Quality of Life Research (2007) 16: 203–215
DOI 10.1007/s11136-006-9111-2

Health-related quality of life: Hepatocellular carcinoma, chronic liver disease, and the general population

Jennifer L. Steel[1], Kapil Chopra[2], Marion C. Olek[3] & Brian I. Carr[1]
[1]*University of Pittsburgh, School of Medicine; Starlz Transplantation Institute, Liver Cancer Center, 3459 Fifth Avenue; Montefiore 7 S, Pittsburgh, PA 15213, USA (E-mail: steeljl@msx.upmc.edu);* [2]*University of Pittsburgh, Center for Liver Disease, Pittsburgh, PA, USA;* [3]*University of Pittsburgh, Liver Cancer Center, Pittsburgh, PA, USA*

Accepted in revised form 12 August 2006

Abstract

Health related quality of life (HRQL) has become an important endpoint in testing the efficacy of treatments for chronic liver disease (CLD) and the consequences of CLD which include hepatocellular carcinoma (HCC) and liver failure. However, a paucity of research on HRQL has been conducted with these patient populations. The aims of the present study were to compare persons diagnosed with HCC to persons diagnosed with CLD as well as with the general population (GP) on a disease-specific instrument measuring HRQL. If significant and clinically meaningful differences in HRQL exist, HRQL may be used as a corroborative indicator of disease progression in patients with CLD. Two hundred and seventy-two people participated in the present study. Of these participants, 83 were diagnosed with HCC, 51 with CLD, and 138 were from the GP. None of the patients in the HCC or CLD samples were actively receiving chemotherapeutic treatments for the CLD or HCC. A sociodemographic questionnaire and the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) was administered to participants. The results of the study suggested that people diagnosed with HCC, prior to treatment, had a poorer overall HRQL when compared to those persons with CLD and the general population, as expected. The differences in HRQL were statistically significant as well as clinically meaningful. People diagnosed with CLD and HCC respectively, reported better social and family well-being than the general population. Furthermore, people with CLD reported equivalent emotional well-being as the general population sample. HRQL subscale scores, with the exception of social and family well-being, discriminated group membership.

Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of death from cancer worldwide [1] and more than 19,000 adults in the United States (U.S.) die from HCC each year. The primary etiology of HCC is hepatitis B and/or C with which more than five million people are chronically infected in the U.S. alone [1]. Chronic liver disease (CLD), as a result of infection with hepatitis B and/or C, results in HCC in approximately 15% of this population [1]. The remainder of the population often succumbs to liver failure unless orthotopic liver transplantation is an option [2]. The goal of treating CLD, and particularly HCC, is to ameliorate symptoms, prolong survival, and improve or maintain health related quality of life (HRQL). Until recently, instruments designed specifically to measure HRQL in patients with hepatobiliary disease have not been available [3]. As a result a paucity of research has been conducted examining HRQL in patients with HCC and CLD.

The majority of the studies that have been conducted concerning HRQL in patients with

hepatobiliary carcinoma included persons diagnosed with non-liver primary tumors with metastases to the liver [4, 5] or patients who had surgical resection for HCC [6, 7]. Few studies have addressed HRQL in patients with unresectable HCC [8–10]. Due to the increasingly number of people affected by this disease, two instruments have recently been developed specifically for people diagnosed with heptobiliary carcinomas, the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep; 11) and the European Organization for Research and Treatment of Cancer (EORTC) QLQ-HCC18 [12].

Health related quality of life has also recently become an important endpoint in the treatment of CLD, secondary to the decrements in quality of life that are often experienced when treated with interferon [13]. Research concerning patients diagnosed with CLD has also advanced where instruments measuring specific symptoms of CLD have also recently been developed [14–17].

The research that has been conducted concerning patients diagnosed with HCC and CLD often employs general HRQL instruments in prospective studies investigating the effects of treatment on HRQL [18–19]. Few studies have compared HRQL of patients with HCC and CLD even though HCC often occurs in the context of CLD. Furthermore, we have no data concerning how HRQL in these populations compares to other chronic diseases or to the general population. If HRQL can discriminate between medical conditions such as HCC and CLD, HRQL may be used as an additional indicator for the early detection of disease progression in patients diagnosed with CLD.

