Liver Histological Abnormalities Were Better Reflected by Virus Level in Chronic Hbv Infected Patients Aged ≤ 30 Years, Hbeag-Positive and Persistently Normal Alt

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Research Article

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Abstract

Background: We analyzed correlations between significant liver histological characteristics and clinical variables in HBV-infected patients and provided recommendations on treatment decisions for patients age younger than 30-year-old.

Methods: Liver biopsy was performed on 161 chronic HBV-infected patients with ALT $\leq$ 40 U/L from July, 2000 – November, 2019. Median age was 39(18-70) years old. Histologic assessment was based on the Scheuer scoring system.

Results: Significant necroinflammation and fibrosis were observed in 65.2% (105/161) and 52.2% (84/161) patients of all cases. The pathological abnormality was significantly negatively correlated with viral level in HBeAg-positive subjects, and based on ROC curve analysis, the viral level to predict obvious liver pathological changes was 6.7 log₁₀ IU/ml in those patients. Threshold value of ALT (25 U/L) based on the distribution of ALT and virus levels. Patients younger than 30 years old, almost all had significant pathological alteration with HBV-DNA < 6.7 log₁₀ IU/ml; However, the ratio of insignificant liver's inflammation and fibrosis were 65% and 70% with HBV-DNA levels $\geq$ 6.7 log₁₀ IU/ml respectively, on that basis, it could have a further rising, reaching 67.5% and 75% combining with ALT $\leq$ 25 U/L.

Conclusion: Viral load was a better factor to reflect hepatic histological abnormality in Chronic HBV-infected patients with HBeAg-positive and persistently normal ALT whose age $\leq$ 30 years, 5000000 IU/ml was a suitable threshold.

Introduction

Hepatitis B virus (HBV) infection is a major public health problem worldwide. China has the world's largest burden of HBV infection, the absolute number of HBV - infected people is around 70 million, most of them are carried without immediate treatment (1).

Alanine Transaminase (ALT) level usually indicated liver function. International guidelines recommended observation rather than treatment for patients with ALT levels within the upper limit of normal (ULN) (2–5). However, the 2015 updated guideline of The Asian Pacific Association for the Study of the Liver (APASL) on the management of chronic hepatitis B (CHB), most HBV-infected subjects would not develop hepatic complications. However, 15–40% would develop cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease (2), and these highly related to persistent viraemia (6). A meta-analysis revealed that approximately one fifth of chronic hepatitis B patients with ALT $\leq$ 40 IU/L might have significant hepatic fibrosis, the approach to such patients should be individualized (7). Moreover, studies from Korea and Indonesia had shown that patients in Immune tolerant phase (IT) had liver histologic damages more or less (8–9), the same phenomenon presented to HBeAg-negative cases (10).

In the latest domestic and foreign practice guidelines for CHB, there was no consensus on the age at treatment or liver biopsy for chronic HBV infection with persistently normal ALT levels (PN-ALT). Age over

35-year-old in guideline of APASL in 2015(2), over 40-year-old in The American Association for the Study of Liver Diseases (AASLD) upgraded in 2018(5) and over 30-year-old in Chinese Society of Hepatology in 2019(3) should evaluate histological severity by liver biopsy or noninvasive tests. Patients with age over 30 years old and high HBV-DNA levels were considered to start antiviral therapy in the 2017 European Association for the Study of the Liver (EASL)(4). The opinions given by most studies were mainly for patients older than 30 years old (11, 12). There was not a clear-cut recommendation to perform drug therapy or liver biopsy before 30 years old.

We analyzed the liver pathological characteristics of chronic HBV-infected patients with PN-ALT and relationships with clinical variables to determine the optimal HBV-DNA threshold value reflecting significant liver tissue damage, and provided recommendations, especially for the HBeAg-positive patients under 30 years of age.

Patients And Methods

Patients

Patients with chronic HBV infection with PN-ALT underwent ultrasonography-guided percutaneous liver biopsy in the Second Affiliated Hospital of Chongqing Medical University during Between July 2000 and November 2019. Inclusion criteria and exclusion criteria as shown in the Fig 1.

