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Impact of hepatic steatosis on the efficacy of antiviral treatment for chronic hepatitis B and the establishment of predictive model: a cohort study

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Abstract

Aim Metabolic dysfunction-associated steatotic disease (MASLD) and chronic hepatitis B (CHB) are prevalent liver disorders. Ongoing discussions investigate the impact of MASLD on the therapeutic outcomes of CHB.

Methods A cohort of 320 CHB patients on antiviral therapy (including NAs and PEG IFNα) were included and categorized into CHB + MASLD (n = 125) and CHB group (n = 195). The treatment response rates, Kaplan–Meier survival analysis, and Cox regression were assessed between the two groups to investigate the impact of MASLD on antiviral responses in patients with CHB.

Results At weeks 24 and 48, the CHB + MASLD group displayed a higher HBsAg response rate than the CHB group (24 weeks: 11.5% vs. 3.8%, p = 0.026; 48 weeks: 24.4% vs. 8.4%, p = 0.001). The pgRNA response was also higher in the CHB + MASLD group at both time points (24 weeks: 30.9% vs. 19.7%, p = 0.163; 48 weeks: 48.8% vs. 28.3%, p = 0.049). Kaplan–Meier survival analysis revealed a shorter median time to HBsAg response at 48 weeks for the CHB + MASLD group (HR = 3.251, 40 weeks vs. 42.5 weeks, p = 0.002). This is particularly evident among individuals who are negative for HBeAg (48w: 24.2% vs 12.2%, p = 0.005). KM survival analysis demonstrated that the CHB + MASLD group was more likely to achieve HBsAg response (HR = 2.428, p = 0.039).COX regression analysis identified age (HR = 0.948, p = 0.005), antiviral regimen (NAs + PEG IFNα: HR = 5.33, p < 0.001; PEG IFNα: HR = 1.099, p = 0.93), baseline HBsAg level (HR = 0.648, p = 0.009), and MASLD presence (HR = 3.321, p = 0.002) as independent predictors for HBsAg response. Time-ROC analysis showed that these factors effectively predicted HBsAg decline (24 weeks: AUC = 0.902; 48 weeks: AUC = 0.890). The model demonstrated strong discriminative power, calibration, and clinical relevance.

Conclusion In CHB patients without significant liver fibrosis who receive antiviral therapy, concurrent MASLD enhances HBsAg response, particularly in HBeAg-negative patients. Factors like younger age, NAs with PEG IFNα therapy, lower initial HBsAg levels, and MASLD presence predict treatment success. Further investigations are required to elucidate the impact of diverse metabolic disorders on the advancement of liver fibrosis.

Trial registration Registry and the registration No. Of the study/trial: ChiCTR23000 74064(2023-07-28).

Keywords Hepatic steatosis, Chronic hepatitis B, HBsAg, Antiviral treatment, Predictive model

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Introduction

Chronic hepatitis B (CHB) is a prevalent liver disease, with a global incidence of approximately 3.2% in 2022. In China, the situation is more severe, with a prevalence rate of 5.6%, which translates to nearly 80 million individuals living with HBV infection [1]. If left untreated, patients with CHB have a significant risk, about 30% to 40% of progressing to serious conditions such as cirrhosis or liver cancer [1]. This underscores the importance of effective antiviral therapy in improving health outcomes for these patients. In 2016, the WHO set a goal to eliminate viral hepatitis by 2030. This initiative aims for a 90% reduction in new HBV and HCV infections and the eradication of this public health threat [2]. HBV infects the human body by entering liver cells through the NTCP protein on the cell membrane. The viral genome, known as relaxed circular DNA (rcDNA), enters the cells and integrates into the host DNA, forming covalently closed circular DNA (cccDNA). The remarkable stability of cccDNA significantly contributes to the challenges associated with eliminating the hepatitis B virus [3]. CHB treatment encompasses two primary outcomes: complete cure and clinical cure. A complete cure requires eradicating cccDNA from liver cells, which is often difficult to accomplish. Clinical cure, or functional cure, indicates that serum levels of HBsAg and HBV DNA are consistently undetectable, regardless of HBsAg seroconversion. Although some residual cccDNA may persist, the risk of progressing to end-stage liver disease significantly decreases [4].

Metabolic dysfunction-associated steatotic disease (MASLD) affects approximately 38.77% of the global population [5]. MASLD primarily arises from the accumulation of lipids in the liver, insulin resistance, imbalances in gut microbiota, and oxidative stress. These factors can lead to serious complications, including liver fibrosis, cirrhosis, and hepatocellular carcinoma. Concurrent CHB and MASLD affect over one-third of the population, with variable findings on their correlation. Some studies indicated that hepatitis B patients who also have MASLD exhibit reduced levels of viral expression [6]. Cohort studies suggested MASLD may facilitate hepatitis B virus clearance [7]. Mechanisms likely involve immune activation [8] and autophagy [9]. Our preliminary study found that patients with MASLD and CHB have lower levels of HBV DNA, pgRNA, HBsAg, and HBeAg than those with isolated CHB [6]. HBsAg serves as an indirect marker of HBV cccDNA, with serum levels reflecting the status of cccDNA in hepatocytes [10, 11]. Current estimates indicate that the HBsAg prevalence in our country is 6.1% [12], which poses risks for liver disease progression and hepatocellular carcinoma. Furthermore, HBsAg clearance is associated with better liver function and prognosis. This research focuses on HBsAg response as a primary endpoint, using a retrospective cohort study to investigate how MASLD affects antiviral treatment outcomes in CHB and the factors that influence these outcomes. The study aims to develop a predictive model for antiviral therapy response, offering insights for clinical cure.

