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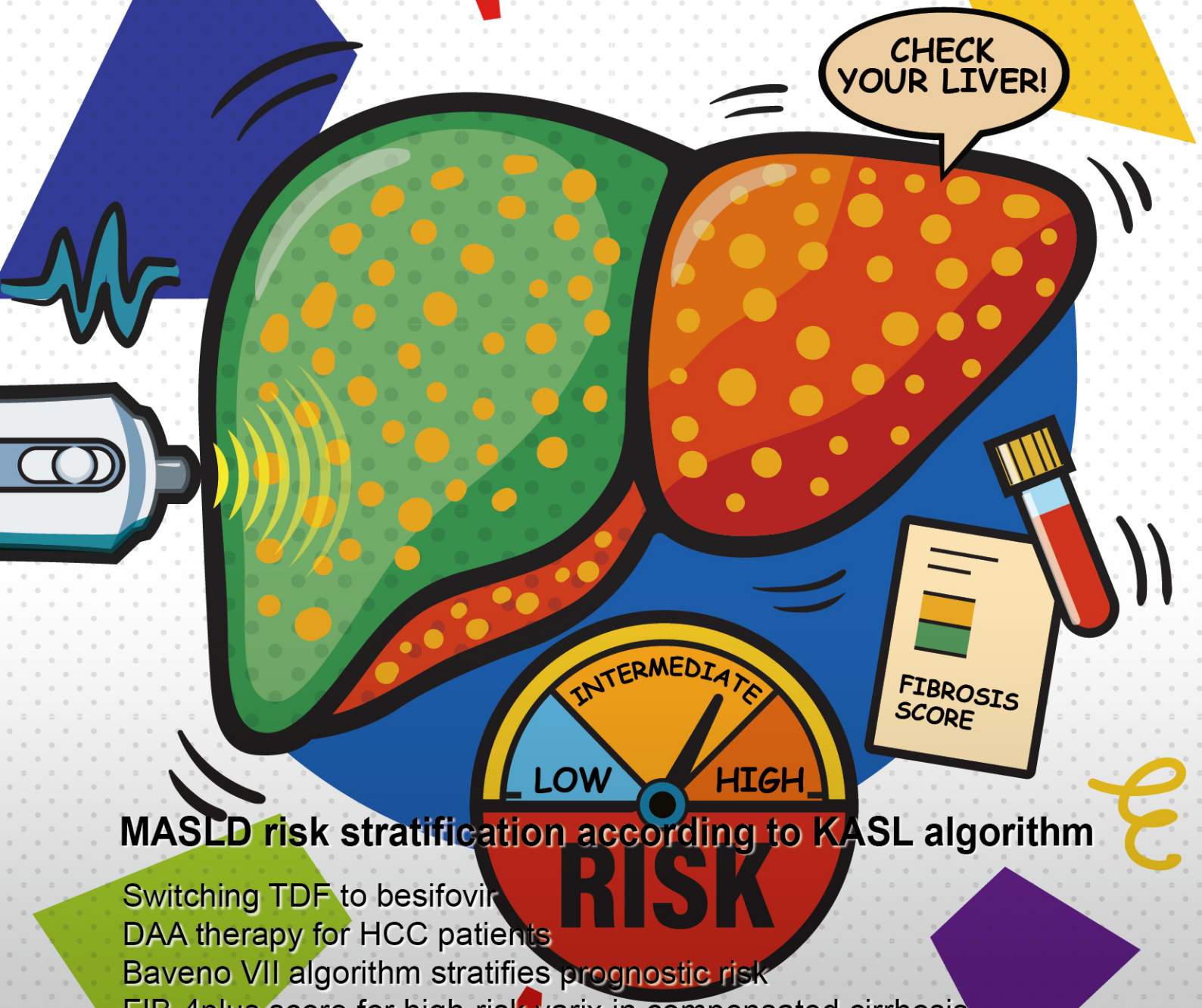

MASLD risk stratification according to KASL algorithm

Switching TDF to besifovir
DAA therapy for HCC patients
Baveno VII algorithm stratifies prognostic risk
FIB-4plus score for high-risk varix in compensated cirrhosis

KASL

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Original Article

Impacts of metabolic syndrome diseases on long-term outcomes of chronic hepatitis B patients treated with nucleos(t)ide analogues

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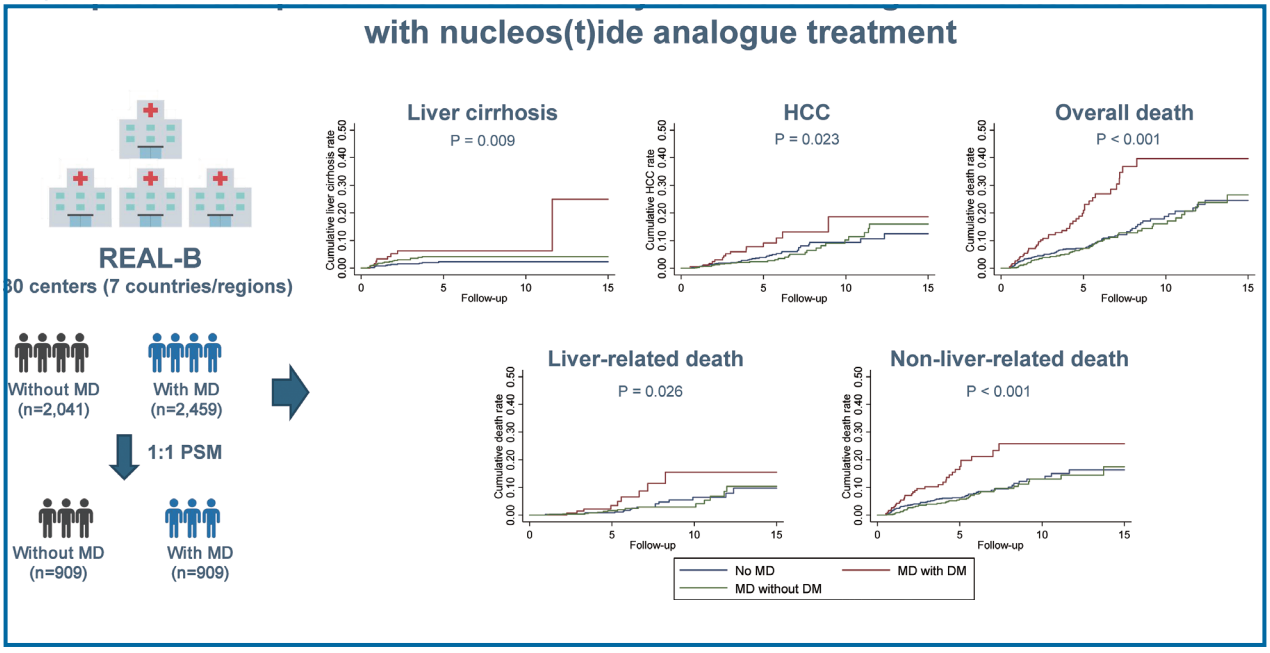
Graphical Abstract



