World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i30.4950

World J Gastroenterol 2013 August 14; 19(30): 4950-4957
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Validation of the chronic liver disease questionnaire in Serbian patients

Dusan Dj Popovic, Nada V Kovacevic, Darija B Kisic Tepavcevic, Goran Z Trajkovic, Tamara M Alempijevic, Milan M Spuran, Miodrag N Krstic, Rada S Jesic, Zobair M Younossi, Tatjana D Pekmezovic

Dusan Dj Popovic, Nada V Kovacevic, Tamara M Alempijevic, Milan M Spuran, Miodrag N Krstic, Rada S Jesic, Clinic for Gastroenterology, Clinical Centre of Serbia, Belgrade 11000, Serbia
Nada V Kovacevic, Tamara M Alempijevic, Darija B Kisic Tepavcevic, Goran Z Trajkovic, Miodrag N Krstic, Rada S Jesic, Tatjana D Pekmezovic, Faculty of Medicine, University of Belgrade, Belgrade 11000, Serbia
Darija B Kisic Tepavcevic, Tatjana D Pekmezovic, Institute of Epidemiology, Faculty of Medicine, University of Belgrade, Belgrade 11000, Serbia
Goran Z Trajkovic, Institute of Statistics and Informatics, Faculty of Medicine, University of Belgrade, Belgrade 11000, Serbia
Zobair M Younossi, Center for Liver Diseases, Department of Medicine, Inova Fairfax Hospital, Falls Church, Annandale, VA 22003-6800, United States
Author contributions: Popovic DD gave an substantial contributions to conception of the study, as well as in acquisition of data and drafting the article; Kovacevic NV and Younossi ZM gave substantial contributions to conception and design of the research; Kisic Tepavcevic DB had significant contributions in interpretation of data and revising the article critically for important intellectual content; Trajkovic GZ gave essential contributions in analysis and interpretation of data; Alempijevic TM, Spuran MM, Krstic MN and Jesic RS had important contributions in acquisition of data; Pekmezovic TD revised the article critically for important intellectual content and gave a final approval of the version to be published.
Supported by Grant from the Ministry of Education and Science of the Republic of Serbia, No. 175087 to Pekmezovic TD, Kisic Tepavcevic DB and Trajkovic GZ
Correspondence to: Tatjana D Pekmezovic, MD, Chief, Professor of Medicine, Institute of Epidemiology, Faculty of Medicine, University of Belgrade, Visegradska 26A, Belgrade 11000, Serbia. pekmezovic@sezampro.rs
Telephone: +381-11-3607062 Fax: +381-11-3607062
Received: April 15, 2013 Revised: June 5, 2013
Accepted: June 19, 2013
Published online: August 14, 2013

Abstract

AIM: To translate into Serbian and to investigate the validity of the cross-culturally adapted the chronic liver disease questionnaire (CLDQ).

METHODS: The questionnaire was validated in 103 consecutive CLD patients treated between October 2009 and October 2010 at the Clinic for Gastroenterology, Clinical Centre of Serbia, Belgrade (Serbia). Exclusion criteria were: age < 18 years, psychiatric disorders, acute complications of CLD (acute liver failure, variceal bleeding, and spontaneous bacterial peritonitis), hepatic encephalopathy (grade > 2) and liver transplantation. Evaluation of the CLDQ was done based on the following parameters: (1) acceptance is shown by the proportion of missing items; (2) internal reliabilities were assessed for multiple item scales by using Cronbach alpha coefficient; and (3) in order to assess whether the allocation of items in the domain corresponds to their distribution in the original questionnaire (construction validity), an exploratory factor analysis was conducted. Discriminatory validity was determined by comparing the corresponding CLDQ score/sub-score in patients with different severity of the diseases.

RESULTS: The Serbian version of CLDQ questionnaire completed 98% patients. Proportion of missing items was 0.06%. The total time needed to fill the questionnaire was ranged from 8 to 15 min. Assistance in completing the questionnaire required 4.8% patients, while 2.9% needed help in reading, and 1.9% involved writing assistance. The mean age of the selected patients was 53.8 ± 12.9 years and 54.4% were men. Average CLDQ score was 4.62 ± 1.11. Cronbach's alpha for the whole scale was 0.93. Reliability for all domains was above 0.70, except for the domain "Activity" (0.49). The exploratory factor analysis model revealed 6 factors with eigenvalue of greater than 1, explaining 69.7% of cumulative variance. The majority of the items (66%) in the Serbian version of the CLDQ presented the highest loading weight in the domain assigned by the CLDQ developers: "Fatigue" (5/5), "Emotional function" (6/8), "Worry" (5/5), "Abdominal symptoms" (0/3), "Activity"

(0/3), "Systemic symptoms" (3/5). The scales "Fatigue" and "Worry" fully corresponded to the original. The factor analysis also revealed that the factors "Activity" and "Abdominal symptoms" could not be replicated, and two new domains "Sleep" and "Nutrition" were established. Analysis of the CLDQ score/sub-score distribution according to disease severity demonstrated that patients without cirrhosis had lower total CLDQ score (4.86 ± 1.05) than those with cirrhosis Child's C (4.31 ± 0.97). Statistically significant difference was detected for the domains "Abdominal symptoms" [F (3) = 5.818, P = 0.001] and "Fatigue" [F (3) = 3.39, P = 0.021]. *Post hoc* analysis revealed that patients with liver cirrhosis Child's C had significantly lower sub-score "Abdominal symptoms" than patients without cirrhosis or liver cirrhosis Child's A or B. For domain "Fatigue", patients with cirrhosis Child's C had significantly lower score, than non-cirrhotic patients.

