Implementing Health Related Quality of Life Measurement in Clinical Practice:

A prospective study in patients with chronic liver disease

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Implementatie van kwaliteit van leven metingen in de klinische praktijk: een prospectief onderzoek bij patiënten met chronische leverziekte

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Contents

Introduction and aims of the studies

Health related quality of life (HRQoL), or psychological-, social-, and physical functioning (1), has become an important outcome measure in medical care. A literature search in PubMed in July 2007 for 'health related quality of life' showed close to 14.000 hits. Until recently, HRQoL measurement has predominantly been restricted to a research environment, with most studies comparing HRQoL scores of specific patient populations with scores of healthy norm populations. Subsequently, impaired HRQoL has now been established for many patient populations. However, this information does not give insight in the HRQoL of individual patients. Therefore, a useful next step in HRQoL measurement seems to be its application in clinical practice, with the goal of improving individual patients' well-being.

The conclusion of a recent thesis on the HRQoL of patients with chronic liver disease subscribes this move from using HRQoL in a research environment to clinical practice (2). In that thesis, it was concluded that "During consultations, besides attention for physical impairments of patients with chronic liver disease (CLD), attention should be given to psychological impairment…" (2). With the application of HRQoL measurement in clinical practice, both physical and psychological impairment will be addressed. Considering the reduced HRQoL that has been found in patients with CLD and the large prevalence and severity of CLD, patients with this disease were included in the present thesis on the application of HRQoL measurement in clinical practice.

The first aim of this thesis was to assess the effectiveness of computerized measurement of HRQoL in clinical practice. To that end, we performed a prospective, randomised controlled study on the use of HRQoL data in a large sample of patients with CLD recruited from the recruited from the outpatient clinic of hepatology of a single academic centre in the Netherlands. The results are described in the first part of this thesis (chapter 2 and 3).

The second aim of the study was to identify predictors of HRQoL in patients with CLD. In order for the identification of impairment, as described in the first part of the thesis, to lead to an adjustment in treatment it is imperative to know which factors influence HRQoL of patients with CLD. With knowledge of these factors, physicians can be assisted in further management of patients presenting with impaired HRQoL. Despite the many studies that have shown a reduced HRQoL in hepatology, relatively few studies have investigated which factors influence liver patients' HRQoL. Therefore, second aim of this thesis was to determine physical and psychological factors that are closely related to HRQoL in patients with chronic liver disease. The results of this investigation are addressed in the second part of the thesis (chapter 4 - 6).

The last chapter describes the development of a liver disease-specific questionnaire to assess patient satisfaction with the consultation (chapter 7).

This thesis starts with an overview on HRQoL, giving its definition, describing the use of HRQoL assessments in health care, HRQoL in patients with chronic liver disease, and implementation of HRQoL measurement in clinical practice (chapter 1).

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Part

Feasibility and effectiveness of implementing computerized HRQoL measurement in clinical practice

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 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 of 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.

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 70796 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 will take 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

Health related quality of life has been deducted 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. The researchers of this study 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 concern (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, 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 to ask 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 patients, but 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 standardized, self-administered questionnaires. Note that the patients' judgments about their own HRQoL is 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 norm population. A disadvantage is that generic instruments are not designed to identify disease-specific domains that may be important to identify 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 change 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 to patients with relatively mild conditions, we recommend the use of the SF-36, which is applicable to

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 et al. 1980, 1985 (20, 21)	Ware et al. 1992 (88). (Validation study Brazier et al. 1992 (22)).	Bergner et al. 1981 (19)
Nr. of items	38	36	136
Nr. of subscales	7	8	12
Total score	No	Yes	Yes
Reliability	IC: Cronbach's α = 0.70 - 0.85 (Dutch population (86)) TRT: r = 0.75 – 0.88	IC: Cronbach's α > 0.84 (social functioning, α=0.73) TRT: r = 0.60 – 0.81	IC: Cronbach's α = 0.94 TRT: r = 0.87-0.97
Validity*	CV: Ill versus 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 - -0.93). DV: Correlations between non-comparable dimensions of SF-36 and NHP were low (r=-.018 - -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.

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 employed thoroughly (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 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 one is interested in

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 et al. 1998 (9)	Younossi et al. 1999 (10)	Gralnek et al. 2000 (11)	Unal et al. 2001 (7)
Nr. of items	69	29	101	18
Nr. 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 table 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 table 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.

a large amount 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.

Utility measures

Utility measures have originated in health economics, and form an important subgroup of generic measures that are used in cost-effectiveness studies (24) and medical decision-making analyses (25). With utility measures, Quality Adjusted Life Years (QALY's) 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 '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 like Standard Gamble and Time Trade-Off are used to estimate the utility values between 0.00 (a bad health state) and 1.00 (normal health) (24, 25). Besides using these sophisticated but labour-intensive methods, there are generic 'of 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-6D (27) and the EuroQoL EQ-5D (28) (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).

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. Side effects of interferon may include fever, sore 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 HRQoL of these patients to be impaired (30-34). Studies including CLD patients with other disease etiologies than HCV also show impaired HRQoL (35-39). Of all patients with CLD, patients with HCV seem to have the worst HRQoL (35).

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 et al. 1995 (26)	Brazier et al. 2002 (27)
Nr. of items	5	31	10
Nr. of dimensions	5	8	6
Nr. of unique health states	243	972000	18000
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, Intra Class 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.

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 amount 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, anemia (47) and low physical activity (48) 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). Standardized 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 in patients results in reference to adequate treatment like psychotherapy or social work, whereas no recognition of 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, 76), 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 of symptom control, and better HRQoL and emotional functioning have been observed in association with the availability of HRQoL information to 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 used measures to detect small changes (82) 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 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 recognized 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, that 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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Logistic feasibility of health related quality of life measurement in clinical practice: results of a prospective study in a large population of chronic liver patients

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Submitted

Abstract

Background

The objective of the present study was to provide a complete and detailed report of technical and logistical feasibility problems with the implementation of routine computerized HRQoL measurement at a busy outpatient department of hepatology that can serve as a tool for future researchers interested in the procedure.

Methods

Practical feasibility was assessed by observing problems encountered during the development of the computer program, observing patients' ability to complete the HRQoL questionnaires, monitoring the number of times that patients completed the HRQoL questionnaires and observing logistics at the outpatient department. Patients' reasons for not completing the HRQoL questionnaires were assessed retrospectively by means of a mailed questionnaire. Physicians' attitudes towards the availability of computerized HRQoL information about their patients were assessed by means semi-structured interviews and by means of checklists administered after each consultation with a study participant.

Results

All physicians (n=11) and 587 patients agreed to participate in the study. Practical feasibility problems concerned complicated technical aspects of developing a user-friendly computer program and safe data transmission over the Internet, patients' lack of basic computer skills and patients' lack of compliance (completion of questionnaires on only 43% of the occasions). The main reason given for non-compliance was simply forgetting, which seemed to be related to reception employees' passive attitude towards sending patients to the computer. Physicians were generally positive about the instant computerized availability of HRQoL information. They requested the information in 92% of the consultations and found the information useful in 45% of the consultations, especially when it provided them with new information.

Conclusions

This study was among the first to implement the complete procedure of routine computerized HRQoL measurements in clinical practice and to subsequently describe the feasibility issues encountered. It was shown that the attitudes of physicians were generally positive. Several barriers towards successful implementation were encountered and, subsequently, solutions were provided. Most importantly, when implementing routine computerized HRQoL measurements in clinical practice, assistance of an IT professional for the development of a tailor-made computer program, availability of

questionnaires in multiple languages and the use of touch-screen computers to optimise patient participation are essential. Also, all staff of the department concerned should approve of the intervention and consider it as part of standard clinical routine if successful implementation is to be obtained.

Introduction

The importance of patients' health related quality of life (HRQoL) in medical practice is nowadays beyond dispute. Two decades ago a committee of the American College of Physicians specifically supported the view that maintenance of a patient's functional well-being is a fundamental goal of medical practice. They also noted that the assessment of the physical, psychological, and social functioning of the patient in terms of the impact of disease is "an essential part of clinical diagnosis, a major determinant of therapeutic choices, a measure of their efficacy, and a guide in planning long-term care…"[1].

Since 2001, several impact high impact articles have been published on the effectiveness of HRQoL measurement in clinical practice, which have presented positive results such as more frequent discussion and identification of HRQoL related problems, improved emotional functioning, improved HRQoL, a decrease in depression, a decrease in debilitating symptoms, and expressed interest in continued use of the information by both physicians and patients [2-6]. Despite these positive results, standard measurement and feedback of HRQoL has as of yet not been widely implemented in clinical practice. This may be explained by the initial lack of convincing data regarding the effectiveness of standardized HRQoL measurement in actually improving HRQoL or psychosocial outcomes [2, 7-10], and by practical and attitudinal barriers that have been associated with the implementation of HRQoL measurement in clinical practice. Practical barriers that have been reported include general lack of time, money and human resources, impracticality of instruments, disruption of clinical routine, lack of IT support and health professionals' lack of knowledge in this area. Attitudinal barriers may include health professionals' scepticism of the validity of HRQoL questionnaires, and ability to intervene should the questionnaires reveal any problems [10-16].

To the best of our knowledge, only two studies have actually implemented the procedure of HRQoL measurement in clinical practice and subsequently described the issues encountered in terms of feasibility. In one of the studies, the main finding was that higher compliance occurred when the computerized data collection was integrated into routine care. However, it should be noted that the follow-up time was very short (12 weeks), resulting in a large number of patients attending only once which makes it difficult to draw any firm conclusions on patient compliance in the long run [17]. In the

other study, only 18 patients participated and the questionnaires were not computerized [18]. A previous study has shown that pen-and-paper versions of HRQoL questionnaires, which have to be scored by hand, take too much time and are costly in the long term [19]. Providing clinicians with instant information about their patients' HRQoL at busy outpatient clinics can only be obtained if this HRQoL is assessed by means of computers that can generate an output which can instantly be accessed by clinicians.

The aim of the present study was to gain more insight in the practical and attitudinal feasibility problems encountered during the process of implementing computerized HRQoL measurement at a busy outpatient department of hepatology (liver disease) (Erasmus MC, Rotterdam, the Netherlands). Chronic liver disease is one of the most prevalent diseases in the world, affecting over 560 million people (www.epidemic.org, 4-12-2006). It is a serious disease that is associated with impaired HRQoL [20, 21]. Chronic liver disease is an appropriate example of a typical chronic disease, with patients experiencing substantial comorbidity and possibly mortality as is the case in many other chronic diseases.

This study was among the first to actually implement the complete procedure of routine computerized HRQoL measurement at an outpatient department, and to subsequently describe all feasibility issues encountered throughout the process. The focus was on technical as well as logistic feasibility issues such as optimization of patient compliance in the long run, rather than effects of the intervention on patient well-being which have been presented elsewhere [2-6]. Practical suggestions for researchers and health care workers interested in implementing assessment of HRQoL in clinical practice were given.

Methods

Patient inclusion

This study was performed at the Department of Gastroenterology and Hepatology of the Erasmus MC (Rotterdam, the Netherlands), which is one of three specialised centres for liver disease in the Netherlands. With patients visiting the outpatient department on average once every four months, the recruitment phase was set at four months. Between September 2004 and January 2005 all patients of 18 years and older with chronic liver disease (CLD) attending the department of hepatology and all physicians working at the department of hepatology were invited to participate in the study verbally and in writing. Patients who agreed to participate received an explanation of the purpose and procedure of the study from the researcher and, consequently, signed an informed consent form. The protocol was in accordance with the ethical guidelines of the modi-

fied 1975 Declaration of Helsinki and approved by the Medical Ethics Committee of the Erasmus MC.

Study design and intervention

The first three months of the study consisted of a pilot-testing phase during which problems with the computer program were detected and solved. After these three months, the actual intervention started.

Physicians were randomly assigned to either the intervention group (who had access to a graphical representation of the HRQoL data of their patients) or the control group (who conducted their consultations as usual). The physicians in the intervention group were asked to use the HRQoL data in all consultations for the duration of one year. Physicians in both the control group and the intervention group were asked to complete a checklist about the content of the consultation after each consultation with a participating patient.

All participating patients were asked to complete computerized versions of a generic (Short Form-12 [22]) and a disease-specific HRQoL questionnaire (Liver Disease Symptom Index 2.0 [23]), and the first part of a pen-and-paper questionnaire on patient satisfaction with the consultation (QUOTE-Liver [24]), before each consultation for the duration of one year. After the consultation, they completed the second part of the satisfaction questionnaire. For a more elaborate description of the study design and intervention we refer to Gutteling et al. (2008)[6] (chapter 3).

In order to optimise participation, study participants were given instructions on the study procedure both verbally and in writing at the beginning of the study, and eye-catching posters were put up in the waiting room to remind them of the study. In addition, the reception employees were instructed to refer study participants to the computer. With a study-duration of 1 year, it was estimated that this would yield on average three measurement moments per patient.

Measurement instruments

Practical feasibility

Practical feasibility of computerized HRQoL measurement was assessed throughout the study by a) observing problems encountered during the development of the computer program, b) observing patients' ability to complete the HRQoL questionnaires, c) by monitoring the number of times that patients completed the HRQoL questionnaires, and d) by observing logistics at the outpatient department on a daily basis.

A questionnaire was administered retrospectively to assess participants' reasons for not completing the HRQoL assessments in the clinic. This questionnaire included the following questions: 1) Did you complete the questionnaires with each visit during the

past year?, and 2) If not, please indicate why not. This last question had several response categories of which more than one could be checked: a) I forgot to complete the questionnaires, b) I was too late, or there was not enough time before the consultation to complete the questionnaires, c) I did not feel like completing the questionnaires, d) I was too ill to complete the questionnaires and e) other…

Attitudinal barriers

Attitudinal barriers of physicians were explored by semi-structured interviews with all physicians that were conducted midway through the study and at the end of the study. In these interviews physicians were asked, amongst others, whether they would be interested in continued use of the information and whether there were any items that they would like to be included in future versions of the computer program.

Secondly all physicians in the experimental group were asked to complete a checklist at the end of a consultation of each participating patient, which consisted of four important questions:, a) Did you request the HRQoL information?, b) Did you use the information? c) Did you find the information useful? and d) Why (not)?

Attitudinal barriers on the part of the reception employees were inventorized while observing the process of care at the outpatient department on a daily basis.

Data analysis

The retrospective questionnaire administered to patients on reasons for not completing the assessment at the clinic and the checklist completed by physicians after each consultation were analysed quantitatively in SPSS 11.0, in terms of frequencies and percentages. Descriptive data is presented on the observed practical feasibility. Descriptive data on the interviews with physicians, which were intended to provide global information about physicians' experiences with, and opinions on, the HRQoL information, is also presented.

Results

Patients' and physicians' characteristics

All physicians working at the department of hepatology (n=11, 1 female) agreed to participate in the study. Their mean age was 39 years (range 27-55). The average working experience of the physicians was 8.7 years (range 0 – 27 years). Five hundred and eighty seven patients gave informed consent to participate (Fig. 1) of which 327 completed the measurements once or more. 260 patients who had consented to participate did not complete the measurements once. Demographic characteristics of the 327 participants are presented in Table 1, and comparisons were made with the 260 nonresponders.

Table 1. Demographic characteristics of patients in the study

	Respondents (n=327)	Non-respondents (n=260)	P
Gender (n, %)			
Women	144 (44)	108 (76)	0.46
Men	183 (56)	135 (42)	
Age (mean, range)	48.1 (20-81)	47.4 (18-80)	0.70
Diagnosis (n, %)			
Hepatitis B	47 (14)	43	0.00
Hepatitis C	47 (14)	54	
Cholestatic liver disease	33 (10)	31	
Pre-transplantation	18 (6)	1	
Post-transplantation	110 (34)	52	
Auto-immune hepatitis	23 (7)	16	
Other	49 (15)	47	
Disease Severity (n,%)			
No cirrhosis	206 (63)	153 (63)	0.95
Compensated cirrhosis	87 (27)	63 (26)	
Decompensated cirrhosis	34 (10)	28 (11)	
Nationality (n, %)			
Dutch	270 (83)	207 (85)	0.54
Moroccan	5 (2)	2 (1)	
Turkish	7 (2)	7 (3)	
Surinam	10 (3)	4 (2)	
Europe other	6 (2)	4 (2)	
World other	25 (7)	20 (7)	
Unknown	4 (1)	0 (0)	

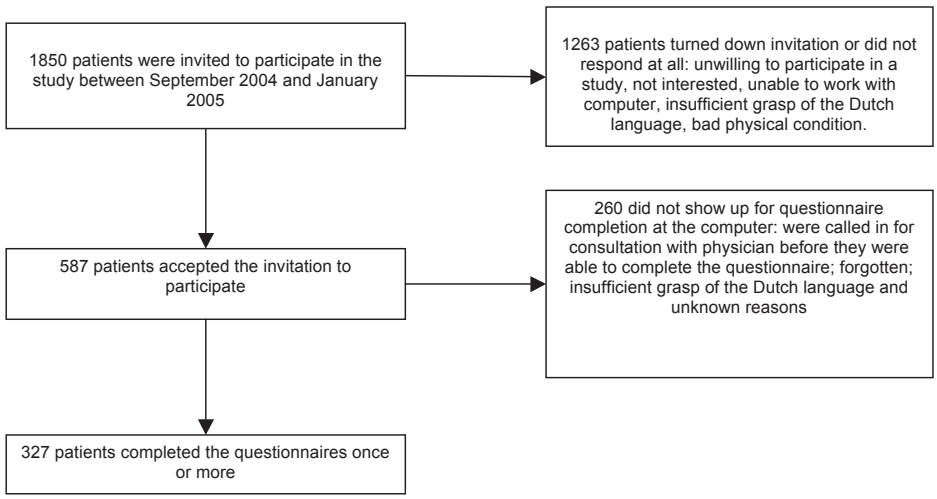
Differences were assessed by means of Chi-square tests (except for age: t-test)

Practical feasibility

Problems encountered during the development of the computer program

Developing a tailor-made computer program that met our needs with regard to the inclusion of our questionnaires of choice, lay-out, and instant availability of computerized graphical representations of the results to the physicians without violating patients' privacy, proved to be time-consuming and more costly than planned. Expertise of an IT professional was required. During the pilot testing phase, we discovered that administering the Short Form-36, the complete LDSI 2.0 and the complete first part of the QUOTE-Liver interfered with clinical routine. Consequently, we included shorter versions of the questionnaires in the actual trial [6]. Completion time was now on average 7.5 minutes, which we found acceptable since it did no longer interfere with clinical routine.

Figure 1. Patients in the study



Patients' ability to complete the HRQoL questionnaires

During the pilot testing phase, problems with patients' basic computer skills such as mouse handling, scrolling and entering digits in a designated field became apparent. Although participants with such limited knowledge of computers formed a minority, they required substantial assistance. The computer program used in the trial was amended in order to overcome these problems by making checkboxes larger and the entry field for the patient number more easily identifiable. In addition, a mouse pad was used that provided step-by-step instructions for the completion of the questionnaires. These improvements did not visibly improve patient participation. The mouse pad was mostly ignored, and entering the patient number remained difficult, mostly because patients did not know their number (estimation of ½). Basic mouse handling also remained problematic for a significant amount of patients (estimation of 1/5), which consequently required substantial assistance.

HRQoL questionnaire completion rate

At the end of the study, the HRQoL assessment in the clinic had occurred on 43% of the occasions (756 times out of the estimated 1761 times, which is a rough estimation based on the assumption that patients visited the outpatient department on average three times during the study (587x3=1761)). 260 participants never completed the HRQoL assessment on the computer at all, of which 16 due to substantial language problems. Only 105 patients completed the HRQoL questionnaires three times or more (Table 2). A retrospective exploration of the reasons for this low response rate was performed by means of a mailed questionnaire (response rate = 55%, 170 males, 145 females, mean age 50.0 years). The

main reason that was given for not completing the retrospective questionnaires was 'simply forgetting'. Other important reasons included 'no time' and 'did not feel like it'. Less often, reasons such as 'the computer was broken', 'there was no-one there to help me complete the HRQoL questionnaires', 'no-one told me to complete the HRQoL questionnaires' and 'the computer was occupied', were given. For an overview of all reasons given we refer to Fig. 2.

Figure 2. Participants' reasons for not completing the questionnaires

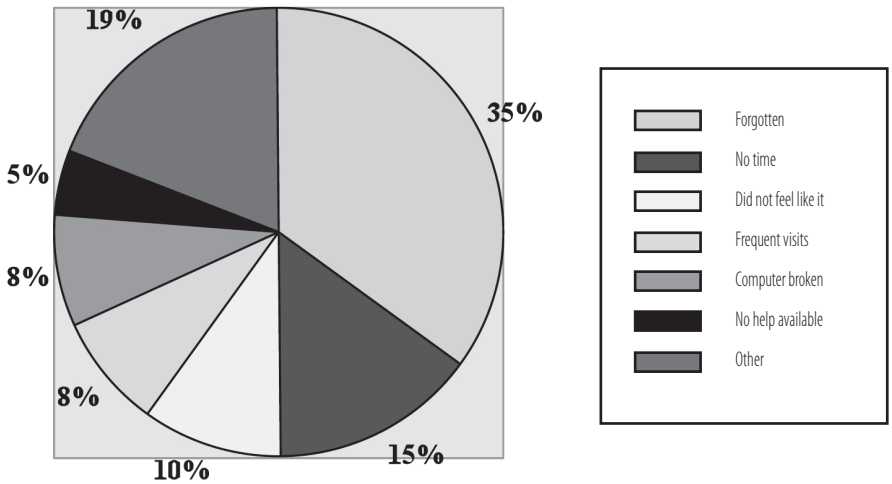


Table 2. Number of times that patients completed the questionnaires

	Times that questionnaires were completed									
	1	2	3	4	5	6	7	8	9	>9
Patients (n)	327	181	105	58	33	20	13	10	5	4

Logistical issues

Logistical issues that were observed at the outpatient department were forgetfulness of the reception employees to send patients to the computer and the computer being out of sight of the waiting room area.

Attitudinal barriers

Interviews with physicians

The interview data showed that all physicians would like to use the HRQoL information again in the future, especially for patients awaiting liver transplantation, patients with HCV, and nonnative speakers (mostly patients with HBV). They suggested embedding

the information in the existing patient information system and adding a screening tool for depression, especially for patients with HCV and/or patients awaiting liver transplantation, diagnostic questions (e.g. allergies, use of medication), questions about the social situation of younger people (e.g. school, friends, pass-times), and questions about expectations of the consultation.

Physician checklists

The physicians in the experimental group requested the information in 92% of the consultations, discussing it with their patients in 58% of the consultations. They indicated finding the HRQoL information useful in 45% of the consultations, mostly because it provided new information but also because it saved time and because it confirmed the verbal information and their own clinical impressions of patients who were doing well physically. These last two statements were also relevant for the one physician who claimed to know his patients well and did therefore not find the HRQoL information particularly useful. All physicians found the information less useful when patients were doing well, when they knew patients well and when patients were very talkative (Fig 3).

Observations

Attitudinal barriers were encountered on the part of the reception employees. Their busy schedule did not allow for much time to identify study participants and refer them to the computer. The importance to do so was not clear to them, and when no firm instructions were given, they often forgot to send patients to the computer.

Figure 3. Physicians' evaluations of the HRQoL information

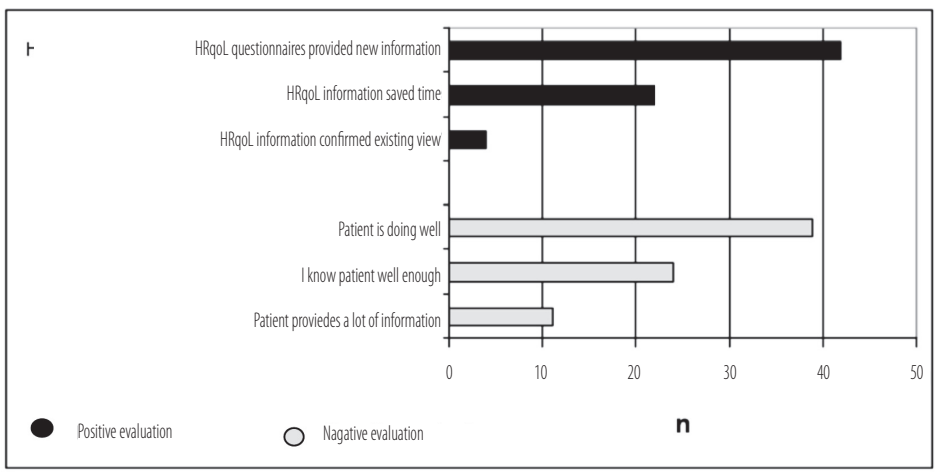


Table 3 . Advice to improve HRQoL measurements in clinical practice

Technical issues
For psychometric purposes, computerized questionnaires should resemble pen-and-paper versions as closely as possible
Hire an IT expert
Allow for development costs
Logistical issues
Location in the vicinity of the waiting room area (ideally the computer can be seen from the waiting room area)
Enough privacy
Availability of internet/network connection
Easily accessible to patients
Optimal patient participation
use of a touch-screen computer
very easy log-on procedure, eg. scanning the patient's punch card
questionnaires in multiple languages
short questionnaires
HRQoL assessment is considered part of clinical routine
Physicians and front desk employees ask patients to complete the questionnaires
Optimal physician participation
HRQoL data embedded in the existing patient information system
Add screening for depression
Bring in a local clinical leader as a spokesman for the importance of HRQoL measurement
Provide clear data output and clear instructions on how to interpret the data
Make clear that the data should not be used as clear cut-off points for treatment of referral decisions, but rather as a base for more directed discussion of psychosocial topics
Provide management options

Advice

The most important advice to improve HRQoL measurements in clinical practice that resulted from the current study is summarized in Table 3.

