Quality of Life Research (2007) 16:375–388
DOI 10.1007/s11136-006-9131-y
© Springer 2006

Generic and disease-specific health related quality of life of liver patients with various aetiologies: A survey

Simone M. van der Plas[1], Bettina E. Hansen[1,2], Josien B. de Boer[3], Theo Stijnen[2], Jan Passchier[3], Rob A. de Man[1] & Solko W. Schalm[1]
[1]*Department of Gastroenterology and Hepatology, Erasmus Medical Centre Rotterdam, P.O. Box 2040, 3000 CA, Rotterdam, The Netherlands;* [2]*Department of Epidemiology and Biostatistics, Erasmus Medical Centre Rotterdam, Rotterdam, The Netherlands;* [3]*Department of Medical Psychology and; Psychotherapy, Erasmus Medical Centre Rotterdam, Rotterdam, The Netherlands*

Accepted in revised form 17 September 2006

Abstract

Most studies on health related quality of life (HRQoL) of chronic liver patients were done in small clinical populations or restricted to one aetiology or disease stage. There is still a need for a study in a large liver patient population with 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 we compared HRQoL and fatigue between aetiological groups and healthy Dutch controls. Members of the Dutch liver patient association completed the Liver Disease Symptom Index, 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 linear, ordinal and logistic regression, corrected for disease stage and other significant factors. Viral hepatitis patients showed a worse mental health than other aetiological groups. Hemochromatosis patients demonstrated 17% more bodily pain than viral hepatitis patients and the strongest decrease in role emotional health with increasing age. Aetiological groups showed a worse generic HRQoL and more fatigue than controls. In conclusion, viral hepatitis and hemochromatosis patients have a more impaired HRQoL than patients of other liver disease aetiological groups.

Key words: Autoimmune hepatitis, Cholestatic disease, Hemochromatosis, Quality of life, Viral hepatitis

Abbreviations HRQoL – Health Related Quality of Life; LDSI – Liver Disease Symptom Index; MFI-20 – Multidimensional Fatigue Index-20; NLV – Nederlandse Leverpatiënten Vereniging (Dutch liver patient association); OR – Odds ratio; SF-36 – Short Form-36

Introduction

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]. To date, many patient associations, including the Dutch liver patient association (Nederlandse Leverpatiënten Vereniging, NLV), continue to fight for recognition of disease related physical, mental and social problems of chronically

ill 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 were the first to compare the HRQoL of liver patients with hepatitis B or C. Their study demonstrated that hepatitis C patients showed significantly more impairment in 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 among cirrhotic cholestatic liver patients than among cirrhotic patients with hepatocellular disease [3]. Other studies reported no effect of aetiology on HRQoL of cirrhotic patients or on quality of life adjusted life years of liver patients regardless of disease stage [4, 5]. Although these studies contributed substantially to our understanding of HRQoL of 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 HRQoL there is still a need for a study in a large research population with a broad variety of aetiologies. This study should use a generic as well as a disease-specific questionnaire. While the generic HRQoL questionnaire gives a broad insight in the general functioning of the patient, the disease-specific questionnaire can give additional insight in specific complaints related to the underlying disease, which can be of extra explanatory value when comparing different aetiologies [6, 7].

Our collaboration with the Dutch liver patient association gave us the opportunity to study the HRQoL of a chronic liver patient population with sufficient variation regarding aetiology, disease stage and other factors potentially influencing HRQoL, permitting maximum adjustment for potential confounders. Our aim was to evaluate the adjusted impact of liver disease aetiology on generic HRQoL, disease-specific HRQoL and fatigue among patients with viral hepatitis, autoimmune hepatitis, cholestatic diseases, hemochromatosis or other liver diseases. For this study we used the disease-specific Liver Disease Symptom Index 2.0 (LDSI) and the generic Short Form-36 (SF-36), as recommended in the literature [7, 8]. Since fatigue is an important complaint of chronic liver patients [9–11] we added the domain-specific Multidimensional Fatigue Index-20 (MFI-20).

Methods

Study population

We conducted our study among all members of the Dutch liver patient association NLV. Before the study, the board of the NLV informed all members by mail about the aim of our study and the way in which quality of life would be measured. A week later (October 2000) all 2020 members of the NLV received a patient information form and a questionnaire by mail. The form again, provided information about the aim of the study, content of the questionnaires, privacy arrangements, voluntary participation, and the way to express either their informed consent or refusal to participate in the study (through their response to the first question in the questionnaire). 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 2 months non-responders received a new questionnaire. We closed the response period 5 months after the first mailing. Inclusion criteria were: (1) Informed consent and (2) aged 18 years or older at the moment of administration (3) and having a (history of) liver disease. Non-patient members were excluded and were not used as controls since involvement with liver patients could influence their HRQoL. 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 conformed to the ethical guidelines of the 1975 Declaration of Helsinki and approved by the Ethics Committee of the Erasmus MC Rotterdam, the Netherlands.

Measurement instruments

We investigated the HRQOL of chronic liver patients by means of three questionnaires: The extended version of the disease-specific Liver Disease Symptom Index 1.0 (the LDSI 2.0), the Dutch Short-Form 36, and the MFI-20.

