Health Related Quality of Life of Chronic Liver Patients

A Dutch Population-Based Study

ACKNOWLEDGEMENTS

The work presented in this thesis was conducted at the Department of Hepatology and Gastroenterology in close collaboration with the Department of Epidemiology and Biostatistics, the Dutch liver patient association (Nederlandse Leverpatiënten Vereniging (NLV)) and the Department of Medical Psychology and Psychotherapy. The author gratefully acknowledges the principal investigators, the board of the NLV and of course all NLV-members. Furthermore, the author gratefully acknowledges E. Smets and M. Müller for providing respectively the MFI-20 and the SF-36 Dutch norm data.

This study was supported by The Dutch Digestive Diseases Foundation (MLDS), grant WS 98-39. Financial support for the publication of this thesis, provided by the Dutch Digestive Diseases Foundation and the Department of Epidemiology and Biostatistics of the Erasmus MC is gratefully acknowledged.

ISBN: 90-77595-23-6

Cover design: Jan Carlier
Print and lay-out: Optima Grafische Communicatie Rotterdam

Health Related Quality of Life of Chronic Liver Patients
A Dutch Population-Based Study

Gezondheid Gerelateerde Kwaliteit van Leven van Chronische Leverpatiënten

Een Nederlands Populatie-Onderzoek

Proefschrift
ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
Op gezag van de Rector Magnificus
Prof.dr. S.W.J. Lamberts
en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
woensdag 31 maart 2004 om 13.45 uur

door

Simone Maria van der Plas
geboren te Bleiswijk

PROMOTIECOMMISSIE

Promotoren:	Prof.dr. S.W. Schalm Prof.dr. Th. Stijnen
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MANUSCRIPTS BASED ON THE STUDY DESCRIBED IN THIS THESIS

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Van der Plas SM, Hansen BE, de Boer JB, Stijnen Th , Passchier J, de Man RA, Schalm SW. The Liver Disease Symptom Index 2.0; validation of a disease-specific questionnaire. Quality of life Research. Accepted for publication

Chapter 3

Van der Plas SM, Hansen BE, de Boer JB, Stijnen Th, Passchier J, de Man RA, Schalm SW. Generic and disease-specific health related quality of life of non-cirrhotic, cirrhotic and transplanted liver patients: a cross-sectional study.
BMC Gastroenterology 2003, 3: 33

Chapter 4

Van der Plas SM, Hansen BE, de Boer JB, Stijnen Th, Passchier J, de Man RA, Schalm SW. Generic and disease-specific health related quality of life of chronic liver patients with various aetiologies. Submitted.

Chapter 5

Van der Plas SM, Hansen BE, de Boer JB, Stijnen Th, Passchier J, de Man RA, Schalm SW. Generic and disease-specific health related quality of life of patients with viral hepatitis B or C. Submitted.

Chapter 6

Van der Plas SM, Hansen BE, de Boer JB, Stijnen Th, Passchier J, de Man RA, Schalm SW. Health related quality of life of chronic liver patients; a survey in Dutch patients. Submitted.

1

Introduction

Chronic illnesses form a spectrum of diseases. Some chronic illnesses are poorly understood and unpredictable, some are understood and manageable, some are progressively disabling and some are life threatening. Nevertheless, for all chronic patients chronic illnesses have one thing in common: The patient will never again return to the pre-illness state of invulnerability of obliviousness to the body's functioning. In chronic patients, symptoms may interfere to varying degrees with the ability to work, to carry out family and social roles and to rest [1]. It is in this light that a measure like Health Related Quality of Life (HRQoL) can be of great use.

HRQoL is a psychosocial outcome that reflects a person's health and how a disturbance of a person's health influences his or her functioning in daily life [2]. HRQoL provides information about the physical, social and mental burden of disease and is complementary to the clinical, biochemical and physiologic outcomes, which provide information about the pathological course of the disease [3]. Although clinicians may be more concerned about the traditional biological outcomes, patients are more concerned about the impact of disease and related treatments on quality of life [4].

Chronic liver disease is associated with significant morbidity and mortality. Patients may suffer from complications of cirrhosis like ascites, variceal bleedings and hepatic encephalopathy, which are easily evaluated by traditional clinical measures. Yet, many chronic liver patients are put up with non-specific symptoms like fatigue, abdominal discomfort, nausea and depression. These symptoms are hard to evaluate, however [5,6]. Therefore, in clinical practice the severity of these symptoms may get less attention than required, although these symptoms may have a significant impact on HRQoL.

In the past decades, research by means of generic and liver disease-specific HRQoL questionnaires has increased our insight in the HRQoL of chronic liver patients. Many of these studies compared the HRQoL between pre-transplanted and post-transplanted liver patients or focused on the impact of a certain therapy, such as interferon therapy on HRQoL [7-10]. Others compared the HRQoL of patients with various disease stages or aetiologies or were directed to the HRQoL impact of a specific aetiology like hepatitis C or cholestatic diseases [11-14]. However, the majority of these studies were conducted in relatively small clinical populations or restricted to a certain disease stage or aetiology, leaving limited space for correction for other potentially disturbing factors of HRQoL. Furthermore, the used liver disease-specific questionnaires were predominantly directed to measurement of symptom severity, but disregarded the measurement of experienced hindrance of symptoms during daily activities [15-18].

The research on HRQoL of chronic liver patients described in this thesis was conducted in collaboration with the Dutch liver patient association (Nederlandse Leverpatiënten Vereniging (NLV)). In contrast to earlier studies, our investigation approached a population-based study since our large population of NLV members merely represented a general population of chronic liver patients. Moreover, the population-size and the amount variation in the population regarding aetiology and disease stage permitted extensive adjustment for potential confounders. This enabled us to evaluate the impact of disease stage and aetiology on the HRQoL (generic HRQoL, disease-specific HRQoL and fatigue) of chronic liver patients.

Before we started the analyses we aimed for, we validated the construct validity of the Liver Disease Symptom Index 2.0, a disease-specific questionnaire developed at our Department of Gastroenterology and Hepatology at the Erasmus Medical Center Rotterdam (chapter 2).

Our main aim was to evaluate the impact of disease stage (non-cirrhosis, compensated cirrhosis and decompensated cirrhosis) and liver transplantation (chapter 3), aetiology (viral hepatitis, autoimmune hepatitis, cholestatic diseases, hemochromatosis and other liver diseases) (chapter 4) and more specifically the impact of viral hepatitis B and C (chapter 5) on the HRQoL of chronic liver patients. Finally, we integrated the findings described in former chapters, to put the HRQoL of specific liver patient subgroups in perspective with the HRQoL of other liver patients, non-liver patients and healthy controls (chapter 6).

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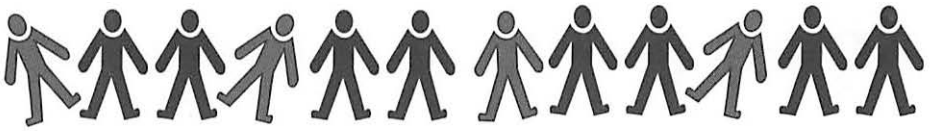
2

Validation of the Liver Disease Symptom Index 2.0



ABSTRACT

Background: The available liver disease-specific questionnaires do address severity of symptoms but hardly evaluate how patients experience these specific symptoms during daily activities. The Liver Disease Symptom Index 2.0 (LDSI) includes 18 items that measure symptom severity and symptom hindrance in the past week.
Methods: In a large survey (n=1175) conducted in collaboration with the Dutch liver patient association, we evaluated the convergent and divergent construct validity of the LDSI with the SF-36 and the MFI-20 and the surplus value of including both symptom severity *and* symptom hindrance items in the LDSI.
Results: The LDSI items showed expected convergent and divergent correlations with Short Form-36 (SF-36) and Multidimensional Fatigue Index-20 (MFI-20) scales. Correlations revealed only a slight to moderate overlap between LDSI items and SF-36 and MFI-20 scales. With respect to the surplus value of the symptom severity and symptom hindrance items, we found that the impact of symptom hindrance on generic HRQoL varied in a different way across different levels of generic HRQoL than symptom severity. This indicated that symptom severity items and symptom hindrance items measured different aspects of HRQoL.
Conclusions: We conclude that the LDSI provides information complementary to the information given by the SF-36 and the MFI-20 and that it is psychometrically sound to include both symptom severity items and symptom hindrance items in the LDSI.

In the past decades, most research on HRQoL of chronic liver patients focused on treatment induced change in HRQoL, the variation of HRQoL across disease stages and the comparison of HRQoL between aetiologies. For these purposes, a liver disease-specific questionnaire has been recommended [1]. However, many studies investigated the HRQoL of chronic liver patients by means of a generic questionnaire [2-5]. Turning point has been the development of the Hepatitis Quality of Life Questionnaire. This questionnaire includes eight generic and two disease-specific scales, which measure limitations in physical, role- and social activities and distress due to hepatitis [6-8]. Severity of specific symptoms or hindrance of specific symptoms in daily functioning has not been addressed in this questionnaire. In contrast, the Chronic Liver Disease Questionnaire, the Liver Disease Quality of Life Questionnaire and the Liver Transplantation Database Quality Of Life questionnaire do address symptom severity but hardly evaluate how patients experience these specific symptoms during daily activities [6-8]. Still, information about the way liver patients experience their symptoms and how these symptoms affect their daily activities could be important for individual disease management. In clinical practice, objective physiological and clinical outcomes do not always match the patient's health perceptions [9-11]. As a consequence, hepatologists may experience difficulties in understanding their patients. Therefore, a disease-specific questionnaire that measures the experienced severity and hindrance of specific symptoms may provide important additional information. For this reason, we developed the Liver Disease Symptom Index (LDSI).

In an earlier study we evaluated the psychometric properties of the LDSI [12]. Several adjustments have followed from the first psychometric evaluation, which led to the LDSI 2.0. A pilot study, conducted in a clinical population pointed out that the LDSI 2.0 had an adequate feasibility and test-retest reliability, which allowed us to take the next step in the validation process: To evaluate the construct validity of the Liver Disease Symptom Index 2.0.

METHODS

The Liver Disease Symptom Index 2.0 (appendix 1)

The psychometric properties of the first LDSI version have been evaluated in a clinical population of chronic liver patients. Results were promising with respect to the feasibility, reliability and the discrimination between compensated cirrhotic and decompensated cirrhotic patients. However, difficulties arose with respect to the discrimination between compensated cirrhotic and non-cirrhotic patients. Therefore, we changed the response categories to a five-point scale. We gave the LDSI a more multidimensional character by adding items on depression and worry about the family situation. Since we intended to use the LDSI in a large survey on the HRQoL of chronic liver patients organised in collaboration with the Dutch liver patient association (Nederlandse Leverpatiënten Vereniging (NLV), we consulted the board of the NLV for important disease-specific items still lacking in the LDSI. The NLV board included various chronic liver patients who, based on their experience and contact with other liver patients stressed the importance of itch as a cause of sleep

deprivation and the hindrance of jaundice in social contacts. Especially the item on itch was supported by the literature [13,14]. However, we decided to include both items into the LDSI to improve our insight in the impact of these two symptoms.

The LDSI version 2.0 includes 18 items. Nine items measured severity of: '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'. Nine other items measure the hindrance of these symptoms to daily activities. The item 'Fear of complications' has no accompanying hindrance item. The symptom 'Itch' has two accompanying hindrance items (hindrance of itch during the day and during sleep). All items have 'the last week' as time frame and are scored on a 5-point scale ranging from 'not at all' to 'to a high extent'. The single items have not been combined into multi-item scales, as we are of the opinion that in clinical practice results of separate symptom severity and symptom hindrance items are easier to interpret and more valuable for patient management.

Extra NLV items

Apart from the LDSI 2.0 six extra NLV items were developed, which in the experience of the board of the NLV were important aspects of the HRQoL of chronic liver patients (appendix 2). The items concern: 'Memory problems', 'Change of personality', 'Hindrance in financial affairs', 'Involuntary change in use of time', 'Decreased sexual interest' and 'Decreased sexual activity'. These items are scored on a 5-point scale ranging from 'not at all' to 'to a high extent'.

Background questionnaire

A background questionnaire was used to determine gender, age, education level, marital status, aetiology, duration of the liver disease, status of the liver disease(s) (cured, non-cured), liver transplant history, presence of cirrhosis, presence or history of splenomegaly, ascites or oesophageal variceal bleedings, presence of oesophageal variceal bleedings or ascites in the year 2000, history of complications of cirrhosis (liver cancer or imminent coma), comorbidity (defined as diseases or disorder other than the liver disease that limit the respondent's daily activities), medication use and the amount of hours per week spent on work and activities with and without physical effort.

Other questionnaires

For the validation of the construct validity of the LDSI and the extra NLV items, we used the Short Form-36 (SF-36) and the Multidimensional Fatigue Index-20 (MFI-20) [15,16]. Both questionnaires proved to be reliable and valid instruments in a chronic liver patient population [12]. The SF-36 includes 8 scales: Physical Functioning, Role limitations due to Physical problems, Bodily Pain, General Health, Vitality, Social Functioning, Role limitations due to Emotional problems and Mental Health. The scale scores range from 0 to 100. A higher score indicates a better generic HRQoL. The domain-specific MFI-20 measures 5 types of fatigue: General Fatigue, Physical Fatigue, Reduction in Activity, Reduction in Motivation and Mental Fatigue. Scale scores range from 4 to 20. A higher score indicates more fatigue. The MFI-20 questionnaire was used because fatigue is an important complaint of chronic liver patients [17,18].

Pilot-testing of the LDSI 2.0

Preparatory to a large survey on HRQoL of chronic liver patients in the Netherlands in collaboration with the NLV, we tested the feasibility and test-retest reliability of the LDSI 2.0 and the background questionnaire in a pilot study at the outpatient clinic of our Hepatology department at the Erasmus Medical Center Rotterdam, The Netherlands. During routine visits, hundred consecutive chronic liver patients received two copies (a test and a retest questionnaire) of the LDSI and the background questionnaire. Patients were asked to complete the questionnaires at home with an interval of three days. All respondents signed an informed consent form. In total 34 respondents completed the questionnaires in three days. Sixty-nine respondents returned the test and the retest questionnaire (mean time-interval 4.4 days, SD 2.9). Six patients returned just one questionnaire, while 25 patients did not respond.

We evaluated the test-retest reliability of the LDSI and the extra NLV items by means of *weighed* kappas in respondents with a test-retest interval of three days (n=34). We chose this short interval to decrease the potential variation in symptom severity so that a potential low agreement between the test and the retest could be predominantly attributed to change of item interpretation. Kappas < 0.20 were defined as 'poor', 0.21-0.40 as 'fair', 0.41-0.60 as 'moderate', 0.61-0.80 as 'good' and 0.81-1.00 as 'very good' [19]. Thirteen LDSI items showed a good to very good test-retest reliability ($\kappa_{weighed}$ 0.63 to 0.99). Three items (severity and hindrance of depression and hindrance of decreased appetite) showed a moderate test-retest reliability ($\kappa_{weighed}$ 0.55 to 0.57). One item (hindrance of worry about the family situation) showed a fair test-retest reliability ($\kappa_{weighed}$ 0.32). Of the extra NLV items 5 showed a good test-retest reliability ($\kappa_{weighed}$ 0.66 to 0.82), while the item on memory problems showed a very good test-retest reliability ($\kappa_{weighed}$ 0.91).

We evaluated the feasibility of the LDSI and extra NLV items in the 69 respondents who returned test and retest questionnaires. Items with 5% missing values or less were defined as having a good feasibility. We defined items as missing if no answer was provided or if multiple responses were given when only one was required. The LDSI items in both the test and retest questionnaires showed a good feasibility. In the test questionnaire the extra NLV items on financial affairs and sexuality demonstrated a slightly decreased feasibility of 5.8%.

In the same 69 respondents, we evaluated the reliability of respondent-reported clinical symptoms (presence of cirrhosis and presence or history of splenomegaly, ascites and oesophageal variceal bleedings) and respondent-reported aetiology in the background questionnaire. We used kappas to evaluate the agreement between test- and retest questionnaires and the agreement between reported data and data in the hospital file. Furthermore, we used kappas to evaluate the disease stage definitions that were based on reported clinical symptoms. We defined respondents without any of the clinical symptoms as non-cirrhotic. Respondents who reported cirrhosis and/or a history of splenomegaly and/or ascites were defined as compensated cirrhotic. Respondents with oesophageal variceal bleedings were defined as decompensated cirrhotic.

The items concerning presence of cirrhosis and presence or history of splenomegaly, ascites and oesophageal variceal bleedings, showed very good test-retest reliabilities (κ 0.85 to 0.97). Reported splenomegaly, ascites and oesophageal variceal bleedings showed a good agreement with hospital data with kappas of respectively 0.71, 0.71 and 0.68. A moderate agreement was shown between reported cirrhosis and

the hospital data (κ 0.52) as respondent's misunderstood cirrhosis for fibrosis. The reported aetiologies showed a good agreement between the test questionnaire and the retest questionnaire (κ 0.71) and a good agreement with the hospital data (κ 0.63).

The assigned disease stages based on our disease stage definitions showed only a fair agreement with the disease stages based on hospital data of the patients (κ 0.37). The hospital data revealed that our disease stage definitions disregarded the temporary state of the decompensated cirrhotic stage. With the current treatment modalities (diuretics or surgical interventions) decompensated cirrhotic patients often reverse to an apparently compensated state. During the survey in the NLV population, we took this temporary state of decompensated cirrhosis into account by including the item concerning: The presence of ascites or oesophageal variceal bleedings *in the year 2000* (the year of the study) into the background questionnaire. This extra criterion distinguished recent decompensated cirrhotic patients from reversed decompensated cirrhotic patients.

Validation of Liver Disease Symptom Index 2.0 and NLV items

As the LDSI 2.0 showed an adequate feasibility and test-retest reliability, we used a large survey on HRQoL of chronic liver patients in the Netherlands to evaluate the convergent and divergent construct validity of LDSI and the extra NLV items and the surplus value of including symptom severity and symptom hindrance items in the LDSI 2.0.

In October 2000, 2020 NLV members received a questionnaire by mail. The questionnaire included the LDSI, the extra NLV items, the SF-36, the MFI-20 and the background questionnaire. Non-responders received a second mailing. We closed the response period 5 months after the first mailing. Respondents completed the questionnaire anonymously and gave their informed consent by confirming their willingness to participate in the first question of the background questionnaire.

Statistical methods

We performed all analyses in SPSS 10.0.

We used Spearman correlations to evaluate convergent and divergent construct validity between LDSI's symptom severity and symptom hindrance items. We expected that a specific symptom severity item and its accompanying symptom hindrance item would show stronger convergent relations than other symptom severity and symptom hindrance item combinations. For these calculations solely symptomatic respondents were selected, since we assumed that solely symptomatic patients have symptom hindrance.

We also used Spearman correlations to evaluate the convergent and divergent construct validity between LDSI items or extra NLV items and the SF-36 or the MFI-20 scales. By means of these correlations we evaluated if the LDSI items showed convergent and divergent relations with the expected scales and if the LDSI offered HRQoL information additional to the information provided by the SF-36 or MFI-20. Spearman correlations < 0.4 were regarded as low, 0.4 to 0.7 as moderate, ≥ 0.7 as high [19]. Significance level was $p < 0.0002$ to correct for multiple comparisons.

To investigate the surplus value of including symptom severity as well as symptom hindrance items in the LDSI, we evaluated if symptom severity items and

symptom hindrance items differed with respect to their impact on generic HRQoL. If the impact (odds ratio) differed between symptom severity and symptom hindrance, this would indicate that symptom severity items measure another aspect of HRQoL than symptom hindrance items. We expected that these impacts would change across different levels of generic HRQoL. Therefore, we divided the generic HRQoL of liver patients in three levels, based on cut off values of generic HRQoL in healthy controls.

We assumed that the 10-25% healthy controls with the lowest generic HRQoL scores could be considered as controls with a poor generic HRQoL. Consequently, we considered liver patients with a generic HRQoL score equal or lower than the HRQoL score of the 25th percentile of the healthy controls, as liver patients with a poor generic HRQoL. In healthy controls we calculated for each SF-36 scale, the score corresponding to the ≤10th, 11th-25th and >25th percentile. In liver patients we used these scores as cut off values for categorisation of their scale specific HRQoL. Thus, for every SF-36 scale, the score range was split up in group A: liver patients with scale scores corresponding to the ≤10th percentile of healthy controls; Group B: liver patients with scale scores corresponding to the 11th-25th percentile of healthy controls; and Group C (reference): liver patients with scale scores corresponding to the >25th percentile of healthy controls. For the analyses, we used multinomial regression, which allows outcomes with more than 2 categories. The three categories of generic HRQoL (A, B and C) served as dependent outcome. Group C served as the reference group. The symptom severity items or the symptom hindrance items were independent determinants. For every LDSI item we calculated two odds ratios: The odds ratio of a HRQoL score in group A relatively to a score in group C and the odds ratio of a HRQoL score in group B relatively to a score in group C.

We conducted similar analyses to evaluate if symptom severity items and symptom hindrance items differed with respect to their impact on fatigue.

RESULTS

Characteristics of the clinical liver patient population and the Dutch liver patient population

Table 1 shows the characteristics of the clinical pilot population, the NLV population and the characteristics of the SF-36 and MFI-20 healthy controls.

In total 2020 NLV members received a questionnaire of which 1617 were returned. Of these, 374 respondents were non-patient member who joined the NLV because of involvement with liver patients in family, circle of acquaintances or work. In total 1243 had a (history of) liver disease. Of these, 1222 gave informed consent, but 47 were younger than 18 years of age. In total 1175 respondents were included in the analysis. Assuming that the percentage of patient members is equal in non-responders and responders (76%), than the total number of patient members is 1553 and the response rate (n=1243) would be around 80%.

The NLV population was significantly different from the clinical pilot population with respect to gender, disease stage and aetiology.

Table 1: Demographic and clinical characteristics of the clinical population, the NLV population and the SF-36 and MFI-20 controls.

Characteristic	Clinical liver pt. population (n=69)	NLV liver pt. population (n=1175)	SF-36 healthy controls (n=1715)	MFI-20 healthy controls (n=139)
Age				
Mean age ± SD, yr.	48 ± 14	48 ± 12	48 ± 17	46 ± 16
Gender				
Men, n (%)	40 (58.0)[a]	497 (42.3)	967 (56.6)	60 (44.4)
Women, n (%)	29 (42.0)	678 (57.7)	740 (43.4)	75 (55.6)
Education				
None/elementary education	7 (10.6)	109 (9.3)	212 (12.6)	11 (8.1)
Lower secondary education	25 (37.9)	446 (38.1)	569 (33.8)	90 (66.7)
Upper/post secondary education	21 (31.8)	329 (28.1)	477 (28.4)	34 (25.2)
1st/2nd stage tertiary education	13 (19.7)	287 (24.5)	424 (25.2)	0 (0)
Marital status				
Married / Living together	47 (69.1)	866 (74.0)	1278 (74.8)	
Single / Widow(er) / Divorced	21 (30.9)	304 (26.0)	431 (25.2)	
Disease stage				
Non-cirrhosis	24 (34.8)[b]	489 (42.5)		
Compensated cirrhosis	31 (44.9)	391 (34.0)		
Decompensated cirrhosis	14 (20.3)	84 (7.3)		
Liver transplant	-	186 (16.2)		
Aetiology				
Viral hepatitis	31 (47.7)[c]	275 (24.6)		
Autoimmune hepatitis	10 (15.4)	142 (12.7)		
PBC/PSC	12 (18.5)	175 (15.7)		
Hemochromatosis	-	98 (8.3)		
Other liver diseases	8 (12.3)	171 (14.6)		
Liver transplants	-	186 (16.6)		
Liver diseases reported as cured	4 (6.1)	71 (6.4)		

[a]Significantly different between the clinical population and the NLV population p=0.011
[b]Significantly different between the clinical population and the NLV population p=0.000
[c]Significantly different between the clinical population and the NLV population p=0.000 (when hemochromatosis and transplants excluded p > 0.05).

Symptom severity and symptom hindrance frequencies

Table 2 shows the frequency of symptomatic patients and the frequency of patients with symptom hindrance among the symptomatic patients. More than 50% of the patients experienced joint pain (58%), sleepiness (71%) during the day and worry about the family situation caused by the liver disease (51%). Other symptoms were less common. Of the liver patients experiencing symptoms, often more than 50% was hampered by the symptoms in daily activities.

Table 2: Frequencies of symptomatic respondents per LDSI or NLV item and within these groups the percentage respondents with symptom hindrance to daily activities in the NLV population (n=1175).

LDSI items	Symptomatic n (%)	% with symptom hindrance among symptomatic
Itch	451 (39.6)	50.5
Joint pain	654 (57.5)	83.8
Pain in right upper abdomen	451 (39.3)	63.1
Sleepiness during day	817 (71.2)	85.1
Worry about family situation	578 (50.5)	66.6
Decreased appetite	370 (32.3)	71.4
Depression	544 (47.5)	77.6
Fear of complications	507 (44.1)	Not applicable
Jaundice	113 (9.9)	41.1
Extra NLV items		
Memory problems	639 (56.3)	Not applicable
Change of personality	787 (69.6)	Not applicable
Hindrance in financial affairs	505 (44.8)	Not applicable
Involuntary change in use of time	789 (69.3)	Not applicable
Decreased sexual interest	518 (46.0)	Not applicable
Decreased sexual activity	574 (51.4)	Not applicable

Construct validity

Construct validity is one of the most important characteristics of a measurement instrument. It assesses the degree to which an instrument measures what it was supposed to measure and relies upon expressing opinions about expected relations amongst constructs. Convergent relations anticipate correlations between a postulated HRQoL item or dimension and all other dimensions that theory suggests should be related to it. Divergent relationships anticipate that some items or dimensions of HRQoL are relatively unrelated. Additionally, these correlations indicate if items are redundant because they overlap or duplicate the information contained in other items [19].

Table 3 shows the Spearman correlations between specific symptom severity items and their accompanying symptom hindrance item. As expected, symptom severity items showed stronger convergent relations with their accompanying symptom hindrance item than with other symptom hindrance items. Most of these item-pair correlations were of moderate strength. Items regarding the severity of joint pain, sleepiness during the day and depression showed high correlations with their accompanying hindrance item, suggesting overlap between the information provided by these items.

Table 4 and 5 show that all LDSI items are low to moderately correlated with the SF-36 and MFI-20 scales, indicating a slight to moderate overlap between the information given by the LDSI and the other two questionnaires. As expected, '(hindrance of) joint pain' showed convergent relations with particularly the physical scales of the SF-36. Joint pain hampers activities like bending, kneeling, walking and climbing stairs. Items, which are specifically measured by the physical functioning scale. Logically, these limitations hamper in daily activities and affect vitality, as

Table 3: LDSI construct validity. Spearman correlations between a specific symptom severity item and the accompanying symptom hindrance item in a selected NLV population of symptomatic patients (for n, see table 2).

Severity and Hindrance item pairs concerning:	R^2 Spearman
Itch	0.61
Joint Pain	0.80
Pain in the right upper abdomen	0.66
Sleepiness during the day	0.79
Worry about the family situation	0.66
Decreased appetite	0.61
Depression	0.75
Jaundice	0.52

shown by the correlations between hindrance of joint pain and the role physical, vitality, general fatigue and physical fatigue scales. '(Hindrance of) depression' was expected to show convergent relations with multiple SF-36 scales, as depression, could affect the overall burden of patients with a chronic medical illness [20]. Similarly, '(Hindrance of) worry' showed multiple convergent relations. '(Hindrance of) sleepiness showed expected convergent relations with most MFI-20 scales and the SF-36 vitality scale that evaluates feelings like 'being worn out' and 'feeling full of pep', but also with the role physical and social functioning scale which measure interference of physical problems in daily and social activities. '(Hindrance of) itch', '(Hindrance of) decreased appetite', and '(Hindrance of) jaundice' predominantly showed divergent relations as these symptoms are not measured in the SF-36 or MFI-20, although decreased appetite' and 'vitality' were unexpectedly associated.

The extra NLV-items all showed low to moderate correlations with LDSI items and the SF-36 and MFI-20 scales. The item concerning memory problems showed convergent relations with mental fatigue, while 'change of personality' was associated with social functioning, which measures interference of emotional problems with social activities. The item concerning the 'involuntary change in use of time due to the liver disease', was moderately associated with LDSI's worry, depression and sleepiness and almost all SF-36 and MFI-20 scales, but not with the role emotional, mental health, reduction in motivation and mental fatigue scale.

Figure 1a and 1b respectively show the *significant* associations between symptom severity or symptom hindrance and poor generic HRQoL. In these figures, poor HRQoL of liver patients corresponds to the HRQoL level of the 10% healthy controls with the lowest HRQoL (group A). Symptom hindrance was associated with larger odds ratios of poor generic HRQoL than symptom severity. For instance, being hampered by joint pain demonstrated odds ratios of 9.43, 2.77, 12.51 and 2.89 for respectively a poor physical functioning, poor role physical functioning, severe bodily pain and a poor general health, while an increasing severity of joint pain demonstrated odds ratios of 2.53, 1.64, 5.17 and 1.87 on the same SF-36 scales. Furthermore, hindrance of depression was associated with higher odds ratios of poor physical functioning (OR 2.90), poor general health (OR 2.10), poor social functioning (OR 8.13), poor role emotional functioning (OR 4.26) and poor mental health (8.72) than an increasing severity of depression (OR range: 1.57 in physical functioning to 4.00 in mental health). Similar results were found with respect to hindrance of

abdominal pain, hindrance of decreased appetite, hindrance of worry about the family situation and hindrance of sleepiness during the day.
Figure 1c and 1d respectively show the *significant* relations between symptom severity or symptom hindrance and a poor generic HRQoL, which corresponds to the HRQoL of healthy controls in the 10th to 25th percentile (group B). These figures show the same tendency as the former two. Odds ratios of symptom severity and symptom hindrance for this HRQoL level (B) were often significantly lower than the odds ratios for the poorer HRQoL level (A). However, the impact of symptom severity on HRQoL was still lower than the impact of symptom hindrance.

When we evaluated the impact of symptom severity items and symptom hindrance on various levels of fatigue, the same tendency as described was found (not shown).

Table 4: Construct validity of LDSI items in relation to SF-36 scales by means of Spearman correlations (R^2) in the NLV population (n=1175).
$R^2 < 0.4$=slight information overlap between LDSI item and SF-36 scale, $0.40 \leq R^2 < 0.7$=moderate information overlap, $R^2 \geq 0.7$=strong information overlap.