CONCLUSION: The Serbian version of CLDQ is well accepted and represents a valid and reliable instrument in Serbian sample of CLD patients.

Key words: Chronic liver disease; Quality of life; Questionnaire; Validation; Factor analysis

Core tip: The Serbian validation of the chronic liver disease questionnaire (CLDQ) confirmed the 6-domain structure of the original United States version. However, in our investigation the original structure was only partially reproduced. The most prominent changes are related to the fact that the factors "Activity" and "Abdominal symptoms" could not be replicated, and two new domains "Sleep" and "Nutrition" were established Moreover, the domain "Nutrition" has been introduced for the first time. Our results of factors analysis gave the evidence that at list some items from the original version of CLDQ should be allocated or eliminated from the questionnaire because of the multiple loadings.

Popovic DD, Kovacevic NV, Kisic Tepavcevic DB, Trajkovic GZ, Alempijevic TM, Spuran MM, Krstic MN, Jesic RS, Younossi ZM, Pekmezovic TD. Validation of the chronic liver disease questionnaire in Serbian patients. *World J Gastroenterol* 2013; 19(30): 4950-4957 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i30/4950.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i30.4950

INTRODUCTION

The concept of health-related quality of life (HRQoL) incorporates many aspects of an individual's experience, the general well-being, satisfaction, social and physical functioning[1]. Chronic liver disease (CLD) includes a wide range of disorders that are characterized by chronic inflammation and often progress to the cirrhosis. This group of diseases has a significant impact on HRQoL, and therefore its assessment is widely used as important outcome in clinical trials[2,3]. The most widely used general questionnaire is the short form health survey-36[4]. Furthermore, the liver disease-specific instruments comprise items that are specific for patients with CLD, and therefore they are more sensitive for capturing all relevant disease-burdened quality of life domains than a generic measure. These disease-specific questionnaires such as the CLD questionnaire (CLDQ)[5], liver disease quality of life instruments[6] and hepatitis quality of life questionnaire[7] are more sensitive and responsive to changes in HRQoL.

The CLDQ is a specific quality of life instrument designed for patients with liver disease, regardless of the underlining severity and etiology of CLD[5]. Its original version was developed by Younossi *et al*[5] and has demonstrated appropriate validity and reliability. The CLDQ has already been cross-culturally adapted and validated into different languages in previously published studies[8-18].

Up to now, there is no CLD-specific quality of life instruments adapted for Serbian patients. Therefore, the aim of this study was to investigate the validation of the translated and culturally adapted CLDQ questionnaire on a group of Serbian CLD patients.

MATERIALS AND METHODS

A cross-sectional study has been performed at the Clinic for Gastroenterology, Clinical Centre of Serbia, Belgrade. Between October 2009 and October 2010, consecutive inpatients and outpatients with CLD were considered for inclusion. Inclusion criteria were chronic hepatitis or liver cirrhosis. Diagnosis of liver disease was made by medical doctor-specialist in hepatology. Chronic hepatitis was defined as elevation of aminotransferases for 1.5 times greater than the upper limit of the reference interval, for more than 6 mo duration, and/or presence of histopathologic criteria for chronic hepatitis. The diagnosis of cirrhosis was based on clinical, laboratory, echo sonographic, endoscopic and histopathological criteria[9,19]. Ascites was diagnosed by ultrasound. Hepatic encephalopathy was assessed clinically, and patients were graded on a scale from 1 to 4. The presence of hypersomnia indicated grade 1, somnolentia grade 2, severe somnolence or stupor grade 3 and severe stupor or coma grade 4[8]. Exclusion criteria were: age < 18 years, psychiatric disorders (psychosis or dementia), acute complications of CLD (acute liver failure, variceal bleeding, and spontaneous bacterial peritonitis), hepatic encephalopathy (grade > 2) and liver transplantation. We also excluded the patients undergoing antiretroviral therapy because of a very small number of these subjects.

Severity of liver cirrhosis was determined by the Child-Pugh classification[20,21]. According to the severity of the diseases, patients were categorized into the following groups: non-cirrhotic, cirrhotic Child's A, cirrhotic Child's B and cirrhotic Child's C. According to the etiol-

ogy of the diseases, patients were categorized into the following categories: alcoholic, viral (viral hepatitis B and viral hepatitis C), autoimmune (autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing hepatitis) and other (non-alcoholic steatohepatitis, Wilson's disease, hereditary hemochromatosis and cryptogenic).

This study was approved by the Ethics Committee of the Faculty of Medicine, University of Belgrade. All subjects gave written consent to participate in the study. Permission to use and validate CLDQ questionnaire was obtained by author of the original version (Younossi ZM).

The demographic data (age, gender, education, occupation, employment, marital status), clinical information (duration of the liver disease, haematemesis, ascites, hepatic encephalopathy), as well as the results of hematological, biochemical, virological and immunological analyses, were obtained from medical records.

The CLDQ was developed in 1999, by Younossi *et al*[5]. The questionnaire consists of 29 questions, which are divided into 6 domains as follows: "Fatigue", "Activity", "Emotional function", "Abdominal symptoms", "Systemic symptoms" and "Worry". Scores for each question were ranked from 1 (the worst quality of life - "All of the time") to 7 (the best quality of life - "None of the time"), for to the period of 2 wk ago. These scores were created using the Likert method. Domain scores are the means of the items contained. A summary score is calculated by the mean value of all subscale scores. The scores range from 1 to 7, whit higher values indicating better quality of life[5]. The CLDQ questionnaire was self-administered for all types of patients and filled in by the patients. In case of help in understanding and/or writing, the physician provided assistance when necessary.

