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Original Article

Prognostic Relevance of Metabolic Dysfunction-associated Steatohepatitis for Patients with Chronic Hepatitis B

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Abstract

Background and Aims: Metabolic dysfunction-associated fatty liver disease (MAFLD) is prevalent in patients with chronic hepatitis B (CHB). The effect of the histologic MAFLD phenotype on long-term CHB outcomes is unknown. We performed a longitudinal study to determine the prognostic relevance of biopsy-proven hepatic steatosis and steatohepatitis for CHB patients. ***Methods:*** Clinical and laboratory data were obtained from CHB patients who underwent liver biopsy during 2002–2008 and were treated with antiviral drugs. A hepatopathologist reviewed the biopsy specimens. Cox proportional hazards regression was used to estimate the adjusted hazard ratio (aHR) of outcomes, including all-cause mortality, liver transplantation, and liver-related events. ***Results:*** In accordance with Brunt's classification, 408 patients had steatohepatitis (*n*=34), "steatosis but not steatohepatitis" (*n*=118), or "non-steatosis" (*n*=256). All steatohepatitis patients had features of metabolic dysfunction. Over a mean follow-up of 13.8±3.1 years, 18 patients died or underwent liver transplantation. In multivariate-adjusted analysis, steatohepatitis (aHR, 6.37; 95% confidence interval [CI]: 1.59–25.5) compared with non-steatosis and advanced fibrosis (aHR, 11.3; 95% CI: 1.32–96.3) compared with no fibrosis were associated with overall mortality/liver transplantation. Thirty-five patients developed 43 liver-related events, among which 32 were hepatocellular carcinoma. These events were associated with steatohepatitis (aHR, 5.55; 95% CI: 2.01–15.3) compared with non-steatosis and advanced fibrosis (aHR, 6.23; 95% CI: 1.75–22.2) compared with no fibrosis. The steatosis but not steatohepatitis group had a non-significantly higher risk of overall mortality and liver-related events. ***Conclusions:*** Metabolic dysfunction-associated steatohepatitis increased the risk of long-term mortality/transplantation and liver-related events in CHB patients.

Keywords: Chronic hepatitis B; Steatohepatitis; Liver histology; Long-term prognosis.

Abbreviations: aHR, adjusted hazard ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CHB, chronic hepatitis B; CI, confidence interval; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD activity score.

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Introduction

Chronic hepatitis B virus (HBV) infection is a global public health problem affecting more than 250 million people who are at high risk of death from cirrhosis and liver cancer.[1] The goal of therapy for patients with chronic hepatitis B (CHB) is to improve survival by preventing disease progression to cirrhosis, liver decompensation, and hepatocellular carcinoma (HCC).[2–4] That can be achieved by eliminating HBV or through sustained suppression of viral replication using antiviral treatment. Metabolic dysfunction-associated fatty liver disease (MAFLD) has become more prevalent in patients with CHB owing to the growing prevalence of obesity.[5,6] The coexistence of CHB and MAFLD, particularly the histologic phenotype of steatohepatitis, can augment liver damage and increase the risk of liver fibrosis. That was supported by a histological study that revealed an association between steatohepatitis and advanced fibrosis in CHB patients.[7]

Metabolic syndrome and hepatic steatosis have been shown to increase the risk of fibrosis progression in patients with CHB receiving antiviral treatment.[8] A follow-up study of cirrhotic patients treated with tenofovir disoproxil fumarate for CHB showed that patients with concurrent fatty liver disease had a lower likelihood of fibrosis regression despite suppression of HBV.[9] Another prospective study demonstrated that a lower body mass index (BMI) was independently associated with fibrosis regression in CHB patients who achieved an undetectable HBV viral load during long-term therapy with nucleoside analogues.[10] Therefore, monitoring the development of unfavorable outcomes is recommended in this population. However, there are limited data on the impact of MAFLD on clinical outcomes (e.g., cirrhotic complications, HCC, and death) during comprehensive treatment for CHB. This cohort study aimed to determine the long-term effect of concurrent fatty liver disease, particularly a histologic phenotype of steatohepatitis on overall survival and liver-related com-

plications in patients with CHB receiving antiviral therapy to improve our understanding of the prognostic value of MAFLD in these patients.

Methods

Study cohort

We conducted a retrospective analysis of prospectively collected data from consecutive patients with chronic HBV infection who underwent a liver biopsy to determine the need for antiviral treatment between 2002 and 2008 at our institution. The study cohort included patients who had at least moderate necroinflammation and/or liver fibrosis stage 2 or higher in accordance with the METAVIR system and were treated with antiviral agents. Patients were excluded from analysis if they had hepatitis C virus or human immunodeficiency virus co-infection, alcohol dependence, less than 6 months of follow-up data in our clinic, no available liver histology for review, or intermittent or persistent HBV DNA >2000 IU/mL after stopping antiviral agents during follow-up.

Data acquisition

Extensive clinical and laboratory data were collected at the time of the liver biopsy. Clinical information included age, sex, any medications, BMI, and metabolic dysfunction in accordance with the international expert consensus statement for MAFLD.[6] All laboratory variables were obtained within 6 months of biopsy and included liver biochemistry, complete blood count, fasting glucose, lipid profile, HBV DNA levels, and viral serology: hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and antibodies against HBsAg and HBeAg.

Histopathology

All biopsies were stained with hematoxylin and eosin and Masson's trichrome. If the tissue stains had faded, stored paraffin-embedded tissue blocks were cut and restained. Liver biopsies were reviewed by a single experienced hepatopathologist (AP) who was blinded to the clinical information. The NASH Clinical Research Network scoring system for nonalcoholic fatty liver disease (NAFLD) was used to grade the histological lesions.[11] The histological features included steatosis grade (0–3), lobular inflammation grade (0–3), hepatocyte ballooning grade (0–2), and portal inflammation grade (0–2). The individuals with < 5% and ≥5% of hepatocytes with visible lipid droplets were classified as "non-steatosis" and "hepatic steatosis," respectively. Patients with hepatic steatosis were then categorized into "steatohepatitis" and "steatosis but not steatohepatitis" groups. The histological diagnosis of steatohepatitis was established using characteristic features of steatosis, hepatocyte ballooning, mixed lobular acute and chronic inflammation, and intra-acinar perisinusoidal fibrosis using Brunt's classification.[12] Other features included the NAFLD activity score (NAS), Mallory-Denk bodies, microgranuloma, and acidophil bodies. The liver fibrosis stage was assessed in accordance with the METAVIR scoring system.[13]

Long-term outcomes

Patients were assessed at 3- to 6-month intervals after the baseline liver biopsy and more frequently as clinically indicated. During each visit, clinical events, metabolic assessments, and virologic measurements were recorded. HCC surveillance with liver imaging every 6 months was offered to patients with cirrhosis and at-risk individuals without cirrhosis as recommended by international guidelines.[2–4] The study outcomes were all-cause mortality or liver transplantation and liver-related complications (e.g., HCC, spontaneous bacterial peritonitis, variceal hemorrhage, portosystemic encephalopathy, and hepatorenal syndrome). The cause of death and all complications that occurred during the follow-up were reviewed.

