CME

Health-related Quality of Life in Pediatric Patients With Chronic Hepatitis B Living in the United States and Canada

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ABSTRACT

Objectives: The aim of the study was to determine whether selected sociodemographic and hepatitis B virus (HBV)-specific clinical factors are associated with health-related quality of life (HRQoL) among pediatric patients chronically infected with HBV.

Methods: Children with chronic HBV enrolled in the Hepatitis B Research Network completed the Child Health Questionnaire at study entry. Caregivers of children 5 to <10 years completed the parent-reported form (CHQ-Parent Report Form); youth 10 to <18 years completed the child-reported CHQ-Child Report Form. We examined univariable associations of the Child Health Questionnaire scores with selected independent variables: sex, adoption status, maternal education, alanine aminotransferase (U/L), aspartate aminotransferase-to-platelet ratio index, and HBV-specific symptom count.

Results: A total of 244 participants (83 young children 5–<10 years, 161 youth 10–<18 years) were included, all HBV treatment-naïve. Among young children, increased alanine aminotransferase level was negatively associated with CHQ-Parent Report Form psychosocial summary *t* score ($r = -0.28$, $P = 0.01$). No other subscale comparisons for young children were statistically significant. Among youth, adoption was associated with better physical functioning and general health ($P < 0.01$). Higher maternal education was associated with better role/functioning-physical and -emotional scores ($P < 0.05$). Maternal education and adoption status were linked with adoption associated with higher maternal education. Increased symptom count in youth was associated with worse HRQoL in subscales measuring bodily pain, behavior, mental health, and self-esteem ($P < 0.01$).

Conclusions: Although overall HRQoL is preserved in children with chronic HBV, some sociodemographic and HBV-related clinical factors were associated with impaired HRQoL in our pediatric patients at baseline. Measurement of HRQoL can focus resources on education and psychosocial support in children and families most in need.

Key Words: adoption, Child Health Questionnaire, children, chronic medical condition, hepatitis B, quality of life, refugee

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Chronic hepatitis B virus (HBV) infection is associated with significant morbidity and mortality, with 25% of infected individuals developing cirrhosis and/or hepatocellular carcinoma (1,2). Universal vaccination and prenatal screening in the United States and Canada have decreased the incidence of chronic HBV in children born in these countries. New cases of childhood hepatitis B are, however, seen in North America in children of immigrants and children adopted internationally (3–5). On average, 53,800 chronic HBV cases were imported to the United States annually during 2004–2008 (4).

Adults with chronic HBV experience decreased health-related quality of life (HRQoL) (6), but there is little information about HRQoL in children with HBV. HRQoL is a complex and inherently subjective measure that is an important outcome of disease management. Impaired HRQoL has been associated with poor medication adherence, depression, anxiety, and worse health outcomes (7). Importantly, patients and their families may make treatment decisions for chronic disease management based upon how treatments affect HRQoL and life functioning (8). The measurement of HRQoL in children with chronic HBV has the potential to allow early interventions that may reduce adult depression and increase adherence to therapies for HBV.

The Hepatitis B Research Network (HBRN) (9) provides a unique opportunity to study a large, well-characterized cohort of children with chronic HBV infection in the United States and Canada (5). Using this cohort, we assessed HRQoL in children and youth with chronic HBV using an age-appropriate instrument, the Child Health Questionnaire (CHQ) (10). In this exploratory study, our aim was to describe the HRQoL of children with chronic HBV and their families and to examine selected sociodemographic and disease-related factors associated with HRQoL in our cohort. This will contribute to the overarching goal of the Pediatric HBRN to improve the lives of children with chronic HBV.

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METHODS

Seven pediatric hepatology centers in the United States and Canada participated in the HBRN Pediatric Cohort study (5,9). Subject inclusion criteria included age 6 months to <18 years and hepatitis B surface antigen-positive. Exclusion criteria included history of hepatic decompensation, hepatocellular carcinoma, solid organ, or bone marrow transplant, coinfection with human immunodeficiency virus, current HBV anti-viral therapy, or social or medical factors that would make follow-up difficult.

The HRQoL substudy included pediatric HBRN participants ≥5 to <18 years of age who were HBV treatment naive. English literacy was required for caregivers of children <10 years of age and for children ≥10 years of age because translations were not available for several of the more common languages in the HBRN cohort. Participants for this analysis were enrolled between December 2010 and September 2015.

All sites had institutional review board approval. Written informed consent was obtained from parents or legal guardians; assent was obtained from children according to the requirements of the local institutional review board.

What Is Known

- Chronic hepatitis B virus affects children of international adoption and refugees from countries where hepatitis B virus is endemic.
- Adults with hepatitis B virus have poor health-related quality of life and are at risk for depression and other psychosocial disorders.

What Is New

- In North American children with chronic hepatitis B virus, some sociodemographic and clinical factors were associated with impaired health-related quality of life, including elevated alanine-amino-transferase in young children and symptom-reporting, maternal education, and adoption status in youth.
- Measuring health-related quality of life may alert clinicians to children and families needing psychological support and education to dispel anxiety and reduce risk of nonadherence to therapy and behavioral and mood problems.

Measures

Socioeconomic and Demographic Characteristics

Demographic variables collected at entry into the study included age, sex, race, adoption status, and measures of family socioeconomic status (eg, maternal education).

