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Liver disease symptoms are associated with higher risk of adverse clinical outcomes: A longitudinal study of North American adults with chronic Hepatitis B

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Summary

Background: Symptoms of chronic hepatitis B (CHB) are not well characterised.

Aims: To evaluate CHB symptoms and associations with disease activity and clinical outcomes.

Methods: Longitudinal data from 1576 participants in the Hepatitis B Research Network Cohort Study who completed symptom assessments were analysed. A composite symptom score was calculated using a Symptom Checklist (0 = none to 40 = extreme). Multivariable mixed models assessed variables associated with symptom change over time. Latent class symptom trajectories were evaluated. The cumulative probability of long-term clinical outcomes (new onset cirrhosis, hepatic decompensation, hepatocellular carcinoma, liver transplantation, death) was examined by baseline symptom groups.

Results: Participants median age was 42 (range: 18-80), 51% were male, 75% Asian, (68% of whom were born outside North America) with a median follow-up of 4.2 years. On average, symptoms did not significantly change over time. The multivariable model identified several variables associated with higher symptoms during follow-up: being female, non-Asian, born in the United States/Canada, lower education, higher AST, lower platelets and more comorbidities. Two patient subgroups were identified based on longitudinal symptom trajectories: a low symptom group (92%, n = 1451) with symptom scores averaging 2.4 over time and a moderate symptom group (8%, n = 125) with symptom scores averaging 11.5. During follow-up, 7.3% in

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the moderate symptom group, but only 3.2% of the low symptom group, developed adverse outcomes ($P = 0.02$).

Conclusions: In this large cohort of CHB patients, symptoms were generally mild and stable over time. However, in some patients with moderate symptoms at baseline, deleterious clinical outcomes were more frequent at follow-up.

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1 | INTRODUCTION

Over one million people living in the United States and Canada are affected by chronic hepatitis B infection (CHB) and the burden of disease is significantly higher amongst those who are foreign-born.[1,2] CHB is a dynamic disease as the course may change and fluctuate over time. Longitudinal studies are needed to better understand the natural history of CHB and evolution of patients' experiences with the disease. While several studies have evaluated the health-related quality of life of patients with CHB, only a few cross-sectional studies have explored patient-reported symptoms of CHB.[3-6]

We previously published a cross-sectional analysis of data from 876 adults living in the United States and Canada who participated in the Hepatitis B Research Network (HBRN) Adult Cohort Study.[7] Overall, this multi-ethnic North American cohort had mild liver disease and reported favourable HRQoL on the SF-36 and minimal CHB symptoms on a 10-item Symptom Checklist developed by the NIDDK. One-quarter of patients reported no symptoms. The most frequent symptoms amongst those who had symptoms were fatigue (60%), irritability (32%) and itching (32%) but most symptoms were only mildly bothersome.

An unexpected and interesting finding was that the Symptom Checklist score explained substantial variation in SF-36 HRQoL scores after controlling for several patient, clinical and disease-related variables. These preliminary findings suggested that CHB-associated symptoms may have unrecognised impact on patient-reported outcomes and CHB clinical management, worthy of investigation, in and of themselves. Furthermore, whether CHB symptoms are associated with viral fluctuation, CHB flares, disease progression, antiviral treatment, or long-term clinical outcomes, remains unknown.

The HBRN Adult Longitudinal Cohort Study provides an ideal opportunity to evaluate the trajectory of CHB symptoms and their associations with patient, virological, disease and long-term clinical outcomes.[8] The objectives of this longitudinal analysis were to characterise CHB-associated symptoms over time and explore associations with changes in virological and clinical outcomes during 7 years of follow-up.

2 | METHODS

2.1 | Study design

This was a prospective longitudinal study of patients diagnosed with CHB infection and enrolled in the Hepatitis B Research Network (HBRN) Adult Cohort study. The Hepatitis B Research Network is an NIH-funded consortium of investigators from 21 geographically diverse adult clinical centres across the United States and one clinical centre in Canada.[8] All protocols were approved by the HBRN Steering Committee, the Institutional Review Boards or Research Ethics Boards of the participating sites, as well as a Data Safety and Monitoring Board appointed by the NIDDK to oversee the Network. All participants provided written informed consent. The HBRN adult cohort study is registered on ClinicalTrials.gov (NCT01263587).

2.2 | Participants

From 2011 to 2018, the HBRN Adult Cohort study enrolled 2032 adults with CHB who were *not* on HBV therapy at enrollment, of whom 2018 were HBsAg+ eligible participants (Figure S1). Participants were excluded from this analysis if they had acute HBV infection or co-infection with human immunodeficiency virus, hepatitis C virus, or hepatitis D virus. Participants who were on HBV therapy within 24 weeks prior to their first symptom assessment were excluded. Participants were evaluated at baseline, week 12 and every 24 weeks. Follow-up visits were censored for women who were pregnant at that visit or within 24 weeks after giving birth. Follow-up visits were also censored after entering one of the HBRN clinical treatment trials. Participants were excluded if they did not have at least two eligible symptom assessments at protocol follow-up visits. Participants who were put on HBV treatment by their local hepatologist after their first symptom assessment were included in the analysis. The final analytic sample included 1576 participants who were HBsAg (+) at first assessment and who collectively completed 14 966 symptom assessments over the course of the 7-year cohort study with a median follow-up of 4.2 years.

