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Predictive value of early changes in HBsAg and CD4+T cells for clinical cure of chronic hepatitis B treated with Peg-IFN α-2b.

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SUMMARY: *The purpose of the present research was to find out early prognostic elements for clinical remission in patients who have chronic hepatitis B virus (HBV)-related liver illness receiving treatment by pegylated interferon-α-2b (Peg-IFN-α-2b) and to establish a clinical prediction model. We have conducted a retrospective cohort research investigation. During the time period from May 2024 to January 2026, 91 patients that have chronic HBV infection which satisfied the inclusion and exclusion criteria were one after another recruited from the outpatient clinic of the Department of Infectious Diseases which is at Suining Central Hospital. We divided the patients into two groups according to whether HBsAg clearance was obtained in the 48 weeks of the treatment course. The group which obtained successful treatment is called the effective group (n=38), hence the group which did not obtain successful treatment is the ineffective group (n=53). The measurement of virus carrying capacity, liver function situation, and immune label things was carried out before the treatment was done, and at 12, 24, 48 weeks after the treatment. We used univariate and multivariate logistic regression analyses to carry out screening for independent predictor variables and thus construct a prediction model. The forecast ability of this model has been evaluated by making use of a receiver operating characteristic (ROC) curve. Between the group with effective curative effect and the group with ineffective curative effect, the baseline log10HBsAg levels have a notable difference (P<0.001). When the treatment reaches the 24-week time point, both the decreasing degree of HBsAg (Δlog10HBsAg) (P<0.001) and the number of CD4+ T cells (P=0.04) in the effective group, they are obviously higher than the corresponding values in the ineffective group. Multivariate statistical analysis has indicated that Δlog10HBsAg (OR=5.506, 95%CI 2.775 - 10.926, P<0.001) and the quantity of CD4+ T cells at 24 weeks (OR=1.008, 95%CI 1.001 - 1.015, P=0.018) therefore are independent prediction factors. The area under the ROC curve (AUC) of the combined model for predicting clinical cure was 0.935, and this was higher than that of any individual indicator. Conclusion: A rapid decline in HBsAg early after starting treatment and an elevated count of CD4+ T cells at 24 weeks can be predicted as indicators of clinical cure for patients with chronic HBV infection treated with Peg-IFN α-2b. The constructed combined prediction model has good discrimination and clinical utility.*

KEYWORDS: *Chronic HBV infection; Clinical cure; Polyethylene glycol interferon alpha-2b; HBsAg; CD4+T cells*

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1 Introduction

Chronic hepatitis B (CHB) is a problem for public health around the world. According to the World Health Organisation, there were about 254 million people with chronic HBV infection around the world in 2022, and about 1.1 million died each year from HBV-related cirrhosis and hepatocellular carcinoma (HCC). At present, the goals of treatment recommended by domestic and foreign experts include achieving clinical cure. Clinical cure will reduce the risk of long-term injury to the patient and improve their quality of life to near normal after a recovery. Pegylated interferon alpha-2b (Peg IFN alpha-2b) is a typical example of a treatment to induce a clinical cure due to its dual effects of direct antiviral action and immune regulation [1]. However, there are significant differences in how patients respond to Peg-IFN α-2b treatment individually, and only some of them achieve HBsAg clearance. Therefore, in the early days of treatment, it is necessary to identify the good responders accurately to adjust the course of treatment and avoid wasting medical resources or causing harm to the patient. The basic predictive indicators of traditional predictive indices are baseline HBsAg levels and HBV DNA concentrations, and they have poor prognostic value. Recently, many scholars have started to build flexible and high-dimensional prediction systems. Dynamic changes in HBsAg after the start of treatment have been found to be strong predictors of HBsAg clearance, and a drop in HBsAg from baseline at 12 or 24 weeks after treatment can indicate the onset of a host immune response [2, 3]. At the same time, the health of the host also affects how well the virus is suppressed. Chronic HBV-infected individuals often show a reduction in the function of HBV-specific T cells, and the functional recovery of T cell subsets during treatment, particularly for $CD4^+$ T cells as auxiliary cores of the immune response, is closely related to clinical cure [4]. ALT is a general index for damage to liver cells; therefore, any change in its value after treatment is also considered to be due to immune activation and the breakdown of infected liver cells. Based on retrospective cohort analysis, we have studied the predictive value of early HBsAg decline, peripheral blood CD^4 T cell count, and dynamic changes in ALT for clinical cure among CHB patients treated with Peg IFN α-2b. A multi-dimensional joint prediction model has been built to assist in the early identification of favourable populations and realise personalised precision medicine.