Disease Characteristics

Serum alanine aminotransferase (ALT, U/L) was recorded within 6 months of the baseline study visit. HBV DNA (IU/mL), and hepatitis e antigen (HBeAg) status were tested by a central laboratory. When central laboratory results were unavailable (eg, due to inadequate sample), the most recent clinical results obtained within 1 year (HBV DNA) or 2 years (HBeAg) of baseline were used. Other laboratory values, including international normalized ratio (INR), albumin (g/dL), and direct bilirubin (mg/dL), were based on the latest values obtained within 1 year of baseline. On average, laboratory results were taken <1.5 months before the baseline visit. Liver biopsies were not required as part of the cohort study; AST-to-platelet ratio index (APRI) (11) was calculated for each subject, with an AST of 40 U/L used as the upper limit of normal for this calculation to facilitate comparison with other studies using this index (12,13). Symptom counts (0, 1, 2, 3+) were based on the following HBV-specific symptoms during the last month: fatigue, pain over liver, nausea, poor appetite, weight loss, itching, irritability, depression/sadness, jaundice, and dark urine.

Child Health Questionnaire

The CHQ was completed at the baseline visit. The CHQ is a validated instrument that measures generic HRQoL in the physical, psychological, and social domains in children, including physical functioning (PF), bodily pain/discomfort (BP), general health (GH), general behavior (BE), mental health (MH), self-esteem (SE); role/social limitations as a result of physical (RP), emotional/behavioral (REB, PF50), emotional (RE), and behavioral (RB) problems (CF87); and the impact on parental time (PT), parental emotion (PE), and family activities (FA) (10). The CHQ-Parent Report Form (PF50) includes 11 subscales, while the CHQ-Child Report Form (CF87) includes 10 subscales. Each subscale is calculated by summing items to a total score of 0 to 100; higher scores reflect better HRQoL. Specifically for the PF50, 2 additional summary *t* scores (physical and psychosocial) were derived by aggregating 10 individual scales (omitting the family activities subscale) and were standardized using a linear *t* score transformation (mean 50, standard deviation 10) from the combined general US sample (N = 391) and 6 clinical samples (N = 563) (14). The PF50 was administered to biological or adoptive parents or legal guardians, henceforth referred to as caregivers of young children 5 to <10 years of age. Children who were at least 10 years of age (identified below as ''youth'') completed the CF87 themselves.

Statistical Analysis

Summary statistics were used to describe demographic and disease-related characteristics. Mean with standard deviation (SD), or median with (25th percentile, 75th percentile) and (minimum, maximum) were reported for continuous variables. Frequencies and proportions were reported for categorical variables. Mean (SD) and

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95% confidence intervals (CI) were calculated for each CHQ subscale and summary *t* score. CHQ subscales were presented as radar plots to allow easy visualization of the range of mean scores across multiple subscales. The plot radius indicates the score (much like a *y*-axis); points farther out on the radar plot indicate higher scores (ie, higher HRQoL). Descriptive characteristics are presented for the overall sample and separately by age group. For descriptive comparison, we included summary scores from a group of adolescent liver transplant recipients (7.5 ± 5.7 years post-transplant) (7) and a healthy pediatric population (15).

We examined univariable associations of CHQ scores with selected independent variables: sex, adoption status, maternal education, ALT (U/L), APRI, and HBV-specific symptom count. For categorical independent variables, CHQ summary *t* scores were presented as mean (SD) by category; because subscale scores were skewed, median (25th percentile, 75th percentile) were presented. Moreover, because >75% of participants obtained the maximum score (100) on several subscales, we also presented the frequency and percent of participants with subscale scores below 100. Kruskal-Wallis nonparametric tests were used to compare the distribution of CHQ scores across levels of categorical variables. Spearman correlation coefficients, with corresponding *P* values, were used to assess the correlation of CHQ scores with continuous independent variables (ALT and APRI).

Sensitivity Analysis

Because flares are associated with increased liver enzymes, and may be associated with increased symptoms and decreased HRQoL, we repeated our analysis after excluding 1 younger and 5 older children with ALT flares, which was defined as an ALT more than 10 times the upper limit of normal using the following age- and sex-specific upper limit of normal cutpoints: 25 U/L for boys and girls 5 to <13 year-olds, 25 U/L for boys ≥13 years, and 22 U/L for girls ≥13 years (16,17). Results for these sensitivity analyses were similar to those obtained with the full sample, and thus are not reported.

Statistical significance was determined as $P < 0.05$. For subscale score comparisons, Bonferroni-Holm adjusted *P* values were calculated to indicate statistical significance after accounting for multiple comparisons across the 11 and 10 subscales for the PF50 and CF87, respectively. SAS 9.3 (SAS Institute, Cary, NC) was used for statistical analyses.

RESULTS

Demographic and Clinical Characteristics

As of September 2015, 395 children were enrolled in the HBRN Pediatric Cohort study; 330 were at least 5 years of age. Of these, 280 were treatment naïve, and thus eligible to participate in the HRQoL study. A total 244 of these had CHQ data and were included in the analysis. The PF50 was available for 83 children 5 to <10 years old, and the CF87 was available for 161 youth 10 to <18 years old (Table 1).

Demographic characteristics of 5 to <10 year olds are found in Table 1. Serum ALT levels ranged from 12 to 365 (median 39) U/L. The majority were HBeAg positive (91%), and 72% had HBV DNA levels $\geq 10^8$ U/mL. INR ranged from 0.9 to 1.2, albumin 1.1 to 5.4 g/dL, and direct bilirubin 0.0 to 0.99 mg/dL. APRI median score was 0.37; 4 subjects (5.8%) had values above 1.0. Presumed mode of HBV transmission was vertical in 97%. Two or more of the queried symptoms were reported in 14% within the past 4 weeks of the baseline visit, most commonly itching (n = 15), irritability (n = 11), fatigue (n = 7), depression/sadness (n = 6), and nausea (n = 6). None of the queried comorbid conditions were noted, although 6 children were currently taking medications, including bronchodilators (n = 1), antihistamines (n = 1), and attention deficit hyperactivity disorder medications (n = 4).