Patients and methods

Participants

This study examined 320 cases of CHB patients retrospectively who received treatment at the Hepatology Outpatient Department of Dalian Medical University First Affiliated Hospital between July 2021 and September 2024. Patients were categorized into two groups based on hepatic steatosis presence: the CHB group (n = 195) and the CHB + MASLD group (n = 125). Inclusion criteria: (1) Age ≥ 18 years; (2) CHB diagnosis conforming to the " Guidelines for the prevention and treatment of chronic hepatitis B (version 2022)"[13]; (3) MASLD diagnosis in line with the " Guidelines for the prevention and treatment of metabolic dysfunction-associated fatty liver disease (Version 2024)"[14]; (4) Receipt of antiviral therapy comprising either nucleos(t)ide analogs (NAs) monotherapy (including entecavir, tenofovir disoproxil fumarate, tenofovir alafenamide fumarate, and tenofovir amibufenamide), PEG interferonα−2b (PEG IFNα) monotherapy, or a combination of NAs and PEG IFNα; (5) Participation in at least one follow-up evaluation. Exclusion criteria: (1) Co-infection with other viral hepatitis or significant liver fibrosis; (2) Presence of autoimmune liver disease, cholestatic liver disease, Wilson's disease, significant alcohol use, or drug-induced liver disease; (3) Use of medications known to induce hepatic steatosis (e.g., corticosteroids, tamoxifen); (4) Pregnant or lactating individuals; (5) Incomplete clinical records. Laboratory results and FibroScan findings from patients were collected for analysis. Serum samples were collected from patients and stored at − 80 °C for HBV RNA analysis. A follow-up period of 48 weeks was implemented for the enrolled participants, with data collection occurring at 24-week and 48-week intervals. Of the 320 patients, 267 (83.4%) pursued monotherapy utilizing NAs, 7 (2.2%) opted for PEG IFNα monotherapy, while 46 (14.4%) engaged in NAs combined with PEG IFNα therapy. More than 80% of patients received NAs as monotherapy, while the yearly HBsAg clearance rate stayed below 3%. Thus, HBsAg response was defined as a reduction of ≥ 0.5 log from baseline. The pgRNA response was defined as a decrease of ≥ 0.5 log from baseline as well. The baseline HBeAg status indicated that 214 patients (66.9%) were negative for HBeAg, while 106(33.1%) were positive. The enrollment flowchart is provided in Fig. 1.

This research was approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University (PJ-KS-KY-2023–339) and followed the guidelines established in the Declaration of Helsinki. All participants provided written informed consent for the anonymous use of their data and blood samples in this study.

Laboratory examination

Retrieve patient data from the hospital information system. Collect demographic details, such as gender, age, and family history of hepatitis, diabetes, and hypertension. Collect medical history and biochemical liver function results, blood glucose levels (FBG), lipid profiles, serum uric acid (UA), serum insulin, HBsAg, and HBV DNA. Record anthropometric data, including weight and height, and calculate Body Mass Index (BMI) as weight/height2. Evaluate serum HBV DNA using HBV nucleic acid quantification kits (Hunan Shengxiang Biotechnology, China) with rt-PCR, detecting down to 20 IU/mL. Quantify serum HBsAg with the Abbott Architect i2000 (Abbott, Chicago, USA), having a detection limit of 0.05 IU/mL. Assess serum HBeAg via Roche e801 automated immunoassay (Roche, Basel, Switzerland), with a detection limit of 1.0 (S/Co). Analyze serum pgRNA with the SAT isothermal amplification kit (Rendu Biotechnology, Shanghai, China), which detects concentrations between 2–8 log copies/mL and has a minimum detection limit of 50 copies/mL.

FibroScan Test

For the evaluation of the Controlled Attenuation Parameters (CAP) and liver stiffness measurement (LSM), the FibroScan®502 and M-type probe (Echosens, Paris,

France) were utilized. The procedure involves obtaining ten successful measurements from one site. The median of these valid results is used as the final metric. This assessment adheres to the "Guidelines for the Prevention and Treatment of Metabolic Dysfunction-Associated Fatty Liver Disease (Version 2024)" [14]. CAP values were classified as follows: no steatosis (Grade 0 (S0)), CAP < 248 dB/m; Mild steatosis (Grade 1 (S1)), 248 dB/m ≤ CAP < 268 dB/m; Moderate steatosis (Grade 2 (S2)), 268 dB/m ≤ CAP < 294 dB/m; Severe steatosis (Grade 3 (S3)), CAP ≥ 294 dB/m.

Statistical analysis

Continuous variables that follow a normal distribution are expressed as mean ± standard deviation. The median and interquartile range represent variables that do not follow a normal distribution. Independent sample t-tests or non-parametric tests, such as the Mann–Whitney U test, are used to conduct intergroup comparisons.