2 Data and Methods

2.1 Research subjects

This is a single-center, retrospective cohort study which we conducted on patients who bear the chronic HBV infection. These patients got a treatment that uses Peg-IFN alpha-2b at the Outpatient Office of the Infection Section in Suining Central Hospital from May 2024 to January 2026.

Included Standards1.

The sick people must satisfy the diagnostic norms established in the "Guiding Documents for the Prevention and Cure of Chronic Hepatitis B (2022 Version)".2. It is required that they possess the positive HBsAg test result for no less than 6 months, and their HBsAg level is not higher than 3000 IU/ml.3. The age of the patients ought to be situated in the interval of 18 to 60 years of age.4. Before the patients enter this study, they either have never used interferon or have ceased the use of it for over six months.

Excluding Standards1.

The patients who have co-infection of hepatitis A, C, D, E viruses or HIV were all excluded.2. The persons who are diagnosed with or are suspected to get hepatocellular

carcinoma have not been included.3. The patients who have decompensated cirrhosis or serious liver function damage (ALT that surpasses 10 times of the upper bound of normal range or total bilirubin that exceeds 2 times of the upper bound of normal range) are to be excluded.4. The people who have serious heart, brain, kidney, endocrine, autoimmune diseases or malignant tumors were not included in this research.5. Females who are in pregnant or lactating periods have been excluded.6. The patients who have the history of alcohol or drug abuse are not included in this study.7. The persons who had serious whole-body bad responses or cannot bear the injection-place bad responses following the treatment were all excluded.

Treatment Scheme

Peg-IFN α2b (180 μg each week, it is given by subcutaneous injection) was adopted either alone or together with nucleoside(t)ide analogues (NAs) for the treatment.

Grouping of Patients

Patients were divided into two groups on basis of whether serum HBsAg clearance (HBsAg < 0.05 IU/ml) and no HBV DNA detection took place in 48 weeks of treatment. We call these two groups the effective group and the ineffective group. This research has gotten the permission from the Medical Ethics Committee of Suining Central Hospital (approval number KYLLKS20250212), and all patients have signed the written informed consent document.

2.2 Data collection

Collect patient demographic information, treatment plans and laboratory indicators such as HBsAg, HBsAb, HBeAg (chemiluminescence method, Abbott i2000), HBV DNA (fluorescence quantitative PCR method, detection limit of 10 IU/ml, Roche COBAS TaqMan), ALT (rate method), albumin (bromocresol green method), and absolute values of peripheral blood $CD3^+CD4^+$ T cells and $CD3^+CD8^+$ T cells (flow cytometry, BD FACSCAN II) from the hospital electronic medical record system at baseline, 12 weeks, 24 weeks and 48 weeks after treatment. All of the above tests were conducted in the Laboratory Department of Suining Central Hospital, and all operations followed the standard operating procedures. Data processing: Natural-log transformation was used to improve the distribution of HBsAg data. However, because there are negative values (0 IU/ml) in the original data, we cannot directly take the logarithm. Based on a study in South Korea [6], a value of 0 was replaced with 0.001 IU/ml (about 10% of the detection limit), and the converted variable was recorded as log10HBsAg for the following linear regression analysis. Calculate the decrease in HBsAg from baseline to week 24: $\Delta \log_{10}$ HBsAg=baseline $\log_{10}$ HBsAg - week 24 $\log_{10}$ HBsAg.

2.3 Statistical Methods

Statistically analyze the data in R language (version 4.3.2). Periodically obtain the above data and save them. Shapiro-Wilk tests were used to check whether the normality of the data met the conditions, and those that were normally distributed were presented in the form of mean ± standard deviation ($x \pm s$). Two independent sample t-tests were conducted for intergroup comparisons; non-normally distributed data were expressed as the median (interquartile range) [M (Q, R)], and a Mann-Whitney U test was employed for intergroup comparison. Count data are expressed as frequency (percentage) [n (%)], and the chi-squared test is employed for inter-group comparisons. Univariate analysis is performed to screen the predictive factors for the screen, and then the odds ratios (ORs) and 95% confidence intervals (CIs) of these factors are calculated. Include many factors in a multiple-choice logistic regression model and use stepwise selection to build the first model. Draw the working characteristic curve of the

subjects, calculate the area under the curve, and then determine the discriminative ability of single-index and combined models based on the maximum Jordan index to find the optimal cutoff value. To verify the stability of the model and prevent overfitting, five-fold cross-validation was employed to assess the reproducibility of the model coefficients, and among the various models of different variable combinations, the one with the lower AIC and BIC values was selected as the optimal prediction model. The bilateral test level is α=0.05, and a value of P<0.05 is considered statistically significant.

