Association Between the Presence of Metabolic Comorbidities and Liver-Related Events in Patients With Chronic Hepatitis B

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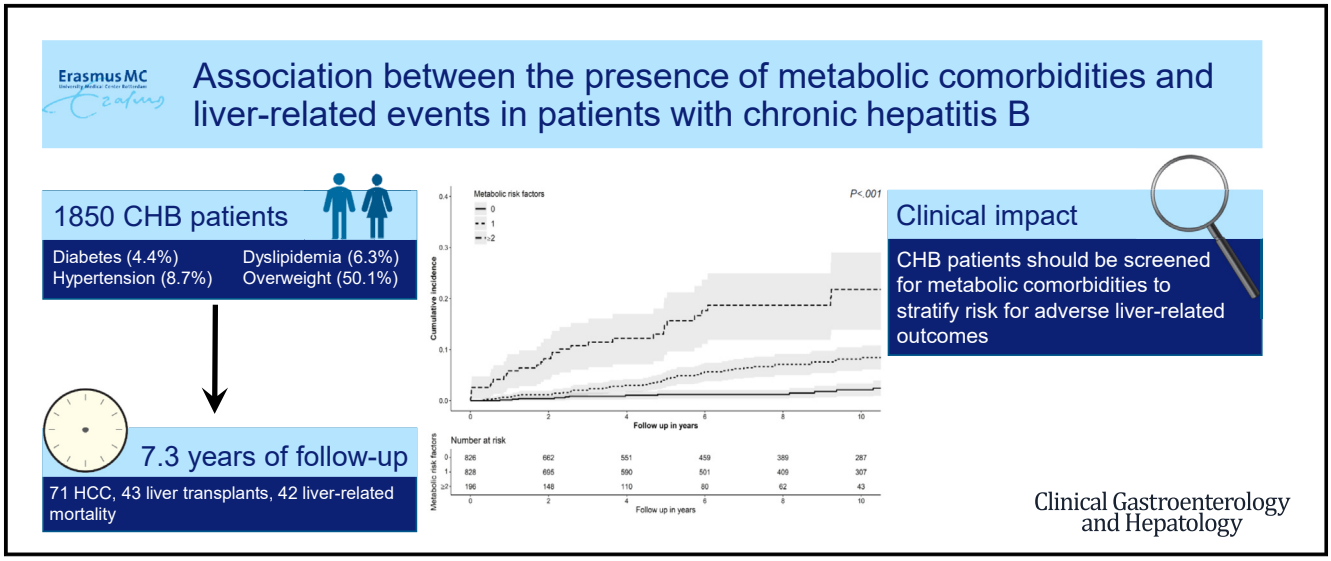

BACKGROUND & AIMS: **Patients with chronic hepatitis B (CHB) are at increased risk of hepatocellular carcinoma and (liver-related) mortality. In addition to hepatitis B–related factors, metabolic comorbidities may contribute to the progression of fibrosis. Therefore, we studied the association between metabolic comorbidities and adverse clinical outcomes in patients with CHB.**

METHODS: **We conducted a retrospective cohort study of CHB patients attending the Erasmus MC University Medical Center (Rotterdam, The Netherlands) and CHB patients who underwent liver biopsy at the Toronto General Hospital (Toronto, Canada). The presence of metabolic comorbidities (ie, overweight, diabetes mellitus, hypertension, and dyslipidemia) was assessed based on chart review. The primary end point was liver-related events, defined as the first composite of hepatocellular carcinoma, liver transplantation, or liver-related mortality.**

RESULTS: **We analyzed 1850 patients, of whom 926 (50.1%) were overweight, 161 (8.7%) had hypertension, 116 (6.3%) had dyslipidemia, and 82 (4.4%) had diabetes. During a median follow-up period of 7.3 years (interquartile range, 2.9–11.5 y), a total of 111 first events were recorded.**

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Abbreviations used in this paper: aMAP, age, male, albumin–bilirubin, and platelets; CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; IQR, interquartile range; LSM, liver stiffness measurement.

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Hypertension (hazard ratio [HR], 8.3; 95% CI, 5.5–12.7), diabetes (HR, 5.4; 95% CI, 3.2–9.1), dyslipidemia (HR, 2.8; 95% CI, 1.6–4.8), and overweight (HR, 1.7; 95% CI, 1.1–2.5) were associated with an increased risk for liver-related events. The presence of multiple comorbidities further increased the risk. Findings were consistent for patients with and without cirrhosis, among noncirrhotic hepatitis B e antigen–negative patients with hepatitis B virus DNA less than 2000 IU/mL and in multivariable analysis adjusting for age, sex, ethnicity, hepatitis B e antigen status, hepatitis B virus DNA, use of antiviral therapy, and the presence of cirrhosis.