Discussion

The present study is, to the best of our knowledge, the first to describe a variety of feasibility issues encountered during the implementation of computerized HRQoL measurement in clinical practice, in a population of patients with chronic liver disease. Feasibility problems concerning technical aspects of developing a user-friendly computer program with safe data transmission over the Internet, patients' computer skills, and patients' compliance were encountered. Physicians were generally positive about the instant computerized availability of HRQoL information.

Technical problems that we encountered during the developmental phase of the computer program were substantial and cost substantial time and effort to correct.

Assistance from an IT professional is advised if one intends to develop a computer program that includes the particular questionnaires of interest, is easy for patients to complete, and transmits the information to the physicians' computer in such a way that privacy is assured.

With regard to patients' lack of basic computer skills, the use of touch-screen computers, which have been shown to be easy to handle by various patient populations [19, 25-29], is recommended when implementing HRQoL measurement in clinical practice. This may optimise patient participation, and the quality of the answers, which will be less biased by the presence of family members or friends that help with completing the questionnaires such as found in the study of Velikova et al (2002) [30].

A limitation of the present study was the high number of nonparticipants. Part of the explanation may lie in the fact that patients themselves were responsible for contacting their physician if they were interested in participating in the study. In addition, the number of non-Dutch speaking patients visiting the department of hepatology of the Erasmus MC is relatively large (Hepatitis B for example, is most common among people from North Africa). These patients were also invited to partcipate, but were not able to participate since the questionnaires in this study were only available in Dutch. Future studies should aim at including nonnative speakers, whose data are of particular interest to the physicians in this study.

The low compliance of patients that did participate in our study, is in accordance with findings of a previous study showing deterioration of compliance with longer follow-up [17]. Bad timing and other priorities were given as possible explanations. In our study, an explanation may lie in the small window of opportunity to complete the questionnaires before each consultation. Indeed, patients mentioned in the retrospective questionnaire that lack of time was one of the main reasons for not completing the questionnaires. Simply forgetting to complete the questionnaires was the most important reason, despite eye-catching posters that were put up in the waiting room. The fact that the retrospective question 'have you completed the questionnaires with each visit' was answered with 'no' in 57% of the cases supposes an honest attitude of the respondents, who were informed about the anonymity of their responses.

Considering these results, it seems that patient participation cannot be left to patients themselves, who may be nervous about the upcoming consultation and/or used to going to the waiting room after announcing themselves at the reception desk. To optimise participation it is, in our opinion, of vital importance that all staff of the department concerned, especially the reception desk personnel but also the nurses and physicians, approves of the intervention, considers it as part of standard clinical routine, and acts accordingly by sending patients to the computer before each consultation.

Attitudinal barriers to the successful implementation of computerized HRQoL measurement in clinical practice that have previously been described, concerned physi-

cians scepticism about the validity and importance of self-rated health, preferences for physiological outcomes over psychological outcomes, unfamiliarity with questionnaire scores, and doubts of their ability to intervene should the questionnaires reveal any problems (8, 15). We found only sporadic indications of such barriers. Bringing in a local clinical leader as a spokesman for the importance of self-rated health, clear data output and clear instructions on how to interpret the data, and instructions to use the HRQoL data as a basis for more directed discussion of psychosocial topics seemed to have conquered most of these barriers in our study.

The positive attitudes of the physicians in our study towards the availability of instant computerized HRQoL information during the consultation are in accordance with previous studies in oncology [18, 30], and advocate the continued use of such a procedure in patients with chronic liver disease. However, future studies should aim at including more liver specialists in order to substantiate these findings. Expressed concerns of an increase in workload as a result of the HRQoL data [30] were absent in our study. These positive findings in liver specialists, treating patients with a disease that is generally less acute and life threatening than cancer for instance, give incentive to further exploration of routine computerized HRQoL measurement in other specialisations within internal medicine such as nephrology or gastroenterology. When implementing such a procedure, it should be stressed to physicians that standardized HRQoL information should never replace the clinical dialogue between patient and physician, as important symptoms may then be overlooked, or exaggerated [30]. Rather, the HRQoL information should be seen as an indication of possible problems worth discussing and exploring further during the consultation.

Conclusions

This study addressed practical feasibility issues associated with routine computerized measurement of HRQoL at a busy outpatient department of Hepatology. Feasibility is an important requirement for more widespread implementation of such an intervention. Another requirement is that the intervention is effective in improving patients´ well-being and/or medical treatment. The current study has directly contributed to the first requirement by showing that the attitudes of physicians were generally positive, by identifying probable barriers towards successful implementation, and by providing solutions on how to overcome these barriers. These include hiring an IT expert, involving all personnel and using touch-screen computers. While the findings of the current study are encouraging they also emphasise that these implementation processes are complex and should not be underestimated. Further studying of the feasibility and ef-

fectiveness of routine computerized HRQoL measurements in clinical practice is needed before widespread implementation can be achieved.

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Effectiveness of measurement of health related quality of life in clinical practice: a randomised controlled trial in patients with chronic liver disease and their physicians

3

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Qual Life Res. 2008 Mar; 17 (2): 195-205.

Abstract

Background/Aims

This study assessed the effectiveness of computerized measurement and feedback of health related quality of life (HRQoL) in daily clinical practice, in patients with chronic liver disease.

Methods

162 patients (61% male; mean age = 47,5 years) regularly completed computerized HRQoL questionnaires before each consultation for the duration of one year. Six physicians were randomly assigned to the experimental group who received an instant online graphical output of the data. Five other physicians were randomly assigned to the control group who conducted their consultations as usual. Differences between both groups on generic- and disease-specific HRQoL, patient management, and patient satisfaction with the consultation were assessed, as were physicians' experiences with the HRQoL data and effects on their consultations.

Results

No direct effect of the experimental condition on patients' HRQoL was found. However, an interaction effect of the experimental condition and age was found: older patients in the experimental group had significantly better disease-specific HRQoL (F=4.16; p=0.04), and generic mental HRQoL (F=4.62; p=0.03) than patients in the control group. Also, male patients in the experimental group had better generic mental HRQoL than patients in the control group (F=6.10; p=0.02). Physicians in the experimental group altered their treatment policy significantly more often than did physicians in the control group (z=-3.73, p=0.00), and their experiences with the availability of HRQoL information were generally positive. The scores on patient satisfaction with the consultation did not differ significantly between patients in the experimental group and patients in the control group (z=-1.20, p=0.23).

Conclusions

Computerized measurement and feedback of HRQoL in a daily clinical practice of an outpatient department of Hepatology did not improve HRQoL for the whole group of chronic liver patients but, rather, improved disease-specific HRQoL of older patients with chronic liver disease and mental HRQoL of older patients and male patients with chronic liver disease. It also had an effect on patient management.

Introduction

Health related quality of life (HRQoL), or psychological-, social-, and physical functioning (1), has become an important outcome measure in medical care. Standardized assessment of HRQoL preceding each consultation may potentially provide physicians with valuable information. Several studies have shown that physicians vary in their ability to elicit psychosocial information, or that they underestimate patients' HRQoL (2-5). Furthermore, 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 (6-8).

Nevertheless, relatively few studies have assessed the value of HRQoL measurement in clinical practice. Some have shown positive results with regard to the acceptance by patients and physicians, or a significant increase in the identification and/or discussion of HRQoL related issues (9-14). Less consistent and favourable results have been obtained with regard to the effectiveness of standardized HRQoL measurement in actually improving HRQoL or psychosocial outcomes. Even though decreased depression (15), improved overall and emotional functioning (10), improved mental health (16), and a decrease in disease-specific debilitating symptoms of patients undergoing chemotherapy (13) have been associated with HRQoL measurement in clinical practice, several other studies did not find any significant improvement in HRQoL or psychosocial outcomes (9, 17-20). A possible explanation might be that the majority of the existing studies assessing the effectiveness of HRQoL measurement in clinical practice with regard to patients' psychosocial functioning or HRQoL have included oncological patients or patients from general practice. Oncological patients can be considered a special group due to the life threatening nature of the disease. Patients from general practice, on the other hand, may be too diverse and often presenting with generally minor complaints, which may hamper the discovery of beneficial effects. Both groups impede generalization of results to other chronic patient populations.

Two important studies (9, 10) used study designs where physicians were part of both the control and the experimental group, either by using a cross-over design (physicians were first assigned to one group, than crossed over to the other group halfway through the study) (9) or by assigning patients rather than physicians to the different groups (10). This may possibly have caused bias. Two systematic reviews have stressed the need for further research evaluating the effectiveness of repeated measurements of HRQoL in clinical practice (18, 20), and the need for further research to help health care professionals identify those patients that would benefit most from such interventions (20).

The study reported here differs from previous studies by including a patient population with chronic liver disease (CLD) in order to study the effects of HRQoL use in

clinical practice in a population which is more representative of other patients with a chronic disease. 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 the second most common reason for liver transplantation in the United States (21). CLD is a serious disease that is associated with significant physical and psychological symptoms such as impaired cognition, hepatic coma, fluid in the abdomen, abdominal pain, joint pain, fatigue, depression and anxiety (22-28). Not surprisingly, HRQoL in patients with chronic liver disease has been shown to be impaired (29, 30). Chronic liver disease is an appropriate example of a typical chronic disease, with patients experiencing substantial comorbidity and possibly mortality as is the case in other chronic diseases such as kidney disease and chronic obstructive pulmonary disease.

Our study also differs from previous studies by assessing the benefits of HRQoL measurement for patients with different demographic characteristics (e.g. men and women, young and old), which is essential for determining which patients are most likely to benefit from HRQoL measurement in clinical practice, a point recently reiterated in a systematic review on this topic (20). In addition, in our study, physicians rather than patients are assigned to the control- or the experimental group. This assigning of physicians to only one group prevents the bias of physicians being focused on discussing HRQoL when seeing patients in the control group.

The aims of the present study were twofold: the first was to assess the effectiveness of real-time computerized measurement of HRQoL in various patients with chronic liver disease (CLD) and presentation of the results to physicians before the consultation, in terms of improvement in patient HRQoL, patient management, and patient satisfaction with the consultation, by means of a randomised trial with repeated measurements. The second aim was to assess hepatologists' experiences with the availability of real-time HRQoL data of their patients, and to measure the possible effect(s) it had on their consultations.

Patients and Methods

Patient recruitment

This study was performed at the Department of Gastroenterology and Hepatology of the Erasmus Medical Centre, Rotterdam, where HRQoL measurement on a regular basis, was implemented for the duration of one year. All patients older than 17 years of age with chronic liver disease visiting the department between September 2004 and

January 2005 were invited to participate in the study. Written information about the study was sent to the patients three days before their consultation at the outpatient department. Patients interested in participating in the study informed their physician, who consequently directed them to the researcher for further explanation of the study and to sign an informed consent form. For this effectiveness study, we included all patients with two or more measurement moments. All physicians working at the department of Hepatology participated in the study. The protocol was in accordance with the ethical guidelines of the modified 1975 Declaration of Helsinki and approved by the Medical Ethics Committee of the Erasmus MC.

Study objectives

The primary aim of this study was to assess the effectiveness of computerized measurement of HRQoL in clinical practice. The primary outcome measures were patients' generic HRQoL (physical and mental component score separately) and disease-specific HRQoL. Secondary outcome measures were patient satisfaction with the consultation and patient management. The secondary aim of this study was to assess hepatologists' experiences with the availability of real-time HRQoL data of their patients.

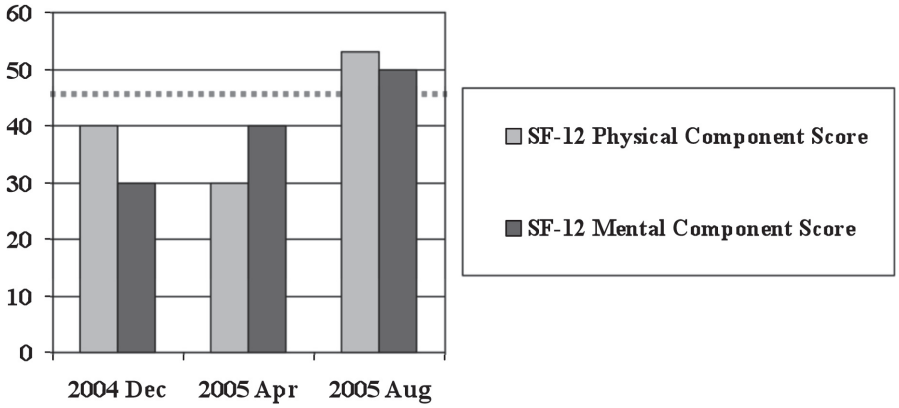
Study design and intervention

Physicians

Physicians were randomly assigned to either the experimental group or the control group by means of a restricted randomisation procedure called blocking. To ensure an equal amount of physicians in each group, it was decided to include six physicians in the experimental group and five physicians in the control group. We used a random sequence table to assign physicians to one of the conditions. Due to the nature of the intervention, it was impossible to blind physicians to group assignment.

Physicians in the experimental group were able to obtain an instant computerized graphical output of the HRQoL data of their patients, which also included data from previous measurement moments so that changes in patients' HRQoL could be monitored (Fig. 1). Prior to the study, physicians received instructions from a psychologist with expertise in the field of HRQoL measurement on how to interpret this output. First, the physicians were shown the questionnaires in order to familiarize them with the content. Second, they were informed that the red line in the graph was the average score of patients with chronic liver disease on the Short Form-36 measuring generic HRQoL, and that scores under this line were to be considered low. They were also told that the average score of healthy people on this questionnaire is 50. The physicians were instructed to interpret the disease-specific Liver Disease Symptom Index 2.0 (LDSI 2.0) at item level, with scores ranging from 1 (not at all), to 5 (to a large extent). The

Fig. 1 Example of the graphical output of patients' health-related quality of life as presented to physicians in the intervention group. A score of 50 is the average score of a healthy norm population. The *dashed line* represents the mean score for patients with chronic liver disease



physicians were asked to use the HRQoL data in all consultations for the duration of one year. No recommendations for specific responses were given. Instead, they were instructed to use their clinical experience to choose an appropriate treatment. After seeing a participating patient, physicians in both groups completed a checklist about the content of the consultation. Physicians in the control group conducted their consultations as usual.

Patients

Through the random assignment of physicians, patients were indirectly allocated to either group. Patients were initially blinded to the group assignment. All patients participating in the study completed a computerized generic- and disease-specific HRQoL questionnaire, and the first part of a pen-and-paper questionnaire on patient satisfaction with the consultation before each consultation at the outpatient Department of Hepatology for one year. They also completed the second part of the satisfaction questionnaire after the consultation. More specific information on the content of the questionnaires is provided in the section 'Study measures'. To ascertain good completion of the questionnaires, a researcher was always available at the outpatient department to answer questions about the computer and/or questionnaires at patients' request.

Study measures

HRQoL

Disease-specific HRQoL: This was assessed by means of theLDSI 2.0, which measures severity and hindrance of nine symptoms: itch, joint pain, pain in the right upper abdomen, decreased appetite, jaundice, fatigue, depressed mood, worries about fam-

ily situation and fear of complications (24). Because of time constraints, only items measuring severity of symptoms were included in this study (n = 9). The physicians were instructed to interpret the questionnaire at item level, with scores ranging from 1 (not at all) to 5 (to a large extent). For data analysis, a total score, ranging from 9 to 45, was computed by summing the scores of each item. The reliability of the LDSI 2.0 is good (internal consistency α>0.79), as is the construct validity (30).

Generic HRQoL: This was assessed by means of the Short Form-12 version 1 (SF-12). The SF-12 produces a Physical Component Summary (PCS) and Mental Component Summary (MCS), representing physical and emotional functioning respectively. The mean score of the PCS and MCS in the general population is 50 (standard deviation (SD) 10) with higher scores representing better HRQoL. The mean scores and standard deviations of the PCS and MCS of CLD patients was calculated from a large database (n=1175) (29, 31) (PCS: mean 43.2, SD 10.7; MCS: mean 44.4, SD 12.8). These means were used as a reference point (red line) in the graphical representation for the physicians, so they could easily identify patients scoring below average within the CLD group. The SF-12 has been shown to be reliable between test and re-test (MCS r=0.76, PCS r=0.89), and median relative validity estimates of 0.67 - 0.97 for the PCS and MCS, respectively, have been found (32).

Patient satisfaction with the consultation

Patients' satisfaction with the consultation was measured with the QUOTE-Liver, a newly developed questionnaire consisting of 20 items that assesses the discrepancy between patients' needs/expectations (importance: measured before the consultation, and the actual care that they receive (performance: measured after the consultation). The internal consistency of the overall QUOTE-Liver was excellent (α=0.90), as was the face validity: all patients (n=152) in the validation study, and three psychologists and a hepatologist agreed that the items of the QUOTE-Liver adequately reflected the most important aspects of care for CLD patients. Construct validity, as measured by the correlation between a VAS measuring overall satisfaction and the total score on the QUOTE Liver was good (r=0.69; p<0.01). Content validity was also good: none of the 152 patients in the validation study suggested new items to be included (Gutteling et al 2006, unpublished). A reduced version consisting of the nine items ranked by patients as most important and the two liver disease-specific items, was used in the present study. Using a formula applied for all QUOTE-instruments (10 - importance X performance), a total satisfaction score can be computed ranging from 0 tot 10, with 0 meaning not satisfied at all and 10 meaning completely satisfied (33).

Patient management

The effect of the intervention on patient management was measured by means of a checklist that physicians completed after each consultation with a study participant, including the question: "have you changed your treatment in any way?" and a subquestion: "If so, what have you done?" followed by several options: "Prescription of antidepressants", "Referral to psychosocial care", "Altering the frequency of consultations", and "Other".

Physicians' experiences

Experiences of physicians with the experimental condition were assessed through the checklists that they completed after each consultation with a study participant, asking the question: "Did you find the HRQoL information useful? Why?" with the answering options: "Yes it provided new information," "Yes it saved time," "yes,…," "No, the patient is doing well," "No, I know this patient well enough," "No, the patient tells me a lot," "No,…". Also, a semistructured interview was conducted six months into the study and at the end of the study. The interview included questions about the effort to request the HRQoL information, the usefulness of the information, whether the availability of HRQoL information increased the duration of the consultation and whether participating patients addressed HRQoL issues more often than patients who did not participate. Physicians were also asked if there were certain subgroups of patients whose HRQoL information they would find particularly useful. Opinions of physicians in the control group towards possible future availability of HRQoL information during the consultation were assessed by means of the same semistructured interview at 6 months only.

Statistical analysis

Sample size

A nonclustered power analysis based on a 'medium effect size' (Cohen's D = 0.50) with a 5% significance level and 80% power indicated that at least 64 patients were needed in each group in order to detect a statistically significant difference.

Data selection

For patients who were included in both groups because they had consultations with physicians from the control group as well as physicians from the experimental group during the year of the study, the data from the condition that they had been in most often was included (n=33). For patients who had been in both conditions equally (n=19), all data were excluded. The first measurement moment of all patients (T1) was

considered a baseline measure since no HRQoL data had yet been presented to the physicians.

Data analysis

Differences on the variables gender, diagnosis, disease severity and age between participants and non-participants were assessed by means of ^{2} tests or t tests. The same was done for assessing differences between patients in the control group and patients in the intervention group. Scores of participating patients on measurement moments (T2 - Ti) were summarized into one overall score per variable in the study. Univariate analyses of variance were performed in SPSS 11.0. Fixed factors were: age, gender, disease severity, presentation of HRQoL data to the clinicians (feedback), and interactions between these variables.

Differences in diagnoses between patients in both groups were controlled for by entering one propensity score of the variable diagnosis as a covariate in the analyses. Propensity scores were especially designed for situations where study participants could not be randomly assigned to groups, and their characteristics were therefore not balanced among the groups. A propensity score is defined as the conditional probability of assignment to a certain treatment group, given a set of observed pretreatment characteristics and is usually estimated by means of a logistic regression analysis (34). Thereby, the background characteristic(s), in this case diagnosis, is reduced to one single score, the propensity score. In the current study, we calculated the propensity score by entering the different diagnoses (HBV, HCV, cholestatic liver disease, pré-transplantation, post-transplantation, autoimmune hepatitis and other as dummy variables (M-1) in a logistic regression analysis. The unstandardized logistic regression weights were then multiplied by the relevant dummy variable and summed, together with the constant. This score was used in the univariate analysis to adjust for baseline confounding.

Univariate analyses of variance were performed for each outcome variable (disease-specific HRQoL and generic HRQoL MCS and PCS) separately. A forward technique was used in which the main effects of the fixed factors were assessed in the first block, and the interactions between feedback of HRQoL data and each of the other fixed factors (age, gender, disease severity) were explored in the second block. Differences between the two groups on patient management variables and satisfaction with the consultation were assessed by means of Mann-Whitney tests.

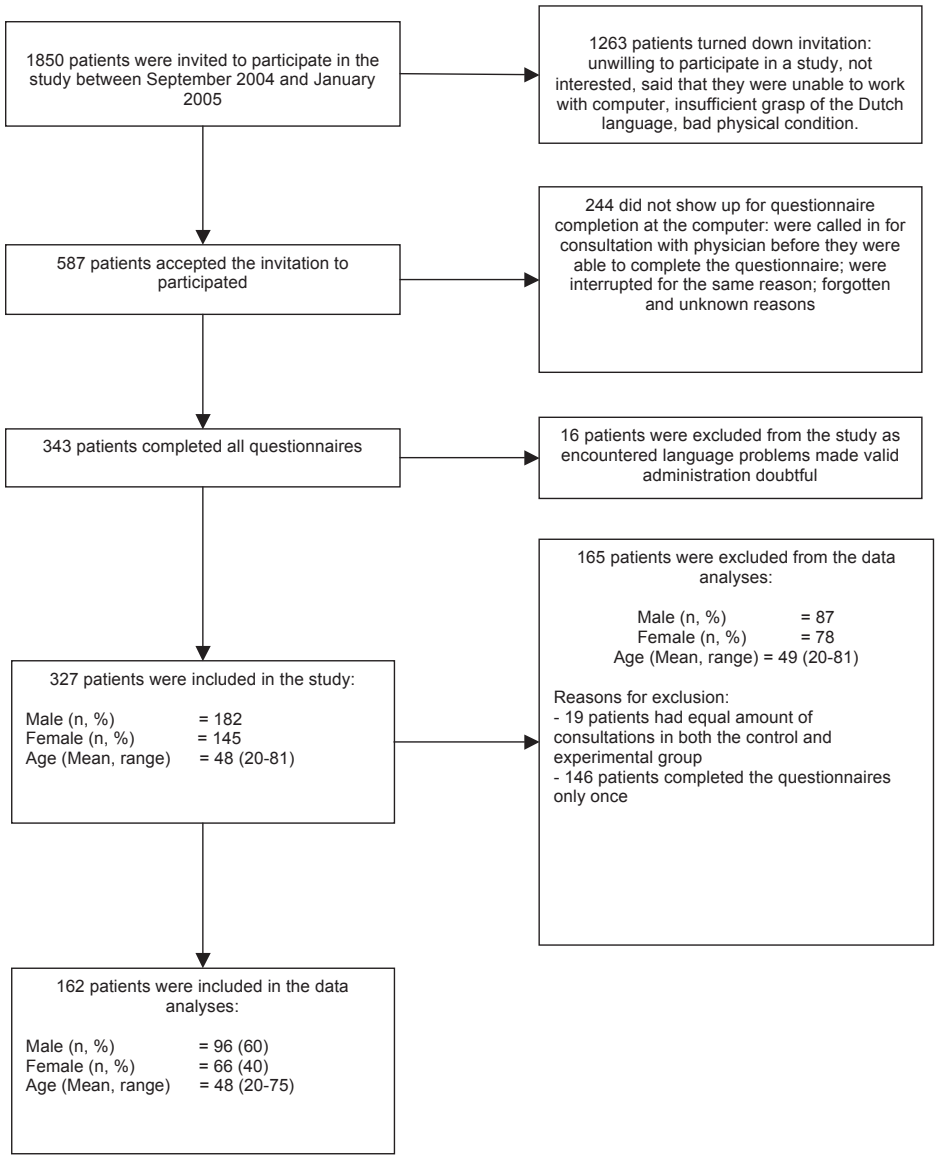
Hepatologists' experiences with the availability of real-time patient HRQoL data was assessed by means of semistructured interviews and checklists. These data were of a descriptive nature and are presented as such.