2.3 | Primary outcome

Symptoms were assessed using a National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Liver Disease Symptom Checklist (SCL) at enrollment and every 24 weeks during follow-up. The SCL is a 10-item instrument originally developed by the NIDDK to quantify symptoms associated with chronic liver disease. It has been modified for utilisation in several NIDDK-funded research networks of various liver disease populations.[7,9] Participants were asked, "*During the last month, how much have you been bothered by the following symptom: fatigue, itching, pain over liver, irritability, depression/sadness, nausea, poor appetite, weight loss, dark urine, jaundice*." For each symptom, the participant marked a box to indicate how bothered they were by the symptom in the last month: None at all (0), A little bit (1), moderately (2), quite a bit (3), or extremely (4). If they did not have the symptom, they marked "None at all." For this analysis, a total CHB symptom score was created at each study visit by summing the 10 symptom scores with a possible range from 0 to 40, with higher scores indicating worse symptoms.[7]

2.4 | Independent variables

The following baseline patient characteristics were explored: age, sex, race, place of birth and education. Clinical and virological data collected at the same follow-up visit as the Symptom Checklist were evaluated: serum alanine aminotransferase (ALT, U/L), aspartate aminotransferase (AST, U/L), albumin (g/dL), platelets ($\times 10^3/mm^3$), AST-platelet-ratio index (APRI), fibrosis-4 (FIB-4) index, cirrhosis status, CHB phenotypes, HBV DNA (log_{10} IU/mL), HBeAg (positive, negative), quantitative HBsAg (qHBsAg log_{10} IU/mL), number of medical comorbidities (0, 1, 2+), number of medications (0, 1, 2+) and HBV treatment status. HBV phenotypes were defined based upon HBeAg status and HBV DNA and ALT levels as previously defined by the HBRN and included inactive carriers, immune active HBV, immune tolerant HBV and an indeterminant HBV phenotype.[10] Upper limit of normal for ALT was set at 30 U/L for males and 20 U/L for females.[2,11,12]

2.5 | Clinical outcomes

Clinical outcomes in this analysis included the development of new-onset or diagnosis of cirrhosis, hepatic decompensation, hepatocellular carcinoma, liver transplantation, or death during follow-up. All outcomes were pre-defined in the study protocol and the occurrence and timing of each clinical event were adjudicated by a committee of HBRN clinical investigators to determine if criteria for these outcomes were met. Diagnosis of cirrhosis at baseline and during follow-up was based on histology, hepatic decompensation or CTP score ≥7; and in the absence of the above criteria by two of the following: splenomegaly or nodular liver on radiological imaging, or platelet count <120 000/mm^3.[13] At the time of first symptom assessment, 18 patients had a diagnosis of cirrhosis and were not concurrently on HBV therapy. These 18 patients were excluded from the analysis of predictors of subsequent clinical outcomes. A binary variable for the incidence of clinical outcomes (Yes = 1) was created for patients who developed any of the clinical events noted above after their first symptom assessment.

2.6 | Statistical analyses

Data were summarised using frequencies (percentages) for categorical variables and medians (25th and 75th percentiles) for continuous variables. The total SCL score was analysed as a continuous outcome. A mixed-effects model was used to identify demographics and clinical markers that were associated with the total SCL score over time at the population level. Because the total symptom score was right-skewed and not normally distributed, regular linear mixed models could not be used; negative binomial mixed models with random intercepts to account for within-participant correlation across time were used.[14] The statistical methods used for variable selection using LASSO (least absolute shrinkage and selection operator) and mixed-effects models are presented in the Supplementary Information. Second, latent class mixed models were used to examine individual symptom trajectories over time and to identify subgroups of participants with different patterns of change in symptom scores. The best latent class mixed model was selected based on the smallest Bayesian information criterion (BIC) and with at least 5% of participants in each class. The Kruskal-Wallis test or Pearson's chi-square test was used to test whether distributions of continuous or categorical characteristics at baseline differed by trajectory groups. The cumulative probability of clinical outcomes by Kaplan-Meier method and incidence rates per 100 person-years of clinical outcomes by Poisson regression models were evaluated. All analyses were conducted in statistical software packages SAS (version 9.4; SAS Institute Inc) and R (version 3.5.3; R Foundation for Statistical Computing). All tests were two-sided and a P value < 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Participant characteristics

The study flowchart of patients included and excluded in this analysis is shown in Figure S1. Patients who were excluded from this analysis included those with acute HBV or co-infection with human immunodeficiency virus, hepatitis C virus, or hepatitis D virus; those with incomplete or ineligible symptom assessments; and those who were on treatment for HBV prior to the first symptom assessment. The majority of patients (93%) completed their first symptom assessment at week 0 (baseline) into the cohort study.

The characteristics of the 1576 participants are summarised in Table 1. The median age was 42 years (range: 18-80). Men and

women were equally represented. Patients were predominantly Asian (75%) and 83% were born outside of the United States and Canada. The median HBV DNA level was 3.8 $\log_{10}$ IU/mL and the majority of patients (73%) had HBeAg-negative status. In regard to HBV phenotype, 22% were inactive carriers, 40% had active disease, 4% were immune tolerant and 35% had indeterminant phenotypes. Five percent of participants had APRI scores ≥1.5 and 3% had FIB-4 scores ≥3.25 suggestive of advanced fibrosis but less than 1% (n = 18) were clinically diagnosed as having cirrhosis at baseline. Most patients had no medical comorbidities (74%).

3.2 | CHB symptoms over time

Figure 1 depicts average symptom scores over the course of 18 research visits for the entire cohort. On average, patients reported minimal symptoms of CHB (a total symptom score averaging <4) at baseline and during the 7-year follow-up. While symptom scores for some individuals varied over time, the average score for the total cohort did not change significantly during the course of the study nor did average scores vary by age or time since baseline. (Table S1).

