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Validation and Performance of Chronic Liver Disease Questionnaire (CLDQ-RO) in the Romanian Population

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ABSTRACT

Background & Aims: Health-related quality of life is an essential part of managing chronically ill patients, including patients with chronic liver disease. Various methods are used to try to assess the quality of life ranging from generic to disease-specific questionnaires. Some of the results may reveal a novel connection to the disease's evolution, which is observed directly by the patient. This study aimed to validate and assess the chronic liver disease questionnaire (CLDQ-RO) performance in the Romanian population.
Methods: A two-phase study was designed. The first phase consisted of linguistic validation of CLDQ-RO (translation and piloting), while in the second phase, the questionnaire was applied to patients with various chronic liver diseases. Statistical validation (reliability, structural, and construct validity) was performed using SPSS v20.0, and statistical significance was considered $p<0.05$.
Results: The CLDQ-RO was applied to 231 patients with chronic liver disease (14.3% with chronic hepatitis, 35.5% with compensated cirrhosis, and 50.2% with decompensated cirrhosis). The questionnaire showed excellent overall reliability (Cronbach's alpha=0.93) and good structural and construct validity, with most of the items in CLDQ-RO fitting in the domains of the original version of the questionnaire. There was a significant decrease in the overall score of the CLDQ-RO with the progression of disease ($p<0.001$), indicating a substantial impact of the decompensation event on health-related quality of life. Regarding the type of decompensation, ascites accurately predicted a lower quality of life ($p=0.004$).
Conclusions: The CLDQ-RO is a valid and disease-specific method for assessing patients' health-related quality of life with liver disease. Among the decompensation events, it seems that ascites seriously impacts the quality of life.

Key words: chronic hepatitis – liver failure – ascites – quality of life – health-related quality of life – patient health questionnaire – the patient-reported outcome measures.

Abbreviations: AA: activity; AS: abdominal symptoms; CCI: Charlson comorbidity index; CLD: chronic liver disease; CLDQ: CLD questionnaire; CLDQ-RO: CLDQ in Romanian population; CP: Child-Pugh; EF: emotional function; FA: fatigue; HCV: hepatitis C virus; HRQOL: health-related quality of life; MELD: model for end-stage liver disease; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; QOL: quality of life; SS: systemic symptoms; WO: worry.

INTRODUCTION

Maintaining a good quality of life (QOL) is crucial in patients with chronic liver disease (CLD) [1]. Health-related quality of life (HRQOL) reflects the physical, emotional, and lifestyle implications of illness. It is recognized as an essential component of CLD where it is negatively influenced by the severity and progressive nature of the disorder [1-3]. Because CLD could affect a younger age group and patients with CLD live a considerable time with their illness, it is crucial to quantify and improve their HRQOL [2, 4].

Questionnaires that reflect HRQOL are a valuable tool in evaluating novel therapies which aim to improve specific symptoms for patients with CLD [2].

There is a great variety of methods that quantify HRQOL. Generic (non-disease specific) questionnaires quantify any chronic disease's physical and mental components [1, 5]. Generic measurement scales have the advantage of being widely used in different conditions, but they lack patients' clinical status sensitivity [2].

Disease-specific scales have been developed to measure the impact of symptoms in specific diseases and should not be applied to other disorders [3]. To correctly assess HRQOL, both generic and disease-specific instruments should be used because they gather complementary information [3].

There are several problems assessing the QOL as the patient-reported outcome, including subjectivity and cross-cultural comparability [6]. To retain the original purpose and ensure comparability of an instrument's results developed in one language or culture, it needs to be adapted, translated, and validated in other countries and cultures [7].

The most commonly used disease-specific questionnaire in CLD is the chronic liver disease questionnaire (CLDQ) [2, 8]. The CLDQ has been translated and validated in a considerable number of languages [9-17]. Also, it has undergone validation in patients infected with hepatitis C virus (HCV), cholestatic liver disease, and non-alcoholic fatty liver disease (NAFLD), including non-alcoholic steatohepatitis (NASH) [3, 18-20].

