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Patients with chronic hepatitis B exhibiting significant inflammation and fibrosis should pay particular attention to the status of hepatic steatosis during antiviral therapy

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Abstract

Objective This study aims to explore the effects of various hepatic steatosis conditions on histological outcomes in patients with significant inflammation and fibrosis in chronic hepatitis B (CHB) and analyze their impact on HBV virological suppression outcomes and biochemical improvement.

Method This retrospective study included 219 chronic hepatitis B (CHB) patients receiving nucleos(t)ide analogues therapy. Each of these patients underwent two liver biopsies. Patients were categorized into four groups based on hepatic steatosis status: sustained non-hepatic steatosis ($n=118$), new-onset hepatic steatosis ($n=33$), sustained hepatic steatosis ($n=37$), and disappeared hepatic steatosis ($n=31$). We compared the liver biochemical parameters and histological changes before and after treatment. Logistic regression analysis was performed to evaluate characteristics associated with the improvement of significant liver inflammation ($G \geq 2$), significant fibrosis ($S \geq 2$), and the persistence of hepatic steatosis.

Results After treatment, the sustained non-steatosis group exhibited the highest rate of improvement in baseline significant inflammation (75.31%), while the sustained steatosis group had the lowest (42.31%, $p=0.008$). The sustained steatosis group also had the highest rate of inflammation progression (15.38%, $p=0.020$) and was identified as a risk factor for inadequate baseline inflammation improvement ($p=0.006$, OR=0.244, 95% CI 0.090–0.665). In terms of baseline significant liver fibrosis improvement, the sustained non-hepatic steatosis group showed the highest improvement rate (67.14%), while the sustained hepatic steatosis group had the lowest (28.00%, $p=0.006$). The new-onset steatosis group had the highest rate of liver fibrosis progression (15.00%, $p=0.027$), and sustained hepatic steatosis was a risk factor for poor baseline fibrosis improvement ($p=0.001$, OR=0.180, 95% CI 0.064–0.507). Furthermore, the sustained hepatic steatosis group showed the smallest decrease in liver enzyme markers ALT, GGT,

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and ALP post-treatment, with reductions of 22.11% ($p=0.023$), 13.86% ($p=0.003$), and 1.98% ($p=0.025$), respectively. Logistic regression analysis revealed that high baseline BMI and LDL-C levels were significantly associated with persistent fatty liver, with high BMI ($p=0.042$, OR = 1.109, 95% CI 1.004–1.226) and high LDL-C ($p<0.001$, OR = 2.570, 95% CI 1.524–4.332).

Conclusion In CHB patients with significant inflammation and fibrosis, the persistence of hepatic steatosis during antiviral treatment may impede the improvement of inflammation and fibrosis, leading to disease progression and biochemical abnormalities.

Keywords Antiviral therapy, Chronic hepatitis B, Hepatic steatosis, Significant liver inflammation, Significant fibrosis

Introduction

According to the World Health Organization, approximately 257 million people worldwide are infected with the hepatitis B virus (HBV) [1]. Meanwhile, changes in lifestyle and dietary habits have contributed to hepatic steatosis, which may progress to metabolic-associated fatty liver disease (MASLD), currently the most prevalent chronic liver disease globally, surpassing chronic hepatitis B (CHB) as the primary cause [2, 3]. The co-occurrence of chronic hepatitis B (CHB) and metabolic-associated steatotic liver disease (MASLD) is a widespread phenomenon worldwide. Both diseases can lead to liver fibrosis, cirrhosis, and even hepatocellular carcinoma (HCC), significantly affecting patient prognosis [4, 5]. Several clinical and basic studies have demonstrated a negative correlation between hepatic steatosis and chronic HBV infection. CHB patients with hepatic steatosis often exhibit lower HBV DNA levels and higher rates of HBsAg clearance [6–8]. A recent study found that individuals with chronic hepatitis B and hepatic steatosis face a higher risk of liver-related events and mortality [9]. Currently, evidence on the impact of hepatic steatosis on histological improvement following antiviral treatment in CHB patients with varying degrees of histological inflammation and fibrosis remains limited.

Two prospective studies found that, in CHB patients receiving nucleos(t)ide analog antiviral therapy, hepatic steatosis was associated with a decrease in ALT normalization rate and HBV DNA clearance [10, 11]. However, these studies relied on ultrasound, controlled attenuation parameter (CAP), and liver stiffness measurement (LSM) to assess the degree of steatosis and fibrosis. Therefore, additional evidence from the gold standard of liver biopsy is required [12]. On the other hand, previous studies have shown that patients with significant inflammation ($G\geq 2$) and significant fibrosis ($S\geq 2$) are more likely to progress to cirrhosis, hepatocellular carcinoma, and end-stage liver disease. Thus, risk stratification based on the severity of liver inflammation and fibrosis is crucial for disease prognosis [13, 14]. Currently, there is limited research on the impact of hepatic steatosis on histological improvement during antiviral treatment. A study by Sun et al. found that new-onset and persistent NAFLD significantly

reduced the rate of fibrosis improvement during antiviral treatment in CHB patients [15]. You et al. included 239 CHB patients who underwent paired liver biopsies before and after antiviral treatment, and found that persistent steatosis was associated with a reduced rate of fibrosis resolution during antiviral treatment in CHB patients [16]. Unfortunately, neither of these studies specifically investigated the impact of hepatic steatosis on the post-treatment histological outcomes of CHB patients with severe inflammation or fibrosis at baseline.

Our study retrospectively included CHB patients who received antiviral treatment and underwent two liver biopsies (LBx). The grading of liver inflammation and staging of fibrosis severity were determined based on histological results. This study aims to explore the effects of various hepatic steatosis conditions on histological outcomes in CHB patients with significant inflammation and liver fibrosis, as well as their impact on HBV virological suppression and biochemical improvement.

Materials and methods

Study population

This study retrospectively included chronic hepatitis B (CHB) patients who received antiviral treatment at Beijing Ditan Hospital, Capital Medical University, between January 2010 and December 2021, and underwent two liver biopsies for pathological analysis for various reasons. The inclusion criteria were: (1) age >18 years; (2) HBsAg positive for ≥ 6 months; (3) treatment with nucleos(t)ide analogues (NAs), including entecavir (ETV), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide fumarate (TAF), or telbivudine. The exclusion criteria included: (1) concomitant chronic liver diseases, such as chronic hepatitis C, autoimmune liver disease, drug-induced liver injury, hereditary metabolic liver diseases, or unexplained liver injury or steatosis; (2) excessive alcohol consumption: women ≥ 20 –50 g/day, men ≥ 30 –60 g/day; (3) pregnancy, malignant tumors, severe cardiopulmonary diseases, or renal insufficiency; (4) missing clinical data; (5) use of traditional Chinese medicines for anti-fibrosis.

The study was conducted by the ethical standards of the Declaration of Helsinki and its later amendments,

approved by the Institutional Review Board of Capital Medical University at Beijing Ditan Hospital.

Clinical data collection and hepatic pathology examination

Clinical information, laboratory results, and diagnostic results for each patient were obtained from the electronic records of Beijing Ditan Hospital. The data collected included age, gender, height, weight, hepatitis B surface antigen (HBsAg), hepatitis B e-antigen (HBeAg), hepatitis B virus DNA (HBV DNA), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin (TBIL), direct bilirubin (DBIL), cholesterol (CHOL), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid (UA), and fasting blood glucose (FG).

