = 0.191), and cirrhosis (R = 0.303) was linearly related to age ($P < 0.01$) and increased with age ($P < 0.001$).

Antiviral treatment

Antiviral treatment status

The majority (71.73%) of the patients with CHB were taking entecavir (ETV), followed by TDF (16.22%). Among the remaining 12.05% of the patients, 2.68% were taking telbivudine (LDT), 2.15% were taking ADV combined with lamivudine (LAM), 2.14% were taking ADV, 1.31% were taking LAM, and 3.77% were taking other antiviral

drugs. At the same time, a total of 22.16% of patients are taking treatment containing ADV or TDF.

Medium- or long-term antiviral treatment

Among the 8309 patients with CHB, the median duration of antiviral treatment was 24.00 (11.00–44.00) months. The antiviral status of patients treated for less and more than 24 months is listed in Table 2. For patients treated for > 24 months, the proportion of patients taking ETV was higher (75.76% vs. 67.93%; P < 0.001) and the proportion taking TDF was considerably lower (8.25% vs. 23.74%; P < 0.001) than for patients treated for < 24 months.

Among patients with CHB treated for > 24 months, the rate of ALT normalization (< 40 U/L in males and < 35 U/L in females) was 86.24%, and that of an undetectable serum HBV DNA level (< 30 IU/mL) was 89.11%. Among patients with CHB, the majority (75.76%) were taking ETV, whereas 25.21% had a history of exposure to LAM, 33.34% a history of exposure to nucleotide-based antivirals, and 35.92% had used two or more antivirals. A history of exposure to nucleotide-based antivirals was defined as having taken or currently taking TDF or ADV.

Kidney function

General kidney function

Of the patients with CHB, 5332 had relatively complete renal function data. The median serum creatinine level and eGFR were 69.00 (59.00–80.00) μmol/L and 105.60 (92.64–114.57) mL/min/1.73m^2, respectively. Of patients with relatively complete data, patients with an eGFR of < 60 mL/min/1.73m^2 accounted for 4.14%, and patients with proteinuria for 8.33%. According to the definition of CKD, the proportion of patients with CKD was 11.37%. The prevalence of CKD increased with age (P < 0.001). Of the patients with CKD, 44.39% (269/606) had been treated for > 24 months, 17.66% (107/606) had a history of LAM exposure, 34.65% (210/606) had a history of exposure to nucleotide-based antivirals. Among them, 135 patients with hepatitis B had a history of ADV exposure and 87 patients had a history of TDF exposure. And the median duration of their antiviral treatment was 61.00(37–84) and 12.00 (6.00–24.25) months, respectively.

Risk factors for CKD

The relationship between CKD and related factors as deter mined by univariate and multivariate analyses is summarized in Table 3. Age group (18–44, 45–59, 60–74, and 75–89 years), HBsAg level (> 250 vs. ≤ 250 IU/mL), presence of HBeAg (positive vs. negative), diabetes mellitus, hypertension, hepatic cirrhosis, PLT count, and exposure to ADV were significantly associated with CKD (P < 0.001). ALT normalization rates were different between groups, but the difference was not statistically significant (P = 0.062). In a multivariate analysis, age group (odds ratio [OR] = 2.387, P < 0.001), diabetes mellitus (OR = 1.486, P = 0.025), hypertension (OR = 2.557, P < 0.001), hepatic cirrhosis (OR = 1.295, P = 0.008), and a history of exposure to ADV (OR = 1.644, P < 0.001) were significantly associated with CKD.

Microalbuminuria

Of the patients with CHB, 651 were examined for urinary microalbumin, of which 19.35% (126/651) had microalbuminuria. The incidence of microalbuminuria increased with age (P < 0.001). The incidence of CKD was significantly higher in patients with CHB with microalbuminuria (P < 0.001), whereas 64.29% (81/126) of the patients with microalbuminuria had no comorbidity of CKD. Among the patients with CHB and microalbuminuria, 50.00% (63/126) had normal eGFRs (> 90 mL/min/1.73m^2) and urinary protein levels. The patients with diabetes mellitus (P < 0.001), hypertension (P = 0.001), or cirrhosis (P < 0.001) had a higher incidence of microalbuminuria. In terms of antiviral status, patients with CHB with a history of exposure to TDF had a higher incidence of microalbuminuria (27.07.30% vs. 17.37%; P = 0.014),

