Infection and Drug Resistance

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Effects of Non-Alcoholic Fatty Liver Disease on Baseline Histology and 96-Week Entecavir Response in Treatment-Naïve Chronic Hepatitis B

Xiaohui Gu[1,*], Weiguang Yang[2,*], Yue Hu[3], Yixin Li[4], Liwei Zheng[5], Bei Jiang[3]

[1]The Fifth Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, People's Republic of China; [2]Department of Cardiovascular Surgery, Tianjin Medical University General Hospital, Tianjin, People's Republic of China; [3]Tianjin Second People's Hospital, Tianjin Institute of Hepatology, Tianjin, People's Republic of China; [4]School of Medical Technology, Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, People's Republic of China; [5]Division of Infectious Diseases, Anschutz Medical Campus, University of Colorado School of Medicine, Aurora, CO, USA

*These authors contributed equally to this work

Correspondence: Bei Jiang, Tianjin Second People's Hospital, Tianjin Institute of Hepatology, Tianjin, People's Republic of China, Email beier0131@163.com; Liwei Zheng, Division of Infectious Diseases, Anschutz Medical Campus, University of Colorado School of Medicine, Aurora, CO, USA, Email liwei.zheng@cuanschutz.edu

Background and Aims: The coexistence of chronic hepatitis B (CHB) and non-alcoholic fatty liver disease (NAFLD) is increasingly common, yet their combined impact on antiviral outcomes remains unclear. This study aimed to compare baseline histopathological features and longitudinal virological responses to entecavir (ETV) therapy in CHB patients with and without NAFLD.

Methods: From October 2014 to January 2022, 299 treatment-naïve CHB patients (130 with NAFLD, 169 without NAFLD) were enrolled in a real-world observational cohort at Tianjin Second People's Hospital. NAFLD diagnosis was confirmed by liver biopsy and (or) ultrasound examination following AASLD guidelines. Baseline characteristics (histopathology, metabolic profiles, HBV markers) and serial virological outcomes (HBV DNA seroconversion, HBsAg/HBeAg loss rate) were analyzed over 96 weeks of ETV therapy. Statistical comparisons utilized Mann–Whitney U and chi-square tests.

Results: At baseline, NAFLD-comorbid patients exhibited milder hepatic inflammation (G≥3: 6.9% vs 17.2%, P =0.022) and fibrosis (S≥3: 10.8% vs 17.2%, P =0.020) despite higher metabolic dysregulation (BMI: 24.8 vs 21.5 kg/m^2, TG: 1.05 vs 0.89 mmol/L, P <0.001). While early virological responses (4–48 weeks) were comparable, NAFLD patients showed significantly lower HBV DNA seroconversion rates at 96 weeks (82.7% vs 92.1%, P =0.038) and persistently reduced HBsAg levels (3.17±1.07 vs 3.57±0.67, P = 0.017).

Conclusion: Despite milder baseline histology, NAFLD comorbidity predicts suboptimal 96-week HBV DNA seroconversion and slower HBsAg decline during entecavir therapy, underscoring the need for intensified, integrated metabolic-antiviral management in this cohort.

Keywords: NAFLD, chronic hepatitis B, clinical cohort study, virological response, entecavir

Introduction

Non-alcoholic fatty liver disease (NAFLD), a spectrum of liver disorders, is characterized by excessive hepatic fat accumulation, contributing to the pathogenesis of non-alcoholic steatohepatitis (NASH), progressive fibrosis, and even hepatocellular carcinoma (HCC).[1] Over the past 30 years, as a result of economic development and lifestyle habit changes, NAFLD has become an emerging global health problem.[2] While in Asian countries and areas, chronic hepatitis B virus (HBV) infection (CBI) still remains a leading cause of end-stage liver diseases, including liver cirrhosis (LC) and HCC.[3] With the wide popularization of HBV vaccines and antiviral drugs, the number of new cases of HBV infection is dramatically decreasing, yet the cure of CBI remains hard to achieve.[3]

With the growing burden of NAFLD, the clinical co-occurrence of NAFLD and CBI has gained great interest in their interplay.[4] Evidence from observational studies suggests that NAFLD-related hepatic steatosis could

Received: 26 August 2025
Accepted: 7 December 2025
Published: 23 December 2025

impair HBV replication.[5,6] However, the effect of NAFLD on HBV-related liver disease progression remains controversial. The impacts of metabolic disorder on HBV replication might accelerate viral clearance, while several studies indicate that the co-occurrence of CBI and NAFLD is associated with increased risk for advanced liver injury.[7,8] The complex pathology involves a bidirectional interplay where HBV infection modifies host lipid metabolism, while NAFLD-driven metabolic dysfunction (particularly insulin resistance and lip toxicity) can independently exacerbate hepatic inflammation and fibrosis, presenting a unique challenge in patient management.