The disease-specific Liver Disease Symptom Index 1.0 was developed at the Department of Hepatology and Gastroenterology of the Erasmus MC in Rotterdam, The Netherlands. Its content was based on interviews with chronic liver patients about disease-specific symptoms and the adverse impact of symptoms on daily activities (further referred to as 'hindrance caused by symptoms'). The LDSI 1.0 was validated in a clinical population of chronic liver patients and showed a good feasibility and reliability, but failed to discriminate between non-cirrhotic patients and patients with compensated cirrhosis [8]. Therefore, we revised the response categories (from a 4-point scale to a 5-point scale). In addition, we gave the LDSI a more multidimensional character by adding items concerning depression and worry. 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 caused by these symptoms to daily activities. All items have 'the last week' as time frame and were scored on a 5-point scale ranging from 'not at all' to 'to a high extent'. The LDSI 2.0 was supplemented with six extra NLV items. The board of the NLV selected these items as important aspects of HRQoL of chronic liver patients based on frequent contact with other liver patients and their own experience as chronic liver patients. 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'. These items were also scored on a 5-point scale ranging from 'not at all' to 'to a high extent'. We evaluated feasibility (n = 69) and test–retest reliability (3-day interval, n = 34) of the LDSI 2.0 and the extra NLV items among outpatients of our Hepatology department. Items generally showed a good feasibility (< 5% missing values) and a fair (one item concerning worry, $\kappa_{weighted}$ 0.32) to very good test-retest reliability ($\kappa_{weighted}$ 0.91). In the NLV population, low (< 0.4) to moderate (0.4–0.7) Spearman correlations evaluating convergent and divergent construct validity between LDSI items or extra NLV items and the SF-36 or the MFI-20 scales, indicated a slight to moderate overlap between the information given by the questionnaires used. For details regarding the psychometric evaluation and the final version of the LDSI 2.0, we refer to our article published in 2004 in this journal [12].

The generic SF-36, version 1.2, includes 8 multi-item scales on 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. Translation of the SF-36 into Dutch followed the stepwise, iterative procedures developed by the IQOLA Project [13]. The originally Dutch 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 among Dutch chronic liver patients [8]. Crude SF-36 and MFI-20 scale scores were calculated according to the SF-36 and MFI-20 scoring algorithms [14, 15].

A separate questionnaire was used to determine sex, age, aetiology (appendix), 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 or without physical effort. For each item questioning the presence of a clinical characteristic (ascites, cirrhosis, etc) a

simplified description of this clinical symptom was given: cirrhosis: advanced scarring of the liver; ascites: accumulation of liquid in the abdomen; splenomegaly: enlarged spleen; oesophageal variceal bleeding: bleeding from a varicose vein in the gullet.

All questionnaires were self-reported.

Comparison groups

Respondents were categorised in aetiological groups and disease stage groups. The categorisations were respectively based on self-reported aetiologies or clinical characteristics. Since members participated anonymously, self-reported clinical data was not verified by reference to their medical records. For more detailed information regarding the reliability of the reported aetiologies and clinical characteristics, we refer to an earlier article published in this journal [12]. We investigated the HRQoL of liver disease aetiological groups that were distinct with respect to clinical background. We hypothesised that the infectiousness of a viral liver disease could have a different impact on HRQoL than a disease that is often induced by an external toxic factor (autoimmune hepatitis), or a disease with a more physiologic background (cholestatic diseases, haemochromatosis). This resulted in the following five aetiological 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. Cirrhosis is an advanced form of scarring or liver damage as a result of chronic hepatitis. In the compensated cirrhotic stage, the liver is still functioning well despite the distorted architecture of the liver. Decompensation occurs when accumulated liver damage prevents the liver from functioning properly and interferes with other body systems. Respondents who reported no cirrhosis and had never had splenomegaly, ascites or oesophageal variceal bleeding were classified as non-cirrhotic. Respondents who reported cirrhosis *or* ever had splenomegaly *or* ascites *or* 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. By using the criterion 'in the year 2000', we took the temporary state of decompensated cirrhosis into account. Decompensated cirrhotic patients often reverse to an apparently compensated state in response to medication or surgical interventions. The NLV population showed 43 compensated cirrhotic patients who 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 (a beta-blocker to prevent bleeding from oesophageal varices) at the moment of our study. The HRQoL level of the *reversed* decompensated cirrhotic patients was comparable to the HRQoL level of the compensated cirrhotic group and not the HRQoL level of decompensated patients. This group was therefore categorised as compensated cirrhotic.

Statistical methods

For the SF-36, healthy Dutch controls (n = 1715) came from a nationwide, population based health status survey among adults of Dutch households, randomly drawn from the national telephone registry [13]. For the MFI-20, healthy Dutch controls (n = 139) were adults randomly drawn from households in telephone directories as a comparison group for a study on fatigue among cancer patients [16]. Data of SF-36 controls (SF-36 scale scores, sex, age, educational level and marital status) and MFI-20 controls (MFI-20 scale scores, sex, age and educational level) were added to the our liver patient database. We used general linear regression to estimate mean SF-36 scale scores (corrected for sex, age, education level and marital status) and mean MFI-20 scale scores (corrected for sex, age and education level) for aetiological groups and Dutch healthy controls. SF-36 scales or MFI-20 scales served as dependent outcome variables and aetiological groups (including the healthy controls as reference group) as independent determinants.