All patients underwent ultrasound-guided liver biopsy. The biopsy specimens were fixed in 10% formalin, routinely embedded in paraffin, and sections were stained using Hematoxylin and Eosin (H&E) and Masson's trichrome staining techniques. Experienced hepatopathologists further evaluated these sections. All liver biopsy sections met the criteria for histological feature scoring.

The severity of hepatic steatosis was graded according to the NAFLD Activity Score (NAS) in the Nonalcoholic Steatohepatitis Clinical Research Network (NASH-CRN) scoring system. Steatosis <5% was scored as 0, 5–33% as 1, 33–66% as 2, and >66% as 3 [17]. The Scheuer scoring system was used to assess liver inflammation grading and fibrosis staging [18]. Liver inflammation was classified into five stages: G0, no inflammation; G1, inflammation without necrosis; G2, focal necrosis or necrotic bodies; G3, severe focal cell injury; G4, widespread bridging necrosis; and fragmentary necrosis. Clinically significant liver inflammation was defined as inflammation graded G2 to G4. The liver fibrosis staging system is as follows: S0, no fibrosis; S1, portal fibrosis without septa; S2, portal fibrosis with rare septa; S3, multiple septa without cirrhosis; S4, cirrhosis. Clinically significant liver fibrosis was defined as fibrosis staged S2 to S4 [19]. The screening criteria for type 2 diabetes (T2DM), hypertension, and obesity were based on their respective diagnostic standards [20–22].

Patients with persistently no hepatic steatosis maintained a steatosis score of 0 both before and after treatment. New-onset hepatic steatosis patients had a steatosis score of 0 before treatment and a score of ≥ 1 after treatment. Patients with sustained hepatic steatosis consistently scored ≥ 1 both before and after treatment. Patients in whom hepatic steatosis resolved had a steatosis score of ≥ 1 before treatment and returned to a score of 0 after treatment.

Changes in liver inflammation after treatment were defined as improvement (G score decrease ≥ 1), no

change (G score remained unchanged), or progression (G score increase ≥ 1). Changes in liver fibrosis after treatment were defined as improvement (S score decrease ≥ 1), no change (S score remained unchanged), or progression (S score increase ≥ 1).

Statistical analysis

For continuous data, data that follow a normal distribution are expressed as mean $\pm$ standard deviation ($\bar{x} \pm SD$), while data that do not follow a normal distribution are expressed as median and interquartile range [M (P25, P75)]. Categorical variables are described by frequency and percentage (n, %). Differences between continuous variables were analyzed using the Kruskal-Wallis test, while categorical variables were analyzed using the χ^2 test or Fisher's exact test. Univariate and multivariate logistic regression analyses were conducted to identify factors associated with improvement in significant liver inflammation, significant fibrosis, and the persistence of hepatic steatosis. All statistical analyses were performed using SPSS software version 26.0, and graphical analysis was done using GraphPad Prism 9 and Origin 2022. A two-tailed p -value < 0.05 was considered statistically significant.

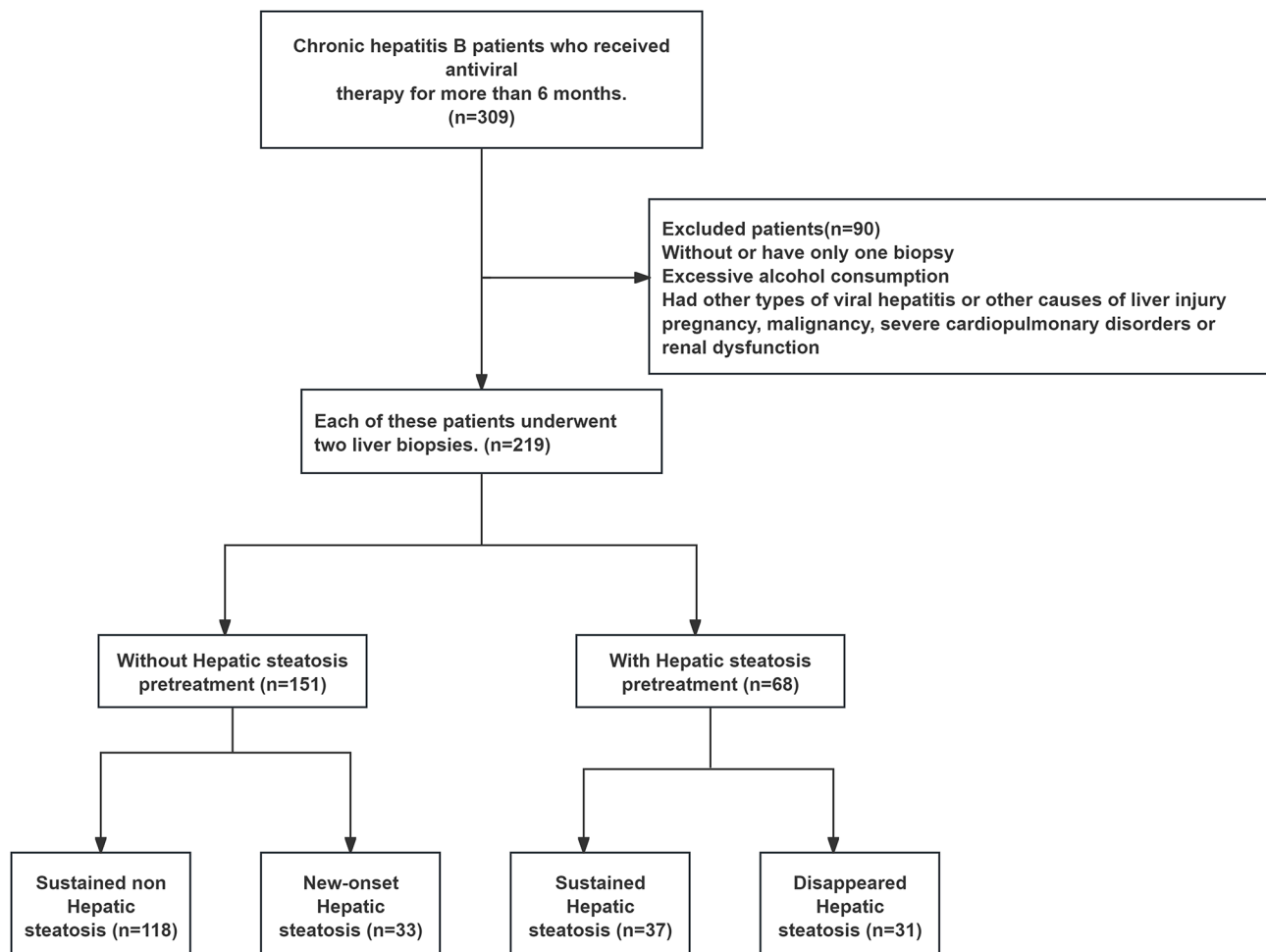
Results

Clinical characteristics of patients with different hepatic steatosis conditions

This study retrospectively included 219 patients with chronic HBV infection. Based on liver biopsy results, we observed changes in the distribution of hepatic steatosis during follow-up. The patients were divided into four groups based on the presence of hepatic steatosis: sustained non-hepatic steatosis group ($n = 118$, 53.88%), new-onset hepatic steatosis group ($n = 33$, 15.07%), sustained hepatic steatosis group ($n = 37$, 16.89%), and disappeared hepatic steatosis group ($n = 31$, 14.16%) (see Fig. 1).

