Effectiveness of antiviral treatment in HBeAg-negative patients with normal or mildly elevated alanine aminotransferase: a retrospective study

Sufang Wei
Southern Medical University
Meixin Hu
Southern Medical University
Hongjie Chen
Southern Medical University
Qiuli Xie
Shunde Hospital of Southern Medical University
Peng Wang
Shunde Hospital of Southern Medical University
Hong Li
Shunde Hospital of Southern Medical University
Jie Peng (pjie138@163.com)
Southern Medical University

Research Article

Keywords: alanine aminotransferase, antiviral therapy, hepatitis B e-antigen

Posted Date: April 19th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1513335/v1

Abstract

Background

Few studies have assessed the effects of antiviral treatment in hepatitis B e-antigen (HBeAg)-negative patients with normal or mildly elevated alanine aminotransferase (ALT). This study aimed to investigate the effects of antiviral treatment in these patients.

Methods

We retrospectively analysed the outcomes of antiviral treatment in HBeAg-negative patients with normal or mildly elevated ALT who were treated nucleoside/nucleotide analogues (NAs) for up to 96 weeks.

Results

Overall, 128 patients were enrolled, including 74 patients with normal ALT and 54 patients with mildly elevated ALT. The total cumulative rates of viral suppression were 64.06%, 81.97% and 96.39%, at week 24, 48 and 96, respectively. The cumulative rates of viral suppression in normal and mildly elevated ALT groups were 67.86% versus 58.97%, 86.39% versus 76.31% and 93.13% versus 97.04%, at week 24, 48 and 96, respectively. The serum HBV DNA levels at week 12 and the hepatitis B surface antigen (HBsAg) levels at week 24 were significant predictors of the 96-week virological response. Compared with the values at baseline, liver stiffness values significantly decreased at week 48 (8.26 kPa vs 6.60 kPa, $p < 0.001$), and 96 (8.68 kPa vs 6.33 kPa, $p < 0.001$), respectively.

Conclusions

HBeAg-negative patients with normal or mildly elevated ALT could benefit from antiviral therapy with NAs. Antiviral treatment is strongly recommended for these patients.

Background

Chronic hepatitis B virus (HBV) infection remains a major public health problem worldwide and can lead to cirrhosis and hepatocellular carcinoma (HCC), contributing to high mortality and morbidity among humans [1]. The natural history of chronic HBV infection is variable, but it is generally divided into five stages based on hepatitis B e-antigen (HBeAg) status, serum HBV DNA levels, alanine aminotransferase (ALT) levels and staging of liver disease severity, including HBeAg-positive chronic HBV infection, HBeAg-positive chronic hepatitis B, HBeAg-negative chronic HBV infection, HBeAg-negative chronic hepatitis B and hepatitis B surface antigen (HBsAg)negative phase [2]. Ideally, an adult patient with chronic HBV infection should be treated early to improve chance of survival by preventing disease progression. Nevertheless, to date, determining treatment initiation for patients with chronic HBV infection has

traditionally been based on serum ALT levels; ALT ≥ 2 upper limit of normal (ULN) is regarded as a threshold for antiviral therapy, and regular monitoring is recommended for HBeAg-negative individuals with alanine aminotransferase (ALT) < 2 ULN under current guidance [2–4]. Antiviral treatment is not indicated in HBeAg-negative patients with normal ALT for having the following: a low incidence of histological progression, high rates of HBsAg clearance and a very low risk of cirrhosis and HCC [5]. Although ALT elevation remains a critical indicator of hepatic necroinflammation [6], an increasing number of studies reveal that significant abnormalities in the liver tissues frequently occurs in patients without significantly elevated ALT [7, 8]. Previous trials detected necroinflammation in 11.8% of patients with normal ALT, and 22.2% of those with mildly elevated ALT, while the incidence of serious fibrosis was 49.0% and 55.6%, respectively [9]. The incidence of significant liver disease in HBeAg-negative patients was 38.2% [10]. Moreover, some studies have found that untreated HBeAg-negative patients with normal or mildly elevated ALT are at an increased risk of HCC and death [11, 12].

Nucleoside/nucleotide analogues (NAs) are first-line therapeutic drugs for the treatment of chronic hepatitis B patients in most clinical practice guidelines and have been applied in patients due to their robust antiviral activity and safety [11, 12]. There is evidence that NAs can prevent the transmission of HBV, as well as the infection of transplanted livers, by reducing viral loads and producing non-infectious variations of HBV virions [15].

To date, however, there is insufficient data on the antiviral outcomes of NAs in HBeAg-negative patients with normal or mildly elevated ALT. We aimed to evaluate the efficacy of antiviral therapy in patients with ALT < 2 ULN in China.

