



Baseline Characteristics and Treatment Patterns of the Patients Recruited to the China Registry of Hepatitis B

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Abstract

Background and Aims: Chronic hepatitis B virus (HBV) infection remains a major public health problem globally. Here, we describe the baseline characteristics and treatment profiles of HBV-infected patients recruited to the China Registry of Hepatitis B. **Methods:** Inclusion criteria were patients with different stages of chronic HBV infection and complete key data. Exclusion criteria were patients with hepatocellular carcinoma. The baseline clinical, laboratory and treatment profiles were analyzed. **Results:** Finally, 40,431 patients were included. The median age was 43 years, with 65.2% being men and 51.3% being positive for hepatitis B e antigen (HBeAg). The most common initial diagnosis was chronic hepatitis B (81.0%), followed by cirrhosis (9.3%), inactive carrier of hepatitis B surface antigen (HBsAg) (6.7%), and immune tolerant phase of hepatitis B infection (3.0%). Among the 21,228 patients who were on treatment, 88.0%, 10.0% and 2.0% received nucleos(t)ide analogues (NAs), interferon or combination of NAs and interferon, respectively. The proportion of patients who received preferred NAs (entecavir or tenofovir disoproxil fumarate) had increased from 13.5% in 2003 to 79.7% in 2016. **Conclusions:** We concluded that middle-aged men accounted for most of the patients with chronic hepatitis B in this cross-sectional study. About half of the patients were HBeAg-positive. NAs were the most commonly used therapy, and use of the preferred NAs had steadily increased in the past decade.

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Introduction

Universal vaccination against hepatitis B virus (HBV) in infants has achieved great success but chronic HBV infection remains a major public health problem globally.¹ The 2017 World Health Organization (WHO) Global Hepatitis Report estimates that 257 million persons, or 3.5% of the population, are chronically infected by HBV,² with the highest hepatitis B surface antigen (HBsAg) prevalence (6.2%) being in the Western Pacific region.^{3–5} Chronic HBV infection is asso-

ciated with a considerable burden of liver morbidity and mortality, and can lead to cirrhosis, decompensation and hepatocellular carcinoma (HCC).⁶

In China, with high coverage of HBV vaccination in infants, the estimated prevalence of HBsAg declined to 6.1% in the general population.^{7,8} However, historical HBV endemicity built a large reservoir of chronically infected persons. It is estimated that there are more than 70 million persons with chronic HBV infection in China.³ To facilitate real-world clinical study of chronic HBV infection, we have established a national HBV registry platform, the China Registry of Hepatitis B (known as the CR-HepB),⁹ which was launched in July 2012. Currently, it consists of 47 tertiary hospitals in mainland China (ClinicalTrials.gov registry number: NCT03108794).⁹

In the present cross-sectional study, we described the demographic, baseline characteristics, and treatment profiles of patients recruited in CR-HepB from June 2012 through June 2017.

Methods

Data sources

The CR-HepB was launched in June 2012 but retrospectively captured data of patients from 2000. The current study retrieved data from CR-HepB registrants prospectively or retrospectively from June 2012 to June 2017. The key information includes patients' age, gender, diagnosis, laboratory results, liver biopsy results, and antiviral treatment profiles.

Patient population

Inclusion criteria were patients with different stages of chronic HBV infection and available information on hepatitis B e-antigen (HBeAg) status and HBV DNA and alanine transaminase levels. Exclusion criteria were patients with HCC.

The diagnostic criteria for immune tolerant phase, HBeAg-positive chronic hepatitis B (CHB), HBeAg-negative CHB, inactive HBsAg carriers, cirrhosis, and HCC were in line with major international and national guidelines¹⁰ and described in our previous paper.⁹

Statistical analyses

We use proportions and percentages to describe the demographic and clinical characteristics of the patients. We present the proportions of patients by their age, sex, HBeAg status, diagnosis, liver biopsy results, and type(s) of treatment received. Descriptive statistics are expressed as medians, lower quartiles, and upper quartiles, or as a number and percentage of patients. All statistical analyses were performed using SPSS v19.0.

Results

After excluding 530 individuals with HCC, 40,431 patients with confirmed diagnoses of immune tolerant phase hepatitis B,

Keywords: Hepatitis B; Treatment; Registry.

Abbreviations: CHB, chronic hepatitis B; CR-HepB, China Registry of Hepatitis B; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NAs, nucleos(t)ide analogues; WHO, World Health Organization.