3.3 | Associations between longitudinal symptom score and patient characteristics and HBV disease markers

Univariable associations between total symptom score and independent variables in the total cohort (n = 1576) are shown in Table S1. The final multivariable model (Table 2) found six variables independently associated with variability in longitudinal total symptom scores: sex, race/place of birth, education, AST levels (expressed as times ULN), platelet counts and number of comorbidities. (The process of variable selection for the multivariate model is described in the Supplemental Information). These six variables helped to explain some of the variability in symptom scores shown for the total population (Figure 1). For instance, symptom scores were 16% higher in females compared to males ($P = 0.01$; Table 2). Non-Asian patients born in the United States/Canada had 54% higher symptom scores compared to Asians born outside the United States/Canada ($P < 0.01$). Patients with lower education levels had 35% higher symptom scores than those with college degrees or higher ($P < 0.01$). Having an AST level of >5 times ULN during follow-up was associated with a 41% higher total symptom score compared to AST levels ≤1 ULN ($P < 0.01$). ALT levels >5 times ULN was also associated with higher symptom scores in the LASSO model but AST was chosen for the final model due to larger effect size. Lower platelet counts (<150 ($\times 10^3/mm^3$)) were associated with an 11% higher average symptom score compared to higher counts ($P = 0.01$). Participants with two or more comorbidities had 17% higher total symptom scores compared to patients with no comorbidities ($P = 0.002$). We conducted a sensitivity analysis excluding patients with comorbidities from the prediction of worse symptom scores, higher AST ($P = 0.02$) and lower platelet counts ($P < 0.01$) remained significantly associated with worse symptoms (data not shown). Notably, HBV treatment, HBV phenotype and change in HBV DNA, HBsAg and albumin during follow-up were *not* selected in the final multivariate model as significant predictors that explained symptom variability.

In a secondary mixed effects model informed by LASSO, AST levels and platelet counts were replaced with FIB-4, while age, sex, race/place of birth, education and comorbidities were retained from the initial multivariable model. In this secondary model, a FIB-4 score of >3.25 (reflecting advanced fibrosis) was associated with a 29% higher total symptom score compared to FIB-4 score <1.45 ($P = 0.001$) (Table S2).

3.4 | Longitudinal symptom trajectories

Whereas the mixed-effects regression models helped to identify factors that explained variability in symptom scores over time at the *population level*, latent class trajectory models were used to examine symptom trajectories over time at *the individual level*. A two-class latent trajectory model was selected that identified two clusters of patients who had different types of symptom trajectories over time (Figure 2). Most patients (92%; n = 1451) reported low symptom scores at baseline and throughout follow-up (average symptom score over time = 2.4) (herein referred to as the "low symptom group"). The second cluster of patients (8%; n = 125) reported moderate symptoms at baseline and during follow-up (average symptom score = 11.5 over time) (herein referred to as the "moderate symptom group"). Figure 3 shows all 10 individual symptoms rated as "Moderately," "Quite a bit" or "Extremely" bothersome over time stratified by the two symptom groups. The moderate symptom group consistently experienced worse symptom scores compared to the low symptom group.

3.5 | Baseline characteristics associated with symptom trajectories

Baseline characteristics associated with the moderate symptom group, relative to the low symptom group, are shown in Table 1. At baseline, patients in the moderate symptom group were more frequently non-Asian (38% vs 24%), with lower education levels (74% vs 50%), having been born in the United States/Canada (27% vs 16%) and having cirrhosis (3% vs 1%), abnormal AST levels (33% vs 23%), higher APRI scores >1.5 (10% vs 5%), higher FIB-4 scores >3.25 (9% vs 3%) and a higher number of comorbidities ≥2 (18% vs 10%) and concomitant medications ≥2 (15% vs 7%) (all *P*-values < 0.05).

3.6 | Baseline symptom group and probability of adverse clinical outcomes

Because low and moderate symptom trajectories were relatively stable from baseline through follow-up, we re-classified patients

TABLE 1 Baseline characteristics associated with low and moderate symptom clusters

Variable	All n = 1576	Low symptom group n = 1451 (92%)	Moderate symptom group n = 125 (8%)	*P*-value
Age at current study visit	n = 1576	n = 1451	n = 125	0.46
Median(25th:75th)	41.5 (33.1:51.5)	41.4 (33.1:51.4)	43.3 (33.2:54.3)	
Sex	n = 1576	n = 1451	n = 125	0.09
Male	796 (51%)	742 (51%)	54 (43%)	
Female	780 (49%)	709 (49%)	71 (57%)	
Race	n = 1573	n = 1448	n = 125	0.003
White	164 (10%)	142 (10%)	22 (18%)	
Black	193 (12%)	175 (12%)	18 (14%)	
Asian	1174 (75%)	1096 (76%)	78 (62%)	
Other/mixed	42 (3%)	35 (2%)	7 (6%)	
Education level	n = 1565	n = 1440	n = 125	<0.001
Below Bachelor	818 (52%)	726 (50%)	92 (74%)	
Bachelor or Higher	747 (48%)	714 (50%)	33 (26%)	
Born in the United States or Canada	n = 1573	n = 1449	n = 124	0.001
No	1305 (83%)	1215 (84%)	90 (73%)	
Yes	268 (17%)	234 (16%)	34 (27%)	
HBV phenotype	n = 1464	n = 1350	n = 114	0.44
Immune tolerant	52 (4%)	48 (4%)	4 (4%)	
HBeAg+ CHB	318 (22%)	287 (21%)	31 (27%)	
HBeAg− CHB	270 (18%)	252 (19%)	18 (16%)	
Inactive carrier	317 (22%)	298 (22%)	19 (17%)	
Indeterminant	507 (35%)	465 (34%)	42 (37%)	
Cirrhosis prior/at current visit	n = 1576	n = 1451	n = 125	0.024
No	1558 (99%)	1437 (99%)	121 (97%)	
Yes	18 (1%)	14 (1%)	4 (3%)	
ALT × ULN	n = 1543	n = 1422	n = 121	0.23
≤1 ULN	461 (30%)	427 (30%)	34 (28%)	
>1 to ≤3 ULN	860 (56%)	798 (56%)	62 (51%)	
>3 to ≤5 ULN	112 (7%)	100 (7%)	12 (10%)	
>5 ULN	110 (7%)	97 (7%)	13 (11%)	
AST × ULN	n = 1503	n = 1387	n = 116	0.09
≤1 ULN	1147 (76%)	1069 (77%)	78 (67%)	
>1 to ≤3 ULN	295 (20%)	265 (19%)	30 (26%)	
>3 to ≤5 ULN	33 (2%)	29 (2%)	4 (3%)	
>5 ULN	28 (2%)	24 (2%)	4 (3%)	
AST × ULN (normal vs abnormal)	n = 1503	n = 1387	n = 116	0.017
Normal AST	1147 (76%)	1069 (77%)	78 (67%)	
Abnormal AST	356 (24%)	318 (23%)	38 (33%)	
HBeAg	n = 1527	n = 1409	n = 118	0.10
Negative	1121 (73%)	1042 (74%)	79 (67%)	
Positive	406 (27%)	367 (26%)	39 (33%)	
HBV DNA (log_{10} IU/mL)	n = 1563	n = 1439	n = 124	0.10
Median(25th:75th)	3.8 (2.7:6.2)	3.8 (2.7:6.1)	4.2 (3.0:6.6)	
qHBsAg (log_{10} IU/mL)	n = 1395	n = 1286	n = 109	0.37

