Health-related quality of life in cirrhotic patients: a case-control study

Qualité de vie chez les patients cirrhotiques : étude cas-témoins

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RÉSUMÉ

Introduction : L'évaluation de la qualité de vie chez les patients cirrhotiques est de plus en plus fréquemment rapportée dans la littérature.

Objectifs : Comparer les scores de qualité de vie des patients cirrhotiques par rapport à ceux des témoins sains et de déterminer les facteurs associés à l'altération de la qualité de vie chez les patients cirrhotiques.

Méthodes : La qualité de vie chez les patients cirrhotiques a été mesurée en utilisant la version tunisienne du questionnaire MOS 36-item Short-Form Health Survey (SF-36) et la version arabe du questionnaire Liver Disease Symptom index 2.0 (LDSI2.0). Un seul questionnaire, le SF-36, a été administré aux témoins qui étaient appariés selon l'âge et le sexe aux patients. Les scores du SF-36 ont été comparés entre les patients cirrhotiques et les témoins et les scores LDSI2.0 ont été comparés chez les patients cirrhotiques en fonction des caractéristiques de la cirrhose. Les facteurs associés à l'altération de la qualité de vie ont été identifiés en utilisant une régression logistique.

Résultats : Cinquante patients cirrhotiques et 50 témoins ont été inclus dans l'étude. Les patients cirrhotiques avaient des scores SF-36 significativement plus bas que ceux des témoins concernant les 8 dimension (p<0,001). Les items les plus altérés du LDSI2.0 étaient la sévérité de la crainte des complications (item 8), le changement de la gestion du temps (item 13), la diminution de l'intérêt pour l'activité sexuelle (item 14) et la diminution de l'activité sexuelle (item 15). L'analyse par régression logistique multiple a mis en évidence que le sexe féminin (p=0,009), le diabète (p= 0,046), le traitement diurétique (p=0,022), la bilirubinémie élevée (p=0,045) et le temps de prothrombine allongé (p=0,041) étaient associés à l'altération de la qualité de vie.

Conclusions: La qualité de vie chez les patients cirrhotiques était significativement plus altérée que celle des témoins. Le sexe féminin, le diabète, le traitement diurétique, la bilirubinémie élevée et le temps de prothrombine allongé étaient significativement associés à l'altération de la qualité de vie.

Mots-clés

Evaluation de l'impact sur la santé ; état de santé ; hépatopathie ; questionnaire

SUMMARY

Background: Assessment of health-related quality of life (HRQOL) in patients with cirrhosis has been increasingly reported in literature.

Aims: To compare quality of life scores between cirrhotic patients and healthy controls and to assess factors associated with the impairment of quality of life in cirrhotic patients.

Methods: HRQOL was measured in cirrhotic patients by the Tunisian version of MOS 36-item short-form health survey (SF-36) and the Arabic version of the Liver Disease Symptom index 2.0 (LDSI2.0). Age-and sex- matched controls were asked to complete only the SF36. The SF36 scores were compared between cirrhotic patients and controls and LDSI2.0 scores were compared across cirrhotic patients according to the characteristics of cirrhosis. Factors associated with poor perceived health status were identified by logistic regression.

Results: Fifty cirrhotic patients and fifty controls were enrolled in the study. The cirrhotic group had significantly lower SF36 scores than healthy controls in all 8 dimensions (p<0.001). Most impaired LDSI items were severity of fear of complications (item 8), change in use of time (item 13), decreased sexual interest (item 14) and decreased sexual activity (item 15). Multiple logistic regression analysis showed that female sex (p=0.009), diabetes (p=0.046), treatment with diuretics (p=0.022), increased levels of serum bilirubin (p=0.045) and prolonged prothrombin time (p=0.041) were associated with poorer HRQOL.

Conclusions: HRQOL was significantly more impaired in cirrhotic patients than controls. Female sex, diabetes, treatment with diuretics, increased levels of serum bilirubin and prolonged prothrombin time were important factors in reducing HRQOL.