Study Highlights

- Having ≥2 metabolic diseases increased the risk of cirrhosis and death in CHB patients treated with NAs.
- Diabetes as a single metabolic disease was associated with all adverse outcomes in CHB patients treated with NAs.
- Prevention and management of diabetes should be considered in CHB patients treated with NAs.

Background/Aims: Given the increase in prevalence of metabolic diseases, we investigated their long-term impacts on the outcomes of chronic hepatitis B (CHB) patients receiving nucleos(t)ide analogue (NA) treatment.

Methods: We analyzed data from CHB patients for whom initiated NA treatment from 30 centers. We balanced patient characteristics with and without metabolic disease (diabetes, obesity, dyslipidemia, and hypertension) via propensity-score matching (PSM) to evaluate adverse outcomes.

Results: The study included 4,500 patients. PSM yielded 909 pairs of patients with balanced characteristics. When stratified by the number of metabolic diseases, only patients with ≥2 metabolic diseases had an increased cumulative incidence of cirrhosis and overall death. However, when stratified by the presence of diabetes (regardless of the presence or number of other metabolic diseases), patients with diabetes (versus those without) had a significantly higher cumulative incidence of all outcomes: cirrhosis (P=0.009), hepatocellular carcinoma (HCC, P=0.023), and overall, liver-related, and non-liver-related death (P<0.001, P=0.026 and P<0.001, respectively). Having ≥2 metabolic diseases was associated with cirrhosis, overall death, and non-liver-related death but not HCC or liver-related death, while diabetes was significantly associated with a higher risk of all outcomes: cirrhosis (hazard ratio [HR]=3.75, P=0.004), HCC (HR=2.02, P=0.020), and overall, liver-related, and non-liver-related death (HR=2.53, P<0.001; HR=2.65, P=0.016; HR=2.38, P<0.001).

Conclusions: Having two or more metabolic diseases was associated with a higher risk of cirrhosis, overall death, and non-liver-related death, but having diabetes as a single metabolic disease was significantly associated with all adverse outcomes including cirrhosis, HCC, and overall, liver-related, and non-liver-related death. **(Clin Mol Hepatol 2025;31:1003-1017)**

Keywords: Chronic hepatitis B; Metabolic diseases; Nucleos(t)ide analogues; Hepatocellular carcinoma; Death

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INTRODUCTION

Hepatitis B virus (HBV) infection is a major global health threat with over 290 million people chronically infected and 820,000 deaths per year, mainly due to cirrhosis and hepatocellular carcinoma (HCC).[1] Nucleos(t)ide analogue (NA) treatment is now widely available and has been shown to be effective at suppressing HBV replication and reducing the risk of adverse liver-related outcomes.[2-4]

In recent decades, the prevalence of metabolic diseases including obesity, hypertension, diabetes, and dyslipidemia has increased rapidly in the general population as well as in patients with chronic hepatitis B (CHB).[5-7] The presence of concurrent metabolic diseases with CHB has been reported to be associated not only with increased cardiovascular risk but also adverse liver events,[8] though data regarding the association with liver adverse events are currently conflicting.[9-17] A recent prospective study with a median follow-up of 5.9 years found that not only DM but also glycemic burden and glycemic control influenced the risks of adverse CHB outcomes.[18] However, this was a single center study and included a mixed population of patients who received antiviral treatment and patients who were not treated for CHB. Other prior studies also had single-center study designs, small sample sizes, evaluated mixed populations of treated and untreated patients, and/or generally focused on the number of metabolic factors rather than specific types of metabolic disease, thus limiting their conclusions.

In this study, leveraging data from a large cohort of patients from the Real-World Evidence from the Global Alliance for the Study of HBV consortium (REAL-B),[19-21] a well-defined population of previously treatment-naïve CHB patients for whom first-line NA treatment was initiated at 30 sites in 7 countries/regions with longitudinal data up to 15 years, we investigated the impacts of the number and specific type of metabolic disease on the long-term outcomes of NA-treated CHB patients.

MATERIALS AND METHODS

Study population

This was a retrospective multinational cohort study of previously treatment-naïve CHB patients for whom entecavir (ETV), tenofovir disoproxil fumarate (TDF), or tenofovir alafenamide (TAF) treatment was initiated. CHB was defined as the presence of serum hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), or detectable serum HBV DNA for at least 6 months. Metabolic disease was defined as the presence of at least one component of metabolic syndrome (as defined below) by the time of ETV, TDF, or TAF initiation. Patients were enrolled at 30 REAL-B study centers in Argentina, Mainland China, Japan, Singapore, South Korea, Taiwan, and the U.S.A. Data were collected using a unified structured data frame at each study site and transferred to the data coordinating center at Stanford University as described previously.[19-21] Patients were excluded if there was co-infection with hepatitis C, D, or human immunodeficiency virus, HCC or death within 6 months of treatment initiation, or missing data. This study was approved by the institutional review boards of Stanford University and of each study site with waiver of the requirement for informed consent and was conducted in accordance with the Declarations of Helsinki.

