The Impact of Chronic Hepatitis C and Comorbid Psychiatric Illnesses on Health-related Quality of Life

Joseph K. Lim, MD,* Ruth Cronkite, PhD,† Mary K. Goldstein, MD MSc,‡ and Ramsey C. Cheung, MD*

Goals: To determine the relative impact of chronic hepatitis C (CHC) and comorbid psychiatric illness on the health-related quality of life (HRQoL).

Background: Psychiatric conditions are more common among patients with CHC but their relative influence on HRQoL is not well understood.

Study: We identified 864 veterans who had previously completed a veteran-specific HRQoL questionnaire (SF-36V) as part of the 1999 VA Large Health Survey with known HCV antibody (anti-HCV) status before the survey. For 201 anti-HCV(+) and 663 anti-HCV(−) patients, we compared the HRQoL status and the prevalence of 6 major psychiatric diagnoses. We conducted multiple regression analyses to measure the effect of anti-HCV status and psychiatric comorbidity.

Results: Compared with the anti-HCV(−) group, anti-HCV(+) veterans were more likely to have alcohol dependence ($P < 0.001$), depression ($P = 0.01$), or posttraumatic stress disorder (PTSD) ($P < 0.004$). The anti-HCV(+) group also reported lower HRQoL on 4 of the 8 SF-36V subscales ($P < 0.01$) and the mental component summary scale ($P < 0.001$). Even after adjusting for demographic variables and comorbid psychiatric illness, anti-HCV(+) patients reported a significantly lower mental component summary score ($P < 0.01$) than did anti-HCV(−) patients. Multiple regression analysis found that depression and PTSD predicted lower HRQoL scores for all 8 HRQoL subscales ($P < 0.01$) and both the physical ($P < 0.001$) and mental component ($P < 0.03$) summary scales independent of anti-HCV status.

Conclusions: The HRQoL is significantly impaired in veterans with CHC, particularly the mental health components of HRQoL. In contrast, comorbid depression and PTSD are associated with both lower physical and mental components of HRQol, independent of CHC.

Key Words: hepatitis C, quality of life, psychiatric disorders, veterans

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C hronic hepatitis C (CHC) is an important public health problem, affecting over 2.7 million individuals in the United States and over 170 million worldwide.[1,2] CHC accounts for 8000 to 10,000 deaths annually and is the leading indication for liver transplantation.[3] It has been projected that between 2010 and 2019, 165,000 hepatitis C virus (HCV)-related deaths will result from chronic liver disease, including 27,200 from hepatocellular carcinoma at a cost of $10.7 billion in direct medical expenditures.[4] Since the initial discovery of HCV in 1989,[5] significant advances have been made in our understanding of the disease and therapy.

Clinical symptoms of CHC tend to be mild and nonspecific (eg, fatigue, malaise, abdominal pain). Patients with CHC have a lower health-related quality of life (HRQoL),[6–15] which improves after achieving sustained virologic response to antiviral therapy or undergoing liver transplantation.[6–9,16–20] These impairments are not associated with age, sex, mode of transmission, substance use, serum ALT levels, or social support.[21,22] Although previous studies have shown that psychiatric illnesses are common in patients with CHC,[6,23] their relative impact on HRQoL is poorly understood.

Drug and alcohol use, depression, post traumatic stress disorder (PTSD), anxiety, and CHC are more common among veterans than in the general population.[24–28] Veterans who receive care from the Veterans Health Affairs (VHA) facilities are more likely to have greater disability with more complex medical and mental health problems than veterans using other facilities or the general population.[15,29] Not surprisingly, HRQoL is significantly lower across multiple domains in veterans than in the general population.[30–32] We hypothesize that HRQoL is significantly impaired among veterans with CHC compared with those who are anti-HCV negative, and that comorbid psychiatric illnesses contribute significantly to these changes independent of HCV status.

MATERIALS AND METHODS

Study Population

The sample comprised 864 veterans enrolled in the VA Palo Alto Health Care System (VAPAHCS), who participated in the 1999 Large Health Survey and had been tested for anti-HCV before December 1998. We targeted veterans who had a documented HCV antibody status for at least 6 months before completion of the Large Health Survey, which began in July 1999, so that the veterans would be aware of their HCV status before completing the survey. We determined anti-HCV status from laboratory records of more than 20,000 veterans at the VAPAHCS who were tested for HCV antibody between July 1992 and December 1998 using either second or third generation enzyme-linked immunoassay EIA II or EIA III assays (Abbott Laboratories, Abbott Park, IL).