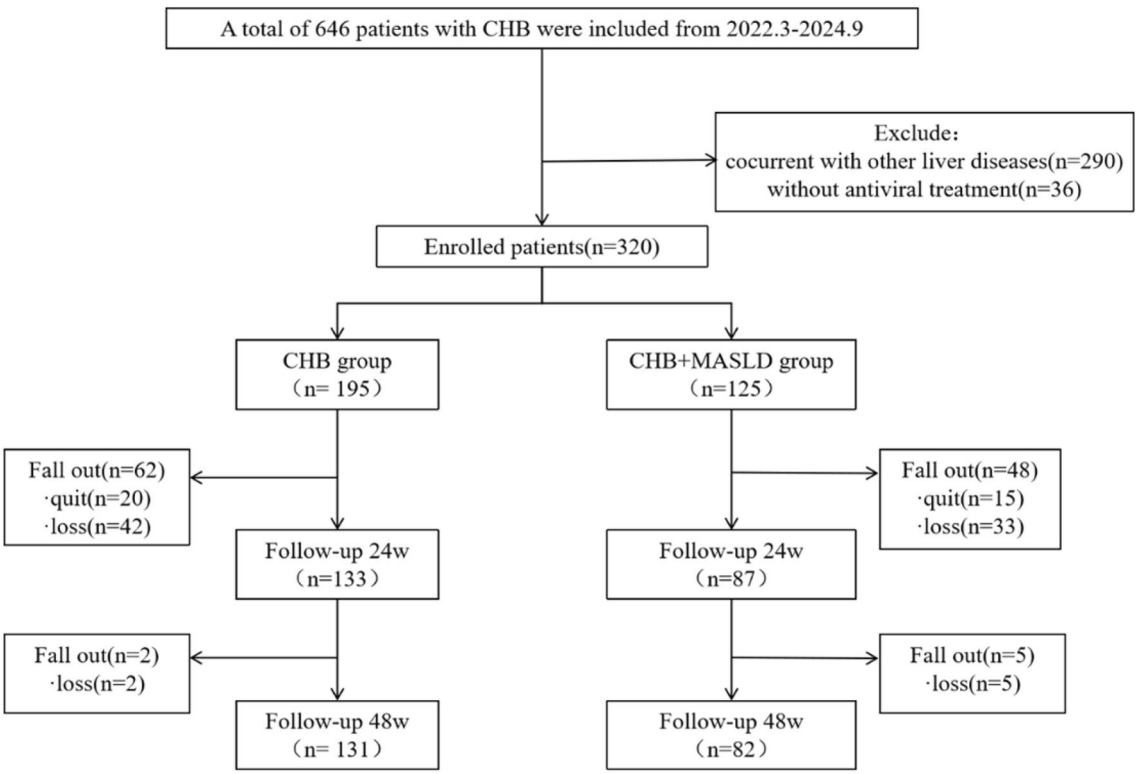

Fig. 1 Enrollment flow chart

Categorical variables are quantified as frequencies and percentages (%). The chi-square test and Fisher's exact test assess group differences. The impact of MASLD on the response to HBV antiviral treatments is assessed using Kaplan–Meier survival analysis. Predictive factors influencing HBV antiviral treatment response undergo analysis through Cox proportional hazards regression, ultimately leading to the establishment of a prediction model for HBV response rates among CHB patients at weeks 24 and 48. An effective prognostic NOMO chart is created. The prediction model's sensitivity, specificity, and clinical applicability are evaluated using bootstrap methods, C-index, time-AUC curve, and decision Curve Analysis (DCA) curve. All data are analyzed using IBM SPSS (version 26.0) and R language. A p-value of less than 0.05 indicates statistical significance.

Results

Baseline characteristics

A total of 320 patients participated in this study. Based on the presence or absence of hepatic steatosis, patients were divided into the CHB + MASLD group (n = 125) and the CHB group (n = 195). The two groups were similar regarding age, gender, other general data, HBV DNA, and HBsAg levels. In the CHB + MASLD group, the HBeAg positive rate and HBeAg level were significantly lower than in the CHB group. In contrast, the levels of ALT, total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), UA, and Homeostasis model assessment of insulin resistance (HOMA-IR) were significantly higher in the CHB + MASLD group (Table 1). According to the medical records detailing antiviral therapy, the patients were segregated into two groups: 91 cases (28.4%) were identified as individuals undergoing initial treatment (NAs: n = 82, 90.1%; NAs + PEG IFNα: n = 5, 5.5%; PEG IFNα: n = 4, 4.4%), whereas 229 cases (71.6%) underwent NAs therapy. According to the level of HBV DNA, 140 cases (43.8%) had HBV DNA < 20IU/ml and 180 cases (56.2%) had HBV DNA ≥ 20IU/ml. In the CHB + MASLD group, 59 cases (47.2%) were classified as mild (S1), 30 cases (24.0%) as moderate (S2), and 36 cases (28.8%) as severe (S3). Based on the baseline levels of HBeAg, 320 patients were divided into 214 HBeAg-negative patients (66.9%) and 106 HBeAg-positive patients (33.1%). Baseline characteristic analysis for both groups showed that among HBeAg-negative patients, the CHB + MASLD group exhibited significantly higher levels of TC, TG, LDL, and HOMA-IR compared to the CHB group. In HBeAg-positive patients, the CHB + MASLD group demonstrated significantly elevated levels of UA and HOMA-IR compared to the CHB group (Table 2).

Antiviral therapy response

The HBsAg response rate in the CHB + MASLD group was significantly higher than in the CHB group (24 weeks: 11.5% vs 3.8%, p = 0.026; 48 weeks: 24.4% vs 8.4%, p = 0.001). The pgRNA response rate was higher than in the CHB group at 24 weeks (30.9% vs 19.7%), and significantly higher at 48 weeks (48.8% vs 28.3%, p = 0.049) (Table 3). The results indicated that among HBeAg-negative patients, the HBsAg response rate at 48 weeks was significantly higher in the CHB + MASLD group compared to the CHB group (24 weeks: 11.9% vs 6.2%, p = 0.217; 48 weeks: 24.2% vs 12.2%, p = 0.005). Among HBeAg-positive patients, the HBsAg response rate was also higher in the CHB + MASLD group than in the CHB group (24 weeks: 15.0% vs 7.7%, p = 0.349; 48 weeks: 25.0% vs 9.6%, p = 0.112) (Table 4).

KM survival analysis

The HBsAg response rate and time required for CHB + MASLD group and CHB group at 48 weeks were analyzed using the log-rank test. The findings revealed that individuals in the CHB + MASLD group were significantly more likely to achieve an HBsAg response compared to those in the CHB group (HR = 3.251, p = 0.002). Additionally, the median time required to reach this response was notably shorter for the CHB + MASLD group than CHB group (40 weeks vs. 42.5 weeks) (Fig. 2a). Further analysis indicated that an increase in the severity of MASLD correlated with a higher likelihood of CHB patients achieving an HBsAg response (HR = 11.17, p = 0.01) (Fig. 2b). Stratified results highlighted that HBeAg-negative patients from the CHB + MASLD group had a greater likelihood of achieving an HBsAg response compared to those in the CHB group (HR = 2.428, p = 0.039) (Fig. 2c). Additionally, HBeAg-positive patients in the CHB + MASLD group also showed a tendency to achieve an HBsAg response (p = 0.251) (Fig. 2d).