Liver biopsy is regarded as the gold standard for assessing fibrosis or cirrhosis in patients with CHB; however, it is an invasive and expensive approach. Liver stiffness measurement (LSM) is recommended by previous studies as an alternative and non-invasive technique for evaluating liver fibrosis [3, 16, 17]. Therefore, in the present study, we used a FibroScan device to estimate antiviral outcomes in these patients.

Methods

Patients

A total of 432 HBeAg-negative patients from Nanfang Hospital and Shunde Hospital of Southern Medical University in Guangdong province, China, between 2010 and 2020 were enrolled in this retrospective study. The selection criteria were as follows: 1) HBV DNA load ≥ 2000 IU/ml 2) serum hepatitis B surface antigen (HBsAg) positivity for > 6 months 3) HBeAg-negative and treatment-naïve patients 4) ALT level < 2 times the ULN twice in 6 months (a cut-off of 40 U/L was used for serum ALT levels) and 5) treated with NA therapy only without interruption. The exclusion criteria were as follows: 1) co-infection with hepatitis C virus or human immunodeficiency virus 2) decompensated cirrhosis 3) HCC at enrolment or a previous

history of HCC 4) other chronic liver diseases 5) cardiovascular disease, cancer, autoimmune disorders or renal dysfunction 6) pregnant women and 7) alcoholism.

Ultimately, 128 HBeAg-negative patients were identified for the current study and divided into normal ALT (n = 74) and mildly elevated ALT (n = 54) groups according to baseline serum ALT levels. The study design was approved by the appropriate ethics review board of Nanfang Hospital and Shunde Hospital. Written informed consent was obtained from all patients for their clinical data to be used in this study, and their information was anonymised and de-identified prior to analysis. And a**ll methods were performed in accordance with the relevant guidelines** and regulations.

Virologic and liver function tests

We reviewed the medical records and collected the laboratory data of all patients. First, serum HBV DNA load was measured using a real-time polymerase chain reaction. Second, HBV markers, serum HBV DNA load was measured using a real-time polymerase chain reaction. Second, HBV markers, HBeAg and hepatitis B e-antibody (anti-HBe) levels were determined using commercially available enzyme immunoassays (Alisei Quality System; RADIM, Rome, Italy). Third, serum HBsAg levels were quantitatively measured using Elecsys HBsAg II immunoassays (Roche Professional Diagnostics, Rotkreuz, Switzerland). Fourth, liver biochemistry, including serum ALT, AST, albumin, total bilirubin (TBil) and direct bilirubin (DBil) levels, was examined via the colorimetric method (MODULAR EVO; Hoffmann-La Roche Ltd, Basel, Switzerland). Finally, parameters of haematopoietic function, including platelet count and lymphocyte count, were recorded.

LSM

A FibroScan device (Echosens, Paris, France) was employed by trained operators according to the manufacturer’s instructions to assess the severity of liver fibrosis using transient elastography for each patient. Paired liver stiffness measurements were taken in patients before and after antiviral therapy. The median value from at least 10 successful measurements was considered reliable. The results are expressed as kilopascals (kPa).

Study endpoints

The primary efficacy endpoint of this study was the cumulative incidence of the virological response (VR), which is defined as undetectable HBV DNA in patients with chronic HBV infection. The secondary outcomes were the decline in HBV DNA and HBsAg levels, rate of HBsAg loss, and decrease in LSM. We defined HBsAg loss as HBsAg < 0.05 IU/ml.

Statistical analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) 25.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p < 0.05$. All p-values were two-tailed.

Serum HBsAg and HBV DNA levels were transformed to $\log_{10}$ IU/mL for analysis. The time to response was defined as the time between the start of treatment and the first instance HBV DNA was undetectable. The data are displayed as mean ± standard deviation or median (interquartile range) for numerical data and number (proportion) for nominal data. Differences between the two groups were assessed using the t-test for numerical parameters, Mann-Whitney test for continuous parameters, and chi-squared test for categorical parameters. The comparison of cumulative rates was assessed using the Kaplan–Meier analysis and log-rank test. The factors involved in VR and HBsAg loss were investigated using Cox's regression analysis. The hazard ratio (HR) and 95% confidence intervals (CIs) were calculated to evaluate relative risk confidence. Receiver operating characteristic (ROC) curves were generated to examine the diagnostic capability of diverse serum biochemical markers.

