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ORIGINAL ARTICLE

Fatigue in Patients with Chronic Hepatitis B Living in North America: Results from the Hepatitis B Research Network (HBRN)

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Abstract

Background Fatigue is a common symptom of liver disease but not well characterized in patients with chronic hepatitis B virus (HBV).

Aims We assessed the rate of fatigue using a validated instrument in patients with HBV and identified demographic, virologic, and clinical features associated with fatigue in a cross-sectional cohort study from the Hepatitis B Research Network.

Methods Participants were English- and Spanish-speaking adults with chronic HBV who were not pregnant nor on treatment. Fatigue was measured using the PROMIS® Fatigue 7-item Short Form.

Results The sample included 948 adults: median age 42; 51 % female; 71 % Asian; 74 % college educated; 77 % employed; 41 % inactive HBV carriers; 36 % with active chronic disease; and 2 % with advanced fibrosis, defined as AST–platelet ratio index (APRI) > 1.50. Patients with chronic HBV had a mean fatigue T-score of 46.8 ± SD = 7.9, compared to a mean fatigue T-score of 50.0 ± 10 in the US general population ($p < .0001$). In univariate analyses, greater fatigue was associated with demographic and clinical features such as female sex, lower income, more comorbidities, higher APRI score, and poorer mental health ($p < 0.05$). In multivariate analysis, female sex ($p < .001$), poorer mental health ($p < .001$), APRI score ($p = .005$), and history of diabetes ($p = .039$) were the strongest independent predictors.

Conclusions The frequency of fatigue in this large cohort of North American chronic HBV patients may be equal to or lower than that reported in the US general population. Patients with advanced fibrosis, more comorbidities, and poorer mental health report worse fatigue.

Keywords Liver · Mental health · Patient-reported outcomes · PROMIS · Symptoms

For the Hepatitis B Research Network (HBRN).

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Abbreviations

HBRN	Hepatitis B Research Network
PROMIS	Patient Reported Outcomes Measurement Information System
APRI	AST–platelet ratio index
HBV	Hepatitis B virus
NIH	National Institutes of Health
SD	Standard deviation
ALT	Alanine aminotransferase test

BMI	Body mass index
MOS SF-36	Medical Outcomes Study 36-item Short Form
HrQOL	Health-related quality of life

Introduction

Chronic infection with the hepatitis B virus (HBV) affects approximately 1.25 million individuals in North America, at least 10 % of whom will develop cirrhosis, liver failure, or liver cancer in their lifetime [1]. In addition to being at increased risk of liver-related mortality and morbidity, patients with chronic HBV may also have disease-related symptoms such as fatigue [2–6]. Fatigue is the most commonly reported symptom in patients with chronic viral hepatitis and is associated with reductions in health-related quality of life (HRQOL) [3, 7, 8]. In chronic hepatitis C, fatigue scores are higher than in the general population [7, 9] and often associated with demographic factors and poor mental health functioning [9–11]. Moreover, patients with advanced liver disease or markers of cirrhosis have more pronounced decrements in HRQOL [8, 9, 11, 12].

Patient-reported outcomes such as fatigue are relatively understudied in patients with chronic hepatitis B compared to those with hepatitis C. The majority of studies that specifically evaluate fatigue in HBV come from Asian or Middle Eastern countries where the findings may not be applicable to individuals living in North America because of sociocultural differences including health perceptions about what it means to have HBV [2, 13–15]. Studies assessing fatigue in HBV generally have been limited in sample size and often have been part of larger studies that combined patients with various forms of liver disease [2, 4, 13, 15, 16]. Other studies have used single item questions, assessment of serious adverse events, or subscales of HRQOL instruments to measure fatigue [3]. Almost all studies have had a primary emphasis on the broader construct of HRQOL which can be affected by numerous patient and environmental characteristics confounding the relationship with disease state [17]. Symptoms, such as fatigue, are more directly associated with disease state, but often measured secondarily to HRQOL [2, 4, 14–16, 18]. Taken together, standardized measures of fatigue have not been examined as a primary endpoint in any large North American cohort of patients with chronic HBV infection.

The National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System® (PROMIS®) initiative has developed a comprehensive set of highly reliable, rigorously validated, precise tools to measure physical, mental, and social functioning and associated symptoms in the general US population and across a wide range of chronic illnesses [19, 20]. Fatigue is one of the core symptoms assessed by PROMIS because it is such a pervasive feature of many illnesses and treatments. The PROMIS fatigue surveys are highly reliable and have been validated in several disease states [19, 21], countries, and ethnic groups [22, 23]. Although not previously studied in chronic HBV infection per se, PROMIS measures have been used to measure patient-reported outcomes in other liver disease populations [24–26].

