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Development and initial validation of the chronic hepatitis B quality of life instrument (CHBQOL) among Chinese patients

Lin Zhu[1,2] · Jingxia Kong[1] · Yingjing Zheng[1] · Mengna Song[1] · Xiao Cheng[1] · Li Zhang[1] · Donald L. Patrick[3] · Hongmei Wang[1,2]

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Abstract

Purpose This study developed and tested preliminary measurement properties of a Chinese scale specifically designed to measure HRQOL in patients with chronic hepatitis B (CHBQOL).

Methods We conducted 94 individual interviews with CHB patients to solicit items and five hepatitis expert interviews along with three rounds of cognitive interviews to identify problems with relevance and understanding of content. A cross-sectional validation study was then conducted to evaluate measurement properties ($n = 578$). Factor analysis was used to determine the latent structure of the scale. Reliability was evaluated through Cronbach's alpha coefficients and intra-class correlation coefficients (ICCs). Measurement model adequacy, convergent, discriminant, and known-groups validity were also examined.

Results A scale of 30 items was drafted. After item reduction, the remaining 23 items were assigned to the CHBQOL Somatic symptoms, Emotional symptoms, Belief and Social stigma domains, which had acceptable goodness of fit ($\chi^2/df = 3.13$, GFI = 0.90, AGFI = 0.88, RMSEA = 0.06, SRMR = 0.05). All the CHBQOL domains had satisfactory reliability with Cronbach's α coefficients ranging from 0.73 to 0.91 and ICCs were higher than 0.70 except for Belief domain (ICC = 0.54). Convergent and discriminant validity were acceptable as supported by significant item-domain correlations (0.64–0.90). In general, the correlations between CHBQOL and the SF-36 dimensions met hypotheses. Significant differences were found by mean scores in the subgroups of demographic and clinical variables, supporting the known-groups validity.

Conclusions The CHBQOL instrument proved to be an appropriate tool for assessing HRQOL among Chinese CHB patients.

Keywords Chronic hepatitis B · Health-related quality of life · Reliability · Validity · Instrument development

Introduction

The World Health Organization estimated that in 2015, 257 million people in the world, or 3.5% of the general population, were living with chronic hepatitis B infection (CHB) [1]. CHB is a potentially life-threatening liver disease that results in 0.5 to 1.2 million deaths a year [2], mostly from complications of hepatitis B virus (HBV)-related chronic liver disease including cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC). This mortality rate is comparable to the number of deaths from tuberculosis and HIV [3]. China is a high endemic area of hepatitis B with the prevalence of 7.18% of hepatitis B surface antigen (HBsAg) in the population aged 1–59 years [4]. About 120 million current HBV carriers reside in China, which accounts for almost one-third of the global total, and more than half a million Chinese people die annually from end-stage liver diseases [5, 6].

Lin Zhu and Jingxia Kong have contributed equally to this work.

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✉ Hongmei Wang
rosa@zju.edu.cn

[1] Department of Social Medicine of School of Public Health, Zhejiang University School of Medicine, 866 Yuhang Tang Road, Hangzhou 310058, Zhejiang, People's Republic of China

[2] Department of Pharmacy of the First Affiliated Hospital, Zhejiang University School of Medicine, 866 Yuhang Tang Road, Hangzhou 310058, Zhejiang, People's Republic of China

[3] Department of Health Services, University of Washington, Seattle, WA, USA

Over the past 20 years, following the advent of several new antiviral agents, improved therapeutic outcomes of CHB delay the progression of cirrhosis, thereby reducing the incidence of HCC and lengthening survival [3, 7]. Oral nucleoside analogues (NAs) are effective in inhibiting HBV replication, but they seldom result in cure, and total clearance of HBsAg is rare [3, 8]. Although pegylated interferon (PEG-IFN) achieves higher rates of HBsAg and hepatitis B e antigen (HBeAg) loss, low treatment response, severe side effects, and high cost preclude its wide use [3]. Therefore, long-term (potentially lifelong) NA therapy is required in the majority of CHB management, which associates with the increasing use of healthcare resources and costs. The disease burden of HBV infection and HCC in China is also believed to be among the world's largest [9]. In light of this disease burden, the prevention and treatment of CHB is a high priority.

CHB not only imposes a burden on the healthcare system, but also has a significant impact on individuals' daily life activities and health status [10], particularly their perceived quality of life. Perceived quality of life is defined as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns" [11]. Health-related quality of life (HRQOL) assesses how individual' well-being can be clearly affected by a disease and its treatment. Previous studies indicated that patients with CHB reported lower-functioning and well-being (HRQOL) scores than the general population [12, 13]. However, most of these studies used generic instruments for assessment [12–15]. The 36-Item Short-Form Health Survey (SF-36) and its shorter version (SF-12) were the most used instruments in studies worldwide [16]. Generic instruments are not designed to identify disease-specific domains that may be sensitive to clinical changes specific to the condition and therefore may fail to capture the most important components of HRQOL related to HBV [17, 18].

