Predictors of liver histological changes and a sustained virological response to peginterferon among chronic hepatitis B e antigen-positive patients with normal or minimally elevated alanine aminotransferase levels

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Summary
A proportion of chronic hepatitis B patients with normal or only minimally elevated alanine aminotransferase (ALT) levels display significant histologic changes and would benefit from antiviral therapy. We aim to evaluate the histologic abnormalities seen in these patients and then determine which of them would most likely respond to peginterferon therapy. One hundred and thirteen hepatitis B e antigen (HBeAg)-positive patients with a normal or minimally elevated ALT level and moderate-to-severe histologic changes in their liver tissue were selected to receive peginterferon monotherapy and participate in a follow-up analysis. A multiple logistic regression analysis indicated that increasing age ($P = .049$) and lower hepatitis B virus (HBV) DNA levels ($P = .038$) were associated with significant histological abnormalities in patients with a normal or minimally elevated ALT. Our predictive model which incorporated HBeAg testing at treatment week 12 combined with hepatitis B surface antigen (HBsAg) testing at treatment week 24 was able to identify which patients with a normal ALT level would achieve a sustained virological response (SVR) (positive predictive value [PPV]: 66.7%, negative predictive value [NPV]: 90.0%). Lower HBsAg and HBeAg levels at treatment week 24 were associated with a SVR in patients with a minimally elevated ALT level (PPV: 100.0%, NPV: 100.0%). A liver biopsy and antiviral therapy should be strongly considered when treating HBeAg-positive patients with a normal or minimally elevated ALT level, low HBV DNA level, and aged >35 years. On-treatment quantification of combined HBsAg and HBeAg test results may be useful for predicting a SVR to peginterferon monotherapy in these patients.

KEYWORDS
alanine aminotransferase, chronic hepatitis B, hepatitis B, histological activity, peginterferon, sustained virological response

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1 | INTRODUCTION

Chronic hepatitis B (CHB) remains a major health problem in China, and a persistent hepatitis B virus (HBV) infection can lead to severe liver disorders, such as liver cirrhosis, hepatic failure and hepatocellular
carcinoma. However, intervention with antiviral agents may prevent the progression of hepatitis B to these severe diseases and improve the functional capacity of remaining viable liver tissue. A recent study showed that treatment of CHB should start earlier than recommended by current guidelines.

In clinical practice, physicians have primarily used alanine aminotransferase (ALT) levels as a convenient surrogate marker of liver damage. However, some studies have demonstrated that a substantial proportion of patients with a normal or only minimally elevated ALT level (1-2× upper limit of normal (ULN)) may not show clinical symptoms of liver disease, but still display significant abnormalities in their liver tissue during a histological examination. Such patients should be started on a CHB treatment protocol appropriate for their level of disease.

Due to its durable viral response and finite treatment course, peginterferon remains an important first-line treatment option for CHB. Because peginterferon functions as an immune mediator, high levels of ALT (two- to fivefold ULN) were determined to be an important pretreatment predictor of patient response in a previous study, and twofold ULN for ALT suggested as a reasonable threshold for initiating therapy even without liver biopsy. While another published report found 20% of patients with lower ALT levels, < twofold ULN would achieve a sustained response to treatment. Furthermore, as a substantial proportion of such patients do have suffered significant liver damage, a single normal or only mildly increased ALT value might lead to an unnecessary delay in initiating antiviral therapy. However, the aforementioned studies do not describe methods for identifying which patients with a normal or minimally elevated ALT level would most likely benefit from peginterferon therapy.

The current study was performed to identify which CHB patients with a normal or minimally elevated ALT level should receive antiviral therapy and then investigate the efficacy of peginterferon in these patients. We also developed a robust model for use in predicting a successful outcome of antiviral therapy.