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Abbreviations:

AASLD, American Association for the Study of Liver Disease; ALT, alanine aminotransferase; anti-HBs, antibodies to HBsAg; BMI, body mass index; CHB, chronic hepatitis B; CI, confidence interval; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; IPTW, inverse probability treatment weighting; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NA, nucleos(t)ide analogue; PSM, propensity-score matching; SD, standard deviation; SHR, subdistribution hazard ratios; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; VR, virologic response

Definitions

Metabolic syndrome components included type 2 diabetes mellitus, obesity, hypertension, and dyslipidemia. Diabetes and hypertension were defined by medical history or use of antidiabetic or antihypertensive medication, respectively. Obesity was defined as a body mass index (BMI) of ≥25 kg/m^2 for Asian patients and ≥30 kg/m^2 for non-Asian patients.[22-26] Dyslipidemia was diagnosed by a medical history of dyslipidemia, hyperlipidemia, hypertriglyceridemia, or hypercholesterolemia, lipid-lowering drug use, serum total cholesterol ≥200 mg/dL (>5.17 mmol/L), triglycerides ≥150 mg/dL (1.7 mmol/L), low-density lipoprotein cholesterol ≥160 mg/dL (4.1 mmol/L), or decreased serum high-density lipoprotein cholesterol <40 mg/dL (<1.03 mmol/L) for men and <50 mg/dL (<1.29 mmol/L) for women.[27,28] The presence of liver steatosis was assessed by imaging modalities such as FibroScan®, ultrasound, magnetic resonance imaging, computed tomography, or liver histology.

Study outcomes

Study outcomes included the development of cirrhosis, HCC, death (overall, liver-related and non-liver-related), and HBsAg loss. Surveillance of HCC and cirrhosis was generally carried out every 6 months. Presence of cirrhosis was defined by histologic and/or radiologic evidence of cirrhosis or liver stiffness (>12.5 kPa)[1] or imaging, endoscopic, or clinical evidence of portal hypertension or hepatic decompensation (e.g., splenomegaly, ascites, hepatic encephalopathy, gastroesophageal varices, or a platelet count <120×10^3/μl).[19,20] HCC diagnosis was based on practice guidance criteria provided by the American Association for the Study of Liver Disease (AASLD).[29] Overall death was defined as death from any cause. Liver-related death was defined as death resulting from HCC, liver failure, or complications of liver cirrhosis. HBsAg loss was defined as the loss of serum HBsAg with or without the development of antibodies to HBsAg. Time to occurrence of clinical outcomes was defined from NA initiation to the date of the outcome event occurrence. Censoring criteria included the end of the study observation period, occurrence of the study outcome, or loss to follow-up, whichever came first. All patients were treated with NAs and did not discontinue treatment during the study period.

Statistical analysis

Continuous variables are presented as means (±standard deviations [SD]) or medians (interquartile range) and the statistical significance of differences in these variables between groups was evaluated by Student's *t*-test or the rank sum test. Categorical variables are reported as counts and percentages and were compared using chi-squared tests. Patients with or without metabolic diseases were matched for background characteristics by propensity-score matching (PSM) with a caliper of 0.2 of the SD of the logit of the propensity score. Incidence of outcome events of interest among groups was assessed in the total and PSM cohorts using the Kaplan–Meier method and compared using the log-rank test. We compared study outcomes with stratification by the overall number of metabolic diseases versus no metabolic disease. Given the importance of diabetes as a major driver of poor clinic outcomes based on prior reports,[30-32] we also stratified outcome analyses by the presence of diabetes regardless of the presence or number of other metabolic diseases versus patients with metabolic disease but without diabetes and those without any metabolic disease. Pair-wise log-rank tests were performed to evaluate the significance of differences between two groups with different outcomes with *P*-values adjusted by Bonferroni's correction.[33] To identify potential factors associated with study outcomes, we performed Cox proportional hazards regression to estimate the hazard ratios (HRs) relating potential factors with study outcomes in the PSM cohort.

We also performed several subgroup and sensitivity analyses to evaluate the robustness of the study results. For subgroup analyses, we stratified the data by age, sex, HBeAg status (positive or negative), alanine aminotransferase (ALT) level (> or ≤2 times the upper limit of normal [defined as 35 U/L for men and 25 U/L for women]), HBV DNA level (≥ or <20,000 IU/mL), presence of cirrhosis (yes or no), and type of antiviral medications (ETV or TDF/TAF). For one sensitivity analysis, we excluded patients with hepatic steatosis since its presence can affect CHB outcomes.[34,35] We also performed Cox regression analyses to examine hepatic steatosis as an independent variable. In another sensitivity analysis, though the distribution of cirrhosis was matched between study groups in the PSM cohort, we adjusted for the presence of cirrhosis as a poten-

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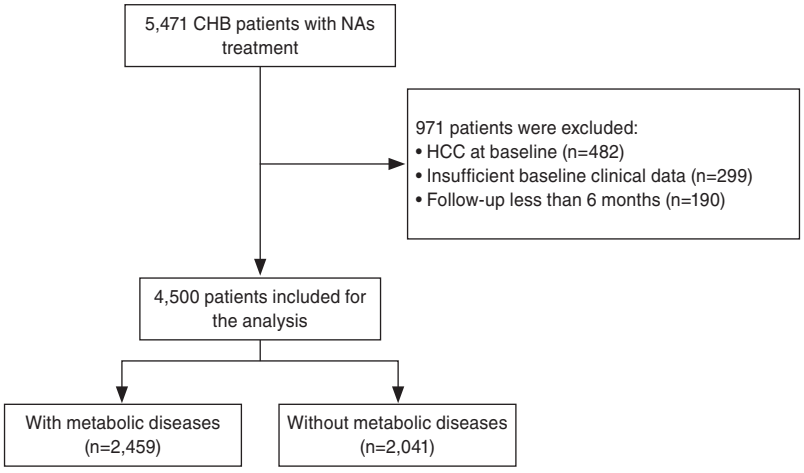

Figure 1. Flow chart of patient selection. CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; NA, nucleos(t)ide analogue.

tial residual confounding factor because it is a major factor affecting clinical outcomes of patients with CHB. We also performed Fine–Gray competing risks analyses in the PSM cohort using death as a competing risk to evaluate incidence and subdistribution hazard ratios (SHRs) for liver cirrhosis and HCC. Finally, as an additional sensitivity analysis, we performed regression analysis to evaluate factors associated with study outcomes in cohorts matched by inverse probability treatment weighting (IPTW).

All statistical analyses were performed using Stata software (version 14.0, StataCorp, College Station, TX, USA). A 2-tailed *P*-value of <0.05 was considered to indicate statistical significance.