The CLDQ adaptation was based on internationally accepted methodology for cultural adaptation of HRQoL questionnaires[22,23]. We used a standard methodology for the production of the Serbian version and it's included: (1) "Foward translation" - translation of the original version from English to Serbian language, so that the Serbian's version, semantically and conceptually corresponds to the original questionnaire. Translation was conducted by two independent, professional translators. Following review and editing by translators and experts, one single translation was formed; (2) "Backward translation" implied translation of the Serbian's version of CLDQ into English. Conducted by two translators, one an expert in quality of life and another one a clinician, with discussion on controversial items, it resulted in the final version of CLDQ culturally corresponding with Serbian's patients with CLD chronic disease liver; (3) Serbian version CLDQ questionnaire was tested on five patients with CLD who have had the opportunity to present their comments and suggestions. Test results are discussed by the group of experts, who created the final Serbian's version of the CLDQ (CLDQ-S); and (4) the final version was tested in 15 patients with CLD. During adaptation and pretesting of the CLDQ, there were no disputed items and any change from the original questionnaire items. Patients had no difficulty in understanding and completing the questionnaire.

Statistical analysis

In the data analysis, descriptive and analytical statistics were used. Continuous variables were described as mean ± SD, while the categorical variables were presented as proportions (percentages). For comparison of continuous variables between groups one-way Analysis of variance was used, including Bonferroni post hoc test for multiple comparisons.

Evaluation of the CLDQ was done through the following parameters: (1) acceptance is shown by the proportion of missing items; (2) internal reliabilities of Serbian version CLDQ were assessed for multiple item scales by using Cronbach alpha coefficient, ranges from 0-1, latter meaning perfect reliability; (3) in order to assess whether the allocation of items in the domain corresponds to their distribution in the original questionnaire (construction validity), an exploratory factor analysis (principal component analysis with varimax rotation) was conducted. A factor was considered as important if its eigenvalue exceeded 1.0; and (4) discriminatory validity was determined by comparing the corresponding CLDQ score/sub-score in patients with different severity of the diseases.

RESULTS

Out of 107 patients who met the inclusion criteria, 96.2% (n = 103) patients agreed to participate in the study. The reason for not accepting participation was a lack of interest or time. The mean age of the selected patients was 53.8 ± 12.9 years (range 21-79 years) and 54.4% were men (Table 1). According to the etiology of CLD the largest proportion was alcoholic liver disease (35%), and then autoimmune liver disease (28.2%). CLD in the stage of cirrhosis had 77.6% (n = 80) patients (Table 1).

The Serbian version of CLDQ questionnaire was completed by 98% (n = 101) patients. Proportion of missing items was 0.06% (2/2987). Two patients filled the questionnaire, but did not answered to all questions, for the "Systemic symptoms" domain (one for Question No.6 and one for No.27). The total time needed to fill the questionnaire ranged from 8 to 15 min. Assistance in completing the questionnaire was required by 4.8% (n = 5) patients, while 2.9% (n = 3) needed help in reading, and 1.9% (n = 2) involved writing assistance.

Analysis of distribution characteristics and reliability of the Serbian version of CLDQ showed that the average CLDQ score was 4.62 ± 1.11 and varied from 1.90 to 6.78. Cronbach's alpha for the whole scale (items 1-29) was 0.93. Reliability for all domains was above 0.70, except for the domain "Activity" (0.49) (Table 2).

In our validation study the exploratory factor analysis model revealed 6 factors with eigenvalue of greater than 1, explaining 69.7% of cumulative variance (Table 3). The majority of the items (66%) in the Serbian version of the

Table 1 Demographic and clinical characteristics of patients with chronic liver disease *n* (%)

Characteristics	Statistics
Age[1] (yr)	53.8 ± 12.9
Gender	
Male	56 (54.4)
Female	47 (45.6)
Education	
Unqualified[2]	6 (5.8)
Primary school	18 (17.5)
Secondary school	43 (41.7)
High school	17 (16.5)
University	18 (17.5)
Missing data	1 (1.0)
Current employment status	
Employed	29 (28.2)
Unemployed	25 (24.3)
Retired	49 (47.5)
Profession	
Housewife	13 (12.6)
Peasant	3 (2.9)
Worker	40 (38.8)
Official	21 (20.4)
Expert	21 (20.4)
Missing data	5 (4.9)
Marital status	
Single	15 (14.6)
Married/cohabiting	68 (66.0)
Separated/divorced	13 (12.6)
Widowed	7 (6.8)
Alcohol consumption	56 (54.4)
Smoker	32 (31.1)
Disease severity	
Non cirrhotic	23 (22.3)
Cirrhotic Child's A	25 (24.3)
Cirrhotic Child's B	30 (29.1)
Cirrhotic Child's C	25 (24.3)
Etiology	
Alcoholic	36 (35.0)
Viral	16 (15.5)[3]
Autoimmune/cholestatic	29 (28.2)
Other	22 (21.3)

[1]mean ± SD; [2]Without primary school; [3]Four patients with hepatitis B surface antigen positive chronic liver disease (CLD) and 12 patients with anti-hepatitis C virus positive CLD.