SF36	Itch	Hitch	Jp	Hjp	Abp	Habp	Slp	Hslp	Wor	Hwor	Dap	Hdap	Dpr	Hdpr	Fear	Jau	Hjau
PF	-0.26	-0.25	**-0.51**	**-0.53**	-0.29	-0.32	-0.34	-0.35	-0.25	-0.32	-0.31	-0.30	-0.36	-0.39	-0.24	-0.19	-0.16
RP	-0.28	-0.25	-0.38	**-0.41**	-0.28	-0.33	**-0.45**	**-0.47**	-0.38	**-0.43**	-0.37	-0.37	**-0.49**	**-0.50**	-0.33	-0.23	-0.15
BP	-0.29	-0.25	**-0.67**	**-0.67**	**-0.43**	**-0.44**	-0.36	-0.37	-0.32	-0.39	-0.32	-0.34	**-0.40**	**-0.43**	-0.33	-0.19	-0.17
GH	-0.31	-0.27	**-0.42**	**-0.42**	-0.33	-0.36	**-0.43**	**-0.43**	**-0.43**	**-0.45**	-0.34	-0.34	**-0.47**	**-0.48**	-0.37	-0.23	-0.18
VI	-0.28	-0.25	**-0.40**	**-0.41**	-0.38	-0.37	**-0.54**	**-0.54**	**-0.41**	**-0.46**	**-0.40**	-0.38	**-0.55**	**-0.55**	-0.35	-0.24	-0.17
SF	-0.30	-0.27	-0.34	-0.34	-0.33	-0.35	**-0.42**	**-0.43**	**-0.45**	**-0.49**	-0.35	-0.35	**-0.55**	**-0.59**	-0.38	-0.22	-0.19
RE	-0.19	-0.18	-0.21	-0.24	-0.24	-0.23	-0.34	-0.32	-0.37	**-0.42**	-0.28	-0.29	**-0.50**	**-0.54**	-0.32	-0.15	-0.14
MH	-0.21	-0.18	-0.24	-0.25	-0.32	-0.29	-.035	-0.34	**-0.47**	**-0.46**	-0.30	-0.29	**-0.61**	**-0.59**	**-0.40**	-0.15	-0.14

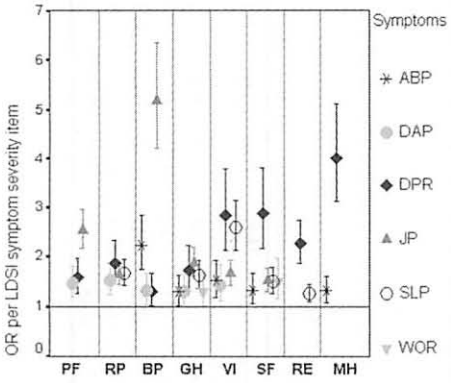
All correlations are highly significant ($p \leq 0.0002$).
Itch=Severity of itch, **Hitch**=Hindrance of itch in daily activities, **Jp**=Severity of joint pain, **Hjp**=Hindrance of joint pain in daily activities, **Abp**=Severity of pain in right upper abdomen, **Habp**=Hindrance of pain in right upper abdomen in daily activities, **Slp**=Severity of sleepiness during the day, **Hslp**=Hindrance of sleepiness during the day in daily activities, **Wor**=Severity of worry about the family situation, **Hwor**=Hindrance of worry about the family situation in daily activities, **Dap**=Severity of decreased appetite, **Hdap**=Hindrance of decreased appetite in daily activities, **Dpr**=Severity of depression, **Hdpr**=Hindrance of depression in daily activities or social contacts, **Fear**=Severity of fear of complications of disease, **Jau**=Severity of jaundice, **Hjau**=Hindrance of jaundice in daily activities or social contacts.
PF=physical functioning; **RP**=role limitations due to physical problems, **BP**=bodily pain, **GH**=general health, **VI**=vitality, **SF**=social functioning, **RE**=role limitations due to emotional problems, **MH**=mental health.

Table 5: Construct validity of LDSI items in relation to MFI-20 scales by means of Spearman correlations in the NLV population (n=1175).
$R^2 < 0.4$=slight information overlap between LDSI item and MFI-20 scale, $0.40 \leq R^2 < 0.7$=moderate information overlap, $R^2 \geq 0.7$=strong information overlap.

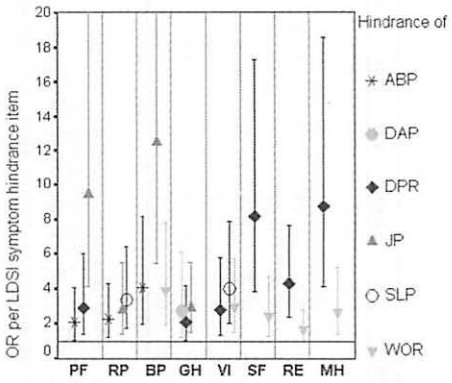
MFI-20	Itch	Hitch	Jp	Hjp	Abp	Habp	Slp	Hslp	Wor	Hwor	Dap	Hdap	Dpr	Hdpr	Fear	Jau	Hjau
GF	0.32	0.27	**0.43**	**0.42**	0.38	0.35	**0.60**	**0.59**	**0.41**	**0.44**	0.39	0.36	**0.53**	**0.52**	0.33	0.25	0.18
PhF	0.31	0.26	**0.44**	**0.45**	0.35	0.36	**0.50**	**0.50**	0.39	**0.43**	0.38	0.36	**0.51**	**0.51**	0.32	0.24	0.18
RA	0.24	0.22	0.29	0.30	0.31	0.28	**0.47**	**0.45**	0.37	**0.40**	0.34	0.31	**0.49**	**0.48**	0.32	0.20	0.15
RM	0.22	0.20	0.29	0.29	0.28	0.27	**0.40**	0.37	0.32	0.35	0.31	0.29	**0.46**	**0.44**	0.26	0.15	0.12
MF	0.23	0.20	0.29	0.31	0.26	0.25	**0.44**	**0.43**	0.36	0.37	0.30	0.27	**0.43**	**0.47**	0.30	0.17	0.16

All correlations are highly significant ($p < 0.0002$)
For the legend of the LDSI items, see table 4.
GF=general fatigue, **PhF**=physical fatigue, **RA**=reduction in activity, **RM**=reduction in motivation, **MF**=mental fatigue

Figure 1a and 1b: The effect (OR) of increasing symptom severity (a) and presence of symptom hindrance (b) on poor generic HRQoL. The level of poor generic HRQoL of chronic liver patients, corresponds to the HRQoL of the 10% healthy controls with the worst generic HRQoL (10th percentile). For the legend of the LDSI items and the SF-36 scales, see table 4.

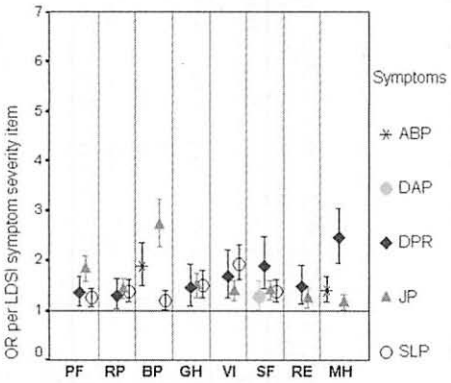


a)Not significant: itch, fear, jau

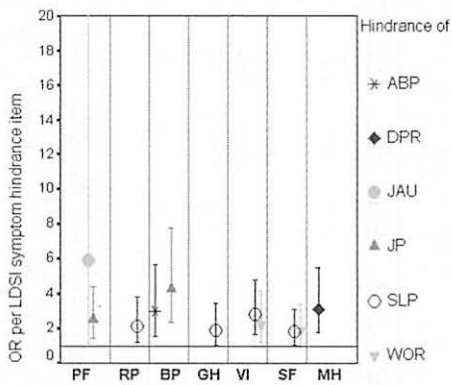


b) Not significant: hitch, hjau

Figure 1c and 1d: The effect (OR) of increasing symptom severity (c) and presence of symptom hindrance (d) on poor generic HRQoL. The level of poor generic HRQoL of chronic liver patients corresponds to the level of generic HRQoL of healthy controls in the 10th to 25th percentile. For the legend of the LDSI items and the SF-36 scales, see table 4.



c) Not significant: itch, wor, fear, jau



d) Not significant: hitch, hdap

DISCUSSION

The Liver Disease Symptom Index is a disease-specific questionnaire for chronic liver patients. As validation is an ongoing process, several adjustments have followed from the first psychometric evaluation of the LDSI, which led to the LDSI 2.0. A pilot study convinced us that the LDSI 2.0 had an adequate feasibility and test-retest reliability, which allowed further validation of this disease-specific questionnaire.

In this study we aimed to evaluate the construct validity of the Liver Disease Symptom Index 2.0. The convergent and divergent relations between the LDSI and the SF-36 and MFI-20 revealed that there is only a slight to moderate overlap between LDSI items and the SF-36 and MFI-20 scales. Therefore, the disease-specific information given by the LDSI can be regarded as complementary to the generic and domain specific HRQoL information. The additional explanatory value of the LDSI can be illustrated by convergent relations between 'joint pain', 'sleepiness', 'worry' and 'depression' items and multiple SF-36 and MFI-20 scales. These symptoms seem to play an important part in the HRQoL of general chronic liver patient population, but the moderate correlations with the scales indicate that these symptoms are only partly measured by the SF-36 and the MFI-20. Therefore, the additional information provided by the LDSI may deepen our insight in the HRQoL of chronic liver patients and may support individual liver disease management.

Worth mentioning is that the construct validity of the first LDSI version was evaluated in a clinical population of outpatients and hospitalised patients (33%). The LDSI then showed mainly convergent relations between SF-36/MFI-20 scales and 'Abdominal pain', 'Fear' and 'Decreased appetite', probably due to the more severe condition of hospitalised patients. Apparently, these symptoms played a less important part in the current general population of chronic liver patients. This indicates that the construction of the LDSI is valid for both clinical and general populations of chronic liver patients.

A potential weakness of the LDSI 2.0 seemed to be the high correlations between the severity of 'Joint pain', 'Sleepiness during the day' and 'Depression' and their accompanying hindrance item. Because of the high correlations one would expect that the symptom severity item and the symptom hindrance item give similar information. However, our analysis with respect to the associations between LDSI items and poor generic HRQoL or severe fatigue demonstrated that presence of symptom hindrance has a larger impact on poor generic HRQoL or severe fatigue than increasing symptom severity. This indicates that the symptom severity items and symptom hindrance items do measure different aspects of HRQoL.

Furthermore, we demonstrated that the impact of symptom severity and symptom hindrance varied across liver patients. The impact of symptom severity and symptom hindrance was often significantly higher in liver patients with the poorest generic HRQoL and the most severe fatigue. Moreover, we found that when the generic HRQoL was less poor or the fatigue less severe, the impact of symptom hindrance decreased stronger than the impact of symptom severity. Nonetheless, both impacts were still significantly higher compared to the impact of symptom severity and hindrance in liver patients with a normal generic HRQoL or normal fatigue. These findings point out that the impact of symptom severity varies in a different way

across liver patients than the impact of symptom hindrance. This supports the value of including symptom severity items as well as symptom hindrance items in the disease-specific questionnaire.

A limitation of our validation process is that it was conducted in a general population of chronic liver patients. The NLV population significantly differed from the clinical pilot-population with respect to gender, disease stage and aetiology. Therefore, extrapolation of our findings to other (clinical) chronic liver patient populations should be done with caution.

Moreover, the NLV may attract liver patients with a *low* HRQoL seeking social support, although the social support received from other members may influence their HRQoL positively. In a post-hoc analysis, we found that the NLV population had a higher symptom hindrance prevalence than the clinical population. This is surprising, as the clinical pilot population included relatively more patients with a compensated and decompensated disease stage. The higher symptom hindrance prevalence may have influenced our results regarding the impact of symptom severity and symptom hindrance on HRQoL and therefore may not be representative for a clinical population of chronic liver patients. When we checked the impact of symptom severity and symptom hindrance on HRQoL in our clinical population, we found that symptom severity and symptom hindrance alternately showed the largest impact across the SF-36 scales. Although these findings do not reflect the tendency found in the NLV population, it nevertheless indicates that symptom severity items and symptom hindrance items do measure different aspects of HRQoL.

Future studies are needed for further psychometric refinement of the LDSI. In another study we evaluated the known groups validity of the LDSI for disease stages groups [21]. Summary scores of symptom severity and symptom hindrance could be developed in order to facilitate population comparisons. Additionally, the responsiveness of the LDSI needs to be examined, since the establishment of minimal important changes will support a better understanding of the LDSI results in clinical practice.

We conclude that the Liver Disease Symptom Index 2.0 provides HRQoL information complementary to the HRQoL information given by the SF-36 and the MFI-20. The impact of symptom severity and symptom hindrance on HRQoL varies in a different way across liver patients, which suggests that symptom severity items and symptom hindrance items measure different aspects of HRQoL. These findings indicate that it is psychometrically sound to include both symptom severity items and symptom hindrance items into the LDSI 2.0.

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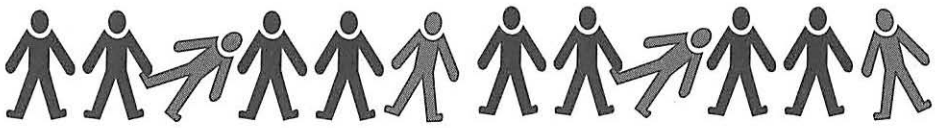
3

Health related quality of life of non-cirrhotic, cirrhotic and transplanted liver patients



ABSTRACT

Background: Studies on Health Related Quality of Life (HRQoL) of chronic liver patients were performed in clinical populations. These studies included various disease stages but small variations in aetiology and no transplanted patients. We performed a large HRQoL study in non-cirrhotic, cirrhotic and transplanted liver patients with sufficient variety in aetiology. We compared the generic HRQoL and fatigue between liver patients and healthy controls and compared the disease-specific and generic HRQoL and fatigue between non-cirrhotic, cirrhotic and transplanted liver patients, corrected for aetiology.

Methods: Members of the Dutch liver patient association received the Short Form-36, the Liver Disease Symptom Index 2.0 and the Multidimensional Fatigue Index-20. Based on reported clinical characteristics we classified respondents (n=1175) as non-cirrhotic, compensated cirrhotic, decompensated cirrhotic or transplants. We used linear, ordinal and logistic regression to compare the HRQoL between groups.

Results: All liver patients showed a significantly worse generic HRQoL and fatigue than healthy controls. Decompensated cirrhotic patients showed a significantly worse disease-specific and generic HRQoL and fatigue than non-cirrhotic patients, while HRQoL differences between non-cirrhotic and compensated cirrhotic patients were predominantly insignificant. Transplanted patients showed a better generic HRQoL, less fatigue and lower probabilities of severe symptoms than non-cirrhotic patients, but almost equal probabilities of symptom hindrance.

Conclusions: HRQoL in chronic liver patients depends on disease stage and transplant history. Non-cirrhotic and compensated cirrhotic patients have a similar HRQoL. Decompensated patients showed the worst HRQoL, while transplanted patients showed a significantly better HRQoL than cirrhotic *and* non-cirrhotic patients.

In the year 2000, 40.9% of the Dutch population suffered from a chronic disease. In that same year, more than 800 Dutch men and women died of a chronic liver disease (0.6% of year specific total mortality) [1]. Until today, the Dutch liver patient association (Nederlandse Leverpatiënten Vereniging (NLV)) and many other patient associations wwwwwht for recognition of disease related physical, mental and social problems of chronic patients. Quality of life research could contribute to a better understanding of these problems and may fulfil this quest for recognition.

One of the first studies done on Health Related Quality of Life (HRQoL) of chronic liver patients was conducted in 1979 and studied the effect of liver transplantation on HRQoL of chronic liver patients [2]. The study demonstrated that the quality of life of liver patients after transplantation ranged from poor to superior. In 1998, Foster et al compared the HRQoL of liver patients with viral hepatitis B and C and reported that social functioning, energy and fatigue and role limitations due to physical problems were significantly more impaired in hepatitis C patients [3]. In more recent studies, the HRQoL of different stages of liver disease were compared. Younossi et al found an increasing impairment of generic HRQoL with increasing disease severity, while Marchesini et al found that the most relevant determinants of impaired health status were severity of disease and muscle cramps [4-6].

These studies contributed substantially to our knowledge of the physical, social and mental problems of chronic liver patients. However, the majority of these studies was conducted in relatively small clinical populations and the comparisons between disease stages were adjusted for small or few aetiological groups. Moreover, none of these studies included liver transplant recipients in the study population.

Therefore, to get a better understanding of the differences in HRQoL between the various disease stages and the relation with transplanted liver patients, one must study a large liver patient population with a broad variety with respect to disease stage and aetiology. Furthermore, the HRQoL should be measured by a generic as well as a disease-specific questionnaire to give a profound insight in the differences in HRQoL between disease stages [7 8].

Our study offers an extensive overview of the HRQoL of chronic liver patients. In contrast to the clinical populations in earlier studies, our collaboration with the Dutch liver patient association gave us the opportunity to study the HRQoL of large number liver patients, approaching a population level. The study population of 1175 members included various stages of cirrhosis and aetiologies as well as a large number of transplanted liver patients. It provided us with sufficient varied information to realise an HRQoL comparison between non-cirrhotic, compensated cirrhotic, decompensated cirrhotic and transplanted liver patients, corrected for aetiology.

Another distinguishing feature of this study is that the HRQoL information was generated by means of the Liver Disease Symptom Index 2.0 (LDSI), the Short Form-36 (SF-36) and the Multidimensional Fatigue Index-20 (MFI-20). Other studies already used a combination of a generic and a disease-specific questionnaire [4,5]. However, the LDSI provides, in contrast to other liver disease-specific questionnaires, information about the severity of symptoms *and* hindrance of these symptoms during daily activities. In an earlier study we demonstrated that the LDSI provides additional information on top of the SF-36 and the MFI-20 (S.M. van der Plas, Quality of life

Research, accepted for publication). The SF-36 and MFI-20 were both validated in a clinical chronic liver patient population [9]. Therefore, the combination of these instruments forms a reliable and valid method to accomplish the following aims:1) To compare the generic HRQoL and fatigue between chronic liver patients and healthy Dutch controls and 2) to evaluate the differences in disease-specific HRQoL, generic HRQoL and fatigue between non-cirrhotic, compensated cirrhotic, decompensated cirrhotic and transplanted liver patients, corrected for aetiology. By evaluating the differences in disease-specific HRQoL, we addressed the known groups validity of the LDSI across the various subgroups. The known groups validity is based on the principle that certain specified groups of patients, may be anticipated to score differently from others. We evaluated LDSI's sensitivity for these differences.

METHODS

Study population

In October 2000, all 2020 members of the NLV were approached for participation in this study and received a questionnaire by mail. The members included patients with a (history of) liver disease as well as non-patients who joined the NLV because of involvement with liver patients in family, circle of acquaintances or work. After two months, non-responders received a new questionnaire. We closed the response period 5 months after the first mailing. As requested by the Ethics Committee, members gave their informed consent by confirming their willingness to participate in the first question of the questionnaire.

Inclusion criteria were: 1) Informed consent, 2) having a (history of) liver disease and 3) aged 18 years or older at the moment of the study. To preserve the anonymity of the participants, the NLV withheld the coding of respondent numbers and member names, while the researcher withheld the completed questionnaires. The protocol was conform the ethical guidelines of the 1996 Declaration of Helsinki and has been approved by the Ethics Committee of the Erasmus Medical Centre Rotterdam, the Netherlands.

Measurement instruments

The disease-specific LDSI 2.0 includes 18 items. Nine items measure the severity of: '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'. Nine other items measure the hindrance of these symptoms during daily activities. All items have 'the last week' as time frame and are scored on a 5-point scale ranging from 'not at all' to 'to a high extent'.

Apart from the LDSI, 6 additional items recommended by the NLV, were scored on the same 5-point scale. These items concerned: 'Memory problems due to liver disease', 'Change of personality due to liver disease', 'Hindrance in financial affairs due to liver disease', 'Involuntary change in use of time due to liver disease', 'Decreased sexual interest' and 'Decreased sexual activity'. The LDSI as well as the extra NLV items have recently been validated in chronic liver patients and showed a

good feasibility, test-retest reliability and construct validity (Van der Plas, Quality of life Research, accepted for publication).

The generic (Dutch) SF-36 version 1.2, includes 8 multi-item scales on Physical Functioning, Role limitations due to Physical problems (Role Physical), Bodily Pain, General Health, Vitality, Social Functioning, Role limitations due to Emotional problems (Role Emotional) and Mental Health. The scale scores range from 0 to 100. A higher score indicates a better generic HRQoL. SF-36 data of Dutch healthy controls was available [10].

The domain-specific MFI-20 includes five 4-item scales: General Fatigue, Physical Fatigue, Reduction in Activity, Reduction in Motivation and Mental Fatigue and scale scores range from 4 to 20. Higher scores indicate more fatigue. MFI-20 data of Dutch healthy controls was available [11]. Both the SF-36 and the MFI-20 proved to be reliable and valid in Dutch chronic liver patients [9].

A separate questionnaire was used to determine gender, age, marital status, education level, aetiology, duration of the liver disease, status of the liver disease(s) (cured, non-cured), presence of a liver transplant, presence of cirrhosis, presence or history of splenomegaly, ascites or oesophageal variceal bleedings, presence of oesophageal variceal bleedings or ascites in the year 2000, history of complications of cirrhosis (liver cancer or imminent coma), comorbidity (defined as the presence of diseases or disorders other than the liver disease that limit the respondent's daily functioning), medication use and the amount of hours per week spent on work and activities with and without physical effort.

Liver patient comparison groups

Due to the design of the study, respondents originated from all over the country and participated anonymously. Therefore, we based the categorisation of respondents in disease stage groups (non-cirrhotic (NC), compensated cirrhotic (CC), decompensated cirrhotic (DC)) or the liver transplant group (LTX) on respondent-reported clinical characteristics (table 1).

Furthermore, we categorised respondents in 5 aetiology groups based on reported aetiologies: Viral Hepatitis, Autoimmune Hepatitis, Cholestatic diseases, Hemochromatosis and other liver diseases. Transplanted respondents and respondents who considered themselves as cured were assigned to the groups 'Liver transplants' and 'Cured liver diseases' respectively.

We have validated the reliability of respondent-reported clinical characteristics, disease stage definitions and reported aetiologies in a pilot study conducted at our Hepatology outpatient clinic. Respondent-reported clinical characteristics and aetiologies demonstrated a good agreement between the test and the retest questionnaire (clinical characteristics: κ 0.85 [0.71, 0.94] to 0.97 [0.91, 1.03]; aetiologies: κ 0.71 [0.63, 0.79]) and a good agreement with hospital data (clinical characteristics: κ 0.68 [0.45, 0.90] to 0.71 [0.53, 0.88]; aetiologies: κ 0.63 [0.55, 0.78]). Reported presence of cirrhosis showed a moderate agreement with hospital data (κ 0.52 [0.31, 0.73]). The assigned disease stage groups showed a lower agreement with the disease stages based on hospital data of the patients. The hospital data revealed that our disease stage definitions (which during the pilot did not include the criterion of *recent* ascites or variceal bleeding), disregarded the temporary state of the decompensated cirrhotic

stage: patients may become decompensated due to flare up of disease activity or inflammation, but can reverse to an apparently compensated state after treatment with diuretics or surgical interventions.

During the current study, we took this temporary state of decompensated cirrhosis into account by including the criterion concerning: The presence of ascites or oesophageal variceal bleedings *in the year 2000* (the year of the study), as extra item into the background questionnaire. This extra criterion distinguished recent decompensated cirrhotic patients from *reversed* decompensated cirrhotic patients. In the NLV population 43 compensated cirrhotic were defined as *reversed* decompensated cirrhotic patients (based on the absence of ascites and/or variceal bleedings in the year 2000 and the use of diuretics and/or propanolol at the moment of our study). The HRQoL level of these patients fitted the HRQoL level of the compensated cirrhotic group and not the HRQoL level of decompensated patients. This indicated that these patients were correctly categorised as compensated cirrhotic patients.

Controls

Healthy Dutch controls for the SF-36 (n=1715) originated from a nationwide, population-based health status survey with the standard version of the SF-36, conducted by the Dutch Organisation for Applied Scientific Research (TNO). Controls were adult members of a random sample of Dutch households, drawn from the national telephone registry. This registry included a somewhat larger percentage of men and a smaller category in the age of 15-25 years than the adult population in the Netherlands. TNO corrected for this imbalance by stating in the introductory letter that any adult member of the household could complete the questionnaire. A random set of introductory letters requested that the questionnaire had to be completed by a member of the household in the age of 15-25 years [10].

Healthy Dutch controls for the MFI-20 (n=139) originated from a study on fatigue and radiotherapy in cancer patients. Controls were adults from a non-selective sample of households taken from the telephone directories. As women are more frequently at home, researchers of this study prevented overrepresentation of women by interviewing the next person to have a birthday within that household [11].

Statistical methods

We compared the generic HRQoL of NC, CC, DC and LTX with the generic HRQoL of the general Dutch population. SF-36 scale scores were calculated by SF-36 scoring algorithms [12]. We estimated mean SF-36 scale scores by general linear regression, in which we used the SF-36 scales as dependent outcome. A variable, which included the disease stage groups, transplanted group and controls served as independent determinant. Means were corrected for gender, age, marital status and education level. Furthermore, we compared fatigue between NC, CC, DC and LTX and the general Dutch population. The MFI-20 scale scores were calculated by MFI-20 scoring algorithms [13]. We used general linear regression with the MFI-20 scales as outcome to estimate mean MFI-20 scale scores. Again, the variable that included the various subgroups served as independent determinant. Means were corrected for gender, age and education level.

To compare the generic HRQoL and fatigue between NC, CC, DC and LTX, we performed a linear regression in SPSS 10.0 and in SAS 8.0. SF-36 scales or MFI-20 scales served as dependent outcomes. Mean differences in SF-36 scale scores or mean differences in MFI-20 scale scores were calculated between NC (reference) and CC, DC and LTX. Of each scale, model-based standard errors in SPSS were compared with robust standard errors provided by PROC MIXED using the 'empirical'-option in SAS 8.0. Model-based standard errors in SPSS were similar as robust standard errors in SAS.

We evaluated the known groups validity of the LDSI symptom severity items across disease stages and the transplanted group by means of a proportional odds model for ordinal outcome with the PLUM procedure in SPSS 10.0. In every LDSI symptom severity item, the mean probability to score one of the five response categories (1='no symptom' to 5='severe symptom') was estimated per disease stage group or transplant group. We used the same model to evaluate the known groups validity of the extra NLV items.

We evaluated the known groups validity of the LDSI symptom hindrance items across disease stages and the transplanted group by means of binary logistic regression. We estimated for each subgroup the odds ratio of being hampered by symptoms in daily activities (score=2 to 5), relatively to not being hampered (score=1) by these symptoms. We selected respondents who actually had the symptom (symptom severity score >1), since we assumed that only those respondents could have symptom hindrance.

Estimated differences, probabilities and odds ratios between subgroups were corrected for gender, age, education level, aetiology, use of liver disease medication, use of psychopharmaca and comorbidity. Determinants were regarded as significant when $p < 0.05$.

RESULTS

Selection of the population

Of the 2020 members approached for this survey, 1617 members returned the questionnaires. Of these, 374 respondents were non-patient member, who joined the NLV because of involvement with liver patients in family, circle of acquaintances or work. In total 1243 patients had a (history of) liver disease. According to the regulations of the Ethics Committee, we excluded 21 patients who did not give informed consent. Furthermore, we excluded forty-seven patients younger than 18 years of age. In total 1175 respondents were included in the analysis. When we assumed that the percentage of patient members was equal in non-responders and responders (77%), than the total number of patient members in the total NLV population would be 1553 and the actual response (n=1243) would be around 80%.

Population characteristics

Table 2 shows the baseline characteristics of the study population for non-cirrhotic, cirrhotic and transplanted liver patients and the characteristics of Dutch healthy controls for the SF-36 and the MFI-20. The total population of 1175 respondents of

Table 1: Classification of disease stage groups and the transplanted group based on respondent-reported clinical characteristics.

	Cirrhosis	Splenomegaly	Ascites	Variceal bleeding	Recent ascites and/or variceal bleeding (during year of the study)	Transplant
Non-Cirrhosis	No	No	No	No	No	No
Compensated Cirrhosis* Clinical situation 1	Yes	-	-	-	No	No
Compensated Cirrhosis* Clinical situation 2	-	Yes	-	-	No	No
Compensated Cirrhosis* Clinical situation 3	-	-	Yes	-	No	No
Compensated Cirrhosis* Clinical situation 4	-	-	-	Yes	No	No
Decompensated Cirrhosis	-	-	-	-	Yes	No
Transplanted	-	-	-	-	-	Yes

*) Patients can be defined as compensated cirrhotic in four clinical situations.
Legend clinical characteristics:
No: *Absence* of the clinical characteristic is an absolute condition for the concerning disease stage group or transplant group.
Yes: *Presence* of the clinical characteristic is an absolute condition for the concerning disease stage group or transplant group.
- : Presence or absence of the clinical characteristic is *no* absolute condition.

Table 2 Demographic and clinical characteristics of liver patients and controls.

Characteristic	NC (n=489)	CC (n=391)	DC (n=84)	LTX (n=186)	Dutch SF-36 controls (n=1715)	Dutch MFI-20 controls (n=139)
Age						
Mean age ± SD, yr.	48 ± 12	49 ± 14	50 ± 12	49 ± 13	48 ± 17	46 ± 16
Gender						
Men, n (%)	214 (43.8)	162 (41.4)	36 (42.9)	78 (41.9)	967 (56.6)	60 (44.4)
Women, n (%)	275 (56.2)	229 (58.6)	48 (57.1)	108 (58.1)	740 (43.4)	75 (55.6)
Education						
None/elementary education	33 (6.8)	39 (10.0)	15 (18.1)	18 (9.7)	212 (12.6)	11 (8.1)
Lower secondary education	178 (36.5)	157 (40.2)	27 (32.5)	74 (40.0)	569 (33.8)	90 (66.7)
Upper/post secondary education	141 (28.9)	106 (27.1)	24 (28.9)	48 (25.9)	477 (28.4)	34 (25.2)
1st/2nd stage tertiary education	136 (27.9)	89 (22.8)	17 (20.5)	45 (24.3)	424 (25.2)	0 (0)
Marital status						
Married / Living together	360 (73.9)	292 (75.1)	57 (67.9)	139 (75.1)	1278 (74.8)	
Single / Widow(er) / Divorced	127 (26.1)	97 (24.9)	27 (32.1)	46 (24.9)	431 (25.2)	
Aetiology						
Viral hepatitis	169 (36.3)	77 (20.9)	23 (30.3)			
Autoimmune hepatitis	51 (10.9)	77 (20.9)	11 (14.5)			
PBC/PSC	76 (16.3)	84 (22.8)	13 (17.1)			
Hemochromatosis	58 (12.4)	30 (8.2)	2 (2.6)			
Other liver diseases	58 (12.4)	85 (23.1)	25 (32.9)			
Liver diseases reported as cured	54 (11.6)	15 (4.1)	2 (2.6)			
Liver transplants				186 (100)		

NC=Non-Cirrhosis, CC=Compensated Cirrhosis, DC=Decompensated Cirrhosis, LTX=Liver transplanted.