Large Health Survey

The 1999 Large Health Survey of Veteran Enrollees randomly sampled 1.4 million VHA enrollees between July 1999 and January 2000 for self-reported demographic (age, sex, ethnicity, education levels, and marital status) and health information using a structured questionnaire.[33] The survey response rate was 63.1% for the national sample and 62.4% for the VAPAHCS (VISN 21).

HRQoL

We measured HRQoL using the SF-36V survey, a veteran-specific form of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). The self-administered questionnaire, SF-36, has been validated and widely used as the instrument of choice for assessment of HRQoL.[34] It assesses 8 dimensions of health status divided into 2 major summary component scales representing physical and mental health. The summary scores are weighted averages of all 8 subscales, with the physical functioning, physical role, bodily pain, and general health subscales receiving strong positive weights in the physical component summary (PCS) and the vitality, social functioning, emotional role, and mental health subscales receiving strong positive weights in the mental component summary (MCS). A norm-based score between 0 (worst) and 100 (best) is calculated for each dimension and for the 2 summary components.[35] Each summary component score is expressed as a t score with a mean of 50 and a standard deviation of 10 allowing for comparison across subpopulations and the general US population. The modified SF-36V survey has been validated in the veteran population[36] and normalized to the general US population.[37] It is distinguished from the standard SF-36 by its use of 5 point ordinal choices in assessing physical and emotional role subscales (0 = *none of the time* to 5 = *all of the time*) instead of a dichotomous 2-point choice (*yes, no*) with the purpose of obtaining more precise information.

Comorbid Psychiatric Illnesses

Six major psychiatric diagnoses were drawn from the VHA administrative databases. The diagnoses were based on the Ninth Version of the Clinical Modification of the International Classification of Diseases (ICD-9CM) and included the following psychiatric diagnoses: anxiety (300.0, 300.2), depression (296.2, 296.3, 300.4, 311), bipolar disorder (296.0, 296.1, 296.4, 296.5, 296.7, 296.8, 296.9), schizophrenia (295), PTSD (309.81), and alcohol dependence (303, 305.0).

STATISTICAL ANALYSIS

Comparisons Based on Anti-HCV Status

We compared anti-HCV(+) and anti-HCV(−) veterans on baseline demographic characteristics (age, sex, ethnicity, and marital status), the prevalence of each of 6 comorbid psychiatric diagnoses, the eight HRQoL subscales, and the PCS and MCS. χ^2 tests of association were used for comparisons that involved dichotomous measures although independent group t tests were used for all other nondichotomous measures.

Predictors of HRQoL

We conducted multiple regression analyses to examine the effect of anti-HCV status on HRQoL relative to each of 6 comorbid psychiatric diagnoses. Separate regression equations were estimated for the PCS and MCS scores. The predictor variables included a set of 4 demographic characteristics (age, ethnicity, education, and marital status), a dichotomous variable for anti-HCV status (1 = positive, 0 = negative), and dichotomous variables for the presence of each of 6 psychiatric diagnoses (anxiety, depression, bipolar disorder, schizophrenia, PTSD, and alcohol dependence).

Differential Effects of Psychiatric Illnesses on HRQoL for Each Anti-HCV Subgroup

To examine whether the psychiatric conditions might have a variable effect on HRQoL depending on a veteran's anti-HCV status, 2 separate regression equations (for the PCS and MCS) were estimated for each anti-HCV status subgroup. The same demographic and psychiatric condition variables were used as predictors.

RESULTS

Comparison of Demographic, Comorbid Psychiatric Conditions and HRQoL based on Anti-HCV Status

Compared with the anti-HCV(−) group, anti-HCV(+) veterans were more likely to be significantly younger, male, nonwhite, and unmarried. The anti-HCV(+) group was somewhat less likely to have completed 12 or more years of education compared with the anti-HCV(−) group ($P = 0.057$). The anti-HCV(+) group was significantly more likely to have at least 1 of the 6 psychiatric diagnoses, especially depression, PTSD, or alcohol dependence (Table 1). Individual and summary

TABLE 1. Demographic Characteristics and Psychiatric Diagnoses in Anti-HCV(+) and Anti-HCV(−) Veterans (n = 864)

	Anti-HCV(+) (n = 201)	Anti-HCV(−) (n = 663)	P*
Demographic Characteristics			
Male	99.0%	95.9%	0.034
Nonwhite	45.8%	37.1%	0.027
Unmarried	70.6%	56.9%	< 0.001
Education > 12 years	47.3%	54.9%	0.057
Mean age, years (SD)	51.9 (8.38)	57.9 (13.32)	< 0.001
Psychiatric Diagnoses			
Alcohol dependence	43.8%	29.1%	0.004
Anxiety	15.9%	15.5%	0.895
Bipolar Disorder	11.0%	8.6%	0.312
Depression	43.8%	33.9%	0.001
PTSD	27.9%	18.6%	0.004
Schizophrenia	13.4%	9.2%	0.082
Any psychiatric diagnosisis†	64.7%	51.6%	0.001

*P value based on χ^2 for dichotomous variables and independent groups *t*-test for interval-level variables (age).
†Some veterans have multiple psychiatric diagnosis.