Laboratory assays

All serological measurements were obtained from blood samples three days before the patient underwent liver biopsy. The ULN of serum ALT was defined as 40 U/L. In our study, PN-ALT represented ALT had remained within ULN with at least six months prior to the baseline liver biopsy.

Serum HBsAg, HBeAg were assayed with commercially available enzyme-linked immunosorbent assay (ELISA) kits. Serum HBV viral levels were quantified using real-time (RT)-PCR (Roche Diagnostics), the minimum detection limit was 100 IU/ml or 1000 copy/ml. According to the conversion formula $1 \text{ Copy} \approx 5 \text{ IU}$, all of them were uniformly converted into IU/ml and finally converted into Log10 IU/L for statistical analysis.

Liver histology

The pathological data of liver were extracted from the pathological system of the Second Affiliated Hospital of Chongqing Medical University. According to Scheuer scoring system (13), Fibrosis was classified as stage(S) 0/1/2/3/4, significant liver fibrosis was defined as $S \geq 2$, among which S4 was defined as early cirrhosis or cirrhosis. The grade of inflammatory activity was classified as grade(G) 0/1/2/3/4, Significant inflammation was defined $G \geq 2$.

Statistical analysis

Statistical analysis was performed with using the Statistical Package of Social Science Software program (SPSS), version 24. χ^2 and Fisher tests were used for categorical variables. The Spearman correlation test was used to reflect the correlation, and receiver operating curve (ROC) analysis was used to determine the optimal threshold of serum HBV-DNA. $p < 0.05$ were considered statistically significant.

Results

1. Baseline characteristics

A total of 161 patients were enrolled at baseline (Table1). There were 59.4% (41/69) patients with $G \geq 2$ and 44.9% (31/69) patients with $S \geq 2$ in HBeAg-positive patients, which in HBeAg-negative patients were 69.6% (64/92) and 57.6% (53/92). In the univariate analysis of liver pathology in chronic HBV-infected patients with PN-ALT, HBeAg-positive patients had lower age, lower percentage of men, higher HBV-DNA than the HBeAg-negative patients (Table1).

2. Correlation analysis of liver histopathology and clinical variables in HBeAg-positive and HBeAg-negative patients

In HBeAg-positive patients, the necroinflammation and fibrosis of liver were negatively correlated with viral level ($r = -0.3$, $p < 0.05$) (Fig 2A), while there seemed to be positively correlation between viral load in HBeAg-negative patients, ($p > 0.05$) (Fig 2B). Meanwhile, there were negatively correlation between HBV-DNA and age in HBeAg-positive subjects ($r = 0.23$, $p < 0.05$). No matter how the HBeAg status was, there was no correlation between the histopathological alterations and serum ALT level or age.

3. The HBV-DNA thresholds to reflect significant histological abnormalities in HBeAg-positive patients

Viral levels negatively correlated to significant liver tissue changes in PN-ALT HBeAg-positive patients. Based on ROC curves analysis of serum viral levels, threshold with the optimum sensitivity and specificity for the prediction of significant necroinflammation and fibrosis were determined. The optimum serum HBV-DNA threshold was 6.7 log₁₀ IU/mL (Fig 3A&3B). For HBeAg-positive patients with HBV-DNA ≤ 6.7 log₁₀ IU/ml, 78.8% (33/26) had $G \geq 2$, 57.6% (19/33) had $S \geq 2$. Nevertheless, these patients with HBV-DNA > 6.7 log₁₀ IU/ml, 42% (15/36) had $G \geq 2$, 33.3% (12/36) had $S \geq 2$. (Table 2).

4. The decision tree for histopathological alterations in HBeAg-positive patients

We set the ALT cut-off value as 25 U/L. ALT levels > 25 U/L in 72.7% of the people with HBV-DNA in 4.3 - 6.7 log₁₀ IU/ml and 41.4% of the people with HBV-DNA > 6.7 log₁₀ IU/ml ($p = 0.01$) (Fig 4).