Demographic characteristics of youth ≥10 years of age are found in Table 1. Median ALT level was 41 (range: 13–2067) U/L. 69% were HBeAg positive, with high HBV DNA levels ($\geq 10^8$ IU/mL or above limits of quantification) in 47%. INR ranged from 0.8 to 4.1, albumin 3.4 to 5.2 g/dL, and direct bilirubin 0.0 to 0.82 mg/dL. Median APRI was 0.33, with values above 1.0 in 6 participants (4.3%). Vertical transmission was suspected in 95%. Nearly one-third (29%) reported 2 or more of the queried symptoms within the past 4 weeks, most commonly fatigue (n = 44), irritability (n = 37), itching (n = 24), depression/sadness (n = 20), poor appetite (n = 20), nausea (n = 16), pain over liver (n = 13), and weight loss (n = 10). Queried comorbid conditions were noted in 5 children: anemia (n = 2), anemia and cytopenia (n = 1), diabetes (n = 1), and nonalcoholic fatty liver disease (n = 1). Medication use was noted in 28 (4 of whom used multiple medications): bronchodilators (n = 9), antihistamines (n = 7), antidepressants/anxiolytics/antipsychotics (n = 5), attention deficit hyperactivity disorder medication (n = 4), acne medication (n = 4), estrogen/birth control pills (n = 2), and analgesic/pain medications (n = 1).

Health-related Quality of Life Among Children With Chronic Hepatitis B Virus

Among 5 to <10 year-olds, mean *t* scores for the 2 summary scales (physical [PHS] and psychosocial [PSS]) were 54.1 (SD 6.3) for the PHS, and 52.8 (SD 8.2) for the PSS (not shown). Mean subscale scores for subscales related to physical HRQoL ranged from a low of 71.9 (SD 13.9) for GH, to 97.8 (SD 9.7) for RP (Fig. 1A). For subscales related to psychosocial HRQoL, mean scores ranged from 79.3 (SD 15.3) to 97.2 (SD 10.1) for the BE and REB subscales, respectively. Family-related components ranged from a mean of 74.2 (SD 23.7) to 88.2 (SD 21.1) on the PE and PT subscales, respectively.

In children ≥10 years old, mean physical HRQoL subscale scores ranged from 71.8 (SD 14.2) (GH) to 96.7 (SD 10.9) (RP), whereas mean psychosocial HRQoL subscale scores ranged from 77.8 (SD 14.5) for MH, to 94.1 (SD 16.2) for RB (Fig. 1B). The FA subscale had a mean of 81.5 (SD 20.1).

Tables 2 and 3 present mean (95% CI) PF 50 (a) and CF87 (b) subscale scores for the HBRN Pediatric Cohort, side-by-side with scores from other clinical pediatric populations. Scores from these populations cannot be compared statistically because of important differences in demographic characteristics between the groups. Instead, they provide an understanding of the range of scores in normative and chronically ill populations.

Comparison of Health-related Quality of Life by Selected Characteristics

Summary t Scores for 5 to <10 Year Olds (CHQ-Parent Report Form)

In 5 to <10 year-olds, mean Physical and Psychosocial Summary T-scores were not associated with sex, adoption status, maternal education, symptom count, or APRI ($P > 0.05$, Supplemental Digital Content, Table S1a, *http://links.lww.com/MPG/A909*) Participant characteristics and unadjusted associations with caregiver reported HRQoL (PF50) summary *t* scores among children 5 to <10 years of age in HBRN). Spearman correlation coefficients for ALT with the Physical and Psychosocial Summary *t* scores were −0.08 ($P > 0.05$) and −0.28 ($P = 0.01$), respectively.

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TABLE 1. Demographic and clinical characteristics