SF-36V scores for the anti-HCV(+) and (–) groups are presented in Table 2. Mean HRQoL scores among anti-HCV(+) veterans were lower in 7 of 8 domains with statistically significant differences in 4 domains (role emotional, mental health, general health, and social functioning). The anti-HCV(+) group also had a significantly lower score on the MCS, but not on the PCS. The mean MCS of our study group was lower than the local (Palo Alto), regional (VISN 21), and national average. This is probably because veterans with psychiatric disorders are more likely to have risk factor(s) for HCV and to have consequently undergone antibody testing.

Multiple Regression Analyses of Predictors of HRQoL

The relative contribution of CHC, demographic factors, and comorbid psychiatric diagnoses on HRQoL is summarized in Table 3.

Effect of anti-HCV Status

After adjusting for age, ethnicity, level of education, marital status, and comorbid psychiatric illness, anti-HCV(+) status still demonstrated a negative influence on HRQoL with a statistically significant impairment in the MCS score. Anti-HCV(+) veterans scored 2.64 points lower on MCS than anti-HCV(–) veterans. The PCS score was 0.69 points lower among anti-HCV(+) patients, but this was not statistically significant. Anti-HCV(+) status also demonstrated a negative association with each of the 8 HRQoL subscales and was statistically significant in 5 (data not shown).

Effects of Comorbid Psychiatric Conditions on PCS
Overall

Of the 6 comorbid psychiatric conditions, PTSD had the strongest negative effect on PCS. After controlling

TABLE 2. Health Related Quality of Life (HRQoL) Scores in Anti-HCV(+) and Anti-HCV(−) Veterans (n = 864)

	Anti-HCV(+) (n = 201)	Anti-HCV(−) (n = 663)	P*
Domain (0–100), mean (SD)			
Physical functioning	55.6 (28.5)	55.3 (30.1)	0.887
Role physical	24.5 (39.5)	34.9 (41.1)	0.053
Bodily pain	42.2 (26.8)	45.8 (26.6)	0.096
General health	38.9 (24.2)	45.0 (24.6)	0.002
Vitality	37.4 (23.8)	40.3 (25.2)	0.146
Social functioning	44.6 (30.3)	53.2 (31.2)	0.001
Role emotional	32.5 (44.4)	46.1 (47.7)	< 0.001
Mental health	50.3 (23.7)	59.7 (25.1)	< 0.001
Summary Component Scores (0–100)			
Physical component summary, PCS (SD)	36.2 (10.9)	36.1 (11.8)	0.915
Mental component summary, MCS (SD)	36.1 (13.5)	41.4 (14.4)	< 0.001
Comparison Scores	VA National Average	VISN 21	Palo Alto
Physical component summary, PCS	36.91	38.17	38.37
Mental component summary, MCS	45.08	45.55	45.52

*P value based on *t* test for independent groups.

TABLE 3. Effect of Demographic Characteristics, Psychiatric Diagnoses, and Anti-HCV Status on Physical and Mental Component Score

	Total Sample (n = 864)		Anti-HCV(+) Group (n = 201)		Anti-HCV(−) Group (n = 663)	
	Physical Component Score	Mental Component Score	Physical Component Score	Mental Component Score	Physical Component Score	Mental Component Score
Demographic Characteristics						
Nonwhite (1 = yes, 0 = no)	− 1.84†	0.20	− 1.44	− 0.10	− 1.93†	0.44
Unmarried (1 = yes, 0 = no)	2.64§	0.47	2.46	− 0.10	2.72‡	0.90
Education > 12 y (1 = yes, 0 = no)	2.63§	2.84§	2.89*	2.28	2.61‡	2.88‡
Mean age (y)	− 0.16§	0.10‡	− 0.12	0.11	− 0.17§	0.09†
Psychiatric Diagnoses						
Alcohol dependence (1 = yes, 0 = no)	1.79†	− 1.40	− 0.15	0.33	2.37†	− 2.27†
Anxiety (1 = yes, 0 = no)	0.17	− 1.19	1.34	− 3.27	− 0.08	− 0.05
Bipolar disorder (1 = yes, 0 = no)	− 0.98	− 0.65	− 2.63	4.50	− 0.25	− 2.80
Depression (1 = yes, 0 = no)	− 1.79*	− 7.29§	− 1.87	− 6.98‡	− 1.80	− 7.28§
PTSD (1 = yes, 0 = no)	− 2.38†	− 8.95§	− 0.75	− 6.08‡	− 2.83†	− 10.32§
Schizophrenia (1 = yes, 0 = no)	− 0.49	− 3.14†	2.57	− 2.72	− 1.55	− 3.47*
Anti HCV Status						
Anti HCV(+)	− 0.69	− 2.64‡	—	—	—	—
Constant	44.57	39.40	41.81	34.18	44.82	40.71
Adjusted R^2	0.074§	0.271§	0.01	0.152§	0.085§	0.285§