2 | PATIENTS AND METHODS

2.1 | Patient cohort

Between 2010 and 2014, a total of 416 adult CHB patients who had undergone a liver biopsy were recruited for this study at the Department of Infectious Disease of the Sixth People’s Hospital affiliated with Shanghai JiaoTong University (Shanghai, China) without interruption for 48 weeks. The exclusion criteria included: an active hepatitis C virus infection, hepatitis D virus, or human immunodeficiency virus co-infection; patients who were pregnant; and patients with decompensated liver disease, malignancy, or other liver disease such as alcoholic hepatitis and autoimmune liver disease. Sustained virological response (SVR) was defined as a serum HBV DNA level that was undetectable by real-time polymerase chain reaction (RT-PCR) at 48 weeks post-treatment (<500 copies/mL) and HBeAg seroconversion; HBeAg seroconversion was defined as the disappearance of HBeAg with detectable anti-HBe. The study protocol was approved by the Ethical Committee of the Sixth People’s Hospital of Shanghai JiaoTong University in accordance with the Helsinki Declaration. Each enrolled patient provided a signed written informed consent document.

2.2 | Data collection

The follow-up schedule for all patients was as follows: biochemical, serological, and virological parameters were regularly measured every 3 months at an outpatient clinic, HBV serology, including HBsAg, anti-HBsAg, HBeAg, and anti-HBeAg testing. Serum HBsAg testing was performed using commercial kits (Abbott Laboratories; Lake Bluff, IL, USA). HBV DNA titres were quantified using the Taq-Man probe-based RT-PCR quantification method (Qiagen Bio-Tech Company; Shenzhen, China) with a lower detection limit of 500 copies/mL. A conversion factor (5.26) was used for converting copies/mL to IU/mL. Liver biochemistry was determined at each visit with a routine automated analysis system (Beckman Coulter; Fullerton, CA, USA). HBV genotyping was performed using the PCR-restriction fragment length polymorphism method. The patients were checked for drug compliance and clinical adverse events during each follow-up visit.

2.3 | Liver histology assessments

All liver biopsy specimens were reviewed by experts in gastroenterological pathology who were blinded to the patients’ biochemical and virological results. The degrees of liver necroinflammation and fibrosis were assessed according to criteria used in the Knodell scoring system. Knodell necroinflammatory scores were divided into four categories: minimal (0-3), mild (4-6), moderate (7-9) and severe (10-14) chronic hepatitis. The Knodell fibrosis scores were staged into four categories: minimal (0), mild (1), moderate (2-3), and severe (4). Moderate and severe scores were considered as reasons for starting treatment.

2.4 | Statistical analyses

Serum HBsAg, HBeAg, and HBV DNA levels were logarithmically transformed for analysis. Continuous data are presented as the median (interquartile range). Differences between groups were analysed using the student’s t-test and the nonparametric Wilcoxon signed-rank test for quantitative data, and Pearson’s chi-squared test and Fisher’s exact test were used for analysing qualitative data. Univariate and multivariate logistic regression analyses were performed, and
receiver operating characteristic (ROC) curves were created to evaluate the diagnostic ability of various serum biomarkers. A statistically significant result was defined as a $P$ value < .05, as calculated by a two-sided test. All calculations were performed using SPSS Statistics for Windows, Version 17.0. Chicago, IL: SPSS Inc.

3 | RESULTS

3.1 | Baseline characteristics of patients

Among the 416 screened CHB patients, 23 patients were excluded; therefore, the results from 393 patients were included in our final analysis. Details of the included and excluded patients are shown in Figure 1. One hundred and thirteen of the eligible patients (28.75%) had significant liver inflammation, and 78 (19.85%) had significant fibrosis. The patients with significant liver inflammation were an average of 5 years older than the patients with mild liver inflammation. The sex, genotype, HBsAg results, HBeAg results, HBV DNA levels and ALT levels of the patients were similar, regardless of whether they showed inflammatory changes. Patients with severe fibrosis had lower HBeAg and HBV DNA levels than patients with mild fibrosis (Table 1).