The Hepatitis B Research Network (HBRN), a cooperative network of investigators from clinical centers across the USA and Canada, provided a unique opportunity to evaluate fatigue in patients representing all phases of chronic HBV infection. The specific aims of the current HBRN study analysis were to (a) assess fatigue using one of the PROMIS short form surveys and (b) identify clinical, laboratory, and demographic factors associated with fatigue in a large multiethnic North American population.

Materials and Methods

Study Design

This is a large, multicenter cross-sectional study analyzing data collected from patients enrolled in the HBRN cohort study. The HBRN is a cooperative network of investigators from 21 geographically distinct clinical centers across the USA and one in Canada, a data coordinating center, virology testing laboratory, and immunology center. The goal of the HBRN is to conduct clinical, scientific, epidemiological, and therapeutic research in acute and chronic hepatitis B in both adult and pediatric patients who reside in North America [27]. All protocols were approved by the steering committee and the institutional review boards or research ethics boards of the participating sites, and all participants provided written informed consent.

Participants

The HBRN observational cohort study enrolls participants with hepatitis B who are above the age of 2 years, are not on antiviral therapy, and do not have decompensated chronic hepatitis B nor hepatocellular carcinoma at enrollment. All consenting participants undergo an initial evaluation with collection of demographic information and medical history. In addition, routine laboratory results and virologic testing are done at baseline and at weeks 12, 24, 48, 72, 96, 120, and 144. The NIH PROMIS Fatigue 7-item Short Form (Fatigue SF) was introduced into the observational cohort study after recruitment had begun, and therefore fatigue was assessed at 48 weeks following the

baseline visit. In those participants already completing their 48 weeks visit, fatigue was assessed at the week 72 visit. Administration of the Fatigue SF was limited to adults above the age of 18 years who could speak or read English or Spanish. Among 1654 adult patients who were enrolled in the HBRN at the time of this study, 1118 participants completed the Fatigue SF (893 at week 48 and 225 at week 72). The reasons for not completing the Fatigue SF included study discontinuation ($n = 163$), not reaching week 48 or 72 ($n = 26$), lack of IRB approval ($n = 12$ for whom a site did not have the Fatigue SF approved by IRB prior to week 48 or 72 of the study), language barrier ($n = 175$), and incompletion or missed visit ($n = 160$). Of the 1118 who completed the form, 170 were excluded from the current analyses because they were being treated for hepatitis B, were pregnant, or had acute HBV infection. The remaining 948 patients were included in the analytic dataset. The proportion of patients recruited from each center was approximately 50 % (range 22–73 %). Demographic data from the baseline visit and clinical and virologic data collected at the same visit as the Fatigue SF assessment were used for these analyses. If covariates were not available at the same time point as the Fatigue SF, values from the previous time point were carried forward.

Measures

Fatigue

The PROMIS Fatigue 7-item Short Form (SF) consists of seven questions that assess the experience of fatigue (e.g., "tired," "run out of energy") and interference of fatigue on daily activities (e.g., "work," "take a bath or shower") over the past 7 days (see Appendix 1; http://www.nihpromis.org/science/PubsDomain/Fatigue_adult.aspx). The PROMIS Fatigue 7-item SF includes a subset of items from a larger PROMIS item bank of fatigue items for which the items were selected to capture frequency of fatigue experience and interference (e.g., How often did you feel tired?) with five response options ranging from 1 ("never") to 5 ("always") [28]. Responses are summed so that the final raw score ranges from 7 (lowest possible) to 35 (highest possible). NIH PROMIS provides a scoring table to translate the total raw score into a standardized T-score, which has been calibrated in the US general population to have a mean of 50 and a standard deviation (SD) of 10. The PROMIS T-score metric was based on a sample of 21,133 participants whose internet responses were used to calibrate and derive final T-scores, weighted to the US census norms from 2000 [19, 20, 29]. A subject with a T-score of 40 is one SD below, and a subject with a T-score of 60 is one SD above the US general population mean. Higher fatigue T-scores indicate higher degrees of fatigue. In previous studies, the Fatigue SF correlated with the full item bank of fatigue items ($r = 0.76$), correlated with other measures of fatigue ($r = .89$–$.95$), and the reliability of measurement was greater than 0.91 for scores 2 SD below and 4 SD above the mean [19].

