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ORIGINAL ARTICLE

Retrospective Cohort Study

Influence of nonalcoholic fatty liver disease on the therapeutic effect of nucleoside (acid) analogs for hepatitis B virus

Hua-Dong Li, Ya-Nan Liu, Shuang Wu, Xu-Feng Quan, Xiao-Yan Wang, Tian-Dan Xiang, Shu-Meng Li, Ling Xu, Tong Wang, Hua Wang, Xin Zheng

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Abstract

BACKGROUND

The effect of nonalcoholic fatty liver disease (NAFLD) on the efficacy of nucleoside analogues (NAs) in antiviral therapy for patients with chronic hepatitis B (CHB) remains controversial.

AIM

To investigate the influence of NAFLD on virological response in CHB patients undergoing NAs treatment.

METHODS

Logistic regression analysis was conducted on a cohort of 465 CHB patients from two hospitals to determine whether NAFLD was a risk factor for adverse reactions to NAs. CHB patients were followed up for more than 28 months after initial antiviral treatment, and further validation was performed using different viral load populations.

RESULTS

NAFLD was identified as an independent risk factor for partial virological response following antiviral therapy with NAs (odds ratio = 1.777, P = 0.017). In our subsequent analysis focusing on CHB patients with high viral load, the NAFLD

group exhibited significantly longer virus shedding time and lower proportion of the complete virological response compared with the non-NAFLD group (16.8 ± 6.1 *vs* 13.0 ± 6.8, $P < 0.05$). During the 24-month period of antiviral treatment with NAs, hepatitis B virus (HBV) DNA levels decreased slowly in the NAFLD group, and the negative conversion rate of HBV was notably lower than that observed in non-NAFLD group ($P = 0.001$). Similar results were obtained when analyzing patients with low baseline HBV viral load within the NAFLD group.

CONCLUSION
Coexistence of NAFLD may diminish virological response among CHB patients receiving antiviral treatment with NAs.

Key Words: Nonalcoholic fatty liver disease; Chronic hepatitis B; Nucleoside analogues; Antiviral therapy; Virological response

Core Tip: The effect of nonalcoholic fatty liver disease (NAFLD) on the antiviral therapy with nucleoside analogues (NAs) in patients with chronic hepatitis B (CHB) is controversial. The aim of this study was to investigate the virological response to first-line NAs antiviral treatment in patients with NAFLD and CHB, through dynamically monitoring virology indicators for 96 weeks, to determine the influence of NAFLD on the efficacy of NAs anti- hepatitis B virus treatment. To our knowledge, this is the first grading study based on HBV baseline viral load that confirms a reduction in virological response to NAs antiviral treatment caused by NAFLD.

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INTRODUCTION

Chronic liver diseases, such as chronic hepatitis B (CHB) and nonalcoholic fatty liver disease (NAFLD), are highly prevalent globally[1]. According to the World Health Organization, approximately 257 million individuals worldwide were affected by the hepatitis B virus (HBV) in 2015[2]. In the meantime, the prevalence of NAFLD has been rising over the past decade due to rapid socio-economic growth and improved quality of life[3]. Researches have interpreted that the overall incidence of NAFLD in CHB patients is about 14% to 70%[4,5]. Both HBV infection and NAFLD can induce chronic liver inflammation, aggravate liver injury, and an elevated likelihood of developing liver cirrhosis and hepatocellular carcinoma[6-8]. The implementation of antiviral therapy is crucial in inhibiting the progression of disease among CHB patients.

In recent years, nucleoside analogues (NAs) have been extensively utilized in antiviral treatment of CHB. Previous studies[9-11] have reported a decrease in HBV viral load in non-antiviral CHB patients comorbid with NAFLD, indicating that NAFLD may potentially inhibit HBV replication. However, the impact of NAFLD on the prognosis of antiviral therapy for CHB is a controversial issue. In a retrospective study of 555 CHB patients, Li *et al*[12] found that the presence of NAFLD does not exert any detrimental impact on the complete virological suppression achieved by NAs antiviral therapy, both in the short and long-term. Another retrospective study[13] of the CHB cohort treated with Entecavir (ETV) observed that the virology response rate of patients with NAFLD was similar to CHB patients. However, a separate retrospective study[14] on 524 CHB patients undergoing antiviral therapy showed a negative correlation between concomitant NAFLD and HBV DNA levels. Additionally, a clinical study[15] involving 267 CHB patients treated with ETV demonstrated a significant association between liver steatosis and the failure of antiviral treatment. Currently, there are no specific recommended guidelines for nucleotide antiviral treatment in patients with NAFLD complicated with CHB.

In view of this, we conducted a retrospective analysis on 465 CHB patients who underwent standard antiviral treatment with NAs at two hospitals, aiming to explore the association between NAFLD and virological response to antiviral treatment. Subsequently, these research findings were validated in both high- and low-viral-load CHB populations, while considering the impact of liver fibrosis during the course of antiviral treatment, aiming to ascertain the influence of NAFLD on virologic response to NAs-based antiviral therapy.

MATERIALS AND METHODS

Study design

We retrospectively analyzed adult patients with CHB who received outpatient treatment at the Department of Infectious Diseases at Wuhan Jinyintan Hospital and Wuhan Union Hospital from January 2011 to January 2022. The demographics, clinical data, abdominal imaging, and laboratory information of the patients were recorded. Initially, we compared various parameters between CHB patients who achieved partial virological response (PVR) and complete virological response (CVR) after 96 weeks of standardized antiviral therapy using NAs, aiming to establish the correlation between NAFLD and the virological response to antiviral therapy.

Subsequently, the high-viral-load (HBV DNA ≥ 10^7 IU/mL) and low-viral-load (1×10^2 IU/mL < HBV DNA < 1×10^5 IU/mL) CHB patients with and without of NAFLD were compared respectively, to determine the influence of NAFLD on the virological response to nucleotide analog ETV or tenofovir disoproxil fumarate (TDF) anti-HBV therapy (Figure 1).