CONCLUSIONS: **Metabolic comorbidities in CHB patients are associated with an increased risk for liver-related events, with the highest risk observed in patients with multiple comorbidities. Findings were consistent in various clinically relevant subgroups, underscoring the need for thorough metabolic assessment in patients with CHB.**

Keywords: Hepatocellular Carcinoma; Liver Transplantation; Liver-Related Mortality; Metabolic Comorbidities.

Chronic hepatitis B (CHB) infection is a major global health problem. According to the World Health Organization, more than 296 million people are chronically infected with hepatitis B, resulting in almost 820,000 deaths per year.[1] The leading causes of death among patients with CHB are hepatocellular carcinoma (HCC) and liver cirrhosis–related complications. Although antiviral treatment is now widely available and can effectively suppress serum hepatitis B virus (HBV) DNA levels, antiviral therapy reduces, but does not eliminate, the risk of adverse clinical outcomes.[2] This partially may be explained by the rapid increase in the prevalence of the metabolic syndrome, comprising overweight, diabetes mellitus, hypertension, and dyslipidemia, in patients with CHB. Several small studies have suggested that the individual components of the metabolic syndrome may increase the risk of fibrosis progression and the development of HCC in CHB patients.[3–5] Moreover, in a recent study we showed that the presence of metabolic-associated fatty liver disease was associated with adverse clinical outcomes, however, the presence of hepatic steatosis alone was not a risk factor.[6] This suggests that the individual components of the metabolic syndrome have an important contributing role. The need for further studies is illustrated by a recent systematic review and meta-analysis that could provide only pooled estimates for diabetes mellitus because of a paucity of data for the other elements of the metabolic syndrome.[7]

Therefore, this study aimed to investigate the association between metabolic comorbidities and liver-related outcomes in CHB.

Methods

Patients and Study Design

This retrospective cohort study included all consecutive CHB patients between 1980 and 2020 from the outpatient clinic of the Department of Gastroenterology and Hepatology of the Erasmus MC University Medical Center (Rotterdam, The Netherlands), and all consecutive CHB patients who underwent liver biopsy at the Toronto General Hospital (Toronto, Canada), who were enrolled in a previous analysis on the association between fatty liver disease and outcomes in CHB.[8] For the current analysis, patients were excluded for the following reasons: (1) presence of viral co-infections (hepatitis D virus, hepatitis C virus, human immunodeficiency virus); (2) presence of other chronic liver disease (alcoholic liver disease, Wilsons disease, primary biliary cholangitis, primary sclerosing cholangitis, and hemochromatosis); (3) HCC diagnosis within 6 months from the first visit; and (4) insufficient data in the medical file for analysis.

Data Collection

Patient charts were reviewed individually by the investigators. Data were collected on patient demographics (date of birth, sex, ethnicity), anthropometric measurements (length and weight), presence of metabolic comorbidities, antiviral treatment, liver biochemistry, and virology. Information on the presence of liver steatosis, fibrosis, and/or cirrhosis was obtained from ultrasound reports, liver stiffness and controlled attenuation parameter assessment, and/or liver histology whenever available.

Variables and Clinical Definitions

Biochemistry and virology obtained within 1 year of the first positive hepatitis B surface antigen test were used for analysis. The following metabolic factors were assessed by chart review: (1) diabetes mellitus, which was based on medical history or use of antidiabetic medication; (2) hypertension, which was based on the medical history or use of antihypertensives; (3) dyslipidemia, which was based on medical history or serum hypercholesterolemia or statin use; and (4) overweight, defined as body mass index 25 kg/m^2 or higher for non-Asians and 23 kg/m^2 or higher for Asians.[9] Metabolic comorbidities were considered present when the

diagnostic criteria were met at the time of or within 3 years after the index date. This cut-off date was chosen because metabolic comorbidities typically present between 4 and 6 years before the formal diagnosis.[10] Cirrhosis was based on liver biopsy showing meta-analysis of histological data in viral hepatitis (METAVIR) score F4, or on a liver stiffness measurement (LSM) greater than 12.2 kPa.[11] In patients without available data on histology or LSM, cirrhosis could be ruled out based on ultrasound findings compatible with cirrhosis and/or portal hypertension. Antiviral treatment was defined as treatment with a potent antiviral agent (including entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide). The age, male, albumin–bilirubin, platelet (aMAP) score was calculated as reported in the original article by Fan et al,[12] and patients were classified as low, intermediate, and high risk based on previously reported cut-off values (0–50, 50–60, 60–100).[12]

Follow-Up Evaluation and Outcomes

The primary end point of the study was the occurrence of a liver-related event, defined as the first of a composite of HCC, liver transplantation, or liver-related mortality. The HCC diagnosis was based on typical radiologic findings and/or histology whenever available. Liver transplantation and mortality were assessed through individual chart review. Liver-related mortality was defined as death resulting from HCC, (acute on chronic) liver failure, and death resulting from complications of cirrhosis (eg, variceal bleeding).