Demographic, Clinical, and Virologic Features

The Fatigue SF scores were analyzed overall in the cohort as well as by multiple demographic features including age, sex, race, marital status, education, employment, income, continent of birth, and years living in the USA and Canada. Clinical features considered in the analyses of fatigue scores included serum alanine aminotransferase (ALT), total bilirubin, albumin, body mass index (BMI), advanced fibrosis as measured by the AST–platelet ratio index (APRI), medication type, and medical comorbidities (i.e., diabetes, hypertension, hyperlipidemia, and other liver diseases such as alcoholic liver disease, nonalcoholic liver disease, autoimmune liver disease, and hepatitis C and D infections). Virologic factors analyzed for association with fatigue included clinically assigned HBV phenotype, presence or absence of HBeAg, HBV DNA level, duration of infection, and presumed source of infection. The HBV phenotype was assigned by clinicians at enrollment based upon common conventions using HBV DNA and ALT levels. The guidelines established by the HBRN are as follows: Inactive HBsAg carriers had HBsAg without HBeAg, normal ALT levels, and no or minimal HBV DNA levels in serum (<1000 IU/mL). Immune active chronic hepatitis B was defined by the presence of HBsAg and raised ALT levels with moderate or high levels of HBV DNA in serum (>10,000 IU/mL) and were also divided into those with and without HBeAg. Immune tolerant chronic hepatitis B was defined by the presence of HBsAg, HBeAg, and high levels of HBV DNA in serum, with normal ALT levels. Patients not fitting into any of these three patterns were considered "indeterminate." Since previous studies in chronic hepatitis C demonstrated that fatigue is often associated with mental health functioning, the Medical Outcomes Study 36-item Short Form (MOS SF-36) mental health functioning subscale was used as one of the clinical correlates [30]. The mental health functioning subscale includes 5 items which assess feeling "down in the dumps," "nervous," "blue/sad," "happy," and "peaceful" in the last 7 days; thus, the subscale is not contaminated with items that measure fatigue or somatic symptoms. Using an algorithm, the raw score is translated into a norm-based standardized T-score, with a mean of 50 and a standard deviation of 10. Higher scores indicate better mental health functioning.

Data Analytic Plan

The raw scores from the Fatigue SF were translated into standardized T-scores which were calculated using the public software package PROMIScore (http://www.nihpromis.org/resources/resourcehome). All PROMIS measures, including the Fatigue SF, were derived from larger item banks which were evaluated in an initial sample of 21,133 respondents [29]. The sample was weighted to have the same distribution of demographic variables as that in the 2000 US Census [29, 31]. After calculation of the T-score, a test of whether the mean T-score deviated from 50 was conducted using a two-sided t test. Subsequently, Fatigue T-scores were described using means, standard deviations, and confidence intervals. Covariates were chosen based upon the previous literature on fatigue in liver disease patients and the clinical judgment and experience of the working group. Across levels of categorical covariates, T-scores were compared using t tests for two-level variables or analysis of variance F tests for variables of three or more levels. Linear regression analysis was used to assess the association between fatigue scores and continuous covariates. Multiple linear regression was employed to identify independent predictors of fatigue significant at $p < 0.05$. Age, race, APRI, and viral load were forced into the multivariable model considering their clinical importance. For other covariates, variables significant at $p = 0.10$ in the univariable regression were considered for inclusion in the multivariable regression model, and a stepwise variable selection method was used to select a final model. Variables omitted (due to their p values being greater than 0.10 in the univariable analysis) were checked further by including them individually in the final model to see whether they become statistically significant when adjusted for other variables.

Results

Participant Characteristics

The characteristics of the 948 participants are summarized in Table 1. Over 88 % of participants who completed the fatigue survey spoke English as a primary language; the remaining 12 % spoke English as a second language and were able to complete the survey. Fifty-one percent ($n = 451$) of participants were female, the median age was 42 years, and the median duration of HBV infection was 31 years. Participants were predominantly Asian (71 %) with only 13 % of Caucasian race. The majority (74 %) had some college education or above. Participants were primarily employed (77 %).

