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ORIGINAL ARTICLE

Depression rather than liver impairment reduces quality of life in patients with hepatitis C

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Objective: Patients with chronic hepatitis C (CHC) have a poorer quality of life than those with other chronic liver diseases. However, some of the factors that determine health-related quality of life (HRQOL) in these patients, such as the degree of liver fibrosis, are still controversial. Therefore, the aim of the present study was to investigate the impact of CHC on HRQOL by conducting clinical, psychiatric, and sociodemographic evaluations.
Methods: One hundred and twenty-four consecutive patients attending a referral center for hepatitis were evaluated using the Mini-International Neuropsychiatry Interview, the Hamilton Depression Rating Scale, the Hospital Anxiety and Depression Scale, and the Medical Outcomes Study 36-Item Short-Form Health Survey. Multiple linear regression analyses were used to quantify independent associations between HRQOL and the clinical, psychiatric, and sociodemographic variables of interest.
Results: Reduced HRQOL was independently associated with major depressive disorder (MDD) and with elevated levels of alanine aminotransferase, but was not associated with hepatic cirrhosis.
Conclusions: MDD rather than the grade of liver fibrosis was strongly associated with HRQOL impairment in patients with CHC. These findings highlight that, in patients with CHC, the psychological effects of the disease deserve more attention and the implementation of integrated medical, psychiatric, and psychological care may be helpful.

Keywords: Chronic hepatitis C; cirrhosis; health-related quality of life; major depressive disorder

Introduction

Approximately 170 million individuals are infected with the hepatitis C virus (HCV) worldwide.[1] HCV is a major cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC), and is responsible for more than 475,000 deaths around the world each year.[1] The natural course of chronic hepatitis C infection (CHC) is slow and insidious; 50-80% of acutely infected individuals will progress to HCV chronic carrier status. Of these, 20% develop cirrhosis and its complications after 20 to 30 years of infection.[2] In addition, HCV infection is associated with a series of extrahepatic manifestations, including depressive and anxiety symptoms, fatigue, and musculoskeletal/joint pain, which have been linked to reduced health-related quality of life (HRQOL).[3]

Issues linked to HRQOL have become remarkably important in the healthcare field.[4] HRQOL is one dimension of broader quality of life that is more directly related to health, and it focuses on the patient's subjective evaluation of well-being, individual experiences, and values regarding the process of being sick.[5] Evaluation of this parameter is essential, because it is known that the distress caused by a disease transcends target organ damage. Consequently, patients with a similar pattern of liver injury might have different degrees of suffering.

Although HRQOL is variably impaired in cirrhotic patients, the results of studies evaluating the impact of the degree of liver fibrosis on HRQOL are still controversial.[6,7] Particularly in patients with CHC, scores indicative of poorer HRQOL have been identified even in the absence of clinically significant hepatic disease when compared with the scores of healthy individuals.[8]

Furthermore, the influence of viral load on HRQOL is unclear. Although it has been suggested that host factors are the major determinants of HRQOL in patients with CHC, some studies have shown that a sustained viral response improves HRQOL in patients receiving specific treatment for HCV.[9]

Despite the fact that CHC has a negative influence on all dimensions of HRQOL, including its physical, psychological, and social aspects,[10] relevant issues should be

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raised, such as the translation of the results measured with generic or specific HRQOL instruments into clinical practice and, consequently, how these findings may influence clinical decision-making. Furthermore, regardless of the stage of liver disease, other potential predictors contribute to impaired HRQOL in patients with CHC, particularly psychiatric illness, which is common among these subjects.[11] The interrelationship between liver function and psychiatric profile may be more multifaceted than suspected.[11,12] Few prospective studies have assessed HRQOL in CHC patients using detailed clinical and psychiatric approaches in combination with semi-structured interviews for psychiatric diagnosis.[13,14]

Depressive symptoms have been extensively identified in adults with chronic health conditions,[15] and correlate negatively with HRQOL. Patients with CHC have a high prevalence of depressive disorders,[11,16] up to 70%, which is seven-fold higher than that found in the general population, independently of the degree of hepatic injury.[8] As described above, CHC interferes not only with physical symptoms but also with psychological and social functioning.[8]

This study focuses on the integration of the patients' medical history, especially the evaluation of aspects beyond liver disease, while simultaneously measuring quality of life in the context of CHC. To this end, a multiprofessional and interdisciplinary approach was used to integrate the diverse health-related, psychological, and social aspects that are strongly linked to HRQOL. Expanding the assessment of these patients enables us to not only enhance knowledge about hepatitis C and other liver diseases, but also to recognize other medical issues, such as comorbid psychiatric difficulties, which, as a whole, may significantly influence the HRQOL of patients with chronic diseases,[17] such as CHC.

Therefore, the aim of this study was to investigate whether variables related to sociodemographic characteristics, degree of liver impairment, clinical comorbidities, and psychiatric illnesses – especially depressive disorders – are independently associated with HRQOL in patients with CHC. We hypothesized that depressive symptoms might be significantly associated with reduced HRQOL in HCV-infected patients, regardless of the presence of clinically significant hepatic disease.