We also used linear regression to estimate adjusted differences between aetiological groups for the separate SF-36 and MFI-20 scales and to estimate adjusted means for the SF-36 Physical and Mental Component Scores. All aetiological

groups were mutually compared. In these analyses we excluded healthy controls and adjusted for gender, age, education level, disease stage, comorbidity, number of liver diseases per patient, use of liver disease medication and use of anti-depressiva/anti-psychotica. We corrected for these factors to establish differences between aetiological groups with the least possible bias due to other confounding factors. All confounding factors were significantly associated with the outcomes in univariate analyses ($p < 0.05$). Correction for some factors can be discussed, since some may have been a consequence of the liver disease, for instance comorbidity. Since it was unclear wether factors, such as comorbidity, predated or followed the diagnosis of the liver disease, we decided to correct for all these factors, taking the risk of underestimating the difference between aetiological groups.

We used a proportional odds model for ordinal outcome by means of PROC LOGISTIC in SAS 8.0. to estimate 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. By means of these probabilities, odds ratios (ORs) associated with severe symptoms were calculated for all specific aetiological groups relative to one of the aetiological groups chosen as the reference group. All aetiological groups were mutually compared.

We used binary logistic regression to estimate, for all specific aetiological groups, the odds ratio of being hampered by symptoms in daily activities (outcome 2–5), relative to one of the aetiological group chosen as the reference group. Again all aetiological groups were mutually compared. For these analyses we selected only respondents with symptoms (symptom severity outcome >1). Estimated ORs were corrected for the same factors as the SF-36 and MFI-20 scales score differences. The observed significance level of determinants was less than 0.05. Interactions were considered significant only if the overall p-value was less than 0.01 to avoid interactions by chance due to multiple testing. The number of respondents in the interacting subcategories was always larger than 5% of the total population.

Results

Selection of the population

Of the 2020 members approached for this survey, 1617 members returned their questionnaires. Of these, 374 respondents were non-patient members. In total 1243 had a (history of) liver disease. If we assume 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%. In reality the proportion of patient members in non-responders is probably lower, leading to a somewhat lower response than 80%. Of the 1243 respondents with a history of liver disease, 1222 gave informed consent, but 47 were younger than 18 years of age. We excluded 186 respondents with transplant and 71 respondents who reported themselves as cured, leaving 918 patient members for analyses.

Baseline characteristics

Table 1 shows the baseline characteristics of the Dutch liver patients and the SF-36 and MFI-20 control comparison groups. The 918 respondents were mostly women (58.4%), had a mean age of 49 years (SD ± 12.6, range 18–81), were married or living with a partner and most patients had lower secondary education level or higher 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 activities requiring physical effort such as 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 remaining aetiological group included patients with parenchymatous non-viral liver diseases (35%), vascular deformations (15%) and congenital metabolic liver diseases (25%). In 57 respondents (6.2%) the aetiology was unknown. In total 102 patients reported more than 1 liver disease. In total 590 (68.8%) of all patients reported comorbidity.

Table 1. Baseline characteristics of the Dutch cross-sectional liver patient population and healthy controls

Characteristic	Dutch 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)	0 (0)
Civil 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)		

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 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, scores of viral hepatitis patients were significantly lower on all SF-36 scales. Score differences between the viral hepatitis patients and cholestatic liver patients

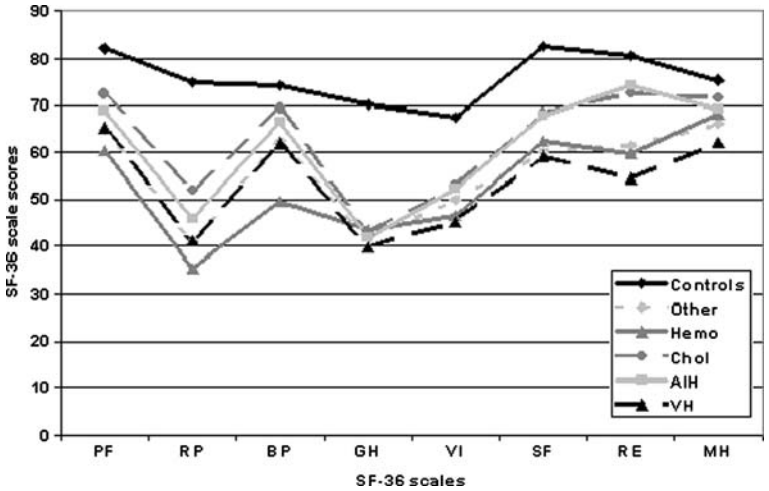

Figure 1. Mean SF-36 scale scores of Dutch healthy controls and chronic liver patients with various aetiologies, adjusted for age, gender, education level and marital status. Legend coding SF-36 scales, controls and aetiological groups: PF = physical functioning, RP = Role limitations due to physical problems, BP = bodily pain, GH = general health, VI = vitality, SF = social functioning, RE = role limitations due to emotional problems, MH = mental health. Controls = Dutch healthy controls, VH = viral hepatitis, AIH = autoimmune hepatitis, CHOL = cholestatic diseases, HEMO = hemochromatosis, Other = other liver diseases.

ranged from −5.2 [95% CI: −10.0, −0.3] with respect to bodily pain to −15.8 [95% CI: −24.2, −7.3] with respect to role limitations due to emotional problems. Compared to patients with autoimmune hepatitis, hemochromatosis and patients with other liver diseases, viral hepatitis patients especially showed significantly lower scores regarding role limitations due to emotional problems and mental health. This finding was also reflected in the Mental Component Score (Figure 2). Hemochromatosis patients scored significantly lower with respect to bodily pain (−9.7 [95% CI: −15.5, −4.0]) than viral hepatitis patients and all other aetiological groups (relative difference of 17% lower bodily pain scores compared to viral hepatitis patients and 24% lower bodily pain scores compared to cholestatic patients). Hemochromatosis patients also showed a significantly lower Physical Component Score than all other aetiological groups, except autoimmune hepatitis. The aetiology dependent differences in role limitations due to emotional problems were modified by age. Figure 3 shows the relationship between role emotional functioning score and age for the various aetiological groups. Hemochromatosis patients experienced a stronger increase of role limitations due to emotional problems with increasing age than other aetiological groups.

