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Effect of dyslipidemia on HBsAg clearance in nucleos(t)ide analogues-experienced chronic hepatitis B patients treated with peginterferon alfa

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Abstract

Background While previous reports have shown that hepatitis B virus (HBV) infection affects lipid metabolism and vice versa, the impact of dyslipidemia on the functional cure of HBV infection following peginterferon alfa (PegIFNα) therapy remains unknown. Hence, this study aimed to investigate the effect of dyslipidemia on hepatitis B surface antigen (HBsAg) clearance and develop a nomogram model for predicting patients for whom PegIFNα therapy is indicated.

Methods A total of 160 nucleos(t)ide analogues (NAs)- experienced chronic hepatitis B (CHB) patients treated with PegIFNα (180 μg/week) were enrolled in this study. The relationship between serum lipid and HBsAg clearance was analysed. Univariate and multivariate COX analyses were used to construct and plot the nomogram model. The area under the receiver operating characteristic curve (AUC) and calibration curve were used to evaluate the discrimination and calibration of the model, respectively.

Results After 48 weeks of PegIFNα therapy, a total of 33 patients in the cohort achieved HBsAg clearance. Univariate and multivariate COX analyses indicated that dyslipidemia was significantly associated with HBsAg clearance and was an independent predictor of HBsAg clearance (HR = 0.243, $P = 0.001$). Kaplan-Meier survival analyses show that cumulative HBsAg clearance was significantly higher in the normolipidemic group than in the dyslipidemia group (log-rank test, $P = 0.007$). During the treatment, triglyceride showed an increasing trend, while the levels of total cholesterol, high-density lipoprotein, low-density lipoprotein, apolipoprotein A1 and apolipoprotein B decreased.

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Dyslipidemia and other indicators independently associated with HBsAg clearance were used to construct the nomogram model. The AUC of the model at 36-week and 48-week were 0.879 and 0.856, and the model demonstrated good discrimination and calibration.

Conclusion Dyslipidemia can affect the antiviral efficacy of PegIFNα in NAs-experienced CHB patients. Our findings suggest that the nomogram model constructed using serum lipid has good predictive power and may help physicians to identify the superior patients for PegIFNα therapy.

Keywords Chronic hepatitis B, Hepatitis B surface Antigen, Peginterferon Alfa, Dyslipidemia, Nomogram

Despite the availability of safe and effective hepatitis B vaccine, hepatitis B virus (HBV) infection remains a major global public health problem, with persistent viral replication and hepatocellular inflammation causing liver fibrosis, cirrhosis, liver failure and hepatocellular carcinoma (HCC). According to the World Health Organization, there were approximately 296 million people worldwide with chronic hepatitis B (CHB) infection in 2019; of whom 820,000 died from liver disease related to HBV [1]. Covalently closed-circular DNA (cccDNA) and HBV integration following liver infection are difficult to clear completely. Hence, the current clinical treatment goal is to pursue functional cure, which means hepatitis B surface antigen (HBsAg) clearance, with or without the presence of anti-HBs and persistent undetectable HBV-DNA. It has been suggested that HBsAg clearance reduces the risk of HCC by 5-fold in CHB patients compared to HBsAg-positive patients [2]; it also makes HBV reactivation very unlikely [3]. However, the functional cure is difficult to achieve. The HBsAg clearance rate does not exceed 3% after treatment with potent nucleos(t)ide analogues (NAs), which are first-line therapeutic agents [4]. Moreover, HBsAg clearance rate after three years of treatment with peginterferon alfa (PegIFNα) in treatment-naive CHB is approximately 8.7–11.0% [1]. Therefore, it is crucial to explore the factors that influence the efficacy of antiviral drugs and identify therapeutically suitable patients in clinical practice.

In Chinese adults, the prevalence of dyslipidemia remains high [5], and HBV infection affects the lipid metabolic status. HBV infection inhibits lipid metabolism, and apolipoprotein (Apo) C3 is negatively correlated with HBV-DNA load in HBeAg-negative patients [6]. An NMR-based metabolomics approach showed that HBx disrupts the metabolism of glucose, lipids and nucleic acids [7]. Similarly, targeted metabolomic analyses have shown that HBV can alter glycerophospholipid and triglyceride synthesis pathways, thereby reducing serum lipid levels [8]. In an in vitro model, researchers have found that HBx-induced beta-d-mannoside-1,4-Nacetylglucosaminyltransferase-III (GnT-III) expression inhibited ApoB secretion, potentially reducing ApoB-containing lipids [9]. Furthermore, HBV was found to inhibit ApoA1 and HDL-C synthesis and secretion, and HBV was speculated to inhibit ApoA1 mRNA and protein expression through downregulation of ApoA1 promoter activity [10]. In turn, lipids can influence the HBV infection process. It has been shown that HBV infection in primary hepatocyte cultures is dependent on the presence of cholesterol in the viral envelope, and cholesterol and lipid rafts play a role in the entry of HBV into hepatocytes [11–13]. PegIFNα is an immunomodulatory agent that regulates the immune system while inhibiting viral replication, and has a unique and irreplaceable role in HBsAg clearance compared to NAs. PegIFNα has been shown to significantly reduce total cholesterol (TC), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels, and significantly increase triglyceride (TG) levels [14, 15]. Whether dyslipidemia affects the antiviral efficacy of PegIFNα is worth exploring. Previous studies [15, 16] have shown that lipids can influence PegIFNα efficacy and predict HBeAg seroresponse in HBeAg-positive patients. However, the effect of dyslipidemia on HBsAg clearance after PegIFNα therapy has not yet been reported. Therefore, the present study selected a cohort of NAs-experienced CHB patients to investigate the effect of dyslipidemia on HBsAg clearance, and a nomogram model was constructed to predict and identify the dominant population of PegIFNα treatment in the early stage.