Results

Characteristics of patients and physicians in the study

Of the 587 patients that agreed to participate in the study, 181 completed the questionnaires more than once. Of these, 19 had been included in the experimental and

Fig. 2 Patients in the study



control conditions equally often and were therefore excluded from the analyses. One hundred and sixty-two patients (control group n=80, experimental group n=82) were included in the analyses (Fig. 2). Differences in age, gender, diagnosis, and disease-severity between patients in the study and nonrespondents are presented in Table 1. Demographic characteristics of the 162 patients included in the analyses are presented in Table 2. Patients in the control and experimental groups were comparable, except for the variables diagnosis and disease severity (Table 2). In the analyses, these differences between the conditions were controlled for. All physicians working at the Department of Hepatology (n=11, ten men) agreed to participate. Their mean age was 39 (range 27-55) years, and their average working experience was 8.7 (range 0 – 27) years.

Descriptives

The amount of times that patients in the control group and patients in the experimental group completed the questionnaires varied between two and 11 (Table 3). Mean scores of patients at T1 and T2-Ti on the outcome variables generic HRQoL and disease-specific HRQoL are presented in table 4.

Table 1. Differences in age, gender, diagnosis, and disease-severity between patients in the study and nonrespondents

	Patients in the analyses (n=162)	Patients excluded from the analysis P* (n=165)		Patients excluded from the study (n=260)	P*
Age (Mean, Range)	47.5 (20-75)	48.6 (20-81)	0.52	47.6 (18-80)	0.92
Gender (n, %)					
Male	96 (59)	87 (53)	0.24	136 (52)	0.21
Female	66 (41)	78 (47)		124 (48)	
Diagnosis (n, %)					
Hepatitis B	22 (13)	25 (15)	0.04	49 (19)	0.00
Hepatitis C	23 (14)	24 (15)		56 (22)	
Cholestatic Liver Dis.	11 (7)	22 (13)		32 (12)	
Pre-Transplantation	11 (7)	7 (4)		1 (0)	
Post-Transplantation	62 (38)	48 (29)		55 (21)	
Auto-Immune Hepatitis	12 (8)	11 (7)		18 (7)	
Other	21 (13)	28 (17)		49 (19)	
Disease Severity (n, %)					
No cirrhosis	101 (62)	105 (64)	0.43	159 (61)	0.96
Compensated cirrhosis	42 (26)	45 (27)		69 (27)	
Decompensated cirrhosis	19 (12)	15 (9)		32 (12)	

Differences were assessed by means of χ^2 tests (except for age: ***t*** test). Reference group for comparison of both P values is the group of patients in the analyses

Table 2. Characteristics of patients included in the data analysis

	Control group (n=80)	Experimental group (n=82)	P Value
Gender (n, %)			
Women	38 (48)	28 (34)	0.08
Men	42 (52)	54 (66)	
Age (mean, range)	47.5 (21 - 74)	47.6 (20 – 74)	0.98
Diagnosis (n, %)			
Hepatitis B	1 (1)	20 (25)	0.00
Hepatitis C	7 (9)	16 (19)	
Cholestatic Liver Disease	4 (5)	6 (7)	
Pre-Transplantation	5 (6)	3 (4)	
Post-Transplantation	43 (54)	23 (28)	
Auto-Immune Hepatitis	6 (7)	6 (7)	
Other	14 (18)	8 (10)	
Disease Severity (n,%)			
No cirrhosis	44 (55)	56 (68)	0.01
Compensated cirrhosis	16 (20)	22 (27)	
Decompensated cirrhosis	20 (25)	4 (5)	

Differences were assessed by means of χ^2 tests (except for age: ***t*** test).

Table 3. Questionnaire completion rate of patients in the control and experimental group

	Number of times questionnaires were completed								Total (n)
	2	3	4	5	6	8	9	11	
Control (n)	22	29	11	7	7	1	2	1	80
Experimental (n)	45	18	9	5	2	2	1	0	82

Effects of the experimental condition on patients' HRQoL and satisfaction with the consultation

Disease-specific HRQoL

There was no main effect for the experimental condition on disease-specific HRQoL. There was a statistically significant interaction effect for the variables age and feedback of HRQoL data on the outcome variable disease-specific HRQoL (Table 5): older patients (>48 years of age, as determined by the median split) in the experimental group had significantly lower total scores on the LDSI 2.0 (meanAdj=18.1, 95%CI: 15.3 – 21.0) ($F=4.18$; $p<0.05$), indicating better disease-specific HRQoL, than other patients, especially older patients in the control group (meanAdj=22.1, 95% CI: 19.9 – 24.3). This difference between older patients in the experimental group and the control group on disease-specific HRQoL is equivalent to a Cohen's D of 0.51, reflecting a "medium difference" (35).

Table 4. Patients' adjusted means and 95% confidence intervals at T1 and T2-Ti

	T1		P	T2-Ti		P
	Control	Experimental		Control	Experimental	
Overall						
SF-12 PCS	41.5 (39.0-43.9)	45.6 (42.0-49.3)	0.06	42.0 (39.6-44.4)	44.8 (41.4-48.3)	0.19
SF-12 MCS	43.4 (40.3-46.5)	46.0 (41.4-50.6)	0.35	43.8 (41.0-46.5)	44.8 (40.8-48.8)	0.69
LDSI 2.0	21.2 (19.0-23.4)	18.9 (15.7-22.2)	0.27	20.4 (18.6-22.2)	18.8 (16.1-21.4)	0.31
Male patients						
SF-12 PCS	10.2 (37.1-43.3)	47.0 (42.9-51.2)	0.10	41.3 (38.2-44.2)	45.7 (41.7-49.7)	0.29
SF-12 MCS	41.6 (37.7-45.4)	45.6 (40.4-50.8)	0.49	41.2 (37.8-44.6)	46.7 (42.1-51.2)	0.02
LDSI 2.0	22.8 (20.0-25.5)	18.1 (14.4-21.8)	0.10	21.4 (19.2-23.6)	18.0 (15.0-21.0)	0.14
Female patients						
SF-12 PCS	42.7 (39.2-46.3)	44.2 (39.8-48.7)		42.8 (39.4-46.2)	44.0 (39.7-48.2)	
SF-12 MCS	45.2 (40.7-49.6)	46.4 (40.8-52.0)		46.3 (42.4-50.2)	42.9 (37.9-47.8)	
LDSI 2.0	19.6 (16.4-22.8)	19.8 (15.8-23.8)		19.4 (16.9-22.0)	19.5 (16.3-22.7)	
Older patients						
SF-12 PCS	41.5 (38.4-44.6)	44.6 (40.7-48.6)	0.49	40.4 (37.4-43.3)	43.4-(39.9-47.5)	0.72
SF-12 MCS	41.5 (37.6-45.4)	46.3 (41.4-51.3)	0.26	41.2 (37.8-44.7)	45.9 (41.6-50.3)	0.03
LDSI 2.0	22.8 (20.0-25.5)	19.1 (15.6-22.7)	0.31	22.1 (19.9-24.3)	18.1 (15.3-21.0)	0.04
Younger patients						
SF-12 PCS	41.4 (37.9-44.9)	46.7 (42.2-48.6)		43.6 (40.3-47.0)	45.9 (41.6-50.3)	
SF-12 MCS	45.3 (40.9-49.7)	45.7 (40.0-51.3)		46.3 (42.5-50.2)	43.6 (38.7-48.6)	
LDSI 2.0	19.6 (16.5-22.7)	18.7 (14.7-22.8)		18.8 (16.2-21.3)	19.4 (16.1-22.6)	

The means at T1 and T2-Ti were obtained from the univariate analyses of variance with fixed factors: age, gender, severity of the disease, study group (control or experimental) and interactions between these variables. Differences in diagnoses between patients in both groups were controlled for. The significance level reflects the group for which the largest difference on the variable was found.

SF-12 Short Form-12, *PCS* Physical Component Summary, *MCS* Mental Component Summary, *LDSI 2.0* Liver Disease Symptom Index 2.0

Generic HRQoL

Mental Component Summary Score

No main effect for the experimental condition on mental HRQoL was found. However, a significant interaction effect for the variables age and feedback of HRQoL data was found. Older patients in the experimental group had higher scores on the SF-12 MCS (meanAdj=45.9, 95% CI: 41.6 – 50.3) ($F=4.62$; $p<0.05$), reflecting better HRQoL, than other patients, especially older patients in the control group (meanAdj=41.3, 95% CI: 37.8 – 44.7) (Table 6). Furthermore, a significant interaction effect was found for the variables gender and feedback of HRQoL data, with male patients in the experimental group showing higher scores on the SF-12 MCS (meanAdj=46.7, 95% CI: 42.1 – 51.2) ($F=6.10$; $p<0.05$) than other patients, especially male patients in the control group (meanAdj=41.2, 95% CI: 37.8 – 44.6) (Table 6).

Table 5. Interaction effects between age, gender, disease severity, and feedback, on the outcome variable disease-specific HRQoL, controlled for diagnosis

Source	F	df	P Value	R^2
Corrected Model	2.11	10	0.03	
Intercept	599.83	1	0.00	
Diagnosis (propensity score)	1.80	1	0.18	
Gender	0.04	1	0.85	
Disease Severity	3.39	2	0.04	
Age	0.84	1	0.36	
Feedback	1.05	1	0.31	0.08
Gender * Feedback	2.17	1	0.14	
Severity * Feedback	0.15	2	0.86	
Age * Feedback	4.18	1	0.04	0.12

Dependent variable: mean total score of the Liver Disease Symptom Index 2.0 (disease-specific health-related quality of life) for the measurement moments T2. . . Ti

Physical Component Summary Score

No significant main effect or interaction effects were found for the variables feedback of HRQoL data and age, gender, and disease severity on the SF-12 PCS.

Patients' satisfaction with the consultation

The scores on patient satisfaction did not differ significantly between the experimental and control group (z=-1.20, p=0.23). Also, no interaction effects of age, gender, and/or disease severity were found on this outcome variable.

Effects of the experimental condition on the consultation and on patient management

Physicians in the experimental group requested the information of their patients in 92% of the consultations, and they discussed it with their patients in 58% of the consultations. They indicated finding the HRQoL information useful in 45% of the consultations, which is generally in accordance with the percentage of patients in the experimental group scoring below average on the MCS (39%) and PCS (42%). They mostly found the HRQoL useless when a patient was doing well. Physicians in the experimental group indicated significantly more often than physicians in the control group that they spent more time than usual discussing psychosocial issues (30.7% versus 6.6% of the consultations, z=-6.65; p<0.001). Treatment policy was altered significantly more often in the experimental group (11% of the consultations vs. 1% of the consultations in the control group; z=-3.73, p<0.001). Most commonly, frequency of consultations was increased (n=5). Other alterations concerned prescription of medication (3), increased attention for physical complaints (4), referral to psychosocial care (1) or occupational health physician (1), and increased attention to explanations/reassurance (2).

Table 6. Univariate analysis of variance with the variables age, gender, disease severity, and feedback, on the outcome variable mental generic HRQoL, controlled for diagnosis

Source	F	df	P Value	R^2
Corrected Model	1.65	10	0.10	
Intercept	1337.05	1	0.00	
Diagnosis (propensity score)	1.34	1	0.25	
Gender	0.14	1	0.71	
Disease Severity	0.40	2	0.67	
Age	0.65	1	0.42	
Feedback	0.16	1	0.69	0.03
Gender * Feedback	6.10	1	0.02	
Severity * Feedback	0.13	2	0.88	
Age * Feedback	4.62	1	0.03	0.10

Dependent variable: mean total score of Short Form-12 Mental Component Summary (SF-12 MCS) (generic mental health-related quality of life) for the measurement moments T2. . . Ti

Physicians' experiences with the availability of HRQoL information in clinical practice

Experiences of the physicians in the experimental group at 6 months and at the end of the study did not differ. All physicians in the experimental condition found the HRQoL information useful, except for one older physician who claimed to know his patients very well. They indicated being better able to understand some of their patients through the extra information that was provided by the questionnaires. These physicians did not perceive requesting the information as an extra effort on their part. Furthermore, they did not think that using the information lengthened their consultations. All physicians in the experimental group indicated that they wanted to continue using the HRQoL information in the future. Physicians in the control group were similarly positive towards the possible availability of HRQoL information during their consultations in the future, on the condition that it would not be time consuming. This specifically concerned patients awaiting liver transplantation, patients with hepatitis C, and nonnative speakers (mostly patients with hepatitis B).

Discussion

Computerized, real-time measurement of HRQoL at a busy outpatient department of Hepatology, and presentation of the results to physicians before each consultation, did not show a main effect on patients' overall HRQoL. However, secondary analyses showed that the HRQoL measurements positively affected disease-specific HRQoL and generic mental HRQoL of older patients (>48 years of age) with CLD and also generic

mental HRQoL of male CLD patients. The results of the present study are among the first to show a beneficial effect of presenting HRQoL data to physicians in clinical practice. Most other studies have failed to show evidence for the actual improvement in HRQoL or psychosocial outcomes (9, 17-20). Of the studies that did find a beneficial effect, one showed a decrease in disease-specific debilitating symptoms (13), and another showed improved emotional functioning (10), which is in line with findings of our study. It should be noted that due to the cross-sectional data analyses, a causal relationship between the intervention and HRQoL could not be demonstrated. Future studies should address this in further detail.

Our study did not find differences between patients in the experimental- and patients in the control group with regard to satisfaction with the consultation, which is in line with findings from previous studies (9, 36, 37). The lack of observed differences between the study groups in this study may have been due to high levels of satisfaction, resulting in a ceiling effect.

This study was among the first to show a significant difference in patient management between the experimental- and the control group, with physicians in the experimental group mostly reporting a significant increase in the frequency of consultations. Our findings were statistically significant and in accordance with the findings of a systematic review (20) and subscribe to the increasingly acknowledged importance of using HRQoL information for the improvement of physician consultations (38). However, it should be noted that even though the differences in patient management between the control group and the experimental were statistically significant, the absolute numbers were small. Therefore, the results should be interpreted cautiously, and further studies using more elaborate methods of data collection - for instance monitoring patients' medical records or administering more detailed checklists - are recommended.

Physicians' experiences with using HRQoL information during the consultation were generally positive; requesting the information was not considered an extra effort on their part and they found the information especially useful for certain groups of patients such as patients awaiting liver transplantation, patients with hepatitis C, and non-native speakers. All physicians but one found the information useful for at least some (45%) of their patients. Physicians indicated finding the information least useful when patients were doing well or when they knew the patient well. These generally positive experiences are in accordance with findings from previous studies (9-14), which assessed oncologists' attitudes towards using HRQoL information in clinical practice. The confirmation of these results in hepatologists suggests that HRQoL information may also be well accepted by physicians treating patients with other chronic conditions. Another result of the present study was that when HRQoL information was available, more time was spent discussing psychosocial issues, and more treatments

were altered. Interview data and checklist data were contradictory about the duration of consultations when HRQoL information was available. In a previous study where the duration of consultations was timed, no increase in consultation time was found (14). Future studies should shed more light on whether the availability of HRQoL information increases the length of consultations in hepatology.

The strength of our study lies in the analyses performed, where benefits for specific groups of liver patients were explored by entering interactions between gender, age, disease severity, and feedback of HRQoL data, rather than solely investigating main effects between the intervention- and the control group. Also, this study included patients with chronic liver disease, rather than patients with cancer or patients from general practice, making it especially relevant to a more general population of patients with a chronic illness.

We are aware of several limitations of this study. First, physicians instead of patients were randomly assigned to either the intervention or control group. Randomisation is a complicated issue in these kinds of implementation studies, and both methods are subject to limitations. An important advantage of the randomisation of physicians is that the control group was not biased towards mentioning HRQoL topics more often than usual. Future studies using the same study design, but including more physicians, are needed in order to further explore possible main effects of HRQoL measurement on patients' overall HRQoL. A second limitation of this study was the high number of non-participants. Part of the explanation may lie in the fact that patients themselves were responsible for contacting their physician if they were interested in participating in the study. In addition, the amount of non-Dutch-speaking patients visiting the department is relatively large (Hepatitis B for example, is most common among people from North Africa). These patients were also invited to partcipate but were less likely to respond. The relatively large amount of patients who completed the questionnaires only once may be explained by the small window of opportunity to complete the questionnaires before each consultation. In addition, for such implementation endeavours, cooperation of al staff members is essential and future research should explore this further. A last limitation of this study was that the checklists that were used to assess the content of the consultations were not very detailed. This was done on purpose, as longer inventories would have compromised physician participation. However, considering the positive outcomes of this study, it is advisable that future studies consider ways to obtain a more detailed view of how the HRQoL information affects the content of the consultations, for example by recording consultations.

In conclusion, although a main effect of the intervention was not found, this study showed a beneficial effect of implementation of HRQoL measurement in clinical practice on the HRQoL of older and male patients with CLD and on patient management. Nevertheless, the study had several shortcomings, and further studies are needed to

substantiate these findings. Physicians' experiences with the availability of HRQoL information were positive, especially for patients awaiting liver transplantation, patients with hepatitis C, and nonnative speakers. They expressed an interest in continued use of HRQoL information. These results advocate the continued use of measuring HRQoL in a clinical practice of hepatology. Including older patients and male patients, who have been shown to benefit most from such a procedure, should be aimed for.

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Part

Determinants of HRQoL in patients with chronic liver disease

Determinants of quality of life in chronic liver patients

4

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Abstract

Background and Aim

Health-related quality of life of patients with chronic liver disease has been shown to be impaired in numerous studies. However, the factors which influence health-related quality of life in treated chronic liver patients are not quite known. This is the first study to assess the impact of physical and psychosocial determinants on a weighted score of health-related quality of life in patients with chronic liver disease.

Methods

The data of 1175 chronic liver patients was used to assess the relationship between items of the disease-specific Liver Disease Symptom Index 2.0 and the Short Form (SF)-6D weighted utility score by means of lineair regression analyses.

Results

Health-related quality of life was most strongly related to disease severity (B= -0.029) and joint pain (B= -0.023). Depression (B= -0.014), pain in the right upper abdomen (B= -0.014), decreased appetite (B= -0.014) and fatigue (B=–0.013) were also strongly related to health-related quality of life. In hepatitis C virus patients, disease severity (B= -0.037) and depression (B= -0.030) were strong determinants of health-related quality of life.

Conclusions

This study shows that health-related quality of life in chronic liver patients is clearly determined by disease severity, joint pain, depression, decreased appetite and fatigue. These patients may benefit most from interventions aimed at improving adaptation to the symptoms described.

Introduction

During the past decades, medical technology has improved dramatically and many otherwise fatal diseases have become chronic. Consequently, increasing attention has been paid to health-related quality of life (HRQoL) to complement clinical outcomes. With the possibility of liver transplantation and the increased success of medication treatment for many liver diseases, this has also been the case in hepatology. HRQoL is often defined as the impact of disease and/or treatment on a patient's physical, emotional and social functioning (1) . Numerous studies have shown that HRQoL is impaired in patients with chronic liver disease (CLD), and within this group, patients with chronic hepatitis C experience the lowest HRQoL (2-18). Despite the many studies that have shown a reduced HRQoL in hepatology, relatively few studies have investigated what factors influence liver patients' HRQoL. Disease severity, as indicated by stage of fibrosis (absent, early or advanced) or Child Pugh scores, seems to determine HRQoL (4, 5, 15). Such a relationship between disease severity and HRQOL seems fairly self-evident. Nevertheless one study did not find this relationship (19). Marchesini et al. (2001) found itch and muscle cramps to be of major concern in patients with cirrhosis (20) . Besides these mainly physical aspects of the illness, the predictive value of psychosocial aspects on HRQoL has also received some attention. Decreased energy and emotional reactions were found to be related to HRQoL in patients with primary billiary cirrhosis (17), although it remains unclear exactly which emotional reactions the authors refer to. Depression, anxiety and illness understanding were all related to HRQoL in patients with hepatitis C and liver patients with various disease aetiologies (3, 14, 17, 19, 21). Depression, anxiety and illness understanding are typically generic features of chronic disease. Other psychosocial factors, which are more specific to suffering from a liver disease, may influence HRQoL as well. These have not been studied previously.

Indeed, a recent study on the development of a disease-specific HRQoL questionnaire in hepatology emphasized that there are many more physical and psychological factors important in determining HRQoL in CLD patients (1). In that study The Liver Disease Symptom Index 2.0 (LDSI 2.0) was developed based on the results from prior studies and interviews with CLD patients about liver disease specific symptoms and health-related disabilities. In conjunction with important predictors such as depression and anxiety, domains such as itch, joint pain, fatigue, pain in the right upper abdomen, memory problems, change of personality, money problems and problems in sexual functioning were found to be of particular importance to CLD patients. The development of the LDSI 2.0 offers the opportunity to determine which specific symptoms for liver disease may influence HRQoL. Therefore the current study proposed to assess the predictive value of these patient-based items in determining HRQoL. These factors were studied in a large sample of patients who presented with a spectrum of diseases,

symptoms and signs, which is broader than that of an in-hospital patient population only.

Besides the dearth of research on factors influencing HRQoL in chronic liver patients, another shortcoming of HRQoL research in CLD patients is that all studies have operationalised HRQoL as a multidimensional, unweighted outcome. Such multidimensional unweighted outcomes make it impossible to compare a burden in different dimensions of HRQoL. For instance, with unweighted scores on different dimensions, it is impossible to ascertain whether a particular decrease in mobility is worse or less of a problem than a particular increase in pain. Typically, these articles present the observations for all HRQoL dimensions measured, which results in a presentation of results which is difficult to interpret. Moreover, the conclusions drawn from such multiple outcomes become contestable, as there is no way of telling if one result is more clinically relevant than the other. This means that it is yet undetermined which variables have the highest impact on the overall HRQoL in hepatology. In this study we use the SF-6D HRQoL questionnaire, which allows for a weighted overall score of HRQoL. The present study will be the first to make use of such 'utility scores' of HRQoL in relation to physical and psychosocial predictors.

Patients and Methods

Study population and measures

In an attempt to include a broad spectrum of chronic liver patients, we developed a cooperation with the Dutch Liver Patient Association (NLV). In October 2000, all 2020 members of the NLV were sent the LDSI 2.0 and the SF-6D on the assumption that they were well-informed patients that received best clinical care for their liver disease. Non-responders received a second mailing. Data collection was stopped five months after the first mailing. Anonymity was guaranteed and participants gave their informed consent by indicating their willingness to participate in the first question of the questionnaire. The protocol was in accordance with the ethical guidelines of the modified 1975 Declaration of Helsinki and approved by the Medical Ethics Committee of the Erasmus MC Rotterdam, the Netherlands.

LDSI 2.0

The LDSI 2.0 consists of 18 items. It measures severity of and hindrance that patients experience from nine symptoms: itch, joint pain, pain in the right upper abdomen, sleepiness during the day, worry about family situation, decreased appetite, depression, fear of complications, and jaundice. In this study, only the symptom severity scores were used. The LDSI 2.0 can be extended with six items considered to be important

by the board of the Dutch Liver Patient Association (NLV): memory problems, change of personality, hindrance in financial affairs, daily time management, decreased sexual interest, and decreased sexual activity. Scores are given on a five-point scale ranging from 'no symptoms at all' (1) to 'symptoms to a high extent' (5). A validation study revealed good feasibility and good test-retest reliability with weighed kappa's ranging from 0.32 to 0.99 with 13 of 18 items showing weighed kappa's of 0.63 or higher (22).

SF-6D

The SF-6D is based on a subset of questions of the SF-36 (23, 24), a widely used measure of HRQoL, and has recently been validated to produce a 'utility score' which ranks health states on a scale with the value 0.00 representing death to 1.00 representing full health (25). The SF-6D has been found to be reliable between test and re-test (26).

Disease severity

The severity of liver disease was determined as follows: respondents who reported having no cirrhosis and not ever having had splenomegaly, ascites or oesophageal variceal bleeding were classified as non-cirrhotic. Respondents who reported having cirrhosis or ever having had either splenomegaly or ascites or oesophageal variceal bleeding, but not in the year of investigation, were classified as compensated cirrhotic. Respondents who reported having had oesophageal variceal bleeding or ascites in the year of investigation were classified as decompensated cirrhotic.

Statistical methods

Lineair regression analyses were performed to investigate the predictive value of liver disease specific physical and psychosocial factors in relation to the utility score of the SF-6D. Demographics, i.e. age and gender, and medical variables i.e. use of interferon and disease severity as indicated by severity of clinical symptoms and fibrosis (no cirrhosis, compensated cirrhosis or decompensated cirrhosis) were controlled for. In order to compare the strength of the relationship between the SF-6D utility score and the various groups of independent variables, the variables were entered stepwise into the regression model in three separate blocks: (1) demographics, (2) medical variables and (3) physical and psychosocial factors. After each step, the total variance explained (R^2) by the included variables was assessed. This way, an increase in variance could be attributed to the added variables. Two separate analyses were run; one for all CLD patients excluding patients with hepatitis C virus (HCV) and one for HCV patients only.