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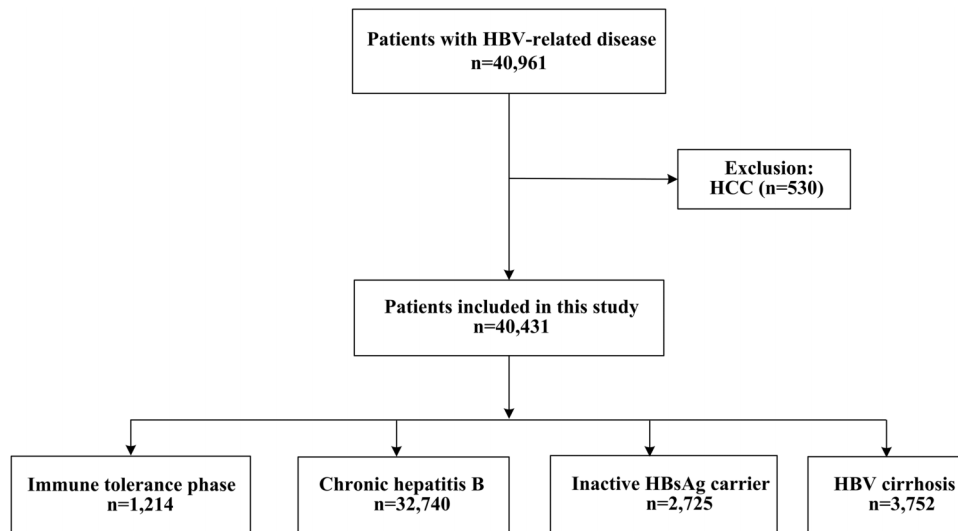


Fig. 1. Flowchart of selection of patients.

CHB, inactive HBsAg carrier status, and cirrhosis were included in the present study (Fig. 1).

Demographic and clinical characteristics of patients

The demographic and clinical characteristics of the patients are shown in Table 1. The median age was 43 years, with a men-to-women ratio of 1.9. Overall, 51.3% were HBeAg-positive. Approximately 81.0% of the patients had initially

been diagnosed with CHB, 9.3% with cirrhosis, 6.7% as inactive HBsAg carriers, and 3.0% with immune tolerant phase hepatitis B.

Age distribution of the 40,431 patients with chronic HBV infection (by sex)

Among the 40,431 patients included in the present study, the 30–49 years-old age group was the most predominant in both

Table 1. Demographic and baseline data of 40,431 patients with hepatitis B virus-related diseases

	Overall, n = 40,431	Immune tolerance phase, n = 1,214	Inactive HBsAg carrier, n = 2,725	Chronic hepatitis B, n = 32,740	Cirrhosis, n = 3,752
Age in years	43 (33, 53)	33 (28, 41)	39 (31, 49)	43 (33, 52)	55 (48, 63)
Sex					
Men, n (%)	26,347 (65.2)	610 (50.2)	1522 (55.9)	21,472 (65.6)	2743 (73.1)
Women, n (%)	14084 (34.8)	604 (49.8)	1203 (44.1)	11,268 (34.4)	1,009 (26.9)
HBeAg-positive, n (%)	20740 (51.3)	1214 (100.0)	0 (0)	17936 (54.8)	1590 (42.4)
HBV DNA (log ₁₀ IU/mL)	3.9 (2.3, 6.6)	7.6 (6.3, 8.1)	0 (0, 2.6)	4.2 (2.7, 6.9)	3.9 (2.0, 5.6)
ALT (IU/mL)	41.7 (24.6, 87.0)	27.0 (21.0, 34.8)	24.0 (18.0, 33.0)	46.0 (26.0, 99.0)	42.0 (27.0, 76.0)
AST (IU/mL)	34.0 (23.0, 63.0)	22.0 (17.0, 26.0)	23.0 (19.0, 28.0)	35.6 (24.0, 67.2)	47.0 (29.5, 83.6)
ALP (U/L)	78.0 (62.0, 101.0)	69.0 (56.0, 85.0)	70.0 (58.0, 86.0)	77.7 (62.0, 99.0)	97.8 (73.0, 133.0)
GGT (U/L)	27.0 (16.0, 55.0)	15.0 (12.0, 21.0)	17.0 (12.0, 25.0)	28.0 (17.0, 55.2)	50.9 (27.9, 99.0)
Bilirubin (μmol/L)	14.8 (10.9, 21.5)	12.1 (9.3, 15.8)	12.8 (9.7, 17.2)	14.4 (10.8, 20.3)	24.5 (15.9, 41.3)
ALB (g/L)	44.0 (39.7, 46.7)	45.2 (43.2, 47.3)	45.4 (43.4, 47.4)	44.2 (40.4, 46.9)	34.8 (29.4, 41.2)
PLT count (×10 ⁹ /L)	165.0 (115.0, 208.3)	200.0 (173.0, 236.0)	188.0 (154.0, 225.0)	171.0 (129.0, 211.0)	81.0 (53.0, 123.0)