Given that Entecavir (ETV) is widely recognized as a first-line therapy for CHB due to its high potency and low resistance barrier, its efficacy in this dual-diagnosis population is critical. Clinical data regarding ETV use in patients with coexisting CHB and NAFLD are conflicting and limited. While some real-world studies suggest that NAFLD may not significantly impact the long-term viral suppression rates of NAs, several other analyses have observed that the presence of hepatic steatosis is an independent risk factor for suboptimal virological and biochemical responses to ETV treatment.[9] These contradictory findings highlight a significant gap in the literature regarding the necessity of a targeted antiviral strategy for CHB patients with metabolic co-morbidities.

Herein, the impact of NAFLD on the viral replication and serum HBsAg, antiviral efficacy of ETV and disease progression among patients with CHB was investigated using our longitudinal cohort.

Methods

Participant Recruitment

From October 2014 to January 2022, 299 adult CHB patients were enrolled in Tianjin second people's hospital. The patients were consecutively treatment-naïve before the collection of liver biopsy. The inclusion criteria of CHB were according to the guideline of prevention and treatment for chronic hepatitis B (version 2022).[10] The exclusion criteria were as follows:[1] co-infection of other viruses such as hepatitis C virus, hepatitis D virus, hepatitis E virus, and human immunodeficiency virus;[2] coexistence with alcohol-associated fatty liver disease, autoimmune hepatitis;[3] concurrence with HCC and other malignancies;[4] complicated with various end-stage diseases;[5] insufficient clinical data in the medical record. Diagnosis criteria of NAFLD were based on NAFLD Practice Guidance from the AASLD.[11] Diagnosis of NAFLD requires the presence of hepatic steatosis, confirmed by either imaging (ultrasound) or histology (macrovesicular steatosis in $\geq$ 5% of hepatocytes), after rigorously excluding steatosis caused by secondary factors, including significant alcohol consumption, Hepatitis C virus (HCV) genotype 3 infection, specific medications, and Wilson's disease. Additionally, the patient exhibits at least one Metabolic Syndrome (MetS) component. The enrolled patients were categorized into two groups: the CHB alone group and the CHB concurrent with NAFLD group. The study was approved by the Ethics Committee of Tianjin Second People's Hospital (No. [2024]43) and written informed consent was obtained from all participants.

Study Design

Demographic, clinical, and routine biochemical data at the time of inclusion were collected. We first compared all the HBV parameters, the degree of hepatic inflammation and fibrosis as well as serum lipid profiles between patients with CHB alone or CHB concurrent with NAFLD for the baseline of antiviral therapy. Enrolled patients who have disciplinary antiviral treatment courses from Oct 2014 to Jan 2022 were followed up for the serum HBV DNA, HBeAg and HBsAg levels. This cohort study is a real-world observational follow-up study, and during the 96-week antiviral therapy period, some indicators may have missing data. HBsAg loss was defined by undetectable serum HBsAg by commercially available assays (<0.05 IU/mL). HBeAg loss was defined by undetectable serum HBeAg (<1 S/CO). HBV DNA below 20 IU/mL was considered undetectable level.

Serological Marker Detection

The levels of serum HBsAg and HBeAg were determined by an Architect I2000SR electrochemistry luminescence immunity analyzer. Serum HBV DNA was extracted and amplified by Roche Cobas TaqMan HBV with a lower limit of detection of 20 IU/mL. Automatic biochemical analyzer-7180 (HITACH1, Japan) was used to detect the patients' biochemical indicators.

Statistical Analysis

Statistical analysis was performed using SPSS software for Windows version 27.0 (SPSS Inc., Chicago, IL, USA). Demographic data and baseline characteristics were presented as median and interquartile range. Continuous variables were compared between each group using nonparametric Mann–Whitney *U*-test, and for categorical variables, using Chi-square test. A two-tailed *P* value<0.05 was considered statistically significant. Binary logistic regression using forward-conditional method was further applied to determine significant variables from univariate analysis.