Results

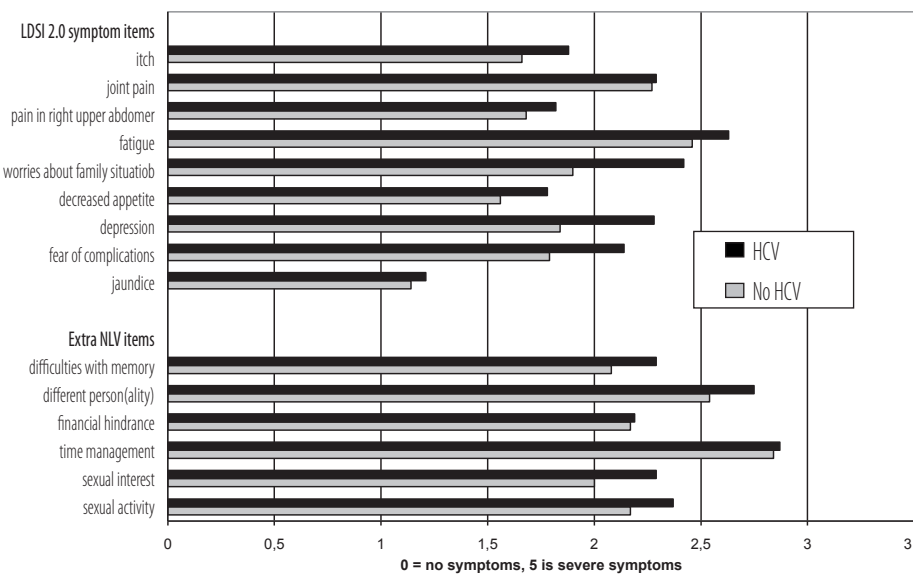
Patient characteristics

Characteristics of the study population are presented in Table 1. 2020 members of the Dutch Liver Patient Association were approached for this study. 374 of them were excluded because they were not patients; they had joined the patient association because of involvement with a family member or acquaintance with a liver disease. Of the members with a liver disease (93.6%) or a history of liver disease (6.4%) who were approached, 1243 responded (response rate = 76%). 1222 gave informed consent, of which 47 were excluded because they were younger than 18 years of age. In total 1175 respondents were included in the study. Demographics of these patients are shown in Table 1.

Determinants of HRQoL

Figure 1 shows the mean scores of experienced symptoms of all CLD patients without HCV and for HCV patients only as measured by the LDSI 2.0. The mean utility scores of both groups are shown in the legend. Table 2 shows the results of the regression analysis that was performed on the symptom items of the LDSI 2.0 and the utility score

Figure 1. Mean scores of patients with and without HCV on the symptom items of the LDSI 2.0



Mean SF-6D utility score of patients with HCV = 0.68

Mean SF-6D utility score of chronic liver patients without HCV = 0.71

Table 1. Patient characteristics

Patients, n	1175
Mean age ± SD, yr.	48 ± 12
Male, n (%)	497 (42.3)
Aetiology, n (%)	
Viral hepatitis	275 (24.6)
Autoimmune hepatitis	142 (12.7)
PBC/PSC	175 (15.7)
Hemochromatosis	98 (8.3)
Other liver diseases	171 (14.6)
Liver transplants	186 (16.6)
Liver diseases reported as cured	71 (6.4)
Disease severity n, (%)	
No cirrhosis	489 (42.5)
Compensated cirrhosis	391 (34.0)
Decompensated cirrhosis	84 (7.3)
Liver transplant	186 (16.2)

of the SF-6D. The total variance explained (R^2) is shown after each step, so that the increase in R^2 represents the contribution of the variables added at that step. The Bs shown in the table represent unstandardized regression weights. These should be interpreted as follows: with each point increase in the predictor variable, HRQoL changes by B, so that, for example, a 1 point increase in joint pain results in 0.02 point decrease in HRQoL in the overall group of CLD patients. Physical and psychosocial variables (step 3) as a whole explained 53% of the variance while demographic and medical variables only explained 7% in this population. Joint pain ($B = –0.023$, $p<0.01$) and disease severity ($B=–0.029$, $p<0.01$) were most strongly related to HRQoL, with more joint pain and worse disease severity resulting in reduced HRQoL. In addition, depression, pain in the right upper abdomen, fatigue and decreased appetite were also strongly related to HRQoL. Daily time management, memory problems, change of personality, age and gender showed a weaker, but nevertheless statistically significant relationship with HRQoL in the overall group of liver patients. In the group of patients with HCV, disease severity ($B= –0.037$, $p<0.001$) and depression were most strongly related to HRQoL ($B= –0.030$, $p<0.001$). Use of interferon, fatigue, joint pain and hindrance in financial affairs were also statistically significantly related to HRQoL in HCV patients, but less strongly than disease severity and depression (Table 2).

Table 2. Unstandardized regression coefficients B from the regression analyses with the SF-6D utility score as the dependent variable, while controlling for demographics and medical variables.

	SF-6D utility score All CLD patients except for hepatitis C B	SF-6D utility score Hepatitis C patients B
Demographics		
Gender male = 0, female = 1	-0.03**	0.016
Age	-0.001**	-0.000
Df	795	199
R^2	0.03	0.00
Medical variables		
Disease severity	-0.029**	-0.037*
Interferon use	-------	-0.081*
Df	795	199
R^2	0.07	0.07
Physical and psychosocial variables		
Itch	0.002	0.002
Joint pain	-0.023**	-0.011*
Pain in right upper abdomen	-0.014**	-0.000
Fatigue	-0.013**	-0.017*
Worries about family situation	-0.004	-0.007
Decreased appetite	-0.014**	-0.008
Depression	-0.014**	-0.030**
Fear of complications	-0.003	0.006
Jaundice	-0.001	-0.017
Memory problems	-0.006*	-0.011
Change of personality	-0.006*	-0.005
Hindrance in financial affairs	0.001	-0.010*
Daily time management	-0.009**	-0.005
Decreased sexual interest	0.001	-0.015
Decreased sexual activity	-0.005	0.001
Df	795	199
R	0.52	0.64

* $p<0.05$
** $p<0.01$

Discussion

This is the first study in which a weighted overall score of HRQoL was related to different physical and psychosocial issues of CLD patients. The regression analyses showed that HRQoL of patients with CLD (excluding hepatitis C) was most strongly determined by joint pain and disease severity. An increase of one point on the joint pain scale or the disease severity scale predicted a 0.023 and 0.029 point decrease in HRQoL respectively. Depression, pain in the right upper abdomen, fatigue, decreased appetite, memory problems, change of personality and daily time management also predicted HRQoL significantly in the overall group of chronic liver patients, but to a smaller extent. Regarding HCV patients, HRQoL was most strongly related to disease severity and depression. Use of interferon, fatigue, joint pain and hindrance in financial affairs were also significantly related to HRQoL in patients with HCV. Note that because of the high number of patients involved in this study, we were able to show that even less obvious items may have a relationship with quality of life. Indeed, many of the extra items of the LDSI 2.0 added on the basis of suggestions of the Dutch Liver Patient Association have a statistically significant relationship with quality of life.

When interpreting the results, it is important to realise that we are looking at associations between symptoms and HRQOL in a population receiving best clinical care. The remaining variance in both symptoms and HRQOL is the variance for which this clinical practice could not control. This explains why, for instance, a variation in disease severity has only a limited influence on HRQOL: most of that variance is controlled for by an apparently successful treatment. What is left of the variance in symptoms and HRQOL and the relation between them suggests room for clinical improvements.

Comparing the results of the present study with those presented in the literature, several considerations may be derived. Some findings were in accordance with the findings from previous studies, such as the relationship of depression and fatigue with HRQoL (14, 15, 19). However, contradictory to other studies, no relationship was found between HRQoL and disease-related worries (21) or itch (20). With regard to worry, it is possible that the difference in measurement instruments accounts for this discrepancy. Also, the 'worry' items could be different. Unfortunately it is not clear from Hauser's study which particular items investigated this dimension. Regarding itch, the difference in findings could be attributed to a sampling issue; the current study contained relatively few patients who experienced itch (2,7%), whereas Marchesini et al. investigated patients with cirrhosis who were therefore more prone to experiencing itch.

Most of the factors that were assessed in this study were neither supported nor contradicted by previous research simply because they have not previously been investigated. Of these factors, some significantly predicted HRQoL, namely: joint pain, pain in the right upper abdomen, decreased appetite, memory problems, change of

personality and daily time management. Factors that failed to determine HRQoL significantly were jaundice, hindrance in financial affairs, decreased sexual activity and decreased sexual interest. As explained above, this does not mean that for example jaundice could not have a influence on HRQOL, but in this patient population no such associations were found, quite possibly because the treatment has already reduced the problems caused by the disease.

A few limitations must be considered. First, this study was conducted in a group of liver patients from the NLV. We concede that becoming a member of a patient association is an action which could possibly induce a selection bias. Indeed, compared to a Dutch in-hospital population which was used in a validation study of the LDSI 2.0, this population differed significantly with respect to gender (more women), disease stage (less severe) and disease aetiology (less viral hepatitis, more liver transplant patients) (22). However, our aim was to include patients with a spectrum of disease and symptoms and signs which was broader compared to an in-hospital patient population only.

A second possible limitation of this study, which is inherent in the selection of the patient population, is that respondents reported the clinical characteristics, disease stage and aetiology of their disease themselves. However, a prior pilot study at the outpatient clinic demonstrated that liver patients are very much aware of the clinical symptoms they have or have had, and what type of liver disease they suffer from (15). Therefore, we are confident that this study provided reliable insight in the HRQoL of chronic liver patients.

A third limitation to this study is that the study population included patients who were transplanted or cured from their liver disease. Considering their limited number (n=71), these patients were included in this study all the same. To control for any bias these patients could cause, additional analyses were conducted without these two groups of patients. No significant differences were found between analyses that included all CLD patients and analyses that excluded transplanted and cured patients, except for the subscale 'change of personality (due to liver disease)', which did not relate statistically significantly to HRQoL when 'cured' and transplanted patients were excluded. This could be explained by the exclusion of transplanted patients that were rejoiced by the life saving treatment and the new life opportunities given.

A fourth limitation is that the physical and psychosocial factors used in this study to predict HRQoL consisted of only one item per dimension, so when it is stated in this study that depression predicts HRQoL significantly, it should be kept in mind that depression was not measured with a questionnaire specifically validated for the purpose of measuring depression. Nonetheless, a question asking to what extent they have felt down during the past four weeks gives a good indication, certainly for research which is based on data from a large sample of patients. Indeed, as emphasized earlier, the

results concerning the relationship between depression and HRQoL in CLD patients are in accordance with previous research (14, 19). It should be noted that the reliability and the validity of the LDSI 2.0, from which the items are derived, are good (22).

With the results of the present study, several suggestions for application in clinical practice can be made. In conjunction with slowing down the progression of the disease, treatment should focus on those aspects that are possibly modifiable and of significant influence on HRQoL, beyond the present treatment level. Strikingly, the factors that were found to determine HRQoL were in fact reasonably modifiable; joint pain, pain in the right upper abdomen, depression, decreased appetite, fatigue, daily time management, memory problems, and change of personality. Providing information on presence or absence of these symptoms to the physician by administering a short checklist to patients right before each visit may prove useful. Consequently, treating the symptoms might obviously be a way to enhance quality of life. For joint pain, institution of (drug) therapy may prove beneficial. Regarding decreased appetite, dietary advice to prevent malnutrition can be considered. For clinically depressed patients, some form of drug therapy or psychotherapy may be beneficial. An alternative, less obvious, intervention might consist of interventions that improve coping with the symptoms associated with chronic liver disease such as memory problems, pain in the right upper abdomen, change in daily time management, fatigue, and change of personality. These are symptoms that are not instantly visible but can have a huge impact on daily functioning. As these cannot easily be treated, patients have to adapt to these problems. As a treating physician, one of the approaches might be to offer participation in a cognitive behavioural programme. Cognitive behavioural treatment is based on the assumption that inappropriate thoughts and behaviors adversely affect well-being. Therefore, teaching patients to adjust their cognitions and behaviors will positively influence quality of life. Interventions based on cognitive behavioral therapy have already been proven to be effective in patients with other chronic diseases (27-30), and may therefore be of most benefit to this patient group.

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Psychological determinants of health related quality of life in patients with chronic liver disease

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Abstract

Objective

To assess the interrelationships of multiple psychological factors and health related quality of life (HRQoL) in patients with chronic liver disease (CLD).

Methods

Both direct and indirect relationships among HRQoL, depression, anxiety, coping and self-efficacy in 164 patients with CLD were assessed.

Results

Depression had a strong direct influence on HRQoL in all three groups of liver patients (β =-0.68). Depression was largely determined by low self-efficacy (β =-0.50) and possibly by use of maladaptive coping strategies (β =0.38).

Conclusion

HRQoL in CLD patients may be positively affected by improving levels of depression, through enhancing coping and self-efficacy skills.

Introduction

The negative impact of chronic liver disease on health related quality of life (HRQoL) of patients with chronic liver disease (CLD) has long been established (1-13). In daily clinical practice, knowledge of this negative association becomes particularly valuable with knowledge of treatable physiological or psychological factors that may potentially influence HRQoL. Recently, several studies have identified psychological factors that are related to HRQoL in patients with chronic liver disease: fatigue, anxiety, depression, and disease related worries (9, 10, 14-24). Many published studies have tended to discuss a limited number of psychological variables at a time, without attempting to examine them in one integrated framework. This complicates the efforts to determine the variable with the strongest relationship with HRQoL. Furthermore, previous studies used multiple scores of HRQoL and therefore multiple outcome variables, which makes the interpretation of the results and the comparability between studies difficult. Finally, previous studies have, to the best of our knowledge, not taken into account two variables that are known to influence HRQoL, namely coping and self-efficacy, which have been shown to affect HRQoL, but never with regard to CLD (23, 25-32).

Considering the size of the patient population that is affected by CLD, the severity of the disease and the chronic nature of the symptoms, there is a need to examine the interaction between psychological variables more closely as they can act as a target for interventions in order to improve HRQoL. Therefore, the aim of the present study was to investigate the relationship of several psychological variables with HRQoL simultaneously in a population of patients with chronic liver disease, with emphasis on establishing a detailed view on the direction of the interplay of the variables.

To that end, three hypotheses about the interrelationships of the psychological variables were integrated into one model. Since no such study has been conducted with chronic liver patients before, the hypotheses were based on clinical practice as well as existing studies with other patient populations (23, 25-27, 33-40).

The three hypotheses which were tested in the model are: (1) depression and anxiety affect HRQoL directly, (2) maladaptive coping may affect HRQoL either directly, or indirectly through elevated anxiety- and depression scores, (3) low perceived self-efficacy may affect HRQoL through its associations with maladaptive coping strategies and elevated depression- and anxiety scores.

Methods

Participants

Questionnaire booklets were sent to 250 patients with the most common forms of chronic liver disease (cholestatic liver disease (n=80), Hepatitis B (HBV) (n=79), Hepatitis C (HCV) (n=91)) who were selected from 15 consecutive consulting hours at the department of Hepatology of the Erasmus MC (Rotterdam, the Netherlands). Their medical data were obtained from the medical database. Patients had to be 18 years of age or older. Informed consent was given by returning the questionnaire booklet. The protocol was in accordance with the ethical guidelines of the modified 1975 Declaration of Helsinki. Since the questionnaire booklets were only administered once and did not include invasive questions, ethical approval was not necessary under Dutch regulations.

Measurement instruments

Health Related Quality of Life

HRQoL was measured with the Short Form-6D (SF-6D), which is based on a subset of questions from the widely used Short Form-36, with good reliability and validity (41, 42). Recently the SF-6D been validated to produce a 'utility score' which ranks health states on a scale with the value 0.00 representing death to 1.00 representing full health (43).

Depression

Depression was measured with the Dutch version of the Beck's Depression Inventory (BDI-II-NL), a 21 item self-report rating inventory (44). The total score ranges between 0 and 63 with scores below 14 considered normal, a score of 14 to 19 indicating mild to moderate depression, a score of 20 to 28 indicating moderate to severe depression and scores higher than 28 indicating severe depression. Validity and reliability of the BDI have been established (45-47).

Anxiety

Anxiety was measured with the State-Trait Anxiety Inventory (STAI), which is one of the most widely used instruments for measuring anxiety in adults. In this study, only trait anxiety was being measured, referring to a general tendency to respond with anxiety to perceived threats in the environment. The trait anxiety scale consists of twenty statements assessing how respondents feel generally. Scores can vary between 20 and 80, with higher scores indicating more anxiety. Norm data are available(48). The STAI has proven to be valid and reliable (48).

Self-Efficacy

Self-efficacy, which refers to the optimistic self-belief that one can perform difficult or new tasks, or that one can cope adequately with adversity, was measured with the 10-item Self-Efficacy Scale (49). Scores vary between 10 and 40, with a higher score indicating more self-efficacy. High reliability and construct validity of the SES were confirmed in earlier studies (50, 51).

Maladaptive coping

Maladaptive coping was derived from the short version of the Cognitive Operations Preference Enquiry called the COPE-Easy, which is a validated questionnaire that assesses individuals' coping responses when confronted with stressful situations and adversity (52, 53). The items comprising maladaptive coping were selected on the basis of principal component analysis with varimax rotation. Items mainly fell into two groups of coping reactions: adaptive and maladaptive coping, which is consistent with prior research (33). Preliminary analysis showed no or weak relationships of adaptive coping with the psychological variables (depression, anxiety, HRQoL and SE) assessed in this study. Maladaptive coping did show statistically significant relationships with these psychological variables and was therefore included in this study. Maladaptive coping consists of four subscales considered detrimental to patients' well being, including: 1) 'getting upset', 2) 'denial', 3) 'behavioural disengagement', which refers to giving up, and 4) 'substance abuse', which refers to alcohol, smoking, and medication.

Statistical modeling

Structural Equation Modeling (SEM) is a statistical methodology that considers a confirmatory (i.e. hypothesis testing) approach to the interdependency of variables. This interdependency distinguishes endogenous variables (i.e. outcome variables, dependent variables) from exogenous variables (determinants, predictor variables, independent variables). SEM enables to identify, to estimate and to test the interdependency in terms of manifest and latent variables. SEM has several advantages over multivariate explorative procedures like regular factor analysis: it takes a strict confirmatory rather than an exploratory approach to data analysis by demanding that the relationships between variables be specified a priori, and it is capable of assessing or correcting for measurement error. In this study the interdependency of manifest variables was explored. A special kind of SEM is path analysis, which was used in this study. Path analysis was originally developed by Wright (1934) (54) and later introduced in the fields of econometrics (55) and social sciences (56). Path analysis is tailored to assess the impact of one variable (i.e. exogenous variable) on another (i.e. endogenous variable) in a non-randomized trial. Typically, in a path model a variable might be both endogenous and exogenous simultaneously. Relationships between variables are specified a priori,

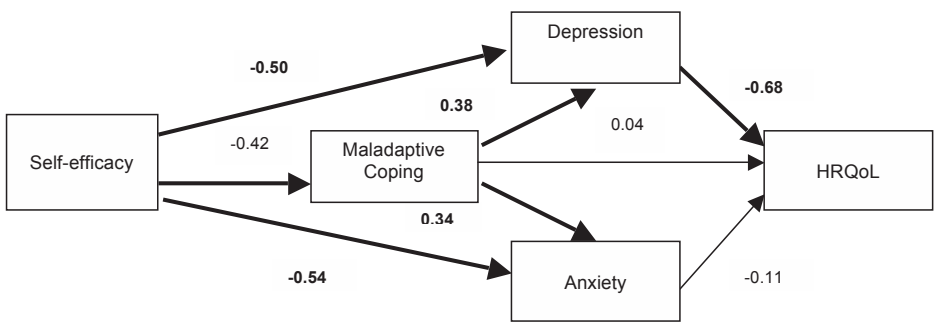
and are one-way. Since the data in this study were cross-sectional, it is not possible to draw conclusions in terms of causality.

To apply the advantages of SEM models at full, the models should be built on substantive grounds and, in addition, be as simple as possible (54). To test the adequacy of the models, Chi-squared tests were used to determine the model-fit. The value of 2, its p-value and the number of degrees of freedom (df) were examined. A non-significant p-value ($p>0.05$; (54)) and the ratio of 2 / df <1.5 represent a good model fit. Four other goodness-of-fit indices were also used: the Comparative Fit Index (CFI) (53) and the Tucker Lewis Index (TLI) (55), the Root Mean Square Error of Approximation (RMSEA) (56) and the Standardized Root Mean Square Residual (SRMR). For the model to fit, the CFI and TLI must be above 0.95, the RMSEA, as well as the SRMR, preferably lower than 0.05. In this study, the interrelationships of the different variables in the model were expressed in terms of standardized regression weights. The regression weights represent the strength of a relationship, while taking into account the other relationships supposed in the model. The direction of the relationship is always one way. The regression weights can be interpreted as follows: for each point increase in z-score of the determining variable the outcome variable will in- or decrease by the standardized regression weight.

Statistical analysis

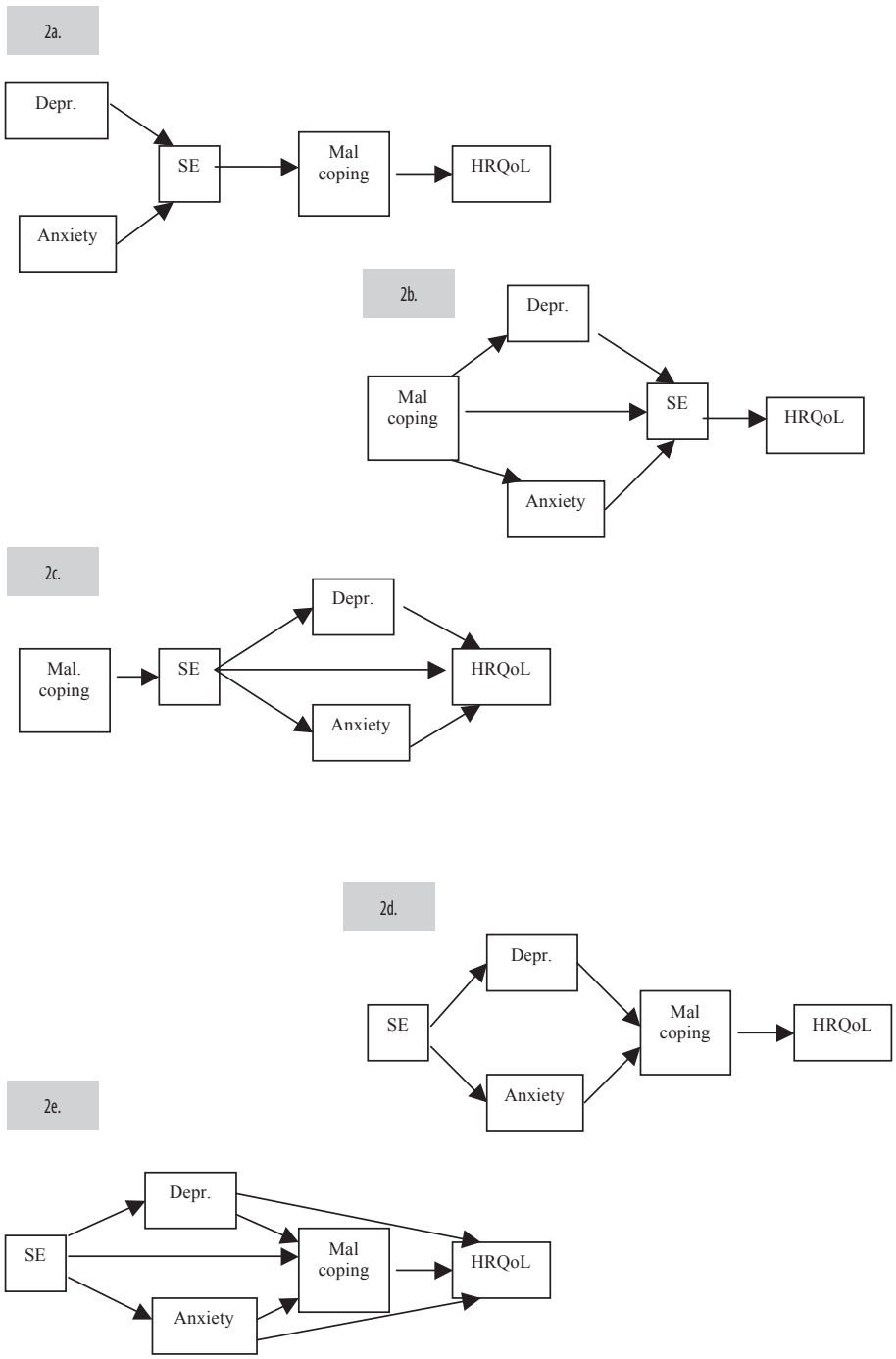
First, the mean scores and standard deviations on HRQoL, depression, anxiety, coping and perceived self-efficacy of patients with HBV, HCV and cholestatic liver disease were described. Figure 1 shows the hypothesized model that tried to estimate the likelihood that HRQoL is influenced by treatable psychological factors.