(Continues)

TABLE 1 (Continued)

Variable	All n = 1576	Low symptom group n = 1451 (92%)	Moderate symptom group n = 125 (8%)	*P*-value
Median(25th:75th)	3.4 (2.7:4.2)	3.4 (2.7:4.2)	3.5 (2.8:4.1)	
Albumin (g/dL)	n = 1474	n = 1361	n = 113	0.015
Median(25th:75th)	4.3 (4.1:4.6)	4.3 (4.1:4.6)	4.3 (4.0:4.5)	
APRI (AST-platelet-ratio index)	n = 1310	n = 1205	n = 105	0.047
≤0.50	971 (74%)	901 (75%)	70 (67%)	
>0.50-1.50	274 (21%)	249 (21%)	25 (24%)	
>1.50	65 (5%)	55 (5%)	10 (10%)	
FIB-4	n = 1310	n = 1205	n = 105	<0.001
<1.45	1023 (78%)	954 (79%)	69 (66%)	
1.45-3.25	247 (19%)	220 (18%)	27 (26%)	
>3.25	40 (3%)	31 (3%)	9 (9%)	
Platelets ($\times 10^3/mm^3$)	n = 1316	n = 1211	n = 105	0.39
Median(25th:75th)	217 (179:257)	217 (180:257)	215 (171:255)	
Number of medical comorbidities	n = 1576	n = 1451	n = 125	0.023
0	1172 (74%)	1088 (75%)	84 (67%)	
1	239 (15%)	220 (15%)	19 (15%)	
2+	165 (10%)	143 (10%)	22 (18%)	
Number of current medications	n = 1576	n = 1451	n = 125	0.005
0	1216 (77%)	1129 (78%)	87 (70%)	
1	237 (15%)	218 (15%)	19 (15%)	
2+	123 (8%)	104 (7%)	19 (15%)	

based solely on their baseline symptom scores and used these baseline groups to estimate the cumulative probability of having a first adverse clinical outcome during follow-up using Kaplan-Meier survival analysis (Figure 4). After excluding 18 patients who had cirrhosis at baseline, 54 patients experienced at least one adverse clinical outcome. The moderate symptom group at baseline included 112 patients (symptom scores ranged from 10 to 26), of whom 8 (7.3%) developed at least one adverse clinical outcome during follow-up, while the low symptom group at baseline included 1446 patients (symptom scores ranged from 0 to 9), of whom 46 (3.2%) developed at least one adverse clinical outcome during a median follow-up time of 4 years ($P = 0.02$; Figure 4). Overall, the incidence of clinical outcomes was 1.81 (0.91-3.63) per 100 person-years in the moderate symptom group and 0.76 (0.57-1.01) in the low symptom group ($P = 0.02$).

Of the 54 patients who experienced at least one adverse event, five experienced a second and one patient a third clinical event during follow-up. The most frequent initial clinical outcome was new-onset diagnosis of cirrhosis which accounted for 40 cases (74%) followed by death in 11 cases (20%: none was considered HBV-related), while HCC accounted for 2 and hepatic decompensation accounted for 1 initial clinical outcome. Events arising after the initial clinical outcome included one case of hepatic decompensation, two HCC, three deaths (two of unknown cause but suspected to be liver-related) and one liver transplant.

