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Relationship Between Metabolic Syndrome, Alanine Aminotransferase Levels, and Liver Disease Severity in a Multiethnic North American Cohort With Chronic Hepatitis B

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OBJECTIVE

Metabolic syndrome (MS) is prevalent and is associated with adverse outcomes of liver disease. We evaluated the prevalence of MS and its influence on alanine aminotransferase (ALT) levels and fibrosis, as estimated by the aspartate aminotransferase–to–platelet ratio index (APRI), in a large, multiethnic North American cohort with chronic hepatitis B (HBV) infection.

RESEARCH DESIGN AND METHODS

Adults with chronic HBV from 21 centers within the U.S. and Canada were evaluated at baseline and for up to 5 years (median 3.7 years) of follow-up. MS was defined as the presence of at least three of five criteria including waist circumference, blood pressure, glucose, triglyceride, and HDL levels.

RESULTS

Analysis included 777 participants, of whom 171 (22%) had MS. Participants with MS (vs. those without MS) were older (median age 54.4 vs. 40.2 years), more often male (61% vs. 51%), and born in the U.S./Canada or had immigrated >20 years ago (60% vs. 43%). MS was not associated with ALT or APRI at baseline. Upon adjusted multivariable analysis of serial ALT values, ALT was significantly higher (mean 12%; $P = 0.02$) among those with MS at baseline and even higher (mean 19%; $P = 0.003$) among those with persistent MS compared with those with persistent absence of MS. MS was not associated with serial APRI on follow-up.

CONCLUSIONS

MS was prevalent in this HBV cohort and was independently associated with higher ALT levels longitudinally. These findings highlight the importance of screening for MS and the potential for MS to influence ALT and its interpretation in the context of HBV treatment decisions.

Hepatitis B virus (HBV) infection is associated with a substantial global health burden: roughly 250 million persons are chronically infected worldwide (1). Recent data suggest that the number of foreign-born individuals with chronic HBV living in the U.S. may be greater than previously reported, and the total number of Americans with chronic HBV

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**A complete list of investigators for the HBRN is presented in Appendix 1 in the Supplementary Data online.*

may be as high as 2.2 million (2). As such, HBV represents a significant public health burden in North America. Chronic HBV has a variable course, ranging from inactive infection with minimal viral replication and/or mild or no liver damage to aggressive disease with severe hepatic inflammation, leading to progressive fibrosis and risk of cirrhosis, liver failure, and hepatocellular carcinoma (HCC) (3). In addition to viral factors, host factors have been identified that influence disease course and long-term prognosis (4).

Metabolic syndrome (MS) is defined as a constellation of metabolic abnormalities including central obesity, hypertriglyceridemia, low HDL, hypertension, and impaired fasting glucose (5). MS has emerged as an important and potentially modifiable risk factor for chronic liver disease progression. In addition to a direct association with nonalcoholic fatty liver disease, MS may influence the outcomes of other chronic liver diseases (4,6). Among patients with chronic hepatitis C virus infection, those with evidence of MS have an accelerated disease course and an increased risk for HCC (7). Although components of MS have been associated with overall patient mortality and HCC risk in HBV (4,8), the effects of MS on other outcomes in chronic HBV infection are not as well documented.

Population-based studies from Asia have reported variable findings; some show an increased prevalence of MS among individuals with HBV infection (9), whereas others find no or a negative association (10). With increasing rates of obesity and its associated metabolic complications, including type 2 diabetes, in North America, the prevalence of MS is also likely to increase among persons with chronic HBV infection (11). Large observational studies have shown that chronic HBV infection is also associated with an increased risk for type 2 diabetes. Although the association of chronic HBV infection and type 2 diabetes was initially observed in Asian but not in U.S. cohorts, we recently reported that the prevalence of type 2 diabetes was higher in HBV-infected individuals than in the general North American population and was associated with longer residence in North America, especially among non-Asians (12). These results suggest that environmental factors, likely primarily dietary, influence the risk for type 2 diabetes and other metabolic risk factors among HBV-infected immigrants. However, limited data exist on whether the presence of MS alters the course of HBV infection (13), especially among North Americans with chronic HBV infection. Moreover, the impact of MS on laboratory tests of liver disease activity and noninvasive markers of liver fibrosis within the context of HBV has not been well defined. Indeed, assessment of the phase of chronic HBV infection, HBV disease monitoring, and decision to initiate HBV therapy rely on serial serum alanine aminotransferase (ALT) levels, HBV viral parameters, and liver disease severity (14). In addition, achieving sustained suppression of HBV viral replication with anti-HBV therapy is associated with normalization of serum ALT (defined as $\leq$19 units/L in females and $\leq$30 units/L in males) and improvement in liver histology (14).