Statistical analysis

Data were summarized using descriptive statistics. Between-group differences in quantitative variables were compared by standard parametric or non-parametric tests, and qualitative variables were compared using chi-squared tests. The cumulative probabilities of mortality or liver transplantation and liver-related complications were estimated by the Kaplan-Meier method and compared using log-rank tests. Hazard ratio (HR) and 95% confidence interval (CI) estimates for the outcomes were calculated by Cox proportional hazard models. All potential confounders, including age, sex, overweight/obese, diabetes mellitus, hypertriglyceridemia, hypertension, and statin use, were considered for multivariable models to identify independent determinants of the study outcomes. Time at risk was defined as the date of liver biopsy to the date of outcome or last follow-up. Statistical analyses were done using SPSS version 18.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics of the study cohort

During the study period, 868 patients with chronic HBV infection who underwent liver biopsy were evaluated. Four hundred sixty patients were excluded from the analysis for the following reasons: no available liver histology for review (n=62), no histologic indication for antiviral therapy (n=174), follow-up less than 6 months (n=151), HBV viremia >2000 IU/mL after discontinuing antiviral treatment (n=56), co-infection with hepatitis C virus (n=11) or human immunodeficiency virus (n=4), and alcohol dependence (n=2, Fig. 1). Thus, 408 patients were included in the analysis.

The mean age of the study cohort was 44±10 years, and the mean BMI was 23.4±4.1 kg/m^2. There was a predominance of men (65%), and 54.2% of the patients had metabolic dysfunction. The mean initial HBV DNA levels were 6.0±1.7 $\log_{10}$ IU/mL, and 34% of patients were HBeAg positive. Histological evidence of hepatic steatosis was observed in 152 patients (37%), and steatosis was mild in 31% and moderate to severe in 6% of patients. A histological diagnosis of "steatohepatitis" was established in 34 (22%) of 152 patients with hepatic steatosis, and the remaining 118 patients were categorized into the "steatosis but not steatohepatitis" group. The baseline clinical, biochemical, and histological characteristics of the study cohort are summarized in Tables 1 and 2.

Compared with patients with non-steatosis, patients with concurrent hepatic steatosis or steatohepatitis were older, predominantly men, overweight/obese, and had higher plasma glucose and triglyceride levels. All patients with steatohepatitis and 77.1% of those with steatosis but not steatohepatitis had metabolic dysfunction, which was defined

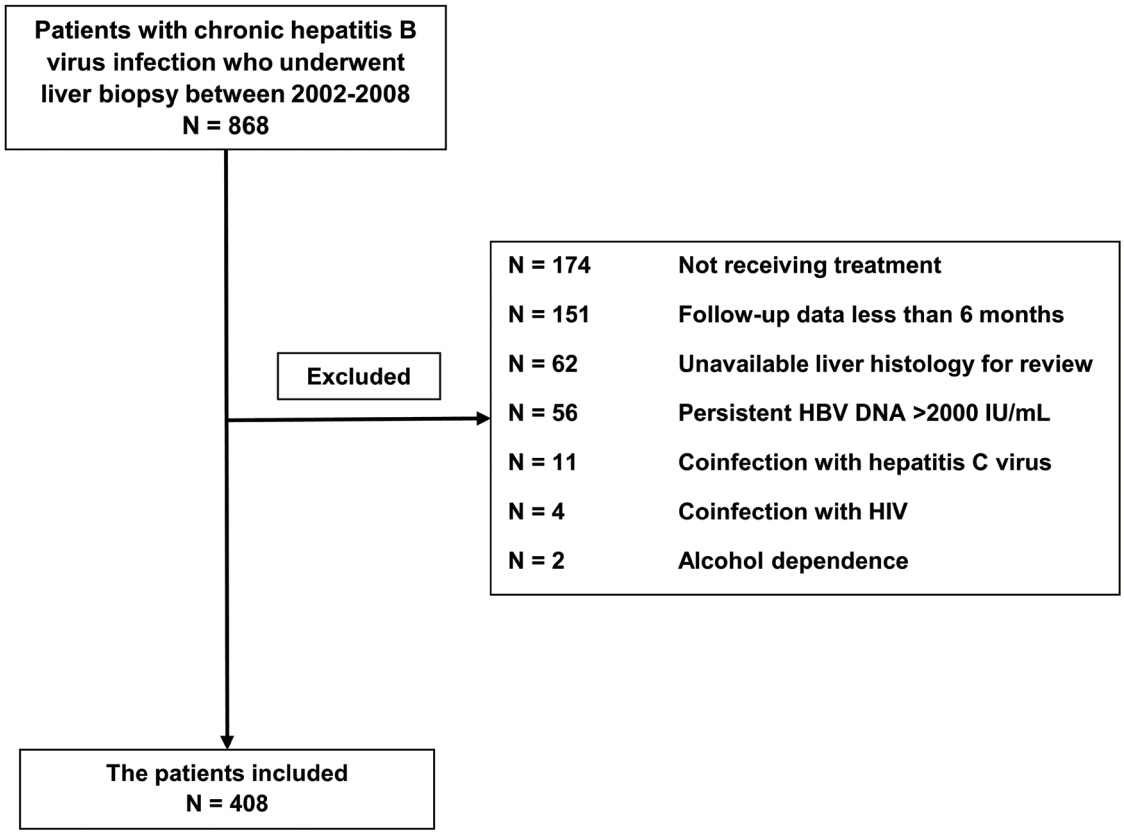

Fig. 1. Flow chart of the selection of the study population.

as meeting one of the following criteria: overweight/obese, type 2 diabetes mellitus, or evidence of metabolic dysregulation. None of the liver biochemistry and viral characteristics, including HBV viral load and HBeAg status, were associated with hepatic steatosis or steatohepatitis in patients with CHB (Table 1). In accordance with the METAVIR scoring system, 238 (58%) of the entire population had fibrosis stages 1–2, and 70 (17%) had advanced fibrosis (stages 3–4). Patients with steatohepatitis had a significantly higher percentage of cytologic ballooning, Mallory-Denk body, microgranuloma, and more lobular inflammation and NAS compared with those with non-steatosis (Table 2). However, there was no significant difference in the portal inflammation grade between the groups.