Of the research that has been conducted using general HRQL instruments for persons diagnosed with CLD [17, 20], researchers have found that people with CLD report lower HRQL than healthy controls from a representative sample of adults in the U.S [2]. Using disease-specific HRQL instruments, Younossi and colleagues reported that in people diagnosed with CLD had significantly lower HRQL than the general population [21]. Severity of disease, etiology of disease, sex, age, and social class did not predict HRQL in patients with CLD or the general population [21, 22]. Only one study, to the authors' knowledge, has compared general HRQL in people diagnosed with HCC and CLD [23]. Bianchi and colleagues reported that patients with HCC who were administered the SF-36 reported significantly greater Bodily Pain, Role Limitation-Physical, and lower physical functioning when compared to patients diagnosed with CLD [23].

The aims of the present study were to compare HRQL, using the same disease-specific instrument, in people diagnosed with primary HCC, CLD, and the general population (GP). It was expected that patients with HCC would have poorer overall HRQL when compared to those diagnosed with CLD and the GP, respectively. We would also expect that some of the demographic (e.g., age) or disease-specific variables (e.g., Child's Pugh score) might predict poorer quality of life in both HCC and CLD patients. Furthermore, discriminant analysis was used to determine if HRQL predicted group membership (CLD, HCC, or GP).

Patients and Methods

Design

The patients in the HCC and CLD samples were part of a prospective, non-randomized study evaluating proxy ratings of HRQL. The GP sample that was recruited as part of this study was randomly selected from the general U.S. population.

Participants studied

A sample of 83 people diagnosed with HCC were recruited for the present study. To be included in the HCC sample, patients must have met the following inclusion criteria: [1] a diagnosis of biopsy proven HCC; [2] age 18 years or older, and [3] no report of suicidal ideation or history of psychosis. Fifty-one patients diagnosed with CLD were recruited for participation. Inclusion criteria for this sample was [1] diagnosis of chronic liver disease that was based on blood tests (e.g., presence of hepatitis C) or CT scan and/or biopsy (e.g., cirrhosis); [2] age 18 years or older, and [3] no report of suicidal ideation or history of psychosis.

At the time of assessment, patients in the HCC and CLD samples had not received treatment for their liver-related conditions (e.g., chemotherapy, interferon). The purpose of the study was to determine if either sample had differences in

HRQL prior to treatment. We know clinically that both the HCC and CLD groups have significant decrements in quality of life when they undergo treatment. The HCC sample was newly diagnosed patients that had not received chemotherapy, radiation, or transplant prior to their initial evaluation of HRQL. The CLD patients were not currently receiving treatment for their liver disease, with the exception of the patients with hemochromatosis who may have received phlebotomy. The patients that were included in the CLD sample had not previously received liver transplantation. Many of the CLD patients, and a few of the HCC patients were referred for evaluation for liver transplantation, and some of the patients later received a liver transplant, but several months or years after the assessment of quality of life. The patients may have been taking alternative or complementary interventions (e.g., herbs) or treatments for comorbid disease processes (e.g., hypertension).

Patients evaluated for CLD and HCC are part of the same Institute, the Starzl Transplantation Institute, but separate centers (Center for Liver Disease and Liver Cancer Center) and therefore a close working relationship between the clinicians evaluating and treating these patients exists. The patients diagnosed with CLD are evaluated for HCC every 6 months, or less, with a CT scan annually or if blood work (e.g., rise in alpha fetoprotein) and/or symptom presentation indicates. At the time of HRQL assessment, the patients that were included in the CLD group were not diagnosed or referred for evaluation for HCC by radiological report, pathology, or blood work. If the clinician had a suspicion that the patient may be diagnosed with HCC based on their findings, s/he would have been referred to the Liver Cancer Center where the HCC sample was recruited. The only possibility of the CLD patients having HCC is if the disease was undetectable by current methods of diagnosis (e.g., rising AFP or lesion found on CT scan).