Key-words

Health impact assessment; health status; liver disease; questionnaire

INTRODUCTION

Cirrhosis is considered a major public health problem worldwide. The natural history of cirrhosis includes mainly two phases: compensated cirrhosis where patients remain asymptomatic and decompensated cirrhosis which is characterized by development of ascites and complications such as variceal bleeding, encephalopathy, hepatocellular carcinoma and hepato-renal syndrome (1). Thus, cirrhosis may have a significant negative impact on all aspects of well-being and health-related quality of life (HRQOL). Over the past two decades, HRQOL has been considered an important outcome measure in research and clinical care of patients with cirrhosis (2). The concept of HRQOL is defined by the World Health Organization as "individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (3). Many tools have been developed to assess HRQOL. The generic instruments can be used across a wide range of populations and conditions. The most commonly used generic instrument is the Medical Outcomes Study 36-Item Short Form (SF-36) (4). Other tools are more sensitive and more specific than generic ones and can only be valid to a specific disease: the disease-specific questionnaires. The most widely used liver disease specific questionnaires are the Hepatitis Quality of Life Questionnaire (HQLQ)", "The Chronic Liver Disease Questionnaire (CLDQ)", "The Liver Disease Quality of Life Questionnaire (LDQOL)" and "The Liver Disease Symptom Index2.0 (LDSI2.0). Thus far, only few data are available on HRQOL in cirrhotic patients, limited to viral infection or liver transplantation (5, 6). The aims of our study were to assess HRQOL in cirrhotic patients in comparison with controls and to identify factors that could be associated with the impairment of quality of life in cirrhotic patients.

METHODS

The study was performed in accordance with the Declaration of Helsinki of the World Medical Association and was approved by the local ethics committee. All patients gave their informed consent prior to the study inclusion.

Study population

A cross-sectional study was carried out over a period of 6 months. Patients were selected from the outpatient clinics. They were eligible for inclusion if they had established diagnosis of cirrhosis based on clinical findings, laboratory tests, and/or histological examination. Excluding criteria were age <18 years old, overt hepatic encephalopathy at inclusion, cancer of whatever tissue type including hepatocellular carcinoma, a history of psychiatric or neurological disorders and severe co-morbidities. The control group consisted of healthy volunteers who were matched by age and sex with the patients. Controls were selected from the general population and include friends and relatives of patients.

Data collection

Main data items that were collected from study patients were demographics, education, marital status, professional occupation, characteristics of cirrhosis such as etiology, disease duration, severity according to Child-Pugh score, previous decompensation episodes, prior complications and current therapy. Associated diseases were diagnosed on the basis of previous medical records or specific drug treatment.

Measurement instruments

Patients were asked to complete two questionnaires: the Tunisian version of MOS 36-item Short-Form health survey (SF-36) (7) and the Arabic version of the Liver Disease Symptom Index 2 .0 (LDSI2.0) (8). Controls were asked to complete only the MOS 36-item short-form health survey (SF-36).

- *Short Form-36 health survey (SF-36):*

The SF-36 is a generic, self-administered instrument that assesses HRQOL. It is a short form of the Medical Outcomes Study composed of 149 items (9). SF-36 consists of 36 multiple-choice-questions. It measures 8 domains: physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE) and mental health (MH). Two summary scores can also be calculated: a mental component summary (MCS) and a physical component summary (PCS). Questions are scored on a scale from 0 to 100. Higher scores indicate better HRQOL. The SF-36 has been translated into Tunisian dialect and was validated to assess HRQOL in Tunisian population (7).

- *The Liver Disease Symptom Index 2 .0 (LDSI2.0):*

The LDSI2.0 is a disease specific questionnaire developed in the Netherlands in 2004 (10). It assesses

HRQOL in patients with chronic liver disease. The LDSI2.0 is composed of 24 questions divided into two subscales: symptom severity and limitation of daily life due to symptoms. All items have "the last week" as their time frame and are scored on a five-point scale ranging from 0 "not at all" to 4 to "a high extent". Lower scores demonstrate better quality of life. The Arabic version of LDSI2.0 was validated in 2012 (8). We considered patients who answered 1 to 2 have moderate symptoms (or hindrance) and those who answered 3 to 4 have severe symptoms (or hindrance).