3 Results

3.1 Comparison of Characteristics between Effective and Invalid Group Data

A total of 91 patients with chronic HBV infection met the inclusion and exclusion criteria for this study, and 38 (41.8%) in the response group and 53 (58.2%) in the non-response group were included. In terms of baseline characteristics, the two groups of patients did not differ significantly (P > 0.05) in demographic information, selection of the treatment plan, or other viral and liver function markers, such as HBsAb, HBeAg, HBV DNA positivity rate, ALT, and ALB. The baseline log10HBsAg levels of the effective group were lower than those in the ineffective group [1.87 (1.12, 2.57) vs. 2.69 (1.91, 3.07) log10 IU/ml, Z=-3.372], and the distribution of baseline HBsAg levels was also significantly different (P<0.001). In the effective group, 57.9% were HBsAg <100IU/ml, and only one person (2.6%) had HBsAg <3000IU/ml. After treatment, the effective group had a significantly larger decrease in HBsAg (Δ log10HBsAg) from the baseline at week 0 to week 24 than the ineffective group [3.31 (2.42, 4.56) vs. 0.69 (0.08, 1.25) log10 IU/ml, Z=6.857, P<0.001], and the absolute value of peripheral blood CD3+CD4+T cells at week 24 was also higher in the effective group than in the ineffective group (408.00 ± 168.16 vs. 343.68 ± 99.96 cells/μ l, t=2.1, P=0.040). ΔALT in the two groups was not significantly different (P=0.161). Therefore, according to the change in ALT, all sorts of patterns appeared. The ALT levels of the patients in the effective group showed an upward trend at 12 weeks after treatment, followed by a decline at 24 weeks; they exhibited a pattern of "first increasing and then decreasing", while the ALT changes in the ineffective group were relatively minor. See Table 1 and Figure 1 for details.

Table 1: Comparison of Characteristics for Effective and Invalid Group Data

Project	Effective group (n=38)	Invalid group (n=53)	Statistical value	*P value*
Treatment plan[*n*(%)]				
Peg-IFN α-2b	14(36.84)	12(22.64)	x^2=2.187	0.139
Peg-IFN α-2b Joint NA (s)	24(63.16)	41(77.36)		
Baseline $\log_{10}$HBsAg [M(P25,P75)$\log_{10}$IU/ml]	1.87 (1.12,2.57)	2.69 (1.91,3.07)	*Z*=-3.372	<0.001
HBsAg[*n*(%)]				
<100IU/ml	22(57.9)	16(30.2)	x^2=17.366	<0.001
(100, 500]IU/ml	13(34.2)	11(20.8)		
(500, 1500]IU/ml	2(5.3)	16(30.2)		
(1500, 3000]IU/ml	1(2.6)	10(18.9)		
Baseline HBsAb [M(P25,P75)IU/ml]	1.11 (0.49,1.56)	0.92 (0.28,1.87)	*Z*=0.419	0.675
Baseline HBeAg [M(P25,P75)IU/ml]	0.42 (0.38,0.47)	0.4 (0.37,0.45)	*Z*=0.725	0.468
Baseline HBV DNA [*n*(%)]				
Positive	8(21.1)	16(30.2)	x^2=0.951	0.329
Negative	30(78.9)	37(69.8)		
Δ$\log_{10}$HBsAg [M(P25,P75)$\log_{10}$IU/ml]	3.31 (2.42,4.56)	0.69 (0.08,1.25)	*Z*=6.857	<0.001
Baseline ALT [M(P25,P75)U/L]	18.5 (14,30.25)	25 (19.5,37)	*Z*=-1.909	0.056
Baseline ALB [$\bar{x}\pm s$ g/L]	46.35±2.77	46.30±2.54	*t*=0.087	0.931
ΔALT [M(P25,P75)U/L]	39.5 (20,83)	31 (12,58)	*Z*=1.541	0.161
Absolute value of CD3+CD4+cells at 24 weeks [$\bar{x}\pm s$ cell/μl]	408.00±168.16	343.68±99.96	*t*=2.1	0.040

Note: $\Delta\log_{10}$HBsAg refers to baseline $\log_{10}$HBsAg – 24 week $\log_{10}$HBsAg, and ΔALT refers to 12 week ALT – baseline ALT.