Fatigue in chronic liver patients and Dutch healthy controls

All aetiological groups showed a significantly worse score for fatigue than healthy Dutch controls on all MFI-20 scales (Figure 4).

The lower diagonal of Table 2 shows which MFI-20 scales have significantly different scores when the various aetiological groups are compared. Again, significant scale score differences were most often found when the viral hepatitis group was compared with the other aetiological groups. In these cases, viral hepatitis patients had a significantly higher fatigue score, thus showing more fatigue. Compared to cholestatic patients, viral hepatitis patients had significantly higher scores for fatigue on all scales and score differences ranged from +1.3 [95% CI: 0.25, 2.4] with respect to general fatigue, to +1.9 [95% CI: 0.8, 2.9] with respect to physical fatigue. Patients with autoimmune hepatitis demonstrated significantly lower scores regarding the scales reduction in activity' (−1.5 [95% CI: −2.7, −0.3]) and reduction in motivation (−1.4 [95% CI: −2.4, −0.4]) than viral hepatitis patients, but a similar level of general, physical and mental fatigue. Hemochromatosis patients experienced the same level of fatigue on all MFI-20 scales as viral hepatitis patients.

Table 2. Adjusted *significant* ($p < 0.05$) score differences regarding generic HRQoL (SF-36, upper diagonal) and fatigue (MFI-20, lower diagonal) between liver disease aetiological groups

Significantly higher or lower SF-36 scale scores (scale 0–100) compared to the aetiological reference group[a]					
	Viral hepatitis (reference)	Autoimmune hepatitis (reference)	Cholestatic diseases (reference)	Hemochromatosis (reference)	Other liver diseases (reference)
Viral hepatitis		VI(−7.3), SF(−8.5), RE(−18.8)	PF(−6.5), RP(−10.1), BP(−14.9), GH(−5.2), VI(−8.4), SF(−10.5), RE(−15.8), MH(−7.0)	BP(9.7), RE(−12.0), MH(−7.2)	GH(−6.9), VI(−5.9), MH(−4.6)
Autoimmune hepatitis	RA(−1.5), RM(−1.4)			BP(11.0), VI(6.9)	RE(10.8)
Cholestatic diseases	GF(−1.3), PhF(−1.9), RA(−1.6), RM(−1.4), MF(−1.7)			PF(9.8), RP(13.9), BP(14.9), VI(8.0)	SF(7.2)
Hemochromatosis			PhF(1.8)		PF(−6.6), BP(−13.1)
Other liver diseases	GF(−1.1), RA(−1.2), RM(−1.3), MF(−1.8)				
	Viral hepatitis (reference)	Autoimmune hepatitis (reference)	Cholestatic diseases (reference)	Hemochromatosis (reference)	Other liver diseases (reference)
Significantly higher or lower MFI-20 scale scores (scale 4–20) compared to the aetiological reference group[b]					

[a]Positive differences: Aetiological group has a significant higher scale score (=better HRQoL) than the reference group. Negative differences: Aetiological group has a significant lower scale score (=worse HRQoL) than the reference group.
[b]Positive differences: Aetiological group has a significant higher scale score (=more fatigue) than the reference group. Negative differences: Aetiological group has a significant lower scale score (=less fatigue) than the reference group.
Legend: *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.

Comparison of symptom severity and symptom hindrance between aetiologies

The upper diagonal of Table 3 shows adjusted significant ORs associated with severe symptoms. All aetiological groups were mutually compared with respect to the chance of getting a severe symptom. Viral hepatitis patients demonstrated significantly higher odds of reporting severe worry about the family situation (Range of odds ratios in the comparisons of viral hepatitis with other aetiological groups: OR 2.02 [95% CI: 1.37, 3.00] relative to 'other liver diseases' to OR 2.8 [95% CI: 1.78, 4.29] relative to cholestatic patients), severe depression (Range of odds ratios: OR 1.72 [95% CI: 1.16, 2.55] relative to other liver diseases to OR 2.67 [95% CI: 1.70, 4.19] relative to cholestatic diseases) and severe fear of complications (Range of odds ratios: OR 1.54 [95% CI: 1.03, 2.29] relative to 'Other liver diseases' to OR 2.65 [95% CI: 1.69, 4.17] relative to cholestatic diseases). The odds of severe fear were influenced by gender and comorbidity. In men, comorbidity significantly increased the odds of severe fear of complications compared to men without comorbidity (OR 2.62 [95% CI: 1.62, 4.25]). Additionally, men with comorbidity demonstrated significantly higher odds of fear of complications compared to women with comorbidity (OR 1.54 [95% CI: 1.09, 2.16]). Among hemochromatosis patients the odds of severe joint pain were significantly higher compared to all other aetiological groups (Range