HRQOL questionnaires reflect disease severity, as it is associated with Child-Pugh (CP) and Model for End-Stage Liver Disease (MELD) scores [21]. In patients with CLD, CLDQ is significantly different between different CP classes [22]. Contrary to the CP score, the MELD score does not reflect QOL in patients awaiting liver transplantation [23].

This study aimed to validate the CLDQ and assess its correlation with liver disease severity in the Romanian population (CLDQ-RO).

METHODS

Chronic liver disease questionnaire

Developed by Younoussi et al. [8], CLDQ is a standardized, self-administered, disease-specific questionnaire, which assesses the HRQOL of patients with CLD. The CLDQ contains 29 questions split into six domains: abdominal symptoms (AS), fatigue (FA), systemic symptoms (SS), activity (AA), emotional function (EF), and worry (WO). All items refer to symptoms in the previous two weeks and are scored from 1 to 7, a higher score corresponding to a better HRQOL. Median scores are reported for each domain and, the overall score is the mean of the six domains in the questionnaire.

Adaptation of CLDQ in Romanian

The linguistic validation process was conducted following a standard method [24]:

1) Forward translation (English to Romanian) was performed independently by two bilingual researchers (V.T. and M.I.) whose mother tongue was Romanian. A Romanian standard version was obtained after the consensual debate.

2) Backward translation was performed by two bilingual independent researchers (A.F. and O.F.). An expert committee, formed of one public health researcher (R.C.), one psychologist, and two hepatologists (B.P. and H.S.), rated the equivalence between the Romanian standard version, backward translation version, and the original to identify differences or ambiguities. Item no. 8 („How much of the time in the last two weeks have you been bothered by having decreased strength?") was poorly rated and modified to maintain clinical relevance.

3) Prefinal version of the translated questionnaire was administered to a piloting sample of 12 patients (who were not included in the validating sample) with CLD, aged 41-67 years: 8 male and 4 females; 3 patients with chronic hepatitis, 3 Child-Pugh A patients, 3 with cirrhosis CP class A patients, 3 with cirrhosis CP class B and 3 with cirrhosis CP class C. Two independent researchers (V.T. and M.I.) interviewed the patients in the piloting sample about the applicability and comprehensibility of the questionnaire.

Finally, the different language-specific modifications were made to the patient's better understanding of CLDQ-RO (Suppl File 1 and available online at https://lirec.ro/cldq-ro/).

Study design and patients

Consecutive patients with various CLD, hospitalized or followed in our tertiary healthcare hepatology clinic (Regional Institute of Gastroenterology and Hepatology in Cluj-Napoca, Romania) between June 2018 and July 2019 were included in this prospective cross-sectional study. Patients with CLD, regardless of the etiology or disease's severity, were included after signing the informed consent. Patients with acute hepatitis and unstable condition, previous admission in the past month, and overt hepatic encephalopathy were excluded. According to the Geneva Universal Declaration of Human Rights, the study was conducted and was approved by the local Ethics Committee (the approval no. 63/14.03.2016).

Examination and measures

To evaluate the severity of the liver disease, CP and sodium MELD scores were calculated [25, 26]. Patients were administered the Romanian CLDQ in a quiet room by a trained examiner. If patients had reading difficulties, the examiner read the questions aloud and wrote the answers for them.

To quantify the possible interference of comorbidities other than a liver disease with the CLDQ scores, a modified Charlson comorbidity index (CCI) was calculated [27]. This index assessed 17 different comorbidities: age, congestive heart failure, peripheral vascular disease, stroke or transient ischemic attack, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, chronic kidney disease, solid tumor, leukemia, lymphoma, and AIDS, with scores ranging from 0 to 37 to offer a 10-year estimated survival. In this study, CCI was calculated adding the values allocated for each comorbidity, except for liver disease.

Statistical analysis

Statistical analyses were performed using SPSS (version 20.0 for Windows; IBM SPSS™, Chicago, IL, USA). To test the normality of distribution for continuous variables, the Shapiro-Wilk test was performed. Continuous variables were expressed as mean ± standard deviation (SD) for normally distributed variables, median [Interquartile range (IQR)] for non-normally distributed variables, and categorical variables as counts and percentages. Categorical variables were analyzed using the Chi-squared test. According to the normality distribution in the compared groups, continuous variables were analyzed using the unpaired t-test or Mann-Whitney U test.

