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Case Control Study

Soluble programmed death-1 is predictive of hepatitis B surface antigen loss in chronic hepatitis B patients after antiviral treatment

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Abstract**BACKGROUND**

Hepatitis B surface antigen (HBsAg) loss, a functional cure in patients with chronic hepatitis B (CHB) undergoing antiviral therapy, might be an ideal endpoint of antiviral treatment in clinical practice. The factors that contribute to the functional cure remain unclear, and the predictors of functional cure are worth exploring. The concentration and kinetics of soluble programmed death-1 (sPD-1) in patients with CHB may play an important role in elucidating the immune response associated with functional cure after nucleos(t)ide analogs therapy.

AIM

To investigate the factors associated with HBsAg loss and explore the influence of sPD-1 Levels.

METHODS

This study analyzed the data and samples from patients with CHB who underwent antiviral treatment in a non-interventional observational study conducted at Peking University First Hospital in Beijing (between 2007 and 2019). All patients were followed up: Serum samples were collected every 3 mo during the first year of antiviral treatment and every 6 mo thereafter. Patients with positive hepatitis B e antigen levels at baseline and with available sequential samples who achieved HBsAg loss during antiviral treatment served as the case group. This case group ($n = 11$) was further matched to 44 positive hepatitis B e anti patients without HBsAg loss as controls. The Spearman's rank correlation test and receiver operating characteristic curves analysis were performed.

RESULTS

The sPD-1 Levels were higher in patients with HBsAg loss than in those without

of Peking University First Hospital. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Shanghai Jing An District Central Hospital (Approval No. 090f51e6809a26e1 v1.0).

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HBsAg loss from baseline to month 96, and the differences were significant between the groups at baseline ($P = 0.0136$), months 6 ($P = 0.0003$), 12 ($P < 0.0001$), 24 ($P = 0.0007$), 48 ($P < 0.0001$), and 96 ($P = 0.0142$). After 6 mo of antiviral treatment, the sPD-1 levels were positively correlated with alanine transaminase (ALT) levels ($r = 0.5103$, $P = 0.0017$), and the sPD-1 levels showed apparent correlation with ALT ($r = 0.6883$, $P = 0.0192$) and HBV DNA ($r = 0.5601$, $P = 0.0703$) levels in patients with HBsAg loss. After 12 mo of antiviral treatment, the sPD-1 levels also showed apparent correlation with ALT ($r = 0.8134$, $P = 0.0042$) and HBV DNA ($r = 0.6832$, $P = 0.0205$) levels in patients with HBsAg loss. The sPD-1 levels were negatively correlated with HBsAg levels in all patients after 12 mo of antiviral treatment, especially at 24 ($r = -0.356$, $P = 0.0497$) and 48 ($r = -0.4783$, $P = 0.0037$) mo. After 6 mo of antiviral treatment, the AUC of sPD-1 for HBsAg loss was 0.898 ($P = 0.000$), whereas that of HBsAg was 0.617 ($P = 0.419$). The cut-off value of sPD-1 was set at 2.34 log pg/mL; the sensitivity and specificity were 100% and 66.7%, respectively.

CONCLUSION

The sPD-1 levels at 6 mo can predict HBsAg loss after 144 mo of antiviral treatment.

Key Words: Programmed cell death 1 protein; Hepatitis B surface antigen; Chronic hepatitis B; Antiviral; Nucleos(t)ide analogs; Hepatitis B e antigen

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Core Tip: This study analyzed the data and samples from patients with chronic hepatitis B who underwent antiviral treatment and were followed up for 12 years to investigate the factors associated with hepatitis B surface antigen (HBsAg) loss and explore the impact of soluble programmed death-1 (sPD-1) levels. The sPD-1 levels were significantly different between patients with and without HBsAg loss during antiviral treatment. The sPD-1 levels at 6 mo can predict HBsAg loss after 12 years of antiviral treatment.

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INTRODUCTION

More than 240 million individuals worldwide are infected with chronic hepatitis B (CHB)[1]. Among them, 15%-40% of untreated CHB cases progress to cirrhosis that may result in liver failure and even liver cancer[2]. Nucleos(t)ide analogues (NAs) were widely used for antiviral treatment because of their none contraindications and high tolerability in patients with CHB[2]. Hepatitis B surface antigen (HBsAg) levels and other virological indicators such as hepatitis B virus (HBV) DNA and hepatitis B e antigen (HBeAg) are measured to monitor the effects of antiviral treatment during the follow-up of patients with CHB[3]. Since HBsAg levels reflect the transcriptional activity of covalently closed circular DNA, especially in HBeAg-positive patients, HBsAg loss, a functional cure in CHB patients undergoing antiviral therapy, might be an ideal endpoint of antiviral treatment in clinical practice[4]. However, only 1%-12% of CHB patients are cured in response to NA therapy within 5-7 years[5]. The factors that contribute to the cure remain unclear, and the predictors of functional cure are worth exploring.