The general population sample (n = 138) was randomly selected from a list of names and addresses obtained from a registry of U.S. residents. The general population sample was stratified by gender, age, and population by state of residence. Of 1,000 surveys mailed to participants, 14% returned completed surveys. The general population sample was not originally recruited or administered the FACT-Hep for the purposes of this study, therefore this sample was not screened for CLD or HCC. The GP sample was recruited to obtain normative data on the FACT-G prior to the time the normative data was available. No inclusion or exclusion criteria was used in recruiting participants for the GP sample therefore, participants could have had suicidal ideation or had symptoms of thought disorder, psychosis, or delusions.

Instruments/Assessment

The patient battery included a number of instruments to assess sociodemographic, quality of life, psychological functioning, and sexual health; however for the purposes of this study the following questionnaires were included: (1) Sociodemographic Questionnaire which included items related to the patient's age, gender, ethnicity (only for CLD and HCC patients), marital status, educational level, and occupation; and (2) the Functional Assessment of Cancer Therapy-Hepatobiliary Carcinoma (FACT-Hep; [11], [24]) which consists of the FACT-General and the Hepatobiliary module. The FACT-General is a multidimensional 27-item instrument that measures four dimensions of quality of life, namely: 'physical well-being (PWB-7 items); social and family well-being (SFWB-7 items); emotional well-being (EWB-7 items); functional well-being (FWB-7 items); an overall HRQL score (QoL) can also be calculated which includes the total for the four subscales. It is one of the most widely utilized quality of life questionnaires employed in clinical trials for new cancer treatments and has been demonstrated to be valid and reliable [25]. The Hepatobiliary module of the FACT includes 18 additional items specific for patients with Hepatobiliary disease. The module includes questions that pertain to symptoms of the disease as well as side effects of the treatment.

The FACT-Hep was scored according the FACIT manual [25]. All FACT scales are scored so that a high score reflects good quality of life in that domain with the exception of the Additional Concerns scale in which a high score for this study suggested more symptoms and side effects from treatment. If a participant skipped an item, scores were prorated using the average of the other answers

in the scale. When there are missing data, prorating subscale scores is acceptable as long as more than 50% of the items were answered. Computing the overall HRQL score is considered appropriate if the item response rate is greater than 80%.

The FACT-Hep has been demonstrated to be reliable and valid [11]. The internal consistency was between 0.72 and 0.94 for the FACT-Hep and test-retest ranged between 0.84 and 0.91 [11]. Convergent and divergent validity were demonstrated by examining the FACT subscales with scales measuring mood (POMS), social support (ISEL), and social desirability (Marlowe-Crowne Social Desirability Scale). The FACT-Hep also was found to differentiate between groups on performance and treatment status [25].

Normative data for the FACT-G has been published by the authors of the FACIT measurement system [26]. The means for the FACT-G for the general U.S. adult population are as follows: PWB = 23; SFWB = 19; EWB = 20; FWB = 19 and overall HRQL = 80. Normative data for people diagnosed with mixed cancer types has been reported and the means are as follows: PWB = 21; SFWB = 22; EWB = 19; FWB = 19 and overall HRQL = 81 [26].

Prior research suggests that the FACT-Hep was found to be sensitive to changes to clinical indicators (alkaline phosphate, alpha-fetoprotein, hemoglobin, and survival) that reflect disease progression and response to treatment in this cancer type [27]. Combined results from distribution-based and cross-sectional anchor-based analyses provided information regarding the clinical meaningfulness of scores between groups [27]. Clinically meaningful differences between subscales of the FACT-Hep (PWB, SFWB, EWB, and FWB) have been reported to be between 2–3 points, for the FACT-Hepatobiliary Additional Concerns subscale a change of 5–6 points is clinically meaningful, and a difference between 6–7 points on the FACT-G overall score is clinically meaningful [27].

Procedure

After Institutional Review Board approval, patients diagnosed with HCC and CLD who met the inclusion criteria were approached by their treating health care provider to determine their interest in learning more about the purpose, risk and benefits of the study. If the patient agreed to learn more about the study they were introduced to a research associate, trained in psychology, to explain the study in detail and ask for the patients' written informed consent. Upon receipt of written informed consent, the patient was asked to complete a battery of questionnaires. The research associate was available to answer questions and to assess questionnaires for missing data before the participant left the appointment. Disease-specific information was gathered from the patients' electronic medical record. The general population sample participants were mailed an informed consent form and battery of questionnaires that included the sociodemographic questionnaire and the FACT-Hep. The participants from the GP sample were provided contact information in the case they had questions regarding the items in the battery of questionnaires they were mailed.