The Hepatitis B Quality of Life instrument, version 1.0 (HBQOL V1.0) is the first disease-targeted HRQOL instrument in non-cirrhotic HBV; however, the instrument was validated in an English-speaking US population [18]. Besides, multiple items of the HBQOL V1.0 instrument convey similar meanings, for instance, both "Your hepatitis B may flare up at any time" and "Your health might unexpectedly get worse because of hepatitis B" ask patients about their concern with disease deterioration. Several HRQOL measures have been adapted into Chinese for assessment in the hepatitis B patients, such as Chronic Liver Disease Questionnaire (CLDQ) and the Hepatitis Quality of Life Questionnaire (HQLQ) [19, 20], while the content validation for most of the Chinese adaptations is not evaluated. Moreover, the original instruments have their own weaknesses. For example, CLDQ is unable to discriminate between more advanced stages of liver disease [16]. HQLQ excludes patients with other chronic liver diseases than HCV, which has some similarities with HBV but is distinctively different [21].

Culture influences how people come to perceive, cope with health problems, and use healthcare services (i.e., health beliefs and behaviors). The findings from a qualitative study showed patients with hepatitis B infection bore more social impacts than a virus [22]. CHB patients in China used to have limited access to education and employment. Many patients had to choose sub-optimal drugs due to the economic burden arising from inadequate reimbursement for treatment in China. Besides, the challenges of living with CHB and developing intimate relationships greatly bothered patients [22]. HRQOL is culture- and value- dependent, therefore, it will be particularly important to develop a HRQOL instrument for CHB patients in the most widely spoken language in China, Mandarin. The main objective of this study was to develop a culturally grounded HRQOL instrument for assessing the impact of CHB and its cure in China. Based on the source instrument (Chinese version), adaptations for other Asian countries with the highest prevalence could be further developed to help estimate disease burden and evaluate clinical outcomes in these countries.

Methods

Study design

The study was conducted in two phases from July 2016 to February 2018 in Zhejiang Province, China, with the approval of Zhejiang University School of Public Health Ethics Committee. In phase I, qualitative research was conducted to guide construction of HRQOL items for patients with CHB using concept elicitation and cognitive interviewing. Psychometric validation of measurement properties of this new instrument was then tested in Phase II. Informed consent was obtained from all participating subjects during each phase of the study, and all data were analyzed anonymously. Besides, a 100 RMB (≈ 14.5 USD) reimbursement was given to each participant as compensation for time and travel.

Sample sites and participants selection

Six tertiary hospitals were selected for recruiting patients from six cities with varying socioeconomic status according to GDP per capita (two high, two medium, and two low level, respectively). CHB patients from both outpatient and inpatient departments of these hospitals were eligible when meeting all the following inclusion criteria:

(1) Adult male or non-pregnant, non-lactating female subjects, 18–70 years of age, able to read, write, and communicate in Mandarin and comply with the study requirements.
(2) Physician-documented evidence of chronic HBV infection (i.e., HBsAg positive for more than 6 months).
(3) Pre-cirrhotic active CHB with ongoing hepatic inflammation from all stages of treatment (i.e., pre-, intra-, post-oral antiviral therapy with approved NAs including tenofovir, entecavir, adefovir, lamivudine, or telbivudine, either as single agents or in combination).
(4) No co-infection with HCV, HDV, or HIV, no significant cardiovascular, pulmonary, or neurological disease, never underwent liver transplantation or had any end-stage illnesses.

The above study design and inclusion criteria applied to both the qualitative and quantitative phases. Clinical diagnoses of HBV-related diseases were made following the recommendations set forth by Guideline of Prevention and Treatment for Chronic Hepatitis B (2015 Update) [23].

Qualitative phase

Ninety-four in-depth semi-structured interviews with CHB patients were conducted to explore areas of life, goals, concerns, and worries associated with CHB based on an initial conceptual framework involving physical, emotional, social, and environmental well-being. Interviews with five experienced hepatitis clinicians were simultaneously conducted to help understand the clinical characteristics of the CHB disease and how it affects patients' health and life from clinicians' perspective. Interviews were audio-taped and transcribed verbatim for use in thematic content analysis to identify, categorize, and classify themes in the data. Coding was done by two independent researchers. Items were initially drafted applying item development processes used before by the research group [24]. Relevance, importance, comprehensibility, and potential redundancy of items, as well as the suitability of the questionnaire items, recall periods, and response options were evaluated in the additional cognitive interviews in one hospital with up to three round (ten patients in each round) before creating the draft CHBQOL instrument tested here.

Quantitative phase

Participants recruitment

The target sample consisted of around 600 CHB patients from six hospitals divided into three treatment groups: newly diagnosed not on treatment, currently on treatment with virus suppressed, and currently on treatment with no virus suppressed. Eligible participants were recruited according to strict inclusion and exclusion criteria with disease-related information verified by clinicians. Taking the gender, age, education, and treatment condition into consideration, recruitment aimed for a sample broadly representative of the socio-demographic profile of the Chinese CHB population. Five hundred and seventy-eight participants were finally recruited, with less CHB patients in treatment with no viral suppression.

Study measures

Socio-demographic information was self-reported and clinical data were collected from the hospital information system. The socio-demographic information included gender, age, education, marital status, employment status, per capita annual disposable income, and health insurances. The CHB-related characteristics consisted of HBV DNA level, HBeAg status, alanine aminotransferase (ALT) level, and categorized treatment conditions according to clinically meaningful cut-off points [3].

