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ORIGINAL RESEARCH—CLINICAL

Severe Hepatic Steatosis Is Associated With Low-Level Viremia and Advanced Fibrosis in Patients With Chronic Hepatitis B in North America

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BACKGROUND AND AIMS: The obesity epidemic has increased the risk of nonalcoholic fatty liver disease (NAFLD) in both the general and chronic hepatitis B (CHB) populations. Our study aims to determine the prevalence of NAFLD in patients with CHB based on controlled attenuation parameter (CAP) and the epidemiological, clinical, and virological factors associated with severe hepatic steatosis. **METHODS:** The Canadian Hepatitis B Network cohort was utilized to provide a cross-sectional description of demographics, comorbidities, antiviral treatment, and hepatits B virus (HBV) tests. Liver fibrosis and steatosis were measured by transient elastography and CAP, respectively. Any grade and severe steatosis were defined as CAP >248 and >280 dB/m, respectively. Advanced liver fibrosis was defined as transient elastography measurement >10.7 kPa. **RESULTS:** In 1178 patients with CHB (median age: 47.4%, 57.7% males, 75.7% Asian, 13% African, 6.5% White, 86% HBV e antigen negative, median HBV DNA of 2.44 $\log_{10}$IU/mL, 42.7% receiving treatment), the prevalence of any grade and severe steatosis was 53% and 36%, respectively. In the multivariate analysis, obesity was a significant predictor for severe steatosis (adjusted odds ratio: 5.046, 95% confidence interval: 1.22–20.93). Severe steatosis was a determinant associated with viral load (adjusted odds ratio: 0.385, 95% confidence interval: 0.20–0.75, $P < .01$; r = −0.096, $P = .007$) regardless of antiviral therapy, age, and alanine aminotransferase levels. **CONCLUSION:** In this large multiethnic CHB population, hepatic steatosis is common. Severe steatosis is independently associated with higher fibrosis, but negatively with HBV DNA, regardless of antiviral therapy history.

Keywords: Hepatitis B; Hepatic Steatosis; Controlled Attenuated Parameter (CAP); Transient Elastography (TE); Fatty Liver Disease

Introduction

The global increase in risk factors associated with the metabolic syndrome (MetS) such as obesity, sedentary lifestyle, Western dietary pattern, insulin resistance, and hyperlipidemia has led to an epidemic of nonalcoholic fatty liver disease (NAFLD).[1,2] NAFLD is clinically diagnosed as greater than 5% hepatic steatosis without heavy alcohol use (based on the definition by the National Institute on Alcohol Abuse and Alcoholism, ie, an average of more than 1 unit of alcohol per day in female and more than 2 units of alcohol per day in males). In parallel, the prevalence of NAFLD is increasing in the ∼260 million people living with chronic hepatitis B (CHB), affecting between 22% and 51% of patients.[3–5] Despite the availability of an effective vaccine and oral antiviral treatment, CHB remains a global health burden as the seventh highest cause of mortality worldwide and responsible for about 687,000 deaths per year.[6] Liver fibrosis is a shared pathological process in CHB and NAFLD. It is particularly important to understand the concurrent impact of hepatic steatosis, especially severe steatosis, on the efficacy of CHB therapy, fibrosis progression, and hepatocellular carcinoma (HCC) development.[7–11] Previous studies on the relationship between hepatic steatosis and CHB report conflicting findings in a single ethnic cohort. Few have reported an inverse relationship between hepatic steatosis and hepatitis B virus (HBV) viral load (HBV DNA), whereas others have reported no significant association. Investigating the interaction between hepatic

Abbreviations used in this paper: **ALT, alanine aminotransferase; APRI, AST-platelet index; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; CHB, chronic hepatitis B; FIB-4, fibrosis-4; HBeAg, HBV e antigen; HBsAg, HBV surface antigen; HBV, hepatitis B virus; HBx, HBV X protein; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; MetS, metabolic syndrome; MRI, magnetic resonance imaging; NA, nucleos(t)ide analog; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; qHBsAg, quantitative HBsAg; TE, transient elastography; US, ultrasound.**

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steatosis and HBV-related factors, especially in more diverse CHB populations, may inform clinical management and monitoring recommendations.[12]

Liver biopsy is the gold standard for assessment of hepatic steatosis and fibrosis but is limited by invasiveness, potential serious complications, and sampling error. Noninvasive imaging such as ultrasound (US) and magnetic resonance imaging (MRI) have varying utility; MRI is costly, and US is more accessible but has high observer variability and low sensitivity especially when hepatic fat content is < 30%.[13] More recently, liver stiffness assessment with transient elastography (TE, FibroScan®) and controlled attenuation parameter (CAP) are convenient noninvasive tests that are validated to quantify hepatic fibrosis and steatosis. CAP utilizes an algorithm to measure US attenuation with vibration-controlled elastography to calculate the attenuation of the ultrasound signal, expressed in decibels per meter (dB/m).[14,15] In clinical practice, CAP is useful for screening and serial assessment of hepatic steatosis. CAP correlates with the grade of hepatic steatosis, assessed by hepatic US, and has been validated using the gold standard of liver histology.[16–18] In Asian (Chinese) patients with CHB, one study demonstrated that CAP was highly accurate in the detection of severe steatosis (>66%) with a >90% sensitivity and specificity and hence may be of high predictive value to screen for NAFLD in patients with CHB.[19] Several studies have reported outcomes in patients with NAFLD and CHB, mainly in single centre and/or Asian cohorts (ie, Hong Kong, Israel, Malaysia).[12,20,21] However, there are limited published data on the utility of CAP in viral hepatitis, especially in a more diverse patient cohort.[18,22,23] Liver inflammation in patients with CHB and NAFLD may have a synergistic impact on the risk of fibrosis and liver-related mortality. In this large cross-sectional, multisite study in Canada, we evaluated a diverse cohort of patients with CHB for hepatic steatosis using CAP. The objectives of this study are to determine the prevalence of NAFLD in patients with CHB based on CAP measurement and the epidemiological features, clinical, and virological factors (ie, HBV DNA levels) associated with concurrent severe hepatic steatosis.

Methods

Study Design

This was a cross-sectional, retrospective cohort study of patients followed up in 11 hepatology or infectious disease clinics in 6 provinces across Canada, involved in the Canadian Hepatitis B Network. Each site conducted data collection by reviewing electronic and paper patient charts. Deidentified information was entered into a web-based database registry hosted by the University of Calgary, Canada (ie, REDCap®). Eligible participants provided informed consent to participate, or were included with a waiver of consent, based on each site's local research ethics board (REB) approval. All data received were anonymous and collected under an approved University of Calgary Conjoint Ethics Research Board–approved protocol (Ethics ID # REB16-0041) and analyzed under Conjoint Ethics Research Board Ethics ID REB19-0189.[24]