COX regression analysis

COX regression analysis was used to analyze the baseline-related factors of HBsAg response, and a related model was established to predict the response of CHB patients to antiviral therapy. A total of 320 patients were enrolled and followed up for 48 weeks. Of these patients, 31 (9.7%) achieved a positive HBsAg response by week 48. By integrating all relevant baseline factors, our univariate regression analysis identified several influencing factors for HBsAg response: age (HR = 0.969, p = 0.008), antiviral regimen (NAs + PEG IFNα: HR = 8.246, p < 0.001; PEG IFNα: HR = 2.696, p = 0.338), baseline HBsAg level (HR = 0.529, p < 0.001), and combined MASLD (HR = 3.013, p = 0.003). Additionally, different degrees of MASLD were significant

Table 1 Baseline Characteristics of 320 patients

Parameters	CHB + MASLD (n = 125)	CHB (n = 195)	Total (n = 320)	*P* value
Age (years)	45.57 ± 10.61	46.21 ± 11.43	45.96 ± 11.11	0.617
Male (n, %)	76(60.8%)	106(54.4%)	182(56.9%)	0.256
BMI (kg/m^2)	25.50 ± 2.58	23.36 ± 4.06	24.35 ± 3.58	0.056
Family History (n, %)	62(49.6%)	100(51.3%)	162(50.6%)	0.769
T2DM (n, %)	4(3.2%)	7(3.6%)	11(3.4%)	0.852
Hypertension (n, %)	8(6.4%)	6(3.1%)	14(4.4%)	0.156
Antiviral regimen (n, %)				0.067
NAs	101(80.8%)	166(85.1%)	267(83.4%)	
IFN	6(4.8%)	1(0.5%)	7(2.2%)	
IFN + NAs	18(14.4%)	28(14.4%)	46(14.4%)	
Follow-up time (w)	48(31.50,48.00)	48(36.00,48.00)	48(33,48)	0.714
HBV DNA (log_{10}IU/ml)	1.50(0,2.92)	1.37(0,2.30)	1.44(0,2.63)	0.210a
pgRNA (log_{10}copies/ml)	1.97(1.31,3.03)	2.28(1.10,4.68)	2.03(1.27,3.73)	0.438[a]
HBsAg (log_{10}IU/ml)	3.29(2.68,3.71)	3.35(2.82,3.83)	3.31(2.73,3.78)	0.123a
HBcAb (S/Co)	0.007(0.007,0.009)	0.007(0.007,0.009)	0.007(0.007,0.009)	0.075[a]
HBeAg (S/Co)	0.11(0.10,0.70)	0.18(0.11,17.05)	0.12(0.10,6.70)	< 0.001*[a]
HBeAg positive (n, %)	26(21.3%)	76(41.1%)	102(31.9%)	< 0.001*
ALT (U/L)	27.5(21,52)	22.0(15,35)	25.0(17.0,40.39)	< 0.001*[a]
AST (U/L)	25(20,33)	24(19,31)	24.0(20.0,31.0)	0.238
ALB (g/L)	46.65(44.98,48.50)	46.20(44.40,47.80)	46.40(44.45,48.15)	0.057
TBil (umol/L)	13.70(11.15,17.83)	14.60(11.50,20.30)	14.40(11.35,18.80)	0.074
HbA1c (%)	6.00 ± 0.85	7.29 ± 2.19	6.77 ± 1.75	0.500
TC (mmol/L)	4.87(4.38,5.67)	4.61(3.80,5.31)	4.8(4.27,5.51)	0.016*[a]
TG (mmol/L)	1.31(1.00,1.91)	1.02(0.81,1.33)	1.22(0.87,1.64)	0.003*[a]
LDL (mmol/L)	2.84 ± 0.72	2.49 ± 0.70	2.71 ± 0.73	0.008*
UA (umol/L)	372.96 ± 94.12	335.09 ± 78.66	353.24 ± 88.22	0.005*
HOMA-IR	3.00(2.01,4.98)	1.55(0,2.94)	2.58(0,4.31)	< 0.001*
FBG (mmol/L)	5.58 ± 1.03	5.96 ± 1.57	5.73 ± 1.28	0.129
LSM (kPa)	5.25 ± 1.14	5.13 ± 1.16	5.18 ± 1.15	0.507
CAP (dB/m)	277.56 ± 31.30	199.08 ± 32.87	234.57 ± 50.62	< 0.001*

Non-normal distribution was expressed as midth (IQR), normal distribution was expressed as mean ± SD, non-normal distribution was expressed as a, and non-parametric test was used. *lindicates p < 0.05

(mild: HR = 2.916, p = 0.012; moderate; HR = 2.218, p = 0.172; severe: HR = 2.691, p = 0.067). The multivariate regression analysis included significant univariate indicators, revealing that younger age (HR = 0.948, p = 0.005), an antiviral regimen combining NAs with PEG IFNα (NAs + PEG IFNα: HR = 5.33, p < 0.001), a lower baseline HBsAg level (HR = 0.648, p = 0.009), and combined MASLD (HR = 3.321, p = 0.002) were independently linked to HBsAg response in CHB patients (Table 5).

Construction and validation of prognostic model

Using the Cox proportional hazards regression model, a prognostic model was developed, which we illustrated with a nomogram that includes additional scores on the bottom scale indicating the probability of HBsAg responses at 24 weeks and 48 weeks (Fig. 3a). The discrimination C-index and calibration (bootstrap internal validation) were used to verify the accuracy of the model (Fig. 3b). The C-index was calculated to be 0.852(95%CI: 0.795,0.909). The C-index was 0.852 (0.795, 0.909), and the time-ROC curve was generated (24w: AUC 0.902; 48w: 0.890) (FIG. 3c), indicating good fit, sensitivity, and specificity of the model. The DCA curve indicates

