ORIGINAL ARTICLE

Retrospective Cohort Study

Baseline hepatocyte ballooning is a risk factor for adverse events in patients with chronic hepatitis B complicated with nonalcoholic fatty liver disease

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Abstract

BACKGROUND
Although many studies have investigated the impact of chronic hepatitis B virus (HBV) infection and nonalcoholic fatty liver disease (NAFLD) on liver disease, few have investigated the relationship between nonalcoholic steatohepatitis (NASH) defined by liver pathology and the prognosis of chronic HBV infection. Most patients were followed up for a short time. This study aimed to further explore the impact of NAFLD and the pathological changes confirmed by liver pathology in patients with chronic HBV infection.

AIM
To study the effect of NAFLD confirmed using liver pathology on the outcomes of long-term serious adverse events [cirrhosis, hepatocellular carcinoma (HCC), and death] in patients with chronic hepatitis B (CHB) virus infection.

METHODS
We enrolled patients with chronic hepatitis B virus (HBV) infection who underwent liver biopsy at the Third People's Hospital of Zhenjaing Affiliated Jiangsu University between January 2005 and September 2020. Baseline clinical and pathological data on liver pathology and clinical data at the end of follow-up were collected. Propensity score matching (PSM) was used to balance baseline parameters, Kaplan-Meier (K-M) survival analysis was used to evaluate the risk of clinical events, and Cox regression was used to analyze the risk factors of events.

RESULTS
Overall, 456 patients with chronic HBV infection were included in the study, of whom 152 (33.3%) had histologically confirmed NAFLD. The median follow-up time of the entire cohort was 70.5 mo. Thirty-four patients developed cirrhosis, which was diagnosed using ultrasound during the follow-up period. K-M

survival analysis showed that NAFLD was not significantly associated with the risk of cirrhosis (log-rank test, $P > 0.05$). Patients with CHB with fibrosis at baseline were more prone to cirrhosis (log-rank test, $P = 0.046$). After PSM, multivariate analysis showed that diabetes mellitus, ballooning deformation (BD), and platelet (PLT) were independent risk factors for cirrhosis diagnosed using ultrasound ($P < 0.05$). A total of 10 patients (2.2%) developed HCC, and six of these patients were in the combined NAFLD group. K-M survival analysis showed that the cumulative risk of HCC in the NAFLD group was significantly higher (log-rank test, $P < 0.05$). Hepatocyte ballooning, and severe liver fibrosis were also associated with an increased risk of HCC (log-rank test, all $P < 0.05$). Cox multivariate analysis revealed that hepatocyte ballooning, liver fibrosis, and diabetes mellitus were independent risk factors for HCC.

CONCLUSION
There was no significant correlation between chronic HBV infection and the risk of cirrhosis in patients with NAFLD. Diabetes mellitus, BD, and PLT were independent risk factors for liver cirrhosis. Patients with chronic HBV infection and NASH have an increased risk of HCC. BD, liver fibrosis, and diabetes mellitus are independent risk factors for HCC.

Core Tip: A total of 456 patients with chronic hepatitis B virus infection were included in the study, of whom 152 (33.3%) had histologically confirmed nonalcoholic fatty liver disease (NAFLD). The median follow-up time of the entire cohort was 70.5 mo. Kaplan-Meier (K-M) survival analysis showed that NAFLD was not significantly associated with the risk of cirrhosis. Patients with chronic hepatitis B with fibrosis at baseline were more prone to cirrhosis. After PSM, multivariate analysis showed that diabetes mellitus, ballooning deformation, and platelet were independent risk factors for cirrhosis. A total of 10 patients (2.2%) developed hepatocellular carcinoma (HCC). K-M survival analysis showed that the cumulative risk of HCC in the NAFLD group was significantly higher. Cox multivariate analysis revealed that hepatocyte ballooning, liver fibrosis, and diabetes mellitus were independent risk factors for HCC.

INTRODUCTION

Chronic hepatitis B (CHB) virus infection and nonalcoholic fatty liver disease (NAFLD) are important causes of liver-related complications and death. With the increasing prevalence of NAFLD, the number of patients with combined NAFLD and hepatitis B virus (HBV) infections is also on the increase. In Asia, the prevalence of NAFLD in patients with hepatitis B virus infection is approximately 14%-67%, which is not different from the data of western countries[1,2]. In recent years, there have been many studies on hepatitis B complicated with NAFLD; however, the interaction between these two diseases is still elusive.

It is understandable that in the case of combined NAFLD, the overall prognosis of these patients seems to be worse. Both NAFLD and CHB can aggravate liver injury and increase the risk of cirrhosis and liver cancer[3-7]. Recently, a cohort study evaluated the FibroScan liver transient elastography results of 459 hepatitis B e antigen (HBeAg)-negative patients over a 10-year period, and found that hepatic steatosis in patients with CHB was associated with the progression of fibrosis[8]. Based on FibroScan examination, a study of 1202 patients with CHB found that the proportion of patients with moderate to severe fibrosis among patients with severe steatosis was significantly higher than that in patients with mild or moderate steatosis (23.2% *vs* 12.6%)[9,10]. A retrospective cohort study of 270 patients with CHB showed that liver steatosis confirmed by biopsy was an independent risk factor for hepatocellular carcinoma (HCC) in patients with CHB[5]. Another large multicenter multi-ethnic cohort study of 1089 patients with CHB showed that liver steatosis confirmed by biopsy was not significantly associated with clinical outcomes (HCC and death).

Although many studies have investigated the impact of chronic HBV infection and NAFLD on liver disease, few have investigated the relationship between nonalcoholic steatohepatitis (NASH) defined by liver pathology and the prognosis of chronic HBV infection. Most patients were followed up for a short time. This study aimed to further explore the impact of NAFLD and the pathological changes confirmed by liver pathology in patients with chronic HBV infection.

MATERIALS AND METHODS

Research objective

All patients with chronic HBV infection who underwent liver biopsy at The Third Hospital of Zhenjiang Affiliated Jiangsu University from January 2005 and September 2020 were selected. Chronic HBV infection was defined as continuous positive serum hepatitis B surface antigen (HBsAg) or HBV DNA results for more than 6 mo. The inclusion criterion was a follow-up time greater than 6 mo. The exclusion criteria were a history of excessive alcohol consumption (defined as alcohol intake ≥ 20 g/day for men and ≥ 10 g/day for women)[11], history of schistosomiasis of the liver, autoimmune hepatitis, primary biliary cirrhosis, malignancy, immunodeficiency virus infection, viral hepatitis C or D, long-term use of drugs that can cause hepatic steatosis (amiodarone, sodium valproate, tamoxifen, dexamethasone, or methotrexate), and incomplete clinical data. This study was approved by the ethics committee of The Third People's Hospital Affiliated to Zhenjiang, Jiangsu University. It was registered in the Chinese Clinical Trial Registry (No: chictr2200060304).