3.2 | Parameters associated with liver histological abnormalities

To select parameters which might predict histological abnormalities, multivariate analysis was performed using the following factors as they existed at baseline: age, gender, viral genotype, serum ALT, HBsAg, HBeAg and HBV DNA levels. Our analysis showed that among patients with a normal or minimally elevated ALT level, increasing age

![FIGURE 1](image-url) Flow chart showing the patient screening and selection process

| TABLE 1 | Patient characteristics categorized by histological changes |
|---------------------------------------------|---------------------------------------------|
| Characteristics | Histological inflammation | Fibrosis |
| No. of patients | Mild (71.25%) | Significant (28.75%) | Mild (80.15%) | Significant (19.85%) |
| Age | 34.50 (24.50-41.75) | 37.00 (32.00-44.00) | 35.00 (27.50-42.00) | 37.00 (32.00-47.00) |
| Gender (male/female) | 203/77 | 78/35 | 220/95 | 60/18 |
| Genotype (B/C) | 111/169 | 48/65 | 121/194 | 31/47 |
| ALT (U/L) | 46.00 (35.50-74.50) | 53.00 (34.00-81.00) | 50.00 (36.50-75.50) | 38.60 (27.00-107.00) |
| HBsAg ($\log_{10}$ IU/mL) | 3.69 (3.07-4.68) | 3.69 (3.39-4.61) | 3.72 (3.31-4.73) | 3.58 (3.19-3.74) |
| HBeAg ($\log_{10}$ PEIU/mL) | 2.13 (1.36-3.14) | 1.75 (0.90-2.90) | 2.77 (1.46-3.12) | 1.02 (0.62-1.44) |
| HBV DNA ($\log_{10}$ IU/mL) | 6.16 (4.44-6.59) | 6.06 (4.36-6.56) | 6.25 (4.72-6.81) | 4.55 (3.15-6.42) |

Data are expressed as median (interquartile range) or proportion.
ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBV DNA, hepatitis B virus DNA.
was associated with significant necroinflammation, and lower HBV DNA levels were associated with significant fibrosis (Table 2).

### 3.3 Parameters associated with a clinical response in patients stratified by ALT

Among 393 patients, 113 patients met the criteria for receiving peginterferon treatment. These included 57 patients with a normal ALT level and 56 patients with a minimally elevated ALT level. At the final evaluation during treatment and follow-up period, there were no significant differences in total HBeAg seroconversion rates between patients with a normal ALT level and those with a minimally elevated ALT level at different time points (patients with a normal ALT level vs patients with a minimally elevated ALT level: 48 weeks, 35.09% vs 41.07%, \( P = .564 \); 96 weeks, 19.29% vs 32.14%, \( P = .136 \)). SVR rates were higher among patients with a minimally elevated ALT level than those with a normal ALT level at 96 weeks (28.57% vs 17.54%, \( P = .186 \)), but no significant difference was observed.

Among patients with normal ALT levels, the characteristics of age, gender, genotype distribution, histological damage, and baseline HBsAg, HBeAg, and HBV DNA levels were similar in the SVR and non-SVR groups. However, during the treatment period, the serum HBeAg levels at weeks 12 (\( P = .034 \)) and 24 (\( P = .037 \)), as well as the HBsAg levels at week 24 (\( P = .004 \)), were significantly lower in the SVR group than in the non-SVR group (Table 3). Our multivariate analysis indicated that lower HBeAg levels at treatment week 12 (OR=1.75, 95% CI, 1.00-2.19; \( P = .039 \)) and lower HBsAg levels at treatment week 24 (OR=3.56, 95% CI, 0.97-9.27; \( P = .009 \)) were accurate predictors of a SVR (Table 4).