Data analyses

Data was analyzed using SPSS.v13. Descriptive statistics were calculated to provide information regarding demographic and disease specific characteristics. To test the reliability of the FACT-Hep in each of the samples, Cronbach's alpha [28] was employed. Difference in demographic and disease specific characteristics were tested using Analysis of Variance (ANOVA) and Chi-Square analyses for continuous and categorical variables, respectively. Kruskal–Wallis and Mann–Whitney *U*-tests were employed to test differences between samples. The nonparametric tests were used secondary to the skewed distribution found on the subscales of the FACT-Hep. Discriminant analysis was performed to determine if HRQL classified patients according to the group membership (i.e., HCC, CLD, and GP). Discriminant analysis was used to facilitate the development of a predictive model of group membership based on observed characteristics of each case. The analysis is based on linear combinations of predictor variables that provides information regarding the variables that discriminates between groups.

Results

The response rate for each of the samples varied with 93% (n = 83) of the HCC sample, 80% (n = 51) of the CLD sample, and 14% (n = 134) of the GP sample responding to our request to participate in the study and complete questionnaires. Sociodemographic and disease specific (for the HCC and CLD samples) characteristics can be found in Table 1 and 2.

Using ANOVA, significant differences in age were found between samples [$F(2,274) = 35$, $p < 0.001$]. Using Chi-Square analyses, significant differences across samples were found according to gender [Chi-Square = 47.9, $p = 001$], etiology of disease [Chi-Square = 36.6, $p < 0.001$], presence of cirrhosis [Chi-Square = 5.2, $p < 0.001$], and Child's Pugh score [Chi-Square = 16.3, $p = 0.001$].

Using Cronbach's alpha, the reliability of each of the FACT-Hep subscale was tested across samples. All subscales of the FACT were found to have adequate reliability (0.71–0.96) with the exception of the SFWB scale for the CLD sample (0.50), the EWB subscale for the GP sample (0.58), and the overall QoL scale for the CLD sample (0.60). See Table 3.

Between group differences were tested using Kruskal–Wallis nonparametic test. Table 4 depicts significant differences were found on all subscales when comparing the three samples for PWB [Chi-Square = 40.8, $p < 0.001$]; SFWB [Chi-Square = 9.8, $p = 0.007$]; EWB [Chi = Square = 8.8, $p = 0.012$]; FWB [Chi-Square = 36.9, $p = 0.001$]; AC [Chi-Square = 67.8, $p = 0.001$]; and the overall HRQL [Chi-square = 24.8, $p = 0.001$]. Mann–Whitney *U*-tests were used to compare between groups. Significant differences were found between the HCC and CLD samples for PWB subscales [Mann–Whitney $U = 1704$, $p = 0.02$] and the overall quality of life [Mann–Whitney $U = 1747.5$, $p = 0.03$]. Significant differences on all the subscales were found between the HCC and GP samples comprised the PWB [Mann–Whitney $U = 3599$, $p = 0.001$]; SFWB [Mann–Whitney $U = 4882$, $p = 0.02$], EWB [Mann–Whitney $U = 4557$, $p = 0.002$]; FWB [Mann–Whitney $U = 3144$, $p = 0.001$]; AC subscales [Mann–Whitney $U = 2229.5$, $p = 0.001$] and overall quality of life [Mann–Whitney $U = 3559.5$, $p = 0.001$]. Significant differences between the CLD and GP samples comprised the PWB [Mann–Whitney $U = 2408.5$, $p = 0.001$]; SFWB [2748.5, $p = 0.006$]; FWB [Mann–Whitney $U = 2694.5$, $p = 0.007$]; and AC [Mann–Whitney $U = 1870.5$, $p = 0.001$] subscales. Figure 1 provides medians, interquartiles, and outliers of data for all three samples side by side.

Clinically meaningful differences between samples were found between the HCC and GP and the CLD and GP samples on the PWB, FWB, AC, and overall HRQL subscales. A clinically meaningful difference was found between the CLD and GP samples on the SFWB. Clinically meaningful differences were also found between the HCC and CLD samples on the SFWB, EWB, FWB, and overall HRQL scales. See Table 4.

