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The combined polymorphisms of interleukin-6-174GG genotype and interleukin-10 ATA haplotype are associated with a poor quality of life in patients with chronic hepatitis C

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Abstract

Purpose Chronic hepatitis C (CHC) is associated with a decreased health-related quality of life (HRQOL). More recent studies have pointed toward a genetic basis of patient-reported quality of life outcomes. Taking into account that the influence of single-nucleotide polymorphisms (SNPs) on the HRQOL of CHC patients has not been studied, we investigated the combined *IL10*-1082G/A, −819C/T, and −592C/A SNPs, and *IL6*-174G/C SNP. We also evaluated the association between demographic, clinical, psychiatric, virological, and genetic variables with domains and summaries of HRQOL in CHC patients.

Methods 132 consecutive CHC patients and 98 controls underwent psychiatric evaluation by using the Mini International Neuropsychiatric Interview. HRQOL was assessed by a generic questionnaire, the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), and by the specific Liver Disease Quality of Life Questionnaire (LDQOL). *IL*6 and *IL*10 polymorphisms were evaluated by Taqman SNP genotyping assay. Multivariate analysis was used to evaluate the associations.

Results Major depressive disorder was associated with lower SF-36 and LDQOL scores in seven and ten domains, respectively. Diabetes and hypertension were also associated with reduced HRQOL. CHC patients carrying the combination of *IL*10 ATA haplotype/*IL*6-GG genotype had lower scores in the SF-36—physical functioning domain, and reduced scores in the LDQOL effects of liver disease on activities of daily living, quality of social interaction, and sexual function domains than the non-carriers of the combined haplotype/genotype.

Conclusion This is the first study to demonstrate that combined *IL*6 high-producer GG genotype and *IL*10 low-producer ATA haplotype is associated with poorer HRQOL in CHC patients.

Keywords Chronic hepatitis C · Health-related quality of life · *IL*6 gene polymorphism · *IL*10 gene polymorphism

Introduction

The hepatitis C virus (HCV) infection is a worldwide public health burden that affects around 71 million people [1, 2]. Hepatic-associated diseases, such as cirrhosis and

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hepatocellular carcinoma, are well-recognized complications of chronic hepatitis C (CHC) [1, 2]. Furthermore, CHC has been considered a systemic disease, and several extrahepatic manifestations of the disease such as fatigue, anorexia, myalgia, arthralgia, irritability, and headaches [3, 4] may result in a poor health-related quality of life (HRQOL). CHC is also associated with depression and anxiety symptoms [5, 6], which impair the patient's HRQOL [3, 4, 7, 8].

HRQOL is one dimension of a broader quality of life concept that is more directly related to health, and it focuses on the patient's subjective evaluation of well-being, individual experiences, and values [9]. Assessment of this parameter is essential, because it is known that the distress caused by a disease transcends target organ damage. Therefore, patients with a similar pattern of liver injury might have different degrees of suffering [7].

The core of HRQOL is consolidated in multidimensional aspects, including individual's health perception, functional status, social support, and socioeconomic status [9, 10]. Based on these aspects, several factors may be responsible for HRQOL decrement in patients with CHC [11]. It has been suggested that host factors are the major determinants of HRQOL in patients with CHC [12]; among them, clinical comorbidities, psychological, and psychiatric aspects have to be emphasized [5–7, 13]. In addition, studies have demonstrated that sustained virological response (SVR) improves HRQOL in patients receiving specific treatment for HCV [8]. However, neither the influence of the viral load nor the impact of aspects related to the host on HRQOL has been completely understood. Particularly, the association between polymorphisms in anti- and pro-inflammatory cytokine genes and the domains and summaries of HRQOL as well as overall quality of life should not be disregarded.

There is growing evidence for a genetic basis of patient-reported quality of life outcomes [14, 15]. Several investigations have demonstrated an association between the scores of HRQOL domains and candidates' molecular markers such as genes, inflammatory mediators, and biological pathways [16]. Among them, polymorphisms in pro- and anti-inflammatory cytokine genes, as well as specific cytokine profiles should be highlighted [17–20]. In the setting of hepatitis C, specific cytokine single-nucleotide polymorphisms (SNPs) such as interleukin (IL) *IL*6 and *IL*10 SNPs have been associated with a greater risk of hepatic cirrhosis [21–25]. The *IL*10 SNPs located in the promoter region at the positions − 1082A/G (rs1800896), − 819C/T (rs1800871), and − 592C/A (rs1800872) have been associated with different expressions of this cytokine [26, 27]. Among the *IL*10 haplotypes, GCC, ACC, and ATA are associated with high, intermediate, and low production of IL-10, respectively [26, 27]. In addition, the *IL*6 SNP located in the promoter region at the position − 174G/C (rs1800795) confers two distinct phenotypes, i.e., the genotypes − 174GG and − 174GC are associated with higher circulating levels of IL-6 while the genotype − 174CC is linked to a low production of this cytokine [28–30].