Results

Baseline Demographic and Clinical Information

A total of 299 CHB patients were enrolled in this study, with 130 (43.5%) exhibiting comorbid NAFLD and 169 (56.5%) without NAFLD. As shown in Table 1, baseline characteristics revealed significant differences between the two groups. Patients with CHB and NAFLD showed a male predominance (55.0% vs 45.0% in non-NAFLD group, *P*<0.001), older median age (37 vs 35 years, *P*=0.011), and higher BMI (24.8 kg/m^2 vs 21.5 kg/m^2, *P*<0.001). Metabolic parameters differed markedly: NAFLD patients had elevated triglyceride (TG: 1.05 vs 0.89 mmol/L, *P*<0.001), lower high-density lipoprotein (HDL: 1.20 vs 1.43 mmol/L, *P*<0.001), and higher low-density lipoprotein (LDL: 2.50 vs 2.06 mmol/L, *P*<0.001). Liver-related biomarkers demonstrated that NAFLD patients had higher gamma-glutamyl transferase (GGT: 34.0 vs 26.0 U/L, *P*=0.028) and albumin levels (46.1 vs 43.7 g/L, *P*=0.019), while no significant differences were observed in HBV DNA load, HBsAg levels, or HBeAg positivity (all *P*>0.05). Histopathological analysis revealed distinct patterns: non-NAFLD patients exhibited more severe hepatic inflammation (G≥3: 17.2% vs 6.9%, *P*=0.022) and advanced fibrosis (S≥3: 17.2% vs 10.8%, *P*=0.020) compared to NAFLD patients. These findings suggest that NAFLD comorbidity in CHB patients is associated with distinct metabolic profiles and milder histopathological severity

Table 1 Baseline Characteristics of Enrolled CHB Patients Before Treatment

Characteristics		Total (n=299)	CHB with NAFLD (n=130)	CHB without NAFLD (n=169)	*P*
Sex	Men	151 (50.5%)	83 (55.0%)	68 (45.0%)	<0.001
	Women	148 (49.5%)	47 (31.8%)	101 (68.2%)	
Age, years		36 (30,46)	37 (32,49)	35 (30,43)	0.011
BMI (Kg/m^2)		23.4 (21.3,26.2)	24.8 (23.0,27.8)	21.5 (19.5,22.9)	<0.001
HBV DNA (log_{10} IU/mL)		6.13 (3.55,8.09)	5.33 (3.06,8.23)	6.30 (3.91,8.00)	0.312
HBsAg (IU/mL)		6301.23 (1790.11,22,130.23)	7157.07 (1607.7,24,493.75)	5980.48 (1846.06,20,475.70)	0.874
HBeAg positivity (n, %)		158 (52.8%)	65 (50.0%)	93 (55.0%)	0.864
ALT (U/L)		36.0 (20.0,58.4)	38.0 (24.0,74.0)	34.5 (18.9,53.3)	0.337
AST (U/L)		33.0 (23.0,51.0)	36.0 (23.4,58.0)	30.2 (22.2,45.0)	0.067
GGT (U/L)		30.0 (18.0,53.0)	34.0 (23.0,60.0)	26.0 (16.8,50.0)	0.028
Albumin (g/L)		45.0 (41.0,47.5)	46.1 (43.6,47.9)	43.7 (40.7,46.9)	0.019
CHO (mmol/L)		4.37 (3.89,4.92)	4.55 (4.00,5.07)	4.25 (3.83,4.86)	0.184
TG (mmol/L)		0.96 (0.74,1.25)	1.05 (0.87,1.58)	0.89 (0.67,1.16)	<0.001
HDL (mmol/L)		1.34 (1.11,1.58)	1.20 (1.01,1.43)	1.43 (1.21,1.67)	<0.001
LDL (mmol/L)		2.22 (1.82,2.69)	2.50 (1.96,2.89)	2.06 (1.80,2.47)	<0.001
Metabolic Comorbidities					
Diabetes mellitus (n, %)		17 (5.7%)	8 (6.1%)	9 (5.3%)	0.26
Hypertension (n, %)		46 (15.4%)	24 (18.5%)	22 (13.0%)	0.13
Obesity (n, %)		44 (14.7%)	27 (20.8%)	17 (10.1%)	<0.001
Inflammation (n, %)	G (0–1)	38 (12.7%)	19 (14.6%)	19 (11.2%)	0.022
	G (1–2)	223 (74.6%)	102 (78.5%)	121 (71.6%)	
	G≥3	38 (12.7%)	9 (6.9%)	29 (17.2%)	
Fibrosis (n, %)	S (0–1)	135 (45.1%)	67 (51.5%)	68 (40.2%)	0.020
	S (1–2)	121 (40.5%)	49 (37.7%)	72 (42.6%)	
	S≥3	43 (14.4%)	14 (10.8%)	29 (17.2%)	