HBV phenotype was clinician-assigned at the time of enrollment into HBRN: 40.7 % were considered inactive carriers, 36 % had chronic hepatitis B with disease activity (9.9 % with HBeAg and 25.6 % without HBeAg), 10.1 % had immune tolerant hepatitis B, and 13.6 % were designated as "indeterminate." The median HBV DNA was 3.4 $\log_{10}$ IU/mL, the median ALT was 30 U/L, and 2 % of participants had APRI scores (>1.5) suggestive of advanced fibrosis or cirrhosis. Comorbid conditions were not very frequent with only 27.8 % of participants having another medical condition besides hepatitis B. The SF-36 mental health functioning subscale norm-based score had a median value of 54.2, with the middle 50 % of participants being between 47.2 and 58.5.

Evaluation of Fatigue in the Cohort

There was excellent internal consistency (over Cronbach's $\alpha = 0.84$) for the fatigue short form with individual item's alpha ranging from 0.79 to 0.89. In the HBRN cohort, the mean fatigue raw score was 14.13 (SD = 4.48) and the transformed standardized T-score was 46.8 (95 % CI 46.3–47.3), which was lower than that of the reference mean for the US general population ($T = 50$). Prior studies suggest that one-half of a SD is equivalent to a moderate effect size and the minimally important difference (MID) in PROMIS scores ranges from 2 to 5 points [32]. Although the 3.2 difference between the HBRN and PROMIS samples was statistically significant ($p < 0.0001$), it may or may not represent a clinically meaningful difference. The distribution of the fatigue scores in the HBRN cohort is shown in the histogram and density plot of Fig. 1, with 33.3 % (95 % CI 30.3–36.4 %) of participants having a score greater than the average US fatigue T-score of 50 and 15.4 % (95 % CI 13.2–17.9 %) of participants having fatigue T-scores above 55.

Unadjusted and Adjusted Associations Between Fatigue and Demographic and Clinical Patient Characteristics

In unadjusted analyses, female sex, not being married, not being employed, higher BMI, lower income, higher APRI, being born in North or South America, currently taking medications, having comorbid conditions (specifically, hyperlipidemia, diabetes, and other liver diseases such as hepatitis C or D), and lower mental health functioning were all significantly ($p < 0.05$) associated with higher fatigue scores (Table 1). In particular, mean fatigue scores were 2.5 points higher in females than in males, 1.9 points higher in those not employed compared to those who were employed, and 3.1 points higher in patients widowed,

Table 1 Participant characteristics and unadjusted associations with fatigue, $n = 948$

	Median (25th/75th) *n* (%)	Unadjusted mean/slope[b] (95 % CI)	*p* value
Age	$n = 945$		
	42.0 (34.0:52.0)	0.03 (−0.01, 0.07)	0.21
Sex	$n = 940$		
Male	462 (49.1 %)	45.5 (44.79, 46.21)	<0.001
Female	478 (50.9 %)	47.97 (47.27, 48.67)	
Race	$n = 937$		0.19[a]
Asian	666 (71.1 %)	46.67 (46.07, 47.27)	
African-American/other	154 (16.4 %)	46.17 (44.93, 47.42)	0.48
Caucasian	117 (12.5 %)	47.9 (46.47, 49.33)	0.12
Marital status	$n = 925$		0.001[a]
Married or living in a marriage-like relationship	628 (67.9 %)	46.38 (45.76, 46.99)	
Never married	201 (21.7 %)	46.71 (45.62, 47.79)	0.6
Widowed, divorced, or separated	96 (10.4 %)	49.51 (47.94, 51.07)	<0.001
Education	$n = 932$		
Some grade school through HS	242 (26.0 %)	46.82 (45.83, 47.82)	0.91
Some college and above	690 (74.0 %)	46.75 (46.16, 47.34)	
Employment	$n = 936$		
Part-time/full-time	722 (77.1 %)	46.37 (45.79, 46.94)	
Homemaker/retired/unemployed/other	214 (22.9 %)	48.22 (47.17, 49.27)	0.002
Income	$n = 776$		0.003[a]
$0–$49.9 K	338 (43.6 %)	47.8 (46.97, 48.64)	
$50–$99.9 K	212 (27.3 %)	47.09 (46.04, 48.14)	0.3
100 –$199.9 K	161 (20.7 %)	45.56 (44.35, 46.76)	0.003
$200 K+	65 (8.4 %)	44.91 (43.01, 46.8)	0.006
Continent at birth	$n = 937$		0.002[a]
Asia	606 (64.7 %)	46.78 (46.16, 47.4)	
North/South America	201 (21.5 %)	47.96 (46.88, 49.05)	0.06
Africa	92 (9.8 %)	44.1 (42.5, 45.7)	0.002
Europe/Australia	38 (4.1 %)	46.49 (44, 48.97)	0.82
Years in USA/Canada	$n = 856$		0.07[a]
≤10 years ago	192 (22.4 %)	46.03 (44.91, 47.14)	0.05
>10–20 years ago	208 (24.3 %)	46.13 (45.06, 47.2)	0.07
>20 years ago	456 (53.3 %)	47.34 (46.61, 48.06)	
ALT (IU/L)	$n = 942$		
	30.0 (21.0:45.0)	0 (−0.01, 0.01)	0.56
TBili (mg/dL)	$n = 940$		
	0.6 (0.5:0.9)	−1.21 (−2.64, 0.22)	0.1
Albumin (g/dL)	$n = 937$		
	4.3 (4.1:4.5)	−2.08 (−3.62, −0.55)	0.008
HBV DNA (log10 IU/mL)	$n = 945$		
	3.4 (2.4:4.9)	−0.14 (−0.35, 0.07)	0.2
BMI (kg/m^2)	$n = 934$		
	24.1 (21.8:27.1)	0.11 (0.01, 0.21)	0.029
Years of HBV infection	$n = 641$		
	31.0 (20.0:42.0)	0.05 (0.01, 0.09)	0.008
Phenotype	$n = 938$		0.61[a]
Inactive carrier state	382 (40.7 %)	46.91 (46.12, 47.7)	
HBeAg-negative chronic hepatitis B	240 (25.6 %)	47.14 (46.15, 48.14)	0.72