At baseline, the sustained non-hepatic steatosis group had the lowest body mass index (BMI) of 22.39 kg/m², while the sustained hepatic steatosis group had the highest BMI of 26.06 kg/m² ($p < 0.001$). Furthermore, the disappeared hepatic steatosis group exhibited the highest levels of gamma-glutamyl transferase (GGT) and uric acid (UA), with values of 38.20 U/L ($p = 0.02$) and 339.00 μ mol/L ($p < 0.001$), respectively. The sustained hepatic steatosis group showed the highest levels of triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C), with values of 1.29 mmol/L ($p = 0.001$) and 3.24 mmol/L ($p < 0.001$), respectively.

No significant differences were observed between the four groups in terms of gender, age, diabetes, hypertension prevalence, HBV virological characteristics (such as HBsAg and HBV DNA levels), and other clinical

**Fig. 1** Flowchart

characteristics, including liver enzymes and blood lipids (see Table 1).

Changes in liver enzymes and blood lipids under different hepatic steatosis conditions after HBV treatment

After antiviral treatment, liver enzyme biomarkers (ALT, AST, TBIL, DBIL, GGT, ALP) significantly decreased in all groups ($p < 0.05$) (see Supplementary Fig. 1). Among these, the sustained hepatic steatosis group showed the smallest reductions in ALT, GGT, and ALP, with reductions of 22.11% ($p = 0.023$), 13.86% ($p = 0.003$), and 1.98% ($p = 0.025$), respectively. After treatment, there were no significant differences in the reductions of AST, TBIL, and DBIL between the four groups ($p > 0.05$) (see Table 2).

After treatment, the disappeared hepatic steatosis group exhibited significant decreases in triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C), with reductions of 22.45% ($p < 0.001$) and 17.48% ($p = 0.002$), respectively, while the new-onset hepatic steatosis group showed significant increases in TG and LDL-C, with increases of 19.05% ($p < 0.001$) and 10.97%

($p = 0.002$), respectively. Additionally, the disappeared hepatic steatosis group showed a significant increase in high-density lipoprotein cholesterol (HDL-C), with an increase of 14.16% ($p = 0.012$). These changes suggest that the presence or resolution of hepatic steatosis may be associated with the degree of change in blood lipids.

Before treatment, there were no significant differences in glucose (GLU) levels between the subgroups ($p > 0.05$); after treatment, the sustained hepatic steatosis group had the highest GLU level and the largest increase (6.10 mmol/L, $p < 0.001$) (8.85%, $p = 0.039$) (see Supplementary Fig. 2 and Table 2).

Analysis of the relationship between hepatic steatosis status and virological response after HBV treatment

After antiviral treatment, HBsAg and HBV DNA significantly decreased in all groups compared to before treatment ($p < 0.05$) (see Supplementary Fig. 1). The rate of undetectable HBV DNA reached 72.60% in the overall population. After treatment, there were no significant differences in the decrease of HBsAg and HBV DNA

Table 1 Comparison of baseline clinical characteristics among subgroups based on different hepatic steatosis distributions

	Total (n = 219)	Sustained non- hepatic steatosis (n = 118)	New-onset he- patic steatosis (n = 33)	Sustained hepatic steatosis (n = 37)	Disappeared he- patic steatosis (n = 31)	P value
Male, n (%)	168(76.71)	85 (72.03)	26 (78.79)	29 (78.38)	28 (90.32)	0.187
Age*, years	36.00(30.00,46.00)	37.00(30.00,47.00)	35.00(27.50,46.00)	37.00(29.00,45.00)	35.00(31.00,43.00)	0.953
BMI*, kg/m ²	23.39(21.05,25.89)	22.39(20.06,25.06)	23.89(21.60,26.06)	26.06(23.30,28.23)	24.39(23.05,26.73)	<0.001
T2DM*, (n, %)	19(8.68)	10(8.47)	5(15.15)	4(10.81)	0(0.00)	0.178
Hypertension*, (n, %)	34(15.53)	12(10.17)	7(21.21)	8(21.62)	7(22.58)	0.132
Obesity*, (n, %)	31(14.16)	9(7.63)	5(15.15)	10(27.03)	7(22.58)	0.012
Duration of antiviral, weeks	82.00 (80.00,84.00)	82.50(80.00,84.00)	82.00 (80.00,83.00)	82.00 (80.00,84.00)	83.00 (80.00,85.00)	0.597
HBsAg*, log IU/ml	3.53(3.35,3.72)	3.53(3.37,3.74)	3.56(3.41,3.64)	3.56(3.16,3.90)	3.49(3.23,3.58)	0.405
HBV-DNA*, log IU/ml	6.34(5.49,7.18)	6.33(5.47,7.07)	6.27(5.58,7.30)	6.38(5.29,7.21)	6.25(5.56,7.30)	0.978
HBeAg positive*, n (%)	162(73.97)	85(72.03)	28 (84.85)	26 (70.27)	23(74.19)	0.471
ALT*, U/L	64.00(31.80,134.80)	60.95(29.65,138.70)	77.90(33.65,187.80)	61.00(29.90,130.50)	67.00(38.90,133.00)	0.759
AST*, U/L	39.00(26.90,85.80)	38.25(27.15,88.25)	39.60(25.60,117.05)	38.00(24.65,95.70)	42.80(29.60,72.20)	0.947
TBIL*, μmol/L	14.30(11.40,19.60)	14.15(11.40,19.80)	14.90(10.78,23.45)	13.90(12.15,16.95)	14.30(10.10,19.20)	0.875
DBIL*, μmol/L	4.80(3.40,6.30)	4.90(3.40,6.27)	5.10(3.70,7.10)	4.80(3.45,5.90)	4.30(3.00,6.30)	0.600
GGT*, U/L	30.50(23.50,53.00)	25.95(20.88,48.00)	26.67(21.20,53.15)	38.00(27.85,63.10)	38.20(31.10,60.30)	0.020
ALP*, U/L	83.40(67.20,89.50)	82.20(68.55,83.85)	83.40(69.20,111.90)	83.40(57.50,84.15)	83.40(77.90,113.00)	0.073
TG*, mmol/L	1.13(0.81, 1.45)	0.91(0.74, 1.44)	1.04(0.84, 1.19)	1.29(1.13, 1.51)	1.14(0.94, 1.89)	0.001
CHOL*, mmol/L	4.40(3.90, 5.34)	4.28(3.92, 5.13)	4.71(3.40, 5.43)	4.67(3.91, 5.52)	4.58(4.02, 5.54)	0.544
LDL-C*, mmol/L	2.66(2.31, 3.24)	2.37(2.12, 2.76)	2.42(1.76, 3.69)	3.24(3.07, 3.72)	2.91(2.76, 4.30)	<0.001
HDL-C*, mmol/L	1.13(0.95, 1.34)	1.18(0.98, 1.42)	1.13(0.86, 1.33)	1.14(0.98, 1.35)	1.02(0.94, 1.19)	0.089
UA*, μmol/L	307.00(272.10,365.40)	291.00(258.80,342.50)	307.00(282.50,361.90)	334.90(315.70,429.20)	339.00(298.60,387.50)	<0.001
FG*, mmol/L	5.48(5.11, 6.06)	5.37(5.10, 5.92)	5.71(5.22, 6.32)	5.44(5.13, 5.88)	5.62(5.11, 5.96)	0.284
NAS*	0.00(0.00,1.00)	0.00(0.00,0.00)	0.00(0.00,0.00)	1.00(1.00,2.00)	1.00(1.00,2.00)	<0.001

$P < 0.05$ was shown in bold. * is used to represent at baseline. Non-normal distribution was expressed as midline (IQR), and normal distribution was expressed as mean $\pm$ SD. The comparison among the four groups was performed using non-parametric tests. Abbreviation: BMI, body mass index; T2DM, Type 2 diabetes mellitus; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBV DNA, hepatitis B virus DNA; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, glutamine transpeptidase; ALP, alkaline phosphatase; TBIL, total bilirubin; DBIL, direct bilirubin; TG, triglyceride; CHOL, cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; UA, uric acid; FG, fasting glucose; NAS, Non-alcoholic fatty liver disease activity score

between the groups ($p > 0.05$), indicating that hepatic steatosis in CHB patients does not directly affect the virological response to antiviral treatment (see Supplementary Fig. 1 and Table 2).