In hepatitis C, the mechanisms by which cytokines directly affect HRQOL or indirectly influence symptoms and/or illnesses that negatively impact on quality of life remain unclear [31]. Several studies suggest that an imbalance between pro-inflammatory and anti-inflammatory cytokines might induce an immune activation in the brain, and consequently, generates depression and/or depression-like symptoms such as fatigue, loss of interest in daily activities, and cognitive deficits.

Because the host's immune response against HCV may affect HRQOL in patients with CHC, even before the onset of liver cirrhosis, we hypothesized that *IL*10 ATA haplotype, the IL-10 low-producer phenotype combined with *IL*6 GG genotype, the IL-6 high-producer phenotype, may be linked to a high inflammatory profile that negatively influences HRQOL. Therefore, we investigated the frequency of *IL10* − 1082G/A, − 819C/T, and − 592C/A SNPs and *IL6*-174G/C SNP, separately and in combination, in CHC patients and in healthy subjects of the same ethnicity. We also evaluated the association between demographic, clinical, psychiatric, virological, and genetic variables with domains and summaries of HRQOL in patients with CHC.

Participants and methods

We screened 143 patients with CHC attending the Viral Hepatitis Outpatient Clinic, University Hospital, Belo Horizonte, Brazil. The control group consisted of 98 consecutive volunteer blood donors from the hemocenter of Felício Rocho Hospital (Hemoter - Clínica Romeu Ibrahim de Carvalho), Belo Horizonte, Brazil. All patients and controls signed the informed consent form. The study was designed and conducted in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee of Federal University of Minas Gerais/UFMG (ETIC 0631.0.203.000-09).

The exclusion criteria were pregnancy, breastfeeding, hepatic encephalopathy, HBV/HCV or HCV/HIV co-infection, current antiviral or antidepressant treatment, use of non-steroidal anti-inflammatory drugs or corticosteroids, and the presence of advanced disease such as decompensated liver cirrhosis, chronic kidney disease, heart failure, chronic pulmonary disease, and neoplasia, including hepatocellular carcinoma.

The diagnosis of cirrhosis was based on standard clinical, biochemical, radiological, and histological parameters [32, 33]. The severity of liver dysfunction was assessed by the Child–Pugh–Turcotte score [34]. Compensated cirrhosis was defined as the absence of variceal bleeding, ascites and oedema, jaundice, or symptomatic encephalopathy on

physical examination, and decompensated cirrhosis as the presence of any of these complications [35].

All included individuals, CHC patients and healthy subjects, underwent a psychiatric evaluation, which assessed their psychiatric history and current mental status. Thereafter, the Brazilian version of the Mini International Neuropsychiatric Interview (M.I.N.I. Plus) was administered [36]. This instrument is a semi-structured diagnostic interview comprising the primary Axis I disorders of the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) and the International Classification of Diseases (ICD-10), which was designed for clinical practice and research in psychiatric and primary care settings [37]. The diagnosis of current major depressive disorder was made according to the ICD-10 and the DSM-IV [38]. Furthermore, an in-person interview was conducted using instruments to assess the patients' sociodemographic, clinical characteristics [7], and HRQOL [39–42]. Eleven patients were not included: three patients refused to participate and eight additional patients who had initially agreed to take part in this study failed to complete the questionnaires. One hundred and thirty-two patients and 98 healthy subjects remained in the study.

All participants were from a similar socioeconomic level, as assessed by a previously validated questionnaire [7], which was based on income and educational level, as well as similar cultural habits. All subjects were natives of Minas Gerais, a Brazilian state with the following ethnic background: 56.0% of European ancestry, 32.0% of African ancestry, and 12.0% of Amerindian ancestry, homogeneously present in each subject, irrespective of their phenotype [43].

Generic HRQOL assessment questionnaire

HRQOL was assessed by a generic questionnaire, the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), which is considered to be the most suitable generic instrument for HRQOL measurement in chronic liver disease [39–41]. This multidimensional instrument measures four domains of physical health (General Health Perceptions, Physical Functioning, Physical Role Functioning, and Bodily Pain), and four domains of mental health (Emotional Role Functioning, Social Role Functioning, Vitality, and Mental Health). The first four domains load on a physical component summary (PCS), while the last four load on a mental component summary (MCS). Each domain has a final score of 0–100, in which zero and 100 correspond to the worst and to the best HRQOL, respectively. The SF-36 is validated and yields good psychometric properties [39]. This questionnaire was previously translated into Brazilian Portuguese [44] and validated in the Brazilian population [45, 46].

Specific HRQOL assessment questionnaire

Specific HRQOL was assessed by the Liver Disease Quality of Life Questionnaire (LDQOL1.0) [42], a hybrid questionnaire, an instrument for assessing HRQOL in patients with chronic liver disease, which was previously translated into Brazilian Portuguese and validated in the Brazilian population [47]. The 12 disease-specific scales in LDQOL are Symptoms of Liver Disease (17 items), Effects of Liver Disease (10 items), Concentration (7 items), Memory (6 items), Quality of Social Interaction (5 items), Health Distress (4 items), Sleep Problems (5 items), Loneliness (5 items), Hopelessness (4 items), Stigma of Liver Disease (6 items), Sexual Functioning (3 items), and Sexual Problems (3 items). Each domain has a final score from 0 to 100, in which zero and 100 correspond to the worst and the best HRQOL, respectively [42].