https://doi.org/10.2147/IDR.S563330

compared to CHB alone. Our findings also corroborate previous reports that the presence of hepatic steatosis may suppress HBV viral activity, potentially leading to attenuated liver injury.[12]

The Impact of NAFLD on Virological Response During Antiviral Therapy

Serum HBV DNA levels were measured at 4, 8, 16, 24, 48, 72, and 96 weeks during ETV therapy. A serum HBV DNA level < 20 IU/mL was defined as negative. The cumulative HBV DNA seroconversion rate reached 87.9% at week 96. However, significant differences between the two groups emerged only in the later phases of treatment. No statistically significant differences were observed at early time points (4–48 weeks, all $P > 0.05$). By week 72, the non-NAFLD group showed a higher seroconversion rate than the NAFLD group (83.5% [106/127] vs 76.5% [78/102], $P = 0.184$), although this difference was not statistically significant. At week 96, the non-NAFLD group achieved a significantly higher seroconversion rate (92.1% [116/126]) compared to the NAFLD group (82.7% [81/98]) ($P = 0.038$), indicating that NAFLD may be associated with reduced long-term virological response to ETV therapy. Detailed data are shown in Table 2 and Figure 1A. These results suggest that while both groups exhibited comparable early virological responses, the presence of NAFLD may attenuate sustained HBV DNA suppression during prolonged ETV therapy. Using multivariate regression, with NAFLD was confirmed as an independent factor for basic virological response at only 72 weeks and 96 weeks (Table 3).

Longitudinal Changes in HBsAg Level

We analyzed the serum HBsAg levels in enrolled CHB patients at different follow-up time points. Longitudinal analysis of serum HBsAg levels during ETV therapy revealed distinct patterns between CHB patients with and without NAFLD (Table 4 and Figure 1B). At baseline, both groups exhibited comparable HBsAg levels (NAFLD: 3.41±1.11 vs non-NAFLD: 3.94±0.51 $\log_{10}$ IU/mL, $P = 0.025$). Notably, NAFLD patients consistently demonstrated lower HBsAg levels throughout the 96-week follow-up, with statistically significant differences observed at 4 weeks (3.41±1.11 vs 3.94±0.51, $P = 0.025$), 16 weeks (2.91±1.14 vs 3.65±0.05, $P = 0.003$), 24 weeks (3.46±1.50 vs 3.92±0.84, $P = 0.018$), and all subsequent time points (48–96 weeks, $P < 0.05$).

Despite these intergroup differences, HBsAg levels in both cohorts showed limited decline over time (Total: 3.72 ±0.85 at 4 weeks vs 3.39±0.90 at 96 weeks). Importantly, the results indicated that, with the exception of the 8-week time point during antiviral therapy, where no statistically significant difference was observed between the two groups, the serum HBsAg levels in the NAFLD-comorbid group were significantly lower than those in the non-NAFLD group at all other follow-up time points. This pattern contrasts with the previously observed HBV DNA seroconversion dynamics, where NAFLD-associated differences emerged only at later stages. This suggests that NAFLD may facilitate HBsAg seroclearance.

The presence of NAFLD in CHB patients was associated with a distinct metabolic profile and less severe liver histopathology, but also with a diminished long-term virological response to ETV therapy. While NAFLD patients exhibited lower HBsAg levels throughout treatment, their rates of HBV DNA seroconversion were significantly lower at

Table 2 HBV DNA Seroconversion Rate at 4, 8,16, 24, 48, 72 and 96 weeks During ETV Antiviral Therapy in Enrolled Patients