Statistical Analysis

Cohort characteristics were described as counts with percentages (%) for categoric variables, as means with SD for normally distributed continuous variables, and as the median with the interquartile range (IQR) for non-normally distributed continuous variables. Study differences between subgroups were described using the analysis of variance test for normally distributed continuous data and the Kruskal–Wallis test for non-normally distributed continuous data. For categoric data, the chi-square test was performed.

Life-table methods, the Kaplan–Meier estimator, and univariable and multivariable Cox regression models were used to study the association between metabolic comorbidities and liver-related events. Metabolic comorbidities with a *P* value less than .05 on univariate analysis were combined to assess the cumulative risk effect. Analyses were performed in the overall population, and stratified by ethnicity, presence of cirrhosis, and by aMAP risk categories. A separate analysis also was performed among noncirrhotic hepatitis B e antigen (HBeAg)-negative patients with HBV DNA levels less than 2000 IU/mL at the time of enrollment.

What You Need to Know

Background

In chronic hepatitis B (CHB) patients, the presence of metabolic comorbidities (diabetes, hypertension, dyslipidemia, and overweight) may contribute to the risk of the development of hepatocellular carcinoma and (liver)-related mortality.

Findings

Metabolic comorbidities in CHB patients are associated with an increased risk for liver-related events. The highest risk was observed in patients with multiple comorbidities. Findings were consistent in patients with and without cirrhosis, among noncirrhotic hepatitis B e antigen–negative patients with hepatitis B virus DNA levels less than 2000 IU/mL and in multivariable analysis adjusting for age, sex, ethnicity, hepatitis B e antigen status, hepatitis B virus DNA, use of antiviral therapy, and the presence of cirrhosis.

Implications for patient care

CHB patients should be screened for metabolic comorbidities such as diabetes, hypertension, dyslipidemia, and overweight to stratify their risk of adverse liver-related outcomes.

Multivariable Cox regression models were adjusted for the established predictors of liver-related events (age, sex, ethnicity, cirrhosis, HBeAg status, and use of potent antiviral treatment).

Differences were considered statistically significant when the *P* value was less than .05. For statistical data analysis, IBM SPSS for Windows version 25.0 (SPSS, Inc, Chicago, IL) was used.

Ethics

This study was conducted in accordance with the guidelines of the Declaration of Helsinki and the Principles of Good Clinical Practice. The requirement for informed consent was waived, and the individual institutional review boards gave the necessary approval. The study protocol was reviewed by the Erasmus MC Medical Ethical Committee (MEC-2020-0699).

Results

Patient Characteristics

For this study, 2248 patients were screened for eligibility, of these patients, 398 patients were excluded (Supplementary Figure 1). We analyzed 1850 patients, the majority of whom were male (61.1%), with a median age of 37 years (IQR, 28–47 y) at enrollment. Most of the patients were Asian (42.1%) or Caucasian (40.5%).

In the overall cohort, 1024 (55.4%) patients had 1 or more metabolic comorbidities; 926 (50.1%) patients were overweight, 161 (8.7%) had hypertension, 116 (6.3%) had dyslipidemia, and 82 (4.4%) had diabetes. A total of 186 (10.1%) of the patients had cirrhosis, this was either based on liver biopsy or LSM.

Patients with 1 or more metabolic comorbidities were older, were less frequently HBeAg positive, and more often had cirrhosis (Table 1).

During a median follow-up period of 7.3 years (IQR, 2.9–11.5 y), a total of 111 first events were recorded comprising 71 (3.8%) HCCs, 43 (2.3%) liver transplants, and 42 (2.3%) liver-related deaths. The 5-year and 10-year cumulative incidence of liver-related events was 4.0% (95% CI, 3.0–5.0) and 6.9% (95% CI, 5.5–8.3). The patient characteristics are described in Table 1.

Metabolic Comorbidities Are Associated With an Increased Risk for Liver-Related Events

The presence of hypertension (hazard ratio [HR], 8.3; 95% CI, 5.5–12.7; $P < .001$), diabetes (HR, 5.4; 95% CI, 3.2–9.1; $P < .001$), dyslipidemia (HR, 2.8; 95% CI, 1.6–4.8; $P < .001$), and overweight (HR, 1.7; 95% CI, 1.1–2.5; $P = .007$) were associated significantly with an increased risk for liver-related events (Supplementary Figure 2).

The presence of multiple comorbidities was associated with an additive risk of liver-related events (Figure 1). The 5-year and 10-year cumulative incidence for liver-related events was 1.2% and 2.1% for patients with no comorbidities, 4.2% and 8.2% for patients with 1 metabolic comorbidity, and 14.8% and 21.8% for 2 or more metabolic comorbidities, respectively. These findings were consistent for Caucasians ($P = .001$), Asians ($P = .022$), and others ($P = .005$).