Results

Baseline characteristics

A total of 128 HBeAg-negative CHB patients were enrolled in this retrospective study. Information regarding the patient selection process is displayed in Fig. 1. The baseline characteristics of the included patien

A total of 128 HBeAg-negative CHB patients were enrolled in this retrospective study. Information regarding the patient selection process is displayed in Fig. 1. The baseline characteristics of the included patients are shown in Table 1. Eighty six (67.2%) patients were men, and 54(42.2%) patients had normal ALT. The initial HBV DNA levels in the patients with mildly elevated ALT were significantly higher than those in the patients with normal ALT (5.33 vs 4.66 $\log_{10}$ IU/mL; $p = 0.016$). However, age, TBil, DBil, white blood cell, lymphocyte, platelet, alpha-fetoprotein and HBsAg levels were similar between the patients with normal and mildly elevated ALT.

s are shown in Table 1. Eighty six (67.2%) patients were men, and 54(42.2%) patients had normal ALT. The initial HBV DNA levels in the patients with mildly elevated ALT were significantly higher than those in the patients with normal ALT (5.33 vs 4.66 $\log_{10}$ IU/mL; $p = 0.016$). However, age, TBil, DBil, white blood cell, lymphocyte, platelet, alpha-fetoprotein and HBsAg levels were similar between the patients with normal and mildly elevated ALT.

Table 1
Baseline characteristics of total patients

Characteristics	Normal ALT (n = 74)	Mildly elevated ALT (n = 54)	P-value
Age(yr)	41.7 ± 9.2	41.7 ± 9.9	0.989
Male, n, %	44(59.5%)	42(77.8%)	0.029
ALT (U/L)	25.39 ± 9.03	67.35 ± 20.56	0.000
AST (U/L)	24.71 ± 8.25	41.94 ± 18.00	0.000
ALB (g/L)	45.25 ± 5.69	44.64 ± 5.39	0.592
TBil (μmol/L)	12.65 ± 5.55	12.53 ± 6.39	0.926
DBil (μmol/L)	4.52 ± 2.15	4.71 ± 2.85	0.700
WBC ($\times 10^9$/L)	6.31 ± 1.69	6.15 ± 1.25	0.603
LYM ($\times 10^9$/L)	2.04 ± 0.59	2.12 ± 0.62	0.534
PLT ($\times 10^9$/L)	214.4 ± 49.38	199.8 ± 56.23	0.197
HGB (g/L)	144.2 ± 17.95	151.06 ± 13.08	0.053
HBV DNA ($\log_{10}$IU/mL)	4.66 ± 1.18	5.33 ± 1.74	0.016
HBsAg ($\log_{10}$IU/mL)	3.07 ± 0.63	3.14 ± 0.66	0.589
AFP (ng/mL)	3.37 ± 1.87	4.34 ± 3.44	0.147
LSM (kPa)	7.34 ± 2.31	8.22 ± 3.30	0.207
Notes: continuous data are expressed as the mean ± SD.			
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin; DBil, direct bilirubin WBC, white blood cell; LYM, lymphocyte; PLT, platelet; HGB, hemoglobin; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; AFP, alpha-fetoprotein; LSM, liver stiffness measurement.			

VR

We analysed the outcomes of antiviral therapy in the normal ALT and mildly elevated ALT groups. The total cumulative rates of viral suppression were 46.09%, 64.06%, 77.80%, 81.97%, 89.18% and 96.39% at weeks 12, 24, 36, 48, 72 and 96, respectively. In the normal ALT group, the cumulative rates of viral suppression were 50.00%, 67.85%, 82.98%, 86.39%, 93.19% and 93.19% at weeks 12, 24, 36, 48, 72 and

96, respectively. In the mildly elevated ALT group, the cumulative rates of viral suppression were 40.74%, 58.97%, 71.04%, 76.31%, 85.19% and 97.04% at weeks 12, 24, 36, 48, 72 and 96, respectively. Following the log-rank test, no significant difference in VR was observed between the normal ALT and mildly elevated ALT groups (p = 0.190; Fig. 2).

Associated factors with VR

Univariate and multivariate analyses indicated that the lower HBV DNA levels at week 12 (HR, 0.676; 95% CI, 0.560–0.817; p < 0.001) and HBsAg levels at week 24 (HR, 0.672; 95% CI, 0.485–0.931; p < 0.001) were significantly correlated with VR at week 96 in all patients (Table 2). The relationship between HBV DNA at week 12 and HBsAg levels at week 24 with VR was evaluated using ROC curves. The area under the curve (AUC) for HBV DNA levels at week 12 for predicting VR was 0.845, and the optimal HBV DNA cut-off value was 1.56 $\log_{10}$ IU/mL. The AUC for HBsAg levels at week 24 was 0.772, and the cut-off value for serum HBsAg was 3.57 $\log_{10}$ IU/mL.