Data are expressed as median (range) or n (%).

Abbreviations: ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PLT, platelet.

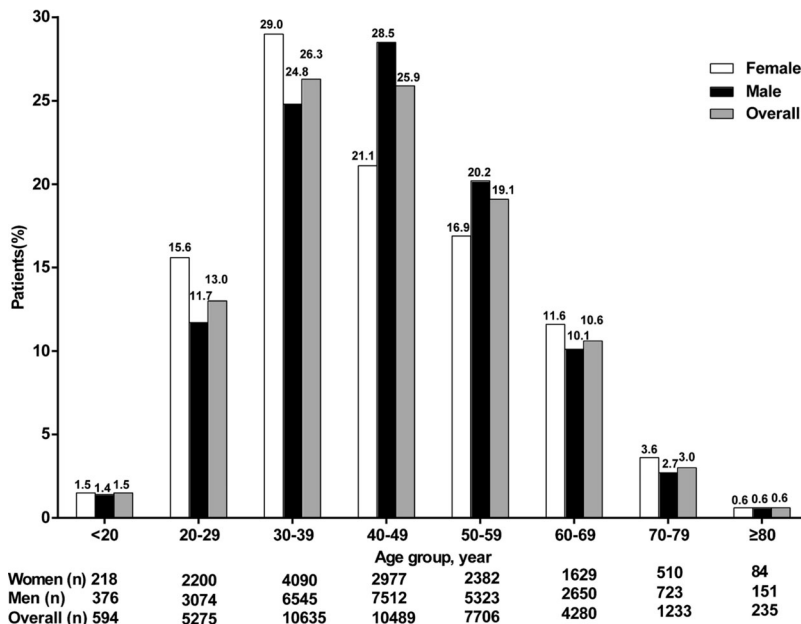


Fig. 2. Age distribution of chronic hepatitis B virus infection by sex in 40,431 patients.

men and women, followed by the 50–59 years-old age group. Patients aged between 30–59 years-old accounted for 71.8% of all patients (Fig. 2).

Disease distribution in different age groups among the 40,431 patients

The proportion of patients diagnosed with cirrhosis was increased with increasing ages, whereas the proportion of patients diagnosed with immune tolerance phase was decreased with increasing age (Fig. 3).

Liver histology of 485 patients

Necroinflammation activity and fibrosis stage were assessed according to the Scheuer grading and staging system.¹¹

Among the 485 patients who underwent liver biopsy, the proportion of patients with liver inflammation grade ≥ 2 or the stage of liver fibrosis ≥ 2 increased with age (Fig. 4).

Treatment profiles of 21,228 patients and the changing prescription of different nucleos(t)ide analogues

Nucleos(t)ide analogues (NAs) were the most common therapy among the 21,228 patients with prescription information. A much smaller proportion of patients were treated with interferon (10.0%) or a combination of interferon and NAs (2.0%).

Lamivudine (15.3%) and adefovir dipivoxil (18.4%) were widely used before 2011, whereas the use of entecavir (51.4%) and tenofovir disoproxil fumarate (2.1%) dramatically increased after 2011 (Fig. 5).