The scores of the CLDQ-RO were presented as mean ± SD. The questionnaire's reliability was estimated by the internal consistency, using the Cronbach's alpha coefficient, which analyses how well a test measures what it should (i.e., QOL in liver disease) [28]. While a Cronbach's alpha coefficient >0.9 is desirable, values >0.7 represent acceptable reliability. The structural validity of the questionnaire was assessed with factor analysis. This was used to identify the domains of the CLDQ-RO. Exploratory factor analysis (principal component analysis with varimax rotation) was used, and factors (domains) were selected for a maximum explained variance at an eigenvalue ≥1, as previously reported in the literature [12].

Construct validity was assessed in relation to CP and MELD scores and was compared to the US original study and German validation study [8, 10]. The German validation study was considered based on European origin, comparable sample size, and disease severity. To assess the status of HRQOL with the progression of liver disease, median scores for each group (according to CP classification, by decompensation status or type) were calculated and compared using Kurskal-Wallis tests with post-hoc analyses. Correlations between domains/overall scores and the CP and MELD scores, respectively, were assessed using Spearman's coefficients. The statistical significance threshold was considered for $p<0.05$.

RESULTS

Patients' characteristics

Two hundred thirty-one patients were enrolled in the study, after excluding 24 patients for refusal to consent, 12 patients for severe acute hepatitis within the past month, and 5 patients for not answering all the questionnaire items. The mean age was 62±10.12 years, 140 (60.6%) being males. The etiology for liver disease was alcohol in 107 (46.3%) patients, viral in 96 (41.6%), and other in 28 (12.1%) (Table I). Chronic liver disease was distributed as follows: chronic hepatitis was

Table I. Demographic and clinical characteristics of patients

			Cirrhosis	
	All patients (N = 231)	Chronic hepatitis (N=33)	Compensated (N = 82)	Decompensated (N= 116)
Age, mean ± SD	62±10.12	64±10.36	63±9.06	60±10.51#
Gender (males), n(%)	140 (60.6%)	12 (33.3%)*	47(57.3%)	81 (69.8%)
Etiology, n (%) *,#				
Alcohol	107 (46.3%)	2 (6%)	28 (34.1%)	77 (66.4%)
Viral	96 (41.6%)	25 (75.8%)	46 (56.1%)	25 (21.5%)
Other	28 (12.1%)	6 (18.2%)	8 (9.8%)	14 (12.1%)
Blood tests, median (IQR)				
Sodium (mEq/l)	139 (5)	140 (4)*	140 (4)	137 (7)#
Creatinine (mg/dl)	0.78 (0.36)	0.72 (0.3)	0.74 (0.24)	0.83 (0.43)#
Hemoglobin (g/dl)	11.9 (4.1)	14.2 (1.67)*	13.4 (3.5)	10.2 (3.45)#
Platlets (10^3/μl)	113 (106)	229 (109)*	114 (93)	94 (84)#
INR	1.4 (0.57)	1.0 (0.16)*	1.22 (1.47)	1.61 (0.5)#
Total Bilirubin (mg/dl)	1.4 (2.35)	0.7 (0.45)*	1.1 (1.05)	2.4 (3.05)#
AST (UI/l)	42 (42)	28.5 (18)*	38 (32)	53 (61)#
ALT (UI/l)	27 (29)	28.5 (30)	26 (28)	28 (30)
Albumin (mg/dl)	3.3 (1.3)	4.3 (0.3)*	3.9 (0.75)	2.9 (0.7)#
Disease severity, n (%) #				
Child-Turcotte-Pugh A	70 (30.3%)	-	60 (73.2%)	10 (8.6%)
Child-Turcotte-Pugh B	70 (30.3%)	-	20 (24.4 %)	50 (43.1%)
Child-Turcotte-Pugh C	58 (25.1%)	-	2 (2.4%)	56 (48.3%)
Sodium-MELD, median (IQR)	-	-	10 (6)	17.5 (10)#
Treatment, n (%)				
Diuretics	-	-	12 (14.6%)	65 (56%)#
Betablockers	-	-	32 (39%)	56 (48.3%)
Lactulose	-	-	14 (17.1%)	56 (48.3%)#
Charlson Comorbidity Index, median (IQR)	3 (3)	3 (3)	3 (2)	2.5 (3)
HCC (BCLC 0/A/B/C/D), n	1/9/12/1/5	0/2/1/0/0	1/4/9/0/3	0/3/2/1/2