Data acquisition

The demographic data of patients (sex, age, height, and weight) were collected along with their clinical history (diabetes mellitus, hypertension, drug use history, drinking history); antiviral treatment; blood routine, biochemistry, and serological examination of hepatitis B pathogen. Other data collected were tumor index results during liver biopsy, including total bilirubin, albumin, prealbumin (PB), alanine aminotransferase (ALT), aspartate aminotransferase, γ-glutamyl transferase, alkaline phosphatase (ALP), fasting blood glucose (GLU), total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein, platelets (PLT), HBsAg, HBeAg, HBV DNA level, alpha fetoprotein (AFP), other types of viral hepatitis indicators, human immunodeficiency virus antibody, and autoantibody test results. Body mass index (BMI) was calculated using each patient's height and weight with the following formula: BMI = weight (kg)/height (m)^2.

The calculation results were graded according to the Asian standard[12], in which overweight and obesity were defined as BMI ≥ 23 kg/m^2 and ≥ 25 kg/m^2, respectively. The detection limit of HBV-DNA was 500 IU/mL.

Pathological evaluation

All liver specimens were evaluated by experienced pathologists and scored according to the nonalcoholic steatohepatitis clinical research network[13] for hepatic steatosis (0-3), lobular inflammation (0-2), portal inflammation (0-3), and ballooning degeneration (0-1). The degree of fibrosis was divided into F0-4 stages according to the METAVIR evaluation system, and the F4 stage was defined as cirrhosis[14]. NAFLD occurs when more than 5% of hepatocytes with steatosis are present in a specimen. The activity score (NAS) of nonalcoholic fatty liver disease was calculated according to the scores of steatosis, lobular inflammation, and ballooning degeneration. NAS ≥ 5 indicates the presence of NASH[13].

Follow up and clinical outcome judgment

The start time of follow-up was the date when the patient underwent liver biopsy. The follow-up endpoint was the date of the last follow-up or the date of the occurrence of clinical outcomes (cirrhosis, HCC, or death). Follow-up of the entire cohort ended in August 2021. The electronic medical record was consulted to obtain the date of the last follow-up, test results (blood routine, HBV pathogen serology, liver function, blood lipids, AFP), and imaging results. The treatment of patients with an interval of more than 6 mo between the last follow-up date and the research deadline (telephone follow-up, regular follow-up) is recommended, and the clinical outcome of those who do not wish to follow up is determined according to the last follow-up record. If there was an out-of-hospital follow-up, the out-of-hospital examination results were obtained, and if there was a death, the time and cause of death were obtained. Those who did not have contact information or could not be contacted were regarded as being lost to follow-up.

The diagnosis of cirrhosis was made by experienced sonographers according to the ultrasound diagnostic criteria of cirrhosis, and computed tomography and magnetic resonance imaging were applied when necessary.

The diagnosis of HCC was based on histological or imaging findings, and the latter was positive lesions detected by at least two imaging techniques (ultrasound, computed tomography, or magnetic

resonance imaging), or the use of imaging technology combined with AFP > 400 ng/mL.

Statistical analysis

The data were analyzed using SPSS version 22.0 (SPSS Inc., Chicago, IL, United States). Continuous variables are expressed as mean ± SD or median (interquartile range), and categorical variables are expressed as percentages. *T*-test was applied when continuous variables were normally distributed, and the Mann–Whitney *U* test was used when they were non-normally distributed. Categorical variables were analyzed using the chi-squared test. Kaplan-Meier (K-M) survival analysis was used to evaluate clinical events, and Cox proportional hazards regression was applied for univariate and multivariate analyses. This study also used 1:1 propensity score matching (PSM) to match the NAFLD and non-NAFLD groups, and the caliper value was set to 0.01. All tests were two-tailed, and statistical significance was set at *P* < 0.05.

RESULTS

Study population

A total of 981 patients with chronic HBV infection underwent liver biopsy at The Third People's Hospital of Zhenjiang between January 2005 and September 2020. After screening based on the inclusion and exclusion criteria, 456 patients were included in the final study, 67 of whom had histologically confirmed cirrhosis at baseline. Figure 1 shows the specific process.

Baseline features

Basic information of the general population: The total number of study patients was 456; of these patients, 152 (33.3%) had histologically confirmed NAFLD. The median follow-up time of the entire cohort was 70.5 mo. The average age of the population was 41 years and 45.1% were female. Regarding BMI, 43% had a normal BMI, 27.9% were overweight (BMI ≥ 23 kg/m^2, < 25 kg/m^2), and 29.2% were obese (BMI > 25 kg/m^2). There were 42 patients with diabetes and 38 with hypertension, accounting for 9.2% and 8.3% of all patients, respectively. Most of the patients (72.4%) received antiviral therapy. At baseline, 358 patients were HBV DNA positive, with a median detection value of 3.63×10^4 ($10^{4.56}$) IU/mL, while in 98 (21.5%) patients the HBV DNA level was below the detection limit. Among all HBV-infected patients, 66% were HBeAg-negative. Table 1 shows the basic information of the total population.

Comparison of baseline data of chronic HBV infection with and without NAFLD: There were 152 patients with chronic HBV infection complicated by NAFLD and 304 patients without NAFLD. Table 2 shows the demographic and main clinical indicators of the two groups. The proportion of female patients in the NAFLD group was higher than that in the NAFLD group (*P* < 0.05), and the median follow-up time was longer than that in the NAFLD group (73 *vs* 63 mo, *P* < 0.05). Compared with the non-NAFLD group, the NAFLD group had a higher prevalence of diabetes and higher BMI (*P* < 0.001), and its LDL, TG, PB, ALT levels were also significantly higher (*P* < 0.05). However, there were no differences in age, prevalence of hypertension, proportion of liver cirrhosis, HBV DNA, and other indicators (*P* > 0.05).

Comparison of clinical characteristics of patients with chronic HBV infection without cirrhosis at baseline with NAFLD and those without NAFLD: Taking patients without cirrhosis at the time of liver biopsy as the research object, the demographic and main clinical indicators of the NAFLD and non-NAFLD groups were compared (Table 3). There were significant differences in sex, BMI, prevalence of diabetes, follow-up duration, HBV DNA, ALT, TC, TG, LDL, and other indicators between the two groups (all *P* < 0.05). However, there was no difference in the antiviral status and other indicators (*P* > 0.05). The prevalence of diabetes, follow-up duration, and ALT levels in the two groups were 1:1 PSM. There were 109 patients in the NAFLD and non-NAFLD groups. After PSM, there were no significant differences in sex, diabetes prevalence, follow-up duration, HBV DNA, ALT, and other indicators between the two groups (*P* > 0.05); however, there were differences in BMI, PA, and TG (*P* < 0.05). Moreover, the NAFLD group was divided into the NASH (21 cases) and non-NASH (88 cases) groups.

Comparison of the pathological characteristics of chronic HBV infection with and without NAFLD: Among patients with NAFLD, 58.6% had mild hepatic steatosis, 31.6% had moderate hepatic steatosis, and 9.9% had severe hepatic steatosis. Differences were observed between the NAFLD group and non-NAFLD group in the degree of liver fibrosis, portal inflammation, and NAS score (*P* < 0.05). There was no difference in lobular inflammation or ballooning deformation (BD) between the two groups (*P* > 0.05) (Table 4).