Table 2 Distribution and reliability of the chronic liver disease guestionnaire

Scale	*n*	mean ± SD	Min value	Max value	Missing items[1]	Cronbach alpha
Abdominal symptoms	103	4.75 ± 1.63	1.33	7	0%	0.82
Fatigue	103	4.20 ± 1.60	1.60	7	0%	0.90
Systemic symptoms	101	5.27 ± 1.60	1.60	7	1.94%	0.74
Activity	103	4.47 ± 1.33	1.33	7	0%	0.49
Emotional function	103	4.61 ± 1.62	1.62	7	0%	0.89
Worry	103	4.24 ± 1.61	1.00	7	0%	0.85
CLDQ total	101	4.62 ± 1.11	1.90	6.78	1.94%	0.93

[1]Proportion of patients with missing any item on the subscale. CLDQ: Chronic liver disease questionnaire.

CLDQ presented the highest loading weight in the domain assigned by the CLDQ developers: "Fatigue" (5/5), "Emotional function" (6/8), "Worry" (5/5), "Abdominal symptoms" (0/3), "Activity" (0/3), "Systemic symptoms" (3/5). The scales "Fatigue" and "Worry" corresponded fully to the original. An important difference compared to the original version was inclusion of two new factors, "Sleep" and "Nutrition". A new factor named "Sleep" was derived from the two items, No. 16 ("difficulty sleeping") and No. 20 ("incapable to fall asleep"), of the original subscale "Emotional function". An additional new factor "Nutrition" consisted of two items, No. 7 ("not able as much as would like") and 14 ("restriction of diet"), belonging to the "Activity" domains in original version of CLDQ. Furthermore, the factor "Activity", which consists of three items (No. 7, 9 and 14), could not be reproduced at all. Items No. 7 and 14 constructed the new factor "Nutrition", and item No. 9 had highest loading on "Fatigue". Also, the factor "Abdominal symptoms", which consists of three items (No. 1, 5 and 17) was not be replicated in the form like in the original version. Namely, in the Serbian version of CLDQ all of these three items had the highest loading in the same group and jointly with questions 3, 21 and 23 constituted a factor called "Systemic symptoms". In the original version of the questionnaire items No. 3, 21 and 23 are also part of the domain "Systemic symptoms", with the difference that in Serbian CLDQ questionnaire the two issues (No. 6 and 27) from the original version showing higher loadings on more than one other factors rather than the factor "Systemic symptoms". Explicitly, the item No. 6 ("shortness of breath in daily activities") showed higher loadings on "Fatigue", and "Nutrition", while the question No. 27 ("itching") revealed a higher degree of belonging to the domains of "Nutrition", "Worry" and "Sleep" (Table 3).

The analysis of etiology-specific scores of CLDQ have shown that the lowest total quality of life score (4.45 ± 1.11) was registered in the group of autoimmune/cholestatic origin of CLD, while the highest total score (4.84 ± 0.91) was observed in the CLD subcohort with the causes different from alcoholic, viral and autoimmune/cholestatic. However, there were no statistically significant differences between etiology-specific total quality of life scores, as well, as, among etiology-specific domain scores of CLDQ (data was not shown).

Analysis of the CLDQ scores distribution according to disease severity demonstrated that patients without cirrhosis had lower the total CLDQ score than those with cirrhosis Child's C, but without statistic significance [F (3) = 0.97, P = 0.402]. Statistically significant difference was detected for the domains "Abdominal symptoms" [F (3) = 5.818, P = 0.001] and "Fatigue" [F (3) = 3.39, P = 0.021]. *Post hoc* analysis revealed that patients with liver cirrhosis Child's C had significantly lower sub-score "Abdominal symptoms" than patients without cirrhosis or liver cirrhosis Child's A or B. For domain "Fatigue", patients with cirrhosis Child's C had significantly lower

Table 3 Exploratory factor analysis of the serbian version of the chronic liver disease questionnaire

Original CLDQ items	Factor 1 Systemic symptoms	Factor 2 Emotional function	Factor 3 Fatigue	Factor 4 Worry	Factor 5 Sleep	Factor 6 Nutrition
Fatigue						
(2) tired or fatigued	0.542	0.173	0.636[1,2]	0.271	0.018	0.140
(4) sleepy during the day	0.105	0.200	0.868[1,2]	0.004	0.156	-0.012
(8) reduced strength	0.489	0.119	0.595[1,2]	0.310	-0.019	0.220
(11) decreased level of energy	0.374	0.159	0.600[1,2]	0.385	0.055	0.282
(13) drowsy	0.168	0.287	0.824[1,2]	0.114	0.172	-0.085
Emotional function						
(10) anxious	0.313	0.521[1,2]	0.354	0.358	0.022	0.267
(12) unhappy	0.034	0.677[1,2]	0.283	0.284	0.096	0.264
(15) irritable	0.118	0.823[1,2]	0.157	0.082	0.036	0.091
(16) difficulty sleeping	0.256	0.184	0.175	0.229	0.745[1,3]	0.096
(19) mood fluctuations	0.127	0.794[1,2]	0.178	0.248	0.139	-0.042
(20) incapable to fall asleeP	0.252	0.183	0.123	0.155	0.822[1,3]	0.046
(24) felt depressed	0.162	0.815[1,2]	-0.003	0.288	0.203	0.092
(26) problem concentrating	0.161	0.697[1,2]	0.078	0.240	0.089	0.224
Worry						
(18) impact on family	0.237	0.269	0.037	0.760[1,2]	0.081	0.036
(22) symptoms developing into major problems	0.153	0.361	0.170	0.696[1,2]	0.229	0.015
(25) condition getting worse	-0.028	0.269	0.188	0.791[1,2]	0.240	0.152
(28) never feeling any better	0.005	0.293	0.162	0.659[1,2]	0.151	0.232
(29) availability of a liver	-0.142	-0.018	0.103	0.599[1,2]	0.460	0.127
Abdominal symptoms						
(1) abdominal bloating	0.763[1,3]	0.098	0.242	0.063	-0.041	0.074
(5) abdominal pain	0.785[1,3]	0.050	0.136	-0.054	0.207	0.110
(17) abdominal discomfort	0.811[1,3]	0.228	0.138	0.205	0.072	-0.049
Activity						
(7) not able to eat as much as would like	0.186	0.406	0.175	0.066	-0.079	0.543[1,3]
(9) trouble lifting or carrying heavy objects	0.389	-0.105	0.481[1,3]	0.162	0.116	0.236
(14) restriction of diet	-0.073	0.182	0.100	0.212	0.199	0.703[1,3]
Systemic symptoms						
(3) bodily pain	0.798[1,2]	0.103	0.116	0.097	0.121	-0.053
(6) shortness of breath in daily activities	0.367	0.296	0.433[1,3]	-0.047	0.083	0.389
(21) muscle cramps	0.470[1,2]	0.223	0.102	0.046	0.422	0.350
(23) dry mouth	0.556[1,2]	0.305	0.261	-0.065	0.316	0.172
(27) itching	0.252	0.011	-0.193	0.370	0.358	0.481[1,3]