*$p< 0.05$, from Chi-squared, T-tests (normally distributed variables) or Mann-Whitney tests (non-normally distributed variables) used for comparison between hepatitis and cirrhosis groups. #$p<0.05$, from Chi squared, T tests (normally distributed variables) or Mann-Whitney tests (non-normally distributed variables) used for comparison between compensated and decompensated subgroups. BCLC: Barcelona-Clinic Liver-Cancer Staging System; HCC: hepatocellular carcinoma.

Table II. Spearman's correlation coefficients between Child Pugh, MELD and modified Charlson comorbidity index scores with the scales of the CLDQ-RO

Domains	Child-Pugh (Spearman's rho)	MELD (Spearman's rho)	Modified Charlson comorbidity index (Spearman's rho)
Abdominal Symptoms	-0.29**	-0.17*	0.026
Fatigue	-0.30**	-0.27**	-0.052
Systemic Symptoms	-0.22*	-0.18*	-0.085
Activity	-0.15*	-0.14	0.041
Emotional Function	-0.19**	-0.12	0.023
Worry	-0.16**	-0.16	0.092
Overall	-0.26**	-0.18*	0.025

*p<0.05 , **p<0.01. CLDO-RO: chronic liver disease questionnaire in Romanian population; MELD: model for end-stage liver disease; .

present in 33 (14.3%), compensated cirrhosis in 82 (35.5%), and decompensated cirrhosis in 116 (50.2%). Among the compensated patients, 14 (7.1%) had at least one previous decompensation episode. Of the decompensated patients, 45 (22.7%) were at the first episode of decompensation, and 71 (35.9%) had had multiple episodes before inclusion. Twenty-five (12.6%) cirrhotic patients had hepatocellular carcinoma (Table I). The type of decompensation at inclusion was only ascites in 53 (45.7%) patients, only variceal bleeding in 40 (35.5%), and 23 (19.8%) patients had at least two types of decompensation (one of them being ascites). In the cirrhosis group, 77 patients (38.9%) were under diuretic treatment, 88 patients (44.4%) under beta-blockers, and 70 patients (35.4%) under lactulose. Patients who received treatment with lactulose had an overall poorer QOL compared to those who did not receive lactulose (p=0.026), affecting abdominal symptoms (p=0.004), fatigue (p=0.05), and activity (p=0.048). When we analyzed eventual comorbidities' influence on QOL, we found no correlation between the CCI and the CLDQ-RO different domains (Table II). Also, the CCI was not different between different groups (p>0.05) (Table II).

Validation of the questionnaire's results

The scores distribution and reliability of CLDQ-RO are presented in Table III. Most patients completed the questionnaire independently, while only 19% needed assistance from the interviewer. Mean scores of the CLDQ-RO varied between 3.77 to 4.68 across the scale. The overall reliability calculated as Cronbach's alpha coefficient was 0.93, and it was >0.7 for 4 out of 6 domains (Table III). The theoretical (from 1 to 7) and observed ranges matched most of the scores, and the percentages of floor and ceiling effects were below 10%.

Preliminary analysis for exploratory factor analysis included Kaiser-Meyer-Olkin measure of sampling adequacy (KMO=0.91) and Bartlett's test of sphericity (p < 0.001). The exploratory factor analysis revealed six factors (Eigenvalue > 1) and total variance explained of 61%. Most of the items in the CLDQ-RO matched 5 out of 6 domains of the original version: AS (2/3), FA (5/5), AA (2/3), EF (5/8), WO (3/3). Items in Factor 3 overlapped between 2 domains (abdominal symptoms and systemic symptoms) of the original version (Supplement Table I). There were two items („Feeling depressed" and „Problems concentrating") which loaded heavily on factor 5 (mental status).