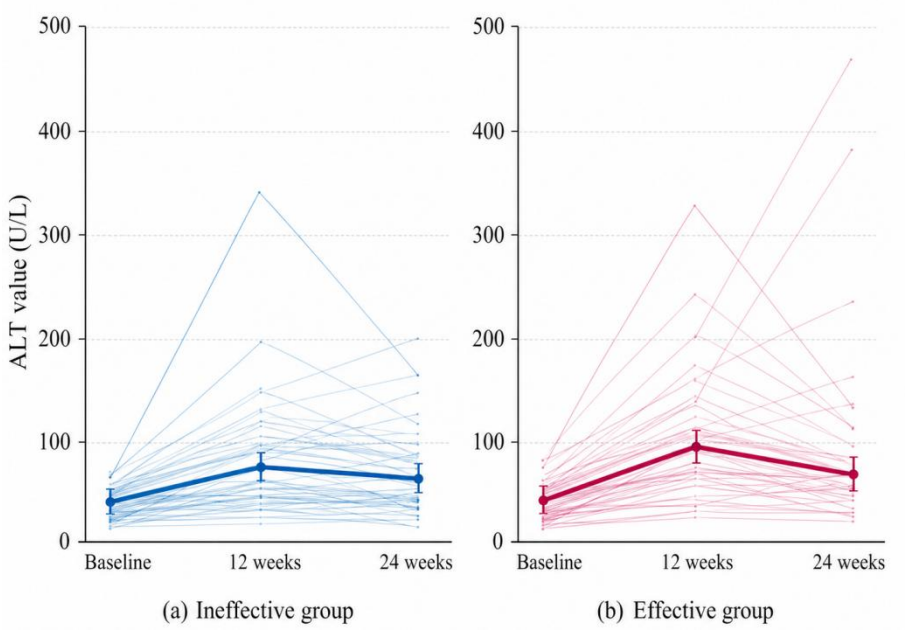

Figure 1: Trend of ALT over Time

3.2 Single factor regression analysis

The change of the base-10 logarithm of Hepatitis B surface antigen (Δ $\log_{10}$ HBsAg) has displayed a positive correlation relation with clinical cure, with an Odds Ratio (OR) of 5.009 (95% Confidence Interval [CI]: 2.648 - 9.475, p-value<0.001). In like manner, the 24-hour $CD4^+$ T cell number likewise possessed a positive correlation with clinical healing, which has an OR of 1.004 (95% CI: 1.000 - 1.007, p=0.031). By comparison, the alteration of alanine aminotransferase (ΔALT) did not get the statistical meaning in the single-factor analysis (p=0.191). When we faced prediction of treatment response, the area below the Receiver Operating Characteristic (ROC) curve for Δ$\log_{10}$ HBsAg was 0.924 (95% CI: 0.864 - 0.983). According to the rule of the maximum Youden exponent, the optimal cut point for forecast was set at 2.64 $\log_{10}$ IU/ml. On this particular threshold value, the forecast model displayed a sensitivity of 73.7 percent and a specificity of 98.1 percent. With respect to the number of $CD4^+$ T cells at 24 weeks, the area under the curve is 0.598 (95% CI: 0.468 - 0.728). The optimum cut-off value that is got through Youden index calculation was 490 cells per microliter. Under this cut-off value, the prediction model possesses a sensitivity that is 39.5% and a specificity that is 94.3%. In order to obtain more detailed information, you may refer to Table 2, Figure 2, and Figure 3.