Table 2 Baseline characteristics of patients with different expression of HBeAg

Parameters	HBeAg Negative			HBeAg Positive		
	CHB + MASLD (n = 98)	CHB (n = 116)	*P* value	CHB + MASLD (n = 27)	CHB (n = 79)	*P* value
Age (years)	46.85 ± 10.82	48.35 ± 10.71	0.309	40.93 ± 8.48	42.99 ± 11.86	0.408
Male (n, %)	59(60.2%)	64(55.2%)	0.458	17(63.0%)	41(52.6%)	0.349
BMI (kg/m^2)	25.36 ± 2.94	23.84 ± 4.41	0.300	25.26 ± 1.15	23.43 ± 3.67	0.183
Family History (n, %)	47(48.0%)	59(50.9%)	0.672	15(55.6%)	40(51.3%)	0.702
T2DM (n, %)	3(3.1%)	5(4.3%)	0.631	1(3.7%)	2(2.6%)	0.759
Hypertension (n, %)	5(5.1%)	3(2.6%)	0.334	3(11.1%)	3(3.8%)	0.161
Antiviral regimen (n, %)			0.098			0.230
NAs	74(75.5%)	92(79.3%)		27(100%)	74(94.9%)	
IFN	6(6.1%)	1(0.9%)		0	0	
IFN + NAs	18(18.4%)	23(19.8%)		0	4(5.1%)	
HBV DNA (log_{10}IU/ml)	1.35(0, 2.30)	0(0, 1.89)	0.128	2.31(1.49,6.44)	1.94(0,5.71)	0.378[a]
pgRNA (log_{10}copies/ml)	1.88(1.18,2.51)	1.88(0,2.91)	0.848[a]	6.89(3.65,7.32)	5.16(3.93,7.12)	0.230[a]
HBsAg (log_{10}IU/ml)	2.95(2.42,3.47)	3.11(2.50,3.53)	0.207[a]	3.97 ± 0.55	3.71 ± 0.81	0.125
HBcAb (S/Co)	0.007(0.007,0.008)	0.007(0.007,0.009)	0.281[a]	0.007(0.006,0.010)	0.007(0.007,0.009)	0.483[a]
ALT (U/L)	25.00(20.0,42.0)	19.00(14.0,32.0)	0.098[a]	34.0(23.50,56.00)	25.0(18.00,41.50)	0.059[a]
AST (U/L)	24.00(20.0,31.0)	23.00(19.0,28.75)	0.394[a]	28.0(20.00,44.00)	24.0(19.25,31.00)	0.141[a]
ALB (g/L)	46.60(45.20,48.58)	46.40(44.00,47.90)	0.140[a]	46.8(44.30,48.18)	46.1(44.40,47.70)	0.431[a]
TBil (umol/L)	14.20(11.25,17.98)	15.65(12.33,21.10)	0.057[a]	12.9(9.63,15.93)	13.9(10.50,18.00)	0.377[a]
TC (mmol/L)	4.97 ± 0.99	4.53 ± 0.86	0.038*	5.09(4.75,5.86)	4.91(3.23,5.45)	0.126[a]
TG (mmol/L)	1.25(0.97,1.79)	1.00(0.83,1.30)	0.014*[a]	1.93 ± 1.40	1.17 ± 0.64	0.070
LDL (mmol/L)	2.80 ± 0.73	2.47 ± 0.60	0.033*	3.04 ± 0.64	2.53 ± 0.90	0.083
UA (umol/L)	371.60 ± 97.10	347.67 ± 79.83	0.154	380.08 ± 79.68	317.69 ± 75.67	0.023*
HOMA-IR	2.87(1.83,4.86)	1.58(0,2.94)	0.041*[a]	4.13 ± 2.37	1.59 ± 1.60	0.020*
CAP (dB/m)	279.41 ± 32.60	198.52 ± 35.35	< 0.001*	270.65 ± 25.29	199.97 ± 28.83	< 0.001*

Non-normal distribution was expressed as midth (IQR), normal distribution was expressed as mean ± SD, non-normal distribution was expressed as a, and non-parametric test was used. * indicates $p < 0.05$

Table 3 Comparison of HBsAg and pgRNA response rates between CHB + MASLD and CHB group

Time (w)	Parameters	HBsAg Response (n, %)	pgRNA Response (n, %)
24w	CHB + MASLD (n = 87)	10/87(11.5%)	17/55(30.9%)
	CHB (n = 133)	5/133(3.8%)	12/61(19.7%)
	P value	0.026*	0.163
48w	CHB + MASLD (n = 82)	20/82(24.4%)	20/41(48.8%)
	CHB (n = 131)	11/131(8.4%)	13/46(28.3%)
	P value	0.001*	0.049*

HBsAg response was defined as a ≥ 0.5log decrease in HBsAg from baseline and pgRNA response as a ≥ 0.5log decrease in pgRNA from baseline. * indicates $p < 0.05$

Table 4 Comparison of 24w and 48w HBsAg response rates in two groups of patients with different HBeAg expression

Time (w)	HBeAg Neagtive (n,%)			HBeAg Postive (n,%)		
24w	CHB + MASLD (n = 67)	CHB (n = 81)	*P* value	CHB + MASLD (n = 20)	CHB (n = 52)	*P* value
	8(11.9%)	5(6.2%)	0.217	3(15.0%)	4(7.7%)	0.349
48w	CHB + MASLD (n = 66)	CHB (n = 79)	*P* value	CHB + MASLD (n = 16)	CHB (n = 52)	*P* value
	16(24.2%)	6(12.2%)	0.005*	4(25.0%)	5(9.6%)	0.112

HBsAg response was defined as a ≥ 0.5log decrease in HBsAg from baseline and pgRNA response as a ≥ 0.5log decrease in pgRNA from baseline. * indicates $p < 0.05$