The relationship between hepatic steatosis and improvement of hepatitis severity after HBV treatment

After antiviral treatment, hepatitis severity significantly improved in all groups compared to before treatment ($p < 0.05$) (see Fig. 2A). We compared the changes in hepatitis severity after treatment in patients with significant inflammation ($G \geq 2$) at baseline. In terms of improvement, the sustained non-hepatic steatosis group showed the highest rate of improvement (75.31%), while the sustained hepatic steatosis group had the lowest rate of improvement (42.31%, $p = 0.008$). Furthermore, the sustained hepatic steatosis group had the highest rate of significant inflammation progression (15.38%, $p = 0.020$) (see Fig. 3A). Further analysis revealed that among patients with a ≥ 2 -point improvement in inflammation after treatment, the sustained non-hepatic steatosis group

had the highest proportion (44.00%), while the sustained hepatic steatosis group and new-onset hepatic steatosis group had the lowest proportion (16.67%, $p = 0.047$) (see Supplementary Tables 1 and Fig. 4A). Univariate logistic regression analysis indicated that improvement in significant inflammation was associated with baseline ALT, GGT, degree of liver inflammation, new-onset hepatic steatosis during treatment, and sustained hepatic steatosis ($p < 0.1$). In multivariate analysis, the results showed that sustained hepatic steatosis was associated with difficulty in achieving significant improvement in hepatitis ($p = 0.006$, OR = 0.244, 95% CI 0.090–0.665) (see Table 3).

The relationship between hepatic steatosis and improvement of liver fibrosis after HBV treatment

After antiviral treatment, liver fibrosis significantly improved in all groups compared to before treatment ($p < 0.05$) (see Fig. 2B). We compared the changes in liver fibrosis in patients with significant fibrosis at baseline. In terms of improvement of significant liver fibrosis, the sustained non-hepatic steatosis group showed the

Table 2 Comparison of Post-Treatment clinical characteristics among subgroups based on different hepatic steatosis distributions

	Total (n = 219)	Sustained non-hepatic steatosis (n = 118)	New-onset hepatic steatosis (n = 33)	Sustained hepatic steatosis (n = 37)	Disappeared hepatic steatosis (n = 31)	P value
HBV-DNA undetectable ^a , n (%)	159(72.60)	87(73.73)	25(75.76)	24(64.86)	23(74.19)	0.707
HBeAg positive ^a , n (%)	129(58.90)	65 (55.08)	21 (63.64)	20 (54.05)	23 (74.19)	0.224
HBSAg ^a , logIU/ml	3.28(2.91,3.43)	3.28(2.93,3.38)	3.24(2.90,3.44)	3.41(2.69,3.62)	3.20(2.90,3.38)	0.363
ΔHBSAg (post-pre)/ pre, %	-7.26(-15.82,-2.62)	-7.35(-15.84,-2.57)	-10.67(-19.75,-1.27)	-4.97(-12.19,-2.22)	-8.60(-15.10,-4.48)	0.610
HBV-DNA ^a , logIU/ml	1.30(1.30,1.35)	1.30(1.30,1.41)	1.30(1.30,1.32)	1.30(1.30,1.47)	1.30(1.30,1.35)	0.685
ΔHBV-DNA (post-pre)/ pre, %	-78.37(-80.94,-72.22)	-78.33(-80.76,-67.26)	-78.90(-81.71,-75.60)	-77.98(-80.26,-70.16)	-78.69(-81.10,-75.99)	0.413
ALT ^a , U/L	31.70(20.90,49.00)	25.70(19.53,39.63)	33.50(21.65,51.15)	48.80(33.70,68.50)	47.07(20.80,80.20)	<0.001
ΔALT(post-pre)/ pre, %	-42.36(-77.39,2.23)	-48.27(-80.04,-11.23)	-62.89(-84.28,37.50)	-22.11(-56.37,45.17)	-33.25(-57.59,22.51)	0.023
AST ^a , U/L	25.60(21.10,34.00)	24.40(20.13,31.20)	26.30(23.20,34.90)	27.90(22.75,36.70)	30.90(21.30,43.80)	0.056
ΔAST(post-pre)/ pre, %	-30.63(-70.12,0.53)	-40.27(-73.77,2.55)	-25.74(-75.82,49.37)	-19.77(-58.40,18.06)	-29.39(-53.64,-7.11)	0.324
TBIL ^a , μmol/L	13.30(10.40,16.50)	12.90(10.63,16.65)	14.50(10.75,17.30)	12.60(10.30,15.60)	13.30(9.20,15.50)	0.576
ΔTBIL(post-pre)/ pre, %	-11.61(-32.69,14.77)	-9.87(-33.84,10.54)	-11.61(-31.57,27.34)	-15.67(-33.33,15.26)	-10.14(-31.05,15.10)	0.988
DBIL ^a , μmol/L	4.15(3.20,5.50)	4.15(3.30,5.75)	4.70(3.40,5.55)	3.90(3.00,5.00)	4.10(2.80,4.90)	0.324
ΔDBIL(post-pre)/ pre, %	-15.31(-30.56,13.16)	-14.25(-29.47,13.61)	-17.10(-22.32,10.44)	-15.84(-36.28,8.04)	-16.42(-32.26,14.29)	0.926
GGT ^a , U/L	21.30(15.70,30.90)	18.30(15.15,22.43)	22.80(19.70,34.60)	31.40(28.75,48.15)	26.90(17.10,39.40)	<0.001
ΔGGT(post-pre)/ pre, %	-25.20(-51.39,-0.61)	-34.82(-66.54,8.31)	-15.63(-48.33,9.14)	-13.86(-32.69,16.07)	-21.10(-52.27,3.44)	0.003
ALP ^a , U/L	73.71(61.50,77.90)	73.71(57.58,73.71)	73.71(67.25,87.45)	73.71(59.55,83.75)	73.71(65.90,84.90)	0.120
ΔALP(post-pre)/ pre, %	-11.62(-26.88,1.65)	-11.62(-31.77,2.43)	-10.91(-35.09,1.75)	-1.98(-13.47,10.65)	-13.10(-19.87,-4.93)	0.025
TG ^a , mmol/L	1.13(0.72,1.56)	0.81(0.68,1.37)	1.23(0.90,1.53)	1.37(1.28,1.87)	1.04(0.65,1.49)	<0.001
ΔTG(post-pre)/ pre, %	0.00(-24.14,28.47)	-8.33(-26.95,21.80)	19.05(-2.69,53.28)	5.09(-6.07,37.50)	-22.45(-30.57,3.17)	<0.001
CHOL ^a , mmol/L	4.25(3.59,4.95)	4.00(3.42,4.77)	4.41(3.63,5.41)	4.80(4.15,5.21)	4.22(3.69,4.79)	0.006
ΔCHOL(post-pre)/ pre, %	-4.86(-18.60,9.47)	-6.25(-16.99,5.40)	2.94(-28.51,49.14)	0.22(-12.88,15.26)	-9.07(-21.60,2.54)	0.086
LDL-C ^a , mmol/L	2.57(2.24,3.19)	2.46(2.00,2.72)	2.89(2.25,3.59)	3.53(2.82,3.55)	2.81(2.16,3.20)	<0.001
ΔLDL-C(post-pre)/ pre, %	-2.43(-20.21,16.44)	0.05(-19.13,16.58)	10.97(-14.72,46.13)	2.85(-18.53,14.02)	-17.48(-34.66,-1.43)	0.002
HDL-C ^a , mmol/L	1.13(0.93,1.34)	1.19(0.93,1.42)	1.10(0.88,1.53)	1.02(0.93,1.17)	1.14(0.94,1.61)	0.094
ΔHDL-C(post-pre)/ pre, %	-2.58(-22.90,28.97)	-5.50(-23.02,28.31)	3.31(-24.52,47.15)	-14.16(-27.92,11.40)	14.16(-5.88,42.50)	0.012
UA ^a , μmol/L	342.00(288.00,384.00)	313.00(267.00,374.50)	349.00(308.50,400.15)	371.00(327.50,392.00)	345.00(320.00,366.00)	0.007
ΔUA(post-pre)/ pre, %	5.82(-10.65,23.70)	5.34(-9.05,27.93)	17.92(-5.45,38.64)	4.64(-12.59,20.61)	1.77(-20.77,12.23)	0.068
FG ^a , mmol/L	5.63(5.33,6.10)	5.54(5.14,5.91)	5.59(5.34,6.73)	6.10(5.66,6.51)	5.52(5.16,5.92)	<0.001
ΔFG(post-pre)/ pre, %	1.38(-6.38,10.71)	0.40(-6.43,9.27)	0.76(-9.18,10.68)	8.85(0.90,19.95)	0.18(-9.15,7.82)	0.039
NAS ^a	0.00(0.00,1.00)	0.00(0.00,0.00)	1.00(1.00,1.00)	1.00(1.00,2.00)	0.00(0.00,0.00)	<0.001