3.7 | Exploratory analyses

We conducted several additional exploratory analyses to evaluate perturbations to the Kaplan-Meier analyses relative to the initial results in Figure 4. First, we evaluated time to first HBV-related outcome and only HBV-related deaths (rather than all-cause death) (Figure S2). The results were similar; the probability of HBV clinical outcomes in the moderate symptom group was twice as high as the low symptom group. Second, we explored the probability of adverse clinical outcomes after excluding patients with comorbidities at baseline (Figure S3). The total number of patients with clinical outcomes during follow-up decreased from 54 to 18; however, the results were similar: the moderate symptom group had a significantly higher risk of HBV-related adverse clinical outcomes compared to the low symptom group at the 4th year of follow-up (5% vs 1%; Log-rank $P = 0.003$). Next, we grouped patients into low and moderate symptom clusters based upon symptom scores collected (a) during the first year of follow-up and (b) those obtained during the entire follow-up period. These analyses produced similar results to those obtained using just the baseline symptom data alone (Table S3). Finally, we evaluated each of the 10 individual symptoms, rather than the Total SCL score to see which symptoms were most associated with adverse outcomes (Table S4). We found that liver-related symptoms (ie, weight loss, nausea, pain over the liver, dark urine) that were rated "A little bit" or above, were significantly associated

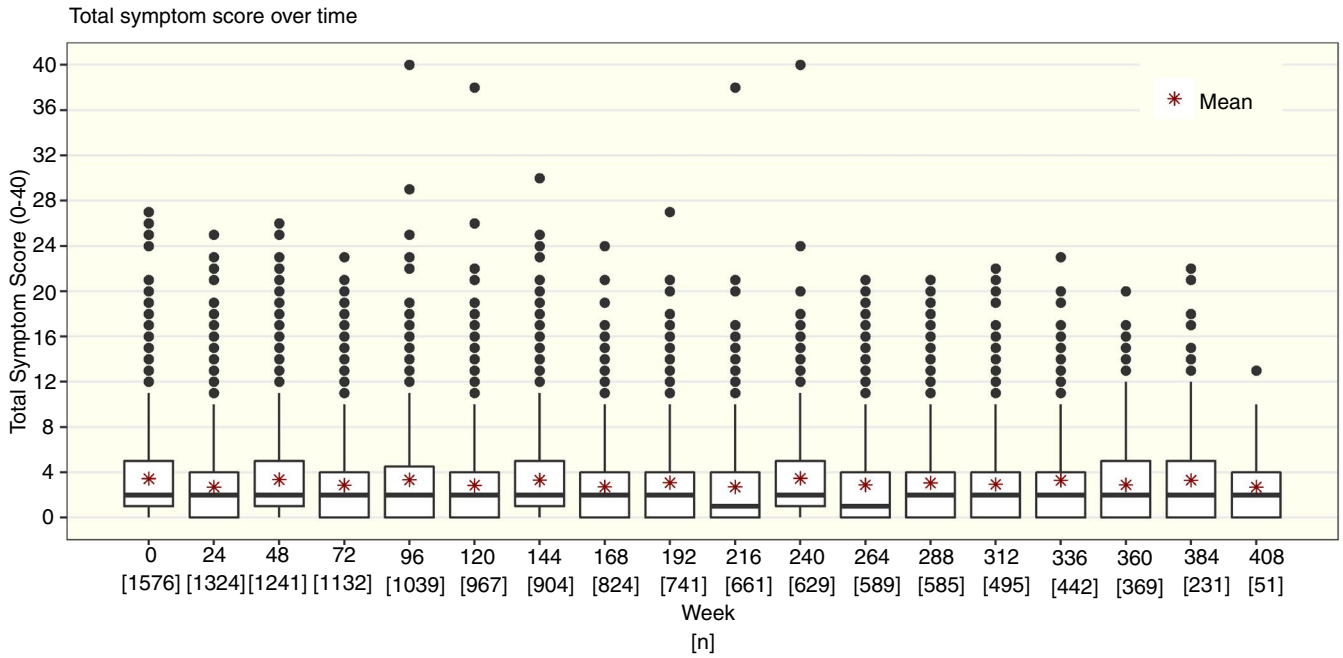

FIGURE 1 Boxplot of total symptom score by time points over 7-year follow-up in total cohort. Note: Horizontal axis shows the number of weeks into the Adult Cohort Study and sample size included in each SCL total symptom score at each time point. Total Symptom Score is a composite of 10 HBV-associated symptoms (fatigue, itching, pain over liver, irritability, depression/sadness, nausea, poor appetite, weight loss, dark urine, jaundice), each rated on 0-4 scale from Not at all bothersome = 0 to extremely bothersome = 4. Total SCL score created by summing the 10 symptom scores for possible range = 0-40 with higher scores indicating worse symptoms. Boxplots: asterisk = mean; bar = median; box = 25th and 75th percentiles, black dots = outliers of SCL scores that were greater than 1.5 times interquartile range (75th-25th)

with adverse clinical outcomes. More nonspecific symptoms such as fatigue and poor appetite rated as "Moderately" or above, were significantly associated with clinical outcomes. Moreover, the relatively nonspecific symptoms of irritability, depression and itch were not predictive of adverse clinical outcomes.

4 | DISCUSSION

Chronic HBV infection is a dynamic and clinically variable disease that may impact quality of life and aspects of functioning and life satisfaction.[15] Although there have been many studies of quality of life in patient cohorts with HBV infection, few have focused upon patient-reported symptoms or attempted to correlate symptoms with virological, biochemical and histologic features of disease or with clinical outcomes. This report represents an attempt to characterise the presence and severity of patient-reported symptoms during the natural history of CHB and expands upon our previous cross-sectional analysis.[7] Using 7 years of longitudinal data collected from adult patients who participated in the HBRN Adult Cohort Study, several key findings were observed related to population-level estimates, symptom trajectories and patient subgroups at risk for worse symptoms and future adverse events.