[1]Highest factor loadings for each factor; [2]Factor loadings corresponding to the factors in the original version; [3]Factor loadings indicate highest loadings on other factors than the original ones. The factors "activity" and "abdominal symptoms" could not be reproduced; a new factors "sleep" and "nutrition" were found. CLDQ: Chronic liver disease questionnaire.

score, than non-cirrhotic patients. Significant difference was not detected for the following domains: "Systemic symptoms", "Activity", "Emotional function" and "Worry" (Table 4).

DISCUSSION

The CLDQ is a disease-specific instrument for assessment HRQoL in patients with CLD. It is reliable, reproducible, valid, short, easy to administer and economic questionnaire, which is validated and cross-culturally adapted into many different languages[8-18].

According to internationally accepted methodology for the validation of HRQoL questionnaires, we developed a Serbian version of CLDQ. Patients had no difficulty in understanding and completing the questionnaire. Only 4.8% of the patients required assistance in filling the questionnaire. The frequency of missing items is 0.06%, although this parameter seen in other studies varied from 0.4% to 23.5%[8,24].

In all validation studies CLDQ questionnaire shows outstanding reliability which ranged up to 0.96[9]. In our study, Cronbach's alpha is 0.93, for the overall scale which is the same as in Lithuanian[14], Greece[11], and the Spanish[10] versions. For all domains, internal reliability is acceptable, except for "Activity" where it is 0.49. However, this finding is in accordance with those obtained in Spanish[10] and Germany[8] validation study, where the Cronbach's alpha is 0.57 and 0.69, respectively. High reliability for this domain was found in Thais[9] and Pakistani[15] study.

The domain "Activity" includes three questions: No. 7 ("Not able to eat as much as you would like"), No. 9 ("Trouble lifting or carrying heavy objects") and No. 14 ("Limitation of diet"). The reason for the low internal reliability of this domain could be a cultural relationship between diet and disease in our population.

Exploratory factor analysis was carried out to establish whether the changes introduced in the Serbian version of CLDQ affected the structure of the questionnaire. The Serbian validated version confirmed the 6-domain structure of the original United States ver-

Table 4 Distribution of chronic liver disease questionnaire-S score/sub-score according disease severity

	n	Abdominal symptoms	Fatigue	Systemic symptoms	Activity	Emotional function	Worry	Total score
Non cirrhotic	23	5.37 ± 1.39[1]	4.81 ± 1.38[1]	5.54 ± 1.14	4.80 ± 1.32	4.40 ± 1.52	4.23 ± 1.54	4.86 ± 1.05
Child's class A	25	5.08 ± 1.65[1]	4.35 ± 1.30	5.34 ± 1.38	4.40 ± 1.39	4.62 ± 1.31	4.36 ± 1.70	4.69 ± 1.22
Child's class B	30	4.88 ± 1.58[1]	4.18 ± 1.51	5.25 ± 1.34	4.37 ± 1.59	4.77 ± 1.30	4.27 ± 1.61	4.63 ± 1.17
Child's class C	25	3.68 ± 1.46	3.52 ± 1.45	4.95 ± 0.99[2]	4.40 ± 1.37	4.60 ± 1.24	4.09 ± 1.65	4.31 ± 0.97
P value[3]		0.001	0.021	0.442	0.68	0.808	0.952	0.402

[1]Significantly better score compared with "cirrhosis Child's C" score (*post hoc* analysis); [2]For domain "systemic symptoms" (n = 23); [3]*P* value for Analysis of variance.