P<0.05 was shown in bold. ^a is used to represent post-treatment; Δ is used to represent the difference before and after treatment; Non-normal distribution was expressed as median (IQR), normal distribution was expressed as mean ± SD. The comparison among the four groups was performed using non-parametric tests. Abbreviation: BMI, body mass index; HBeAg, hepatitis B e antigen; HBV DNA, hepatitis B virus DNA; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, glutamine transpeptidase; TBIL, total bilirubin; DBIL, direct bilirubin; TG, triglyceride; CHOL, cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; UA, uric acid; FG, fasting glucose; NAS, Non-alcoholic fatty liver disease activity score

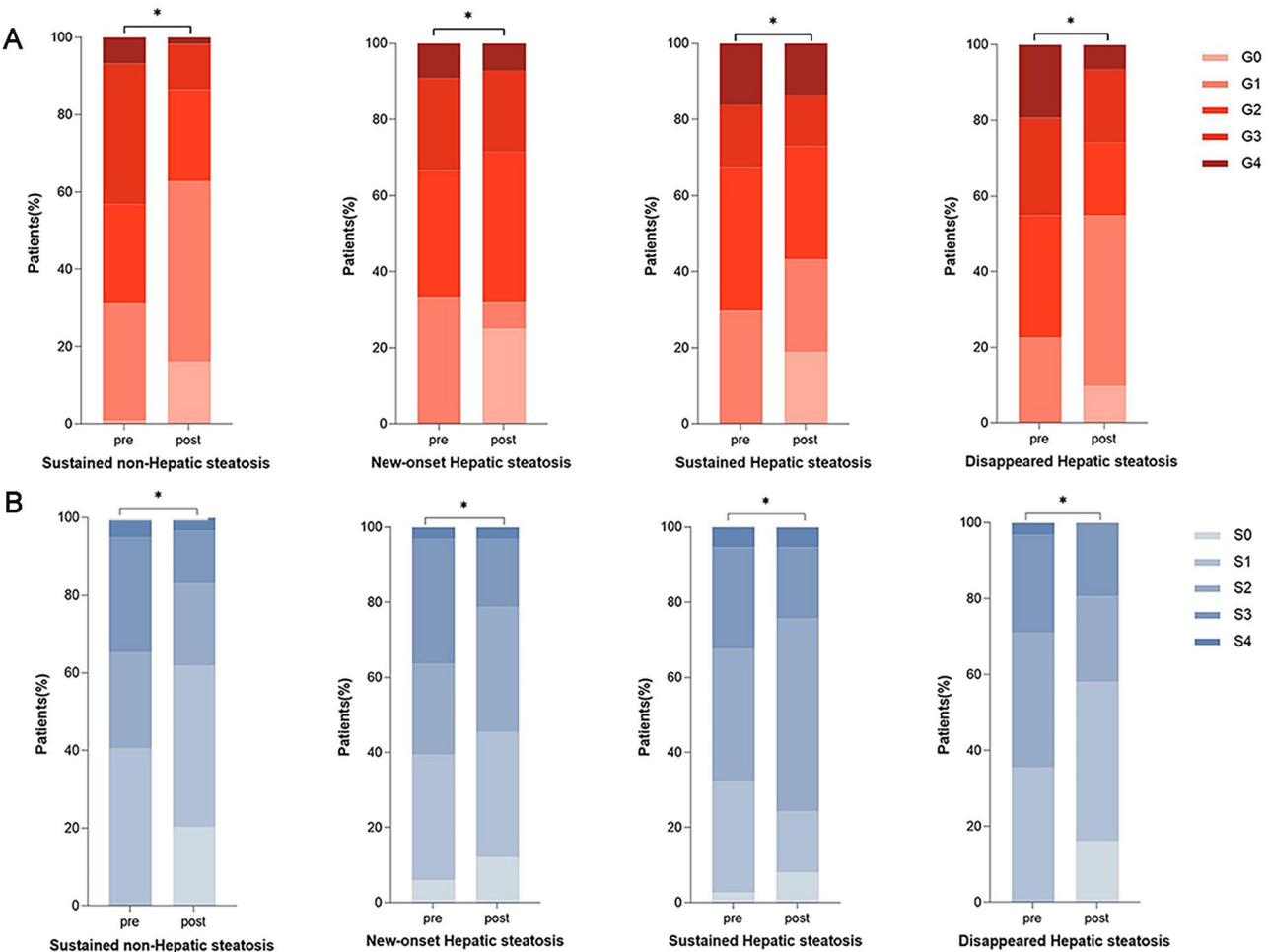


Fig. 2 Histological Degree Before and After Treatment in Subgroups Based on Different hepatic steatosis Distributions. **(A)** Liver inflammation grading based on different hepatic steatosis distributions. **(B)** Liver fibrosis staging based on different hepatic steatosis distributions. (* $P < 0.05$)