Statistical analysis

Statistical analysis was performed with Statistical Package for Social Science (SPSS) software version 21.0 (IBM Corp., Armonk. New York, USA). Data were summarized as mean and percentage. The comparison of qualitative variables was carried out by the chi-square test and in case of non-validity by the Fischer test. The Mann-Whitney U test was used to compare quantitative variables. Univariate logistic regression analysis was conducted to investigate the association between characteristics of cirrhosis and impaired quality of life. Variables that had a p-value of less than or equal to 0.2 through the univariate logistic regression were selected to perform a multiple logistic regression analysis. A p-value ≤ 0.05 was deemed to denote statistical significance.

RESULTS

Patient characteristics

Fifty cirrhotic patients and 50 controls were included in the study. The mean age of patients was 59.3 ±10.5 years and 32 (64%) were women. Almost 76% (n=38) were married and more than half of the sample were unemployed (58%; n= 29). Nearly 60% (n=30) of patients were suffering from at least one comorbidity such as diabetes (44%; n=22) and hypertension (38%; n=19). Main etiology of cirrhosis was viral hepatitis B and C (62%; n=31) and roughly two-thirds of patients had at least 1 previous episode of decompensation (66%; n=33). Demographic and clinical variables are described in Table 1.

Table 1: Demographic and clinical characteristics of the patients

Variables	N (%)
Age; mean ± SD	59.3±10.5
Gender	
Male	18 (36)
Female	32 (64)
Marital status	
Single (never married ; divorced ; widowed)	12 (24)
Married	38 (76)
Education	
Illiterate	23 (46)
Elementary school	17 (34)
Secondary school	8 (16)
Higher education (university)	2 (4)
Current employment status	
Employed	13 (26)
Unemployed	29 (58)
Retired	8 (16)
Comorbidities	
No comorbidities	20 (40)
Diabetes mellitus	22 (44)
Hypertension	19 (38)
Others	10 (20)
Etiology of cirrhosis	
Viral hepatitis (B/C)	31 (62)
Others	10 (20)
Undetermined etiology	9 (18)
Severity of cirrhosis	
Child-Pugh A	27 (54)
Child-Pugh B	18 (36)
Child-Pugh C	5 (10)
Ascites	
No	17 (34)
Controlled (mild)	33 (66)
Complications	
Variceal bleeding	39 (78)
Prior hepatic encephalopathy	9 (18)
Medications	
Diuretics	28 (56)
Beta-blockers	40 (80)
Lactulose	9 (18)
PT (%); mean ± SD	65.7±18.1
BUN (g/L) ; mean ± SD	0.03±0.07
Serum bilirubin(mg/L); mean ± SD	16±10.1

SD: Standard deviation; PT: prothrombin time; BUN: blood urea nitrogen

SF-36 scales and subscales

The domains most affected in patients with cirrhosis were RP, VT and RE. The largest percentage of subjects (50%) with below average scores were encountered in the VT

and MH subscales. On the other side, RP subscale had the best evaluation with 70% of the subjects with above average scores (Table 2). Compared with controls, patients scored significantly lower on all the SF36 subscales ($p \leq 0.001$) (Figure 1).