Consistent with another cross-sectional analysis,[3] we found that CHB symptoms tend to be mild and nondistressing and, on average, did not significantly change over time (median of 4 years) in the total cohort. The mild nature of symptoms in this cohort is consistent with the low rates of cirrhosis (1%), comorbidities (25%) and concomitant medications (23%) in this population, as well younger age (median age of 42) and potential ethnic-cultural factors that could affect symptom reporting (eg, 83% born outside the United States/Canada).[16] The low rate of cirrhosis in this cohort is due in part to the inclusion criteria to enroll only untreated compensated patients into the HBRN cohort study.[8]

While the average number of symptoms did not change substantially over time in the total cohort, the overall variability in symptoms was associated with several virological and clinical factors in unadjusted analyses (ie, AST, ALT, platelets, APRI, FIB-4, HBeAg, HBV DNA). The most reliable variables associated with symptom variation were AST levels and platelets using a conservative statistical technique that adjusts for high correlations amongst variables. Patients whose AST levels were greater than five times ULN during follow-up had a 41% greater score of total symptoms and patients whose platelet counts were below 150 ($\times 10^3/mm^3$) had an 11% higher symptom score. An increase in ALT levels greater than five times ULN, consistent with HBV flares, was also associated with worsening symptoms during follow-up, although AST was ultimately selected for inclusion in the final model. These results suggest that patients complaining of worsening symptoms may be experiencing changes in HBV disease activity or worsening liver disease; conversely, patients with rising AST and ALT levels and reductions in platelets may experience worsening of physical and emotional symptoms and warrant closer

TABLE 2 Multivariable model predicting total symptom score

Predictors	Total symptom score, mean ratio (95% CI)[a] Multivariable model
Participants (n) and observations (obs)	n = 1492, obs = 10 561
Bayesian information criterion (BIC)	BIC = 42 321
Age (year)	*P* = 0.79
Per 10 y	0.99 (0.96, 1.03)
Sex	*P* = 0.01
Male	Reference
Female	1.16 (1.04, 1.29)
Asian race and place of birth	*P* < 0.01
Asian born outside of the United States/Canada	Reference
Asian born in the United States/Canada	1.02 (0.82, 1.27)
Non-Asian born outside of the United States/Canada	0.79 (0.68, 0.92)
Non-Asian born in the United States/Canada	1.54 (1.29, 1.84)
Education	*P* < 0.01
Below Bachelor	1.35 (1.21, 1.50)
Bachelor or Higher	Reference
AST × ULN	*P* < 0.01
≤1 ULN	Reference
>1-3 ULN	1.06 (1.00, 1.12)
>3-5 ULN	1.19 (1.01, 1.41)
>5 ULN	1.41 (1.17, 1.69)
Platelets (×10^3/mm^3)	*P* = 0.01
≥150	Reference
<150	1.11 (1.03, 1.20)
Number of comorbidities	*P* = 0.002
0	Reference
1	1.10 (1.03, 1.17)
2+	1.17 (1.06, 1.29)

Note: g Variables used for model selections: sociodemographic variables at baseline (sex, Asian race and place of birth, education) and time-varying variables (age at each visit, ALT × ULN, categorical ALT × ULN, AST × ULN, categorical AST × ULN, HBeAg, HBV DNA, quantitative HBsAg, albumin, categorical platelets, FIB-4, comorbidities, medications, and currently on HBV treatment).

[a]If a 95% confidence interval (CI) for a mean ratio does not include 1, the mean of T-SCL is significantly different between groups or per unit change in a continuous predictor.

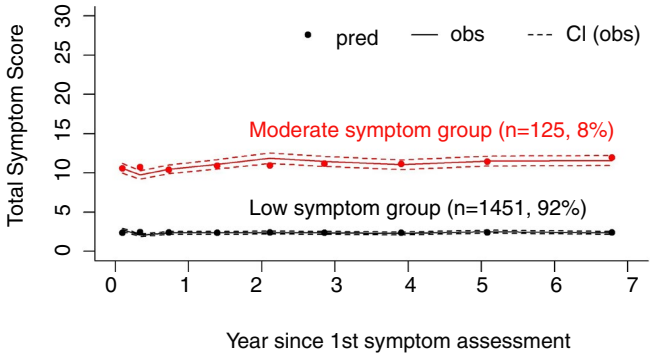

FIGURE 2 Total symptom scores over 7-year follow-up for patients clustered by low symptom and moderate symptom trajectories. Note: A two-class latent trajectory model was selected based on the smallest Bayesian information criterion (BIC) and with at least 5% of participants in each class. Latent trajectory 1 represents patients with low symptoms, where black dot represents predicted trajectory and black line represents observed trajectory. Latent trajectory 2 represents patients with moderate symptoms, where red dot represents predicted trajectory and red line represents observed trajectory

monitoring and management. Symptom assessment tools used as part of the clinical encounter may lead to on-the-spot symptom management rather than waiting for blood work to evaluate objective disease parameters. Patients more likely to experience worsening symptoms over time include women, those born within the United States/Canada and those with more medical comorbidities.

It is noteworthy that in this cohort, we did not find that CHB symptoms varied according to HBV phenotypes, being on HBV treatment, or change in HBV DNA or HBsAg levels. We had anticipated that HBV treatment may impact symptoms; however, the majority of patients (n = 373) were prescribed nucleotides, while only a handful (n = 8) were treated with peginterferon; indeed, the latter group did experience worse symptoms consistent with previous studies of interferon therapies (Table S1).[17,18]

Our second objective was to identify subgroups of patients who may experience different types or patterns of symptoms over time. Two patient clusters were identified whose symptoms at baseline and during follow-up remained fairly stable over time. While the vast majority of patients reported minimal nondistressing symptoms at baseline and during follow-up; a smaller subset reported elevated, moderately distressing symptoms at baseline that persisted over time. These patients had greater elevations in general symptoms such as fatigue, psychological symptoms such as irritability and also symptoms of advanced liver disease such as pruritus and poor appetite. These patients tended to be non-Asian, born in the United States/Canada, had more advanced liver disease and a higher number of medical comorbidities and medication use. These findings may help clinicians identify patients at risk for worse symptoms during the course of their CHB; it is also possible that patients' symptoms are aggravated by an interaction of multimorbidity and/or concomitant medications, not solely liver disease.[19] However, when we conducted a sensitivity analysis excluding patients with comorbidities from the prediction of worse symptoms, higher AST and lower platelet counts remained significantly associated with worse symptoms, thus providing evidence that CHB disease changes are partially responsible for worse symptoms.