Study subjects and definition

Patients enrolled in this study were required to meet both the diagnostic criteria for CHB and NAFLD. According to the "Guidelines of prevention and treatment for chronic hepatitis B (2019 version)"[16], CHB was defined as hepatitis B surface antigen (HBsAg) or/and HBV DNA presence for over 6 months. The diagnosis of NAFLD was in accordance with AASLD's practice guide "Diagnosis and Management of Nonalcoholic Fatty liver Disease"[17], which was demonstrated by imaging or histology as evidence of hepatic steatosis, without any secondary causes such as excessive alcohol consumption, use of hepatotoxic medications, or genetic disease. Due to the limited operation of liver biopsies during clinical diagnosis and treatment, all subjects underwent confirmation through liver ultrasound and liver elasticity detection. Complete virological response was defined as undetectable serum HBV DNA levels (polymerase chain reaction) or below the detection limit (100 IU/mL) after 24 weeks of standard NAs antiviral treatment. Partial virological response referred to CHB patients with good compliance and no resistance to NAs after 24 weeks of standard antiviral therapy, where HBV DNA decreased by ≥ 2 Log10 IU/mL but remained detectable using sensitive methods.

We excluded patients with the following conditions from this study: Liver disease caused by non-HBV infections or combined with other hepatitis virus infections; patients with immune deficiency diseases, autoimmune hepatitis, or those receiving systemic immune regulation treatment for related diseases; pregnant or lactating women; and individuals undergoing other anti-HBV therapies such as interferon.

Statistical analysis

Statistical analysis was conducted using Univariate and Multivariate Logistic regression tests, Student's *t*-test, and Pearson's χ^2 test. Continuous variables were reported as median (interquartile range) or mean ± SD. while categorical variables were described by numbers and proportion (%). For the analysis of continuous variables that follow a normal distribution, we employed the student's *t*-test, while for categorical variables, Pearson's χ^2 test was utilized. Mann-Whitney *U* tests were performed to analysis of nonnormally distributed variables with two independent samples. Kaplan-Meier method was used to determine the negative conversion rate (NCR) of HBV DNA, and the normalization rates of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). GraphPad Prism (Version 8.0, SanDiego, California, United States) and SPSS (version 25, IBM, United States) software were employed for charting and statistical analysis. A *P*-value of ≤ 0.05 was regarded as statistically significant.

RESULTS

Patient characteristics

A total of 1405 adults with CHB were assessed during the study period, and 465 individuals met the inclusion criteria. Among those who received antiviral therapy with NAs, 139 subjects obtained CVR, while 326 subjects experienced PVR, and the risk factors of PVR were observed. Subsequently, to verify the relationship between NAFLD coexisting with CHB and virological response, we conducted a dynamic analysis of viral response to NAs antiviral treatment in patients with high and low HBV DNA viral load levels (Figure 1).

Table 1 presents the baseline demographic data and clinical characteristics of all enrolled subjects, who were monitored for an average duration of 28 months. In the study population, men accounted for a higher proportion than women (68.8% *vs* 31.2%), with an average age was 35 years.

Based on the virological response outcome, patients were divided into two groups: The CVR group and the PVR group. The gender composition did not show any significant difference between these two groups ($P = 0.94$). However, it was observed that patients in the CVR group had a higher age compared to those in the PVR group (38.1 *vs* 34.4, $P = 0.0005$). Significant differences were found between the PVR and CVR groups regarding baseline levels of HBsAg and HBV DNA, duration of HBV shedding, and HBeAg positivity rate. These parameters were all higher in the PVR group than in the CVR group. Interestingly, our findings revealed a greater proportion of NAFLD patients in the PVR group when compared to the CVR group (31.9% *vs* 20.9%). Moreover, this particular group also exhibited higher baseline levels of triglyceride and total cholesterol (1.4 *vs* 1.2 for triglyceride; 4.9 *vs* 4.4 for total cholesterol), suggesting a potential association with NAFLD development. However, no significant differences were observed when comparing fibrosis-4 (FIB-4) scores and AST to platelet ratio index (APRI) scores reflecting liver fibrosis or cirrhosis between the CVR and PVR groups respectively ($P > 0.05$).

Table 1 Baseline demographic data and clinical characteristics of chronic hepatitis B patients, *n* (%)/mean ± SD/95%CI