In this study we examined the prevalence of MS and its association with liver disease parameters in a large cohort of ethnically diverse North American patients with chronic HBV infection who were followed for a median of 3.7 years.

RESEARCH DESIGN AND METHODS

Subjects enrolled in the Hepatitis B Research Network (HBRN) Adult Cohort Study from January 2011 to February 2014 were considered for inclusion in this analysis. The HBRN Adult Cohort Study is a prospective study of hepatitis B surface antigen–positive adult patients sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, and it comprises 21 adult liver centers in the U.S. and Canada, as previously described (15). In brief, the HBRN Adult Cohort Study enrolled hepatitis B surface antigen–positive persons 18 years of age or older who did not have a history of hepatic decompensation, HCC, solid organ or bone marrow transplantation, or HIV coinfection and who were not receiving hepatitis B antiviral therapy. If antiviral therapy was initiated any time after enrollment, subjects continued in the study. Participants were evaluated at enrollment, week 12, week 24, and every 24 weeks thereafter. For this study we excluded participants who had acute hepatitis B infection, who were pregnant, or in whom the presence/absence of MS, as defined below, could not be assessed. Up to 240 weeks (5 years) of follow-up were included in this analysis.

All protocols were approved by the HBRN Steering Committee and the institutional review boards (research ethics board in the case of the Toronto site) of the participating sites. All participants provided written informed consent.

Assessment of Clinical Variables

MS was defined as the presence of at least three of five factors at baseline (5): *1*) abnormal glucose metabolism (fasting glucose $\geq$100 mg/dL, use of antidiabetes agents, and/or a history of diabetes); *2*) high-risk waist circumference ($\geq$80 cm for Asian women and $\geq$88 cm for women of all other races, $\geq$90 cm for Asian men and $\geq$102 cm for men of all other races); *3*) low HDL cholesterol level ($<$50 mg/dL for women and $<$40 mg/dL for men); *4*) elevated triglyceride level (fasting value $\geq$150 mg/dL or taking lipid-lowering agents at baseline); and *5*) elevated blood pressure (systolic pressure $\geq$130 mmHg and/or diastolic pressure $\geq$85 mmHg, taking antihypertensive medications at baseline, and/or a history of hypertension). Alcohol consumption was graded as none or minimal ($<$1 drink/month), moderate (more than none or minimal but $\leq$4 drinks/day or 14 drinks/week in men, $\leq$3 drinks/day or 7 drinks/week in women), or heavy (more than moderate or binge drinking, defined as $\geq$5 drinks on at least 1 day in the previous month) (16). The upper limit of normal (ULN) for ALT was 30 units/L for males and 20 units/L for females. Because transient elastography was only approved for use in the United States in 2013, this noninvasive assessment of liver fibrosis was not available when the HBRN Adult Cohort Study was initiated. Therefore, the aspartate aminotransferase (AST)–to–platelet ratio index (APRI) score was used to estimate liver fibrosis. The APRI was calculated using the equation (17)

$$\text{APRI} = \frac{\text{AST (units/L)} \div \text{AST ULN}}{\text{Platelet count } (10^9/\text{L})} \times 100$$

APRI score was chosen over the Fibrosis-4 score for evaluating fibrosis to avoid collinearity with age that was used in the models assessing the impact of MS on fibrosis. Cirrhosis was defined as APRI $>$2.0.

Histological Evaluation

Biopsies performed for clinical indication within 1 year of entry into the HBRN Adult Cohort Study were reviewed by a central

pathology committee comprising pathologists from participating clinical centers. Hematoxylin and eosin and Masson trichrome stains were available for all cases. Biopsies were scored for inflammation and fibrosis using the method described by Ishak et al. (18). Steatosis was graded based on the proportion of steatotic hepatocytes assessed at low magnification: grade 0 indicates no steatosis; grade 1, <5% steatosis; grade 2, from 5% to 33% steatosis; grade 3, >33% to 67% steatosis; and grade 4, >67% steatosis. Perisinusoidal fibrosis was assessed as 0 for none, 1 for mild (visible only with trichrome staining), and 2 for moderate (evident with hematoxylin and eosin staining). The presence of concurrent steatohepatitis was based on findings of steatosis, ballooning injury with or without Mallory-Denk bodies, and perisinusoidal fibrosis in an appropriate architectural pattern (19). Possible steatohepatitis was distinguished from definite steatohepatitis based on the quality of the characteristic features.