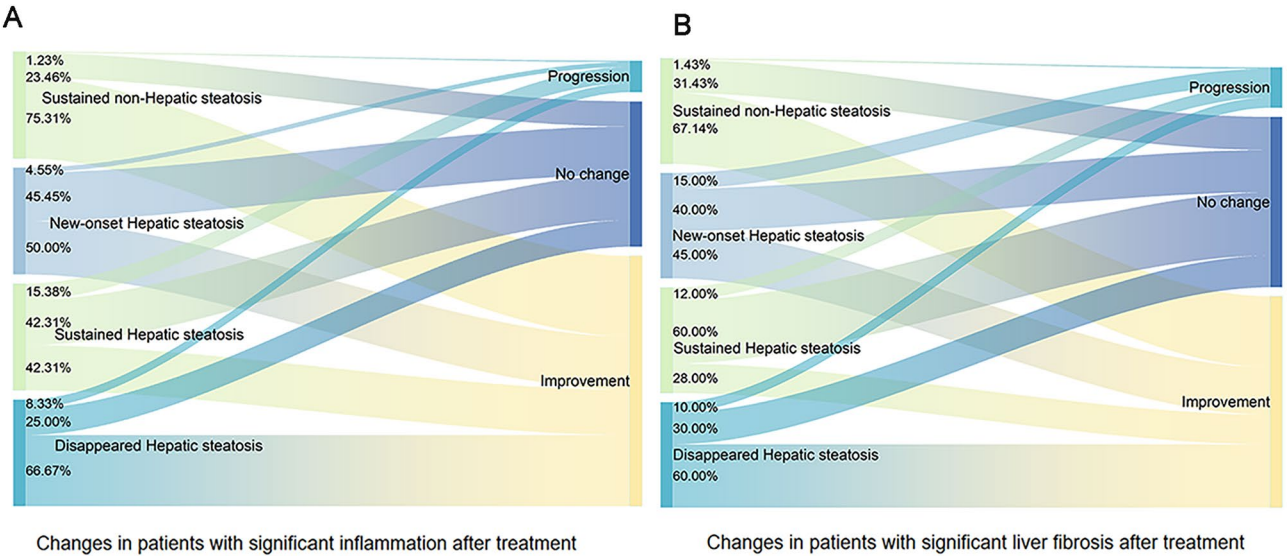


Fig. 3 Histological changes in liver tissue among subgroups with different hepatic steatosis distributions during antiviral therapy. **(A)** Dynamics of significant liver inflammation grading after treatment. **(B)** Dynamics of significant liver fibrosis staging after treatment

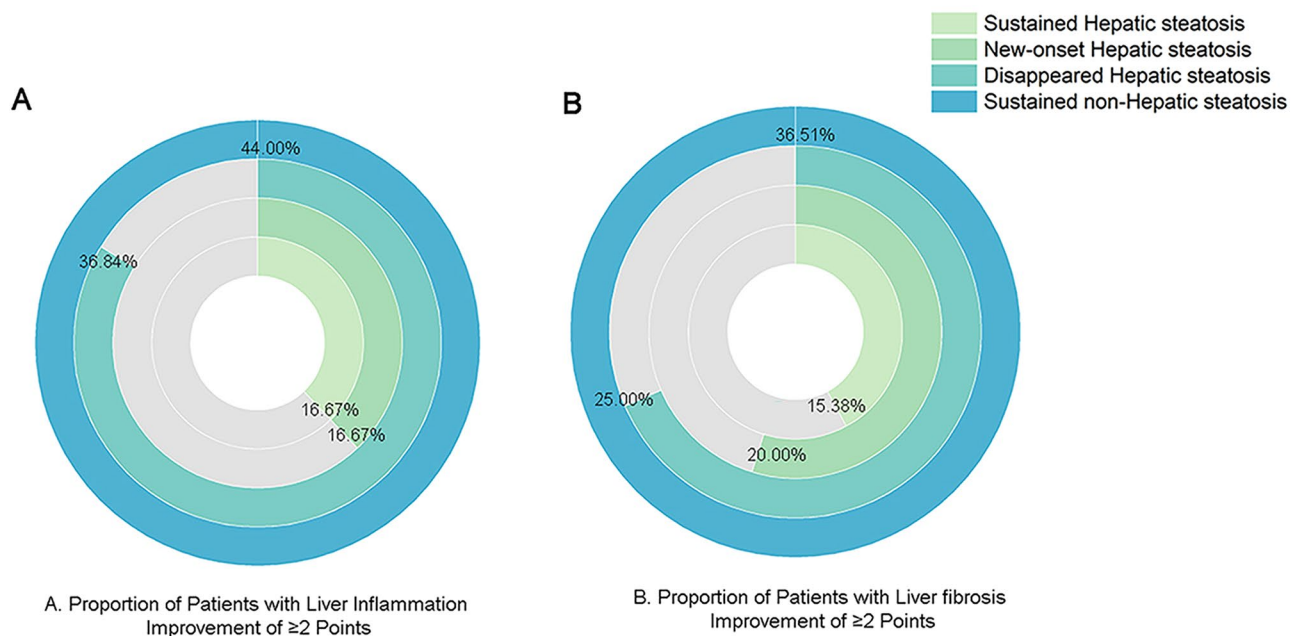


Fig. 4 Proportion of Patients with Liver Histological Improvement of ≥ 2 Points Based on Different hepatic steatosis Distributions. **(A)** The proportion of Patients with Liver Inflammation Improvement of ≥ 2 Points. **(B)** The proportion of Patients with Liver fibrosis Improvement of ≥ 2 Points)

Table 3 Predictive factors for improvement of significant inflammation after antiviral therapy

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Gender	1.300 (0.598–2.825)	0.508		
Age*, years	0.992 (0.961–1.024)	0.634		
BMI*, kg/m ²	0.961 (0.881–1.049)	0.375		
Duration of antiviral, weeks	0.915 (0.803–1.043)	0.184		
HBsAg*, logIU/ml	1.270 (0.659–2.446)	0.476		
HBV-DNA*, logIU/ml	0.957 (0.744–1.232)	0.735		
ALT*, U/L	1.003 (1.000–1.005)	0.073		
AST*, U/L	1.002 (0.999–1.005)	0.298		
TBIL*, μ mol/L	1.010 (0.957–1.065)	0.720		
DBIL*, μ mol/L	1.048 (0.899–1.223)	0.546		
ALP*, U/L	0.999 (0.989–1.008)	0.796		
GGT*, U/L	1.006 (0.999–1.012)	0.088		
Δ TG (post-pre)/ pre, %	0.996 (0.989–1.002)	0.209		
Δ CHOL(post-pre)/ pre, %	0.992 (0.979–1.005)	0.216		
Δ LDL-C(post-pre)/ pre, %	0.992 (0.981–1.004)	0.208		
Δ HDL-C(post-pre)/ pre, %	1.000 (0.992–1.009)	0.962		
Δ UA(post-pre)/ pre, %	1.003 (0.992–1.015)	0.564		
Δ FG(post-pre)/ pre, %	1.016 (0.997–1.037)	0.105		
liver inflammation score*	4.055 (2.085–7.884)	<0.001	4.066 (2.056–8.039)	<0.001
liver fibrosis score*	1.095 (0.770–1.558)	0.613		
NAS*	0.884 (0.578–1.352)	0.569		
Hepatic steatosis status change				
Sustained non-hepatic steatosis	1 (Reference)	-	1 (Reference)	-
New-onset hepatic steatosis	0.328 (0.123–0.871)	0.025		
Sustained hepatic steatosis	0.240 (0.095–0.608)	0.003	0.244 (0.090–0.665)	0.006
Disappeared hepatic steatosis	0.656 (0.244–1.760)	0.402		