Antiviral treatment and long-term follow-up evaluation

The mean duration of follow-up for the study cohort was 13.8±3.1 years (range, 2.6–21.4 years), with 5,636 person-years of follow-up. Initially, 356 of the cohort (87.3%) received nucleos(t)ide analogues, and 52 (12.7%) were treated with pegylated interferon. During follow-up, 25 patients (6.1%) experienced HBsAg seroclearance, which is defined as two negative HBsAg assays at least 6 months apart, and 356 patients (87.2%) maintained suppression of viral replication (HBV DNA <20 IU/mL) during long-term treatment with lamivudine (13.5%), entecavir (40.4%), and tenofovir disoproxil fumarate (33.3%). Additionally, 27 (6.6%) patients entered the HBeAg-negative inactive state, which is defined as negative HBeAg with persistent viremia < 2000 IU/mL and normal aminotransferase levels after discontinuing antiviral agents. Concurrent hepatic steatosis or steatohepatitis was not associated with treatment-induced HBsAg seroclearance (Table 1). Thirty-five patients (8.6%) experienced 43 liver-related events, among which 32 events were HCC (Table 3). Overall, one patient received a liver transplant, and 17 patients died; nine of the deaths were caused by liver-related complications (HCC and variceal hemorrhage) and eight deaths had non-liver-related causes.

Histologic features associated with the development of clinical outcomes

The fibrosis stage, NAFLD category, NAS category, and grade of steatosis and hepatocyte ballooning but not lobular inflammation were histologic features that were significantly associated with outcomes (Table 4). In the multivariate-adjusted Cox regression, NAFLD category and fibrosis stage were histologic features that were independently associated with mortality/liver transplantation and liver-related events (Supplementary Table 1).

Factors associated with the development of overall mortality/liver transplantation

The mean survival free of liver transplantation was significantly shorter in the steatohepatitis group than in the non-steatosis group (16.0 vs. 20.9 years, respectively, log-rank test, $p<0.001$; Fig. 2A). No significant difference in survival free of liver transplantation was found between the steatosis but not

Table 1. Baseline characteristics of patients with chronic hepatitis B and their HBV status with long-term antiviral therapy

Variable	Non-steatosis (*n*=256)	Hepatic steatosis			*p*-value*
		All steatosis (*n*=152)	Steatosis but not steatohepatitis (*n*=118)	Steatohepatitis (*n*=34)	
Age, year	42.2±10.6	47.7±8.5†	46.5±8.6	51.9±6.4	<0.001
Male sex, *n* (%)	151 (59.0)	116 (76.3)†	93 (78.8)	23 (67.6)	<0.001
Body mass index, kg/m^2	21.8±3.3	25.9±3.9†	25.6±3.8	27.2±4.0	<0.001
Metabolic dysfunctionΩ, *n* (%)	96 (37.5)	125 (82.2)†	91 (77.1)	34 (100)	<0.001
Overweight/obese, *n* (%)	85 (34.6)	110 (73.8)†	81 (70.4)	29 (85.3)	<0.001
Diabetes mellitus, *n* (%)	17 (6.7)	47 (30.9)†	30 (25.4)	17 (50.0)	<0.001
Hypertension, *n* (%)	42 (16.4)	66 (43.4)†	52 (44.1)	14 (41.2)	<0.001
Hypertriglyceridemia, *n* (%)	21 (8.2)	38 (25.0)†	28 (23.7)	10 (29.4)	<0.001
Statin use, *n* (%)	57 (22.3)	61 (40.1)†	45 (38.1)	16 (47.1)	<0.001
AST, IU/mL	46 (31, 73)	42 (28, 73)	40 (27, 66)	60 (33, 77)	0.131
ALT, IU/mL	63 (38, 125)	64 (38, 107)	62 (36, 107)	68 (54, 107)	0.620
Total bilirubin, mg/dL	0.7 (0.6, 1.0)	0.7 (0.5, 0.9)	0.7 (0.6, 0.9)	0.65 (0.5, 1.0)	0.454
Albumin, g/dL	4.3±0.4	4.3±0.4	4.4±0.4	4.3±0.4	0.160
Globulin, g/dL	3.5±0.6	3.5±0.6	3.5±0.6	3.7±0.6	0.271
Creatinine, mg/dL	0.8 (0.7, 1.0)	0.9 (0.8, 1.0)	0.9 (0.8, 1.0)	0.9 (0.7, 1.1)	0.567
Glucose, mg/dL	95±22	107±37†	99±18	127±58	0.004
Total cholesterol, mg/dL	195±50	199±42	200±33	194±63	0.826
Triglyceride, mg/dL	96±87	141±109†	143±119	138±81	<0.001
HDL-cholesterol, mg/dL	61±19	58±35†	60±41	54±10	0.751
HBeAg positive, *n* (%)	92 (35.9)	46 (30.3)	36 (30.5)	10 (29.4)	0.500
HBV DNA, $\log_{10}$IU/mL	6.1±1.7	5.8±1.6	5.9±1.7	5.5±1.4	0.129
HBV status on the last follow-up, *n* (%)					
HBsAg seroclearanceΦ	15 (5.9)	10 (6.6)	10 (8.5)	0 (0.0)	0.184
Sustained HBV suppression#	223 (87.1)	133 (87.5)	101 (85.6)	32 (94.1)	0.419
HBeAg-negative inactive stateΨ	18 (7.0)	9 (5.9)	7 (5.9)	2 (5.9)	0.909

Data are means (standard deviation), median (interquartile range) or number (proportion) of patients with a condition. ALT, alanine aminotransferase; AST, aspartate aminotransferase. **p*-value for comparisons of groups of non-steatosis, steatosis but not steatohepatitis, and steatohepatitis. †There was a statistically significant difference between non-steatosis and hepatic steatosis. ΩMetabolic dysfunction was diagnosed as the presence of at least one of the following: (1) overweight/obese (body mass index ≥23 kg/m^2), (2) type 2 diabetes mellitus, or (3) at least two metabolic risk abnormalities. Metabolic risk abnormalities consisted of (1) waist circumference ≥90 cm for men and ≥80 cm for women, (2) blood pressure ≥130/85 mmHg or specific drug treatment, (3) fasting plasma triglycerides ≥150 mg/dL or specific drug treatment, (4) plasma HDL-cholesterol <40 mg/dL for men and <50 mg/dL for women or specific drug treatment, and (5) prediabetes (fasting glucose 100–125 mg/dL) according to the international expert consensus for MAFLD. ΦHBsAg seroclearance was defined as two negative HBsAg assays at least 6 months apart. #Sustained HBV suppression was defined as undetectable HBV DNA (<20 IU/mL) during treatment with nucleos(t)ide analogues. ΨHBeAg-negative inactive state was defined as negative HBeAg with viremia <2000 IU/mL and normal aminotransferase levels after discontinuing antiviral agents.

steatohepatitis and non-steatosis groups (p=0.090). There was a significant difference between the steatohepatitis, steatosis but not steatohepatitis, and non-steatosis groups in the proportion of patients who died from liver-related complications (8.8% vs. 3.4% vs. 0.8%, respectively, p=0.007).

