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Quality of Life Issues for Patients with Cirrhosis

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In recent years, evaluating the impact of chronic liver disease and the success of its treatment has expanded beyond only measuring clinical outcomes. These assessments now include measuring patients' perspective of their disease, and the effect treatment has on their quality of life [1–13]. In this context, health-related quality of life (HRQOL) has become a very important outcome for measuring patient's perspective about their health and treatment.

HRQOL falls under the broader category of quality of life which accounts for many other aspects of a person's life besides simply health, including the influence of environment, freedom, economy as well as aspects of their culture, values, and spirituality [2, 5, 6, 14, 17, 18, 19]. Therefore, HRQOL has been very succinctly defined as a broad multidimensional concept that includes self-reported measures of physical and mental health as well as the ability to be socially active (social well-being) [1–13].

Although HRQOL and patient-reported outcomes (PROs) can be interchangeable terms, PROs may include other outcomes reported by and important to patients. Alternative terms that are commonly used to define a patient's perspective (self-report) of their physical, mental, and social functioning include health status and well-being [20–22]. In general, HRQOL tools or instruments are divided into general measures (generic instruments) and disease-specific instruments [1–24]. In the following paragraphs, we describe some of the most common generic and disease-specific instruments used to measure HRQOL in patients with cirrhosis.

Tools Used to Measure HRQOL (Tables 34.1 and 34.2)

The Short Form-36 Version 2 (SF-36v2)

The Short Form-36 version 2 (SF-36v2) is a widely used instrument for HRQOL evaluation [6]. It assesses eight HRQOL scales (ranging 0–100 with higher values corresponding to a better health status): physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). The two summary scores summarize the physical and mental health components of the SF-36: the Physical Component Summary score (PCS) and Mental Component Summary score (MCS). The SF-36 scales and summary scores are calculated

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Table 34.1 Health-related quality of life tools for patients with chronic hepatitis C virus

Name of tool	Health domains measured	Number of items	Strengths and limitations	Generic or disease specific	How administered
SF-36	Eight domains measuring functional health and well-being: general health, vitality, role emotional, role physical, social well-being, mental health, and physical functioning. Two summary scales of physical composite and mental composite scores	36 items	Most widely used tool worldwide. Established population norms for comparison. It is generic and disease specific. Asks for recall of how the patient is feeling over past week/month	Generic-general health	Self-administered or can be done in person or over the telephone. Takes 5 to 10 minutes to complete
Sickness impact profile (SIP), also the SIP-68	Investigates a change in behavior as a consequence of illness, Covers 12 categories of daily living sleep and rest, eating, work, home management, ambulation, mobility, body care and movement, social integration, alertness behavior, emotional behavior and communication	136 items/68 items	Items are scored on a numeric scale with higher scores reflecting greater dysfunction. An aggregate psychosocial score is derived from four categories and an aggregate physical score from three categories	Generic-general health	Paper and pencil takes approximately 30–40 min for the full survey and 15–20 min of the SIP-68
Chronic liver disease questionnaire (CLDQ) and CLDQ-HCV	The CLDQ has six domains (abdominal symptoms, activity, emotional function, fatigue, systemic symptoms, and worry). CLDQ applies to all patients with chronic liver disease CLDQ-HCV is specific for HCV patients and measures four domains: activity and energy, emotional, worry, systemic. CLDQ-HCV assesses HRQOL in patients with HCV	Both CLDQ and CLDQ-HCV have 29 items with scores ranging from 1 to 7; higher scores indicate better health-related quality of life (HQRL)	Widely used and validated tool; translated into many languages—see website	Disease specific	Paper and pencil: self-administered Electronic version: e-CLDQ
Post–liver transplant quality of life (pLTQ)	8 domains which include: emotional function, worry, medications, physical function, healthcare, graft rejection concern, financial, pain	32 items with the first 28 items scored on a scale of 1–7 and higher scores reflect better HRQOL	Stable over time but a relatively new measurement	LT	Self-administered

Table 34.1 (continued)

Name of tool	Health domains measured	Number of items	Strengths and limitations	Generic or disease specific	How administered
Liver disease quality of life (LDQOL)—short form	9 domains and measures symptoms of liver disease and the effects of liver disease. Shown to correlate highly with SF-36 scores, symptom severity, disability, days and global health	36 items	Translated into several languages to include Spanish and Korean	Disease specific	Self-administered
Hepatitis quality of life questionnaire (HQLQv2)	Two-part survey to assess functional health and well-being of patients with chronic HCV, Includes the SF-36v2® Health Survey (36 questions) and 15 additional questions which measure generic health concepts relevant to assessing the impact of hepatitis (health distress, positive well-being) and disease-specific concepts (e.g., hepatitis-specific functional limitations, hepatitis-specific distress)	51 items	Is available in a fixed form or interview (telephone/face-to-face) format	Disease specific	It can be administered in clinical settings, at home or in other locations
Liver disease symptom index 2.0 (LDSI 2.0)	Measures symptom severity and symptom hindrance in the past week	18 items	Measures symptom severity and symptom hindrance in the past week. Considered an additive tool when researching HRQOL with the liver disease population. Responses are on a five-point scale from “not at all hindered” to “hindered a high extent.” Translated into several languages	Disease specific	Self-administered
Multidimensional fatigue inventory	Measures that cover: general fatigue, physical, fatigue, mental fatigue, reduced motivation and reduced anxiety	20 items use a 5-point Likert scale from 1 to 5 (yes that is true to no that is not true). Higher scores mean less fatigue	Valid and reliable tool	Generic for fatigue	Self-report