Methods

Study population and design

A total of 1100 CHB patients treated with PegIFNα (180 μg/week) at Fujian Medical University Affiliated First Quanzhou Hospital (Quanzhou, China) from January 2019 to March 2024 were retrospectively screened. Inclusion criteria were as follows: (1) serum HBsAg present for ≥6 months; (2) age between 18 and 70 years; (3) previous treatment with NAs for ≥3 months; and (4) PegIFNα treatment for ≥48 weeks with complete follow-up data. Exclusion criteria were as follows: (1) co-infection with hepatitis C virus, hepatitis D virus, hepatitis E virus or human immunodeficiency virus; (2) discontinuation or change in treatment regimen; (3) concomitant history of cirrhosis, hyperthyroidism, thyroiditis, autoimmune hepatitis, pregnancy or any type

of tumor and (4) incomplete relevant test data and information. Ultimately, 160 patients were analyzed in the present study.

First, the patients were divided into the normolipidemia group and the dyslipidemia group according to the status of baseline serum lipids. Dyslipidemia refers to hypertriglyceridemia (TG≥1.7mmol/L), hypercholesterolemia (TC≥5.2mmol/L), or mixed hyperlipidemia. The diagnosis was based on the Chinese Guidelines for Lipid Management (2023) [5]. The PegIFNα treatment strategy involved "add-on" and "switch-to". According to The expert consensus on clinical cure (functional cure) of chronic hepatitis B [17] and the optimizing-seroconversion sequential treatment (OSST) trial from China [18, 19], the 'add-on' strategy means that patients receive NAs treatment together with PegIFNα, while the 'switch-to' strategy involves switching patients to PegIFNα monotherapy. Thereafter, all patients were divided into the HBsAg clearance (SC) group and the non-HBsAg clearance (NSC) group according to the treatment outcomes at the end of 48 weeks of PegIFNα. HBsAg clearance was defined as the disappearance of HBsAg in previously HBsAg positive patients (<0.05 IU/ mL); HBV-DNA negative was defined as HBV-DNA below the lower limit of detection (<20 IU/ mL).

Data collection

General information about all patients, including name, gender, age, height, weight, body mass index (BMI), HBeAg status, HBV-DNA status and treatment regimen, was collected. HBsAg, anti-HBs, HBeAg, anti-HBe and anti-HBc were quantified by chemiluminescent particulate immunoassays using the Architect i2000 SR platform and Abbott Architect reagents (Abbott Laboratories, Chicago, IL). COBAS AmpliPrep/COBAS TaqMan system (Roche Diagnostics, Mannheim, Germany) was used to detect serum HBV DNA by quantitative PCR, with a lower limit of detection of 20 IU/mL. During PegIFNα treatment, HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc, HBV-DNA, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), globulin (GLO), total bilirubin (TBIL), alkaline phosphatase (ALP), glutamyl transpeptidase (GGT), TG, total cholesterol (TC), HDL, LDL, ApoA1, ApoB, and other clinical data were recorded at 12 week intervals after the initiation of treatment until the end of 48 weeks of treatment. In addition, the time of baseline data collection refers to before initiation of PegIFNα treatment.

Statistical analysis

Statistical analysis was performed using SPSS 27.0 (IBM Corporation, USA) and R (version 4.2.2) softwares. Categorical variables were expressed as frequencies or percentages (%). Continuous variables conforming to a normal distribution were expressed as mean±standard deviation, and not conforming to a normal distribution were expressed as median (M) and interquartile range (IQR). Depending on the distribution of the data, categorical variables were compared using a chi-square test or Fisher's exact probability method, and the significance of differences in continuous variables was checked using a non-parametric test (Mann-Whitney U test) or a t-test for two independent samples. Two-factor repeated analysis of variance (ANOVA) or generalized estimating equations were used to compare the dynamics of lipid markers between the groups. Kaplan-Meier survival analysis and log-rank tests were used to describe cumulative HBsAg clearance and cumulative HBsAg seroconversion rates. The potential factors affecting HBsAg clearance were first screened out using univariate COX regression analysis ($P<0.20$). Subsequently, multivariate COX analysis and stepwise regression analysis were performed to identify the independent predictors of HBsAg clearance after initiating PegIFNα therapy in CHB patients. Next, a nomogram model was constructed to predict HBsAg clearance probability. Internal validation of the predictive model was then performed using the bootstrap method. The model's discrimination was evaluated with the ROC curve and concordance index (C-index), while its calibration was assessed using a calibration curve. Statistical significance was set at $P<0.05$.