Factors significantly associated with mortality/liver transplantation included age (p=0.005), diabetes mellitus (p=0.031), NAFLD category (p=0.011), and fibrosis stage (p=0.005) (Table 5). The type of antiviral drugs and HBsAg seroclearance were not significantly associated with overall mortality/liver transplantation. A multivariate analysis adjusted for potential confounders showed that the steatohepatitis group [HR, 6.37, (95% CI: 1.59–25.5); p=0.009] compared with the non-steatosis group and advanced fibrosis [HR, 11.3 (95% CI: 1.32–96.3); p=0.027] compared with fibrosis stage 0 were prognostic factors associated with mortality/liver transplantation.

Factors associated with the development of liver-related events

The observed survival free of liver-related events was significantly lower among CHB patients with either steatohepatitis or steatosis but not steatohepatitis than among those with non-steatosis (p<0.001; Fig. 2B). There was a significant difference between the steatohepatitis, steatosis but not steatohepatitis, and non-steatosis groups in the proportion of patients who developed HCC (23.5% vs. 11.0% vs. 4.3%, respectively, p<0.001). After discontinuing antiviral

Table 2. Liver biopsy features of the study cohort with chronic hepatitis B

Variable	Non-steatosis (*n*=256)	Hepatic steatosis			*p*-value*
		All steatosis (*n*=152)	Steatosis but not steatohepatitis (*n*=118)	Steatohepatitis (*n*=34)	
Steatosis, *n* (%)					<0.001
<5%	256 (100)	0 (0)	0 (0)	0 (0)	
5%-33%	0 (0)	126 (82.9)	106 (89.8)	20 (58.8)	
>33%-66%	0 (0)	23 (15.1)	11 (9.4)	12 (35.3)	
>66%	0 (0)	3 (2.0)	1 (0.8)	2 (5.9)	
Lobular inflammation, *n* (%)					0.010
0 – No foci	42 (16.4)	9 (5.9)	9 (7.6)	0 (0)	
1 – <2 foci	160 (62.5)	113 (74.3)	89 (75.4)	24 (70.6)	
2 – 2–4 foci	49 (19.1)	30 (19.7)	20 (16.9)	10 (29.4)	
3 – >4 foci	5 (2.0)	0 (0)	0 (0)	0 (0)	
Hepatocyte ballooning, *n* (%)					<0.001
0 – None	254 (99.2)	106 (69.7)	106 (89.8)	0 (0)	
1 – Few	2 (0.8)	38 (25.0)	11 (9.3)	27 (79.4)	
2 – Many	0 (0)	8 (5.3)	1 (0.8)	7 (20.6)	
Portal inflammation, *n* (%)					0.091
0 – None	26 (10.2)	6 (3.9)	6 (5.1)	0 (0)	
1 – Mild	121 (47.3)	79 (52.0)	64 (54.2)	15 (44.1)	
2 – More than mild	109 (42.6)	67 (44.1)	48 (40.7)	19 (55.9)	
NAFLD activity score, *n* (%)					<0.001
0–2	251 (98.0)	80 (52.6)	80 (67.8)	0 (0)	
3–4	5 (2.0)	62 (40.8)	38 (32.2)	24 (70.6)	
5–8	0 (0)	10 (6.6)	0 (0)	10 (29.4)	
Mallory-Denk body, *n* (%)	0 (0)	26 (17.1)	0 (0)	26 (76.5)	<0.001
Microgranuloma, *n* (%)	1 (0.4)	5 (3.3)	3 (2.5)	2 (5.9)	0.023
Acidophil body, *n* (%)	2 (0.8)	5 (3.3)	3 (2.5)	2 (5.9)	0.071
Fibrosis stage, *n* (%)					0.008
0	68 (26.6)	32 (21.1)	24 (20.3)	8 (23.5)	
1	68 (26.6)	44 (28.9)	43 (36.4)	1 (2.9)	
2	72 (28.1)	54 (35.5)	38 (32.2)	16 (47.1)	
3	33 (12.9)	15 (9.9)	9 (7.6)	6 (17.6)	
4	15 (5.9)	7 (4.6)	4 (3.4)	3 (8.8)	

Data are number (proportion) of patients with a condition. NAFLD, non-alcoholic fatty liver disease. **p*-value for comparison of non-steatosis, not steatohepatitis, and steatohepatitis.

agents, no patient with a low level of detectable viral load developed any liver-related events during follow-up.

Factors significantly associated with developing liver-related complications included age ($p<0.001$), overweight/obese ($p=0.033$), NAFLD category ($p<0.001$), and fibrosis stage ($p<0.001$; Table 5). The types of antiviral drugs and seroclearance of HBsAg were not significantly associated with a lower risk of liver-related outcomes. Multivariate analysis adjusted for potential confounders showed that the steatohepatitis group [HR, 5.55 (95% CI: 2.01–15.3), $p=0.001$] compared with the non-steatosis group and advanced fibrosis [HR, 6.23 (95% CI: 1.75–22.2), $p=0.005$] compared with fibrosis stage 0 were prognostic factors associated with liver-related events. The steatohepatitis group [HR, 5.08 (95% CI: 1.72–15.0), $p=0.003$] compared with the non-steatosis group and advanced fibrosis [HR, 5.09 (95% CI: 1.39–18.6), $p=0.014$] compared with fibrosis stage 0 were independently associated with developing HCC after adjusting for potential confounders.

Long-term outcomes of patients with early histologic fibrosis stage

Because patients with advanced fibrosis had a higher mortality and more liver-related events, the long-term out-

Table 3. Causes of death and liver-related events

Outcome	Number
Death or liver transplantation	(*n*=18)
Hepatocellular carcinoma	8 (44.4%)
Variceal hemorrhage	1 (5.6%)
Infections	3 (16.7%)
Non-liver cancer	5 (27.7%)
Liver transplantation	1 (5.6%)
Liver-related events	(*n*=35)
Hepatocellular carcinoma	32 (91.4%)
Varices hemorrhage	4 (11.4%)
Portosystemic encephalopathy	3 (8.6%)
Hepatorenal syndrome	3 (8.6%)
Spontaneous bacterial peritonitis	1 (2.9%)

Data are number (percentage) of a condition.

comes of patients with early fibrosis stages were analyzed. We eliminated 70 patients with advanced fibrosis, leaving 338 patients with no or mild fibrosis (stage 0–2). Among them, ten died, four of whom died due to liver-related events. Patients with steatohepatitis [HR, 2.73 (95% CI: 0.44–17.1), p=0.283] and steatosis but not steatohepatitis [HR, 1.44 (95% CI: 0.32–6.51), p=0.638] did not have a significantly increased risk of death compared with those with non-steatosis after adjusting for fibrosis stage and other confounders (Fig. 3A).