Antiviral conditions

There was no significant difference in the proportion of patients receiving antiviral treatment, types of antiviral drugs, and duration of antiviral treatment between the NAFLD group and non-NAFLD group

Table 1 Basic information of total chronic hepatitis B (*n* = 456), *n* (%)	
Parameters	**Results**
Age (yr)	41.08 ± 10.41
Sex female	160 (45.1)
BMI (kg/m^2)	
< 23	196 (43.0)
23-25	127 (27.9)
≥ 25	133 (29.2)
Diabetes	42 (9.2)
Hypertension	38 (8.3)
NAFLD	152 (33.3)
Duration of follow-up (mo)	70.5 (29-133)
Antiviral therapy	330 (72.4)
HBV DNA (+), log$_{10}$ (IU/mL)	4.56 (3-6.92)
HBV DNA (-)[1]	98 (21.5)
HBeAg (-)	301 (66.0)

[1]Hepatitis B virus DNA (-): < 500 IU/mL.

NAFLD: Nonalcoholic fatty liver disease; BMI: Body mass index; HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen.

(P > 0.05). At the last follow-up, 302 (91.2%) patients who received antiviral therapy were HBV DNA-negative, including 102 (78.9%) in the NAFLD group and 200 (93%) in the non-NAFLD group. There was no significant difference in the proportion of HBV DNA negativity between the two groups (P > 0.05). A total of 275 (83.1%) patients had normal ALT levels: 90 (77.6%) in the NAFLD group and 185 (56%) in the NAFLD group. There was no significant difference in the proportion of normal ALT levels between the two groups (P = 0.05) (Table 5).

Risk of cirrhosis in patients with chronic HBV infection

Occurrence of cirrhosis: Patients without cirrhosis at the time of liver biopsy were selected as research participants, and the risk of progression to cirrhosis was observed. During the follow-up period, 34 patients developed liver cirrhosis diagnosed by ultrasound, with a median follow-up time of 72 (30-134) mo, including 10 (7.8%) in the NAFLD group and 24 (9.2%) in the NAFLD group. This study was conducted during the follow-up period.

K-M survival analysis of NAFLD and the risk of cirrhosis: The results of the K-M survival analysis showed that there was no significant increase in the risk of liver cirrhosis diagnosed using ultrasound in the combined NAFLD group before and after PSM (log-rank, P = 0.69). The results of the K-M survival analysis after PSM are shown in Figure 2A. F0, 1, 2 was regarded as mild fibrosis, while F3, 4 was regarded as severe fibrosis. Patients with fibrosis after PSM had an increased risk of cirrhosis diagnosed using ultrasound (log rank, P < 0.05). The results of K-M survival analysis after matching are shown in Figure 2B. Figure before PSM. In the NAFLD group, three out of 21 cases in the NASH group and seven out of 88 patients in the non-NASH group developed cirrhosis. The results of K-M survival analysis after PSM are shown in Figure 2C. There was no statistical difference between the two groups (P = 0.17).

Univariate and multivariate Cox regression analysis of cirrhosis: Cox regression univariate analysis showed that age, antiviral duration, lobular inflammation, BD, liver fibrosis, ALP, LDL, and PLT were related to cirrhosis (P < 0.05). Multivariate analysis showed that age, ballooning degeneration, liver fibrosis, and PLT were independent risk factors for cirrhosis diagnosed using ultrasound (all P < 0.05) (Table 6).

Univariate and multivariate Cox regression analysis of cirrhosis after PSM: Cox regression univariate analysis showed that age, hypertension, diabetes mellitus, lobular inflammation, portal inflammation, liver fibrosis, ALT, and PLT were related to cirrhosis diagnosed using ultrasound (P < 0.1). Multivariate analysis showed that diabetes mellitus, BD, and PLT were independent risk factors for liver cirrhosis diagnosed using ultrasound (P < 0.05) (Table 7).

Table 2 Comparison of baseline characteristics of chronic hepatitis B patients with and without nonalcoholic fatty liver disease, *n* (%)

Parameters	NAFLD	No NAFLD	P value
	n = 152	*n* = 304	
Age (yr)	41.87 ± 9.44	40.69 ± 10.85	0.24
< 40	67 (44.1)	141 (46.4)	0.64
40-60	77 (50.7)	148 (48.7)	
≥ 60	8 (5.3)	15 (4.9)	
Sex female	41 (27)	119 (39.1)	0.01
BMI (kg/m^2)			< 0.001
< 23	31 (20.4)	165 (54.3)	
23-25	49 (32.2)	78 (25.7)	
≥ 25	72 (47.4)	61 (20.1)	
Diabetes	27 (17.8)	15 (4.9)	< 0.001
Hypertension	18 (11.8)	20 (6.6)	0.07
Cirrhosis	24 (15.8)	43 (14.1)	0.64
Duration of follow-up (mo)	71 (27-118)	73 (32-114)	0.08
HBV DNA (IU/mL)			0.08
< 500 IU/mL	29 (19.1)	69 (22.7)	
< 4 log10	21 (13.8)	60 (19.7)	
≥ 4 log10	102 (67.1)	175 (57.6)	
HBeAg (-)	91 (59.9)	210 (69.1)	0.05
TBil (μmol/L)	15.69 ± 9.06	15.91 ± 9.1	0.8
ALB (g/L)	44.22 ± 3.42	43.62 ± 3.81	0.1
PB (mg/L)	241.53 ± 67.19	224.74 ± 73.69	0.02
ALT (U/L)	85 (32-275)	77 (26-263)	0.002
≤ 40	67 (44.1)	172 (56.6)	0.012
> 40	85 (55.9)	132 (43.4)	
AST (U/L)	76 (27-248)	83 (26.5-247)	0.28
ALP (U/L)	84.7 ± 26.3	83.92 ± 31.68	0.8
GGT (U/L)	40.88 ± 36.95	36.31 ± 38.17	0.23
GLU (mmol/L)	5.48 ± 1.07	5.34 ± 1.02	0.2
TC (mmol/L)	4.32 ± 0.88	4.17 ± 0.71	0.08
TG (mmol/L)	1.54 ± 1.04	1.23 ± 0.5	0.001
LDL (mmol/L)	2.7 ± 0.68	2.56 ± 0.7	0.049
HDL (mmol/L)	1.32 ± 0.4	1.35 ± 0.31	0.27
PLT (× 10^9/L)	167.05 ± 54.18	159.13 ± 56.02	0.15
AFP (ng/mL)	3.25 (2.15-5.83)	2.93 (2.03-5.81)	0.33

NAFLD: Nonalcoholic fatty liver disease; BMI: Body mass index; TBil: Total bilirubin; ALB: Albumin; PB: Prealbumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ-glutamyl transferase; ALP: Alkaline phosphatase; GLU: Fasting blood glucose; TC: Total cholesterol; TG: Triglyceride; LDL: Low density lipoprotein; HDL: High density lipoprotein; PLT: Platelet; AFP: Alpha-fetoprotein; HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen.