Table 2: Results of Single-factor Logistic Regression Analysis

Variable	Regression coefficient	Standard error	OR value	OR95% CI lower limit	OR95% CI upper limit	*P* value
Δ$\log_{10}$HBsAg	1.611	0.325	5.009	2.648	9.475	<0.001
CD4+T cell count at 24 weeks	0.004	0.002	1.004	1.000	1.007	0.031
ΔALT	0.005	0.003	1.005	0.998	1.011	0.191

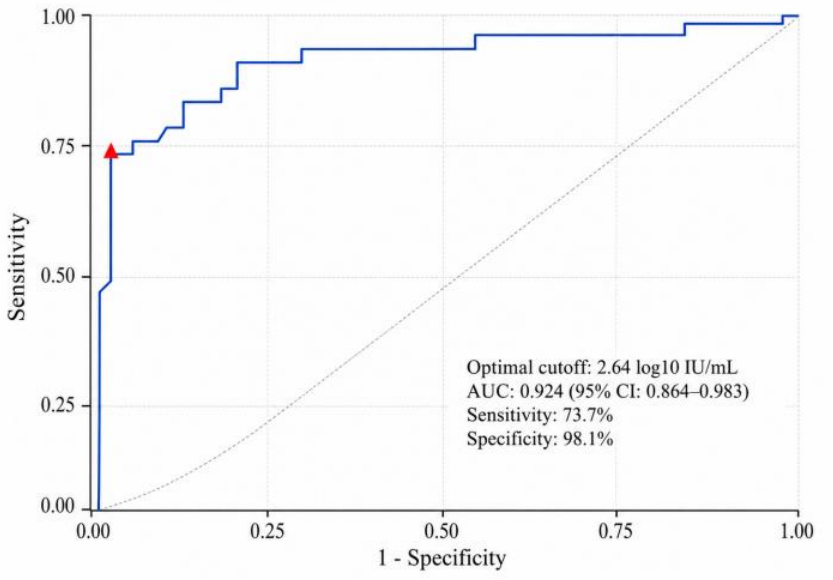

Figure 2: ROC Curve of log10HBsAg decline from baseline to week 24

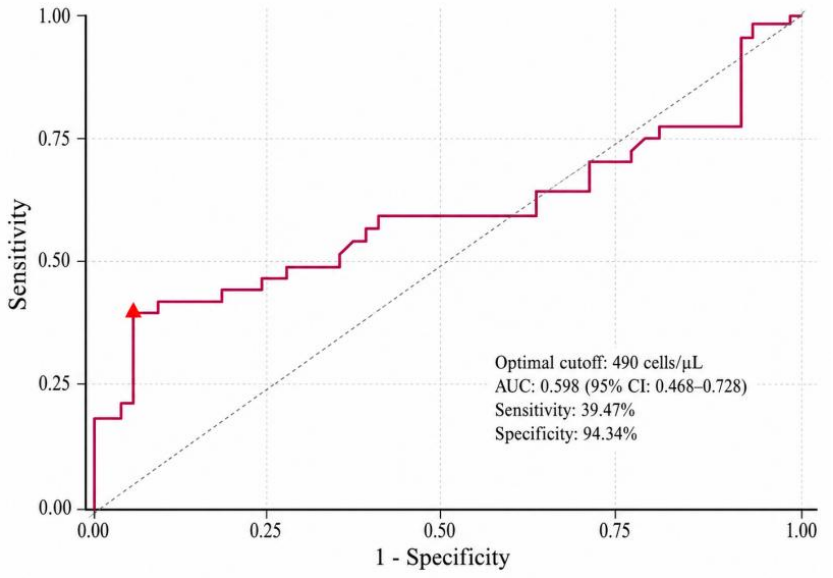

Figure 3: ROC Curve of CD4+ T cells at 24 weeks

3.3 Multivariate logistic regression analysis and model construction

Δ $\log_{10}$HBsAg (OR=5.506, 95% CI 2.775-10.926, P<0.001) and 24-hour $CD4^+$ T cell count (OR=1.008, 95% CI 1.001-1.015, P=0.018) are independent predictors of clinical cure, and ΔALT does not have an independent predictive value (OR=0.994, 95% CI 0.983-1.005, P=0.310). See Table 3 for more information.