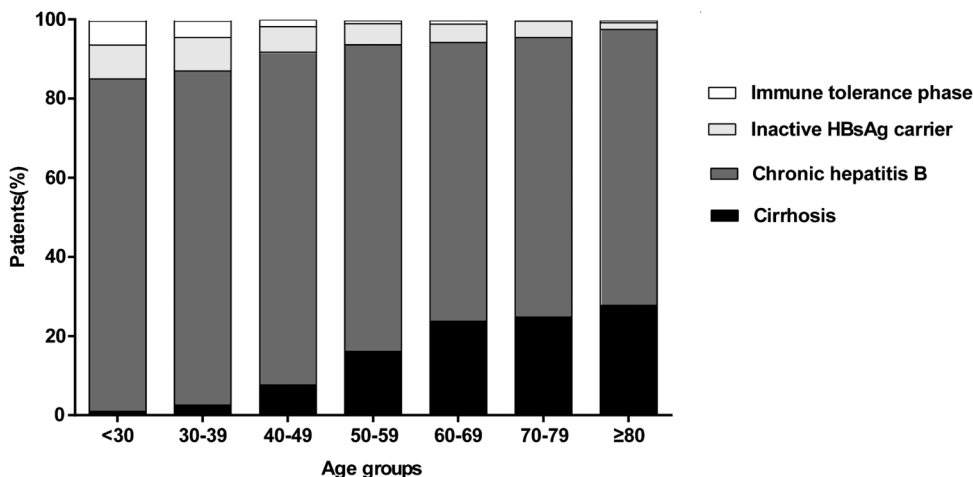


Fig. 3. Disease distribution in different age groups among the 40,431 patients.

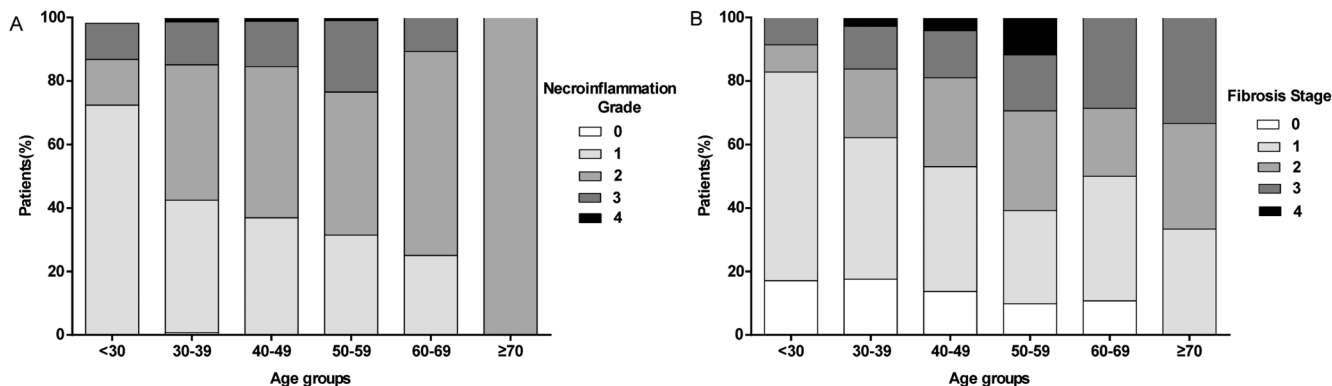


Fig. 4. Distribution of (A) the necroinflammation grade and (B) fibrosis stage in 485 patients.

Discussion

In the present study, with large number of patients, we found that middle-aged men represented the major proportion of this cohort. About half of the patients were HBeAg-positive. The most common initial diagnosis was CHB, followed by cirrhosis, inactive HBsAg carrier, and immune tolerant phase of hepatitis B infection. The proportion of patients diagnosed with cirrhosis was increasing with increasing age. Among the patients with prescription information, nearly 90% received NAs and the use of preferred NAs have increased dramatically in the past decade.

Our study showed that men accounted for a significantly higher proportion (65.2%) than women (34.8%), and about half of patients were HBeAg-positive. This is similar to the result of a recent multicenter, real-world study conducted in tier-2 city hospitals in China, which showed that 74% of 3,408 patients with CHB were men, with an overall mean age of 40 years, and that 60% of patients were HBeAg-positive.¹² Not surprisingly, patients with HBeAg-negative infection were older than those with HBeAg-positive infection, also similar to that reported from the USA.¹³

In our study, the middle-aged group was the most predominant in both men and women. This is in line with the recent reports that the prevalence of HBsAg in childbearing-aged men and women still being around 6% in rural and endemic areas in China.¹⁴ Therefore, prevention of mother-to-child transmission is still of paramount importance.^{3,15,16}

Not surprisingly, the proportion of patients diagnosed with cirrhosis was increased with increasing age. Similarly, among the 485 patients who underwent liver biopsy, the majority of these patients had mild to moderate necroinflammation and fibrosis. This may be due to the fact that patients with more disease activity and advanced fibrosis could be identified easily by noninvasive modalities, making them under-represented among patients who received liver biopsy.

