

Overview of research on health-related quality of life in patients with chronic liver disease

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ABSTRACT

Health-related quality of life (HRQoL) has become an important outcome measure in patients with chronic liver disease (CLD). In this article, an overview is given of the most common measurement instruments of HRQoL, determinants of HRQoL in patients with CLD, and current developments in the implementation of routine measurement of HRQoL in daily clinical practice. Well-developed generic instruments of HRQoL are the Short Form-36 (SF-36), the Nottingham Health Profile (NHP) and the Sickness Impact Profile (SIP). Well-developed liver disease-specific HRQoL instruments are the Hepatitis Quality of Life Questionnaire (HQLQ), the Chronic Liver Disease Questionnaire (CLDQ), the Liver Disease Quality Of Life Questionnaire (LDQOL), and the Liver Disease Symptom Index 2.0 (LDSI 2.0). Commonly used HRQoL measures in cost-effectiveness studies are the Health Utilities Index (HUI), Short Form-6D (SF-6D) and the EuroQol-5D (EQ-5D). HRQoL of patients with chronic liver disease has been shown to be impaired, with patients with hepatitis C showing the worst HRQoL. Disease severity, pruritis, joint pain, abdominal pain, muscle cramps, fatigue, depression and anxiety have been associated with HRQoL in patients with CLD. Recently, 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 of actual improvement in HRQoL. Furthermore, logistic and attitudinal barriers seem to impede successful implementation. Nevertheless, given the importance of HRQoL in liver patients, we should persist in measuring and subsequently improving HRQoL in clinical practice.

KEYWORDS

Hepatitis, liver, quality of life

INTRODUCTION

Due to continuously improving medical treatment, many formerly lethal diseases have nowadays become chronic. It has been calculated that one quarter to one third of the adult population in the Netherlands has a chronic disease (van den Berg & van den Bos 1989, Monthly Indicators, Statistics Netherlands (CBS) 3, 4-21). The increasing prevalence of chronic disease in developed countries has led to an increased focus on the emotional and social well-being of patients as well as their physical well-being, referred to as health-related quality of life (HRQoL). To illustrate the increasing interest in HRQoL in medical treatment, a count of hits in PubMed when entering the search term 'quality of life' in title and/or abstract shows an increase of over 31-fold in the past 20 years (from 2266 articles in 1986 to 70,796 articles in 2006). Despite this increase in research, the impact on clinical practice has been limited: to date, HRQoL assessment has largely been restricted to patients in a research environment. However, the importance of using HRQoL information for the improvement of physician consultations is increasingly being acknowledged. In 1992, a large conference was dedicated to the topic of 'Applications of health status assessment measures in clinical practice',¹ and in June of 2007, another conference on this topic took place (www.isoqol.org). Furthermore, several high-impact articles have been published on this topic since 2001.²⁻⁴ This article will discuss HRQoL specifically for patients with chronic liver disease (CLD), its measurement, and current developments in the implementation of routine measurement of HRQoL in clinical practice.

CHRONIC LIVER DISEASE

CLD is one of the most prevalent diseases in the world. The most common causes of CLD, hepatitis B virus (HBV) and hepatitis C virus (HCV), have been estimated to affect 360 million and 200 million people worldwide respectively (www.epidemic.org, 4-12-2006). In addition, alcohol is another main cause of end-stage liver disease worldwide, and alcoholic liver disease is the second most common reason for liver transplantation in the United States.⁵ In the Netherlands, CLD affects approximately one in 400 people (www.statline.cbs.nl, 4-12-2006). CLD is a serious disease that is associated with significant morbidity and mortality. Patients may suffer from specific complications of cirrhosis such as hepatic encephalopathy, ascites and variceal bleedings. Furthermore, fatigue, joint pain, pruritis, loss of appetite, depression, abdominal pain, worries about complications of the disease, decreased sexual interest/activity, loneliness, hopelessness, problems with social interaction and problems with memory/concentration have been associated with CLD.⁶⁻¹² Given the many effects that CLD may have on patients, HRQoL should be considered an important outcome measure in the treatment of CLD patients.