Note: $P < 0.05$ was shown in bold. *indicated at baseline; Δ is used to represent the difference before and after treatment; Logistic regression analysis was used to identify factors associated with Significant Inflammation, calculating odds ratios (ORs), 95% confidence intervals (95% CIs) and p values

Table 4 Predictive factors for improvement of significant fibrosis after antiviral therapy

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	Pvalue	OR (95% CI)	Pvalue
Gender	1.038 (0.464–2.325)	0.927		
Age*, years	1.013 (0.981–1.046)	0.440		
BMI*, kg/m ²	0.997 (0.915–1.085)	0.941		
Duration of antiviral, weeks	0.949 (0.829–1.086)	0.446		
HBsAg*, logIU/ml	1.073 (0.606–1.899)	0.810		
HBV-DNA*, logIU/ml	0.932 (0.718–1.211)	0.600		
ALT*, U/L	1.001 (0.998–1.004)	0.441		
AST*, U/L	1.001 (0.998–1.004)	0.613		
TBIL*, µmol/L	0.987 (0.934–1.042)	0.637		
DBIL*, µmol/L	0.933 (0.795–1.096)	0.401		
ALP*, U/L	0.996 (0.985–1.006)	0.390		
GGT*, U/L	1.000 (0.995–1.006)	0.853		
Δ TG (post–pre)/ pre, %	0.998 (0.991–1.005)	0.550		
Δ CHOL(post–pre)/ pre, %	0.993 (0.980–1.007)	0.313		
Δ LDL-C(post–pre)/ pre, %	1.003 (0.990–1.016)	0.679		
Δ HDL-C(post–pre)/ pre, %	0.997 (0.989–1.004)	0.386		
Δ UA(post–pre)/ pre, %	1.016 (1.002–1.029)	0.021		
Δ FG(post–pre)/ pre, %	0.999 (0.981–1.018)	0.938		
liver inflammation score*	1.583 (0.983–2.549)	0.059		
liver fibrosis score*	1.763 (1.077–2.888)	0.024	1.858 (1.105–3.123)	0.019
NAS*	0.923 (0.601–1.418)	0.714		
Hepatic steatosis status change				
Sustained non-hepatic steatosis	1 (Reference)	-	1 (Reference)	-
New-onset hepatic steatosis	0.400 (0.145–1.102)	0.076		
Sustained hepatic steatosis	0.190 (0.070–0.520)	0.001	0.180 (0.064–0.507)	0.001
Disappeared hepatic steatosis	0.734 (0.264–2.044)	0.554		

Note: *indicated at baseline; Δ is used to represent the difference before and after treatment; Logistic regression analysis was used to identify factors associated with Significant fibrosis, calculating odds ratios (ORs), 95% confidence intervals (95% CIs) and *p* values

highest improvement rate (67.14%), while the sustained hepatic steatosis group showed the lowest improvement rate (28.00%, $p = 0.006$). Among patients with significant fibrosis, the sustained non-hepatic steatosis group had the lowest rate of fibrosis progression (1.43%), while the new-onset hepatic steatosis group had the highest progression rate (15.00%, $p = 0.027$) (see Fig. 3B). Among patients with cirrhosis ($S = 4$) at baseline, no significant differences were observed in liver fibrosis changes between the subgroups ($p > 0.05$) (see Supplementary Table 2).

Univariate logistic regression analysis showed that improvement of significant liver fibrosis was associated with baseline liver inflammation activity, severity of liver fibrosis, changes in uric acid during treatment, new-onset hepatic steatosis, and sustained hepatic steatosis ($p < 0.1$). Multivariate logistic regression analysis indicated that sustained hepatic steatosis during treatment was associated with difficulty in improving liver fibrosis ($p = 0.001$, OR = 0.180, 95% CI 0.064–0.507) (see Table 4).

Baseline abnormal BMI and LDL-C levels as independent risk factors for persistent hepatic steatosis in CHB patients

Univariate logistic regression analysis showed that the incidence of sustained hepatic steatosis in CHB patients before and after treatment was associated with baseline BMI, TG, LDL-C, and uric acid (UA) levels ($p < 0.10$). Multivariate logistic regression analysis revealed that baseline high BMI and LDL-C levels were independently associated with sustained hepatic steatosis in CHB patients before and after treatment, specifically: high BMI ($p = 0.042$, OR = 1.109, 95% CI 1.004–1.226) and high LDL-C ($p < 0.001$, OR = 2.570, 95% CI 1.524–4.332) (see Supplementary Table 3).

Discussion

The impact of steatohepatitis on the long-term prognosis of chronic hepatitis B (CHB) patients has been the subject of several studies. Van Kleef et al. assessed steatohepatitis via ultrasound and found that it was associated with overall mortality and cancer risk in CHB patients, highlighting the potential impact of steatohepatitis on patient prognosis [9]. Additionally, Rugivarodom et al. pointed out that steatohepatitis is closely related to the

progression of liver fibrosis in CHB patients, providing further evidence that steatohepatitis may exacerbate liver damage via metabolic pathways, leading to worse clinical outcomes [23].

The study also indicates that patients with chronic hepatitis B (CHB) combined with non-alcoholic fatty liver disease (NAFLD) demonstrate more severe lobular and portal inflammation, hepatocellular ballooning, and fibrosis. Compared to patients who are only infected with HBV, they are more likely to develop significant inflammation and more advanced liver fibrosis [24–26]. However, there is still insufficient research on the impact of hepatic steatosis on histological changes after treatment in CHB patients with different levels of hepatic histological inflammation and fibrosis. Liver biopsy is a commonly used method to assess liver lesions in chronic hepatitis B patients, especially liver fibrosis and cirrhosis. For patients receiving nucleos(t)ide analog therapy, liver biopsy helps monitor treatment efficacy and adjust the treatment plan [27]. Although non-invasive methods, such as liver elastography, are becoming more widely used, liver biopsy remains an irreplaceable tool in certain cases [12]. Therefore, studying the impact of hepatic steatosis on significant histological changes in the liver, especially in CHB patients with varying degrees of hepatitis and fibrosis, is critical for assessing clinical outcomes after treatment.

Our study divided patients into four groups based on changes in hepatic steatosis observed in liver biopsy results: sustained non-hepatic steatosis group, new-onset hepatic steatosis group, sustained hepatic steatosis group, and disappeared hepatic steatosis group. The results showed that, after antiviral treatment, in patients with significant liver fibrosis ($S \geq 2$) at baseline, the changes in liver fibrosis were closely associated with the presence and progression of hepatic steatosis. The sustained hepatic steatosis group had the lowest rate of liver fibrosis improvement, while the sustained non-hepatic steatosis group had the highest improvement rate. The new-onset hepatic steatosis group had the highest rate of liver fibrosis progression, while the sustained non-hepatic steatosis group had the lowest progression rate. Multivariate logistic regression analysis confirmed that sustained hepatic steatosis is an independent risk factor for liver fibrosis improvement during antiviral treatment in patients with baseline significant fibrosis. Therefore, we recommend that CHB patients with significant liver fibrosis should actively treat hepatic steatosis to delay liver disease progression [28]. Furthermore, although there were no significant differences in the liver fibrosis improvement rate among groups in patients with cirrhosis ($S = 4$) at baseline, this may be related to the shorter follow-up period. Future studies should further explore

the impact of hepatic steatosis on the long-term prognosis of cirrhosis patients.