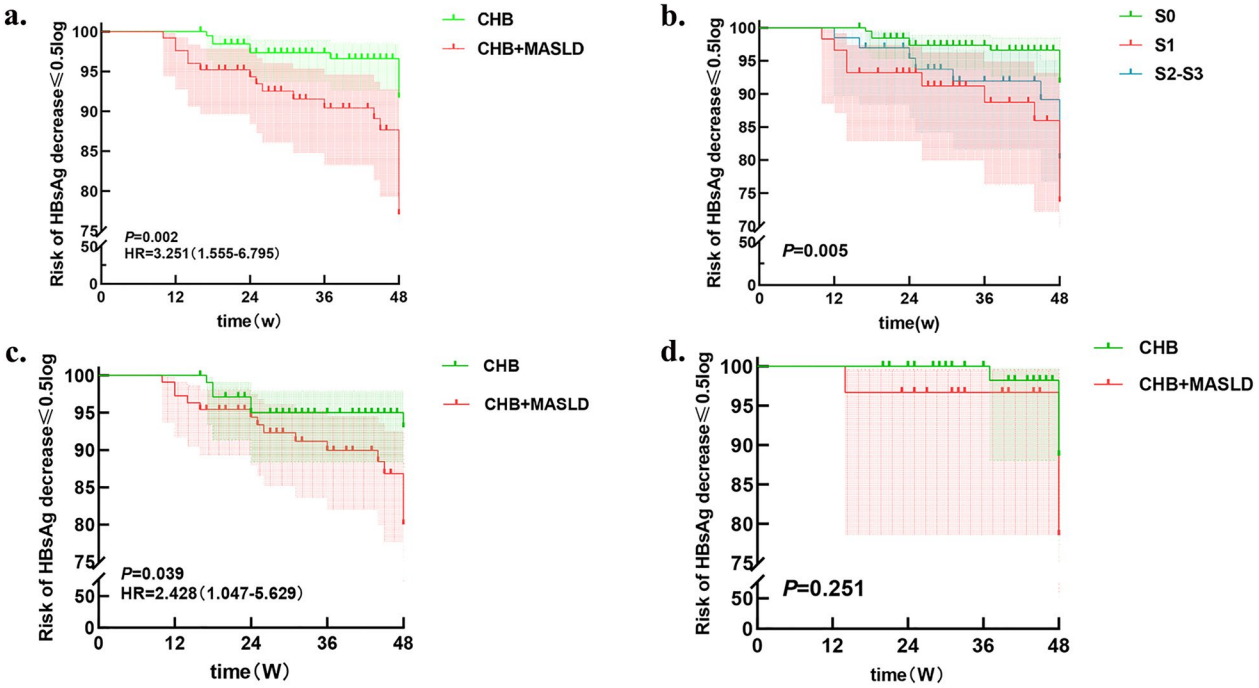

Fig. 2 Kaplan–Meier survival analysis of HBsAg response occurrence. **a** K-M survival analysis of HBsAg response rate between CHB + MASLD group and CHB group; **b** K-M survival analysis of the incidence of HBsAg response with different degrees of MASLD in the CHB + MASLD group; **c** K-M survival analysis of the incidence of HBeAg-negative HBsAg responses; **d** K-M survival analysis of the incidence of HBeAg-positive HBsAg responses

(Fig. 3d) that this model is likely to have broad clinical applicability (Fig. 3).

Table 5 COX regression analysis of factors related to HBsAg response in CHB patients

Parameters	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age (years)	0.969	0.936–1.004	0.008*	0.948	0.913–0.984	0.005*
Male (n, %)	0.634	0.298–1.346	0.235			
LSM (kPa)	0.940	0.840–1.051	0.275			
HBeAg positive (%)	0.651	0.291–1.455	0.296			
ALT (U/L)	1.004	0.998–1.010	0.154			
HOMA-IR	0.871	0.624–1.214	0.871			
T2DM (%)	0.793	0.108–5.819	0.820			
Hypertension (%)	2.461	0.748–8.098	0.138			
BMI (kg/m^2)	0.952	0.737–1.228	0.704			
Dyslipidemia (%)	0.423	0.147–1.218	0.111			
Antiviral regimen						
NAs	Reference			Reference		
NAs + PEG IFNα	8.246	4.017–16.925	< 0.001*	5.33	2.248–12.637	< 0.001*
PEG IFNα	2.696	0.354–20.516	0.338	1.099	0.135–8.912	0.93
Baseline HBsAg (log_{10}IU/ml)	0.529	0.404–0.692	< 0.001*	0.648	0.467–0.899	0.009*
With MASLD	3.013	1.443–6.288	0.003*	3.321	1.567–7.04	0.002*
No MASLD	Reference					
Mild (S1)	2.916	1.264–6.727	0.012*			
Moderate (S2)	2.218	0.706–6.968	0.172			
Severe (S3)	2.691	0.934–7.749	0.067			

Dyslipidaemia was defined as the presence of at least one abnormality in TC, TG, and LDL. *Indicates p < 0.05