Metabolic Comorbidities Are Associated With an Increased Risk for Liver-Related Events in Patients With and Without Cirrhosis

The overall 5-year and 10-year cumulative incidence for liver-related events among patients without cirrhosis were 2.9% and 5%, and 12.5% and 21.9%, respectively, among patients with cirrhosis.

The presence of 1 or more metabolic comorbidities was associated with an increased risk of liver-related events for patients with and without cirrhosis at the start of follow-up evaluation. Among patients without cirrhosis, the 5-year and 10-year cumulative probability of liver-related events were 1% and 1.6%, 3.1% and 6.5%, and 11.5% and 14.5% in those without metabolic comorbidities, those with 1 metabolic comorbidity, and those with 2 or more metabolic comorbidities, respectively ($P < .001$) (Figure 2*A*).

The cumulative probabilities of liver-related events at the 5-year and 10-year follow-up evaluation among patients with cirrhosis were 4.4% and 8.3% for those without metabolic comorbidities, vs 13.2% and 22% in case of 1 metabolic comorbidity, and 21.9% and 39.8% in case of 2 or more comorbidities, respectively ($P = .009$) (Figure 2*B*).

Metabolic Comorbidities Are Associated With an Increased Risk for Liver-Related Events in Patients With Intermediate and High Age, Male, Albumin–Bilirubin, Platelet Scores

The median aMAP risk score was 44 (IQR, 39–50), and 1328, 388, and 134 patients were classified as low, intermediate, and high risk. Patients with a low aMAP score had virtually no risk for liver-related events at 10 years (1.2%), compared with 8.5% among patients with an intermediate aMAP score and 50.2% among patients with a high aMAP score ($P < .001$) (Figure 3*A*). The presence of 1 or more metabolic comorbidities was associated with an increased risk for liver-related events among patients with an intermediate or high risk aMAP score ($P < .001$ for both) (Figure 3*B*).

Metabolic Comorbidities Are Associated With an Increased Risk for Liver-Related Events in Noncirrhotic Hepatitis B e Antigen–Negative Patients With Low Viral Load

The presence of metabolic comorbidities was associated with an increased risk of liver-related events among noncirrhotic HBeAg-negative patients with HBV DNA level less than 2000 IU/mL without antiviral treatment at the start of follow-up evaluation (n = 471). We observed no liver-related events among patients without metabolic comorbidities. In contrast, the 5-year and 10-year cumulative probabilities of liver-related events among patients with 1 metabolic comorbidity were 3.7% and 6.3%, and 15.6% and 21.6% among patients with 2 or more metabolic comorbidities, respectively ($P < .001$) (Figure 2*C*).

Presence of Metabolic Comorbidities Is Associated With an Increased Risk of Liver-Related Events in Multivariable Analysis

In a multivariable Cox regression analysis adjusting for age, sex, ethnicity, HBeAg status, HBV DNA, use of potent antiviral therapy, and presence of cirrhosis, we obtained similar results: presence of 1 metabolic comorbidity (adjusted HR, 2.6; 95% CI, 1.5–4.6) or 2 or more metabolic comorbidities (adjusted HR, 4.5; 95% CI, 2.3–8.5) were associated independently with an increased risk for liver-related events ($P < .001$) (Table 2).