Table 3: Mean SF-36 scores of Dutch healthy controls, non-cirrhotic, compensated cirrhotic, decompensated cirrhotic and transplanted liver patients. Mean scores are corrected for gender, age, education level and marital status.

SF-36 scale	Dutch controls (CI 95%) n=1715	LTX (CI 95%) n=186	NC (CI 95%) n=489	CC (CI 95%) n=391	DC (CI 95%) n=84
Physical Functioning	82 (81-83)	69 (66-72)	70 (68-72)	65 (63-67)	50 (66-72)
Role Physical	75 (73-76)	53 (47-59)	48 (45-52)	44 (40-48)	21 (13-29)
Bodily Pain	74 (73-75)	73 (69-76)*	66 (64-68)	64 (61-66)	48 (43-53)
General Health	70 (69-71)	56 (53-59)	46 (44-48)	41 (39-43)	31 (26-35)
Vitality	67 (66-68)	62 (59-65)	51 (49-53)	50 (48- 52)	39 (35-43)
Social Functioning	82 (81-83)	73 (69-76)	65 (63-67)	64 (61-66)	47 (42-52)
Role Emotional	80 (78-82)	74 (68-79)	67 (63-70)	63 (59-67)	49 (42-57)
Mental Health	75 (74-76)	74 (71-76)*	67 (65-68)	67 (66-69)	61 (57-65)

For legend of disease stages, see table 2.
*) Not significantly different from the score in Dutch healthy controls.

Table 4: Mean MFI-20 scores of Dutch healthy controls, non-cirrhotic, compensated cirrhotic, decompensated cirrhotic and transplanted liver patients. Mean scores are corrected for gender, age and education level.

MFI-20 scales	Dutch controls (CI 95%) n=139	LTX (CI 95%) n=186	NC (CI 95%) n=489	CC (CI 95%) n=391	DC (CI 95%) n=84
General Fatigue	9.6 (8.7-10.4)	11.0 (10.3-11.8)	13.9 (13.3-14.2)	14.6 (14.1-15.1)	16.6 (16.0-17.7)
Physical Fatigue	8.6 (7.7-9.4)	11.0 (10.2-11.7)	13.0 (12.6-13.4)	13.5 (13.0-14.0)	16.2 (15.2-17.3)
Reduction Activity	8.5 (7.7-9.4)	10.1 (9.4-10.8)	11.5 (11.1-12.0)	11.7 (11.2-12.2)	14.3 (13.2-15.3)
Reduction Motivation	7.8 (7.2-8.7)	8.6 (8.0-9.3)*	10.5 (10.1-10.9)	10.5 (10.0-10.9)	12.4 (11.4-13.4)
Mental Fatigue	7.9 (7.0-8.7)	10.0 (9.3-10.7)	11.1 (10.6-11.5)	11.7 (11.2-12.2)	13.3 (12.3-14.5)

For legend of disease stages, see table 2.
*) Not significantly different from the score in Dutch healthy controls.

which 678 (57.7%) were women had a mean age of 48.6 years (SD ± 12.7, range 18-81). In total 76% of these respondents spent on average 24.5 (SD ± 16.3) hours per week on a paid and/or voluntary job and spent on average 6.5 (SD ± 6.7) hours per week on physical activities like walking, cycling and gardening.

All respondents with a liver transplant were assigned to the liver transplant group (n=186, 16.2%). The remaining respondents were mainly non-cirrhotic (42.5%) and compensated cirrhotic (34.0%). Twenty-five respondents were not classified in one of the three disease stage groups or in the transplant group because of missing values in the classification items.

More than one-fifth of the 1175 respondents had viral hepatitis (23.4%). Of the 57 (4.7%) respondents categorised as missing, 23 respondents reported cirrhosis as their liver disease, while 31 gave an unclear or insufficient description of their liver disease.

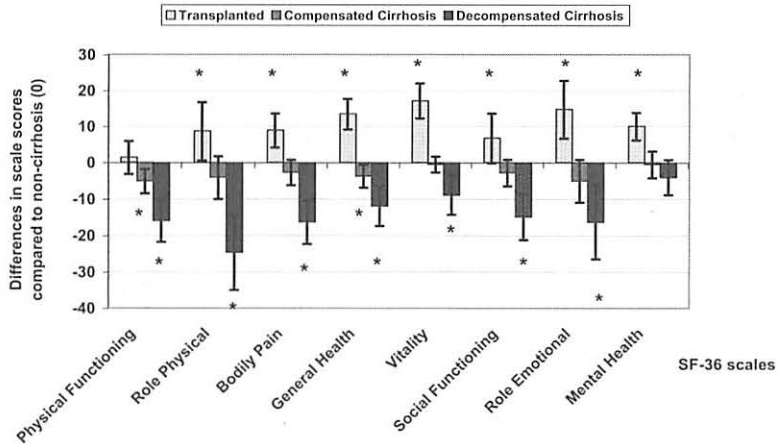
Comparison of generic HRQoL and fatigue with Dutch healthy controls

Respectively Table 3 and 4 show the generic HRQoL and fatigue of chronic liver patients compared to Dutch healthy controls. The majority of the chronic liver patients reported a significantly impaired generic HRQoL and significantly more fatigue compared to healthy controls ($p < 0.05$). Only transplanted liver patients showed a similar level of mental health, bodily pain and reduction in motivation as healthy controls.

Comparison of generic HRQoL and fatigue between non-cirrhotic, cirrhotic and transplanted patients

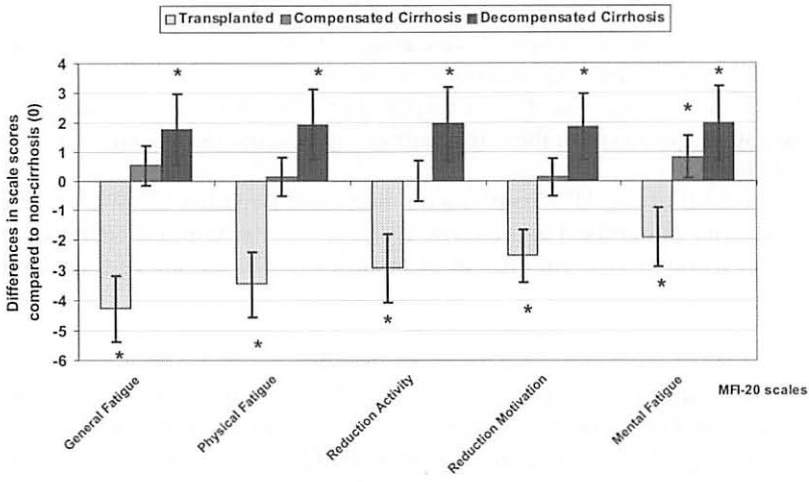
Figure 1 shows the mean differences in SF-36 scale scores between non-cirrhotic, cirrhotic and transplanted liver patients. The generic HRQoL of chronic liver patients

Figure 1: SF-36 scale score differences between non-cirrhotic (reference, set to zero), compensated cirrhotic, decompensated cirrhotic and transplanted liver patients. Differences are corrected for gender, age, education level, aetiology, comorbidity, use of liver disease medication and use of psychopharmaca.



Negative differences: Scale score of subgroup is lower (worse) than the scale score of non-cirrhotic patients.
Positive differences: Scale score of subgroup is higher (better) than the scale score of non-cirrhotic patients.
*) Scale score of subgroup is significantly lower or higher than the scale score of non-cirrhotic patients ($p < 0.05$).

Figure 2: MFI-20 scale score differences between non-cirrhotic, compensated cirrhotic, decompensated cirrhotic and transplanted liver patients. Differences are corrected for gender, age, education level, aetiology, comorbidity, use of liver disease medication and use of psychopharmaca.



Negative differences: Scale score of subgroup is lower (less severe) than the scale score of non-cirrhotic patients.
Positive differences: Scale score of subgroup is higher (more severe) than the scale score of non-cirrhotic patients.
*) Scale score of subgroup is significantly lower or higher than the scale score of non-cirrhotic patients ($p < 0.05$).

worsened with a worsening disease stage. Non-cirrhotic and compensated cirrhotic patients showed few significant HRQoL differences. Patients with decompensated cirrhosis mostly demonstrated a significantly worse generic HRQoL than non-cirrhotic patients. In contrast, transplanted patients scored on seven of the eight SF-36 scales a significantly *better* HRQoL than non-cirrhotic patients. Fatigue showed the same pattern across the disease stages and the transplanted group (figure 2).

Known groups validity of the LDSI items

Figure 3a to 3i illustrate the known groups validity of the LDSI symptom severity items. The probability to score higher than 1 on itch, pain in the right upper abdomen, sleepiness, worry about the family situation, decreased appetite, depression, fear and jaundice were highest for liver patients with decompensated cirrhosis. These probabilities were all significantly higher than the probabilities of the non-cirrhotic group ($p=0.000$ to $p=0.002$). Probabilities to score higher than 1 on joint pain were similar for all disease stages. Compensated cirrhotic patients had a significantly higher probability to score higher than 1 on itch ($p=0.03$), sleepiness ($p=0.014$) and jaundice ($p=0.008$) than non-cirrhotic patients. Transplanted liver patients demonstrated significantly lower probabilities to score higher than 1 on itch, joint pain, pain in the right upper abdomen, sleepiness, worry about the family situation, decreased appetite, depression and fear of complications than non-cirrhotic patients ($p=0.000$ to $p=0.002$).

Figure 4 shows the known groups validity of the LDSI symptom hindrance items. Decompensated cirrhotic patients demonstrated for most symptoms significantly

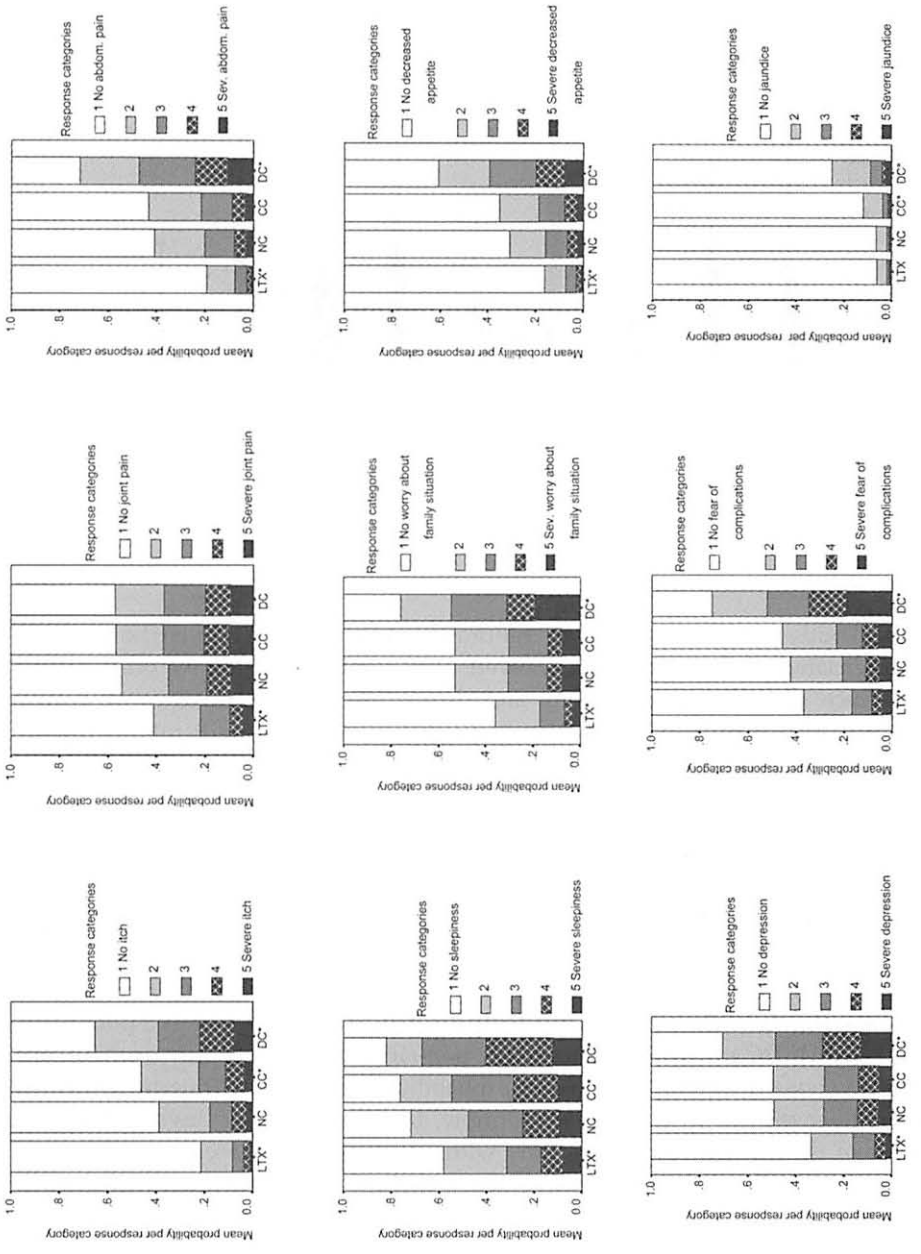
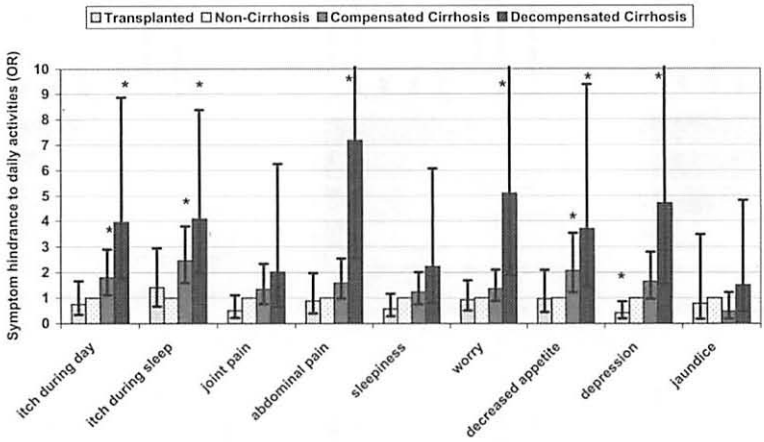


Figure 3a-i: Probabilities per LDSI symptom severity item per response category for all liver patients subgroups.
Probabilities are corrected for gender, age, education level, aetiology, comorbidity, use of liver disease medication and use of psychopharmaca.
NC=Non-Cirrhosis, CC=Compensated Cirrhosis, DC=Decompensated Cirrhosis, LTX=Liver transplanted.
*) Probabilities of subgroup are significantly different from probabilities of non-cirrhosis ($p < 0.05$).

Figure 4: Odds ratios (OR) for presence of symptom hindrance of transplanted and cirrhotic patients relatively to non-cirrhotic patients. Odds ratios are corrected for gender, age, education level, aetiology, comorbidity, use of liver disease medication and use of psychopharmaca.



*) Odds ratio of subgroup is significant relatively to non-cirrhosis ($p < 0.05$).

higher odds ratios of symptom hindrance relatively to non-cirrhotic patients. Compensated cirrhotic patients showed only significantly higher odds ratios for hindrance of itch during the day and during sleep and hindrance of decreased appetite. Transplanted patients showed a significantly lower odds ratio of hindrance of depression relatively to non-cirrhotic patients.

Known groups validity of extra NLV items.

Finally, we evaluated the known groups validity of the extra NLV items. The analysis showed that decompensated and compensated cirrhotic patients have a significantly higher probability of memory problems than non-cirrhotic patients (CC p=0.009, DC p=0.00), while transplanted patients show a significantly lower probability (p=0.009). The probability of a change in personality was, relatively to non-cirrhotic patients, significantly higher in the compensated and decompensated patient group (CC p=0.011, DC p=0.000). Compared to non-cirrhotic patients only decompensated patients showed significantly higher probabilities of financial limitations as a result of the liver disease (p=0.000). Furthermore, the probability of 'involuntary change in use of time' increased significantly with a worsening disease stage (CC p=0.019, DC p=0.000). Transplanted patients showed the lowest probability that the liver disease resulted in 'involuntary change in use of time' (p=0.000). The probabilities of decreased sexual interest were not significantly different between transplanted, compensated cirrhotic and non-cirrhotic patients, but decompensated cirrhotic patients showed a significantly higher probability of decreased sexual interest (p=0.000). Decompensated as well as transplanted patients showed a significantly higher probability of decreased sexual activity compared to non-cirrhotic patients (DC p= 0.016, LTX p=0.001).

DISCUSSION

The aims of this study were: 1) the comparison of the generic HRQoL and fatigue between chronic liver patients and healthy Dutch controls and 2) to give a profound insight in the differences in disease-specific HRQoL, generic HRQoL and fatigue between non-cirrhotic, compensated cirrhotic, decompensated cirrhotic and transplanted liver patients, corrected for various aetiologies.

We have shown that after correction for aetiology and other factors, generic HRQoL, disease-specific HRQoL and fatigue worsened with a worsening liver disease stage.

However, non-cirrhotic and compensated cirrhotic patients mostly showed insignificant differences with respect to generic and disease-specific HRQoL and fatigue. Decompensated cirrhotic patients revealed a significantly lower generic HRQoL, a higher probability of a worse disease-specific HRQoL and more fatigue than non-cirrhotic patients. Transplanted liver patients demonstrated a better generic HRQoL, a lower probability of severe symptoms and less fatigue than non-cirrhotic and cirrhotic liver patients. However, their probability of symptom hindrance was often not significantly different from the non-cirrhotic group.

The worsening HRQoL across disease stages found in our study is in line with earlier studies [4-6,14]. Also Unal et al infrequently found significant differences in generic and disease-specific HRQoL and fatigue between non-cirrhotic and compensated cirrhotic patients, although the trend across these two disease stages was reversed (compensated cirrhotic patients showed a better HRQoL than non-cirrhotic) compared to the trend found in our study [9]. Even after we had analysed the Unal data with more advanced statistical methods, corrected for factors like sex, age, education and aetiology, the reversed trend remained. It should however be noted that this study and other earlier studies used different disease stage criteria (Child's-Pugh's score and histological data), which hampered the inter-study comparison.

The results of the current study indicate that the LDSI has a moderate to good known groups validity for the three disease stages and the transplanted liver patient group. The symptom severity items easily discriminated the decompensated patients and the transplanted patients from the non-cirrhotic patients. However, difficulties occurred regarding the discrimination between compensated cirrhotic and non-cirrhotic patients. The same problem emerged in the discrimination between compensated and non-cirrhotic patients by the symptom hindrance items.

It is unclear if these difficulties should be attributed to a lack of sensitivity of the LDSI or to the natural characteristics of the compensated cirrhotic disease stage. After all, compensated cirrhotic patients may be asymptomatic for years or decades: Ascites and neurological abnormalities are often absent and in general these patients have a good nutritional state. This may explain the similar HRQoL in non-cirrhotic and compensated cirrhotic patients [6,15]. One study already demonstrated the absence of a significant difference in HRQoL between these two groups in a mixed population of chronic liver patients [14]. But a significant difference between the disease-specific HRQoL of non-cirrhotic and compensated cirrhotic was reported as well, although this study only included cholestatic liver patients [5]. Nevertheless, the LDSI items

more frequently distinguished between NC and CC patients than the various SF-36 or MFI-20 scales, which illustrated the disease-specific character of the LDSI.

Until now, no other study directly compared the generic and disease-specific HRQoL between transplanted liver patients and non-cirrhotic and cirrhotic liver patients. Earlier studies repeatedly demonstrated that post-transplanted liver patients have a much better HRQoL than pre-transplanted liver patients [16,17]. However, our study specifically revealed that transplanted patients also have a better generic HRQoL and less fatigue than non-cirrhotic and cirrhotic liver patients. Nevertheless, the HRQoL of transplanted patients was often significantly impaired, compared to the HRQoL level of healthy controls.

These results are in line with earlier research, which revealed that transplanted liver patients do have some physical problems, which indeed are experienced as limitations in daily life. Although these limitations barely seem to affect their overall HRQoL as transplanted patients have minimum of concern about physical problems, the presence of limitations may explain the impaired HRQoL of transplanted patients [18-22]. The mental health of transplanted patients was comparable with the mental health of the healthy controls, which confirms earlier literature stating that the tension, depression and anger prevalence rates in transplanted patients were not notably different from the rates in controls [18,23].

The high HRQoL of transplanted liver patients compared to non-transplanted cirrhotic and non-cirrhotic patients may be explained by the difference in acquired social support. Social support is of utmost importance as a resource of coping with chronic illness and may be beneficial for health outcome regardless of age [24,25]. For transplant recipients the psychological support in the transplantation and rehabilitation period provided by medical staff and family, is considered as one of the essentials of the transplant program, as social support influences the post transplantation survival and HRQoL [18,26]. However, for other chronic liver patients the enhancement of social support may be less considered as essential part of treatment. Nevertheless, it could positively influence the HRQoL by addressing negative feelings like low self-esteem or hopelessness resulting from the irreversibility of the pathological process and related disability. This potential hiatus in chronic liver disease management could be bridged by Social Network Mapping, which establishes a dialogue regarding individuals' needs and possible sources of support [27].

Despite of the fact that this study included a large population of chronic liver patients, this study design also had certain limitations. Since 90% of our respondents originated from The Netherlands, our study population could be regarded as a selected population. In another quality of life study conducted at our outpatient clinic, nearly a quarter of the participants were not originally Dutch. Due to the absence of other ethnic groups in our population, extrapolation of our results to outpatient populations should be done with caution.

Additionally, it is unclear which liver patients are attracted by the patient association and how membership influences their HRQoL. Over representation of liver patients with a *low* HRQoL, seeking contact with other liver patients may have led to an underestimation of HRQoL, while other members' social support may have influenced the measured HRQoL in our population positively. Furthermore, we lacked information about non-responders due to the design of the study. Therefore,

responders may have been a selection of relatively healthy patients who felt well enough to complete the questionnaire, which may have led to an overestimation of HRQoL.

A last possible limitation of this study is that we had to depend on the respondents' knowledge with respect to data about clinical symptoms and aetiologies. However, our 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. As we have no reason to expect that members of a liver patient association are less informed, we are confident that this population-based study provided a reliable insight in the HRQoL of chronic liver patients in Western countries.

We conclude that even after correction for aetiology and other factors, the generic and disease-specific HRQoL and fatigue of chronic liver patients depends on the patient's disease stage or transplant history. Although the HRQoL worsened with a worsening disease stage, non-cirrhotic and compensated cirrhotic patients barely showed significant differences in generic and disease-specific HRQoL or fatigue. Decompensated cirrhotic patients showed a significantly worse HRQoL compared to non-cirrhotic patients. The HRQoL of transplanted patients exceeded the HRQoL of all other chronic liver patients, although it was still impaired compared to the HRQoL of healthy controls. Thus, chronic liver patients cannot be considered as one group for whom disease related problems have equal impact on their daily functioning. For a good medical treatment and an honest approach of chronic liver patients it is therefore important that the disease stage or the transplant history are taken into account. Enhancing social support given by medical staff or family as part of chronic liver disease management may partly close the HRQoL-gap between non-cirrhotic, cirrhotic and transplanted liver patients.

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4

Health related quality of life of liver patients with various aetiologies

ABSTRACT

Background: Most studies on Health Related Quality of Life (HRQoL) of chronic liver patients were conducted in small clinical populations or restricted to one aetiology or disease stage. There is still a need for a large study conducted in a liver patient population of various aetiologies and disease stages, approaching a population-based study. We evaluated the impact of liver disease aetiology on generic HRQoL, disease-specific HRQoL and fatigue and compared the generic HRQoL and fatigue between aetiological groups and healthy Dutch controls.

Methods: Members of the Dutch liver patient association completed the Liver Disease Symptom Index 2.0, Short Form-36, and Multidimensional Fatigue Index-20. We compared the HRQoL between patients with viral hepatitis, autoimmune hepatitis, cholestatic diseases, hemochromatosis and other liver diseases by multivariate linear, ordinal and logistic regression.

Results: Prominent differences between aetiological groups were especially found in comparisons with viral hepatitis and hemochromatosis patients. In the SF-36, viral hepatitis patients revealed a worse mental health than most other aetiological groups, whereas the LDSI showed significantly higher odds ratios of severe depression, severe worry and severe fear of complications. Hemochromatosis patients demonstrated significantly more joint pain and more limitations due to emotional problems with increasing age.

Conclusions: Severe joint pain, impaired role emotional functioning and impaired mental health distinguish hemochromatosis patients and viral hepatitis patients from other chronic liver patients.

In the year 2000, 40% of the Dutch population suffered from a chronic disease and more than 800 Dutch men and women died of a chronic liver disease [1]. Until today, many patient associations, including the Dutch liver patient association (Nederlandse Leverpatiënten Vereniging (NLV)), fight for recognition of disease related physical, mental and social problems of chronic liver patients. Quality of life research may contribute to a better understanding of these problems and may fulfil this quest for recognition.

Until now, research has given limited insight in the Health Related Quality of Life (HRQoL) differences between liver disease aetiologies. Foster et al was the first to compare the HRQoL of liver patients with hepatitis B or C. This study demonstrated that hepatitis C patients showed significantly more impairment of social functioning, energy and fatigue and role limitations due to physical problems than hepatitis B patients [2]. Later studies reported variable results concerning the effect of aetiology on HRQoL. Younossi et al found no significant HRQoL differences between various aetiologies without cirrhosis, but did find significantly less impairment in cirrhotic cholestatic liver patients than in cirrhotic patients with hepatocellular disease [3]. Other studies reported no effect of aetiology on HRQoL in cirrhotic patients and no effect of aetiology with respect to utility decrement regardless of the disease stage [4,5].

Although these studies contributed substantially to our understanding of HRQoL in chronic liver patients, the majority of these studies were conducted in relatively small clinical populations or analyses were restricted to a certain disease stage. To increase our knowledge about the impact of various liver disease aetiologies on the HRQoL there is still a need for a study in a large research population with a broad variety of aetiologies and various disease stages. This study should use a generic as well as a disease-specific questionnaire to get a profound insight in the HRQoL differences between aetiologies [6,7].

Our collaboration with the Dutch liver patient association gave us the opportunity to evaluate the HRQoL of chronic liver patients, approaching a population-based study. Our study population of NLV members enabled us to evaluate the impact of various liver disease aetiologies on HRQoL, since the population-size and the amount variation in the population regarding, aetiology, disease stage and other factors potentially influencing HRQoL, permitted extensive correction for potential confounders. As recommended in the literature [6-8], we used the disease-specific Liver Disease Symptom Index and the generic Short Form-36. Since fatigue is an important complaint of chronic liver patients [9-11], we added the domain-specific Multidimensional Fatigue Index-20.

Our aim was to evaluate the impact of liver disease aetiology on generic HRQoL, disease-specific HRQoL and fatigue in patients with viral hepatitis, autoimmune hepatitis, cholestatic diseases, hemochromatosis and other liver diseases. Therefore, we compared the disease-specific HRQoL, generic HRQoL and fatigue between the various aetiological groups, corrected for disease stage, use of liver disease medication, number of liver diseases per patient, comorbidity, gender, age, education level and use of psychopharmaca. Additionally, we compared the generic HRQoL and fatigue between the various aetiological groups and healthy Dutch controls.

The impact of viral hepatitis B and C infection on HRQoL will be described in a separate paper.

METHODS

Study population

In October 2000 all 2020 members of the NLV received a questionnaire by mail. The questionnaire consisted of the Liver Disease Symptom Index 2.0 (LDSI), the Dutch Short Form-36 (SF-36), and the Multidimensional Fatigue Index-20 (MFI-20). NLV members included patients with a (history of) liver disease as well as non-patients who joined the NLV because of involvement with liver patients in family, circle of acquaintances or work. After two months non-responders received a new questionnaire. We closed the response period 5 months after the first mailing. Members gave their informed consent by confirming their willingness to participate in the first question of the questionnaire. Inclusion criteria were: 1) Informed consent and 2) aged 18 years or older at the moment of the study 3) and having a (history of) liver disease. To preserve the anonymity of the participants, the NLV withheld the coding of respondent numbers and member names, while the researcher withheld the completed questionnaires. The protocol was conform the ethical guidelines of the 1975 Declaration of Helsinki and approved by the Ethics Committee of the Erasmus MC Rotterdam, the Netherlands.

Measurement instruments

The disease-specific LDSI 2.0 includes 18 items. Nine items measure severity of: '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'. Nine other items measure the hindrance of these symptoms to daily activities. All items have 'the last week' as time frame and are scored on a 5-point scale ranging from 'not at all' to 'to a high extent'. Apart from the LDSI, 6 additional items recommended by the Dutch liver patient association, were scored on the same 5-point scale. These extra NLV items concern: 'Memory problems due to liver disease', 'Change of personality due to liver disease', 'Hindrance in financial affairs due to liver disease', 'Involuntary change in use of time', 'Decreased sexual interest' and 'Decreased sexual activity'. The LDSI as well as the extra NLV items have recently been validated in chronic liver patients at the outpatient clinic and in the NLV-population (Van der Plas, Quality of life Research, accepted for publication).

The generic SF-36, version 1.2, includes 8 multi-item scales on Physical Functioning, Role limitations due to Physical problems (Role Physical), Bodily Pain, General Health, Vitality, Social Functioning, Role limitations due to Emotional problems (Role Emotional) and Mental Health. The scale scores range from 0 to 100. A higher score indicates a better generic HRQoL.