Liver disease severity and CLDQ-RO score

According to CP and MELD scores, there is a good/fair correlation between CLDQ-RO and liver disease stage (Table II). All scales correlated significantly with CP and MELD scores, except for EF for the latter. Median scores for each severity stage of the liver disease (hepatitis, Child-Pugh class A, Child-Pugh class B, Child-Pugh class C) are presented comparatively in Fig. 1. There were significant differences between subgroups regarding AS (p<0.001), FA (p<0.001), SS (p=0.001), EF (p=0.049), WO (p=0.015) and overall score (p<0.001). The post-hoc comparison revealed significant differences between chronic hepatitis and CP class C in 3 domains (AS, FA, WO) and the overall score; CP class A vs. CP

Table III. Scores distribution and reliability of the CLDQ-RO

Scales	Median	Interquartile range (IQR)	Observed range	Floor* (%)	Ceiling* (%)	Cronbach's alpha
Overall	4.24	1.72	1.86-6.79	0	0	0.93
Abdominal symptoms	4.67	2.33	1-7	9.5	2.16	0.75
Fatigue	3.80	2.00	1-7	2.16	0	0.86
Systemic symptoms	4.80	1.80	1.20-7	2.60	0	0.64
Activity	4.67	2.33	1-7	7.36	0.87	0.65
Emotional function	4.38	2.00	1.50-7	0.43	0	0.86
Worry	4.40	2.60	1-7	6.93	3.03	0.85

CLDO-RO: chronic liver disease questionnaire in Romanian population.

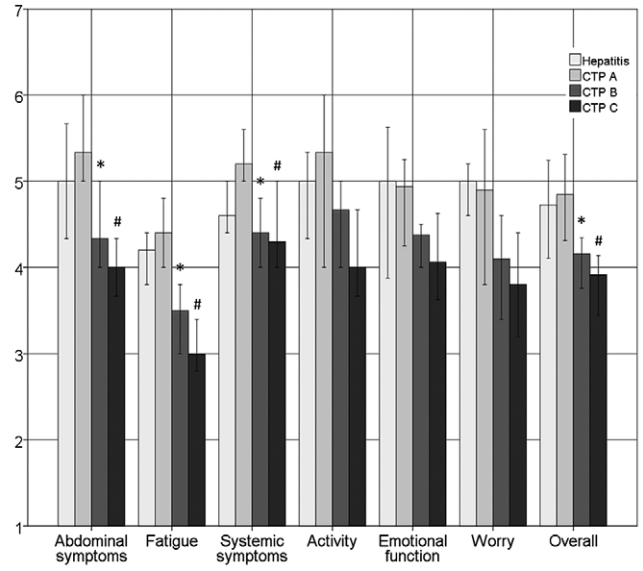

Fig. 1. Chronic liver disease questionnaire in Romanian population scores of each subgroup of patients classified by Child-Pugh classification. Each bar shows the median score (95% CI) for the following stages of liver disease: hepatitis (N=33), CP A (N=70), CP B (N=70) and CP C (N=58). *p<0.05 – group CP A vs group CP B; #- P<0.05- group CP A vs CP C.