Table 1. Patient Characteristics at Baseline

Characteristics	Overall (n = 1850)	Number of metabolic comorbidities			*P* value
		0 (n = 826)	1 (n = 828)	≥2 (n = 196)	
Age, *y*	37 (28–47)	32 (25–41)	38 (30–48)	48 (40–58)	<.001
Male gender, n (%)	1131 (61.1)	432 (52.3)	561 (67.8)	138 (70.4)	<.001
Ethnicity, n (%)					
Caucasian	749 (40.5)	316 (38.3)	341 (41.2)	92 (46.9)	.216
Asian	779 (42.1)	365 (44.2)	337 (40.7)	77 (39.3)	
Other	322 (17.4)	145 (17.6)	150 (18.1)	27 (13.8)	
Platelets, $\times 10^9$/L	207 (67)	208 (59)	208 (66)	204 (99)	.759
ALT, *U/L*	43 (26–81)	40 (23–84)	44 (29–77)	46 (32–89)	.006
Albumin, *g/L*	43 (4.6)	43 (3.9)	43 (4.6)	41 (6.7)	<.001
Total bilirubin, *μmol/L*	10 (7–15)	10 (10–14)	10 (7–14)	11 (8–17)	.014
ALBI score	-3.0 (0.4)	-3.0 (0.3)	-3.0 (0.4)	-2.7 (0.7)	<.001
HBeAg positive, n (%)	636 (34.4)	347 (42.0)	246 (29.7)	43 (21.9)	<.001
HBV DNA, log_{10} *IU/mL*	4.8 (3.2–7.3)	5.4 (3.5–8.0)	4.4 (3.0–7.0)	4.1 (2.8–6.0)	<.001
Cirrhosis, n (%)	187 (10.1)	50 (6.1)	83 (10.0)	54 (27.6)	<.001
Diabetes, n (%)	82 (4.4)	–	13 (1.6)	69 (35.2)	<.001
Dyslipidemia, n (%)	116 (6.3)	–	25 (3.0)	91 (46.4)	<.001
Hypertension, n (%)	161 (8.7)	–	41 (5.0)	120 (61.2)	<.001
Overweight, n (%)	926 (50.1)	–	749 (90.5)	177 (90.3)	.000
BMI	24.3 (22.0–27.6)	21.1 (20.0–22.7)	26.2 (24.1–28.8)	27.2 (25.0–29.4)	<.001
Antiviral therapy, n (%)	769 (41.6%)	303 (36.7)	365 (44.1)	101 (51.5)	<.001
Events, n (%)	111 (6.0)	16 (1.9)	63 (7.6)	32 (16.3)	<.001
HCC	71 (3.8)	15 (1.8)	41 (5.0)	15 (7.7)	<.001
Ltx	43 (2.3)	2 (0.2)	23 (2.8)	18 (9.2)	<.001
Liver-related death	42 (2.3)	5 (0.6)	27 (3.3)	10 (5.1)	<.001
aMAP risk groups, n (%)					<.001
Low	1328 (71.8)	682 (82.6)	558 (67.4)	88 (44.9)	
Intermediate	388 (21)	119 (14.4)	204 (24.6)	65 (33.2)	
High	134 (7.2)	25 (3.0)	66 (8.0)	43 (21.9)	

NOTE. Data are presented as means (SD), median (IQR), and n (%). Analysis of variance was used to study differences for normally distributed continuous data, the Kruskal–Wallis test was used for non-normally distributed continuous data, and the chi-square test was used for categoric data.
ALBI, albumin-bilirubin; ALT, alanine aminotransferase; BMI, body mass index; HBeAg, hepatitis B virus e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LTx, liver transplantation; aMAP, age, male, albumin–bilirubin, platelet.

Discussion

In this multicenter study of 1850 patients with CHB, the presence of metabolic comorbidities was associated with an increased risk for liver-related events, with the highest risk observed in patients with multiple metabolic comorbidities. Findings were consistent among various clinically relevant subgroups (ethnicity, noncirrhotic and cirrhotic, aMAP categories, and noncirrhotic HBeAg-negative patients with a low viral load) and in multivariable analysis adjusting for other potential predictors.

Although currently available antivirals are highly effective at suppressing HBV DNA levels, CHB patients remain at risk for disease progression and HCC.[2] In a recent study we showed that the presence of metabolic-associated fatty liver disease was an independent risk factor for adverse clinical outcomes among patients with CHB.[6] Importantly, the presence of hepatic steatosis without other signs of metabolic dysfunction was not associated with an increased risk of liver-related outcomes, suggesting that other processes associated with the metabolic syndrome may be important contributing factors. One such factor may be insulin resistance, which plays a pivotal role in the metabolic syndrome, and indeed has been associated with inflammation, the development of fibrosis, and the risk of cancer, including HCC.[13–15] In this study, we therefore assessed the

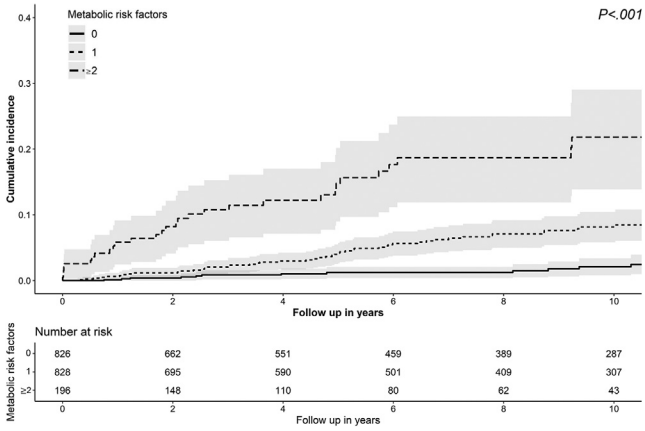

Figure 1. Cumulative incidence of liver-related events in the overall study population.

association between components of the metabolic syndrome and liver-related outcomes.