Data Elements, Inclusion/Exclusion

Adult participants older than 18 years with confirmed chronic HBV infection (ie, hepatitis B surface antigen [HBsAg] positive for greater than 6 months) who were seen by a physician affiliated with the Canadian HBV Network after January 1st, 2012, were included in this study. Patients were excluded if they had a history of alcohol misuse disorder, coinfection with hepatitis C, hepatitis D infection, human immunodeficiency virus (HIV), no liver stiffness measured by TE, or no CAP measurement (Figure 1). Available data elements included age, sex, ethnicity, country of birth, family history of liver disease, alcohol intake, smoking and recreational drug use, psychiatric comorbidities, extrahepatic cancer, and other non–liver-related chronic disease (ie, cardiovascular disease) considered clinically significant by local site investigator. Standard laboratory tests included alanine aminotransferase (ALT) (upper limit of normal >25 U/L in females and >30 U/L in males),[25] HBV DNA, HBV eAg (HBeAg), and if available, quantitative (q) HBsAg and genotype were recorded. A history of MetS and associated comorbidities, including diabetes, obesity, cardiovascular disease, hypertension, and dyslipidemia, was noted. MetS was classified based on the World Health Organization criteria of insulin resistance and at least 2 of the following: hypertension, low high-density lipoprotein levels, plasma triglyceride levels greater than 1.7, or central obesity based on waist circumference. Diabetes mellitus was defined as glycosylated hemoglobin >6.5%, fasting plasma glucose >7.0 mmol/L, or specific treatment for diabetes mellitus. Clinical outcomes including end-stage liver disease complications (portal hypertension, cirrhosis, liver decompensation with variceal bleeding and ascites, and hepatocellular carcinoma) were noted from clinician reports and other medical records including diagnostic imaging. Treatment was defined as a patient who received anti-HBV therapy at any time point (ie, nucleos(t)ide analog [NA] or interferon) including those who received multiple treatment courses or prior treatment that were since discontinued.

Liver Stiffness and CAP Measurements by TE

Fasting liver stiffness and CAP measurements were obtained by TE (FibroScan®, Echosens, Paris, France) and performed by experienced operators at each center as per standard procedures using either the standard M probe or the XL probe (ie, minimum of 10 valid readings, with at least 60% success rate and an interquartile range of <30% of the median value). CAP was calculated simultaneously as liver stiffness, and the reading was considered reliable only when successful and reliable stiffness measurements were obtained.[15] The TE cutoffs used for F2 and F3 fibrosis were 7.3 kPa and 10.7 kPa, respectively. Hepatic steatosis was defined as CAP >248 dB/m. Mild/moderate steatosis (10%–66%) and severe steatosis (>66%) were defined as CAP 248–279 dB/M and CAP >280 dB/m, respectively, based on the recent meta-analysis correlating CAP measurements with histologic steatosis grading.[17]

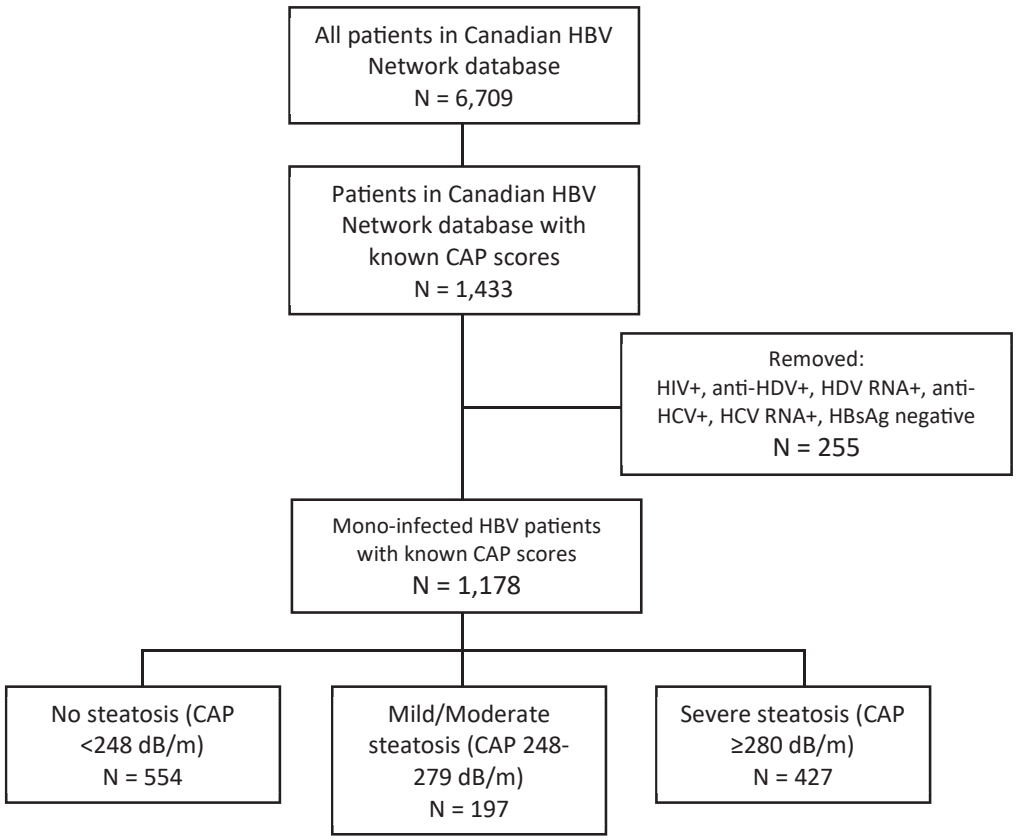

Figure 1. Flowchart of inclusion and exclusion criteria.

Statistical Analyses

Logistic regression models were used to identify independent determinants associated with severe steatosis (CAP ≥280 dB/m) and detectable HBV DNA levels. These models adjusted for demographic and clinical variables such as age, sex, ethnicity, history of smoking, metabolic syndrome, laboratory variables (HBeAg and ALT), and antiviral treatment. All regression estimates are reported as adjusted odds ratio (aOR) with corresponding 95% confidence interval (CI). Correlation of steatosis (based on the CAP score) and HBV DNA levels with demographic and clinical variables were performed using Pearson's correlation method. Data were summarized with the r and corresponding *P* values, and $P < .05$ was considered significant. Simple and multiple linear regressions of the significant findings were performed, and significant findings displayed with scatterplots. Logistic regression and correlation statistical analysis were performed using IBM SPSS Statistics 27.0.1.0.

Continuous data were summarized with the mean, 95% CI, and count (n). For comparisons between all 3 steatosis groups (no, mild/moderate, and severe steatosis), one-way analysis of variance was used. For dichotomous comparison between no-steatosis vs severe-steatosis groups, a 2-tailed t test was used. Severe steatosis (CAP > 280 dB/m) was chosen for our statistical comparisons because there were some emerging data suggesting higher CAP cutoffs might be needed to detect moderate to severe steatosis in individuals with higher body mass index (BMI).[26] Furthermore, CAP >280 dB/M was used based on published data showing this cutoff was independently associated with severe liver fibrosis in treatment-naïve and on-treatment Hep cohorts.[9] Categorical data were summarized as proportion using mean % (n/n known). Chi-squared tests were used for comparisons in 3 groups. For both continuous and categorical variables, all missing data were excluded. A *P* value $< .05$ was considered to be statistically significant. GraphPad Prism 9.0.0 (San Diego, CA) was used for statistical analysis.