Variable	Chronic hepatitis B (*n* = 465)	Complete virologic response (*n* = 139)	Partial virologic response (*n* = 326)	*t*/χ^2	*P* value
Gender (*n* = 465)				χ^2 = 0.006	0.940
Male	320 (68.8)	96 (69.1)	224 (68.7)		
Female	145 (31.2)	43 (30.9)	102 (31.3)		
Age (years), *n* = 465	35.5 ± 10.5	38.1 ± 11.7	34.4 ± 9.7	*t* = 3.514	0.0005
HBV DNA baseline level, log10 (IU/mL), *n* = 465	6.1 ± 6.0	5.6 ± 1.9	6.4± 2.0	*t* = 3.661	0.0003
Virus shedding time (months), *n* = 428	9.8 ± 8.7	6.9 ± 5.8	11.2 ± 9.5	*t* = 4.919	< 0.0001
HBsAg baseline level, log10 (IU/mL + 1), *n* = 461	3.4 ± 1.0	3.0 ± 0.9	3.6 ± 1.0	*t* = 5.479	< 0.0001
HBeAg				χ^2 = 14.57	< 0.0001
Positive	298 (64.1)	71 (51.1)	227 (69.6)		
Negative	167 (35.9)	68 (48.9)	99 (30.4)		
NAFLD				χ^2 = 5.815	0.016
Yes	133 (28.6)	29 (20.9)	104 (31.9)		
No	332 (71.4)	110 (79.1)	222 (68.1)		
Leucocytes (G/L), *n* = 396	5.5 ± 1.7	5.4 ± 1.8	5.6 ± 1.6	*t* = 0.7417	0.4587
Haemoglobin (g/L), *n* = 396	148.2 ± 18.2	148.6 ± 17.2	147.9 ± 18.7	*t* = 0.3339	0.7386
Neutrophils (G/L), *n* = 396	3.2 ± 1.4	3.2 ± 1.4	3.3 ± 1.4	*t* = 0.6343	0.5263
Lymphocytes (G/L), *n* = 396	1.8 ± 0.6	1.8 ± 0.6	1.8 ± 0.6	*t* = 0.0444	0.9646
Total bilirubin log10 (μmol/L), *n* = 464	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	*t* = 0.8594	0.3906
Alanine aminotransferase log10 (U/L), *n* = 464	1.7 ± 0.4	1.7 ± 0.4	1.7 ± 0.4	*t* = 0.6270	0.5310
Aspartate aminotransferase log10 (U/L), *n* = 464	1.6 ± 0.3	1.6 ± 0.3	1.6 ± 0.3	*t* = 1.432	0.1527
Albumin (g/L), *n* = 464	44.9 ± 3.3	44.9 ± 3.5	44.9 ± 3.2	*t* = 0.0135	0.9892
Uric acid (umol/L), *n* = 447	337.5 ± 92.8	327.7 ± 76.5	341.6 ± 98.8	*t* = 1.454	0.1467
Fasting glucose (mmol/L), *n* = 229	5.5 ± 1.1	5.6 ± 1.5	5.4 ± 0.9	*t* = 1.283	0.2009
Triglyceride (mmol/L), *n* = 264	1.4 ± 1.1	1.2 ± 0.6	1.4 ± 1.2	*t* = 2.056	0.0408
Total cholesterol (mmol/L), *n* = 264	4.5 ± 1.0	4.4 ± 1.0	4.9 ± 0.9	*t* = 3.694	0.0003
High-density lipoprotein (mmol/L), *n* = 264	1.2 ± 0.3	1.2 ± 0.3	1.1 ± 0.3	*t* = 1.761	0.0794
Low-density lipoprotein (mmol/L), *n* = 264	2.8 ± 0.9	2.82 ± 0.90	2.8 ± 0.9	*t* = 0.1163	0.9075
Treatment follow-up period (months), *n* = 465	28.3 ± 17.5	39.8 ± 16.9	22.9 ± 15.0	*t* = 10.52	< 0.0001
[a]APRI score, *n* = 396	0.42 (0.28-0.81)	0.41 (0.27-0.90)	0.43 (0.29-0.81)	Z = -0.571	0.568
Low (< 0.5)	226 (57.07)	68 (58.62)	158 (56.43)	*t* = 0.161	0.688
Intermediate (0.5-1.5)	128 (32.32)	36 (31.03)	92 (32.86)	*t* = 0.125	0.724
High (> 1.5)	42 (10.61)	12 (10.35)	30 (10.71)	*t* = 0.012	0.913
[b]Fibrosis-4 score, *n* = 395	0.93 (0.52-1.82)	1.00 (0.50-1.94)	0.89 (0.54-1.74)	Z = -0.232	0.816
Low (< 1.45)	266 (67.34)	74 (63.79)	192 (68.82)	*t* = 0.940	0.332
Intermediate (1.45-3.25)	82 (20.76)	22 (18.97)	60 (21.50)	*t* = 0.321	0.571
High (> 3.25)	47 (11.90)	20 (17.24)	27 (9.68)	*t* = 4.472	0.034

[a]Aspartate aminotransferase to platelet ratio index score = [(aspartate aminotransferase (U/L)/upper limit of normal)/platelet (10^9/L)] × 100
[b]Fibrosis-4 score = [Age (years) × aspartate aminotransferase (U/L)]/[platelet (10^9/L) × square root alanine aminotransferase (U/L)]
APRI: Aspartate aminotransferase-to-platelet ratio index; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; NAFLD: Nonalcoholic fatty liver disease.