sion[5]. Such composition of the questionnaire has also been supported by the Hamburg[20] and Chinese (Hong Kong)[17]. The Italian version has five factors versions[13], while Spanish[10] and Greek[11] validated CLDQ revealed 7 factors. However, in our investigation the original structure was only partially reproduced. The most prominent changes are related to the fact that the factors "Activity" and "Abdominal symptoms" could not be replicated, and two new domains "Sleep" and "Nutrition" were established. In the validation studies of the CLDQ carried out in Italy[13], Spain[10], Germany[24] and Chinese (Hong Kong)[17] a new factor described as "Sleep" has already been found and composed of the same two items as in our analysis. Ferrer *et al*[10] pointed out that sleeping habits could vary among cultures (napping habits and bed-times) and therefore influenced cluster potential of sleeping-related items. Moreover, in Serbian version of CLDQ, the domain "Nutrition" has been introduced for the first time. This domain consisted of two items ("Not able to eat as much as would like" and "Restriction in diet") belonging to the "Activity" in original version of CLDQ. Keeping in mind the fact that the original factor "Activity" contains one additional question ("Trouble lifting or carrying heavy objects") that is not strictly related to the previous two, special allocation of the domain of nutrition makes the assessment of quality of life more sensitive. In accordance with our findings, the factor "Activity" could not also be reproduced in investigations conducted in Germany[24] and Italy[13]. Furthermore, majority of the studies dealing with the validation of this questionnaire have shown that the factor "Systemic symptoms" was difficult to be fully reproduced[10-13,24]. In our exploratory analysis the factor "Systemic symptoms" was also partially confirmed (3/5). In Serbian version two of five items in this original domain revealed a higher degree of belonging to the other factors. Namely, the item No. 6 ("Shortness of breath in daily activities") showed higher loadings on "Fatigue", and "Nutrition", while the question No. 27 ("Itching") revealed a higher degree of belonging to the domains of "Nutrition", "Worry" and "Sleep". Ferrer *et al*[10] found that three questions (No. 3, 6 and 23) derived from original "Systemic symptoms" had considerably higher loadings on more than one other factor. Additionally, in Spanish validated version, two items (No. 3 and 6) showed multiple loading on different factors. The other studies also confirmed the hypothesis that the original domain of "Systemic symptoms" consisted of items that could not be assigned clearly and strictly to any particular dimension[11,13].

Our results of factors analysis gave the evidence that at least some items from the original version of CLDQ should be allocated or eliminated from the questionnaire because of the multiple loadings. However, we do not yet want to recommend a change of domains because direct comparisons between the validated versions of CLDQ in different populations would no longer be possible.

The decreasing in total CLDQ score with increasing disease severity was shown in several studies[5,9-11,14,16,25-28]. Reduction of the total CLDQ-S score, between patients without cirrhosis and those with cirrhosis Child's C is 0.55 points, but without statistically significance. However, Younossi *et al*[5] described that a change of 0.5 points on the 1 to 7 point scale approximates the important difference in questionnaire score. Significant reduction of the CLDQ-S sub-score, with severe CLD is detected for the subscales "Abdominal symptoms" and "Fatigue".

In Germany validation study[8] a significant reduction of the CLDQ sub-score was detected for the domains "Abdominal symptoms", "Systemic symptoms", "Activity" and "Worry", while in Spanish validation[10] this finding was obtained for "Fatigue", "Activity" and "Worry". The US validation study reported a significant reduction of the CLDQ score and sub- score for domains: "Fatigue", "Systemic symptoms" and "Activity"[5]. Additionally, Sobhonslidsuk *et al*[9] has shown that severity of CLD affecting the quality of life in all domains of CLDQ, while Ray *et al*[16] confirmed these results for all subscales except for "Worry".

In our research, the etiology of CLD did not significantly affect the HRQoL, which is consistent with previously published results[14,28-30]. In patients with early stages of CLD, etiology does not affect HRQoL, while in patients with cirrhosis, cholestatic etiology is associated with better HRQoL, than hepatocellular CLD[25]. Ray *et al*[16] described that the etiology of CLD did not affect the overall score and most CLDQ sub-score, but had effect on sub-score "Abdominal symptoms" as well as the average scores for some questions. Etiology associated with a worse HRQoL are: chronic viral hepatitis C[16,31], nonalcoholic etiology[27] and non-alcoholic fatty liver disease[32]. In our validation sample, these results could not be reproduced, probably due to the small number of patients with chronic viral hepatitis C included in our study. Besides the impact of chronic hepatitis C and interferon therapy

has an impact on HRQoL[33]. However, data on its effects are controversial[7,33,34].

In conclusion, our results provide considerable support to the appropriate metric properties of the Serbian version of CLDQ. Therefore, it could be emphasized that the questionnaire might be reliable and valid instrument for indentifying HRQoL among liver disease patients and it can be used by health professionals in their clinical practices to improve assessment of patients, especially those with low scores of quality of life. Furthermore, the results reconfirmed psychometric characteristics of the questionnaire observed in other CLD patients populations.

COMMENTS

Background

Chronic liver disease (CLD) has a significant impact on health-related quality of life (HRQoL), and therefore its assessment is widely used as important outcome in clinical trials. The CLD questionnaire (CLDQ) is a specific quality of life instrument designed for patients with liver disease, regardless of the underlining severity and etiology of CLD. Its original version was developed by Younossi *et al* and has demonstrated appropriate validity and reliability.

Research frontiers

The CLDQ has already been cross-culturally adapted and validated into different languages in previously published studies. Up to now, there is no CLD-specific quality of life instruments adapted for Serbian patients. Therefore, the aim of this study was to investigate the validation of the translated and culturally adapted CLDQ questionnaire on a group of Serbian CLD patients.

Innovations and breakthroughs

The Serbian validation of the CLDQ confirmed the 6-domain structure of the original United States version. However, in our investigation the original structure was only partially reproduced. The most prominent changes are related to the fact that the factors "Activity" and "Abdominal symptoms" could not be replicated, and two new domains "Sleep" and "Nutrition" were established Moreover, the domain "Nutrition" has been introduced for the first time. Their results of factors analysis gave the evidence that at list some items from the original version of CLDQ should be allocated or eliminated from the questionnaire because of the multiple loadings.