Risk of HCC in patients with chronic HBV infection

Characteristics of patients with HCC: During the follow-up period, 10 patients (2.2%) developed HCC (Table 7), and two died (one died due to HCC and the cause of death in the other case was not related to

Table 3 Comparison of baseline characteristics of chronic hepatitis B patients (without cirrhosis) with and without nonalcoholic fatty liver disease, *n* (%)

Parameters	*P* values before PSM	PSM		*P* value
		NAFLD	No NAFLD	
		(*n* = 109)	(*n* = 109)	
Age (yr)	0.58			0.63
< 40		52 (47.7)	47 (43.1)	
40-60		51 (46.8)	58 (53.2)	
≥ 60		6 (5.5)	4 (3.7)	
Sex female	< 0.05	29 (26.6)	37 (33.9)	0.24
BMI (kg/m^2)	< 0.05			< 0.05
< 23		21 (19.3)	58 (53.2)	
23-25		35 (32.1)	30 (27.5)	
≥ 25		53 (48.6)	21 (19.3)	
Diabetes	< 0.05	4 (3.7)	4 (3.7)	1
Hypertension	0.07	12 (11)	6 (5.5)	0.14
Duration of follow-up (mo)	< 0.05	71 (28-119.5)	52 (25-111)	0.3
Antiviral drugs	0.59			0.3
Entecavir		49 (61.3)	56 (71.8)	
Tenofovir		26 (32.5)	19 (24.4)	
Other		5 (6.3)	3 (3.8)	
Antiviral duration	0.48			0.46
Never		29 (26.6)	31 (28.4)	
< 5 yr		50 (45.9)	54 (49.5)	
≥ 5 yr		30 (27.5)	24 (22)	
HBV DNA (IU/mL)	< 0.05			0.06
< 500 IU/mL		18 (19.3)	24 (22)	
< 4 log10		13 (32.1)	21 (19.3)	
≥ 4 log10		78 (48.6)	64 (58.7)	
HBeAg (-)	0.12	65 (59.6)	75 (68.8)	0.16
TBil (μmol/L)	0.94	15.73 ± 7.17	14.25 ± 5.73	0.09
ALB (g/L)	0.21	44.15 ± 3.32	44.29 ± 3.78	0.78
PB (mg/L)	0.28	243.24 ± 65.74	225.67 ± 62.19	< 0.05
ALT (U/L)	< 0.05			0.89
≤ 40		43 (19.3)	44 (40.4)	
> 40		66 (32.1)	65 (59.6)	
AST (U/L)	0.16	36 (27.5-49.5)	37 (26.5-50)	0.95
ALP (U/L)	0.1	85.55 ± 26.37	82.82 ± 22.08	0.41
GGT (U/L)	0.12	37.44 ± 25.34	34.76 ± 33.13	0.5
GLU (mmol/L)	0.06	5.25 ± 0.68	5.41 ± 0.89	0.15
TC (mmol/L)	< 0.05	4.37 ± 0.88	4.22 ± 0.64	0.16
TG (mmol/L)	< 0.05	1.47 ± 0.75	1.22 ± 0.51	< 0.05
LDL (mmol/L)	< 0.05	2.77 ± 0.65	2.62 ± 0.61	0.09

HDL (mmol/L)	0.38	1.31 ± 0.36	1.32 ± 0.3	0.82
PLT (× 10^9/L)	0.12	174.29 ± 51.81	162.83 ± 47.49	0.09
AFP (ng/mL)	0.29	3.1 (2.1-5.3)	2.9 (2.1-5.5)	0.74
NASH		15 (13.7)		

PSM: Propensity score matching; BMI: Body mass index; TBil: Total bilirubin; ALB: Albumin; PB: Prealbumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ-glutamyl transferase; ALP: Alkaline phosphatase; GLU: Fasting blood glucose; TC: Total cholesterol; TG: Triglyceride; LDL: Low density lipoprotein; HDL: High density lipoprotein; PLT: Platelet; AFP: Alpha-fetoprotein; NASH: Nonalcoholic steatohepatitis; HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen.

Table 4 Comparison of pathological features of chronic hepatitis B patients with and without nonalcoholic fatty liver disease, *n* (%)

| Pathological features	Total (*n* = 456)	NAFLD (*n* = 152)	No NAFLD (*n* = 304)	*P* value
Fibrosis				0.045
F0	109 (23.9)	30 (19.7)	79 (26)	
F1	129 (28.3)	36 (23.7)	93 (30.6)	
F2	93 (20.4)	41 (27)	52 (17.1)	
F3	58 (12.7)	21 (13.8)	37 (12.2)	
F4	67 (14.7)	24 (15.8)	43 (14.1)	
Steatosis				
0	304 (66.7)		304 (100)	
1	89 (19.5)	89 (58.6)		
2	48 (10.5)	48 (31.6)		
3	15 (3.3)	15 (9.9)		
Portal tract inflammation				< 0.001
0	35 (7.7)	8 (5.3)	27 (8.9)	
1	275 (60.3)	79 (52)	196 (64.5)	
2	117 (25.7)	50 (32.9)	67 (22)	
3	29 (6.3)	15 (9.9)	14 (4.6)	
Lobular inflammation				0.13
0	91 (20)	28 (18.4)	63 (20.7)	
1	315 (69.1)	101 (66.4)	214 (70.4)	
2	50 (11)	23 (15.1)	27 (8.9)	
Ballooning degeneration				0.004
0	153 (33.6)	58 (38.2)	165 (54.3)	
1	195 (42.8)	61 (40.1)	96 (31.6)	
2	108 (23.7)	33 (21.7)	43 (14.1)	
NASH	32 (21.1)	32 (21.1)		
NAS score	1.7 ± 1.2	2.7 ± 1.2	1.2 ± 0.8	< 0.001

NASH: Nonalcoholic steatohepatitis; NAS: Activity score of nonalcoholic fatty liver disease; NAFLD: Nonalcoholic fatty liver disease.

liver disease). The median time interval between liver biopsy and HCC diagnosis was 100.5 mo (68.5-128.0). HCC occurred in six patients (3.3%) with NAFLD and four patients (1.6%) without NAFLD. Seven patients developed cirrhosis at the time of liver biopsy, and one of the other three developed cirrhosis before HCC.

Table 5 Comparison of antiviral data of chronic hepatitis B virus infection with and without nonalcoholic fatty liver disease, *n* (%)

Parameters	NAFLD	No NAFLD	*P* value
	(*n* = 152)	(*n* = 304)	
Antiviral	116 (76.3)	215 (70.7)	0.21
Antiviral drugs			0.5
Entecavir	73 (62.9)	131 (60.9)	
Tenofovir	35 (30.2)	68 (31.6)	
Others	8 (6.9)	16 (7.4)	
Antivirus duration			0.31
< 5 yr	70 (46.1)	129 (42.4)	
≥ 5 yr	46 (30.3)	86 (28.3)	

NAFLD: Nonalcoholic fatty liver disease.