Table 1 continued

	Median (25th/75th) *n* (%)	Unadjusted mean/slope[b] (95 % CI)	*p* value
Indeterminate	128 (13.6 %)	46.83 (45.46, 48.2)	0.92
Immune tolerant chronic hepatitis B	95 (10.1 %)	45.85 (44.26, 47.44)	0.24
HBeAg-positive chronic hepatitis B	93 (9.9 %)	46.08 (44.48, 47.69)	0.36
APRI (AST–platelet ratio index)	$n = 887$		0.004[a]
≤0.50	704 (79.4 %)	46.67 (46.09, 47.25)	
>0.50–1.50	165 (18.6 %)	47.03 (45.82, 48.23)	0.6
>1.50	18 (2.0 %)	52.99 (49.34, 56.64)	<0.001
Presumed source of hepatitis B	$n = 948$		0.86[a]
Vertical transmission	415 (43.8 %)	46.67 (45.91, 47.44)	
Horizontal transmission	175 (18.5 %)	46.49 (45.31, 47.67)	0.8
Sexually transmitted	37 (3.9 %)	47.79 (45.23, 50.35)	0.41
Other	70 (7.4 %)	47.38 (45.52, 49.25)	0.49
Unknown/missing	251 (26.5 %)	46.77 (45.79, 47.75)	0.88
Currently taking any prescription medication	$n = 945$		
Yes	224 (23.7 %)	47.89 (46.85, 48.92)	0.017
No		46.44 (45.87, 47.02)	
Medical comorbidities	$n = 945$		
At least one	263 (27.8 %)	47.96 (47, 48.91)	0.005
None		46.34 (45.74, 46.93)	
Hx diabetes	$n = 945$		
Yes	46 (4.9 %)	50.43 (48.15, 52.71)	0.001
No		46.6 (46.09, 47.12)	
Hx hypertension	$n = 945$		
Yes	151 (16.0 %)	47.77 (46.51, 49.03)	0.1
No		46.6 (46.05, 47.15)	
Hx hyperlipidemia	$n = 944$		
Yes	128 (13.6 %)	48.77 (47.4, 50.13)	0.002
No		46.48 (45.94, 47.02)	
Hx liver disease	$n = 948$		
Yes	61 (6.4 %)	48.81 (46.82, 50.8)	0.034
No		46.60 (46.07, 47.13)	
SF-36 mental health functioning	$n = 940$		
	54.2 (47.2:58.5)	−0.46 (−0.5, −0.41)	<0.001

[a] For testing equality of T-scores across all categories

[b] For discrete variables, unadjusted category mean fatigue score. For continuous variables, change in mean fatigue score per unit change in variable

divorced, or separated compared to those who were married.