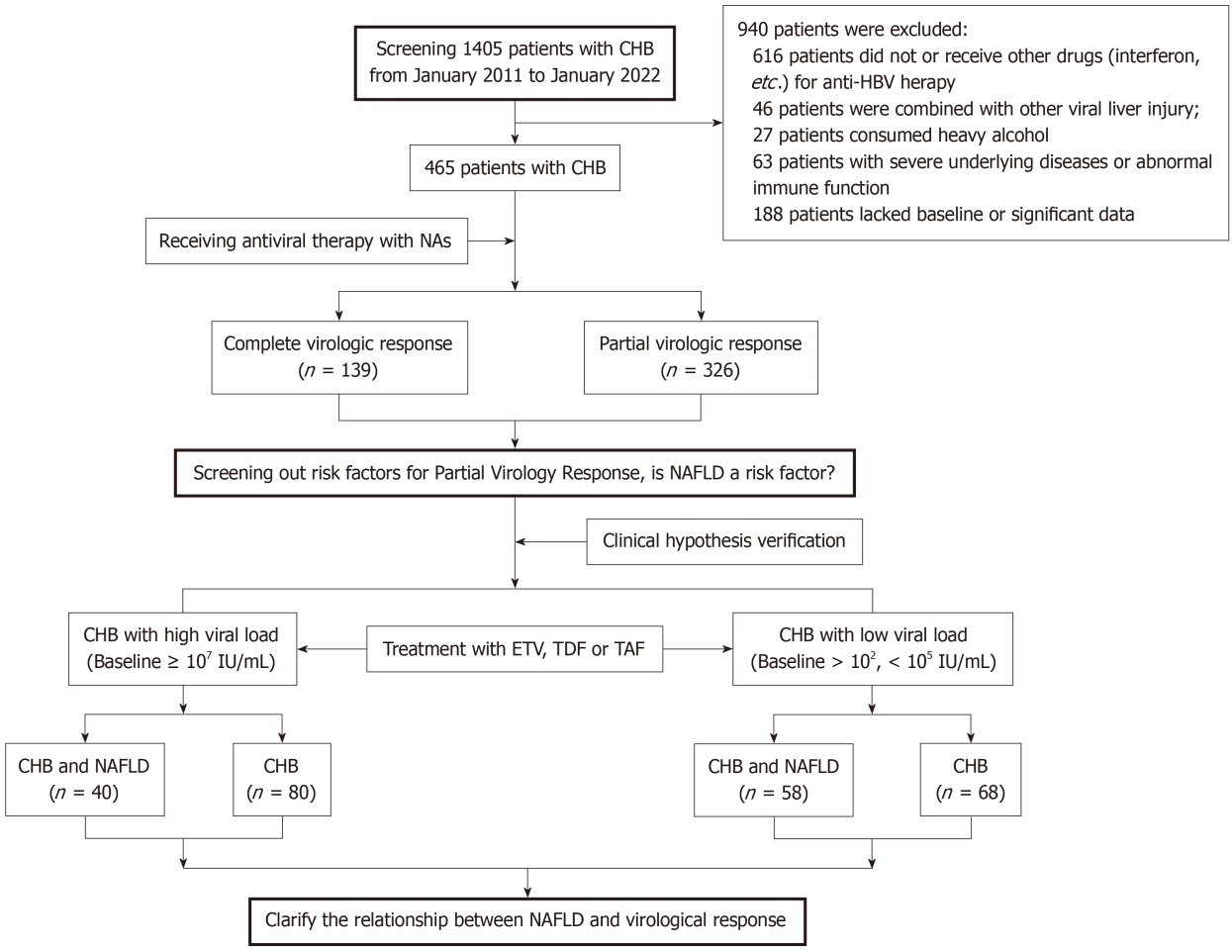


Figure 1 Flow chart of the chronic hepatitis B subjects enrolled in the study. A total of 1405 adults with chronic hepatitis B (CHB) were assessed during the study period, and 465 met the inclusion criteria. Among those who received antiviral therapy with NAs, 139 subjects obtained complete virological response, 326 subjects got partial virological response (PVR), and the risk factors of PVR were observed. Subsequently, to verify the relationship between nonalcoholic fatty liver disease coexisting with CHB and virological response, we conducted a dynamic analysis of viral response to NAs antiviral treatment from patients with hepatitis B virus DNA high viral load and low viral load. CHB: Chronic hepatitis B; NAs: Nucleos(t)ide analogues; NAFLD: Nonalcoholic fatty liver disease; ETV: Entecavir; TDF: Tenofovir disoproxil fumarate; TAF: Tenofovir alafenamide fumarate.

Subsequently, we conducted multivariate logistic regression analysis, and found that NAFLD, Virus shedding time, and HBsAg baseline level were independent predictors of PVR after antiviral therapy with NAs in CHB patients, respectively. Notably, the presence of NAFLD was positively associated with PVR following antiviral treatment, as CHB patients with NAFLD had a 1.792-fold higher likelihood of developing PVR compared to those without NAFLD. To assess the influence of liver fibrosis on the antiviral response to NAs, we established Univariate analysis and Multivariate analysis model II and III; however, no significant correlations were observed between FIB-4 or APRI scores and PVR outcomes (Table 2).

Relationship between NAFLD and poor response to anti-HBV treatment with nucleotide analogues

Previously, our findings indicated that NAFLD was associated with a reduced virological response to NAs antiviral treatment in CHB patients. Therefore, we enrolled CHB patients with elevated viral load to undergo a follow-up period exceeding 30 months after initiation of NAs antiviral therapy (33.8 *vs* 35.1 months, $P = 0.7233$). The results indicated that the male population in NAFLD patients was significantly higher compared to the non-NAFLD group (92.5% *vs* 66.3%, $P = 0.004$), while there was no noteworthy distinction in age between the two groups (29.5 *vs* 31.0, $P = 0.2480$). Regarding the utilization rate of antiviral drugs ETV and/or TDF, there were no notable disparities observed between the two groups, however, due to poor treatment efficacy, 60% of study subjects in the NAFLD group required switching or combination therapy with two NAs compared to 48.7% in the non-NAFLD group. We evaluated baseline levels of HBsAg and HBV

Table 2 Logistic regression analysis of risk factors for partial virological response to antiviral therapy of chronic hepatitis B

Variable	Univariate analysis			Multivariate analysis model I			Multivariate analysis model II			Multivariate analysis model III		
	β	OR (95%CI)	*P* value	*β*	OR (95%CI)	*P* value	*β*	OR (95%CI)	*P* value	*β*	OR (95%CI)	*P* value
Age (years)	-0.033	0.968 (0.949-0.986)	0.001	-0.013	0.987 (0.965-1.009)	0.253	-0.004	0.996 (0.971-1.021)	0.746	-0.003	0.997 (0.973-1.023)	0.842
HBV DNA baseline level, log10 (IU/mL)	0.183	1.201 (1.086-1.328)	< 0.001	0.017	1.017 (0.886-1.168)	0.809	0.011	1.011 (0.87-1-176)	0.884	0.008	1.008 (0.867-1.173)	0.913
Virus shedding time (months)	0.063	1.065 (1.033-1.097)	< 0.001	0.033	1.033 (1.001-1.067)	0.046	0.038	1.039 (1.002-1.078)	0.039	0.039	1.04 (1.002-1.078)	0.037
HBeAg positive (*vs* negative)	0.787	2.196 (1.461-3.302)	< 0.001	-0.18	0.836 (0.468-1.492)	0.544	-0.06	0.942 (0.501-1.773)	0.853	-0.083	0.92 (0.488-1.736)	0.797
HBsAg baseline level, log10 (IU/mL+1)	0.624	1.866 (1.5-2.322)	< 0.001	0.507	1.661 (1.254-2.2)	< 0.001	0.517	1.677 (1.237-2.273)	0.001	0.52	1.682 (1.239-2.282)	0.001
NAFLD (*vs* non-NAFLD)	0.575	1.777 (1.11-2.845)	0.017	0.583	1.792 (1.068-3.006)	0.027	0.92	2.508 (1.368-4.6)	0.003	0.9	2.459 (1.34-4.514)	0.004
APRI score	-0.069	0.934 (0.836-1.043)	0.224				-0.052	0.949 (0.853-1.056)	0.34			
FIB-4 score	-0.041	0.96 (0.92-1.002)	0.061							-0.023	0.977 (0.939-1.016)	0.247

HBV DNA: Hepatitis B virus deoxyribonucleic acid; NAFLD: Nonalcoholic fatty liver disease; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; APRI: Aspartate aminotransferase-to-platelet ratio index; FIB-4: Fibrosis-4 index; OR: Odds ratio.

DNA, along with the rates of seroconversion for HBsAg and HBeAg, but observed no disparities between the two cohorts. Surprisingly, virological shedding time was significantly prolonged in the NAFLD group compared to the non-NAFLD group (16.8 *vs* 13 months, $P = 0.0033$), and there was a significantly lower proportion of CVR compared to that observed in the non-NAFLD group (12.5% *vs* 38.8%, $P = 0.003$). In terms of biochemical markers, there was no significant difference in baseline ALT levels between the two groups ($P = 0.0722$). However, AST levels were observed to be lower in the NAFLD group compared to the non-NAFLD group ($P = 0.0122$) (Table 3).