Currently, both domestic and international guidelines recommend guiding antiviral treatment in CHB patients based on the extent of liver damage, emphasizing that treatment should be initiated when significant inflammation or fibrosis is present [12, 29, 30]. Our study further indicates that patients with significant inflammation and liver fibrosis should particularly focus on hepatic steatosis during antiviral treatment.

Our findings show that after antiviral treatment, in patients with significant inflammation ($G \geq 2$) at baseline, liver inflammation changes were strongly associated with hepatic steatosis. The sustained hepatic steatosis group had the lowest rate of hepatitis improvement, while the sustained non-hepatic steatosis group had the highest improvement rate. The new-onset hepatic steatosis group had the highest rate of hepatitis progression, while the sustained non-hepatic steatosis group had the lowest progression rate. Importantly, among patients with at least a 2-point improvement in liver inflammation, the sustained hepatic steatosis group had the lowest proportion, while the sustained non-hepatic steatosis group and new-onset hepatic steatosis group had higher proportions. Multivariate logistic regression analysis confirmed that sustained hepatic steatosis is an independent risk factor for inflammation improvement during antiviral treatment in patients with baseline significant hepatitis.

These results suggest that sustained hepatic steatosis is an important risk factor for difficulty in achieving improvement in inflammation and may hinder the improvement of liver inflammation during antiviral treatment. Therefore, for CHB patients receiving antiviral treatment, a comprehensive assessment should be performed to determine if abnormal liver enzymes are associated with concurrent hepatic steatosis, in order to effectively address unresolved hepatitis issues.

Previous studies have shown that approximately 25% of chronic hepatitis B (CHB) patients with abnormal liver enzymes have non-alcoholic fatty liver disease (NAFLD) [31]. We found that after antiviral treatment, the sustained hepatic steatosis group showed the smallest reduction in liver enzyme markers (ALT, ALP, and GGT), indicating that hepatic steatosis may hinder the normalization of liver enzymes in CHB patients, thereby affecting the improvement of liver function during antiviral treatment. Therefore, managing and treating hepatic steatosis is crucial for improving liver function in CHB patients.

According to the latest guidelines from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver, the goal of antiviral treatment for CHB patients is to achieve serum HBV DNA levels below the detection limit as early as

possible and to maintain normalization of ALT levels [12, 29]. However, the effect of hepatic steatosis on the antiviral response in CHB patients remains a subject of debate [32, 33]. Our study did not observe a correlation between hepatic steatosis and virological response, which is consistent with the findings of Li et al. [34]. Nevertheless, hepatic steatosis may influence treatment outcomes in CHB patients; therefore, for patients with concurrent hepatic steatosis, antiviral therapy should be intensified, and virological response should be monitored regularly.

Hepatic steatosis is frequently associated with metabolic abnormalities [35, 36]. Multivariate logistic regression analysis showed that the persistent presence of hepatic steatosis was significantly associated with higher BMI and LDL-C levels before treatment. This suggests that addressing the metabolic imbalance in patients with hepatic steatosis is urgent. Therefore, for patients with CHB and hepatic steatosis, lifestyle modifications should be prioritized, aiming to improve cardiovascular metabolic health and overall well-being. Weight reduction can improve blood pressure, blood glucose, and blood lipid levels, reduce the risk of cardiovascular diseases, and provide additional benefits [37, 38].

Our study has the following limitations. First, it is a retrospective, single-center study, which may introduce some bias. Future studies should include a larger sample size and a multi-center, prospective design to validate these findings. Second, the study lacks long-term follow-up on clinical outcomes. Future research should implement longer follow-up periods and collect detailed information on patients' lifestyles to comprehensively assess the antiviral response, clinical outcomes, and factors associated with hepatic steatosis in CHB patients.

Conclusion

First, our study found that during antiviral treatment of CHB patients with significant inflammation and fibrosis, sustained hepatic steatosis may make the improvement of inflammation and fibrosis difficult and could even lead to the progression of hepatitis and liver fibrosis. Second, patients with sustained hepatic steatosis are more likely to exhibit biochemical abnormalities after treatment, including lesser reductions in liver enzyme markers such as ALT, ALP, and GGT, as well as increased levels of lipids, uric acid, and fasting glucose.

Abbreviations

CHB	Chronic hepatitis B
MASLD	Metabolic dysfunction-associated steatotic liver disease
HBV	Hepatitis B virus
NAFLD	Nonalcoholic fatty liver disease
HCC	Hepatocellular carcinoma
CAP	Controlled attenuation parameter
LSM	Liver stiffness measurement
LBx	Liver biopsies
HBsAg	Hepatitis B surface antigen
NAs	Nucleos(t)ide analogues

HBeAg	Hepatitis B e antigen
HBV DNA	Hepatitis B virus DNA
WBC	White blood cells
PLT	Blood platelet count
AST	Aspartate transaminase
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
GGT	Gamma-glutamyl transferase

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12985-025-02703-z>.

Supplementary Material 1: S1 Table: Changes in Liver Inflammation and Severity Based on Hepatic Steatosis Status Pre- and Post-Treatment. **S2 Table:** Changes in Liver fibrosis and Severity Based on Hepatic Steatosis Status Pre- and Post-Treatment. **S3 Table:** Predictive Factors for Sustained Hepatic Steatosis in Patients with Chronic Hepatitis B.

Supplementary Material 2: S1 Fig: Dynamic changes in clinical indicators before and after treatment across subgroups with different hepatic steatosis distributions. (A.ALT; B.AST; C.GGT; D.TBIL; E.DBIL; F.ALP; G.HBsAg; H.HBV DNA) (* $P < 0.05$).

Supplementary Material 3: S2 Fig: Dynamics of Lipid Profile Markers Before and After Treatment in Subgroups Based on Different hepatic steatosis Distributions. (A.TG; B.LDL-C; C.CHO; D.HDL-C; E.FG; F.UA) (* $P < 0.05$).

Acknowledgements

We would like to express our sincere gratitude to Dr. Peng Wang, Dr. Lei Sun, and Dr. Xingang Zhou from the Pathology Department of Beijing Ditan Hospital for their invaluable support.

Author contributions

Yang BQ and Yang TY contributed equally to this work and shared the first authorship; Wang Q and Li Y provided idea for this research and were co-corresponding authors; Yang BQ, Yang TY, Hou CX and Li Y critically revised the manuscript; Yang BQ, Yang TY and Wang Q wrote the manuscript and performed the statistical analyses; All authors read and approved the final manuscript.

Funding

This work was supported by the High-level Public Health Technical Personnel Construction Project (Discipline backbone-02-29).

Data availability

All data collected during the study are available from the corresponding author at wangqid04@ccmu.edu.cn.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration and its subsequent amendments and was approved by the Institutional Review Board of Beijing Ditan Hospital, Capital Medical University (NO.DTEC-KY2021-046-04). This is a retrospective study involving no diagnostic or therapeutic interventions, and the data were anonymized. Therefore, the research centre's ethics committee waived the requirement for patient informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT 4.0 in order to improve readability and language. After using this tool, the author(s) reviewed

and edited the content as needed and take(s) full responsibility for the content of the publication.

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Received: 3 October 2024 / Accepted: 11 March 2025

Published online: 27 May 2025

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