Characteristics	All N = 244	Young children 5 to <10 years N = 83	Youth 10 to <18 years N = 161
Age, y*	N = 244	N = 83	N = 161
	11.89 (3.58)	7.68 (1.49)	14.05 (2.10)
Sex†	N = 244	N = 83	N = 161
Male	95 (38.9%)	21 (25.3%)	74 (46.0%)
Female	149 (61.1%)	62 (74.7%)	87 (54.0%)
Race†	N = 242	N = 82	N = 160
White	15 (6.2%)	3 (3.7%)	12 (7.5%)
Black/African-American	30 (12.4%)	7 (8.5%)	23 (14.4%)
Asian	188 (77.7%)	68 (82.9%)	120 (75.0%)
Other	9 (3.7%)	4 (4.9%)	5 (3.1%)
Adopted†	N = 244	N = 83	N = 161
	131 (53.7%)	57 (68.7%)	74 (46.0%)
Maternal education†,‡	N = 217	N = 71	N = 146
Less than high school	26 (12.0%)	0 (0.0%)	26 (17.8%)
High school or equivalent	25 (11.5%)	4 (5.6%)	21 (14.4%)
Some college or equivalent	45 (20.7%)	17 (23.9%)	28 (19.2%)
Bachelor's degree or higher	121 (55.8%)	50 (70.4%)	71 (48.6%)
ALT (U/L)§	N = 240	N = 82	N = 158
	40 (28, 54)	38 (26, 51)	40 (30, 54)
	(12, 2067)	(12, 365)	(13, 2067)
HBeAg†	N = 228	N = 76	N = 152
Negative	54 (23.7%)	7 (9.2%)	47 (30.9%)
Positive	174 (76.3%)	69 (90.8%)	105 (69.1%)
HBV DNA ($\log_{10}$ IU/mL)‖	N = 229	N = 75	N = 154
Median (25th percentile, 75th percentile)	8.1 (5.3, 8.5)	8.2 (7.8, 8.7)	7.9 (4.0, 8.4)
< 3	32 (14.0%)	6 (8.0%)	26 (16.9%)
3 to < 6	31 (13.5%)	2 (2.7%)	29 (18.8%)
6 to < 8	40 (17.5%)	13 (17.3%)	27 (17.5%)
≥8	126 (55.0%)	54 (72.0%)	72 (46.8%)
International normalized ratio (INR)§	N = 189	N = 56	N = 133
	1.0 (1.0, 1.1)	1.0 (1.0, 1.0)	1.00 (1.0, 1.1)
	(0.8, 4.1)	(0.9, 1.2)	(0.8, 4.1)
Albumin (g/dL)§	N = 218	N = 74	N = 144
	4.4 (4.2, 4.6)	4.4 (4.2, 4.6)	4.3 (4.2, 4.6)
	(1.1, 5.4)	(1.1, 5.4)	(3.4, 5.2)
Direct Bilirubin (mg/dL)§	N = 180	N = 59	N = 121
	0.08 (0.00, 0.10)	0.10 (0.0, 0.10)	0.00 (0.00, 0.12)
	(0.00, 0.99)	(0.00, 0.99)	(0.00, 0.82)
APRI (AST-platelet-ratio index)§	N = 208	N = 69	N = 139
	0.34 (0.26, 0.52)	0.37 (0.30, 0.52)	0.33 (0.25, 0.50)
	(0.14, 12.31)	(0.15, 2.31)	(0.14, 12.31)
Total symptom count	N = 244	N = 83	N = 161
0	135 (55.3%)	49 (59.0%)	86 (53.4%)
1	51 (20.9%)	22 (26.5%)	29 (18.0%)
2	25 (10.2%)	7 (8.4%)	18 (11.2%)
3+	33 (13.5%)	5 (6.0%)	28 (17.4%)

*Mean (SD).

†The first row gives the number of non-missing observations, followed by N (%) in each category.

‡For one child with 2 adoptive mothers, maternal education for the mother with 'some college or equivalent' was randomly selected for inclusion in this analysis; the other mother had a Master's Degree. Maternal education level was set to missing for one child with a mother who was deceased.

§The first row gives the number of non-missing observations. The second row gives median (25th percentile, 75th percentile), and the third row gives the (minimum, maximum).

‖The first row gives the number of non-missing observations. The second row gives median (25th percentile, 75th percentile), and the remaining rows give N (%) for each category.

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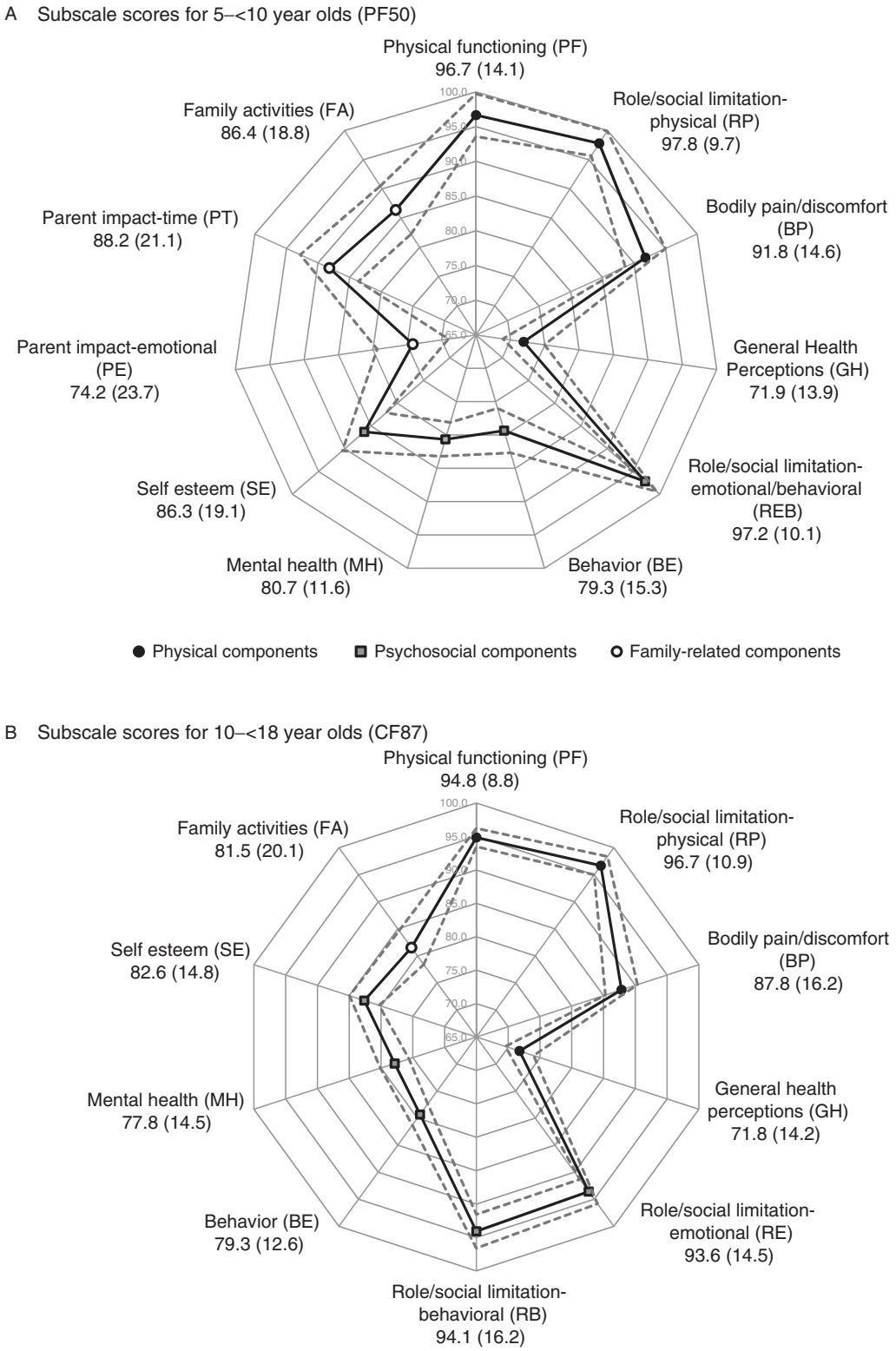