Laboratory parameters

Blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes.

DNA extraction and genotyping of *IL*6 and *IL*10

DNA was extracted from the leukocytes with the QIAamp DNA mini kit (QIAGEN GmbH, Hilden, Germany) according to the manufacturer's recommendations. *IL*-10 and *IL*-6 genotyping were Taqman assayed (Real Time PCR 7500 System Applied Biosystems, Foster City, CA) by using oligonucleotide primers previously described by Turner et al. [26] and Fishman et al. [28]. The sequences of synthetic probes and reaction conditions are described in Table S1 (Supplementary Material).

Statistical analysis

Data were analyzed with SPSS (SPSS Inc., Chicago, IL) statistical software package version 17.0. Descriptive statistics were used to provide information regarding demographic, clinical, psychiatric, virological, and genetic data. The Shapiro–Wilk test was used to evaluate whether the data were normally distributed. The asymptotic Pearson's χ^2 test was used to compare the percentages. The Student's t test or ANOVA was used to compare the means, and the two-tailed Mann–Whitney U test was used for medians. Because significant departures from normality were observed for all HRQOL domain and summary scores, comparisons between the groups were made by the two-tailed Mann–Whitney U test.

The Hardy–Weinberg equilibrium of alleles at individual *loci* was assessed by two-tailed Chi-square test or Fisher's Exact test in both case and control groups. Haplotype

frequencies for pairs of alleles and linkage disequilibrium between the *loci* were estimated by using the program EH (available from ftp://linkage.rockefeller.edu/software/eh/).

Quality of life analysis

For HRQOL scores assessed by the generic questionnaire, we first transformed the SF-36 mean scores of CHC patients into standard scores, based on the scores of the age- and gender-matched control group [19]. The standard scores were calculated by dividing the difference between the mean scores of the CHC patients and the scores of the age- and gender-matched control group by the standard deviation of this control group. Based on Cohen, the effect sizes were interpreted as small ($d=0.2$), medium ($d=0.5$), and large ($d=0.8$) [48]. Second, all these described steps were also performed using the SF-36 mean scores of the age- and gender-matched Brazilian population as the reference population [45, 46]. Additionally, the MCS and PCS scores were compared to the mean of the control group and the mean of the Brazilian reference population [45, 46] using two *t* tests. The level of significance was set at $P \leq 0.05$.

Because previous studies have demonstrated that both medical and/or psychiatric comorbidities have a relevant impact on HRQOL of patients with CHC [7, 49–52], we included hypertension, diabetes, and major depressive disorder in addition to cytokine polymorphisms as variables in the linear regression analyses. The association between HRQOL and CHC patients' following variables—demographic (sex and age), clinical comorbidities (hypertension and diabetes mellitus), liver fibrosis stage (chronic hepatitis and compensated cirrhosis), psychiatric comorbidity (current major depressive disorder), and genetic (*IL10* − 1082G/A, − 819C/T, and − 592C/A SNPs and *IL6* − 174G/C SNP, separately and in combination) was evaluated. As a first step, several linear regression analyses were employed to select the variables potentially associated ($P \leq 0.10$) with each one of the HRQOL outcomes (dependent variable, i.e., each of the eight SF-36 domains, the two SF-36 subscales, and the twelve LDQOL domains). Subsequently, to assess the independent associations between patient characteristics and HRQOL, all variables with $P \leq 0.10$ in the univariate analysis were included in the multivariate linear regression analyses. The analyses were separately performed for each of the HRQOL outcomes. The R^2 (adjusted coefficient of determination) and the ANOVA were used to assess the adequacy of the models. Variables that had missing data > 10% were not selected for the models of linear multivariate analysis. The level of significance was set at *P* values ≤ 0.05.

Results

Characteristics of the study population and distribution of the *IL*10 and *IL*6 genotypes

The characteristics of individuals included in the study were CHC patients [$n=132$; mean age 52.6 ± 11.4 years; 72/132 (54.5%) females] and controls [$n=98$; mean age 36.0 ± 10.4 years; 47/98 (48.0%) females] (Table 1). Patients with CHC (33.3%) were more likely to have current major depressive disorders ($P<0.001$) than controls (1.0%) (Table 1).

Among CHC patients, 24 (18.2%) had compensated cirrhosis [Child–Turcotte–Pugh score A5, 16 (66.7%) and A6, 8 (33.3%)].