In our study, more than half of the patients were prescribed treatment, and nearly 90% of them received NAs due to their favorable efficacy and safety as well as ease of administration. All major international guidelines recommend highly potent entecavir and tenofovir disoproxil fumarate as preferred therapy,^{10,17-19} since accumulating evidence indicates that long-term therapy with entecavir or tenofovir disoproxil fumarate can prevent or reverse liver fibrosis and

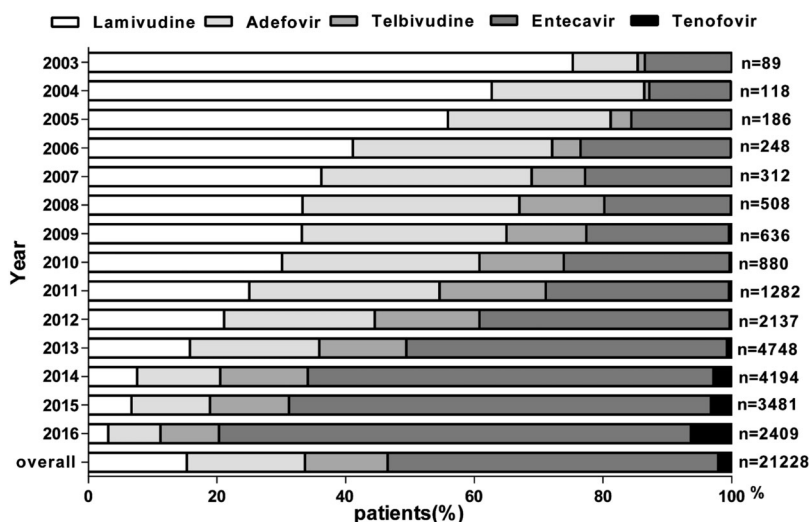


Fig. 5. Changes in proportion of each nucleos(t)ide analogue use, 2003–2016.

reduce risk of HCC.^{20–22} However, in real-world practice, lots of patients had been treated with lamivudine, adefovir dipivoxil and telbivudine, which are not preferred therapy, due to their low antiviral potency and low genetic barrier. This discrepancy between guideline recommendations and real-world clinical practice may be influenced by many factors, including doctors' knowledge, reimbursement policy, and patients' economic status and compliance.^{22–24}

Fortunately, this study showed the prescription of different NAs has favorably changed in the past years, with entecavir prescription increased from less than one-third to more than half. This trend may reflect the following facts: 1) evidence from clinical trial and real-world studies convincingly demonstrates the efficacy and safety of antiviral therapy,^{12,25,26} 2) update of evidence-based national guidelines recommends entecavir and tenofovir disoproxil fumarate as first-line therapy,¹⁰ 3) evolving national and local reimbursement policy offers more potent antiviral therapy for people who are covered by basic social medical insurance. All these improved the standard of care in clinical practice for CHB treatment. Tenofovir disoproxil fumarate was used only in less than 10%, simply because it had not been proved for HBV until mid-2014 in mainland China.

We hope this large nationwide database could provide a point of view of clinical profiles of chronic HBV infection and the treatment landscape in mainland China. However, several limitations in our study need to be mentioned. First, since CR-HepB is a hospital-based registry system, the proportion of inactive HBsAg carriers may be underestimated, as these patients are usually asymptomatic and may not seek medical service. Second, the cross-sectional design made it difficult to identify factors associated with disease progression or regression. However, CR-HepB registrants are advised to received follow-up visits every 3 to 6 months, so we could expect this limitation may be solved in the future. A final limitation is potential selection bias, as the majority of patients in the CR-HepB are from tertiary hospitals, therefore not necessarily reflecting the clinical practice in secondary or primary medical care settings where the resources and expertise are far less privileged.

Conclusions

In conclusion, this hospital-based cross-sectional study provides a snapshot of demographic and baseline profiles of Chinese patients with different stage of chronic HBV infection, as well as the landscape of clinical management.

Ethics Approval

The registry protocol was reviewed and approved by the ethics committee of Beijing Friendship Hospital, Capital Medical University (Approval Number: BJFH-EC/2014-044). Each participating institution also obtained approval from its institutional ethics committee.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Designed the study (JJ, HY, HZ, LW, JH, ZD), drafted the manuscript (SS), data management (YK). Served as the project leader and extensively and critically revised this manuscript (JJ). The other authors are the team members. All authors have read and approved the final version of the manuscript.

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