The domain-specific MFI-20 includes five 4-item scales: General Fatigue, Physical Fatigue, Reduction in Activity, Reduction in Motivation and Mental Fatigue and scale scores range from 4 to 20. Higher scores indicate more fatigue. Both the SF-36 and the MFI-20 proved to be reliable and valid in Dutch chronic liver patients [8]

A separate questionnaire was used to determine gender, age, education level, aetiology, duration of the liver disease, status of the liver disease(s) (cured, non-cured), presence of a liver transplant, presence of cirrhosis and presence or history of splenomegaly, ascites or oesophageal variceal bleedings, presence of oesophageal

variceal bleedings or ascites in the year 2000, history of complications of cirrhosis (liver cancer or imminent coma), comorbidity (defined as diseases or disorders other than the liver disease which limit the respondent's daily functioning), medication use and the amount of hours per week spent on work and activities with and without physical effort.

Liver patient comparison groups

We categorised respondents into 5 aetiology groups: Viral Hepatitis, Autoimmune Hepatitis, Cholestatic liver diseases, Hemochromatosis and Other liver diseases. Furthermore, we categorised respondents into three disease stage groups: non-cirrhosis, compensated cirrhosis and decompensated cirrhosis. As a consequence of the study design and anonymity of respondents, we based the categorisation in aetiology and disease stage groups on respondent-reported aetiologies and clinical characteristics in the questionnaire.

Respondents who reported to have no cirrhosis and did not ever have splenomegaly, ascites or oesophageal variceal bleeding were classified as non-cirrhotic. Respondents who reported cirrhosis *or* ever had splenomegaly *or* ever had ascites *or* ever had oesophageal variceal bleeding, but not in the year 2000 (the year of investigation), were classified as compensated cirrhotic. Respondents who had had oesophageal variceal bleeding or ascites in the year 2000 were classified as decompensated cirrhotic.

In a pilot study conducted at our Hepatology outpatient clinic, reported aetiologies and clinical characteristics of disease stage demonstrated a good agreement between the test and the retest questionnaire (aetiologies: κ 0.71; clinical characteristics: κ 0.85 to 0.97) and a good agreement with hospital data (aetiologies: κ 0.63; clinical characteristics: κ 0.68 to 0.71). The assigned disease stage groups showed however a lower agreement with the disease stages based on hospital data of the patients. The hospital data revealed that our disease stage definitions disregarded the temporary state of the decompensated cirrhotic stage. With the current treatment modalities (diuretics or surgical interventions) decompensated cirrhotic patients often *reverse* to an apparently compensated state.

In the current study we took this temporary state of decompensated cirrhosis into account by adding the criterion concerning: The presence of ascites or oesophageal variceal bleedings *in the year 2000* (the year of the study), as extra item to the background questionnaire. In the NLV population 43 compensated cirrhotic patients could be defined as *reversed* decompensated cirrhotic patients based on the absence of ascites and/or variceal bleedings in the year 2000 and the use of diuretics and/or propanolol at the moment of our study. The HRQoL level of the *reversed* decompensated cirrhotic patients fitted the HRQoL level of the compensated cirrhotic group and not the HRQoL level of decompensated patients and were therefore categorised as compensated cirrhotic patients.

Controls

Healthy Dutch controls for the SF-36 (n=1715) originated from a nationwide, population-based health status survey with the standard version of the SF-36, conducted by the Dutch Organisation for Applied Scientific Research (TNO). Controls were adult members of a random sample of Dutch households, drawn from the

national telephone registry. This registry included a somewhat larger percentage of men and a smaller category in the age of 15-25 years than the adult population in the Netherlands. TNO corrected for this imbalance by stating in the introductory letter that any adult member of the household could complete the questionnaire. A random set of introductory letters requested that the questionnaire had to be completed by a member of the household between the ages of 15-25 years [12].

Healthy Dutch controls for the MFI-20 (n=139) originated from a study on fatigue and radiotherapy in cancer patients. Controls were adults from a non-selective sample of households taken from the telephone directories. As women are more frequently at home, researchers of this study prevented overrepresentation of women by interviewing the next person to have a birthday within that household [13].

Statistical methods

Crude SF-36 and MFI-20 scale scores were calculated according to the SF-36 scoring algorithms [14 15].

We used a general linear regression to estimate marginal mean SF-36 and MFI-20 scale scores for the aetiological groups and Dutch healthy controls. SF-36 scales or MFI-20 scales served as dependent outcome and aetiological groups (including the healthy controls as reference) as independent determinant. SF-36 scale scores were corrected for gender, age, education level and marital status. MFI-20 scale scores were corrected for gender, age and education level.

We also used linear regression to estimate the differences in generic HRQoL or fatigue between aetiological groups. In this analysis we excluded healthy controls and corrected for gender, age, education level, disease stage, comorbidity, number of liver diseases per patient, use of liver disease medication and use of psychopharmaca.

We used a proportional odds model for ordinal outcome by means of PROC LOGISTIC in SAS 8.0. to estimate for each aetiological group the probability of a certain symptom severity outcome (1=no symptom, 2, 3, 4 or 5=severe symptom) measured by the LDSI. We used the same model to estimate for each aetiological group the probability of a certain outcome of the extra NLV items.

Binary logistic regression estimated for each aetiological group the odds ratio of being hampered by symptoms in daily activities (score 2 to 5), relatively to not being hampered (score=1). For these analyses we selected only respondents with symptoms (symptom severity score >1). Probabilities and odds ratios were corrected for the same factors as the SF-36 and MFI-20 scales score differences. Interactions were significant if the overall p-value < 0.01 to avoid interactions by chance due to multiple testing. Moreover, the number of respondents in the interacting subcategories should be larger than 5% of the total population.

RESULTS

Selection of the population

Of the 2020 members approached for this survey, 1617 members returned the questionnaires. Of these, 374 respondents were non-patient member, who joined the NLV because of involvement with liver patients in family, circle of acquaintances or

work. In total 1243 had a (history of) liver disease. Assuming that the percentage of patient members is equal in non-responders and responders (77%), the total number of patient members would be 1553 and the actual response (n=1243) would be around 80%. Of the 1243, 1222 gave informed consent, but 47 were younger than 18 years of age. For this analysis we excluded 186 transplanted respondents and 71 respondents who reported them selves as cured, leaving 918 patient respondents for analyses.

Population characteristics

Table 1 shows the baseline characteristics of the study population and the Dutch healthy controls for the SF-36 and the MFI-20. The 918 respondents selected for analysis were mostly women (58.4%), had a mean age of 49 years (SD ± 12.6, range 18-81), were married or living together and had lower secondary education level according to the ISCED classification (UNESCO General conference 1997). In total 76% of these respondents spent on average 16.6 (SD ±22.7) hours per week on a paid and/or voluntary job and spent on average 7.2 (SD ±8.3) hours on physical activities like walking, cycling and gardening.

A third of the respondents suffered from some form of viral hepatitis, mostly hepatitis C (66.9%) and B (29.5%). The cholestatic group included patients with primary biliary cirrhosis (63.4%) and primary sclerosing cholangitis (36.6%). The group 'other liver diseases' included patients with parenchymatous non-viral liver diseases (35.1%), vascular deformations (14.6%), congenital metabolic liver diseases (24.6%) and a mix of congenital anatomic liver diseases, benign and malignant malformations, cholelithiasis and secondary biliary cirrhosis (25.7%). Fifty-seven respondents (6.2%) were classified as missing. In total 102 patients reported more than 1 liver disease. In total 590 (68.8%) of the patients reported next to their liver disease other comorbidity.

Generic HRQoL in chronic liver patients and Dutch healthy controls

All aetiologies showed a significantly worse generic HRQoL than healthy Dutch controls on all SF-36 scales (figure 1).

The upper diagonal of table 2 shows which SF-36 scales are significantly different between the aetiological groups. Most significant scale score differences were found when the viral hepatitis group was compared with one of the other aetiological groups. Scale scores of the viral hepatitis group were often significantly lower indicating a worse HRQoL than other aetiological groups. Compared to cholestatic liver patients, viral hepatitis patients scored significantly lower (worse) on all SF-36 scales with score differences ranging from (-5.2 [-10.0,-0.3] with respect to bodily pain to -15.8 [-24.2, -7.3,] with respect to role limitations due to emotional problems). Viral hepatitis patients showed a significantly worse vitality (-7.2 [-12.4, -2.1]), social functioning (-8.5 [-14.9, -2.0]) and more role limitations due to emotional problems (-18.9 [-28.2, -9.5]) than patients with autoimmune hepatitis. Furthermore, viral hepatitis patients scored significantly lower (worse) with respect to mental health than patients with cholestatic diseases (-7.0 [-10.9, -3.04]), hemochromatosis (-7.7 [-11.8, -2.5]) and patients with other liver diseases (-4.6 [-8.6, -0.6]).

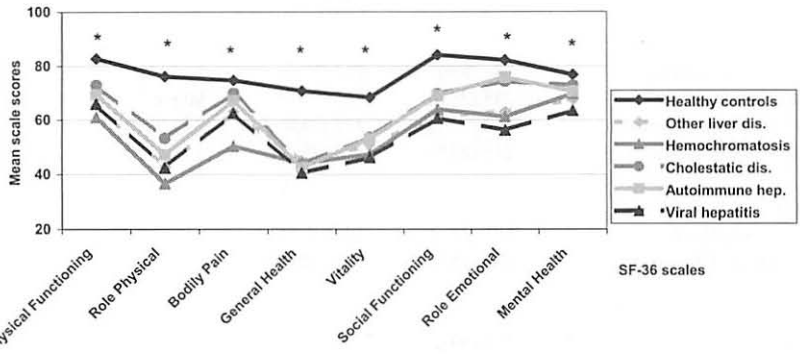
Hemochromatosis patients experienced significantly more bodily pain than all other aetiological groups (range bodily pain score differences: (-9.7 [-15.5, -4.0])

Table 1: Demographic and clinical characteristics of liver patients and controls.

Characteristic	NLV liver pt. population (n=918)	SF-36 healthy controls (n=1715)	MFI-20 healthy controls (n=139)
Age			
Mean age ± SD, yr.	49 ± 13	48 ± 17	46 ± 16
Gender			
Men, n (%)	382 (41.6)	967 (56.6)	60 (44.4)
Women, n (%)	536 (58.5)	740 (43.4)	75 (55.6)
Education			
None/elementary education	88 (9.6)	212 (12.6)	11 (8.1)
Lower secondary education	348 (38.0)	569 (33.8)	90 (66.7)
Upper/post secondary education	264 (28.9)	477 (28.4)	34 (25.2)
1st/2nd stage tertiary education	215 (23.5)	424 (25.2)	-
Marital status			
Married / Living together	681 (74.5)	1278 (74.8)	
Single / Widow(er) / Divorced	233 (25.5)	431 (25.2)	
Aetiology			
Viral hepatitis	275 (30.0)		
Autoimmune hepatitis	142 (15.5)		
PBC/PSC	175 (19.1)		
Hemochromatosis	98 (10.7)		
Other liver diseases	171 (18.6)		
Disease stage			
Non-cirrhosis	435 (48.7)		
Compensated cirrhosis	376 (42.1)		
Decompensated cirrhosis	82 (9.2)		
Comorbidity			
Patients with comorbidity	590 (68.8)		
Cardiovascular	124 (22.0)		
Neurological	17 (4.1)		
Respiratory	98 (16.6)		
Muscular	149 (25.4)		
Joints	241 (43.2)		
Urological	51 (10.2)		
Gastrointestinal	117 (21.0)		
Diabetes	47 (8.0)		
Visual	73 (12.5)		
Psychological	84 (14.7)		
Other	45 (7.6)		

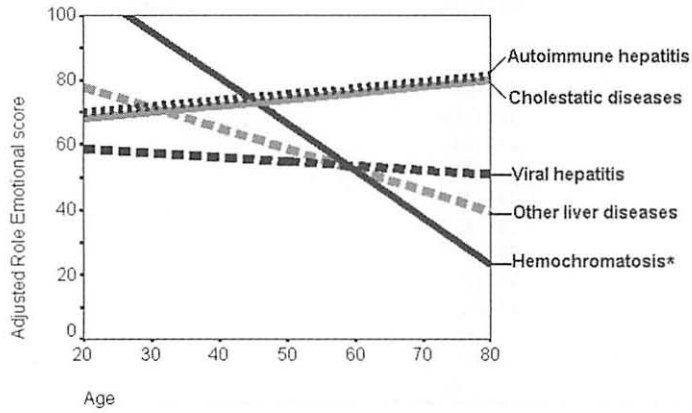
compared to patients with viral hepatitis to (-14.9 [-21.1, -8.7]) compared to patients with cholestatic diseases). The aetiology dependent differences in role limitations due to emotional problems were modified by age. Figure 2 shows the development of role emotional functioning by age for the various aetiologies. Hemochromatosis patients experienced a significantly stronger increase of role limitations due to emotional problems with increasing age than other aetiological groups ($p < 0.006$).

Figure 1: Mean SF-36 scale scores of Dutch healthy controls and chronic liver patients with various aetiologies, corrected for age, gender, education level and marital status.



*) Aetiological groups have a significantly lower (worse) score than healthy controls on that specific scale ($p < 0.05$).

Figure 2: The adjusted Role Emotional score by age (in years) for patients with autoimmune hepatitis, cholestatic diseases, viral hepatitis, other liver diseases and hemochromatosis. Adjusted for gender, age, education level, disease stage, comorbidity, number of liver diseases, use of liver disease medication and use of psychopharmaca.



*) The steep decline in role emotional scores, especially observed in hemochromatosis patients (n=98) indicates: significantly more limitations in work or other daily activities due to emotional problems with increasing age than in other aetiological groups ($p \leq 0.006$).

Fatigue in chronic liver patients and Dutch healthy controls

All aetiologies showed a significantly worse fatigue than health Dutch controls on all MFI-20 scales (figure 3).

The lower diagonal of table 2 shows which MFI-20 scales are significantly different between the aetiological groups. Again, the most significant scale score differences were found when the viral hepatitis group was compared with one of the other aetiological groups. In these cases viral hepatitis patients showed significantly higher scores, thus more fatigue. Compared to cholestatic patients, viral hepatitis patients showed significantly more fatigue on all scales ranging from +1.3 [0.25, 2.4] with respect to general fatigue to +1.9 [0.8, 2.9] with respect to physical fatigue. Patients with autoimmune hepatitis demonstrated a significantly smaller reduction in activity (-1.5 [-2.7, -0.3]) and a smaller reduction in motivation (-1.4 [-2.4, -0.4]) than viral hepatitis patients, but a similar general, physical and mental fatigue. Hemochromatosis patients experienced on all MFI-20 scales the same level of fatigue as viral hepatitis patients.

Comparison of symptom severity and symptom hindrance between aetiologies

The upper diagonal of table 3 shows which aetiological groups differ significantly with respect to the odds ratios (OR's) of severe symptoms. Relatively to other aetiological groups viral hepatitis revealed significantly higher OR's of severe worry about the family situation (range: OR 2.02 [1.37, 3.00] relatively to other liver diseases

Table 2: *Significant* differences in generic HRQoL (SF-36, upper diagonal) and fatigue (MFI-20, lower diagonal) between liver disease aetiological groups ($p < 0.05$). Differences were corrected for gender, age, education level, disease stage, comorbidity, number of liver diseases, use of liver disease medication and use of psychopharmaca.

	Significantly higher or lower SF-36 scale scores compared to the aetiological reference group.				
	Viral hepatitis *(Reference)*	**Autoimmune hepatitis** *(Reference)*	**Cholestatic diseases** *(Reference)*	**Hemochromatosis** *(Reference)*	**Other liver diseases** *(Reference)*
Viral hepatitis		VI -, SF-, RE-	PF-, RP-, BP-, GH-, VI-, SF-, RE-, MH-	BP+ RE-, MH-	GH-, VI-, MH-
Autoimmune hepatitis	RA-, RM-			BP+, VI+	RE+
Cholestatic diseases	GF-, PhF-, RA-, RM-, MF-			PF+, RP+, BP+, VI+	SF+
Hemochromatosis			PhF+		PF-, BP-
Other liver diseases	GF-, RA-, RM-, MF-				
	Viral hepatitis *(Reference)*	**Autoimmune hepatitis** *(Reference)*	**Cholestatic diseases** *(Reference)*	**Hemochromatosis** *(Reference)*	**Other liver diseases** *(Reference)*
Significantly higher or lower MFI-20 scale scores compared to the aetiological reference group.					

SF-36: PF=physical functioning, RP=role limitations due to physical problems, BP=bodily pain, GH=general health, VI=vitality, SF=social functioning, RE=role limitations due to emotional problems, MH=mental health. *MFI-20:* GF=general fatigue, PhF=physical fatigue, RA=reduction in activity, RM=reduction in motivation, MF=mental fatigue.

SF-36 scales:

+) Significantly higher score than reference group (=better HRQoL on that scale).

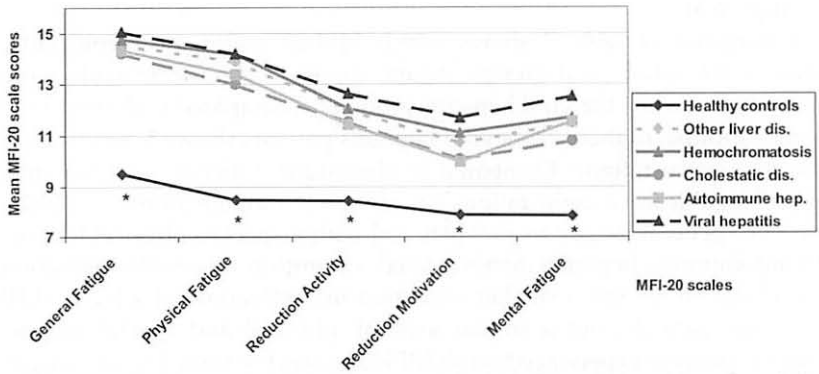
-) Significantly lower score than reference group (=worse HRQoL on that scale).

MFI-20 scales:

+) Significantly higher score than reference group (=more severe fatigue on that scale).

-) Significantly lower score than reference group (=less severe fatigue on that scale).

Figure 3: Mean MFI-20 scale scores of Dutch healthy controls and chronic liver patients with various aetiologies, corrected for age, gender and education level.



*) Fatigue in aetiological groups is significantly more severe than in healthy controls on that specific scale ($p < 0.05$).

to OR 2.8 [1.78, 4.29] relatively to cholestatic patients), severe depression (range: OR 1.72 [1.16, 2.55] relatively to other liver diseases to OR 2.67 [1.70, 4.19] relatively to cholestatic diseases) and severe fear of complications (range: OR 1.54 [1.03, 2.29] relatively to 'other liver diseases' to OR 2.65 [1.69, 4.17] relatively to cholestatic diseases). The OR of severe fear was influenced by gender and comorbidity. In men, comorbidity significantly increased the OR of severe fear of complications relatively to men without comorbidity (OR 2.62 [1.62, 4.25]). Additionally, men with comorbidity demonstrated significantly more fear of complications relatively to women with comorbidity (OR 1.54 [1.09, 2.16]). In hemochromatosis patients, the OR of severe joint pain was significantly higher relatively to all other aetiological groups (range: OR 1.89 [1.11, 3.22] relatively to autoimmune hepatitis to OR 4.28 [2.59, 7.05] relatively to cholestatic diseases). Aetiological groups did not show significant differences with respect to severity of sleepiness during the day or severity of jaundice.

The lower diagonal of table 3 shows which aetiological groups differ significantly with respect to the OR's of symptom hindrance. Patients with autoimmune hepatitis, cholestatic diseases and other liver diseases demonstrated significantly lower OR's of symptom hindrance than viral hepatitis patients. Symptom hindrance was not significantly different between viral hepatitis and hemochromatosis patients in any of the symptoms.

Table 4 shows which aetiological groups have significantly higher or lower OR's for the various complaints mentioned in the extra NLV items. Viral hepatitis patients showed a significantly higher OR of severe change of personality due to the liver disease relatively to patients with hemochromatosis, cholestatic or other liver diseases (range: OR 1.56 [1.06, 2.29] relatively to other liver diseases to OR 2.21 [1.44, 3.40] relatively to cholestatic diseases). OR's of severe memory problems, severe decreased sexual interest and severe decreased sexual activity were not significantly different among patients with viral hepatitis, autoimmune hepatitis, hemochromatosis or cholestatic diseases.

Table 3: *Significant* odds ratios for symptom severity (upper diagonal) or symptom hindrance (lower diagonal) between aetiological groups ($p < 0.05$). Odds ratios were corrected for gender, age, education level, disease stage, comorbidity, number of liver diseases, use of liver disease medication and use of psychopharmaca.

Aetiological groups showing significantly higher or lower odds ratios of *severe symptoms* than the reference group					
	Viral hepatitis *(Reference)*	**Autoimmune hepatitis** *(Reference)*	**Cholestatic diseases** *(Reference)*	**Hemo-chromatosis** *(Reference)*	**Other liver diseases** *(Reference)*
Viral hepatitis		Itch + Worry about family situation + Decreased appetite + Depression + Fear of complications +	Joint pain + Worry about family situation + Decreased appetite + Depression + Fear of complications +	Itch + Abdominal pain + Worry about family situation + Depression + Fear of complications + Joint pain -	Worry about family situation + Depression + Fear of complications +
Autoimmune hepatitis	Worry about family situation -		Joint pain + Itch -	Abdominal pain + Joint pain - Decreased appetite -	Joint pain + Decreased appetite -
Cholestatic diseases	Itch during daily activities - Joint pain - Worry about family situation -			Abdominal pain + Itch - Joint pain -	Fear of complications -
Hemo-chromatosis			Itch during daily activities + Joint pain + Worry about family situation +		Joint pain + Abdominal pain -
Other liver diseases	Itch during daily activities - Joint pain - Sleepiness during day - Depression - Jaundice -	Worry about family situation + Sleepiness during day - Depression -		Worry about family situation + Joint pain - Sleepiness during day - Depression -	
	Viral hepatitis *(Reference)*	**Autoimmune hepatitis** *(Reference)*	**Cholestatic diseases** *(Reference)*	**Hemo-chromatosis** *(Reference)*	**Other liver diseases** *(Reference)*
Aetiological groups showing significantly higher or lower odds ratios of *symptom hindrance* than the reference group.					

Symptom severity items:
+) The chance of a severe symptom for that specific aetiological group is significantly higher than for the reference group.
-) The chance of a severe symptom for that specific aetiological group is significantly lower than for the reference group.
Symptom hindrance items:
+) The chance of being hampered by the symptom is significantly higher for that specific aetiological than for the reference group.
-) The chance of being hampered by the symptom is significantly lower for that specific aetiological than for the reference group.

Table 4: *Significant* odds ratios between liver disease aetiological groups for complaints mentioned in the extra NLV items ($p < 0.05$). Odds ratios were corrected for gender, age, education level, disease stage, comorbidity, number of liver diseases, use of liver disease medication and use of psychopharmaca.

Aetiological groups showing significantly higher or lower odds ratios of *severe complaints* than the reference group				
	Autoimmune hepatitis *(Reference)*	**Cholestatic diseases** *(Reference)*	**Hemochromatosis** *(Reference)*	**Other liver diseases** *(Reference)*
Viral hepatitis		Personality change + Change in time spending +	Personality change +	Memory problems + Personality change + Decr. sexual interest+ Decr. sexual activity +
Autoimmune hepatitis				Memory problems +
Cholestatic diseases			Change in time spending -	
Hemochromatosis				Memory problems + Decr. sexual interest+

+) The chance of a severe symptom for that specific aetiological group is significantly higher than for the reference group.
-) The chance of a severe symptom for that specific aetiological group is significantly lower than for the reference group.

Other determinants associated with outcomes of the SF-36, LDSI and MFI-20

In general: the female sex, a lower secondary education level or less, comorbidity, having more than 1 liver disease, use of liver disease medication and use of psychopharmaca are associated with a worse HRQoL, more severe fatigue and higher OR's of severe symptoms and symptom hindrance.

DISCUSSION

Our aim was to evaluate the impact of liver disease aetiology on generic HRQoL, disease-specific HRQoL and fatigue in chronic liver patients. Corrected for various factors including disease stage, patients with viral hepatitis showed generally a worse HRQoL, but especially a worse mental health than other aetiological groups. Viral hepatitis patients demonstrated significantly higher odds ratios of mental symptoms like worry about the family situation, depression and fear of complications. Additionally, this patient group revealed significantly higher odds ratios of being hampered by various mental and physical symptoms during daily activities. Hemochromatosis patients revealed a significantly worse bodily pain, higher odds ratios of severe joint pain and their role emotional functioning steeply worsened with increasing age. Cholestatic liver patients generally showed a better generic HRQoL and less fatigue than most other aetiological groups. All aetiological groups showed a significantly worse generic HRQoL and more fatigue than healthy controls.

In our view, our study had the power to provide additional insight in the HRQoL of chronic liver patients. The large study population included sufficient variation in aetiology and disease stage to allow HRQoL comparisons by means of sophisticated statistical methods. A potential weakness of our study may be that the categorisation in aetiological and disease stage groups depended on data reported by the respondent. However, in our pilot study we demonstrated that inconsistencies between reported

data and hospital data were few. Therefore, we are confident that our respondents provided us with correct data about their aetiology and clinical characteristics.

Nevertheless, our results may have been influenced by potential selection biases. Due to the design of the study no information about non-responders was available. Responders may have been a selection of relatively healthy patients who felt well enough to complete the questionnaire, which may have led to an overestimation of HRQoL. Furthermore, the patient association may attract liver patients with a *low* HRQoL, although the social support given by other members may influence HRQoL positively. These potential selection biases may have led to an over- as well as an underestimation of HRQoL in our population.

Various other studies compared the HRQoL differences between aetiologies. One study, conducted in chronic liver patients with various aetiologies (n= 353), reported that patients without cirrhosis (n=127) have a similar HRQoL (measured by SF-36), regardless of the aetiology (viral or cholestatic). In cirrhotic patients, a significantly different HRQoL was found between cholestatic patients and patients with hepatocellular liver disease, but not between cholestatic and viral hepatitis patients [3]. However, our post hoc analysis within the non-cirrhotic group showed that viral hepatitis patients do have a significantly worse physical functioning, vitality, social functioning, role emotional functioning and mental health than cholestatic patients. In cirrhotic patients, we found that viral hepatitis patients have a significantly worse HRQoL than cholestatic patients in all SF-36 scales, except the bodily pain scale. Differences in disease stage definitions as well as statistical methods may explain the different results of Younossi et al.

The same author measured utilities in chronic liver patients by means of the Health Utility Index-2. No significant differences between utility scores given by patients with viral, cholestatic and other liver diseases were found. However, the HUI-2 may measure a slightly different concept than the SF-36, as indicated by correlations between the HUI-2 and SF-36 results ranging from 0.59 to 0.71 [4]. Finally, Marchesini et al pooled patients with viral hepatitis, PBC, autoimmune diseases and other liver diseases as non-alcoholic liver patients to compare their HRQoL with the HRQoL of alcoholic liver patients. No significant difference between alcoholic and non-alcoholic liver patients was found [5].

In hemochromatosis patients, joint pain is a known complaint. Twenty to fifty percent of the hemochromatosis patients older than 50 years of age develop arthritis in finger joints, which cannot be reversed and often progresses to other joints. [16-19]. We hypothesized that this progressive pain might play a part in the worsening role emotional functioning with increasing age, since negative feelings like depression and fear could *follow* from the adverse consequences of accumulating health problems (disability hypothesis) [20]. Additionally, progressive pain might result in more emotional distress due to the dose-response relationship between pain and quality of life [21,22]. A linear regression analysis in hemochromatosis patients showed indeed a significant positive relation between the bodily pain scale and the role emotional scale, although this finding does not allow conclusions about the direction of the relation between these two dimensions.

With respect to viral hepatitis patients we demonstrated that these patients mostly suffered from an impaired mental health. Prominent differences with other

aetiological groups concerning the physical dimension were found less often. The relative importance of impaired mental health in viral hepatitis patients points at the possibility that mental impairment might induce physical health problems (psychosomatic hypothesis) in this patient group [20]. Intervention studies in viral hepatitis and hemochromatosis patients are needed to clarify if improvement of the impaired dimensions leads to improvement of other dimensions.

In conclusion, this study increased our insight in the impact of liver disease aetiology on generic and disease-specific HRQoL. Prominent differences between aetiological groups were especially found in comparisons with viral hepatitis and hemochromatosis patients. Viral hepatitis patients revealed especially a worse mental health than all other aetiological groups, whereas hemochromatosis patients demonstrated significantly more bodily pain and more limitations due to emotional problems with increasing age. The potential interactions between physical and mental HRQoL dimensions in these patient groups require more attention in research and clinical practice.

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5

Health related quality of life of patients with viral hepatitis B or C

ABSTRACT

Background: Health Related Quality of Life (HRQoL) of chronic hepatitis C patients has found to be impaired in clinical study populations. Few studies directly compared the impact of hepatitis B or C infection on HRQoL or have put the HRQoL of viral hepatitis patients into perspective with other chronic diseases. We selected hepatitis B and C patients from a general liver patient population. Our aim was to evaluate the impact of hepatitis B and hepatitis C infection on generic and disease-specific HRQoL and fatigue. Furthermore, we put the generic HRQoL of viral hepatitis patients in perspective with other chronic liver patients and patients with diabetes mellitus and cancer.

Methods: Members of the Dutch liver patient association completed the Liver Disease Symptom Index 2.0, Short Form-36, and Multidimensional Fatigue Index-20. Our population (n=258) included patients with hepatitis B or hepatitis C with and without interferon therapy. We compared HRQoL between the three subgroups by multivariate linear-, ordinal- and logistic regression.

Results: Hepatitis C patients without interferon therapy showed an impaired role emotional functioning and mental health compared to hepatitis B patients, but also compared to other chronic liver and non-liver patients. Interferon therapy significantly aggravated this impaired role emotional functioning and mental health and led to additional impairments of other HRQoL dimensions.

Conclusions: The difference in HRQoL between hepatitis B patients and hepatitis C patients without interferon therapy was explained by the impaired emotional functioning and mental health found in hepatitis C patients. In hepatitis C patients with interferon therapy, additional and more severely affected HRQoL elements contributed to this difference.

Infection with the hepatitis B virus as well as infection with the hepatitis C virus are major causes of chronic hepatitis. In immunocompetent adults, acute exposure to the hepatitis B virus leads in 2-10% percent to chronic hepatitis B, while acute exposure to hepatitis C leads in the vast majority (around 75%) to chronic hepatitis C [1,2].

A cross-sectional population-based study on sera of 7373 Dutch men and women in 1995-1996, demonstrated that 2.1% of the population had a history of hepatitis B infection. Of these 0.2% was still infectious. Almost 1 in thousand participants had a history of hepatitis C infection [3].