Statistical Analysis

Descriptive statistics included median and range and mean ± SD, as appropriate. Continuous variables were compared between those with and those without MS using the nonparametric Kruskal-Wallis test, and categorical variables were compared using the χ^2 test or Fisher exact test, as appropriate. Linear regression models were used to estimate the adjusted (for age, sex, race, alcohol consumption, HBV DNA levels, and hepatitis B e antigen [HBeAg] status) association between MS and both ALT level and the APRI score at baseline. Linear mixed models were used for a similar analysis that included ALT values and APRI scores both at baseline and during follow-up. All the ALT values and APRI scores were analyzed as individual and separate dependent variables in these models. Note, however, that to meet normality assumptions, the $\log_2$ scale for both ALT and the APRI score was used in the models, and therefore results are presented as ratios rather than differences. All HBV DNA levels included in the models were assessed serially during follow-up. All the other predictor variables were assessed at baseline.

RESULTS

Of the 1,547 subjects enrolled in the HBRN Adult Cohort Study during the study period who met the study inclusion criteria, the presence or absence of MS could be ascertained in 777 (50.2%). The inability to ascertain MS was typically due to a lack of fasting glucose or lipid levels at enrollment. The participants for whom MS could (n = 777) or could not (n = 770) be ascertained did not differ significantly with respect to age (median 43.5 vs. 42.2 years; P = 0.82), sex (47.2% vs. 46.9% female; P = 0.89), race (72.6% vs. 69.7% Asian; P = 0.21), or APRI score (3.5% vs. 3.4% with APRI >2; P = 0.90).

Of 777 participants included in the analysis, 171 (22%) had MS at baseline. Table 1 summarizes the characteristics of participants with and those without MS at baseline. The participants with MS were older, more likely to be born in the U.S. or Canada or to have been immigrants longer in these countries, and more likely to have a known family history of diabetes. With respect to HBV viral parameters, those with MS had significantly lower prevalence of HBeAg (14.2% vs. 30.3%; P = 0.0002) and lower HBV DNA levels (median $\log_{10}$ value 3.23 vs. 3.96; $P < 0.0001$) than those without MS, presumably as a result of their older age and longer estimated duration of HBV infection. No significant differences were found between groups with respect to baseline ALT or AST levels and APRI scores. However, a significantly larger proportion of participants with MS at baseline had an indeterminant HBV phenotype (20) (those who do not meet the criteria for immune-active HBeAg positive or negative, immune-tolerant, or inactive carrier states, 41.5% vs. 29.5%). This difference was primarily related to a larger proportion of participants with MS at baseline who were HBeAg negative, with low levels of HBV DNA ($\leq 10^4$ IU/mL) but elevated ALT values (38% vs. 23.8% in those without MS at baseline). Of note, nearly one-third of participants with this type of indeterminant phenotype had MS—a proportion significantly larger than that with HBeAg-negative immune-active and inactive carrier HBV phenotypes combined (31.1% vs. 23.1%; P = 0.046).

With respect to histology, liver biopsy within a year of study entry was available for 73 participants (50 without MS and 23 with MS). Median time elapsed from liver biopsy to study entry was similar among those participants without and those with MS (−123 vs. −117 days; P = 0.5). Participants with MS had higher grades of steatosis and higher scores for perisinusoidal fibrosis, and were more likely to have definite steatohepatitis, than those without MS (30% vs. 2%), consistent with the presence of metabolic liver disease. However, scores for inflammation and Ishak fibrosis were similar in the two groups.

Association Between MS and ALT and APRI Scores at Baseline

Of the 777 participants included in the data analysis, a total of 734 participants had available baseline ALT levels (of whom 160 had MS) and 687 had available baseline APRI scores (of whom 148 had MS) (Supplementary Fig. 1). In multivariable regression analysis, the presence of MS at baseline was not associated with ALT value or APRI score at baseline. HBV DNA level was positively associated with baseline ALT (1 $\log_{10}$ higher HBV DNA was associated with 14% higher ALT) and APRI score (1 $\log_{10}$ higher HBV DNA was associated with 10% higher APRI score). Women had, on average, lower ALT and APRI scores than men (Table 2). In addition, older age was associated with higher baseline APRI scores (8% higher for every decade greater age).