Nineteen (5.6%) patients experienced a liver-related complication during the follow-up evaluation, and all had HCC. These patients achieved sustained viral suppression with long-term nucleos(t)ide analogues but had no HBsAg seroclearance. The observed survival free of liver-related event (HCC) showed a significant difference in the NAFLD category (Fig. 3B). Adjusting for fibrosis stage and other confounders, the steatohepatitis group had an increased risk of HCC compared with the non-steatosis group [HR, 4.49 (95% CI: 1.05–19.1), p=0.043], while the steatosis but not steatohepatitis group was not significantly associated with a higher risk of HCC [HR, 2.40 (95% CI: 0.78–7.37), p=0.126] compared with the non-steatosis group.

Discussion

In this longitudinal cohort study of 408 CHB patients receiving antiviral treatment, concurrent biopsy-proven steatohepatitis and advanced fibrosis were independently associated with long-term overall mortality, liver transplantation, and liver-related events despite attaining control of the underlying viral infection. Metabolic dysfunction-associated steatohepatitis is strongly associated with a higher rate of developing HCC among patients with CHB, regardless of the liver fibrosis severity. The increased risk we measured was independent of other well-defined risk factors, such as metabolic factors and virologic status.

Considering the epidemic of obesity, MAFLD among patients with chronic HBV infection has become a research focus. Some evidence suggests that the metabolic alterations in MAFLD may hamper HBV replication in CHB or enhance antiviral responses through activation of innate immunity.[14–16] However, our data showed that concurrent steatosis and steatohepatitis were not associated with HBV characteristics or treatment-induced HBsAg seroclearance. The existing evidence is inconclusive, and further well-designed studies are needed. Previous studies have reported metabolic syndrome as a risk factor for liver fibrosis progression in patients with CHB, independent of the viral load.[17,18] Additionally, elevated BMI is recognized as an independent risk factor for liver-related mortality in these patients.[19] The underlying mechanism of liver disease progression with metabolic abnormalities could be attributable to the occurrence of concurrent MAFLD.

Currently, there are limited data on the effects of MAFLD on clinical outcomes following comprehensive treatment for CHB. In a cohort study by Peleg *et al.*,[20] liver steatosis, which was measured by ultrasonography, was associated with all-cause mortality and cancer in patients with CHB. A multiethnic cohort of CHB patients found associations between clinical outcomes of all-cause death and HCC and steatohepatitis, which was defined by the NAS values recorded in pathology reports.[21] Patients with probable NASH (NAS 3–4) and definite NASH (NAS ≥5) constituted the steatohepatitis cohort. The NAS system was designed exclusively to measure changes in NAFLD during clinical trials.[11] Some of the NAS histological components, such as lobular inflammation and cytologic ballooning, are not specific to steatohepatitis and can be found as necroinflammatory features in most patients with CHB.[22,23] The presence of steatohepatitis based on NAS values and concurrent hepatic steatosis identified by imaging might lead to misclassification in CHB patients. Approximately one-third to two-thirds of both cohorts received antiviral therapy,[20,21] and therefore, the findings should interfere with the heterogeneity of HBV infection throughout follow-up. Thus, the effect of MAFLD, particularly steatohepatitis, on long-term clinical outcomes in CHB patients is not well determined. The current investigation, which used a systematic pathologic protocol to define the presence of hepatic steatosis and steatohepatitis in CHB patients after attaining control of the viral infection, should be pivotal in examining the prognostic relevance of MAFLD.

To unequivocally establish coexisting steatohepatitis in a CHB background, we carefully selected histopathologic criteria for steatohepatitis. Only patients exhibiting the constellation of steatosis, mixed lobular inflammation, hepatocyte ballooning, zone 3 perisinusoidal fibrosis, and overall liver injury pattern were considered to be diagnostic for steatohepatitis, as proposed by Brunt *et al*.[23] Therefore, to identify the histologic candidate with the long-term prognosis for CHB patients with concurrent fatty liver disease, Cox regression models, including each histologic lesion of NAFLD, NAS category, steatohepatitis that was diagnosed in accordance with Brunt's pathological criteria, and fibrosis stage were created for each outcome. The analyses revealed that although a NAS of ≥5 appeared significant in univariate analysis, it did not have long-term prognostic significance in multivariable analysis. The histopathological definition of steatohepatitis as proposed by Brunt *et al*.[23] and its components of steatosis and hepatocyte ballooning but not lobular inflammation showed significance for the outcomes in univariate analysis. When the features of steatohepatitis and its determinants were analyzed in multivariate models, the diagnosis of steatohepatitis by Brunt's criteria was the only relevant histologic feature of MAFLD that provided meaningfully long-term prognostic information for patients with CHB when adjusted for liver fibrosis stage. These results strengthen the histologic categorization of a group of CHB patients with concurrent steatohepatitis, as defined in this study.

In patients with chronic HBV infection, a liver biopsy is useful for determining the extent of necroinflammatory damage and liver fibrosis to determine the need for antiviral treatment and to detect possible coexistent lesions.[23] Using Brunt's pathological criteria, steatohepatitis was histologi-

Table 4. Cumulative events and univariate-unadjusted hazard ratio estimates for the outcomes by histological feature among patients with chronic hepatitis B