FIGURE 1. Mean scores (standard deviation) and 95% confidence interval of (A) subscale scores for 5 to <10 year olds (CHQ-Parent Report Form [PF50]) and (B) subscale scores for 10 to <18 year olds (CHQ-Child Report Form [CF87]). Solid lines demonstrate mean scores and dashed lines indicate 95% confidence intervals.

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TABLE 2. Parent-reported health-related quality of life (CHQ-Parent Report Form) in young children with chronic hepatitis B, chronic hepatitis C, and normative sample

Population	Clinic based chronic hepatitis B	Clinic based chronic hepatitis C	Normative sample
Country	United States and Canada (HBRN, current study)	United States (24)	United States (15)
Sample size	83	114	391
Mean age (range)	7.7 (5 to <10) years	11 years	11.5 years (5 to <18) years
Race/ethnicity of the sample	83% Asian, 6% White	4% Asian, 75% White	1% Asian, 83% White
CHQ-PF50	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Physical summary score	54 (53–55)	52 (51–53)	53 (52–54)
Psychosocial summary score	53 (51–55)	52 (50–54)	51 (50–52)
Physical components			
PF	97 (94–100)	96 (94–98)	96 (95–97)
Role functioning physical	98 (96–100)	97 (95–99)	94 (92–96)
Bodily pain	92 (89–95)	82 (79–85)	82 (80–84)
General health	72 (69–75)	66 (63–69)	73 (71–75)
Psychosocial components			
Role functioning emotional/behavior	97 (95–99)	95 (92–98)	93 (91–95)
Behavior	79 (76–82)	79 (76–82)	76 (74–78)
MH	81 (78–84)	80 (78–82)	79 (78–80)
SE	86 (82–90)	83 (80–86)	80 (78–82)
Family-related components			
Parent-impact-emotional	74 (69–79)	65 (60–70)	80 (78–82)
Parent-impact-time	88 (83–93)	88 (85–91)	88 (86–90)
Family activities	86 (82–90)	85 (82–88)	90 (88–92)

TABLE 3. Child-reported health-related quality of life (CHQ-Child Report Form) in youth with chronic hepatitis B, youth after liver transplantation, and normative sample

Population	Clinic based chronic hepatitis B	Clinic based liver transplant recipients	School based
Country	United States and Canada (HBRN, current study)	United States (7)	United States (10)
Sample size	161	28	232
Mean age (range)	14.1 (10 to <18) years	15.1 (12 to <18) years	13.0 (10–15) years
Race/ethnicity of the sample	75% Asian, 7.5% White	72% White	Predominantly African-American
CHQ-CF87	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Physical components			
PF	94.8 (93.5–96.2)	90.2 (85.0–95.4)	88.8 (87.0–90.6)
Role functioning-physical	96.7 (95.0–98.4)	88.4 (80.3– 96.5)	88.3 (85.6–91.0)
Bodily pain	87.8 (85.3–90.3)	72.4 (63.6–81.2)	74.4 (71.4–77.3)
General health	71.8 (69.6–74.0)	60.3 (55.4–65.2)	66.4 (64.5–68.3)
Psychosocial components			
Role functioning-emotional	93.6 (91.3–95.8)	87.6 (79.9–95.3)	85.9 (83.2–88.6)
Role functioning-behavioral	94.1 (91.5–96.6)	87.6 (79.6–95.6)	86.5 (83.8–89.3)
Behavior	79.3 (77.4–81.3)	81.0 (75.4–86.6)	76.6 (74.7–78.5)
MH	77.8 (75.6–80.1)	77.2 (70.3–84.1)	72.7 (70.6–74.8)
SE	82.6 (80.3–84.9)	81.8 (77.3–86.3)	81.8 (79.8–83.9)
Family-related components			
Family activities	81.5 (78.4–84.7)	79.7 (73.6–85.8)	–

*Family activities scale was not provided in these samples (10).

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That is, increasing ALT levels were associated with decreased psychosocial HRQoL.

Subscale Scores for 5 to <10 Year Olds (CHQ-Parent Report Form)

For boys, the lowest median scores were observed for GH (72.5) and parent impact-emotional (66.7) subscales. For girls, the lowest median scores were observed for GH (71.7) and MH (80.0) (Supplemental Digital Content, Table S1b, *http://links.lww.com/MPG/A909*). For children living with biological parents, the GH subscales had the lowest median score (69.6), with all other components above 80.0. For adoptees, median scores were below 80.0 for both GH (72.5) and parent impact-emotional (75.0). Among children of mothers who did not have at least a bachelor's degree, 4 subscales had median scores below 80.0: GH (70.8), behavior (72.5), MH (75.0), and parent impact-emotional (66.7). For children of mothers with a bachelor's degree or higher, only the GH subscale median (72.5) was below 80.0. Little variability was observed for the PF, role functioning-physical, bodily pain, role functioning-emotional/behavioral and parent impact-time subscales: each had a median score of 100.0 across categories of sex, adoption status and maternal education (Supplemental Digital Content, Table S1b, *http://links.lww.com/MPG/A909*) Participant characteristics and unadjusted associations with caregiver reported HRQoL (PF-50) domains among children 5 to <10 years of age in HBRN). In fact, ≥85% of participants obtained the maximum score of 100 for the PF, role functioning-physical and role functioning-emotional/behavioral subscales, regardless of sex, adoptions status, or maternal education. Despite the association of lower psychosocial *t* score with increasing ALT, none of the PF50 subscale comparisons, including those by symptom count or ALT, were statistically significant.