Our study shows that the individual components of the metabolic syndrome are risk factors for liver-related events, with an additive effect observed among patients with multiple metabolic comorbidities. Our findings corroborate other recent studies. One study from Taiwan,[5] in which 1690 male civil servants with CHB were included, suggested an increased risk for HCC and liver-related death in patients with metabolic comorbidities. However, this study included only male patients, had no data on antiviral treatment or HBV-related factors available, and only a few patients had multiple metabolic comorbidities. Another study from the Republic of Korea,[16] which used the Korean National Health Insurance Service database to estimate the risk of HCC, non-HCC cancer, and all-cause mortality in CHB patients, reported a 1.23-fold higher risk for HCC in patients with the highest metabolic risk profile (≥3 metabolic comorbidities). Our study adds to this emerging body of evidence by now providing solid data on the association between metabolic dysfunction and adverse liver-related outcomes in both Asians and non-Asians, among patients with and without cirrhosis, and adjusted for other HBV-related factors.

The primary aim of this study was to assess the association between metabolic comorbidities and liver-related outcomes, as opposed to the association with cardiovascular morbidity and mortality, which is well established. To make sure that the association with cardiovascular mortality would not drive any associations identified in this study, we focused on liver-related outcomes alone. Because patients with advanced liver disease are at risk of both HCC and liver-related death (either of which may necessitate liver transplantation), we believe the use of a composite of these end points that share the same pathophysiological pathways, is the most logical. However, we performed additional sensitivity analyses for incident HCC and all-cause mortality and found consistent results.

In our cohort, the patients with 2 or more metabolic comorbidities had a higher likelihood of cirrhosis, were more often HBeAg negative, and had slightly lower HBV DNA levels compared with subjects without metabolic comorbidities. This mainly is owing to the association of age with both metabolic dysfunction and higher prevalence of HBeAg-negative CHB, which is associated with lower HBV DNA levels. However, as can be judged from Table 1, mean HBV DNA levels still were higher than 4 log IU/mL in this subset of the cohort and the majority had HBV DNA levels higher than 2000 IU/mL; these patients therefore had significant HBV replication and are at risk of HBV-related disease progression. To confirm that the presence of metabolic comorbidities increases the risk of liver-related events independently of age we adjusted for age in multivariable regression analysis, and performed sensitivity analyses for patients aged 45 years and older; both showed consistent results.

Another important finding was that the presence of metabolic comorbidities was associated independently with adverse clinical outcomes across aMAP risk categories. We observed a negligible risk of adverse events in the low aMAP risk group during a follow-up period of 10 years. However, among patients with intermediate and high predicted risk, we observed a significantly increased risk for liver-related events in the presence

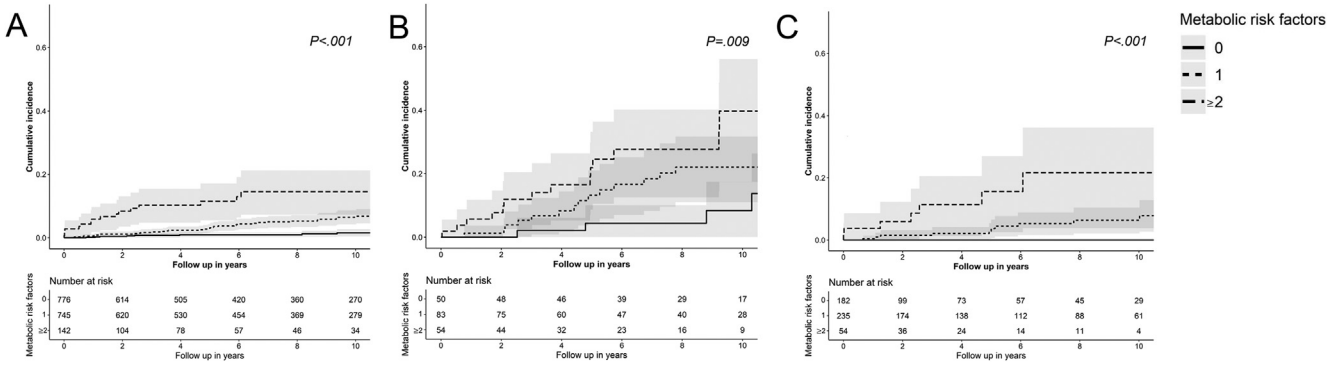

Figure 2. Cumulative incidences of liver-related events in (*A*) noncirrhotic patients, (*B*) cirrhotic patients, and (*C*) noncirrhotic HBeAg-negative patients with HBV DNA levels less than 2000 IU/mL.