Results

Baseline characteristics of patients

A total of 160 CHB patients (113 male and 47 female), of whom 70 were HBeAg-positive and 82 were anti-HBe positive, aged 18–67 years, were enrolled in this study. Of these, 101 patients received the "add-on" treatment strategy, and the rest received the "switch-to" treatment strategy. Among the 160 patients, 92 had normal lipid levels, 23 had hypertriglyceridemia, 31 had hypercholesterolemia, and 14 had mixed hyperlipidemia. As shown in Table 1, BMI, GGT, TG, TC, LDL, ApoA1 and ApoB were significantly lower in the normolipidemia group than in the dyslipidemia group; however, HDL levels were similar between the two groups. In addition, although the proportion of patients taking tenofovir disoproxil fumarate was slightly higher in the normolipidemia group, there was no statistical significance. No significant differences were observed in the other indices between the two groups.

Lipid metabolism and therapeutic effect of PegIFNα

After 48 weeks of PegIFNα treatment, 33 patients achieved HBsAg clearance, with an HBsAg clearance rate of 20.63% and an HBsAg seroconversion rate of 10.63%. In the SC group, the percentage of HBeAg-positive patients and level of baseline HBsAg was lower, and the

Table 1 Baseline characteristics of patients

Characteristic	Normolipidemia Group ($n=92$)	Dyslipidemia Group ($n=68$)	*P* value
Age (years)	36.50 (31–44)	40 (33–45)	0.185
Male (%)	68.5%	73.5%	0.488
BMI (kg/m^2)	23.73 ± 3.21	24.87 ± 3.41	**0.032**
HBeAg-positive (%)	47.8%	38.2%	0.227
Anti-HBe positive (%)	50.0%	52.9%	0.713
HBV-DNA positive (%)	54.3%	50.0%	0.586
Add-on treatment (%)	65.2%	60.3%	0.523
NAs classification			0.066
ETV (%)	30.4%	44.1%	
TDF (%)	40.2%	23.5%	
TAF (%)	29.3%	32.4%	
Duration of NAs treatment (weeks)	59.40 ± 13.50	57.01 ± 15.54	0.301
Drugs for dyslipidemia (%)	1.1%	4.4%	0.183
HBsAg (lg, IU/mL)	3.02 ± 0.82	2.93 ± 0.82	0.516
anti-HBs (mIU/mL)	0.43 (0.05–0.91)	0.34 (0.01–0.70)	0.260
HBeAg (S/CO)	0.73 (0.37–22.23)	0.48 (0.34–8.56)	0.117
anti-HBe (S/CO)	0.99 (0.02–2.40)	0.78 (0.02–1.97)	0.586
anti-HBc (S/CO)	8.23 (7.50–9.25)	8.84 (7.46–10.01)	0.201
HBV-DNA (lg, IU/mL)	1.82 (1.04–3.75)	1.30 (1.00-4.60)	0.968
ALT (U/L)	39.00 (25–94)	42.5 (26.5–92)	0.794
AST (U/L)	33 (24-61.25)	31 (24.25–59.75)	0.945
GLO (g/L)	30.70 (27.73–33.20)	30.25 (28.90–33.80)	0.362
GGT (U/L)	26.00 (17.25-41.00)	39.00 (21.00–64.00)	**0.003**
ALP (U/L)	78.50 (65.25–98.25)	77.50 (68.25–95.75)	0.942
TBIL (umol/L)	14.45 (11.75–18.98)	14.80 (11.28–19.93)	0.959
ALB (g/L)	45.15 (42.23–46.95)	44.65 (43.03-46.00)	0.713
TG (mmol/L)	0.91 (0.70–1.13)	1.73 (1.20–2.10)	**< 0.001**
TC (mmol/L)	4.28 (3.88–4.59)	5.42 (4.89–6.08)	**< 0.001**
HDL (mmol/L)	1.08 (0.90–1.26)	1.11 (0.97–1.46)	0.054
LDL (mmol/L)	2.69 (2.40–3.01)	3.53 (2.80–3.93)	**< 0.001**
ApoA1 (g/L)	1.27 ± 0.17	1.34 ± 0.20	**0.009**
ApoB (g/L)	0.97 (0.81–1.06)	1.22 (0.94–1.37)	**< 0.001**