Results

Study Population Demographics

Among the 6709 patients in the Canadian Hepatitis B Network database,[24] 1433 (21.4%) had CAP scores recorded. Two hundred fifty-five patients were excluded owing to other viral coinfections (ie, hepatitis C, hepatitis D, and HIV),[27,28] alcohol misuse disorder, other liver disease (eg, autoimmune), or HBsAg clearance.[29] In total, 1178 patients mono-infected with HBV were included for analysis (median age: 47.4 years, 57.7% male, 75.7% Asian, 13% African, 6.5% White, and 5.1% other ethnicity), out of whom 86% were HBeAg negative, median HBV DNA of 2.44 $\log_{10}$IU/mL (interquartile range: 2.55interquartile range), and 42.7% underwent antiviral treatment (Table 1). Based on CAP measurement, 554 patients with CHB infection had no steatosis (CAP < 248 dB/m), 197 had mild/moderate (CAP 248–279 dB/m), and 427 had severe steatosis (CAP ≥ 280 dB/m, Figure 1). Compared with the group with no steatosis, individuals with severe steatosis were older (50.5 years vs 46.2 years, $P < .001$), male (63.3% vs 52.5%, $P < .001$), White (9.2% vs 4.3%, $P = .003$),

with smoking history (18.3% vs 11.7%, $P = .004$), as well as higher BMI (28.0 vs 23.1, $P < .001$, Table 1).

Analysis of Association Between Hepatic Steatosis, HBV DNA, and Liver Fibrosis

Most patients were HBeAg negative. Steatosis status was not influenced by HBeAg status (Table 1). Patients with severe steatosis had lowest HBV DNA levels compared with the other groups (HBV DNA 2.74–2.45–2.36 $\log_{10}$IU/mL in none, mild/moderate, and severe steatosis respectively, $P = .04$ and .01).

A higher proportion of patients with ALT above the upper limit of normal was found in the no-steatosis vs severe-steatosis group (64.9% vs 49.5%, $P < .001$, Table 1). ALT was one of the independent predictors of detectable HBV DNA (odds ratio [OR]: 1.952; 95% CI: 1.41–2.71, $P < .001$; aOR 3.661, 95% CI: 1.82–7.35, $P < .001$, Table 2). A positive correlation was also observed between ALT and HBV DNA level by linear regression analysis ($r = 0.319$, $P < .001$, Figure 2A and Figure A1A). Other independent determinants associated with detectable HBV DNA levels include age >60 years (OR: 0.393, 95% CI: 0.28–0.55;

Table 1. Summary of Demographics, History, and Comorbidities/Hepatic Complications in Individuals Without Hepatic Steatosis (CAP < 248 dB/M, n = 554), Mild/Moderate Steatosis (CAP: 248–279 dB/M, n = 197), and Severe Steatosis (CAP: ≥ 280 dB/M, n = 427) Followed in the Canadian HBV Network

Baseline characteristics	No steatosis (n = 554)	Mild/moderate steatosis (n = 197)	Severe steatosis (n = 427)	*P* value (all 3 groups)[a]	*P* value (no steatosis vs severe steatosis)[b]
Age (y)	46.2 (45.1–47.3, 554)	51.0 (49.1–52.8, 197)	50.5 (49.3–51.7, 427)	<.001[e]	<.001[e]
Male sex	52.5% (289/551)	59.9% (118/197)	63.3% (269/425)	.002[e]	<.001[e]
Country of birth					
Born in Canada	4.1% (18/436)	1.9% (3/158)	6.2% (23/371)	.080	.182
Born outside Canada	95.9% (418/436)	98.1% (155/158)	93.8% (348/371)	.080	.182
Ethnicity					
Asian	77.3% (394/510)	76.8% (142/185)	73.5% (297/404)	.400	.191
Black (African/Caribbean)	14.9% (76/510)	10.8% (20/185)	11.6% (47/404)	.214	.151
White	4.3% (22/510)	7.6% (14/185)	9.2% (37/404)	.012[e]	.003[e]
Other ethnicity (Incl. Indigenous)	4.1% (21/510)	5.9% (11/185)	5.9% (24/404)	.390	.206
Other sociodemographic factors					
Alcohol use history[f]	21.1% (117/554)	21.3% (42/197)	23.7% (101/427)	.613	.344
Smoking history	11.7% (65/554)	14.2% (28/197)	18.3% (78/427)	.016[e]	.004[e]
Body mass index (kg/m^2)	23.1 (22.7, 23.6, 263)	25.6 (24.8–26.4, 105)	28.0 (27.4–28.7, 200)	<.001[e]	<.001[e]
Comorbidities					
NAFLD and/or steatosis on US/MRI/biopsy	24.5% (136/554)	46.7% (92/197)	67.7% (289/427)	<.001[e]	<.001[e]
Diabetes	5.1% (28/554)	12.2% (24/197)	15.0% (64/427)	<.001[e]	<.001[e]
Hypertension	14.3% (79/554)	24.9% (49/197)	26.0% (111/427)	<.001[e]	<.001[e]
Dyslipidemia	10.6% (59/554)	19.8% (39/197)	20.6% (88/427)	<.001[e]	<.001[e]
Cardiovascular disease	0.9% (5/554)	4.6% (9/197)	2.3% (10/427)	.006[e]	.069
Chronic kidney disease	2.3% (13/554)	4.1% (8/197)	2.1% (9/427)	.326	.802
Osteoporosis	2.0% (11/554)	2.5% (5/197)	1.6% (7/427)	.750	.689
Cancer (excl. HCC)	3.4% (19/554)	3.6% (7/197)	2.6% (11/427)	.701	.441
Psychiatric	2.5% (14/554)	5.1% (10/197)	6.3% (27/427)	.013[e]	.003[e]
Hepatic complications					
Cirrhosis	5.4% (30/554)	5.6% (11/197)	7.2% (31/427)	.462	.236
Hepatocellular carcinoma	1.3% (7/554)	3.0% (6/197)	1.6% (7/420)	.249	.623
Liver fibrosis/steatosis					
TE (kPa)	5.8 kPa (5.4–6.2, 554)	6.3 kPa (5.6–7.0, 197)	6.8 kPa (6.4–7.3, 424)	.003[e]	<.001[e]
CAP (dB/m)	206 (203–209, 554)	261 (261–234, 197)	324 (321–327, 427)	<.001[e]	<.001[e]
>F2 fibrosis (TE > 7.3 kPa)	12.5% (69/553)	15.2% (30/197)	23.8% (102/424)	<.001[e]	<.001[e]
>F3 fibrosis (TE > 10.7 kPa)	4.5% (25/553)	6.1% (12/197)	9.0% (38/424)	.019[e]	.005[e]
Laboratory					
qHBsAg (IU/mL)	6146 (2439–9853, 80)	10,511 (2646–18,377, 36)	4886 (1925–7847, 66)	.261	.608
ALT % above ULN[d]	64.9% (307/473)	66.3% (122/184)	49.5% (189/382)	<.001[e]	<.001[e]
HBeAg-	85.0% (364/428)	85.5% (130/152)	87.3% (283/324)	.659	.368
HBV DNA ($\log_{10}$IU/mL)	2.74 (2.5–2.9, 448)	2.45 (2.1–2.8, 170)	2.36 (2.2–2.6, 350)	.035[e]	.013[e]