Applications

The authors' results provide considerable support to the appropriate metric properties of the Serbian version of CLDQ. Therefore, it could be emphasized that the questionnaire might be reliable and valid instrument for indentifying HRQoL among liver disease patients and it can be used by health professionals in their clinical practices to improve assessment of patients, especially those with low scores of quality of life.

Terminology

Cross-cultural adaptation and validation procedures create a version of the original questionnaire in a target language that is conceptually equivalent to the origin instrument and psychometrically valid to allow for data pooling and cross-national comparisons.

Peer review

The manuscript investigated the validation of a CLDQ in Serbian CLD patients. The study is of clinical significance. The manuscript from Popovic *et al* reports the validation of a CLDQ in Serbian patients. Evaluation of health related quality of life is a very relevant issue as life expectancy for several chronic diseases has increased significantly. Adaptation of a preexisting questionnaire instead of proposing an alternative procedure allows comparison with results from other patient communities allowing cross-cultural validations and future refinements. Congratulations on this article which is well written and is a good initiative to better understnd the repercussions of CLD on the quality of life of these patients.

REFERENCES

1 **Glise H**, Wiklund I. Health-related quality of life and gastrointestinal disease. *J Gastroenterol Hepatol* 2002; **17** Suppl: S72-S84 [PMID: 12000595 DOI: 10.1046/j.1440-1746.17.s1.6.x]

2 **Simpson KJ**, Finlayson ND. Clinical evaluation of liver disease. *Baillieres Clin Gastroenterol* 1995; **9**: 639-659 [PMID: 8903798 DOI: 10.1016/0950-3528(95)90054-3]

3 **Younossi ZM**, Guyatt G. Quality-of-life assessments and chronic liver disease. *Am J Gastroenterol* 1998; **93**: 1037-1041 [PMID: 9672326 DOI: 10.1016/S0002-9270(98)00206-8]

4 **Ware JE**, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; **30**: 473-483 [PMID: 1593914 DOI: 10.1097/00005650-199206000-00002]

5 **Younossi ZM**, Guyatt G, Kiwi M, Boparai N, King D. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. *Gut* 1999; **45**: 295-300 [PMID: 10403745 DOI: 10.1136/gut.45.2.295]

6 **Gralnek IM**, Hays RD, Kilbourne A, Rosen HR, Keeffe EB, Artinian L, Kim S, Lazarovici D, Jensen DM, Busuttil RW, Martin P. Development and evaluation of the Liver Disease Quality of Life instrument in persons with advanced, chronic liver disease--the LDQOL 1.0. *Am J Gastroenterol* 2000; **95**: 3552-3565 [PMID: 11151892 DOI: 10.1016/S0002-9270(00)02168-7]

7 **Ware JE**, Bayliss MS, Mannocchia M, Davis GL. Health-related quality of life in chronic hepatitis C: impact of disease and treatment response. The Interventional Therapy Group. *Hepatology* 1999; **30**: 550-555 [PMID: 10421667]

8 **Häuser W**, Schnur M, Steder-Neukamm U, Muthny FA, Grandt D. Validation of the German version of the Chronic Liver Disease Questionnaire. *Eur J Gastroenterol Hepatol* 2004; **16**: 599-606 [PMID: 15167163]

9 **Sobhonslidsuk A**, Silpakit C, Kongsakon R, Satitpornkul P, Sripetch C. Chronic liver disease questionnaire: translation and validation in Thais. *World J Gastroenterol* 2004; **10**: 1954-1957 [PMID: 15222044]

10 **Ferrer M**, Córdoba J, Garin O, Olivé G, Flavià M, Vargas V, Esteban R, Alonso J. Validity of the Spanish version of the Chronic Liver Disease Questionnaire (CLDQ) as a standard outcome for quality of life assessment. *Liver Transpl* 2006; **12**: 95-104 [PMID: 16382456 DOI: 10.1002/lt.20551]

11 **Kollia Z**, Patelarou E, Vivilaki V, Kollia E, Kefou F, Elefsiniotis I, Dourakis SP, Brokalaki H. Translation and validation of the Greek chronic liver disease questionnaire. *World J Gastroenterol* 2010; **16**: 5838-5844 [PMID: 21155005 DOI: 10.3748/wjg.v16.i46.5838]

12 **Mucci S**, Citero Vde A, Gonzalez AM, De Marco MA, Nogueira-Martins LA. [Cross-cultural adaptation of the Chronic Liver Disease Questionnaire (CLDQ) to the Brazilian population]. *Cad Saude Publica* 2010; **26**: 199-205 [PMID: 20209224]

13 **Rucci P**, Taliani G, Cirrincione L, Alberti A, Bartolozzi D, Caporaso N, Colombo M, Coppola R, Chiaramonte M, Craxi A, De Sio I, Floreani AR, Gaeta GB, Persico M, Secchi G, Versace I, Mele A. Validity and reliability of the Italian version of the Chronic Liver Disease Questionnaire (CLDQ-I) for the assessment of health-related quality of life. *Dig Liver Dis* 2005; **37**: 850-860 [PMID: 16221576 DOI: 10.1016/j.dld.2005.02.014]

14 **Sumskiene J**, Sumskas L, Petrauskas D, Kupcinskas L. Disease-specific health-related quality of life and its determinants in liver cirrhosis patients in Lithuania. *World J Gastroenterol* 2006; **12**: 7792-7797 [PMID: 17203522]

15 **Atiq M**, Gill ML, Khokhar N. Quality of life assessment in Pakistani patients with chronic liver disease. *J Pak Med Assoc* 2004; **54**: 113-115 [PMID: 15129867]