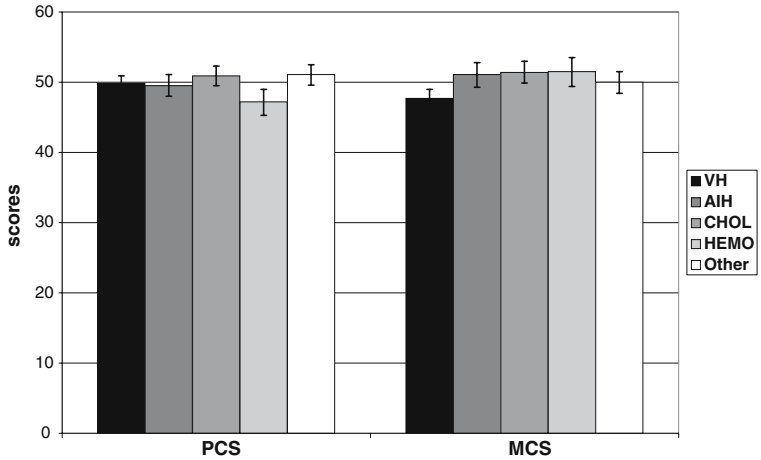

Figure 2. Mean MFI-20 scale scores of Dutch healthy controls and chronic liver patients with various aetiologies, adjusted for age, gender and education level. Legend coding MFI-20 scales, controls and aetiological groups: GF = general fatigue, PhF = physical fatigue, RA = reduction in activity, RM = reduction in motivation, MF = mental fatigue. For legend of aetiological groups, see legend Figure 1.

of odds ratios: OR 1.89 [95% CI: 1.11, 3.22] relative to autoimmune hepatitis to OR 4.28 [95% CI: 2.59, 7.05] relative 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 the significant odds ratios associated with being hampered by symptoms. Again all aetiological groups were mutually compared. Patients with autoimmune hepatitis, cholestatic diseases and other liver diseases often demonstrated significantly lower odds of symptom hindrance relative to viral hepatitis patients. Viral hepatitis and hemochromatosis did not differ with respect to their odds of symptom hindrance.

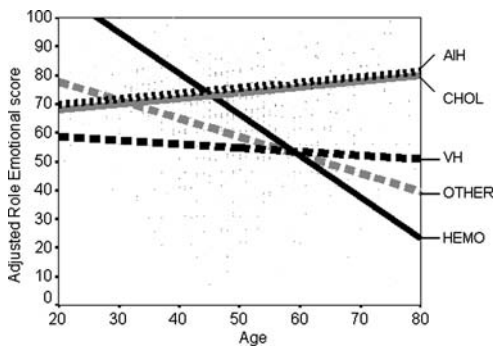

Figure 3. Mean SF-36 Physical and Mental Component Scores for chronic liver patients with various aetiologies, adjusted for gender, age, education level, disease stage, comorbidity, number of liver diseases per patient, use of liver disease medication and use of anti-depressiva/anti-psychotica. Legend coding for SF-36 component scores: PCS = Physical Component Scores, MCS = Mental Component Scores. For legend of aetiological groups, see legend Figure 1.

Table 4 shows the significant odds ratios associated with severe complaints mentioned in the various NLV items. Viral hepatitis patients showed significantly higher odds of severe change of personality due to the liver disease relative to patients with hemochromatosis, cholestatic or other liver diseases (Range of odds ratios: OR 1.56 [95% CI: 1.06, 2.29] relative to 'Other liver diseases' to OR 2.21 [95% CI: 1.44, 3.40] relative to cholestatic diseases). Odds of severe memory problems, severe decreased sexual interest and severe decreased sexual activity were not significantly different for patients with viral hepatitis, autoimmune hepatitis, hemochromatosis or cholestatic diseases.

Discussion

Our aim was to evaluate the impact of liver disease aetiology on generic HRQoL, disease-specific HRQoL and fatigue of chronic liver patients. Corrected for various factors, including disease stage, patients with viral hepatitis generally showed a worse HRQoL, but especially a worse mental health than other aetiological

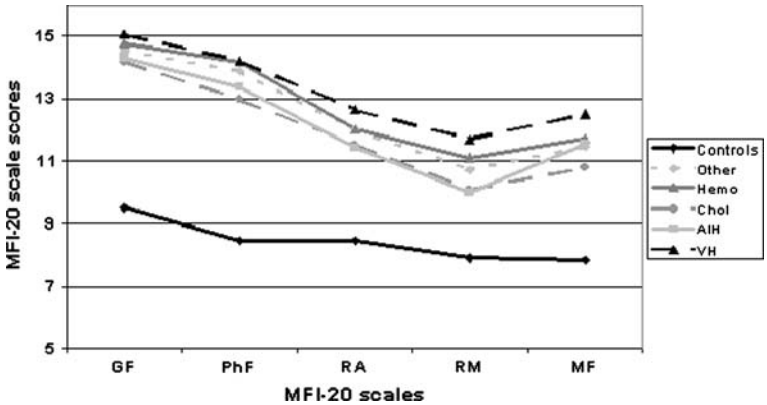

Figure 4. Per aetiological group the adjusted Role Emotional score (RE) by age. Lower RE scores indicate: more limitations in work or other daily activities due to emotional problems. For legend of aetiological groups, see legend Figure 1.

groups. Viral hepatitis patients demonstrated significantly higher odds of severe mental symptoms such as worry about the family situation, depression and fear of complications and significantly higher odds of being hampered by various mental and physical symptoms during daily activities. A new finding was that compared to other aetiological groups hemochromatosis patients demonstrated an impaired physical HRQoL, with prominent elements regarding fatigue and bodily pain. Hemochromatosis patients demonstrated significantly more bodily pain, higher odds of severe joint pain and their role emotional functioning steeply worsened with increasing age. All aetiological groups showed a significantly worse generic HRQoL and more fatigue than healthy controls.