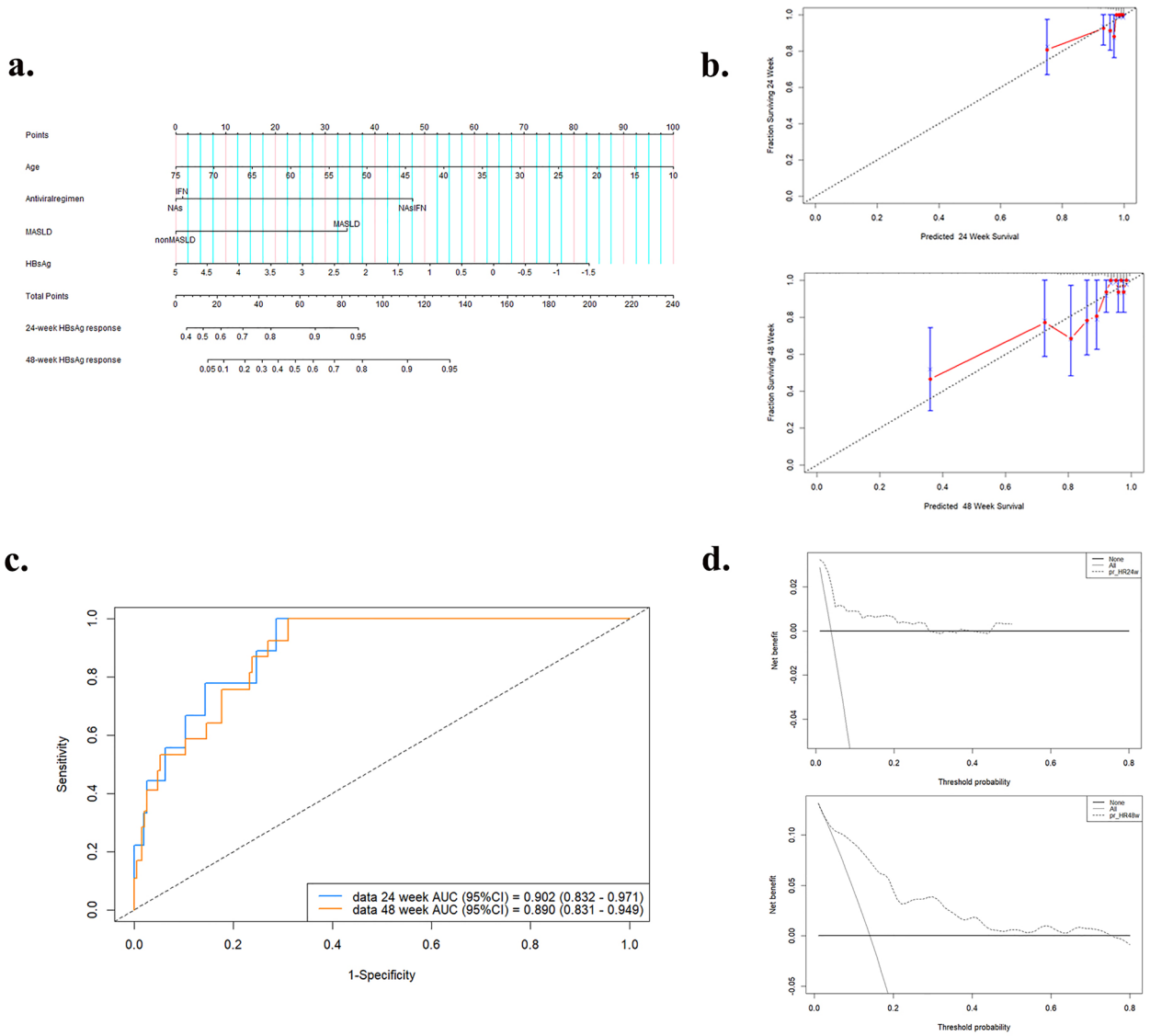

Fig. 3 Construction and validation of prognostic model. **a** NOMO chart; **b** Calibration curve; **c** Time-ROC curve; **d** Clinical practicability DCA curve

Discussion

The annual prevalence of CHB alongside MASLD is increasing. Currently, there is no agreement on how MASLD affects the outcomes of antiviral treatment for CHB. Previous studies suggested that hepatic steatosis could aid in the clearance of the hepatitis B virus [7], while others indicated it had no effect on this clearance [15]. In this study, we established a cohort of CHB patients through continuous follow-up. Results revealed that hepatic steatosis, in combination with antiviral therapy using NAs and PEG IFNα, could enhance the HBsAg response. Conversely, higher baseline HBsAg levels and older age adversely affected the HBsAg response in patients receiving antiviral therapy for CHB.

Hepatitis B surface antigen (HBsAg) is a complex comprising large surface antigen (LHBsAg) generated by a 2.4 kb mRNA derived from cccDNA, along with middle surface antigen (MHBsAg) and small surface antigen (SHBsAg) produced by a 2.1 kb mRNA. These antigens are capable of being discharged directly into the bloodstream, and their concentrations in the blood can serve as an indirect indicator of the condition of cccDNA in hepatic cells [10, 11]. Research showed that a decrease in HBsAg during antiviral therapy indicates a reduction in intrahepatic cccDNA. This finding suggested that there is a lasting therapeutic response during long treatment periods [16]. Additionally, the absence of HBsAg indicates that the body has gained immune control over

the virus [17]. Some investigations revealed that host immune function can experience partial restoration when patients' HBsAg levels drop below 3000 IU/ml [18, 19]. The gradual reduction in serum HBsAg during antiviral therapy exhibits a slow decline and a low negative conversion rate. Therefore, it is infrequently utilized as a marker to assess early antiviral efficacy. However, a quantitative decline in HBsAg may predict long-term antiviral success [20]. Reports indicated that the annual HBsAg clearance rate remains at or below 1% among patients receiving ETV/ Lamivudine (LAM) therapy for CHB [21]. In China, the prevalence of chronic hepatitis B is significant, approximately 5.6%(1). With a vast population base, around 80% of patients receive NAs treatment, and a majority achieve virological response, defined as HBV DNA remaining beneath the threshold of detection [22]. In this investigation, a reduction of HBsAg exceeding 0.5 log from baseline was designated as the primary endpoint. This decision arose from the fact that the population of patients receiving treatment for CHB has surged, comprising 71.6% of the cohort. Notably, over 80% of these patients underwent NAs therapy, yet the rate of HBsAg clearance among NAs-treated individuals remained suboptimal.

Hepatic steatosis primarily arises from lipid accumulation, imbalances in intestinal flora, oxidative stress, insulin resistance, and other factors. Disruptions in lipid metabolism, especially lipid accumulation, are a key mechanism in the onset and progression of related diseases. Recent research showed that the prevalence of hepatic steatosis among Chinese adults correlates with increased levels of TG and UA. This investigation found that TC, TG, UA, and HOMA-IR were significantly elevated in patients with CHB and MASLD. UA, a byproduct of purine metabolism, has been shown in animal studies to trigger reactive oxygen species (ROS), c-Jun N-terminal kinase (JNK), and activator protein 1 (AP-1) signaling pathways, which promote hepatic fat accumulation [23].

At baseline, the CHB + MASLD group had significantly lower HBeAg positivity and levels compared to the CHB group, which is consistent with previous studies [6]. The survival analysis indicated that CHB patients with MASLD were more likely to achieve an HBsAg response and did so in a shorter time compared to the CHB group. Different severities of MASLD were independently correlated with HBsAg response in CHB patients, consistent with findings from Mak et al. [7] and Kacar et al. [24]. A recent meta-analysis [25] found a significant correlation between hepatic steatosis and higher HBsAg clearance. This correlation enhances the chances of clinical cure in CHB patients. Metabolic dysfunction also contributes to CHB functional cure [26]. To explore the underlying mechanisms, we should consider the roles of organelle dysfunction and immune activation associated with lipid metabolism disorders. In vitro studies showed that stearic acid and oleic acid enhance p-PERK and p-eIF2α expression, inducing endoplasmic reticulum stress, which inhibits HBV DNA, HBsAg, and pgRNA in hepatocytes [27]. Immune activation plays a vital role in how steatosis influences HBsAg expression. Fat accumulation in hepatocytes, along with metabolic stress, may enhance the innate immunity that is usually suppressed by HBV. This enhancement promotes antiviral agents such as interferon and tumor necrosis factor-α, which activate lymphocytes that help clear HBsAg [28]. Purine metabolism may also affect HBsAg synthesis and secretion. In the BABL/c HBV mouse model, UA increases T cell proliferation, raises IFN-γ levels, and strengthens the immune response to dendritic cells activated by HBsAg [29]. Exploring lipid metabolism disorders and immune mechanisms in MASLD may offer new insights for treating CHB patients. However, studies have shown that the presence of steatosis can exacerbate complications such as liver fibrosis and cirrhosis in CHB patients [30]. A longitudinal study led by Professor Hong You found that ongoing fatty degeneration during antiviral treatment in CHB patients is closely linked to reduced regression of fibrosis [31]. Moreover, a large case–control study revealed that severe fatty degeneration is associated with a higher incidence of severe fibrosis than mild or moderate cases [32]. Thus, further prospective cohort studies with larger sample sizes are essential. These studies should explore how fatty degeneration inhibits hepatitis B virus replication and leads to complications in the liver. Recently, our research team has been putting together data on liver fibrosis, and we'll share more details in our upcoming studies.