No significant differences were observed between CHC patients without cirrhosis and those with compensated cirrhosis concerning the mean age (52.5 ± 12.1 years vs. 52.9 ± 7.7 years; $P=0.84$), female sex, (55.6% vs. 50.0%, $P=0.62$), arterial hypertension (35.2% vs. 29.2%, $P=0.57$), and current major depressive disorder (23.1 vs. 29.2, $P=0.53$). Diabetes mellitus tended to be more frequent ($P=0.08$) in CHC patients with compensated cirrhosis (33.3%) than in those without cirrhosis (17.6%). There was no significant difference ($P=0.37$) in viral load between patients without cirrhosis [HCV-RNA log10 (IU)/ml 5.76 (5.30–6.15)] and those with compensated cirrhosis [5.51 (5.10–6.03)]. The frequency of HCV Genotype 1 in patients without cirrhosis [75/87 (86.2%)] did not differ ($P=0.18$) from that of patients with compensated cirrhosis [14/19 (73.7%)]. The viral load quantification and the HCV genotyping were available for 106/132 (80.3%) patients.

The frequencies of *IL*10 SNPs and *IL*6 SNP, separately and in combination, did not differ between CHC patients and blood donors (Table 1). All alleles were in Hardy–Weinberg equilibrium in both patients and controls as shown in Table 1.

Generic health-related quality of life questionnaire scores

Because the scores of the SF-36 may vary according to age and gender, their mean values were analyzed in a subgroup of age- and gender-matched patients ($n=55$) and controls ($n=55$) (Table S2; Supplementary Material). The characteristics of the age- and gender-matched 110 individuals were shown in Table S3 (Supplementary Material). CHC patients had significantly lower scores in all SF-36 domains (Fig. 1a) and summaries than controls. When SF-36 domains of CHC patients were compared to that of the age- and gender-matched Brazilian population [40, 41, 45, 46], all SF-36 subscales (domains/summaries) were diminished (Table S2 and Fig. 1b).

Table 1 Interleukin genotype distribution, demographic, and clinical characteristics in patients with chronic hepatitis C ($n=132$) and healthy controls ($n=98$)

Variables	CHC *n* (%)	Control *n* (%)	*P* value
*IL*6 genotypes			
− 174			
C/C	09 (6.8)	07 (7.2)	
G/C	38 (28.8)	41 (41.8)	0.11
G/G	85 (64.4)	50 (51.0)	
Total	132 (100)	98 (100)	
HEW	0.18	0.91	
*IL*10 genotypes			
− 1082			
G/G	22 (16.7)	16 (16.3)	
A/G	54 (40.9)	38 (38.8)	0.93
A/A	56 (42.4)	44 (44.9)	
Total	132 (100)	98 (100)	
HEW	0.22	0.19	
− 819/− 592			
TT/AA	19 (14.4)	11 (11.2)	
CC/CC	54 (40.9)	41 (41.8)	0.78
CT/CA	59 (44.7)	46 (47.0)	
Total	132 (100)	98 (100)	
HEW	0.34	0.90	
*IL*10 haplotypes[a]			
GCC (high producer)	48/104 (46.2)	29/73 (39.7)	0.40
ATA (low producer)	50/104 (48.1)	32/73 (43.8)	0.58
Combined *IL*10 ATA haplotype/*IL*6-174 GG genotype[b]			
ATA + GG (High inflammatory profile)	35/94 (37.2)	14/59 (23.7)	0.08
Demographic			
Male	60 (45.5)	51 (52.0)	0.32
Female	72 (54.5)	47 (48.0)	
Age (years)[c]	52.6 ± 11.4	36.0 ± 10.4	< 0.001
Clinical comorbidities			
DM	27 (20.5)	0 (0.0)	< 0.001
HTN	45 (34.1)	0 (0.0)	< 0.001
Psychiatric comorbidity			
Current MDD	44 (33.3)	1 (1.0)	< 0.001

CHC chronic hepatitis C, *n* number of subjects, *IL*6 interleukin-6 gene, *HEW* Hardy–Weinberg Equilibrium, *IL10* interleukin-10 gene

[a]Carriers of diplotypes (*IL*10) GCC/ATA [cases ($n=28$) and controls ($n=25$)] were removed from the analysis

[b]Carriers of diplotypes (*IL*10) GCC/ATA [cases ($n=28$) and controls ($n=25$)] and carriers of haplotype (*IL*10)/genotype (*IL*6) ATA/GC [cases ($n=10$) and controls ($n=14$)], respectively, were removed from the analysis

[c]Mean ± standard deviation (SD); *DM* diabetes mellitus, *HTN* hypertension, *MDD* major depressive disorder; *P* values ≤ 0.05 were considered significant. The asymptotic Pearson's χ^2 test was used to compare categorical variables. The *t* test and Mann–Whitney *U* test were used for comparison of means and medians, respectively