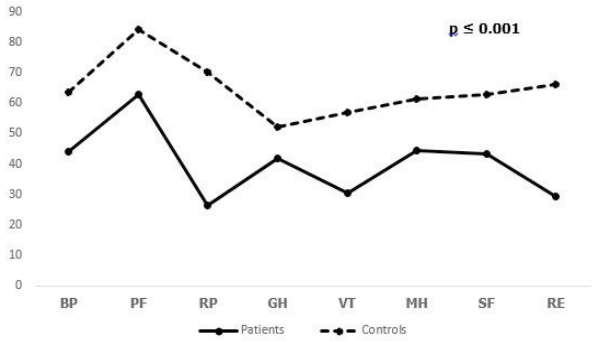

Figure 1: SF-36 scores of cirrhotic patients compared with controls
BP: bodily pain, PF: physical functioning, RP: role limitations due to physical problems, GH: general health, VT: vitality, MH: mental health SF: social functioning, RE: role limitations due to emotional problems

Table 2: Central tendency and dispersion of subscales of SF36

	Median	P25	P50	P75	Below average subjects N (%)
PF	70±25.9	45	70	85	23 (46%)
RP	25±23.9	0	25	50	15 (30%)
BP	45±32.6	10	45	77.5	24 (48%)
GH	45±9.9	40	45	46.25	23 (46%)
VT	27.5±18	15	27.5	41.25	25 (50%)
SF	37.5±29.4	25	37.5	62.5	21 (42%)
RE	33.3±29.8	0	33.3	33.3	20 (40%)
MH	46±16.7	36	46	56	25 (50%)

PF: physical functioning, RP: role limitations due to physical problems, BP: bodily pain, GH: general
health, VT: vitality, SF: social functioning, RE: role limitations due to emotional problems and MH: mental health P25:25th percentile, P50:50th percentile, P75:75th percentile

Descriptive item analysis of the LDSI 2.0

Aspects of HRQOL most impaired in cirrhotic patients were severity of fear of complications (item 8), change in use of time (item 13), decreased sexual interest (item 14) and decreased sexual activity (item 15) since most patients experienced severe symptoms and/or hindrance. In contrast, pain in the right upper abdomen (items 3A and 3B), sleeping during the day (items 4A and 4B) and jaundice (items 9A and 9B) were minimally affected as nearly all patients had low scores. Distribution of LDSI2.0 item scores is detailed in table 3.

Table 3: Distribution of LDSI2.0 item scores

Items /subscales	Score distribution (N=50)					Severe symptoms/ hindrance N (%)
	0	1	2	3	4	
Itch						
1A. Severity	30	7	7	4	2	6 (12)
1B. Hindrance in daily activity	32	10	4	3	1	4 (8)
1C. Hindrance in sleeping	40	2	2	3	3	6 (12)
Joint pain						
2A. Severity	5	16	17	7	5	12 (24)
2B. Hindrance in daily activity	10	13	15	8	4	12 (24)
Pain in the right upper abdomen						
3A. Severity	26	8	14	2	0	2 (4)
3B. Hindrance in daily activity	29	10	11	0	0	0 (0)
Sleeping during the day						
4A. Severity	36	7	4	1	2	3 (6)
4B. Hindrance in daily activity	37	4	7	2	0	2 (4)
Worry about family situation						
5A. Severity	3	19	11	13	4	17 (34)
5B. Hindrance in daily activity	14	17	7	10	2	12 (24)
Decreased appetite						
6A. Severity	20	14	7	8	1	9 (18)
6B. Hindrance in daily activity	26	9	7	8	0	8 (16)
Depression						
7A. Severity	5	17	19	8	1	9 (18)
7B. Hindrance in daily activity	14	13	17	5	1	6 (12)
Fear of complication						
8. Severity	1	7	17	18	7	25 (50)
Jaundice						
9A. Severity	43	6	1	0	0	0 (0)
9B. Hindrance in daily activity	43	5	1	1	0	1 (2)
Other aspects of HRQOL						
10. Memory problems	15	10	18	6	1	7 (14)
11. Change of personality	1	14	21	9	5	14 (28)
12. Hindrance in financial affairs	16	11	8	6	9	15 (30)
13. Change in use of time	2	10	15	18	5	23 (46)
14. Decreased sexual interest	9	4	8	5	24	29 (58)
15. Decreased sexual activity	0	4	11	3	32	35 (70)