RESULTS

Characteristics and long-term outcomes of the total patient cohort

Of the 5,471 previously treatment-naïve patients in the REAL-B consortium for whom first-line NA treatment was initiated, a total of 4,500 patients met our study inclusion criteria (Fig. 1). The cohort was majority male (62.8%) and Asian (97.4%). Over half (54.6%) had at least one metabolic disease (11.7% with diabetes, 33.7% with obesity, 17.6% with dyslipidemia, 20.9% with hypertension; 33.2% had 1 metabolic disease, 14.9% had 2 metabolic diseases, and 6.5% had 3 or more metabolic diseases). Patients with metabolic disease were older (52.8±12.6 years vs. 48.2±12.8 years), more likely to be male (66.7% vs. 58.1%), and had a higher proportion of hepatic steatosis (33.9% vs. 19.2%) than patients without metabolic disease (all *P*<0.001). Median follow-up times were similar between patients with and without metabolic disease (4.5 years vs. 4.3 years, *P*=0.088) (Table 1).

Overall, there was a significantly higher 15-year cumulative incidence of cirrhosis (*P*=0.006), HCC (*P*<0.001), overall death (*P*<0.001), and non-liver related death (*P*<0.001) in patients with metabolic disease compared with patients without metabolic disease, but not liver-related death (*P*=0.127) (Supplementary Fig. 1). When comparing patients without metabolic disease with patients with metabolic disease but without diabetes and patients with diabetes (regardless of the presence or number of other metabolic diseases), patients with diabetes consistently had higher 15-year incidence of study outcomes including liver cirrhosis, HCC, as well as overall, liver-related, and non-liver related death (Supplementary Fig. 2, all *P*=0.002 to <0.001). There were few HBsAg seroclearance events and we found no significant difference in the rates of HBsAg seroclearance between patients with and without metabolic disease regardless of whether the comparisons were stratified by the number of metabolic disease or by the presence of diabetes (Supplementary Fig. 3A).

PSM cohort

Patient characteristics and long-term outcomes

PSM yielded 909 pairs of patients with well-matched

Table 1. Baseline characteristics of patients with and without metabolic diseases

Patient characteristics	Before PSM				After PSM*			
	With metabolic diseases (n=2,459)	Without metabolic diseases (n=2,041)	*P*-value	Standardized difference	With metabolic diseases (n=909)	Without metabolic diseases (n=909)	*P*-value	Standardized difference
Age (yr)	52.8±12.6	48.2±12.8	<0.001	0.363	49.6±12.1	50.4±11.9	0.152	0.067
Male	1,641 (66.7)	1,185 (58.1)	<0.001	0.179	563 (61.9)	564 (62.0)	0.961	0.002
Asian	2,403 (97.7)	1,979 (96.9)	0.112	0.047	881 (96.9)	884 (97.3)	0.676	0.019
Significant alcohol intake (n=4,005)	685 (31.1)	492 (27.3)	0.008	0.084	292 (32.1)	304 (33.4)	0.549	0.028
Diabetes	526 (21.4)	-	-	-	192 (21.1)	-	-	-
Hypertension	939 (38.2)	-	-	-	294 (32.3)	-	-	-
Dyslipidemia	791 (32.2)	-	-	-	256 (28.2)	-	-	-
Obesity	1,518 (61.7)	-	-	-	573 (63.0)	-	-	-
Hepatic steatosis (n=3,994)	741 (33.9)	347 (19.2)	<0.001	0.338	177 (19.5)	204 (22.4)	0.120	0.073
Antiviral treatment			0.177	0.040			0.312	0.047
ETV	1,553 (63.2)	1,249 (61.2)			567 (62.4)	546 (60.1)		
TDF/TAF	906 (36.8)	792 (38.8)			342 (37.6)	363 (39.9)		
Positive HBeAg (n=3,900)	677 (31.6)	669 (38.1)	<0.001	0.138	301 (33.1)	304 (33.4)	0.881	0.007
Cirrhosis (n=4,469)	752 (30.9)	448 (22.0)	<0.001	0.201	237 (26.1)	248 (27.3)	0.560	0.027
HBV DNA (log_{10} IU/mL)	5.7 (4.3, 7.1)	5.9 (4.4, 7.4)	<0.001	0.100	5.8 (4.4, 7.3)	5.8 (4.3, 7.2)	0.630	0.020
ALT (U/L)	68 (38, 137)	71 (36, 154)	0.799	0.037	75 (37, 144)	64 (36, 152)	0.234	0.031
AST (U/L) (n=4,351)	53 (34, 102)	55 (32, 109)	0.851	0.033	54 (33, 106)	53 (33, 112)	0.881	0.025
Platelet counts (10^3/μL) (n=3,784)	170 (122, 219)	182 (138, 230)	<0.001	0.136	177 (132, 225)	176 (131, 223)	0.809	0.019
Fib-4 (n=3,661)	2.2 (1.3, 4.3)	1.9 (1.1, 3.7)	<0.001	0.083	2.0 (1.1, 3.7)	2.0 (1.2, 3.9)	0.238	0.020
Fib-4 categories			<0.001	0.172			0.231	0.048
Low (<1.45) (n=1,218)	617 (30.4)	601 (36.9)			328 (36.1)	296 (32.6)		
Intermediate (1.45–3.25) (n=1,265)	696 (34.2)	569 (35.0)			315 (34.6)	344 (37.8)		
High (>3.25) (n=1,178)	720 (35.4)	458 (28.1)			266 (29.3)	269 (29.6)		
Follow-up period (yr)	4.5 (2.5, 7.0)	4.3 (2.5, 6.5)	0.088	0.055	4.4 (2.5, 6.6)	4.6 (2.8, 6.6)	0.165	0.045
Metabolic diseases								
1 disease	1,496 (60.8)	-			603 (66.3)	-		-
2 diseases	670 (27.3)	-			219 (24.1)	-		-
≥3 diseases	293 (11.9)	-			87 (9.6)	-		-

Values are presented as mean±standard deviation, number (%), or median (interquartile range).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ETV, entecavir; Fib-4, fibrosis-4; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; PSM, propensity-score matching; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

*Matched for sex, age, HBeAg status, baseline HBV DNA, platelet counts, and ALT level, AST level, ethnicity, alcohol use, liver cirrhosis, hepatic steatosis, and follow-up time.

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background characteristics including sex, age, race, alcohol use, liver cirrhosis, hepatic steatosis, HBeAg status, baseline HBV DNA, platelets, ALT and aspartate aminotransferase levels, and duration of treatment (Table 1).