Table 2
Factors associated with VR* at week 96 in total NAs-treated patients

Variable	Univariate analysis		Multivariate analysis	
	HR (95.0%CI)	P-value	HR (95.0%CI)	P-value
Age	1.002 (0.982–1.021)	0.892		
Male (sex)	0.823 (0.549–1.255)	0.366		
Baseline ALT(U/L)	0.994 (0.986–1.002)	0.120		
Baseline AST(U/L)	0.993 (0.983–1.004)	0.209		
HBV DNA ($\log_{10}$IU/mL)				
Baseline	0.774 (0.710–0.845)	< 0.001	0.893 (0.780–1.023)	0.104
12 week	0.569 (0.487–0.665)	< 0.001	0.676 (0.560–0.817)	< 0.001
HBsAg ($\log_{10}$IU/mL)	0.657 (0.555–0.778)	< 0.001	1.004 (0.688–1.465)	0.985
Baseline	0.568 (0.470–0.686)	< 0.001	0.672 (0.485–0.931)	0.017
24 week				

*Defined as undetectable HBV DNA by sensitive PCR assay during the treatment and follow-up period. NAs, nucleoside/nucleotide analogues; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; HBV, Hepatitis B virus; HBsAg, hepatitis B surface antigen; HR, Hazard ratio; CI, Confidence interval.

Variation in HBV DNA and HBsAg levels

HBV DNA load significantly decreased among all the CHB patients who underwent antiviral treatment during the study period, regardless of ALT levels (Fig. 3). The extent of HBV DNA decline was calculated. In all patients, mean HBV DNA decreased by 3.28 ± 1.78 IU/mL and 4.08 ± 1.31 IU/mL after 48 weeks and 96 weeks of treatment, respectively. In the normal ALT group, mean HBV DNA decreases of 2.86 ± 1.93 IU/mL and 3.71 ± 1.05 IU/mL were observed after 48 weeks and 96 weeks of treatment, respectively. In the mildly elevated ALT group, these values were 3.73 ± 1.54 and 4.38 ± 1.48 IU/mL, respectively. There was no meaningful effect on HBV DNA decrease in the two group of patients. HBsAg loss was not observed in the present study. Furthermore, HBsAg levels did not differ significantly between the normal and mildly elevated ALT groups at any time point. The mean decline in HBsAg levels at weeks 48 and 96 in these two groups were 0.041 vs 0.259 $\log_{10}$ IU/mL ($p = 0.112$) and 0.137 vs 0.222 $\log_{10}$ IU/mL ($p = 0.412$), respectively (Fig. 4).

LSM improvement

There were 36 CHB patients who received antiviral therapy and underwent FibroScan at treatment initiation and week 48. The results showed that liver stiffness index significantly improved (8.17 kPa vs 6.57 kPa, $p < 0.001$; Fig. 5a). Fibroscan was also performed among 23 patients at week 96 and showed significant improvement of liver stiffness post treatment (8.87 kPa vs 6.43 kPa, $p < 0.001$; Fig. 5b).

Discussion

This research indicates that antiviral therapy can effectively suppress replication of the HBV virus in HBeAg-negative patients with normal or mildly elevated ALT. The decline in HBV DNA and HBsAg levels between the two groups was comparable in this study. Liver stiffness significantly improved after antiviral therapy, which may prevent deterioration of liver histology.

The HBV DNA level in patients with mildly elevated ALT was higher than those in patients with normal ALT in our study, which was in line with the natural history of chronic HBV infection that patients in the phase of HBeAg-negative chronic HBV infection have relatively low HBV DNA levels accompanied by persistently normal ALT; while, patients in the phase of HBeAg-negative chronic hepatitis B have persistent or fluctuating moderate to high levels of serum HBV DNA as well as fluctuating or persistently elevated ALT values [2].

Virologic response may be important when assessing antiviral efficacy of NAs in patients. Sustained suppression of HBV replication has been shown to have a protective effect against liver fibrosis progression and related clinical outcomes [18, 19]. The low incidence of a VR to antiviral treatment was one of the reasons for therapy deferment in HBeAg-negative patients with ALT < ULN. In our study, however, the VR rate at week 96 in the normal ALT group was parallel to the mildly elevated ALT group. In a previous study of HBeAg-negative patients without significantly elevated ALT by Zhao et al. [8], it was

found that patients with normal ALT can achieve a VR rate similar to that of participants with a mild elevation in ALT. In addition, compared with the reported rates of VR to NAs in HBeAg-negative patients with ALT > 2 ULN (range: 88.0– 96.6% at 24 months) [20–23], our data demonstrated that the VR rate of patients with normal ALT and mildly elevated ALT who received antiviral treatment may be comparable to that of patients with ALT > 2 ULN.