Functional HBV-specific T cells (with helper or cytotoxic effects) are considered as crucial factors that influence the prognosis of HBV-infected patients[6]. However, HBV-specific T cell function is progressively impaired by exposure to chronic inflammation and high viral load[7]. Programmed death-1 (PD-1) is considered a critical

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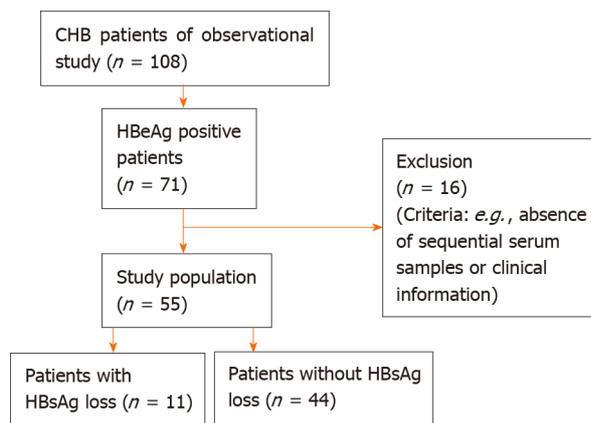


Figure 1 Overview of the inclusion process of the study population. CHB: Chronic hepatitis B; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen.

factor for T cell exhaustion in chronic infections[8]. Studies have shown that HBV-specific T cells express PD-1, and the blockade of PD-1 and programmed death-ligand 1 (PD-L1) partially restores the function of T cells[8].

Recent studies measured serum PD-1 levels and considered whether serum PD-1 might compete with PD-L1 expressed on the cell surface and impair the inhibitory effects of PD-1/PD-L1 interactions on T cells[9]. Nevertheless, the potential functional effects of serum PD-1 are not clear owing to the lack of relevant data. The concentration and kinetics of soluble PD-1 (sPD-1) in patients with CHB may play an important role in elucidating the immune response associated with functional cure after NA therapy. This study analyzed the data and samples from patients with CHB who underwent antiviral treatment and were followed up for 12 years to investigate the factors associated with HBsAg loss and explore the influence of sPD-1 Levels.

MATERIALS AND METHODS

Subjects and samples

Patients with CHB (HBsAg positive ≥ 6 mo) who initiated NA therapy in a non-interventional observational study conducted at Peking University First Hospital in Beijing (between 2007 and 2019) were enrolled in this study. All patients were followed up: Serum samples were collected every 3 mo during the first year of antiviral treatment and every 6 mo thereafter. Patients with human immunodeficiency virus, hepatitis C virus, hepatitis D virus, hepatitis E virus, other liver diseases, hepatocellular carcinoma, cardiovascular disease, diabetes, pregnancy, or autoimmune disease were excluded. Patients who consumed alcoholic beverages were excluded. Patients with steatosis were also excluded according to ultrasound[10]. HBeAg-positive patients before NA treatment with available sequential samples and HBsAg loss during antiviral treatment served as the case group. This case group ($n = 11$) was further matched to 44 positive HBeAg patients without HBsAg loss (Figure 1). These 55 patients were treated with NAs: Lamivudine 100 mg per day ($n = 3$), adefovir dipivoxil 10 mg per day ($n = 17$), or entecavir 0.5 mg per day ($n = 35$) as monotherapy for 144 mo. All participants provided written informed consent, and the study was approved by the ethics committee of Peking University First Hospital. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Shanghai Jing'an District Central Hospital (Approval No. 090f51e6809a26e1 v1.0).

