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ORIGINAL ARTICLE

Retrospective Cohort Study

# Association of serum gamma-glutamyl transferase with treatment outcome in chronic hepatitis B patients

Rui Huang, Chen-Chen Yang, Yong Liu, Juan Xia, Ran Su, Ya-Li Xiong, Gui-Yang Wang, Zhen-Hua Sun, Xiao-Min Yan, Shan Lu, Chao Wu

Rui Huang, Juan Xia, Ran Su, Ya-Li Xiong, Gui-Yang Wang, Zhen-Hua Sun, Xiao-Min Yan, Chao Wu, Department of Infectious Diseases, Nanjing Drum Tower Hospital, Nanjing University Medical School, Nanjing 210008, Jiangsu Province, China

Chen-Chen Yang, Department of Infectious Diseases, Qidong People's Hospital, Qidong 226200, Jiangsu Province, China

Yong Liu, Department of Laboratory Medicine, Nanjing Drum Tower Hospital, Nanjing University Medical School, Nanjing 210008, Jiangsu Province, China

Shan Lu, Department of Medicine, University of Massachusetts Medical School, Worcester, MA 01605, United States

Author contributions: Wu C and Lu S designed the research; Huang R, Yang CC, Liu Y, Xia J, Su R, Xiong YL, Wang GY, Sun ZH, and Yan XM performed the research; Huang R and Yang CC analyzed the data; Huang R wrote the paper; all authors have read and approved the final version for submission.

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Correspondence to: Chao Wu, MD, PhD, Department of Infectious Diseases, Nanjing Drum Tower Hospital, Nanjing University Medical School, 321 Zhongshan Road, Nanjing 210008, Jiangsu Province, China. dr.wu@nju.edu.cn
Telephone: +86-25-83105890
Fax: +86-25-83307115

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## Abstract

**AIM:** To investigate the association of serum gamma-glutamyl transferase (GGT) levels with chronic hepatitis B infection and hepatitis B e antigen (HBeAg) seroconversion.

**METHODS:** A retrospective study was performed on clinical data collected from patients who had been positive for hepatitis B surface antigen for > 6 mo and who were antiviral-treatment naïve ($n$ = 215) attending the Hepatitis Clinic at Nanjing Drum Tower Hospital between August 2010 and December 2013. Healthy individuals without liver disease ($n$ = 83) were included as controls. Patients were categorized into four groups based on disease status as recommended by the European Association for the Study of the Liver: immune tolerance (IT; $n$ = 47), HBeAg-positive hepatitis (EPH; $n$ = 93), HBeAg-negative hepatitis (ENH;

*n* = 20), and inactive carrier (IC; *n* = 55). Prediction of complete response (CR) based on serum GGT was also examined in EPH patients (*n* = 33) treated for 48 wk with nucleos(t)ide analogue (NA) therapy, including lamivudine plus adefovir combination therapy (*n* = 20) or entecavir monotherapy (*n* = 13). CR was defined as a serum hepatitis B virus DNA level < 500 copies/mL and HBeAg seroconversion by 48 wk of treatment.

**RESULTS:** Serum GGT levels were significantly increased in EPH and ENH patients relative to the IT, IC, and healthy control groups ($P < 0.01$ for all). However, no significant difference in serum GGT levels was found between the EPH and ENH groups. Baseline serum GGT levels were significantly higher in patients who achieved CR (7/33; 21.2%) compared to patients in the non-CR group (26/33; 78.8%; $P = 0.011$). In addition, the decline in serum GGT was greater in CR patients compared to non-CR patients after 24 wk and 48 wk of treatment ($P = 0.012$ and $P = 0.008$, respectively). The receiver operating characteristic curve yielded a sensitivity of 85.71% and a specificity of 61.54% at a threshold value of 0.89 times the upper limit of normal for baseline serum GGT in the prediction of CR following NA therapy.

**CONCLUSION:** Serum GGT is significantly elevated in EPH and ENH patients and is a potential biomarker for the prediction of HBeAg seroconversion following NA therapy.

**Key words:** Gamma-glutamyl transferase; Hepatitis B e antigen; Hepatitis B; Natural history; Nucleos(t)ide analogues; Seroconversion



**Core tip:** Serum gamma-glutamyl transferase (GGT) levels have been associated with treatment response in chronic hepatitis C patients. However, whether serum GGT levels are associated with chronic hepatitis B infection is unknown. This study provides evidence that serum GGT levels are significantly elevated in patients with hepatitis B e antigen (HBeAg)-positive and HBeAg-negative hepatitis patients. Furthermore, serum GGT levels were investigated as a potential biomarker for the prediction of HBeAg seroconversion in patients with HBeAg-positive hepatitis following a 48-wk course of nucleos(t)ide analogue treatment.