Baseline serum HBV DNA levels have been found to correlate with an increased risk of liver necroinflammation and fibrosis in HBeAg-negative individuals [24, 25]. In our current study, HBV viral load in the two groups decreased notably after antiviral treatment. These observations provide further evidence that HBeAg-negative patients without significantly elevated ALT could benefit from antiviral therapy.

Furthermore, the factors associated with 96-week VR in HBeAg-negative patients with normal or mildly elevated ALT and ROC curve analyses were evaluated in this study. Our results indicate that when evaluating these patients based on the areas under the ROC curves for HBV DNA and HBsAg levels during treatment, the HBV viral load at week 12 is a more accurate predictor of 96-week VR than HBsAg levels at week 24. HBV viral load < 1.56 $\log_{10}$ IU/mL at week 12 had favourable virological outcomes. In this study, however, the serum ALT levels failed to predict VR, which supports the conclusion that there is a need to initiate antiviral therapy for these patients, regardless of ALT level.

The low rate of HBsAg loss and depressed HBsAg reductions during treatment with NAs remain a noteworthy issue [26, 27]. Previous studies have demonstrated that the cumulative rate of HBsAg clearance in HBeAg-negative patients was 2.2% at year 5 [28], that the median annual decline of HBsAg levels over 5 years was 0.098 log IU/ml/year and the decline amplitude of HBsAg level was 5.9% at year 2 under treatment with low-genetic barrier NAs [29]. In the current study, no patients achieved HBsAg loss, and the decline amplitude of HBsAg level at week 96 was 6.2% in the total HBeAg-negative patients, which was similar to the result in the study mentioned above.

Another favourable finding in our study was the histological amelioration compared with baseline measurements that was observed in patients following antiviral therapy. Paired FibroScan measurements exhibited obvious changes in liver stiffness at the 48- and 96-week time points. Du et al [30] and Yan et al [31] reported that fibrosis scores decrease significantly after long-term therapy in HBeAg-negative patients with either normal or elevated ALT. These similar outcomes indicate that antiviral treatment for such patients could achieve histological improvement.

Limitations

First, one limitation of the present study is its retrospective design. Nevertheless, this study included patients in two teaching hospitals in China, and the sample size was large. Consequently, the data was representative and reliable. Second, the liver biopsy had not been performed on patients. However, LSM was used as a non-invasive method for the evaluation of liver fibrosis in the study. Third, the follow-up time of antiviral treatment only lasted 96 weeks. More abundant data about the efficacy of antiviral

treatment and the loss of HBsAg will be explored in future studies. Despite these limitations, our current findings provide a novel strategy for managing CHB with ALT < 2 ULN.

Conclusions

NAs were effective for HBV DNA suppression in HBeAg-negative patients with normal or mildly elevated ALT, and were found to improve histologic manifestation. Therefore, antiviral therapy is recommended for HBeAg-negative patients regardless ALT level.

Abbreviations

ALT Alanine aminotransferase

Anti-HBe Hepatitis B e-antibody

AST Aspartate transaminase

AUC Area under the curve

CI Confidence interval

DBil Direct bilirubin

HBeAg Hepatitis B e-antigen

HBsAg Hepatitis B surface antigen

HBV Hepatitis B virus

HCC Hepatocellular carcinoma

HR Hazard ratio

LSM Liver stiffness measurement

NA Nucleoside/nucleotide analogue

TBil Total bilirubin

ROC Receiver operating characteristic

ULN Upper limit of normal

VR Virological response

Declarations

Availability data and materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The study was approved by the ethics committee of Nanfang Hospital and Shunde Hospital of Southern Medical University. Written informed consent was obtained from all patients for their clinical data to be used in this study, and their information was anonymised and de-identified prior to analysis.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Sufang Wei and Meixin Hu analysed and interpreted the patients’ data regarding chronic hepatitis B, and the former was the major contributor in writing the manuscript. Hongjie Chen was responsible for constructing the tables and figures. All authors read and approved the final manuscript.

Acknowledgements

We acknowledge the contributions of all patients and staff from Nanfang Hospital and Shunde Hospital affiliated to Southern Medical University.

Funding

This work was supported by grants from the National Natural Science Foundation of China (81971949).

References

1. Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol. 2018;3:383–403.
2. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370–98.

3. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67:1560–99.
4. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HLY, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10:1–98.
5. Invernizzi F, Viganò M, Grossi G, Lampertico P. The prognosis and management of inactive HBV carriers. Liver Int. 2016;36;Suppl 1:100–4.
6. Kao JH, Hu TH, Jia J, Kurosaki M, Lim YS, Lin HC, et al. East Asia expert opinion on treatment initiation for chronic hepatitis B. Aliment Pharmacol Ther. 2020;52:1540–50.
7. Liao B, Wang Z, Lin S, Xu Y, Yi J, Xu M, et al. Significant fibrosis is not rare in Chinese chronic hepatitis B patients with persistent normal ALT. PLOS ONE. 2013;8:e78672.
8. Zhao Q, Liu K, Zhu X, Yan L, Ding Y, Xu Y, et al. Anti-viral effect in chronic hepatitis B patients with normal or mildly elevated alanine aminotransferase. Antiviral Res. 2020;184:104953.
9. Gong X, Yang J, Tang J, Gu C, Huang L, Zheng Y, et al. A mechanistic assessment of the discordance between normal serum alanine aminotransferase levels and altered liver histology in chronic hepatitis B. PLOS ONE. 2015;10:e0134532.
10. Wang H, Ru GQ, Yan R, Zhou Y, Wang MS, Cheng MJ. Histologic disease in Chinese chronic hepatitis B patients With low viral loads and persistently normal alanine aminotransferase levels. J Clin Gastroenterol. 2016;50:790–6.
11. Kim HC, Nam CM, Jee SH, Han KH, Oh DK, Suh I. Normal serum aminotransferase concentration and risk of mortality from liver diseases: prospective cohort study. BMJ. 2004;328:983.
12. Sharma SK, Saini N, Chwla Y. Hepatitis B virus: inactive carriers. Virol J. 2005;2:82.
13. Su SY. The impact of national viral hepatitis therapy program and hepatitis B vaccination program on mortality from acute and chronic viral hepatitis in Taiwan. Hepatol Int. 2019;13:157–64.
14. Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, et al. Entecavir versus lamivudine for Patients with HBeAg-Negative Chronic hepatitis B. N Engl J Med. 2006;354:1011–20.
15. Liu Y, Liu H, Hu Z, Ding Y, Pan XB, Zou J, et al. Hepatitis B virus virions produced Under Nucleos(t)ide analogue treatment are mainly not infectious because of irreversible DNA chain termination. Hepatology. 2020;71:463–76.
16. Li Q, Chen L, Zhou Y. Diagnostic accuracy of liver stiffness measurement in chronic hepatitis B patients with normal or mildly elevated alanine transaminase levels. Sci Rep. 2018;8:5224.
17. Seo YS, Kim MY, Kim SU, Hyun BS, Jang JY, Lee JW, et al. Accuracy of transient elastography in assessing liver fibrosis in chronic viral hepatitis: A multicentre, retrospective study. Liver Int. 2015;35:2246–55.
18. Zoutendijk R, Reijnders JG, Zoulim F, Brown A, Mutimer DJ, Deterding K, et al. Virological response to entecavir is associated with a better clinical outcome in chronic hepatitis B patients with cirrhosis. Gut. 2013;62:760–5.