Tests

HBsAg [hepatitis surface antibody (anti-HBs)] and HBeAg (anti-HBe) levels were measured using chemiluminescence assay kits (Roche Diagnostics GmbH, Mannheim, Germany). The COBAS TaqMan assay (Roche Diagnostics, Basel, Switzerland) was used to quantify serum HBV DNA levels (lower limit of detection, 100 IU/mL). Serum sPD-1 levels in CHB patients were measured using an enzyme-linked immunosorbent assay (ELISA) kit (DuoSet Human PD-1, R&D Systems, Minneapolis, MN, United States) according to the manufacturer's instructions, and absorbance was measured at

450 nm. Serum alanine transaminase (ALT) levels were assessed at the Peking University First Hospital using a standard procedure. The upper limit of normal ALT level was 50 U/L in men and 40 U/L in women.

Statistical analysis

Baseline was defined as the time at which NA therapy was initiated. Continuous variables were expressed as median (interquartile range, IQR). Categorical variables were expressed as values. Continuous variables were compared using a two-tailed Student's *t*-test or Mann-Whitney *U* test depending on the distribution. Correlations between sPD-1 and detection markers were assessed using the Spearman's rank correlation test. The predictive value of different biomarkers for HBsAg loss during treatment was summarized using receiver operating characteristic (ROC) curves. Data were analyzed using the SPSS software, version 25 [SPSS Inc. (IBM Corp., Armonk, NY, United States)]. Statistical tests were two-sided; $P < 0.05$ was considered statistically significant.

Patient and public involvement statement

Neither the patients nor the public were involved in the design, conduct, report, or dissemination of our research.

RESULTS

Baseline data characteristics

Before treatment, the patient's baseline period was defined. The baseline characteristics of the 55 patients are presented in [Table 1](#). The median age of patients with HBsAg loss was 35 years (IQR: 23.00–38.00) and that of patients without HBsAg loss was 36.5 (IQR: 28.00–42.75). In the patients with HBsAg loss, 10 were male and 1 was female. In the patients without HBsAg loss, 37 were male and 7 were female. The median values of ALT, HBV DNA, HBsAg, and sPD-1 in patients with HBsAg loss were 140 IU/mL, 8.447 log IU/mL, 3.331 log IU/mL, and 2.766 Log IU/mL, respectively. There were no statistical differences in age, sex, ALT, HBV DNA, HBsAg levels, and response to antiviral therapy between the two groups at baseline.

Dynamics of HBV DNA, ALT, and HBsAg levels during NA treatment

During NA treatment, HBV DNA levels decreased in all patients with similar kinetics, and there were no statistical differences at different time points between the two groups ([Figure 2A](#)). HBV DNA was undetectable in patients with HBsAg loss after 60 mo of antiviral treatment. After 132 mo of antiviral treatment, HBV DNA levels were undetectable in all patients. The time to HBV DNA undetectable of each patient from baseline was calculated, and there was no statistical difference between two groups of patients ($P = 0.0805$).

ALT levels decreased after antiviral treatment in the two groups of patients, and there was no statistical difference between two groups at different time points in ALT levels ([Figure 2B](#)). The time to the normalization of ALT levels from baseline of each patient showed no statistical difference between the two groups of patients ($P = 0.3678$). ALT levels in patients with HBsAg loss normalized after an average of 7.91 mo, whereas that in patients without HBsAg loss normalized after an average of 13.77 mo.

The median HBsAg level (log₁₀ IU/mL) in patients with or without HBsAg loss was similar between the two groups before month 12 ([Figure 2C](#)). HBsAg levels were statistically different between the two groups after 12 mo of antiviral treatment ($P = 0.0022$). In patients with HBsAg loss, HBsAg level (log₁₀ IU/mL) showed a significant decline from 3.33 (2.83–4.58) log₁₀ IU/mL before treatment to 2.973 (0.9415–3.748) log₁₀ IU/mL after 12 mo ([Figure 2C](#)), and it decreased gradually thereafter. HBsAg in patients without HBsAg loss remained high during NA treatment.

HBeAg seroconversion after antiviral treatment

All patients with HBsAg loss achieved HBeAg seroconversion after 120 mo. Among patients without subsequent HBsAg loss, 18 did not achieve HBeAg seroconversion during 144 mo of follow-up. Among patients with HBeAg seroconversion, the average time of HBeAg seroconversion was 43.09 mo in patients with HBsAg loss and 48.596 mo in patients without HBsAg loss and showed no statistical difference between the two groups.