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## INTRODUCTION

Hepatitis B virus (HBV) infection remains one of the most serious health problems worldwide despite the widespread availability of safe and effective vaccines. Individuals with chronic HBV infection (CHB) are at an increased risk for developing hepatic cirrhosis, hepatocellular carcinoma (HCC), and even death[1]. As more than 2 billion people have been infected with HBV, and an estimated 350-400 million are chronically infected[1,2], advances in the detection of biomarkers specifically associated with the development of HBV-related diseases might impact patient treatment and outcome.

Recently, gamma-glutamyl transferase (GGT) has emerged as a potential biomarker in the diagnosis and treatment of HBV infection. GGT, a key enzyme in glutathione metabolism, is a cell-surface heterodimeric glycoprotein that is highly expressed in the biliary epithelium, kidney tubules, and brain capillaries[3]. To date, serum GGT levels have been routinely used as a biomarker for hepatobiliary diseases and as an indicator of alcohol intake[4], and yet, its diagnostic value remains unclear[5]. Results from several recent studies, however, have indicated that serum GGT might be of diagnostic value[5,6]. First, elevated GGT has been shown to be associated with increased mortality in liver diseases, cancer, and diabetes in the general population of the United States[6]. Second, serum GGT levels are elevated in patients with chronic hepatitis C[5,7-10]. In some studies, low baseline GGT levels have been shown to be an independent predictor of a sustained virologic response to therapy in chronic hepatitis C[11-15]. Finally, serum GGT might also be associated with the development of HCC more generally, as well as specifically, in patients with chronic hepatitis C. Therefore, GGT might be predictive in the development of HCC in non-cirrhotic patients even after successful eradication of hepatitis C virus[16-18].

Whether serum GGT levels are associated with CHB is less well understood. Here, serum GGT levels during various phases of CHB in a cohort of Chinese patients were retrospectively analyzed and investigated as a potential serum marker predictive for hepatitis B e antigen (HBeAg) seroconversion in response to nucleos(t)ide analogue (NA) therapy for CHB.

## MATERIALS AND METHODS

### *Ethics statement*

This study was approved by the Ethics Committee of Nanjing Drum Tower Hospital (Nanjing, China) and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participating individuals.

**Table 1 Clinical characteristics of patients and healthy controls**

| Characteristic | HC ($n$ = 83) | IT ($n$ = 47) | EPH ($n$ = 93) | ENH ($n$ = 20) | IC ($n$ = 55) |
|---|---|---|---|---|---|
| Age (yr) | 30.0 (22.0-49.6) | 26.0 (20.0-32.2)[a] | 29.0 (23.0-40.0) | 41.0 (20.2-57.8) | 32.0 (23.6-46.0) |
| Sex (male/female) | 49/34 | 29/18 | 70/23 | 15/5 | 30/25 |
| HBV DNA ($log_{10}$ copies/mL) | ND | 7.78 (6.77-8.62)[c] | 7.07 (5.67-8.05)[c] | 4.99 (3.76-7.52) | UD |
| ALT (ULN) | 0.42 (0.26-0.77) | 0.59 (0.43-0.90) | 3.80 (1.94-14.14)[b] | 2.99 (1.99-11.75)[b] | 0.59 (0.31-0.89) |
| Tbil (μmol/L) | 13.90 (9.10-21.62) | 12.80 (8.60-30.20) | 19.20 (12.80-42.90) | 16.55 (10.73-28.08) | 15.40 (9.38-25.66) |

Data shown are the median (10%-90% percentile); [a]$P < 0.05$ *vs* all groups; [b]$P < 0.05$ *vs* IT and IC; [c]$P < 0.01$ *vs* ENH. ALT: Alanine aminotransferase; EPH: HBeAg-positive hepatitis; ENH: HBeAg-negative hepatitis; HBV: Hepatitis B virus; HC: Healthy control; IC: Inactive carrier; IT: Immune tolerance; ND: Not determined; Tbil: Total bilirubin; UD: Undetectable; ULN: Upper limit of normal.

### *Study subjects*

A retrospective study was performed on data collected from patients who had been positive for the hepatitis B surface antigen (HBsAg) for > 6 mo and were antiviral-treatment naïve ($n$ = 215) that attended the Hepatitis Clinic at Nanjing Drum Tower Hospital between August 2010 and December 2013. Healthy individuals without liver disease ($n$ = 83) were included as controls. Based on the levels of alanine aminotransferase (ALT), HBeAg, hepatitis B e antibody, and HBV DNA, the patients were categorized into four groups according to the recommendations by the European Association for the Study of the Liver: immune tolerance (IT), HBeAg-positive hepatitis (EPH), HBeAg-negative hepatitis (ENH), and inactive carrier (IC)[2].