When stratified by the number of metabolic disease without specifying the presence of diabetes, cumulative incidence only differed significantly for incidence for cirrhosis (*P*=0.002) and overall death (*P*=0.014). Pairwise comparisons with statistical significance levels adjusted using Bonferroni correction showed consistent results, with significant difference between those patients with two metabolic disease or ≥3 metabolic diseases for cirrhosis and between ≥3 metabolic diseases for overall death as compared to no metabolic disease (*P*<0.001, *P*=0.016, 0.006, respectively; threshold of the Bonferroni correction *P*-value: 0.025) (Supplementary Fig. 2A, 2C). There were no statistically significant differences in the incidence of HCC, liver-related death, non-liver related death, or HBsAg seroclearance according to the number of metabolic diseases (*P*=0.537, 0.371, 0.099, 0.286, respectively; Fig. 2B, 2D, 2E and Supplementary Fig. 3B).

However, when stratified according to the presence of diabetes, patients with diabetes (regardless of the presence or number of other metabolic diseases) as compared to those with metabolic disease(s) but without diabetes or without any metabolic disease had the highest 15-year cumulative incidence of cirrhosis (25.0% vs. 4.1% vs. 2.3%, respectively, *P*=0.009), HCC (18.6% vs. 16.0% vs. 12.4%, respectively, *P*=0.023), overall, liver-related, and non-liver-related death (39.7% vs. 26.5% vs. 24.5%, respectively, *P*<0.001; 15.5% vs. 10.4% vs. 9.7%, respectively, *P*=0.026; 25.8% vs. 17.5% vs. 16.4%, respectively, *P*<0.001). Pairwise comparisons of corrected significance levels using the Bonferroni method resulted in similar findings for comparisons between patients with diabetes versus no metabolic disease and those with diabetes versus those with a metabolic disease(s) but without diabetes (Fig. 3). Additionally, results were consistent in sensitivity analyses excluding patients with hepatic steatosis (Supplementary Fig. 4). Trends were also similar in most subgroup analyses although statistical power was limited in some instances due to small subgroup sample sizes (Supplementary Fig. 5–11).

Factors associated with adverse long-term outcomes

In Cox regression analyses, there were significant associations between the presence of two or ≥3 metabolic diseases (vs. no metabolic disease) and higher risk of liver cirrhosis development (HR=4.00, 95% confidence interval [CI] 1.77–9.08, *P*=0.001; HR=3.78, 95% CI 1.22–11.74, *P*=0.021, respectively) and overall death (HR=1.55, 95% CI 1.03–2.33, *P*=0.037; HR=2.09, 95% CI 1.22–3.56, *P*=0.007, respectively), but not with HCC development or liver-related death. Only patients with ≥3 metabolic diseases had a significantly higher risk of non-liver-related death than those without metabolic disease (HR=1.99, 95% CI 1.08–3.69, *P*=0.027) (Supplementary Table 1).

However, in Cox regression analysis stratified by the presence of diabetes, we observed significant associations between diabetes (regardless of the presence or number of metabolic diseases) and higher risks of all adverse outcomes including cirrhosis (HR=3.75, 95% CI 1.53–9.18, *P*=0.004), HCC (HR=2.02, 95% CI 1.12–3.65, *P*=0.020), overall death (HR=2.53, 95% CI 1.75–3.66, *P*<0.001), liver-related death (HR=2.65, 95% CI 1.19–5.86, *P*=0.016), and non-liver related death (HR=2.38, 95% CI 1.56–3.65, *P*<0.001) (Table 2). Conversely, a significant association between hepatic steatosis and a lower risk of cirrhosis (HR=0.15, 95% CI 0.04–0.64, *P*=0.010), HCC (HR=0.28, 95% CI 0.11–0.70, *P*=0.006), and liver-related death (HR=0.12, 95% CI 0.02–0.88, *P*=0.037) was observed (Supplementary Table 2).

Consistent results were also observed in a sensitivity analysis of the PSM cohort after excluding patients with hepatic steatosis (Table 3). In another sensitivity analysis adjusting for cirrhosis, the presence of diabetes remained significantly associated with higher risks of overall death (adjusted HR [aHR]=2.44, 95% CI 1.68–3.53, *P*<0.001) and non-liver-related death (aHR=2.42, 95% CI 1.58–3.71, *P*<0.001) (Supplementary Table 3). In further evaluation using Fine–Gray competing risks analysis with death as a competing risk in the PSM cohort, patients with diabetes (regardless of the presence or number of other metabolic diseases) remained the group with the higher risk of liver cirrhosis (SHR=3.51, 95% CI 1.36–9.05, *P*=0.009) and HCC (SHR=2.02, 95% CI 1.11–3.67, *P*=0.022) (Supplementary Table 4, Supplementary Fig. 12). We obtained consistent results in an analysis excluding patients with hepatic steatosis (Supplementary Table 5, Supplementary Fig. 13). Similar trends were observed in most subgroup analyses although some analyses were limited by small subgroup sample sizes (Supplementary