The SF-36 is a generic HRQOL instrument with established reliability and validity for assessing the functioning and well-being of CHB patients [13, 14, 25]. It consists of 36 items belonging to eight scales scoring from 0 to 100: physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health(MH), which can be aggregated to form two summary scores: physical component summary (PCS) and mental component summary (MCS) scores [26, 27]. The PCS and MCS are standardized on the basis of a normative Chinese general population dataset, with the mean set at 50 (SD 10) [27]. Higher scale or summary scores indicate a better health status.

The draft CHBQOL instrument consisted of an item pool with 30 CHB-specific items based on patient interviews and expert opinions. The questionnaire was self-administered with an average completion time of 3.8 min. Each item was rated on a 6-point Likert scale with anchors from 0 ("not at all") to 5 ("very much") to distinguish how CHB patients feel and the severity of symptoms. There were no labels for the other response options (1–4). Responses to the items in negative wording (item 1–7, 9, 11–16, 19–26, 28) were recoded so that a higher score represents a better quality of life. The sum of all the responses to items within the same domain represents the CHBQOL domain score, and the domain scores were then transformed to a 0–100 scale to facilitate analysis and interpretation.

Statistical analysis

Outliers and missing values were checked against the original paper questionnaires and inconsistencies were corrected before data analysis. Missing data were assessed and replaced individually by the mean score of the other items in the domain if at least 50% of items in a domain had been answered [26, 27]. Descriptive analysis was used in frequency tables of socio-demographic and clinical data. Candidate items and final domains of CHBQOL were characterized in terms of item means, standard deviations (SD), skewness, kurtosis, percentage of responses at the floor and ceiling.

Measurement properties of this new developed instrument, including conceptual and measurement model, reliability, validity, and respondent burden were evaluated in this stage. To explore the measurement model, both exploratory factor analysis (EFA) and Confirmatory factor analysis (CFA) were used. A principal axis factoring analysis, a Pearson correlated factors model with an oblique (Promax) rotation, was selected to extract factors when we desired to obtain parameters reflecting latent constructs [28–30]. The eigenvalues for each factor were set as greater than 1.0 [28, 31]. Items with lower factor loadings were dropped one by one in an ascending order until all the remaining items have a loading of 0.4 or higher on the only one factor [29]. Scree plot was also used to support the number of factors.

CFA was conducted to test the dimensionality of the CHBQOL instrument and compare the model fits of different hypothetical structures. The maximum likelihood method was used to estimate parameters. A series of common goodness-of-fit indices were computed to assess the model fit, including Chi-square divided by degree of freedom (χ^2/df), Goodness-of-Fit index (GFI) and its adjusted value, Root Mean Square Error of Approximation (RMSEA), and Standardized Root Mean Square Residual (SRMR). The measurement model of $\chi^2/df < 3$, GFI > 0.9, AGFI > 0.9, RMSEA < 0.05, SRMR < 0.05 was considered representative of a well-fitting model [32].

Cronbach's alpha coefficient and inter-class correlation coefficient (ICC) were applied to estimate the reliability. A Cronbach's alpha [33] and ICC of 0.7 or above was considered appropriate for group comparisons [34, 35]. To assess test–retest reliability, a random sample of 60 CHB patients (ten from each hospital) were asked to complete the CHBQOL questionnaire again a week after their first test (approximately 7–10 days) in an electronic format via internet. Patients was verbally confirmed whether their health status was stable during the test and retest period.

In addition to the factor analyses, construct validity of the CHBQOL instrument was further evaluated by convergent, discriminant, and criterion validity evidence. Item-domain Pearson's correlations were calculated to test the convergent and discriminant validity. The coefficient of each item correlated with its respective domain was expected to larger than 0.50 and higher than those coefficients with other domains, indicating a good convergent and discriminant validity. Spearman's correlation was used to measure the correlations among the four CHBQOL domains and their association with the SF-36. It was hypothesized that comparable dimensions, e.g., CHBQOL Emotional symptoms domain and SF-36 MH scale, would have a stronger correlation, while less comparable dimensions, such as CHBQOL Emotional symptoms domain and SF-36 PF scale, would have a weak correlation [36]. Pearson's correlation coefficients of 0.50 or above were regarded as strong, 0.30–0.49 as moderate, and lower than 0.30 as weak [37].

Known-groups validity tests were used to examine how well the HRQOL domain scores discriminated among subgroups of participants with differing self-reported overall health and clinical conditions [38]. Previous studies have found the HRQOL of patients with chronic liver disease was poorer for females [13, 19, 39], those with financial burden [39], and those at older age [39, 40], the known groups to be tested in our study. In addition, we hypothesized patients with impaired liver function would have worse quality of life, particularly in physical and emotional health. Patients were divided into subgroups according to HBV DNA level, alanine aminotransferase (ALT) level, and HBeAg status, which were often used as a guide to antiviral treatment [3]. One-way ANOVA or independent sample *t* test was performed to assess group differences.

All statistical analyses were carried out using IBM SPSS version 20.0 and Amos 20.0 software (SPSS Inc., Chicago, IL, USA). A *p* value of smaller than 0.05 was set as the statistically significant level.