DEFINITION OF HEALTH-RELATED QUALITY OF LIFE

HRQoL was adapted from the more general and wide-ranging concept 'quality of life' (QoL). Because this is such a broad concept, there is no universally accepted definition for QoL. In this study we have adopted the WHO definition of the multidimensional concept of QoL: 'individuals' perceptions of their position in life in the context of the culture and value system in which they live and in relation to their goals, standards, and concerns'.¹³ Due to the multidimensionality of the concept, it is not practical (or perhaps not possible) to assess all that is meant by QoL simultaneously. Therefore, a more limited and focused assessment should be undertaken. With regard to chronic illness, QoL should be determined by health parameters, and not by more general parameters such as economic status or environment since these are often distant from health or medical concerns.¹⁴ This has led to the concept of HRQoL. HRQoL ranges from negatively valued aspects of life, including death, to the more positively valued aspects such as role function or happiness. The general consensus is that it consists of three core domains: psychological functioning (well-being and emotional status), social functioning, and physical functioning.¹⁵ It should be noted that this definition of HRQoL is from a patient or clinical perspective, which is the main focus of this article. HRQoL can also be

looked at from a cost-effectiveness perspective. This will be described more elaborately in the paragraph on utility measures.

USE OF HRQOL ASSESSMENTS IN HEALTH CARE

In general, there are four main uses of HRQoL assessments in health care: 1) treatment comparisons in clinical trials, 2) patient population studies to evaluate the burden of the disease in terms of HRQoL, 3) health economics evaluations to determine the best use of health care resources, and 4) treatment choices in individual patient care.¹⁴ This article will focus on elements mentioned in point two, i.e. levels of HRQoL in patient populations with various forms of liver disease, and elements mentioned in point four, i.e. HRQoL assessment at individual patient level.

Measurement of HRQoL

HRQoL includes a physical, a social, and a mental component, each of which consist of multiple subcomponents. For example, the mental component can consist of depression, but also of anxiety. Typically, these components can not be readily observed. Indeed, one of the arguments for asking patients to judge their own HRQoL with the use of questionnaires is that it has been shown that physicians are generally unable to adequately judge their patients' HRQoL.¹⁶ Judgements of physicians do not only deviate from those of patients, they also differ between physicians.¹⁶ Especially this last variability makes it difficult to obtain 'objective' judgements of HRQoL. Measurement of HRQoL is therefore done by means of standardised, self-administered questionnaires. Note that the patients' judgements about their own HRQoL are still subjective: patients with the same physical state might give us different views about their HRQoL, but this outcome no longer depends on the observer. There are two basic types of HRQoL questionnaires that measure HRQoL from this patient perspective: generic questionnaires and disease-specific questionnaires. A third type of HRQoL questionnaires exists that measures HRQoL from a cost-effectiveness perspective. These are called utility measures.

Generic questionnaires

Generic HRQoL questionnaires include a spectrum of domains of HRQoL that apply equally to various patient populations. Generic questionnaires have the advantage that the scores of the patients can be compared with the scores of other patient populations and/or a healthy control population. A disadvantage is that generic instruments are not designed to identify disease-specific domains that may be important to establish clinical changes.¹⁷ The most

generic form is just one question 'how is your quality of life today', with for instance a visual analogue scale (VAS) as answering mode. The three most commonly used generic HRQoL instruments, according to a recent review,¹⁸ are the Nottingham Health Profile (NHP), the Medical Outcomes Study Short Form-36 (SF-36) and the Sickness Impact Profile (SIP) (*table 1*). The SIP has a broad coverage of topics, but is therefore very long.¹⁹ The NHP focuses on more severe levels of disability and has thus been known to be less sensitive to changes in conditions where effects are relatively mild.^{20,21} The SF-36 is sensitive to a wider range of disability levels, from the general population to patients with severe levels of disability.²² All three instruments have sufficient psychometric properties, as shown in *table 1*. For health care workers interested in a broad range of HRQoL topics, we recommend using the SIP if it is feasible for the patients to complete this lengthy instrument. Shorter instruments are the NHP and the SF-36. Since the NHP is less sensitive in patients with relatively mild conditions, we recommend the use of the SF-36, which is applicable to a broader range of conditions. Furthermore, the SF-36 is currently the most used HRQoL instrument in studies worldwide, and shorter versions are available.