The patients were excluded if they met any of the following criteria: (1) coinfection with hepatitis C virus, hepatitis D virus, or HIV; (2) pre-existing comorbidities that are related to elevated GGT (*e.g.*, hepatobiliary tract, pancreatic, and/or heart disease or alcohol abuse); (3) evidence of malignant disease including HCC; (4) treated with anti-HBV therapy before admission; and (5) evidence of cirrhosis based on histologic examination or any clinical feature of portal hypertension, such as esophagogastric varices, ascites, or anomalies as revealed by imaging with sonography or CT.

EPH patients ($n$ = 33) who received NAs, either lamivudine (LAM) plus adefovir (ADV) or entecavir (ETV) alone, and were followed for 48 wk were also included. These patients were classified into two groups: complete response (CR) and non-complete response (NCR). Patients in the CR group had serum HBV DNA levels < 500 copies/mL and had undergone HBeAg seroconversion by week 48, whereas patients in the NCR group had reduced serum HBV DNA but remained HBeAg positive. Various clinical parameters were compared between the CR and NCR groups.

Serum ALT and GGT levels were measured with the Beckman CX-7 Biochemical Autoanalyser (Beckman Coulter, Inc., Brea, CA, United States). HBV serologic markers were detected with the Abbott Architect System (Abbot Laboratories, Chicago, IL, United States). Serum HBV DNA levels were quantified using Cobas Taqman (F. Hoffmann-La Roche AG, Basel, Switzerland).

### *Statistical analysis*

Data analyses were performed with SPSS version 22.0 (IBM Corp., Armonk, NY, United States), and MedCalc version 11.4.2.0 (MedCalc Software, Mariakerke, Belgium). Continuous variables are presented as either the median ($10^{th}$-$90^{th}$ percentile) or the mean ± SE, and categorical data are expressed as percentages. A Student's $t$-test or the Mann-Whitney $U$ test was used for group comparisons. Categorical data were analyzed by the $\chi^2$ or Fisher's exact test. Comparisons of variance between groups were performed by analysis of variance or the Kruskal-Wallis $H$ test. Interclass comparisons of repeated sample data were analyzed with the general linear model repeated-measures procedure. Correlation analysis between variables was conducted using Pearson's or Spearman's correlation analysis. To identify the optimal threshold values for predicting a CR to treatment, receiver-operating characteristic (ROC) curves were constructed. The sensitivity and specificity of predictions at these values were calculated, and a two-tailed $P < 0.05$ was considered to be statistically significant.

## RESULTS

### *Clinical characteristics of patients with CHB vary between different phases*

In order to effectively evaluate treatment modalities, clinical characteristics of antiviral-treatment-naïve patients ($n$ = 215) with CHB were compared between groups. Patients were classified based on the phase of CHB as follows: IT ($n$ = 47), EPH ($n$ = 93), IC ($n$ = 55), and ENH ($n$ = 20). Thus, the EPH group consisted of the most patients. All baseline clinical parameters evaluated are presented in Table 1. First, IT patients were significantly younger than other groups ($P < 0.05$ for all). Second, serum ALT levels were significantly elevated in EPH and ENH patients relative to IT and IC patients ($P < 0.05$ for all). Finally, serum HBV DNA levels were significantly higher in patients in the IT and EPH groups compared to the ENH group ($P < 0.01$ for both), but were undetectable in the IC group.

### *GGT levels differ between phases of CHB*

In order to determine the value of GGT for clinical evaluation and prognosis, levels were first examined

**Table 2 Comparisons of the baseline characteristics between non-complete response and complete response patients**

| Characteristic | All patients ($n$ = 33) | NCR ($n$ = 26) | CR ($n$ = 7) | $P$ value[1] |
|---|---|---|---|---|
| Age (yr) | 28.0 (23.0-41.8) | 26.5 (22.7-37.0) | 33.0 (24.0-53.0) | 0.060 |
| Sex (male/female) | 27/6 | 20/6 | 7/0 | 0.301 |
| HBV DNA ($log_{10}$ copies/mL) | 7.41 (6.13-8.17) | 7.33 (6.29-8.17) | 7.41 (5.65-8.66) | 0.736 |
| ALT (ULN) | 3.47 (1.79-16.27) | 3.39 (1.90-8.82) | 6.88 (1.58-51.20) | 0.011 |
| GGT (ULN) | 0.89 (0.36-2.48) | 0.85 (0.34-1.78) | 1.48 (0.70-3.14) | 0.011 |

[1]Comparison made between NCR and CR groups. Data shown are the median ($10^{th}$-$90^{th}$ percentile). ALT: Alanine aminotransferase; CR: Complete response; GGT: Gamma-glutamyl transferase; HBV: Hepatitis B virus; NCR: Non-complete response; ULN: Upper limit of normal.