*$P \leq 0.10$.
†$P \leq 0.05$.
‡$P \leq 0.01$.
§$P \leq 0.001$.

for anti-HCV status and demographics, veterans with PTSD had PCS scores 2.38 points lower than veterans without PTSD ($P = 0.033$). Depression was also associated with a trend toward a lower PCS score (− 1.79, $P = 0.069$) whereas alcohol dependence was associated with a slightly higher PCS score (1.79, $P = 0.045$). When looking at the overall pattern of effects, 4 of the 6 psychiatric diagnoses (alcohol dependence, bipolar disorder, depression, and PTSD) demonstrated stronger effects on PCS than anti-HCV status. The overall explained variance (R^2) for the total sample was 0.074, suggesting that approximately 7% of the variation in the PCS scores was accounted for by the 11 predictor variables in the model.

Based on Anti-HCV Status

To assess whether psychiatric diagnoses might have a differential effect on the PCS score depending on HCV status, separate regression models were estimated for the anti-HCV(+) and anti-HCV(–) groups. The demographic and psychiatric disorder variables remained the same. Among anti-HCV(+) individuals, none of the 6 psychiatric diagnoses had a significant effect on PCS. Among anti-HCV(–) individuals, PTSD had a negative effect on PCS (− 2.83, $P = 0.036$) whereas alcohol dependence had a positive effect (2.37, $P = 0.024$).

Effects of Comorbid Psychiatric Conditions on MCS
Overall

Three of the 6 psychiatric diagnoses had significant negative effects on the MCS: depression, PTSD, and schizophrenia. The negative effects for depression and PTSD were considerably stronger than their effects on PCS. After controlling for demographics, other psychiatric diagnoses, and CHC, depression was associated with a MCS score 7.29 points lower than what was observed for veterans without depression. Veterans with PTSD scored 8.95 points lower on MCS than those without PTSD. These 3 psychiatric conditions had negative effects on MCS that were stronger than the effect of CHC (− 2.64). Taken together, the 11 predictor variables (4 demographic, 6 psychiatric diagnosis, HCV) account for 27% of the variation in MCS, which is almost 4 times greater than that for the PCS model (7%).

Based on Anti-HCV Status

When separate regression models were estimated for the 2 anti-HCV subgroups, the pattern of effects was relatively consistent across the two subgroups. Both depression and PTSD had strong negative effects on MCS that were similar to those observed for the total sample. Alcohol dependence seemed to have a significant negative effect on MCS among anti-HCV(–) veterans, but not among anti-HCV(+) veterans. Taken together, the predictors account for about 15% of the variation in MCS for the anti-HCV(+) group and 29% of the variation in MCS for the anti-HCV(–) group.

DISCUSSION

HRQoL is markedly diminished in veterans who are anti-HCV(+) and is further reduced among patients with comorbid depression and PTSD. The impairment

associated with being anti-HCV(+) is predominantly on the mental components, whereas psychiatric disorders seem to have a broader effect. Patients with CHC have been found to have a significantly reduced HRQoL that is lower than that of patients with other liver diseases of similar severity.[10] Co-morbid conditions more commonly seen in patients who are anti-HCV(+) could provide a possible explanation for this observation. One of the few studies addressing this issue found that HRQoL was significantly lower among 63 otherwise healthy patients with CHC than among the general population, and further reduced among 157 CHC patients with coexisting medical or psychiatric illness ($P < 0.001$); the lowest scores were observed among the 7 CHC patients with comorbid psychiatric illness. Although strongly suggestive of an important cumulative effect of CHC and comorbid psychiatric disorders, this study was limited by small numbers and the absence of a comparable HCV negative control group. Most published studies addressing HRQoL in CHC infection have examined highly selected populations, typically within specialty referral clinics or large clinical trials. In contrast, the VHA Large Health Survey was administered on randomly selected VHA enrollees, thereby minimizing selection and referral bias. The use of this survey in conjunction with administrative files provided a unique opportunity to address the relative effects in a more broad and representative population.

