Annals of Hepatology

ORIGINAL ARTICLE

October-December, Vol. 9 No.4, 2010: 419-427

Fatigue and depressive symptoms associated with chronic viral hepatitis patients' health-related quality of life (HRQOL)

Katerina Karaivazoglou,* Gregoris Iconomou,* Christos Triantos,** Thomas Hyphantis,*** Konstantinos Thomopoulos,** Maria Lagadinou,**** Charalambos Gogos,**** Chryssoula Labropoulou-Karatza,** Konstantinos Assimakopoulos*

* Department of Psychiatry, University of Patras School of Medicine, Rion Patras, Greece.
** Department of Internal Medicine (Hepatology Unit), University of Patras School of Medicine, Rion Patras, Greece.
*** Department of Psychiatry, Medical School, University of Ioannina, Greece.
**** Department of Internal Medicine (Infectious Diseases Unit), University of Patras School of Medicine, Rion Patras, Greece.

ABSTRACT

Background and rationale. It is well established that chronic viral hepatitis (CVH) negatively affects patients' health-related quality of life (HRQOL). The aim of the present study was to assess the extent to which fatigue and depressive symptoms are associated with CVH patients' HRQOL. **Methods.** Eighty-four adult CVH outpatients [45 with hepatitis B virus (HBV) and 39 with hepatitis C virus (HCV) infection] participated in the study. The Short Form-36 Health Survey (SF-36), the Beck Depression Inventory-II (BDI-II) and the Fatigue subscale of the Functional Assessment of Cancer Therapy-Anemia Scale (FACT-F) were used to assess HRQOL, depression and fatigue, respectively. **Results.** All aspects of HRQOL perceived by CVH patients were significantly impaired compared to the general population, as a comparison with Greek population-based normative data revealed. HBV patients presented similar HRQOL with HCV patients. Clinical parameters including infection activity, fibrosis stage or inflammation grade, as well as depressive symptoms and fatigue were found to be significantly associated with HRQOL. Multivariate analyses showed that older age ($p < 0.001$) and higher fatigue scores ($p < 0.001$) were the variables most closely associated with the physical HRQOL, whereas higher rates on depressive symptoms ($p < 0.0005$) and fatigue ($p < 0.020$) scales were the variables most closely associated with the mental HRQOL. **Conclusions.** In conclusion, CVH is associated with impaired HRQOL. Fatigue and impaired psychological functioning is associated with diminished HRQOL in CHV, independent of the disease etiology. Consequently, management of fatigue and depressive symptoms should be considered a priority, in order to improve HRQOL in CVH patients.

Key words. CVH. HRQOL. Fatigue. Depression.

INTRODUCTION

Chronic viral hepatitis (CVH) affects a sizeable proportion of patients, who are referred to Hepatology Departments seeking specialized care.[1] The management of the disease requires a multi-disciplinary approach, considering both biological and psychosocial aspects. Although CVH usually runs an asymptomatic course or is accompanied by minor non specific symptoms, there are a proportion of patients with advanced disease who present serious complications. In addition, the diagnosis of CVH seems to exert a labelling effect on patients,[2-4] modifying their way of living, increasing their psychological burden[5-10] and negatively affecting their well-being.[1,7,9-13] Furthermore, antiviral treatment has been found to augment psychiatric co-morbidity and adversely affect several domains of HRQOL, which could compromise patients' continuity of care, adherence to medical advice, and even their prognosis.[14-18]

A resent comprehensive review by Foster[19] showed that independently of liver disease, hepatitis C (HCV) infection reduces the HRQOL of most chronically infected patients. Surprisingly few studies, however, have assessed the HRQOL of chronic hepatitis B patients (HCB).[1,11,20] A recent study of Tillmann, *et al.*,[21] reported that HCV-positive patients scored worse in the mental aspects of HRQOL compared to other liver diseases, except for hepatitis B infection

Correspondence and reprint request: Katerina Karaivazoglou, MD
Department of Psychiatry, University of Patras School of Medicine
Rion Patras, Greece 26504. Tel.: +30-2610999731
E-mail: karaivaz@hotmail.com

Manuscript received: July 18, 2010.
Manuscript accepted: August 30, 2010.