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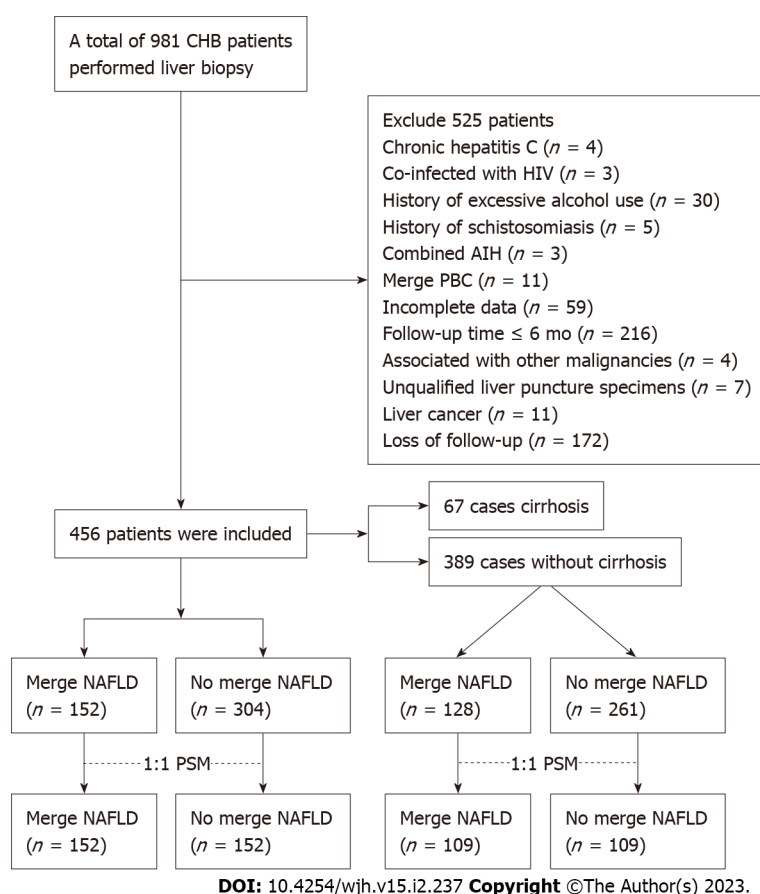
Figure 1 Flow chart of patient screening and grouping. CHB: Chronic hepatitis B; NAFLD: Nonalcoholic fatty liver disease; HIV: Human immunodeficiency virus; AIH: Autoimmune hepatitis; PBC: Primary biliary cholangitis.

K-M survival analysis of HCC risk: Patients with baseline cirrhosis were included in the K-M survival analysis of HCC risk. It was found that the cumulative risk of HCC in the NAFLD group was significantly higher than that in the non-NAFLD group (log rank, *P* = 0.02) (Figure 3A). At the same time, the risk of HCC in patients with severe liver fibrosis (F3-4) was also significantly increased (log rank, *P* = 0.005) (Figure 3B). When the NAFLD group was divided into the NASH group with 32 patients (3 HCCs) and the non-NASH group with 120 patients (3 HCCs), the risk of HCC in the NASH group was increased (log rank, *P* = 0.03) (Figure 3C), and the risk of HCC in patients with hepatic ballooning was significantly increased (log rank, *P* = 0.01) (Figure 3D). There was no significant difference in the risk of HCC among patients with steatosis, lobulitis, and portal inflammation (log rank,

Table 6 Univariate and multivariate Cox regression analysis of cirrhosis

Parameters	Univariate HR (95%CI)	*P* value	Multivariate HR (95%CI)	*P* value
Clinical factors				
Sex	1.36 (0.63-2.92)	0.43		
Age (yr)	1.08 (1.04-1.12)	< 0.001	1.06 (1.02-1.10)	0.003
BMI (kg/m²)	0.96 (0.64-1.45)	0.86		
Diabetes	2.57 (0.78-8.52)	0.12		
Hypertension	2.71 (0.95-7.76)	0.06		
Duration of antiviral (≥ 5 yr/never or < 5 yr)	1.65 (1.07-2.54)	0.02	1.32 (0.84-2.06)	0.23
Pathological factors				
NAFLD	1.12 (0.53-2.37)	0.76		
NASH	1.38 (0.33-5.86)	0.66		
Lobular inflammation	2.35 (1.19-4.66)	0.01	0.77 (0.33-1.80)	0.54
Portal tract inflammation	1.40 (0.90-2.20)	0.14		
Ballooning degeneration	3.34 (1.65-6.75)	0.001	2.57 (1.05-6.28)	0.04
Fibrosis	1.49 (1.08-2.06)	0.02	1.39 (1.04-1.87)	0.028
Laboratory examination				
TBil (μmol/L)	0.99 (0.95-1.04)	0.8		
ALB (g/L)	0.94 (0.85-1.04)	0.25		
PB (mg/L)	1.00 (0.997-1.00)	0.83		
ALT (> 40/≤ 40U/L)	1.00 (0.996-1.00)	0.64		
AST (U/L)	1.00 (0.99-1.01)	0.54		
ALP (U/L)	1.01 (1.00-1.02)	0.008	1.01 (1.00-1.02)	0.08
GGT (U/L)	1.01 (1.00-1.01)	0.13		
GLU (mmol/L)	1.31 (0.96-1.78)	0.09		
TG (mmol/L)	0.57 (0.28-1.18)	0.13		
TC (mmol/L)	0.95 (0.61-1.49)	0.83		
HDL (mmol/L)	1.71 (0.65-4.49)	0.28		
LDL (mmol/L)	0.46 (0.27-0.79)	0.005	0.76 (0.45-1.29)	0.31
PLT (× 10⁹/L)	0.99 (0.98-0.99)	0.001	0.98 (0.97-0.99)	0.001
AFP (ng/mL)	0.99 (0.96-1.03)	0.63		
HBeAg (-)	0.91 (0.43-1.90)	0.79		
HBV DNA (≥ 4 log IU/mL)	0.82 (0.55-1.23)	0.34		

BMI: Body mass index; TBil: Total bilirubin; ALB: Albumin; PB: Prealbumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ-glutamyl transferase; ALP: Alkaline phosphatase; GLU: Fasting blood glucose; TC: Total cholesterol; TG: Triglyceride; LDL: Low density lipoprotein; HDL: High density lipoprotein; PLT: Platelet; AFP: Alpha-fetoprotein; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen.

P > 0.05) (figures ignored).

Univariate and multivariate Cox regression analysis of HCC: Cox regression univariate analysis showed that diabetes mellitus, NAFLD, NASH, lobular inflammation, BD, liver fibrosis, GLU, TC, TG, and PLT were correlated with HCC (all *P* < 0.05). Multivariate analysis of factors with *P* < 0.10 in the Cox regression univariate analysis showed that ballooning, liver fibrosis, and diabetes were

Table 7 Univariate and multivariate Cox regression analysis of cirrhosis after propensity score matching

Parameters	Univariate		Multivariate	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age (yr)	1.06 (1.01-1.11)	0.02	1.05 (0.99-1.11)	0.11
Hypertension	3.26 (0.89-11.90)	0.07	0.59 (0.12-2.97)	0.52
Diabetes	6.74 (0.77-58.81)	0.08	12.21 (1.1-134.4)	0.04
Lobular inflammation	2.63 (1.02-6.82)	0.046	1.20 (0.26-5.57)	0.82
Ballooning degeneration	4.33 (1.01-5.15)	0.006	1.80 (0.86-4.48)	0.02
Portal tract inflammation	2.37 (1.18-4.75)	0.02	72.61 (2.16-2436)	0.48
Fibrosis	1.57 (0.96-2.56)	0.07	1.03 (0.48-2.25)	0.93
ALT(U/L)	1.00 (1.00-1.01)	0.06	1.00 (0.99-1.01)	0.26
PLT ($\times 10^9$/L)	0.98 (0.96-0.99)	< 0.001	0.98 (0.96-0.99)	0.001