An unexpected yet clinically useful discovery was that patient-reported moderate symptoms (SCL score >10) at baseline predicted future adverse clinical outcomes. Notably, this relationship persisted

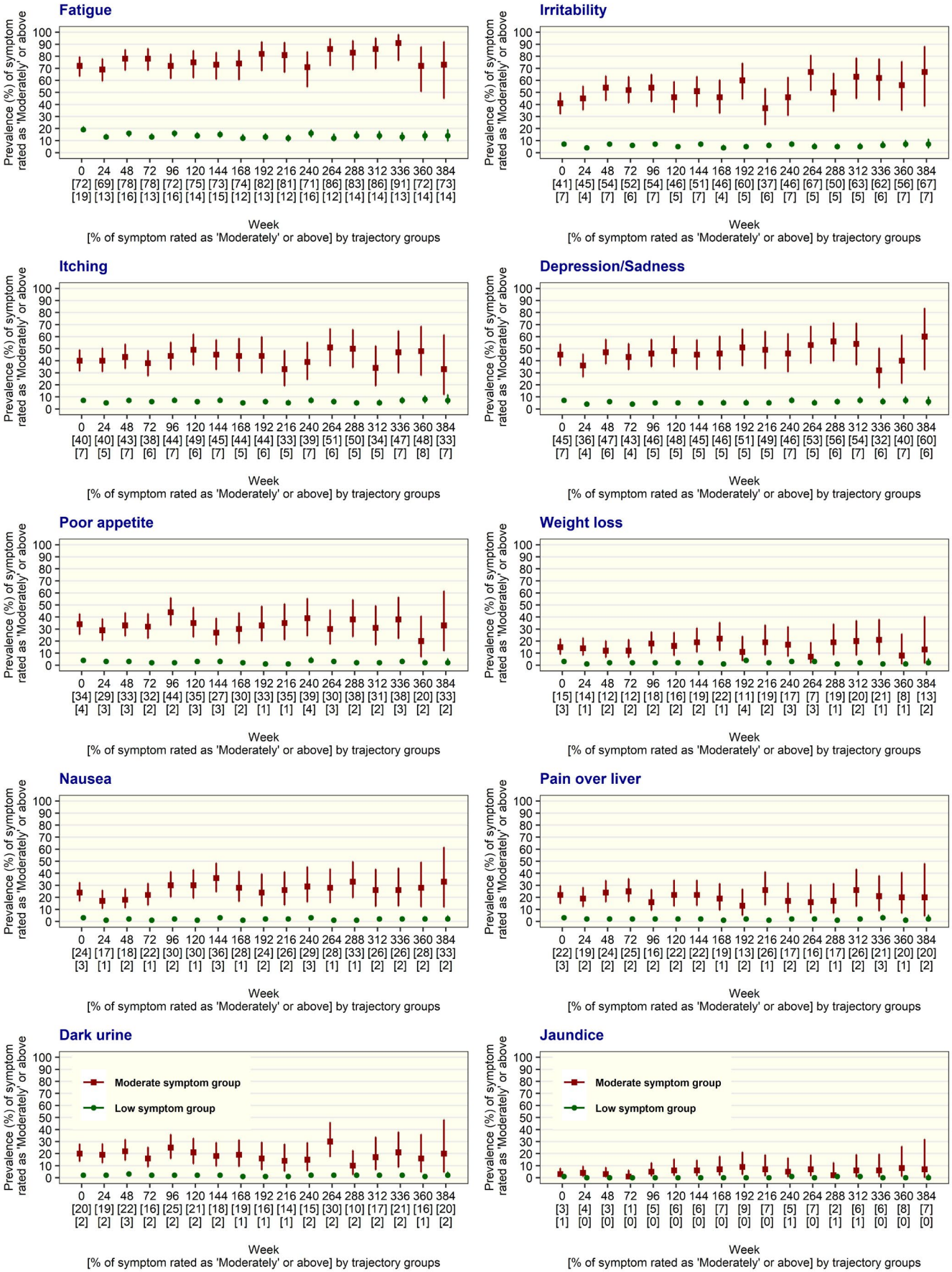

FIGURE 3 Prevalence of 10 individual symptoms from SCL rated as "moderate" or above over time by moderate and low symptom groups. Note: SCL, Symptom Checklist