Table 3: Initial Prediction Model Logistic Regression Analysis Results

Variable	Regression coefficient	Standard error	OR value	OR95% CI lower limit	OR95% CI upper limit	P value
Δlog10HBsAg	1.789	0.367	5.982	2.913	12.286	<0.001
ΔALT	-0.006	0.006	0.994	0.983	1.005	0.310
CD4+T cell count at 24 weeks	0.008	0.003	1.008	1.001	1.015	0.023

3.4 Model construction and validation

Perform an internal validation of the first model using five-fold cross-validation. The model has good and stable predictive discrimination based on the above results, and the AUC is 0.935. The optimised model shows that Δ $\log_{10}$ HBsAg is the best independent predictor of treatment response (OR=5.506, 95% CI 2.775-10.96, P<0.001), and 24-hour $CD4^+$ T cell count is still independently predictive (OR=1.008, 95% CI 1.001-1.015, P=0.018). The final regression equation is Logit (P)=-6.198531 + 1.706 × Δlog_{10} HBsAg + 0.008 × 24-week CD4+T cells. The AUC of the model is 0.935. Table 4 and Figure 4 are as follows.

Table 4: Results of Optimized Model Logistic Regression Analysis

Variable	Regression coefficient	Standard error	OR value	OR95% CI lower limit	OR95% CI upper limit	P value
Δlog10HBsAg	1.706	0.350	5.506	2.775	10.926	<0.001
CD4+T cell count at 24 weeks	0.008	0.003	1.008	1.001	1.015	0.018

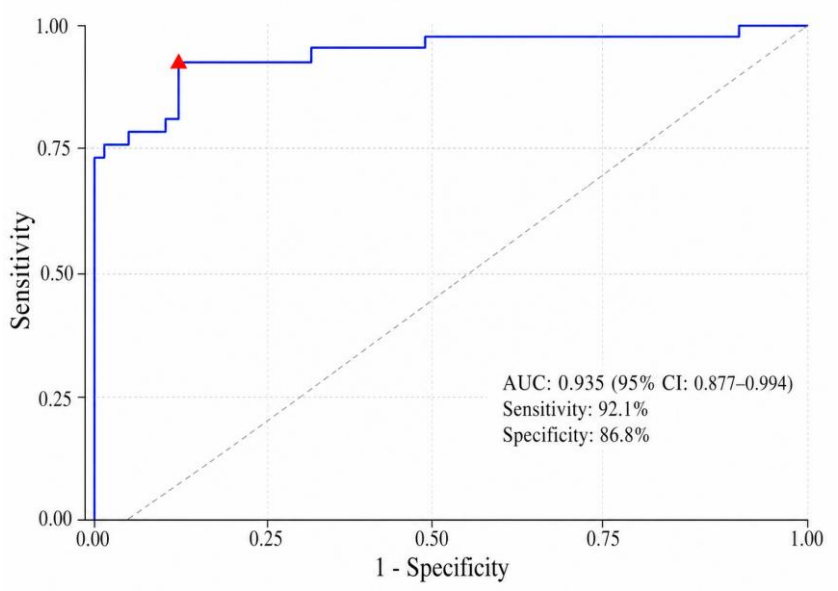

Figure 4: ROC Curve of the $\Delta\, log_{10}\, HBsAg^+\, CD4^+ Tcell$ Combination Model

4 Conclusions

Systematically study the early predictive factors of clinical cure in chronic HBV-infected patients receiving Peg-IFN alpha-2b treatment and successfully build a joint prediction model based on virology and immunology. Based on the above studies, a considerable reduction in

HBsAg at the beginning of treatment and an increase in peripheral blood $CD4^+$ T cell count by 24 weeks after starting treatment are strong, independent indicators of HBsAg clearance. The joint model of the two has shown good predictive performance.

Several clinical trials have used HBsAg $\le$ 3000 IU/ml as an index to determine whether a person is a suitable candidate for interferon treatment. Patients with a baseline HBsAg below this threshold are more likely to achieve a higher sustained virological response and are thus generally not suitable for interferon therapy [7]. This study will extend the range of inclusion to HBsAg $\le$ 3000 IU/ml. However, the sample size of the 1500-3000 IU/ml group is relatively small, and only one case (2.6%) had HBsAg seroconversion. This result is not the same as in a recent randomised controlled trial [8]; this study also set the lower bound for HBsAg $\leq$ 3000 IU/ml. After 96 weeks of combined treatment with entecavir and Peg IFNα-2b, the conversion rate of HBsAg is approximately 30.12%. This may be due to the length of treatment, treatment plan, sample size, and baseline characteristics of the patients at the time of enrollment. Δlog10HBsAg was chosen as a strong indicator (AUC=0.924) in this study, which is in line with the conclusions of Professor Pan Chen's and Professor Zheng Qi's groups about the benefits of early monitoring for HBsAg changes. It is also in line with the conclusion of a large meta-analysis of 27 studies and almost 8,000 patients [9]. At both the baseline and 12 and 24 weeks after treatment, a lower value of HBsAg is independently associated with the clearance of HBsAg. Its decline is not only the result of reduced viral replication, but also serves to disrupt the state of immune suppression induced by high antigen loads and enables the subsequent $CD4^+$ T cell-mediated immune restoration phase [10, 11]. In addition, a higher baseline HBsAg level indicates a greater antigen load that needs to be suppressed in order to clear HBsAg, and thus the "threshold of decline amplitude" for the induction of an effective immune response is relatively high.