16 **Ray I**, Dutta D, Basu P, De BK. Quality of life assessment of patients with chronic liver disease in eastern India using a Bengali translation chronic liver disease questionnaire. *Indian J Gastroenterol* 2010; **29**: 187-195 [PMID: 20740340 DOI: 10.1007/s12664-010-0036-x]

17 **Lam ET**, Lam CL, Lai CL, Yuen MF, Fong DY. Psychometrics of the chronic liver disease questionnaire for Southern Chinese patients with chronic hepatitis B virus infection. *World J Gastroenterol* 2009; **15**: 3288-3297 [PMID: 19598306 DOI: 10.3748/wjg.15.3288]

18 **Wu CH**, Deng QW, Ji XS, Yan LM. Preliminary Use of the CLDQ in Chronic Hepatitis B Patients. *Zhongguo Linchuang Xinlixue Zhazhi* 2003; **11**: 60-62

19 **McCormick PA**. Hepatic Cirrhosis. In: Dooley SJ, Lok SFA, Burroughs KA, Healthcote EJ. Sherlock's Diseases of the liver and billiary system. 12th ed. Oxford: Wiley-Blackwell, 2011: 103-120

20 **Pugh RN**, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646-649 [PMID: 4541913]

21 **Sterling R**, Mattar W, Kwo P. Cirrhosis. In: Conn HF, editor. Conn's current therapy 2009. Philadelphia: Saunders Elsevier, 2009: 496-504

22 **Acquadro C**, Conway K, Hareendran A, Aaronson N. Literature review of methods to translate health-related quality of life questionnaires for use in multinational clinical trials. *Value Health* 2008; **11**: 509-521 [PMID: 18179659 DOI: 10.1111/j.1524-4733.2007.00292.x]

23 **Wild D**, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value Health* 2005; **8**: 94-104 [PMID: 15804318 DOI: 10.1111/j.1524-4733.2005.04054.x]

24 **Schulz KH**, Kroencke S, Ewers H, Schulz H, Younossi ZM. The factorial structure of the Chronic Liver Disease Questionnaire (CLDQ). *Qual Life Res* 2008; **17**: 575-584 [PMID: 18389385 DOI: 10.1007/s11136-008-9332-7]

25 **Younossi ZM**, Boparai N, Price LL, Kiwi ML, McCormick M, Guyatt G. Health-related quality of life in chronic liver disease: the impact of type and severity of disease. *Am J Gastroenterol* 2001; **96**: 2199-2205 [PMID: 11467653 DOI: 10.1016/S0002-9270(01)02519-9]

26 **Younossi ZM**, Kiwi ML, Boparai N, Price LL, Guyatt G. Cholestatic liver diseases and health-related quality of life. *Am J Gastroenterol* 2000; **95**: 497-502 [PMID: 10685757 DOI: 10.1016/S0002-9270(99)00833-3]

27 **Les I**, Doval E, Flavià M, Jacas C, Cárdenas G, Esteban R, Guardia J, Córdoba J. Quality of life in cirrhosis is related to potentially treatable factors. *Eur J Gastroenterol Hepatol* 2010; **22**: 221-227 [PMID: 19794311 DOI: 10.1097/MEG.0b013e3283319975]

28 **Zuberi BF**, Memon AR, Afsar S, Qadeer R, Kumar R. Correlation of quality of life in patients of cirrhosis of liver with etiology and disease severity using disease-specific quality of life questionnaire. *J Ayub Med Coll Abbottabad* 2007; **19**: 7-11 [PMID: 18183709]

29 **Gao R**, Gao F, Li G, Hao JY. Health-related quality of life in chinese patients with chronic liver disease. *Gastroenterol Res Pract* 2012; **2012**: 516140 [PMID: 22701477 DOI: 10.1155/2012/516140]

30 **Kalaitzakis E**, Josefsson A, Björnsson E. Type and etiology of liver cirrhosis are not related to the presence of hepatic encephalopathy or health-related quality of life: a cross-sectional study. *BMC Gastroenterol* 2008; **8**: 46 [PMID: 18922174 DOI: 10.1186/1471-230X-8-46]

31 **Tillmann HL**, Wiese M, Braun Y, Wiegand J, Tenckhoff S, Mössner J, Manns MP, Weissenborn K. Quality of life in patients with various liver diseases: patients with HCV show greater mental impairment, while patients with PBC have greater physical impairment. *J Viral Hepat* 2011; **18**: 252-261 [PMID: 20337922 DOI: 10.1111/j.1365-2893.2010.01292.x]

32 **Dan AA**, Kallman JB, Wheeler A, Younoszai Z, Collantes R, Bondini S, Gerber L, Younossi ZM. Health-related quality of life in patients with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2007; **26**: 815-820 [PMID: 17767465 DOI: 10.1111/j.1365-2036.2007.03426.x]

33 **Younossi Z**, Kallman J, Kincaid J. The effects of HCV infection and management on health-related quality of life. *Hepatology* 2007; **45**: 806-816 [PMID: 17326207 DOI: 10.1002/hep.21565]

34 **Bianchi G**, Loguercio C, Sgarbi D, Abbiati R, Chen CH, Di Pierro M, Disalvo D, Natale S, Marchesini G. Reduced quality of life in patients with chronic hepatitis C: effects of interferon treatment. *Dig Liver Dis* 2000; **32**: 398-405 [PMID: 11030185 DOI: 10.1016/S1590-8658(00)80260-1]

P- Reviewers Chen JL, Corrales FJ, Ferreira CN
S- Editor Gou SX **L- Editor** A **E- Editor** Ma S

百世登
Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

ISSN 1007-9327