Relationship of Baseline MS With ALT and APRI Scores Over Time

During a median follow-up of 3.7 years, 634 participants (501 without MS and 133 with MS) did not undergo HBV therapy. Overall, relatively small proportions of these participants (18% without MS and 12% with MS) met the American Association for the Study of Liver Diseases (AASLD) laboratory criteria for treatment initiation based on ALT level, HBV DNA, and HBeAg status at baseline. The proportion of untreated participants who met treatment criteria decreased over time to 4% by the 5th year of follow-up. However, a larger percentage of participants with MS received HBV therapy compared with those without MS (23% vs. 16%; P = 0.03). Figure 1 shows ALT levels in the participants in whom HBV therapy was not initiated during the entire follow-up period. ALT levels tended to be higher at most follow-up time points in participants with MS at baseline compared with those without MS. However, this difference was predominantly seen among women (Supplementary Fig. 2), and the absolute value of the differences between the two groups was small. In

Table 1—Characteristics of subjects with and without MS at baseline

Characteristics	No MS (*n* = 606)	MS (*n* = 171)	*P* value
Host-related characteristics			
Age, median (range), years	40 (18–78)	54 (23–80)	<0.0001
Female sex	49.5	39.2	0.02
Race			0.054
White	10.4	11.7	
Black	11.7	19.3	
Asian	74.3	66.7	
Other	3.6	2.3	
Continent of birth			0.005
Africa	9.7	9.9	
Asia	69.3	63.7	
Europe	4.6	1.2	
North America	15.5	23.4	
South America	0.8	0.6	
Australia	0.0	1.2	
Birth and immigration status			<0.0001
Born in the U.S. or Canada	14.5	21.1	
Foreign-born and immigrated >20 years ago	28.2	39.2	
Foreign-born and immigrated ≤20 years ago	53.1	32.7	
Foreign-born but immigration date unknown	4.1	7.0	
Race-adjusted BMI category			<0.0001
Normal (*n* = 341)	49.9	9.6	
Overweight (*n* = 345)	38.7	42.2	
Obese (*n* = 170)	11.3	48.2	
Alcohol use in past 12 months*			0.7
None	72.6	75.9	
Moderate	20.5	18.2	
At risk	6.9	5.9	
Known family history of diabetes	32.2	49.1	<0.0001
Laboratory and HBV-related characteristics			
Platelets, median (IQR), $\times 10^3/mm^3$	219 (182–255) (*n* = 565)	228 (183–271) (*n* = 156)	0.20
Total bilirubin, median (IQR), mg/dL	0.64 (0.50–0.90) (*n* = 597)	0.60 (0.41–0.80) (*n* = 597)	0.006
Albumin, median (IQR), g/dL	4.3 (4.1–4.6) (*n* = 585)	4.3 (4.1–4.6) (*n* = 169)	0.74
Fasting glucose, median (IQR), mg/dL	84.0 (79.0–90.1) (*n* = 588)	99.0 (87.0–111.7) (*n* = 127)	<0.0001
ALT, median (IQR), units/L	33 (23–53)	36 (26–50)	0.25
ALT			0.9
Normal	30.3	28.8	
>1 to <2 × ULN	41.8	42.9	
≥2 × ULN	27.8	28.2	
AST, median (IQR), units/L	28 (22–39)	27.5 (23–37)	0.74
AST			0.11
Normal	73.5	79.4	
Abnormal	26.5	20.6	
Log_{10} HBV DNA, median (IQR), IU/mL	3.96 (2.8–6.2)	3.23 (2.3–4.6)	<0.0001
HBeAg status			0.0002
Negative	69.5	85.8	
Positive	30.3	14.2	
Equivocal	0.2	0.0	
HBV genotype			0.06
A	14.2	18.7	
B	36.1	30.4	
C	33.3	25.1	
D	7.6	4.7	
Other/multiple	2.8	5.3	
Unknown	5.9	15.8	
HBV phenotype			0.001
Immune tolerant	5.1	1.2	
HBeAg-positive chronic hepatitis B	19.8	11.1	
HBeAg-negative chronic hepatitis B	17.8	15.2	
Inactive carrier	19.0	24.0	
Indeterminant	29.5	41.5	