Table 1. Continued

Baseline characteristics	No steatosis (n = 554)	Mild/moderate steatosis (n = 197)	Severe steatosis (n = 427)	*P* value (all 3 groups)[a]	*P* value (no steatosis vs severe steatosis)[b]
Treatment (at any time)					
On treatment at any time	41.7% (231/554)	47.7% (94/197)	41.5% (177/427)	.283	.939
Tenofovir-based regimen[c]	28.3% (157/554)	32.0% (63/197)	26.2% (112/427)	.330	.463
Lamivudine	15.5% (86/554)	13.7% (27/197)	12.4% (53/427)	.376	.170
Entecavir	8.5% (47/554)	16.8% (33/197)	11.0% (47/427)	.006[e]	.183
Interferon	1.6% (9/554)	1.5% (3/197)	2.1% (9/427)	.814	.576

Outcomes were compared between 2 groups (none vs severe steatosis). Continuous data are shown as mean (95% CI, n known). Categorical data are shown as mean % (n/n known).
[a]For statistics comparing all 3 groups, one-way analysis of variance tests were used for continuous data and chi-square tests were used for categorical data.
[b]For statistics comparing no-steatosis and severe-steatosis groups, a 2-tailed t-test was used for continuous data and chi-square tests were used for categorical data. For both continuous and categorical variables, missing data were excluded.
[c]Tenofovir-based regimen refers to treatment regimen that contains tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF).
[d]Normal ALT <25 U/L in females, <35 in males.
[e]$P < .05$.
[f]Alcohol consumption with <1 unit of alcohol/d for female and <2 units of alcohol/d for male.

$P < .001$), higher fibrosis stage based on TE (>F2 fibrosis, OR: 0.503, 95% CI: 0.35–0.72; >F3 fibrosis, OR: 0.401, 95% CI: 0.24–0.67, both $P < .001$), >2 metabolic comorbidities (OR: 0.639, 95% CI: 0.43–0.94, $P < .05$), diabetes (OR: 0.516, 95% CI: 0.33–0.8, $P < .01$), hypertension (OR: 0.661, 95% CI: 0.47–0.94, $P < .05$), cirrhosis (OR: 0.256, 95% CI: 0.15–0.43, $P < .001$), and HCC (OR: 0.242, 95% CI: 0.10–0.60, $P < .01$) (Table 2).

After accounting for cofounding effects of treatment, age, and elevated ALT levels, severe steatosis was found to be a significant determinant associated with detectable HBV DNA levels (aOR: 0.385, 95% CI: 0.20–0.75, $P < .01$, Table 2 and Figure 3A). Patients with severe steatosis who received NA treatment had lower mean HBV DNA levels. However, patients with steatosis who were not treated with NA also had lower HBV DNA levels (Figure 3A). This supports the finding that the effect of severe steatosis on HBV DNA levels are independent from the effects of NA treatment (ie, no significant interaction, $P = .662$). This finding is also supported by linear regression analysis where a negative correlation between the CAP score and HBV DNA was observed ($r = -0.096$, $P = .007$, Figure 2A, B). Collectively, this suggests that patients with severe steatosis are more likely to have undetectable HBV DNA.

Patients with CHB with severe steatosis had more advanced fibrosis (>stage 2–3 fibrosis, F2-F3) based on TE measurement (ie, >7.3 or >10.7 kPa) than those with no steatosis (23.8% vs 12.5%, $P < .001$; 9.0% vs 4.5%, $P = .019$, respectively, Table 1). Overall mean TE scores were higher in the severe-steatosis group (6.8 kPa [95% CI: 6.4–7.3] vs 5.8 kPa [95% CI: 5.4–6.2], $P < .001$). Furthermore, severe steatosis is an independent risk factor for liver fibrosis, regardless of treatment status (Figure 3B). However, there were no significant differences between the incidence of cirrhosis or HCC between groups (Table 1).

Correlation Between CAP, Imaging, and Liver Biopsy

Patients with higher CAP were more likely to have US or MRI report of hepatic steatosis or clinical note of NAFLD (ie, 24.5%, 46.7%, and 67.7% [no/mild-moderate/severe steatosis], $P < .001$, Table 1). Liver biopsy data were only available in 18 patients, and among them, only 5 have steatosis; hence, analysis could not be performed to determine how well the CAP and TE correlate to the histology. However, histological descriptions (ie, hepatocyte ballooning, steatosis, and lobular inflammation) corresponded to the noninvasive test results (data not shown).

Metabolic Syndrome Comorbidities and Risk Factors Associated With Severe Hepatic Steatosis in Patients With CHB

There were significantly more patients with diabetes, hypertension, and dyslipidemia among patients with CHB with severe steatosis than among those without steatosis (Table 1). Thus, with increasing hepatic steatosis, as determined by CAP, a concurrent increase in the prevalence of diabetes (ie, 5.1% vs 12.2% vs15.0%, $P < .001$), hypertension (14.3% vs 24.9% vs 26.0%, $P < .001$), and dyslipidemia (10.6% vs19.8% vs 20.6%, $P < .001$) was observed. Patients with moderate to severe steatosis also had more reported psychiatric illness (2.5% in no steatosis, 5.1% in moderate, 6.3% severe steatosis, $P = .003$). No significant differences

Table 2. Determinants Associated with Detectable HBV DNA Levels in Patients With CHB and NAFLD (n = 1178)

Variable	Univariate analysis Odds ratio (95% CI)	Multivariate analysis Adjusted odds ratio (95% CI)
Age ≥ 60 y	0.393 (0.28–0.55)[c]	0.809 (0.39–1.70)
Male sex	0.750 (0.55–1.02)	0.912 (0.50–1.67)
Born in Canada	0.662 (0.32–1.36)	0.430 (0.11–1.71)
Ethnicity		
White	Ref	Ref
Asian	0.436 (0.29–0.66)[c]	0.610 (0.17–2.15)
Black (African/Caribbean)	3.322 (1.75–6.29)[c]	1.64 (0.36–7.49)
Other ethnicity	1.140 (0.56–2.32)	0.599 (0.18–1.99)
Liver tests		
Elevated ALT[d]	1.952 (1.41–2.71)[c]	3.661 (1.82–7.35)[c]
>F2 fibrosis (TE > 7.3 kPa)	0.503 (0.35–0.72)[c]	0.568 (0.26–1.22)
>F3 fibrosis (TE > 10.7 kPa)	0.401 (0.24–0.67)[c]	–
Comorbidities		
0 metabolic comorbidities[e]	Ref	Ref
1 metabolic comorbidity[e]	1.127 (0.77–1.65)	0.338 (0.05–2.16)
≥2 metabolic comorbidities[e]	0.639 (0.43–0.94)[a]	0.221 (0.01–3.81)
CAP score (≥ 280 dB/m)	0.886 (0.65–1.20)	0.385 (0.20–0.75)[b]
Diabetes	0.516 (0.33–0.80)[b]	0.728 (0.15–3.45)
Hypertension	0.661 (0.47–0.94)[a]	1.285 (0.26–6.34)
Obesity (BMI > 30 kg/m^2)	2.083 (1.06–4.10)[a]	2.539 (0.47–13.85)
Dyslipidemia	0.966 (0.65–1.44)	1.120 (0.25–5.06)
Cardiovascular disease	0.832 (0.33–2.12)	0.229 (0.03–2.15)
HCC	0.242 (0.10–0.60)[b]	0.291 (0.05–1.63)
Cirrhosis	0.256 (0.15–0.43)[c]	–

Odds ratios shown with 95% confidence intervals.
[a]$P < .05$.
[b]$P < .01$.
[c]$P < .001$.
[d]Normal ALT <25 U/L in females, <35 in males.
[e]Metabolic comorbidities included are diabetes, obesity, hypertension, cardiovascular disease, and dyslipidemia.

were observed for other comorbidities such as chronic kidney disease, osteoporosis, and extrahepatic cancers (Table 1).