Follow-up period	HBV DNA seroconversion rate			
	Total	CHB with NAFLD	CHB without NAFLD	*P*
4w	43/149 (28.9%)	19/59 (32.2%)	24/90 (26.7%)	0.580
8w	38/107 (35.5%)	16/47 (34.0%)	22/60 (36.7%)	0.687
16w	54/122 (44.3%)	24/49 (49.0%)	30/73 (41.1%)	0.574
24w	114/239 (47.7%)	49/100 (49.0%)	65/139 (46.8%)	0.895
48w	172/243 (70.8%)	74/103 (71.8%)	98/140 (70.0%)	0.886
72w	184/229 (80.3%)	78/102 (76.5%)	106/127 (83.5%)	0.184
96w	197/224 (87.9%)	81/98 (82.7%)	116/126 (92.1%)	0.038

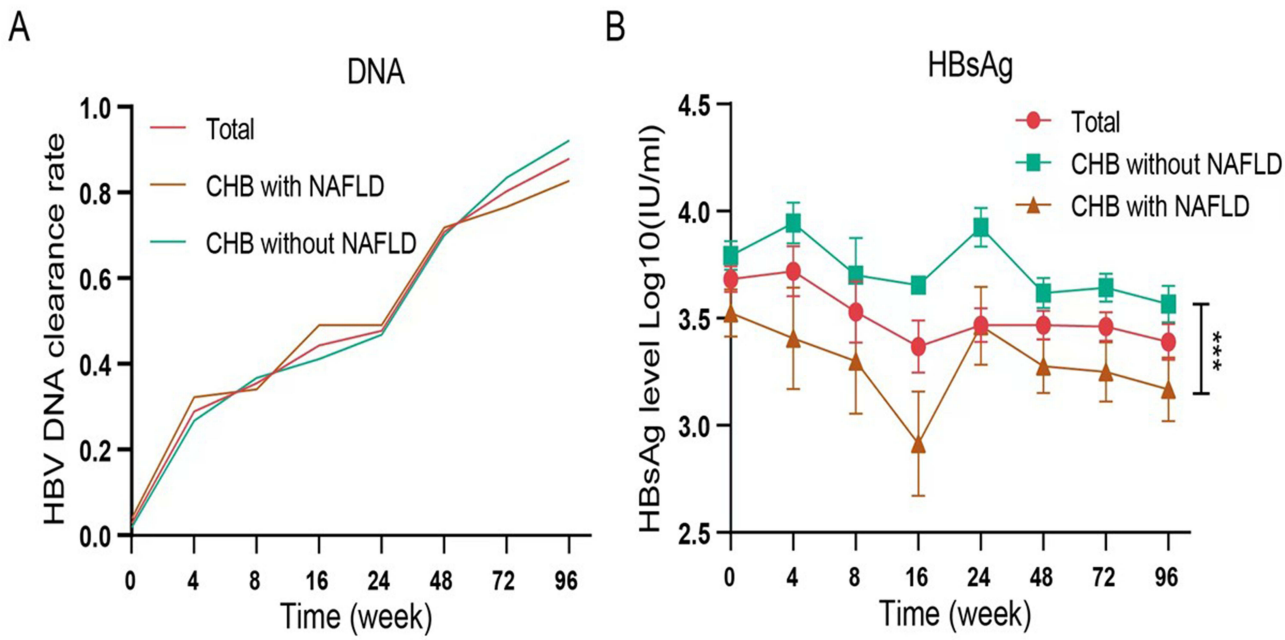

Figure 1 HBV DNA seroconversion rate and serum HBsAg level at 4, 8, 16, 24, 48, 72 and 96 weeks during ETV antiviral therapy in enrolled patients. (**A**). Comparison of HBV DNA seroconversion rates between CHB with NAFLD and without NAFLD Patients; (**B**). Comparison of serum HBsAg level between CHB with NAFLD and without NAFLD Patients. *** $P<0.0001$).

week 96 compared to non-NAFLD patients. These findings align with previous reports suggesting that hepatic steatosis may suppress HBV replication but also attenuate response to antiviral therapy, highlighting the complex interaction between NAFLD and CHB.