†: HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; BMI, body mass index

‡: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; GLO, globulin; TBIL, total bilirubin; ALP, alkaline phosphatase; GGT, glutamyl transpeptidase;

§: TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; APO, apolipoprotein

percentage of normolipidemic patients was higher (Table S1). Univariate COX regression analyses of baseline clinical indicators identified potential influences on HBsAg clearance ($P<0.20$), including serum lipid, age, HBeAg status, HBsAg, anti-HBe, and TC (Table S2). These factors were further evaluated through multivariate Cox regression and stepwise regression analyses, which demonstrated that serum lipid remained an independent predictor of HBsAg clearance after adjusting for confounding variables such as age, HBeAg status, and HBsAg (Table 2). The predictive value of serum lipid for HBsAg clearance was assessed using ROC curves, with AUC of 0.614 and 0.634 at 36-week and 48-week, respectively (Figure S1).

According to serum lipid, the patients were classified into normolipidemic and dyslipidemia groups. The Kaplan-Meier survival analysis showed that the cumulative HBsAg clearance rate was significantly higher in the normolipidemia group than in the dyslipidemia group during PegIFNα treatment, with a log-rank test result of $P=0.007$ (Fig. 1A). No significant difference was found between the cumulative HBsAg seroconversion rate of the two groups, with a log-rank test result of $P=0.07$ (Fig. 1B). In addition, age, HBeAg status and HBsAg were also independent factors in predicting HBsAg clearance.

Dynamic changes in serum lipids

There was no significant difference in six lipid indexes between the SC and NSC groups. Of these, TG levels showed an overall upward trend during PegIFNα treatment, with the NSC group showing significantly higher TG levels than baseline at each time point after starting

Table 2 Univariate and multivariate analysis of factors associated with HBsAg clearance

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Baseline				
Age (years)	0.962(0.962-1.000)	0.048	0.951(0.913–0.991)	0.017
HBeAg status, negative (%)	3.748(1.547–9.079)	0.003	4.365(1.763–10.806)	0.001
Serum lipid, dyslipidemia (%)	0.345(0.150–0.795)	0.012	0.243(0.104–0.566)	0.001
HBsAg, < 1500 IU/ml (%)	7.579(2.312–24.843)	< 0.001	8.016(2.428–26.470)	< 0.001
Anti-HBe (S/CO)	0.962(0.916–1.010)	0.119	–	–
TC (mmol/L)	0.677(0.461–0.995)	0.047	–	–

†: HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen

‡: TC, total cholesterol

§: HR, hazard ratio; CI, confidence interval

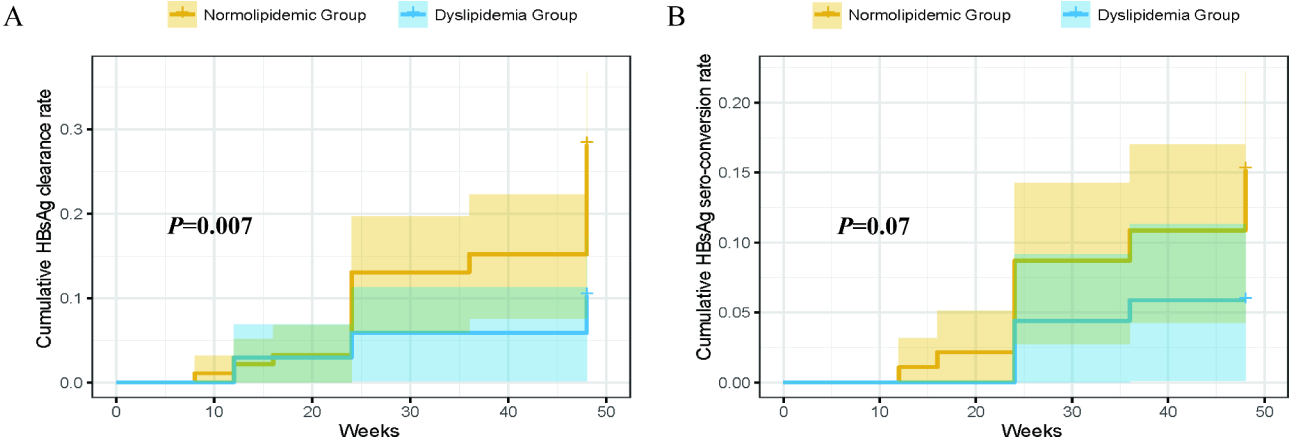

Fig. 1 Comparison of (**A**) cumulative HBsAg clearance rate and (**B**) cumulative HBsAg seroconversion rate between normolipidemic group and dyslipidemia group

treatment and the SC group showing higher TG levels than baseline at 36 and 48 weeks after starting treatment. TC, HDL, LDL, ApoA1 and ApoB levels were significantly lower after starting treatment than those at baseline, showing a decreasing trend (Fig. 2). Furthermore, there was no significant difference with respect to BMI between the SC and NSC groups. There was no significant change in the BMI of patients in each group during the treatment (Figure S2).