Patients and methods

Design

This cross-sectional study was conducted between February 2010 and April 2012. We prospectively screened 152 consecutive outpatients aged $>$ 18 years. Each had been referred to the Viral Hepatitis Outpatient Clinic of Hospital das Clínicas da Universidade Federal de Minas Gerais, Belo Horizonte, Brazil, and met the inclusion criteria of the study for CHC, which was confirmed by the presence of specific anti-HCV antibodies and HCV-RNA. The exclusion criteria were refusal to participate in the study, age $<$ 18 years, pregnancy, hepatic encephalopathy, HBV/HCV or HCV/HIV co-infection, renal failure, current antiviral treatment, past or present use of antidepressants, presence of any physical or mental condition that might exert an undue influence on the interview process, and patients with advanced disease. Patients with clinical liver decompensation or hepatocellular carcinoma were also excluded. Twenty-eight patients were not included in the sample. Patients with hepatitis C virus antibody (anti-HCV$^+$) but HCV-RNA$^-$ were excluded (n=9). Other patients were excluded for spontaneous viral clearance following acute hepatitis C infection (n=1), hepatic encephalopathy (n=1), HBV/HCV co-infection (n=2), and chronic renal failure (n=8). In addition, one individual refused to participate and a further six patients who had initially agreed to take part in this study failed to complete the questionnaire and were thus excluded from analysis.

Participants

A total of 124 patients (72 [58.1%] female and 52 [41.9%] male, mean age 53.2$\pm$11.0 years) remained in the study. The patients underwent clinical and psychiatric evaluation. At the time of assessment, these individuals were not receiving antiviral treatment. The study was approved by the institutional Research Ethics Committee, and all of the included patients provided written informed consent.

Laboratory parameters

HCV status was evaluated by a third-generation ELISA (AxSYM HCV, version 3.0; Abbott GmbH & Co., Wiesbaden, Germany). HCV-RNA was detected by an AMPLICOR 2.0 assay (Roche Diagnostics, Branchburg, NJ) according to the manufacturer's instructions. Viral load was determined using a commercial test (Cobas TaqMan HCV test V.2.0; Roche Molecular Systems, Pleasanton, CA). HCV genotyping was performed by using a line probe assay (VERSANT HCV genotyping assays; Bayer Diagnostics, Tarrytown, NY) according to the manufacturer's recommendation. Patients testing positive for HCV-RNA were defined as having CHC. Viral load quantification and the HCV genotyping were available for 76% of patients. According to our treatment protocol, only those patients who met all criteria for antiviral therapy underwent investigation of viral load and HCV genotyping.

Sample size calculation

The sample size was calculated using the statistical program Power and Sample Size Calculations version 3.0.[18] A sample consisting of 120 patients was required for a multiple linear regression analysis with 12 predictors, a significance level of $p \leq 0.05$, and a statistical power of 0.80.

Measures/instruments

During recruitment, an in-person interview was conducted using instruments to assess the patients' sociodemographic and clinical characteristics, psychiatric comorbidities,

and HRQOL. The following questionnaires were included: a sociodemographic questionnaire that included items related to the patient's gender, age, educational level, family income, lifestyle factors (smoking, alcohol abuse [$>$ 20 g/day for females and $>$ 40 g/day for males], and illicit drug use); the Mini-International Neuropsychiatry Interview (MINI-Plus 5.0), consisting of a brief standardized diagnostic interview comprising the primary axis I disorders of the DSM-IV and the ICD-10; and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), which measures HRQOL.

Psychiatric diagnoses were established by using the Brazilian version of the MINI-Plus 5.0,[19] which was designed for clinical practice and research in psychiatric and primary care settings. Although the MINI-Plus is a satisfactory instrument for diagnosing psychiatric disorders, a semi-structured interview was also used for detailed psychiatric evaluations of these patients. This interview was conducted by two psychiatrists and one psychologist (RAF, LRC, and CCC) and included a clinical psychiatric approach in combination with a predetermined set of open-ended questions.

To assess the rate of depression, the patients who were initially diagnosed with major depressive disorders (MDD) were evaluated using the 21-item Hamilton Depression Rating Scale (HDRS)[20] and the 14-item Hospital Anxiety and Depression Scale (HADS).[21] The HDRS scores classify the rate of depression as follows: 0-7, absence of depression or depression remission; 8-17, mild depression; 18-24, moderate depression; and $\geq$ 25, severe depression. The overall 14-item HADS consists of two subscale items, seven of which evaluate anxiety (HADS-A) and seven of which evaluate depression (HADS-D), with each of the seven items being graded on a four-point scale. The responses to the HADS were used to assess the frequency and severity of anxiety and depression. A score cutoff of $\geq$ 9 was used for both the HADS-A and HADS-D subscales.