Table 3 Multivariate Analysis of Baseline Factors Significantly Associated with NAFLD

Factors	Exp (B)	95% CI	SE	P
Baseline factors associated with antiviral response at 72 weeks				
With NAFLD	0.464	0.220–0.982	0.382	0.040
Baseline factors associated with antiviral response at 96 weeks				
With NAFLD	0.410	0.174–0.962	0.436	0.045

Table 4 Serum HBsAg Level at 4, 8, 16, 24, 48, 72 and 96 weeks During ETV Antiviral Therapy in Enrolled Patients

Follow up period	HBsAg level (log_{10}IU/mL)			
	Total	CHB with NAFLD	CHB without NAFLD	*P*
4w	3.72±0.85	3.41±1.11	3.94±0.51	0.025
8w	3.53±0.95	3.30±1.04	3.70±0.85	0.176
16w	3.37±+0.94	2.91±1.14	3.65±0.05	0.003
24w	3.47±0.99	3.46±1.50	3.92±0.84	0.018
48w	3.47±0.88	3.28±1.06	3.62±0.69	0.003
72w	3.46±0.81	3.25±1.12	3.64±0.56	0.009
96w	3.39±0.90	3.17±1.07	3.57±0.67	0.017

https://doi.org/10.2147/IDR.S563330

Discussion

CHB and NAFLD represent two most common liver diseases worldwide. HBV complicated with NAFLD is thus common based on the high prevalence of both diseases. Despite a widely observed association between CHB and NAFLD, their causal relationship remains obscure. This study provides novel insights into the complex interplay between NAFLD and CHB progression under long-term ETV therapy. Our findings reveal a paradoxical relationship: while CHB patients with NAFLD exhibited milder hepatic histopathology at baseline, they demonstrated attenuated virological responses and distinct serological profiles during antiviral treatment. These observations challenge the conventional view of NAFLD as a universally aggravating factor in chronic liver diseases and highlight the need for nuanced management strategies in this comorbid population. It is noteworthy that the conclusions drawn in this study are consistent with those of previous observational studies, which suggest that hepatic steatosis may accelerate spontaneous HBsAg clearance and serve as a protective factor against chronic HBV infection.[13–15] Additionally, although still debated, most studies suggest that HBV infection may reduce the incidence of NAFLD.[16–18] Evidence based on cell and animal models indicates that hepatic steatosis inhibits viral replication and augments anti-HBV immunity.[19,20] In summary, the influence of hepatic steatosis on CHB remains highly intricate. Mounting evidence consistently points to an inverse correlation between steatosis and viral replication, which manifests clinically as lower HBV DNA titers and, notably, a higher propensity for HBsAg seroclearance. This phenomenon suggests that steatosis per se may exert a suppressive or even protective effect against viral persistence. However, this perspective is drastically complicated by the underlying metabolic context, encapsulated by the definition of NAFLD. While the viral-suppressing effect of fat accumulation may theoretically reduce liver injury, the metabolic risk factors central to NAFLD are independently established as potent drivers of fibrosis progression and hepatocarcinogenesis in CHB patients. Therefore, the clinical outcome is not dictated by steatosis alone, but by the competing balance between its potential benefit in promoting HBsAg clearance and the significant, additive risk stemming from concurrent metabolic derangement.[21]

The crosstalk between viral replication, antiviral therapy efficacy and lipid metabolism has been well documented, through both experimental and clinical studies.[22,23] To this end, we aimed to elucidate the impact of NAFLD on the efficacy of anti-HBV treatment. Our findings showed that under long-term ETV treatment, CHB patients complicated with NAFLD have lower HBV DNA seroclearance rate. However, it seems that NAFLD inhibits serum HBsAg levels in CHB patients, which might be accounted by the complex origin of serum HBsAg, from majorly subviral particles and minorly infectious DNA containing virions, and, from both covalently closed circular DNA (cccDNA) and integrated HBV DNA.[24] Additionally, since HBsAg is a membrane-anchored protein that constitutes HBV envelope, its egress can be easily disturbed by NAFLD-associated lipid composition alteration.[25]

These findings advocate for dual-target therapeutic strategies in NAFLD-comorbid CHB: optimizing metabolic control (eg, weight loss, statins) alongside antiviral therapy to improve long-term outcomes. The differential HBsAg kinetics further suggest that current serological thresholds for predicting functional cure may require adjustment in NAFLD populations. However, this study has limitations: its single-center design, absence of cccDNA quantification, and lack of dietary/metabolic intervention data. Future research should integrate multi-omics approaches to unravel the molecular crosstalk between lipid metabolism and HBV persistence. Furthermore, another key limitation is the data cut-off date of January 2022. Although the conclusions are based on complete follow-up data up to this point, the exclusion of events and observations occurring after January 2022 is a temporal constraint. Future studies are planned to address this by extending the follow-up period.