The size of our study population had sufficient power and variation in aetiology and disease stage to allow HRQoL comparisons by means of sophisticated statistical methods. Since our study was the first Dutch observational study on HRQoL among patient members of the Dutch liver patient association, information regarding the size of the presented aetiological groups and their level of HRQoL was unknown and therefore an a priori power analysis could not be conducted. However, the information presented above, allowed us to estimate a sample size in the case a new study would be held among members of the NLV; Based on the current PCS standard deviation of our population, the significantly different mean PCS scores of viral hepatitis patients and hemochromatosis patients, a power of 0.80 and a significance level of 0.01, the sample size per aetiological group should be at least 63 (313 chronic liver patients in total), to find a significantly different PCS score. The number of patients of the aetiological groups in the current study clearly exceeds this sample size.

The fact that categorisation in aetiological and disease stage groups depended on self-reported data could be a potential weakness of our study, although in our pilot study inconsistencies between reported data and hospital data were few [12]. Nevertheless, there still could have been misclassification biases. Furthermore, our results may have been influenced by potential selection biases. Responders may have been a selection of relative healthy patients who felt well enough to complete the questionnaire, which may have led to an overestimation of HRQoL. This may also explain the high percentage of respondents engaged in low levels of work and leisure activities with physical effort. Furthermore it is unclear which patients are attracted by the patient association and how membership influences HRQoL. We compared the mean SF-36, and MFI-20 scores of our study population with the scores of an earlier study conducted at our outpatient and inpatient clinic [8]. Despite the fact that the earlier study also included hospitalised patients, our study population generally showed a worse generic HRQoL and more fatigue, suggesting that our study population may not be a representative sample of all chronic liver patients. Furthermore, it is unclear if the controls sample included a representative sample of liver patients for The Netherlands. Overrepresentation may have led to

Table 3. Adjusted *significant* ($p < 0.05$) odds ratios for symptom severity (upper diagonal) or symptom hindrance (lower diagonal) between aetiological groups

Aetiological groups showing significantly higher or lower odds ratios of *severe symptoms*					
	Viral hepatitis (reference)	Autoimmune hepatitis (reference)	Cholestatic diseases (reference)	Hemochromatosis (reference)	Other liver diseases (reference)
Viral hepatitis		Itch (2.09) Worry about family situation (2.23) Decr. appetite (2.27) Depression (2.36) Fear of complications (2.44)	Joint pain (1.88) Worry about family situation (2.76) Decr. appetite (1.98) Depression (2.67) Fear of complications (2.65)	Itch (1.88) Abdominal pain (1.90) Worry about family situation (2.75) Depression (1.83) Joint pain (0.44) Fear of complications (2.36)	Worry about family situation (2.02) Depression (1.72) Fear of complications (1.53)
Autoimmune hepatitis	Worry about family situation (0.41)		Joint pain (2.26) Itch (0.52)	Abdominal pain (2.44) Joint pain (0.53) Decreased appetite (0.45)	Joint pain (1.78) Decreased appetite (0.53)
Cholestatic diseases	Itch during daily activities (0.60) Joint pain (0.32) Worry about family situation (0.29)			Abdominal pain (2.12) Itch (1.72) Joint pain (0.23)	Fear of complications (0.58)
Hemochromatosis		Worry about family situation (4.85)	Itch during daily activities (2.48) Joint pain (9.16) Worry about family situation (6.82)		Joint pain (3.37) Abdominal pain (0.35)
Other liver diseases	Itch during daily activities (0.51) Joint pain (0.42) Sleepinessduring day (0.48) Depression (0.30) Jaundice (0.27)	Sleepiness during day (0.36) Depression (0.42)	Worry about family situation (2.47)	Joint pain (0.14) Sleepiness during day (0.29) Depression (0.27)	
	Viral hepatitis (reference)	Autoimmune hepatitis (reference)	Cholestatic diseases (reference)	Hemochromatosis (reference)	Other liver diseases (reference)
Aetiological groups showing significantly higher or lower odds ratios of symptom *hindrance*					

Table 4. Adjusted *significant* ($p < 0.05$) odds ratios between liver disease aetiological groups for complaints mentioned in the extra NLV items

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 (2.21) Change in time spending (1.57)	Personality change (1.68)	Memory problems (1.76) Personality change (1.56) Decr. sexual interest(1.96) Decr. sexual activity (1.75)
Autoimmune hepatitis				Memory problems (1.80)
Cholestatic diseases				
Hemochromatosis				Decr. sexual interest (1.77)

underestimation of the HRQoL differences between controls and liver patients.

One earlier study, conducted among chronic liver patients with various aetiologies (n = 353), reported that patients without cirrhosis (n = 127) have a similar HRQoL (measured by SF-36), regardless 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. Analysis within our non-cirrhotic group showed that viral hepatitis patients do show a significantly worse physical functioning, vitality, social functioning, role emotional functioning and mental health than cholestatic patients. Also our cirrhotic group demonstrated that viral hepatitis patients have a significantly worse HRQoL than cholestatic patients. Differences in disease stage definitions as well as statistical methods may explain the different results of Younossi et al. [3].