(HBC). In the latter study, HRQOL was also significantly impaired in patients with viral clearance after interferon therapy but not after spontaneous clearance, indicating the complex interplay between several disease and treatment-related parameters with psychological distress and other psychosocial factors in the formation of CVH patients' HRQOL. Given, however, that HRQOL has now been identified as an outcome of great importance in research and clinical practice in several diseases, the investigation of its determinants emerges as a significant necessity.[22]

Several studies have attempted to link HRQOL impairment of hepatitis patients to specific demographic, clinical and psychosocial parameters of the disease. However, the existing evidence is suggestive rather than conclusive, as there are still conflicting findings about the extent to which each parameter independently contributes to HRQOL. Certain researchers have associated severity of liver disease and presence of cirrhosis with a greater impairment in HRQOL,[1,23,24] but others found that no such relationships exist.[9,11] Other clinical indices of liver disease including ALT levels, virus type and viral load were also found not related to HRQOL impairment.[1,9,11-12,25] With respect to gender differences, recent investigations have indicated that HCV-infected women present with decreased levels of physical, emotional and social well being compared to men.[18,26] The discrepancies between studies could be attributed to the method and timing of assessment, and heterogeneous CVH populations.

On the other hand, fatigue, depression and cognitive impairment are among the most common complaints of patients and occur independently of liver disease or treatment status;[11,19,27-30] all these symptoms have the potential to impair patients' ability to function at work or in society.[5,19,31] Several studies have shown that psychosocial distress symptoms, fatigue and medical co-morbidity are associated with CVH patients' HRQOL.[9,10,23,32-34] However, most of these studies focus on HCV-infected patients and scarce studies investigated the impact of these parameters in HCB-infected patients' HRQOL.[10,35] In addition, although it is well known that, apart from its physical origins, fatigue could also be a manifestation of psychological disturbances including depression,[34,36,37] very few studies investigated the concurrent impact of both depression and fatigue on CVH patients' HRQOL.[34] Thus, further research is needed to assess the complex relationships between clinical parameters, fatigue and psychological distress symptoms with HRQOL impairment and its implications, as has been suggested.[38]

Prompted by these facts, the aim of the present study was to investigate the independent relationships of demographic, clinical and psychological distress variables with HRQOL in a sample of Greek patients infected with chronic viral hepatitis, and whether both fatigue and depressive symptoms are independently associated with several aspects of HRQOL in both HCV- and HBC-infected patients. It should be noted that hepatitis B remains a major health priority in Western Balkans.[39] In addition, evidence suggests that ethnicity and social parameters may influence hepatitis patients' HRQOL.[34,40] Since studies have shown that Greek patients adopt illness behaviour and passive attitude towards their well-being which is largely influenced by psychosocial parameters compared to other European citizens,[41] we maintain that assessing psychosocial factors associated with HRQOL in CVH patients of a different social and cultural background in which hepatitis B is still a major health priority, may expand the clinical usefulness of the existing evidence and could contribute to devising appropriate treatment strategies that would enhance patients' total functioning.

METHOD

Participants and procedure

The current study was conducted at the Hepatology Unit and at the Infectious Diseases Unit, Department of Internal Medicine of the University of Patras Medical School, Greece between May 2004 and September 2006. The study protocol was approved by the Institutional Review Board of the University Hospital of Patras, and all participants gave written informed consent before study entry. Male and female consecutive outpatients aged 18 years or older, infected with chronic hepatitis B or C, were approached during their scheduled visit to the Hepatology Unit and invited to take part in the study. Participants were selected after thorough screening of their medical records to exclude co-morbid factors that could independently impair HRQOL. Exclusion criteria were: illicit drug use or alcohol abuse during the last 12 months, current treatment with psychotropic medication, stroke, cancer, cerebrovascular disease, mental retardation, dementia, seizure disorder, HIV infection, other chronic liver disease, cirrhosis, child B/C, hepatic encephalopathy, interferon treatment during the last six months, and lack of fluency in the Greek language. Hepatitis B and hepatitis C diagnosis was confirmed based on criteria published by the American Association for the Study of Liver Diseases.[42,43]