Liver histologic features	Mortality/liver transplantation			Liver-related events		
	Cumulative events, *n*	Unadjusted HR (95% CI)	*P*-value	Cumulative events, *n*	Unadjusted HR (95% CI)	*P*-value
Steatosis, grade						
<5%	6/256	1 (reference)		12/256	1 (reference)	
5%-33%	10/126	3.43 (1.24–9.43)	0.017	21/126	3.70 (1.82–7.53)	<0.001
>33%	2/26	3.13 (0.63–15.5)	0.163	2/26	1.64 (0.37–7.34)	0.516
Lobular inflammation, grade						
No foci	1/51	1 (reference)		3/51	1 (reference)	
<2 foci	14/273	2.73 (0.36–20.8)	0.331	27/273	1.85 (0.56–6.12)	0.311
>2 foci	3/84	1.84 (0.19–17.7)	0.599	5/84	1.07 (0.26–4.48)	0.926
Hepatocyte ballooning, grade						
None	12/360	1 (reference)		23/360	1 (reference)	
Few	5/40	3.89 (1.37–11.0)	0.011	8/40	3.40 (1.52–7.62)	0.003
Many	1/8	4.53 (0.59–34.9)	0.147	4/8	9.88 (3.40–28.7)	<0.001
Portal inflammation, grade						
None	1/32	1 (reference)		1/32	1 (reference)	
Mild	5/200	0.72 (0.08–6.18)	0.766	10/200	1.48 (0.19–11.5)	0.711
More than mild	12/176	2.07 (0.27–16.0)	0.484	24/176	4.33 (0.59–32.1)	0.151
NAS category						
0–2	11/331	1 (reference)		22/331	1 (reference)	
3–4	5/67	2.38 (0.83–6.85)	0.108	11/67	2.68 (1.30–5.53)	0.008
5–8	2/10	5.94 (1.32–26.9)	0.021	2/10	3.27 (0.77–13.9)	0.109
NAFLD category						
Non-steatosis	6/256	1 (reference)		12/256	1 (reference)	
Steatosis but not steatohepatitis	7/118	2.49 (0.84–7.40)	0.102	13/118	2.36 (1.08–5.17)	0.032
Steatohepatitis	5/34	6.72 (2.05–22.0)	0.002	10/34	7.34 (3.16–17.1)	<0.001
Fibrosis stage						
0	1/100	1 (reference)		3/100	1 (reference)	
1	4/112	3.51 (0.39–31.4)	0.262	6/112	1.74 (0.43–6.96)	0.436
2	5/126	3.90 (0.45–33.4)	0.215	10/126	2.64 (0.73–9.62)	0.140
3	4/48	9.27 (1.03–83.1)	0.040	11/48	8.78 (2.45–31.5)	<0.001
4	4/22	19.3 (2.15–173.0)	0.008	5/22	8.67 (2.07–36.3)	0.003

CI, confidence interval; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis.

cally established in 22% of our CHB patients with hepatic steatosis, which is comparable to previous studies involving CHB patients.[7,24] We found that CHB patients with concurrent steatohepatitis share characteristics with CHB patients with "non-steatosis" and individuals with "steatosis but not steatohepatitis," but there are some differences. Compared with non-steatosis patients and those with steatosis but not steatohepatitis, CHB patients with steatohepatitis did not display a different prevalence and grade of portal inflammation, which is a histologic feature of antiviral therapy. However, CHB patients with steatohepatitis differed from those with non-steatosis or steatosis but not steatohepatitis regarding higher rates of metabolic dysfunction and a more advanced stage of fibrosis. We also showed that metabolic dysfunction-associated steatohepatitis and advanced fibrosis are associated with overall mortality/liver transplantation or liver-related events after adjusting for age, sex, metabolic risk factors, and statin use. Nevertheless, the long-term prognostic importance of steatohepatitis on overall mortality was reduced when patients with advanced fibrosis were excluded. This finding suggests that advanced fibrosis is the primary driver of poor outcomes for patients, although steatohepatitis contributes to an increased risk of HCC in treated CHB patients with or without advanced fibrosis when adjusted for age, sex, metabolic features, statin use, and fibrosis stage. Taken together, the presence of metabolic dysfunction-associated steatohepatitis in CHB patients with advanced fibrosis can ascertain the subgroup of