Results

Basic characteristics of the participants

Of the 578 participants included in this validation study, 74.2% were male patients. The mean age was 39.22 years, with a standard deviation (SD) of 11.07. Most of the participants were married, full-time employed, and had high school diploma or below. Forty-eight (8.3%) patients had no health insurance. Participants with HBV DNA below 2000 IU/ml occupied 68.1%. 44.8% patients were with HBeAg negative and 67.0% participants had normal ALT level (Table 1).

Item descriptive statistics

Eleven items (item 2, 3, 4, 6, 13, 14, 15, 16, 18, 19, 21) had responses from only one participant (0.17%), item 7 had two, and the other 18 items were all answered. Item means ranged

Table 1 Participants' socio-demographic and disease characteristics ($n=578$)

Variable	N^a	Percentage (%)
Gender		
Male	429	74.2
Female	149	25.8
Age (years)		
< 30	149	25.8
31–40	174	30.2
41–50	163	28.2
> 50	91	15.8
Education		
Elementary school or below	68	11.8
Middle school	198	34.3
High school	122	21.1
Junior college	66	11.4
College or above	124	21.4
Marital status		
Single	79	13.7
Married/cohabitation	482	83.4
Separated/divorced	13	2.2
Widowed	4	0.7
Employment status		
Full-time employed	382	66.1
Part-time employed	38	6.6
Retired	34	5.9
Homemaker	54	9.3
Others	70	12.1
Per capita annual disposable income (RMB) (1USD ≈ 6.7 RMB)		
< 21,000	137	23.7
21,000–60,000	237	41.1
> 60,000	203	35.2
City		
Hangzhou	138	23.9
Ningbo	81	14.0
Huzhou	88	15.2
Yiwu	100	17.3
Linhai	96	16.6
Quzhou	75	13.0
Health insurance[b]		
Urban employee basic medical insurance	295	51.0
Urban resident basic medical insurance	56	9.7
New cooperative medical scheme	193	33.4
Commercial medical insurance	50	8.7
No insurance	48	8.3
Treatment group		
Newly diagnosed not on treatment	148	25.6
Currently on treatment with virus suppressed	356	61.6
Currently on treatment with no virus suppressed	74	12.8
HBV DNA level (IU/ml)		
< 100	268	48.8
100–1999	106	19.3
2000–19,999	43	7.8
20,000–199,999	35	6.4
≥ 200,000	97	17.7
HBeAg status		
Negative	228	44.8
Positive	281	55.2
ALT level (U/L)		
≤ 40	367	67.0
41–79	98	17.9
≥ 80	83	15.1

[a]Sample sizes within characteristics may not sum to $n=578$ due to missing values

[b]One participant can have multiple health insurances

from 2.58 to 4.43 with a possible range of 0–5 (Table 2). The percentage of response at the floor (score = 0) ranged from 0.90 to 18.70%, and the percentage of response at the ceiling (score = 5) ranged from 17.60 to 69.60%, indicating that our sample of CHB patients tended to response at the upper end of the QOL continuum. The skewness coefficient of all items ranged from − 2.03 to − 0.01, which showed a negativity skewed distribution. Item kurtosis ranged from − 1.37 to 3.70, and both skewness and kurtosis seemed acceptable between the limits of ± 2.0 and ± 7.0, respectively, in which case, the data could be considered normal [30].

Item reduction and factor analysis

Based on the Kaiser–Meyer–Olkin (KMO) test of sampling adequacy of 0.929 and Bartlett's test of Sphericity coefficient ($\chi^2=8291.311$, $df=435$, $p<0.001$), there were a sufficient number of significant correlations among the items to perform a factor analysis [41]. Principle axis analysis based on Pearson correlations using oblique rotation (Promax) was administrated to extract factors. Firstly, a five-factor model was developed with oblique solution, which tended to group items into four main factors and a small factor with two items (item 8 and 9) relevant to physical limitations. The items were sorted by descending order of factor loads on each factor. According to the results, item 30 (The hospital will let out my disease information) was first dropped due to the lowest factor loading of 0.245. Items 27, 1, 9, 29, 10, and 8 were then dropped one by one until the four-factor model was eventually achieved with all the retained items yielding to their latent factors loading above 0.4 (Table 3), accounting for 61.27% of the accumulative variance.

The CFA was firstly undertaken to test the one-factor model with all 30 items, however, the factor loadings of

Table 2 Content, domain assignment, and descriptive statistics of CHBQOL item pool ($n = 578$)