In univariate analysis, independent risk factors associated with severe steatosis in patients with CHB were male sex (OR: 1.445, 95% CI: 1.13–1.84, $P < .001$), metabolic syndrome comorbidities (1 metabolic comorbidity, OR: 1.820, 95% CI: 1.36–2.43; >2 metabolic comorbidities, OR 2.337; 95% CI: 1.68–3.25, both $P < .001$), hypertension (OR: 1.710, 95% CI: 1.28–2.28, $P < .001$), dyslipidemia (OR: 1.730, 95% CI 1.26–2.37, $P < .001$), obesity (OR: 4.975, 95% CI: 3.00–8.25, $P < .001$), smoking history (OR: 1.581, 95% CI: 1.14–2.20, $P < .01$), psychiatric illness (OR: 2.045, 95% CI: 1.16–3.59, $P < .05$), and higher fibrosis stages determined by TE >F2 (OR: 2.056; 95% CI 1.51–2.80, $P < .001$) >F3 (OR: 1.897, 95% CI: 1.19–3.03, $P < .001$, Table 3). In the multivariate analysis, obesity was a significant determinant associated with severe steatosis (aOR: 3.862, 95% CI: 2.02–7.34, $P < .001$). In linear regression analysis, higher CAP was positively correlated with older age (r = 0.152, $P < .0001$), BMI (r = 0.388, $P < .0001$), ALT (r = 0.090, $P = .011$), and TE (r = 0.253, $P < .0001$, Figure 2A, and Figure A1C–F).

Discussion

This multisite nationwide cross-sectional study examined the prevalence and factors associated with hepatic steatosis in a large, multiethnic CHB population in North America. Based on a validated noninvasive testing method (ie, CAP score), NAFLD was very common in patients with CHB, with 53% showing at least moderate to severe steatosis, which is much higher than in other studies predominantly in single-center Asian populations (ie, 21.5%–40%).[7,30] This finding is likely due to the presence of higher percentages of non-Asian populations (eg, White) and the impact of North American lifestyle (ie, high-fat diet, more sedentary lifestyle). Similar to the general population with hepatic steatosis, patients with CHB in Canada with hepatic steatosis were more likely to be male sex, White, and older age and with higher BMI. As expected, metabolic syndrome risk factors including diabetes and hypertension were common in moderate- to severe-steatosis group, but psychiatric illness and smoking history were also notable comorbidities. The complex inter-relationship between these factors and NAFLD and the impact of medications and/or other lifestyle factors (ie, exercise, diet) is yet to be

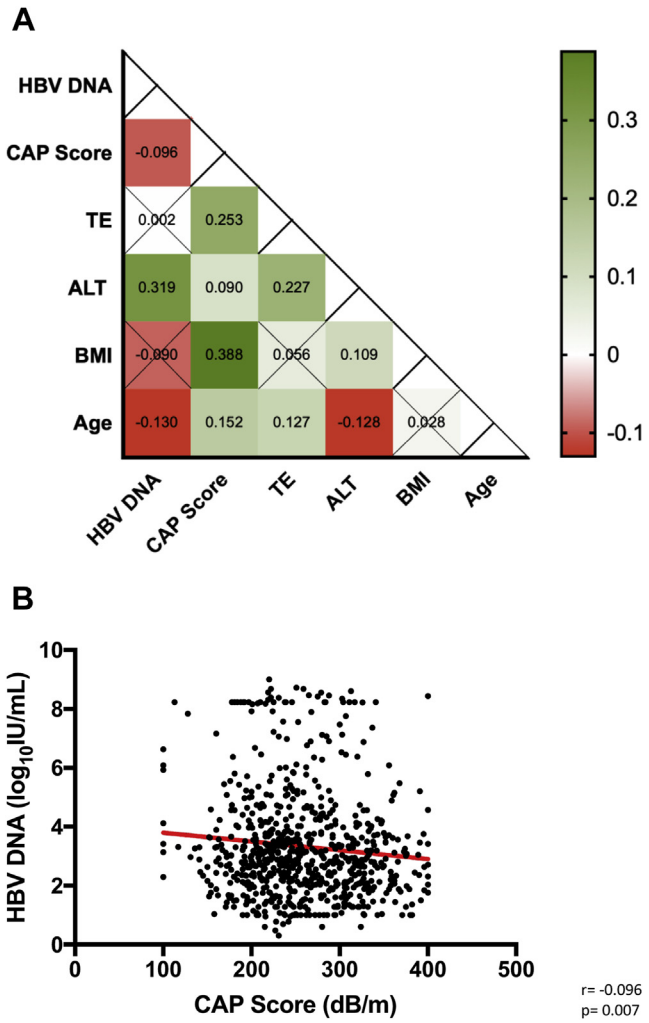

Figure 2. (A) Correlation between the CAP score (dB/m), HBV DNA (log_{10}IU/mL), transient elastography (kPa), ALT (U/mL), body mass index (kg/m^2), and age (years) using Pearson's correlation method. The numbers represent the obtained r values. Insignificant r values are crossed off. Scatterplots of significant findings from Pearson's correlation test are plotted. In (B) is the scatterplot of the CAP score vs HBV DNA levels. Corresponding regression lines are plotted.

determined. However, NAFLD likely shares common pathogenesis with these other conditions, based on shared lifestyle and environmental risks, mediated by dysregulation of oxidative stress, inflammation pathways, and mitochondrial function.[31]

Obesity was a significant independent factor associated with severe steatosis in the CHB cohort in the current study, which parallels known NAFLD risk factors in non-HBV patients.[32,33] Additionally, the association between severe steatosis (determined by CAP) and hepatic fibrosis, regardless of antiviral therapy, is consistent with findings of a large prospective study conducted in 1606 Asian patients with CHB in Hong Kong[9] and a multicenter study in North American and European patients with biopsy proved nonalcoholic steatohepatitis.[34] However, in contrast to other studies, we did not demonstrate any significant difference in the incidence of cirrhosis and HCC between the different steatosis groups. We speculate that this might be due to a higher percentage of non-Asian, younger populations and more receiving antiviral therapy in our cohort. The current sample size and the retrospective cross-sectional study design instead of prospective long-term follow-up also limit analysis for these outcome differences. Similarly, we did not note any association with chronic kidney disease, although an increased prevalence has been noted in other cohorts,[35] which might be due to younger age and management of other lifestyle risk factors. Patients with more severe steatosis unexpectedly were also less likely to have elevated ALT. One possible explanation is that this group might be more likely to be on treatment for their metabolic comorbidities (ie, dyslipidemia, diabetes); however, data were incomplete regarding treatment for concomitant metabolic comorbidities.