According to the decision tree, 53.8% of patients under 30 years old had little inflammation and 57.7% had barely fibrosis. When HBV-DNA was lower than 6.7 log₁₀ IU/ml, obvious inflammation or fibrosis was found in 83% (5/6). When HBV-DNA > 6.7 log₁₀ IU/ml, rate of $G < 2$ increased to 65%, and the proportion $S < 2$ increased to 70%. While ALT was further considered, the incidence of scarcely any inflammation or fibrosis was increased to 67.5% and 75% when ALT ≤ 25 U/L. (Fig 5).

Discussion

In whole study, there were totally 65.2% with $G \geq 2$, 52.2% with $S \geq 2$, even 9.3% with early cirrhosis. The histopathological alterations of liver were similarly with research of Kumar M et al (10) and Gui HL et al (14). Previous studies had shown CHB patients with PN-ALT had definitively increased risk of long-term cirrhotic complications and HCC (15, 16). Although there was no consensus on treatment for chronic HBV-infected cases with PN-ALT, early interventions were needed in patients before it progressed to cirrhosis or liver cancer. The current international guidelines for the management of HBV recommended regularly monitor indications mostly the same for chronic HBV-infected, mainly based on serum HBV DNA, ALT levels, the severity of the liver diseases by non-invasive testing and so on (2–5). In addition to, Age was another essential factor, it had been agreed upon in current international guidelines. The most remarkable finding of the present study revealed that recommendations for patients younger than 30 years of age.

In HBeAg-positive infection phase generally with higher HBV-DNA levels and younger age than HBeAg-negative. Chen YC et al (17) concluded patients with HBeAg seroconversion before age 30 had excellent prognosis. In that study, patients with HBeAg seroconversion after age 40 were at significantly higher risk for HBeAg negative hepatitis, cirrhosis, and HCC. That seemed to explain why such high prevalence of liver histopathological abnormalities occurred in our study. In our cohort, the average age of HBeAg-positive patients was younger than HBeAg-negative, 34.4 versus 42.4 years, respectively. This indicated that the age of HBeAg serological conversion was about 40 years old, whereas underlying liver histological changes had occurred in this population, about 60% of HBeAg-positive and 70% of HBeAg-negative patients occurred liver damage, respectively.

At present research, there was a negative relationship in HBeAg-positive patients between serum viral levels and hepatic histopathological alterations, which was consistent with Xie Q et al study (18). In their study showed that patients with HBV DNA levels $< 4 \log_{10}$ IU/ml all had significant fibrosis, whereas the prevalence of significant fibrosis decreased to 35.9% in patients with HBV DNA level $\geq 7 \log_{10}$ IU/ml. Previous studies had shown a positive relationship between HBV DNA levels and liver fibrosis or inflammation among HBeAg-negative patients (19, 20), our study was inconsistent with that. This might be related to the small sample size. Although the HBeAg-negative HBV-infected patients were older, asymptotically about 30-40 years, the spontaneous recovery was rare and the long-term prognosis was poor with rapid evolution to cirrhosis and HCC, the annual incidence of cirrhosis was 8–10% (21–22). Therefore, it might reveal that antiviral therapy was needed to all HBeAg-negative HBV-infected patients with PN-ALT without regard to serum viral levels.

Persistent viremia increasing the risk of cirrhosis and Hepatic carcinoma cell had been well documented in a number of studies. The maximal suppression of HBV-DNA as early as possible could reduce the risk of disease progression (23, 24). At our research, we investigated the relationships between clinical variables and hepatic pathology in HBeAg-positive patients. We used ROC to identify the optimal cut-off value of HBV-DNA that reflects obvious hepatic inflammation and fibrosis in HBeAg-positive patients, the

value was 6.7 log₁₀ IU/ml, it also reflected the lower limit of viral load of the IT phase. Although the sensitivity and specificity are not perfect, they could guide the clinician in deciding whether to initiate antiviral therapy or more closely followed up. Yenilmez E et al (25) thought HBV-DNA levels between 10⁶ and 10⁸ IU/mL more likely to be in chronic infection stage in HBeAg-positive CHB. Chinese Xie Q's team (18) study also found the optimal serum HBV DNA cut-off value to evaluate low risk of significant fibrosis was $\geq 6.7 \log_{10}$ IU/ml, patients with serum HBV DNA levels $\geq 8.5 \log_{10}$ IU/ml all had no significant fibrosis.