Instruments

HRQOL was assessed using the Short Form 36 Health Survey (SF-36). It is a self-report, generic HRQOL instrument, which includes eight multi-item scales (36 items) that evaluate the extent to which an individual's health limits his or her physical, emotional, and social well-being. The SF-36 covers eight domains of HRQOL, namely physical functioning, role limitations due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems, and mental health. Scores on each subscale range from 0 to 100, with higher scores indicating a better HRQOL results.[44] Summary scores for physical health (physical component score-PCS) and mental health (mental component score-MCS) can also be derived.[45] SF-36 has been widely used in liver disease and has exhibited satisfactory psychometric properties.[1,10,11,25,38] The Greek version of the SF-36 was used, which also provides population-based normative data.[46]

Depressive symptoms were assessed using the Greek version of the 21-item Beck Depression Inventory-BDI-II.[47,48] Higher scores indicate elevated depressive symptoms, while a total score of 0-13 is considered minimal range, 14-19 is indicative of mild depression, 20-28 is indicative of moderate, and 29-63 of severe depression.

Fatigue was assessed by the Greek standardized version of the the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F), a 13-item self-administered instrument rated on a 5-point scale from 0 (Not at all) to 4 (Very much).[49,50] Although the FACIT-F has not previously been used in CVH patients, it has found wide application across diverse medical fields and populations, including the general population,[51] patients with cancer,[51,52] rheumatoid arthritis,[53] psoriatic arthritis,[54] and chronic obstructive pulmonary disease.[55] FACIT-F scores range from 0 to 52, with higher values indicating less fatigue. Scores in the range of 30 and below are in general suggestive of significant fatigue.[56]

Statistical analysis

All the statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 15.0 (SPSS Inc., Chicago, IL, USA) for Windows. Summary statistics for all variables were calculated. Normality was tested by the Kolmogorov-Smirnov test.[57] Univariate comparisons were first conducted to assess differences in demographic, psychological and HRQOL variables between HBV and HCV patients. Student's t-tests and chi-square tests were calculated as appropriate. All the p-values were two-tailed. Univariate comparisons were also conducted to assess the relationships between all independent variables and the physical as well as mental HRQOL separately for HBV and HCV patients. Two-tailed t-tests were carried out and Pearson's or Spearman's correlations were calculated, as appropriate.

To assess factors associated with chronic viral hepatitis patients' HRQOL, univariate comparisons were first conducted to assess the relationship of major demographic, clinical and psychological variables with HRQOL in the entire sample. Two-tailed t-tests, Pearson's or Spearman's correlations were also calculated, as appropriate. Subsequently, to assess factors most closely associated with HRQOL, two independently produced multiple regression analyses were performed. The dependent variables were the physical (PCS) and mental (MCS) components of the SF-36. Independent variables were the virus aetiology (i.e., HBV or HCV), the major demographic variables and the statistically significant variables of the previous univariate analyses. Colinearity between independent variables was tested based on variance inflation factors (VIF) and tolerances for individual variables.[58]

Patient Characteristics

A total of 84 eligible patients were enrolled into the study, 45 with HBV and 39 with HCV infection. Demographic and clinical characteristics are provided in table 1. The majority were males (65.5%); median age was 46 years and median education was 8 years. No statistically significant differences were observed between HBV and HCV patients regarding the major demographic variables. Thirty patients (35.7%) had recently undergone liver biopsy (17 with HBV and 13 with HCV). Each biopsy specimen was evaluated according to the grading and staging system described by Goodman and Ishak.[59] Median fibrosis stage of those patients who had undergone liver biopsy was 3, and median inflammation grade was five. Twenty-seven patients (32.1%) presented abnormal ALT/AST rates at the time of the assessment. There were no statistically significant differences between the two types of infection with respect to the severity or activity of the disease (Table 1).