Nomogram model for predicting HBsAg clearance

Using these four independent factors influencing HBsAg clearance, we constructed a nomogram model to visually predict the probability of achieving HBsAg clearance in CHB patients at 36-week and 48-week after initiating PegIFNα therapy (Fig. 3). The AUC of this model at 36-week and 48-week were 0.879 and 0.856, respectively, and the C-index generated by Bootstrap internal validation was 0.836 (95% CI: 0.773–0.883), confirming the model's good discriminatory power (Fig. 4). The calibration curves at 36-week and 48-week showed good calibration (Fig. 5).

In addition, we also compared the nomogram model with another model without serum lipid using ROC curves. The results showed that dyslipidemia could improve the AUC of the model from 0.752 to 0.879 at 36-week, and from 0.674 to 0.856 at 48-week, indicating that dyslipidemia plays an important role in the nomogram model and that the addition of dyslipidemia can improve the model's prediction of HBsAg clearance effectively (Figure S3).

Discussion

Although PegIFNα has shown better efficacy than NAs in achieving functional cure in CHB patients, its clinical use is limited by numerous drawbacks, such as higher costs and more adverse effects [20]. Moreover, the efficacy of PegIFNα is not only directly influenced by the drug itself but also by the characteristics of the HBV virus, the metabolic status of the patient, body mass, the degree of liver tissue lesions, and other factors. Therefore, it is important to fully understand the factors affecting the efficacy of antiviral therapy and to apply the drug appropriately according to the various influencing factors in order to improve the efficacy and prognosis of patients. Our