The finding that NAFLD is an independent predictor of poorer long-term virological response, even in patients with mild baseline liver damage, highlights the complex influence of metabolic factors on antiviral efficacy.[9] We attribute this result, which emerged significantly at the 96-week endpoint, to several interwoven mechanisms: First, metabolic dysfunction (insulin resistance and lip toxicity) creates an unfavorable microenvironment that compromises the host's anti-HBV immune response and may provide the virus with alternative metabolic pathways for replication, thereby weakening treatment effectiveness. Second, hepatic fat accumulation may alter the intracellular pharmacokinetics of nucleos(t)ide analogues, potentially resulting in suboptimal drug concentrations at the site of HBV polymerase. Finally, the milder baseline inflammation in the NAFLD group may reflect a compromised immune state linked to metabolic stress, leading to a slower kinetic of viral suppression. This underscores the need for personalized treatment that addresses both viral suppression and underlying metabolic risk in CHB patients with coexisting NAFLD.

Conclusion

Our clinical cohort study showed that CHB patients with concurrent NAFLD exhibited significantly lower levels of hepatic inflammation and fibrosis compared to those with CHB alone. Additionally, cumulative HBV DNA seroclearance rates at 96 weeks were higher in CHB patients without NAFLD than in those with concurrent NAFLD. Interestingly, NAFLD appears to facilitate HBsAg seroclearance in CHB patients undergoing ETV therapy.

NAFLD may impact the efficacy of antiviral therapy differently for HBV DNA and HBsAg seroclearance. This highlights the importance of considering NAFLD status in the management of CHB and suggests that tailored treatment approaches may be beneficial for patients with both conditions.

Abbreviations

HBV, hepatitis B virus; CHB, chronic hepatitis B; CBI, chronic hepatitis B virus infection; NAFLD, non-alcoholic fatty liver disease; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B s antigen; NASH, non-alcoholic steatohepatitis; HCC, hepatocellular carcinoma; ETV, entecavir.

Data Sharing Statement

The individual participant data reported in this publication will be available and can be reviewed upon request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Tianjin Second People's Hospital (No. [2024]43). Informed consent was obtained from all participants.

Acknowledgments

We are grateful to every patient who took part in this study, and we would like to express our appreciation to our colleagues, Minghui Li and Guiwen Guan, for them valuable contributions to the discussions related to this research.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the National Natural Science Foundation of China (62301362).

Disclosure

The authors declare that they have no competing interests.

References

1. Huang DQ, El-Serag HB, Loomba R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol*. 2021;18(4):223–238. doi:10.1038/s41575-020-00381-6
2. Lonardo A, Byrne CD, Caldwell SH, Cortez-Pinto H, Targher G. Global epidemiology of nonalcoholic fatty liver disease: meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2016;64(4):1388–1389. doi:10.1002/hep.28584
3. Jeng WJ, Papatheodoridis GV, Lok ASF. Hepatitis B. *Lancet*. 2023;401(10381):1039–1052. doi:10.1016/S0140-6736(22)01468-4
4. Huang J, Jing M, Wang C, et al. The impact of hepatitis B virus infection status on the prevalence of nonalcoholic fatty liver disease: a population-based study. *J med virol*. 2020;92(8):1191–1197. doi:10.1002/jmv.25621
5. Liu J, Yang HI, Lee MH, et al. Incidence and determinants of spontaneous hepatitis B surface antigen seroclearance: a community-based follow-up study. *Gastroenterology*. 2010;139(2):474–482. doi:10.1053/j.gastro.2010.04.048
6. Mak LY, Hui RW, Fung J, et al. Diverse effects of hepatic steatosis on fibrosis progression and functional cure in virologically quiescent chronic hepatitis B. *J Hepatol*. 2020;73(4):800–806. doi:10.1016/j.jhep.2020.05.040