Table 1 Baseline data characteristics of all patients

Patients characteristics	HBsAg loss (n = 11)	w/o HBsAg loss (n = 44)	P value
Age	35.00 (23.00-38.00)	36.5 (28-42.75)	0.3243
Gender	10/1	7/37	0.515
ALT (IU/mL)	140 (77-245)	116 (75-219)	0.9590
HBV DNA (log IU/mL)	8.447 (6.923-8.614)	8.024 (6.909-8.934)	0.8844
Antiviral therapy (first-line/second-line) ¹	6/5	29/15	0.488
ADV/LAM	4/1	13/2	0.400
HBsAg (log IU/mL)	3.331 (2.826-4.582)	3.856 (3.526-4.347)	0.1274
sPD-1 (log pg/mL)	2.766 (2.622-2.903)	2.657 (2.540-2.765)	0.0136

¹Patients were treated with NAs: entecavir (first-line), lamivudine and adefovir dipivoxil (second-line). HBsAg: Hepatitis B surface antigen.

Association between sPD-1 levels before and during NA treatment and subsequent HBsAg loss

The sPD-1 levels were higher in patients with HBsAg loss than in those without HBsAg loss from baseline to month 96 (Figure 2D), and the differences were significant between the two groups at baseline ($P = 0.0136$), months 6 ($P = 0.0003$), 12 ($P < 0.0001$), 24 ($P = 0.0007$), 48 ($P < 0.0001$), and 96 ($P = 0.0142$).

After antiviral treatment, the sPD-1 levels of all patients decreased, especially in patients without HBsAg loss, showing a significant decline in sPD-1 levels from baseline to month 3 ($P < 0.0001$, Figure 2E). The sPD-1 levels in patients without HBsAg loss decreased significantly from 2.12 (1.87–2.29) at month 24 to 1.19 (0–1.70) at month 48, whereas that in patients with HBsAg loss stayed above 2 logs until month 72 (Figure 2F).

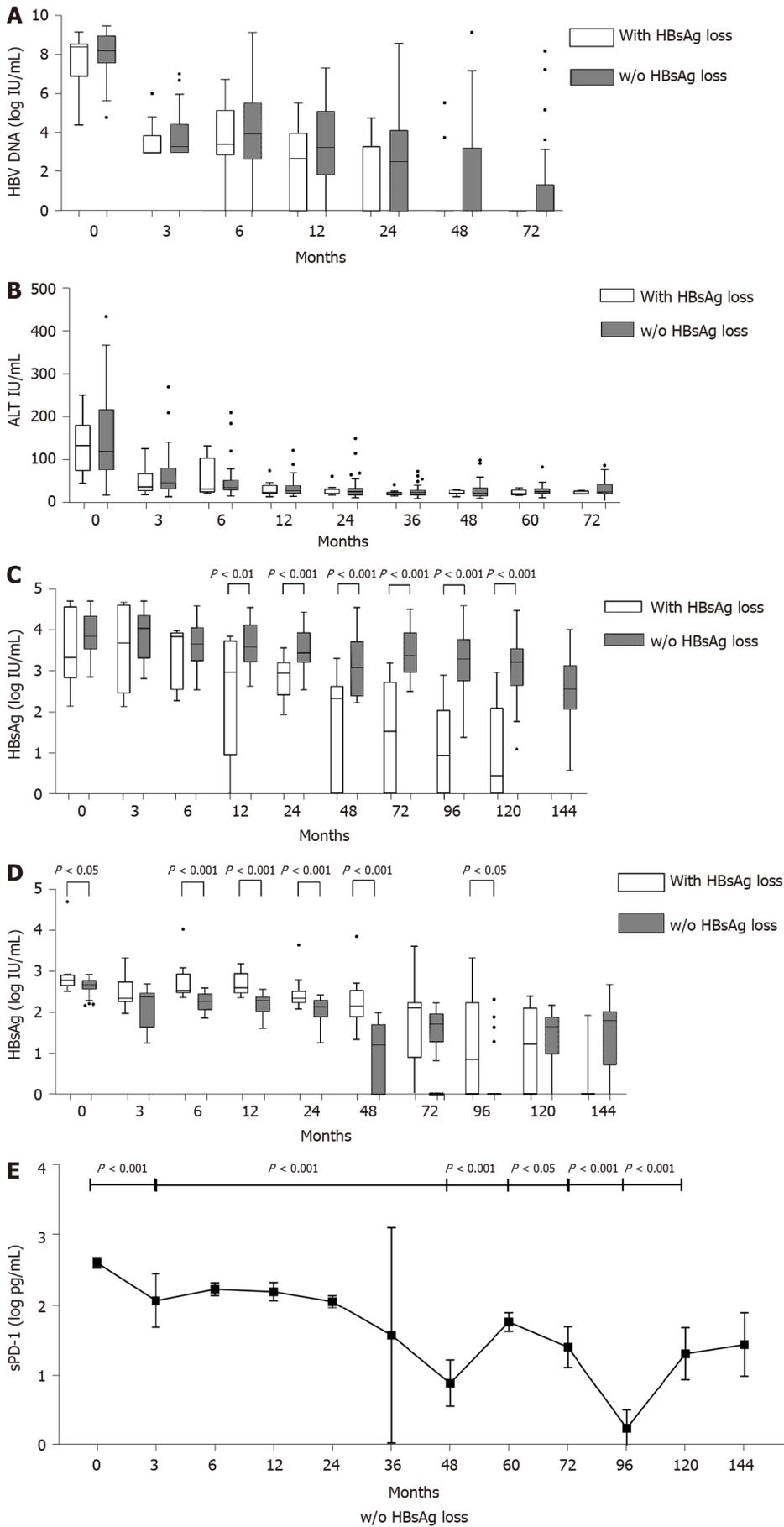
The sPD-1 levels showed no significant correlation with HBsAg, serum HBV DNA, or ALT levels at baseline. After 6 mo of antiviral treatment, the sPD-1 levels were positively correlated with ALT levels ($r = 0.5103$, $P = 0.0017$, Figure 3A) and showed weak correlation with HBsAg and HBV DNA levels. For further study, correlation analysis was conducted in patients with or without subsequent HBsAg loss after 144 mo of follow-up, respectively. The sPD-1 levels showed apparent correlation with ALT ($r = 0.6883$, $P = 0.0192$, Figure 3B) and HBV DNA ($r = 0.5601$, $P = 0.0703$, Figure 3C) levels in patients with HBsAg loss. After 12 mo of antiviral treatment, the sPD-1 levels also showed apparent correlation with ALT ($r = 0.8134$, $P = 0.0042$, Figure 3D) and HBV DNA ($r = 0.6832$, $P = 0.0205$, Figure 3E) levels in patients with HBsAg loss.