Figure 1. Hypothesized model with standardized regression coefficients of patients with chronic liver disease.



Statistically significant ($p<0.05$) relationships are marked in bold.

Figure 2. Competing models



Our data analysis strategy was the following: The interrelationships of the variables HRQoL, depression, anxiety, coping and self-efficacy, as represented in Figure 1, were analyzed in Mplus, version 5 for all CLD patients (58). The exogenous variable was self-efficacy and the endogenous variable was HRQoL. The other variables in the model were both endogenous and exogenous. In order to assess the influence of disease severity on HRQoL, the model was tested again with a dummy variable representing the presence of absence (value=0) of (de)compensated cirrhosis (value=1).The hypothesized model was explored for differences in diagnosis (HBV, HCV and cholestatic liver disease) by simultaneously adding these as subgroups in the analysis. It was explored which relationships between the parameters were the same for all subgroups, and which relationships differed, by fixing as many relationships as possible while maintaining adequate model fit.

In order to test the hypothesized model, the goodness of fit of this model was compared to the goodness of fit of several "competing models". These competing models are shown in figure 2 and were constructed by varying the interrelationships of the variables. Since findings from the literature and clinical experience were already incorporated in the original model (Fig. 1), the competing models could only be based on common sense and may therefore be less convincing, but nevertheless plausible. Model 2a and 2b reflect the hypothesis that depression and anxiety influence self-efficacy instead of the other way around such as in the original model. In model 2c, it is hypothesized that maladaptive coping influences self-efficacy. Model 2d reflects the hypothesis that depression and anxiety influence HRQoL only indirectly, via maladaptive coping, instead of directly which is hypothesized in the original model. Model 2e states that, contrary to the original model, depression and anxiety influence maladaptive coping instead of the other way around.

Results

Patient characteristics

Of the 250 patients that were sent a questionnaire booklet, 175 responded (response rate = 70%). The non-respondents were mostly male (68%) with an average age of 47.2 years. Of these, 13 were diagnosed with cholestatic liver disease, 22 with HBV and 40 HCV (Table 1). Eleven respondents used interferon, which can induce a temporary state of depression, and were therefore excluded from the analyses. One hundred and sixty-four patients were included in the analyses (89 (54%) male, 75 (46%) female). Of these, 55 had HBV, 43 had HCV, and 66 had cholestatic liver disease. Their mean age was 45.8 (Table 1). Differences on the variables age, gender and diagnosis between respondents and nonrespondents were assessed by means of χ^2 tests or a t test. Respondents and nonrespondents differed significantly on the variable diagnosis, with a significantly larger percentage of HCV patients in the nonrespondent group (Table 1).

Table 1. Demographic characteristics of the respondents included in the analyses and nonrespondents.

	Respondents (n=164)	Non-respondents (n=75)	P
Gender (n,%)			
Male	89 (54)	51 (68)	0.05
Female	75 (46)	24 (32)	
Age			
Mean (SD)	45.8 (12.9)	47.2 (12.3)	0.18
Diagnosis (n, %)			
Hepatitis B	55 (34)	22 (43)	0.00
Hepatitis C	43 (26)	40 (53)	
Cholestatic liver disease	66 (40)	13 (17)	

Of the 164 patients who participated in the study, 161 patients (98%) completed the BDI-II-NL and 160 (98%) completed the STAI and the self-efficacy questionnaire. The COPE-Easy was completed by 157 (96%) and the SF-36 by 154 patients (94%). The mean scores of patients with HBV, HCV and cholestatic liver disease on HRQoL, depression, anxiety, self-efficacy and maladaptive coping are presented in Table 2. Correlations between HRQoL, depression, anxiety, self-efficacy and maladaptive coping are shown in Table 3. The mean reliability coefficients of the variables were: BDI-II-NL α=0.94, STAI α=0.33, maladaptive coping α=0.83, HRQoL α=0.81.

Table 2. Mean scores of patients with HBV, HCV and cholestatic liver disease on HRQoL, depression, anxiety, self-efficacy and maladaptive coping.

	HBV (N=55)		HCV (N=43)		Cholestatic (N=66)	
	Mean	SD	Mean	SD	Mean	SD
HRQoL	0.77	(0.14)	0.66	(0.14)	0.75	(0.13)
Depression	11.68	(11.24)	18.87	(13.51)	10.00	(7.63)
Anxiety	40.94	(13.47)	45.80	(14.10)	38.57	(11.49)
Self-Efficacy	30.80	(6.24)	29.28	(7.06)	31.85	(5.65)
Maladaptive coping	1.75	(0.65)	1.83	(0.62)	1.58	(0.52)

Table 3. Correlations between HRQoL, depression, anxiety, self-efficacy and maladaptive coping.

	HRQoL	Depression	Anxiety	Self-efficacy	Maladaptive Coping
HRQoL		-0.75**	-0.67**	0.48**	-0.45**
Depression			0.85**	-0.66**	0.60**
Anxiety				-0.68**	0.57**
Self-efficacy					-0.42**
Maladaptive Coping					

** p<0.01 (2-tailed)

Structural Equation Modeling

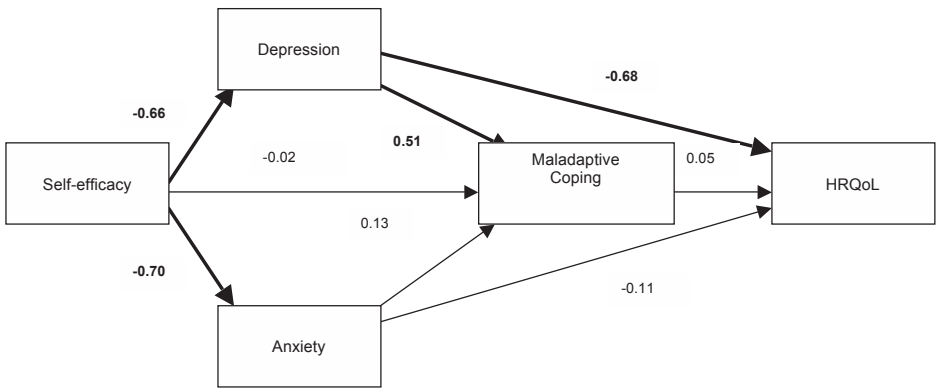
The hypothesized model showed good model fit ($\chi2$=0.63, df=1, p=0.43, CFI=1.00, TLI=1.00, RMSEA=0.00, SRMR=0.00) and is presented in Figure 1. The standardized regression weight that accompanies each arrow in the models represents the strength of the relationship between the variables. Statistically significant relationships (p<0.05) between variables are marked in bold. Depression had the strongest direct relationship with HRQoL (β=-0.68). Self-efficacy was related to depression (β=-0.50) as was maladaptive coping (β=0.38).The model testing was rerun including a variable representing disease severity (absence (value=0) or presence of (de)compensated cirrhosis (value=1)). Disease severity had a modest but statistically insignificant relationship with HRQoL β=0.08, p>0.05). Subsequently, the model was tested for patients with cholestatic liver disease, HBV, and HCV by adding these as subgroups in the analysis. We fixed the relationships between self-efficacy and depression, self-efficacy and maladaptive coping, self-efficacy and anxiety, anxiety and HRQoL and depression and HRQoL. Adequate model fit was maintained ($\chi2$=19.32, df=13, p=0.11, CFI=0.99, TLI=0.97, RMSEA=0.10, SRMR=0.11). The path coefficients in the model were similar for all three subgroups of patients except for the relationships between maladaptive coping and HRQoL (range of β = -0.01 – 0.17), maladaptive coping and depression (range of β = -0.48 – 0.58) and maladaptive coping and anxiety (range of β = 0.23 – 0.42). Depression showed the strongest direct relationship with HRQoL (β = -0.58). The final model (Figure 1) was compared with five competing models (Figure 2a to 2e). Four of

these had bad model fit (Table 4). However, one competing model (Fig. 2, model 2e) had adequate model fit (χ2=0.32, df=1, p=0.57, CFI=1.0, TLI=1.01, RMSEA=0.00, RMSR=0.01) and is shown in more detail in Figure 3. This model was largely similar to the hypothesized model. The difference lies therein that the relationships between maladaptive coping and depression and anxiety were inversed.

Table 4. Goodness-of-fit indices of the competing models

Model	X2	df	p	CFI	TLI	RMSEA	SRMR
1	0.63	1	0.43	1.00	1.00	0.00	0.00
2a	133.00	5	0.00	0.56	0.22	0.42	0.22
2b	82.40	3	0.00	0.84	0.46	0.42	0.13
2c	44.27	3	0.00	0.92	.072	0.31	0.11
2d	89.23	4	0.00	0.83	0.57	0.38	0.15
2e	0.32	1	0.57	1.00	1.01	0.00	0.01

Figure 3. Competing model with good model fit



Statistically significant (p<0.05) relationships are marked in bold

Discussion

The main objective of this study was to test the hypothesis that various potentially treatable psychological variables are related to HRQoL in patients with chronic liver disease. The hypothesized model tested for patients with HBV, HCV and cholestatic liver disease showed good model-fit, meaning that the a priori hypothesized relationships between the variables are plausible: depression had a direct effect on HRQoL in all patients with chronic liver disease. Self-efficacy and maladaptive coping, had an indirect effect on HRQoL, through depression. Direct relationships between HRQoL and anxiety and coping were present in the model, but they were very weak, indicat-

ing a negligible direct contribution of these factors to HRQoL. Disease severity was of modest influence on HRQoL while not significantly altering the proposed model. This is in line with previous research, which has also shown a relationship between disease severity and HRQoL in this specific patient population (4). The model did not differ between patients with different diagnoses (HBV, HCV or cholestatic liver disease). Path coefficients generally were similar, with depression showing the strongest relationship with HRQoL. Relationships of maladaptive coping with HRQoL, depression and anxiety did differ. This suggests that maladaptive coping has a different influence on these variables for these subgroups of patients. This finding of an unclear role of coping in the model also emerges from the competing model. Further research is needed to explore these findings.

These findings are in accordance with previous studies using different patient populations, which showed direct relationships between depression an HRQoL (24, 33, 34, 62), and indirect relationships between HRQoL and negative/ maladaptive coping and self-efficacy through depression (33, 34). This previous finding of a direct relationship between maladaptive coping and depression suggests that maladaptive coping affects depression, and not vice versa, as our alternative model proposed. A direct relationship between anxiety and HRQoL, which was found in one previous study in patients with coronary artery disease (62), was not replicated in our study with CLD patients. The acute nature of a stroke or heart attack compared to the more chronic nature of liver failure, may explain this finding. The finding of a previous study of a direct effect of HRQoL on depression (instead of vice versa) in patients with psoriasis (63), was not tested in the current study in which HRQoL was the outcome measure, and can therefore not be confirmed nor rejected. The possibility of such a relationship existing in patients with CLD is one that needs further exploration in future studies.

A limitation of SEM, and therefore of the present study, is that not all models imaginable can be tested since one has to choose which models to test, often based on theory and/or clinical experience. As a result, the finding of a plausible model (with good model fit) does not mean that no other models are plausible. Suggesting and testing several so called 'competing models' can rule out or identify other plausible models. In the current study, we tested several competing models and found that besides the hypothesized model, competing model 2e was plausible. Future studies should be conducted to determine which of these models provides the best fit to the data in other samples. A limitation of this cross-sectional study is that no conclusions can be drawn in terms of causality. In order to really test causality, a study comparing several data points should be conducted. Another limitation is the fact that only patients with CLD were included, which limits generalization of the results to other patient populations. However, the results of the present study are in accordance with previous studies with other patient populations, and therefore strengthen the hypothesis that

depression is the most important determinant of HRQoL, and that self-efficacy and maladaptive coping affect HRQoL through depression. Since depression scores of the patients in the study did not reflect clinical levels of depression, but rather depressive symptomatology, focusing treatment solely on depression seems unadvisable. Instead, the relationship between coping and depression should be observed. Improved HRQoL may be obtained by improving levels of coping and self-efficacy, which will in turn reduce levels of depression.

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Health related quality of life and psychological correlates in patients listed for liver transplantation

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Abstract

Purpose

Given the increasing waiting time for liver transplantation and the amount of possible stressors associated with it, assessment of psychological well-being and health related quality of life (HRQoL) in these patients is warranted in order to optimise pre-transplant care.

Patients and Methods

Patients with chronic liver disease (n=32) awaiting transplantation completed a series of questionnaires measuring HRQoL, depression, anxiety, coping and self-efficacy. Comparisons were made with other patients with liver disease with and without cirrhosis, and a healthy norm population. Relationships between these psychological variables were explored and subgroup analyses were performed to assess possible differences in coping strategies.

Results

Compared to other patients with liver disease without cirrhosis, liver transplant candidates had statistically significantly lower HRQoL scores on the subscales physical functioning ($p<0.001$) and general health ($p<0.001$). Their HRQoL did not differ from patients with liver disease with cirrhosis. Overall, patients awaiting liver transplantation had significantly reduced HRQoL ($p<0.001$) and increased depression scores ($p<0.001$) compared to healthy controls. Levels of depression, anxiety, self-efficacy and coping did not differ between liver transplant candidates and other patients with liver disease. Depression correlated significantly with HRQoL. Patients without depression made significantly more use of active coping strategies than patients with elevated depression levels.

Conclusions

Patients awaiting liver transplantation are not experiencing worse physical and psychological HRQoL than other liver patients with cirrhosis of the liver. Therefore, there is currently no indication to increase the level of psychosocial care for liver transplant candidates.

Introduction

With the increase in patients with liver disease in need of a liver transplantation (748% between 1991 and 2003) outnumbering the increase in available donor organs (195% between 1991 and 2003), European liver patients' time spent on the waiting list increases each year. There is evidence from research on heart or lung transplant patients that the time on the waiting list can be stressful, with patients expressing fear of death and worries about deteriorating health, among others (1-3). Nevertheless, extensive data on the well being of patients listed for a liver transplantation is currently not available. Levels of health related quality of life (HRQoL) are known to be lower before liver transplantation compared to after (4-11), but there is little knowledge of the influence of psychological variables on the experienced HRQoL of these patients. Levels of anxiety and depression have been reported to be elevated in different transplant patient populations, including patients with liver disease (11). While these studies have given insight into psychological variables that are important, it is not yet clear which variables contribute to possible decreased levels of HRQoL in patients awaiting liver transplantation. Moreover, limited data is available on actual levels of HRQoL for patients on the liver transplant list, and whether these are significantly lower than patients with liver disease who are not in need of a new liver.

Therefore the first aim of this study was to assess the relative levels of HRQoL of patients awaiting liver transplantation, and to compare them to other patients with chronic liver disease and a norm population of healthy persons. Given the stressful experience of awaiting transplantation, it was hypothesized that levels of HRQoL would be significantly lower in liver transplant candidates. The second aim of the current study was to assess the relationships between HRQoL and several psychological variables such as anxiety, depression and coping in liver transplant candidates. The levels of HRQoL and their psychological correlates will give an answer to the question whether this patient group is in need of additional care in light of the stressful experience.

Materials and Methods

Patient population

Questionnaire booklets were sent to all (N=61) patients with chronic liver disease who are more than 16-year old, awaiting liver transplantation at the Erasmus MC (Rotterdam, the Netherlands) in May 2004. The indication for liver transplantation was end-stage liver failure due to cirrhosis with or without hepatocellular carcinoma. The waiting time for transplantation at that moment was dependent on time on the waiting list in combination with medical urgency criteria. Informed consent was given by

returning the questionnaire booklet. The protocol was in accordance with the ethical guidelines of the modified 1975 Declaration of Helsinki. Since the questionnaire booklets were only administered once and did not include invasive questions, ethical approval was not necessary under Dutch regulations.

Measurement instruments

Short Form-36

The Short Form-36 (SF-36) is a widely used generic health-related quality of life questionnaire consisting of 36 questions that are combined into 8 scales on physical functioning, role limitations due to physical functioning, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health. The scale scores vary between 0 and 100, with a higher score indicating a better generic health-related quality of life. An overall score can also be computed, with a range between 0.00 and 1.00, with higher scores indicating better HRQoL (12). Reliability and validity of the SF-36 have long been established (13-16).

Beck's Depression Inventory

The Beck's Depression Inventory (BDI-II-NL) is a 21-item self-report rating inventory measuring characteristic attitudes and symptoms of depression (17). The total score ranges between 0 and 63 with scores below 14 considered normal, a score of 14-19 indicating mild to moderate depression, a score of 20-28 indicating moderate to severe depression and scores higher than 28 indicating severe depression. Since physical symptoms associated with end-stage liver disease such as poor appetite and fatigue are also associated with depression, the scores of liver transplant candidates on the three separate factors of the BDI-II-NL (somatic, cognitive, and affective) were also computed. The cognitive- and affective subscales do not include items pertaining to physical symptoms. Validity and reliability of the BDI-II-NL have been established (18-20).

State-Trait Anxiety Inventory

The State-Trait Anxiety Inventory (STAI) is one of the most widely used instruments for measuring anxiety in adults. In this study, only trait anxiety was measured, which refers to a general tendency to respond with anxiety to perceived threats in the environment. The trait anxiety scale consists of twenty statements that assess how respondents feel "generally." Scores can vary between 20 and 80, with higher scores indicating more anxiety. The STAI has been proven to be valid and reliable (21).

Self-Efficacy Scale

Self-efficacy reflects an optimistic self-belief that one can perform difficult or new tasks or that one can cope with adversity. The Self-Efficacy Scale (SES) consists of 10-items that are scored on a 4-point scale ranging from "not at all true" to "exactly true". Scores vary between 10 and 40, with a higher score indicating better self-efficacy. Good reliability and construct validity of the SES were found in earlier studies (22-24).

Cognitive Operations Preference Enquiry-Easy

The Coping Operations Preference Enquiry-Easy (COPE-Easy) consists of 32 questions that incorporate 15 distinct coping strategies (25, 26). Scores range between 2 and 8, with a higher score on a coping strategy indicating more use of that specific coping strategy. The 15 coping strategies can be grouped into three subscales: active problem focused coping, avoidant coping, and seeking social support (27). Good reliability (Cronbach's α=0.67 - 0.91) for all coping strategies except for mental disengagement (Cronbach's α=0.57) has been established for the Dutch version of the COPE-Easy (27).

Statistical analysis

First, descriptive statistics were derived to explore the scores of liver transplant candidates on HRQoL, anxiety, depression, self-efficacy and coping. Second, t-tests were performed to compare the scores of liver transplantation candidates to norm scores of a healthy population (13, 21, 23, 28) and the scores of other patients with and without cirrhosis of the liver which were randomly selected from the medical database of the Erasmus MC (Rotterdam, the Netherlands) (n=164), controlled for age and gender (Gutteling et al. submitted). With the large amount of variables and comparison groups in this study, there was a reasonable chance of occurrence of false positives if the p-value at which test statistics were considered statistically significant was not adjusted. Therefore, a new p-value was calculated using the Bonferroni method: the amount of t-tests in this study was 41, the average Pearson correlation between the variables in the study was 0.43. A calculation (29) showed that test statistics with a p-value of 0.006 and lower could be considered statistically significant, comparable with a p-value of 0.05 for one t-test. Third, Pearson correlations between an overall score of HRQoL on the one hand and depression, anxiety, coping, and self-efficacy on the other hand, were assessed to identify factors that showed a significant relationship with HRQoL. The correlation between HRQoL and length of waiting time was also computed. Additional analyses on subsamples were performed to assess possible differences in coping strategies and self-efficacy between patients with low and high depression and anxiety scores. Because of the small sample size, Mann-Whitney tests were performed.

Results

Patient characteristics

Out of the 61 patients that were sent a questionnaire booklet, nine did not want to participate for unknown reasons. Two patients were transplanted and two patients died before completing the questionnaires. One patient was physically ill to the extent that completion of the questionnaire booklet was impossible. Three patients did not speak Dutch well enough. In total, 44 patients participated (response rate = 72%). Of these 44 patients, nine were considered nontransplantable due to improvement of their liver disease during conservative medical management and were, therefore, excluded from the analyses. Three patients spent considerably more time on the waiting list than the other 32 (average of 727 days compared to 177 days), and were therefore not included in the analyses. The selection of patients is shown in Fig. 1. Table 1 shows the baseline characteristics of the respondents, and Table 2 shows the mean scores of liver transplant candidates on HRQoL, depression, anxiety, self-efficacy and coping.

Figure 1. Patients in the study

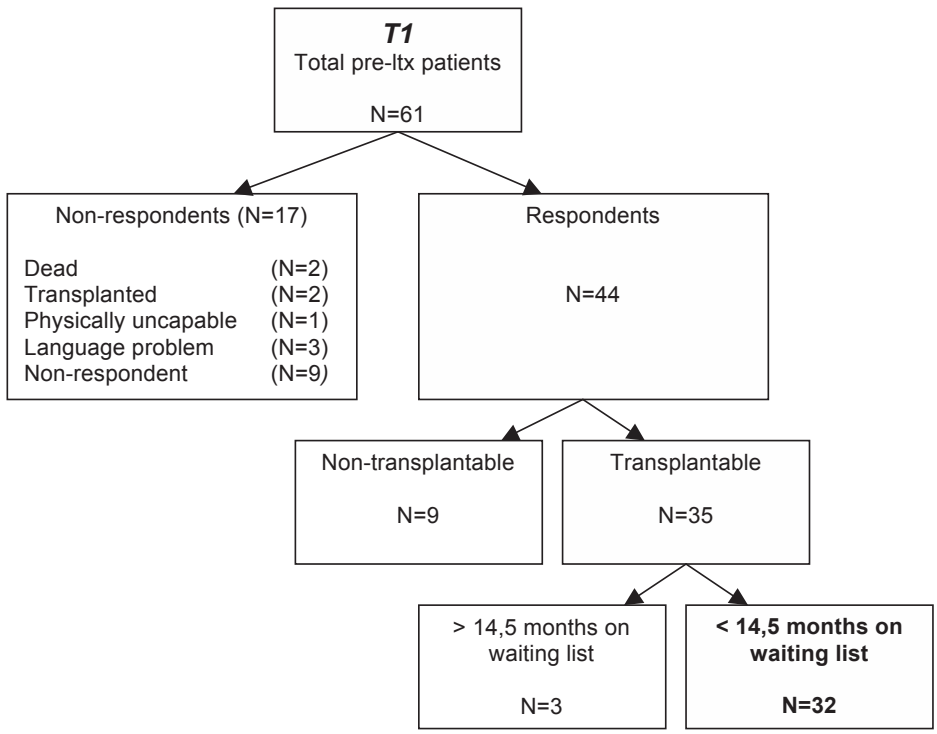

Table 1. Demographic characteristics of pre-ltx patients, other liver patients without cirrhosis, other liver patients with cirrhosis, and a healthy norm population [32].

	Pre-ltx	Other liver patients		Healthy population
		No cirrhosis	Cirrhosis	
	(n=32)	(n=101)	(n=62)	(n=1742)
Gender (n, %)				
Male	22 (69)	51 (51)	37 (60)	976 (56)
Female	10 (31)	50 (49)	25 (40)	766 (44)
Age				
Mean (SD)	52.5 (11.1)	44.0 (12.6)	49.4 (12.8)	47.6 (18.0)
Range	(23-65)	(18-72)	(23-78)	(16-94)
Nationality (n, %)				
Dutch	28 (87,5)	91 (90.1)	59 (95.2)	1655 (95)
Other	4 (12.5)	10 (9.9)	3 (4.8)	87 (5)
Time on waiting list in days				
(median, range)	165 (1 - 436)	----------	----------	----------
Disease aetiology (n, %)				
Post-Alcoholic	6 (19)	----------	----------	----------
Cholestatic PBC PSC	7 (22)	38 (37,6)	28 (45.2)	----------
Viral	10 (31)	63 (62.4)	34 (54.8)	----------
Metabolic	2 (6)	----------	----------	----------
Liver cancer	1 (3)	----------	----------	----------
Other	6 (19)	----------	----------	----------

Statistical analysis

Comparison of liver transplant candidates with a norm population of healthy persons

Compared to a norm population of healthy persons, patients awaiting liver transplantation had significantly worse scores on all subscales of HRQoL, except the subscale 'role emotional functioning', reflecting the degree to which emotional problems interfere with work or other daily activities. Their mean depression score was also significantly worse. With regard to the distribution of scores, 13 patients had a mean score reflecting no depression, 10 patients had mild depression, 6 patients had moderately severe depression, and 3 patients had severe depression. The scores of liver transplant candidates on the subscales of the BDI-II-NL compared to the scores of a norm population of healthy persons can be seen in Table 3. Fifty-two percent of the liver transplant candidates had above average scores on the cognitive and somatic subscales, and 60% of these patients had above average scores on the affective subscale. There were no differences in the scores on mean anxiety and self-efficacy between patients awaiting liver transplantation and the norm population of healthy persons. However, eight

Table 2. Mean scores and standard deviations on HRQoL, depression, anxiety, self-efficacy, and coping of pre-ltx patients, other liver patients with and without cirrhosis, and a healthy norm population (Gutteling et al., submitted) and a healthy norm population (13, 21, 23, 28).