Table 34.1 (continued)

Name of tool	Health domains measured	Number of items	Strengths and limitations	Generic or disease specific	How administered
Multidimensional fatigue symptom inventory- short form (MFSI-SF)	Assesses global, somatic, affective, cognitive, and behavioral manifestations of fatigue	30 items	Shorter version of the original 83 items—Multidimensional fatigue symptom inventory. Takes less time but maintains the integrity of original survey	Generic	Self-report
Quality well-being scale	Combines preference-weighted values for symptoms and functioning. Symptoms are assessed by questions that ask about the presence or absence of different symptoms (yes or no). Functioning is assessed by a series of questions designed to record functional limitations over the previous three days, within three separate domains (mobility, physical activity, and social activity). The four domain scores are combined into a total score that provides a numerical point-in-time expression of well-being that ranges from 0 for death to 1 for asymptomatic optimum functioning	3 pages—58 questions	Can be self-administered, used in a face-to-face interview, answered by proxy and administered online	Generic	Self-administered (see strengths and limitations)
Health utilities index (HUI)	A generic multi-attribute preference-based measure of health status and HRQOL	HU13 consists of eight attributes/dimensions: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Scores range from highly impaired to normal	Can be used in clinical studies, population-based surveys, in the estimation of quality-adjusted life years and economic analysis	Generic	Self-administered then scored by investigator

Table 34.1 (continued)

Name of tool	Health domains measured	Number of items	Strengths and limitations	Generic or disease specific	How administered
Short form-6D (SF-6D)	To calculate the true value of a treatment, the scores from the SF-36v2$^{®}$ or the SF-12v2$^{®}$ Health Surveys can be converted into a utility index, called the SF-6D, which considers not only how many years a medical intervention can add to a patient's life, but also the quality of that life	–	Get a better understanding of a patient's real preference for a treatment. Helps select the best course of action for a patient. Compares two interventions based on quality-adjusted life years and cost. Assesses the cost effectiveness of a medical product, procedure, or health and wellness program. Allocates health-care resources most efficiently	Generic for quality of years added. Used for the economic impact of a disease	The SF form is self-administered then the investigator will convert the scores to a utility score
Euro-QOL (EQ-5D)	A standardized instrument for use as a measure of health outcome	Measures five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels: no problems, some problems, extreme problems. Incorporates a visual analog scale to obtain the respondent's self-rated health on a vertical, visual analog scale where endpoints are labeled 'best imaginable health sate' and 'worst imaginable health state	Cognitively simple, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire	Generic	Self-completion by respondents and is ideally suited for use in postal surveys, in clinics and face-to-face interviews

HCV hepatitis C virus, *HRQOL* health-related quality of life, *LT* liver transplant, *HU13* health utilities index mark 3

Table 34.2 URLs for health-related quality of life tools used for patients infected with the hepatitis C virus (www.cldq.org)

Name of tool	Short name	URL	URL2
SF-36 (ware)	SF36	http://www.sf-36.org/tools/SF36.shtml#VERS	–
Sickness impact profile (SIP) also the SIP-68	SIP/SIP-68	http://www.outcomes-trust.org/instruments.htm	http://www.scirepro-ject.com/outcome-
Chronic liver disease questionnaire (CLDQ)	CLDQ	https://www.cldq.org/	–
Post-liver transplant quality of life (pLTQ)	pLTQ	http://onlinelibrary.wiley.com/doi/10.1002/lt.22267/full	–
Liver disease quality of life (LDQOL)- short form	LDQOL SF	http://www.ncbi.nlm.nih.gov/pubmed/11151892	–
Hepatitis quality of life questionnaire (HQLQv2)	HQLQv2	http://www.qualitymetric.com/WhatWeDo/DiseasespecificHealthSurveys/HepatitisQualityofLifeQuestionnaireHQLQv2/tabid/193/Default.aspx	–
Liver disease symptom index 2.0 (LDSI 2.0)	LDS!2.0	http://www.ncbi.nlm.nih.gov/pubmed/15503842	–
Multidimensional fatigue inventory	Multidimensional fatigue inventory	http://www.ncbi.nlm.nih.gov/pubmed/7636775	–
Multidimensional fatigue symptom inventory-short form (MFSI-SF)	MFSI-SF	http://www.cas.usf.edu/~jacobsen/HANDOUT.FSI&MFSI.pdf	–
Quality well-being scale	Quality well-being scale	http://www.healthmeasurement.org/pub_pdfs/_QUESTIONNAIRE_QWB-SA,%20version%201.04.pdf	–
Health utilities index (HUI)	HUI	www.researchgate.net/utilityhealth_utilities_index/d9	–
Short form 6D (SF-6D)	SF-6D	–	–
Euro-QOL (EQ-5D)	EQ-5D	www.euroqol.org	–

URL uniform resource locator

using the QualityMetric Health Outcomes Scoring Software 4.5 (Lincoln, RI, USA) and the 2009 US population norms [6].