HRQOL was assessed by a generic questionnaire, the SF-36, which is considered to be the most suitable generic instrument for HRQOL measurement in chronic liver diseases.[22] This multidimensional instrument measures four domains of physical health (General Health Perceptions, Physical Functioning, Physical Role Functioning, Bodily Pain) and four domains of mental health (Emotional Role Functioning, Social Role Functioning, Vitality, Mental Health). Each domain has a final score of 0-100, in which zero corresponds to the worst and 100 to the best HRQOL, respectively. The SF-36 domains can also be grouped into two subscales: the physical component summary (PCS) and the mental component summary (MCS).

Clinical comorbidities

Hypertension (HTN) was diagnosed using the 2013 European Society of Hypertension/European Society of Cardiology (ESH/ESC) Guidelines,[23] and diabetes mellitus (DM) was defined using the 2014 American Diabetes Association (ADA) diagnosis and classification of DM.[24]

Data analyses

Data were entered into a Microsoft Access database, verified by the double-entry method, and analyzed using SPSS version 20.0.

The reliability of the SF-36 was analyzed by administering the questionnaire to a subgroup of 20 patients on two separate occasions, 1-3 weeks apart. The degree of agreement between the SF-36 domain component summary evaluated on these two occasions was determined using Spearman's correlation. The internal consistency of the disease-specific dimensions was obtained using Cronbach's alpha, and the test-retest reliability was assessed using the intraclass correlation coefficient (ICC).[25] The ceiling and floor effects (the percentage of patients with maximum and minimum scores, respectively) were also calculated for each domain.

The SF-36 summary components were calculated following a standardized three-step procedure according to *SF-36® Physical and Mental Health Summary Scales: A User's Manual*.[5,26] The z scores were calculated using data from the SF-36 sample of Brazilian households.[27]

Descriptive statistics were calculated to provide information regarding demographic and disease-specific characteristics. The Shapiro-Wilk test was used to evaluate whether the data were normally distributed. The asymptotic Pearson's chi-square test and the Mann-Whitney *U* test were used to compare percentages and medians, respectively.

Various models were created for each of the eight domains of the SF-36 (dependent variable). The independent variables were grouped into sociodemographic characteristics (age, sex, family income, and educational attainment), clinical characteristics (liver cirrhosis, HTN, and DM), psychiatric comorbidities (MDD, anxiety disorders, alcohol abuse/dependence, current or past illicit drug abuse/dependence), and biochemical data (alanine aminotransferase [ALT]). Variables with a p-value $<$ 0.20 on univariate analysis were selected for the multivariate analysis. In each group of variables (sociodemographic characteristics, clinical characteristics, psychiatric comorbidities and biochemical data), when more than one variable had a p-value $<$ 0.20, hierarchical linear regression models were created for the selection of variables that were truly associated with the reduction of scores in each domain. Only those variables with a p-value $<$ 0.05 were included in the final multivariate linear regression model. The adjusted coefficient of determination (R^2) and ANOVA were used to assess the adequacy of the models. Variables that had more than 10% missing data were not selected for the multivariate analysis models. Finally, several models were created for each of the two summary components of the SF-36 (dependent variable): PCS and MCS.

The influence of the severity of MDD on the scores of each SF-36 domain summary component was evaluated by Spearman's test, with p-values $<$ 0.05 considered significant.

To evaluate the association between age and quality of life, patients were stratified into three age ranges: 18-45, 46-65, and $>$ 66 years.

Results

The internal consistency of the disease-specific dimensions of the SF-36 was good, with all coefficient values exceeding 0.79. The test-retest reliability was also good in all dimensions, and the ICC values were statistically significant (0.68-0.94; $p < 0.05$). In the group of patients interviewed at two different times, the agreement between domains was satisfactory ($r = 0.94$, $p < 0.0001$).

Correlations among the SF-36 domains ranged from 0.28 (General Health Perceptions and Emotional Role Functioning, $p = 0.002$) to 0.70 (Mental Health and Vitality, $p < 0.0001$). The mean scores of the PCS and the MCS were 49.1±2.8 and 52.8±11.5, respectively.

Sociodemographic and clinical profile

The sociodemographic profile of the study population is shown in Table 1. Clinical, biochemical, virological, and liver histology findings are summarized in Table 2.

Twenty-one patients showing clinical signs of compensated cirrhosis, classified as having a Child-Pugh score of A, B or C, did not undergo liver biopsy. Current MDD was the most common psychiatric disorder observed (38/30.6%). Of the 124 patients, 29 (23.4%) were diagnosed with some type of anxiety disorder. Current/past alcohol dependence/abuse and illicit drug use were observed in 28 (22.6%) and 31 (25.0%) patients, respectively. HTN and DM were diagnosed in 44 (35.5%) and 23 (18.5%) patients, respectively. Twenty-five (20.2%) patients had normal ALT concentrations at the time of assessment. The majority of the patients (79/94, 84.0%) were infected with HCV genotype 1. A liver biopsy was available for 81 (65.3%) patients, and 42 (51.9%) showed moderate to severe inflammatory activity. Staging of hepatic fibrosis showed the following results: none (24.7%), mild (28.4%), moderate (22.2%), and severe (24.7%). Among the patients enrolled, 14 (11.3%) had received previous treatment for HCV, but all had finished the treatment at least 12 months before the start of the study.