Depressive symptoms, fatigue and health-related quality of life

Twelve out of the 84 patients (14.3%) presented with scores on BDI-II scale indicative of mild depression, while one patient presented with a score indica-

tive of moderate and another one of severe depression. Mean depressive symptoms, fatigue and HRQOL scores are presented in table 2. As shown in this Table, HBV patients presented similar to HCV patients' rates in fatigue and HRQOL components scores, while HCV patients presented higher rates in BDI-II scores, although the latter difference failed to reach statistical significance ($p < 0.083$). SF-36 domain scores were also compared with the respective scores obtained from the Greek adult sample from the general population (N = 1007) of the Greek validation study,[46] which provides population-based normative data. Although a formal statistical test was not performed because of the different sampling methods, certain differences relevant to all domains of the SF-36 were observed between patients and the general

Table 1. Clinical and demographic patients' characteristics.

Characteristic	Total (N = 84)	HBV (N = 45)	HCV (N = 39)	p-value
Age, years				
Range	19-78	19-77	22-78	
Mean ± SD	46.0 ± 16.7	44.1 ± 15.6	48.1 ± 17.7	0.279*
Educational level, years				
Mean ± SD	8.8 ± 4.4	8.7 ± 4.7	8.9 ± 4.1	0.809*
Sex (*N, %*)				
Male	55 (65.5%)	33 (73.3%)	22 (56.4%)	0.104**
Female	29 (34.5%)	12 (26.7%)	17 (43.6%)	
Fibrosis stage***				
Median	3	3	3	
Mean ± SD	3.2 ± 2.0	3.2 ± 1.9	3.4 ± 2.1	0.841*
Inflammation grade***				
Median	5	6	4.5	
Mean ± SD	5.3 ± 2.3	5.7 ± 2.5	4.8 ± 2.2	0.340*
Serum ALT levels				
Mean ± SD	77.0 ± 84.9	80.8 ± 109.0	72.9 ± 45.3	0.687*
Serum AST levels				
Mean ± SD	55.8 ± 61.8	52.2 ± 5.1	60.1 ± 42.9	0.580*

* Two-tailed t-tests. ** Chi-square test. *** Fibrosis stage and inflammation grade were calculated only in those patients who had recently undergone liver biopsy, i.e., N = 30.

Table 2. CVH patients' fatigue, depressive symptoms and health-related quality of life.

Variable	Total (N = 84)	HBV (N = 45)	HCV (N = 39)	p-value*
Fatigue				
FACT-F† (Mean ± SD)	8.3 ± 6.6	7.9 ± 7.0	8.8 ± 6.2	0.533
Depressive symptoms				
BDI-II‡ (Mean ± SD)	7.1 ± 6.2	6.1 ± 4.9	8.4 ± 7.3	0.083
Health-Related QOL				
Physical functioning	52.6 ± 5.6	53.1 ± 5.4	52.1 ± 5.9	0.396
Role limitations due to physical problems	50.4 ± 9.2	51.5 ± 8.7	49.1 ± 9.7	0.230
Bodily pain	52.1 ± 8.6	52.3 ± 8.2	51.9 ± 9.1	0.829
General health	47.4 ± 7.8	47.8 ± 7.6	46.9 ± 8.1	0.574
Vitality	50.9 ± 10.0	51.1 ± 11.1	50.8 ± 8.7	0.912
Social functioning	50.6 ± 9.0	50.7 ± 9.2	50.4 ± 9.0	0.882
Role limitations due to emotional problems	48.0 ± 9.6	47.1 ± 10.4	49.2 ± 8.5	0.328
Mental health	48.8 ± 9.8	49.2 ± 9.2	48.3 ± 10.5	0.660
PCS§	51.9 ± 6.6	52.8 ± 6.4	50.9 ± 6.7	0.197
MCS‖	48.1 ± 9.5	47.7 ± 10.2	48.6 ± 8.7	0.665