Continued on p. 1255

Table 1—Continued

Characteristics	No MS (n = 606)	MS (n = 171)	P value
APRI score			0.3
<1	90.4	92.9	
1–2	6.2	3.2	
>2	3.4	3.8	
Liver histology, n†	50	23	
Ishak inflammation, total score			
1–4	34.0	30.4	0.4
5–8	42.0	60.9	
9–12	16.0	8.7	
13–18	8.0	0.0	
Steatosis grade			
None	24.0	13.0	0.004
<5	60.0	34.8	
5–33%	10.0	17.4	
>33–67%	4.0	34.8	
>67%	2.0	0.0	
Steatohepatitis			
Absent	92.0	56.5	0.0003
Possible	6.0	13.0	
Definite	2.0	30.4	
Ishak fibrosis stage			
0–2	76.0	73.9	1.0
>2	24.0	26.1	
Perisinusoidal fibrosis			
0	74.0	52.2	0.003
1	24.0	17.4	
2	2.0	30.4	

Data are percentages unless otherwise indicated. IQR, interquartile range. *Alcohol consumption was graded as none/minimal (<1 drink/month), moderate (more than none/minimal but ≤4 drinks/day or 14 drinks/week in men, ≤3 drinks/day or 7 drinks/week in women), or at risk (more than moderate or binge drinking, latter defined as ≥5 drinks on at least 1 day in the previous month). †Liver biopsy specimens were available for 73 subjects (50 without MS and 23 with MS) for histologic evaluation.

multivariable models that included all participants and controlled for years of follow-up, receipt and duration of HBV therapy, and other covariates (age, sex, race, alcohol intake, HBV DNA, and HBeAg status), MS was independently associated with higher ALT levels over time, with a magnitude of association similar to that seen at baseline (Table 3). Participants with MS at baseline had, on average, 12% higher ALT levels during follow-up (when combining all time points) compared with those without MS (P = 0.02). As expected, women had on average 27% lower ALT levels during follow-up than men ($P <$ 0.0001), and higher HBV DNA levels were also associated with higher ALT levels over time (21% higher for every $\log_{10}$ HBV DNA increase; $P <$ 0.0001).

Given the influence of sex on ALT levels, we further evaluated the primary effects of both MS and sex, and the interactions between them, in the same multivariable model that included all participants and controlled for years of follow-up, receipt and duration of HBV therapy, and other covariates (age, sex, race, alcohol intake, HBV DNA, and HBeAg status). This showed that MS at baseline was significantly associated with higher ALT levels in women (ratio 1.26; 95% CI 1.10–1.45; P = 0.0011) but not in men (ratio 1.03; 95% CI 0.92–1.16; P = 0.6). In the multivariable model for ALT shown in Table 3, HBeAg positivity seems to be associated with lower ALT values compared with those observed in HBeAg-negative participants. While it should be noted that the linear relationship between HBV DNA and ALT levels is preserved for both the HBeAg-positive and HBeAg-negative groups, the data suggest that the magnitude of this relationship is attenuated in the HBeAg-positive group.

APRI scores during follow-up were associated with older age (8% higher for every decade increase in age; $P <$ 0.0001) and female sex (19% lower; $P <$ 0.0001). However, no statistically significant association was found between MS at baseline and APRI scores over time (P = 0.06).

We recognized that MS status can change during follow-up, so we repeated the multivariable modeling for the longitudinal analysis using only data from participants whose baseline MS status remained constant over time. For this modeling, a total of 624 subjects with available data and unchanged MS status during follow-up were included for the ALT outcome analysis and 587 participants were included for the APRI outcome analysis (Supplementary Fig. 1). When evaluating participants whose MS status remained constant during the follow-up period, the presence of MS was associated with even higher ALT levels—an average of 19% higher (P = 0.003)—whereas the estimates for APRI scores did not change (Supplementary Table 1). Sex did not have a statistically significant differential influence on the relationship between MS and ALT (P = 0.08) or APRI (P = 0.7) in these models.