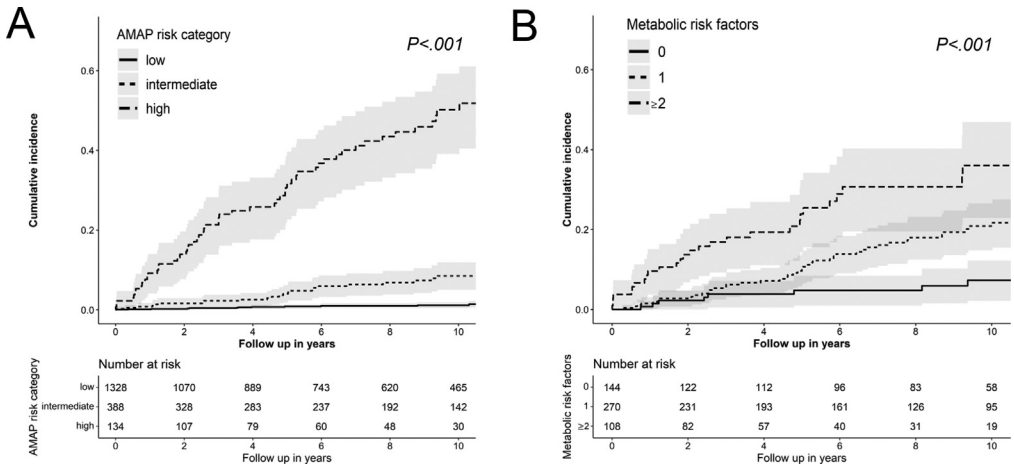

Figure 3. Cumulative incidences of liver-related events in (*A*) different age, male, albumin–bilirubin, platelet (aMAP) risk categories and (*B*) intermediate and high-risk aMAP score patients, all with 95% confidence shading.

of 1 or more metabolic comorbidities. This suggests that the presence of metabolic comorbidities should be taken into consideration when applying such risk scores to guide management aimed at improving liver-related outcomes.

Finally, and perhaps most importantly, our study shows that among noncirrhotic HBeAg-negative patients with low viral load, typically considered inactive HBV carriers at low risk of adverse outcomes, the risk of liver-related events remains increased in the presence of metabolic comorbidities. These findings suggest that thorough metabolic evaluation should be considered mandatory before patients are discharged from further follow-up evaluation.

Despite the fact that this was a large multicenter multi-ethnic cohort with a long follow-up period, there were some limitations. First, this was a retrospective cohort study involving only 2 centers and metabolic comorbidities potentially could have been underdiagnosed. Second, we assessed metabolic comorbidities at baseline and patients developing signs of metabolic dysfunction over time remained in the no-metabolic-comorbidity group in our analyses. However, such misclassification would result in bias toward finding no association, and it therefore is unlikely to have influenced the outcomes of this study. Third, despite our large cohort the number of patients in the different subgroup analysis were limited. Fourth, because of the retrospective design the primary indication for the use of statins or antihypertensive drugs, mostly started by the general practitioner, was not always clear. In addition, alcohol use may be a relevant risk factor for liver-related complications in patients with CHB. We excluded patients with a history of alcohol abuse, but concede that information on alcohol use may not always be reliable in retrospective studies. Finally, although we enrolled patients with a range of ethnicities, the majority were Caucasian or Asian, and external validation of our findings remains necessary for other ethnicities.

In conclusion, the presence of metabolic comorbidities is associated with an increased risk of liver-related events in patients with CHB, with the highest risk observed in patients with multiple comorbidities. Findings were consistent for patients with and without cirrhosis at study entry, across aMAP risk categories, and among noncirrhotic HBeAg-negative patients with a low viral load. Our findings support the need for thorough metabolic assessment in patients with CHB.

Table 2. Cox Proportional Hazard Regression Analysis

Variable	HR (95% CI)	*P* value
Gender, male vs female	1.99 (1.12–3.53)	.018
Age (per year)	1.06 (1.04–1.08)	<.001
Ethnicity		.011
Caucasian	Reference	
Asian	0.50	
Other	0.50	
Cirrhosis, yes vs no	2.36 (1.46–3.84)	<.001
Antiviral treatment, yes vs no	1.15 (0.72–1.83)	.559
HBeAg status, positive vs negative	1.02 (1.00–1.05)	.026
HBV DNA, *log IU/mL*	0.95 (0.89–1.02)	.167
Cumulative comorbidities		
1 comorbidity	2.80 (1.50–5.21)	.001
2 comorbidities	3.55 (1.71–7.36)	.001

HBeAg, hepatitis B virus e antigen; HBV, hepatitis B virus; HR, hazard ratio.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2023.03.024.

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Conflicts of interest

These authors disclose the following: Keyur Patel consults for, advises, and has received research grants from Gilead; Adriaan J. van der Meer has received research grants from Zambon, Gilead, and CymaBay, has received consultancy fees from Intercept and AOP Health, and has received speakers fees from AOP Health; Rob J. de Knegt is a speaker for Echosens, consults for AbbVie, and has received grants from AbbVie, Gilead, and Janssen; Bettina E. Hansen has received personal fees for consulting from Intercept, Cymabay, Mirum, Albireo, Chemomab, and Caliditas, and research support from Intercept, Cymabay, Mirum, and Albireo; Jordan J. Feld has received personal fees for consulting from AbbVie, Enanta, Gilead, Janssen, and Roche, and research funding from AbbVie, Abbott, Gilead, and FUJIFILM Wako Chemicals; Harry L. A. Janssen has received grants from AbbVie, Arbutus, Bristol Myers, Squibb, Gilead Sciences, Janssen, Merck, and Roche, and is a consultant for Aligos, Arbutus, Arena, Eiger, Enyo, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, Regulus, Roche, VBI Vaccines (Variation Biotechnologies), Vir Biotechnology, Inc, and Viroclinics; and Milan J. Sonneveld has received speaker's fees and research support from Fujirebio, and has received grants from Gilead. The remaining authors disclose no conflicts.