Disease-specific questionnaires

Disease-specific questionnaires are designed to be valid only for a specified condition and have the advantage of providing greater specificity and sensitivity.²³ Four liver disease-specific HRQoL questionnaires have been developed and used extensively (*table 2*). The first liver disease-specific HRQoL questionnaire to be systematically developed and employed was the Hepatitis Quality of Life Questionnaire (HQLQ),⁹ followed by the Chronic Liver Disease Questionnaire (CLDQ),¹⁰ the Liver Disease Quality Of Life questionnaire (LDQOL),¹¹ and lastly, the Liver Disease Symptom Index 2.0 (LDSI 2.0).¹² All four instruments have strengths and weaknesses. The HQLQ consists of the widely validated generic SF-36 with five added disease-specific subscales, but it excludes patients with other chronic liver disease than HCV. The CLDQ is a short and therefore feasible questionnaire, but is unable to discriminate between more advanced stages of liver disease. The LDQOL addresses a variety of domains, but is therefore very long (101 items). This may be a problem when completion time is limited, or multiple questionnaires are being administered. The LDSI 2.0 is a short questionnaire that measures nine possible liver disease-specific symptoms, as well as the *hindrance* that

Table 1. Specifications of the three most commonly used generic HRQoL instruments

	Nottingham Health Profile (NHP)	Medical Outcomes Study Short Form-36 (SF-36)	Sickness Impact Profile (SIP)
Authors	Hunt <i>et al.</i> 1980, 1985 ^{20, 21}	Ware <i>et al.</i> 1992 ⁸⁸ (Validation study Brazier <i>et al.</i> 1992 ²²)	Bergner <i>et al.</i> 1981 ¹⁹
No. of items	38	36	136
No. of subscales	7	8	12
Total score	No	Yes	Yes
Reliability	IC: Cronbach's $\alpha = 0.70 - 0.85$ (Dutch population (86)) TRT: $r = 0.75 - 0.88$	IC: Cronbach's $\alpha > 0.84$ (social functioning, $\alpha = 0.73$) TRT: $r = 0.60 - 0.81$	IC: Cronbach's $\alpha = 0.94$ TRT: $r = 0.87 - 0.97$
Validity*	CV: Ill <i>versus</i> healthy people DV: Between groups with various health statuses in a Dutch population ⁸⁵	Conv. V: Correlations between four comparable dimensions of SF-36 and NHP were high ($r = -0.55$ to -0.93) DV: Correlations between non-comparable dimensions of SF-36 and NHP were low ($r = -0.018$ to -0.35)	Conv. V: E.g. Activity of Daily Living Index: $r = 0.55 - 0.61$ DV: E.g. explained variance of Speech Pathology Ratings: $R^2 = 0.30$) Clinical validity Descriptive validity
Subscales	Energy Pain Emotional reactions Sleep Social isolation Physical mobility	Physical functioning Role limitations due to physical problems Role limitations due to emotional problems Mental health Vitality Bodily pain General health perception Social functioning	Ambulation Body care/movement Mobility Social interaction Alertness behavior Emotional behavior Communication Sleep and rest Eating Work Home management Recreation/pastimes
IC = internal consistency; TRT = test-retest reliability; CV = construct validity; Conv. V = convergent validity; DV = discriminant validity. *All reported validities have been established.			

patients experience from having these symptoms. The LDQOL, HQLQ and CLDQ fail to address this hindrance, even though having a certain symptom does not always automatically mean that HRQoL is impaired. Psychometric properties of the four instruments are sufficient, as shown in *table 2*. The LDQOL can be used when administration of a lengthy questionnaire is not an issue, and the aim is to obtain information on a wide range of liver disease-specific HRQoL domains. When a short questionnaire is preferred, the LDSI 2.0 is recommended over the CLDQ since it takes symptoms *and* hindrance of these symptoms into account. The HQLQ may be an efficient instrument for health care professionals interested in the HRQoL of patients with HCV, since it comprises generic and disease-specific items simultaneously.