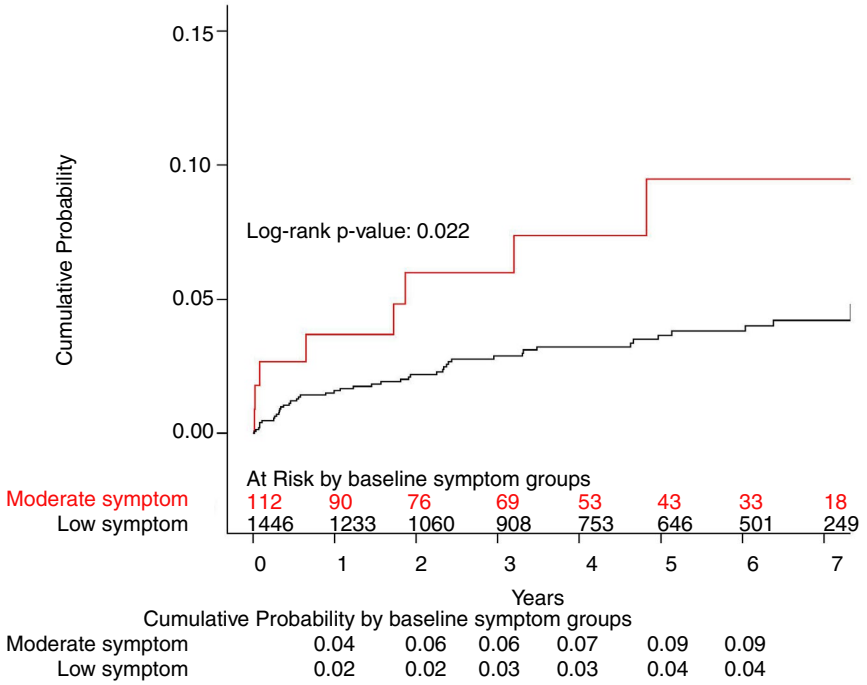

FIGURE 4 Cumulative probability of clinical outcomes (cirrhosis, decompensation, HCC, liver transplant, or all-cause of death) by baseline symptom latent groups

regardless of whether we examined all-cause deaths, HBV-related outcomes/deaths or when patients with other comorbidities were excluded. Moreover, while the total SCL score predicted adverse outcomes, individual symptoms such as "a little bit" of weight loss, nausea, pain over the liver, or dark urine, or a "moderate amount" of fatigue or poor appetite were also predictive of adverse clinical outcomes. We also observed that collecting symptom measurements over the course of 1 year or more did not significantly enhance predictability, suggesting that an initial assessment of baseline symptoms may be an efficient strategy to predict the risk of future adverse events. While the incidence of clinical outcomes was very low in this cohort, these findings may have significant clinical and research implications. A brief 10-item symptom instrument completed by patients during clinic encounters may be an effective tool to identify patients who are suffering, require better symptom management and blood work to evaluate objective disease parameters and who appear at risk for both HBV-related and unrelated adverse clinical outcomes.

We can speculate about the relationship between moderate symptoms at baseline and worse clinical outcomes during follow-up. The relationship between worse CHB liver disease and comorbidities with worse symptoms could be related to physiological mechanisms (eg, systemic inflammation) underlying liver or other disease processes that lead to symptoms and worse health outcomes. It is also plausible that a larger culture of health behaviours associated with place of birth influences both symptoms and worse health outcomes. Our data suggest that patients reporting worse symptoms at baseline were more likely to be born in the United States/Canada (27% vs 16%) and were White or Black. A previous study by the HBRN found that patients who were White and born in the United States/Canada had higher rates of risky health behaviours (risky alcohol and tobacco use),[20] which ostensibly may predispose people to worse health status, more symptoms and more susceptibility for worse health outcomes. Different rates of lifestyle behaviours may partially explain symptoms and outcomes, but it is very difficult to disentangle factors associated with the larger socio-cultural-ethnic context.

The study has limitations, primarily with regard to the generalisability of findings given that this primarily Asian, North American cohort was relatively healthy and the proportion with cirrhosis and adverse clinical events was low. The negligible rate of cirrhosis is a result of the study eligibility criteria that sought to specifically enroll untreated patients into the HBRN cohort study.[8] Therefore, due to the low overall rate of clinical outcomes and patients with moderate symptoms in this primarily untreated cohort, there is a need for additional prospective cohort studies to confirm our findings. A second limitation is that the psychometric properties of the NIDDK SCL instrument have not been properly evaluated and remains an important area of future investigation. Unfortunately, there are no CHB-specific symptom instruments; however, our findings shed light on important symptom domains that should be measured by a CHB-specific instrument. Despite this limitation, the SCL was translated into three languages (Spanish, Chinese and Korean) for this study and was completed by over 1500 patients. A final limitation is that other factors that might be associated with symptom-reporting (eg, psychiatric disorders, anticipated and actualised stigmatisation, specific medical conditions, transmission of HBV to offspring, other sociodemographic variables) were not evaluated.[15,21] Study strengths include the large multi-ethnic sample size, multi-site enrollment, extensive number of serial symptom assessments and seven years of follow-up. In addition, the robust analytical methods (trajectory analysis, LASSO selection) instil greater confidence in our final results.

To conclude, this study evaluated patient-reported symptoms in a large population of patients followed for chronic hepatitis B

in North America. Most patients had few comorbidities, mild liver disease and reported minimal symptoms unless they had more advanced liver disease (higher AST levels, lower platelet count) or more comorbidities. While the majority of patients in this cohort had minimal and stable symptoms, a small subgroup of patients experienced moderate symptoms that endured throughout follow-up. Patients with moderate symptoms were at increased risk to develop adverse clinical outcomes, both HBV and non-HBV related, during follow-up, although the absolute rate of disease progression was low in this relatively healthy cohort. It is difficult to tease apart the underlying causes of symptoms in patients with CHB, some appearing due to the underlying chronic liver disease and some due to other comorbidities. Symptoms should be evaluated in studies of the natural history and treatment of CHB as they may reflect more advanced liver disease or poorer prognosis and should be considered important therapeutic endpoints on par with improvements in aminotransferase levels and HBV DNA. Future research endeavours that seek to develop robust predictive models of poor health outcomes in the CHB population should include a symptom checklist, AST, platelets, comorbidities and demographic variables. If validated in other independent cohorts, a brief symptom checklist might complement objective laboratory values to identify patients at greater risk for adverse clinical outcomes. Symptom assessments may also lead to a better understanding of patient suffering, immediate symptom management, need for additional testing and foster a more holistic patient-centred approach.

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ETHICAL APPROVAL

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received. The study conformed to the US Federal Policy for the Protection of Human Subjects.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data will be provided to the NIDDK repository (https://repository.niddk.nih.gov/home/) within 6 months of the final publication.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX 1

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