Many chronic hepatitis B patients are healthy carriers (50%). These patients have normal liver enzymes, a normal or near-normal liver histology, are asymptomatic and have an excellent prognosis. However, the other half of the chronic carriers may have evidence of continuous or intermittent active viral replication. Of these patients, 15-20% will develop cirrhosis within 5 years, which increases the risk of complications of the liver disease: ascites, variceal bleeding, encephalopathy and hepatocellular carcinoma. Similar to chronic hepatitis B infections, chronic hepatitis C infections can be subclinical for at least two decades. As disease progression is mostly silent, the most frequent complaint is fatigue. Also in chronic hepatitis C patients, the development of cirrhosis implies an increasing risk of liver related complications [1].

Few studies directly compared the impact of hepatitis B or C infection on HRQoL or have put the HRQoL of viral hepatitis patients in perspective with other chronic liver and non-liver diseases. Foster et al compared the HRQoL of these patient groups by means of the SF-36 and revealed that hepatitis C patients are significantly more impaired with respect to social functioning, energy and fatigue and role limitations due to physical problems than hepatitis B patients [4]. Another study demonstrated that musculoskeletal pain and fatigue was more frequent in hepatitis C than in hepatitis B patients [5]. These studies increased our knowledge about HRQoL and symptom differences between these patient groups. However, to get a good insight in the impact of hepatitis B or C infection on HRQoL, a larger population of viral hepatitis patients is needed with sufficient variation in disease stage and other factors influencing HRQoL, to allow extensive adjustment. Furthermore, a generic as well as a disease-specific questionnaire should be used to get a profound insight in the important symptoms and dimensions contributing to the HRQoL of hepatitis B and C patients [6,7]. Based on this knowledge, disease management could be adapted to the specific needs of these patient groups.

Our collaboration with the Dutch liver patient association gave us the opportunity to study the HRQoL of patients with hepatitis B and C, selected from a general population of Dutch chronic liver patients. Our study population of NLV members enabled us to evaluate the adjusted impact of viral hepatitis B and C infection on HRQoL, since the population-size and the amount variation in the population, permitted extensive adjustment for other factors. We used the disease-specific Liver Disease Symptom Index 2.0 and the generic Short Form-36. Additionally, we used the Multidimensional Fatigue Index-20, as fatigue is an important complaint of patients with chronic hepatitis C [1,5,8].

Our first aim was to evaluate the impact of hepatitis B and hepatitis C infection on generic HRQoL, disease-specific HRQoL and fatigue. Our second aim was to put the

HRQoL of viral hepatitis B and C patients into perspective, by comparing the HRQoL of patients with viral hepatitis with the HRQoL of patients with other chronic liver and non-liver diseases such as diabetes mellitus and cancer.

METHODS

Study population

In October 2000, all 2020 members of the Dutch liver patient association (Nederlandse Leverpatiënten Vereniging (NLV)) were approached for participation in this study and received a questionnaire by mail. The members included patients with a (history of) liver disease as well as non-patients who joined the NLV because of involvement with liver patients in family, circle of acquaintances or work. After two months non-responders received a new questionnaire. We closed the response period 5 months after the first mailing.

Members gave their informed consent by confirming their willingness to participate in the first question of the questionnaire. Inclusion criteria for the current study were: 1) Informed consent and 2) aged 18 years or older at the moment of the study 3) having a (history of) liver disease, 4) reported viral hepatitis B or C. Patients who had a liver transplant and patients who reported themselves as cured were excluded.

To preserve the anonymity of the participants, the NLV withheld the coding of respondent numbers and member names, while the researcher withheld the completed questionnaires. The protocol was conform the ethical guidelines of the 1996 Declaration of Helsinki and approved by the Ethics Committee of the Erasmus Medical Center Rotterdam, the Netherlands.

Liver patient comparison groups

We categorised respondents into two viral hepatitis groups: hepatitis B or hepatitis C.

Hepatitis C patients were categorised in patients with and without interferon therapy at the moment of the study. Furthermore we categorised respondents in disease stage groups (non-cirrhosis, compensated cirrhosis and decompensated cirrhosis).

As a consequence of the study design and anonymity of respondents, we based the categorisation in aetiology and disease stage groups on respondent-reported aetiologies and clinical characteristics in the questionnaire. Respondents who reported to have no cirrhosis and did not ever have splenomegaly, ascites or oesophageal variceal bleeding were classified as non-cirrhotic. Respondents who reported cirrhosis *or* ever had splenomegaly *or* ever had ascites *or* ever had oesophageal variceal bleeding, but not in the year 2000 (the year of investigation), were classified as compensated cirrhotic. Respondents who had had oesophageal variceal bleeding or ascites in the year 2000 were classified as decompensated cirrhotic.

In a pilot study conducted at our Hepatology outpatient clinic, reported aetiologies and clinical characteristics of disease stage demonstrated a good agreement between the test and the retest questionnaire (aetiologies: κ 0.71; clinical characteristics: κ 0.85 to 0.97) and a good agreement with hospital data (aetiologies:

κ 0.63; clinical characteristics: κ 0.68 to 0.71). The assigned disease stage groups (non-cirrhosis, compensated cirrhosis and decompensated cirrhosis) showed however a lower agreement with the disease stages in hospital files of patients. The hospital data revealed that our disease stage definitions during the pilot, disregarded the temporary state of the decompensated cirrhotic stage, e.g. due to flare up of disease activity or inflammation. The current treatment modalities (diuretics or surgical interventions) help decompensated cirrhotic patients to *reverse* to an apparently compensated state. During the current study we took this temporary state of decompensated cirrhosis into account by adding the criterium concerning: The presence of ascites or oesophageal variceal bleedings *in the year 2000* (the year of the study), as extra item to the background questionnaire. This item would discriminate *reversed* decompensated cirrhotic patients from recent decompensated cirrhotic patients.

Other comparison groups

We compared the generic HRQoL of viral hepatitis patients with the generic HRQoL of patients with diabetes mellitus and cancer. Patients with diabetes mellitus (n=60) originated from a sample of 4024 patients older than 18 years of age, approached by 60 general practitioners in the southern and eastern parts of The Netherlands [9]. Patients with cancer (n=485), originated from a sample of patients with breast, colorectal or lung cancer with a life expectancy of at least 4 months, recruited from the outpatient clinics of the departments of internal medicine and radiotherapy of the Antoni van Leeuwenhoek hospital in Amsterdam [10].

Measurement instruments

For HRQoL measurement we used the Dutch versions of the Liver Disease Symptom Index version 2.0 (LDSI), the Short Form-36 (SF-36), version 1.2 and the Multidimensional Fatigue Index (MFI-20). In addition, we obtained personal background information by a separate questionnaire.

The disease-specific LDSI 2.0 includes 18 items. Nine items measure severity of: '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'. Nine other items measure the hindrance of these symptoms to daily activities. All items have 'the last week' as time frame and are scored on a 5-point scale ranging from 'not at all' to 'to a high extent'. Apart from the LDSI, 6 additional items recommended by the Dutch liver patient association, were scored on the same 5-point scale. The items concern: 'Memory problems due to liver disease', 'Change of personality due to liver disease', 'Hindrance in financial affairs due to liver disease', 'Involuntary change in use of time', 'Decreased sexual interest' and 'Decreased sexual activity'. The LDSI as well as the extra items have recently been validated in chronic liver patients at the outpatient clinic and in the NLV-population (Van der Plas, Quality of life Research, accepted for publication).

The generic SF-36 includes 8 multi-item scales on Physical Functioning, Role limitations due to Physical problems (Role Physical), Bodily Pain, General Health, Vitality, Social Functioning, Role limitations due to Emotional problems (Role Emotional) and Mental Health. The scale scores range from 0 to 100. A higher score indicates a better generic HRQoL. SF-36 data of Dutch healthy controls are available [10].

The domain-specific MFI-20 includes five 4-item scales: General Fatigue, Physical Fatigue, Reduction in Activity, Reduction in Motivation and Mental Fatigue. Scale scores range from 4 to 20. Higher scores indicate more fatigue. MFI-20 data of Dutch healthy controls are available [11]. Both the SF-36 and the MFI-20 proved to be reliable and valid in Dutch chronic liver patients [12].
A separate questionnaire was used to determine gender, age, education level, marital status, aetiology, duration of the liver disease, status of the liver disease(s) (cured, non-cured), presence of a liver transplant, presence of cirrhosis and presence or history of splenomegaly, ascites or oesophageal variceal bleedings, presence of oesophageal variceal bleedings or ascites in the year 2000, history of complications of cirrhosis (liver cancer or imminent coma), comorbidity (defined as the presence of diseases or disorders other than the liver disease that limit the respondent's daily functioning), medication use and the average number of hours per week spent on work and activities with and without physical effort.

Statistical methods

Demographic and clinical characteristics were compared between hepatitis groups by t-test (approximate normal variables), Mann-Whitney test (for continuous non-normal variables) and χ^2-test (for categorical variables). Crude SF-36 and MFI-20 scale scores were calculated according to the SF-36 and MFI-20 scoring algorithms respectively [13,14]. Crude SF-36 and MFI-20 scale scores were compared between hepatitis B and C patients per disease stage. Differences were regarded as significant when $p \leq 0.005$ to prevent significant results due to multiple testing.

To estimate adjusted differences in generic HRQoL or fatigue between patients with viral hepatitis B and viral hepatitis C patients with and without interferon therapy, we performed a general linear regression. SF-36 scales or MFI-20 scales served as dependent variables. The hepatitis groups and correction factors served as independent determinants.

We compared the LDSI symptom severity between hepatitis B and hepatitis C with and without interferon therapy with a proportional odds model for ordinal outcome by means of PROC LOGISTIC in SAS 8.0. This model estimated for each viral hepatitis group the probability of a certain symptom severity outcome (1=no symptom, 2, 3, 4 or 5=severe symptom). The same model was used to analyse the extra NLV items.

Binary logistic regression estimated for each of the three viral hepatitis groups the odds ratio of being hampered by symptoms in daily activities (score 2 to 5), relatively to not being hampered (score=1) by these symptoms. We assumed that only respondents with symptoms could have symptom hindrance, therefore we selected respondents who actually had the symptom (symptom severity score > 1). The symptom hindrance variables served as the dependent outcomes, viral hepatitis groups and correction factors as independent determinants. Odds ratios for symptom hindrance were estimated per subgroup.

Differences, probabilities and odds ratios were regarded as significant when $p < 0.05$ and were corrected for gender, age, education level, average number of hours paid work conducted per week, disease stage, comorbidity, number liver diseases, use of liver disease medication and use of psychopharmaca. Interactions were regarded

as significant if the overall p-value < 0.01. Additionally, the number of respondents in the interacting subcategories should be larger than 5% of the total population.

RESULTS

Selection of the population

Of the 2020 members approached for this survey, 1617 members returned questionnaires. Of these, 374 respondents were non-patient member who joined the NLV because of involvement with liver patients in family, circle of acquaintances or work. In total 1243 had a (history of) liver disease. In total 258 patients met the inclusion criteria for the current study.

Population characteristics

Table 1 shows the baseline characteristics of the liver patient population and the Dutch healthy controls for the SF-36 and the MFI-20. Patients with viral hepatitis C were significantly (p=0.04) older and had a higher education (p=0.04) than patients with hepatitis B. The hepatitis B group included significantly more men (p=0.03). Other demographic characteristics were not significantly different between the

Table 1: Demographic and clinical characteristics of liver patients.

Characteristic	Hepatitis B (n=74)	Hepatitis C (n=184)
Age		
Mean age ± SD, yr.	45 ± 11[a]	49 ± 11
Gender		
Men, n (%)	50 (67.6)[b]	97 (52.7)
Women, n (%)	24 (32.4)	87 (47.3)
Education		
None/elementary education	15 (20.5)[c]	18 (9.8)
Lower secondary education	16 (21.9)	65 (35.3)
Upper/post secondary education	27 (37.0)	57 (31.0)
1st/2nd stage tertiary education	15 (20.5)	44 (23.9)
Marital status		
Married / Living together	53 (72.6)	117 (63.9)
Single / Widow(er) / Divorced	20 (27.4)	66 (36.1)
Disease stage		
Non-cirrhosis	44 (61.1)	116 (64.1)
Compensated cirrhosis	22 (30.6)	51 (28.2)
Decompensated cirrhosis	6 (8.3)	14 (7.7)

[a] Significantly different between hepatitis B and hepatitis C patients, p=0.04
[b] Significantly different between hepatitis B and hepatitis C patients, p=0.03
[c] Significantly different between hepatitis B and hepatitis C patients, p=0.04

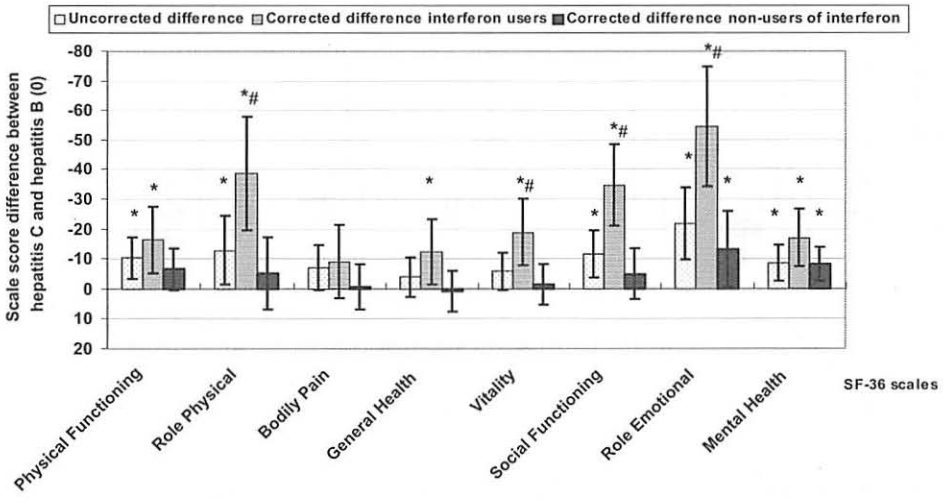
two patient groups. Hepatitis B patients spent per week significantly more hours on a paid job (25.8 hours, p=0.01) than hepatitis C patients (16.3 hours). Hepatitis B as well as hepatitis C patients spent 6.5 hours per week on physical activities like walking, cycling and gardening. At the time of the study, 22 hepatitis C patients used interferon. None of the hepatitis B patients used interferon.

With respect to the non-liver chronic patients, more than half of the sample (54.2%) that included the diabetes mellitus patients had an age lower than 50. The total sample included 67.6% women, but the mean age and gender distribution of the diabetes mellitus patients is unknown. The mean age of cancer patients originating from the Antoni van Leeuwenhoek hospital was 57.3 (± 12.1) years and the sample included 58% women. The majority of these patients had breast cancer (35%) or lung cancer (31%).

Generic HRQoL and fatigue in patients with viral hepatitis B and C

Figure 1 and figure 2 respectively, show the uncorrected and corrected difference in generic HRQoL and fatigue between patients with viral hepatitis B and C. Hepatitis C patients were categorised in hepatitis C patients with and without interferon therapy. Compared to hepatitis B patients, hepatitis C patients with interferon therapy showed significant impairments on almost all SF-36 and MFI-20 scales ($p < 0.03$). The most severe impairment concerned the amount of limitations due to emotional problems. Also hepatitis C patients without interferon therapy reported a significantly impaired mental health (p=0.005) and more limitations due to emotional problems (p=0.041)

Figure 1: Uncorrected difference in generic HRQoL between patients with hepatitis B and hepatitis C (overall) and corrected differences in generic HRQoL between patients with viral hepatitis B, hepatitis C with interferon therapy and hepatitis C patients without interferon therapy. Corrected for gender, age, education level, disease stage, use of liver disease medication, comorbidity, number liver diseases per patient, use of psychopharmaca and average number of hours paid work conducted per week.



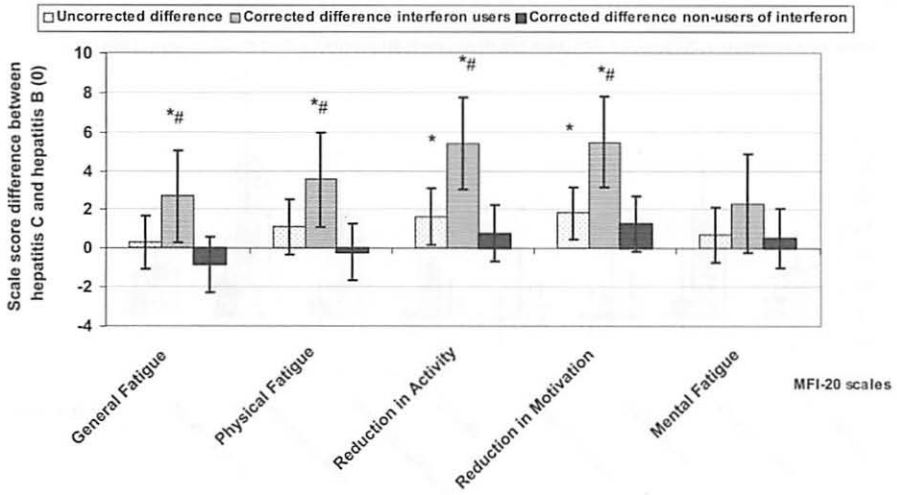
Negative difference: lower (worse) scale score than scale score of hepatitis B patients.
*) Scale score is significantly lower (worse) than scale score of hepatitis B patients ($p < 0.05$).
#) Scale score of hepatitis C patients with interferon therapy is significantly lower (worse) than scale score of hepatitis C patients without interferon therapy ($p \leq 0.001$).

than hepatitis B patients. However, the impairments regarding vitality, social functioning, role emotional functioning, role physical functioning and four of the five fatigue scales found in hepatitis C patients with interferon therapy were significantly worse than in hepatitis C patients without interferon therapy ($p \leq 0.002$).

Table 2 shows the comparison of crude SF-36 and MFI-20 scores between patients with hepatitis B and C per disease stage. In non-cirrhotic patients, hepatitis C patients showed a significantly worse physical and social functioning and more role limitations due to emotional problems ($p \leq 0.005$) than hepatitis B patients. None of the disease stages showed significant differences in fatigue between hepatitis B and C.

After correction for baseline factors and categorisation by interferon use, non-cirrhotic hepatitis C patients with interferon (n=14) showed a worse social functioning (p=0.000), more limitations due to emotional problems (p=0.002) and a worse mental health (p=0.047) than non-cirrhotic hepatitis B patients. Hepatitis C patients without interferon (n=146) and hepatitis B showed no significant differences. In the compensated cirrhotic group, 6 hepatitis C patients used interferon. No differences were found between this group and hepatitis B patients, but hepatitis C patients without interferon (n=67) did show a worse mental health (p=0.014) and a more severe reduction in activity (p=0.009) and motivation (p=0.018) than hepatitis B patients in the same disease stage. In decompensated cirrhotic patients, we only corrected for gender due to small numbers. Solely hepatitis C patients without interferon therapy showed a significantly impaired mental fatigue compared hepatitis B patients (p=0.049).

Figure 2: Uncorrected difference in fatigue between patients with hepatitis B and hepatitis C (overall) and corrected differences in fatigue between patients with viral hepatitis B, hepatitis C with interferon therapy and hepatitis C patients without interferon therapy. Corrected for gender, age, education level, disease stage, use of liver disease medication, comorbidity, number liver diseases per patient, use of psychopharmaca and average number of hours paid work conducted per week.



Positive difference=higher scale score (more severe fatigue) than scale score of hepatitis B patients.
Negative difference=lower scale score (less severe fatigue) than scale score of hepatitis B patients.
*) Scale score is significantly higher (more severe) than scale score of hepatitis B patients ($p < 0.05$).
#) Scale score of hepatitis C patients with interferon therapy is significantly higher (more severe) than scale score of hepatitis C patients without interferon therapy ($p \leq 0.002$).

Table 2: Uncorrected SF-36 and MFI-20 scale scores of hepatitis B and C patients per disease stage.

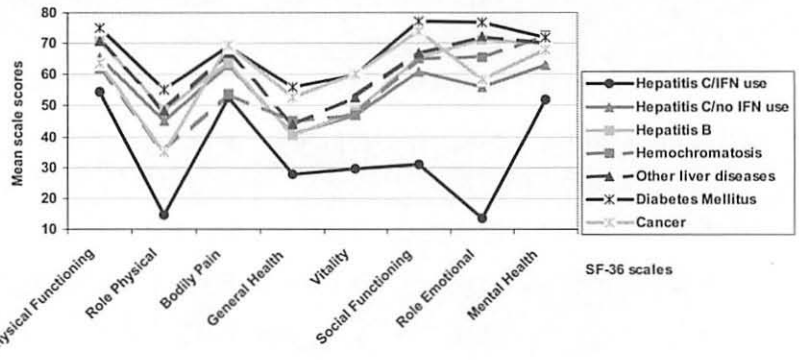
	Non-Cirrhosis		Compensated Cirrhosis		Decompensated Cirrhosis	
	Hepatitis B (n=44)	Hepatitis C (n=116)	Hepatitis B (n=22)	Hepatitis C (n=51)	Hepatitis B (n=6)	Hepatitis C (n=14)
Physical Functioning	81.1 (19.3) ‡	69.4 (24.1)	65.7 (28.1)	57.6 (28.4)	57.4 (23.5)	44.9 (26.9)
Role Physical	58.3 (36.7)	43.5 (41.5)	44.0 (44.7)	34.6 (42.0)	37.5 (34.5)	14.3 (36.3)
Bodily Pain	70.8 (24.7)	66.0 (25.4)	73.0 (22.9)	56.7 (29.5)	36.7 (27.6)	36.4 (26.6)
General Health	46.6 (23.0)	43.6 (24.5)	43.7 (20.7)	33.2 (22.8)	21.1 (20.1)	26.4 (23.5)
Vitality	52.6 (20.5)	47.2 (23.4)	50.3 (23.5)	42.8 (22.5)	42.5 (31.3)	34.9 (23.3)
Social Functioning	75.0 (23.3) ‡	60.4 (29.5)	58.5 (24.8)	52.9 (31.1)	60.4 (36.6)	43.8 (31.3)
Role Emotional	76.2 (36.2) ‡	53.8 (45.3)	65.1 (41.5)	43.8 (45.9)	66.7 (42.1)	40.5 (45.6)
Mental Health	68.7 (15.4)	62.4 (22.6)	72.9 (19.1)	59.3 (23.5)	61.3 (33.3)	56.0 (25.4)
General Fatigue	14.1 (5.1)	14.3 (4.9)	15.4 (5.2)	15.9 (4.9)	16.3 (4.9)	17.4 (4.9)
Physical Fatigue	13.2 (5.0)	13.7 (5.3)	12.8 (4.6)	15.1 (5.1)	15.7 (5.4)	16.7 (4.8)
Reduction Activity	11.1 (4.7)	12.2 (5.5)	10.9 (4.2)	14.3 (5.4)	14.3 (4.2)	13.8 (5.0)
Reduction Motivation	10.5 (4.7)	11.9 (5.1)	9.7 (4.1)	12.5 (4.7)	11.5 (2.9)	13.0 (6.1)
Mental Fatigue	11.6 (5.5)	11.8 (5.1)	12.6 (4.3)	13.7 (5.1)	12.0 (6.4)	16.5 (3.8)

‡) Scores are significantly different between hepatitis B and C ($p \leq 0.005$).

Symptom severity and symptom hindrance in patients with viral hepatitis B and C

Also with respect to symptom severity we categorised hepatitis C patients by interferon use. Both interferon users and non-users showed a significantly higher odds ratio of severe depression than hepatitis B patients (OR users: 10.67 [3.72, 30.57], OR non-users: 2.13 [1.10, 4.13]). Furthermore, hepatitis C patients with interferon showed a significantly higher OR of severely decreased appetite (OR 3.28 [1.17, 9.15])

Figure 3: Corrected mean SF-36 scale scores for patients with viral hepatitis B, hepatitis C with interferon therapy, hepatitis C patients without interferon therapy, hemochromatosis patients and patients with other liver diseases (cholestatic diseases, autoimmune hepatitis and remaining liver diseases) compared with crude mean SF-36 scale scores for patients with diabetes mellitus and cancer. Means of liver patients are corrected for gender, age, education level, disease stage, use of liver disease medication, comorbidity, number liver diseases per patient, use of psychopharmaca and average number of hours paid work conducted per week.



Hepatitis C patients with and without interferon therapy showed a significantly worse mental health and role emotional functioning than most other chronic liver patients ($p < 0.05$). Role emotional functioning was not significantly different between hepatitis C patients and hemochromatosis patients. Compared to diabetes mellitus and cancer patients, both hepatitis C subgroups reported more limitations due to emotional problems and a worse mental health.

and a significantly higher OR of involuntary change in time spending (OR 3.04 [1.05, 8.82]), while non-users reported a significantly higher odds ratio of being hampered by joint pain during daily activities (OR 3.37 [1.05, 10.8]) compared to hepatitis B patients.

Comparison of generic HRQoL between patients with viral hepatitis and chronic patients with liver and non-liver diseases

We compared the corrected mean HRQoL measured by the SF-36, between patients with viral hepatitis B and C (with and without interferon) and other chronic liver patients. Furthermore, we used the crude SF-36 scale means for cancer and diabetes mellitus to put the HRQoL of hepatitis B and C patients in perspective (figure 3). Hepatitis C patients without interferon showed a significantly worse mental health and role emotional functioning than other chronic liver patients, although hemochromatosis patients revealed a similar role emotional functioning. Also compared to patients with diabetes mellitus and cancer, these hepatitis C patients reported more limitations due to emotional problems and a worse mental health. Interferon therapy significantly aggravated the generic HRQoL of hepatitis C patients. In contrast, hepatitis B patients reported a similar emotional functioning and mental health as other liver patients and a better emotional functioning and mental health than cancer patients.

DISCUSSION

The aims of this study were to evaluate the impact of hepatitis B and hepatitis C infection on generic HRQoL, disease-specific HRQoL and fatigue and to compare the generic HRQoL between patients with viral hepatitis, other chronic liver patients and patients with chronic non-liver diseases, such as diabetes mellitus and cancer.

As interferon or interferon-based therapy could influence the mental health of hepatitis C patients [15-17], we compared the HRQoL of hepatitis B patients with the HRQoL of hepatitis C patients with interferon therapy or without interferon therapy. The HRQoL of hepatitis C patients with interferon therapy was significantly more severly affected than the HRQoL of hepatitis C patients without interferon therapy. Yet, hepatitis C patients with interferon as well as without interferon therapy showed a significantly impaired role emotional functioning and mental health compared to hepatitis B and other chronic liver patients. Hepatitis C patients with and without interferon also showed an impaired role emotional functioning and mental health compared to patients with diabetes mellitus and cancer.

Few other studies compared the HRQoL between hepatitis B and hepatitis C patients. Foster et al compared the HRQoL measured by the SF-36, of non-cirrhotic patients with viral hepatitis B or C, who had not taken antiviral medication within the past 6 months. Hepatitis C patients revealed a significantly worse social functioning, vitality and more role limitations due to physical problems than hepatitis B patients [4]. However, these findings were uncorrected for confounders. In the current study, we found no significant differences between non-cirrhotic hepatitis B and hepatitis C patients without interferon. In the compensated cirrhotic group we did find a significantly more severe reduction in activity and motivation and a significantly worse mental health in hepatitis C patients without interferon.

It is still unclear why the mental/emotional health of hepatitis B patients is less affected. In hepatitis C patients changes in brain metabolism, may cause cognitive impairments like impaired concentration and speed of working memory. These cognitive problems could result in less effective performance in daily activities, that could indirectly cause depression and anxiety [18-21]. Hepatitis B patients demonstrated less signs of altered cerebral metabolism than hepatitis C patients [22].

Furthermore, it has also been reported that hepatitis B patients experienced less frequently an interferon-induced depression than hepatitis C patients [23]. The effect of interferon use on mental health of hepatitis C patients might be confounded by a chronic condition predating the onset of viral infection and the use of interferon [24]. A recent study reported that almost 50% of the 630 patients with the diagnosis HCV, used anti-depressant in the pre-diagnostic period, against 38.4% in controls ($p < 0.001$) [25]. Moreover, depressive symptoms and psychiatric morbidity have been associated with intravenous drug use, whereas intravenous drug use has been associated with hepatitis C infection. Therefore, history of drug usage could confound the impaired mental health found in hepatitis C patients [24,26,27]. In our study we did not investigate the intravenous drug history of respondents.

Another factor that could play an important part in the impairment of mental health of hepatitis C patients is the diagnosis of hepatitis C its self. A recent study, based on a screening among women who received hepatitis C virus contaminated

blood products in 1977, included 87 PCR positive women with a chronic HCV infection and 68 PCR negative women considered to have a spontaneous self-limited infection. Despite the PCR negative status of the 68 women, a similar proportion of women reached the criteria for depression and anxiety (9.8%) as in the PCR positive group (9.6%). This suggest that the sudden diagnosis with an infectious chronic disease, associated with intravenous drug usage, may have caused great concern to these women and can be regarded as a stressful event which could influence mental / emotional health [28].

Furthermore, we lacked insight in the social network of hepatitis C patients. In a qualitative study, hepatitis C patients showed distress due to actual loss or fear of losing partners, friends and family due to perceived social stigma, associated with societal fear of contagions or the relation of hepatitis C with intravenous drug use [29,30]. Another study showed that of the 257 hepatitis C patients, 147 experienced stigmatisation that they attributed to their disease. The likelihood of stigmatisation was independent of mode of infection, professional status, education and age, but was significantly associated with depression, anxiety and worsened quality of life [31].

A final factor that may have influenced the mental health of hepatitis might be the hepatitis C awareness campaigns. Hepatitis C awareness campaigns may create, next to awareness, also fear of cirrhosis, hepatocellular carcinoma and liver transplantation, although around 80% of all chronic hepatitis C patients will never develop cirrhosis and 95% will never develop hepatocellular carcinoma [32].

In conclusion, hepatitis C patients without interferon therapy showed an impaired emotional functioning and mental health compared to hepatitis B patients, but also compared to other chronic liver patients and patients with diabetes mellitus and cancer. Interferon therapy significantly aggravated this impaired emotional functioning and mental health and led to additional impairments of other HRQoL dimensions. During hepatitis C consultations, besides attention for physical impairments, attention should be given to psychological impairments in this patient group.

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Health related quality of life of chronic liver patients; Integration of findings

ABSTRACT

Background: Since most studies on Health Related Quality of Life (HRQoL) of chronic liver patients were conducted in small clinical populations, there is still a need for a large study on HRQoL of chronic liver patients of various aetiologies and disease stages that approaches a population-based study.