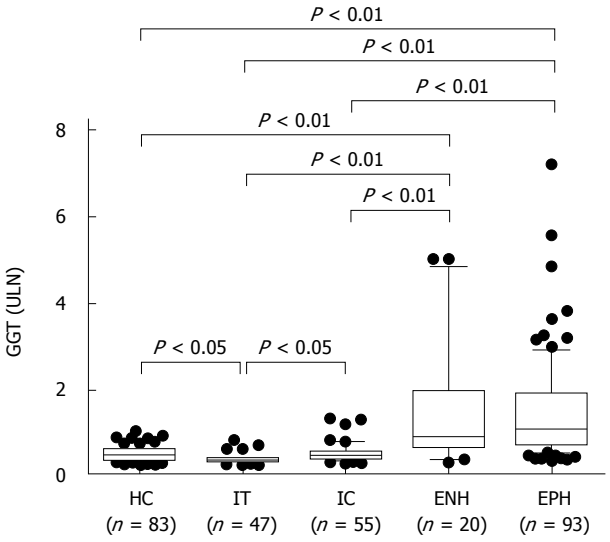


**Figure 1 Baseline serum gamma-glutamyl transferase levels are increased in hepatitis B e antigen-negative and hepatitis B e antigen-positive hepatitis B patients.** Data are shown as a median value ($10^{th}$-$90^{th}$ percentile). EPH: Hepatitis B e antigen-positive hepatitis; ENH: Hepatitis B e antigen-negative hepatitis; GGT: Gamma-glutamyl transferase; HC: Healthy control; IC: Inactive carrier; IT: Immune tolerance; ULN: Upper limit of normal.

for differences between patient groups. The results revealed that GGT levels were significantly different in patients at different phases of CHB (Figure 1). Specifically, the GGT levels reached as high as about 8 × upper limit of normal (ULN) and were about 2-4 × higher in the EPH and ENH groups compared to IT and IC patients as well as healthy controls ($P$ < 0.01 for all). However, the GGT levels were comparable in the EPH and ENH groups. Interestingly, GGT levels in the IC patients and healthy controls were about 1.5 × higher than in the IT group, but all values remained within the normal range.

Associations between GGT levels and the other clinical parameters were also investigated. A significant positive correlation was found between serum GGT levels and serum ALT levels within the entire cohort of 215 patients with CHB ($r$ = 0.747, $P$ < 0.001). However, no significant correlation between serum GGT levels and HBV DNA levels was observed ($r$ = 0.037).

### *Clinical outcomes for HBeAg-positive patients treated with NAs*

Baseline clinical parameters including GGT levels were evaluated in the context of patient outcome, CR or NCR following NA therapy. This cohort consisted of EPH patients ($n$ = 33) who had received LAM + ADV combination therapy (20/33; 60.6%) or ETV monotherapy (13/33; 39.4%), and outcome was assessed after 48 wk. Baseline characteristics of the patients are presented in Table 2. The median age of the patients in the cohort was 28.0 years, and most of the patients (27/33; 81.8%) were men. After 48 wk of NA therapy, undetectable serum HBV DNA was achieved in 30/33 (90.9%) patients, and a subset (7/33; 21.2%) were in CR. Age and gender were similar between the CR and NCR groups. Baseline ALT levels were about 2 × higher in the CR group compared to NCR group, and this difference was statistically significant ($P$ = 0.011). Furthermore, the baseline GGT levels were also found to be significantly higher in the CR group compared to the NCR group ($P$ = 0.011). However, the relative HBV DNA levels did not differ between these two groups before treatment.

### *HBV DNA, ALT, and GGT levels decrease following NA therapy*

The same clinical parameters were analyzed following the 48 wk of treatment with NAs. Serum levels of HBV DNA, ALT, and GGT all decreased significantly over 48 wk of treatment for both the CR and NCR groups ($P$ < 0.05 for all) (Figure 2). The values at intermediate time points during therapy were also used to assess the rate at which levels decreased from baseline with treatment (Figure 3). For HBV DNA and ALT levels in both groups, decreases in response to therapy occurred dramatically within the first 12 wk. HBV DNA levels in the CR group and the rate of decrease closely paralleled values of the NCR group at weeks 0, 12, 24, and 48 (Figure 2A and Figure 3A). ALT levels in the CR group were, however, significantly higher than those in the NCR group at baseline ($P$ = 0.011), and also showed a greater decline at weeks 12 ($P$ = 0.009), 24 ($P$ = 0.011), and 48 ($P$ = 0.009; Figure 2B and Figure 3B). GGT levels also decreased significantly in