Table 1 Sociodemographic characteristics of patients with CHC (n=124)

Parameters	Patients
Age (years), mean ± SD	53.2±11.7
Age (years), range	20-74
Gender	
Male	52 (41.9)
Female	72 (58.1)
Educational attainment	
≤ 9 years of study	63 (51.0)
9-12 years of study	41 (33.0)
> 12 years of study	10 (8.0)
Illiterate	10 (8.0)
Total family income/year*	113 (100.0)
≤ US$ 4,000	48 (42.5)
US$ 4,001-12,000	33 (29.2)
> US$ 12,000	32 (28.3)

Data expressed as n (%), unless otherwise specified.
CHC = chronic hepatitis C; SD = standard deviation.
* Data from 113 (91.1%) patients. The national minimum wage in 2011 was equivalent to US$ 4,000 per year.

Table 2 Clinical, laboratory, virological, and liver histology findings of patients with CHC (n=124)

Variables	n (%)
Medical comorbidities	
Chronic hepatitis	103 (83.1)
Cirrhosis	21 (16.9)
Child-Pugh class	21 (100.0)
A	10 (47.6)
B	8 (38.1)
C	3 (14.3)
HTN	44 (35.5)
DM	23 (18.5)
Psychiatric diagnoses (DSM-IV)*	
Current major depressive disorder	38 (30.6)
Anxiety disorders	29 (23.4)
Current/past alcohol abuse/dependence	28 (22.6)
Current/past illicit drug abuse/ dependence	31 (25.0)
Biochemical parameters	
ALT (U/L), mean ± SD (range)	77.2±53.8 (18.0-317.0)
Virological parameters	
Viral load† [HCV-RNA (IU/mL)], mean ± SD	2,027,090±4,161,843
HCV genotype†	94 (100.0)
1a	35 (37.2)
1b	42 (44.7)
3a	12 (12.8)
Others‡	5 (5.3)
Histology§	
Grading	81 (100.0)
No activity (A0)	7 (8.6)
Mild activity (A1)	32 (39.5)
Moderate activity (A2)	39 (48.2)
Severe activity (A3)	3 (3.7)
Staging	81 (100.0)
No fibrosis (F0)	20 (24.7)
Mild fibrosis (F1)	23 (28.4)
Moderate (F2)	18 (22.2)
Severe fibrosis (F3/F4)	20 (24.7)

Data expressed as n (%), unless otherwise specified.
ALT = alanine aminotransferase (reference value: 13-40 U/L); CHC = chronic hepatitis C; DM = diabetes mellitus; HCV = hepatitis C virus; HTN = hypertension; SD = standard deviation.
* Psychiatric interviews were conducted using the Brazilian version of the MINI Plus.
† Data from 94 (76.0%) patients.
‡ 1a + 1b (n=2), 2b, 2a + 2b.
§ Data from 81 (65.3%) patients. Staging and grading were performed according to the METAVIR classification.

Factors associated with changes in HRQOL scores

Univariate analysis

A poorer HRQOL was found in patients aged ≥ 65 years for the following domains (median [interquartile range], p-value): General Health Perceptions (57.0 [45.0] vs. 87.0 [30.0], $p = 0.001$), Physical Functioning (75.0 [65.0] vs. 95.0 [16.3], $p < 0.0001$), and Physical Role Functioning (75.0 [75.0] vs. 100.0 [25.0], $p = 0.004$). Decreased SF-36 domain scores were also associated with female gender:

Physical Functioning (90.0 [25.0] vs. 95.0 [15.0], p = 0.004), Bodily Pain (72.0 [48.0] vs. 84.0 [38.8], p = 0.03), Vitality (70.0 [30.0] vs. 80.0 [25.0], p = 0.001), and Mental Health (76.0 [33.0] vs. 80.0 [24.0], p = 0.05). Conversely, increased SF-36 domain scores were associated with higher levels of education (≤ 9 years of study vs. > 9 years of study) for the following domains: General Health Perceptions (72.0 [45.0] vs. 90.0 [20.0], p < 0.0001), Physical Functioning (85.0 [30.0] vs. 95.0 [10.0], p < 0.0001), Physical Role Functioning (87.5 [75.0] vs. 100.0 [10.0], p < 0.0001), Emotional Role Functioning (66.6 [100.0] vs. 100.0 [66.0], p = 0.03), Social Role Functioning (87.5 [50.0] vs. 100.0 [25.0], p = 0.03), and Bodily Pain (62.0 [49.8] vs. 84.0 [34.0], p < 0.0001). Moreover, better SF-36 domain scores were associated with higher family income in all SF-36 domains.