Among patients with minimally elevated ALT levels, the SVR group had higher liver inflammation scores (\( P = .046 \)) and HBeAg levels (\( P = .045 \)) before treatment when compared with the non-SVR group. Additionally, the sustained responders showed significantly lower HBsAg, HBeAg and HBV DNA levels during treatment when compared with the nonsustained responders (Table 3). A step-wise multiple regression analysis revealed that lower HBeAg levels at treatment week 12 (OR, 2.92, 95% CI, 0.97-6.71; \( P = .011 \)) and 24 (OR, 2.85, 95% CI, 0.93-7.16; \( P = .025 \)), as well as decreased HBsAg levels at treatment week 24 (OR, 1.69, 95% CI, 1.00-2.82; \( P = .047 \)), were independently correlated with a SVR (Table 4).

#### TABLE 2 Multivariate analysis of baseline parameters associated with significant abnormalities

| Parameter                          | OR  | 95% CI      | \( P \) value |
|------------------------------------|-----|-------------|---------------|
| Significant inflammation            |     |             |               |
| Age                                | 1.09| 0.99-1.19   | .049          |
| Significant fibrosis               |     |             |               |
| HBV DNA at baseline                | 0.39| 0.16-1.01   | .038          |

#### TABLE 3 Changes in HBsAg, HBeAg, and HBV DNA levels in HBV patients according to their treatment response

| Characteristics          | Normal ALT                      | Minimally elevated ALT                      | \( P \) value |
|--------------------------|---------------------------------|---------------------------------------------|---------------|
|                         | SVR (17.54%)                    | 10 (17.54%)                                 |               |
|                         | Non-SVR (82.46%)                | 47 (82.46%)                                 |               |
| No. of patients          |                                 |                                             |               |
| Age                      | 30.50 (28.00-34.00)             | 34.00 (27.00-45.00)                         | .070          |
| Gender (male/female)     | 7/3                             | 30/17                                       | 1.000         |
| Genotype (B/C)           | 4/6                             | 20/27                                       | 1.000         |
| Necroinflammation score  | 7.50 (6.25-8.75)                | 6.00 (4.00-7.00)                            | .066          |
| Fibrosis score           | 2.00 (2.00-2.00)                | 2.50 (2.00-3.25)                            | .052          |
| HBsAg (log10 IU/mL)      |                                 |                                             |               |
| Baseline                 | 4.00 (3.33-4.10)                | 3.64 (3.29-4.09)                            | .740          |
| 12 week                  | 3.51 (3.04-3.90)                | 3.49 (3.24-4.19)                            | .136          |
| 24 week                  | 3.23 (2.36-3.44)                | 3.46 (3.14-4.28)                            | .004          |
| HBeAg (log10 PEIU/mL)    |                                 |                                             |               |
| Baseline                 | 1.96 (0.27-2.82)                | 2.46 (1.82-2.93)                            | .064          |
| 12 week                  | 0.92 (0.18-2.09)                | 1.88 (0.72-2.86)                            | .034          |
| 24 week                  | 0.67 (-0.15-1.64)               | 1.45 (0.75-2.83)                            | .037          |
| HBV DNA (log10 IU/mL)    |                                 |                                             |               |
| Baseline                 | 6.23 (4.93-6.81)                | 6.02 (5.58-7.08)                            | .179          |
| 12 week                  | 4.20 (2.88-6.65)                | 5.75 (2.55-6.24)                            | .686          |
| 24 weeks                 | 2.00 (2.00-4.16)                | 3.03 (2.00-5.35)                            | .337          |

Data are expressed as median (interquartile range) or proportion. 
SVR, sustained virological response; ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBV DNA, hepatitis B virus DNA.
3.4 Prediction of a SVR for patients stratified by ALT