However, the number of patients with a normalization of ALT levels or undetectable HBV DNA increased over time. After 12 mo of antiviral treatment, the sPD-1 levels were negatively correlated with HBsAg levels in all patients, especially at 24 ($r = -0.356$, $P = 0.0497$, Figure 3F) and 48 ($r = -0.4783$, $P = 0.0037$, Figure 3G) mo.

Prediction of HBsAg loss by sPD-1 levels before and during NA treatment

To analyze the predictive value of the different available virologic biomarkers at baseline for HBsAg loss, ROC curve analysis was performed. Before NA treatment, the strongest predictor was sPD-1 [area under the curve (AUC) = 0.700, Figure 4A), whereas HBsAg (AUC = 0.6458) and HBV DNA (AUC = 0.5589) showed no significant prediction of response to NA therapy.

The above results suggested that statistical differences were only observed in sPD-1 levels between the two groups of patients within 12 mo of NA treatment. To explore the predictive value of sPD-1 for HBsAg loss, ROC curve analysis was performed. After 6 mo of antiviral treatment, the AUC of sPD-1 for HBsAg loss was 0.898 ($P = 0.000$, Figure 4B), whereas that of HBsAg was 0.617 ($P = 0.419$). The cut-off value of sPD-1 was set at 2.34 log pg/mL; the sensitivity and specificity were 100% and 66.7%, respectively.