Comparison of LDSI2.0 scores among cirrhotic patients

In univariate analysis, factors increasing scores of the LDSI2.0 were gender, age below 50 years, comorbidities (diabetes and hypertension), non-viral etiology of cirrhosis, advanced liver disease (Child-Pugh B/C), portal hypertensive gastropathy, use of diuretics, increased levels of blood urea nitrogen (BUN) and bilirubin and decreased levels of albumin and prothrombin (PT). These factors were associated with the impairment of itch (items 1A, 1B and 1C), joint pain (item 2A), sleeping during the day (item 4B), decreased appetite (items 6A and 6B), depression (item 7A), hindrance in financial affairs (item 12), change in use of time (item 13) and decreased sexual interest (item 14) (Table 4).

Table 4: Factors associated with poorer quality of life (subscores 3 and 4) according to LDSI2.0 scale (univariate analysis)

	1A	1B	1C	2A	4B	6A	6B	7A	12	13	14
Male sex									+		
Female sex				+							+
Age < 50							+		+		
Diabetes	+	+	+								
Hypertension			+								+
Non-viral etiology						+	+				
Child-Pugh B/C										+	
Portal hypertensive gastropathy										+	
Diuretics									+	+	
BUN >0.45g/L						+	+				
Albumine <30 g/L								+			
Bilirubin > 340 umol/L							+				
PT <40%					+	+					

1A: Severity of itch; 1B: Hindrance of itch in daily activity; 1C: Hindrance of itch in sleeping; 2A: severity of joint pain; 4B: hindrance of sleeping during the day in daily activity; 6A: severity of decreased appetite; 6B: hindrance of decreased appetite in daily activity; 7A: severity of depression; 12: Hindrance in financial affairs; 13: Change in use of time; 14: Decreased sexual interest ; BUN: blood urea nitrogen; PT: prothrombin time
+: indicates those associations with p<0.05

In multivariate analysis, the independent variables associated with severe symptoms and/or hindrance were female sex *(p=0.009)*, diabetes *(p=0.046)*, use of diuretics *(p=0.022),* increased levels of BUN *(p=0.045)* and decreased PT *(p=0.041)* (Table 5).

Table 5: Factors associated with poorer quality of life (subscores 3 and 4) according to LDSI2.0 scale (multivariate analysis)

	6A	12	13	14
Female sex				+
Diabetes			+	
Diuretics		+		
BUN >0.45g/L	+			
PT <40%	+			

6A: severity of decreased appetite; 12: Hindrance in financial affairs; 13: Change in use of time; 14: Decreased sexual interest; BUN: blood urea nitrogen; PT: prothrombin time +: indicates those associations with p<0.05

DISCUSSION

The current study showed that cirrhotic patients perceive significantly more impaired HRQOL compared with matched controls. Female sex, diabetes, treatment with diuretics, increased levels of bilirubin and decreased PT were independent factors associated with poorer HRQOL. This conclusion is based on two questionnaires: the SF-36 and the LDSI2.0. To our knowledge, our study is the first at the national level to assess the HRQOL by means of two validated questionnaires in Arabic language: the SF36 and the LDSI2.0. However, some limitations of the present study should be considered. The main one is the small number of cirrhotic patients. Moreover, patients were recruited from a tertiary center and therefore may not be representative of all patients with chronic liver disease. Then, carefulness is required before extrapolating results to the general population.

Cirrhosis is an example of chronic disease that could deeply alter patients' functioning and well-being. Most studies investigating HRQOL in patients with chronic liver disease have been performed using the SF-36 as a generic instrument (4).

In the present study, the most affected domains were RP (Role limitations due to physical problems), RE (Role limitations due to emotional problems) and VT (vitality). The highest scores were encountered in 2 dimensions: PF (physical functioning) and MH (mental health).

The current study showed that the cirrhotic group had significantly lower SF36 scores than healthy controls in all 8 dimensions. The results observed in our study are similar to those observed in previous research showing lower SF-36 scores in patients with chronic liver disease (11, 12).