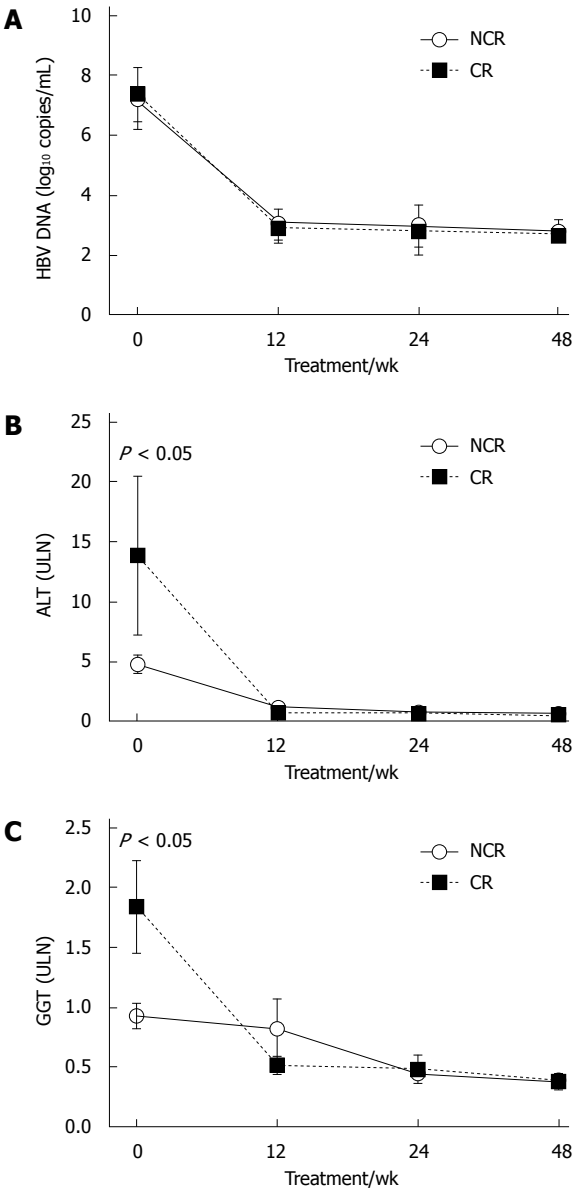


**Figure 2 Serum levels of hepatitis B virus DNA, alanine aminotransferase, and gamma-glutamyl transferase decrease in complete response and non-complete response groups after 48 wk of treatment.** A: HBV DNA; B: ALT; C: GGT. Data are shown as the mean ± SE. ALT: Alanine aminotransferase; CR: Complete response; GGT: Gamma-glutamyl transferase; HBV: Hepatitis B virus; NCR: Non-complete response; ULN: Upper limit of normal.