Table 2 Antiviral treatment status

Variable	Total (n = 8309)	Treatment duration ≤ 24 months (n = 4275)	Treatment duration > 24 months (n = 4034)	P value
Treatment duration (months)	24.00 (11.00–44.00)	11.00 (5.00–17.00)	46.00 (35.00–62.00)	–
ETV, n(%)	5960 (71.73)	2904 (67.93)	3056 (75.76)	< 0.001
TDF, n(%)	1348 (16.22)	1015 (23.74)	333 (8.25)	< 0.001
Others, n(%)	1001 (12.05)	356 (8.33)	645 (15.99)	< 0.001
LAM exposure, n(%)	1094 (13.17)	77 (1.80)	1017 (25.21)	< 0.001
Nucleotide analogue exposure n(%)	2556 (30.76)	1211 (28.33)	1345 (33.34)	< 0.001

ETV entecavir, *TDF* tenofovir disoproxil fumarate, *LAM* lamivudine

Table 3 Univariate and multivariate analysis of CKD

Variables	Univariate analysis	Multivariate analysis		
	P value	*B*	OR (95% CI)	P
Age groups	< 0.001*	0.870	2.387 (2.118–2.691)	< 0.001*
Gender	0.322	–	–	–
HBsAg > 250 IU–mL	< 0.001*	–	–	–
HBeAg positive	< 0.001*	–	–	–
HBV DNA undetectable	0.407	–	–	–
ALT normalization	0.062	–	–	–
Diabetes mellitus	< 0.001*	0.396	1.486 (1.052–2.099)	0.025*
Hypertension	< 0.001*	0.939	2.557(1.915–3.412)	< 0.001*
Hepatic cirrhosis	< 0.001*	0.259	1.295(1.070–1.567)	0.008*
WBC (10^9/L)	0.439	–	–	–
PLT (10^9/L)	< 0.001*	–	–	–
Treatment duration	0.304	–	–	–
ADV-experienced	< 0.001*	0.497	1.644(1.321–2.046)	< 0.001*
TDF-experienced	0.542	–	–	–

OR odds ratio, *HBsAg* hepatitis B virus surface antigen, *HBeAg* hepatitis B e antigen, *HBV* hepatitis B virus, *ALT* alanine transaminase, *WBC* white blood cell, *PLT* platelet, *ADV* adefovir dipivoxil, *TDF* tenofovir diester fumarate

*Statistical significance

whereas a history of exposure to ADV (P = 0.0254), ALT normalization rate (P = 0.097), an undetectable HBV DNA level (P = 0.838), HBsAg level > 250 IU/mL (P = 0.307), and treatment for > 24 months (P = 0.0879) were not significantly related to microalbuminuria. In a multivariate analysis, CKD (OR = 5.212, P < 0.001), diabetes mellitus (OR = 2.908, P = 0.002), hepatic cirrhosis (OR = 2.089, P = 0.001), and a history of exposure to TDF (OR = 2.066, P = 0.004) were significantly associated with microalbuminuria.

Discussion

This real-world study reflects the current status of patients with CHB in China. The median age of the patients with CHB was 46 years, and almost 16% were more than 60 years of age. Compared with two previous studies in China [5, 6] the patients with CHB were significantly older. Also, the incidence of hepatic cirrhosis and several non-liver complications increased with age. In patients older than 60 years of age, the incidence of complications, including hepatic cirrhosis, hypertension, diabetes, and CKD, was high. To some extent, this reflects the increasing age and incidence of complications of patients with CHB.

ETV was used by most of the patients. Because of its high viral suppression ability and low risk of resistance, the proportion of patients taking TDF has increased recently [21, 22]. Due to lower antiviral capacity, kidney and bone safety, drug resistance, and other factors, some antivirals have been relegated to second-line status [23, 24].

Many of the patients with CHB had a complicated medication history. Notably, some patients with CHB, particularly those treated for > 24 months, had achieved HBV suppression but > 25% had been exposed to LAM or nucleotide analogues. The history of previous medication might cause pre-existing mutations and lead to drug resistance [25–27]. And long-term use of ADV and TD might cause kidney damage [28].