'values' of health states are typically determined by asking healthy people to rate HRQoL of hypothetical health states, for instance characteristic health states of liver patients, instead of the patients themselves. Consequently, coping is not included. Sophisticated techniques such as Standard Gamble and Time Trade-Off are used to estimate the utility values between 0.00 (a poor state of health) and 1.00 (normal health).^{24,25} Besides using these sophisticated but labour-intensive methods, there are generic 'off the shelf' quality of life instruments that provide the utility value as additional outcome. The three most used utility measures are the Health Utilities Index (HUI),²⁶ the SF-6D²⁷ and the EuroQoL EQ-5D²⁸ (*table 3*). We prefer the EQ-5D and HUI over the SF-6D, as the SF-6D has shown a floor effect, especially in liver patients.²⁹

UTILITY MEASURES

Utility measures originated in health economics, and form an important subgroup of generic measures that are used in cost-effectiveness studies²⁴ and medical decision-making analyses.²⁵ With utility measures, quality adjusted life years (QALYs) can be computed, which can provide an indication of the benefits gained from a variety of medical procedures in terms of quality of life and survival of the patient. Utility

HRQOL IN PATIENTS WITH CHRONIC LIVER DISEASE

The vast majority of studies assessing HRQoL in patients with CLD have focused on patients with chronic HCV infection. This interest of the research community in HCV may be explained by the severity of this form of CLD as well as by the debilitating side effects of interferon, which is used to treat some of these patients.

Table 2. Specifications of the four liver disease-specific HRQoL measures

	Hepatitis quality of life questionnaire (HQLQ)	Chronic liver disease questionnaire (CLDQ)	Liver disease quality of life questionnaire (LDQOL)	Liver disease symptom index 2.0 (LDSI 2.0)
Authors	Bayliss <i>et al.</i> 1998 ⁹	Younossi <i>et al.</i> 1999 ¹⁰	Gralnek <i>et al.</i> 2000 ¹¹	Unal <i>et al.</i> 2001 ⁷
No. of items	69	29	101	18
No. of subscales	13	6	20	9
Total score	No	Yes	No	Yes
Reliability	IC: Cronbach's $\alpha > 0.80$	TRT: ICC = 0.59	IC: Cronbach's $\alpha > 0.70$ (1 subscale $\alpha = 0.62$)	IC: Cronbach's $\alpha > 0.79$
Validity*	CV: E.g. correlations between limitations and physical factor of the SF-36 ($r = 0.69$) DV	CV: Worse CLDQ scores with increased disease severity	CV: Worse LDQOL scores with increased disease severity for all subscales	CV: Correlations between symptom severity items and their accompanying hindrance items: $r = 0.52 - 0.80$
Subscales	8 subscales of the SF-36 (see <i>table 1</i>) + Limitations due to chronic hepatitis C Health distress due to chronic hepatitis C Positive well-being Sleep somnolence Health distress	Fatigue Activity Emotional function Abdominal symptoms Systemic symptoms Worry	8 subscales of the SF-36 (see <i>table 1</i>) + CLD-related symptoms CLD-related effects on activities of daily living Concentration Memory Sexual functioning Sexual problems Sleep Loneliness Hopelessness Qual. of social interaction Health distress Self-perceived stigma of CLD	Itch Joint pain Pain in the right upper abdomen Sleepiness during the day Worry about family situation Decreased appetite Depression Fear of complications Jaundice
IC = internal consistency; ICC = intra class correlation; TRT = test-retest reliability; CV = construct validity; DV = discriminant validity. *All reported validities have been established.				