Item no. brief item content	Domain	Mean ± SD	Skewness	Kurtosis	Floor (%)	Ceiling (%)
2 Feel nauseated	Somatic	4.43 ± 1.04	− 2.02	3.70	0.90	69.60
3 Abdominal distension	Somatic	4.12 ± 1.29	− 1.58	1.74	2.60	56.20
4 Abdominal pain	Somatic	4.39 ± 1.06	− 1.94	3.39	0.90	66.80
5 Lose one's appetite	Somatic	4.21 ± 1.23	− 1.68	2.18	2.10	60.00
6 Sleep is affected	Somatic	3.84 ± 1.48	− 1.22	0.48	5.50	48.60
7 Decreased sexual function	Somatic	3.97 ± 1.39	− 1.33	0.88	3.80	52.20
11 Feel depressed	Emotional	3.74 ± 1.44	− 1.01	0.02	3.80	41.50
12 Feel sad	Emotional	3.88 ± 1.41	− 1.21	0.54	3.80	48.40
13 Feel self-abased	Emotional	3.91 ± 1.45	− 1.27	0.59	4.50	51.40
14 Feel fidgety	Emotional	3.75 ± 1.41	− 1.04	0.20	3.80	40.80
15 Feel hopeless	Emotional	4.25 ± 1.24	− 1.75	2.24	1.60	63.10
16 Worry about getting worse	Emotional	3.05 ± 1.74	− 0.46	− 1.10	13.00	27.70
17 Believe hepatitis B can be cured	Belief	2.98 ± 1.86	− 0.35	− 1.35	14.70	32.90
18 Live long	Belief	3.05 ± 1.64	− 0.40	− 1.01	9.30	26.10
19 Transmission to others	Social	2.78 ± 1.85	− 0.23	− 1.37	18.70	26.50
20 My family will despise me	Social	4.11 ± 1.46	− 1.60	1.41	5.20	64.00
21 Intimacy	Social	3.66 ± 1.69	− 0.97	− 0.43	8.30	50.50
22 Others avoid meeting with me	Social	3.84 ± 1.48	− 1.19	0.39	5.20	48.80
23 Others talk about me	Social	3.60 ± 1.65	− 0.92	− 0.42	8.30	45.70
24 Reduce my chances in life	Social	3.44 ± 1.65	− 0.75	− 0.72	8.00	38.80
25 Decreased social activities	Social	3.57 ± 1.52	− 0.76	− 0.53	4.50	40.50
26 Treatment is troublesome	Social	2.69 ± 1.76	− 0.13	− 1.29	16.10	21.80
28 Not allowed to do certain jobs	Social	3.34 ± 1.74	− 0.65	− 0.96	9.70	39.30
1 Feel fatigue	Dropped	3.23 ± 1.32	− 0.55	− 0.36	3.80	17.60
8 Take care of myself	Dropped	3.27 ± 1.67	− 0.65	− 0.80	10.20	32.20
9 Can't do what I want to do	Dropped	3.21 ± 1.67	− 0.54	− 0.95	9.70	31.30
10 As healthy as peers	Dropped	2.58 ± 1.70	− 0.01	− 1.26	14.50	19.00
27 Cost is affordable	Dropped	3.02 ± 1.71	− 0.36	− 1.14	11.10	29.10
29 Have access to disease information	Dropped	3.06 ± 1.69	− 0.46	− 1.02	11.60	27.30
30 Hospital let out my disease information	Dropped	4.30 ± 1.28	− 2.03	3.42	4.00	67.60

All items were administered with a 6-point scale with anchored by "not at all" (0) and "very much" (5). There were no labels for the other response options (1–4)

Items in bold font were finally eliminated in the subsequent factor analysis

items 29, 8, 27, 10, 17, 18, 30 were far away from 0.50 [42]. After dropping these items, the one-factor model still had a poor fit ($\chi^2/df = 9.31$, GFI = 0.67, AGFI = 0.61, RMSEA = 0.12), that confirmed the multidimensionality of the CHBQOL. We secondly inspected the three-factor model based on the review of the contents of remaining items. After allowing correlations between error covariance 23 and 24, 3 and 4, and 11 and 12, model fit indices were found to be acceptable ($\chi^2/df = 3.52$, GFI = 0.89, AGFI = 0.87, RMSEA = 0.07, SRMR = 0.06). Thirdly, the four-factor structure derived form EFA was also tested. The four-factor model achieved a good fit ($\chi^2/df = 3.12$, GFI = 0.90, AGFI = 0.88, RMSEA = 0.06, SRMR = 0.05), with the factor loadings of all 23 items ranging from 0.55 to 0.90 (see Supplemental Fig. 1), which were fairly good (> 0.50). Comparing the results of all hypothetical models, the four-factor model was preferred by the researchers. One of the factors reflected something special, although it had only two items (item 17 and 18). The scree plot was also graphically displayed to support the four predominant factors. The four factors were finally named Somatic symptoms, Emotional symptoms, Belief, and Social stigma domains, respectively, on the basis of the interpretation of grouped items. Descriptive statistics of four domains are shown in Table 3.