In our study we corrected for factors that could potentially explain the generally low HRQoL of patients with viral hepatitis. Despite these adjustments, viral hepatitis patients demonstrated a lower physical HRQoL and especially a lower mental HRQoL than most other aetiological groups. Our cross-sectional study design does not allow definite conclusions about the origin of the low HRQoL and especially the impaired mental health of viral hepatitis patients. Various hypotheses have been raised about the relation between negative feelings and somatic complaints. According to the *disability hypothesis*, personality changes including negative feelings such as depression and fear can *follow* from adverse consequences of accumulating health problems. But, according to the *psychosomatic hypothesis*, high levels of negative feelings may also *cause or worsen* physical health problems [17]. Viral hepatitis patients mostly suffered from impaired mental health, whereas various aspects of physical health (physical functioning, limitations due to physical problems) were often not significantly more impaired compared to other aetiological groups. This could be in line with the fact that disease progression in the case of viral hepatitis is largely silent. With regard to hepatitis C infection, the period between acute infection and manifestation of chronic liver disease is typically 20–30 years [18]. However, the fact that the majority of the cases of chronic viral hepatitis B, C (or D) cure at a very slow rate or do not cure [19] may put a strain on the mental health of these patients. This may especially be true for hepatitis C patients of whom 70% develop chronic hepatitis with 20% of this subgroup developing cirrhosis. With hepatitis B, chronic hepatitis develops in 5% of the formerly healthy adults and cirrhosis predominantly develops in 50% of the chronic hepatitis B patients with active viral replication. However, with hepatitis B as well as

hepatitis C, cirrhosis may lead to hepatic insufficiency, portal hypertension and hepatocellular carcinoma [18, 20]. The influence of impaired mental health on physical aspects of HRQoL may therefore be stronger than the influence of physical problems on mental health, which could support the *psychosomatic hypothesis*.

The *disability hypothesis* may support the strongly decreasing emotional health with increasing age in hemochromatosis patients. 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 [21–24]. As time passes, progressive pain may result in more emotional distress due to the dose–response relationship between pain and quality of life [25, 26]. Analysis of hemochromatosis patients indeed showed a significant positive relation between the bodily pain scale and the role emotional scale.

In conclusion, this study increased our insight in impact of liver disease aetiology on generic and disease specific HRQoL. After extensive correction, viral hepatitis patients showed a significantly worse HRQoL, but especially a worse mental health than all other aetiological groups. Particularly hemochromatosis patients demonstrated an impaired physical HRQoL and experienced significantly more bodily pain and more limitations due to emotional problems with increasing age. Potential interactions between physical and mental health require a multidimensional view during management of viral hepatitis and hemochromatosis patients.

Acknowledgements

Our study was supported by the Dutch foundation of Hepatogastroenterology (Maag Lever Darm Stichting), grant number WS 98–39. We wish to thank the NLV for their organisational support and their input in the development of various items and moreover all the NLV members for their enthusiastic participation in our study. Without their help this study would not have been possible. Finally we thank E. Smets and M. Müller for providing respectively the MFI-20 and the SF-36 Dutch norm data.

Appendix

List used for registration of patient aetiology in the background questionnaire.
For each liver disease in the list below, the following four questions were asked:

1. In which year was/were your liver disease(s) diagnosed by the medical specialist?
2. Was the duration of the liver disease longer than 6 months? (yes/no)
3. Are you using medication to suppress the liver disease? (yes/no)
4. Has the liver disease been cured? (yes/no)

Viral Hepatitis: Hepatitis A; Hepatitis B; Hepatitis C; Hepatitis D; Hepatitis E; Hepatitis G; Hepatitis CMV (Cytomegalo virus); Hepatitis EBV (Epstein-Barr virus); **Parenchymal liver disease, non-viral:** Autoimmune hepatitis; Alcoholic hepatitis; Drug induced hepatitis; Toxic hepatitis; Hepatitis due to an unknown cause; Steatosis (fatty degeneration of the liver); Granulomatous hepatitis; Sarcoidosis; Reye's syndrom; **Vascular disease:** Budd-Chiari syndrome; Venous congestion; Veno-occlusive disease; Porta-thrombosis; Idiopatic (or primary) portal hypertension; Cardiac cirrhosis; **Cholestatic liver diseases:** Primary Biliary Cirrhosis (PBC);Primary Sclerosing Cholangitis (PSC); Secondary Biliary Cirrhosis; **Congenital liver diseases, metabolic:** Wilson's disease (copper storage disease); Hemochromatosis; Alpha -1-antitrypsin-deficiency; Porphyria; Gilbert's syndrome; Dubin-Johnson syndrome; Crigler-Najjer disease; Primary glyceric aciduria; Rotor's syndrome; Galactosemia; Niemann-Pick disease; Gaucher's disease; **Congenital diseases, anatomical:** Congenital liver cysts; Choledochus-cyst(s); Congenital liver fibrosis; Biliary atresia; Allagille's syndrome; Arteriovenous malformation; Osler-Weber-Rendu disease; Caroli's syndrome; **Malignant malformations:** Hepatocellular carcinoma; Cholangiocarcinoma; APUD-oma; Carcinoid syndrome; Metastasis of the liver; Cholangiocellular carcinoma; **Benign malformations:** Hepatocellular adenoma; Hemangioma; Focal nodular hyperplasia; Nodular regenerative hyperplasia; **Parasitic liver diseases:** Amoeba abcess; Schistosomiasis; Echinococcus-cyst(s); **Cholelithiasis:** Cholecystolithiasis (Gallbladder stone disease); Choledocholithiasis (Bile

duct stone disease); Intrahepatic gall stones; **Other liver diseases:** Hepatic encephalopathy; **My liver disease has not been mentioned in the table. My liver disease(s) is/are:**1....,2....,3.....