The absolute number of peripheral blood CD4+ T cells at week 24 after treatment is also an independent prognostic factor for clinical remission. Although the predictive power of a single index is relatively weak (AUC=0.598), its specificity is still quite high at 94.3%, and it is independent of other predictors (OR=1.008). Professor Boni and others have successfully extended the original study of interferon therapy for restoring T cell function to regular clinical practice in this research. CD4+ T cells are negatively correlated with HBsAg and HBV DNA levels, and their early activation may serve as a "switch" to establish an effective immune response [12]. Venzin and others [13] recently presented in 2025 that CD4+T cells "allow" Kupffer cells in the liver to produce IL-12 and thus restore the function of depleted CD8+T cells. An increase in the number of peripheral CD4+ T cells can be seen as an indirect indicator that a strong immune response in the liver has been triggered. Single-cell sequencing studies have also shown that the effective treatment induces a shift in differentiation for CD4+ T cells towards a more cytotoxic effector type [14, 15].

No independent statistical prediction for ΔALT was achieved in the quantitative analysis, and this result is contrary to some previous studies showing that an early increase in ALT predicts a good response to treatment [16, 17]. However, this difference also shows that ALT is not directly correlated with the risk. Studies have shown that the predictive value of ALT is relatively high in patients with elevated baseline inflammatory indices or those receiving NAs sequential/combined treatments. The median baseline ALT of the enrolled patients in this study was only 24 U/L; therefore, the immune-quiescent population was relatively larger, and the frequency of flare events may be lower. However, this study found that the response group showed a characteristic dynamic trajectory of "first rising and then falling" in ALT levels, whereas the non-response group had relatively flat changes. Together with the stable low-fluctuation pattern of ALT associated with HBsAg clearance identified by Professor Zeng

Jianyong's team through trajectory clustering [18], this is the overall predictive value of ALT.

The "Δ $\log_{10}$ HBsAg+$CD4^+$ T cell" bivariate model finally constructed in this study can capture the early synchronisation of virus clearance and immune reconstruction, the two main healing processes. This is in line with Peng and others' [19] study of integrating virology (HBsAg) and inflammatory markers (dALT2). Given that only 4% of the HBV treatment coverage rate in China has been achieved [20], selecting Peg-IFN α-2b as the model for recognising "advantageous responders" will be more cost-effective and can serve as an intelligent application of the "treat as you please" approach. At the critical point of the 24th week of treatment, quantitative tools can be used for clinical decision-making to increase the confidence in high-probability predictors of treatment and provide a reasonable explanation for ALT fluctuations. For low-probability predictors, at the right time, adjustments can be made to the plan to avoid an inefficacious treatment [21-23].

There are also certain limitations of this study: ① This study is a single-center study with a relatively small sample size, and the generalizability of the conclusion to different races or populations with higher baseline HBsAg needs to be externally validated by multi-center, large-scale studies. ② The primary endpoint is HBsAg clearance at 48 weeks after treatment, and there is a lack of long-term follow-up data after discontinuing treatment to assess the predictive value of the model for persistent clinical cure and long-term clinical outcomes (risk of cirrhosis and HCC). ③ To ensure clinical applicability, the model used conventional detection indicators and undoubtedly overlooked more potential emerging biomarkers.

In short, this study has found that the clinical cure of chronic HBV-infected patients treated with Peg-IFN $\alpha_2\beta$ is associated with a significant drop in HBsAg early in the treatment period and an increase in peripheral blood CD4+ T cell count at 24 weeks. The joint prediction model built based on the two above indicators also has good discriminative ability and has been verified to be stable and reliable.

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