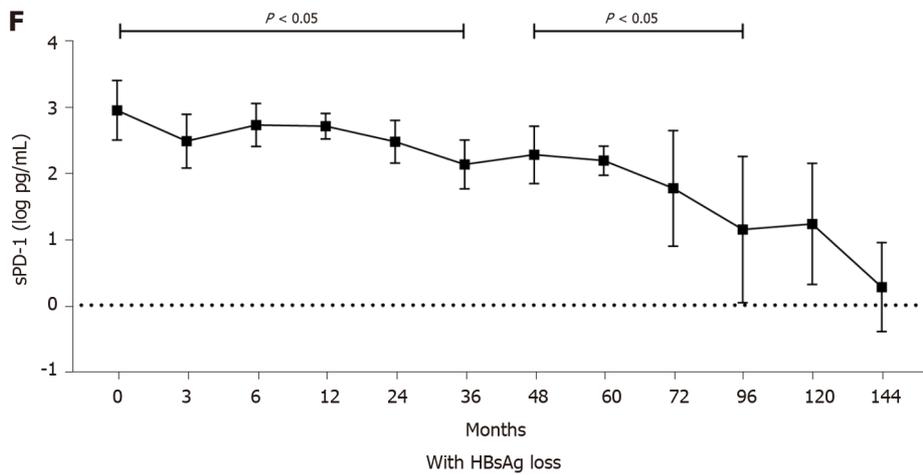


Figure 2 Dynamics during nucleos(t)ide analogue treatment. A: Hepatitis B virus (HBV) DNA; B: Alanine transaminase (ALT); C: Hepatitis B surface antigen (HBsAg); D: Soluble programmed death-1 (sPD-1) levels; soluble programmed death-1; E, F: Levels in patients without (E)/with (F) HBsAg loss at different time points.

DISCUSSION

Patients with HBsAg loss after antiviral treatment were not different from patients without HBsAg loss in terms of HBV DNA, ALT, and HBsAg levels at baseline. The sPD-1 levels were significantly different between the two groups of patients during antiviral treatment, especially after 6 mo of antiviral treatment. This study examined the predictive value of sPD-1 levels for HBsAg loss in patients with CHB under NA treatment and found that sPD-1 levels at 6 mo had higher AUC values than HBsAg associated with HBsAg loss. The sPD-1 levels at 6 mo can better predict HBsAg loss during antiviral treatment than HBsAg levels.

Different ELISA kits could contribute to discrepant results. Xia *et al*[11] used different ELISA kits for dosing sPD-1 Levels. There was a significant correlation between the sPD-1 levels and ALT levels at baseline in Zhou *et al*[9], but a weak correlation in Xia *et al*[11]. However, their research showed similar results that patients with CHB had higher levels of sPD-1 than healthy controls. Consistent with Xia *et al* [11], our results showed that the sPD-1 levels were positively correlated with ALT and HBV DNA levels at 6 and 12 mo. The sPD-1 levels decreased in all patients after baseline, which might be associated with lower viral load and lower expression of viral antigen after antiviral treatment. Meanwhile, patients with subsequent HBsAg loss had higher sPD-1 levels until month 96 than patients without HBsAg loss. The sPD-1 levels in patients with subsequent HBsAg loss remained at high levels of two logs from baseline to month 72, whereas those in patients without HBsAg loss decreased quickly from baseline to month 48. These results suggested that patients with higher sPD-1 levels during antiviral treatment were more likely to develop HBsAg loss.

We found that sPD-1 levels were negatively correlated with HBsAg levels after 24 and 48 mo of antiviral treatment, and other studies have not explored sPD-1 levels for this long time period. Other virological and biochemical biomarkers, such as HBV DNA and ALT levels, showed no significant correlation with sPD-1 levels. This might associate with the increasing number of patients with the normalization of ALT levels or undetectable HBV DNA over time. And HBsAg levels were obviously different between patients with or without HBsAg loss after 12 mo of antiviral treatment.

Zhou *et al*[9] found that the sPD-1 levels in patients in the immune-active phase were the highest among all CHB disease stages. Therefore, the high sPD-1 levels were associated with immune activation[12,13]. The sPD-1 could interact with the membrane bound PD-L1 and counteract the inhibition of PD-1/PD-L1 signal path on virus-specific T cells[14]. The sPD-1 levels at 6 mo might reflect the immune activity, and high levels of sPD-1 at that time might benefit the HBV-specific immunity. HBsAg loss could reflect the suppression of HBV covalently closed circular DNA expression [15,16]. Therefore, the sPD-1 levels at 6 mo could predict HBsAg loss, and the cut-off value of sPD-1 was set at 2.34 Log pg/mL; the sensitivity and specificity were 100% and 66.7%, respectively.