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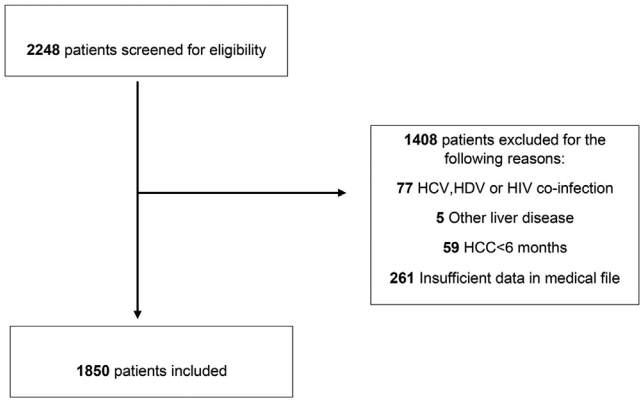
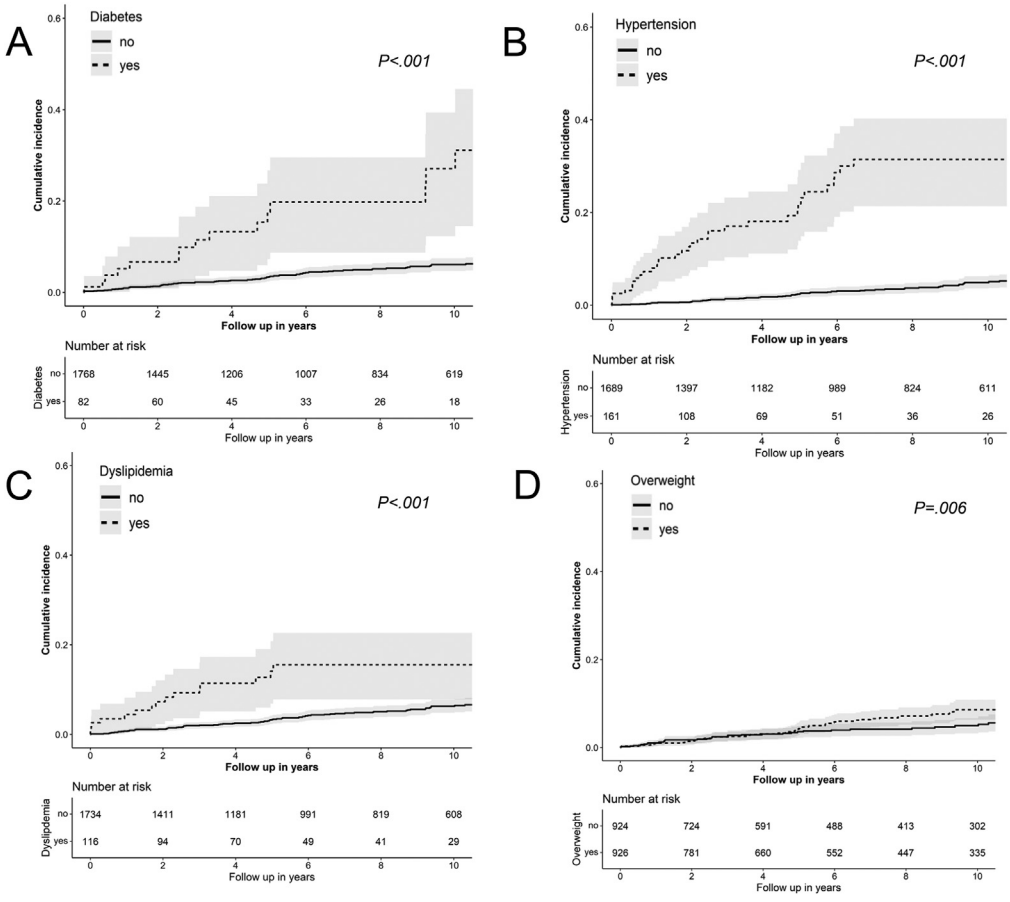


Supplementary Figure 1. Flow diagram of participants for the study. HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus.



Supplementary Figure 2. Cumulative incidences of liver-related events in (*A*) patients with and without diabetes, (*B*) patients with and without hypertension, (*C*) patients with and without dyslipidemia, and (*D*) patients with and without overweight.