Table 1. Demographic characteristics of the samples

Variable	HCC (n = 83)	CLD (n = 51)	General (n = 138)
Gender (%)***[13]			
Male	77	44	30
Female	23	56	70
*Age****[123]			
Mean	58	54	40
Range	18–83	32–79	18–80
Marital status (%)			
Single	15	20	59
Married	56	69	10
Divorced	9	8	6
Widowed	11	4	17
Ethnicity (%)			
Caucasian	81	84	–
African American	8	10	–
Asian-American	6	2	–
Native American	2	4	–
Hispanic/Latino(a)	1	0	–
Non US citizen	1	0	–
Education (%)			
High School	54	56	1
Vocational	20	20	16
Four years of college	17	12	6
Graduate/Professional	9	12	31
Income (%)			
Under 10,000	21	17	10
11–20,000	24	17	14
21–40,000	37	33	33
41–60,000	11	14	19
61–80,000	3	12	11
81–100,000	1	5	7
Over 100,000	4	2	6

[12] = HCC versus CLD; [13] = HCC versus GP; [23] = CLD versus GP; [123] = HCC, CLD, and GP ***$p < 0.001$.

Table 2. Disease specific characteristics

Variable	HCC (n = 83)	CLD (n = 51)
Etiology (%)**		
Hepatitis B	9	4
Hepatitis C	30	43
Alcohol-related	28	8
NASH	0	8
Cryptogenic	28	8
Autoimmune	0	8
Primary biliary cirrhosis	0	4
Primary schlerosing cholangitis	0	4
Hemochromatosis	0	2
Child's Pugh Score (%)		
A	51	60
B	26	30
C	1	10
None	16	–
Unknown	6	–
Cirrhosis (%)**		
Yes	76	93
No	24	7
Stage of disease (%)		
I-II	20	–
III-IV	80	–
Tumor size (cm)		
Mean	6.8	–
Range	1–20	–
Number of lesions		
Mean	3.2	–
Range	1–6	–
Vascular invasion (%)	42	–
Vascularity of lesion		
Hypovascular	18	–
Hypervascular	77	–
Mixed	5	–
Survival (months)		
Median	7.4	–
Range	0.4–91.2	–
Alpha fetoprotein		
Median	44	5
Range	2–129,750	2–62
Albumin		
Median	3.3	3.4
Range	2.1–4.3	2.5–4.3
GGTP		
Median	183	106
Range	23–750	29–655
HCT		
Median	37.5	36.6
Range	24.5–46.7	27.9–45.6
HgB		
Median	12.1	12.8
Range	8.1–15.0	9.2–16
Bilirubin		
Median	1.0	0.7
Range	0.20–3.5	0.3–4.5
WBC		
Median	5.4	5.1
Range	2.5–12.8	1.8–11.1

**$p = 0.001$.

In comparison to the norms for the U.S adult population [26], the scores for the GP sample of this study were higher on all subscales of the FACT-G including the PWB (23 versus 24), SFWB (19 versus 21), EWB (17 versus 20), FWB subscales (19 versus 22), and overall HRQL (80 versus 86). Although not statistically tested, the HCC sample reported lower scores on all subscales of the FACT-G with the exception of the SFWB subscale when compared to other cancer types [26].

Discriminant analyses were performed and several of the FACT-Hep subscales were found to significantly predict group membership [Wilks' Lambda = 0.71, $p = 0.001$]. The PWB [Chi Square = 19.4, $p = 0.001$], EWB [Chi-Square = 7.8, $p = 0.02$], FWB [Chi-Square = 48.0, $p = 0.001$], Additional Concerns [Chi-Square = 65.4, $p = 0.001$] subscales, and the overall HRQL [Chi-Square = 29.5, $p < 0.001$] all predicted group membership (i.e., HCC, CLD, GP). See Table 5.

Discussion

The results of the present study were consistent with expectations and prior research suggesting patients with HCC reported poorer overall HRQL when compared to people diagnosed with CLD and the GP, respectively. It should be noted that this sample of HCC patients had lower overall HRQL (Mean = 74) on the FACT-General than previous studies (Mean = 83) [6]. The patients in the present study had more advanced disease when compared to a study by Poon and colleagues where patients were treated with surgical resection [6].