An additional EFA on a random half of the sample ($N = 280$) demonstrated similar factor structure found from the full sample except that one more item (item 1 fatigue) was grouped into Somatic symptoms domain. CFA performed on the other half dataset ($N = 298$) also provided

Table 3 Exploratory factor analysis for the CHBQOL four-factor model and scale descriptive statistics ($n=578$)

Item no. brief item content	Pattern matrix			
	Somatic symptoms	Emotional symptoms	Belief	Social stigma
2 Feel nauseated	**0.66**	0.07	− 0.13	− 0.01
3 Abdominal distension	**0.79**	− 0.10	− 0.01	0.05
4 Abdominal pain	**0.79**	− 0.07	0.00	− 0.03
5 Lose one's appetite	**0.66**	0.10	− 0.05	− 0.05
6 Sleep is affected	**0.46**	0.20	0.08	− 0.07
7 Decreased sexual function	**0.55**	0.02	0.08	0.09
11 Feel depressed	0.09	**0.81**	− 0.04	− 0.04
12 Feel sad	− 0.03	**0.94**	− 0.02	− 0.04
13 Feel self-abased	− 0.06	**0.75**	0.02	0.19
14 Feel fidgety	0.17	**0.67**	0.05	0.10
15 Feel hopeless	0.14	**0.44**	0.08	0.13
16 Worry about getting worse	0.01	**0.46**	0.04	0.26
17 Believe hepatitis B can be cured	− 0.07	0.02	**0.69**	− 0.03
18 Live long	0.01	0.01	**0.85**	− 0.02
19 Transmission to others	− 0.14	0.14	− 0.11	**0.54**
20 My family will despise me	0.07	0.23	− 0.03	**0.43**
21 Intimacy	0.04	0.04	0.03	**0.63**
22 Others avoid meeting with me	0.06	-0.10	0.05	**0.81**
23 Others talk about me	− 0.11	0.14	− 0.07	**0.77**
24 Reduce my chances in life	− 0.09	− 0.06	0.02	**0.95**
25 Decreased social activities	0.16	− 0.07	0.05	**0.65**
26 Treatment is troublesome	0.04	0.14	− 0.06	**0.46**
28 Not allowed to do certain jobs	0.06	− 0.11	0.01	**0.68**
Mean ± SD (range from 0 to 100)	83.1 ± 18.5	75.2 ± 24.0	60.3 ± 31.1	69.0 ± 23.8
Floor (%)	0.0	0.2	5.9	0.3
Ceiling (%)	23.5	18.0	19.4	6.9

an acceptable goodness of fit ($\chi^2/df=2.19$, GFI = 0.87, AGFI = 0.84, RMSEA = 0.06, SRMR = 0.05).

Reliability

The CHBQOL instrument demonstrated a quite good reliability, with Cronbach's α coefficients ranging from 0.73 to 0.91 within each domain, which were above the acceptable cut-off value of 0.70. The ICCs were 0.84, 0.82, and 0.79 for Somatic symptoms, Emotional symptoms, Social stigma domain, respectively, while 0.54 for Belief domain (Table 4).

Table 4 Cronbach's α coefficients and test–retest reliability of the CHBQOL instrument

Domain (number of items)	Cronbach's α coefficient ($n=578$)	ICC (95% CI) ($n=59$)
Somatic symptoms (6)	0.83	0.84 (0.72–0.90)
Emotional symptoms (6)	0.91	0.82 (0.69–0.89)
Belief (2)	0.73	0.54 (0.23–0.73)
Social stigma (9)	0.89	0.79 (0.65–0.88)

ICC intra-class correlation coefficient

Construct validity

Concerning item-domain correlations, each item correlated with its respective domain with coefficients ranging from 0.64 to 0.90 ($p<0.01$). Additionally, all the items revealed a higher correlation with their respective domains than with other domains, indicating a good convergent and discriminant validity (see Supplemental Table 1). There were significant correlations among the four CHBQOL domains. The correlations between CHBQOL Emotional symptoms domain and Somatic symptoms and Social stigma domains were strong, while those between CHBQOL Belief domain and other three domains were weak. The Spearman correlation coefficients between the CHBQOL and the SF-36 were stronger between more comparable dimensions (e.g., 0.59 between CHBQOL Emotional symptoms domain and SF-36 MH scale, 0.46 between CHBQOL Somatic symptoms

domain and SF-36 GH scale) than those between less comparable dimensions (e.g., 0.32, 0.13, and 0.28 between CHBQOL Emotional symptoms, Belief and Social stigma domains, and SF-36 PF scale, respectively). Generally, criterion validity of the CHBQOL was considered to be satisfactory (Table 5).

Known-groups validity

Table 6 shows the mean CHBQOL domain scores by subgroups. Female participants had significantly lower scores in Emotional symptoms domain than males. Increasing age was negatively associated with Somatic symptoms and Belief scores, but positively with Social stigma scores. Compared with young CHB patients aged below 30 years, older people performed better in Social stigma domain, but there was no significant difference between any two groups of age over 30. Patients with lowest per capita annual disposable income (< 21,000 RMB) had lowest CHBQOL scores in all domains although statistical significance were only found in Somatic symptoms and Emotional symptoms domains, compared with those with per capita annual disposable income more than 60000 RMB.

Patients with abnormal ALT had lower mean scores in Emotional symptoms and Social stigma domains than patients with normal ALT values (Table 6). A significant effect was found for different HBeAg status on Social stigma scores ($t = -2.060$, $p < 0.05$). In addition, it is interesting to find that impaired liver function (such as higher HBV DNA level, HBeAg-positive, abnormal ALT) was associated with significant higher scores in Belief domain. Biological indicators had no significant effect on CHBQOL Somatic symptoms domain.