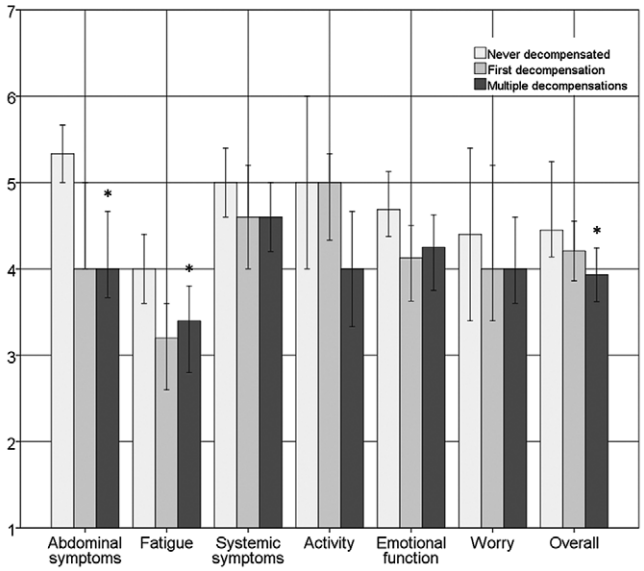

Fig. 2. Scores of subgroups of cirrhotic patients classified by status of decompensation. Each bar shows the median score (95% CI) for patients: never decompensated (N=68), at first decompensation (N=45) and with multiple decompensations at admission (N=71). *p<0.05 – pairwise comparison between never decompensated vs multiple decompensation.

class C and, CP class A vs. CP class B differed in 3 domains (AS, FA, SS) and the overall score (Fig. 1). No significant differences were observed between chronic hepatitis and CP class A or CP class B and CP class C groups.

Type of decompensation and CLDQ-RO score

The post hoc analysis indicated significant differences when comparing: the groups of never decompensated vs. multiple decompensations in 2 domains (AS and FA) and overall (Fig. 2). According to the type of decompensation, there were significant differences when comparing patients with no decompensation vs. patients with ascites regarding AS (p<0.001), FA (p=0.046) and overall score (p=0.041), and patients with no decompensation vs. multiple in AS (p=0.008) and FA (p=0.047) (Fig. 3).

A linear regression analysis was performed, including CLDQ-RO overall score as a dependent variable and the presence of ascites, variceal bleeding, and hepatocellular carcinoma as covariates (ANOVA, p=0.02). Ascites was the only variable (β=-0.48, p=0.004) to impact the CLDQ-RO overall score significantly.

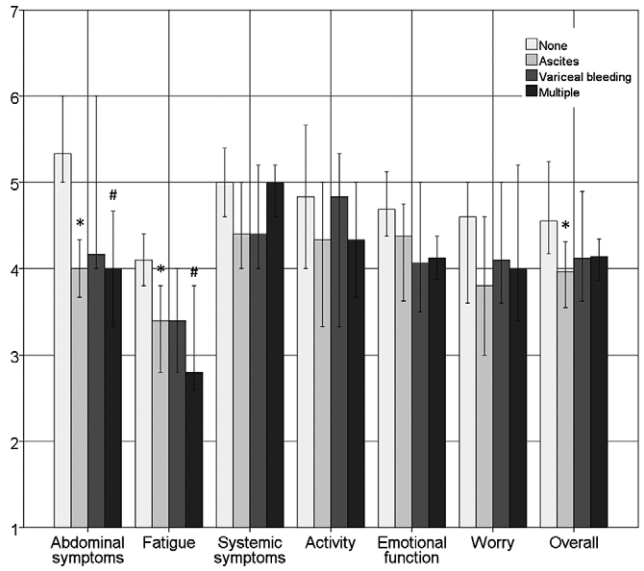

Fig. 3. Scores of subgroups of cirrhotic patients according to the type of decompensation. Each bar shows the median score (95% CI) for the following type of decompensation: none (N=82), ascites (N=53), variceal bleeding (N=40) and multiple (N=23). *p<0.05- compensated group vs ascites group; #-p<0.05- compensated group vs multiple decompensation group.

DISCUSSION

This study, conducted on a large cohort, validates the first disease-specific instrument for reporting the QOL in patients with CLD in Romania. The CLDQ-RO identified a decrease in the HRQOL with the liver disease progression and parallel to the ascites occurrence in cirrhotic patients.

Liver cirrhosis is a progressive disease marked by severe complications associated with increased mortality. Thus, it is likely to have a substantial negative impact on the daily QOL [1]. The ultimate goal of managing patients with liver cirrhosis is to extend survival with a poor quality of living and improve and maintain a reasonably good QOL [4].

The CLDQ-RO was easily administered (less than 5 minutes) and demonstrated a high response rate (>90%). Internal consistency of the construct ranged from good (for most domains) to excellent (for the entire construct). Only two scales (SS and AA) reached acceptable reliability. The distribution of responses fitted well in the original 7 points Likert scale. These results are congruent with the original US version of the questionnaire [8].