Among clinical laboratory variables analyzed as continuous variables, serum ALT, AST, bilirubin, and alkaline phosphatase levels were not significantly associated with fatigue scores. The calculated APRI score, however, was significantly associated with fatigue scores, being on average 6.3 points higher in participants with APRI > 1.5 ($T = 53$) compared to those with levels of ≤0.5 ($T = 46.7$) or 0.5–1.5 ($T = 47.0$). Serum albumin levels were also significantly associated with fatigue scores, with a 2.1-point reduction in fatigue for a 1 g/dL increase in albumin. Notably, there were no significant associations between fatigue scores and any virologic feature of hepatitis B such as HBeAg status and HBV DNA levels. In addition, fatigue scores were almost identical among the clinically assigned HBV phenotypes with no differences between inactive HBsAg carriers (46.9) compared to those with HBeAg-positive (46.1) or HBeAg-negative immune active disease (47.1), or immune tolerant hepatitis B (45.9). In contrast, both the presence of other medical comorbidities and worse mental health functioning were significantly associated

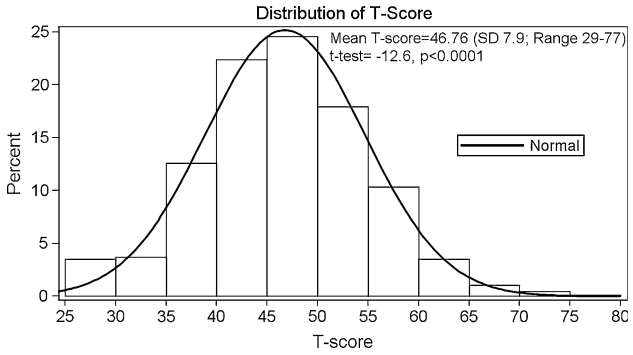

Fig. 1 Distribution of fatigue T-score in HBV patients in the cohort

with higher levels of fatigue. Participants with one or more comorbidities had 1.6 points higher average fatigue scores compared to those without any comorbidities. For every 10-point decrease in the mental health functioning score, the mean fatigue score increased by 4.6 points.

Table 2 shows results for adjusted regression models with race, age, APRI, and viral load forced into the model. Sex, mental health functioning, and having a history of diabetes remained significant independent predictors of fatigue. In the adjusted analysis, the estimated mean fatigue score for females was 2.18 units (95 % CI 1.29–3.06) higher than for males ($p < 0.0001$). The estimated mean fatigue score for those with APRI > 1.50 (advanced fibrosis) was 4.41 units (95 % CI 1.32–7.50) higher than for those with APRI $\leq$ 0.50 ($p = .005$). Those with a history of diabetes had a mean fatigue score that was 2.22 (95 % CI 0.11–4.32) units higher than those without a history of diabetes ($p = 0.039$). Finally, as mental health functioning deteriorated, mean fatigue scores increased (Fig. 2). A 10-unit decrease in mental health functioning was associated with a 4.4 (95 % CI 4.0–4.9)-unit increase in mean fatigue score ($p < 0.0001$).

Discussion

Fatigue is a common symptom of many medical conditions including diseases of the liver. In this study, fatigue was assessed using a reliable and validated instrument in a large multiethnic cohort of patients with chronic HBV infection residing in North America. We utilized the PROMIS Fatigue 7-item Short Form to measure the frequency and intensity of fatigue. The PROMIS measure was selected because of its precision in measuring the unidimensional construct of fatigue without being confounded by items that tap other symptoms (e.g., depression) or domains (e.g., HRQOL). Further, it is short, easily utilizable and patient-friendly and has been applicable to a wide range of disease states, including liver disease [26]. The main findings of this study suggest that fatigue is unrelated to most virologic and disease markers of HBV, and however, it is associated with liver disease severity (i.e., APRI score suggestive of advanced fibrosis), as well as female sex, mental health functioning, and comorbidities such as diabetes.