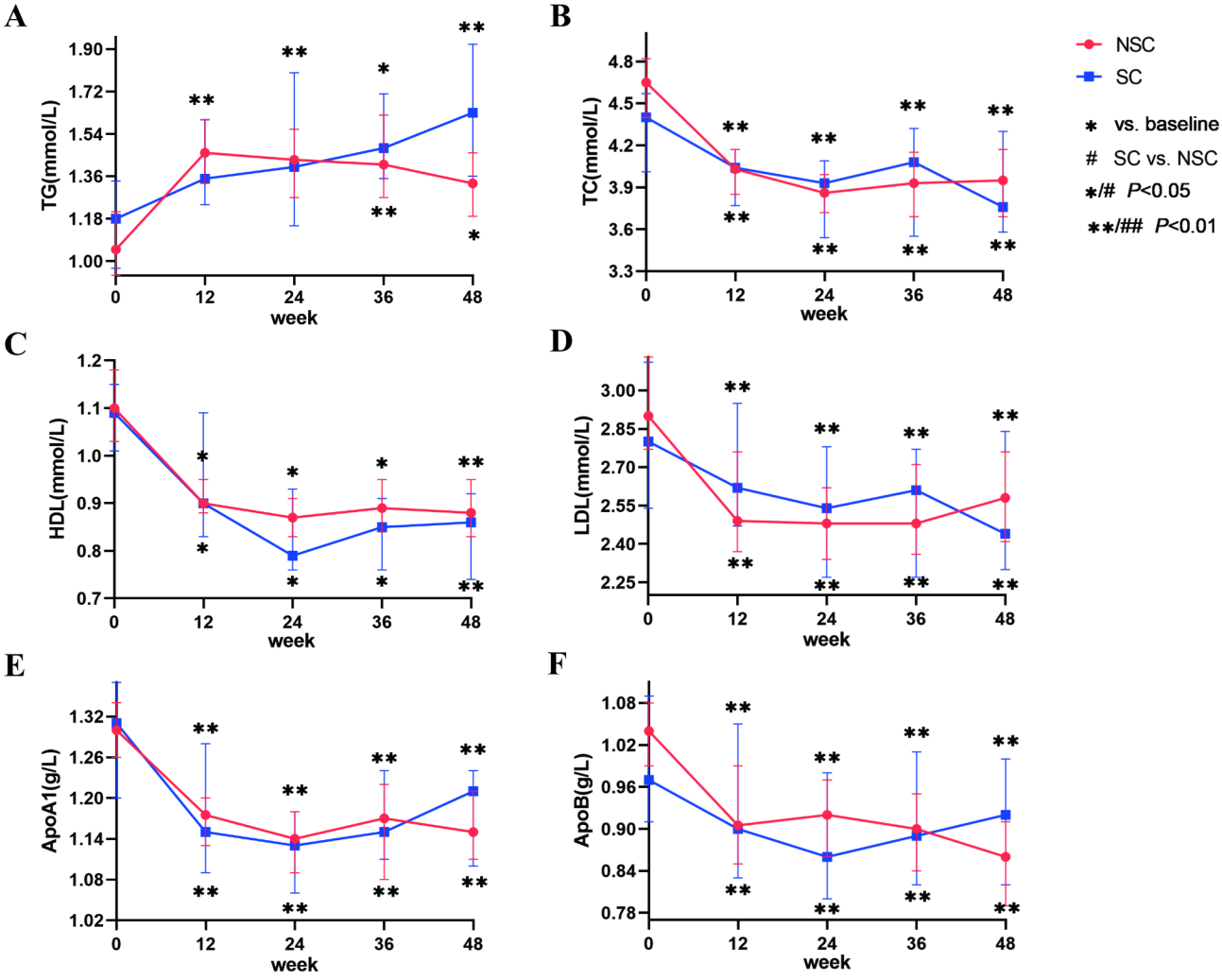

Fig. 2 Dynamic changes of serum lipids between NSC group and SC group. Dynamic changes of TG(**A**), TC(**B**), HDL(**C**), LDL(**D**), ApoA1(**E**), and ApoB(**F**) between the NSC and SC groups during treatment. TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B

retrospective study demonstrated that CHB patients with normal lipids were more likely to achieve HBsAg clearance during PegIFNα treatment. Four factors—namely age, HBeAg status, dyslipidemia, and HBsAg—were independently associated with HBsAg clearance. Based on the lipid metabolism, a nomogram model was constructed to predict HBsAg clearance. After evaluation and verification, this model showed good performance.

In a recent study [21] of CHB patients treated with NAs, the HBeAg seroconversion rate was found to be significantly lower in the dyslipidemia group than in the normolipidemic group in the fifth year of treatment (27.9% vs. 43.2%, $\chi^2=4.216$, $P<0.05$), and dyslipidemia was demonstrated to be an independent risk factor for HBeAg seroconversion. Similarly, the present study also showed that dyslipidemia interferes with the efficacy of antiviral therapy in CHB patients, but the outcome events, antiviral drug, and study population in our study were different. Moreover, we found no difference in HBsAg seroconversion rate between the two different lipid groups. These findings suggest that lipid metabolic status can influence PegIFNα antiviral efficacy. Therefore, the lipid profile of patients, whether they are hypertriglyceridemia, hypercholesterolemia or mixed hyperlipidemia, should be closely monitored before the initiation of antiviral therapy, and the lipid levels can be normalized through several interventions, including lifestyle interventions and pharmacological treatments. In addition, by separately comparing the dynamics of the six lipid markers in the SC and NSC groups, we observed that the cohort showed an overall increase in TG levels over time, while TC, HDL, LDL, ApoA1, and ApoB levels were lower than the baseline levels, which is in agreement with previous studies [15, 22]. However, individual lipid levels did not show significant differences between the two groups at each follow-up.

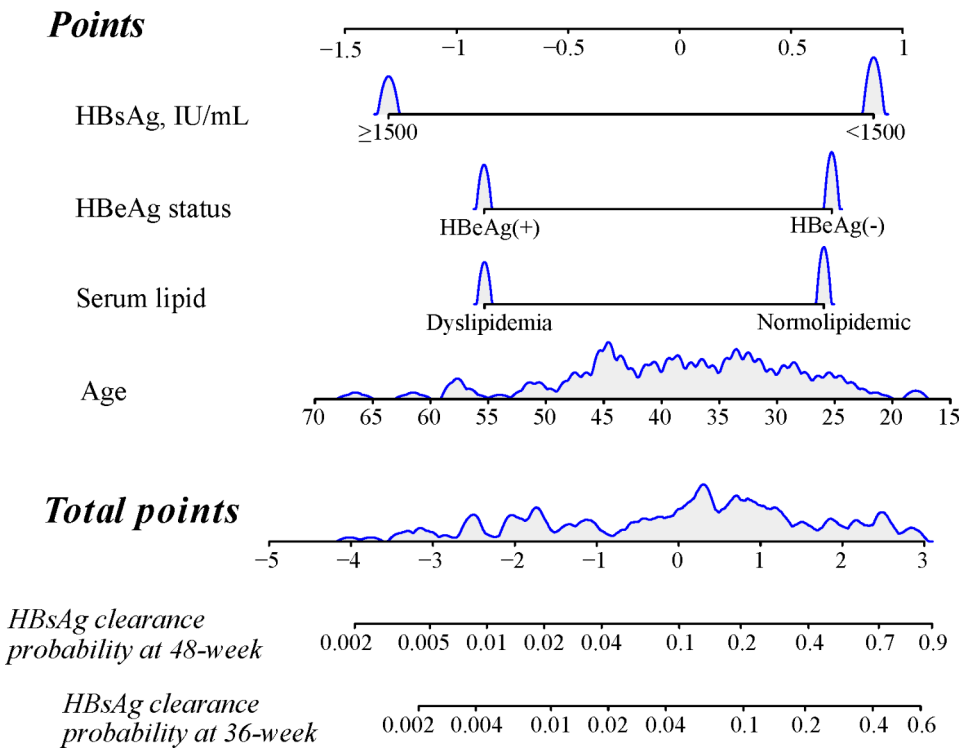

Fig. 3 Nomogram model for predicting HBsAg clearance in CHB patients treated with PegIFNα