Studies had shown that using such a definite HBV-DNA cut-off value for treatment was inappropriate, needing to combine with age. At present study, the histopathological inflammation and fibrosis not correlated with age in HBeAg-positive cases, which seemed to be at odds with previous research, in those studies, age was associated independently with significant fibrosis in HBeAg-positive patients (10, 26). This might be related to small number of the population in our study. Andreani et al revealed the median age of loss of tolerance was 30.7 years (27). In Asian countries, most of HBV infection was acquired during the perinatally/early childhood period, and the onset of IT at age 30 or older indicated a prolonged status of infection and might predispose to complications. It had been reported that HBeAg-positive patients over age 30 with generally higher HBV-DNA levels were at significantly higher risk of developing HCC (11). Vlachogiannako's review suggested that HBeAg-positive patients over 30 years old with viral load more than 20,000 IU/mL should be treated without regard to ALT levels or liver histology (28).

Patients were usually young age during IT stage. The recent Turkish study focused on naive, male and young population. The average age was 22.91 years. All cases, 53.5% had significant fibrosis, 34.4% had significant inflammation (25). As in this study, patients with HBV-DNA $> 2 \times 10^8$ IU/mL, the most frequent Fibrosis score was 2 (46.1%), HAI was 4 (22.1%). However, the drawback of this study was that it was highly selective among the population. From our decision tree, patients younger than 30 years of age, HBV-DNA $\geq 6.7 \log_{10}$ IU/ml showed insignificant liver's inflammation in 65% and insignificant fibrosis in 70%. This is at least a 10% improvement over age and ALT alone in identifying liver tissue damage.

According to guidelines, there was controversial to decrease the treatment threshold for ALT level. And in the literature, high risk of liver fibrosis in HBeAg-positive patients with an ALT level > 0.5 ULN (ULN, 58 IU/L) (29). Lai M et al reported that ALT levels between 25-40 U/L was regarded as high normal, in which histopathological abnormalities were more likely to occur (30). It was clear from the literature mentioned above that the decision to initiate antiviral therapy should not be based on a specific ALT threshold. However, lowering the ALT threshold was worthwhile. According to decision tree, patients younger than 30 years of age, who HBV-DNA levels $\geq 6.7 \log_{10}$ IU/ml showed 67% were insignificant liver inflammation, 75% were insignificant fibrosis with ALT ≤ 25 U/L. This suggested that the evaluation of liver tissue changes in chronic HBV-infected patients under 30 years old was mainly based on the virus level, pathological abnormalities could be further defined by adding the ALT level.

There were several limitations in our study, it's a retrospective, single-center study, with small sample size, existing unavoidable selective bias. At the same time, the cross-sectional span was relatively long, almost

nearly 20 years. In the past, ALT was the main indicator for antiviral treatment of CHB, the data was complete, and patients lack of other indicators' data, so we did not include more serological indicators.

In conclusion, it usually required to consider age, viral loads and ALT levels comprehensively when evaluating histopathological abnormality of liver. For chronic HBV-infected patients whose age ≤ 30 years old with PN-ALT and HBeAg-positive, patients with HBV-DNA lower than $6.7 \log_{10}$ IU/ml should perform liver biopsy to assess the severity of the disease. For patients whose HBV-DNA $>6.7 \log_{10}$ IU/ml, histology could be further assessed in conjunction with ALT, 25U/L seemed the considerable threshold. The majority of chronic HBV-infected patients with PN-ALT with HBeAg-negative had severe liver histopathological damage, timely viral therapy was necessary.

Declarations

Data Availability: All data included in this study are available upon request by contact with the corresponding author.

Animal research Not Applicable.

Consent to Participate: This study had been approved by ethics Committee of the Second Affiliated Hospital of Chongqing Medical University. All patients undergoing liver biopsy had signed Informed consent before the procedure.

Consent to publish: All authors have read and approved the content, and agree to submit this manuscript for consideration for publication in this journal.

Plant Reproducibility: Not applicable.

Clinical Trials Registration: Not applicable.