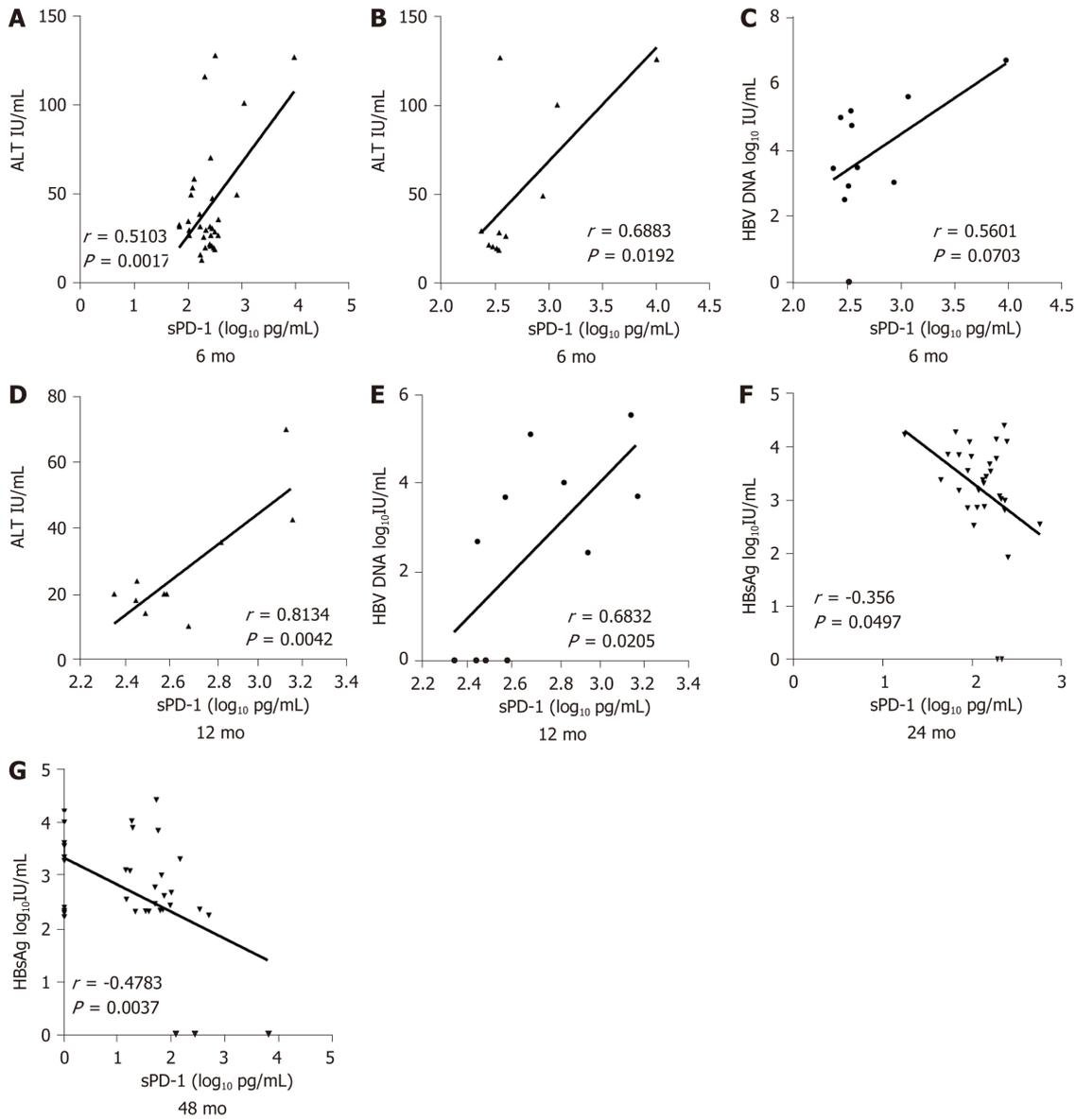


Figure 3 Soluble programmed death-1 levels. A: Levels were positively correlated with alanine transaminase (ALT) levels in all patients after 6 mo; B, C: Levels were positively correlated with ALT (B) and hepatitis B virus (HBV) DNA levels (C) in patients with hepatitis B surface antigen (HBsAg) loss after 6 mo; D, E: Levels were positively correlated with ALT (D) and HBV DNA levels (E) in patients with HBsAg loss after 12 mo; F, G: Levels were negatively correlated with HBsAg levels in all patients after 24 mo (F) and 48 mo (G). sPD-1: Soluble programmed death-1.

In consequence, patients with higher sPD-1 levels before and during the early stage of antiviral treatment could develop more effective immune response to HBV infection.

There were some limitations in this study. The correlation between sPD-1 levels and HBsAg loss depended on the immune response of functional HBV-specific T cells to HBV infection. The T cell function of patients from this study needed to be detected. In addition, this study was done on a smaller number of cases. Next, we plan to set up a cohort of 300 patients with CHB and divide them into different groups by sPD-1 levels at baseline to explore the prognosis of two groups of patients.