19. Sun Y, Wu X, Zhou J, Meng T, Wang B, Chen S, et al. Persistent low level of hepatitis B virus promotes fibrosis progression During therapy. Clin Gastroenterol Hepatol. 2020;18:2582–2591.e6.
20. Suzuki F, Suzuki Y, Hosaka T, Sezaki H, Akuta N, Fujiyama S, et al. Efficacy of long-term tenofovir-based rescue therapy in patients with chronic hepatitis B refractory to nucleoside/nucleotide analogs. J Gastroenterol. 2017;52:641–51.
21. Xie YD, Ma H, Feng B, Wei L. Efficacy of real-world entecavir therapy in treatment-naïve chronic hepatitis B patients. Chin Med J (Engl). 2017;130:2190–7.
22. Viganò M, Loglio A, Grossi G, Lampertico P. Tenofovir alafenamide (TAF) treatment of HBV, what are the unanswered questions? Expert Rev Anti Infect Ther. 2018;16:153–61.
23. Ibragimov EK, Abdurakhmanov DT, Rozina TP, Nikulkina EN, Tanaschuk EL, Odintsov AV, et al. Efficacy and safety of long-term therapy with nucleos(t)ide analogues in chronic hepatitis B. Ter Arkh. 2019;91:40–7.
24. Diktas H, Karacaer Z, Özturk II, Cicek H. Comparison of relationship between histopathological, serological and biochemical parameters in patients with chronic hepatitis B infection. Postgrad Med J. 2016;92:693–6.
25. Liu C, Wang L, Xie H, Zhang L, Wang B, Luo C, et al. The relationship between serum hepatitis B virus DNA level and liver histology in patients with chronic HBV infection. PLOS ONE. 2018;13:e0206060.
26. Lam YF, Seto WK, Wong D, Cheung KS, Fung J, Mak LY, et al. Seven-year treatment outcome of entecavir in a real-world cohort: effects on clinical parameters, HBsAg and HBcrAg levels. Clin Transl Gastroenterol. 2017;8:e125.
27. Suzuki F, Hosaka T, Suzuki Y, Sezaki H, Akuta N, Fujiyama S, et al. Long-term outcome of entecavir treatment of nucleos(t)ide analogue-naïve chronic hepatitis B patients in Japan. J Gastroenterol. 2019;54:182–93.
28. Hosaka T, Suzuki F, Kobayashi M, Seko Y, Kawamura Y, Sezaki H, et al. Clearance of hepatitis B surface antigen during long-term nucleot(s)ide analog treatment in chronic hepatitis B: results from a nine-year longitudinal study. J Gastroenterol. 2013;48:930–41.
29. Seto WK, Lam YF, Fung J, Wong DK, Huang FY, Hung IF, et al. Changes of HBsAg and HBV DNA levels in Chinese chronic hepatitis B patients after 5 years of entecavir treatment. J Gastroenterol Hepatol. 2014;29:1028–34.
30. Du X, Wang J, Shao L, Hu X, Yang C, Shen L, et al. Histological improvement of long-term antiviral therapy in chronic hepatitis B patients with persistently normal alanine aminotransferase levels. J Viral Hepat. 2013;20:328–35.
31. Yan JY, Li ZQ, Yu ZJ, Kan QC. Management of individuals with chronic hepatitis B virus infection and persistent normal or mildly elevated aminotransferase levels. J Cell Biochem. 2019;120:6632–41.

Figures

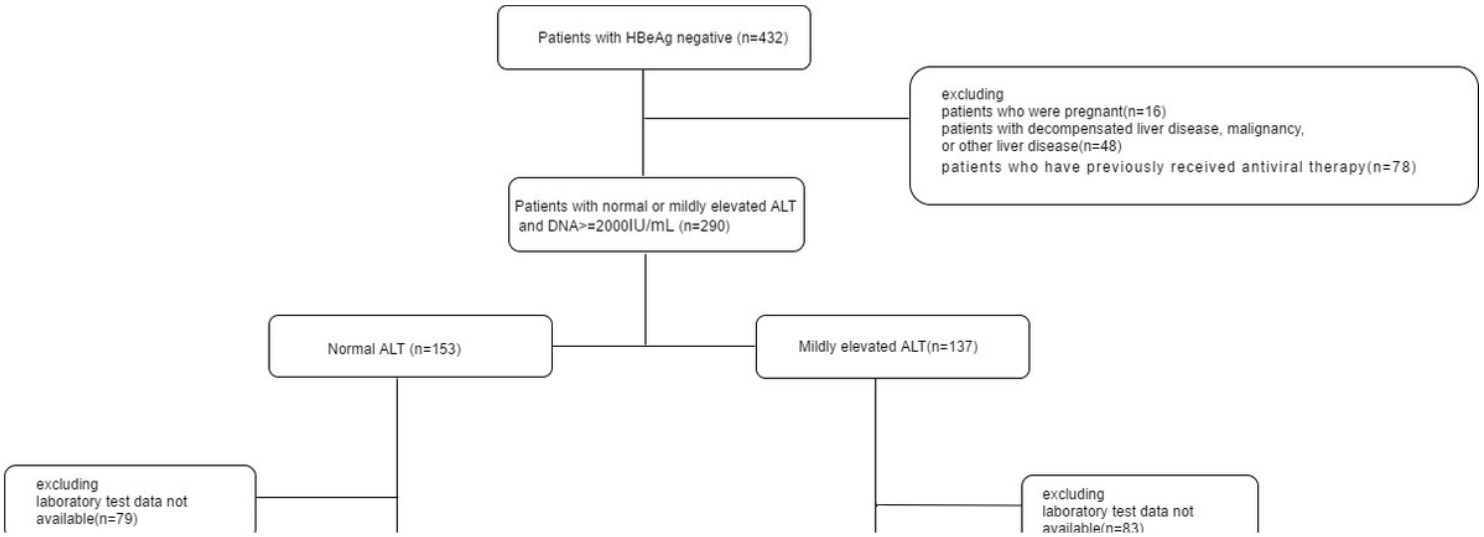

Figure 1

A flow chart of the patient selection process (CHB, chronic hepatitis B; ALT, alanine aminotransferase; HBeAg, hepatitis B e-antigen).