ALT: Alanine aminotransferase; PLT: Platelet.
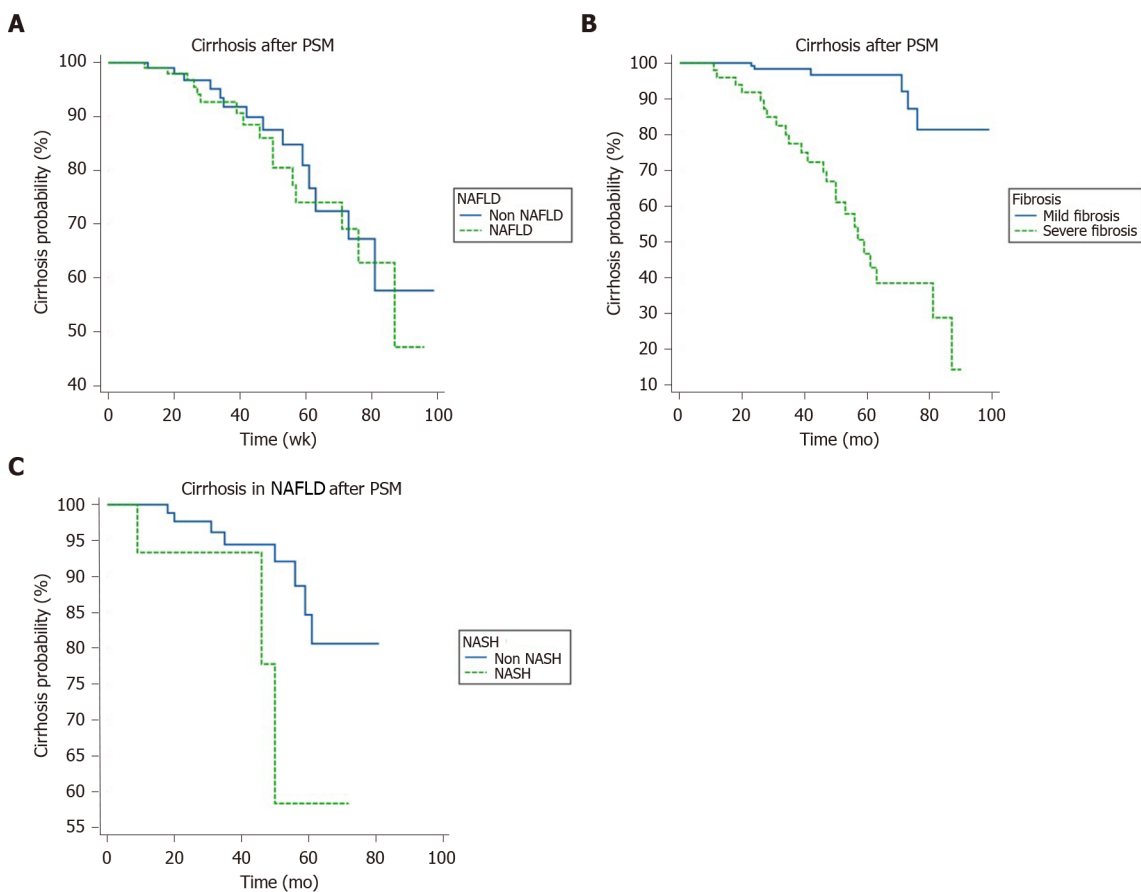
DOI: 10.4254/wjh.v15.i2.237 **Copyright** ©The Author(s) 2023.

Figure 2 Kaplan-Meier survival analysis of nonalcoholic fatty liver disease and the risk of cirrhosis. A: Results of the Kaplan-Meier (K-M) survival analysis of the risk of cirrhosis after propensity score matching (PSM) in nonalcoholic fatty liver disease (NAFLD) and non NAFLD with chronic hepatitis B; B: Results of K-M survival analysis of the risk of cirrhosis after PSM in patients with mild fibrosis and in those with severe fibrosis; C: Nonalcoholic steatohepatitis (NASH) and non-NASH stratification of NAFLD and K-M survival analysis of the risk of cirrhosis. NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; PSM: Propensity score matching.

independent risk factors for HCC (Table 8).

Table 8 Univariate and multivariate Cox regression analysis of hepatocellular carcinoma occurrence

Parameters	Univariate	P value	Multivariate	P value
	HR (95%CI)		HR (95%CI)	
Clinical factors				
Sex	40.03 (0.17-9369.3)	0.19		
Age (yr)	1.06 (0.99-1.13)	0.054	0.29 (0.03-2.50)	0.26
BMI (kg/m^2)	0.97 (0.78-1.21)	0.8		
Diabetes	14.36 (4.01-51.47)	< 0.001	34.8 (2.27-534.1)	0.01
Hypertension	1.99 (0.25-15.71)	0.52		
Antivirus duration (≥ 5 yr, never or < 5 yr)	1.32 (0.38-4.56)	0.66		
Pathological factors				
NAFLD (steatosis ≥ 5%)	4.29 (1.20-15.41)	0.025	2.28 (0.44-11.69)	0.33
NASH	4.36 (1.35-24.80)	0.002	0.53 (0.01-1.84)	0.39
Lobular inflammation	7.2 (2.16-23.91)	0.001	5.16 (0.53-49.96)	0.16
Portal tract inflammation	2.02 (0.98-4.15)	0.056	0.49 (0.31-1.85)	0.29
Ballooning degeneration	8.69 (1.57-29.64)	0.008	5.16 (0.83-19.96)	0.03
Fibrosis stage	14.25 (13.68-55.14)	< 0.001	8.37 (1.39-50.44)	0.02
Laboratory examination				
TBil (μmol/L)	1.02 (0.97-1.09)	0.37		
PB (mg/L)	0.998 (0.99-1.01)	0.64		
LB (g/L)	0.97 (0.82-1.14)	0.69		
ALT (> 40/≤ 40 U/L)	0.999 (0.99-1.01)	0.71		
AST (U/L)	0.999 (0.98-1.01)	0.89		
ALP (U/L)	1.01 (0.99-1.03)	0.42		
GGT (U/L)	0.99 (0.96-1.02)	0.46		
GLU (mmol/L)	1.45 (1.08-1.94)	0.01	0.64 (0.37-1.12)	0.12
TG (mmol/L)	0.18 (0.04-0.92)	0.04	0.085 (0.004-1.7)	0.11
TC (mmol/L)	0.36 (0.15-0.85)	0.02	0.39 (0.15-1.01)	0.053
HDL (mmol/L)	0.39 (0.04-3.67)	0.41		
LDL (mmol/L)	0.47 (0.18-1.26)	0.13		
PLT (× 10^9/L)	0.97 (0.96-0.99)	0.004	0.99 (0.97-1.01)	0.26
AFP (ng/mL)	0.99 (0.91-1.07)	0.77		
HBeAg (-) (%)	1.43 (0.40-5.08)	0.58		
HBV DNA (≥ 4 log IU/mL)	1.49 (0.39-5.77)	0.56		

BMI: Body mass index; TBil: Total bilirubin; ALB: Albumin; PB: Prealbumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ-glutamyl transferase; ALP: Alkaline phosphatase; GLU: Fasting blood glucose; TC: Total cholesterol; TG: Triglyceride; LDL: Low density lipoprotein; HDL: High density lipoprotein; PLT: Platelet; AFP: Alpha-fetoprotein; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen.