Lower scores in several SF-36 domains were associated with DM: General Health Perceptions (71.0 [35.5] vs. 87.0 [32.0], p = 0.004), Physical Functioning (65.0 [55.0] vs. 95.0 [15.0], p < 0.0001), Bodily Pain (60.0 [78.0] vs. 66.0 [34.5], p = 0.03), Vitality (60.0 [43.7] vs. 75.0 [30.0], p = 0.001), and Mental Health (66.0 [46.0] vs. 80.0 [24.0], p = 0.05). HTN was associated with decreased scores in all SF-36 domains, except for Mental Health (68.0 [35.0] vs. 69.0 [40.0], p = 0.07). Current MDD and anxiety disorders were also associated with reduced scores in all SF-36 dimensions (p < 0.007). In addition, worse SF-36 domain scores were found in other psychiatric disorders, such as current/past alcohol abuse/dependence: Physical Functioning (85.0 [35.0] vs. 95.0 [16.5], p = 0.02), Physical Role Functioning (50.0 [100.0] vs. 100.0 [25.0], p < 0.0001), Emotional Role Functioning (50.0 [100.0] vs. 100.0 [33.4], p < 0.004), Bodily Pain (61.0 [49.0] vs. 75.0 [30.0], p = 0.003), and Mental Health (68.0 [36.0] vs. 80.0 [28.0], p = 0.002); and current/past illicit drug abuse/dependence: Bodily Pain (51.0 [31.0] vs. 72.0 [38.0], p = 0.05).

A poorer HRQOL was found in patients with higher ALT concentration (≤ 40 U/L vs. > 40 U/L), as demonstrated by lower scored in the Social Role Functioning (75.0 [62.5] vs. 100.0 [25.0], p = 0.02) and Vitality (65.0 [40.0] vs. 85.0 [37.5], p = 0.03) domains.

When the summary components of SF-36 were evaluated, higher family income was associated with increased PCS scores. Neither cirrhosis nor HTN/DM was associated with lower scores on the SF-36 summary components. However, both current MDD and anxiety disorder were associated with lower scores in both PCS and MCS, regardless of the stage of liver disease.

Multivariate analysis

Current MDD (p < 0.01) was associated with lower SF-36 scores in all domains (Table 3). Furthermore, the poorest HRQOL was observed in the patients with current/previous alcohol abuse/dependency and in those with HTN. ALT concentration was inversely associated with lower SF-36 scores in five domains (Table 3). Otherwise, higher levels of education and higher family income were associated with increased SF-36 domain scores.

The results of the multiple linear regression analyses in which each of the summary scores of the SF-36 was used as the dependent variable, including clinical, psychiatric, and sociodemographic factors influencing HRQOL, are shown in Table 4. The associations remained even when either patients with cirrhosis (n=21) or those who had previously received interferon therapy (n=14) were excluded from the analysis.

Correlation between the degree of depression measured by the HDRS and HADS scales and SF-36 domain and summary component scores

When degree of depression was assessed by the HDRS, patients with moderate to severe depression had lower SF-36 scores than those with mild depression in all domains: General Health Perceptions, r = -0.44 (p < 0.0001); Physical Functioning, r = -0.34 (p < 0.0001); Physical Role Functioning, r = -0.36 (p < 0.0001); Bodily Pain, r = -0.30 (p = 0.002); Emotional Role Functioning, r = -0.44 (p < 0.0001); Social Role Functioning, r = -0.40 (p < 0.0001); Vitality, r = -0.41 (p < 0.0001); and Mental Health, r = -0.67 (p < 0.0001) (Figure 1A). When depression severity was evaluated by the HADS (HAD-A and HAD-D), moderate to severe depression also correlated with lower SF-36 scores in all domains: General Health Perceptions, r = -0.45 (p < 0.0001); Physical Functioning, r = -0.33 (p = 0.001); Physical Role Functioning, r = -0.36 (p < 0.0001); Bodily Pain, r = -0.34 (p = 0.0001); Emotional Role Functioning, r = -0.33 (p = 0.001); Social Role Functioning, r = -0.50 (p < 0.0001); Vitality, r = -0.59 (p < 0.0001); and Mental Health, r = -0.75 (p < 0.0001) (Figure 1B).

A correlation between PCS scores and the degree of depression, both on the HDRS (r = -0.63, p < 0.0001) and on the HADS (r = -0.75, p < 0.0001), was also observed.

Degree of histological abnormalities, HCV viral load, and SF-36 scores

The degree of hepatic necroinflammatory activity and the stage of hepatic fibrosis did not influence scores in any SF-36 dimensions or in the SF-36 summary components (Table 5).

Neither viral load nor HCV genotype was associated with the scores of the SF-36 domains and summary components.