Our study highlights the limitations of US for diagnosing NAFLD/hepatic steatosis. Only 67.8% of patients with severe steatosis and 46.7% with moderate steatosis were noted to have an US report of steatosis. The available data together with clinician diagnosis of NAFLD highlight the importance of liver biopsy and histological diagnosis, but CAP can be useful as a convenient and standardized measurement of hepatic steatosis in patients with CHB, especially for serial measurements.

Our results demonstrated an interesting inverse relationship between HBV DNA levels and hepatic steatosis (ie, increased CAP was associated with lower HBV DNA levels), which confirms findings from others, suggesting that increasing hepatic steatosis has a negative effect on HBV replication. Hui et al[12] found significantly lower median serum HBV DNA levels only in the treatment-naïve, steatotic patients, but there were no significant differences in the NA-treated patients. In contrast, patients with steatosis in our cohort, regardless of their treatment status, had lower HBV DNA levels. There are a few postulations for underlying mechanism behind this paradoxical relationship between HBV DNA levels and hepatic steatosis. First, it is possible that the metabolic alterations in NAFLD may directly inhibit HBV replication or indirectly boost antiviral responses through activation of innate immunity.[36] The presence of fat within the hepatocytes and the associated abnormal lipid metabolism may alter HBsAg cytoplasmic distribution, which may induce hepatocyte apoptosis, leading to inhibition of viral replication.[37–39] Furthermore, in vivo and in vitro models have also demonstrated the steatogenic effects of the HBV X protein. It is possible that HBV has antisteatogenic effects that overtake the known steatogenic effects of HBx, leading to protection against steatosis.[40–42]

Previous studies had shown that hepatic steatosis has a favorable effect on HBsAg seroclearance and lower qHBsAg levels; however, our study did not show lower qHBsAg in the moderate- to severe-steatosis groups.[43] This might be due to younger age and higher HBeAg positivity rates in our cohort (eg, 13%–15% HBeAg positivity vs 2% in the study

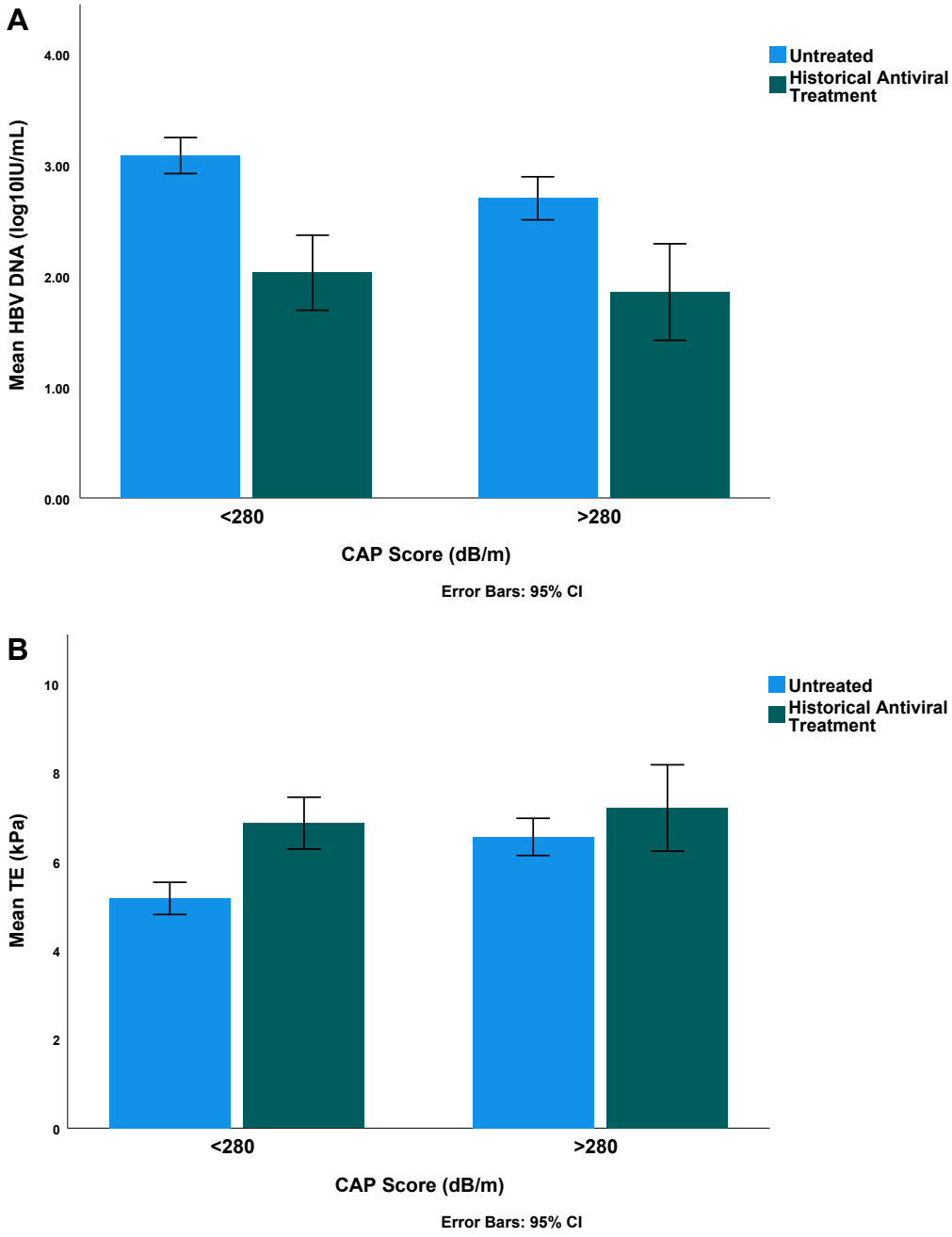

Figure 3. Impact of the CAP score on (A) HBV DNA levels and (B) liver fibrosis in relation to hepatitis B antiviral treatment in patients with and without a history of antiviral history. The error bars represent 95% CI.

by Mak et al).[43] We do not have serial qHBsAg levels in most patients, and those patients who lost HBsAg throughout study follow-up were excluded from the analysis.

Our study has several strengths. First, it includes a large multiethnic cohort within a universal (single-payer) Canadian healthcare system, nationwide clinical data collection, including nonliver comorbidities and lifestyle risk factors. Second, although most patients in this cohort are Asian, they represent a diverse population from 45 different countries including multiple Asian regions (ie, Western, Eastern, and Central Asian) as well as White and Black patients compared with other single-center studies. Third, our study adds knowledge to the existing literature on inverse relationship between HBV DNA and hepatic steatosis, regardless of the treatment status.