Table 3. Specifications of the mostly used utility measures

	EuroQol-5D (EQ-5D)	Health utilities index (HUI 3)	Short form-6D (SF-6D)
Authors	EuroQol Group 1990, Brooks 1996 ²⁸	Feeney <i>et al.</i> 1995 ²⁶	Brazier <i>et al.</i> 2002 ²⁷
No. of items	5	31	10
No. of dimensions	5	8	6
Nr. of unique health states	243	972,000	18,000
Total score	Yes	Yes	Yes
Reliability	TRT: ICC = 0.81	TRT: ICC = 0.87	TRT: ICC = 0.83
Validity*	CV: Spearman correlation with HUI 3 = 0.80 Spearman correlation with SF-6D = 0.70 DV: Able to discriminate between mildly, moderately, severely and very severely disabled patients	CV: Spearman correlation with EQ-5D = 0.80 Spearman correlation with SF-6D = 0.69 DV: Able to discriminate between mildly, moderately, severely and very severely disabled patients	CV: Spearman correlation with EQ-5D = 0.70 Spearman correlation with HUI 3 = 0.69 DV: Able to discriminate between mildly, moderately, severely and very severely disabled patients
Dimensions	Mobility Self-care Usual activity Pain/discomfort Anxiety/depression	Vision Hearing Speech Ambulation Dexterity Emotion Cognition Pain	Physical functioning Role limitations Social functioning Pain Mental health Vitality
TRT = test-retest; ICC = intraclass correlation; CV = construct validity; DV = discriminant validity. All tests of reliability and validity were performed in a sample of patients with multiple sclerosis. ⁸⁷ *All reported validities have been established.			

Side effects of interferon may include fever, aching muscles, fatigue, depression, aggression, impotence, hair loss and eczema. These side effects often have consequences for family life, work, and other aspects of daily living. Indeed, studies assessing HRQoL in HCV patients with and without interferon treatment have shown the HRQoL of these patients to be impaired.³⁰⁻³⁴ Studies including CLD patients with other disease aetiologies than HCV also show impaired HRQoL.³⁵⁻³⁹ Of all patients with CLD, those with HCV seem to have the worst HRQoL.³⁵

Determinants of HRQoL in patients with chronic liver disease

Despite the many studies that have shown a reduced HRQoL in hepatology, relatively few studies have investigated which factors influence liver patients' HRQoL. That is a problem when we want to move from just measuring HRQoL towards treatments that improve HRQoL. Disease severity, as indicated by stage of fibrosis (absent, early or advanced) or Child Pugh scores, seems to determine HRQoL.^{8,37,39,40} Such a relationship between disease severity and HRQoL seems fairly self-evident as we are dealing with 'health related' quality of life. Nevertheless some studies did not find this relationship.^{32,41,42} This may have been due to the relatively small number of patients with CLD in a more advanced stage that were included in these studies: Foster *et al.* (1998) did not include patients with cirrhosis, Kramer

et al. (2005) excluded patients with decompensated cirrhosis and most patients in the study had mild chronic hepatitis (Child Pugh stage A without ascites). Over 70% of the patients in the study performed by Hauser *et al.* (2004) did not have cirrhosis. Besides disease severity, physical symptoms of CLD such as pruritis, joint pain, abdominal pain, and muscle cramps have been shown to be related to HRQoL.^{8,38,43} Fatigue is also of concern in patients with CLD.^{8,36,42,44-46} Lastly, anaemia⁴⁷ and low physical activity⁴⁸ have been associated with poorer HRQoL in HCV patients.