CONCLUSIONS

This large, prospective cohort study of individuals with chronic HBV infection in North America followed for up to 5 years offers a unique opportunity to assess the relationship between MS and serum ALT and surrogate markers of liver disease severity at baseline and longitudinally. We found that the overall prevalence of MS was 22% in this largely Asian (~70%)

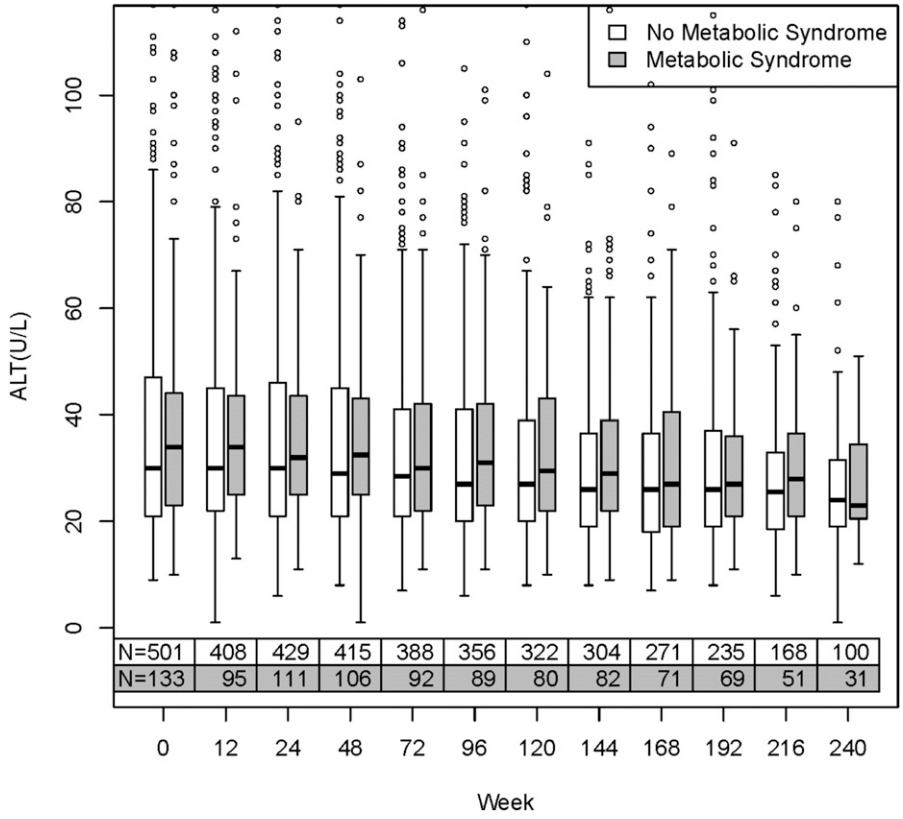

Figure 1—Baseline and longitudinal ALT levels (units [U]/L) in participants with or without MS at baseline who had not received HBV antiviral therapy. Each box represents the first (lower end) to third (upper end) quartiles of ALT values (interquartile range [IQR]), and the horizontal line in each box represents the median ALT value. The vertical line at either end of the box extends to the most extreme value or is cut off at 1.5 times the IQR; observations beyond this cutoff are displayed as circles.

cohort. This observed prevalence is similar to those in reports of other Asian populations, in which MS prevalence ranged from 18% to 23% (21). While baseline ALT levels were not increased in the overall cohort in the presence of MS, nearly one-third of patients with high ALT but low HBV DNA levels ($\leq 10^4$ IU/mL) had MS, a proportion that was significantly

Table 2—Associations of MS at baseline with baseline ALT values and APRI scores using multivariable analysis

	Baseline ALT (n = 734)			Baseline APRI score (n= 687)		
Variables	Ratio*	95% CI	P value	Ratio*	95% CI	P value
MS (vs. no MS)	1.10	0.97–1.26	0.14	0.89	0.79–1.02	0.09
Age, per decade (years)	0.99	0.95–1.04	0.69	1.08	1.03–1.13	0.0006
Female sex (vs. male sex)	0.70	0.63–0.77	<0.0001	0.76	0.69–0.84	<0.0001
Race (vs. white)						
Asian	0.93	0.79–1.10	0.39	0.91	0.77–1.07	0.24
Black	0.84	0.69–1.03	0.09	0.90	0.73–1.10	0.29
Other	0.83	0.61–1.14	0.25	0.92	0.68–1.26	0.61
Alcohol use in past 12 months (vs. none)						
Moderate	1.00	0.91–1.09	0.97	1.06	0.93–1.19	0.39
At risk	1.04	0.90–1.20	0.62	1.05	0.86–1.28	0.66
Birth and immigration status (vs. foreign-born and immigrated ≤20 years ago)						
Born in U.S./Canada or foreign-born and immigrated >20 years ago	0.94	0.85–1.05	0.29	0.92	0.83–1.02	0.10
Foreign-born but unknown date of immigration	1.03	0.79–1.33	0.85	1.02	0.80–1.30	0.89
Family history of diabetes (vs. none)	1.08	0.98–1.20	0.12	1.01	0.91–1.12	0.87
Log_{10}HBV DNA (IU/mL)	1.14	1.11–1.18	<0.0001	1.10	1.07–1.14	<0.0001
HBeAg positive (vs. negative)	0.93	0.79–1.10	0.39	1.07	0.91–1.25	0.44