Sickness Impact Profile (SIP)

The SIP is a generic health measurement tool that is used to investigate a change in behavior as a consequence of illness. It contains a 136 items divided by 12 categories covering activities of daily living (sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care and movement, social interaction, alertness behavior, emotional behavior, and communication). Items are scored on a numeric scale with higher scores reflecting greater dysfunction. In addition to individual category scores, an aggregate psychosocial score is derived from four categories, and an aggregate physical score is calculated from three categories [5, 12, 14].

Chronic Liver Disease Questionnaire (CLDQ)

The CLDQ is another widely used and validated HRQOL instrument developed specifically for assessment of HRQOL in chronic liver disease patients [7, 13, 14, 18]. It includes 29 items and 6 HRQOL scales: fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry. CLDQ has a summary score, CLDQ total score [7]. These scales are averaged to the total CLDQ score that ranges 1–7 with higher values representing better HRQOL [7, 17, 18]. In addition to CLDQ, a hepatitis C-specific version was also developed and validated (CLDQ-hepatitis C virus (HCV)). CLDQ-HCV consists of four scales that measure: activity/energy (AE), emotion (EM), worry (WO), and systemic (SY) as well as a CLDQ-HCV total score (CLDQ-HCV Tot) [25]. Both CLDQ and CLDQ-HCV are now widely used throughout the world to assess HRQOL for patients with liver disease and HCV [15, 20, 26–32].

Liver Disease Quality of Life (LDQOL)

The short form of liver disease quality of life instrument (SF-LDQOL) is a questionnaire that comprises 36 disease-targeted items representing nine domains, symptoms of liver disease, and the effects of liver disease. The SF-LDQOL has been shown to correlate highly with SF-36 scores, symptom severity, disability days, and global health [6, 14].

Post-Liver Transplant Quality of Life (pLTQ) Instrument

The pLTQ instrument is a relatively new measurement tool developed to measure health-related quality of life in posttransplant patients. After 12 liver experts and transplant recipients were interviewed, a thorough literature search was conducted, and factor analysis and testing in more than 200 liver transplant (LT) patients was performed, the pLTQ was formulated. The tool includes 32 items which covers eight domains (emotional function, worry, medications, physical function, health care, graft rejection concern, financial, and pain) and has been determined to be stable over time [35–39].

Hepatitis Quality of Life Questionnaire (HQLQv2)

The Hepatitis Quality of Life Questionnaire™ Version 2 (HQLQv2™) is a two-part survey designed to assess the functional health and well-being of patients with chronic hepatitis C. It includes the SF-36v2® Health Survey and 15 additional questions that measure other generic health concepts particularly relevant in assessing the impact of hepatitis (e.g., health distress, positive well-being), and disease-specific concepts (e.g., hepatitis-specific functional limitations, hepatitis-specific distress) [5, 14].

The HQLQv2 was developed to help patients and clinicians monitor the effects of hepatitis C and its treatment as well as screening and monitoring changes in disease impact. The HQLQv2 is available in a fixed form or interview (telephone/face-to-face) format. It can be administered in clinical settings, at home, or in other locations. The HQLQv2 is intended for adults 18 years of age and older, and is available in multiple language translations with a standard 4-week recall period [5, 14].

Liver Disease Symptom Index 2.0 (LDSI 2.0)

The Liver Disease Symptom Index 2.0 (LDSI) developed in a Dutch cohort of patients includes 18 items that measure symptom severity and symptom hindrance in the past week [5, 11, 14] Through convergent and divergent construct validity, the investigators determined that the information from the LDSI provided complementary information to the information gleaned from the SF-36 and the multidimensional fatigue inventory (MFI)-20 and it should be considered an additive tool when researching HRQOL in a population with liver disease [5, 11, 14].

Quality of Well-Being Scale (QWB)

The QWB-self-administered (SA) combines preference-weighted values for symptoms and functioning. Symptoms are assessed by questions that ask about the presence or absence of different symptoms or conditions. Functioning is assessed by a series of questions designed to record functional limitations over the previous 3 days, within three separate domains (mobility, physical activity, and social activity). The four domain scores are combined into a total score that provides a numerical point-in-time expression of well-being that ranges from zero (0) for death to one (1.0) for asymptomatic optimum functioning [5, 14].

Health Status/Utility Assessment (The Health Utilities Index (HUI), EuroQol-5D (EQ-5D), and the Short Form-6D (SF-6D))

One of the most important applications for quality of life assessment is in economic analysis. In fact, outcomes, such as life years gained or lost by an intervention, are usually qualified in terms of the quality-adjusted years of life gained or lost. Health utility assessment is the method used to obtain quality-of-life adjustments. The direct assessment of health utilities uses the technique of time trade-off or standard gamble, while the indirect assessment utilizes questionnaires designed to assess health status. Some of the important questionnaires that are available to assess health utilities are discussed below [5, 14].

To calculate the true value of a treatment, the scores from the SF-36v2® or the SF-12v2® Health Surveys can be converted into a utility index, called the SF-6D, which considers not only how many years a medical intervention can add to a patient's life, but also the quality of that life. The SF-6D can then be used to obtain a better understanding of a patient's real preference for a treatment, select the best course of action for a patient, compare two interventions based on quality-adjusted life years (QALYs) and cost, assess the cost-effectiveness of a medical product, procedure, or health and wellness program, and allocate health-care resources most efficiently [5, 6].