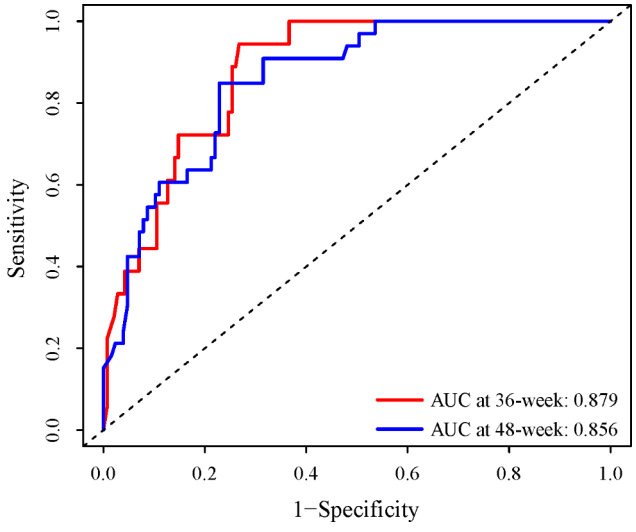

Fig. 4 ROC curves for validating the discrimination power of the nomogram. AUC, area under the receiver operating characteristic curve

Several previous studies [18, 23–25] have shown that patients with low HBsAg levels (<1500 IU/ml) and negative HBeAg prior to interferon initiation are more likely to achieve functional cure with sequential interferon therapy. In conjunction with the above findings, our study identified HBeAg status, serum lipid, HBsAg and age as independent predictors of HBsAg clearance. Chu et al. [26] observed that among HBeAg-negative patients receiving combination therapy with PegIFN and NAs, increasing age was an independent risk factor for HBsAg clearance, consistent with our findings. Previously, limited studies have reported the impact of lipids on antiviral therapy in CHB patients. Cao et al. [15] found an independent positive correlation between the rate of change in TC at 24 weeks after treatment initiation and HBeAg seroconversion at 72 weeks in HBeAg-positive patients who received 48 weeks of PegIFNα monotherapy. In another study [16] with the same patient inclusion conditions and a treatment regimen consisting of 48 weeks of PegIFNα monotherapy and PegIFN add-on NAs therapy, Xun et al. found a negative correlation between baseline TC and HBeAg seroconversion. Similarly, our study found dyslipidemia to be an independent risk factor for HBsAg clearance, which implies a negative correlation between them. However, some studies [27–29] observed that metabolic dysfunction-associated steatotic liver disease (MASLD) could improve HBsAg clearance. The reasons for these differences may be that, first, MASLD is characterised by hepatic steatosis, obesity, diabetes mellitus and metabolic abnormalities. Huang et al. [27] and Mak et al. [28] used controlled attenuation parameter(CAP) or abdominal ultrasound to define MASLD, and they found that hepatic steatosis had a positive effect on HBV clearance. However, hepatic steatosis and dyslipidemia are not exactly equivalent, and a distinction needs to be made regarding their relationship to HBV clearance. Second, and more importantly, all

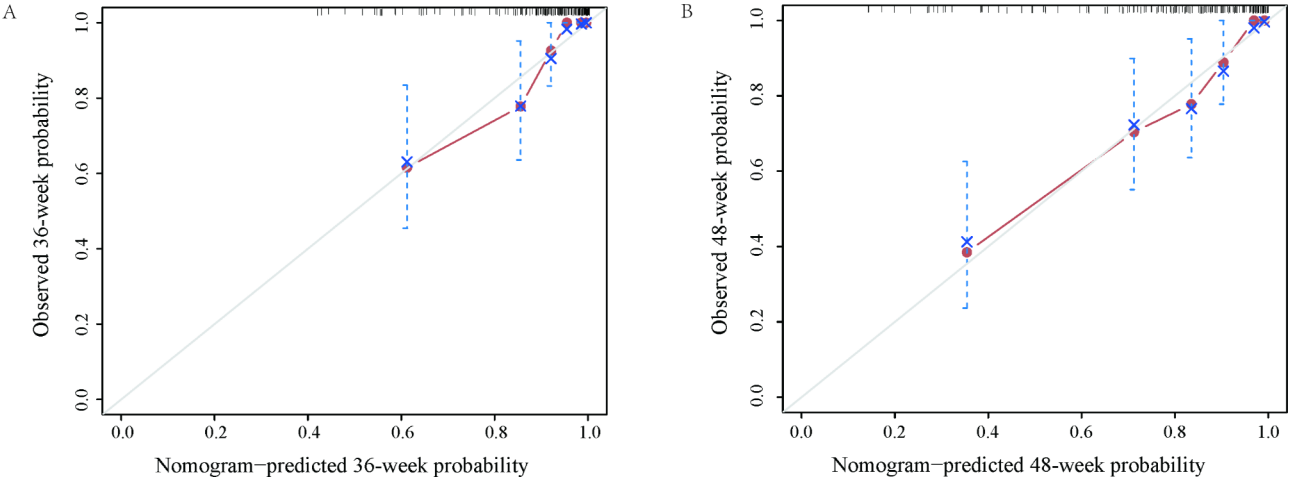

Fig. 5 Calibration plots of the nomogram for 36-week (**A**) and 48-week (**B**) HBsAg clearance probability prediction