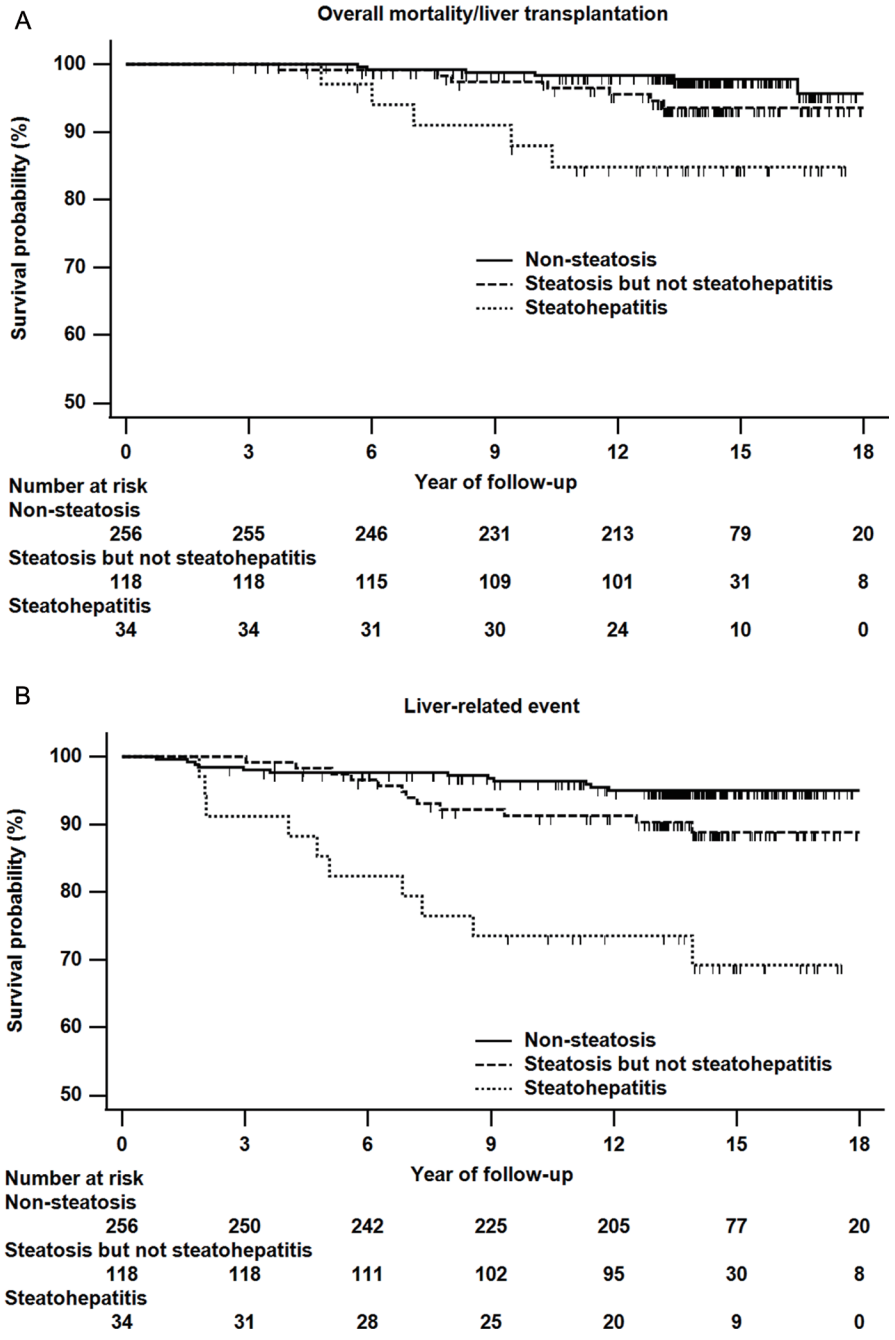

Fig. 2. Kaplan-Meier analysis of transplant-free survival (A) and survival free of liver-related events (B) among the entire population. Patients with steatohepatitis had higher probabilities of death/liver transplantation (log-rank, $p<0.001$) and liver-related events (log-rank, $p<0.001$) than those with non-steatosis. Patients with steatosis but not steatohepatitis had higher probabilities of liver-related events than those with non-steatosis (log-rank, $p=0.027$).

patients who require medications to suppress HBV replication and intensive lifestyle changes to improve liver-related outcomes.

Seroclearance of HBsAg is the desired endpoint for managing patients with CHB; this is known as a functional cure. In a meta-analysis of 28 studies that enrolled 188,316 patients with chronic HBV infection, HBsAg seroclearance was significantly associated with improved patient outcomes, including HCC, liver decompensation, liver transplantation, and all-cause mortality.[25] However, our analysis shows that HBsAg seroclearance was not associated with a significantly lower risk of overall mortality/liver transplantation and liver-related complications. The type of antiviral agents for our cohort changed over time, and any bias in the results would be nondifferential, leading to an underestimation of the true magnitude of the association.

In contrast to the NAFLD population, most of our CHB patients died from complications related to liver disease and extrahepatic cancers, and no mortality related to cardiovascular events occurred in this cohort. Although previous studies reported that cardiovascular disease is the leading cause of death in patients with NAFLD,[26,27] we observed

Table 5. Risk factors for mortality/liver transplantation and liver-related events among patients with chronic hepatitis B

Variable	Mortality/liver transplantation				Liver-related event			
	Univariate analysis		Multivariate analysis*		Univariate analysis		Multivariate analysis*	
	HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
Age, year	1.08 (1.02–1.13)	0.005	1.07 (1.01–1.13)	0.021	1.11 (1.07–1.16)	<0.001	1.10 (1.06–1.15)	<0.001
Male sex	1.82 (0.60–5.54)	0.290	3.26 (0.94–11.3)	0.064	1.01 (0.50–2.03)	0.981	1.94 (0.87–4.34)	0.107
Overweight/obese	1.73 (0.67–4.46)	0.258	0.66 (0.22–1.92)	0.443	2.14 (1.06–4.30)	0.033	0.89 (0.39–2.02)	0.774
Diabetes mellitus	2.95 (1.11–7.88)	0.031	2.10 (0.65–6.80)	0.216	1.41 (0.62–3.24)	0.413	0.60 (0.22–1.66)	0.324
Hypertension	1.82 (0.71–4.70)	0.215	1.24 (0.37–4.16)	0.729	1.71 (0.86–3.39)	0.127	1.20 (0.51–2.82)	0.668
Hypertriglyceridemia	0.33 (0.04–2.49)	0.284	0.18 (0.02–1.44)	0.105	1.16 (0.48–2.80)	0.742	0.83 (0.32–2.14)	0.693
Statin use	0.48 (0.14–1.66)	0.248	0.33 (0.09–1.22)	0.097	0.49 (0.20–1.18)	0.111	0.33 (0.13–0.82)	0.017
HBeAg-positive	0.83 (0.32–2.14)	0.698			1.02 (0.51–2.05)	0.962		
Long-term antiviral therapy								
Lamivudine	1 (reference)				1 (reference)			
Entecavir	0.55 (0.15–1.94)	0.352			1.17 (0.46–2.94)	0.747		
Tenofovir	0.87 (0.26–2.90)	0.823			0.85 (0.31–2.29)	0.742		
HBsAg seroclearance	0.84 (0.11–6.31)	0.866			0.41 (0.06–2.96)	0.374		
NAFLD category								
Non-steatosis	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Steatosis but not steatohepatitis	2.49 (0.84–7.40)	0.102	2.73 (0.78–9.55)	0.117	2.36 (1.08–5.17)	0.032	2.32 (0.98–5.50)	0.057
Steatohepatitis	6.72 (2.05–22.0)	0.002	6.37 (1.59–25.5)	0.009	7.34 (3.16–17.1)	<0.001	5.55 (2.01–15.3)	0.001
Fibrosis stage								
0	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
1–2	3.71 (0.47–29.4)	0.214	2.61 (0.32–21.5)	0.372	2.21 (0.64–7.60)	0.208	1.79 (0.51–6.30)	0.364
3–4	12.5 (1.56–100)	0.017	11.3 (1.32–96.3)	0.027	8.75 (2.55–30.0)	<0.001	6.23 (1.75–22.2)	0.005

Data are expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). Overweight (BMI 23–24.9 kg/m^2) and obese (BMI ≥25 kg/m^2) were categorized following the Asian-specific criteria. BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis. *Multivariate-adjusted hazard ratio estimates for the outcomes were calculated by Cox proportional hazard models to control for potential confounding factors such as age, sex, overweight/obese, diabetes mellitus, hypertension, and statin use.