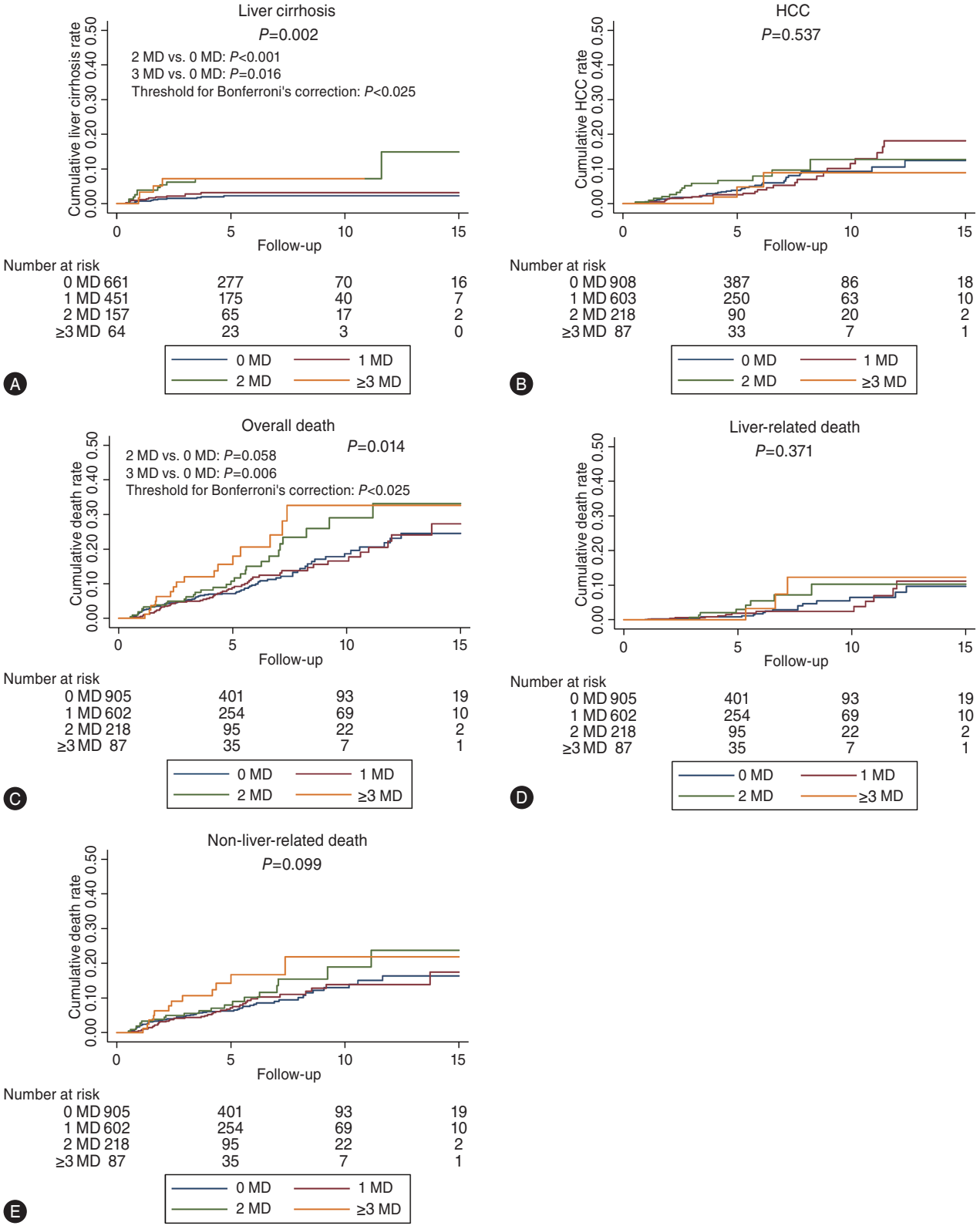

Figure 2. Cumulative incidence of liver cirrhosis, hepatocellular carcinoma, and death in CHB patients with different numbers of metabolic diseases in a propensity-score matched cohort. (A) Liver cirrhosis; (B) HCC; (C)Overall death; (D) Liver-related death; (E) Non-liver-related death. CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; MD, metabolic disease.

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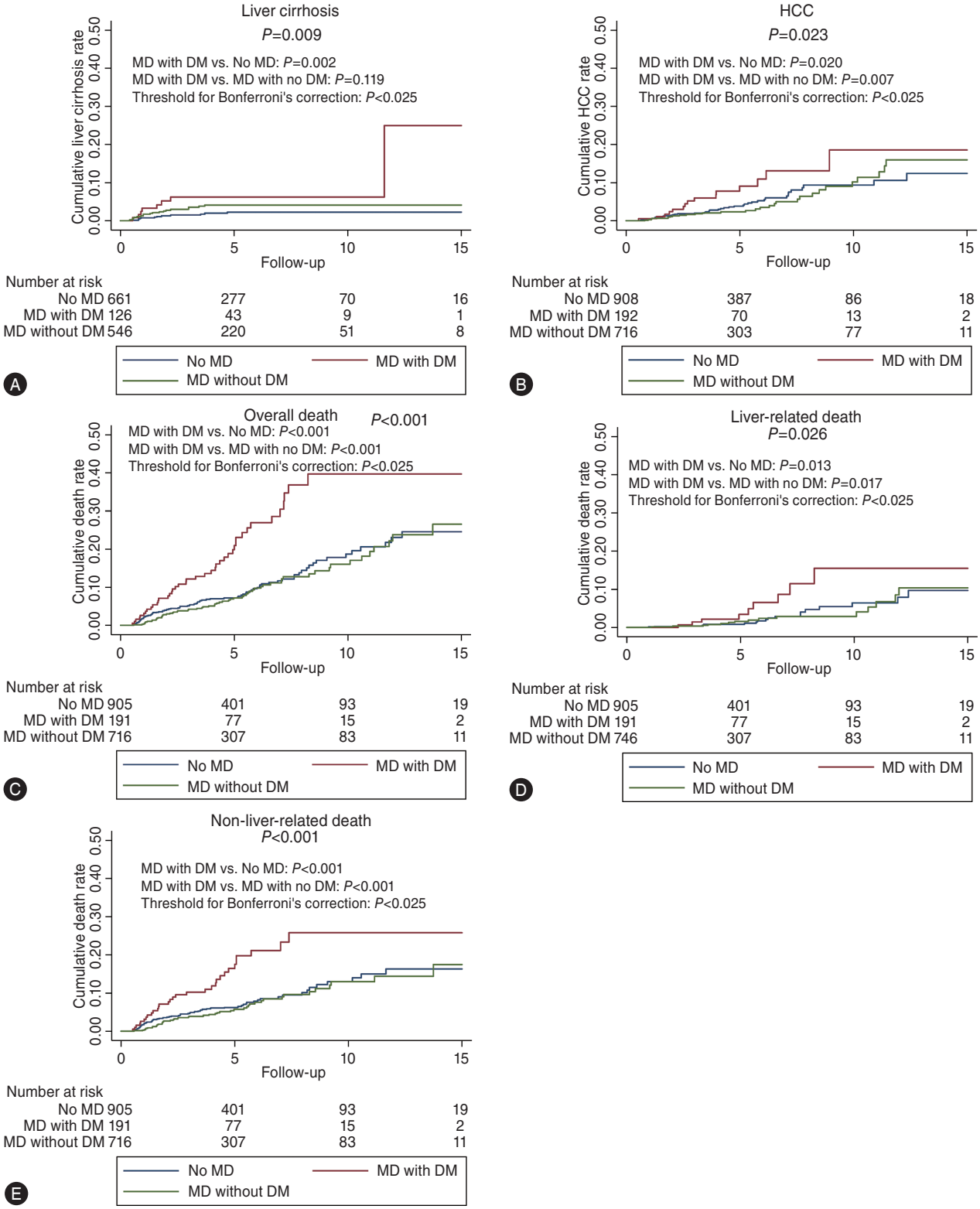

Figure 3. Cumulative incidence of cirrhosis, hepatocellular carcinoma, and death in CHB patients without metabolic diseases, with diabetes (regardless of the presence or number of other metabolic diseases) and with metabolic diseases but without diabetes in a propensity-score matched cohort. (A) Liver cirrhosis; (B) HCC; (C)Overall death; (D) Liver-related death; (E) Non-liver-related death. CHB, chronic hepatitis B; DM, diabetes mellitus; HCC, hepatocellular carcinoma; MD, metabolic diseases.