The approach most commonly used in the European community is the EQ-5D, which has been advanced by a collaborative group from Western Europe known as the EuroQol group. This group, originally formed in 1987, comprises a network of international, multidisciplinary researchers, originally from seven centers in England, Finland, the Netherlands, Norway, and Sweden. More recently, researchers from Spain as well as researchers from Germany, Greece, Canada, the USA, and Japan have joined the group. The intention of this effort is to develop a generic currency for health that could be used commonly across Europe. The original version of the EuroQol had 14 health states in six different domains. More current versions of the EuroQol, the EQ-5D, are now in use in a substantial number of clinical and population studies [5, 14].

HRQOL Findings in Patients with Chronic Liver Disease

Patients with chronic liver disease (CLD) report significant impairment of their HRQOL [1–22]. Although this impairment is applicable to most patients with CLD, patients with HCV, primary biliary cirrhosis (PBC) and non-alcoholic fatty liver disease (NAFLD) seem to have more impairment [1, 2]. In fact, several recent studies have reported that patients with HCV have a dramatically reduced HRQOL due to extreme fatigue and depression [2, 7, 18, 19, 25]. A number of studies of patients living with PBC report impairment of the physical health component related to fatigue. In fact, fatigue in PBC is so overwhelming that some have questioned whether it should be an indication for LT in this group of patients [39]. Carbone and group found that LT improved the HRQOL in patients with PBC; however, fatigue, though improved, persisted 2 years posttransplant calling into question the appropriateness of this symptom as an indication for transplant given the scarcity of donated organs [40]. Patients with cirrhosis have also demonstrated a significantly reduced HRQOL related to numerous clinical and demographic features in addition to suffering from depression and anxiety [1–25].

Specific Studies of HRQOL in Cirrhotics

In addition to etiology of CLD, severity of liver disease accounts for the majority of impairment in patients' HRQOL. There are multiple publications suggesting that patients with compensated cirrhosis have more impairment than CLD patients without significant hepatic fibrosis. Worsening hepatic dysfunction in patients with cirrhosis, as documented by higher model for end-stage liver disease (MELD) scores, and the development of complications, such as ascites and hepatic encephalopathy, account for severe impairment of HRQOL [2, 3, 4, 9, 17, 20, 23, 30, 40–44].

When compared with the national norm for healthy subjects, HRQOL, as measured by SF-36 [6], shows severe impairment of HRQOL in patients with cirrhosis. In fact, this impairment occurs in every aspect of their well-being [17, 19, 45]. Marchesini and colleagues assessed HRQOL using 2 generic HRQOL tools (SF-36 and the Nottingham Health Profile) in a large cohort of Italian patients with cirrhosis and compared their results to norm-based results [46]. They found that the cirrhotic group had significantly lower HRQOL than the Italian population norms as a result of muscle cramps and pruritus associated with cirrhosis. It was noted that clinicians' and patients' perceptions of the importance of certain symptoms on well-being may differ [18]. Therefore, it is imperative that clinicians spend sufficient time to determine what is causing the most problems for patients so that an appropriate intervention plan will be developed [18].

Other investigators have explored the role of HRQOL in predicting mortality. Kenwal and associates administered the SF-LDQOL questionnaire to 156 patients who were awaiting LT [29, 47]. Using Cox proportional hazard modeling to measure the independent effect of baseline HRQOL on survival after adjusting for MELD scores and other covariates, they found that higher-baseline HRQOL predicted lower mortality (hazard ratio, 0.96; 95 % confidence interval, 0.94–0.99). Specifically, for each one-point increase in HRQOL, there was a 4 % decrease in mortality. These results did not change after adjusting for MELD scores, patient demographics, or psychosocial characteristics [47]. It was also interesting to note that the MELD score accounted for only 1 % of the variation in HRQOL scores ($p=0.18$). Survival was most strongly predicted by activities of daily living, health distress, sleep disturbance, and perceived disease stigma. Based on these results, the authors concluded that measuring HRQOL may have a role in predicting survival of patients with advanced liver disease [47].

Sleep disturbances have long been associated with patients living with cirrhosis [48]. These changes are a multifactorial phenomenon [48]. Recently, Mostacci et al. evaluated daytime somnolence and sleep complaints in a group of 178 patients with cirrhosis compared to a control group using the Basic Nordic Sleep Questionnaire (BNSQ) and the Epworth Sleepiness Scale (ESS). Compared to controls, patients with cirrhosis complained of more daytime sleepiness ($p<0.005$), sleeping badly at least three times a week ($p<0.005$), difficulties falling asleep ($p<0.01$) and frequent nocturnal awakening ($p<0.005$). The study authors concluded that insomnia and daytime sleepiness are major complaints for this group of patients [48].

Studies assessing the feasibility and effectiveness of measuring HRQOL in daily clinical practice have been performed, generally showing positive results regarding the discussion of HRQOL-related topics, but mixed results regarding the added value to clinical practice of any actual improvement in HRQOL. In one study, which assessed the use of computerized measurement and feedback of HRQOL in the daily clinical practice of an outpatient hepatology department, results demonstrated that there was no improvement in HRQOL for the entire group of chronic liver patients. However, HRQOL showed an improvement in the mental subscale of older patients and male patients with CLD, which had an effect on patient management of this subgroup of patients [21]. Logistic and attitudinal barriers also seem to impede successful implementation of measuring HRQOL in clinical practice settings [22]. However, despite these, HRQOL remains important and relevant in helping to guide clinical decision making.