*Factor by which the mean ALT value or APRI score differs for the comparator vs. the reference. For example, the baseline ALT in women is, on average, 70% of that in men with all other factors kept constant, and the mean baseline APRI is 10% higher in people with a 1 log_{10} higher HBV DNA level.

Table 3—Associations of MS at baseline with baseline and longitudinal ALT values and APRI scores using multivariable analysis*

	Baseline and longitudinal ALT levels (n = 734)			Baseline and longitudinal APRI scores (n = 687)		
Variables	Ratio†	95% CI	P value	Ratio†	95% CI	P value
MS (vs. no MS)	1.12	1.02–1.22	0.02	0.91	0.82–1.01	0.06
Age, per decade (years)	1.00	0.97–1.03	0.87	1.08	1.04–1.12	<0.0001
Female sex (vs. male sex)	0.73	0.68–0.78	<0.0001	0.81	0.76–0.88	<0.0001
Race (vs. white)						
Asian	0.89	0.79–1.00	0.052	0.81	0.77–0.99	0.03
Black	0.87	0.75–1.00	0.056	0.84	0.71–0.98	0.03
Other	0.94	0.76–1.17	0.59	0.99	0.78–1.26	0.95
Alcohol use in past 12 months (vs. none)						
Moderate	1.00	0.92–1.10	0.92	1.01	0.92–1.11	0.84
At risk	1.05	0.91–1.21	0.52	1.03	0.88–1.21	0.67
Birth/immigration status (vs. foreign-born and immigrated ≤20 years ago)						
Born in U.S./Canada or foreign-born and immigrated >20 years ago	0.95	0.88–1.03	0.20	0.99	0.91–1.07	0.71
Foreign-born but unknown date of immigration	0.98	0.81–1.18	0.83	0.94	0.77–1.14	0.53
Family history of diabetes (vs. none)	1.03	0.96–1.11	0.36	0.98	0.91–1.06	0.65
Log_{10} HBV DNA (IU/mL)‡	1.21	1.20–1.22	<0.0001	1.16	1.15–1.18	<0.0001
HBeAg positive (vs. negative)	0.85	0.78–0.93	0.0006	0.91	0.82–1.00	0.0500

*Analysis was also controlled for duration of follow-up, receipt of HBV therapy, and duration of HBV therapy. †Factor by which the mean ALT value or APRI score differs for the comparator vs. the reference. ‡Measured at baseline and longitudinally.

higher than that in other HBeAg-negative groups with chronic HBV infection. Another important finding was an association between MS at baseline and higher ALT levels over time, even after controlling for patient and viral factors including age, sex, HBV DNA levels, and HBeAg status. This relationship was stronger among those with persistent MS status. While the difference in the absolute values of ALT was numerically small in those with MS and those without MS over time (e.g., at year 1, median ALT 34.5 vs. 30.0 units/L; at year 2, median ALT 32.5 vs. 29 units/L; at year 3, median ALT 28.0 vs. 26.5 units/L), it is recognized that small changes may lead to patients with chronic HBV infection falling within versus outside the cutoff values recommended by treatment guidelines for the initiation of antiviral therapy (14,22,23).

AASLD guidelines recommend the use of ALT levels ≥2 × ULN (the ULN for ALT in healthy adults is defined as 30 units/L for males and 19 units/L for females) as one of the criteria for HBV therapy (14). The risks and benefits of treatment versus observation in persons who are in the "gray zone," with ALT 1–2 × ULN and low HBV DNA level, have not been well defined. Thus it is recommended that the severity of liver disease (defined by biopsy or noninvasive testing for fibrosis) be considered in treatment decisions for patients in the gray zone (14). Our results highlight the contribution of MS to modest ALT changes and call attention to the need for clinicians to consider metabolic profiles when interpreting changes in ALT. In addition, identification and optimal management (including lifestyle modification and weight loss) of common metabolic abnormalities such as diabetes and hyperlipidemia are critical for those with coexisting HBV disease. In our study, a larger proportion of participants with MS (23% vs. 16% with no MS) received HBV therapy. Although the reasons for treatment initiation per se were not assessed, it is possible that a higher percentage of participants with MS met the ALT criterion for initiating therapy despite HBV DNA levels that may have been below the guideline cutoff or within the gray zone. Alternatively, participants with MS may have had more persistent ALT elevations that prompted a higher rate of treatment initiation when HBV DNA criteria were met.