Table 2. Cox regression of long-term outcomes of CHB patients with metabolic diseases with or without diabetes in the PSM cohort

	Events	HR (95% CI)	*P*-value
Liver cirrhosis			
No metabolic diseases	12/661	Reference	
Metabolic without diabetes	19/546	1.97 (0.96, 4.06)	0.066
Metabolic with diabetes	8/126	3.75 (1.53, 9.18)	0.004
HCC			
No metabolic diseases	41/908	Reference	
Metabolic without diabetes	29/716	0.89 (0.55, 1.43)	0.618
Metabolic with diabetes	15/192	2.02 (1.12, 3.65)	0.020
Overall death			
No metabolic diseases	87/905	Reference	
Metabolic without diabetes	63/716	0.92 (0.67, 1.27)	0.620
Metabolic with diabetes	42/191	2.53 (1.75, 3.66)	<0.001
Liver-related death			
No metabolic diseases	19/904	Reference	
Metabolic without diabetes	15/715	0.99 (0.50, 1.95)	0.981
Metabolic with diabetes	9/189	2.65 (1.19, 5.86)	0.016
Non-liver-related death			
No metabolic diseases	67/904	Reference	
Metabolic without diabetes	47/715	0.89 (0.62, 1.30)	0.563
Metabolic with diabetes	31/189	2.38 (1.56, 3.65)	<0.001

CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; CHB, chronic hepatitis B; PSM, propensity-score matching.

Figs. 14, 15). Lastly, in an additional sensitivity analysis using the IPTW method where relevant background characteristics of the study groups (e.g., sex, age, race, alcohol use, liver cirrhosis, hepatic steatosis, HBeAg status, baseline HBV DNA, platelets, ALT level, and duration of treatment) were balanced, consistent results with higher risk of all adverse outcomes were again observed in patients with diabetes (Supplementary Table 6).

DISCUSSION

In this multinational cohort of 4,500 NA-treated CHB patients from both the East and West, we found that the presence of diabetes (regardless of the presence or number of other metabolic diseases) was consistently associated with a comprehensive range of adverse liver outcomes (cirrhosis, HCC, and liver-related deaths) as well as overall death and non-liver related death, rather than the numerical numbers of metabolic diseases *per se*. Patients with diabetes had an almost 4-fold higher risk of liver cirrhosis, 2-fold higher risk of HCC, and 2 to 2.5-fold higher risk of overall, liver-related, or non-liver related death compared to patients without metabolic disease, but not patients with metabolic disease(s) without diabetes.

Our study findings are congruent with prior knowledge that while NAs are effective at reducing the incidence of adverse liver-related events in CHB, these patients remain at risk for adverse liver-related events such as HCC.[36-39] By using PSM and IPTW to balance the background characteristics of our comparative patient groups and performing multiple sensitivity and subgroup analyses, our study expands on prior knowledge[11,40] and provides robust evidence of the negative impact of metabolic diseases, especially diabetes, on both liver outcomes and overall and non-liver related mortality among patients treated with first-line NAs. Prior studies were limited by small sample sizes, single-center study designs, and/or a focus mainly on liver outcomes.[11,40] Our study cohort was based on patients from 30 centers across different world regions and our sample size

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Table 3. Cox regression of long-term outcomes of CHB patients with metabolic diseases with or without diabetes after excluding patients with hepatic steatosis in the PSM cohort

	Events	HR (95% CI)	*P*-value
Liver cirrhosis			
No metabolic diseases	10/497	Reference	
Metabolic without diabetes	19/409	2.26 (1.05, 4.86)	0.037
Metabolic with diabetes	8/94	4.33 (1.71, 10.97)	0.002
HCC			
No metabolic diseases	37/704	Reference	
Metabolic without diabetes	28/574	0.91 (0.55, 1.48)	0.695
Metabolic with diabetes	15/157	2.15 (1.18, 3.93)	0.012
Overall death			
No metabolic diseases	75/702	Reference	
Metabolic without diabetes	56/574	0.91 (0.64, 1.29)	0.601
Metabolic with diabetes	36/156	2.41 (1.62, 3.59)	<0.001
Liver-related death			
No metabolic diseases	18/701	Reference	
Metabolic without diabetes	15/573	1.00 (0.50, 1.99)	0.997
Metabolic with diabetes	9/155	2.69 (1.21, 5.99)	0.016
Non-liver-related death			
No metabolic diseases	56/701	Reference	
Metabolic without diabetes	40/573	0.88 (0.58, 1.32)	0.526
Metabolic with diabetes	26/155	2.29 (1.43, 3.64)	0.001

CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; CHB, hepatitis B; PSM, propensity-score matching.

was large to allow for evaluation of a more comprehensive range of outcomes and robust adjustment for potential confounders.