Discussion

In the present study, depressive disorder had a deeper impact on the HRQOL of patients with CHC than did the severity of liver disease. These results confirm that depressive symptoms have a negative influence on quality of life in individuals with chronic infection, as observed elsewhere.[8,28,29] Additionally, our results demonstrated that not only the presence of MDD but also the severity of depressive disorder was associated with lower scores in all SF-36 domains, as well as in the

Table 3 Multiple linear regression including variables influencing health-related quality of life (measured by SF-36) in patients with CHC (n=124)

SF-36 domains/variables	Beta coefficient	*t*	95%CI	Adjusted R^2	F-value	df	p-value
General Health Perceptions							
Current MDD	-0.43	-4.98	-29.80 to -12.93	0.22	16.88	2	< 0.0001
Educational level	0.18	2.18	0.61 to 12.71				0.03
Physical Functioning							
Current MDD	-0.31	-3.08	-22.78 to -4.92	0.29	12.04	4	< 0.0001
HTN	-0.23	-3.05	-21.52 to -4.55				0.003
Total family income/year	0.27	3.77	4.48 to 14.41				0.003
ALT	-0.29	-2.70	-0.18 to -0.03				0.008
Physical Role Functioning							
Current MDD	-0.32	-2.95	-37.38 to -7.36	0.18	7.31	3	0.004
Current/previous alcohol abuse/dependency	-0.33	-2.66	-38.58 to -5.66				0.009
Total family income/year	0.07	2.36	1.60 to 18.49				0.02
Bodily Pain						2	
Current MDD	-0.32	-3.8	-28.56 to -9.19	0.12	8.79		< 0.0001
ALT	-0.19	-2.25	-0.18 to -0.01				0.03
Emotional Role Functioning							
Current MDD	-0.32	-3.78	-45.33 to -14.20	0.12	9.23	2	< 0.0001
Current/previous alcohol abuse/dependency	-0.18	-2.09	-35.70 to -0.94				0.04
Social Role Functioning							
Current MDD	-0.53	-5.86	-45.95 to -24.44	0.24	18.79	2	< 0.0001
ALT	-0.21	-2.56	-0.18 to -0.03				0.008
Vitality							
Current MDD	-0.48	-6.36	-38.46 to -20.13	0.26	21.33	2	< 0.0001
ALT	-0.19	-2.29	-0.17 to -0.01				0.03
Mental Health							
Current MDD	-0.73	-10.94	-45.69 to -31.72	0.51	61.10	2	< 0.0001
ALT	-0.20	-3.02	-0.150 to -0.030				0.003

ALT = alanine aminotransferase; CHC = chronic hepatitis C; CI = confidence interval; df = degrees of freedom; MDD = major depressive disorder; HTN = hypertension; SF-36 = 36-Item Short-Form Health Survey; *t* = computed by dividing the estimated value of the β coefficient by its standard error.
Linear regression models were adjusted as appropriate according to the ANOVA F-test ($p < 0.05$).

physical component summary. It should be emphasized that the SF-36 domain scores and summary component scores were analyzed in combination. Several studies have demonstrated that the SF-36 summary component scores are not independent, i.e., the PCS and MCS may be partially measuring the same constructs.[26] Therefore, the PCS/MCS scoring method imprecisely summarizes the scores of the SF-36 domains, and must be carefully analyzed and interpreted in combination with the domain scores.[26]

In health care, an alternative manner of assessing the HRQOL of patients would be to use instruments that are targeted at specific aspects of a particular disease. These disease-specific questionnaires are designed to identify disease-specific domains with high specificity and sensitivity.[30] In addition to hepatic disease severity, other factors that influence CHC patients' HRQOL should be recognized. The administration of an instrument able to detect small changes in quality of life may increase identification of HRQOL-related issues. Among them, the diagnosis of psychological factors, such as depressive symptoms and anxiety, should be emphasized. Moreover, this process also permits physicians to make changes in patient management. In the present study, when a specific instrument was used to evaluate HRQOL in patients with CHC, MDD was strongly associated with poorer HRQOL, independently of the stage of liver disease.[31] Altogether, these findings highlight the significance of psychiatric issues in HRQOL impairment in CHC patients.

The high prevalence of MDD (30.6%) observed in the present study is consistent with the results of previous investigations using structured psychiatric interviews in CHC patients.[14] However, the pathogenesis of HCV-related psychiatric symptoms has not been completely clarified. Several lines of evidence have demonstrated that the virus is able to cross the blood-brain barrier. Recently, studies focusing on the analysis of quasispecies have allowed the identification of HCV-RNA in brain tissue.[32] Otherwise, the role played by the host's immune response (especially cytokine-related effects) on psychiatric disorders in CHC should not be disregarded.[33]

In addition to depression, CHC has been shown to be associated with other psychiatric comorbidities that may themselves contribute to a poorer HRQOL.[4,16,34] Despite the results of multivariate analyses in this study, the

Table 4 Multiple linear regression including variables influencing health-related quality of life (as measured by SF-36, summary scores) in patients with CHC (n=124)