	Pre-ltx (Mean, SD) N (n=	**Other liver patients** (Mean, SD) No cirrhosis	Cirrhosis	**Healthy norm** (Mean, SD)
SF-36 Overall score	0.70 (0.09)	0.73 (0.14)	0.74 (0.14)	----------
SF-36 Physical functioning	58.2 (23.1)	76.4 (22.8)*	73.5 (23.7)	74.9 (23.4)*
SF-36 Role physical functioning	31.5 (37.6)	55.0 (45.1)	52.4 (44.3)	76.4 (36.3)*
SF-36 Bodily pain	59.1 (26.8)	68.8 (27.0)	66.8 (26.8)	74.9 (23.4)*
SF-36 General health	30.6 (18.0)	50.3 (23.4)*	42.5 (22.6)	70.7 (20.7)*
SF-36 Vitality	44.2 (16.8)	50.6 (24.9)	53.9 (24.4)	68.6 (19.3)*
SF-36 Social functioning	66.0 (19.6)	67.9 (29.4)	74.4 (27.1)	84.0 (22.4)*
SF-36 Role emotional functioning	67.8 (36.6)	67.3 (42.4)	61.2 (45.2)	82.3 (32.9)
SF-36 Mental health	66.3 (18.4)	66.9 (21.8)	68.8 (23.6)	76.8 (17.4)*
Depression overall (range 0-63)	16.0 (7.9)	12.6 (10.7)	13.1 (12.0)	6.2 (6.20)*
Anxiety (range 20-80)	41.7 (10.9)	41.1 (12.98)	41.2 (13.37)	38.4 (9.90)
Self-Efficacy (range 0-40)	29.9 (6.04)	31.1 (6.09)	30.3 (6.67)	29.28 (5.09)
Active coping (range 1-4)	2.63 (0.55)	2.67 (0.64)	2.52 (0.74)	----------
Seeking support (1-4)	2.40 (0.61)	2.41 (0.76)	2.24 (0.77)	----------
Avoidant coping (1-4)	1.89 (0.57)	1.84 (0.66)	1.89 (0.60)	----------

Note: The ***t***-tests were performed with Bonferroni correction. Age and gender were controlled for.
*p<0.05

patients (25%) had anxiety scores falling in the 10th percentile of a comparison group of healthy persons, reflecting clinical anxiety.

Comparison of liver transplant candidates with other patients with liver disease

Compared to other patients without liver cirrhosis, patients awaiting liver transplantation had significantly lower HRQoL scores on the subscales physical functioning ($p<0.001$) and general health ($p<0.001$). The scores on the subscales of the SF-36 reflecting bodily pain, role physical functioning, and the psychosocial domains of HRQoL did not differ for liver transplant candidates without cirrhosis and other patients with chronic liver disease. Compared to patients with liver cirrhosis, liver transplant candidates did not have statistically significantly lower HRQoL scores, but the subscale physical functioning did show a trend ($p<0.007$; remember that due to the Bonferroni correction, a $p<0.006$ was required). With regard to self-efficacy, anxiety, depression

Table 3. Scores of pre-liver transplantation patients on the subscales of the BDI-II-NL

BDI-II-NL	N	Pre-liver transplantation patients Mean (SD)	Healthy controls Mean	25%ile	50%ile	75%ile	90%ile
Cognitive	29	3.83 (3.60)	1.4	7	7	7	8
Affective	30	2.3 (2.09)	0.9	0	12	5	13
Somatic	29	9.76 (3.87)	4.0	4	10	6	9

BDI-II-NL – Beck Depression Inventory

Table 4. Pearson correlations between the overall score of HRQoL, time on waiting list and psychological variables in liver patients awaiting transplantation

	HRQoL (overall)	Time on waiting list
Time on waiting list	-0.34	1.00
Depression	-0.43*	-0.20
Anxiety	-0.32	-0.14
Self-efficacy	0.16	0.18
Active coping	-0.02	0.04
Seeking social support	-0.16	0.18
Avoidant coping	-0.11	0.14

HRQoL - Health-related quality of life

* $p<0.05$

and coping between liver transplant candidates and hepatology patients with and without cirrhosis of the liver, there were no statistically significant differences.

Correlations between HRQoL, time on waiting list and psychological variables

The results of the correlation analysis are shown in Table 4. Of all the psychological variables in the analysis, HRQoL of liver transplant candidates was only statistically significantly correlated with depression ($r=0.43$, $p<0.05$). Length of waiting time was not significantly correlated with HRQoL or with any of the psychological variables.

Subgroup analyses

Liver transplant candidates without depression (n=13) made significantly more use of active coping ($Z=-3.14$, $p<0.01$) than liver transplant candidates with higher depression scores (n=19). A trend was seen for avoidant coping, with non-depressed patients making less use of maladaptive coping than patients with higher depression scores ($Z=-1.95$, $p = 0.05$). Patients without depression had significantly higher scores on self-efficacy ($Z=-3.12$, $p<0.05$) than patients with higher depression scores. With regard to anxiety, it was shown that patients with low anxiety scores (n=24) had significantly higher self-efficacy scores than patients with high anxiety scores (n=8) ($Z=-2.27$, $p<0.05$). No differences were found between patients with low and higher depression scores on the coping strategy of social support seeking. This was also true for patients

with low and higher anxiety scores. Furthermore, these patients did not differ in their use of active and avoidant coping strategies.

Discussion

In comparison with other patients with liver disease without cirrhosis of the liver, physical HRQoL was impaired, while the level of physical HRQoL of patients with cirrhosis of the liver and liver transplant candidates was comparable. Overall, liver transplant candidates did not have worse mental HRQoL and were not more depressed than patients with less advanced liver disease. They were also not more anxious, and their coping and self-efficacy styles did not differ. However, nine (15%) of the liver transplant candidates had moderate to severe depression, and 25% had anxiety scores reflecting clinical anxiety. HRQoL correlated significantly with depression, but not with the other psychological variables.

An interesting finding in the current study, contrary to the hypothesis, was the lack of differences between patients with liver disease and transplant candidates on mental HRQoL and several of the psychological variables such as anxiety and coping. While the experience of waiting for a new liver is certainly likely to be stressful, there was no evidence to support that it is significantly more stressful than being diagnosed with chronic liver disease. In addition, it is certainly possible that while the experience is more stressful, the provision of hope through the possibility of liver transplantation counters adverse outcomes in terms of well-being (30). Depression levels were related to HRQoL, which is in line with previous research in other patient populations (31-33). Further subgroup analyses indicated that levels of self-efficacy and active coping were lower for liver transplant candidates with elevated depression scores. This information may prove useful when developing interventions in order to improve HRQoL.

Several limitations of this study should be mentioned. First of all, the sample size of this study was small. However, it must be noted that with a response rate of 72 % of all patients listed for transplantation at the Erasmus Medical Center at a particular point in time, the amount of patients in this study can be considered relatively large. While one should be cautious when drawing any firm conclusions based on the results of this study, it must be noted that the small sample size was taken into consideration when performing the statistical analyses. Furthermore, the results were in line with previous studies. The higher age of, and unequal distribution of, men and women in the sample of transplantation candidates compared to the comparison groups were controlled for in the statistical analysis. A final limitation of this study is the fact that the patients in our sample had been awaiting transplantation for a relatively short period of time (median 165 days, with patients commonly waiting approximately two years to be

transplanted), which may explain the lack of correlation between HRQoL and time on waiting list. Clearly, further research is needed in order to draw conclusions on the effect of waiting time on HRQoL.

Conclusions

Contrary to what was hypothesized, patients awaiting liver transplantation are not experiencing worse HRQoL than patients with advanced liver disease. Their HRQoL and scores on depression and anxiety did not differ from those of other patients with liver disease with cirrhosis. The elevated depression and anxiety scores that were found seem therefore to be inherent in the seriousness of chronic liver disease per se rather than the fact that these patients are awaiting transplantation. The results of the present study imply that there is no indication to routinely provide liver transplant candidates with additional psychosocial care. Instead, physicians should be sensitive to symptoms of anxiety and depression that are to be expected in any patient population with serious chronic disease. Given the relationship of depression and the psychological variables coping and self-efficacy, it is advisable to refer patients awaiting liver transplantation with impaired HRQoL and depression to psychological counselling that focuses on teaching these psychological constructs.

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Quality of health care and patient satisfaction in liver disease: the development and first results of the QUOTE-Liver questionnaire

7

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Submitted

Abstract

Background

Consensus on how to adequately measure patient satisfaction with health care is limited, and has led to the development of many questionnaires with various methodological problems. The objective of this study was to develop a liver disease- and care-specific patient satisfaction instrument on the basis of previously tested methodology in patient satisfaction measurement, the so called QUOTE- series: Quality Of health care services Through the patients' Eyes. QUOTE methodology aims to standardise the measurement of satisfaction as the discrepancy between patients' needs and the extent to which these needs are being met.

Methods

As part of the QUOTE methodology routine, 11 Patients with chronic liver disease from the Erasmus MC (Rotterdam, the Netherlands) participated in focus-group meetings on patient satisfaction with the provided service at the outpatient hepatology clinic. Twenty-eight other patients were invited to rank the items generated during the focus-group meetings according to importance. With this information, the QUOTE-Liver was constructed. Face validity, construct validity, content validity, and reliability of the newly developed questionnaire were assessed in a test sample of 152 patients with chronic liver disease.

Results

Two liver-disease specific, and the 18 items ranked as most important were included in the QUOTE-Liver. Face validity and content validity were acceptable: neither patients (n=152) nor psychologists (n=3) or a hepatologist suggested any extra items to be included. Construct validity was good: the overall score correlated significantly with the Visual Analogue Scale (VAS) measuring overall satisfaction ($r=0.69$, $p<0.01$). The reliability of the QUOTE-Liver was excellent ($\alpha=0.90$).

Conclusion

The QUOTE-Liver is an easy to complete instrument based on standardized state-of-the-art satisfaction measurement methodology. Evidence for its validity and reliability was demonstrated. The QUOTE-liver covers those aspects of satisfaction that CLD patients consider to be important when visiting the outpatient department of hepatology. Even though further substantiating of the favourable psychometric findings is desirable, it seems to be a useful instrument that can be used to identify those aspects of care that need improvement in order to optimise the provision of health care for patients with chronic liver disease.

Introduction

As liver disease is often chronic and progressive, frequent monitoring of medication and progression of the disease is necessary. Therefore, besides the quality of the medical therapy, good quality of care is important to these patients as they frequently interact with their physicians. Besides good medical therapy, good quality of care determines patient satisfaction. Patient satisfaction, in turn, has proven to be important in compliance with treatment, seeking medical advice and maintenance of a continuous relationship with a physician [1, 2]. Also, patient satisfaction and quality of care are increasingly of interest to health insurance companies or health maintenance organisations that wish to negotiate prices when purchasing health care.

Although studies on quality of care/patient satisfaction are numerous, there has until recently been no consensus on how to measure this concept. Most researchers have unjustly dealt with patient satisfaction as an easy concept to measure [3]. This has led to several methodological problems in this field of research. First, the items of the questionnaires or inventories of patients' experiences, have been generated by health care professionals rather than patients, even though several studies have demonstrated that patients' and health care professionals' views about important aspects of satisfaction are often quite different [4-6]. Secondly, there has been a lack of disease- and care-specific items [7]. Finally, when asking patients to answer on a Visual Analogue Scale (VAS) the question "how satisfied are you", 90% tends to be satisfied in [7-9]. This may not be realistic, since a previous study has shown that many patients who reported being satisfied with the care they received, also indicated numerous problems with this same care [10]. Furthermore, this single item question does not give any indication of what needs to be changed when patients are not satisfied.

The lack of consensus on adequate measurement patient satisfaction has led to a proliferation of questionnaires with inadequate measurement properties. A meta-analysis [3] in which 195 articles about patient satisfaction were screened, revealed that the instruments used to measure patient satisfaction were different in almost every study. Data on psychometric properties of the instruments, including their validity and reliability were scarce. A study on the use of patient satisfaction instruments by leading academic medical centres in the United States of America showed little standardization of the instruments currently being used at these centres, particularly for outpatient care [11].

The existence of so many different 'satisfaction' instruments and the lack of data on their reliability and validity does not only cast doubt on the soundness of the instruments, but also makes comparisons of studies impossible and conclusions drawn from studies implausible. For these reasons, the Netherlands Institute for Health Services Research (NIVEL) has developed a state-of-the-art methodology protocol to develop a

standardized series of questionnaires measuring Quality of Care Through the Patient's Eyes (QUOTE) based on market research theory [13], which asserts that consumer satisfaction should be measured by looking at the discrepancy between what consumers need/expect and what they actually receive [14]. QUOTE instruments are now available for a variety of diseases, such as HIV, IBD, and rheumatism. QUOTE instruments consist of two parts: the weight (importance) patients assign to different aspects of health care and patients' experiences with health care (performance). The majority of health care researchers have now distinguished these two basic components of patient (dis) satisfaction [12]. From the combined effect of importance and performance, the quality index can be obtained [12].

The aim of this study was to develop a liver disease- and care-specific version of the QUOTE, called the QUOTE-Liver, which measures quality of care/patient satisfaction in patients with chronic liver disease (CLD). The need for a liver disease- and care-specific instrument was grounded in the fact that CLD affects many people worldwide (560 million people are infected with the hepatitis B or C virus (www.epidemic.org, 4-12-2006), and alcohol-induced end-stage liver disease forms the second most important reason for liver transplantation in the United States [15]. CLD is a serious disease that is associated with significant physical and psychological symptoms such as impaired cognition, hepatic coma, fluid in the abdomen, abdominal pain, joint pain, fatigue, depression and anxiety [16-22]. The development of the QUOTE-Liver was undertaken in order to deal with all aforementioned methodological issues by asking patients rather than health care professionals to define important aspects of care, by including disease- and care-specific items, by focussing on the discrepancy between individual patients' needs and whether these needs have been met, and by having been developed along the lines of a series of similar questionnaires which makes comparison between patient populations possible.

Methods

In order to develop the QUOTE-Liver we followed the QUOTE protocol as described by the Netherlands Institute of Health Services Research (NIVEL, Utrecht, the Netherlands) [23].

Study population

All patients suffering from chronic liver disease (CLD) visiting the outpatient department of Hepatology of the Erasmus Medical Centre in Rotterdam, which is a specialized centre for chronic liver disease in the Netherlands, during the first three months of 2004 were invited to participate in the development of the QUOTE-Liver by mail.

Patients in a given period of time were made aware of the study by letter and invited to contact the researcher if they wanted additional information and if they were considering participating in the study. The phases of the study were done consecutively, each time approaching a new patient sample. Patients were included in each phase of the study on a first-come first-serve basis. Consequently, no information is available on those patients who did not want to take part in the study. Patients who were willing to participate were contacted by the researcher, who provided them with verbal and additional written information. All participants completed an informed consent form. No incentives for participating in the study were given. Travel expenses of the patients participating in the focus group discussions were covered. The study protocol was in accordance with the ethical guidelines of the modified 1975 Declaration of Helsinki. Since patients were invited to participate in one part of the study only, and since the study did not include invasive questions, ethical approval was not necessary under Dutch regulations.

Part one: Focus groups

Focus groups were first mentioned as a market research technique in the 1920's [24, 25]. They are an efficient means to obtain data on opinions and attitudes. Focus groups are qualitative interviews with a small number of people. Unlike one-on-one interviews, focus groups generate information through group discussion, which besides information about what people think, gives insight in why people think the way they do. For good results, just a few focus groups are sufficient, as data become saturated and little new information emerges after the first few groups [26].

The purpose of the focus groups in this study was for patients to generate a list of relevant care aspects at the outpatient department of hepatology of the Erasmus MC. Three focus group meetings were organized at the Erasmus MC (Rotterdam, the Netherlands). During the focus group meetings, patients were asked to name all aspects of their visit to the outpatient department of hepatology that were important to them. Meetings lasted from 70 to 90 minutes. Two researchers, one psychologist and one experienced psychotherapist who could resolve any arising emotional issues, conducted the focus groups.

Part two: Item Ranking

The patients ranked the items to create an order of importance in the aspects named in the focus group meetings [27]. For this ranking exercise, which took place at the outpatient department of hepatology of the Erasmus MC, all aspects mentioned during the focus group meetings were written on separate cards, which patients were asked to divide over five piles, ranging from "most important (1)" to "least important (5)". The piles had to be of nearly equal size in order to force patients to make a choice.

To make sure that no aspects had been missed during the focus group meetings, the patients were asked at this stage whether they thought any important items were missing.

Part three: Selection of items

The QUOTE protocol has no strict guidelines regarding the number of items to be included. Because we wanted an easy to administer questionnaire, we (the authors) opted for a 20-item questionnaire, which is in the lowest range of item numbers of the already existing QUOTE instruments like the QUOTE-IBD (23 items), QUOTE-HIV (27 items), QUOTE-Occupational Therapy short version (23 or 12 items). Since we were interested in the items that were most important to patients, we decided to follow the preferences of patients closely, rather than to chose items belonging to a priori determined aspects of care such as accessibility, waiting room area, etc. Because QUOTE questionnaires are disease- and care-specific, disease- and care-specific items were also included.

Scoring and interpretation of scores

All QUOTE questionnaires, and thus also the final QUOTE-Liver, consist of two parts. The questioning style is deliberately repetitious as it has been reported that this ensures patients' understanding. In part one, the importance of the 20 items is measured. The fact that ordinary Likert scales tend to be highly skewed towards the 'important' dimension was solved by providing 4-point response options (0 = not important at all, 3 = slightly important, 6 = important, 10 = very important), which proved to be a workable solution [12]. In part two, the performance on those same 20 items is measured. Patients are asked what actually happened during the consultation. They can rate items on a four-point scale ranging: no (score=1), not really (0.67), mostly yes (0.33), and yes (0). The QUOTE protocol defines the aspects of care that need improvement when more than 10% of patients are dissatisfied, reflected by a total score of <9.0 (range is 0 – 10), computed by the formula: 10 - importance X performance [28].

Part four: Validation study

Psychometric methods

Principal component analysis was run to explore factors within the questionnaire. Reliability of the QUOTE-Liver was measured by computing the internal consistency of the items and the item-total correlations using the reliability analysis in SPSS 11.0. Face validity, i.e the extent to which experts judge the instrument to measure the intended concept, was determined by presenting it to 152 patients with chronic liver disease, three psychologists and a hepatologist. To guarantee correct measurement of the con-

cept (quality of care from the patients' perspective), construct and content validity were measured. Construct validity, i.e. the degree to which an instrument measures the theoretical construct it is intended to measure, was measured by computing Pearson correlations between a Visual Analogue Scale (VAS), and the total quality impact score of the QUOTE-Liver. The VAS consisted of a horizontal line on which patients had to indicate by means of a cross, to what extent they agreed (no, definitely not – yes, definitely) with the following question: 'Would you recommend a consultation at this outpatient department to your best friend if he/she was in the same circumstances?' Scores were calculated as percentages of the scale, with 0 indicating total disagreement and 100 indicating perfect agreement. To assess content validity, patients were asked to indicate which other items should be included in the QUOTE-Liver. A researcher who was present while patients completed the questionnaire explored the feasibility by looking at the time it took for patients to complete the questionnaire, by reporting patients who failed to complete the questionnaire, and by noting patients' questions regarding the instructions and/or items. In addition, patients were asked whether they had understood the questions, if they thought completing the questionnaire was easy or difficult, and what they thought of the completion time.

Results

Patients in the study

11 patients with CLD participated in the focus group meetings and 28 patients participated in the item-ranking task. 152 patients completed the QUOTE-Liver for validation purposes. The demographic and clinical characteristics of these patients are shown in

Table 1. Demographic and clinical characteristics of the patient population included in the development of the questionnaire.

	Focus Groups	Item Ordering	Validation study
Total number of patients (n)	11	27	152
Male (n, %)	6 (55)	11 (41)	81 (53)
Age (mean, range)	48.3 (18-75)	50.7 (21-74)	46.7 (19-75)
Liver disease (n,%)			
Post-transplantation	5 (45)	5 (19)	24 (16)
Viral Hepatitis	4 (37)	10 (37)	72 (47)
Cholestatic Liver Disease	2 (18)	3 (11)	40 (26)
Other	0 (0)	6 (22)	16 (10)

Part one: Focus groups

The focus group meetings generated 121 partly overlapping aspects that patients found important when visiting the department of hepatology. These were converted into 70 distinct items. Most items (30) concerned competence and social skills of the

physician. 16 items concerned the waiting room area, nine items referred to assisting personnel and making appointments, eight items concerned availability of information, two were about venipuncture and five concerned accessibility of the hospital.

Part two: Item ranking

The mean importance scores of the 70 items ranged from 4.65 for competence of the physician to 1.38 for presence of a cloakroom at the outpatient department. Two disease- and care-specific items were mentioned: "the venipuncture nurses are skilled" and "I don't have to wait long for venipuncture". No items were mentioned when patients were asked if any important items were missing.

Part three: Selection of items

Two disease- and care-specific items were included in the QUOTE-Liver: 'waiting time for venipuncture' and 'skills of the venipuncture nurses'. Besides these two items, the 18 most important items following from the item-ranking task were included. The importance scores did not show a clear difference between important and less important items. Rather, scores for importance decreased gradually (score of item 18 = 3.88, score of item 19 = 3.81). Consequently, the decision to include 20 items in the QUOTE-Liver was made to coincide with the number of items of other QUOTE-instruments. Table 2 shows all items included in the QUOTE-Liver. The scores presented in this table were derived from the validation study conducted with 152 patients. In that study, the average importance and performance scores were computed using the Likert scales, resulting in a range varying from 0 to 10 for the importance scores and a range of 0 to 1 for the performance scores. There were no missing data.

Part four: Validation study

Data analysis

Principal component analysis yielded four factors. 17 items concerning interaction/ contact with the physician loaded high on factor one. One disease- and care-specific item ("How important is it for you that the waiting time for venipuncture is short") loaded high on factor two. The other disease-and care-specific item ("How important is it for you that the venipuncture nurses are skilled" loaded high on factor three. One item ("How important is it to you that the doctor that you visit today is knowledgeable") loaded high on factor four.

The internal consistency of the overall QUOTE-Liver was excellent (=0.90). The item-total correlations of the 17 items concerning interaction with the physician ranged from 0.40 to 0.71 (alpha if item deleted = 0.89 - 0.90). The item-total correlation of the two disease- and care-specific items and of the first item concerning the physician's

Table 2. Items included in the QUOTE-Liver and scores of 152 Dutch patients with chronic liver disease.

		Importance Score	Performance Score	Quality Impact Score
How important is it to you that the doctor that you visit today…				
1	Is knowledgeable	9.46	0.04	9.60
2	Takes time to discuss emotional issues	6.58	0.15	9.21
3	Takes you seriously	9.00	0.04	9.66
4	Makes you feel safe	8.09	0.07	9.50
5	Believes what you say	8.50	0.05	9.57
6	Takes enough time for you	8.05	0.07	9.45
7	Is friendly	7.53	0.03	9.81
8	Is open	8.47	0.05	9.58
9	Listens to you	8.58	0.05	9.59
10	Answers all of your questions	8.67	0.06	9.51
11	Gives you enough information about your disease/treatment	9.01	0.08	9.31
12	Gives you a say in your treatment	7.76	0.10	9.24
13	Answers your questions clearly	8.56	0.07	9.45
14	Gives you medical/technical information about your disease when you ask for it	8.41	0.05	9.62
15	Gives enough explanation about your medication and possible side effects	8.24	0.05	9.56
16	Refers you well when you present with complaints that are not liver disease-related	8.03	0.04	9.61
17	Takes action quickly	8.96	0.04	9.62
How important is it for you that…				
18	You can tell your doctor what's on your mind	7.15	0.05	9.72
19	The venipuncture nurses are skilled	7.78	0.05	9.54
20	The waiting time for venipuncture is short	5.47	0.12	9.12

The QUOTE-Liver consists of the two disease- and care-specific items (19 and 20) and the 18 most important items for quality of care as measured in a population of chronic liver patients. The questioning style is deliberately repetitious, as it has been reported that this ensures patients' understanding. Importance scores can range from 0-10, performance scores can range from 0-1. A 'quality impact score' of <9.0 indicates that more than the usual 10 % of the patients are dissatisfied with the particular aspect of care.

knowledge were 0.08, 0.37 and 0.39 respectively (alpha if item deleted = 0.90-0.91). Face validity was excellent: all patients (n=152) in the validation study and three psychologists and a hepatologist agreed that the items of the QUOTE-Liver adequately reflected the most important aspects of care for CLD patients. Construct validity, as measured by the correlation between the VAS measuring overall satisfaction and the total score on the QUOTE Liver was substantial ($r=0.69$; $p<0.01$). Content validity was also good: none of the 152 patients in the validation study suggested new items to be included. Feasibility was established as all patients in the validation study completed the QUOTE-Liver quickly (average time of 1.5 minutes), and understood the items.