This is the first study to compare patients diagnosed with HCC and CLD using a HRQL instrument that was disease-specific. Although patients with HCC reported worse symptoms than

Table 3 Cronbach's alpha for each scale of the FACT-Hep for each sample

Sample	FACT-Hep subscale					
	PWB	SFWB	EWB	FWB	AC	QOL
HCC	0.88	0.83	0.81	0.89	0.73	0.73
CLD	0.91	0.50	0.86	0.90	0.89	0.60
General	0.96	0.86	0.58	0.83	0.85	0.71

HCC = Hepatocellular carcinoma; CLD = Chronic Liver Disease; General = General Sample Population; PWB = Physical Well-Being; SFWB = Social and Family Well-Being; EWB = Emotional Well-Being; FWB = Functional Well-Being; AC = Additional Concerns module; QOL = Overall health related quality of life.

patients with CLD, this difference was not statistically significant or clinically meaningful. The discriminant analyses successfully differentiated between samples however this was likely secondary to the large differences found between the two medical patient samples (HCC and CLD) when compared to the GP sample. Post hoc analyses also revealed that persons diagnosed with HCC and CLD reported significantly different symptoms on the hepatobiliary module of the FACT but the overall symptom and side effect score was not statistically significant. People diagnosed with HCC reported greater weight loss, difficulties digesting food, greater loss of appetite, and decreased ability to perform usual activities when compared to persons diagnosed with CLD who reported greater fatigue, changes in appearance, and dry mouth.

Table 4 Differences in FACT-Hep subscales across the three samples using Kruskal–Wallis test and post hoc Mann–Whitney *U*-tests

Contrasts	Scale	Median-Median	*p*-value
Overall	PWB		0.001
HCC-General*	PWB	21–26	0.001
CLD-General*	PWB	23–26	0.001
HCC-CLD	PWB	21–23	0.274
Overall	SFWB		0.007
HCC-General	SFWB	24–22	0.021
CLD-General*	SFWB	24–22	0.006
HCC-CLD*	SFWB	24–24	0.402
Overall	EWB		0.012
HCC-General*	EWB	16–18	0.002
CLD-General	EWB	18–18	0.669
HCC-CLD*	EWB	16–18	0.137
Overall	FWB		0.001
HCC-General*	FWB	16–22	0.001
CLD-General*	FWB	20–22	0.007
HCC-CLD*	FWB	16–20	0.019
Overall	AC		0.001
HCC-General*	AC	20-7	0.001
CLD-General*	AC	16-7	0.001
HCC-CLD	AC	20–16	0.155
Overall	QOL		0.001
HCC-General*	QOL	75–87	0.001
CLD-General*	QOL	84–87	0.097
HCC-CLD*	QOL	75–84	0.032

Overall = comparison of all three samples; HCC = Hepatocellular carcinoma; CLD = Chronic Liver Disease; General = General Sample Population; PWB = Physical Well-Being; SFWB = Social and Family Well-Being; EWB = Emotional Well-Being; FWB = Functional Well-Being; AC = Additional Concerns module; QOL = Overall health related quality of life; *Clinically Meaningful Difference.

Our team recently published a paper concerning the clinical meaningfulness of HRQL scores using the FACT-Hep [27]. Distribution-based and cross-sectional anchor-based analyses were performed and as a result minimally important difference estimates (MIDs) were provided. The results of this study suggested that the majority of differences between samples were not only statistically significant but clinically meaningful.