Cirrhosis Complications and HRQOL

Hepatic Encephalopathy and HRQOL

Hepatic encephalopathy (HE) impacts patients' level of consciousness, intellect, personality, neuromuscular activity and survival, thus affecting their ability to carry out activities of daily living and so influencing their HRQOL [41–45, 49, 50]. Recent investigators have studied the impact on HRQOL of new cirrhosis treatments in patient suffering with HE. In one study, investigators reported the outcomes of a clinical trial where patients with HE were randomized to receive either rifaximin or a placebo twice daily for 6 months or until they had a breakthrough episode of HE [51]. Using the CLDQ, patients' HRQOL was followed for the duration of the study. Taking rifaximin significantly improved patients' HRQOL. However, within the group that had a breakthrough of HE, there was a decrease in scores prior to the appearance of HE. The authors concluded that a decrease in HRQOL in patients with a history of HE can signal the onset of a new episode of HE. Therefore, consideration should be given to using a quality of life tool to track a patients' progress [51].

Other investigators have also found that the degree of HE was an independent predictor impacting a patients' HRQOL—the more severe the HE, the lower the HRQOL scores. Results from some studies suggest that complete resolution of an episode of HE may not occur, so over time HRQOL will continue to decrease despite the normal functioning of the patient [41–45, 49–51]. HRQOL results have also helped investigators to determine resolution of the impact of clinically overt HE on a patient's quality of life. Results have indicated that despite the patient appearing to function normally in all areas of daily activities, their HRQL scores have not returned to baseline. This may indicate that a number of these patients may suffer from covert HE, which may not completely resolve. However, further work is necessary to substantiate this finding [41–45, 49–51].

Ascites and HRQOL

Studies examining the impact of ascites caused by cirrhosis on patients' HRQOL have noted similar findings to those found in patients suffering from HE. Sola and colleagues determined that having severe ascites, leg edema, and low serum sodium were all independent predictors for a low HRQOL [9]. Les et al. determined that several potentially treatable variables (ascites, hypoalbuminemia, minimal HE, and anemia) if corrected may positively alter a patients' HRQOL [10].

In another study, Bhogal and Sanjay investigated the impact of using transjugular intrahepatic portosystemic shunts (TIPS) to correct cirrhosis induced complications [51]. Though the TIPS procedure carried potentially significant risks for HE, shunt induced hemolysis, and infection, its success in reducing portal hypertension was superior to paracentesis. However, in a meta-analysis, Albillos et al. found that better control of ascites by TIPS did not translate into improved survival and was associated with worsening of encephalopathy if present [52].

HCV-Related Cirrhosis and HRQOL

Work completed by Younossi et al. and Spiegel et al. suggest that patients infected with HCV have an already diminished quality of life even before reaching the stage of cirrhosis [18, 19, 20, 34, 35, 53]. In fact, Younossi et al. found that assessing HRQOL can be challenging as many of these patients suffer from the indirect effects of fatigue and psychological issues, namely depression and cognitive impairment, which are present early in the disease course [18, 19]. Another issue confounding the assessment of HRQOL is stigmatization resulting from the HCV diagnosis, creating the potential for a psychological disturbance, as well as acting as a barrier to treatment and eroding a patient's social support network [54–56].

Speigel et al. found that achieving a sustained virologic response (SVR) with HCV treatment (i.e., being HCV RNA negative 6 months after completing therapy) was associated with an increase in HRQOL scores as well as a change of 4.2 points in the vitality score from the SF-36, representing a minimally important difference in HRQoL [53]. They also noted that HRQOL in patients with HCV was impaired regardless of the severity of the disease and attributed this impairment to extra hepatic manifestations related to HCV. Their results also confirmed previous observations that patients with HCV had impaired cognitive functioning as well as an increase in symptoms of their comorbid psychosocial issues after contracting HCV, making it difficult to assess the true of effects of cirrhosis alone [53].

The information gleaned from these studies has become invaluable as new treatments are developed for HCV. Recognizing the impact on patients beyond the biologic effects of the virus is now mandatory—therefore, obtaining a baseline HRQOL score prior to treatment is necessary to ensure any changes in the score will be associated with the correct variable(s), including treatment. Several recent studies on new treatment medications called direct acting antiviral agents (DAAs) have been completed [20, 33, 34]. Patients with HCV and cirrhosis who participated in recent phase III clinical trials using DAA's demonstrated decreased scores in their PROs prior to the initiation of treatment. However, during treatment, the researchers found that interferon-free regimens were associated with minimal PRO decrements. On the other hand, PROs were substantially impacted in both cirrhotics and non-cirrhotics by the inclusion of interferon in sofosbuvir-based treatment regimens. The short duration of treatment (12 weeks) appeared to be advantageous, as the decrease in PROs during treatment disappeared and scores returned to baseline after termination of therapy. Finally, patients with cirrhosis who achieved an SVR 12 weeks after stopping treatment, especially with the interferon-free sofosbuvir-based regimens, enjoyed significant improvement in many areas of their PRO scores [20, 33, 34].