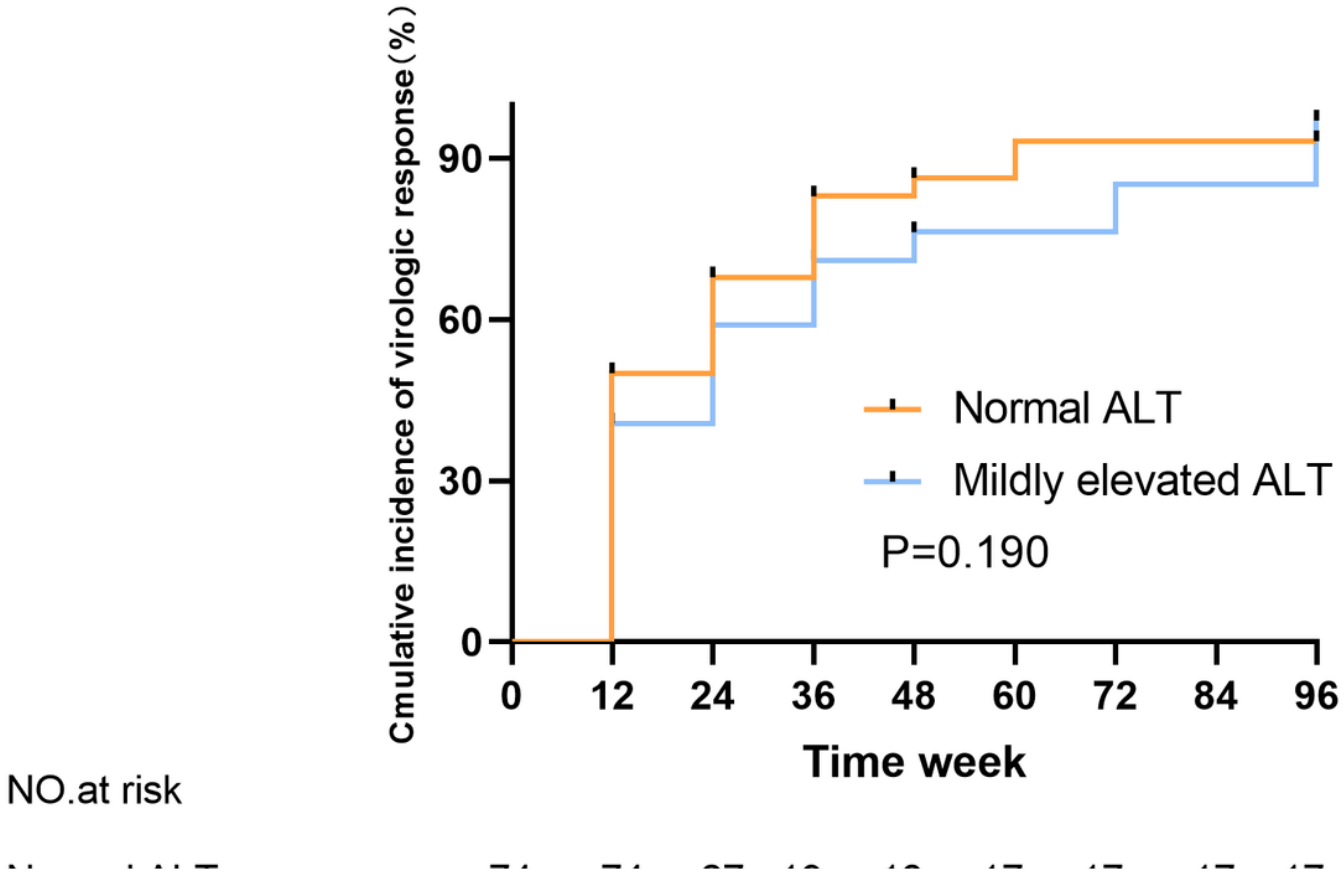

Figure 2

The cumulative incidence of the virological response in the normal and mildly elevated ALT groups; the p-value was determined using log-rank testing (VR: virological response).

Figure 3

HBV DNA levels in patients with normal or mildly elevated ALT levels at each time-point (*, $p<0.05$).

Figure 4

The trend of HBsAg levels in patients with normal or mildly elevated ALT levels across the study time points.

Figure 5

(a). FibroScan before treatment and week 48. Figure 5 (b). FibroScan before treatment and week 96 (***, $p<0.001$).