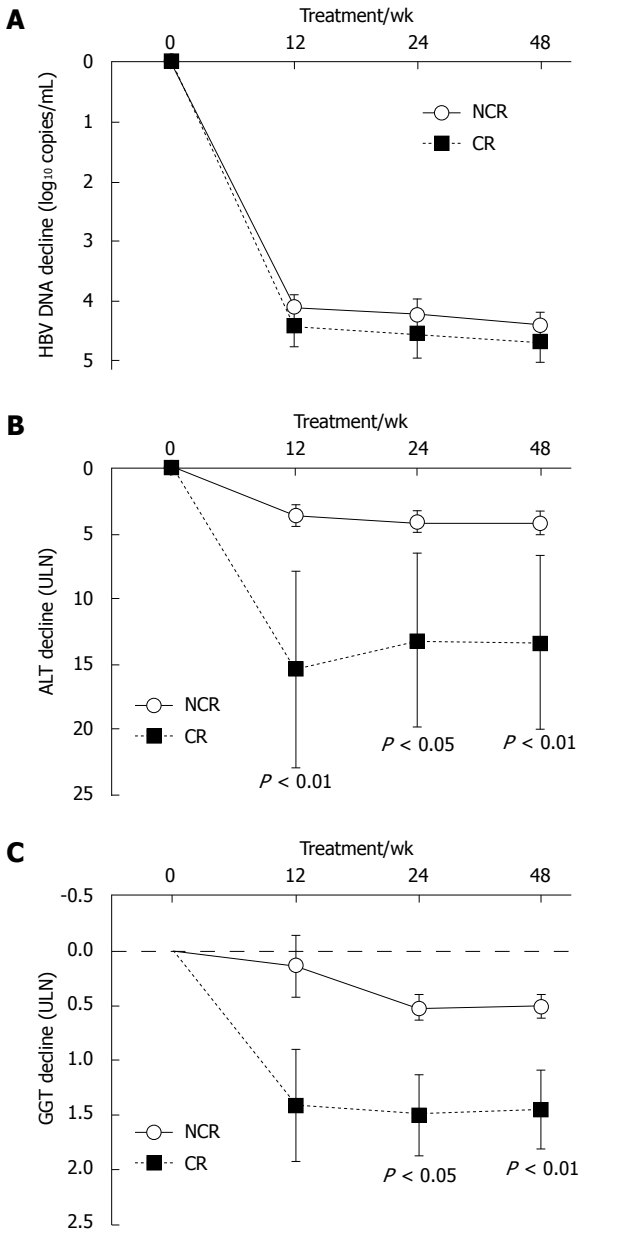


**Figure 3 Decline of serum alanine aminotransferase and gamma-glutamyl transferase from baseline differs between complete response and non-complete response groups after 48 wk of treatment.** Decline of serum levels for A: HBV DNA; B: ALT; C: GGT plotted as a function of time. Data are shown as the mean ± SE. ALT: Alanine aminotransferase; CR: Complete response; GGT: Gamma-glutamyl transferase; HBV: Hepatitis B virus; NCR: Non-complete response; ULN: Upper limit of normal.

CR patients (Figure 2C), and the decline of GGT was significantly greater in the CR group after 24 wk ($P$ = 0.012) and 48 wk ($P$ = 0.008) of treatment (Figure 3C).

### *Antiviral effects are similar for LAM + ADV combination therapy and ETV monotherapy*

The efficacy of LAM + ADV combination therapy and ETV monotherapy was directly compared on the basis of baseline levels of clinical characteristics for the two patient groups and levels after treatment at 12, 24, and 48 wk. Comparisons of baseline levels for ALT and HBV DNA, as well as other clinical parameters, revealed no significant differences between the two treatment groups (Table 3). Results of the analysis of various clinical parameters following treatment also revealed no significant differences between groups. Specifically, undetectable HBV DNA levels were similarly achieved in 55.0% (11/20), 80.0% (16/20) and 85.0% (17/20) of patients at 12, 24, and 48 wk of LAM + ADV treatment, respectively. For ETV therapy, HBV DNA was undetectable in 46.2% (6/13), 69.2% (9/13), and 100% (13/13) of patients at 12, 24, and 48 wk, respectively; the differences were not significant. HBeAg seroconversion was achieved in 25.0% (5/20) of LAM + ADV treated patients and 15.4% (2/13) of the ETV treated patients at 48 wk.

**Table 3 Comparisons of the baseline characteristics between lamivudine plus adefovir and entecavir treated patients**

| Characteristic | LAM + ADV ($n$ = 20) | ETV ($n$ = 13) | $P$ value |
|---|---|---|---|
| Age (yr) | 29.5 (23.0-47.8) | 24.0 (22.4-41.8) | 0.158 |
| Sex (male/female) | 17/3 | 10/3 | 0.659 |
| HBV DNA ($log_{10}$ copies/mL) | 7.25 (5.96-7.98) | 7.56 (6.02-8.44) | 0.334 |
| ALT (ULN) | 3.59 (1.66-16.56) | 3.12 (1.79-17.23) | 0.548 |
| GGT (ULN) | 1.01 (0.60-2.55) | 0.76 (0.33-2.55) | 0.137 |

Data shown are the median ($10^{th}$-$90^{th}$ percentile). ADV: Adefovir; ALT: Alanine aminotransferase; ETV: Entecavir; GGT: Gamma-glutamyl transferase; HBV: Hepatitis B virus; LAM: Lamivudine; ULN: Upper limit of normal.

Finally, an analysis of ALT levels in treated patients over time was performed. LAM + ADV combination therapy similarly led to normalization of ALT levels in 60.0% (12/20), 70.0% (14/20), and 75.0% (15/20) of patients at weeks 12, 24, and 48, respectively. ALT normalization was achieved in response to ETV therapy in 69.2% (9/13), 53.8% (7/13), and 76.9% (10/13) of patients at 12, 24, and 48 wk, respectively. Differences in the rates of ALT normalization in response to either therapy were not statistically significant at any time point.

### *GGT levels are a candidate predictor of HBeAg seroconversion following NA therapy*

Baseline GGT, ALT, and HBV DNA levels were assessed as candidate markers for HBeAg seroconversion following NA therapy in ROC curves. The areas under the ROC curves for each of the clinical parameters demonstrated that only baseline GGT levels achieved significance in the ability to identify patients who had achieved CR after 48 wk of NA therapy (0.788, 95%CI: 0.612-0.911; $P$ = 0.006) (Figure 4). The optimal threshold value for baseline GGT levels was 0.78 ULN, which yielded a sensitivity of 85.71% for detection of CR with a specificity of 61.54%. In contrast, serum ALT and HBV DNA levels failed to predict CR in patients following 48 wk of NA therapy.