Discussion

In the present study, we have developed an easy to complete, self-administered liver disease- and care-specific questionnaire that measures quality of care through the patient's eyes (QUOTE-Liver). Evidence for its validity and reliability was demonstrated. The QUOTE-Liver was developed using a protocol that has recently been applied to develop a series of disease- and care-specific patient satisfaction instruments (QUOTES's) [12]. The QUOTE-Liver consists of two liver disease- and care-specific items, and the 18 most important items out of 70 defined by 28 patients with chronic liver disease.

It is notable that nearly all items included in the QUOTE-Liver concerned aspects related to the physician. Apparently, other aspects of care such as accessibility, cooperation with other health care workers, and accommodation are of lesser importance to patients with chronic liver disease. This may explain the fact that no dissatisfaction, as shown by a score below 9.0, was established. Indeed, other QUOTE instruments found dissatisfaction on items pertaining to accessibility (by telephone) [8, 28-31], doctors' and nurses' psychosocial approach [20, 22, 23], information [8, 28-31], cooperation with other health care workers [29-31], privacy [8, 31], and patient authority [8, 30], rather than medical competence, contact, and communication. Exclusion of these multiple aspects in the development of the QUOTE-Liver was chosen for deliberately since these were of lesser importance to patients with chronic liver disease.

The high satisfaction scores obtained by the QUOTE-Liver in the present study might cast doubt on its sensitivity. Even though it seems plausible that the possible high standard of care at the specialized liver center of the Erasmus MC may account for these scores, further testing of the QUOTE-Liver in its current form, preferably in an experimental setting where 'bad' care is delivered purposefully, is needed in order to draw firmer conclusions on its sensitivity. Another way to assess the sensitivity of the QUOTE-Liver may be to administer it in two different settings, a specialized setting and a less specialized setting. A before and after study, where some aspect of care has been changed, is also a possibility that should be explored.

The method of patient selection used in this study may have caused bias. Even though the most important forms of chronic liver disease (HBV, HCV and cholestatic liver disease) were represented in the patient sample used in the present study, and even though the average age was representative of the overall population of CLD patients [18], no information was available of patients who did not want to participate. Future studies should register characteristics of nonparticipants.

Future studies should also assess the reproducibility of the QUOTE-Liver in terms of test-retest reliability. In addition, other ways should be explored to assess the construct validity of the QUOTE-Liver. A VAS measuring satisfaction was chosen since no adequate alternative was available at the time of the study. Measuring satisfaction by

means of a VAS is relatively crude and possibly influences the subsequent construct validity for which it was used. Future studies could use the generic Dutch version of the QUOTE, which is now available, to assess construct validity. A possible limitation of QUOTE instruments in general that has so far never been mentioned, is that some patients may be reluctant to say no (e.g. no, my physician did not discuss emotional problems) as it may reflect badly on the physician. Indeed, some patients in our study expressed a need for an answering category 'not relevant' for certain items of part two of the QUOTE-Liver. This should certainly be considered, as it will probably increase patient participation without compromising the scoring of the instrument.

Conclusions

In conclusion, the QUOTE-Liver is an easy to complete instrument to assess liver patients' satisfaction with health care at an outpatient department, with evidence of good validity and reliability. The high satisfaction scores that the QUOTE-Liver produced in our validation study may be a result of the items included in the questionnaire, which mostly address physician competence and social behavior. As long as physicians' treatment and communication are good, high scores are to be expected. Further studies are needed to test the responsiveness and generalizability of the QUOTE-Liver to other linguistic and cultural settings.

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08

General discussion

Introduction

As described in the introduction of this thesis, chronic liver disease (CLD) is one of the most prevalent diseases in the world. It is a serious and progressive disease that is associated with various physical and psychosocial symptoms. The health related quality of life (HRQoL) of patients with CLD has been shown to be impaired in numerous studies. In a recent thesis on this topic conducted at the department of Gastroenterology and Hepatology of the Erasmus MC, it was concluded that "During consultations, besides attention for physical impairments of chronic liver patients, attention should be given to psychological impairment and the potential interrelations between these two dimensions". This recommendation advocates the use of HRQoL measures, which incorporate both physical and psychological well-being, in routine clinical practice. Following the general trend of using HRQoL measures in clinical practice, the present thesis describes the research that was conducted on the implementation of HRQoL measurement at a clinical practice of hepatology. The aims of this thesis were twofold. The first was to assess the effect of real-time computerized HRQoL measurement at a clinical outpatient practice of hepatology on the clinical consultation, patient care, and patients' HRQoL. The second aim was to determine more precisely which physical and psychological factors are related to HRQoL in patients with chronic liver disease. If insight in this relationship could be improved, physicians can be provided with more specific indications of potential treatment options to improve impaired HRQoL in chronic liver disease.

In this section of this thesis, a general discussion is provided as a reflection on the results and to guide future research. The outline of this discussion is first a discussion on the feasibility of implementing, and the effectiveness of HRQoL measurement in clinical practice (Part I), then a discussion on the clinical value of determinants found of HRQoL in patients with chronic liver disease (Part II) and finally recommendations for future research (Part III).

PART I: Feasibility and effectiveness of implementing computerized HRQoL measurement in clinical practice

The overview presented in chapter 1 reports a growing amount of studies on HRQoL measurement in clinical practice. This is in line with the growing interest of professionals from various (para)medical disciplines in conferences on this topic (ISOQOL conference 2007). Despite the growing number of scientific publications on the subject and despite the increasing interest in this topic at conferences, it was found that widespread implementation of HRQoL measurement in clinical practice had as of yet not

been forthcoming. In chapter 1, two main reasons were put forward: lack of results (as yet) regarding the effectiveness of standardized HRQoL measurement in actually improving HRQoL or psychosocial outcomes, and practical and attitudinal barriers. This part of the general discussion elaborates further on the difference between intention and implementation, and formulates suggestions to bridge the gap between them.

Feasibility of computerized HRQoL measurement in clinical practice

Two determinants of a successful implementation are 1) a quality of life assessment that is feasible for all patients and 2) direct feedback of the results to the physician. Therefore, we chose for a computerized administration of the HRQoL questionnaires. This means that in our case and similar cases a good computer program is essential for smooth collection and use of the data, and for optimal patient and physician participation. In chapter 2, we were among the first to describe all feasibility issues encountered when implementing real-time computerized HRQoL measurement at an outpatient department. This provided a practical overview of existing and new insights in the requirements for successful implementation of such a procedure. The most decisive requirements were 1) a clear lay-out while resembling the original pen-and-paper version of the questionnaire; 2) instant scoring and conversion of the data into an easy to interpret, online available graphical output, and 3) safe data transmission through the Internet. If these requirements are not met, it is most likely that implementation will fail. Additional pitfalls are patients´ general lack of basic computer skills and sporadic fear of damaging the computer, which therefore necessitate the use of touch-screen computer kiosks. These additional pitfalls may not undermine the implementation completely, but will hamper participation. We found that the development of a computer program that met all of the decisive requirements required extensive knowledge of computer programming language and data transmission processes, and was therefore outsourced to an IT professional. Future studies should anticipate for the costs associated with the indispensable IT expertise. In addition, dedicated monitoring by support staff should be provided, in order to encourage continuous participation. Again, such monitoring should be incorporated in the overall costs of the implementation.

HRQoL measurement in clinical practice makes most sense when done routinely and on longitudinal basis. Compliance is therefore essential. Unfortunately, we often encountered a lack of sufficient compliance. Patients proved to be forgetful of the computer, probably because of anxiety for the upcoming consultation, or their routine of taking place in the waiting room area after announcing themselves at the reception desk. Motivating support staff, such as reception employees, to direct patients to the computer is essential if optimal patient compliance is to be achieved. As the staff of a busy outpatient clinic is likely to work in shifts, optimal staff support is only

likely to be achieved if all staff members are committed to the intervention. Obviously, such an increase of responsibility must be recognized at the work floor. In the present investigation, such an implementation strategy was not yet fully explored and might be suggested in future implementations.

Attitudinal barriers to the successful implementation of computerized HRQoL measurement in clinical practice that have previously been described, concerned physicians scepticism about the validity and importance of self-rated health, preferences for physiological outcomes over psychological outcomes, unfamiliarity with questionnaire scores, and doubts of their ability to intervene should the questionnaires reveal any problems (1, 2). We found only sporadic indications of such barriers. Bringing in a local clinical leader as a spokesman for the importance of self-rated health, clear data output and clear instructions on how to interpret the data, and instructions to use the HRQoL data as a basis for more directed discussion of psychosocial topics seemed to have conquered most of these barriers in our study. Nevertheless, demonstrating the effectiveness of measuring HRQoL in clinical practice, which has been postulated as the most important way to convince physicians of the importance of HRQoL measurement in clinical practice, and a must before widespread adoption of the procedure can be achieved (1, 3), is needed.

Patients' benefits from computerized HRQoL measurement in clinical practice: effectiveness

A beneficial effect of computerized HRQoL measurement in clinical practice was shown for older and male patients with chronic liver disease, especially with regard to disease-specific and mental HRQoL (chapter 3). It should be noted that these beneficial effects were found in the subgroup analyses. The main analysis, which compared overall scores between the group of patients whose HRQoL data was available and the group of patients whose HRQoL data was not available, did not show a beneficial effect. From these results, it can be concluded that real-time computerized HRQoL measurement is only beneficial to older and male patients with chronic liver disease. On the basis of these results it could be hypothesized that the effects are most prominent in populations that have difficulty in expressing HRQoL issues. In that respect we missed a research opportunity by excluding patients who did not speak Dutch. It could well be that in doing so we excluded the population that would have benefited the most. Obviously, it is to be recommended to include this population in future implementations.

The positive results of this thesis regarding the beneficial effect of computerized HRQoL measurement in clinical practice for older and male patients form an important step towards more widespread implementation of computerized HRQoL measurement in clinical practice. Nevertheless, caution is required. Previous studies have been shown mixed results of the beneficial effects of HRQoL measurement in clinical practice. Some

have shown favourable results such as decreased depression (4), improved overall and emotional functioning (5), improved mental health (6), and a decrease in disease-specific debilitating symptoms of patients undergoing chemotherapy (7), but several other studies did not find any significant improvement in HRQoL or psychosocial outcomes (2, 8-11). Therefore, future implementation of computerized HRQoL measurement practice should be conducted in a research setting in order to obtain more results to strengthen the evidence of the procedure. In doing so, these studies should explore beneficial effects for subgroups of patients. Exploring beneficial effects for subgroups of patients has indeed been suggested before (1), and the positive results of our study underline this suggestion. As described above, nonnative speakers and older patients, who were not very well represented in our study, should be included in these studies.

HRQoL measurement may be especially beneficial to the well-being of patients with slowly progressing chronic diseases, such as liver disease, rather than patients with cancer which were included in most previous studies on HRQoL measurement in clinical practice (4, 5, 7, 10, 12). Due to the often acute and life-threatening nature of cancer, psychological factors and HRQoL may be overshadowed by the focus on curing the disease. In other chronic diseases, where symptom control is the main focus of treatment, HRQoL may be of more importance and there may be more room during the consultation to discuss HRQoL-related issues. Future studies should assess whether patients with slowly progressing chronic diseases other than chronic liver disease benefit from HRQoL measurement in clinical practice.

With regard to satisfaction with the consultation, computerized HRQoL measurement before the clinical consultation seemed not to be beneficial for patients, but it must be remarked that satisfaction scores were already high, if not impossible to improve upon. Previously, insufficient measurement instruments were blamed for this ceiling effect, but the fact that a ceiling effect was also found in our study, where the valid and reliable liver disease-specific questionnaire QUOTE-Liver was used (chapter 7), suggests that patients are actually satisfied with the care that they receive. Considering the good quality of care that has been an important focus at the department of hepatology where this study was conducted, this seems plausible. More knowledge about the sensitivity of the QUOTE-Liver to detect changes in patient satisfaction is however needed in order to fully support this hypothesis. This knowledge may be obtained in an experimental design with healthy subjects, where 'bad' care is delivered purposefully. Another way to assess the sensitivity of the QUOTE-Liver may be to administer it in two different settings, a specialized setting and a less specialized setting. A before and after study, where some aspect of care has been changed, is also a possibility that should be explored.

Physicians' benefits from computerized HRQoL measurement in clinical practice

HRQoL has become an important outcome measure in medical care. However, as described in chapter 3, various studies have shown that physicians' ability to initiate a conversation with their patients about the psychological and social aspects of HRQoL varies greatly. Standardized HRQoL measurement preceding each consultation may be a valuable contribution by providing physicians with information about their patients' well-being, and specific topics to discuss during the consultation. The implementation of such assessments will in part depend on physicians' satisfaction with the assessments and the opportunities to employ clinical options on the basis of these assessments. The results in that respect were quite favourable: more time was spent discussing psychosocial issues when HRQoL was available. In addition, the physicians in our study reported that the HRQoL information of their patients sometimes yielded new problems (chapter 3). Furthermore, it was shown that physicians who had access to the HRQoL data of their patients reported having changed their patient management strategies significantly more often than physicians who did not have access to their patients' HRQoL data. Mainly, they reported changing the frequency of consultations, paid increased attention to physical complaints, and changed the prescription of medication. Due to the written reporting of results, socially desirable answers may have caused the differences between the physicians in both groups. Also, due to the cross-sectional analysis of the data from this part of the study, no firm conclusions can be drawn as to whether the disease-specific or generic HRQoL information, or both, are related in a causal way to this change in patient management. Only by audio taping (part of) the consultations in future studies can conclusive answers to these hypotheses been given. In order to overcome possible bias, the audio taping should either be done at random or for a very long period of time so that physicians will not be aware of it as much.

Nevertheless, these positive professional attitudes must be seen as beneficial effects of the availability of HRQoL measurement on the clinical consultation. At a recent conference on this topic, the suggestion was made to have nurses rather than physicians given the task of discussing the HRQoL-related information. Such a suggestion must be seen as undesirable when considering the fact that physicians have generally more ascendancy to reassure patients that their symptoms are a normal consequence of the disease, and that they are the ones who make referral and treatment decisions. Rather than to insulate the physicians of HRQoL information, a facilitation of the HRQoL discussion as in the present study is more appropriate.

PART II: Determinants of HRQoL in patients with chronic liver disease

An important barrier that has been mentioned towards HRQoL measurement in clinical practice, is physicians' scepticism about their ability to intervene should the HRQoL questionnaires reveal any problems (2). This scepticism may be quite realistic: we acknowledge that HRQoL may be a difficult to interpret concept for physicians who are not familiar with this type of outcome measure. Likewise, the responsibility of physicians to address the social and psychological aspects that are part of HRQoL has previously been questioned (ISOQOL conference, 2007). After all, physicians have been trained to treat physical diseases and related physical symptoms, rather than social and psychological problems. Nevertheless, it makes al lot of sense to argue that physicians should assume responsibility for the social and psychological well-being of their patients, because their impairment may be influenced by illness and health interventions. In chronic liver disease for example, treatment of hepatitis C causes significant fatigue and flu-like symptoms, which may lead to unemployment. This, in turn, may affect economic status and psychological well-being. This assuming of responsibility does not imply that physicians should take on the role of psychologists, social workers, or other professionals. However, a brief discussion of HRQoL-related topics may cause patients to feel understood, and help physicians identify potential problems. Consequently, it is their responsibility to refer patients to an appropriate health professional for further diagnosis and treatment. Leaving this to the responsibility of patients themselves is undesirable, since patients may not have the knowledge to determine what kind of help they need, and/or where to find it.

Providing physicians with information about factors that may cause impaired HRQoL may help them steer the conversation in the right direction. Consequently, correct referral for further diagnostic testing and/or treatment may be more easily achieved (6, 13). In the second part of this thesis, several physical and psychological factors were identified that are closely associated with generic HRQoL in various patients with chronic liver disease. The next part of the discussion elaborates on the clinical implications of these findings.

Physical and psychological determinants of generic HRQoL

Results in this thesis show that generic overall HRQoL was most strongly related to disease severity and joint pain. Pain in the right upper abdomen, decreased appetite, and fatigue were also strongly related to HRQoL (chapter 4). The relationship between disease severity and health related quality of life was to be expected, and has been shown in previous studies (14-16). The relationship between fatigue and HRQoL in patients with chronic liver disease has also previously been demonstrated (17-19). The

relationships between joint pain, pain in the right upper abdomen, decreased appetite and HRQoL have never been assessed before. The hindrance that these symptoms may cause and the fact that they are difficult to treat, may explain their impact on HRQoL. However, future studies should substantiate these findings.

Results presented in this thesis showed a strong relationship between depression and HRQoL in patients with various types of chronic liver disease (chapter 4). We also found a prevalence rate of depressive symptoms of 61% in liver patients awaiting transplantation (chapter 6). In chapter 5, we looked at the interrelationships of several psychological variables more closely, and found that depressive symptoms were the most important determinant of HRQoL in patients with chronic liver disease. Self-efficacy and maladaptive coping affected HRQoL indirectly through depression, and anxiety did not affect HRQoL at all. These findings are in accordance with previous studies using different patient populations, which showed direct relationships between depression an HRQoL (20-22), and indirect relationships between HRQoL and negative/ maladaptive coping and self-efficacy through depression (21, 22). High anxiety scores were expected due to the different stressors that have been associated with awaiting organ transplantation, but these were not found in this study. One reason for our found lack of anxiety may lie in the questionnaire used, which was the 'trait' part of the 'State Trait Anxiety Inventory'. This questionnaire may not have been specific enough to the disease-specific anxiety of patients with chronic liver disease. It is advisable for future studies to use the Hospital Anxiety and Depression Scale, which may be more appropriate in this setting. Another explanation may be that anxiety and depression are often interrelated, and that the inclusion of both depression and anxiety simultaneously in the model has caused the lack of a result for anxiety.

Clinical implications

These results indicate that physicians should be especially attentive to physical aspects of chronic liver disease such as disease severity, joint pain, fatigue, decreased appetite and pain in the right upper abdomen in liver patients presenting with impaired HRQoL. However, the treatment of these symptoms is often difficult. Joint pain can be treated with medication and physiotherapy, decreased appetite may be addressed by giving patients dietary advice, and pain in the right upper abdomen may be reduced by controlling the progression of the liver disease, but the success of these interventions varies. Fatigue is even more difficult to treat as it is often interwoven with depression, and its origin is unclear in patients with liver disease (18). A recent study in liver transplant recipients showed that severity of fatigue was related to the level of everyday physical activity, and it was hypothesized that rehabilitation programs aimed at enhancing levels of everyday physical activity can be effective in breaking through the negative spiral of hypo-activity (19). This hypothesis may also apply to other liver patients, and should

be addressed in future studies. The last and most strongly related variable to HRQoL was disease severity, which is impossible to cure. Once cirrhosis has become a reality there is no possibility to return to the pré-cirrhotic state. However, progression of the disease can be slowed down significantly with good adjustment to medication.

A potential concern that has previously been expressed is that patients expect an intervention once symptoms have been inquired. When symptoms can not be treated, as may be the case for the symptoms associated with impaired HRQoL in chronic liver disease mentioned above, expectations may be raised unrealistically, with adverse consequences for the patient-physician relationship (1). If this is the case, one should be cautious about asking patients about (potentially) untreatable symptoms. However, the results of our study do not support this concern. In our study, no adverse consequences for the patient-physician relationship have been reported, even though (potentially) untreatable symptoms were inquired with the liver disease specific HRQoL questionnaire. On the contrary, it seemed that inquiry of disease-specific symptoms was beneficial for older patients, as shown by the positive results in chapter 3. An explanation could be that through the routine HRQoL measurement, new symptoms were discussed and acknowledged. The mere acknowledgement of these new symptoms as a normal consequence of the disease may have caused acceptance and subsequently better HRQoL (23). Future studies should be conducted to see test this hypothesis in patients with chronic liver disease. For now, the results of this thesis advocate inquiring both treatable and (potentially) untreatable symptoms.

Of the psychological variables, depression had the strongest relationship with HRQoL. Therefore, physicians encountering liver patients with low HRQoL scores in their clinical practices should primarily be vigilant for symptoms and signs of depression. However, they should also be cautious not to overlook other symptoms (5). Rather than treating patients with psychosocial problems themselves, physicians should refer patients to other health professionals such as psychologists. Providing physicians with clear referral options for patients whom they suspect to have psychosocial problems is an important next step in the implementation of HRQoL measurement in clinical practice that will likely make an important contribution to optimal patient outcomes and optimal physician compliance.

The next step is then to identify suitable referral options. A previous study in patients with chronic liver disease has shown a positive effect of a psycho-educational intervention consisting of information on the relationship between liver disease and quality of life, adjustment to chronic disease (coping strategies), relaxation, exercise, diet and nutrition, drugs used and possible side effects (24). In addition, possible positive effects of support groups for patients and families coping with hepatitis C have been mentioned, such as better coping and less uncertainty and anxiety (25). The results of this thesis (chapter 5) suggest that with regard to depression, interventions

aimed at improving levels of coping and self-efficacy may be the treatment of choice in the majority of patients with chronic liver disease. Clearly, further studies are needed to determine the effects of various psychosocial interventions on liver patients' HRQoL before these can be considered as suitable referral options. In the meantime, referring patients with impaired HRQoL and suspicion of a serious psychosocial problem to a trained clinical psychologist for individual diagnosis and therapy is indicated. Providing physicians with a list of names and numbers of psychologists who are skilled in the treatment of patients with (psycho) somatic illness will likely contribute to the actual execution of this recommendation.

Part III Methodological considerations and directions for future research

In this discussion section of the thesis, first a discussion was presented on the feasibility of implementing and effectiveness of HRQoL measurement in clinical practice (Part I) and on the clinical value of determinants found of HRQoL in patients with chronic liver disease (Part II). This discussion section will end with recommendations for future research.

Study design

Setting up a well controlled study at a busy outpatient department of hepatology proved to be difficult, as physicians that were assigned to the experimental group would sometimes stand in for physicians that were assigned to the control group and vice versa. Consequently, HRQoL data of patients who were usually seeing a control group physician was discussed during the consultation. The alternative was to assign patients to the study groups, with the consequence that physicians would be part of both the experimental and the control group simultaneously, which is not desirable (10). In order to obtain the best results regarding the effectiveness of HRQoL measurement in clinical practice, future studies should try to aim at including and randomising many physicians in order to obtain the best results.

The data collection period of one year may have been a bit short to obtain convincing results with regard to the effect of computerized HRQoL measurement in clinical practice on patients' well-being. In addition, the cross-sectional analysis of the results and the summarizing of multiple measurement moments into an overall score on an intention-to-treat basis as we did in our study, may be suboptimal. Future studies should try to take on an even more prospective approach when analysing the data. Lengthening the duration of data collection and analysing the differences between measurement moments within the experimental group are advisable. In addition, this

will also aid to determine the long-term effect of computerized real-time HRQoL measurement in clinical practice.

Intervention

The study described in this thesis did not provide physicians with referral and treatment options for patients presenting with impaired HRQoL. Future studies should aim to do so, since this may enlarge the effectiveness of the intervention and decrease physicians' attitudinal barriers. Specific referral and treatment plans may differ for different patient populations and should be determined through the assessment of factors that are closely related to HRQoL in each distinct patient population. Since studies on the effectiveness of psychosocial group interventions for patients with chronic liver disease are still scarce, this is an important research area that deserves further studying. In the meantime, referring patients with impaired HRQoL and suspicion of a serious psychosocial problem to a trained clinical psychologist for individual diagnosis and therapy seems indicated.

The effect of the intervention on patient management was, for reasons of practicality, assessed by means of short checklists. Since positive results were obtained with these checklists, this topic deserves more attention in future studies. Audiotaping (part of) the consultations may provide a more detailed view of the treatment strategies that are being executed and/or discussed. In addition, by relating these data of the consultation to the HRQoL data of each patient, possible relationships between changes in patient management and improvement in patients' HRQoL can be determined.

Patient population

The exclusive inclusion of chronic liver patients impedes generalisation of our results to other chronic patient populations. Even though the results of our study might suggest that measuring HRQoL in clinical practice may be valuable for patients with various chronic diseases, future studies in patients with other chronic conditions should be conducted in order to test this hypothesis. Future studies should also focus on specific subgroups of patients who may benefit most from the procedure and assess the benefits for nonnative speakers.