Methods: Eleven hundred and seventy-five members of the Dutch liver patient association completed the generic Short Form-36 and the disease-specific Liver Disease Symptom Index 2.0. We used multivariate linear, ordinal and logistic regression to compare the HRQoL between disease stages (also including transplanted liver patients) and various aetiologies.

Results: Liver patients demonstrated a significantly reduced HRQoL compared to healthy controls, corrected for gender, age, education and marital status. Compared to non-cirrhotic patients, compensated cirrhotic patients showed few significant reductions in generic HRQoL (2 of 8 SF-36 scales) and infrequently significantly higher odds ratios of severe symptoms (3 of the 9 LDSI symptoms). Decompensated cirrhotic patients showed a marked reduction in generic and disease-specific HRQoL (7 of 8 SF-36 scales, 8 of 9 LDSI symptoms), whereas transplanted patients had a significantly better generic and disease-specific HRQoL than non-cirrhotic patients (7 of 8 SF-36 scales, 8 of 9 LDSI symptoms). With respect to aetiology, we found that hemochromatosis patients experienced significantly more bodily pain and significantly more limitations due to emotional problems with increasing age than other aetiological groups. Hepatitis C patients showed a severely impaired mental health than other chronic liver patients that was significantly aggravated by interferon therapy. The relative contributions of selection, disease-specific factors and environmental factors to the findings in these patient groups were discussed.

Conclusions: This population-based study confirms the reduction in HRQoL in all liver patients and provides additional insight in the relative HRQoL level of specific liver patient groups and in the disease-specific HRQoL reduction in patients with hemochromatosis and hepatitis C.

Most studies on Health Related Quality of Life (HRQoL) of chronic liver patients have been conducted in clinical populations. Many studies assessed the quality of life of liver patients before and after transplantation using standardized quality of life questionnaires. One year after transplantation, most transplanted patients demonstrated a practically normal quality of life, although not as good as the general population [1]. Younossi et al studied the impact of disease severity on HRQoL and found an increasing impairment of generic HRQoL with worsening of disease severity from non-cirrhosis to advanced cirrhosis [2-4]. According to Marchesini et al, muscle cramp was the most relevant determinant of impaired health status in cirrhotic patients [5].

Studies reported variable results concerning the effect of aetiology on HRQoL. Several studies failed to find a significant difference in HRQoL between various aetiological groups, although one study demonstrated significantly less impairment in cirrhotic cholestatic liver patients than in cirrhotic patients with hepatocellular disease [2-5]. Furthermore, several studies compared the HRQoL of hepatitis B or C patients, which revealed that hepatitis C patients are significantly more impaired with respect to social functioning, energy and fatigue and role limitations due to physical problems, musculoskeletal pain and fatigue than hepatitis B patients [6,7].

These studies contributed substantially to our understanding of HRQoL in chronic liver patients. However, the majority of these studies were conducted in relatively small clinical populations or restricted to a certain disease stage, leaving limited space for correction for other potentially confounding factors of HRQoL. For that reason, there was still a need for large study on HRQoL in chronic liver patients that approached a population-based study.

Our collaboration with the Dutch liver patient association gave us the opportunity to study the HRQoL of a large general population of chronic liver patients. Our study population included sufficient variation regarding disease stage, aetiology, and other factors influencing HRQoL, permitting extensive adjustment for confounding factors. Based on this population we evaluated the impact of disease stage, liver transplant and aetiology on the HRQoL of chronic liver patients. Results of sub-studies addressing specific elements have been published previously in specific domains [8]. In this article we give a summary of our findings for the practicing hepatologist.

METHODS

Study population

In October 2000 all 2020 members of the Dutch liver patient association (Nederlandse Leverpatiënten Vereniging (NLV)) were approached for participation in this study and received a questionnaire by mail. The members included patients with a (history of) liver disease as well as non-patients who joined the NLV because of involvement with liver patients in family, circle of acquaintances or work. After two months non-responders received a new questionnaire. We closed the response period 5 months after the first mailing. Members gave their informed consent by confirming their willingness to participate in the first question of the questionnaire. Inclusion criteria were: 1) Informed consent and 2) aged 18 years or older at the moment of the study 3)

and having a (history of) liver disease. To preserve the anonymity of the participants, the NLV withheld the coding of respondent numbers and member names, while the researcher withheld the completed questionnaires. The protocol was conform the ethical guidelines of the 1996 Declaration of Helsinki and approved by the Ethics Committee of the Erasmus MC Rotterdam, the Netherlands.

Measurement instruments

One of the questionnaires we used for this study was the Short Form-36 (SF-36).

This generic quality of life instrument includes 8 multi-item scales on Physical Functioning, Role limitations due to Physical problems (Role Physical), Bodily Pain, General Health, Vitality, Social Functioning, Role limitations due to Emotional problems (Role Emotional) and Mental Health. The scale scores range from 0 to 100. A higher score indicates a better generic HRQoL. SF-36 data of Dutch healthy controls are available [9].

Objective physiological and clinical outcomes are poorly associated with the patient's health perceptions [10,11]. Therefore, additional information about the way liver patients experience their symptoms and how these specific symptoms affect their daily activities could be important for disease management. Moreover, this disease-specific information could be helpful in the interpretation of SF-36 findings. For this reason, we developed the Liver Disease Symptom Index. After validation we adjusted the initial version, which resulted in the Liver Disease Symptom Index 2.0 (LDSI). The LDSI 2.0 includes 18 items. Nine items measure severity of: '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'. Nine other items measure the hindrance of these symptoms to daily activities. All items have 'the last week' as time frame and are scored on a 5-point scale ranging from 'not at all' to 'to a high extent'. The LDSI has recently been validated in chronic liver patients at the outpatient clinic and in the NLV-population (Van der Plas, accepted for publication in Quality of Life Research).

A separate questionnaire was used to determine gender, age, education level, marital status, aetiology, duration of the liver disease, status of the liver disease(s) (cured, non-cured), presence of a liver transplant, presence of cirrhosis and presence or history of splenomegaly, ascites or oesophageal variceal bleedings, presence of oesophageal variceal bleedings or ascites in the year 2000, history of other complications of cirrhosis (liver cancer or encephalopathy), comorbidity (defined as the presence of diseases or disorders other than the liver disease which limit the respondent's daily functioning), medication use and the amount of hours per week spent on work and activities with and without physical effort.

Liver patient comparison groups

Due to the design of the study, respondents originated from all over the country and participated anonymously. Therefore, we based the categorisation of respondents in disease stage groups and aetiological groups on respondent-reported clinical characteristics.

For the categorisation in disease stage groups, we categorised respondents who reported absence of cirrhosis and did not ever have splenomegaly, ascites or

oesophageal variceal bleeding, as non-cirrhotic (NC). Respondents who reported cirrhosis *or* ever had splenomegaly *or* ever had ascites *or* ever had oesophageal variceal bleeding, but not in the year 2000 (the year of investigation), were classified as compensated cirrhotic (CC). Respondents who had had oesophageal variceal bleeding or ascites in the year 2000 were classified as decompensated cirrhotic (DC). Patients with a transplant history were assigned to the transplant group (LTX).

Furthermore, we categorised respondents in 5 aetiology groups, namely: Viral Hepatitis, Autoimmune Hepatitis, Cholestatic diseases, Hemochromatosis and other liver diseases. In this categorisation, transplanted respondents and respondents who considered themselves as cured were excluded. For the final study, we selected in the viral hepatitis group all patients with viral hepatitis B or viral hepatitis C.

We have validated the reliability of respondent-reported clinical characteristics, disease stage definitions and respondent-reported aetiologies in a pilot study conducted at our Hepatology outpatient clinic. Reported clinical characteristics and aetiologies demonstrated a good agreement between the test and the retest questionnaire (clinical characteristics: κ 0.85 [0.71, 0.94] to 0.97 [0.91, 1.03]; aetiologies: κ 0.71 [0.63, 0.79]) and a good agreement with hospital data (clinical characteristics: κ 0.68 [0.45, 0.90] to 0.71 [0.53, 0.88]; aetiologies: κ 0.63 [0.55, 0.78]).

The disease stage groups defined on the basis of clinical characteristics, showed a lower agreement with the disease stages in the patients' hospital records. The hospital data revealed that our initial disease stage definitions (which did not include the criterion of *recent* ascites or variceal bleeding), disregarded the possible temporary state of the decompensated cirrhotic stage: patients may become decompensated due to flare up of disease activity or inflammation, but can *reverse* to an apparently compensated state after treatment with diuretics or surgical interventions. In the current study, we included an extra item concerning: The presence of ascites or oesophageal variceal bleedings *in the year 2000* (the year of the study). This extra criterion distinguished recent decompensated cirrhotic patients from *reversed* decompensated cirrhotic patients.

In the NLV population 43 compensated cirrhotic were defined as *reversed* decompensated cirrhotic patients (based on the absence of ascites and/or variceal bleedings in the year 2000 and the use of diuretics and/or propanolol at the moment of our study). We found that the HRQoL level of these patients fitted the HRQoL level of the compensated cirrhotic group and not the HRQoL level of decompensated patients and categorised these patients as compensated cirrhotic patients.

Other comparison groups

We compared the HRQoL of chronic liver patients with the HRQoL of Dutch patients with other chronic diseases and Dutch healthy controls.

Patients with diabetes mellitus (n=60) originated from a sample of 4024 patients older than 18 years of age, approached by 60 general practitioners in the southern and eastern parts of The Netherlands [12]. Patients with cancer (n=485), originated from a sample of patients with breast, colorectal or lung cancer recruited from the outpatient clinics of departments of internal medicine and radiotherapy of the Antoni van Leeuwenhoek hospital in Amsterdam with a life expectancy of at least 4 months [9].

Healthy Dutch controls for the SF-36 (n=1715) originated from a nationwide, population-based health status survey with the standard version of the SF-36, conducted by the Dutch Organisation for Applied Scientific Research (TNO). Controls were adult members of a random sample of Dutch households, drawn from the national telephone registry [9].

Statistical methods

We used various regression methods to compare generic HRQoL (general linear regression), symptom severity (proportional odds models for ordinal outcome) and symptom hindrance (logistic regression) between disease stage groups (non-cirrhosis, compensated cirrhosis, decompensated cirrhosis and transplanted), between aetiological groups (viral hepatitis, autoimmune hepatitis, cholestatic diseases, hemochromatosis and other liver diseases) and between viral hepatitis groups (viral hepatitis B and C). SF-36 scales and LDSI items served as dependent outcome. The comparison groups served as independent determinants.

Differences, probabilities and odds ratios were corrected for gender, age, education level, disease stage, comorbidity, number of liver diseases per patient, use of liver disease medication and use of psychopharmaca. In case of comparisons between viral hepatitis subgroups, we also corrected for average number of hours paid work conducted per week.

We used general linear regression to estimate the differences in generic HRQoL or fatigue between chronic liver patients and healthy controls. Differences were corrected for gender, age, education level and marital status.

In the results section, a SF-36 scale score difference between a subgroup and the reference group has been expressed as percentage. A percentage expresses how much higher or lower a scale score of a subgroup is relatively to the reference group.

RESULTS

Selection of the population

Of the 2020 members approached for this survey, 1617 members returned the questionnaires. Of these, 374 respondents were non-patient member, who joined the NLV because of involvement with liver patients in family, circle of acquaintances or work. In total 1243 patients had a (history of) liver disease. We excluded 21 patients who did not give informed consent according to the regulations of the Ethics Committee. Forty-seven respondents were excluded due to their age of <18 years. In total 1175 respondents were included in the analysis.

Population characteristics

Table 1 shows the demographic and clinical characteristics of the NLV population.

A large majority (90%) of the respondents reported The Netherlands as country of birth. In total 76% of these respondents spent on average 24.5 (SD ± 16.3) hours per week on a paid and/or voluntary job and spent on average 6.5 (SD ± 6.7) hours per week on physical activities like walking, cycling and gardening. The viral hepatitis groups included mostly hepatitis C (66.9%) and B (29.5%). The cholestatic group

Table 1: Demographic and clinical characteristics of liver patients and controls.

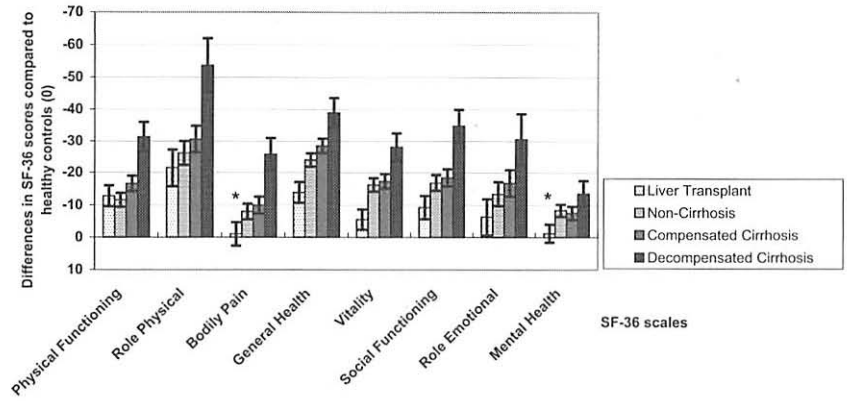
Characteristic	NLV liver pt population (n=1175)	Dutch SF-36 controls (n=1715)
Age		
Mean age ± SD, yr.	49 ± 12.7	48 ± 17
Gender		
Men, n (%)	497 (42.3)	967 (56.6)
Women, n (%)	678 (57.7)	740 (43.4)
Education		
None/elementary education	109 (9.3)	212 (12.6)
Lower secondary education	446 (38.1)	569 (33.8)
Upper/post secondary education	329 (28.1)	477 (28.4)
1st/2nd stage tertiary education	287 (24.5)	424 (25.2)
Marital status		
Married / Living together	866 (74.0)	1278 (74.8)
Single / Widow(er) / Divorced	304 (26.0)	431 (25.2)
Disease stage		Not applicable
Non-cirrhosis	489 (42.5)	
Compensated cirrhosis	391 (34.0)	
Decompensated cirrhosis	84 (7.3)	
Liver transplanted	186 (16.2)	
Aetiology		Not applicable
Viral hepatitis	275 (24.6)	
Autoimmune hepatitis	142 (12.7)	
PBC/PSC	175 (15.7)	
Hemochromatosis	98 (8.8)	
Other liver diseases	171 (15.3)	
Liver transplants	186 (16.6)	
Liver diseases reported as cured	71 (6.4)	

included patients with primary biliary cirrhosis (63.4%) and primary sclerosing cholangitis (36.6%). The group 'other liver diseases' included patients with parenchymatous non-viral liver diseases (35.1%), vascular deformations (14.6%), congenital metabolic liver diseases (24.6%) and a mix of congenital anatomic liver diseases, benign and malignant malformations, cholelithiasis, and secondary biliary cirrhosis (25.7%). Fifty-seven respondents (6.2%) were classified as missing. In total 102 (8.7%) patients reported more than 1 liver disease. Sixty-eight percent (n=746) reported comorbidity apart from their liver disease.

Impact of disease stage and liver transplantation on HRQoL

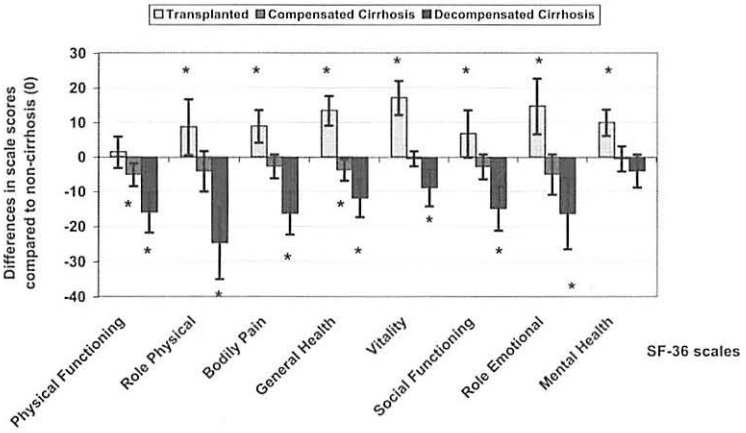
Figure 1a shows the differences in SF-36 scale scores between non-cirrhotic, compensated cirrhotic, decompensated cirrhotic and transplanted patients and the scale scores of Dutch healthy controls, corrected for gender, age, education level and marital status. Scale scores of liver patients were all significantly impaired and

Figure 1a: Differences in SF-36 scale scores between transplanted, non-cirrhotic and cirrhotic liver patients and healthy controls (reference group, set to zero). Differences are corrected for gender, age, education level and marital status.



Negative differences: Scale score of subgroup is lower (worse) than the scale score of healthy controls
*) Scale score in subgroup is *not* significantly lower (worse) than the scale score of healthy controls.

Figure 1b: SF-36 scale score differences between non-cirrhotic (reference, set to zero), compensated cirrhotic, decompensated cirrhotic and transplanted liver patients. Differences are corrected for gender, age, education level, aetiology, comorbidity, use of liver disease medication and use of psychopharmaca.



Negative differences: Scale score of subgroup is lower (worse) than the scale score of non-cirrhotic patients.
Positive differences: Scale score of subgroup is higher (better) than the scale score of non-cirrhotic patients.
*) Scale score of subgroup is significantly lower or higher than the scale score of non-cirrhotic patients ($p < 0.05$).

differences between liver patients and healthy controls increased with an increasing severity of disease stage. Transplanted patients showed in 6 of the 8 SF-36 scales a significantly worse generic HRQoL. Scores of transplanted liver patients were 8.0% (vitality) to 31% (limitations in daily activities due to physical problems (role physical scale)) lower than the scores of healthy controls.

Differences between these three disease stages and the transplanted group were assessed in more detail after correction for gender, age, education level, aetiology, comorbidity, use of liver disease medication and use of psychopharmaca (figure 1b). Transplanted liver patients revealed a 2% (physical functioning) to 36% (general health) better generic HRQoL compared to non-cirrhotic patients. Non-cirrhotic and compensated cirrhotic patients barely showed significant differences, but decompensated cirrhotic patients reported a 6% (mental health) to 66% (role physical) reduction in generic HRQoL compared to non-cirrhotic patients.

Similar observations across these subgroups were found with respect to disease-specific HRQoL [8].

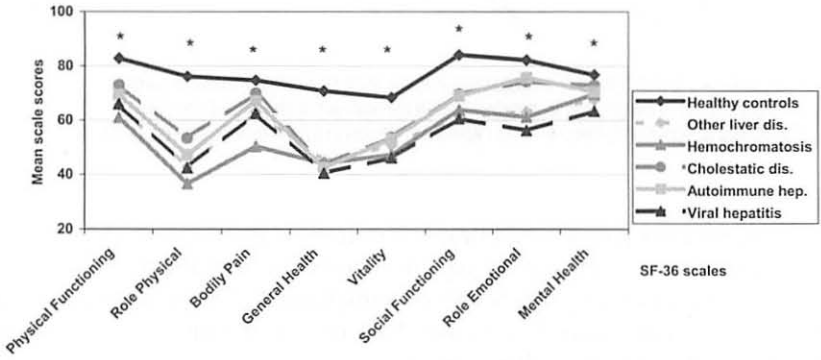
Impact of aetiology on HRQoL

Figure 2a shows the generic HRQoL measured in the various liver disease aetiological groups and healthy controls, corrected for gender, age, education level and marital status. All aetiological groups showed a significantly lower generic HRQoL than healthy controls; the generic HRQoL of patients with hemochromatosis and viral hepatitis was most affected, both with on average 30% lower scores than healthy controls.

Figure 2b shows the differences in generic HRQoL between the various aetiological groups after further correction for baseline factors such as disease stage, comorbidity, number of liver diseases, use of liver disease medication and use of psychopharmaca, and confirms the differences between aetiological groups shown in figure 2a.

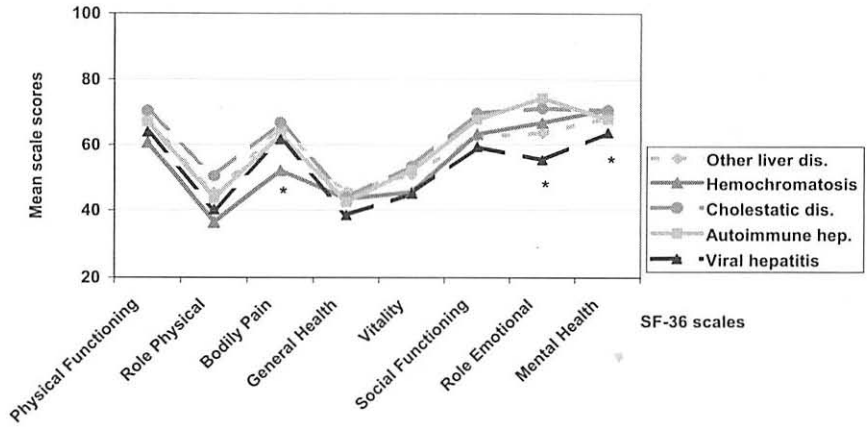
Hemochromatosis patients experienced significantly more bodily pain (16%-23%) than other aetiological groups, while the disease-specific LDSI pointed out that hemochromatosis patients had significantly higher odds ratios of severe joint pain relatively to other aetiological groups (relatively to: Viral hepatitis: OR 2.27 [1.44, 3.57], Autoimmune hepatitis OR 1.89 [1.11, 3.22], Cholestatic diseases: OR 4.28 [2.59, 7.05], Other liver diseases: OR 3.37 [2.03, 5.58]).

Figure 2a: Mean SF-36 scales scores for various aetiological groups and healthy controls. Means are corrected for gender, age, education level and marital status.



*) On all SF-36 scales, aetiological groups have a significantly impaired HRQoL compared to healthy controls ($0.000 \leq p \leq 0.045$).

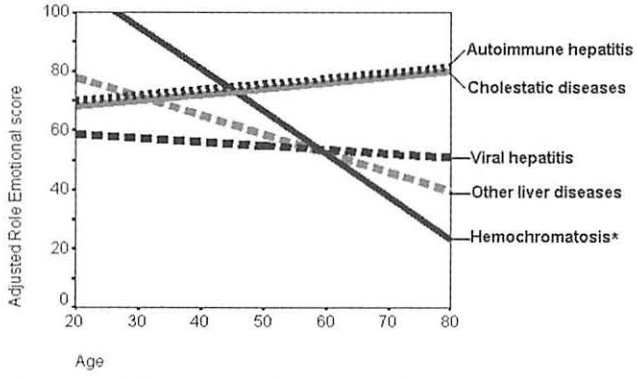
Figure 2b: Mean SF-36 scales scores for various aetiological groups. Means are corrected for gender, age, education level, disease stage, comorbidity, number of liver diseases, use of liver disease medication, use of psychopharmaca.



*) Hemochromatosis patients have significantly more bodily pain than all other aetiological groups ($0.000 \leq p \leq 0.001$). Viral hepatitis patients have a significantly worse role emotional functioning ($0.000 \leq p \leq 0.052$) and significantly worse mental health than most other aetiological groups ($0.001 \leq p \leq 0.06$).

Furthermore, the limitations in daily activities due to emotional problems (role emotional functioning) of hemochromatosis patients increased with increasing age (figure 3). The effect of age on experienced limitations during daily activities due to emotional problems was significantly stronger in hemochromatosis patients than the age effect in other aetiological groups (p=0.000 to p=0.006).

Figure 3: The adjusted Role Emotional score by age (in years) for patients with autoimmune hepatitis, cholestatic diseases, viral hepatitis, other liver diseases and hemochromatosis. Adjusted for gender, age, education level, disease stage, comorbidity, number of liver diseases, use of liver disease medication and use of psychopharmaca.



*) The steep decline in role emotional scores, especially observed in hemochromatosis patients (n=98) indicates: significantly more limitations in work or other daily activities due to emotional problems with increasing age than in other aetiological groups ($p \leq 0.006$).

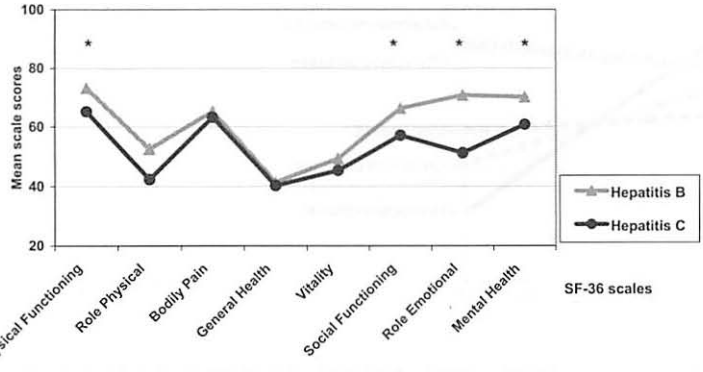
Viral hepatitis patients showed significantly more limitations due to emotional problems (13%-26%) and significantly worse mental health (7-10%) than other aetiological groups.

The disease-specific LDSI specifically pointed out that viral hepatitis patients had significantly higher OR's of severe worry about the family situation, severe depression and severe fear of complications relatively to all other aetiological groups (Worry: OR over all: 2.39 [1.76, 3.24]; Depression: OR over all: 2.01 [1.48, 2.74]; Fear: OR over all: 2.09 [1.54, 2.87]).

The viral hepatitis group included 74 hepatitis B patients and 184 hepatitis C patients. Hepatitis C patients demonstrated significantly lower SF-36 scores regarding physical functioning (-11%), social functioning (-14%), role emotional functioning (-28%) and mental functioning (-14%) than hepatitis B patients (figure 4a). More specifically, the LDSI showed in hepatitis C patients significantly higher odds ratios of severe worry about the family situation (OR 1.84, CI 95% [1.04, 3.29]) and severe depression (OR 2.56, CI95% [1.34, 4.87]) than in hepatitis B patients.

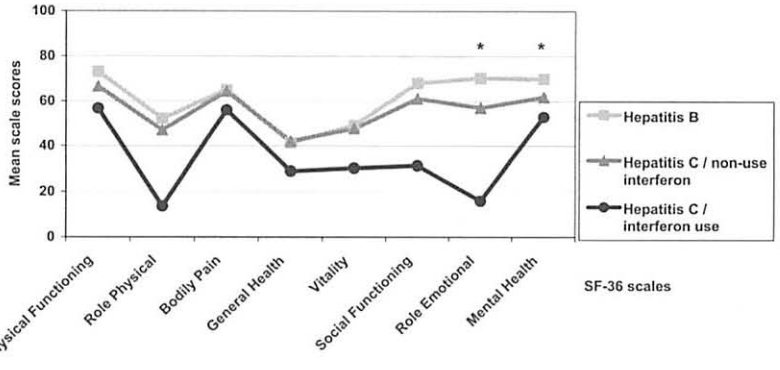
Additionally, we compared the HRQoL of hepatitis B patients with hepatitis C patients with interferon therapy (n=22) and without interferon therapy (n=161) at the moment of the study (figure 4b). Hepatitis C patients with interferon showed significant impairments on almost all SF-36 scales. The most severe impairment concerned the amount of limitations due to emotional problems (score: -77% relatively to hepatitis B). Hepatitis C patients *without* interferon therapy also reported a significantly lower (worse) mental health score (-12%) and role emotional score (-19%) than hepatitis B patients. In line with these findings, both interferon users and non-users showed a significantly higher odds ratio of severe depression than hepatitis B patients (OR users: 10.67 [3.72, 30.57], OR non-users: 2.13 [1.10, 4.13]) in the LDSI.

Figure 4a: Mean SF-36 scales scores for viral hepatitis B (n=74) and viral hepatitis C patients (n=184). Means are corrected for gender, age, education level, disease stage, comorbidity, number of liver diseases, use of liver disease medication, use of psychopharmaca and average number of hours paid work per week.



*) Viral hepatitis C patients demonstrated a significantly worse physical functioning (p=0.022), social functioning (p=0.038), role emotional functioning (p=0.003) and mental functioning (p=0.001) than patients with viral hepatitis B.

Figure 4b: Mean SF-36 scales scores for viral hepatitis B (n=74) and viral hepatitis C patients with interferon therapy (n=22) and without interferon therapy (n=161). Means are corrected for gender, age, education level, disease stage, comorbidity, number of liver diseases, use of liver disease medication, use of psychopharmaca and average number of hours paid work per week.



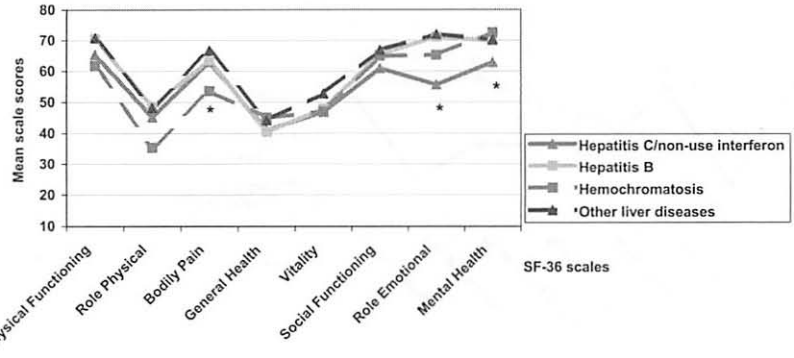
*) Mean scales scores of hepatitis C patients without interferon therapy, were only significantly lower (worse) than scale scores of hepatitis B patients with respect to role emotional functioning (p=0.041) and mental health (p=0.001).
Mean scale scores of hepatitis C patients with interferon therapy, were significantly lower (worse) than all mean scale scores of hepatitis B patients ($0.000 \leq p \leq 0.029$), except regarding bodily pain.
In hepatitis C patients with interferon therapy, scores regarding vitality, social functioning, role emotional functioning and role physical functioning were significantly worse than in hepatitis C patients without interferon therapy ($p \leq 0.002$).

HRQoL of chronic liver patients compared to non-liver patients

In figure 5a, we compared the corrected generic HRQoL measured by the SF-36 between patients with hepatitis B, hepatitis C (without interferon therapy), hemochromatosis and other chronic liver patients (including: cholestatic diseases, autoimmune hepatitis and remaining liver diseases). Hepatitis C patients without interferon showed significantly lower (worse) scores with respect to mental health (on average -11%) and role emotional functioning (on average -23%) than most other liver patient subgroups. The role emotional score of hemochromatosis patients was not significantly different. Hemochromatosis patients still showed significantly more pain than hepatitis C without interferon, hepatitis B and the other chronic liver patients combined.