* Two-tailed t-tests. † Functional Assessment of Cancer Therapy-Anaemia Fatigue Subscale. ‡ Beck Depression Inventory-II. § Physical component summary score of the SF-36. ‖ Mental component summary score of the SF-36.

population (Figure 1). That is to say, chronic viral hepatitis patients, either HBV or HCV, presented much more impaired HRQOL in all SF-36 components compared to the Greek general population. The greatest degree of impairment was observed in role emotional, mental health and general health perception subscales with 41.7%, 52.4% and 67.9% of the patients performing below average, compared to the Greek general population, respectively.

Clinical and Psychological Parameters Associated with HBV and HCV patients' HRQOL

Table 3 presents the results of the analyses performed to assess factors associated with summary scores for physical health (physical component score-PCS) and mental health (mental component score-MCS) separately in HBV and HCV patients. As shown in this table, among HBV patients, impaired physical HRQOL was associated with older age ($p < 0.001$) and higher fibrosis stage ($p < 0.028$), while among HCV patients, impaired physical HRQOL was associated with fewer years of education ($p < 0.003$) and higher fatigue rates ($p < 0.0005$). On the other hand, impaired mental HRQOL among HBV patients was associated with higher rates on depressive symptoms ($p < 0.0005$) and fatigue ($p < 0.006$) scales, and in HCV patients with male gender ($p < 0.001$), higher inflammation grade ($p < 0.025$) and higher rates on depressive symptoms ($p < 0.0005$) and fatigue ($p < 0.001$). In view of these differences among the two infection types, "disease" was included in the subsequent multivariate analyses in the entire sample as independent variable.

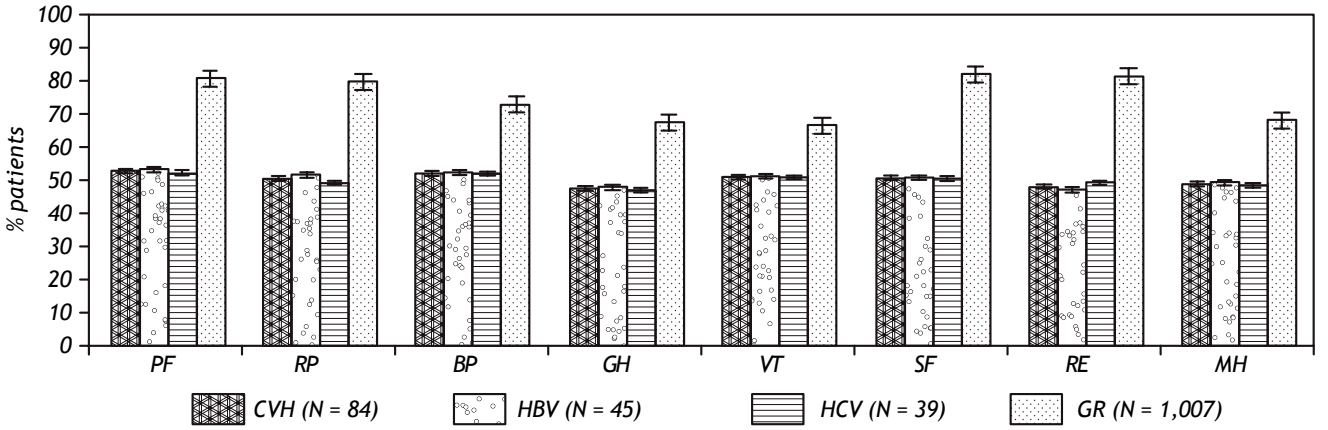

Figure 1. *Health related quality of life rates in each SF-36 component (i.e. physical functioning [PF], Role limitations due to physical problems [RP], bodily pain [BP], general health [GH], vitality [VT], social functioning [SF], role limitations due to emotional problems [RE], mental health [MH]) for CVH, HBV and HCV patients, in comparison to the respective rates of the Greek general population (data were derived from reference 31).*

Table 3. Variables associated with HBV and HCV patients' HRQOL.