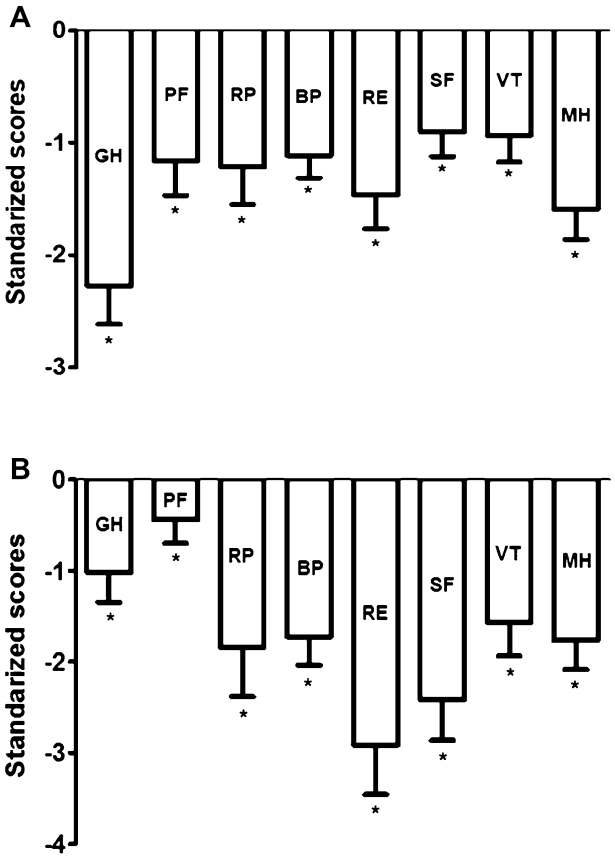

Fig. 1 Standard health-related quality of life (HRQOL) scores on the eight domains of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36). A standardized HRQOL score < 0 indicates a HRQOL score that is worse than the age- and gender-matched control group (blood donors) (**a**) or the age- and gender-matched Brazilian reference population [45, 46] (**b**), and scores > 0 indicates better HRQOL scores [20]. The standardized scores can be interpreted as Cohen's *d*, indicating the effect size [48]. There was a large effect on all quality of life domains when the patients were compared with the age- and gender-matched control group ($d < -0.8$). Moreover, when the patients were compared with age- and gender-matched Brazilian reference population, there was a large effect on GH, RP, BP, RE, SF, VT and MH domains ($d < -0.8$) and a small effect ($d = -0.44$) in PF domain. *VT* vitality, *SF* social functioning, *RE* role emotional, *MH* mental health, *PF* physical functioning, *RP* role physical, *BP* bodily pain, *GH* general health. Domains that significantly ($P \leq 0.05$) differed from the age- and gender-matched control group (blood donors) (**a**) or the age- and gender-matched Brazilian reference population [45, 46] (**b**) are marked with *. The data were analyzed by two-tailed Mann Whitney *U* test

Characteristics of CHC patients with and without *IL*10 ATA haplotype and *IL*6-174GG polymorphisms

The characteristics of CHC patients with and without *IL*10 ATA haplotype and *IL*6-174GG genotype are shown in Supplementary Tables S4 and S5, respectively (Tables S4 and S5). Because of the interactions of cytokine SNPs and their marked effects on the expression profiles of pro- and anti-inflammatory mediators, we analyzed whether the combined SNPs were associated with HRQOL. The carriers ($n = 35$) of the combined *IL*10 ATA haplotype and *IL*6-174GG genotype were more likely to have current major depressive disorder than the non-carriers ($n = 59$) of *IL*10 ATA haplotype/*IL*6-174GG genotype (Table 2). In addition, lower HRQOL scores were observed in the carriers of the *IL*10 ATA haplotype/*IL*6-174GG genotype compared to the non-carriers of the combined haplotype/genotype (Table 2).

The characteristics of healthy individuals ($n = 98$) with and without the *IL*10 ATA haplotype and the *IL*6-174GG polymorphisms are shown in the Supplementary Material (Tables S6, S7 and S8).

Factors associated with changes in HRQOL scores in patients with chronic hepatitis C

Generic HRQOL instrument in chronic hepatitis C patients

In the multivariate analysis, current major depressive disorder was associated with lower SF-36 scores in seven domains and MCS summary (Table 3). Poorer HRQOL was observed for the physical functioning domain in the carriers of combined *IL*10 ATA haplotype and *IL*6-174GG genotype compared to the non-carriers of this haplotype/genotype combination (Table 3). Furthermore, the clinical comorbidities, diabetes mellitus, and arterial hypertension, were associated with reduced scores in the Physical functioning domain and PCS summary (Table 3). The univariate analysis is shown in Supplementary Table S9.

The factors associated with changes in HRQOL scores in healthy individuals ($n = 98$) are shown in Supplementary Material (Tables S10 and S11).

Specific HRQOL instrument in chronic hepatitis C patients

In the multivariate analysis, major depressive disorder was associated with lower LDQOL scores in 11 domains (Table 4). Reduced HRQOL was observed in the carriers of combined *IL*10 ATA haplotype and *IL*6-174GG genotype compared to the non-carriers of this haplotype/genotype combination for the following domains: effects of liver disease on activities of daily living, quality of social interaction, and sexual functions (Table 4). Cirrhosis and diabetes were associated with lower LDQOL scores in the sexual function and sexual problem domains, respectively (Table 4). Univariate analysis is shown in Supplementary Table S12.