Hepatitis B e antigen (HBeAg) is generated by transcribing 3.5 kb mRNA from cccDNA, which is subsequently translated into the protein p22. This protein is then processed in the Golgi apparatus and secreted outside the cell, reflecting the level of cccDNA. This study found that among HBeAg-negative patients, the CHB + MASLD group had a higher HBsAg response rate and was more likely to respond with HBsAg. This lines up with what current research shows. Studies indicated that HBeAg-negative CHB patients exhibit 2.37 times lower cccDNA transcriptional activity and produce 2.28 times fewer viral particles than their HBeAg-positive counterparts [33]. Additionally, the rate of HBV core particle-positive liver cells in HBeAg-negative CHB patients is lower than in HBeAg-positive patients [34]. These findings suggested that HBeAg-negative CHB patients have lower viral loads, which makes it easier for them to

respond with HBsAg when they also have some degree of MASLD.

Antiviral treatments for CHB patients are mainly categorized into two types: NAs and IFNα. This study's results demonstrate that younger age and lower baseline HBsAg levels independently correlate with HBsAg response in CHB patients, aligning with findings from Xueping Yu [35] and Yuanping Zhou [36]. The underlying mechanism likely involves immune activation linked to younger age and lower baseline HBsAg levels. Furthermore, the combination antiviral regimen of NAs and IFNα demonstrates a distinct association with the HBsAg response. A cohort study monitoring CHB patients for 15 years found that only 9.1% achieved cumulative HBsAg clearance after 10 years of NAs treatment [37]. NAs inhibit the reverse transcription of pgRNA into rcDNA by obstructing reverse transcriptase activity, leading to serum HBV DNA levels falling below detectable thresholds. However, these agents do not directly target cccDNA formation [38]. Several studies indicated that HBsAg clearance can reach 20% in patients treated with IFN [39, 40]. This effect arises because IFN enhances immune cell function, induces interferon-stimulating genes and antiviral proteins, promotes the degradation of pgRNA and core particles, and inhibits HBV transcription, thereby reducing HBsAg expression through epigenetic modifications of cccDNA [41]. Recent studies showed that higher baseline UA levels and liver fat accumulation help improve HBsAg clearance in CHB patients treated with 48 weeks of IFN following NAs therapy [42]. Therefore, the combination of NAs and IFN represents a significant therapeutic strategy for enhancing HBsAg clearance rates [43, 44].

However, this study also had several limitations. First, among the 646 patients, only 320 were included in the study, leading to a relatively small sample size, and it was conducted at a single center, which might lead to regional bias. Second, 5% of metabolic indicators in the CHB group were missing in the baseline data; we addressed these gaps through multiple imputations, and the follow-up periods were limited to 24 and 48 weeks. Finally, due to the small sample size, we opted for an internal validation method when establishing the predictive model, without a validation set, which might limit the model's generalizability. Therefore, future research should focus on increasing the sample size, performing subgroup analyses on various treatment plans, extending the follow-up period, and selecting more appropriate endpoints for evaluating antiviral treatment response.

Conclusion

In summary, our findings indicated that MASLD can enhance the antiviral treatment response rate and reduce the time to respond in patients with CHB, particularly in HBeAg-negative patients. Younger patients, antiviral regimens that combine NAs with PEG IFNα, lower baseline HBsAg levels, and the presence of MASLD are effective predictors of treatment response. These factors enhance the efficiency of the antiviral response in CHB patients, leading to quicker clinical cures. Since the study population primarily comprised individuals without significant liver fibrosis, further examination is needed to understand the relationship between MASLD and CHB in the progression of liver fibrosis.

Abbreviations

CHB	Chronic hepatitis B
rcDNA	Relaxed circular DNA
cccDNA	Covalently closed circular DNA
MASLD	Metabolic dysfunction-associated steatotic disease
HCC	Hepatocellular carcinoma
NAs	Nucleos(t)ide analogs
PEG IFNα	Polyethylene glycol interferonα
BMI	Body Mass Index
CAP	Controlled Attenuation Parameters
LSM	Liver Stiffness Measurement
HBsAg	Hepatitis B surface antigen
LHBsAg	Large surface antigen
MHBsAg	Medium surface antigen
SHBsAg	Small surface antigen (SHBsAg)
LAM	Lamivudine
TG	Triglycerides
UA	Uric acid
TC	Total cholesterol
LDL	Low-density lipoprotein
HOMA-IR	Homeostasis model assessment of insulin resistance
ROS	Reactive oxygen species
JNK	C-Jun N-terminal kinase
AP-1	Activator protein 1
SA	Stearic acid
OA	Oleic acid

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Author contributions

G. R. performed the statistical analysis and drafted the manuscript. G. R. and K. J. modified the manuscript together and contributed equally to the manuscript. K. J. and Y. Z. contributed to the research concept and design. G.R., S.Y., Y.G., and Q.C. collected and screened the clinical data. G.R. and Y.Z. were responsible for providing the research thoughts and revising the manuscript. All authors reviewed and approved the final manuscript.

Availability of data and materials

Data from this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Committee of the first affiliated hospital of Dalian Medical University, Approval No. PJ-KS-KY-2023–339. All informed consent was obtained from the subject(s) and/or guardian(s). Written informed consent was obtained from the patients.

Competing interests

The authors declare no competing interests.

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