Since the SF-36 could not assess liver disease specific symptoms such as pruritus and jaundice, determinants of HRQOL in our patients have been assessed using the LDSI2.0 as a specific instrument. To assess the severity of symptoms and their hindrance, we empirically used a binary classification: moderate symptoms (or hindrance) corresponding to scores 1 to 2 and severe symptoms (or hindrance) corresponding to scores 3 to 4.

In some previous research using LDSI2.0 to measure HRQOL, two scores were established by calculating the mean values of symptom severity and symptom hindrance. However, we consider this method not appropriate for assessing severity of symptoms since means and standard deviations (SDs) are not meaningful for qualitative ordinal variables such as the five-point scale LDSI2.0 score (13, 14) Other international studies using the LDSI2.0 focused only on calculating the prevalence of symptoms and then, did not consider symptom severity (15).

In our study, descriptive item analysis demonstrated that most impaired LDSI2.0 items were severity of fear of complications (item 8), change in use of time (item 13), decreased sexual interest (item 14) and decreased sexual activity (item 15). Our findings did not corroborate those of Saffari et al where the means of the items 5A and 12 were higher than other items (14). However, Hunter et al have shown a significantly impaired male sexual function among patients with chronic hepatitis C virus infection. This male sexual dysfunction was related to the severity of liver disease and associated hypoalbuminemia (16).

Our results showed that female sex had a significant negative impact on the perceived severity of symptoms. The most impaired component was decreased sexual interest.

Our findings are consistent with previous studies of patients with chronic liver disease demonstrating that female gender may be an important factor in reducing HRQOL (17, 18). Possible cause was that female patients paid more attention on their health and spent more time on consulting treatment services (17, 19)

Diabetes was also found to be an independent factor associated with impaired HRQOL among our patients. It was mainly associated with change in use of time. Our results are in line with those of other published reports showing that active medical comorbidities mainly diabetes and hypertension were associated with poorer HRQOL in cirrhotic patients (4, 20). Reduced HRQOL in such patients may result from the use of a large number of drugs of various classes and their possible side effects. It could also be explained by the increased risk of psychiatric disorders caused by such chronic physical illnesses (4). Moreover, episodes of hypoglycemia, fear of hypoglycemia and change in life style in diabetic patients may further alter HRQOL (21).

In the current study, use of diuretics was also shown to have a negative impact on HRQOL in cirrhotic patients. Our results corroborate those of Marchesini et al where use of diuretics had effects on most domains of HRQOL measured by the SF-36 and Nottingham Health Profile (NHF) questionnaires (4, 22). This effect could result from adverse effects of diuretics such as fatigue and muscle cramps (23).

Our study also demonstrated that increased serum levels of bilirubin and decreased prothrombin were associated with reduced HRQOL in our study. Our findings are in agreement with those of Gao et al showing hyperbilirubinemia and prolonged prothrombin time were important factors in reducing HRQOL (17). One explanation is that hyperbilirubinemia and prolonged prothrombin time both reflect advanced liver failure. In fact, several studies have disclosed an inverse correlation between HRQOL and Child-Pugh stage demonstrating that advanced liver failure had a negative impact on HRQOL(17, 22, 24). Indeed, it has been established that impaired liver function increases the risk of complications in cirrhotic patients(25). In our study, advanced Child-Pugh stage was univariately associated with impaired HRQOL, mainly with the item change in use of time (item 13). However, we did not found this association in multivariate analysis which is not in accordance with the above studies (17, 22). A possible explanation for the discrepant results is the lack of power of our study due to the small number of the included cirrhotic patients.

In conclusion, findings of our study may be useful to draw physicians' attention to some items. First, studies on factors associated with impaired HRQOL in chronic liver disease should use both generic and liver-specific instruments for more accurate HRQOL assessment. Second, active medical comorbidities should be controlled in patients with cirrhosis since they could have negative effect on HRQOL. Third, physicians should check for adverse effects of drugs, particularly diuretics to prevent further impairment of HRQOL. Further studies are needed to identify appropriate management strategies to improve HRQOL in cirrhotic patients.

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