Table 2 Demographic, clinical, psychiatric, virological, and health-related quality of life data of the patients with chronic hepatitis C, carriers ($n=35$), and non-carriers ($n=59$) of the combined *IL*10 ATA haplotype and *IL*6-174GG genotype

Variables	Combined *IL*10 ATA haplotype and *IL*6 GG genotype[a]		
	ATA + GG High inflammatory profile *n* (%)	Non-ATA + GG Low inflammatory profile *n* (%)	*P*
Demographic			
Male	15 (42.9)	25 (42.4)	0.96
Female	20 (57.1)	34 (57.6)	
Age (years)[b]	50.2 ± 9.8	54.4 ± 12.3	0.09
Clinical comorbidities			
DM	7 (20.0)	13 (22.0)	0.82
HTN	10 (28.6)	25 (42.4)	0.18
Stage of liver disease			
Compensated cirrhosis	8 (22.9)	10 (16.9)	0.48
Psychiatric comorbidity			
Current MDD	13 (37.1)	9 (15.3)	0.02
Virological parameters			
Viral load HCV-RNA [Log10 IU/ml][c]	5.68 (5.32–6.09)	5.52 (4.99–6.08)	0.56
Genotype 1	21 (75.0)	42 (85.7)	0.24
Generic HRQOL questionnaire scores[c]			
PCS SF-36 Summary	48.9 (39.2–54.8)	50.9(42.5–56.6)	0.30
MCS SF-36 Summary	41.3 (28.3–55.8)	50.9 (39.0–58.4)	0.05
Specific HRQOL questionnaire scores (LDQOL)[c]			
Symptoms related to liver disease	76.5 (60.9–85.0)	87.1 (77.1–91.8)	0.01
Effects of liver disease on activities of daily living	70.4 (50.0–87.5)	92.2 (68.8–100)	0.005
Concentration	78.6 (54.5–99.1)	89.3 (71.4–100)	0.18
Memory	70.8 (27.1–100)	77.1 (54.2–91.7)	0.89
Quality of social interaction	66.4 (50.0–80.0)	80.0 (64.6–93.8)	0.02
Health distress	62.5 (32.8–100)	81.3 (62.5–100)	0.09
Sleep problems	55.0 (40.0–80.0)	70.0 (50.0–90.0)	0.11
Loneliness	82.5 (60.0–100)	95.0 (80.0–100)	0.11
Hopelessness	81.3 (59.4–100)	100 (81.3–100)	0.01
Stigma of liver disease	87.5 (57.3–100)	100 (80.2–100)	0.02
Sexual function	55.5 (38.7–72.2)	91.7 (80.5–91.7)	0.001
Sexual problem	77.8 (58.3–100)	88.9 (77.7–100)	0.20

[a]Carriers of diplotypes (*IL*10) GCC/ATA ($n=28$) and haplotype (*IL* 10) ATA/genotype (*IL* 6) GC ($n=10$) were removed from the analysis; *n*, number of subjects

[b]Mean ± standard deviation (SD); *DM* diabetes mellitus, *HTN* hypertension, *MDD* major depressive disorder, *HCV* hepatitis C virus

[c]Median and interquartile range (IQR), 25th–75th percentile; *PCS* Physical Component Summary, *MCS* Mental Component Summary, *SF-36* the Medical Outcomes Study 36-Item Short Form Health Survey, *LDQOL* Liver Disease Quality of Life Questionnaire, *P* values ≤ 0.05 were considered significant. The asymptotic Pearson's χ^2 test was used to compare categorical variables. The *t* test and Mann–Whitney *U* test were used for comparison of means and medians, respectively

HCV viral load, HCV genotype, and HRQOL scores in CHC patients

Neither viral load nor HCV genotype was associated with the scores of the SF-36 and the LDQOL subscales.

Discussion

To the best of our knowledge, this is the first study to demonstrate that the *IL*10 ATA haplotype, low-producer IL-10 phenotype combined with the *IL*6-174GG genotype, high-producer IL-6 phenotype, is associated with poor HRQOL in patients with CHC. Apart from the substantial body of scientific evidence demonstrating that quality of life

Table 3 Variables associated with health-related quality of life (HRQOL) in patients with chronic hepatitis C ($n=132$) using the generic HRQOL instrument

SF-36 domains, summaries[a]/variables	Beta	95%CI	Adjusted R^2	*P* value
MCS summary				
MDD	−17.4	−22.23; −12.05	0.35	<0.001
Mental health				
MDD	−31.98	−42.31; −21.64	0.30	<0.001
Role emotional				
MDD	−34.61	−54.73; −14.47	0.11	0.001
Social functioning				
MDD	−30.49	−41.10; −19.89	0.27	<0.001
Vitality				
MDD	−26.93	−38.74; −15.12	0.19	<0.001
PCS summary				
HTN	−6.58	−10.49; −2.68	0.11	0.001
General health				
MDD	−16.33	−27.46; −5.20	0.08	0.005
Bodily pain				
MDD	−15.09	−27.56; −2.62	0.05	0.02
Physical functioning				
HTN	−15.98	−26.47; −5.50	0.20	0.003
DM	−12.06	−23.93; −0.18		0.05
ATA + GG	−11.35	−21.16; −1.54		0.02
Role physical				
MDD	−26.9	−44.63; −9.18	0.09	0.003