Cirrhosis and Liver Transplantation

Five-and ten-year patient survival after LT is now around 70 and 60 %, respectively. This improvement in life expectancy has shifted the emphasis on follow-up from simple clinical indicators to focusing on how patients cope with everyday life— physically, mentally, and socially [39]. Several studies have investigated the impact of LT on patients' HRQOL [35–40].

Younossi and group determined that patients who underwent LT for complications of cirrhosis had significantly impaired HRQOL [35]. However, after transplantation, their mental health scores rose significantly and were the same or higher than the population norms, while their HRQOL physical component also rose significantly but did not surpass the population norms. They found that HRQOL was clearly associated with the amount of health-care resources expended during their transplant hospitalization such that the more expenses they were perceived to have used, the lower their HRQOL perhaps indicating that patients with a shorter length of stay were healthier [35].

Nutrition has also been found to play a role in patients HRQOL following transplantation. Urano and colleagues determined that after LT, it took at least 6 months for nutritional status, based on laboratory data and energy metabolism, to normalize [37]. Once these parameters normalized, the physical component HRQOL scores improved. They, therefore, concluded that long-term nutritional support is necessary for LT patients in order for them to obtain an optimal level of physical functioning [37]. Others who have studied HRQOL in LT recipients found that patients who were sicker, as noted by their MELD and quality-of-life scores pre-transplant, continued to have low HRQOL scores over time, although their scores improved from baseline [36].

Conclusions

The HRQOL in patients suffering from cirrhosis is significantly decreased when compared to patients without liver disease/cirrhosis. Many tools have been developed to measure the impact of cirrhosis on HRQOL. The most commonly used tools include the CLDQ, the SF-36, the LDQOL, and the EU 5D—for cost-effectiveness studies. HRQOL is influenced by the type of complications arising from cirrhosis. The net overall effect is lower scores, whether such scores are a result of mental impairment or a limitation that had been placed on patients' ability to perform an activity of daily living. Collecting information on HRQOL is helpful in guiding and evaluating the impact of treatment on patients and will be particularly valuable as the management of cirrhosis continues to evolve. Measuring HRQOL in the clinical setting has never been more timely or important.

References

1. Kondo Y, Yoshida H, Tateishi R, Shiina S, Mine N, Yamashiki N, Sato S, Kato N, Kanai F, Yanase M, Yoshida H, Akamatsu M, Teratani T. Health-related quality of life of chronic liver disease patients with and without hepatocellular carcinoma. J Gastroenterol Hepatol. 2007;22(2):197–203.
2. van der Plas SM, Hansen BE, de Boer JB, Stijnen T, Passchier J, de Man RA, Schalm SW. Generic and disease-specific health related quality of life of liver patients with various aetiologies: a survey. Qual Life Res. 2007;16(3):375–88.
3. Sobhonslidsuk A, Silpakit C, Kongsakon R, Satitpornkul P, Sripetch C, Khanthavit A. Factors influencing health-related quality of life in chronic liver disease. World J Gastroenterol. 2006;12(48):7786–91.
4. Gutteling JJ, de Man RA, van der Plas SM, Schalm SW, Busschbach JJ, Darlington AS. Determinants of quality of life in chronic liver patients. Aliment Pharmacol Ther. 2006;23(11):1629–35.
5. The Health Measurement Research Group. Health related quality of life tools. Obtained from the world wide web at: http://www.healthmeasurement.org/Measures.html. Accessed 16 April 2014.
6. Quality Metrics. Hepatitis Quality of Life Questionnaire (HQLQv2). Obtained from the world wide web at: http://www.qualitymetric.com/WhatWeDo/DiseasespecificHealthSurveys/HepatitisQualityofLifeQuestionnaireHQLQv2/tabid/193/Default.aspx. Accessed 15 April 2014.
7. 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(2):295–300.
8. Afendy A, Kallman JB, Stepanova M, Younoszai Z, Aquino RD, Bianchi G, Marchesini G, Younossi ZM. Predictors of health-related quality of life in patients with chronic liver disease. Aliment Pharmacol Ther. 2009;30(5):469–76.
9. Solà E1, Watson H, Graupera I, Turón F, Barreto R, Rodríguez E, Pavesi M, Arroyo V, Guevara M, Ginès P. Factors related to quality of life in patients with cirrhosis and ascites: relevance of serum sodium concentration and leg edema. J Hepatol. 2012;57(6):1199–206. doi:10.1016/j.jhep.2012.07.020. Epub 2012 Jul 20.
10. 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(2):221–7. doi:10.1097/MEG.0b013e3283319975.
11. van der Plas SM1, Hansen BE, de Boer JB, Stijnen T, Passchier J, de Man RA, Schalm SW. The liver disease symptom index 2.0; validation of a disease-specific questionnaire. Qual Life Res. 2004;13(8):1469–81.
12. De Bruin A, Diederiks J, De Witte L, Stevens F, Philipsen H. The development of a short generic version of the sickness impact profile. J Clin Epidemiol. 1994;47:407–12.
13. Two R1, Verjee-Lorenz A, Clayson D, Dalal M, Grotzinger K, Younossi ZM. A methodology for successfully producing global translations of patient reported outcome measures for use in multiple countries. Value Health. 2010;13(1):128–31. doi:10.1111/j.1524-4733.2009.00585.x. Epub 2009 Aug 20.
14. Centers for Disease Control—Health Related Quality of Life. Obtained from the world wide web at http://www.cdc.gov/HRQoL/concept.htm. Accessed 15 April 2014.
15. Gnanasakthy A, Mordin M, Clark M, DeMuro C, Fehnel S, Copley-Merriman C. A review of patient-reported outcome labels in the United States: 2006–2010. Value Health. 2012;15(3):437–42.
16. Loria A, Escheik C, Gerber NL, Younossi ZM. Quality of life in cirrhosis. Curr Gastroenterol Rep. 2013 Jan;15(1):301. doi:10.1007/s11894-012-0301-5. Review.
17. Loria A, Doyle K, Weinstein AA, Winter P, Escheik C, Price J, Wang L, Birerdinc A, Baranova A, Gerber L, Younossi ZM. Multiple factors predict physical performance in people with chronic liver disease. Am J Phys Med Rehabil. 2014 Jan 6;93(6):470-6. (Epub ahead of print).
18. Younossi ZM. Chronic liver disease and health-related quality of life. Gastroenterology. 2001 Jan;120(1):305–7.
19. Afendy A1, Kallman JB, Stepanova M, Younoszai Z, Aquino RD, Bianchi G, Marchesini G, Younossi ZM. Predictors of health-related quality of life in patients with chronic liver disease. Aliment Pharmacol Ther. 2009 Sep 1;30(5):469–76. doi:10.1111/j.1365-2036.2009.04061.x. Epub 2009 Jun 9.