Structural validity assessed by exploratory factor analysis matched the 6-factor model of the original construct. Although

most of the items fitted in the designated domains, there was an overlap between items in the AS and SS domains, indicating poor discrimination between the two. This situation could be explained by assuming that patients did not locate the abdominal area too well. Also, two items („Depressed" and „Problems concentrating") seemed to form a new factor. Cultural differences might explain the problems elicited by the item „depressed," which is not widely known or used. To preserve the original construct, this item was kept in the final version of the CLDQ-RO.

A comparison between CLDQ-RO median scores and those presented in the original US and the German version's validation study is shown in Supplementary File (Table II). Significant differences were observed mainly in the scores of patients with chronic hepatitis, who scored lower in the Romanian cohort. Also, there were differences between the CLDQ-RO and the German version in CP class B patients, but no differences with the original US version.

Using the modified CCI, we proved that CLDQ-RO is truly a disease-specific questionnaire, excluding numerous comorbidities other than liver disease, as confounding factors for decreasing the HRQOL.

Liver disease severity assessed by CP and MELD scores correlated with the worsening of the HRQOL. Looking at similar data from the original US and German validation studies, a similar pattern was observed [8, 10]. While most of the scores were similar, it seems the non-cirrhotic patients in our cohort reported a lower QOL than in the other two studies. These differences might be explained by a predominance of female patients with viral etiology in the chronic hepatitis group. While there were fewer patients in this group, non-cirrhotic patients might be more sensitive and pay more attention to symptoms than cirrhotic ones and suffer from increased anxiety due to bureaucratic delays in the treatment process (especially for HCV).

Progression of liver disease and especially the appearance of decompensation abruptly decreases patients' well-being. These findings are supported by a recent meta-analysis of 7 studies using CLDQ to assess HRQOL [4]. The study reported significant differences between groups in the questionnaire's global score to evaluate the differences between CP classes or compensated and decompensated status of the patients with cirrhosis.

Moreover, in terms of decompensation, ascites was a key factor in worsening cirrhotic patients' QOL. Ascites was identified as an independent predictor of poor QOL compared to variceal bleeding or hepatocellular carcinoma, which seem to weigh less. This is also in concordance with the clinical course of the disease. Nowadays, variceal bleeding and hepatocellular carcinoma may be relatively well controlled by efficient treatment, while ascites is still marked by increased mortality [29]. Tsai et al. [30] conducted a study on patients with liver cirrhosis who did not have hepatocellular carcinoma and reported a high frequency of abdominal symptoms and fluid retention symptoms, with symptoms of distention/bloating ranking first and ascites ranking third among responses [30].

Our study has several weaknesses. First, patients were included from a single tertiary center, which might have led to selected patients. Second, the questionnaire was applied only once, which prevented us from the running of test re-test relatively analysis. Third, a lower number of patients with hepatitis compared to cirrhotic patients were included. This might explain why no significant difference between chronic hepatitis patients and CP class A patients was observed.

One strength of this study is the relatively equal distribution between etiologies and different stages of liver disease. Another particularity of the study was the inclusion of a relatively large number of decompensated patients (half of the patients), which permitted subgroup analyses according to the type of decompensation. Also, a rather large number of patients with hepatocellular carcinoma were included in the analyses.

CONCLUSION

The Romanian chronic liver disease questionnaire (CLDQ-RO) is a disease-specific instrument with a high response rate, good reliability, and good construct validity for the assessment of HRQOL in Romanian patients with CLD. CLDQ-RO proved to assess HRQOL among different stages of liver disease properly. The appearance of decompensation and, particularly ascites, is a pivotal moment in the course of liver disease, determining an abrupt decrease in patients' QOL.

Conflicts of interest: None to declare.

Authors' contributions: V.T., M.I., O.F. and A.F were responsible for the design of the study. V.T., M.I., A.F. and O.F. performed the linguistic validation. V.T., M.I., A.F., B.O. and T.R. collected the data. V.T. performed the statistical analysis, interpretation of results and drafted the manuscript. B.P., H.S. and R.C. supervised the conduction of the study and provided critical feedback. All the authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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