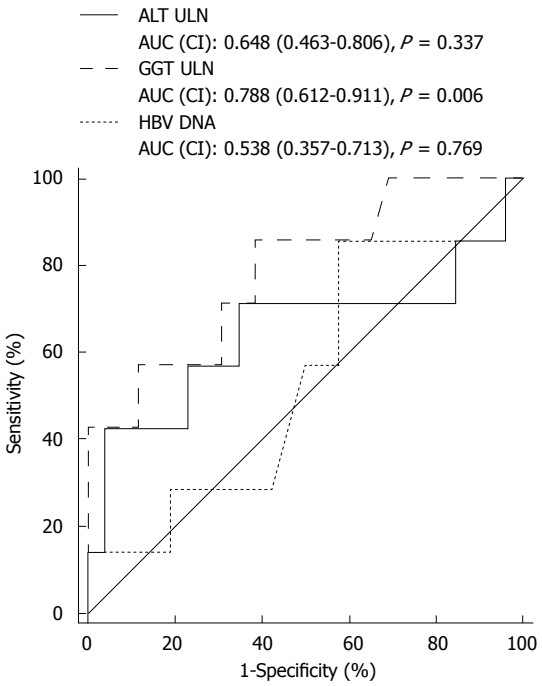


**Figure 4 Receiver operating characteristic curves reveal baseline gamma-glutamyl transferase levels as a predictive marker for complete response in hepatitis B e antigen-positive patients following 48 wk of nucleos(t)ide analogue treatment.** Specificity and sensitivity values are plotted as a function of ALT, GGT, and HBV DNA levels. AUC is calculated with a 95%CI. ALT: Alanine aminotransferase; AUC: Area under the curve; CI: Confidence interval; GGT: Gamma-glutamyl transferase; HBV: Hepatitis B virus; ULN: Upper limit of normal.

## DISCUSSION

The ability to predict outcome in response to antiviral agents on the basis of a clinical parameter(s) is an important component in the development of more personalized therapeutic strategies for CHB patients[19]. Clinical markers that can reliably predict the outcome of antiviral therapy for individual CHB patients are thus highly desirable. For EPH patients, HBeAg seroconversion, defined as the loss of HBeAg from the patient's serum, together with the appearance of neutralizing antibodies (anti-HBe), is the hallmark feature that highly correlated with a favorable long-term outcome in CHB[20-22]. CHB patients who have achieved this disease status usually become an inactive HBsAg carrier[23]. In this study, serum GGT levels were examined as a potential marker for HBeAg seroconversion. The results demonstrate that (1) serum GGT levels differ significantly among the four phases during the natural course of CHB, and levels are significantly higher in EPH and ENH patients compared to IT and IC groups and healthy controls; (2) serum GGT levels are positively correlated with serum ALT levels in patients with CHB; and (3) serum GGT levels are predictive for HBeAg seroconversion in EPH patients treated with NAs. The results support serum GGT levels as a potential biomarker in predicting the activation of antiviral immune responses and HBeAg seroconversion for EPH patients after NA treatment.

HBV is noncytopathic. Liver damage, viral control, and clinical outcome of infection are immunomediated and dependent on the complex interplay between HBV replication and the host immune response[24]. The natural history of CHB can be divided into five phases[2]. While the IT phase is characterized by positive HBeAg, high levels of serum HBV DNA, normal or low levels of ALT, minimum inflammation, and fibrosis on histology[2,25], the EPH phase is often associated with positive HBeAg, a decrease in HBV DNA, an increase in ALT concentrations, and moderate or severe liver necroinflammation[2,26]. Persistent or recurrent increases in ALT with unsuccessful

immune clearance increase the risk of liver cirrhosis and HCC[27]. However, patients in the IC phase usually exhibit very low (generally < 2000 IU/mL) or undetectable serum HBV DNA levels, but normal serum ALT[2]. After HBeAg seroconversion, some patients may experience reactivation of HBV infection with a pattern of fluctuating levels of HBV DNA and serum ALT, developing into the ENH phase[2,24]. It is known that ENH patients have increased risk of liver cirrhosis and HCC[27]. As indications for treatment are based largely on serum HBV DNA and ALT levels and the severity of liver disease[2], EPH and ENH patients are often considered for NA treatment. In the case of EPH patients, HBV DNA levels above 2000 IU/mL, serum ALT levels above the ULN, and complication of other liver diseases are considered as indicators for treatment[2].