Subscale Scores for 10 to <18 Year Olds (CHQ-Child Report Form)

Among youth, median subscale scores ranged from 69.6 to 100.0 and 73.8 to 100.0 for boys and girls, respectively (Table 4). Across all subscales, comparisons by sex, ALT, and APRI were not statistically significant. Median scores ranged from 67.5 to 100.0 and 75.8 to 100.0 for non-adoptees and adoptees, respectively. Adoption status was statistically significantly associated with PF ($P < 0.01$): 15% of non-adoptees and 5% of adoptees scored <100.0. Adoption status was also associated with GH: lower median scores were observed among non-adoptees ($P < 0.001$). Median scores ranged from 70.8 to 100.0 and 73.3 to 100 for children of mothers with less than versus at least a bachelor's degree. Maternal education was statistically significantly associated with role/functioning-physical ($P = 0.02$) and role/functioning-emotional scales ($P = 0.03$). More youth of mothers with less than a bachelor's degree (vs at least a bachelor's degree) scored below 100.0 on the role/functioning-physical (20% vs 3%) and -emotional subscales (33% vs 13%).

As compared to adoptees, non-adoptees were more likely to have mothers with a lower education level (Supplemental Digital Content, Table S2, *http://links.lww.com/MPG/A909*). This was true for both the 5 to <10 year olds (23% of adoptees vs 45% of non-adoptees had mothers with less than a bachelor's degree, $P = 0.051$) but was most striking for youth (23% of adoptees vs 75% of non-adoptees had mothers with less than a bachelor's degree, $P = 0.01$).

The number of reported symptoms (regardless of the specific symptom(s)) was significantly associated with 4 of 10 subscales: bodily pain, behavior, MH, and SE ($P < 0.01$). For behavior, MH and SE subscales, median scores were lowest for those with 3+ symptoms, and highest for those with no symptoms. For the bodily pain subscale, median scores were 100.0 for each group other than those with 3+ symptoms (median 80.0). The proportion of youth scoring <100.0 on the bodily pain subscale was highest for those with the most symptoms (0 symptoms: 36%, 1 symptom: 38%, 2 symptoms: 39%, and 3+ symptoms: 75%).

DISCUSSION

This study examines HRQoL in the largest cohort of children with chronic HBV assembled in the United States and Canada. Our cohort was generally asymptomatic with a low frequency of comorbid conditions and overall HRQoL similar to the normal range for healthy children. Our study, however, showed that clinical factors are associated with HRQoL in children with chronic HBV in several crucial ways. First, among young children, increased ALT levels were negatively associated with children's parent-reported overall psychosocial functioning, an important association for clinicians to consider when caring for young children with HBV and their families. Our data cannot determine whether this results from the direct effect of HBV disease or from the parent's perception of diminished health as a result of knowing the child's ALT levels. Although liver biopsies were not available to stage disease in our cohort, APRI scores were in a normal range in most patients, suggesting the likely absence of significant hepatic fibrosis or inflammation in this cohort (18). Clinicians should know that caregivers of children with chronic hepatitis B and elevated ALT may be experiencing an emotional impact that they may not reveal in the clinical visit.

Second, older children reported more physical symptoms, and the number of these symptoms was associated with reports of worse HRQoL related to bodily pain, MH, SE, and behavior. Report of sadness and depression increased in the older age group and 5 of the children reported medication for these conditions. For clinicians, this means that the well-appearing child with few serologic markers of significant liver disease may still be experiencing impairment in facets of HRQoL. Adults with chronic HBV have a high risk of depression and anxiety (19,20). In adolescents after liver transplantation (predominantly for biliary atresia, autoimmune hepatitis, and hepatitis [type unspecified]), low HRQoL was associated with poor adherence to the prescribed medication regimen (7). Awareness of diminished HRQoL in children with chronic HBV may allow intervention to provide disease-specific education and psychosocial support early in adolescence and young adulthood, to reduce later depression and anxiety, and insure that prescribed antiviral treatments are as successful as possible. There may be benefit in directly addressing the child's and caregiver's fears, which are revealed in the study questionnaires, but rarely openly discussed in the clinical setting. Future studies should explore whether caregivers of children with chronic HBV would benefit from improved education about the disease and its likely course, parent support groups, or clear guidelines regarding any limitations (or lack of limitations) on their child's future.