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Competing Interests: The authors have no conflicts of interest to declare.

Author Contributions: All authors contributed to the study conception and design. Li Wei, Peng Hu and Hu Li were the main investigators. Li Wei, Xiaoqing Liu and Qiao Tang performed Material preparation, data collection and analysis. Li Wei wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

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Tables

Table 1. Baseline data (n=161), univariate analysis of hepatic histological changes in chronic HBV-infected patients with PN-ALT

Variables	Total	G0-1S0-1(47)	G≥2 / S≥2(114)	<i>p</i>
Male, %	101(62.7)	27(57.4)	74(64.9)	0.5
HBV-family history, %	44(27.3)	11(23.4)	33(28.9)	0.4
HBeAg-positive, %	69(42.9)	23(48.9)	46(39)	0.3
age, years	39(18-70)	38±11	39±10	0.12
HBV-DNA (log10), IU/ml	4.4(2.4-8.3)	4.6(2.4-8.3)	4.3(2.4-8.2)	0.2
ALT, U/L	27(9-40)	27(11-40)	27.5(9-40)	0.87
G0/G1/G2/G3/G4, n(%)	0/56(34.8)/82(50.9)/23(14.3)/0			
S0/S1/S2/S3/S4, n(%)	22(13.7)/55(34.2)/45(28)/24(14.9)/15(9.3)			
ALT, Alanine Transaminase; HBV, Hepatitis B virus; PN-ALT, persistently normal ALT level; G, Inflammation grade; S, Fibrosis stage				

Table 2. Characteristics of HBV-DNA subgroup in HBeAg-positive among chronic HBV-infected patients PN-ALT

	HBeAg-positive		
Patient characteristics	HBV-DNA (log10IU/ml)		
	≤6.7	>6.7	<i>p</i>
N	33	36	
Male, n (%)	15(45.5)	15(41.7)	0.75
HBV-Family history, n (%)	12(36.4)	10(27.8)	0.45
Age, years	38±9	31±7.6	0.001
≤30	6(18.2)	20(55.6)	
>30	27(81.8)	16(44.4)	
ALT, U/L	28(9-40)	25(12-40)	0.15
HBV DNA, log10IU/ml	5.8(2.7-6.7)	7.25(6.7-8.3)	/
Inflammation grade			
G0-1	7(21.2)	21(58)	0.002
G2-4	26(78.8)	15(42)	
Fibrosis stage			
S0-1	14(42.4)	24(66.7)	0.04
S2-4	19(57.6)	12(33.3)	

ALT, Alanine Transaminase; HBV, Hepatitis B virus; HBeAg, Hepatitis B e antigen; PN-ALT, persistently normal ALT level;

Figures

Figure 1

Screening flow diagram of the study population; ALT, Alanine Transaminase; HBV, Hepatitis B virus

Figure 2

Correlations of variables with hepatic pathological changes in HBeAg-positive (A) HBeAg-negative (B) patients of chronic HBV infected patients with normal ALT. The circle indicated that the correlation was statistically significant ($p < 0.05$). G, Inflammation grade; S, Fibrosis stage; ALT, Alanine Transaminase; HBV, Hepatitis B virus; HBV-FH, HBV- Family History; HBeAg, Hepatitis B e antigen

Figure 3

ROC curves for $G \geq 2$ (A) (AUROC = 0.704, 95% CI 0.58-0.83) sensitivity = 82%, specificity = 64%, $p = 0.0042$; $S \geq 2$ (B) (AUROC = 0.66, 95% CI 0.53-0.79) sensitivity = 61%, specificity = 68%, $p = 0.0024$) in

HBeAg-positive persistently normal ALT patients. AUROC, area under the receiver operating characteristic curve; ALT, Alanine Transaminase; HBeAg, Hepatitis B e antigen

Figure 4

Distribution of ALT levels and viral loads in in HBeAg-positive subjects ALT, Alanine Transaminase; HBeAg, Hepatitis B e antigen

Figure 5

The decision tree for hepatic pathologic changes in HBeAg-positive patients. ALT, Alanine Transaminase; HBeAg, Hepatitis B e antigen

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