the participants in the above studies were CHB patients who were not receiving antiviral therapy, whereas our study was conducted on patients who initiated PegIFNα therapy. Therefore, their results do not truly reflect the effect of MASLD on antiviral therapy in CHB patients. In addition, several researches [30, 31] have also reported that hepatic steatosis significantly reduces the efficacy of antiviral therapy, either with NAs or interferon therapy. However, the above elaboration of these differences needs to be confirmed with more multicentre studies large-sample in the future.

The mechanisms underlying the relationship between lipid metabolism and interferon efficacy remain unclear. Previous studies [32] have shown that bile acids regulate HBV biosynthesis through multiple molecular receptors. For example, farnesoid X receptor α and the c-Jun N-terminal kinase/c-Jun signal transduction pathway, can promote the transcription and expression of HBV genes in hepatocyte cell lines, and this enhancement of viral gene replication counteracts the antiviral effect of interferon-α. Bile acids are derived from cholesterol; therefore, it is hypothesized that the dyslipidemic state of CHB patients affects the body's bile acid metabolism, which in turn leads to a weakening of the antiviral effect of interferon. On the other hand, as an important component of blood lipids, cholesterol plays a crucial role in regulating the HBV viral life cycle and host infection, and inhibition of cholesterol production may reduce HBV infection [33, 34]. Meanwhile, it has been reported that up or down regulation of the expression of key genes in lipid metabolism can promote HBV clearance. Makokha et al. [35] found that knockdown of sterol regulatory element binding protein cleavage-activating protein (SCAP) not only significantly inhibited viral replication and reduced HBsAg production, but also led to the activation of interferon and interferon-stimulated genes. Schmidt et al. [36] found that inhibition of acyl-CoA: cholesterol acyltransferase (ACAT) rescued depleted T cells, as well as reduced both virions and subviral particles, which ultimately acted as an antiviral agent. In addition, dyslipidemia leads to a stressful state of cellular metabolism in the body, and induces imbalance of the immune system, which may to some extent affect adaptive immunity, specifically the T-cell antiviral response [37, 38]. The above-mentioned possible mechanisms may not be able to fully explain the effect of lipids on PegIFNα therapy, and the complex relationship and specific mechanisms between them need to be investigated and verified through further basic experiments.

This study had some limitations. First, it was a single-center retrospective study, and we only performed internal validation, wherein the prediction model lacked external validation with multi-center, prospective data; future corroboration is needed with the inclusion of more study populations. Second, this study was conducted in a population that was previously treated with NAs, where baseline HBsAg and HBV-DNA levels were not very high. Hence, further studies are needed on the role of lipid metabolism in PegIFNα antiviral efficacy in CHB patients under other background conditions. In addition, HBV genotypes were not included in this study, which we will consider and evaluate in the future.

Conclusion

Dyslipidemia can affect the antiviral efficacy of PegIFNα in NAs-experienced CHB patients, reminding physicians of the need to ensure that patients' lipid metabolism is within the normal range before starting PegIFNα therapy. Furthermore, age, HBeAg status, serum lipid, and HBsAg are independently correlated with HBsAg clearance after PegIFNα therapy. The nomogram model constructed based on the above factors has good predictive power and can be used by clinicians for the initial selection of a superior population for PegIFNα therapy,

thereby avoiding adverse drug reactions and reducing the wastage of healthcare resources.

Abbreviations

HBV	Hepatitis B virus
CHB	Chronic hepatitis B
HBsAg	Hepatitis B surface antigen
PegIFNα	Peginterferon alfa
SC	HBsAg clearance
NSC	Non-HBsAg clearance
ROC	Receiver operating characteristic curve
AUC	Area under the receiver operating characteristic curve
HR	Hazard ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-10093-w.

Supplementary Material 1

Acknowledgements
Not applicable.

Author contributions
K.S., Z.S. and X.Y. conceived the conception of the study. K.S., H.W., Z.G., H.Z., Y.L and Y.Z. acquired the data. K.S., H.W., Z.G., L.R. and Y.Q. participated in data analyses. K.S., L.R. and Y.Q. drafted the manuscript. Z.S. and X.Y. polished this article. X.Y., Z.S., D.Z. and Y.Z. led the project and supervised the study. All authors have read and agreed to the published version of the manuscript.

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Data availability
The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Biomedical Research Affiliated to Fujian Medical University (No. 2014-87), who waived the need for informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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