Also in youth, adoption status was associated with PF and GH, which were worse for non-adoptees. Youth with mothers with less than a bachelor's degree reported more limitations in schoolwork or activities with friends. A similar association of lower maternal education and HRQoL was noted in studies of children after liver transplantation (21,22) and children with kidney disease (22). The majority of our cohort was born outside North America (97%), children of either adoption or immigrant families (23). For both young children and youth, non-adoptees were more likely to have mothers with lower education level. These observations suggest that reduced HRQoL in these youth may not be directly

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TABLE 4. Participant characteristics and unadjusted associations with child-reported health-related quality of life (CF-87) domains among children 10 to <18 years of age in Hepatitis B Research Network

		Physical components				Psychosocial components					Family components
Variables	N	PF	RP	BP	GH*	RE	RB	BE	MH	SE*	FA*
Sex†	161										
Male median (25th, 75th)	74	100.0 (87.5, 100.0)	100.0 (100.0, 100.0)	100.0 (80.0, 100.0)	69.6 (59.2, 77.9)	100.0 (88.9, 100.0)	100.0 (88.9, 100.0)	79.3 (69.1, 89.7)	81.3 (70.3, 89.1)	85.7 (69.6, 92.9)	83.3 (70.8, 100.0)
N (%) <100		34 (46%)	12 (16%)	34 (46%)	71 (97%)	21 (28%)	19 (26%)	73 (99%)	73 (99%)	67 (92%)	50 (68%)
Female median (25th, 75th)	87	100.0 (95.8, 100.0)	100.0 (100.0, 100.0)	100.0 (80.0, 100.0)	73.8 (65.4, 83.3)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	80.0 (70.6, 92.6)	79.7 (65.6, 87.5)	85.7 (75.0, 96.4)	91.7 (70.8, 100.0)
N (%) <100		32 (37%)	6 (7%)	36 (41%)	85 (98%)	15 (17%)	10 (11%)	86 (99%)	84 (97%)	77 (89%)	61 (70%)
Adoption status†	161	‡			‡						
No median (25th, 75th)	87	95.8 (87.5, 100.0)	100.0 (100.0, 100.0)	90.0 (80.0, 100.0)	67.5 (57.1, 77.1)	100.0 (88.9, 100.0)	100.0 (100.0, 100.0)	80.0 (69.7, 90.3)	79.7 (68.8, 87.5)	85.7 (69.6, 92.9)	83.3 (66.7, 100.0)
N (%) <100		45 (52%)	15 (17%)	44 (51%)	85 (99%)	23 (26%)	19 (22%)	86 (99%)	85 (98%)	78 (91%)	64 (74%)
Yes median (25th, 75th)	74	100.0 (95.8, 100.0)	100.0 (100.0, 100.0)	100.0 (80.0, 100.0)	75.8 (69.6, 85.4)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	80.0 (69.7, 89.7)	81.3 (70.3, 90.6)	87.5 (76.8, 96.4)	91.7 (75.0, 100.0)
N (%) <100		21 (28%)	3 (4%)	26 (35%)	71 (96%)	13 (18%)	10 (14%)	73 (99%)	72 (97%)	66 (89%)	47 (64%)
Maternal education†	146										
Bachelor's degree or higher			§			§					
No median (25th, 75th)	75	100.0 (87.5, 100.0)	100.0 (100.0, 100.0)	100.0 (80.0, 100.0)	70.8 (57.1, 80.0)	100.0 (77.8, 100.0)	100.0 (88.9, 100.0)	80.0 (70.6, 91.2)	79.7 (68.8, 87.5)	85.7 (69.6, 92.9)	87.5 (66.7, 100.0)
N (%) <100		33 (44%)	15 (20%)	35 (47%)	74 (99%)	25 (33%)	19 (25%)	74 (99%)	74 (99%)	70 (93%)	54 (72%)
Yes median (25th, 75th)	71	100.0 (95.8, 100.0)	100.0 (100.0, 100.0)	100.0 (80.0, 100.0)	73.3 (66.7, 84.2)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	80.0 (70.6, 92.6)	81.3 (71.9, 90.6)	87.5 (75.0, 98.2)	91.7 (75.0, 100.0)
N (%) <100		24 (34%)	2 (3%)	26 (37%)	67 (96%)	9 (13%)	9 (13%)	70 (99%)	68 (96%)	59 (84%)	46 (66%)
ALT (U/L)¶	158										
Spearman correlation coefficient		0.04	−0.13	−0.02	−0.22	0.06	−0.03	−0.13	0.01	−0.07	−0.03
APRI¶	139										
Spearman correlation coefficient		0.18	0.08	0.00	−0.02	0.07	0.10	−0.06	0.01	0.04	0.05
Symptom count†,‖	161			**				**	**	**	
0 median (25th, 75th)	86	100.0 (95.8,100.0)	100.0 (100.0,100.0)	100.0 (80.0,100.0)	73.8 (66.7,82.1)	100.0 (100.0,100.0)	100.0 (100.0,100.0)	83.4 (70.6,93.2)	82.8 (75.0,92.2)	89.3 (75.0,96.4)	91.7 (70.8,100.0)
N (%) <100		30 (35%)	7 (8%)	31 (36%)	82 (96%)	15 (17%)	10 (12%)	85 (99%)	83 (97%)	73 (86%)	53 (62%)
1 Median (25th, 75th)	29	100.0 (95.8,100.0)	100.0 (100.0,100.0)	100.0 (80.0,100.0)	75.0 (65.4,83.3)	100.0 (88.9,100.0)	100.0 (100.0,100.0)	80.0 (74.1,90.3)	81.3 (75.0,89.1)	92.9 (82.1,96.4)	87.5 (70.8,100.0)
N (%) <100		13 (45%)	5 (17%)	11 (38%)	29 (100%)	8 (28%)	5 (17%)	28 (97%)	29 (100%)	26 (90%)	21 (72%)
2 median (25th, 75th)	18	100.0 (95.8,100.0)	100.0 (100.0,100.0)	100.0 (80.0,100.0)	69.2 (59.2,77.9)	100.0 (100.0,100.0)	100.0 (100.0,100.0)	76.8 (70.6,82.9)	80.5 (68.8,84.4)	79.5 (73.2,87.5)	83.3 (75.0,100.0)
N (%) <100		7 (39%)	1 (6%)	7 (39%)	18 (100%)	3 (17%)	3 (17%)	18 (100%)	17 (94%)	18 (100%)	13 (72%)
3+ median (25th, 75th)	28	93.8 (85.4,100.0)	100.0 (100.0,100.0)	80.0 (65.0,90.0)	62.3 (56.0,71.9)	100.0 (83.3,100.0)	100.0 (83.3,100.0)	69.7 (62.2,75.6)	66.4 (50.8,78.9)	73.2 (63.4,86.6)	83.3 (60.4,91.7)
N (%) <100		16 (57%)	5 (18%)	21 (75%)	27 (96%)	10 (36%)	11 (39%)	28 (100%)	28 (100%)	27 (96%)	24 (86%)