Relationship between NAFLD and clearance of HBV DNA at high viral load

Patients with high viral load were dynamically observed for 24 months following initial antiviral therapy with ETV or TDF, and evaluations were conducted every 3 months to assess the HBV viral load levels and the cumulative rate of HBV DNA negativity. The findings demonstrated a notable disparity in the reduction rate of HBV viral load between the NAFLD and Non-NAFLD groups after 9 months of antiviral treatment. Specifically, at the 9th, 12th, 15th, and 24th months, the log10 levels of HBV viral load (in NAFLD *vs* non-NAFLD) were as follows: 3.1 *vs* 2.7, 2.9 *vs* 2.4, 2.8 *vs* 2.1, and finally at month twenty-four: 2.9 *vs* 2.0 ($P < 0.05$).

In contrast to the non-NAFLD group, where antiviral treatment led to a decrease in HBV DNA levels below detectable limits after fifteen months, no such reduction was observed in the NAFLD group (Figure 2A, Supplementary Table 1). Additionally, it was noted that at twenty-four months post-treatment, patients with NAFLD had a significantly lower NCR for HBV compared to those without NAFLD (62.5% *vs* 86.3%, $P = 0.001$) (Figure 2B, Supplementary Table 2).

Relationship between NAFLD and recovery of ALT and AST in patients with high viral load

However, with regard to biochemical response, when comparing the normalization rates of ALT between NAFLD group and non-NAFLD group, we observed rates of 39.5% *vs* 44.3%, 57.9% *vs* 75.7%, 71.1% *vs* 85.7%, and 84.2% *vs* 92.9% at the 6th, 12th, 18th, and 24th months respectively; however, no significant difference was found at any stage (Figure 3A, Supplementary Table 3).

Similarly, the normalization rates of AST in both NAFLD and Non-NAFLD cohorts were recorded as 63.2% *vs* 76.5% in the 6th month, 79.0% *vs* 96.1% in the 12th month, 89.5% *vs* 98.0% in the 18th month, and 94.7% *vs* 98.0% in the 24th month respectively, there was no notable disparity observed between the two groups in terms of statistical significance (Figure 3B, Supplementary Table 4).

Relationship between NAFLD and the clearance of HBV DNA in patients at low viral load

Similarly, patients with low viral load (1×10^2 IU/mL < HBV DNA < 1×10^5 IU/mL) were dynamically observed for 24 months after initial antiviral therapy with ETV or TDF, and evaluation was conducted every 3 months to monitor the level of HBV viral load level, HBV DNA NCR. The findings suggest that the rate of decline in HBV viral level was co-

Table 3 Baseline demographic data and clinical features of high viral load chronic hepatitis B combined with nonalcoholic fatty liver disease, *n* (%)/mean ± SD

Characteristics	NAFLD (*n* = 40)	Non-NAFLD (*n* = 80)	*t*/χ^2	*P* value
Gender			χ^2 = 8.450	0.004
Male	37 (92.5)	53 (66.3)		
Female	3 (7.5)	27 (33.7)		
Age (years)	29.5 ± 5.6	31.0 ± 7.1	*t* = 1.161	0.2480
HBV DNA baseline level, log10 (IU/mL)	8.1 ± 0.5	8.0 ± 0.5	*t* = 0.3877	0.6990
Virus shedding time (months)	16.8 ± 6.1	13.0 ± 6.8	*t* = 3.003	0.0033
Virology breakthrough time (months)	6.8 ± 5.6	10.9 ± 11.5	*t* = 1.378	0.1735
HBsAg baseline level, log10 (IU/mL)	4.4 ± 0.6	4.2 ± 0.7	*t* = 1.252	0.2148
Antiviral therapy			*t* = 1.985	0.371
ETV	4 (10.0)	15 (18.8)	*t* = 1.532	0.216
TDF	12 (30.0)	26 (32.5)	*t* = 0.077	0.781
ETV and TDF	24 (60.0)	39 (48.7)	*t* = 1.353	0.245
low-level viremia	30 (75.0)	49 (61.3)	*t* = 2.241	0.134
Virological response			χ^2 = 8.750	0.003
Complete virologic response	5 (12.5)	31 (38.8)		
Partial virologic response	35 (87.5)	49 (61.2)		
Serological response (HBsAg)			χ^2 = 0.0000	1.000
Yes	1 (2.5)	2 (2.5)		
No	39 (97.5)	78 (97.5)		
Serological response (HBeAg)			χ^2 = 3.116	0.078
Yes	1 (2.5)	12 (15.0)		
No	39 (97.5)	68 (85.0)		
Leucocytes, (G/L)	6.4 ± 2.1	5.5 ± 1.6	*t* = 2.414	0.0175
Erythrocyte, (T/L)	5.2 ± 0.4	4.9 ± 0.5	*t* = 3.308	0.0013
Platelets, (G/L)	228.5 ± 51.2	200.4 ± 54.2	*t* = 2.489	0.0144
Haemoglobin, (G/L)	155.4 ± 16.6	146.5 ± 16.7	*t* = 2.533	0.0128
Neutrophils, (G/L)	3.8 ± 1.8	3.1 ± 1.3	*t* = 2.232	0.0278
Lymphocytes, (G/L)	2.0 ± 0.5	1.9 ± 0.5	*t* = 1.277	0.2043
Total bilirubin, log10 (μmol/L)	1.2 ± 0.2	1.2 ± 0.2	*t* = 0.2773	0.7820
≤ 19	29 (72.5)	54 (67.5)	*t* = 0.313	0.576
> 19	11 (27.5)	26 (32.5)		
Alanine aminotransferase, log10 (U/L)	1.7 ± 0.3	1.9 ± 0.5	*t* = 1.814	0.0722
≤ 35	6 (15.0)	17 (21.3)	*t* = 0.672	0.412
> 35	34 (85.0)	63 (78.7)		
Aspartate aminotransferase, log10 (U/L)	1.5 ± 0.2	1.7 ± 0.4	*t* = 2.545	0.0122
≤ 40	21 (52.5)	29 (36.3)	*t* = 2.897	0.089
> 40	19 (47.5)	51 (63.7)		
APRI score	0.5 ± 0.4	0.8 ± 0.6	*t* = 2.639	0.0096
Fibrosis-4 score	0.7 ± 0.4	1.0 ± 0.6	*t* = 2.631	0.0098