DISCUSSION

According to the WHO hepatitis report in 2017, 96% of the 1.3 million deaths caused by viral hepatitis worldwide in 2015 were caused by HBV and hepatitis C virus (HCV). In China, 70 million patients with HBV, accounting for 27% of the global population of patients with HBV[14]; furthermore, 68% (95%CI: 60-74) of patients with liver cirrhosis in China are infected with HBV[15]. With the increasing prevalence of obesity and metabolic syndrome, NAFLD has become the most common cause of chronic liver
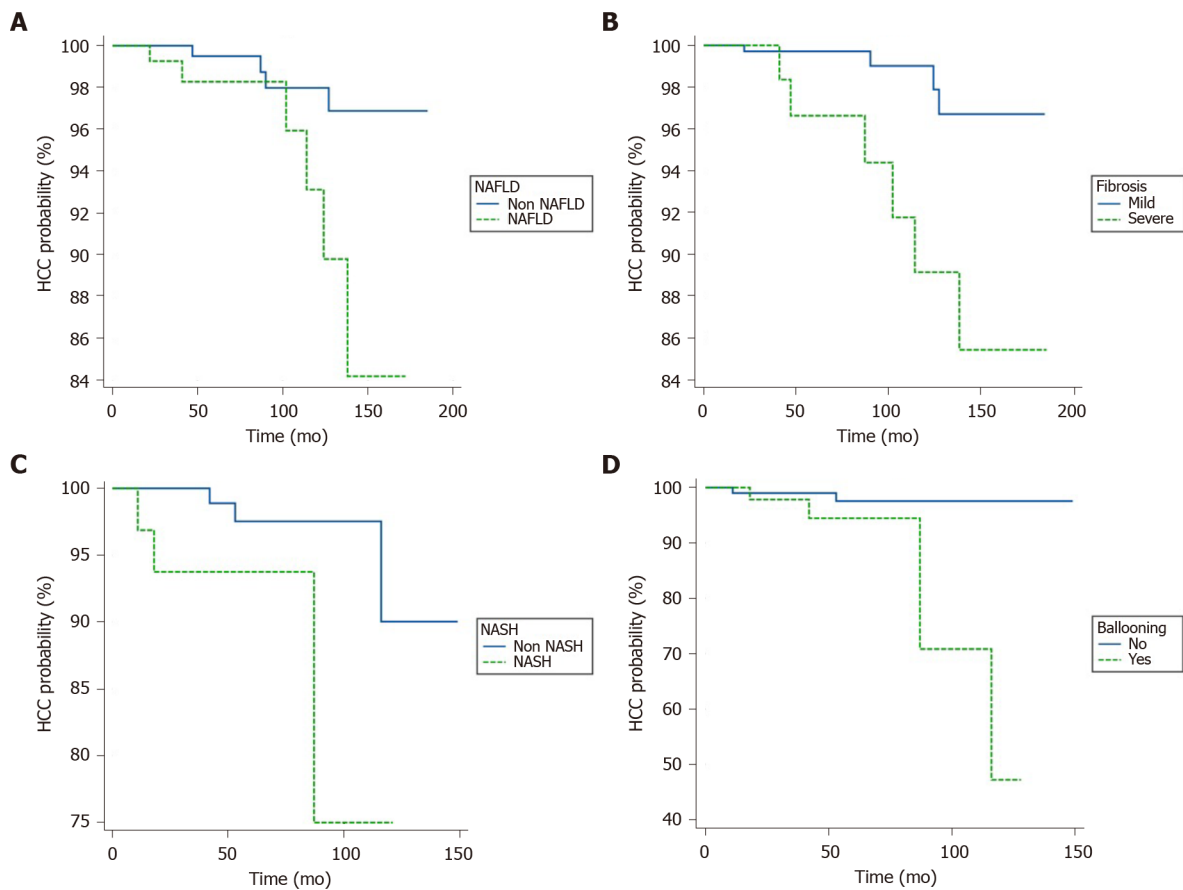
Figure 3 Kaplan-Meier survival analysis of hepatocellular carcinoma risk. A: Results of the Kaplan-Meier (K-M) survival analysis of the risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B and nonalcoholic fatty liver disease (NAFLD) and those without NAFLD; B: Results of K-M survival analysis of the risk of HCC in patients with mild fibrosis and those with severe fibrosis; C: Nonalcoholic steatohepatitis (NASH) and non-NASH stratification of NAFLD and K-M survival analysis of the risk of HCC; D: Ballooning and non-ballooning stratification of NAFLD and K-M survival analysis of the risk of HCC. NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; HCC: Hepatocellular carcinoma.

disease worldwide[14]. Therefore, these two liver diseases are often observed, and with the increasing prevalence of NAFLD, the number of patients with combined NAFLD and HBV infections is also on the increase. Studies have reported that the prevalence of NAFLD, confirmed by biopsy in patients with CHB, ranges from 14% to 52%[5,16-22]. The prevalence of NAFLD in this study was 33.3%, which was also within this range.

NAFLD is associated with metabolic syndrome, and this was also reflected in our study. Compared with those without NAFLD, chronic HBV-infected patients with NAFLD have a higher prevalence of diabetes and BMI, and their low-density lipoprotein, triglyceride, and apolipoprotein B levels were also significantly higher. With the aggravation of hepatic steatosis, the proportion of overweight and obese patients and the average BMI gradually increased. Studies have shown that metabolic syndrome can delay the serum clearance of HBeAg, increase the risk of liver fibrosis and cirrhosis, and thus enhance the development of HCC[8,23,24]. Considering that NAFLD is the main hepatic manifestation of obesity and metabolism-related diseases, chronic HBV infection overlapping with NAFLD may further increase the risk of cirrhosis and HCC. NAFLD is not associated with an increased risk of cirrhosis in patients with chronic HBV infection. After propensity matching for follow-up duration, diabetes mellitus, and ALT, there was no difference in diabetes mellitus and most variables between the two groups, while multivariate analysis still showed that diabetes mellitus was an independent risk factor for the occurrence of liver cirrhosis diagnosed using ultrasound.

In addition, NAFLD, obesity, and hyperlipidemia have been found to be associated with accelerated clearance of HBsAg and lower HBV DNA in many clinical studies[9,15,25]. In our study, it was not found that combined NAFLD was associated with decreased HBV DNA levels, both at baseline and at the last follow-up. However, in the cohort of patients without cirrhosis, we found that the proportion of high-level HBV DNA in the combined NAFLD group was lower than that in the non NAFLD group, although the difference between the two groups was not statistically significant after matching, and the comparison was not stratified by antiviral treatment, age, *etc.* However, NAFLD and CHB can jointly aggravate liver injury, and increase the risk of liver cirrhosis and liver cancer[3-7,26].