Variable	HBV (N = 45)				HCV (N = 39)			
	PCS*		MCS†		PCS*		MCS†	
	r	p-value	r	p-value	r	p-value	r	p-value
Age‡	-0.462	0.001	0.045	0.769	-0.261	0.108	0.043	0.796
Sex§	-	0.320	-	0.841	-	0.403	-	0.001
Years of education‡	0.216	0.154	0.255	0.091	0.460	0.003	0.038	0.820
Fibrosis stage‡,‖	-0.479	0.028	0.081	0.727	-0.184	0.494	-0.391	0.134
Inflammation grade‡,‖	-0.245	0.343	0.110	0.674	-0.133	0.681	-0.638	0.025
Serum ALT levels¶	0.264	0.095	-0.317	0.043	0.215	0.208	0.078	0.678
Serum AST levels¶	0.078	0.630	-0.141	0.378	0.093	0.588	0.045	0.793
BDI-II¶,**	-0.044	0.776	-0.569	0.000	-0.227	0.164	-0.693	0.000
FACT-Fatigue¶,††	-0.202	0.182	-0.406	0.006	-0.612	0.0005	-0.512	0.001

*Physical component summary score of the SF-36. †Mental component summary score of the SF-36. ‡Pearson correlation. §p-values derived from two-tailed t-tests. ‖Fibrosis stage and inflammation grade were calculated only in those patients who had recently undergone liver biopsy, i.e., N = 30 (HCV = 13, HBV = 17). ¶Spearman correlation. **Beck Depression Inventory-II. ††Functional Assessment of Cancer Therapy-Anaemia Fatigue Subscale.

Table 4. Variables associated with CVH patients' Health-Related Quality of Life (N=84).

Variable	PCS*			MCS†		
	Univariate Analyses p-value	Multiple Regression‡ Analysis beta	p-value	Univariate Analysis p-value	Multiple Regression‡ Analysis beta	p-value
Disease (HBV/HCV)§	0.197	-0.085	0.388	0.665	-0.161	0.061
Age‖	0.001	-0.347	0.001	0.659	0.093	0.279
Sex (Male = 1, Female = 2)§	0.138	-0.093	0.348	0.097	-0.026	0.763
Education‖	0.004	0.137	0.186	0.119	0.108	0.237
Fibrosis stage‖,¶	0.034	-	-	0.581	-	-
Inflammation grade‖,¶	0.383	-	-	0.491	-	-
Serum ALT levels**	0.056	0.114	0.240	0.261	-	-
Serum AST levels**	0.424	-	-	0.865	-	-
BDI-II**,††	0.142	-	-	0.0005	-0.564	< 0.0005
FACT-Fatigue**,§§	0.0005	-0.347	0.001	0.0005	-0.223	0.020
Regression Statistics	R Square Adjusted = 0.307 F¶,** = 6.6, p <0.001			R Square Adjusted = 0.451 F¶,** = 12.3, p <0.0005		

* Physical component summary score of the SF-36. †Mental component summary score of the SF-36. ‡Two independently produced multiple regression analyses with dependent variables the PCS HRQOL and MCS HRQOL. Independent variables were the important variables based on the results of the univariate analyses, along with the major demographic variables. § Two-tailed t-test. ‖ Pearson correlation. ¶Fibrosis stage and inflammation grade were calculated only in those patients who had recently undergone liver biopsy, i.e., N = 30; taking into consideration the small sample size, these variables were not included in the regression equation. ** Spearman correlation. †† Beck Depression Inventory-II. §§ Functional Assessment of Cancer Therapy-Anaemia Fatigue Subscale.