Total protein, (g/L)	75.6 ± 5.8	74.3 ± 5.1	t = 1.336	0.1841
Albumin, (g/L)	45.7 ± 2.4	43.7 ± 3.4	t = 3.414	0.0009
Globulin, (g/L)	29.9 ± 5.2	30.6 ± 4.3	t = 0.7613	0.4480
Urea nitrogen, (mmol/L)	4.6 ± 1.3	4.2 ± 1.2	t = 1.599	0.1125
Creatinine, (μmol/L)	76.3 ± 7.5	71.1 ± 11.2	t = 2.542	0.0124
Uric acid, (μmol/L)	413.7 ± 95.7	314.0 ± 86.8	t = 5.546	< 0.0001
Fasting glucose, (mmol/L)	5.3 ± 0.5	5.8 ± 2.4	t = 0.8360	0.4074
Triglyceride, (mmol/L)	1.6 ± 1.6	1.0 ± 0.5	t = 2.085	0.0418
Total cholesterol, (mmol/L)	4.5 ± 0.8	4.2 ± 0.9	t = 1.328	0.1897
High-density lipoprotein, (mmol/L)	1.0 ± 0.2	1.2 ± 0.3	t = 1.886	0.0647
Low-density lipoprotein, (mmol/L)	2.9 ± 0.7	2.5 ± 0.8	t = 1.768	0.0827
Treatment follow-up period, (months)	33.8 ± 16.8	35.1 ± 17.8	t = 0.3550	0.7233

NAFLD: Nonalcoholic fatty liver disease; ETV: Entecavir; TDF: Tenofovir disoproxil fumarate; HBV DNA: Hepatitis B virus deoxyribonucleic acid; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; APRI: Aspartate aminotransferase-to-platelet ratio index.

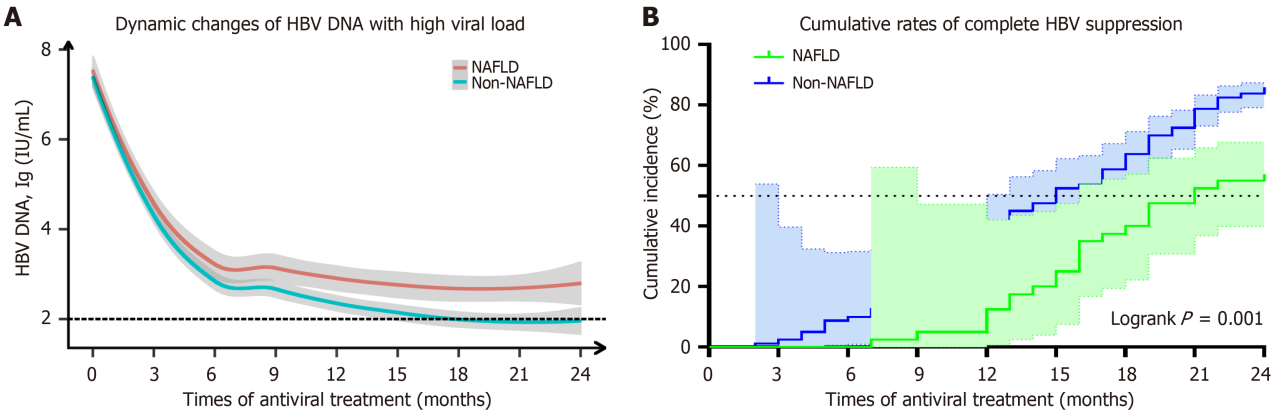


Figure 2 Dynamics of virological response to antiviral therapy over time in chronic hepatitis B patients with and without nonalcoholic fatty liver disease. A: Dynamic change trend of hepatitis B virus viral load; B: Cumulative negative conversion rate of hepatitis B virus. NAFLD: Nonalcoholic fatty liver disease; CHB: Chronic hepatitis B; HBV: Hepatitis B virus; HBV DNA: Hepatitis B virus deoxyribonucleic acid.

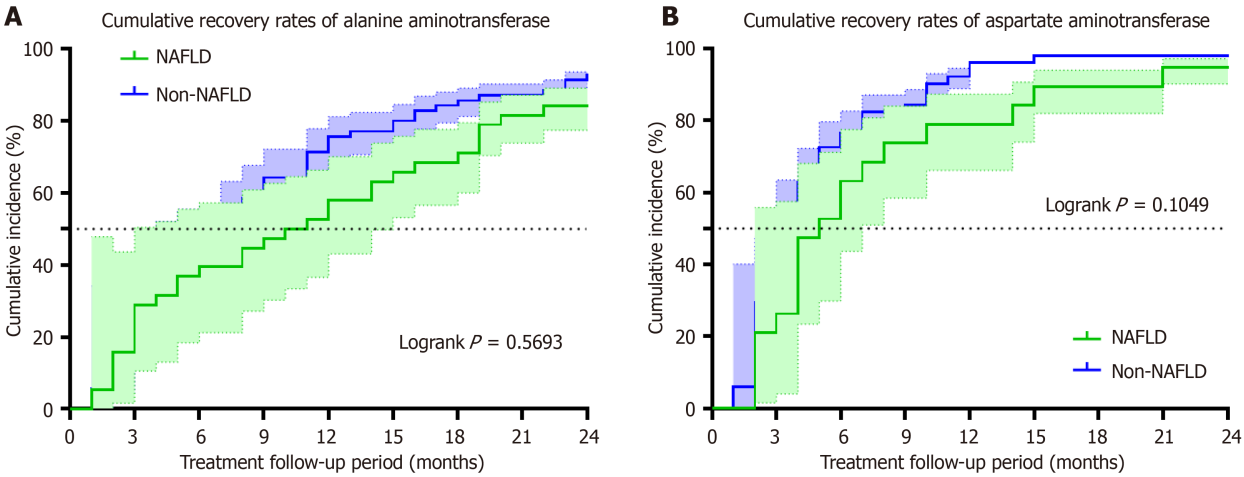


Figure 3 Biochemical response of chronic hepatitis B patients with and without nonalcoholic fatty liver disease by antiviral therapy at 24 months. A: Normalization rate of alanine aminotransferase (≤ 30 U/L and ≤ 19 U/L for males and females); B: Normalization rate of aspartate aminotransferase (≤ 40 U/L for males and females). NAFLD: Nonalcoholic fatty liver disease.

mparatively slower in individuals with NAFLD compared to those without NAFLD. Additionally, after a period of 3 months on antiviral therapy, there was a statistically significant difference observed in the HBV viral load between these two groups. The HBV viral load levels (log10) of CHB patients with NAFLD and Non-NAFLD at 3rd, 6th, and 9th months were 2.3 *vs* 2.1, 2.4 *vs* 2.0, and 2.4 *vs* 2.2, respectively ($P < 0.05$). However, after receiving antiviral therapy for a duration of twelve months, there was no statistically significant difference observed in HBV DNA levels between the two groups ($P > 0.05$) (Figure 4A).