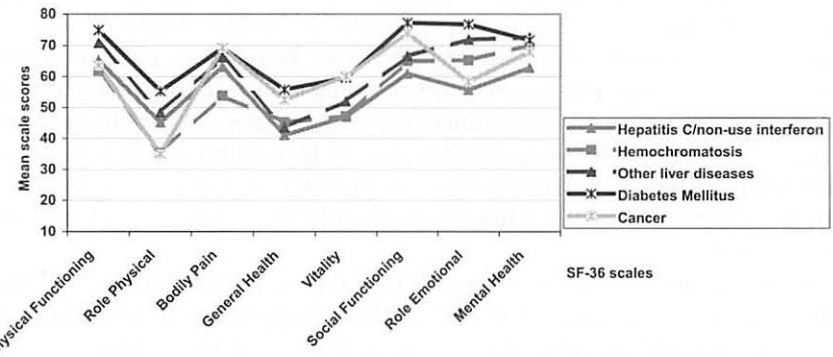
In figure 5b, we used the crude SF-36 scale means for cancer and diabetes mellitus to put the generic HRQoL of chronic liver patients in perspective. Also compared to patients with diabetes mellitus or cancer, hepatitis C patients without interferon therapy reported lower scores regarding limitations due to emotional problems (-33% compared to diabetes mellitus and -5% compared to cancer patients) and mental health (-12% compared to diabetes mellitus and -8% compared to cancer patients), whereas hemochromatosis patients reported lower scores regarding bodily pain (-22% compared to diabetes mellitus and cancer).

Figure 5a: Mean SF-36 scales scores of patients with viral hepatitis C without interferon therapy, viral hepatitis B, hemochromatosis and other liver diseases (cholestatic diseases, autoimmune hepatitis, remaining liver diseases). Means are corrected for gender, age, education level, disease stage, comorbidity, number of liver diseases, use of liver disease medication, use of psychopharmaca and average number of hours paid work per week.



*) Also compared to most other aetiological groups, hepatitis C patients without interferon therapy showed a significantly worse role emotional functioning ($0.000 \leq p \leq 0.014$) and a worse mental health ($0.000 \leq p \leq 0.019$). Role emotional functioning was not significantly different between hepatitis C patients and hemochromatosis patients. Hemochromatosis patients still showed significantly more bodily pain than other groups ($p \leq 0.012$).

Figure 5b: Mean SF-36 scales scores of patients with viral hepatitis C without interferon therapy, hemochromatosis and other liver diseases (cholestatic diseases, autoimmune hepatitis, viral hepatitis B and remaining liver diseases) corrected for gender, age, education level, disease stage, comorbidity, number of liver diseases, use of liver disease medication, use of psychopharmaca and average number of hours paid work per week. Corrected SF-36 scale scores of chronic liver patients are compared with crude SF-36 scale scores of patients with diabetes mellitus and cancer.



Also compared to patients with diabetes mellitus or cancer, hepatitis C patients without interferon therapy reported more limitations due to emotional problems and a worse mental health. Hemochromatosis patients reported more bodily pain than patients with diabetes mellitus and cancer.

DISCUSSION

Main findings

In this survey among Dutch liver patients, approaching a population-based study, the HRQoL of specific liver patient subgroups has been put in perspective with other liver patients, non-liver patients and healthy controls. On the one hand, this study confirmed findings of smaller clinical studies; on the other hand new findings emerged thanks to the large size of the study population and the use of both a generic and a disease-specific questionnaire.

Transplanted liver patients demonstrated a better HRQoL than non-cirrhotic and cirrhotic liver patients, but did not equal the HRQoL level of healthy controls. Non-cirrhotic and compensated cirrhotic patients barely showed significant differences whereas decompensated patients showed the worst HRQoL on all dimensions. Hemochromatosis patients exhibited significantly more bodily pain and with increasing age more limitations due to emotional problems than other aetiological groups. Viral hepatitis C patients without interferon therapy, showed a significantly worse role emotional functioning and mental health than other chronic liver and non-liver patients; interferon therapy was associated with a further significant reduction in HRQoL

Limitations and advantages of the study

Our study had advantages but also limitations compared to earlier and mostly clinical studies. On the one hand, the large study population and the amount of variation regarding disease stage, aetiology and other factors allowed analyses with extensive correction for confounders; additionally the study design prevented referral bias. On the other hand, members of the Dutch liver patients association may have been a selected population of chronic liver patients, and respondents may have been selection of relatively healthy patients.

A final limitation is that for data on clinical characteristics and aetiology we depended on respondent-reported clinical data. To test the potential bias of the latter, we performed a pilot study that showed a good agreement between respondent-reported clinical and aetiological data and data derived from the hospital records, allowing us to rely on respondent-reported data.

Explanation of the findings

Impact of disease stage

Non-cirrhotic and compensated cirrhotic patients showed small and often non-significant differences in generic disease-specific HRQoL. This finding confirmed earlier reports regarding the absence of subjective complaints in compensated cirrhotic patients [13]. In LDSI items, large proportions of non-cirrhotic as well as compensated cirrhotic patients reported absence of symptoms (on average 57% and 53% respectively). However, this may also indicate that the LDSI lacks sensitivity to detect small differences between these groups.

Decompensated cirrhotic patients showed the worst HRQoL in all dimensions. The HRQoL level in decompensated cirrhotic patients may have been overestimated by the classification of *reversed* decompensated cirrhotic patients; i.e. patients with ascites and/or variceal bleeding in the past but not in the year of the study using diuretics and/or propanolol at the moment of our study. We included these patients in the compensated cirrhotic group because their HRQoL level equalled the HRQoL level of compensated cirrhotic patients. Inclusion of *reversed* decompensated cirrhotic patients in the decompensated cirrhotic group would have reduced the abnormalities in both the compensated and the decompensated group.

Impact of liver transplantation

We found that transplanted liver patients demonstrated a far better HRQoL than non-cirrhotic and cirrhotic liver patients. This difference in HRQoL might be explained by the difference in acquired social support. Social support is considered as one of the essentials of the transplant program as it influences post-transplant survival and HRQoL [14-17]. In other chronic liver patients, social support may be less regarded as an essential part of treatment. Furthermore, the high HRQoL level in transplanted patients may have been biased by selection of emotionally stable patients associated with the selection of transplantation candidates [17-19].

Our study confirmed earlier findings that the HRQoL of transplanted patients does not equal the HRQoL of healthy controls [20,21]. After the initial sense of rebirth, the patients' perception of good health may be affected by fear of becoming ill again, medical complications and psychological problems of accepting their new bodily integrity [22]. Nonetheless, other studies associated increasing time since transplantation with improvement of HRQoL, although selection of survivors may have biased these findings [1,23].

Impact of hemochromatosis

Hemochromatosis patients revealed unexpected results with respect to pain and a deteriorating role emotional functioning with increasing age. In twenty to fifty percent of the hemochromatosis patients older than 50 years of age, an irreversible arthritis develops in finger joints that often progresses to other joints [24-27]. Pain caused by arthritis, may have played a part in the worsening emotional functioning with increasing age. Our data showed a significant positive relation between bodily pain and role emotional functioning in hemochromatosis patients.

Impact of viral hepatitis C

We showed that hepatitis C patients without interferon therapy revealed an impaired emotional functioning and mental health compared to other liver patients and non-liver patients. Interferon therapy significantly aggravated these abnormalities. These findings are supported by earlier reports [28-32]. However, the emotional functioning and mental health in both hepatitis C groups might be confounded by a chronic condition predating the onset of viral infection and the use of interferon [31]. A recent study reported that almost 50% of the hepatitis C patients used anti-depressant in the pre-diagnostic period, against 38.4% in controls ($p < 0.001$) [33]. Moreover, depressive symptoms have been associated with intravenous drug use, whereas intravenous

drug use has been associated with hepatitis C infection. Therefore, intravenous drug use could confound the mental health in hepatitis C patients [6,34]. In our study we did not investigate the intravenous drug history of patients.

Other factors that may have influenced the role emotional functioning and mental health of hepatitis C patients are the diagnosis of the hepatitis C associated liver disease, feelings of stigmatisation or biological mechanisms. Hepatitis C infected individuals are relatively young and may suffer from concerns about their insecure and potentially fatal prognosis [35]. Hepatitis C awareness campaigns may support or strengthen these concerns, though around 80% of all chronic hepatitis C patients will never develop cirrhosis and 95% will never develop hepatocellular carcinoma [24]. Furthermore, a hepatitis C status could have a disruptive effect on social networks due societal fears of virus transmission and the association of the disease with intravenous drug use [36,37]. These feelings of stigmatisation are significantly associated with depression, anxiety and worsened quality of life [38]. Finally, the impaired mental health could be due to virus induced altered brain metabolism leading to cognitive impairments that affect daily performance and may indirectly lead to depression and anxiety. Hepatitis B patients demonstrated less signs of altered cerebral metabolism than hepatitis C patients [39-43].

Interaction between physical and emotional/mental elements of HRQoL

While seeking an explanation for HRQoL findings in patients groups, we should not exclude the potential interaction between physical and emotional/mental elements of HRQoL. According to the *disability hypothesis*, negative feelings like depression and fear could *follow* from the adverse consequences of accumulating health problems. In hemochromatosis patients, this hypothesis could support that an important disease-specific factor such as progressive pain may have played a part in the worsening role emotional functioning with increasing age. In contrast, the *psychosomatic hypothesis*, which hypothesizes that severe negative feelings could *cause or worsen* physical health problems, points at the possible consequences of impaired emotional and mental health as found in hepatitis C patients [44-46].

Implications

Our findings underline the importance of multidimensional liver disease management. During consultations, besides attention for physical impairments of chronic liver patients, more attention is needed for psychological impairment and the potential interrelations between these two dimensions. Psychological interventions could lead to reduction in psychological morbidity as well as physical morbidity [47]. Therefore, psychological guidance of vulnerable groups like hemochromatosis and hepatitis C patients should be considered. Randomised clinical trials evaluating the effect of psychological interventions on physical and psychological impairments should be the next step for improvement of liver disease management.

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7

Summary

This thesis describes the differences in Health Related Quality of Life (HRQoL) between liver patient subgroups, originating from a general population of chronic liver patients. Furthermore, this thesis describes the construct validity of the Liver Disease Symptom Index 2.0 (LDSI), a disease-specific questionnaire. The results are based on data obtained in a cross-sectional study conducted by the Department of Gastroenterology and Hepatology and the Department of Epidemiology and Biostatistics of the Erasmus Medical Center Rotterdam in collaboration with the Dutch liver patient association (Nederlandse Leverpatiënten Vereniging (NLV)) and the Department of Medical Psychology and Psychotherapy of the Erasmus Medical Center Rotterdam. This study was supported by the Dutch Digestive Diseases Foundation.

AIMS

The first aim of this study was to investigate the impact of disease stage (non-cirrhosis, compensated cirrhosis and decompensated cirrhosis), liver transplantation, aetiology (viral hepatitis, autoimmune hepatitis, cholestatic diseases, hemochromatosis and other liver diseases) and more specifically the impact of viral hepatitis B and C on the HRQoL of chronic liver patients.

Our second aim was to evaluate the construct validity of the LDSI. The construct validity assesses the degree in which the LDSI measured what it was supposed to measure. We evaluated if expected relations between LDSI items and specific scales of the Short Form-36 (SF-36) or Multidimensional Fatigue Index-20 (MFI-20) could be confirmed. Furthermore, we investigated if specific LDSI items (the LDSI included 9 items concerning severity of specific symptoms and 9 items concerning the hindrance of these specific symptoms in daily activities) could be considered as redundant.

METHODS

In total 2020 members of the NLV received once a questionnaire by mail. The questionnaire included the (Dutch) generic SF-36 version 1.2, the disease-specific LDSI, the domain-specific MFI-20 and a background questionnaire for the collection of demographic and clinical information. Of all members approached, 1617 members returned the questionnaires. In total 1243 respondents had a (history of) liver disease. According to the regulations of the Ethics Committee of the Erasmus Medical Center Rotterdam, we excluded 21 respondents who did not give informed consent. Furthermore, we excluded forty-seven respondents younger than 18 years of age. In total 1175 respondents were included in the analysis.

RESULTS

Validity of the Liver Disease Symptom Index 2.0 (chapter 2)

In a pilot study conducted at the outpatient clinic of our Department of Gastroenterology and Hepatology, we pointed out that the LDSI 2.0 had an adequate feasibility and reliability. With respect to the construct validity evaluated in the study described in this thesis, we found that specific LDSI items mostly showed expected moderate correlations with specific SF-36 or MFI-20 scales. The moderateness of these correlations additionally indicated that the LDSI provided HRQoL information complementary to the HRQoL information provided by the SF-36 and the MFI-20.

Within the LDSI, some symptom severity items showed a high correlation with their accompanying symptom hindrance item, suggesting that one item of this pair was redundant. To investigate this, we estimated of each symptom severity item and each symptom hindrance item the impact on a poor generic HRQoL, measured by the SF-36. We found that symptom hindrance items related differently to generic HRQoL of patients than symptom severity items. This indicated that symptom severity items and symptom hindrance items measured other aspects of HRQoL. Therefore, we concluded that it is psychometrically sound to include both symptom severity items and symptom hindrance items into the LDSI 2.0.

Impact of disease stage and liver transplantation on HRQoL (chapter3)

We evaluated the impact of liver transplantation and disease stage on the generic and disease-specific HRQoL and fatigue of chronic liver patients, corrected for among others gender, age and aetiology. The HRQoL of transplanted liver patients sometimes approached the HRQoL level of healthy controls but was mostly significantly impaired. Nevertheless, the generic and disease-specific HRQoL of transplanted patients was significantly less affected than in non-cirrhotic and cirrhotic liver patients. Non-cirrhotic and compensated cirrhotic patients both revealed a significantly impaired HRQoL compared to healthy controls, although we found few significant HRQoL differences between these two groups. In contrast, decompensated cirrhotic patients showed a significantly worse disease-specific and generic HRQoL and fatigue than non-cirrhotic and compensated cirrhotic patients, transplanted patients and healthy controls. A subgroup of *reversed* decompensated cirrhotic patients, fitted with respect to their generic and disease-specific HRQoL and fatigue better in the compensated cirrhotic group than in the decompensated cirrhotic group.

Impact of aetiology on HRQoL (chapter 4)

We investigated the impact of aetiology on generic and disease-specific HRQoL and fatigue of chronic liver patients, corrected for among others gender, age and disease stage.

Prominent differences between aetiological groups were especially found in comparisons with viral hepatitis and hemochromatosis patients. Hemochromatosis patients experienced significantly more joint pain than other aetiological groups, whereas their role emotional functioning (limitations in daily activities due to emotional problems) worsened significantly with increasing age. Viral hepatitis

patients showed significantly more limitations due to emotional problems and significantly worse mental health than other aetiological groups. In the LDSI, viral hepatitis patients revealed significantly higher odds ratios of severe worry about the family situation, severe depression and severe fear of complications than other aetiological groups.

Impact of viral hepatitis B and C on HRQoL (chapter 5)
We evaluated the impact of viral hepatitis B and C on generic and disease-specific HRQoL and fatigue of chronic liver patients, corrected for among others gender, age and disease stage. Hepatitis C patients showed a significantly worse physical-, social- and role emotional functioning, a significantly worse mental health, a more severe reduction in motivation and significantly higher odds ratios of severe depression and severe worry about the family situation than hepatitis B patients. When we categorised hepatitis C patients into groups with and without interferon therapy, hepatitis C patients without interferon therapy showed an impaired role emotional functioning and mental health compared to hepatitis B patients. Interferon therapy significantly aggravated this impaired emotional functioning and mental health. Moreover, interferon led to additional impairments of other generic and disease-specific HRQoL dimensions and to significantly more fatigue. Also compared to other chronic liver patients and patients with diabetes mellitus or cancer, both hepatitis C subgroups reported more limitations due to emotional problems and a worse mental health.

DISCUSSION

Integration of sub-study findings (chapter 6)
This study, conducted in a large *non-clinical* population approaching a population based study, confirms findings of earlier *clinical* studies in subgroups of liver disease. Additionally, this study puts the impaired HRQoL of liver patient subgroups in perspective. Transplanted patients revealed a significantly better HRQoL than non-cirrhotic and cirrhotic liver patients, while decompensated cirrhotic patients showed the worst HRQoL. Hemochromatosis patients reported significantly more pain than other aetiological groups and a progressive impairment of role emotional functioning with increasing age. In hepatitis C patients, role emotional functioning and mental health proved to be important contributors of impaired HRQoL, especially in hepatitis C patients with interferon therapy.

Selection, disease-specific factors or environmental factors could explain these findings. The high HRQoL level in transplanted patients may have been biased by selection of emotionally stable patients associated with the stringent selection of transplantation candidates. In hemochromatosis patients, an important disease specific factor such as pain may have played a part in the worsening emotional functioning with increasing age; depression or fear could follow from adverse consequences of accumulating health problems (disability hypothesis), while

the dose-response relationship between pain and quality of life may have led to increasing emotional distress in these patients.

With respect to the impaired role emotional functioning and mental health in hepatitis C patients, the explanatory value of selection as well as disease-specific or environmental factors should be considered. The real relationship between mental health and hepatitis C could be obscured by selection of patients with psychiatric morbidity prior to the hepatitis C diagnosis. Additionally, history of intravenous drug use could be an important confounder as this factor might be related to psychiatric morbidity, independent of the hepatitis C infection. Finally, the hepatitis C diagnosis its self, experienced limitations due to the hepatitis C infection such as impaired concentration, feelings of social stigma and fear for future complications of the disease may have played a part in the impaired emotional functioning and mental health of this patient group.

Our findings underline the importance of multidimensional liver disease management in chronic liver patients. 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.

8

Samenvatting

Dit proefschrift beschrijft de verschillen in gezondheid gerelateerde kwaliteit van leven (HRQoL) tussen verschillende groepen leverpatiënten afkomstig van een algemene leverpatiënten populatie. Daarnaast beschrijft dit proefschrift de construct validiteit van de Liver Disease Symptom Index 2.0 (LDSI), een ziekte-specifieke vragenlijst.

De resultaten zijn gebaseerd op een cross-sectioneel onderzoek uitgevoerd door de afdeling Maag- Darm- Leverziekten en de afdeling Epidemiologie en Biostatistiek van het Erasmus Medisch Centrum Rotterdam in samenwerking met de Nederlandse Leverpatiënten Vereniging (NLV) en de afdeling Medische Psychologie en Psychotherapie van het Erasmus Medisch Centrum Rotterdam. Het onderzoek werd financieel gesteund door de Maag Lever Darm Stichting.

DOELSTELLINGEN

Het eerste doel van dit onderzoek was het evalueren van de invloed van ziekte stadium (niet-cirrose, gecompenseerde cirrose en gedecompenseerde cirrose), levertransplantatie, etiologie (virale hepatitis, autoimmuun hepatitis, cholestatische leverziekten, hemochromatose en overige leverziekten) en meer specifiek de invloed van virale hepatitis B en C op de HRQoL van chronische leverpatiënten. Het tweede doel was de evaluatie van de construct validiteit van de LDSI. De construct validiteit beoordeelt in hoeverre de LDSI meet wat het zou moeten meten. We evalueerden of verwachte relaties tussen LDSI items en specifieke schalen van de Short Form-36 (SF-36) en de Multidimensionele Vermoeidheids Index-20 (MVI-20) konden worden bevestigd. Daarnaast werd onderzocht of specifieke LDSI items (de LDSI bestaat uit 9 items betreffende de ernst van specifieke symptomen en 9 items betreffende de hinder van deze specifieke symptomen tijdens dagelijkse activiteiten) als overbodig konden worden beschouwd.

METHODEN

In totaal 2020 leden van de NLV ontvingen eenmalig een vragenlijst via de post.

De vragenlijst bestond uit de (nederlandse) generieke SF-36 versie 1.2, de ziekte-specifieke LDSI, de domein-specifieke MVI-20 en een achtergrond vragenlijst voor de verzameling van demografische en klinische gegevens. Van alle benaderde leden, retourneerden 1617 leden de vragenlijst, waarvan 1243 respondenten een leverziekte of een leverziekte geschiedenis hadden. In overeenstemming met de afspraken gemaakt met Ethische Commissie van het Erasmus Medisch Centrum Rotterdam, excludeerden wij 21 respondenten die geen informed consent hadden gegeven. Bovendien excludeerden we 47 respondenten die jonger waren dan 18 jaar. In totaal namen 1175 respondenten deel aan de analyse.

RESULTATEN

Validiteit van de Liver Disease Symptom Index 2.0 (hoofdstuk 2)
In een pilot onderzoek, uitgevoerd op de polikliniek van de afdeling Maag- Darm-Leverziekten toonden wij aan dat de LDSI een adequate uitvoerbaarheid en betrouwbaarheid heeft. Met betrekking tot de construct validiteit geëvalueerd in het onderzoek beschreven in dit proefschrift, vonden wij dat specifieke LDSI items verwachte correlaties met specifieke SF-36 of MVI-20 schalen vertoonden. Het feit dat deze correlaties laag tot gematigd waren gaf aan dat de LDSI HRQoL informatie oplevert welk complementair is aan de HRQoL informatie geleverd door de SF-36 en de MFI-20.

Binnen de LDSI vertoonden sommige 'ernst van symptoom'-items hoge correlaties met het bijbehorende 'hinder van symptoom'-item, hetgeen suggereerde dat één van de twee items van het item-paar overbodig was. Om dit nader te onderzoeken, schatten we van elk 'ernst van symptoom'-item en elk 'hinder van symptoom'-item zijn effect op slechte generieke HRQoL, gemeten met de SF-36. We vonden dat de relatie tussen 'hinder van symptoom'-items en slechte generieke HRQoL anders was dan de relatie tussen 'ernst van symptoom'-items en slechte generieke HRQoL. Dit gaf aan dat 'ernst van symptoom'-items en 'hinder van symptoom'-items andere aspecten van HRQoL meetten. Met deze reden concludeerden wij dat het psychometrisch verantwoord is om zowel 'ernst van symptoom'-items als 'hinder van symptoom'-items in de LDSI 2.0 te includeren.

Effect van ziekte stadium en levertransplantatie op HRQoL (hoofdstuk 3)
We evalueerden het effect van ziekte stadium en levertransplantatie op de generieke en ziekte-specifieke HRQoL en vermoeidheid van chronische leverpatiënten, gecorrigeerd voor onder andere geslacht, leeftijd en etiologie.

De HRQoL van getransplanteerde patiënten benaderde soms het HRQoL niveau van gezonde controles, maar was meestal significant verminderd. Desalniettemin was de generieke en ziekte-specifieke HRQoL van getransplanteerde patiënten significant minder verstoord dan in patiënten met en zonder cirrose. Patiënten zonder cirrose en patiënten met gecompenseerde cirrose vertoonden beiden een significant verminderde HRQoL in vergelijking met gezonde controles. Onderling vertoonden deze twee subgroepen nauwelijks significante HRQoL verschillen. Gedecompenseerde cirrose patiënten vertoonden een significant slechtere generieke en ziekte-specifieke HRQoL en een ernstigere vermoeidheid dan patiënten zonder cirrose, patiënten met gecompenseerde cirrose, getransplanteerden en gezonde controles. Een subgroep van patiënten die ooit gedecompenseerde cirrose hadden, maar onder invloed van medicatie en/of chirurgische interventies weer *gerecompenseerd* waren, lieten zien dat hun HRQoL (generiek en ziekte-specifiek) en vermoeidheid meer overeenkomst vertoond met de HRQoL en vermoeidheid van gecompenseerde cirrose patiënten dan met de HRQoL en vermoeidheid van gedecompenseerde cirrose patiënten.

Effect van etiologie op HRQoL (hoofdstuk 4)
We onderzochten het effect van etiologie op de generieke en ziekte-specifieke HRQoL en vermoeidheid van chronische leverpatiënten, gecorrigeerd voor onder andere, geslacht, leeftijd en ziekte stadium.

Prominente verschillen tussen etiologieën werden met name gevonden wanneer wij etiologieën vergeleken met hemochromatose en virale hepatitis patiënten. Hemochromatose patiënten ervoeren significant meer gewrichtspijn dan andere etiologieën. Daarnaast nam in hemochromatose patiënten het rol emotioneel functioneren (de mate van beperkingen tijdens het dagelijks functioneren ten gevolge van emotionele problemen) met een toenemende leeftijd signficant sterker af dan in andere etiologieën. Virale hepatitis patiënten vertoonden een significant slechter rol emotioneel functioneren en een slechtere mentale gezondheid dan andere etiologieën. In de LDSI, toonden deze patiënten met virale hepatitis significant hogere odd ratio's voor ernstige zorgen over de thuis/familie stiuatie, ernstige depressie en ernstige angst voor complicaties dan andere etiologieën.

Effect van hepatitis B en C op HRQoL (hoofdstuk 5)
We evalueerden het effect van hepatitis B en C op de generieke en ziekte-specifieke HRQoL en vermoeidheid van chronische leverpatiënten, gecorrigeerd voor onder andere, geslacht, leeftijd en ziekte stadium.

Hepatitis C patiënten hadden een significant slechter fysiek-, sociaal- en rol emotioneel functioneren, een slechtere mentale gezondheid, een ernstigere reductie van de motivatie en significant hogere odd ratio's voor ernstige depressie en ernstige zorgen over de thuis/familie situatie in vergelijking met hepatitis B patiënten.

Na de verdeling van hepatitis C patiënten in een groep met en zonder interferon therapie, toonden hepatitis C patiënten zonder interferon therapie een significant slechter rol emotioneel functioneren en mentale gezondheid dan hepatitis B patiënten. Het rol emotioneel functioneren en de mentale gezondheid verslechterde nog eens in geval van gebruik van interferon therapie. Daarnaast leidde interferon therapie tot additionele verstoringen in andere aspecten van generieke en ziekte-specifieke HRQoL en tot signifcant meer vermoeidheid. Ook in vergelijking met patiënten met diabetes mellitus en kanker, vertoonden beide hepatitis C subgroepen significant meer beperkingen door emotionele problemen (rol emotioneel functioneren) en een slechtere mentale gezondheid.

DISCUSSIE

Integratie van bevindingen (hoofdstuk 6)
Dit onderzoek uitgevoerd in een grote niet-klinische populatie, bevestigt bevindingen van eerdere klinisiche onderzoeken verricht in verschillende groepen leverpatiënten. Dit onderzoek plaatst bovendien de verminderde HRQoL van de verschillende groepen leverpatiënten in perspectief.

Getransplanteerde leverpatiënten hadden een significant betere HRQoL dan leverpatiënten zonder cirrose en met cirrose, terwijl gedecompenseerde cirrose patiënten de slechtste HRQoL vertoonden. Hemochromatose patiënten rapporteerden

significant meer pijn dan andere etiologieën en een progressieve vemindering van het rol emotioneel functioneren met een toenemende leeftijd. In hepatitis C patiënten bleken rol emotioneel functioneren en mentale gezondheid een belangrijke bijdrage te leveren aan de verminderde HRQoL in deze patiënten, met name in hepatitis C patiënten met interferon therapie.

Selectie, ziekte-specifieke factoren en omgevingsfactoren zouden deze bevindingen kunnen verklaren. De goede HRQoL in getransplanteerde patiënten kan gebiased zijn door een selectie van emotioneel stabiele patiënten welke geassocieerd is met de strenge selectie van levertransplantatie kandidaten. In hemochromatose patiënten, kan een ziekte-specifieke factor zoals pijn een rol hebben gespeeld in het verslechterende rol emotioneel functioneren met het toenemen van de leeftijd; depressie en angst kunnen voortkomen uit de negatieve gevolgen van toenemende gezondheidsproblemen (disability hypothese), terwijl de dosis-respons relatie tussen pijn en kwaliteit van leven zou kunnen leiden tot toenemende emotionele stress bij deze patiënten.

Met betrekking tot de verklaring van het verminderd rol emotioneel functioneren en de verminderde mentale gezondheid in hepatitis C patiënten dienen zowel selectie als ziekte-specifieke als omgevingsfactoren overwogen te worden. De werkelijke relatie tussen emotionele/mentale gezondheid en hepatitis C kan vertekend zijn door selectie van patiënten met een psychiatrische morbiditeit welke reeds aanwezig was voor de diagnose van hepatitis C. Bovendien kan intraveneus drugs gebruik een belangrijke confounder zijn, aangezien intraveneus drugs gebruik geassocieerd kan zijn met psychiatrische morbiditeit onafhankelijk van de hepatitis C infectie. Tenslotte kunnen de hepatitis C diagnose zelf, ervaren beperkingen door de hepatitis C infectie zoals verminderde concentratie, gevoelens van sociaal stigma en angst voor toekomstige complicaties van de ziekte een rol hebben gespeeld in het verminderd rol emotioneel functioneren en de verminderde mentale gezondheid van deze groep.

Onze bevindingen onderstrepen het belang van een multi-dimensioneel leverziekte management. Tijdens consulten moet naast aandacht voor fysieke klachten van chronische leverpatiënten ook aandacht zijn voor psychologische klachten en de mogelijke relaties tussen deze twee dimensies.

Appendices

APPENDIX 1: LIVER DISEASE SYMPTOM INDEX 2.0

Vult u de onderstaande vragen in, als u op dit moment een leverziekte heeft of als u ooit een leverziekte heeft gehad.

Met behulp van de onderstaande vragen willen wij een indruk krijgen in welke mate u de afgelopen week bepaalde klachten had en in welke mate u hinder had van deze klachten. Zet een kruisje bij het antwoord dat het best bij uw situatie past.

Bijvoorbeeld:
Wanneer u vindt dat u de afgelopen week geen jeuk had, dan plaatst u bij vraag 1A een kruisje in het meest linkse hokje. Hoe meer jeuk u had de afgelopen week, hoe meer u het kruisje in de richting van "in hoge mate" kunt plaatsen.

Slaat u alstublieft geen vragen over en plaats telkens één kruisje bij elke vraag.

1A. In welke mate had u, de afgelopen week, jeuk?

In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

1B. In welke mate werd u, de afgelopen week, door jeuk gehinderd in uw werk of in uw dagelijkse bezigheden?

In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

1C. In welke mate werd u, de afgelopen week, door jeuk gehinderd in uw slaap?

In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

2A. In welke mate had u, de afgelopen week, gewrichtspijnen?

In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

2B. In welke mate werd u, de afgelopen week, door gewrichtspijnen gehinderd in uw werk of in uw dagelijkse bezigheden?

In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

3A. In welke mate had u, de afgelopen week, pijn in de rechter bovenbuik?