Several virologic and disease markers of HBV were evaluated in this study, including clinically assigned HBV phenotype, HBeAg status, HBV DNA levels, serum aminotransferase levels, and APRI score. Approximately 50 % of the study cohort had immune active HBV disease; however, fatigue was not more severe among these patients compared to those with immune inactive or immune tolerant disease phenotypes. The only clinical variable associated with fatigue in the multivariate model was evidence of advanced liver disease with APRI score of >1.5. The relationship between severity of liver disease and fatigue thus far in the literature has been equivocal, with one study demonstrating no association [13], but a few suggesting that patients with cirrhosis experience greater fatigue [2, 11, 33] and worse quality of life [5]. In a similar

Table 2 Adjusted associations between fatigue and participant characteristics ($n = 876$)

Variable	Regression coefficient (95 % CI)	p value
Race		0.09
African-American/other versus Asian	−1.31 (−2.51, −0.12)	0.032
Caucasian versus Asian	−0.63 (−2.00, 0.74)	0.37
Age	0.01 (−0.02, 0.05)	0.48
APRI		0.012[a]
>1.50 versus ≤0.50	4.41 (1.32, 7.50)	0.005
>0.50–1.50 versus ≤0.50	0.74 (−0.41, 1.89)	0.21
HBV DNA (log10 IU/mL)	−0.15 (−0.35, 0.05)	0.15
Female versus male	2.18 (1.29, 3.06)	<0.001
History of diabetes	2.22 (0.11, 4.32)	0.039
SF-36 mental health functioning score	−0.44 (−0.49, −0.40)	<0.001

Race, age, APRI, and HBV DNA were forced into model

[a] For testing equality of T-scores across all categories

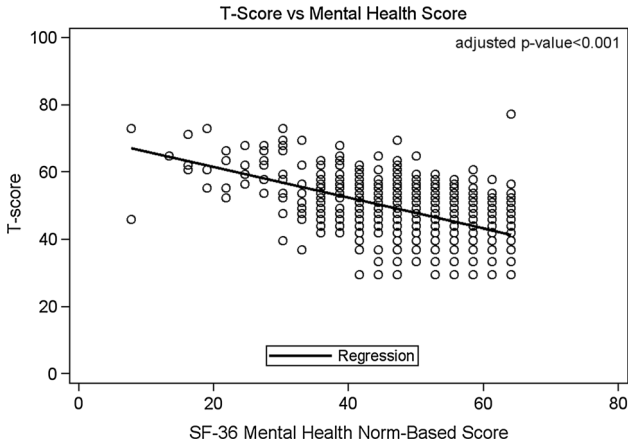

Fig. 2 Association between fatigue T-score and mental health functioning. Scatter plot of fatigue T-score versus SF-36 mental health functioning subscale norm-based score with regression line. *Each circle* represents a participant or overlapping of participant points

population, fatigue levels of patients infected with chronic hepatitis C were not associated with Ishak fibrosis score on liver biopsy, the gold standard for diagnosis of cirrhosis [34]. The finding that only an APRI score of >1.5 is associated with fatigue suggests that serious fatigue issues are uncommon in chronic HBV infection unless advanced fibrosis is present. These findings reinforce the need for routine screening for hepatitis B in high-risk populations, because patients are unlikely to have symptoms indicative of the presence of liver disease. The absence of symptoms of fatigue also places a burden on the treatment for this disease, the endpoints of which should be prevention of disease progression, not necessarily amelioration of symptoms. The lack of association with most virologic or clinical markers indicates that chronic hepatitis B is generally an asymptomatic disease; however, patient-reported fatigue may indicate the presence of advanced fibrosis.

The single, strongest predictor of higher fatigue levels was low mental health functioning, a SF-36 subscale that taps into emotions such as feeling down in the dumps, nervous, blue, sad, happy, and peaceful while not tapping into somatic items, such as fatigue. Other studies have produced similar findings in chronic hepatitis B and C with measures of neuropsychiatric comorbidities, anxiety, and depression predicting higher fatigue levels [4, 5, 10, 11, 13, 14]. Collectively, these findings provide important insight into specific patients who may subjectively experience greater fatigue, namely those with higher rates of depressed or anxious mood.

Importantly, higher levels of fatigue were found in women compared to men. This finding is consistently documented in previous studies, including those using the PROMIS fatigue survey in both normal control and disease populations [35–37] and in women infected with chronic hepatitis C [11]. Predisposing vulnerabilities for women (e.g., endocrine and stress-related factors and social-contextual determinants) have been proposed to explain this phenomenon; however, it remains a commonly observed but not well-understood association [35].