A significant association was not observed between the presence of MS and a surrogate measure of liver disease severity (APRI score) at baseline and upon follow-up. Several potential explanations are available for this lack of association. First, our follow-up duration may be insufficient to detect modest changes in fibrosis. The HBRN Adult Cohort Study excluded patients receiving antiviral therapy at enrollment, thereby selecting for patients with less active or advanced liver disease. Indeed, most participants had milder liver disease (~90% had an APRI score <1.0) at baseline. Second, while APRI has been shown to accurately exclude advanced fibrosis, it is not as accurate in differentiating stages of fibrosis or in detecting small changes in liver disease severity over time (24,25). Use of transient elastography (13) or liver biopsy would have been a more ideal means of capturing modest changes in disease severity, but FibroScan was not approved in the U.S. until 2013. Among the subset with available liver biopsies, however, the participants with MS were more likely to have evidence of concomitant fatty liver disease, including higher grades of steatosis and higher rates of perisinusoidal fibrosis and steatohepatitis, compared with those without MS, supporting our hypothesis that concomitant MS contributes to higher ALT and greater disease severity in chronic HBV infection.

A clear association exists between chronic hepatitis C infection with diabetes and insulin resistance (26), and this in turn likely provides the linkage with MS. By contrast, the relationship between HBV infection and MS remains inconclusive; while some studies show a positive association, most show no or inverse associations (10,27–30). Obesity, diabetes, MS, and HBV infection have all been associated with an increased risk for

cirrhosis and HCC (31,32). In addition, certain components of MS—namely, diabetes and/or insulin resistance—are also associated with overall mortality in chronic HBV infection (4). These findings suggest that MS and its pathogenesis are important to HBV disease, but further longitudinal follow-up of these patients is required to understand better the mechanisms by which MS can influence the natural history of HBV.

This study has several limitations. We used the standard definition of MS that requires the presence of at least three of five clinical and laboratory components, but ~50% of our participants had to be excluded from the analysis because data were missing for two or three of these components. However, no differences were found in age, sex, race, and liver fibrosis (APRI) between participants included in this analysis and those excluded because of missing data related to ascertainment of MS. Contrary to our expectations, the presence of MS at baseline was not associated with baseline serum ALT values or APRI scores. This may reflect the selection criterion of not receiving treatment at study entry, thereby potentially excluding participants with more advanced fibrosis or active chronic HBV infection, for whom antiviral therapy is recommended. Also, we anticipated that both MS and HBV would influence ALT levels at baseline, given that participants were not receiving HBV treatment at enrollment. However, longitudinal ALT data that showed an association between MS and higher ALT over time included participants who received HBV therapy, and longitudinal analyses controlled for receipt of HBV treatment. Thus, by adjusting for treatment (which was not possible at baseline), MS is likely to make a greater contribution to the longitudinal ALT values than to those at baseline. Another limitation of this analysis is that only a limited number of participants had undergone a liver biopsy as a standard of care, requiring reliance on APRI score as a surrogate measure of liver fibrosis. It is reassuring, however, that in the subset of participants who had a liver biopsy, we confirmed that features of steatosis, steatohepatitis, and perisinusoidal fibrosis were more prevalent in participants with MS. Last, the median duration of follow-up of 3.7 years was too short to fully appreciate the impact of MS on the progression of HBV-related liver disease. Nevertheless, this is to our knowledge the largest multiethnic North American cohort with detailed demographic, clinical, and virologic parameters to be prospectively monitored for objective evidence of liver disease progression over time.

In conclusion, approximately one in four North American patients with chronic HBV infection has MS. In evaluating the natural history of the disease in patients with untreated chronic HBV infection, we found MS to be independently associated with higher ALT levels over time. While absolute increases in ALT values were modest, they may be of clinical consequence in persons with ALT values at or near the threshold for consideration of antiviral therapy. Understanding the impact of MS on clinically important end points such as cirrhosis requires a longer duration of follow-up, and our multiethnic population, representative of North American patients with chronic HBV infection, will be useful in this endeavor.

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