Measurement instruments

Because of a lack of practical instruments designed to measure HRQoL at individual patient level, the studies in this thesis made use of the Short Form-12 (SF-12) for the measurement of generic HRQoL in clinical practice (chapter 2&3). We are cognizant of the fact that the SF-12 is a short version of the SF-36 that has been designed to measure HRQoL at group level rather than at individual patient level. However, it may be argued that using HRQoL instruments designed for use at group level is justified as

long as they are used to provide physicians with an indication of the HRQoL of their patients, from which a discussion can be started. In that way, the questionnaires can form a valuable tool for physicians, who have been shown to vary greatly in their ability to elicit psychosocial information (26-34). It should be made extremely clear to physicians that the data that the instruments provide are to be used as such, and never as a cut-off point for treatment or referral decisions. Of course, it is desirable that future studies aim to assess the responsiveness of existing group instruments to monitor changes in individual patients' HRQoL.

Another methodological consideration concerning the use of measurement instruments regards the use of the Liver Disease Symptom Index 2.0 (LDSI 2.0). Due to time constraints, the 'hindrance' items of the LDSI 2.0 were not included, even though the strength of the LDSI 2.0 lies just in these 'hindrance' items since these give a more subjective view of patients HRQoL (one can have symptoms without hindrance). Administering the hindrance items instead of the symptom items was not advisable, since due to word choice, the emphasis on hindrance was not clear without symptom items preceding these questions. By omitting the hindrance items, the LDSI 2.0 resembles the construction of most other HRQoL instruments that assume that having a symptom impairs HRQoL, such as the SF-12. The positive results of this thesis on the symptom items of the LDSI 2.0 suggest that making an inventory of these is already beneficial. However, future studies should aim to also include hindrance items in order to obtain a better view of the subjective HRQoL of patients.

In the second part of this thesis, where determinants of HRQoL were assessed, we made use of the Beck's Depression Inventory (BDI) and the Stait Trait Anxiety Inventory (STAI) to measure depression and anxiety. The BDI comprises physical symptoms such as fatigue and decrease appetite to determine levels of depression. However, chronic liver disease is often accompanied by such symptoms, which may lead to falsely high depression scores. In our study, this was controlled for. However, it is advisable for future studies to use the Hospital Anxiety and Depression Scale (HADS), which has been especially designed for use in patients with physical illness. The anxiety that is measured by the HADS is more disease-specific than the anxiety measured by the STAI. Future studies should also aim to develop a liver disease-specific self-efficacy scale, which was not available for use in our study.

Concluding comments

The beneficial effects of HRQoL measurement in clinical practice as shown in this thesis, together with the generally positive attitudes of physicians towards the availability of HRQoL information during the consultation, advocate more widespread implementa-

tion of such a procedure in other chronic patient populations. To that end, convincing physicians of the importance, feasibility and effectiveness of HRQoL measurement in clinical practice has been mentioned as a must (2, 3). This thesis has made an important contribution in that regard, but future implementation of real-time HRQoL measurement in a research setting with other patient populations and suggestions for treatment/referral options, is essential to substantiate our findings. Only then can the scepticism of physicians' towards the added value of the procedure be overruled, and future widespread implementation facilitated.

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Summary

Introduction

Given that the health related quality of life (HRQoL) of patients with chronic liver disease is reduced compared to healthy persons, the studies described in this thesis set out to investigate ways of improving these patients' HRQoL in the clinical practice of an outpatient department of hepatology. In the Introduction, the origins and aims of this thesis are described. Chapter 1 'Overview of research on health related quality of life in patients with chronic liver disease' provides an overview of the topic of research on health related quality of life in patients with chronic liver disease. The severity of chronic liver disease and the impaired HRQoL in this patient population are described. The growing interest in the topic of implementing HRQoL measurement in clinical practice is shown, and two main reasons for the not being forthcoming of widespread implementation of such a procedure are postulated: lack of results (as yet) regarding the effectiveness of standardized HRQoL measurement in actually improving HRQoL or psychosocial outcomes, and practical and attitudinal barriers.

In the first part of this thesis on the effectiveness of implementing computerized HRQoL measurement in a clinical outpatient practice of hepatology, both these aspects are addressed (Chapters 2 & 3). Chapter 2 focuses on the practical feasibility of implementation of HRQoL measurement in clinical practice, and chapter 3 focuses on the effectiveness of such a procedure in actually improving patients' HRQoL, patient care, and patient satisfaction with the consultation. In the second part of this thesis (Chapters 4 – 6), factors related to HRQoL in patients with chronic liver disease are determined. In chapter 4, physical and psychological factors related to HRQoL in a large sample of 1175 patients with chronic liver disease are assessed. In chapter 5, the relationships between HRQoL and depression, anxiety, coping and self-efficacy are assessed in a sample of patients with hepatitis B, hepatitis C, and cholestatic liver disease. In chapter 6, these relationships are assessed in a sample of patients listed for transplantation. In the final chapter 7, the development of a disease-specific questionnaire to measure patient satisfaction with care at a department of Hepatology and Gastroenterology is described.

PART I: Feasibility and effectiveness of implementing computerized HRQoL measurement in clinical practice

The data for this part of the thesis were obtained as follows. Between September 2004 and January 2005, all patients with chronic liver disease (CLD) attending the department of Gastroenterology and Hepatology of the Erasmus MC (Rotterdam, the Netherlands) were invited to participate in the study. Five hundred and eighty seven patients

and all 11 physicians working at the department of hepatology agreed to participate. All patients participating in the study were instructed to complete a computerized generic (Short Form-12) and disease-specific (Liver Disease Symptom Index 2.0) HRQoL questionnaire before each consultation at the outpatient department of hepatology for the duration of one year. Patients also completed a questionnaire on satisfaction with the consultation (QUOTE-Liver). Physicians were randomly assigned to either the experimental group or the control group. Physicians in the experimental group were able to obtain an instant computerized graphical output of the HRQoL data of their patients, and were instructed to discuss the results with their patients. Physicians in the control group conducted their consultations as usual. After each consultation with a participating patient, physicians in both groups completed a short checklist about the consultation. Midway and at the end of the study, they were interviewed on their views of the availability of the HRQoL data during the consultations.

In chapter 2 'Logistic feasibility of health related quality of life measurement in clinical practice: results of a prospective study in a large population of chronic liver patients', feasibility issues with regard to the implementation of (computerized) HRQoL measurement in clinical practice were described. The study showed that when implementing routine computerized HRQoL measurements in clinical practice, assistance of an IT professional for the development of a tailor-made computer program with safe data transmission over the Internet is essential. Availability of questionnaires in multiple languages and the use of touch-screen computers to optimise patient participation are important. Also, all staff of the department concerned should approve of the intervention and consider it as part of standard clinical routine if successful implementation is to be obtained.

In chapter 3, 'Effectiveness of measurement of health related quality of life in clinical practice: a prospective, randomized controlled trial in patients with chronic liver disease and their physicians', the effectiveness of computerized measurement of HRQoL in daily clinical practice in actually improving patients' well-being was described. Differences in generic and disease-specific HRQoL were assessed between all participating patients whose HRQoL data were available to the physicians and all participating patients who had treatment as usual. Also, differences in HRQoL for specific subgroups of patients were assessed. Differences between older and younger patients, male and female patients, and severely and non-severely ill patients were assessed. The results show no main differences in HRQoL between patients whose HRQoL data was available and patients who received treatment as usual. Subgroup analyses, however, showed that older patients benefited from the availability of HRQoL data, especially with regard to disease-specific and mental HRQoL. Also, male patients benefited from the availability of HRQoL data, especially with regard to mental HRQoL.

In chapter 3, we also assessed the possible effect of availability of HRQoL data on the clinical consultations by analysing the number of changes in patient management. It was found that physicians who had access to the HRQoL data of their patients made significantly more changes in patient management than physicians who did not have access to these data. Most commonly, frequency of consultations was increased. Other alterations concerned prescription of medication, increased attention for physical complaints, referral to psychosocial care or occupational health physician, and increased attention to explanations/reassurance. Physicians were generally positive towards the availability of HRQoL information during their consultations. Patient satisfaction with the consultation did not differ between the experimental and the control group.

PART II: Determinants of HRQoL in patients with chronic liver disease

The second part of this thesis encompasses studies on possible physical and psychological predictors of HRQoL in patients with chronic liver disease. Knowledge of these predictors will enable more concise management strategies to be outlined.

In chapter 4, 'Determinants of quality of life in chronic liver patients', the impact of physical and psychosocial determinants on HRQoL in a sample of 1175 patients with chronic liver disease was assessed. We were the first to use a weighted score of HRQoL rather than multidimensional unweighted outcomes that have been used in previous studies and that make comparisons of results difficult. We found that HRQoL was most strongly related to disease severity and joint pain. Depression, pain in the right upper abdomen, decreased appetite and fatigue, were also strongly related to HRQoL. In patients with hepatitis C, disease severity and depression had strong relationships with HRQoL.

In chapter 5, 'Psychological determinants of health related quality of life in patients with chronic liver disease' we looked at the interrelationships between HRQoL and depression, anxiety, coping and self-efficacy in more detail. 55 Patients with hepatitis B, 43 patients with hepatitis C, and 66 patients with cholestatic liver disease (response rate=70%) completed a questionnaire booklet comprising a generic HRQoL questionnaire (SF-6D), and questionnaires assessing depression (BDI-II-NL), anxiety (STAI), coping (COPE-Easy) and self-efficacy (SES). Both direct and indirect relationships among the psychosocial factors were determined using a Structural Equation Modeling approach. Disease severity was controlled for in the analyses. The results indicated that even though all psychological variables in the model affected HRQoL either directly or indirectly, depression had the most influence on HRQoL in all three groups of liver

patients. Depression, in turn, was largely determined by low self-efficacy and by use of maladaptive coping strategies.

In chapter 6 'Health related quality of life and psychological correlates in patients listed for liver transplantation', we compared HRQoL, anxiety, depression, coping and self-efficacy of 32 patients awaiting liver transplantation with that of other patients with liver disease with and without cirrhosis, and a healthy norm population. It was shown that patients awaiting liver transplantation were not experiencing worse physical and psychological HRQoL than other liver patients with cirrhosis of the liver. Compared to other patients with liver disease without cirrhosis, liver transplant candidates had significantly lower HRQoL scores on the subscales physical functioning and general health. Their overall HRQoL was significantly reduced compared to healthy controls, as were their depression scores. Depression correlated significantly with HRQoL in patients awaiting liver transplantation. Patients without depression made significantly more use of active coping strategies than patients with elevated depression levels. Levels of anxiety, self-efficacy and coping did not differ between liver transplant candidates and the comparison groups.

Chapter 7 'Quality of health care and patient satisfaction in liver disease: the development and first results of the QUOTE-Liver questionnaire' covered the development of a liver disease-specific questionnaire (QUOTE-Liver) that measures quality of care and patient satisfaction in hepatology. The QUOTE protocol as described by the Netherlands Institute of Health Services Research (NIVEL, Utrecht, the Netherlands) was used for this purpose. In total, 39 patients with chronic liver disease participated in the development of the QUOTE-Liver, which consists of 18 generic and two liver disease-specific items. Reliability and validity were tested in a sample of 152 patients with chronic liver disease. Face validity and content validity were satisfactory. Construct validity was good: the overall score correlated significantly with the Visual Analogue Scale measuring overall satisfaction. The reliability of the QUOTE-Liver was excellent.

In the 'Discussion', an overall discussion of the main results of our study in view of results from other studies was presented. Implications and limitations of our study were discussed and recommendations for future research made.

10

Nederlandse samenvatting

Inleiding

Vergeleken met gezonde personen hebben patiënten met een chronische leverziekte een minder goede kwaliteit van leven (KvL). De studies die in dit proefschrift beschreven worden richten zich op het verbeteren van de KvL van deze patiënten in de poliklinische praktijk van een afdeling Maag-, Darm- en Leverziekten. In de 'Inleiding' worden het ontstaan en de doelen van dit proefschrift beschreven. Hoofdstuk 1, 'Overzicht van onderzoek naar ziektegerelateerde kwaliteit van leven bij patiënten met chronische leverziekte', geeft een overzicht van onderzoek naar KvL bij patiënten met een chronische leverziekte. De ernst van chronische leverziekte wordt beschreven, evenals de verminderde kwaliteit van leven in deze patiëntenpopulatie. De toenemende interesse in het meten van KvL in de klinische praktijk wordt belicht en de twee voornaamste redenen voor het uitblijven van een wijdverbreide implementatie van zo'n procedure worden genoemd: gebrek (tot op heden) aan bewijs van het effect van routinematige KvL metingen in de klinische praktijk op de KvL van patiënten, en praktische barrieres en bezwaren van artsen.

In het eerste deel van dit proefschrift over de effectiviteit van het implementeren van geautomatiseerde KvL metingen in de poliklinische praktijk van een Maag-, Darm,-Leverafdeling worden beide aspecten behandeld (hoofdstuk 2 & 3). Hoofdstuk 2 richt zich op de praktische uitvoerbaarheid van implementatie van geautomatiseerde KvL metingen en de klinische praktijk, en hoofdstuk 3 richt zich op de effect van de procedure op de KvL van patiënten, patiëntenzorg en tevredenheid van patiënten met het consult. In het tweede deel van dit proefschrift worden factoren die samenhangen met KvL bij patiënten met een chronische leverziekte in kaart gebracht (hoofdstuk 4-6). In hoofdstuk 4 worden lichamelijke en psychologische factoren die samenhangen met KvL bekeken in een groep van 1175 patiënten met een chronische leverziekte. In hoofdstuk 5 worden de relaties tussen KvL en depressie, angst, coping en self-efficacy bekeken bij patiënten met hepatitis B, hepatitis C en cholestatische leverziekte. In hoofdstuk 6 worden deze relaties bekeken bij patiënten die wachten op een levertransplantatie. Hoofdstuk 7 beschrijft de ontwikkeling van een ziekte-specifieke vragenlijst voor het meten van patiënttevredenheid met de zorg op een afdeling Maag,-Darm-, Leverziekten.

DEEL I: Uitvoerbaarheid en effectiviteit van implementatie van geautomatiseerde KvL metingen in de klinische praktijk

De data voor dit gedeelte van het proefschrift zijn als volgt verkregen. Tussen september 2004 en januari 2005 zijn alle patiënten met een chronische leverziekte van de afdeling Maag-, Darm-, Leverziekten (MDL) van het Erasmus MC (Rotterdam, Nederland) uitgenodigd om deel te nemen aan het onderzoek. 587 patiënten en alle 11 leverartsen werkzaam op de MDL-afdeling stemden toe met deelname. Alle patiënten die deelnamen aan het onderzoek kregen instructie om gedurende een jaar, voor ieder consult op de afdeling MDL, een geautomatiseerde generieke (Short Form-12) en ziekte-specifieke (Liver Disease Symptom Index 2.0) vragenlijst in te vullen. Patiënten vulden ook een vragenlijst in over tevredenheid met het consult (QUOTE-Liver). Artsen werden aselect toegewezen aan de experimentele groep danwel de controle groep. Artsen in de experimentele groep konden onmiddelijk een geautomatiseerde grafische weergave van de KvL data van hun patiënten verkrijgen en zij werden geïnstrueerd om deze resultaten met hun patiënten te bespreken. Artsen in de controle groep voerden hun consult zoals gewoonlijk. Na ieder consult met een deelnemende patiënt vulden de artsen in beide groepen een korte checklist in over het consult. Halverwege en aan het eind van het onderzoek werd hen in een interview gevraagd wat ze vonden van de beschikbaarheid van KvL data tijdens de consulten.

In hoofdstuk 2 'Logistiek van kwaliteit van metingen in de klinische praktijk: resultaten van een prospectief onderzoek bij een grote populatie patiënten met een chronische leverziekte', werden logistieke aspecten van het meten van KvL in de klinische praktijk beschreven. Het onderzoek liet zien dat implementatie van routinematige, geautomatiseerde KvL metingen in de klinische praktijk de hulp van een IT-deskundige vereist die een op maat gemaakt computer programma kan maken en veilige data transmissie over het Internet kan garanderen. Beschikbaarheid van vragenlijsten in meerdere talen en het gebruik van touch-screen computers zijn belangrijk bij het optimaliseren van patiëntenparticipatie. Verder zou, voor een succesvolle implementatie, het personeel van de betreffende afdeling de interventie moeten goedkeuren en beschouwen als onderdeel van de klinische routine.

In hoofdstuk 3 'Effectiviteit van het meten van KvL in de klinische praktijk: een prospectief gerandomiseerd onderzoek bij patiënten met chronische leverziekte en hun artsen', werd beschreven in hoeverre geautomatiseerde KvL metingen in de dagelijkse klinische praktijk effectief zijn in het daadwerkelijk verbeteren van het welzijn van patiënten. Verschillen in generieke- en ziekte-specifieke KvL tussen alle deelnemende patiënten wiens KvL data beschikbaar was voor de artsen en alle deelnemende patiënten die een 'gewoon' consult kregen, werden vastgesteld. Ook werden verschillen

in KvL tussen specifieke subgroepen van patiënten (man/vrouw, jong/oud, niet ziek/ernstig ziek) vastgesteld. De resultaten lieten geen verschillen zien in KvL tussen patiënten wiens KvL data beschikbaar was en patiënten die een 'gewoon' consult kregen. Subgroep analyses lieten echter wel zien dat oudere patiënten baat hadden bij de beschikbaarheid van KvL data, in het bijzonder met betrekking tot ziekte-specifieke en mentale KvL. Ook hadden mannelijke patiënten baat bij de beschikbaarheid van KvL data, in het bijzonder met betrekking tot mentale KvL.

In hoofdstuk 3 keken we ook naar het mogelijke effect van de beschikbaarheid van KvL data op het klinische consult, door het tellen van het aantal veranderingen in patiëntenbeleid. Er werd gevonden dat artsen die toegang hadden tot de KvL data van hun patiënten hun beleid vaker veranderden dan artsen die geen toegang hadden tot deze data. Het vaakst werd de frequentie van consulten verhoogd. Andere veranderingen betroffen het voorschrijven van medicatie, verhoogde aandacht voor lichamelijke klachten, verwijzing naar psychosociale zorg of ergotherapie, en verhoogde aandacht voor uitleg/geruststellen. Artsen waren over het algemeen positief over de beschikbaarheid van KvL informatie tijdens hun consulten. Patiënttevredenheid met het consult verschilde niet tussen patiënten in de experimentele- en patiënten in de controlegroep.

DEEL II: Determinanten van KvL bij patiënten met chronische leverziekte

Het tweede deel van dit proefschrift bevat studies naar mogelijke lichamelijke en psychologische voorspellers van KvL bij patiënten met chronische leverziekte. Kennis van deze voorspellers zal een preciezer behandelbeleid voor patiënten met een lage KvL vergemakkelijken.

In hoofdstuk 4 'Determinanten van KvL bij patiënten met chronische leverziekte', werd de impact van lichamelijke en psychosociale determinanten van KvL vastgesteld in een groep van 1175 patiënten met chronische leverziekte. Wij waren de eersten die gebruik maakten van een gewogen score van KvL in plaats van multidimensionele ongewogen scores, die zijn gebruikt in eerdere studies en die het vergelijken van resultaten moeilijk maken. Wij vonden dat KvL het sterkst samenhing met ziekte-ernst en gewrichtspijn. Depressie, pijn in de rechter bovenbuik, verminderde eetlust en vermoeidheid waren ook sterk gerelateerd aan KvL. Bij patiënten met hepatitis C hadden ziekte-ernst en depressie een sterke relatie met KvL.

In hoofdstuk 5 'Psychologische determinanten van ziektegerelateerde kwaliteit van leven bij patiënten met chronische leverziekte', keken we meer in detail naar de onderlinge relaties tussen KvL en depressie, angst, coping en self-efficacy. 55 Patiënten

met hepatitis B, 43 patiënten met hepatitis C, en 66 patiënten met cholestatische leverziekte (respons rate = 70%) vulden een vragenlijstboekje in met daarin een generieke KvL vragenlijst (SF-6D) en vragenlijsten over depressie (BDI-II-NL), angst (STAI), coping (COPE-Easy) en self-efficacy (SES). Zowel directe als indirecte relaties tussen de psychosociale variabelen werden vastgesteld middels 'Structural Equation Modeling'. In de analyses werd gecontroleerd voor ziekte-ernst. The resultaten laten zien dat hoewel alle psychologische variabelen in het model KvL direct of indirect beïnvloedden, depressie de meeste invloed had op KvL in alle drie de patiëntgroepen. Depressie werd op zijn beurt grotendeels bepaald door lage self-efficacy en het gebruik van ongepaste copingstrategieën.

In hoofdstuk 6 'Ziektegerelateerde kwaliteit van leven en psychologische factoren bij patiënten die wachten op een levertransplantatie', vergeleken we KvL, angst, depressie, coping en self-efficacy van 32 patiënten in die wachtten op een levertransplantatie met andere leverpatiënten met- en zonder levercirrose, en met een gezonde normpopulatie. De resultaten lieten zien dat patiënten die wachtten op een levertransplantatie geen slechtere lichamelijke en psychische KvL hadden dan andere leverpatiënten met levercirrose. Vergeleken met andere leverpatiënten zonder levercirrose hadden levertransplantatiepatiënten significant lagere KvL scores op de subschalen 'lichamelijk functioneren' en 'algemene gezondheid'. Hun overall KvL en depressiescore was significant slechter dan die van gezonde mensen. Depressie hing significant samen met KvL in patiënten die wachtten op een levertransplantatie. Patiënten zonder depressie maakten significant meer gebruik van actieve copingstrategieën dan patiënten met verhoogde depressiescores. Angst, self-efficacy en coping verschilden niet tussen prétransplantatiepatiënten en de vergelijkingsgroepen.

Hoofdstuk 7 'Kwaliteit van de gezondheidszorg en patiënttevredenheid bij leverziekte: de ontwikkeling en eerste resultaten van de QUOTE-Liver vragenlijst', beschreef de ontwikkeling van een leverziektespecifieke vragenlijst (QUOTE-Liver) die de kwaliteit van de zorg en patiënttevredenheid meet bij patiënten met een chronische leverziekte. Daartoe werd gebruik gemaakt van het QUOTE protocol, ontwikkeld door het Nederlands Instituut voor Onderzoek van de Gezondheidszorg (NIVEL, Utrecht, Nederland). In totaal namen 39 patiënten met een chronische leverziekte deel aan de ontwikkeling van de QUOTE-Liver die bestaat uit 18 generieke en twee ziektespecifieke items. Betrouwbaarheid en validiteit werden getoetst op 152 patiënten met een chronische leverziekte. De facevaliditeit en contentvaliditeit waren bevredigend. De constructvaliditeit was goed: de totaalscore correleerde significant met een VAS schaal die totale tevredenheid mat. De betrouwbaarheid van de QUOTE-Liver was uitstekend.

In het hoofdstuk 'Discussie' werden de belangrijkste resultaten van de studies in dit proefschrift beproken in het licht van eerdere resultaten van andere studies. De

implicaties en beperkingen van ons onderzoek werden besproken en er werden aanbevelingen gedaan voor mogelijk toekomstig onderzoek.

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En dan nu het dankwoord. Hoewel wetenschappelijk van geen belang waarschijnlijk het meest gelezen hoofdstuk van ieder proefschrift. Heel graag wil ik in dit hoofdstuk een aantal mensen bedanken die betrokken zijn geweest bij de totstandkoming van dit proefschrift. Het zijn er nogal wat. Waar te beginnen? In de wetenschap dat dankbare mensen alerter, enthousiaster, optimistischer en energieker zijn dan mensen die niet stil staan bij wat ze hebben[1], ben ik maar gewoon begonnen.

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1 McCullough, M. E., Emmons, R. A., & Tsang, J. (2002). The grateful disposition: A conceptual and empirical topography. Journal of Personality and Social Psychology, 82, 112–127

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Curriculum Vitae

Jolie Gutteling was born on the 6th of October 1979 in Alphen aan den Rijn, the Netherlands. From 1989 till 1991 she lived in France where she attended an international school. She graduated from high school (VWO, Scala College, Alphen aan den Rijn) in 1997. After spending a year at Enterprise State Junior College (Alabama, USA), she went on to study clinical psychology at the University of Amsterdam. Her internship was at the Emma Children's Hospital (Amsterdam, the Netherlands), where she learned to administer various (neuro)psychological tests, conduct intake interviews and exit interviews, and perform cognitive behavioral therapy. In 2002 she obtained her master's degree with honor ('met genoegen').

In August of 2003, she started her PhD study at the departments of Gastroenterology and Hepatology / Medical Psychology and Psychotherapy at the Erasmus MC (Rotterdam, the Netherlands). During her PhD, she has worked as a teacher at the faculty of medicine of the Erasmus University. She has also been involved in the development and teaching of a course in quality of life research at the Faculty of Psychology of the Erasmus University. She is currently working as a psychologist at Adhesie GGZ in Deventer, the Netherlands.