Several unique aspects of the current study, compared to the existing literature, are noteworthy. Previously, close examination of fatigue severity in patients with chronic hepatitis B has been hampered by relatively small sample sizes or studies that combine hepatitis B with other chronic liver diseases [6, 38, 39]. In addition, most studies have not focused on the unique situation in North America with its diverse populations reflecting different sources of infection, varying genotypes, and distinct clinical courses of this chronic infection [40]. One qualitative study focused on symptoms among US patients with chronic hepatitis B, but the cohort was comprised largely of non-Asian patients who now represent the minority of patients with this disease in the USA [3]. Moreover, the primary emphasis has been on understanding the effect of chronic HBV infection on the broader construct of HRQOL which is influenced by many patient and environmental characteristics [17], while specific symptoms such as fatigue have been measured secondarily [2, 4, 14–16, 18]. Therefore, the current study broadens our knowledge of patient-reported fatigue in a predominately Asian cohort chronically infected with HBV and residing in North America. It is possible that differences between the HBRN and PROMIS samples, such as race, education, and comorbidities, partially explain the statistical differences in fatigue scores, although it remains unclear whether this difference is clinically meaningful. The HBRN and control PROMIS cohorts differed prominently in racial distribution (74 % Asian vs 1 %), and one might speculate that Asians experience less fatigue than Caucasians. However, we found no significant univariate differences in mean fatigue scores among the Asian ($T = 46.7$), African-American ($T = 46.2$), or Caucasian ($T = 47.9$) patients in the HBRN cohort. Moreover, all three racial groups had median fatigue scores lower than the general US population, suggesting that other factors, not race, likely underlie these differences. On variables available for comparison, the most important difference between the two samples may relate to the fewer comorbidities in the HBRN population (27 %) compared to the general population in the USA (72 %). Nonetheless, no meaningful comparisons can truly be made between the PROMIS sample, which was weighted to have the same distribution of demographics as that in the 2000 US Census, and the HBRN sample of patients who are predominantly Asian, more educated, and have fewer comorbidities.

A few limitations of this study should be noted. Given the specific patient characteristics of this cohort, these

findings may not be generalizable to patients with more advanced liver disease or those engaged in active HBV treatment, non-Asian patients, or individuals residing in other countries where sociocultural perceptions about having HBV or liver disease may differ. Only 2 % of this sample had advanced fibrosis or cirrhosis as estimated by APRI. This may have been because the HBRN did not enroll patients with decompensated cirrhosis or patients who were already on HBV treatment. Further, patients who were on HBV treatment at the time of fatigue assessment were excluded from the current study in order to focus specifically on fatigue that was not caused by treatment side effects. Of the 130 participants who were excluded from this study due to being on treatment and who had an APRI score, 12 (9 %) had APRI scores >1.5, substantially higher than the 2 % reported in our sample. Therefore, the average fatigue level likely would have been higher had the sample included a greater number of patients with advanced liver disease or on HBV treatment. In this study, we employed APRI as a surrogate for liver histology since liver biopsies were neither necessary nor warranted in many study participants and, when available, were rarely concurrent with administration of the PROMIS fatigue survey. Also, only patients who were English or Spanish speaking were recruited for this study because the PROMIS Fatigue Short Form had yet to be translated and tested in other languages. That said, less than a quarter of otherwise eligible patients failed to complete the fatigue instrument due to language barriers. By assessing fatigue at weeks 48 and 72 weeks, we likely missed patients initially diagnosed with more severe disease who required immediate treatment and hence were excluded from these analyses. Our study also did not collect information on antidepressant or antianxiety medication; therefore, the analysis could not be adjusted for the use of these medications. Finally, the external validity of the PROMIS fatigue instrument (or any other fatigue instrument) has not been previously established in individuals with chronic HBV infection or in those from Asian-American descent. We chose the PROMIS fatigue instrument due to its rigorous reliability and validity (e.g., construct, content, and concurrent validity), correlation with items from the larger fatigue bank and other measures of fatigue (e.g., SF-36 vitality scale), validity in other medical populations, and contribution to the overall mission of the NIH PROMIS initiative [20, 41–45]. Future studies of fatigue in patients with HBV should include longitudinal analysis of fatigue before, during, and after HBV treatment to evaluate trends over time, and assessment of other moderator and mediator variables to better understand which patients, and by which pathways, HBV may be related to fatigue.

In conclusion, in this cohort of North American adults participating in the HBRN study, higher fatigue levels are associated with more advanced liver disease and more comorbid conditions, such as diabetes, but no other disease or virologic markers. Women and patients who experience poorer mental health functioning, such as symptoms of depression or anxiety, also appear to be prone to higher levels of fatigue. In patients who complain of fatigue during the clinical encounter, providers should be suspicious of advanced fibrosis or mental health issues and refer accordingly for further evaluation.

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Compliance with ethical standards

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