Factors Associated with Chronic Viral Hepatitis Patients' HRQOL

Table 4 presents the results of the univariate and multivariate analyses performed in the entire sample to assess factors associated with chronic viral hepatitis patients' physical HRQOL and mental HRQOL. As shown in this table, physical component SF-36 score (PCS) was associated with age ($p < 0.001$), education ($p < 0.004$), serum ALT levels ($p < 0.050$), fibrosis stage ($p < 0.034$) and fatigue ($p < 0.0005$). Subsequent multiple regression analysis with dependent variable the PCS and independent variables the major demographic characteristics, the disease (HBV/HCV) and the statistically significant variables based on the previous multivariate analyses (i.e., ALT levels and fatigue) showed that older age ($p < 0.001$) and higher fatigue rates ($p < 0.001$) were the variables most closely associated with physical HRQOL. It should be noted that, due to the small sample size, fibrosis stage was not included in the regression equation. On the other hand, summary mental component SF-36 score (MCS) was associated with both depressive symptoms ($p < 0.0005$) and fatigue ($p < 0.0005$), and these variables were independently closely associated in the subsequent multiple regression analysis (Table 4).

DISCUSSION

The results of the present study showed that all aspects of CVH patients' HRQOL were significantly impaired, compared to the Greek population-based normative data. Clinical parameters such as infection activity, fibrosis stage or inflammation grade, as well as depressive symptoms and fatigue were found to be significantly associated with HRQOL. Multivariate analyses showed that older age and higher fatigue scores were the variables most closely associated with the physical HRQOL, while both fatigue and depressive symptoms were independent correlates of mental HRQOL.

As the results of the present study showed, hepatitis B and hepatitis C patients reported similar scores in fatigue and HRQOL measures, while HCV patients appeared to be more depressed, although the difference was not statistically significant. Despite the absence of significant differences in HRQOL scores between HBV and HCV patients, our analysis revealed that HRQOL correlated with different parameters in these two sub-groups. However, in subsequent multivariate analyses, the type of virus failed to significantly predict HRQOL. In assessing the entire chronic viral hepatitis sample, we found that fatigue was significantly related to both physical and mental HRQOL. In a similar vein, age, educational level, fibrosis stage and ALT levels were correlated with the physical component of HRQOL, while depression was related to the mental aspect of HRQOL. However, in the multivariate analysis, the effect of education and disease severity indices on HRQOL vanished. Fatigue remained a strong determinant of both aspects of

HRQOL independently of depressive symptomatology, while age and depression predicted the physical and mental component, respectively.

The relatively high scores on all HRQOL subscales in our study, compared to previous research,[9,11] and the impairment concerning psychological functioning and general perceptions of health, while sparing the physical domains of SF-36, could be attributed to the application of strict criteria to exclude co-morbidities that might affect HRQOL. Medical conditions co-existing with viral hepatitis have been shown to adversely influence patients' HRQOL.[32,38,60] We used those criteria to describe more accurately the impact of chronic viral hepatitis on patients' physical, emotional and social well being.

Earlier research has shown associations between HRQOL and gender suggesting that women are more likely to report poorer HRQOL than men.[26,38,61] However, other researchers[1,32,60] have demonstrated that gender plays no role in HRQOL. In the current study, no significant differences were noted between men and women in mental and physical health, although females scored lower on both components of the SF-36.