In subgroup analysis, we found that the negative impacts of metabolic diseases, especially diabetes, were consistent across outcomes including liver-related outcomes as well as overall mortality and non-liver related mortality among patients without cirrhosis. However, the effect of diabetes appeared to be more muted with a significant association found only for overall death and non-liver-related death outcomes, but not HCC and liver-related death in an analysis adjusted for the presence of cirrhosis, which could be due to the fact that cirrhosis itself is one of the most important risk factors for HCC and liver-related death.[41]

A strength of the current study is that we provided outcome data based on the type of metabolic disease and not just the number of metabolic diseases. Our study data suggest that there is a hierarchy of metabolic factors in which the presence of diabetes is the most impactful factor in the natural history of CHB. These results have significant clinical implications. First, screening for metabolic diseases, especially diabetes, should be performed in patients with CHB, including those without cirrhosis, as CHB patients with diabetes may be at 2 to 4-fold higher risk of various adverse outcomes including overall mortality as compared to those without metabolic disease. Second, among CHB patients without metabolic disease, patients should be strongly encouraged by their providers to make lifestyles changes to prevent the development of metabolic diseases, especially diabetes. Third, our data highlight the need for a multidisciplinary approach to patients with CHB that should include providers familiar with the management of metabolic diseases, as prior studies have observed reduced HCC risk in diabetic CHB patients with adequate glycemic control.[14,18,42]

Currently, the exact underlying mechanisms linking diabetes and adverse liver and non-liver outcomes among patients with CHB are unclear. However, diabetes has been demonstrated to promote fibrosis progression and HCC via multiple mechanisms.[43,44] Diabetes may contribute to fibrosis

progression and cirrhosis by modulating several key processes implicated in fibrogenesis, including activation of hepatic stellate cells, inflammation, angiogenesis, apoptosis, and hepatic sinusoidal capillarization.[43,45] In addition, hyperglycemia, hyperinsulinemia, insulin resistance, and activation of insulin-like growth factor signaling pathway have been suggested to be involved in the initiation and progression of HCC in diabetes.[44,46] More studies are needed to elucidate the precise mechanisms underlying the observed association between diabetes and CHB disease progression to inform further therapeutic development.

It is also important to note that hepatic steatosis can be a potential confounder when evaluating the impact of metabolic disease on the natural history of CHB. However, the association of hepatic steatosis and poor liver outcomes in CHB remains controversial. A recent meta-analysis found a higher risk of poor liver outcomes in CHB patients with hepatic steatosis,[47] but the estimates in this study were pooled from very heterogeneous measurements (e.g., HR and odds ratios), limiting their conclusions. In our study, hepatic steatosis was associated with a lower risk of cirrhosis, HCC, and liver-related death, which is consistent with results from another recent meta-analysis that included individual patient level data with background risks balanced by IPTW.[34] Nevertheless, we accounted for the effect of hepatic steatosis by matching for this factor in our PSM. We additionally performed sensitivity analyses excluding patients with hepatic steatosis in all study groups and results were consistent with the primary analyses. Together, our findings suggest that the negative impact of diabetes on long-term adverse outcomes in NA-treated CHB patients is likely due to diabetes itself and independent of hepatic steatosis. Our findings are also in line with prior reports noting the distinct effects of hepatic steatosis and metabolic dysfunction on HCC risk in untreated patients with CHB.[35] However, additional studies with larger sample sizes are needed to explore the interactions between hepatic steatosis and metabolic dysfunction on the long-term outcomes of CHB patients treated with NAs.

Our study had several limitations. First, it was retrospective in nature, which could have introduced bias. However, well-defined outcomes and a structured data frame with a unified set of variable definitions were used for data collection across different centers to reduce potential biases. Second, although patients from both the East and West were included in the study, most included patients were of Asian ethnicity independent of geographic location, which is consistent with the disease burden. Thus, more studies of patients of non-Asian ethnicities are needed to validate our findings. Third, our study lacked detailed data on other factors that can impact the risk of adverse liver outcomes in patients with CHB such as statin or metformin use,[48,49] glycemic control,[18] or diabetes that developed later during follow-up, and further studies are needed to evaluate the impact of these factors. Lastly, obesity as defined in general and in this study was based only on BMI, which does not take in account the distribution of visceral fat that might be better measured by waist circumference. However, we lacked detailed data on waist circumference to include in our analyses.

In conclusion, the presence of diabetes rather than the number of metabolic diseases was the major factor associated with a higher risk of adverse long-term outcomes in CHB patients treated with NAs. Prevention and management of metabolic diseases, especially diabetes, is important to consider in the management of patients with CHB.

Authors' contribution

Data collection, data interpretation, manuscript edition, and final approval: All authors. Study design and data analysis: Rui Huang and Mindie H. Nguyen. Manuscript drafting: Rui Huang and Mindie H. Nguyen. Study concept and study supervision: Mindie H. Nguyen.

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Conflicts of Interest

Daniel Q. Huang: Advisory board: Gilead and Roche. Cheng-Hao Tseng: Speaker: Roche. Wan-Long Chuang: Member of Advisory Board: Gilead, AbbVie, BMS, Roche, Vaccitech and PharmaEssentia; Speaker: Gilead, AbbVie, BMS and Roche. Ming-Lung Yu: Research grant from Abbvie, BMS, Gilead, Merck and Roche diagnostics. Consul-

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tant: Abbott, Abbvie, BMS, Gilead, Roche and Roche diagnostics; Speaker: Abbvie, BMS, Eisai, Gilead, Roche and Roche diagnostics. Hidenori Toyoda: Speaker's bureau/fees: AbbVie, Gilead Sciences, Takeda Pharmaceutical, Eisai, Kowa, Terumo, Fujifilm WAKO, Chugai, AstraZeneca, and Bayer. Yasuhito Tanaka: Lecture fee or other financial support: AbbVie GK, Gilead Sciences, Inc., Chugai Pharmaceutical Co., Ltd., ASKA Pharmaceutical Holdings Co., Ltd., OTSUKA Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., GlaxoSmithKline PLC, AstraZeneca, Eisai, HU frontier; Medical research expenses: AbbVie GK., FUJIREBIO Inc., Sysmex Corp, GlaxoSmithKline PLC., Gilead Sciences, Inc., Janssen Pharmaceutical K.K., Scholarship donations: AbbVie GK., OTSUKA Pharmaceutical Co., Ltd. Chao Wu: Research grants: Gilead Sciences. Mindie H. Nguyen: Research grants via Stanford University from Pfizer, Enanta, Astra Zeneca, GSK, Delfi, Innogen, Exact Science, CurveBio, Gilead, Vir Biotech, Helio Health, National Institute of Health, Glycotest and personal fees from consulting/advisory board from Exelixis, Gilead, GSK. Jee-Fu Huang: Consultant of Roche, Gilead, Sysmex, Aligos and speaker for Abbvie, Gilead, Merck, Sysmex, and Novo Nordisk.

SUPPLEMENTARY MATERIAL

Supplementary material is available at Clinical and Molecular Hepatology website (http://www.e-cmh.org).

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