In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

3B. In welke mate werd u, de afgelopen week, door pijn in de rechter bovenbuik gehinderd in uw werk of in uw dagelijkse bezigheden?

In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

4A. **In welke mate was u, de afgelopen week, slaperig overdag?**

In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

4B. **In welke mate werd u, de afgelopen week, gehinderd door slaperigheid overdag in uw werk of in uw dagelijkse bezigheden?**

In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

5A. **In welke mate heeft u zich, de afgelopen week, zorgen gemaakt over de invloed van uw leverziekte op de thuis/gezinssituatie?**

In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

5B. **Hebben zorgen over de invloed van uw leverziekte op de thuis/gezinssituatie u, de afgelopen week, gehinderd in uw werk of in uw dagelijkse bezigheden?**

In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

6A. **In welke mate had u, de afgelopen week, een verminderde eetlust?**

In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

6B. **In welke mate werd u, de afgelopen week, door verminderde eetlust gehinderd?**

In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

7A. **In welke mate heeft u zich, de afgelopen week, door uw ziekte neerslachtig gevoeld?**

In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

7B. **In welke mate werd u, de afgelopen week, door neerslachtigheid ten gevolge van uw ziekte, gehinderd in uw werk, uw dagelijkse bezigheden en/of in uw contacten met andere mensen?**

In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

8. **In welke mate was u, de afgelopen week, bang voor mogelijke complicaties van uw leverziekte?**

In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

9A. **In welke mate was uw huid, de afgelopen week ten gevolge van uw leverziekte geel gekleurd?**

In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

9B. **In welke mate hinderde een gele kleur van uw huid u, de afgelopen week, in uw werk, uw dagelijkse bezigheden en/of contacten met andere mensen?**

In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

APPENDIX 2: EXTRA NLV ITEMS

De volgende vragen gaan over uw kwaliteit van leven sinds u een leverziekte hebt en hebben niet meer specifiek betrekking op uw kwaliteit van leven gedurende de afgelopen week.

10. **Sinds ik een leverziekte heb, heb ik moeite om dingen te herinneren. Bijvoorbeeld: dingen die pas gebeurd zijn, waar ik dingen heb gelaten, afspraken die ik heb gemaakt.**

    In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

11. **Door mijn leverziekte ben ik een andere persoon dan ik vóór mijn leverziekte was.**

    In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

12. **Mijn leverziekte belemmert mij bij financiële zaken. Bijvoorbeeld bij het afsluiten van een verzekering of een hypotheek.**

    In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

13. **Mijn leverziekte dwingt mij om mijn tijd anders in te delen, dan ik zou willen.**

    In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

14. **Mijn seksuele belangstelling is verminderd sinds ik weet dat ik een leverziekte heb.**

    In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

15. **Mijn seksuele activiteit is verminderd sinds ik weet dat ik een leverziekte heb.**

    In het geheel niet ❑ ❑ ❑ ❑ ❑ In hoge mate

APPENDIX 3: SF-36 GEZONDHEIDSTOESTAND VRAGENLIJST (IQOLA SF-36 DUTCH, VERSION 1.2)

Instructie: Deze vragenlijst gaat over uw standpunt t.a.v. uw gezondheid. Met behulp van deze gegevens kan worden bijgehouden hoe u zich voelt en hoe goed u in staat bent uw gebruikelijke bezigheden uit te voeren.

Beantwoord elke vraag door het antwoord op de aangegeven wijze te markeren.
Als u niet zeker weet hoe u een vraag moet beantwoorden, geef dan het best mogelijke antwoord.

1. **Hoe zou u over het algemeen uw gezondheid beoordelen?**

Uitstekend	1
Zeer goed	2
Goed	3
Matig	4
Slecht	5

2. **Hoe beoordeelt u nu uw gezondheid over het algemeen, vergeleken met een jaar geleden?**

Veel beter nu dan een jaar geleden	1
Wat beter nu dan een jaar geleden	2
Ongeveer hetzelfde nu als een jaar geleden	3
Wat slechter nu dan een jaar geleden	4
Veel slechter nu dan een jaar geleden	5

3. **De volgende vragen gaan over dagelijkse bezigheden die u misschien doet op een doorsnee dag. Wordt u door uw gezondheid op dit moment beperkt bij deze bezigheden? Zo ja, in welke mate? (omcirkel één cijfer op elke regel)**

BEZIGHEDEN	Ja, ernstig beperkt	Ja, een beetje beperkt	Nee, helemaal niet beperkt
a. *Forse inspanning*, zoals hardlopen, tillen van zware voorwerpen, een veeleisende sport beoefenen	1	2	3
b. *Matige inspanning*, zoals een tafel verplaatsen, stofzuigen zwemmen of fietsen	1	2	3
c. Boodschappen tillen of dragen	1	2	3
d. Een paar trappen oplopen	1	2	3
e. Eén trap oplopen	1	2	3
f. Bukken, knielen of hurken	1	2	3
g. *Meer dan een kilometer* lopen	1	2	3
h. *Een paar honderd meter* lopen	1	2	3
i. Ongeveer *honderd meter* lopen	1	2	3
j. Uzelf wassen of aankleden	1	2	3

4. **Heeft u in de afgelopen 4 weken één van de volgende problemen bij uw werk of andere bezigheden gehad, ten gevolge van uw lichamelijke gezondheid? (omcirkel één cijfer op elke regel)**

	JA	NEE
a. U besteedde *minder tijd* aan werk of andere bezigheden	1	2
b. U heeft *minder bereikt* dan u zou willen	1	2
c. U was beperkt in het *soort* werk of andere bezigheden	1	2
d. U had moeite om uw werk of andere bezigheden uit te voeren (het kostte u bijv. extra inspanning)	1	2

5. **Heeft u in de afgelopen 4 weken één van de volgende problemen bij uw werk of andere bezigheden gehad, ten gevolge van uw emotionele problemen (zoals depressieve of angstige gevoelens)? (omcirkel één cijfer op elke regel)**

	JA	NEE
a. U besteedde *minder tijd* aan werk of andere bezigheden	1	2
b. U heeft *minder bereikt* dan u zou willen	1	2
c. U deed uw werk of andere bezigheden niet zo *zorgvuldig* als gewoonlijk	1	2

6. **In hoeverrre hebben uw lichamelijke gezondheid of emotionele problemen u gedurende de afgelopen 4 weken gehinderd in uw normale omgang met familie, vrienden buren of bij activiteiten in groepsverband?**

Helemaal niet	1
Enigzins	2
Nogal	3
Veel	4
Heel erg veel	5

7. **Hoeveel lichamelijke pijn heeft u de afgelopen 4 weken gehad?**

Geen	1
Heel licht	2
Licht	3
Nogal	4
Ernstig	5
Heel ernstig	6

8. **In welke mate bent u de afgelopen 4 weken door pijn gehinderd in uw normale werk (zowel werk buitenshuis als huishoudelijk werk)?**

Helemaal niet	1
Een klein beetje	2
Nogal	3
Veel	4
Heel erg veel	5

9. **Deze vragen gaan over hoe u zich voelt en hoe het met u ging in de afgelopen 4 weken. Wilt u a.u.b. bij elke vraag het antwoord geven dat het beste benadert hoe u zich voelde. Hoe vaak gedurende de afgelopen 4 weken: (omcirkel één cijfer op elke regel)**

	Altijd	Meestal	Vaak	Soms	Zelden	Nooit
a. Voelde u zich levenslustig?	1	2	3	4	5	6
b. Was u erg zenuwachtig?	1	2	3	4	5	6
c. Zat u zo in de put dat niets u kon opvrolijken?	1	2	3	4	5	6
d. Voelde u zich rustig en tevreden?	1	2	3	4	5	6
e. Had u veel energie?	1	2	3	4	5	6
f. Voelde u zich somber en neerslachtig?	1	2	3	4	5	6
g. Voelde u zich uitgeput?	1	2	3	4	5	6
h. Was u een gelukkig mens?	1	2	3	4	5	6
i. Voelde u zich moe?	1	2	3	4	5	6

10. **Hoe vaak hebben uw lichamelijke gezondheid of emotionele problemen u gedurende de afgelopen 4 weken gehinderd bij uw sociale actviteiten (zoals vrienden of familie bezoeken, etc)?**

Altijd	1
Meestal	2
Soms	3
Zelden	4
Nooit	5

11. Hoe JUIST of ONJUIST is elk van de volgende uitspraken voor u? (omcirkel één cijfer op elke regel)

	Volkomen juist	Grotendeels juist	Weet ik niet	Grotendeels onjuist	Volkomen onjuist
a. Ik lijk gemakkelijker ziek te worden dan andere mensen	1	2	3	4	5
b. Ik ben even gezond als andere mensen die ik ken	1	2	3	4	5
c. Ik verwacht dat mijn gezondheid achteruit zal gaan	1	2	3	4	5
d. Mijn gezondheid is uitstekend	1	2	3	4	5

APPENDIX 4: MULTIDIMENSIONELE VERMOEIDHEIDS INDEX-20

Vult u de onderstaande vragen in als u op dit moment een leverziekte heeft of als u ooit een leverziekte heeft gehad.

Met behulp van de onderstaande uitspraken, willen wij een indruk krijgen van hoe u zich de laatste dagen voelt.

Bijvoorbeeld
Wanneer u vindt dat de uitspraak voor u helemaal klopt, plaatst u dan een kruisje in het meest linkse hokje. Hoe minder u de uitspraak op uzelf van toepassing vindt, hoe meer u het kruisje naar rechts, richting 'nee, dat klopt niet', kunt plaatsen. Slaat u alstublieft geen vragen over en plaats telkens één kruisje bij elke uitspraak.

Het gaat om hoe u zich de laatste dagen voelt.

1. **Ik voel me fit.**
   Ja, dat klopt ❑ ❑ ❑ ❑ ❑ nee, dat klopt niet

2. **Lichamelijk voel ik me tot weinig in staat.**
   Ja, dat klopt ❑ ❑ ❑ ❑ ❑ nee, dat klopt niet

3. **Ik zit vol activiteit.**
   Ja, dat klopt ❑ ❑ ❑ ❑ ❑ nee, dat klopt niet

4. **Ik heb zin om allerlei leuke dingen te gaan doen.**
   Ja, dat klopt ❑ ❑ ❑ ❑ ❑ nee, dat klopt niet

5. **Ik voel me moe.**
   Ja, dat klopt ❑ ❑ ❑ ❑ ❑ nee, dat klopt niet

6. **Ik vind dat ik veel doe op een dag.**
   Ja, dat klopt ❑ ❑ ❑ ❑ ❑ nee, dat klopt niet

7. **Als ik ergens mee bezig ben, kan ik mijn gedachten er niet goed bijhouden.**
   Ja, dat klopt ❑ ❑ ❑ ❑ ❑ nee, dat klopt niet

8. **Lichamelijk kan ik veel aan.**
   Ja, dat klopt ❑ ❑ ❑ ❑ ❑ nee, dat klopt niet

9. **Ik zie er tegen op om iets te doen.**
   Ja, dat klopt ❑ ❑ ❑ ❑ ❑ nee, dat klopt niet

10. **Ik vind dat ik weinig doe op een dag.**
    Ja, dat klopt ❑ ❑ ❑ ❑ ❑ nee, dat klopt niet

11. **Ik kan me goed concentreren.**
    Ja, dat klopt ❑ ❑ ❑ ❑ ❑ nee, dat klopt niet

12. **Ik voel me uitgerust.**
    Ja, dat klopt ❑ ❑ ❑ ❑ ❑ nee, dat klopt niet

13. **Het kost me moeite ergens mijn aandacht bij te houden.**
    Ja, dat klopt ❑ ❑ ❑ ❑ ❑ nee, dat klopt niet

14. **Lichamelijk voel ik me in een slechte conditie.**
    Ja, dat klopt ❑ ❑ ❑ ❑ ❑ nee, dat klopt niet

15. **Ik zit vol plannen.**
    Ja, dat klopt ❑ ❑ ❑ ❑ ❑ nee, dat klopt niet

16. **Ik ben gauw moe.**
    Ja, dat klopt ❑ ❑ ❑ ❑ ❑ nee, dat klopt niet

17. **Er komt weinig uit mijn handen.**
    Ja, dat klopt ❑ ❑ ❑ ❑ ❑ nee, dat klopt niet

18. **De zin om dingen te ondernemen ontbreekt mij.**
    Ja, dat klopt ❑ ❑ ❑ ❑ ❑ nee, dat klopt niet

19. **Mijn gedachten dwalen gemakkelijk af.**
    Ja, dat klopt ❑ ❑ ❑ ❑ ❑ nee, dat klopt niet

20. **Lichamelijk voel ik me in een uitstekende conditie.**
    Ja, dat klopt ❑ ❑ ❑ ❑ ❑ nee, dat klopt niet

APPENDIX 5: ACHTERGROND VRAGENLIJST

De volgende vragen gaan over uw persoonlijke situatie en uw leverziekte. Zet een kruisje bij het antwoord dat het best bij uw situatie past.

1. **Bent u bereid om aan dit onderzoek mee te doen?**
   - ❑ Ja
   - ❑ Nee

Ook als u niet wilt meedoen aan ons onderzoek, verzoeken wij u, om toch de vragenlijst naar ons terug te sturen door middel van de antwoordenvelop! U hoeft dan uiteraard de rest van de vragenlijst niet in te vullen.

2. **Bent u:**
   - ❑ man
   - ❑ vrouw

3. **Geboortejaar:**

   Jaar.....

4. **Wat is uw geboorteland?**
   - ❑ Nederland
   - ❑ Nederlandse Antillen
   - ❑ Suriname
   - ❑ Turkije
   - ❑ Marokko
   - ❑ Anders, namelijk.....

5. **Wat is uw hoogste volledig afgemaakte opleiding?**

- ❑ Ik heb geen enkele opleiding volledig afgemaakt.
- ❑ Lagere school
- ❑ Lager beroepsonderwijs (huishoudschool, LTS, LEAO)
- ❑ Middelbaar algemeen voortgezet onderwijs (MAVO, IVO, MULO)
- ❑ Middelbare beroepsopleiding (MTS, MEAO, MHNO, INAS)
- ❑ Hoger algemeen en voorbereidend wetenschappelijk onderwijs (HAVO, VWO, HBS, MMS, GYMNASIUM, ATHENEUM)
- ❑ Hoger beroepsonderwijs
- ❑ Universiteit

6. **Wat is uw burgerlijke status?**

- ❑ Getrouwd / Samenwonend
- ❑ Ongetrouwd / Weduwe of Weduwnaar / Alleenstaand

7. **Geeft u een ruwe schatting van het aantal uur dat u, gemiddeld per week, besteedt aan betaald werk, vrijwilligerswerk, huishoudelijk werk en studie. Indien u geen tijd besteedt aan het desbetreffende werk of studie, vult u dan een 0 in.**

Betaald werk	Vrijwilligerswerk	Huishoudelijk werk	Studie (zelfstudie en lessen)
.....	.....	.....	.....

8. **Geeft u een ruwe schatting van het aantal uur dat u, gemiddeld per week, besteedt aan de volgende vrije tijd-activiteiten?**
Indien u geen tijd besteedt aan de betreffende activiteiten-categorie, vult u dan een 0 in.

Activiteiten zonder lichamelijke inspanning. (Bijv. schaken, kaarten, puzzelen, breien, borduren, TV kijken.)	Activiteiten met lichamelijke inspanning. (Bijv. voetballen, fietsen, wandelen, tuinieren.)
.....	.....

9. **Waarom bent u lid van de Nederlandse Leverpatiënten Vereniging?**

- ❑ Ik heb zelf een leverziekte (gehad)
- ❑ Ik ben betrokken bij een persoon die een leverziekte heeft (gehad)
- ❑ Ik ben lid om een andere reden, namelijk

Indien u zelf geen leverziekte heeft (gehad), dan hoeft u de resterende vragen niet te beantwoorden! Wij verzoeken u de vragenlijst naar ons terug te sturen door middel van de antwoordenvelop!

Indien u wel een leverziekte heeft of ooit een leverziekte heeft gehad, gaat u dan door naar vraag 10 en verder.

10. Heeft u op dit moment een leverziekte die reeds meer dan 6 maanden duurt?

- ❑ Ja
- ❑ Nee

11. Graag willen wij van u weten welke leverziekte(n) u heeft (gehad).
In de onderstaande lijst staan verschillende leverziekten in categorieën (dikgedrukt) vermeld. Leest u de lijst eerst rustig door.

Wilt u in deze lijst met een kruisje aangeven welke van de volgende leverziekte(n) u heeft (gehad). Er zijn meerdere antwoorden mogelijk!
Indien uw leverziekte niet in de lijst wordt vermeld, vul dan onder aan de tabel uw leverziekte(n) in. Geeft u vervolgens de maand en het jaar waarin de betreffende leverziekte bij u is vastgesteld en of de duur van de leverziekte wel of niet meer dan 6 maanden is.
Geeft u tenslotte aan of uw leverziekte wel of niet wordt onderdrukt met medicijnen en of de leverziekte wel of niet genezen is.

LET OP: de lijst loopt door op de volgende pagina!

Code	Leverziekten	Jaar waarin de leverziekte bij u werd vastgesteld?	Duur van de leverziekte langer dan 6 maanden? Ja / Nee	Is de leverziekte onderdrukt met medicijnen? Ja / Nee	Is de leverziekte genezen? Ja / Nee
1.0	Virale Hepatitis				
1.01	Hepatitis A				
1.02	Hepatitis B				
1.03	Hepatitis C				
1.04	Hepatitis D				
1.05	Hepatitis E				
1.06	Hepatitis G				
1.07	Hepatitis CMV (Cytomegalo virus)				

1.08	Hepatitis EBV (Epstein-Barr virus)				
2.0	**Parenchymateuze leverziekten, niet viraal**				
2.01	Autoimmuun hepatitis				
2.02	Alcohol hepatitis				
2.03	Geneesmiddelen hepatitis				
2.04	Toxische hepatitis				
2.05	Hepatitis ECI (Hepatitis oorzaak onbekend)				
2.06	Steatose (leververvetting)				
2.07	Granulomateuze hepatitis				
2.08	Sarcoidose				
2.09	Reye syndroom				
3.0	**Vaatafwijkingen**				
3.01	Budd-Chiari syndroom				
3.02	Veneuze stuwing				
3.03	Veno-occlusive disease				
3.04	Porta-thrombose				
3.05	Idiopatische (of primaire) portale hypertensie				
3.06	Cardiale cirrose				
4.0	**Cholestatische leverziekten**				
4.01	Primaire Biliaire Cirrose (PBC)				
4.02	Primaire Scleroserende Cholangitis (PSC)				
4.03	Secundaire Billiaire Cirrose				
5.0	**Congenitale leverziekten, metabool**				
5.01	Ziekte van Wilson (koperstapelings-ziekte)				
5.02	Haemochromatose				
5.03	Alpha -1-antitrypsine-deficiëntie				

5.05	Porfyrie				
5.06	Syndroom van Gilbert				
5.07	Syndroom van Dubin-Johnson				
5.08	Ziekte van Crigler-najer				
5.09	Primaire Oxalose				
5.10	Syndroom van Rotor				
5.11	Galactosemie				
5.12	Ziekte van Niemann-Pick				
5.13	Ziekte van Gaucher (sfingolipidose)				
6.0	**Congenitale ziekten, anatomische afwijkingen**				
6.01	Congenitale levercysten				
6.02	Choledochus-cyste(n)				
6.03	Congenitale leverfibrose				
6.04	Galgang-atresie				
6.05	Syndroom van Allagille				
6.06	Arterio-veneuze malformatie				
6.07	M. Osler-Weber-Rendu				
6.08	Syndroom van Caroli				
7.0	Haardvormige afwijkingen, kwaadaardig				
7.01	Hepatocellulair carcinoom				
7.02	Galgang carcinoom				
7.03	APUDoma				
7.04	Carcinoïd syndroom				
7.05	Levermetastasen				
7.06	Cholangiocellulair carcinoom				
8.0	**Haardvormige afwijkingen, goedaardig**				
8.01	Hepatocellulair adenoom				
8.02	Hemangioom				

8.03	Focale nodulaire hyperplasie				
8.04	Nodulaire regeneratieve hyperplasie				
9.0	Parasitaire leverziekten				
9.01	Amoeben abces				
9.02	Schistosomiasis				
9.03	Echinococcus-cyste(n)				
10.0	Cholelithiasis				
10.1	Cholecystolithiasis (Galblaassteenziekte)				
10.2	Choledocholithiasis (Galgangsteenziekte)				
10.3	Intrahepatische galstenen				
11.0	Andere leverziekten				
11.01	Hepatische encephalopathie				
12.0	Mijn leverziekte(n) wordt/worden niet in de tabel vermeld. Mijn leverziekte(n) is/zijn:				
12.01	1.				
12.02	2.				
12.03	3.				

12. Heeft u een levertransplantatie ondergaan?

- ❑ Ja, namelijk op: dag...../maand...../jaar.....
- ❑ Nee

13. Heeft u cirrose (sterke verlittekening van de lever met een hobbelig leveroppervlak)?

- ❑ Ja
- ❑ Nee

14. Heeft u een vergrote milt (gehad)?

- ❑ Ja
- ❑ Nee

15. **Heeft u een ophoping van vocht in uw buik (ascites) (gehad)?**

- ❑ Ja
- ❑ Nee

16. **Heeft u een bloeding uit spataderen in uw slokdarm (varices bloeding) (gehad)?**

- ❑ Ja
- ❑ Nee

17. **Heeft u in het jaar 2000 nog een bloeding uit spataderen in uw slokdarm of een ophoping van vocht in uw buik gehad?**

- ❑ Ja
- ❑ Nee

18. **Heeft u andere ernstige complicaties van een levercirrose (gehad)?**
Ja, namelijk:

- ❑ leverkanker (hepatocellulair carcinoom)
- ❑ (dreigend) levercoma (encephalopathie)
- ❑ overig, namelijk.....

.....

- ❑ Nee

19. **Heeft u nog andere ziekten/aandoeningen dan uw leverziekte(n), die u belemmeren in het dagelijks functioneren? Meerdere antwoorden zijn mogelijk!**
Ja, namelijk ziekten of aandoeningen van:

- ❑ hart- en vaten (bijv. hoge bloeddruk)
- ❑ het zenuwstelsel (bijv. ziekte van Parkinson)
- ❑ de luchtwegen (bijv. astma)
- ❑ de spieren
- ❑ de gewrichten (bijv. reuma)
- ❑ de urinewegen
- ❑ het maag/darmstelsel (bijv ziekte van Crohn, Colitis Ulcerosa)
- ❑ suikerziekte
- ❑ het oog
- ❑ psychische aandoeningen
- ❑ overige, namelijk.....
- ❑ Nee

20. Heeft u medicijnen in verband met psychische klachten?

- ❑ Ja
- ❑ Nee

21. Gebruikt u slaapmiddelen?

- ❑ Ja
- ❑ Nee

22. Graag willen wij van u weten welke medicijnen u op dit moment gebruikt.
In de onderstaande lijst worden een aantal medicijnen weergegeven.
Leest u de lijst eerst rustig door.

Kruist u de medicijn(en) aan die u **op dit moment** gebruikt.

	Medicijnen	**Gebruik nu**
1	Interferon (Intron A, Roferon)	❑
2	PEG-interferon	❑
3	Lamivudine	❑
4	Famciclovir	❑
5	Entecavir	❑
6	Ribavirine	❑
7	Amantadine	❑
8	Prednison	❑
9	Tacrolimus (Prograft)	❑
10	Ciclosporine (Neoral)	❑
11	Ursodeoxycholzuur (Ursochol, Ursofalk)	❑
12	Budesonide	❑
13	Furosemide (Lasix)	❑
14	Spironolactone (Aldactone)	❑
15	Propanolol (Inderal)	❑
16	Antihypertensiva (tegen hoge bloeddruk)	❑
17	Antidiabetica (tegen suikerziekte)	❑

18 Medicatie tegen luchtweg aandoeningen ❑

19 Slaapmiddelen ❑

20 Middelen tegen psychische klachten (bijvoorbeeld: antidepressiva, middelen tegen angst, etc) ❑

21 Overig, namelijk ❑

1 .....

2 .....

3 .....

4 .....

5 .....

6 .....

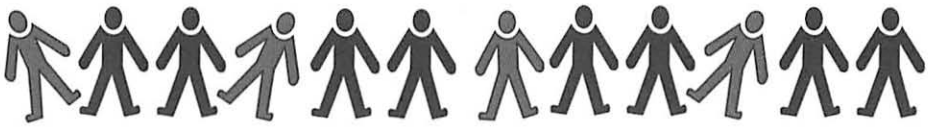
7 .....

8 .....

9 .....

10 .....

Dankwoord



DANKWOORD

Allereerst wil ik alle leden en het bestuur van de Nederlandse Leverpatiënten Vereniging bedanken voor hun medewerking aan dit onderzoek. Zonder hen zou dit boekje niet tot stand zijn gekomen.

Vervolgens wil ik mijn beide promotoren, prof. dr. S.W. Schalm en prof. Dr. Th. Stijnen bedanken voor hun deskundige begeleiding. Beste Solko, jij gaf me de prikkel om altijd net even wat verder te denken en leerde me om vraagstukken simpel te houden. Daar zal ik nog veel aan hebben in de toekomst. Beste Theo, bedankt voor het feit dat ik altijd bij je binnen kon lopen en bedankt voor je oplossingen die, met jou realistische kijk op onderzoek altijd weer in een handomdraai op tafel lagen. Daarnaast ben ik veel dank verschuldigd aan Bettina Hansen, mijn dagelijks begeleider. Beste Bettina, heel erg bedankt voor al je geduld, je ideeën, je statistische advies en natuurlijk je gezelligheid. Mede door jou voelde ik me direct thuis bij de Biostatistiek. Vervolgens dank ik Josien de Boer voor haar goede inhoudelijke adviezen met betrekking tot kwaliteit van leven vraagstukken. Josien, ondanks je drukke nieuwe baan, stond je altijd open voor mijn vragen en was je altijd bereid om zelfs in je vrije tijd nog even wat stukken door te lezen. Dit heb ik altijd zeer gewaardeerd. Tevens dank ik de co-auteurs Rob de Man en Jan Passchier hartelijk voor al hun inhoudelijke adviezen. Daarnaast dank ik de secretaresses van Maag-, Darm-, Leverziekten, Marion Hoogendoorn en Margriet van Dijk, maar natuurlijk ook alle mensen van de polikliniek en iedereen van de IT-afdeling van de afdeling Epidemiologie en Biostatistiek voor hun inspanningen die zij voor mijn onderzoek geleverd hebben.

Dan wil ik al mijn collega's van de Biostatistiek hartelijk bedanken voor hun vriendelijkheid, hun toegankelijkheid en boven al hun statistische humor. Niets is sfeer-verhogender dan statistici in een deuk te zien liggen om een grap over regressie! Daarnaast wil ik mijn collega's van de Epidemiologie bedanken voor hun gezelligheid op de afdeling, maar ook tijdens de gebruikelijke borrels in het Wester Paviljoen. Jullie zorgden voor de broodnodige afwisseling die een onderzoeker zo hard nodig heeft! Ik wens jullie allemaal veel succes met het afronden van jullie eigen proefschrift en ik hoop dat we elkaar in de toekomst nog vaak zullen zien. Speciale dank gaat hierbij natuurlijk uit naar mijn kamergenoot Stephanie Schuit. Stephanie, je kwam precies op het juiste moment. Daarna is het verblijf op kamer 21.83 alleen maar leuker geworden! We houden contact!

Vervolgens wil ik mijn ouders bedanken voor hun sturing en begrip. Mam, ik wil je nog steeds bedanken voor jou suggestie om Gezondheidswetenschappen te gaan studeren. Zonder dat advies had deze promotie nooit plaatsgevonden en had ik nu niet op mijn plek gezeten. Pap, mam, het beste dat jullie in de afgelopen periode voor me konden doen, is me met rust laten. En dat hebben jullie gedaan. Bedankt daarvoor.

Dan almost last, maar verre van least wil ik mijn vriend Matthijs bedanken voor al zijn steun tijdens dit moeilijke traject. Lieve Thijs, jou kan ik eigenlijk nooit genoeg bedanken voor al je begrip en geduld die je de afgelopen jaren met me hebt gehad. Gelukkig kon ik met jou altijd gemakkelijk de leuke draad van het leven weer oppikken en meestal verdween alle stress dan als sneeuw voor de zon. Ik vind

het heerlijk dat deze exercitie nu bijna voorbij is en dat we dadelijk alleen nog maar hoeven te genieten, want.....daar zijn we goed in met zijn tweeën.

Tenslotte wil ik mijn paranymfen Irene van der Meer en Monique van der Plas hartelijk bedanken voor hun hulp in deze laatste fase van mijn promotie. Irene, bedankt voor je gezellige aanwezigheid tijdens onze werk-weekenden op Hoboken en je nuttige promotie-tips. Leuk dat je nu ook mij wilt bijstaan bij het bereiken van deze mijlpaal. Nog even en dan kunnen we eindelijk ongelimiteerd gaan stappen, zonder schuldgevoel! Monique, jou mailtjes uit Kenia waren altijd een goede reden om even pauze te nemen tussen alle analyses door. Ik vind het erg leuk dat je nu samen met mij 'live' het laatste stapje over de streep wilt nemen.

About the Author

ABOUT THE AUTHOR

Simone van der Plas was born at the 7th of February in Bleiswijk. She graduated in 1988 for the HAVO and two years later for the VWO at the Sint-Laurenscollege in Rotterdam. For three years, she studied Law at the Erasmus University Rotterdam where she graduated from the first year examination in 1992. One year later she changed her plans and started the study Health Sciences in Maastricht where she specialised in Biological Health Sciences. Since the metropolis up north still attracted her, she conducted her graduation research project at the Department of Medical Microbiology at the Erasmus MC in Rotterdam. She graduated in 1997.

At the end of this year, she became trainee at the general practice of Schiermonnikoog where she assisted in a research project on the Health Status of the population of this island. In 1998 she started to work as a research co-ordinator for the Aspect-II study, a multi centre trial on the secondary prevention of cardiovascular disease. In November 1999 she started the work described in this thesis at the Department of Gastroenterology and Hepatology (Prof. dr. S.W. Schalm) and the Department of Epidemiology and Biostatistics (Prof. dr. Th. Stijnen) at the Erasmus MC in Rotterdam. During that period she graduated from a Master of Science in Epidemiology at the Netherlands Institute of Health Sciences. Recently, she started as project leader Respiratory Infections at the Centre for Epidemiology of Infectious Diseases at the National Institute of Public Health and the Environment, Bilthoven.