A notable disparity in the HBV NCR between the two groups emerged after twenty-four months of antiviral therapy ($P = 0.006$). Furthermore, we noted that during the initial three to nine months of antiviral treatment, the NAFLD group exhibited a significantly reduced cumulative conversion rate of HBV compared to the non-NAFLD group ($P < 0.05$). Nevertheless, this distinction did not persist beyond twelve months following initiation of antiviral treatment (Figure 4B, Supplementary Table 5).

Impact of different degrees of NAFLD with CHB patients on antiviral therapy effect of nucleotide analogues

This study categorized CHB patients with high viral load and coexisting NAFLD into mild and moderate to severe fatty liver groups based on their abdominal ultrasound and control attenuation parameter (CAP). The control group consisted of CHB patients with high viral load. Initially, all participants were treated with first-line nucleotide analogues antiviral therapy, while monitoring HBV DNA levels every 3 months. The findings revealed that compared to patients with CHB, the decline in HBV DNA levels was slower in those with CHB and NAFLD, particularly those in the mild NAFLD subgroup (Figure 5).

DISCUSSION

In recent years, the prevalence of NAFLD has increased among CHB patients due to improvements in living standards, changes in dietary habits, and the rising rates of obesity and metabolic syndrome[18,19]. Concerns have emerged regarding the impact of NAFLD on the efficacy of antiviral treatment during CHB management, as there are currently no guidelines or recommendations available for reference. Our retrospective analysis involving 465 CHB patients undergoing NAs antiviral therapy revealed that concurrent NAFLD reduced the proportion of complete viral response and delayed HBV clearance. These findings emphasize the need for active attention towards and treatment of NAFLD while also reinforcing monitoring strategies for HBV levels when coexisting with NAFLD.

Furthermore, we stratified the previous study cohort based on viral load levels and HBeAg status. Patients with high viral load and positive HBeAg were selected for treatment with first-line antiviral drugs ETV and TDF. Subsequent dynamic observation and analysis further validated that coexistence of NAFLD delayed HBV clearance and reduced the rate of complete response to antiviral therapy. Our findings are consistent with prior studies[20,21], highlighting a negative association between NAFLD and HBV clearance during oral NAs antiviral therapy in CHB patients, and NAFLD increased the incidence of HBV hypoviremia[22]. Of course, our results are not entirely consistent with some previously reported studies[12,13], given that these studies were conducted over a longer follow-up period, during which participants may have received drug adjustments, interventions for fatty liver, and other confounding factors. Our results are primarily based on studies of antiviral treatment for 24 months. Of particular interest is the emergence of a significant gap after 9 months of antiviral treatment, emphasizing the importance of addressing concerns regarding NAFLD in this patient population.

Meanwhile, we conducted a similar follow-up study to observe the dynamic changes in HBV DNA levels after initial antiviral therapy in CHB patients with low viral load at baseline. Our findings suggest that in the NAFLD group, there was a comparatively gradual decrease in HBV DNA levels and a lower cumulative rate of viral clearance compared to the non-NAFLD group, particularly during the first 9 months of antiviral treatment. These results indicate that coexistence of NAFLD also attenuates the early antiviral treatment response of NAs in individuals with low viral load at baseline.

Patients with CHB may experience liver tissue damage and reduced effectiveness of antiviral treatment due to the potential negative impact of NAFLD. Research indicates that leptin plays a role in modulating T cell function; when this regulation is disrupted, it can hinder the ability of CHB patients to clear the virus, complicating HBeAg seroconversion [23,24]. Insulin resistance serves as a pivotal factor in the pathogenesis of NAFLD, which can impair immune functionality and obstruct viral clearance in CHB patients[25]. In individuals with concurrent NAFLD, hepatic steatosis leads to inflammatory swelling of liver sinusoids and subsequent compression thereof, resulting in altered hepatic microcirculation. Additionally, fat accumulation within hepatocytes exacerbates liver dysfunction, potentially diminishing the bioavailability of antiviral agents within these cells and thereby attenuating their therapeutic efficacy[26].

Recently, a parameter called the CAP has been used to assess the degree of hepatic steatosis. According to the research findings by Chen *et al*[27], CHB patients who were administered ETV as their initial antiviral therapy demonstrated a reduced rate of HBV DNA seroconversion in individuals with significantly elevated baseline levels of CAP, suggesting a limited response to antiviral treatment compared to those with normal CAP. However, another study[28] demonstrated a negative correlation between CAP value and the achievement of CVR. In this research, we performed a comparative examination of the response to antiviral therapy using NA in patients with varying degrees of NAFLD and CHB infection, while including a control group comprising patients with high HBV viral load. The longitudinal monitoring of HBV levels revealed that individuals with NAFLD exhibited a slower decline in HBV levels compared to those with CHB alone, indicating a potential adverse effect of fatty liver on the efficacy of antiviral treatment for NAFLD. These findings are consistent with prior research[20,21,29]. However, it is important to note that patients with mild NAFLD demonstrated the slowest rate of decline in HBV DNA levels, which was even lower than those observed in individuals with