20. Younossi Z, Stepanova M, Henry L, Gane E, et al. Sof paper effects of sofosbuvir-based treatment, with and without interferon, on outcome and productivity of patients with chronic hepatitis C. Obtained from the world wide web at http://www.cghjournal.org/search/quick?restrictName.yjcgh=yjcgh&search_area=journal&search_text1=CLDQ-HCV. Accessed 14 April 2014.
21. Gutteling JJ, Duivenvoorden HJ, Busschbach JJ, de Man RA, Darlington AS. Psychological determinants of health-related quality of life in patients with chronic liver disease. Psychosomatics. 2010;51(2):157–65.
22. Gutteling JJ, de Man RA, Busschbach JJ, Darlington AS. Overview of research on health-related quality of life in patients with chronic liver disease. Neth J Med. 2007;65(7):227–34.
23. Loria A, Escheik C, Gerber NL, Younossi ZM. Quality of life in cirrhosis. Curr Gastroenterol Rep. 2012;15:301.
24. Häuser W, Holtmann G, Grandt D. Determinants of health-related quality of life in patients with chronic liver diseases. Clin Gastroenterol Hepatol. 2004;2(2):157–63.
25. 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(2):221–7. doi:10.1097/MEG.0b013e3283319975.
26. Escheik C, Gerber L, Rover L, Arsalla Z, Otgonsuren M, Younossi ZM. Validation of CLDQ-HCV as a Health Related Quality of Life (HRQOL) instrument for patients with Chronic Hepatitis C (CH-C). Presented at Program No. P240. ACG 2012 Annual Scientific Meeting Abstracts. Las Vegas, NV: American College of Gastroenterology. Accessed from the world wide web at: http://www.eventscribe.com/2012/acg/ajaxcalls/postersinfo.asp?title=7565. Accessed 14 April 2014.
27. Bao ZJ, Qiu DK, Ma X, et al. Assessment of health-related quality of life in Chinese patients with minimal hepatic encephalopathy. World J Gastroenterol. 2007;13:3003–8.
28. Ferrer M, Cordoba J, Garin O, Olive G, Flavia 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 Transplant. 2006;12(1):95–104.
29. Kanwal F, Spiegel BM, Hays RD, Durazo F, Han SB, Saab S, Bolus R, Kim SJ, Gralnek IM. Prospective validation of the short form liver disease quality of life instrument. Aliment Pharmacol Ther. 2008;28(9):1088–101.
30. Sobhonslidsuk A, Silpakit C, Kongsakon R, Satitpornkul P, Sripetch C. Chronic liver disease questionnaire: translation and validation in Thais. World J Gastroenterol. 2004;10(13):1954–7.
31. Hauser 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(6):599–606.
32. Atiq M, Gill ML, Khokhar N. Quality of life assessment in Pakistani patients with chronic liver disease. J Pak Med Assoc. 2004;54(3):113–5.
33. Younossi ZM, Stepanova M, Henry L, Gane E, Jacobson IM, Lawitz E, Nelson D, Gerber L, Nader F, Hunt S. Effects of sofosbuvir-based treatment, with and without interferon, on outcome and productivity of patients with chronic hepatitis C. Clin Gastroenterol Hepatol. 2013 Dec 5;12(8):1349-59.e13. doi:10.1016/j.cgh.2013.11.032.
34. Younossi ZM, Stepanova M, Henry L, Gane E, Jacobson IM, Lawitz E, Nelson D, Nader F, Hunt S. Minimal impact of sofosbuvir and ribavirin on health related quality of life in Chronic Hepatitis C (CH-C). J Hepatol. 2013 Dec 10;60(4):741-7. doi:10.1016/j.jhep.2013.12.006.
35. Younossi ZM1, McCormick M, Price LL, Boparai N, Farquhar L, Henderson JM, Guyatt G. Impact of liver transplantation on health-related quality of life. Liver Transpl. 2000;6(6):779–83.
36. Togashi J, Sugawara Y, Akamatsu N, Tamura S, Yamashiki N, Kaneko J, Sakamoto Y, Aoki T, Hasegawa K, Kokudo N. Quality of life after adult living donor liver transplantation: a longitudinal prospective follow-up study. Hepatol Res. 2013;43:10.
37. Urano E, Yamanaka-Okumura H, Teramoto A, Sugihara K, Morine Y, Imura S, Utsunomiya T, Shimada M, Takeda E. Pre- and postoperative nutritional assessment and health-related quality of life in recipients of living donor liver transplantation. Hepatol Res. 2014;44:3.
38. Neuberger J. What is the real gain after liver transplantation? Liver Transplant. 2009;15(Suppl 2):S1–5.
39. Roberts MS, Angus DC, Bryce CL, Valenta Z, Weissfeld L. Survival after liver transplantation in the United States: a disease-specific analysis of the UNOS database. Liver Transplant. 2004;10:886–97.
40. Carbone M1, Bufton S, Monaco A, Griffiths L, Jones DE, Neuberger JM. The effect of liver transplantation on fatigue in patients with primary biliary cirrhosis: a prospective study. J Hepatol. 2013;59(3):490–4. doi:10.1016/j.jhep.2013.04.017. Epub 2013 Apr 27.
41. Sanyal A1, Younossi ZM, Bass NM, Mullen KD, Poordad F, Brown RS, Vemuru RP, Mazen Jamal M, Huang S, Merchant K, Bortey E, Forbes WP. Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy—a double-blind placebo-controlled study. Aliment Pharmacol Ther. 2011;34(8):853–61. doi:10.1111/j.1365-2036.2011.04808.x. Epub 2011 Aug 17.
42. Company L, Zapater P, Perez-Mateo M, Jover R. Extrapyramidal signs predict the development of overt hepatic encephalopathy in patients with liver cirrhosis. Eur J Gastroenterol Hepatol. 2010;22:519–25.
43. Arguedas MR1, DeLawrence TG, McGuire BM. Influence of hepatic encephalopathy on health-related quality of life in patients with cirrhosis. Dig Dis Sci. 2003;48(8):1622–6.