[a]Health-related quality of life (HRQOL) scores on the eight domains and two summaries of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36); *95% CI* confidence interval, *adjusted* R^2 [explained variance (%)], *MCS* Mental Component Summary, *PCS* Physical Component Summary, *HTN* hypertension, *DM* diabetes mellitus, *MDD* major depressive disorder, *ATA + GG* combined *IL*10 ATA haplotype and *IL*6-174GG genotype. The multivariate linear regression analyses were employed to identify, which of the variables was significantly ($P \leq 0.05$) related to each of the HRQOL outcomes (i.e., the eight HRQOL domains and both HRQOL subscales). The linear regression models were appropriately adjusted according to the *F* test of the ANOVA ($P \leq 0.05$)

is reduced in individuals chronically infected with HCV regardless the severity of hepatic disease [7, 53, 54], factors linked to the reduced HRQOL have not been completely clarified yet.

Recently, several studies have demonstrated a relationship among host genetic, biological pathways, molecular biomarkers, and HRQOL domains [13–20]. Among them, the immune response must be highlighted. Cytokine gene polymorphisms and/or target cytokines have been found to be directly associated with a decrement in HRQOL domains [16–20, 55]; as well as high expression of pro-inflammatory mediators is linked to symptoms that markedly decrease HRQOL scores such as fatigue, pain, and depression [16, 56–59]. Although there are accumulating lines of evidence of genetic involvement in HRQOL [16, 55], we have to bear in mind that quality of life is characterized by a multidimensional nature that engenders a complex analysis [16]. Among the factors that affect HRQOL, an overlap between different aspects might influence the person's subjective perception of his/her state of health, and should be taken into consideration such as genetic background, illnesses, clinical manifestations, and symptoms [16, 54].

Although current major depressive disorder had a strong impact on the HRQOL of patients with CHC [3, 5–8], in the current study, *IL*10 ATA haplotype combined with *IL*6-174GG genotype was retained in the multivariate analysis in both generic and specific HRQOL domains irrespective of the presence of depression covariate. The combined haplotype/genotype was inversely associated with generic and specific HRQOL domains, i.e., with physical functioning score of SF-36 questionnaire and effects of liver disease on activities of daily living, quality of social interaction, and sexual function of LDQOL instrument. Similarly, Rausch et al. found significant associations between cytokine SNPs and symptom burden and quality of life in 1,149 Caucasian survivors of lung cancer [17]. Among all interleukin SNPs evaluated, *IL*6 SNPs were significantly associated with the Lung Cancer Symptom Scale overall quality of life, as well as with the mental health and the emotional health on the Medical Outcomes Study Short Form General Health Survey (SF-8) [17]. Additionally, the authors observed that *IL*10 SNPs were associated with the physical health component summary score of the SF-8 questionnaire.

In hepatitis C, association between HRQOL and genetic variables is marked by a paucity of data, specifically in HCV-infected individuals without evidence of cirrhosis. In line with previous studies [3, 53, 54], we observed a higher decrement in HRQOL in CHC patients in comparison to healthy individuals and the Brazilian population reference [45, 46], irrespective of the degree of hepatic fibrosis. Based on these findings, we might speculate that an imbalance of pro- and anti-inflammatory cytokines may negatively influence HRQOL. The release of inflammatory mediators may contribute to the clinical manifestations of CHC such as fatigue, depression, anxiety, cognitive impairment, muscle pain, and arthralgia [3, 53, 54], which also impact quality of life.

In this study, we report the measurement of HRQOL, particularly focusing on host factors that affect the quality of life of patients with CHC. Among them, current major depressive disorder was associated with lower SF-36 and LDQOL scores in seven (87.5%) and 10 (83.3%) domains, respectively, independently of the liver disease stage. In this context, an important aspect that should be analyzed is the possibility of an overlap between HRQOL domains

Table 4 Variables associated with health-related quality of life (HRQOL) in patients with chronic hepatitis C ($n = 132$) using the specific HRQOL instrument

LDQOL domains[a]/variables	Beta	95% CI for Beta	Adjusted R^2	P
Symptoms related to liver disease				
Sex (female)	−6.81	−13.44; −0.17	0.23	0.04
MDD	−17.54	−25.05; −10.02		<0.001
Effects of liver disease on activities of daily living				
MDD	−12.27	−24.45; −0.30	0.10	0.05
ATA + GG	−11.13	−22.17; −0.09		0.05
Concentration				
MDD	−23.16	−34.14; −12.18	0.17	<0.001
Memory				
MDD	−24.46	−37.20; −11.73	0.14	<0.001
Quality of social interaction				
MDD	−16.16	−24.63; −7.68	0.20	<0.001
ATA + GG	−8.81	−17.52; −0.11		0.05
Health distress				
MDD	−30.05	−43.49; −16.00	0.18	<0.001
Sleep problems				
Sex (female)	−10.94	−20.90; −0.99	0.19	0.03
MDD	−21.70	−32.97; −10.42		<0.001
Loneliness				
MDD	−14.59	−25.76; −3.42	0.06	0.01
Hopelessness				
MDD	−18.96	−29.71; −8.21	0.12	0.001
Stigma of liver disease				
MDD	−24.63	−35.35; −13.90	0.19	<0.001
Sexual function				
Cirrhosis	−18.10	−33.16; −3.05	0.35	0.02
ATA + GG	−25.30	−37.57; −13.03		<0.001
Sexual problem				
DM	−16.61	−31.93; −1.29	0.08	0.03