7. Miyake T, Akbar SM, Yoshida O, et al. Impaired dendritic cell functions disrupt antigen-specific adaptive immune responses in mice with nonalcoholic fatty liver disease. *J Gastroenterol*. 2010;45(8):859–867. doi:10.1007/s00535-010-0218-4
8. Wong SW, Ting YW, Yong YK, et al. Chronic inflammation involves CCL11 and IL-13 to facilitate the development of liver cirrhosis and fibrosis in chronic hepatitis B virus infection. *Scand J Clin Lab Invest*. 2021;81(2):147–159. doi:10.1080/00365513.2021.1876245
9. Jin X, Chen YP, Yang YD, Li YM, Zheng L, Xu CQ. Association between hepatic steatosis and entecavir treatment failure in Chinese patients with chronic hepatitis B. *PLoS One*. 2012;7(3):e34198. doi:10.1371/journal.pone.0034198
10. You H, Wang F, Li T, et al. Guidelines for the prevention and treatment of chronic hepatitis B (version 2022). *J. Clin. Transl. Hepatol*. 2023;11(6):1425–1442. doi:10.14218/JCTH.2023.00320
11. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology*. 2023;77(5):1797–1835. doi:10.1097/HEP.0000000000000323
12. Yao R, Lu S, Xue R, et al. NAFLD is associated with less severe liver fibrosis in chronic hepatitis B: a multi-center, retrospective study. *Ann. Hepatol*. 2024;29(1):101155. doi:10.1016/j.aohep.2023.101155
13. Chu CM, Lin DY, Liaw YF. Does increased body mass index with hepatic steatosis contribute to seroclearance of hepatitis B virus (HBV) surface antigen in chronic HBV infection? *Int J Obesity*. 2007;31(5):871–875. doi:10.1038/sj.ijo.0803479
14. Chu C-M, Lin D-Y, Liaw Y-F. Clinical and virological characteristics post HBsAg seroclearance in hepatitis B virus carriers with hepatic steatosis versus those without. *Dig Dis Sci*. 2013;58(1):1425–1442. doi:10.1007/s10620-012-2343-9
15. Li J, Yang HI, Yeh ML, et al. association between fatty liver and cirrhosis, hepatocellular carcinoma, and hepatitis b surface antigen seroclearance in chronic hepatitis B. *J Infect Dis*. 2021;224(2):294–302. doi:10.1093/infdis/jiaa739
16. Joo E-J, Chang Y, Yeom J-S, Ryu S. Hepatitis B virus infection and decreased risk of nonalcoholic fatty liver disease: a cohort study. *Hepatology*. 2017;65(3):828–835. doi:10.1002/hep.28917
17. Cheng YL, Wang YJ, Kao WY, et al. Inverse association between hepatitis B virus infection and fatty liver disease: a large-scale study in populations seeking for check-up. *PLoS One*. 2013;8(8):e72049. doi:10.1371/journal.pone.0072049
18. Wong VW, Wong GL, Chu WC, et al. Hepatitis B virus infection and fatty liver in the general population. *J Hepatol*. 2012;56(3):533–540. doi:10.1016/j.jhep.2011.09.013
19. Hu D, Wang H, Wang Y, et al. Non-alcoholic hepatic steatosis attenuates hepatitis B virus replication in an HBV-immunocompetent mouse model. *Hepatol Internat*. 2018;12(5):438–446. doi:10.1007/s12072-018-9877-7
20. Zhang Z, Pan Q, Duan XY, et al. Fatty liver reduces hepatitis B virus replication in a genotype B hepatitis B virus transgenic mice model. *J Gastroenterol Hepatol*. 2012;27(12):1858–1864. doi:10.1111/j.1440-1746.2012.07268.x
21. Huang SC, Liu CJ. Chronic hepatitis B with concurrent metabolic dysfunction-associated fatty liver disease: challenges and perspectives. *Clin Mol Hepatol*. 2023;29(2):320–331. doi:10.3350/cmh.2022.0422
22. Lorizate M, Kräusslich HG. Role of lipids in virus replication. *Cold Spring Harbor Perspectives Bio*. 2011;3(10):a004820. doi:10.1101/cshperspect.a004820
23. Chirinos JA, Lopez-Jaramillo P, Giamarellos-Bourboulis EJ, et al. A randomized clinical trial of lipid metabolism modulation with fenofibrate for acute coronavirus disease 2019. *Nat Metab*. 2022;4(12):1847–1857. doi:10.1038/s42255-022-00698-3
24. Meier MA, Calabrese D, Suslov A, Terracciano LM, Heim MH, Wieland S. Ubiquitous expression of HBsAg from integrated HBV DNA in patients with low viral load. *J Hepatol*. 2021;75(4):840–847. doi:10.1016/j.jhep.2021.04.051
25. Piper RC, Katzmann DJ. Biogenesis and function of multivesicular bodies. *Annu Rev Cell Dev Biol*. 2007;23:519–547. doi:10.1146/annurev.cellbio.23.090506.123319