In this study, 72.4% of patients received antiviral therapy, mainly nucleoside analogs; moreover, the 2017 European Association for the Study of the Liver Guidelines proposed long-term inhibition of HBV DNA as the primary endpoint of chronic hepatitis B treatment[27]. Previously, with the development and clinical application of NAs antiviral drugs, HBV replication was effectively controlled[28-31]. In our study, 91.2% of patients with CHB who received antiviral therapy achieved HBV DNA negativity. However, no significant difference was observed in HBV DNA negativity between the NAFLD and non-NAFLD groups. In addition, 83.1% of the patients had normal ALT levels, and there was no significant difference in the normal ALT levels between the two groups. There are conflicting results regarding whether NAFLD affects the efficacy of antiviral therapy in patients with CHB. A recent meta-analysis showed that the efficacy of antiviral therapy decreases in CHB patients with hepatic steatosis[32]. There were significant differences in virological and biochemical reactions between the subgroups with and that without NAFLD, which may be due to the decreased bioavailability of antiviral drugs caused by fat changes, resulting in a significant reduction in the contact area between hepatocytes and antiviral drugs [32]. However, some studies have failed to find an association between hepatic steatosis and the efficacy of antiviral therapy[20,32-35]. Although the impact of hepatic steatosis on antiviral therapy in these patients remains controversial, it is still recommended to monitor the onset or progression of NAFLD during antiviral therapy to prevent potential negative effects.

In recent years, the proportion of patients with cirrhosis caused by NAFLD has increased rapidly. In particular, NASH, defined as the simultaneous presence of steatosis and inflammatory injury in the liver, with or without liver fibrosis[36,37], is an independent risk factor for the development of cirrhosis [38]. Several retrospective studies with long-term follow-up have found that the unadjusted cumulative probability of liver-related events was significantly higher in patients with NASH than in those without NASH[39,40]. A comprehensive analysis of six studies showed that in 41% of patients with NASH fibrosis progressed, with an average annual growth rate of 0.09%[43]; moreover, the progression of fibrosis can lead to the development of cirrhosis and cause other liver-related diseases, such as HCC. The annual incidence of HCC in patients with NASH is 5.29/1000 person years[36,41]. These findings further prove that the risk of HCC in patients with CHB infection complicated by NASH is significantly increased. In our study, NASH did not increase the risk of cirrhosis, but increased the risk of HCC. Furthermore, we observed that the key factor for NASH was ballooning. Ballooning and fibrosis are pre-PSM cirrhosis and HCC risk factors, whereas post-PSM ballooning is still a risk factor for cirrhosis. A previous large-scale cohort study included 1089 cases of NAFLD confirmed by biopsy in North American and European multiethnic CHB populations. After a median follow-up of 10 years, there was no obvious correlation between CHB combined with NAFLD and the risk of liver-related adverse events (cirrhosis or liver cancer), while CHB combined with NASH still led to a higher risk of liver-related adverse events, but was only significant in the population with advanced liver fibrosis[4]. This large-scale study also pointed out that ballooning degeneration and inflammation were important liver-related adverse events, but steatosis was not related to clinical events[4]. This result supports the conclusion of the present study that the combination of NASH will increase the risk of adverse events in patients with chronic HBV infection. Histological determinants of NASH, such as ballooning and lobular inflammation, are important for liver-related adverse events (cirrhosis and HCC).

First, liver fibrosis and subsequent cirrhosis are generally considered to be the prelude to HCC, which is closely related to the occurrence of HCC[26]. Second, diabetes mellitus, blood glucose, and cholesterol, which are components of the metabolic syndrome, are also closely related to the occurrence of HCC. Previous studies have proposed that obesity, diabetes, and metabolic syndrome are independent risk factors for liver fibrosis, cirrhosis, and HCC in patients with chronic hepatitis B, suggesting that metabolic factors and chronic hepatitis B have a synergistic effect in the pathogenesis of liver cancer[23,24,42,43], and extreme obesity and diabetes increase the risk of developing HBV-related HCC by 12.8-fold[45]. A prospective study in Taiwan showed that a high BMI at baseline was associated with the incidence of cirrhosis and HCC[43]; however, the participants were all male patients with chronic HBV infection. In this study, the baseline BMI was not an independent risk factor for HCC occurrence; however, it may be related to different populations, diets, living habits, and grading standards for BMI. Moreover, this may be due to the complex relationship between BMI and HCC. HCC or cirrhosis as a prelude to HCC has an impact on the nutritional status of patients; moreover, nutritional deficiency and sarcopenia can reduce BMI. The impact of a high baseline BMI on the overall prognosis of patients with HCC has also been controversial: some studies have indicated that patients with a high BMI have a worse prognosis, other studies suggest that they may have a better prognosis, and some studies have indicated that there was no significant correlation between the two[44-46].

This study has some limitations. First, the sample size of this single-center retrospective study was reduced after the application of PSM. Because of the influence of the small sample size, we could not match all factors; hence, larger samples and more rigorous prospective studies are needed for further verification. Second, the conclusion of the study is that CHB combined with NAFLD has little effect on the final outcome of liver cirrhosis, which is inconsistent with the results of mainstream studies, and could be due to our short follow-up duration. The study cohort needs to be observed for a longer time, and the conclusion may change if this is done. Third, in the study, identifying adverse events after the diagnosis of liver cirrhosis relied on ultrasound, and ultrasound itself is subject to the subjective understanding of the ultrasonologists; hence, the diagnostic error could be large.

CONCLUSION

In summary, we conducted a long-term follow-up of a cohort of CHB patients with NAFLD based on a diagnosis of liver pathology, and observed that the PSM of baseline influencing factors revealed that the risk of cirrhosis diagnosed using ultrasound was not significantly higher in the group with NAFLD than in the group without NAFLD. Before PSM, age, BD, liver fibrosis, and PLT were independent risk factors for cirrhosis. After PSM, only BD and PLT were found to be independent risk factors for liver cirrhosis diagnosed using ultrasound. The cumulative risk of HCC was significantly higher in patients with NAFLD or NASH. BD, liver fibrosis, and diabetes mellitus were independent risk factors for HCC.

ARTICLE HIGHLIGHTS

Research background

Chronic hepatitis B (CHB) virus infection and nonalcoholic fatty liver disease (NAFLD) are important causes of liver-related complications and death. With the increasing prevalence of NAFLD, the number of patients with combined NAFLD and hepatitis B virus (HBV) infection is also on the increase.

Research motivation

This study aimed to further explore the impact of NAFLD and the pathological changes confirmed by liver pathology in patients with chronic HBV infection.

Research objectives

To study the effect of NAFLD confirmed using liver pathology on the outcomes of long-term serious adverse events in patients with CHB virus infection.

Research methods

Among 456 cases of chronic HBV infection, 152 were confirmed by liver histology to have NAFLD, and 304 were simple chronic HBV infection. The incidence of serious clinical events at the follow-up endpoint was compared by Kaplan-Meier (K-M) survival analysis at baseline using propensity score matching balance parameters.

Research results

After a median follow-up of 70.5 mo, there were 34 cases of ultrasound-diagnosed cirrhosis and 10 cases of HCC. K-M survival analysis showed no significant difference in the occurrence of CHB complicated with NAFLD cirrhosis, and the cumulative incidence of HCC in the NAFLD group was higher than that in the non-NAFLD group (log-rank test, $P < 0.05$). Hepatocyte ballooning and severe liver fibrosis were also associated with an increased risk of HCC (log-rank test, all $P < 0.05$).

Research conclusions

Baseline hepatocyte ballooning is a risk factor for adverse events in patients with CHB complicated with NAFLD.

Research perspectives

Larger samples and more rigorous prospective studies are needed for further verification. The study cohort needs to be observed for a longer time, and the conclusion may change if this is done, in the study.

FOOTNOTES

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