The present study was limited by its cross-sectional retrospective design. Individuals at different stages of HBV infection were included and HBV DNA can be variable at different disease stages; hence, the cross-sectional measurement and analysis might not be reflective of long-term virological outcomes. Furthermore, most patients included were seen at a tertiary liver/infectious disease center, with possible referral bias toward more severe disease and/or comorbid metabolic risk factors for NAFLD than those followed up in the primary care setting. Another limitation of our study is that we did not use ethnicity-specific anthromorphic/BMI cutoffs. As we have an ethnically diverse patient population, we elected to use the standard BMI cutoffs (defined by the World Health Organization) for the entire cohort. Lastly, because our

Table 3. Risk Factors of Severe Steatosis (CAP ≥ 280 dB/m) in Patients With CHB and NAFLD (n = 1178)

Variable	Univariate analysis Odds ratio (95% CI)	Multivariate analysis Adjusted odds ratio (95% CI)
Age ≥ 60 y	1.307 (0.98–1.74)	1.083 (0.64–1.83)
Male sex	1.445 (1.13–1.84)[c]	1.185 (0.77–1.81)
Born in Canada	1.803 (0.98–3.31)	1.015 (0.30–3.46)
Ethnicity		
White	Ref	Ref
Asian	0.829 (0.62–1.10)	0.692 (0.22–2.20)
Black (African/Caribbean)	0.823 (0.57–1.19)	0.255 (0.07–1.00)
Other ethnicity	1.311 (0.76–2.26)	0.242 (0.03–1.79)
Smoking history	1.581 (1.14–2.20)[b]	1.406 (0.82–2.40)
Liver fibrosis		
>F2 fibrosis (TE > 7.3 kPa)	2.056 (1.51–2.80)[c]	1.662 (0.87–3.18)
>F3 fibrosis (TE > 10.7 kPa)	1.897 (1.19–3.03)[b]	–
Comorbidities		
0 metabolic comorbidities[d]	Ref	Ref
1 metabolic comorbidity[d]	1.820 (1.36–2.43)[c]	1.276 (0.76–2.16)
≥2 metabolic comorbidities[d]	2.337 (1.68–3.25)[c]	1.688 (0.92–3.11)
Obesity (BMI > 30 kg/m^2)	4.975 (3.00–8.25)[c]	3.862 (2.02–7.34)[c]
Diabetes	2.37 (1.61–3.49)[c]	0.651 (0.15–2.73)
Hypertension	1.710 (1.28–2.28)[c]	0.376 (0.09–1.62)
Dyslipidemia	1.730 (1.26–2.37)[c]	0.635 (0.16–2.58)
Cardiovascular disease	1.262 (0.56–2.87)	0.174 (0.02–1.66)
HCC	0.946 (0.38–2.39)	1.046 (0.30–3.65)
Cirrhosis	1.356 (0.84–2.20)	–
Psychiatric	2.045 (1.16–3.59)[a]	2.960 (0.76–11.50)

Odds ratios shown with 95% confidence intervals.
[a]$P < .05$.
[b]$P < .01$.
[c]$P < .001$.
[d]Metabolic comorbidities included are diabetes, obesity, hypertension, cardiovascular disease, and dyslipidemia.

study focused on using CAP to define the degree of hepatic steatosis owing to the limited number of liver biopsies, we could not determine whether the patients had simple steatosis or nonalcoholic steatohepatitis. The immunologic environment in the liver could be quite different between these 2 conditions, which could have an impact on the HBV viral load and fibrosis findings. Future prospective study as well as more mechanistic studies (ie, intrahepatic and peripheral HBV-specific immune responses, analysis of novel HBV biomarkers) is needed to better understand the complex relationship between hepatis steatosis, viral replication, and liver fibrosis.

Conclusion

In this large, multiethnic CHB population in Canada, hepatic steatosis is common as defined by noninvasive tests, especially in older age White males. The presence of severe steatosis was independently associated with higher fibrosis, but negatively with HBV viral load, regardless of antiviral therapy history. This study contributes to limited published data on the epidemiology and identification of risk factors associated with NAFLD in diverse patient population living with CHB in North America.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2021.09.005.

References

1. **Seto WK,** Yuen MF. Nonalcoholic fatty liver disease in Asia: emerging perspectives. J Gastroenterol 2017; 52:164–174.
2. **Fung J,** Lee CK, Chan M, et al. High prevalence of non-alcoholic fatty liver disease in the Chinese: results from the Hong Kong liver health census. Liver Int 2015; 35:542–549.
3. **Minkari M,** Molaei M, Shalmani HM, et al. Liver steatosis in patients with chronic hepatitis B infection: host and viral risk factors. Eur J Gastroenterol Hepatol 2009; 21:512–516.