Table 5 Correlations among the CHBQOL domains and their association with the SF-36 ($n = 568$)

CHBQOL domain	CHBQOL domain			
	Somatic symptoms	Emotional symptoms	Belief	Social stigma
Somatic symptoms	1.00			
Emotional symptoms	0.60	1.00		
Belief	0.16	0.18	1.00	
Social stigma	0.45	0.70	0.12	1.00
SF-36 scale/domain				
PF	0.38	0.32	0.13	0.28
RP	0.43	0.39	0.13	0.33
BP	0.42	0.40	0.17	0.28
GH	0.46	0.55	0.34	0.40
VT	0.49	0.51	0.25	0.39
SF	0.40	0.40	0.18	0.36
RE	0.38	0.36	0.10	0.29
MH	0.44	0.59	0.18	0.42
PCS	0.31	0.20	0.03	0.20
MCS	0.44	0.58	0.29	0.42

Sample size was 568 due to missing data in the SF-36 health survey. All correlations were significant except the correlation between CHBQOL Belief domain and SF-36 PCS (Spearman correlation)

Discussion

Our results show that the CHBQOL is a reliable, psychometrically acceptable disease-specific HRQOL measure for patients with CHB in China. Strict procedures were used in the development of the CHBQOL instrument with a mixed method of qualitative and quantitative design. Content validity of the HRQOL questionnaire was assured by an extensive content validation process, including patient individual interviews, expert opinions, and patient cognitive interviews rather than only from literature and investigators themselves. Therefore, both negative and positive aspects of patients' real life were extracted, helping measure overall QOL more accurately.

The ceiling effect was notable on the items of somatic symptoms. Similarly, a high value of 69% for floor effect was reported in another disease-specific HRQOL instrument (Liver Disease Symptom Index 2.0, LDSI 2.0) because of severity of symptoms of patients in the study [43]. Patients with compensated non-cirrhotic disease usually do not have severe physical symptoms, while patients with advanced stages of CHB disease usually have [18]. However, there were few ceiling effects at domain level; therefore, this tool is able to tell the differences between patients with highest scores and improvements in these domains.

Measurement model adequacy, convergent, discriminant, and known-groups validity were assessed in this study. A four-factor model extracted by EFA, with 23 items reflecting Somatic, Emotional, Social, and Belief-related aspects of CHBQOL, explained more than 60% of the total variance. Though the results paralleled the multidimensional conceptualization of CHBQOL, EFA was doubted by its usage as a purely data-driven method [44]. Theory-based CFA was followed to examine whether the obtained dataset is suitable for the model and the criteria for various model fit indices were considered. RMSEA values less than 0.08 are suggested to be reasonable [45]. Therefore, the RMSEA value of 0.06 in this sample indicated an acceptable fit. Moreover, the GFI value of 0.90, AGFI value of 0.88, and SRMR value of 0.05 are considered to be acceptable. Overall, CFA showed that the four-factor model fit the data better than the three-factor and one-factor models. The usefulness of this measure in CHB patients was also confirmed by the high Cronbach's Alpha coefficients, homogeneity, and test–retest reliability. The only exception was for the Belief domain for which the

Table 6 Validity of the CHBQOL instrument assessed by the known-groups method ($n=578$)

Variable	N	Somatic symptoms		Emotional symptoms		Belief		Social stigma	
		Mean (SD)	*t*/F (*p*)	Mean (SD)	*t*/F (*p*)	Mean (SD)	*t*/F (*p*)	Mean (SD)	*t*/F (*p*)
Gender									
Male	429	83.1 (18.5)	− 0.172	76.5 (23.3)	2.212	61.3 (30.8)	1.329	69.4 (23.5)	0.688
Female	149	83.4 (18.5)	(0.864)	71.5 (25.8)	(0.027*)	57.4 (31.7)	(0.184)	67.8 (24.9)	(0.492)
Age (years)									
< 30	149	85.0 (18.7)[a]	4.123	73.5 (24.9)	0.600	69.5 (26.2)[a,b,c]	7.222	63.9 (25.3)[a,b,c]	3.272
31–40	174	85.9 (16.7)[b,c]	(0.007**)	77.1 (22.3)	(0.615)	60.4 (31.4)[a]	(< 0.001**)	71.4 (22.9)[a]	(0.021*)
41–50	163	79.8 (19.6)[a,b]		75.0 (24.8)		55.1 (32.0)[b]		69.4 (24.0)[b]	
> 50	91	80.7 (18.3)[c]		75.0 (24.7)		54.4 (33.0)[c]		71.8 (22.0)[c]	
Per capita annual disposable income (RMB)									
< 21,000	137	78.3 (20.4)[a,b]	6.750	71.6 (25.6)[a]	3.423	57.7 (33.1)	1.721	67.2 (24.3)	1.306
21,000–60,000	237	83.8 (17.9)[a]	(0.001**)	74.8 (24.9)	(0.033*)	59.0 (31.7)	(0.180)	68.2 (24.2)	(0.272)
> 60,000	203	85.6 (17.2)[b]		78.4 (21.6)[a]		63.5 (28.7)		71.1 (23.1)	
HBV DNA level (IU/ml)									
< 2000	374	82.9 (18.6)	− 0.342	76.2 (23.7)	1.347	57.3 (31.5)	− 3.383	70.0 (24.0)	1.312
≥ 2000	175	83.4 (18.1)	(0.733)	73.3 (24.8)	(0.178)	66.9 (30.0)	(0.001**)	67.1 (23.6)	(0.190)
HBeAg status									
Negative	228	81.9 (19.5)	1.242	75.0 (25.5)	− 0.174	56.7 (32.5)	1.990	71.1 (24.3)	− 2.060
Positive	281	84.0 (16.9)	(0.215)	74.6 (23.0)	(0.862)	62.2 (29.7)	(0.047*)	66.7 (23.3)	(0.040*)
ALT level									
Normal	367	83.7 (18.6)	1.486	77.0 (22.9)	2.599	57.3 (32.3)	− 3.689	70.3 (23.5)	2.035
Abnormal	181	81.2 (18.5)	(0.138)	71.1 (26.3)	(0.01*)	67.1 (27.9)	(< 0.001**)	65.8 (24.7)	(0.042*)