Psychiatric disorders are common among CHC patients, especially veterans. In a retrospective analysis of a large VA database of patients hospitalized between 1992 and 1999, El-Serag et al[28] found a high overall incidence of psychiatric disorder among veterans, which was even higher among those with a diagnosis of CHC. Multivariate logistic regression analysis suggested that depression, anxiety disorder, and PTSD were "risk factors" associated with a diagnosis of CHC. Our current study provides further evidence that psychiatric disorders are more common among those who are anti-HCV(+). In a prior study, using well-established and validated questionnaires administered to 120 consecutive veterans with CHC seen in our Liver Clinic, we found depression in 44.2%, anxiety in 38%, PTSD in 20.8%, and alcohol-related problems in 26.7% of the patients in the sample.[38] The prevalence of depression was strikingly similar between the 2 cohorts. The lower prevalence of alcohol-related problems in patients seen in our Liver Clinic illustrates the problem of patient referral bias. The prevalence of psychiatric illness among nonveteran CHC patients also seems to be higher than in the general population with rates of depression and anxiety as high as 22.4% and 15.2%, respectively.[28,39–41]

Accordingly, determining the relative impact of psychiatric illness on HRQoL in CHC patients is clinically important. Our results suggest that US veterans who are anti-HCV(+) experience a significant and independent reduction in HRQoL, and those with comorbid depression or PTSD experience additional impairment. After controlling for 4 demographic vari-

ables and 6 psychiatric diagnoses, we demonstrated that positive anti-HCV status was still associated with a statistically significant negative effect on HRQoL scores along the mental health component (MCS, 2.64 points), with a smaller effect on PCS (0.69). In our multiple regression analyses, the observed explained variance (R^2) in our sample (7% on PCS and 27% on MCS) is similar to than in a recent study on active injection drug users,[42] providing support that our findings may be applicable to nonveteran populations.

This study illustrates the complexity of multiple factors influencing HRQoL. Coexisting psychiatric disorders have the largest negative impact on mental health, with a variable and weaker effect on physical health. The most unexpected finding was the divergent effect of alcohol dependence on physical and mental health among anti-HCV(–) patients. These results mirror previous studies suggesting that alcohol dependence primarily results in impairment in psychologic and role dimensions of HRQoL, whereas physical and functional dimensions remain similar to population norms.[43] Furthermore, our findings suggest that HRQoL may be affected by factors other than medical or psychiatric disorders, such as level of education, marital status, age, and ethnicity. Such factors likely reflect the role of cultural attitudes and social support structures in determining an individual's response to illness.

Our study has several limitations. First, because of its cross-sectional design, caution is required in inferring a causal relationship between HCV status, psychiatric disorders, and HRQoL. We were careful, however, to ensure that a veteran's anti-HCV status was documented before measurement of HRQoL. It is possible that individual awareness of the diagnosis or disease labeling itself may contribute to HRQoL impairment. Two recent studies demonstrated that anti-HCV(+) patients who were unaware of their serostatus reported higher HRQoL measurements than anti-HCV(+) patients who were aware, and similar HRQoL measurements as uninfected controls.[44,45] Second, our measures of psychiatric disorders were derived from ICD-9 diagnoses in the VHA administrative database. However, the prevalence of depression in our cohort was similar to what has been reported in prospective studies.[28,38] Third, our subjects were predominantly male and chose to receive medical care from the VHA, resulting in a unique patient cohort known to have a greater medical and psychiatric disease burden than the general population. Fourth, only anti-HCV was used as a surrogate marker for HCV infection. A small subset of these individuals could represent false-positives, although most patients tested for anti-HCV had 1 or more risk factors for HCV infection, and previous studies have shown that only 3.6% of veterans testing positive for anti-HCV represent false positives.[46] Unfortunately, we do not have information on the severity of liver or psychiatric disease for these patients, but the large sample size and random selection process increases the likelihood that the whole spectrum of each disease was represented.

In summary, CHC is associated with a substantial decrease in HRQoL among US veterans. CHC seems to predominantly affect the mental components, whereas both physical and mental components are impaired by comorbid psychiatric conditions. Depression and PTSD, in particular, contribute significantly to HRQoL impairment in this population, independent of anti-HCV status. Our study suggests that one could improve HRQoL in these patients by treating underlying psychiatric conditions such as depression and PTSD. This is particularly important among individuals who have failed antiviral therapy or are ineligible because of uncontrolled psychiatric disease.

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