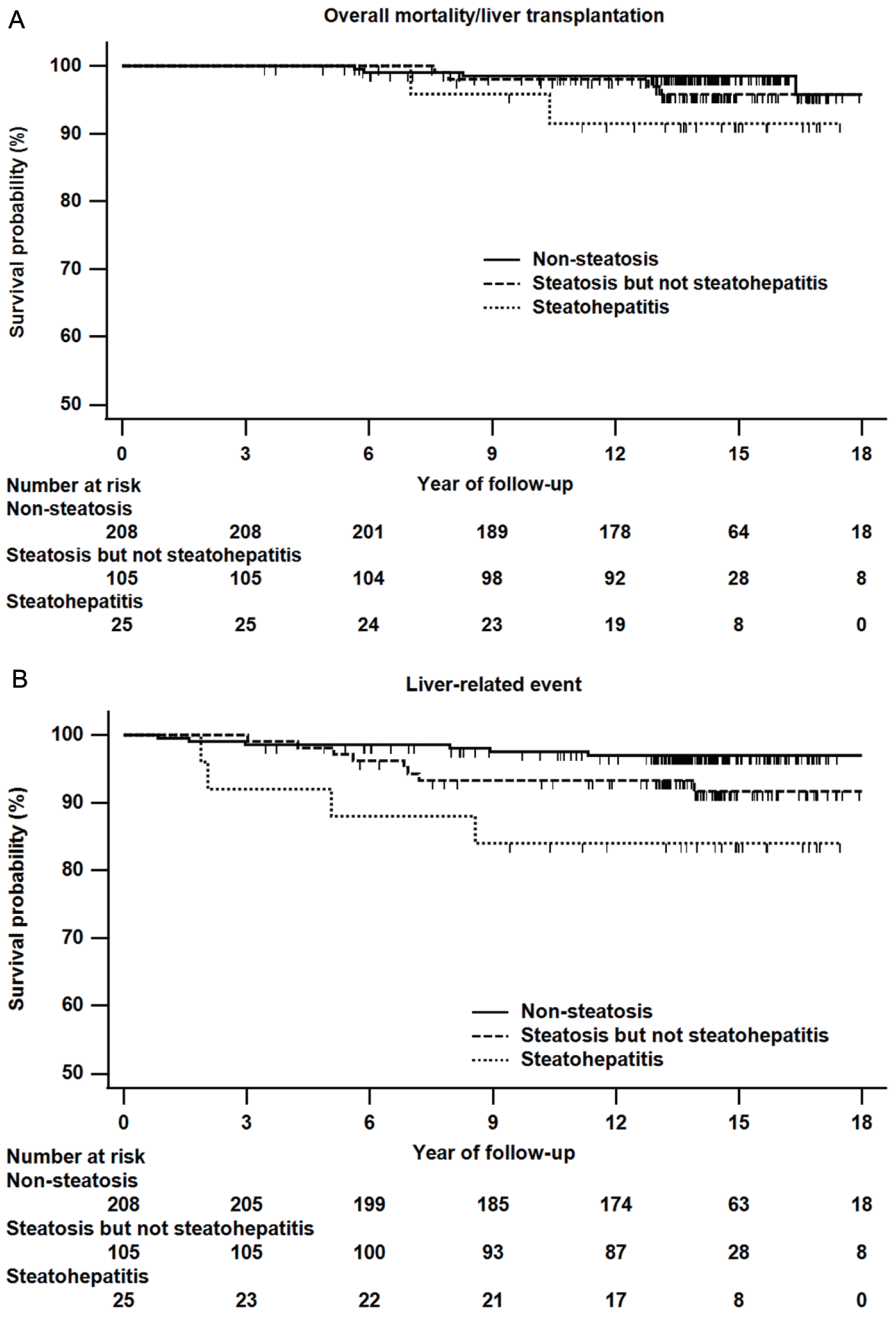

Fig. 3. Kaplan-Meier analysis of overall survival (A) and survival free of liver-related events (B) among chronic hepatitis B patients with early fibrosis stage. Patients with steatohepatitis and steatosis but not steatohepatitis had no difference in overall survival compared with those with non-steatosis (log-rank, p=0.080, and p=0.344, respectively). Patients with steatohepatitis and steatosis but not steatohepatitis had a significantly shorter survival free of liver-related events than those with non-steatosis (log-rank, p=0.002, and p=0.030, respectively).

that HCC was the most common liver-related event and mortality in CHB patients with hepatic steatosis, suggesting a synergistic effect of fatty liver disease on CHB. Our results support findings that hepatic steatosis increases the risk of HCC and mortality among CHB patients.[28,29] The underlying mechanism of carcinogenesis during the course of CHB with hepatic steatosis remains unclear. The pathogenesis of hepatic steatosis-associated HCC is complex and involves inflammatory responses, DNA damage, and fibrogenesis.[30–32] Furthermore, lipotoxicity in steatohepatitis causes a metabolic disturbance, leading to increased reactive oxygen species and driving a procarcinogenic process in the liver, which ultimately accelerates HCC development in CHB.[32,33] Further investigations of this issue to discover specific therapeutic targets for HCC are warranted.

The main strengths of our study included the large sample, an average follow-up of more than a decade per patient, and having an experienced liver pathologist to determine the presence of steatohepatitis and other biopsy features using established histological scoring systems in every case. However, some limitations should be noted, including the lack of a specific protocol for the management of metabolic dis-

eases, which might affect the study results. To compensate for this possible limitation, we adjusted for metabolic parameters and statin use in a multivariate analysis. Although the diagnostic criteria for MAFLD are not required to exclude other liver diseases, CHB patients with coexisting MAFLD and other conditions, such as viral co-infections and significant alcohol use are likely to have distinct pathophysiological circumstances, disease progression, and therapeutic responses compared with CHB individuals with primarily fatty liver disease associated with metabolic dysfunction. Co-infection with hepatitis C virus or human immunodeficiency virus, as well as excessive alcohol consumption, have been recognized as major risk factors for HCC development.[34] Thus, CHB patients with other viral co-infections or alcohol dependence were excluded. Additionally, the present study only included individuals who had HBV control by antiviral drugs or had inactive disease after treatment cessation. This cohort would be more homogeneous using stringent criteria, thereby increasing the likelihood of determining a substantial impact of MAFLD among CHB patients.

In conclusion, this large series of treated patients with CHB demonstrates that metabolic dysfunction-associated steatohepatitis among CHB patients receiving antiviral therapy carries a higher risk of death and the need for liver transplantation and increases the likelihood of liver-related events compared with patients without hepatic steatosis. The higher risk of mortality and liver-related complications in treated CHB patients with steatohepatitis was independent of metabolic conditions and virologic response to antiviral therapy, which could influence these outcomes. We also found that metabolic dysfunction-associated steatohepatitis is independently associated with the occurrence of HCC in CHB patients, even when the virus is controlled by antiviral drugs. This finding supports the evidence that long-term antiviral therapy can halt the progression of viral hepatitis and reduce, but not completely eliminate, the risk of HCC. Therefore, suppression of viral replication or a functional cure should not be the only goal of treatment for this population. Physicians caring for patients with CHB should be alert for signs of metabolic dysfunction-associated steatohepatitis and treat this condition promptly in addition to routine HBV treatment.

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Conflict of interest

PC has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2013, TT has been an associate editor of *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflicts of interest related to this publication.

Author contributions

Study conception and design (PC), collection of the data (MR, AP, SC, SN, WC, TT, PC), analysis of the data (MR, PC), and writing of the manuscript (MR, PC). All authors approved the final version of the article, including the authorship list.

Ethical statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board, and it was registered with ClinicalTrials.gov (NCT05317260).

Data sharing statement

No additional data are available.

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