44. Moscucci F1, Nardelli S, Pentassuglio I, Pasquale C, Ridola L, Merli M, Riggio O. Previous overt hepatic encephalopathy rather than minimal hepatic encephalopathy impairs health-related quality of life in cirrhotic patients. Liver Int. 2011;31(10):1505–10. doi:10.1111/j.1478-3231.2011.02598.x. Epub 2011 Aug 15.
45. Wang JY1, Zhang NP, Chi BR, et al. Prevalence of minimal hepatic encephalopathy and quality of life evaluations in hospitalized cirrhotic patients in China. World J Gastroenterol. 2013;19(30):4984–91. doi:10.3748/wjg.v19.i30.4984.
46. Marchesini G1, Bianchi G, Amodio P, Salerno F, Merli M, Panella C, Loguercio C, Apolone G, Niero M, Abbiati R; Italian Study Group for quality of life in cirrhosis. Factors associated with poor health-related quality of life of patients with cirrhosis. Gastroenterology. 2001;120(1):170–8.
47. Kanwal F, Gralnek IM, Hays RD, Zeringue A, Durazo F, Han SB, Saab S, Bolus R, Spiegel BM. Health-related quality of life predicts mortality in patients with advanced chronic liver disease. Clin Gastroenterol Hepatol. 2009;7(7):793–9.
48. Mostacci B, Ferlisi M, Baldi Antognini A, Sama C, Morelli C, Mondini S, Cirignotta F. Sleep disturbance and daytime sleepiness in patients with cirrhosis: a case control study. Neurol Sci. 2008;29(4):237–40.
49. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy-definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology. 2002;35:716–21.
50. Stewart CA, Malinchoc M, Kim WR, Kamath P. Hepatic encephalopathy as a predictor of survival in patients with endstage liver disease. Liver Int. 2009;29:1365–71.
51. Bhogal HK1, Sanyal AJ. Using transjugular intrahepatic portosystemic shunts for complications of cirrhosis. Clin Gastroenterol Hepatol. 2011;9(11):936–46; quiz e123. doi:10.1016/j.cgh.2011.06.013. Epub 2011 Jun 21.
52. Albillos A1, Bañares R, González M, Catalina MV, Molinero LM. A meta-analysis of transjugular intrahepatic portosystemic shunt versus paracentesis for refractory ascites. J Hepatol. 2005;43(6):990–6. Epub 2005 Jul 5.
53. Spiegel BM, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. Hepatology. 2005;41(4):790–800.
54. Dan AA, Crone C, Wise TN, Martin LM, Ramsey L, Magee S, Sjogren R, Ong JP, Younossi ZM. Anger experiences among hepatitis C patients: relationship to depressive symptoms and health-related quality of life. Psychosomatics. 2007;48(3):223–9.
55. Kallman J, O'Neil MM, Larive B, Boparai N, Calabrese L, Younossi ZM. Fatigue and health-related quality of life (HRQOL) in chronic hepatitis C virus infection. Dig Dis Sci. 2007;52(10):2531–9. Epub 2007 Apr 4.
56. Younossi Z, Kallman J, Kincaid J. The effects of HCV infection and management on health-related quality of life. Hepatology. 2007;45(3):806–16.