In the current investigation, we have focused equally on HCV and HBV patients, considering the impact of both infections on patients' lives. To date, research has rather under-estimated the impact of chronic hepatitis B on patients' HRQOL, since a limited number of relevant studies have been conducted.[1,11,20] The lack of significant differences in SF-36 scores between HCV and HBV-infected patients contradicts the study by Foster, *et al.*,[11] who reported that hepatitis C is associated with global impairment, affecting both physical and mental domains of HRQOL, while hepatitis B was related only to mental functioning decline. However, it is not clear whether the two hepatitis groups in that investigation were well-balanced in background characteristics. Similar to our results, a recent study found no significant differences in HRQOL scores between HBV and HCV patients.[20] It seems that HRQOL impairment does not necessarily depend on the virus itself, but also on common factors of the two liver infections.

Disease severity and activity, including fibrosis stage and ALT levels, negatively correlated with the physical component of SF-36. However, fibrosis stage was not included in multivariate analyses due to the great number of missing values, whereas ALT levels proved not to be a strong predictor of HRQOL. Significant controversy remains regarding the associations between liver disease progression and HRQOL[1,9,11,23,24,32,60] and future investigations are needed to clarify this issue.

Psychological distress affects a significant proportion of chronic disease patients and acts as a major determinant of their HRQOL.[22] In the case of viral hepatitis, psychiatric co-morbidity constitutes an important clinical parameter, which plays a major role to the disease burden imposed on patients.[5,6,10] In a relevant study, Ozkan, *et al.*,[10] found that almost half of viral hepatitis patients suffered from a psychiatric disorder, mainly depression, suggesting that major psychopathology may be the rule rather than the exception in CVH patients. In addition, IFN treatment is often accompanied by psychiatric adverse-effects, which may result to treatment discontinuation possibly compromising patients' prognosis.[14-18] The strong associations observed in this and earlier studies between depression and the mental component of HRQOL,[9,10,32,60] underlines the importance of standard psychiatric evaluation in the clinical setting. Given that the concept of health entails both biomedical and psychosocial well-being, the management of viral hepatitis should aim not only at the normalization of liver enzyme levels and viral clearance, but also at the remission of depressive symptoms and HRQOL improvement. Clarifying the determinants of HRQOL across all phases of viral hepatitis, and developing interventions to restore, maintain and maximize HRQOL are among the tasks confronting research into modern hepatology. Moreover, regular psychiatric assessment during IFN-treatment is mandatory to ensure best adherence and achieve maximum efficacy.

Likewise, fatigue was found to predict both physical and mental summary scores of SF-36. According to the existing literature, fatigue is a common complaint of viral hepatitis patients, especially in those infected by HCV, and it is attributable to both psychological and physiological mechanisms.[62,63] However, being a rather subjective symptom makes its accurate assessment extremely difficult and in standard clinical practice it is often discarded as an unspecific, minor complaint. Our findings, in combination with previous studies,[5,27,33] add further evidence about the significant impact of fatigue on all aspects of HRQOL and emphasize the need for further research to determine its pathogenesis and, subsequently, to devise and implement proper interventions.

The results of the present study are suggestive rather than conclusive. The sample size and the limitation of using only self-reported measures of fatigue and psychological distress prevent us from generalizing the findings. Another major limitation of our study lies in the cross-sectional design and hence conclusions about causality cannot be addressed. The findings need to be

replicated in a prospective study. In addition, due to the unavailability of biopsy data for a significant proportion of patients, we failed to further explore the associations between HRQOL and disease progression, as manifested by fibrosis stage and the presence of cirrhosis. Future studies are needed to address these and other issues in detail, using larger numbers and a prospective longitudinal design.

CONCLUSION

The current investigation met its purpose of delineating the main predictors of HRQOL in a sample of Greek hepatitis patients. Our findings indicate that hepatitis patients perceive themselves as unhealthy compared to the general population and report poor mental health and impaired function due to psychological distress. The decline in HRQOL scores equally affects HBV and HCV patients. In addition, the current results confirm the importance of fatigue and depression as strong predictors of patients' HRQOL, emphasizing the necessity for standard psychiatric evaluation in clinical practice. Managing fatigue and depression through pharmaceutical and/or psychological interventions may not only ameliorate HRQOL but also improve biomedical outcomes in CVH patients.

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