Besides these mainly physical aspects of the illness, the association between psychological aspects of CLD and HRQoL has also received some attention. Depression, anxiety, illness understanding, social stigma, worry about family situation, fear of complications, problems with concentration and memory, and loneliness are all related to HRQoL in patients with CLD.^{8,36,41,49-51} The relative impact of these psychological aspects on HRQoL has, however, not been studied. Furthermore, two important psychological concepts that deserve attention have rarely been assessed in patients with CLD: 'coping' and 'self-efficacy'. 'Coping' refers to the way people deal with stressful situations, such as having a (chronic) disease and the consequences thereof.⁵² 'Self-efficacy' refers to an optimistic self-belief that one can perform difficult or new tasks, or that one can cope adequately with adversity.⁵³ Both coping and self-efficacy have been shown to affect HRQoL in various patient populations,⁵⁴⁻⁵⁸ but this has never been investigated

for patients with CLD. Including measures of coping and self-efficacy in future studies on HRQoL in patients with CLD is advisable.

IMPLEMENTATION OF HRQoL MEASUREMENT IN CLINICAL PRACTICE

Interest in using HRQoL in clinical practice as more than just an outcome measure has increased.¹⁻⁴ Standardised assessment of HRQoL preceding each consultation may potentially provide physicians with valuable information for several reasons. First of all, several studies have shown that physicians vary in their ability to elicit psychosocial information, or that they underestimate patients' HRQoL.^{16,59-66} Secondly, various studies have shown that when communication with the physician encompasses both physical and psychosocial issues, patients have better treatment compliance, are more satisfied with the consultation and report less symptoms.^{3,59,60,65,67-73} Thirdly, timely recognition of psychosocial problems means that patients can be referred for adequate treatment such as psychotherapy or social work, whereas failure to recognise these problems often results in unexplained symptoms and over-utilisation of health care.^{71,73,74}

Studies assessing routine administration of HRQoL in clinical practice have yielded positive findings: availability of HRQoL information to physicians during the consultation was generally well accepted, and physicians expressed an interest in continued use of the information. Furthermore, routine administration of HRQoL in clinical practice has been shown to increase the frequency of: 1) identification and/or discussion of HRQoL-related issues,^{2,3,75-77} 2) identification of patients with moderate to severe health problems and/or anxiety,^{2,78} and 3) actions being taken.^{75,78} A decrease in depression, potential improvement in symptom control, and better HRQoL and emotional functioning have been observed in association with the availability of HRQoL information for the physician,^{3,4,77} even though several other studies have failed to show robust evidence to suggest that routine administration of HRQoL in clinical practice is of benefit in actually improving HRQoL or psychosocial outcomes.^{2,79-81} This may have been due to the lack of sensitivity of the measures used to detect small changes⁸² and/or insufficient clinical relevance of measures to prompt physicians to make changes to patient management.⁷⁹ On the other hand, it may be slightly overzealous to expect HRQoL measurement in clinical practice to cause significant improvement in HRQoL since it encompasses so many dimensions.

For a successful implementation of HRQoL assessment in clinical practice, several practical and attitudinal barriers

have to be overcome, or at least expected, such as general lack of time, money and human resources, impracticability of instruments, lack of IT support, disruption of clinical routine, and health professionals' lack of knowledge in this area and/or scepticism towards the validity of existing measures.^{79,82-85} Efforts should be aimed at optimising practical support such as money and human resources. Furthermore, more research and subsequently additional evidence of the benefits of HRQoL measurement in clinical practice may aid in convincing health professionals of the added value. Any changes in clinical practice are to be expected to be met with some resistance.

CONCLUSION

Studies have shown HRQoL to be impaired in patients with CLD, and many physical and psychological factors have been associated with this impaired HRQoL. However, more conclusive research is desirable on the strength of the relationship of each of these factors with HRQoL in order to be able to determine the focus of treatment. This may also help the clinical decision-making of physicians who use routine HRQoL assessment in clinical practice. With regard to the implementation of HRQoL assessment in clinical practice, and the obstacles experienced in this process, it should be recognised that it is often a long process that requires patience, but the field of HRQoL research has been calling for this move into clinical practice as a logical and needed next step, which will contribute to the improvement of patient care. As long as routine HRQoL assessment is seen as an additional tool for physicians, and the emphasis remains on the clinical experience of the physician and the verbal communication with patients, these barriers should not be a reason to refrain from routine assessment of HRQoL in clinical practice, in our opinion.

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