References

1. CBS. Frequencies of death per primary cause of death and chronic diseases in 2000.
2. Foster GR, Goldin RD, Thomas HC.. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. Hepatology 1998; 27: 209–212.
3. Younossi ZM, Boparai N, Price LL, Kiwi ML, McCormick M, Guyatt G.. Health-related quality of life in chronic liver disease: The impact of type and severity of disease. Am J Gastroenterol 2001; 96: 2199–2205.
4. Marchesini G, Bianchi G, Amodio P, et al. Factors associated with poor health-related quality of life of patients with cirrhosis. Gastroenterology 2001; 120: 170–178.
5. Younossi ZM, Boparai N, McCormick M, Price LL, Guyatt G.. Assessment of utilities and health-related quality of life in patients with chronic liver disease. Am J Gastroenterol 2001; 96: 579–83.
6. Fayers PM, Machin D. Quality of Life, Assessment, Analysis and Interpretation. Chichester: John Whiley & Sons, LTD, 2000.
7. Bayliss MS. Methods in outcomes research in hepatology: Definitions and domains of quality of life. Hepatology 1999; 29: 3S–6S.
8. Unal G, Boer JBde, Borsboom GJ, Brouwer JT, Essink-Bot M, Man RA.de. A psychometric comparison of health-related quality of life measures in chronic liver disease. J Clin Epidemiol 2001; 54: 587–596.
9. Obhrai J, Hall Y, Anand BS. Assessment of fatigue and psychologic disturbances in patients with hepatitis C virus infection. J Clin Gastroenterol 2001; 32: 413–417.
10. Aadahl M, Hansen BA, Kirkegaard P, Groenvold M. Fatigue and physical function after orthotopic liver transplantation. Liver Transpl 2002; 8: 251–259.
11. Goldblatt J, Taylor PJ, Lipman T, et al. The true impact of fatigue in primary biliary cirrhosis: A population study. Gastroenterology 2002; 122: 1235–1241.
12. Plas SMvan der, Hansen BE, Boer JBde, et al. The Liver Disease Symptom Index 2.0; validation of a disease-specific questionnaire. Qual Life Res 2004; 13: 1469–1481.
13. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998; 51: 1055–1068.
14. Ware JE, Snow KK, Kosinski M, Gandek B.. SF-36 Health Survey Manual and Interpretation Guide. Boston: New England Medical Center, The health institute, 2004.
15. Smets EMA, Garssen B, Bonke B. Het meten van vermoeidheid met de multidimensionele vermoeidheidsindex (MVI-20), een handleiding. University of Amsterdam, Department of Medical Psychology, 1995.
16. Smets EM, Visser MR, Willems-Groot AF, Garssen B, Schuster-Uitterhoeve AL, Haes JCde. Fatigue and radiotherapy: (B) experience in patients 9 months following treatment. Br J Cancer 1998; 78: 907–912.
17. Watson D, Pennebaker JW.. Health complaints, stress, and distress: Exploring the central role of negative affectivity. Psychol Rev 1989; 96: 234–254.
18. Feldman M, Scharschmidt BF, Sleisenger M.. Gastrointestinal and Liver Disease. Philadelphia: WB Saunders Company, 1998.
19. Meer Jvan der, Stehouwer C.. Interne Geneeskunde. Houten: Bohn Stafleu Van Loghum, 2001.
20. Ganem D, Prince AM. Hepatitis B virus infection–natural history and clinical consequences. N Engl J Med 2004; 350: 1118–1129.
21. Braunwald E, Fauci AS. Harrison's Principles of Internal Medicine Online. The McGraw-Hill Companies, 2002.
22. Willis G, Scott DG, Jennings BA, Smith K, Bukhari M, Wimperis JZ.. HFE mutations in an inflammatory arthritis population. Rheumatology (Oxford) 2002; 41: 176–179.
23. Vaiopoulos G, Papanikolaou G, Politou M, Jibreel I, Sakellaropoulos N, Loukopoulos D. Arthropathy in juvenile hemochromatosis. Arthritis Rheum 2003; 48: 227–230.
24. McDonnell SM, Preston BL, Jewell SA, et al. A survey of 2,851 patients with hemochromatosis: Symptoms and response to treatment. Am J Med 1999; 106: 619–624.
25. Wang XS, Cleeland CS, Mendoza TR, et al. The effects of pain severity on health-related quality of life: A study of Chinese cancer patients. Cancer 1999; 86: 1848–1855.
26. Katz N.. The impact of pain management on quality of life. J Pain Symptom Manage 2002; 24: S38–S47.

Address for correspondence: Bettina E. Hansen, Department of Gastroenterology and Hepatology, Erasmus Medical Centre Rotterdam, P.O. Box 2040, 3000 CA, Rotterdam, The Netherlands
Phone: +31-10-4088231; Fax: +31-10-4365916
E-mail: b.hansen@erasmusmc.nl