4. **Lesmana LA,** Lesmana CR, Pakasi LS, et al. Prevalence of hepatic steatosis in chronic hepatitis B patients and in its association with disease severity. Acta Med Indones 2012;4:35–39.
5. **Browning JD,** Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 2004; 40:1387–1395.
6. **Stanaway JD,** Flaxman AD, Naghavi M, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. Lancet 2016; 388:1081–1088.
7. **Chen J,** Wang ML, Long Q, et al. High value of controlled attenuation parameter predicts a poor antiviral response in patients with chronic hepatitis B. Hepatobiliary Pancreat Dis Int 2017;16:370–374.
8. **Cai S,** Ou Z, Liu D, et al. Risk factors associated with liver steatosis and fibrosis in chronic hepatitis B patient with component of metabolic syndrome. UEG J 2018; 6:558–566.
9. **Seto WK,** Hui RWH, Mak LY, et al. Association between hepatic steatosis, measured by controlled attenuation parameter, and fibrosis burden in chronic hepatitis B. Clin Gastro Hepatol 2018;16:575–583.
10. **Chan AWH,** Wong GLH, Chan HY, et al. Concurrent fatty liver increases risk of hepatocellular carcinoma among patients with chronic hepatitis B. J Gastroenterol Hepatol 2017;32:667–676.
11. **Lee YB,** Ha Y, Chon YE, et al. Association between hepatic steatosis and the development of hepatocellular carcinoma in patients with chronic hepatitis B. Clin Mol Hepatol 2019;25:52–64.
12. **Hui RWH**, Seto WK, Cheung KS, et al. Inverse relationship between hepatic steatosis and hepatitis B viremia: results of a large case-control study. J Viral Hepat 2018; 25:97–104.
13. **Dasarathy S,** Dasarathy J, Khiyami A, et al. Validity of real time ultrasound in the diagnosis of hepatic steatosis: a prospective study. J Hepatol 2009;51:1061–1067.
14. **Wong GL,** Wong VW. Fat and fiber: how the controlled attenuation parameter complements noninvasive assessment of liver fibrosis. Dig Dis Sci 2015;60:9–12.
15. **Sasso M,** Beaugrand M, de Ledinghen V, et al. Controlled attenuation parameter (CAP): a novel VCTE guided ultrasound attenuation measurement of the evaluation of hepatic steatosis preliminary study and validation in a cohort of patients with chronic liver disease from various causes. Ultrasound Med Biol 2010; 36:1825–1835.
16. **Sasso M,** Miette V, Sandrin L, et al. The controlled attenuation parameter (CAP): a novel tool for the non-invasive evaluation of steatosis using Fibroscan. Clin Res Hepatol Gastroenterol 2012;36:13–20.
17. **Karlas T,** Petroff D, Sasso M, et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. J Hepatol 2017;66:1022–1030.
18. **Sasso M,** Tengher-Barna I, Ziol M, et al. Novel controlled attenuation parameter for non-invasive assessment of steatosis using Fibroscan®: validation in chronic hepatitis B. J Viral Hepat 2012;19:244–253.
19. **Mi YQ,** Shi QY, Xu L, et al. Controlled attenuation parameter for noninvasive assessment of hepatic steatosis using Fibroscan®: validation in chronic Hepatitis B. Dig Dis Sci 2015;60:243–251.
20. **Peleg N,** Issachar A, Sneh Arbib O, et al. Liver steatosis is a strong predictor of mortality and cancer in chronic hepatitis B regardless of viral load. JHEP Rep 2019; 1:9–16.
21. **Wong SW,** Chan WK, Mohamed R. Fatty liver is associated with advanced fibrosis but does not predict adverse outcomes in patients with chronic hepatitis B. J Viral Hepat 2020;27:1297–1305.
22. **Chon YE,** Yung KS, Kim SU, et al. Controlled attenuation parameter (CAP) for detection of hepatic steatosis in patients with chronic liver diseases: a prospective study of a native Korean population. Liver Int 2014;34:102–109.
23. **Myers RP,** Pollett A, Kirsch R, et al. Controlled attenuation parameter (CAP): a non-invasive method for the detection of hepatic steatosis based on transient elastography. Liver Int 2012;32:902–910.
24. **Coffin CS,** Ramji A, Cooper CL, et al. Epidemiologic and clinical features of chronic hepatitis B virus infection in 8 Canadian provinces: a descriptive study by the Canadian HBV Network. CMAJ Open 2019;7:E610–617.
25. **Coffin CS,** Fung SK, Alvarez F, et al. Management of hepatitis B virus infection: 2018 guidelines from the Canadian Association for the Study of the Liver and Association of Medical Microbiology and Infectious Disease Canada. Can Liver J 2018;1:156–217.
26. **Parente DB,** Perazzo H, Paiva FF, et al. Higher cut-off values of non-invasive methods might be needed to detect moderate-to-severe steatosis in morbid obese patients: a pilot study. Sci Rep 2020;10:15007.
27. **Osiowy C,** Swidlins K, Haylock-Jacobs S, et al. Molecular and clinical epidemiology of hepatitis D virus infection in Canada [abstract]. In: The liver meeting 2021 Nov 12-15. Anaheim CA: AASLD, 2021:A226 Oral presentation.
28. **Cooper C,** Driedger M, Wong D, et al. Distinct hepatitis B and HIV co-infected populations in Canada. J Viral Hepat 2021;28:517–527.
29. **Coffin CS,** Haylock-Jacobs S, Doucette K, et al. Association between quantitative hepatitis B surface antigen levels (qHBsAg) and clinical outcomes of Canadian chronic hepatitis B (CHB) patients born in 45 countries: retrospective and prospective rEAL world evidence study of CHB in Canada (REVEAL – CANADA [abstract]). In: The liver meeting; 2021 Nov 12-15. Anaheim, CA; AASLD 2021. A780 Poster presentation.
30. **Shen F,** Zheng RD, Mi YQ, et al. Controlled attenuation parameter (CAP) for detection of hepatic steatosis in patients with chronic liver diseases: a prospective study of a native Korean population. Liver Int 2014;34:102–109.
31. **Soto-Angona O,** Anmella G, Valdes-Florido MJ, et al. Non-alcoholic fatty liver disease (NAFLD) as a neglected

metabolic companion of psychiatric disorders: common pathways and future approaches. BMC Med 2020; 18:261.
32. **Lu FB,** Hu ED, Xu LM, et al. The relationship between obesity and the severity of non-alcoholic fatty liver disease: a systematic review and meta-analysis. Expert Rev Gastroenterol Hepatol 2018;12:491–502.
33. **De Araujo Souza MR,** de Melo Diniz MF, de Medeiros-Filho JEM, et al. Metabolic syndrome and risk factors for non-alcoholic fatty liver disease. Arch Gastroenterol 2012;49:89–96.
34. **Choi HSJ,** Brouwer WP, Zamjir WMR, et al. Nonalcoholic steatohepatitis is associated with liver-related outcomes and all-cause mortality in chronic Hepatitis B. Hepatology 2019;71:539–548.
35. **Lin S,** Wang M, Liu Y, et al. Concurrence of HBV infection and non-alcoholic fatty liver disease is associated with higher prevalence of chronic kidney disease. Clin Res Hepatol Gastroenterol 2021;45:101483.
36. **Zhang J,** Lin S, Jiang D, et al. Chronic hepatitis B and non-alcoholic fatty liver disease: conspirators or competitors? Liver Int 2020;40:496–508.
37. **Chu CM,** Lin Dy, Liaw YF. Clinical and virological characteristics post HBsAg seroclearance in hepatitis B virus carriers with hepatic steatosis versus those without. Dig Dis Sci 2013;58:275–281.
38. **Fung J,** Yuen MJ, Lai CL. The role of steatosis in HBsAg seroclearance for patients with chronic hepatitis B infection: fact or fiction? Dig Dis Sci 2013;58:20–22.
39. **Lim CT,** Kumar R. Hepatitis B and concomitant hepatic steatosis. Ann Transl Med 2017;5:38.
40. **Machado MV,** Oliveira AG, Cortez-Pinto H. Hepatic steatosis in hepatitis B virus infected patients: a meta-analysis of risk factors and comparison with hepatitis C infected patients. J Gastroenterol Hepatol 2011; 26:1361–1367.
41. **Kim KH,** Shin HJ, Kim K, et al. Hepatitis B virus X protein induces hepatic steatosis via transcriptional activation of SREBP1 and PRAR-gamma. Gastroenterology 2007; 132:1955–1967.
42. **Kim K,** Kim KH, Kim HH, et al. Hepatitis B virus X protein induces lipogenic transcription factor SREBP1 and fatty acid synthase through the activation of nuclear receptor LXR alpha. Biochem J 2008;416:219–230.
43. **Mak LY,** Hui RWH, Fung J, et al. Diverse effects of hepatic steatosis on fibrosis progression and functional cure in virologically quiescent chronic hepatitis B. J Hepatol 2020;73:800–806.

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Conflicts of interest:
Hin Hin Ko has acted as speaker for Abbvie, Gilead, Intercept, and Merck and served as an advisory board member for Abbvie, Allergan, Gilead, Intercept, and Lupin. Giada Sebastiani has acted as speaker for Pfizer, Merck, Novonordisk, Novartis, Gilead, and AbbVie; has served as an advisory board member for Merck, Gilead, Pfizer, Allergan, Novonordisk, Intercept, and Novartis; and has received research funding from Merck and Theratec. Carla S. Coffin has received research funding from Gilead, GSK, and Janssen and received speaker fees and advisory board fees from the University of Calgary on behalf of the Canadian HBV Network. All other authors have nothing relevant to disclose. GlaxoSmithKline Biologicals SA was provided the opportunity to review a preliminary version of this manuscript for factual accuracy, but the authors are solely responsible for the final content and interpretation.

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The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
The data and study materials will not be made available to other researchers.