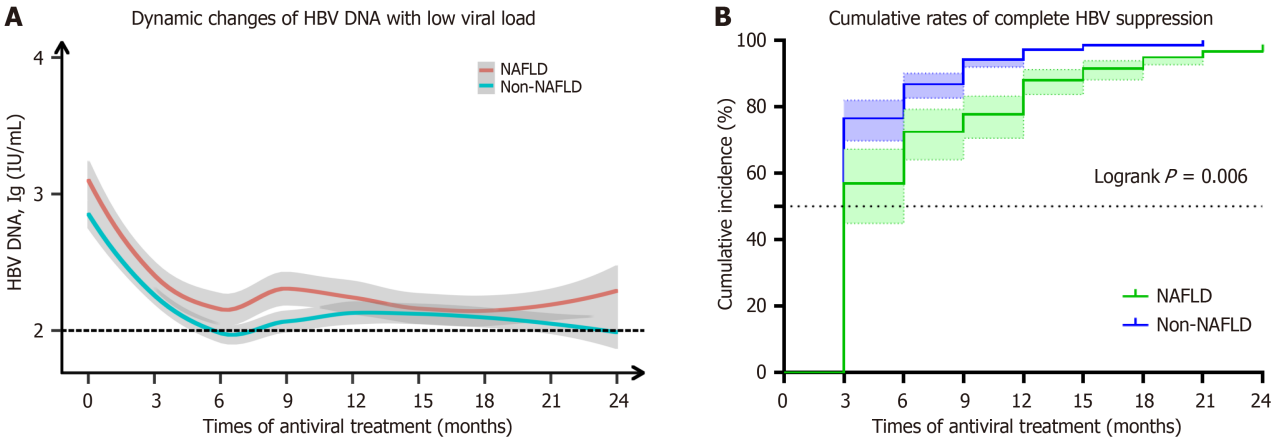
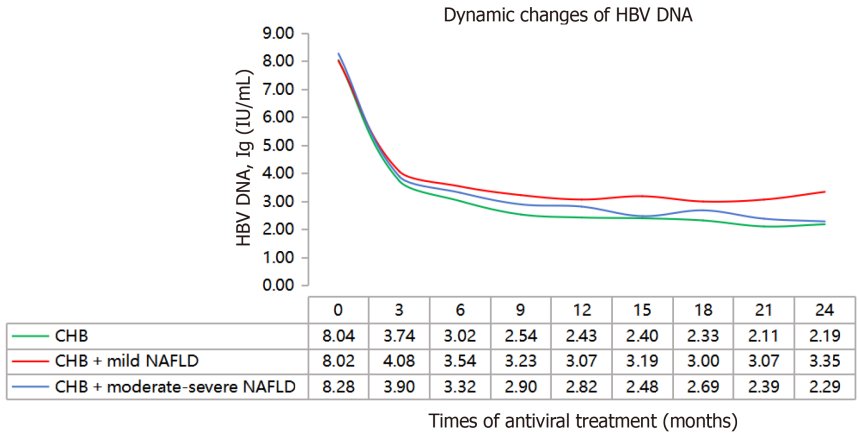


Figure 4 Virological response of chronic hepatitis B patients with and without nonalcoholic fatty liver disease at different antiviral treatment duration. A: Dynamic change trend of hepatitis B virus low viral load; B: Cumulative negative conversion rate of hepatitis B virus low viral load. NAFLD: Nonalcoholic fatty liver disease; HBV: Hepatitis B virus; HBV DNA: Hepatitis B virus deoxyribonucleic acid.



	0	3	6	9	12	15	18	21	24
CHB	8.04	3.74	3.02	2.54	2.43	2.40	2.33	2.11	2.19
CHB + mild NAFLD	8.02	4.08	3.54	3.23	3.07	3.19	3.00	3.07	3.35
CHB + moderate-severe NAFLD	8.28	3.90	3.32	2.90	2.82	2.48	2.69	2.39	2.29

Figure 5 Virological response of chronic hepatitis B patients with different grades of nonalcoholic fatty liver disease at different antiviral treatment duration. Dynamic change trend of hepatitis B virus viral load. NAFLD: Nonalcoholic fatty liver disease; CHB: Chronic hepatitis B; HBV DNA: Hepatitis B virus deoxyribonucleic acid.

moderate to severe fatty liver disease. Further investigations, involving prospective studies with increased sample sizes, is necessary to validate and confirm these observations.

Hepatic fibrosis is a crucial stage in the progression of CHB and NAFLD. In our study, we evaluated the liver non-invasive detection indicators FIB-4 and APRI scores. Surprisingly, no notable disparity was detected in the FIB-4 and APRI scores when comparing the CVR and PVR groups. Furthermore, multivariate analysis revealed that these scores were not identified as risk factors for PVR, which aligns with previous research findings[12]. However, it is intriguing to note that among individuals with high viral load and positive HBeAg status, patients with NAFLD-associated CHB exhibited lower FIB-4 and APRI scores compared to those with simple CHB. Previous research has indicated that the coexistence of NAFLD does not contribute to an increased occurrence of liver fibrosis in CHB patients[18], according to the results of a recent study[30], the presence of NAFLD is considered to be an independent negative factor for significant and advanced liver fibrosis in patients with CHB, although further validation through larger sample sizes is warranted.

This study has several limitations. Firstly, this investigation constitutes a retrospective clinical cohort study, which may be subject to case selection bias. Consequently, the findings necessitate further validation through prospective studies. Secondly, this retrospective clinical study only includes a Chinese ethnic group population, which may not be representative of other ethnic groups worldwide. Additionally, the diagnosis of NAFLD primarily relies on liver imaging results, and outpatient liver biopsy is not readily accepted by patients, thereby limiting the determination of hepatic steatosis severity. This study observed the liver fat status during the initiation of antiviral treatment and the random point liver imaging results during the treatment period, but we do not track the dynamics of liver steatosis in each individual subject. Finally, not all patients in this study received high-sensitivity HBV DNA detection, and we chose a level of 100 IU/mL for HBV DNA as the lower limit of testing for the sake of uniformity between two groups.

CONCLUSION

In conclusion, our study on the CHB patients with varying HBV viral loads, and initial standard 96 weeks of treatment with first-line antiviral drugs further verified that NAFLD can reduce the antiviral response of NAs, highlighting the need for increased attention towards these patients. Moreover, the findings from this retrospective study serve as a valuable point of reference for the development of standardized clinical guidelines, and further prospective studies are warranted to validate these results, provide more scientifically guided antiviral treatment strategies for patients with CHB complicated by NAFLD.

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FOOTNOTES

Author contributions: Li HD was responsible for the data curation, investigation, methodology, writing-original draft, writing-review and editing; Liu YN participated in the data curation, investigation, and editing; Wang H participated in the data curation and methodology; Wu S, Quan XF, Wang XY, Xiang TD, Li SM, Xu L, and Wang T participated in data curation and editing; Zheng X was responsible for methodology, supervision, acquired funding, writing–review and editing.

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Institutional review board statement: This study was performed in accordance with the guidelines of the Helsinki Declaration and had been approved by the Ethics Committee of Wuhan Jinyintan Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology (Approval No. KY-2023-12).

Informed consent statement: As this is a retrospective cohort study and the data is anonymous, the requirement for informed consent has been waived.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Data sharing statement: Data are available from the corresponding author upon reasonable request.

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