SF-36 summary/variables	Beta coefficient	*t*	95%CI	Adjusted R^2	F-value	df	p-value
Physical component summary							
ALT	-0.20	-3.03	-0.02 to -0.003	0.53	20.32	6	0.007
Current MDD	-0.72	-10.37	-5.11 to -3.47				< 0.0001
Current/previous alcohol abuse/dependency	-0.18	-1.70	-1.65 to 0.13				0.09
Educational attainment	-0.05	-0.87	-0.87 to 0.34				0.39
HTN	-0.05	-0.93	-1.13 to 0.42				0.36
Total family income/year	0.12	2.02	0.007 to 0.90				0.05
Mental component summary							
ALT	0.15	2.09	0.01 to 0.07	0.42	29.81	3	0.03
Current MDD	-0.65	-9.10	-20.08 to -12.90				< 0.0001
Current/previous alcohol abuse/dependency	-0.12	-1.72	-7.26 to -0.51				0.09

ALT = alanine aminotransferase; CHC = chronic hepatitis C; CI = confidence interval; df = degrees of freedom; MDD = major depressive disorder; HTN = hypertension; SF-36 = 36-Item Short-Form Health Survey; *t* = computed by dividing the estimated value of the β coefficient by its standard error.
Linear regression models were adjusted as appropriate according to the ANOVA F-test ($p < 0.05$).

influence of anxiety disorder influence on the HRQOL of patients with CHC should not be ignored. The prevalence of anxiety disorders in patients with CHC has been shown to be as high as that of clinical depression.[13,16] Some authors have explained that these elevated levels of psychiatric morbidity are related to coping with stigma and prejudice during the disease process.[35] Overall, these life experiences and feelings may be responsible for increased rates of anxiety and contribute to the negative impact of chronic diseases, such as CHC, on HRQOL.[36] Additionally, in this study, alcohol abuse was another psychiatric comorbidity associated with a reduction in the scores of two domains of the SF-36. This negative impact of alcohol use on HRQOL is consistent with previous studies.[37]

To the best of our knowledge, this is the first study to demonstrate an association between lower scores on the Functional Capacity domain of the SF-36 and HTN in patients with CHC. The high (35.5%) prevalence of HTN may be explained by the older age of the study population. Ethnicity and dietary and cultural habits should also be considered.

In agreement with previous studies, none of the SF-36 scores correlated with presence of cirrhosis, presence of necroinflammatory activity, or viral load.[8,10,38] However, in contrast to previous investigations,[10,38] higher ALT concentrations in this study were associated with decreased SF-36 scores in five domains and in two summary components. As CHC has been associated with several extrahepatic manifestations,[3] one may speculate

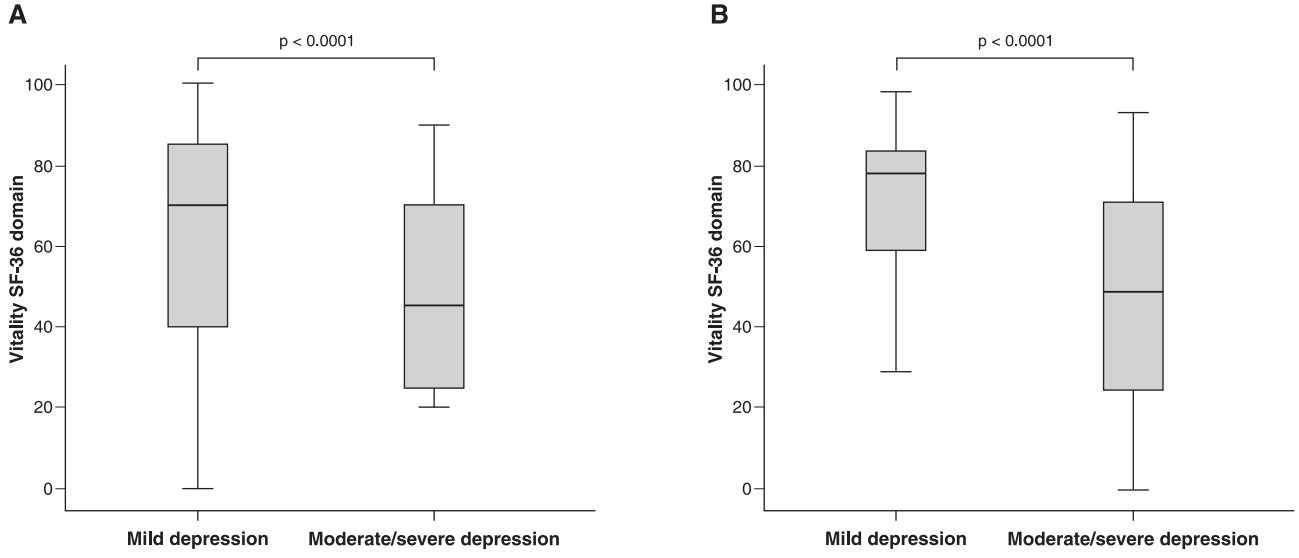

Figure 1 Correlation between the degree of depression, as evaluated by the Hamilton Depression Rating Scale (HDRS) (A) and the Hospital Anxiety and Depression Scale (HADS [HAD-A and HAD-D]) (B), and scores in the Vitality domain of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) in patients with a diagnosis of major depressive disorder (MDD) (n=38). Each box shows the median (horizontal bar) and the lower and upper quartiles. Whiskers indicate the minimum and maximum values.