Renal function is generally neglected during clinical monitoring. Renal function and urine tests were not performed for a considerable number of patients, and only ~ 8% underwent urinary microalbumin testing. In eastern China, routine 24-h urine protein quantitation or urine albumin-creatinine ratio (ACR) analysis is rarely performed, but urine dipstick testing is frequently conducted. Although there is no consensus on which test is superior to the rest [29, 30], because ACR results were lacking the result of the urine dipstick test was used to define proteinuria in this study. Approximately 11.4% of the patients with CHB were at risk of CKD, a larger proportion than in the general population [31]. Age, hypertension, hepatic cirrhosis, and a history of exposure to ADV were independent risk factors for CKD. Among these factors, hypertension had the highest OR and has a complex relationship with CKD. Indeed, hypertension may be both a cause and a result of CKD [32]. Age and diabetes mellitus were also important causes of CKD, consistent with prior studies [33]. Moreover, patients

with CHB, hepatic cirrhosis, and a history of exposure to ADV were at increased risk of CKD. This may be related to hepatorenal syndrome caused by hepatic cirrhosis and the toxicity of some nucleotide antivirals to renal tubules, which leads to secondary osteoporosis and renal dysfunction [34, 35]. However, a history of exposure to TDF seemed to have no effect on renal function, which might be related to the exposure duration. Patients with a history of ADV exposure tended to have longer antiviral treatment time. In addition, the incidence of cirrhosis and rate of exposure to ADV were high among patients with CHB.

Due to the insufficient understanding of renal impairment, economic factors, and the inconvenience of urine retention, urinary microalbumin was tested in only a small proportion of the patients. Approximately 8% of CHB patients underwent urinary microprotein tests, which suggests that there is a huge bias in this study. Clinicians may be more inclined to perform urine microalbumin tests on patients who have already experienced renal impairment. Therefore, the factors that influence the incidence of microalbuminuria were not the same as the independent factors associated with CKD. However, half of the patients with microalbuminuria did not have abnormal urinary protein levels or eGFRs. This may be related to the high sensitivity of the urinary microalbumin test [36, 37].

This study had several limitations. The incidence of non-liver complications, including hypertension, diabetes, and CKD, was lower than in previous reports [38, 39], possibly due to biased selection of the patients with CHB and the lack of auxiliary examinations. The data were collected via medical chart review, and most of the participants were outpatients; thus, information on non-liver complications was frequently unavailable. In China, some patients with CHB return to community or local hospitals to continue their treatment; the relative inaccessibility of the medical records of other institutions resulted in incomplete data. The medications used are affected by the economic status of the patient, the time of drug listing, and the cost of the drug. As a cross-sectional study, it has some unavoidable limitations. We have adopted a multi-center, large sample approach to minimize bias. And no data for a normal population or for other years were available. This should be addressed in future studies.

Conclusions

In conclusion, Chinese patients with CHB are aging (due to the high coverage of hepatitis B vaccination in China) and have an increasing incidence of complications. Therefore, the management of Chinese patients with CHB should take into consideration age, previous medication history, and renal impairment.

Disclosure

The abstract of this paper was presented at the AASLD Conference as a poster with interim findings. The poster's abstract was published in "Poster Abstracts" in Haptology Journal name "Cross-sectional Retrospective Analysis of Chronic Hepatitis B Patients in Eastern China" [ID 137173]: https://aasldpubs.onlinelibrary.wiley.com/doi/full/10.1002/hep.30941

Abbreviations

HBV: Hepatitis B virus; HBsAg: Hepatitis B virus surface antigen; CHB: Chronic hepatitis B; HCC: Hepatocellular carcinoma; CKD: Chronic kidney disease; ADV: Adefovir dipivoxil; TDF: Tenofovir diester fumarate; eGFR: Estimated glomerular filtration rate; DM: Diabetes mellitus; ICD: International statistical classification of diseases; HBeAg: Hepatitis B e antigen; WBC: White blood cell; PLT: Platelet; ALT: Aminotransferase; Scr: Serum creatinine; ANOVA: One-way analysis of variance; SPSS: Statistical Package for the Social Sciences; ETV: Entecavir; LDT: Telbivudine; LAM: Lamivudine; ACR: Albumin-creatinine ratio.

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Authors' contributions

YY, DL, ZT, HS and HC designed the experiment. XZ, SZ, HC, FD, XL, JL, MX and WW collected relevant data. JG, GY, XZ, SZ, HC and CY discussed and analyzed the data. JG wrote the paper. GY and YY revised the paper. All authors read and approved the final manuscript.

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Availability of data and materials

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

Ethical approval and consent to participate

The study protocol was approved by the Ethics Committee of The First Affiliated Hospital, College of Medicine, Zhejiang University (Reference Number: 2018-1034).

Consent to participate

Not applicable.

Competing interests

Not applicable.

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