The Bonferonni-Holm adjustment for multiple comparisons (across the 10 subscales) was used to calculate P values.

All other comparisons were statistically nonsignificant ($P > 0.05$).

BP = bodily pain/discomfort; CHQ-PF50 = CHQ-Parent Report Form; CHQ-CF87 = CHQ-Child Report Form; FA = family activities; GB = general behavior; GH = general health; MH = mental health; PF = physical functioning; PT = parental time; RB = role functioning-behavioral; RE = role functioning-emotional; RP = role/social limitations as a result of physical; SE = self-esteem.

*One participant had missing GH, SE, and FA subscale scores.

†For categorical variables, the first row gives median scores; the second row gives (25th percentile, 75th percentile); the third row gives the frequency (percent) of individuals scoring below 100.0. Kruskal-Wallis non-parametric tests were used to compare the distribution of CHQ scores across categories.

‡Adoption status was statistically significantly associated with better PF ($P < 0.01$) and General Health ($P < 0.001$).

§Higher maternal education was statistically significantly associated with better Role/Functioning-Physical ($P = 0.02$) and Role/Functioning-Emotional ($P = 0.03$).

¶For continuous variables, Spearman correlation was performed to test if HRQoL domain scores were statistically significantly associated with continuous covariates.

‖Symptoms included fatigue, pain over liver, nausea, poor appetite, weight loss, itching, depression/sadness, irritability, jaundice, and dark urine.

**Symptom count was statistically significantly associated with 4 of 10 subscales based on the K-W test: Bodily Pain ($P < 0.01$), Behavior ($P < 0.01$), MH ($P < 0.01$), and SE ($P < 0.01$).

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related to HBV status, but that socioeconomic status, and, perhaps, immigration status, may contribute as well. Providers caring for children with hepatitis B may want to consider the more global health concerns facing this population.

It is tempting to ascribe some reduction in HRQoL in children with chronic HBV to stigma or discrimination perceived by parent or child. Chinese adults with chronic HBV experience more difficulties in interpersonal relationships as a result of stigma—they believe they bring trouble to their families and are less desirable as spouses (24). They also report feeling stigma related to employment and physical relationships. Among Chinese adults living in Canada, stigma associated with chronic HBV infection is a reason for avoiding HBV screening (25). No similar studies have been performed in children.

Our data affirms the usefulness of HRQoL in children with liver disease as a measure of disease impact on the lives of parents and children. A similar study of HRQoL in 114 treatment naive children with chronic hepatitis C virus demonstrated that, relative to normative data, caregivers were more likely to believe their child's health was poor, reported higher concern about their child's health status, and these perceptions limited family activities (26). In studies of children with non-alcoholic fatty liver disease (27) and autoimmune hepatitis (28), decreases in caregivers' HRQoL were found, although use of different HRQoL instruments makes direct comparison difficult. Information on HRQoL in children with chronic HBV is limited. Woo et al (29), found no association of HRQoL and ALT in adults with hepatitis B, although they used a different HRQoL instrument from ours.

Our study has some limitations. Children were enrolled at tertiary medical centers; the population studied may not reflect the United States and Canadian population of HBV-infected children. Children are, however, often referred to tertiary centers for evaluation and management even with asymptomatic HBV. The study was conducted in English because the HRQoL instrument was not translated into some of the languages most common among our non-English speakers. This may impact how well our study reflects the experiences of refugee children with HBV. Despite the large number of children enrolled in this study, our sample of young children with hepatitis B was small, and assessment of a larger cohort may be informative. Although population-normed scores are available for the PF50, there are important sociodemographic differences between the HBRN Pediatric Cohort and our comparison samples, particularly with respect to numbers of immigrant and adopted children, and ethnic and racial composition. Such differences make comparisons between the study and normative populations problematic, and were therefore not undertaken. Information from caregivers of youth was not available for this study, limiting direct comparison of caregivers' impressions of HRQoL from childhood to adolescence. We were unable to evaluate fibrosis in our population; significant fibrosis is rare in children with HBV infection and is unlikely to be a determinant of HRQoL in this cohort.

CONCLUSION

Overall, HRQoL is preserved in children with chronic HBV infection. Some sociodemographic and HBV-related clinical factors were, however, associated with impaired HRQoL in our pediatric cohort study sample at baseline, including elevated ALT in young children and symptom-reporting, maternal education, and adoption status in youth. Measuring HRQoL may alert clinicians to children and families in need of psychological support and education to dispel health-related anxiety and reduce risk of non-adherence to therapy and subsequent behavioral and mood problems. This is crucial, as children with elevated ALT are more likely to need medical therapy for HBV, and early intervention may reduce poor adherence to therapy associated with reduced HRQoL. Future longitudinal studies in this cohort will track changes of HRQoL in children with the evolving clinical state of their chronic HBV.

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