Currently available treatments for CHB include conventional interferon-alpha, pegylated interferon-alpha, and six NAs[2]. The NAs ETV and tenofovir disoproxil are potent HBV inhibitors, and are recommended as first-line monotherapies as resistance to the drugs is slow to develop[2]. However, tenofovir disoproxil has not been approved for CHB treatment in China. Thus, initial therapies involving either a monotherapy or a combination of NA therapies are reasonable strategies for preventing the development of resistance[28]. Both LAM + ADV combination therapy and ETV monotherapy have been demonstrated to be effective in naïve (HBeAg-positive and HBeAg-negative) CHB patients[29,30]. Moreover, the cost of LAM + ADV is less than ETV monotherapy in China. Efficacy of the two treatment strategies was found to be similar in the cohort of 33 EPH patients analyzed in this study. The results are consistent with previous findings, and thus further support this approach in the treatment of CHB patients in China[29,30].

Pretreatment factors previously found to be predictive of HBeAg seroconversion in response to NA treatment were low viral load and high serum ALT levels[2,31-34]. In the present study, serum ALT levels are relatively higher in the CR group compared to the NCR group. However, ROC analysis indicated that serum ALT levels are not predictive for response to NA therapy. This result is possibly due to the relatively small sample size ($n$ = 33) of our cohort. Serum GGT levels of EPH patients at baseline are also significantly higher in the CR group compared to the NCR group. Levels did decrease after NA treatment, and at 24 and 48 wk of treatment, the decline in serum GGT levels was significantly greater in the CR group. High baseline GGT levels thus appeared to be associated with response to NA treatment after 48 wk as well as predictive for HBeAg seroconversion. Therefore, the GGT levels may be an additional predictor of treatment outcome in EPH patients.

Baseline and early decline of HBeAg and HBsAg levels have previously exhibited a high predictive value for virologic response and HBeAg seroconversion in NA-treated EPH patients[35-39]. HBeAg and HBsAg, however, were not quantitated in some of the EPH patients in our study, and therefore, we were unable to evaluate the relative predictive value of GGT and/or quantitative HBeAg and HBsAg.

Why serum GGT levels are linked to NA treatment-induced HBeAg seroconversion in CHB is unclear. It has been reported that elevated serum GGT levels may be related to bile duct damage, severe necroinflammatory activity, advanced fibrosis, or hepatic steatosis[8,40-42]. Elevated serum GGT levels have also been found to be associated with advanced histologic liver damage in patients with HBV[43]. High activity scores on liver biopsy have been reported to be a pretreatment predictor of anti-HBe seroconversion for NA treatment[2]. However, the association between serum GGT levels and activity scores in liver biopsies requires further study.

In conclusion, the results presented here support serum GGT as a potential new biomarker for the design of personalized antiviral therapy for EPH patients. Thus, serum GGT levels should be included in the diagnosis and management of more CHB patients in order to establish the clinical utility of the parameter.

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## COMMENTS

### *Background*

Serum gamma-glutamyl transferase (GGT) has been demonstrated to be associated with treatment response for chronic hepatitis C. However, whether a relationship also exists between serum GGT levels and chronic hepatitis B virus infection (CHB) that could improve the selection of therapeutic modalities remains unclear.

### *Research frontiers*

Predicting outcome with antiviral agents in CHB patients is under intense investigation, as the approach might improve the selection of therapeutic methods. Thus, it is desirable to identify parameters that can reliably predict the outcome of antiviral therapy for individual patients with CHB.

### *Innovations and breakthroughs*

Serum GGT increased significantly in hepatitis B e antigen (HBeAg)-positive hepatitis (EPH) and HBeAg-negative hepatitis patients compared to immune tolerance, inactive carrier, and healthy control groups. High baseline serum GGT levels exhibited a high predictive value for HBeAg seroconversion in EPH patients after 48 wk of treatment with nucleos(t)ide analogues.

### *Applications*

The results indicate that serum GGT is a candidate biomarker for prediction of HBeAg seroconversion in EPH patients treated with nucleos(t)ide analogues. Evaluation of serum GGT may provide additional information critical for improvement in the clinical management of CHB patients.

### Terminology

GGT, a key enzyme involved in glutathione metabolism, is a cell surface heterodimeric glycoprotein that is highly expressed in the biliary epithelium, kidney tubules, and brain capillaries.

### Peer-review

This is a very interesting manuscript with potential clinical implications for improving the management of hepatitis B virus infection through the use of an inexpensive, noninvasive, easy-to-perform test for serum GGT levels. The manuscript is of interest to the field and well presented. The study design is well constructed, and the results contribute novel insight into the development of more personalized therapy for hepatitis B virus patients.

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