[a]Health-related quality of life (HRQOL) scores on the twelve domains of the Liver Disease Quality of Life Questionnaire (LDQOL1.0); *95% CI* confidence interval, *Adjusted* R^2 [explained variance (%)], *HTN* hypertension, *DM* diabetes mellitus, *MDD* major depressive disorder, *ATA + GG* combined *IL*10 ATA haplotype and *IL*6-174GG genotype. The multivariate linear regression analyses were employed to identify the variables that were significantly ($P \leq 0.05$) associated with each of the HRQOL outcomes (i.e., the twelve HRQOL domains). The linear regression models were appropriately adjusted according to the F test of the ANOVA ($P \leq 0.05$)

and psychiatric illnesses, especially depressive disorder. In our study, one may speculate that depressed patients were affected by demotivation, low level of energy, difficulty to concentrate, and reduced self-confidence. These conditions might possibly introduce a bias in the interpretation of the HRQOL domain scores [60, 61]. Nevertheless, Bayliss *et al*. (1998) reported that compared to patients with depression, patients with CHC had seven SF-36 scores equally impaired [62].

In the present study, in addition to major depressive disorder, clinical comorbidities, arterial hypertension, and diabetes mellitus were associated with a reduction in the scores of HRQOL domain. Studies have demonstrated the negative impact of comorbid illness on HRQOL in various clinical scenarios [52, 63]. In our study, arterial hypertension was associated with lower scores on SF-36 physical functioning domain and physical component summary. In our previous study with CHC patients, arterial hypertension also negatively influenced the HRQOL [7]. Interestingly, Trevisol et al. (2012) verified that individuals with arterial hypertension had worse quality of life, particularly when their blood pressure was controlled by medication [63]. Kwan et al., in an investigation with 3023 randomly selected veterans with CHC, reported that hypertension, diabetes, arthritis,

chronic obstructive pulmonary disease, and low back pain had a significant negative effect on the Physical Component Summary (SF-36 questionnaire) on HRQOL score [52].

Concerning diabetes mellitus, a recent study has shown that sexual dysfunction was highly prevalent in men and women with type 2 diabetes and associated with increasing age, clinical depression, and diabetes-related complications [64]. Of note, sexual dysfunction significantly affects the quality of life of patients with CHC [65, 66].

Although HRQOL is variably impaired in cirrhotic patients, the results of studies evaluating the impact of the severity of liver fibrosis on HRQOL are still controversial [67, 68]. In the current study, cirrhosis was associated with lower LDQOL scores in only one domain: sexual function. It has been known that abnormalities of sexual function are prevalent among patients with hepatopathies, especially in subjects with advanced liver failure. In this context, HRQOL may be markedly decreased in cirrhotic patients with sexual dysfunction [69].

It is important to note that this study had some limitations. For instance, the subjects included were recruited from a referral center, and consequently may not be representative of all patients with CHC. In addition, the cross-sectional nature of this investigation precluded the possibility to recognize any cause–effect relationship between low HRQOL and clinical, psychiatric, and genetic cofactors. Furthermore, another limitation is the lack of data regarding patient's and control's plasma levels of IL-6 and IL-10; however, the functional relevance of the studied polymorphisms is well known [26–30].

In summary, this is the first study to demonstrate that *IL*10 ATA haplotype, IL-10 low producer, in combination with *IL*6174GG, IL-6 high producer, is independently associated with poor generic and specific HRQOL domains in CHC patients. The results of the present study indicate that cytokine dysregulation seems to have implications in decrement of quality of life in patients chronically infected with HCV. It should be highlighted that even in the presence of both medical and/or psychiatric comorbidities with a relevant impact on HRQOL of CHC patients [49–52] (such as major depressive disorder, hypertension, and diabetes), cytokine polymorphisms remained associated with certain domains of HRQOL. These findings provide new insight on exploring the factors that predict HRQOL in patients with CHC, and reinforce the need for further studies focusing on the biological mechanisms and the pathogenesis involved in reduced HRQOL in CHC patients. The challenge remains for forthcoming research to identify candidate genes and potential inflammatory markers involved in poorer HRQOL. Moreover, better comprehension of these processes might positively influence the management strategies for increasing the quality of life of subjects with CHC.

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Compliance with ethical standards

Conflict of interest The authors declare they have no conflict of interest.

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