CONCLUSION

The sPD-1 levels were significantly different between the two groups of patients during antiviral treatment, especially within 12 mo after baseline. We found that sPD-1 levels at 6 mo had higher AUC values than HBsAg associated with HBsAg loss.

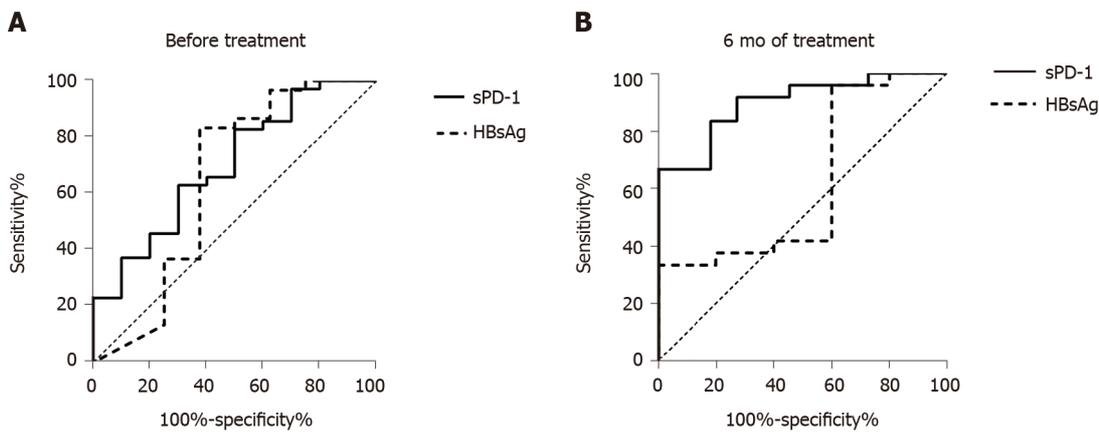


Figure 4 Receiver operating characteristic curves of soluble programmed death-1 and hepatitis B surface antigen levels in the prediction of subsequent hepatitis B surface antigen loss. A: Before treatment; B: After 6 mo of treatment. sPD-1: Soluble programmed death-1; HBsAg: Hepatitis B surface antigen.

ARTICLE HIGHLIGHTS

Research background

Recent studies analyzed serum soluble programmed death-1 (sPD-1) levels and indicated that sPD-1 might play an important role in virus-specific immunity in chronic viral infection.

Research motivation

The factors that contribute to the functional cure in patients with chronic hepatitis B remain unclear, and the predictors of functional cure are worth exploring.

Research objectives

To investigate the factors associated with hepatitis B surface antigen (HBsAg) loss and explore the impact of sPD-1 Levels.

Research methods

Patients with positive hepatitis B e antigen (HBeAg) levels at baseline and with available sequential samples who achieved HBsAg loss during antiviral treatment served as the case group. This case group ($n = 11$) was further matched to 44 positive HBeAg patients without HBsAg loss as controls.

Research results

Patients with HBsAg loss had higher levels of sPD-1 than patients without HBsAg loss from baseline to month 96, and the differences were significant between the groups at baseline ($P = 0.0136$), months 6 ($P = 0.0003$), 12 ($P < 0.0001$), 24 ($P = 0.0007$), 48 ($P < 0.0001$), and 96 ($P = 0.0142$). The sPD-1 levels were positively correlated with ALT and HBV DNA levels in patients with HBsAg loss within 12 mo of antiviral treatment. After 12 mo of antiviral treatment, the sPD-1 levels were negatively correlated with HBsAg levels in all patients, especially at 24 ($r = -0.356$, $P = 0.0497$) and 48 ($r = -0.4783$, $P = 0.0037$) mo. The AUC of sPD-1 levels at 6 mo for HBsAg loss was 0.898 ($P = 0.000$), whereas that of HBsAg was 0.617 ($P = 0.419$). The cut-off value of sPD-1 was set at 2.34 log pg/mL; the sensitivity and specificity were 100% and 66.7%, respectively.

Research conclusions

The sPD-1 levels were significantly different between the two groups of patients during antiviral treatment, especially within 12 mo after baseline. The sPD-1 levels at 6 mo can predict HBsAg loss after 144 mo of antiviral treatment.

Research perspectives

The correlation between sPD-1 levels and HBsAg loss depended on the immune response of functional HBV-specific T cells to HBV infection. The T cell function of patients from this study needed to be detected.

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