Sample sizes with different variables may not sum to $n=578$ due to missing values. Independent sample *t* test for gender, HBV DNA level, HBeAg status, ALT level; one-way ANOVA for age and per capita annual disposable income. The same superscript (a, b, c) represents there is a significant difference between two subgroups in post hoc test. ALT > 40 U/L was diagnosed as abnormal in China. Higher HBV DNA level ≥ 2000 IU/ml, HBeAg-positive, abnormal ALT indicate impaired liver function

**$p < 0.01$, *$p < 0.05$ (two tails)

intra-class correlation coefficient was less than 0.6. That may be because the differences were small between participants' responses in this domain and thus the within-subject variance can easily overwhelm the between-subject variance, leading to low reliability [46].

The Belief factor is unique among the four factors and reflects something more than Emotional symptoms, (e.g., the fear of death and belief in cure). The qualitative interviews gave us a clear picture of CHB patients' feelings ("I think I was sentenced to death"; "I have been dreaming that 1 day my illness could be cured. That is called a miracle."). Regardless of the medical condition, Belief factor is kind of inner faith on life in the particular culture context. There are only two items in this domain, further qualitative study is needed to explore possible unique perceptions in patients' belief [47].

The hypotheses that we would see stronger correlations between comparable CHBQOL and SF-36 dimensions than those between less comparable dimensions were generally met. The correlations between CHBQOL Belief domain and all other CHBQOL domains and SF-36 dimensions but the GH scale were all weak, which also implied its uniqueness in concept. The items in Somatic symptoms domain concern gastrointestinal suffering, sleep, and sexual functioning. Both sleep and sexual functioning often load on other emotional or physical factors. This mixture seems more like psychosomatic symptoms, which possibly resulted in moderate to strong correlations with CHBQOL Emotional symptoms domain and all SF-36 dimensions. Known-groups validity was used to assess if the scale differentiated among different groups. Our hypotheses of gender, age, and income differences on scales were mostly verified. Females reported more and serious emotional symptoms than males, as they tended to be more likely to worry about their illness [13]. Older people had lower Somatic symptoms and Belief domain scores, but they performed better in Social stigma domain probably due to younger CHB individuals suffering more social implications, including education and employment choices, economic opportunities, the development of intimate relationships, and stigma-related things [22]. We also examined known-group validity cross a range

of clinically relevant anchors. We found patients reporting worse clinical performance had significantly higher Belief scores, probably because they have been longing to pull out. Unfortunately, no significant associations were found between any clinical anchors and CHBQOL Somatic symptoms domain scores. One possible reason was that for patients with non-cirrhotic HBV, social and psychosocial aspects other than physical symptoms bothered their daily life [18].

Limitations in this study were several. First, although we recruited CHB patients from cities with diverse socioeconomic status in Zhejiang province, taking gender, age, education, and treatment condition into consideration, the sample inherently was not a perfect representative of target population in China. Although HBV infection is a more common pattern observed in men than in women [48], there might be selection or response bias with the high proportion of male participants, which might affect the generalizability of results across different populations. Second, the difference between paper–pencil and electronic administration of the CHBQOL questionnaire in test–retest survey should not be ignored, though we made two questionnaires appeared to patients almost the same. Third, there was not another independent sample here, so we performed the CFA and EFA on the same dataset, which may overestimate the model fit indices. Fourth, it was a cross-sectional study; therefore, responsiveness to change in virus replication and interpretability of CHBQOL scores remain to be further examined in longitudinal studies. Finally, the analysis above was based on classical test theory, which failed to describe item information functioning. The use of modern test theory including item response theory should be considered in future research to deeply characterize the CHBQOL instrument. Nevertheless, this large study in multiple sites with rigorous analyses provides a strong foundation for future studies using this instrument with different populations and repeated validation analyses.

Conclusions

The CHBQOL instrument revealed acceptable measurement properties including reliability and construct validity in a sample of non-cirrhotic Chinese CHB patients, supporting for use in clinical practice as a disease-specific HRQOL measure among Chinese CHB patients. Further studies will be conducted to confirm the responsiveness over time and to determine the minimally important differences of the CHBQOL using a follow-up cohort.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

Ethical approval All procedures performed in studies were approved by Zhejiang University School of Public Health Ethics Committee.

Informed consent Informed consent was obtained from all individual participants included in the study.

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