Table 5 SF-36 quality of life domain scores according to degree of necroinflammatory activity and stage of liver fibrosis[a] (n=81)

	Hepatic necroinflammatory activity[b]				
	Mild (A1) n=32		Moderate/severe (A2-3) n=42		p-value*
SF-36 domains	Median	IR	Median	IR	
Physical component summary	49.6	4.4	44.8	4.24	0.65
General Health Perceptions	67.0	31.5	82.0	31.3	0.72
Physical Functioning	87.5	41.3	90.0	36.25	0.67
Physical Role Functioning	100.0	93.8	75.0	56.3	0.90
Bodily Pain	61.0	44.25	72.0	46.0	0.72
Mental component summary	50.0	19.5	51.1	20.2	0.67
Emotional Role Functioning	100.0	66.7	100.0	100.0	0.49
Social Role Functioning	81.3	50.0	81.3	62.5	0.84
Vitality	70.0	42.5	65.0	40.0	0.86
Mental Health	70.0	39.0	72.0	38.0	0.64
	Staging of liver fibrosis[c]				
	Mild/moderate (F1/F2) n=41		Severe (F3-4) n=20		p-value*
SF-36 domains	Median	IR	Median	IR	
Physical component summary	49.8	5.1	49.8	4.5	0.77
General Health Perceptions	77.0	37.5	65.0	40.0	0.61
Physical Functioning	90.0	27.5	87.5	32.5	0.55
Physical Role Functioning	100.0	93.8	87.5	75.0	0.75
Bodily Pain	72.0	50.5	61.5	42.8	0.57
Mental component summary	48.6	21.2	53.5	21.5	0.84
Emotional Role Functioning	100.0	66.7	66.7	100.0	0.21
Social Role Functioning	87.5	62.5	75.0	62.5	0.84
Vitality	65.0	40.0	67.5	33.8	0.50
Mental Health	72.0	46.0	72.0	40.0	0.77

IR = interquartile range; SF-36 = 36-Item Short-Form Health Survey.
[a] Metavir classification; [b] no hepatic necroinflammatory activity was observed in the liver fragments of seven patients (A0); [c] no signs of fibrosis were observed in the liver fragments of 20 patients (F0).
* p-values $\leq$ 0.05 were considered significant (Mann-Whitney *U* test).

that elevated ALT concentrations might be associated with the activation of a systemic host immune response. This event might interfere with target organs beyond the liver, including the central nervous system.

Among the sociodemographic variables evaluated in the current study, family income and educational attainment were positively associated with three SF-36 domain scores. Helbling et al. showed that low income was the major factor associated with a reduced HRQOL among patients with CHC.[10] In addition, previous investigations have demonstrated the positive influence of education on the HRQOL of patients with this disease.[3,4]

Of note, regarding host-related variables, it should be emphasized that the majority of studies assessing the HRQOL of patients affected by CHC have taken place in the context of routine medical care and did not use structured psychiatric interviews to confirm anxiety or mood disorders. Our subjects were patients of a university hospital; consequently, a close working relationship between clinicians, hepatologists, psychiatrists, and psychologists evaluating and treating these subjects was enhanced. An interdisciplinary and multiprofessional approach was developed for a better comprehension of CHC patients' clinical/psychiatric manifestations, with a particular focus on evaluating the deleterious effects of HCV that extend beyond liver disease.

The present study has some limitations. First, the subjects included were recruited from a referral center and, consequently, may not be representative of all patients with CHC. Second, although the SF-36 is considered to be the most appropriate generic instrument for HRQOL assessment in patients with chronic liver disease,[22] some issues need to be evaluated. Independent of clinical/psychiatric illnesses, HCV infection alone has been shown to negatively impact HRQOL.[8] Upon receiving a diagnosis of HCV, which is a contagious liver disease, these patients are faced with various challenges, such as adjusting to chronic comorbidity and coping with the stigma and the stress of social and familial relationships.[35] In addition, individuals with CHC live with illness uncertainty, which may become a great psychological stressor for these subjects.[39] Based on these aspects, use of the SF-36 instrument only may be insufficient for an appropriate evaluation of the HRQOL of patients with CHC, which is influenced by multiple complex factors. Furthermore, some studies point to the possibility of an overlap between HRQOL domains and psychiatric abnormalities, especially depressive symptoms. In the present study, the "depressive view" of depressed patients may have introduced bias in the interpretation of the SF-36 domain scores and summary component scores.[40]

In conclusion, we have clearly demonstrated that psychiatric disorders (particularly MDD) and active medical comorbidities, rather than the severity of liver disease, are the determinants of HRQOL impairment in patients with CHC. These findings highlight that the psychological effects of the disease on patients living with CHC deserve more attention, and that implementation of integrated medical, psychiatric, and psychological care may be helpful for patients with CHC.

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Disclosure

The authors report no conflicts of interest.

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