Receiver operating characteristic curves were generated from our univariate and multivariate analyses of serum biomarkers and histological changes to evaluate the predictive values of these variables for a SVR in CHB patients with normal or minimally elevated ALT levels. Among patients with a normal ALT level, the AUC for HBeAg at week 12 for predicting a SVR was only 0.66. The HBeAg cut-off value of 1.54 log_{10} PEIU/mL (35 PEIU/mL) had a sensitivity of 63.2%, specificity of 77.8%, positive predictive value (PPV) of 50.0%, and a negative predictive value (NPV) of 86.7% (Figure 2). Among patients with a minimally elevated ALT level, the AUC for HBeAg at week 12 was 0.79, and the

### TABLE 4 Multivariate analysis of baseline and on-treatment factors associated with a SVR

| Parameter                              | OR   | 95% CI   | P value |
|----------------------------------------|------|----------|---------|
| Normal ALT                             |      |          |         |
| HBeAg at week 12 (log_{10} PEIU/mL)    | 1.75 | 1.00-2.19| .039    |
| HBsAg at week 24 (log_{10} IU/mL)      | 3.56 | 0.97-9.27| .009    |
| Minimally elevated ALT                 |      |          |         |
| HBeAg at week 12 (log_{10} PEIU/mL)    | 2.92 | 0.97-6.71| .011    |
| HBeAg at week 24 (log_{10} PEIU/mL)    | 2.85 | 0.93-7.16| .025    |
| HBsAg at week 24 (log_{10} IU/mL)      | 1.69 | 1.00-2.82| .047    |

OR, odds ratio; CI, confidence interval; ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen.

**FIGURE 2** Flow chart illustrating the use of an HBeAg level of 1.54 log_{10} PEIU/mL at week 12 combined with an HBsAg level of 3.40 log_{10} IU/mL at week 24 (A) among patients with a normal ALT level and an HBsAg level of 2.15 log_{10} IU/mL combined with an HBeAg level of 1.32 log_{10} PEIU/mL at week 24; (B) among patients with a minimally elevated ALT level to predict a sustained response at week 96.
combined HBsAg and HBeAg AUC at week 24 for predicting a SVR was 0.90. When using a cut-off value of \(1.43 \log_{10}\) PEIU/mL (25 PEIU/mL), the sensitivity, specificity, positive predictive value, and negative predictive value of HBeAg for predicting a SVR was 88.9, 63.6%, 45.5%, and 88.0%, respectively. In this regard, the HBSAg value of 2.15 \(\log_{10}\) IU/mL when used in combination with an HBeAg value of 1.32 \(\log_{10}\) PEIU/mL had a sensitivity of 83.3%, specificity of 90.9%, positive predictive value of 100% and negative predictive value of 100% (Figure 2), and was therefore better at predicting a SVR than was either the HBeAg or HBsAg value by itself.

4 | DISCUSSION

Previous investigations have demonstrated that HBeAg-positive patients with normal ALT levels usually display no or only minimal histologic evidence of progressive liver disease; thus, antiviral treatment is not usually recommended for these patients. However, in our study, we found that 28.75% of CHB patients with normal or minimally elevated ALT levels had a significant liver inflammation score, and 19.85% had fibrosis > stage 2. This finding is similar to that in another study from Hong Kong, which found that an elevated ALT does not accurately predict significant liver injury. Additionally, Liao reported that significant fibrosis is not rare among patients with slightly increased ALT levels. Thus, our findings suggest that decisions on whether to initiate antiviral therapy should not be heavily based on a particular ALT threshold. Furthermore, our results showed that being older than 35 years of age and having an HBV DNA load \(<3.94 \log_{10}\) IU/mL was strongly predictive of significant necroinflammation and fibrosis, respectively. These results highlight the need to perform a liver biopsy and make a treatment decision for older CHB patients who have normal or minimally elevated ALT levels and low levels of HBV DNA. Another report recommended performing a liver biopsy when evaluating HBeAg-negative CHB patients >30 years of age and with an HBV DNA level \(\geq 10^4\) copies/mL, regardless of their ALT level.

We also examined various factors that were associated with the long-term clinical outcome of CHB patients with normal and minimally elevated ALT levels. In 1977, a study reported that HBeAg levels were strongly correlated with hepatitis B viral load. Decreased HBeAg levels eventually resulted in reduced HBV DNA replication, and thus, HBeAg seroconversion was considered as a turning point for predicting the efficacy of antiviral therapy. Our results also showed that HBeAg levels decreased more significantly at treatment weeks 12 and 24 among patients who ultimately achieved a SVR, when compared with patients who did not achieve a SVR. However, some evidence also suggests that HBeAg levels do not always correlate with a SVR. Thompson et al. identified the emergence of basal core promoter/precore (BCP/PC) variant quasispecies capable of influencing HBeAg titre independent of viral load. Indeed, if one were to continue treating all patients with the HBeAg cut-off value at week 12, \(\geq 50\)% of the patients who achieved a sustained response in our study population would not have been treated. Hence, changes in HBeAg levels during treatment should not be used as the sole basis to make treatment decisions.

Several recent studies have suggested that HBsAg monitoring might more reliably predict the response to antiviral therapy in patients treated with peginterferon. In fact, envelope protein expression regulates the amplification of covalently closed circular DNA (cccDNA) in HBV by modulating a direct interaction between the nucleocapsid and the L protein. Thus, reduced HBeAg levels are highly correlated with reduced cccDNA levels and can be used to predict a sustained response. Consequently, we sought to combine HBeAg levels and HBeAg levels to formulate a suitable model for predicting a SVR. Our results showed that when evaluating patients with normal ALT levels by comparing the areas under the ROC curve for HBsAg and HBeAg absolute levels during treatment, the HBeAg level at week 24 rather than the HBeAg level at week 12 more accurately predicted a SVR. However, these results have limited clinical significance, because even patients with HBsAg level \(<3.40 \log_{10}\) IU/mL at week 24 have a significant probability of not achieving a SVR. If we had used the HBsAg cut-off value of 3.40 \(\log_{10}\) IU/mL at week 24 as a SVR predictor, only 53.8% of our patient population with a normal ALT level would achieve a SVR. However, when combining a serum HBeAg level of \(\leq 1.54 \log_{10}\) PEIU/mL at week 12 of therapy with an HBsAg level of \(\leq 3.40 \log_{10}\) IU/mL at week 24 of therapy, there was a 66.7% probability of achieving a response. When evaluating patients with minimally elevated ALT levels, combining the predictors of a serum HBsAg level \(\leq 2.15 \log_{10}\) IU/mL and an HBeAg level \(\geq 1.32 \log_{10}\) PEIU/mL at week 24 increased the AUC to 0.90. This AUC had a negative predictive value of 100% for a sustained response, making it better than using either the HBsAg or HBeAg level alone. Accordingly, patients who are likely to be nonsustained responders can be identified by having their HBsAg and HBeAg concentrations evaluated after 24 weeks of optimal peginterferon therapy.

Although our results suggest a promising new strategy for evaluating patients with normal or minimally elevated ALT levels, they still have several limitations. First, the CHB patients who had normal or minimally elevated ALT levels and received antiviral therapy were strictly selected according to specified guidelines; therefore, the number of enrolled patients was relatively small. Second, because the study had a retrospective design, the patient selection process may have been affected by referral bias. Larger well-designed studies are needed to validate our findings.

In summary, a reliance on increased ALT levels underestimates the true proportion of HBeAg-positive patients with normal or only minimally elevated ALT levels who have significant abnormalities in their liver tissue that would only be detected by a histologic examination. This supports the case for performing histologic assessments of liver damage in these patients and especially when evaluating patients of older age and with low HBV DNA levels. The combined use of HBsAg and HBeAg concentrations at 24 weeks of treatment with peginterferon can help physicians to make optimal treatment decisions for this special patient population.

CONFLICT OF INTEREST

The authors who have taken part in this study declare that they do not have anything to disclose regarding conflict of interest with respect to the manuscript.
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