Interestingly, people diagnosed with CLD and HCC reported better SFWB than people from the GP samples. It may be that when a person is diagnosed with a chronic disease such as CLD or HCC, s/he may recognize the support that s/he have in his/her family and friends. Within the GP sample, although it is likely that some of the individuals in the sample had chronic diseases, the sample was likely to have been healthier and as a result did not as readily recognize the support from family and friends that they might have experienced if they had a disease such as CLD or HCC. An alternative explanation may be that those people with less social support completed our questionnaires in our GP sample or those with CLD and HCC who had less support did not present for evaluation and treatment or agree to

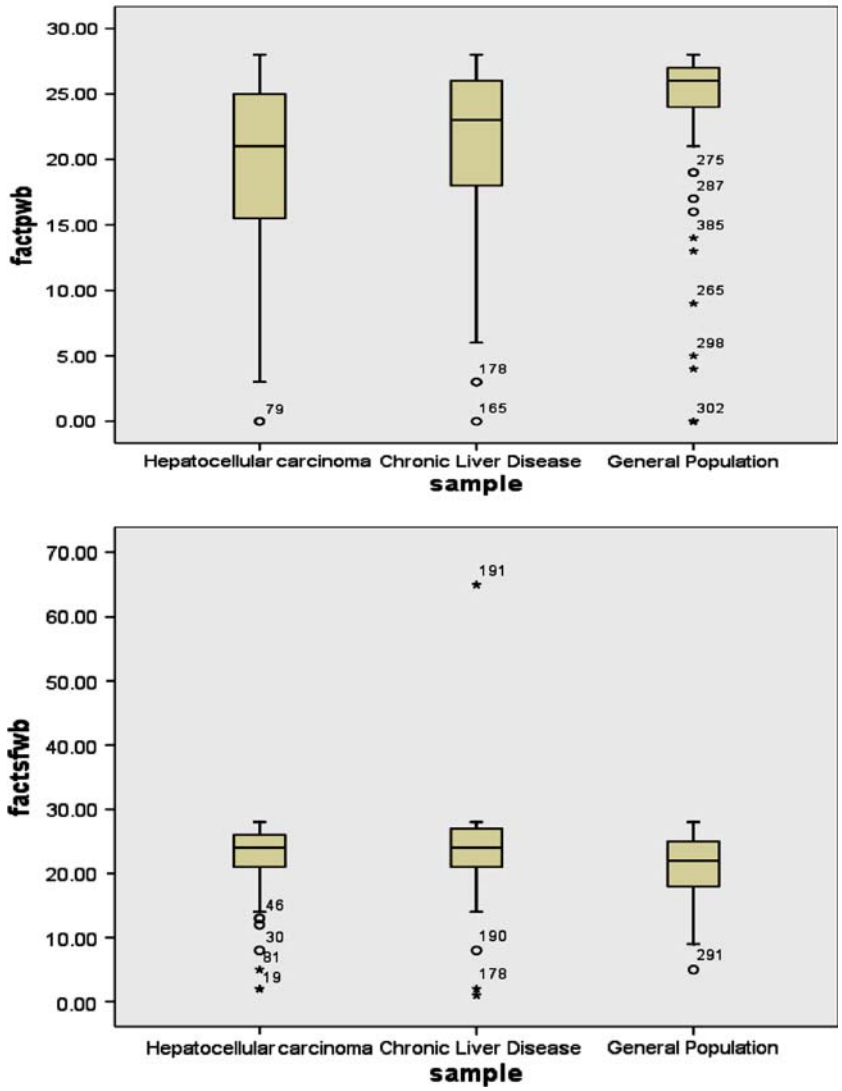

Figure 1. Median, interquartiles, and outliers by sample for each subscale of the FACT-Hep factpwb = FACT Physical well-being scale; factsfwb = FACT Social and family well-being scale; factewb = FACT emotional well-being scale; factfwb = FACT functional well-being scale; factac = FACT Additional concerns scale; factqol = FACT overall quality of life.

participate in our study. Nonetheless, the results are similar to previous studies which have reported that people who have been diagnosed with cancer generally report better social and family well-being than the general population [26].

Arguedas and colleagues, in a sample of patients presenting for transplant evaluation, reported worse HRQL on both physical and mental domains of the SF-36 when compared to the U.S. general population [29]. No differences in HRQL were found with respect to etiology, ethnicity, age, or gender; however differences in HRQL scores in respect of varying levels of severity of liver disease based on Child-Pugh were reported in that study. Our results were consistent with that study in that patients with CLD reported worse HRQL than the general population and sociodemographic or disease-specific variables were not found to be associated with HRQL.

The HCC sample of patients reported statistically lower emotional functioning than people in the GP sample and the general population norms as anticipated. This difference was also clinically meaningful. It would be expected that a diagnosis

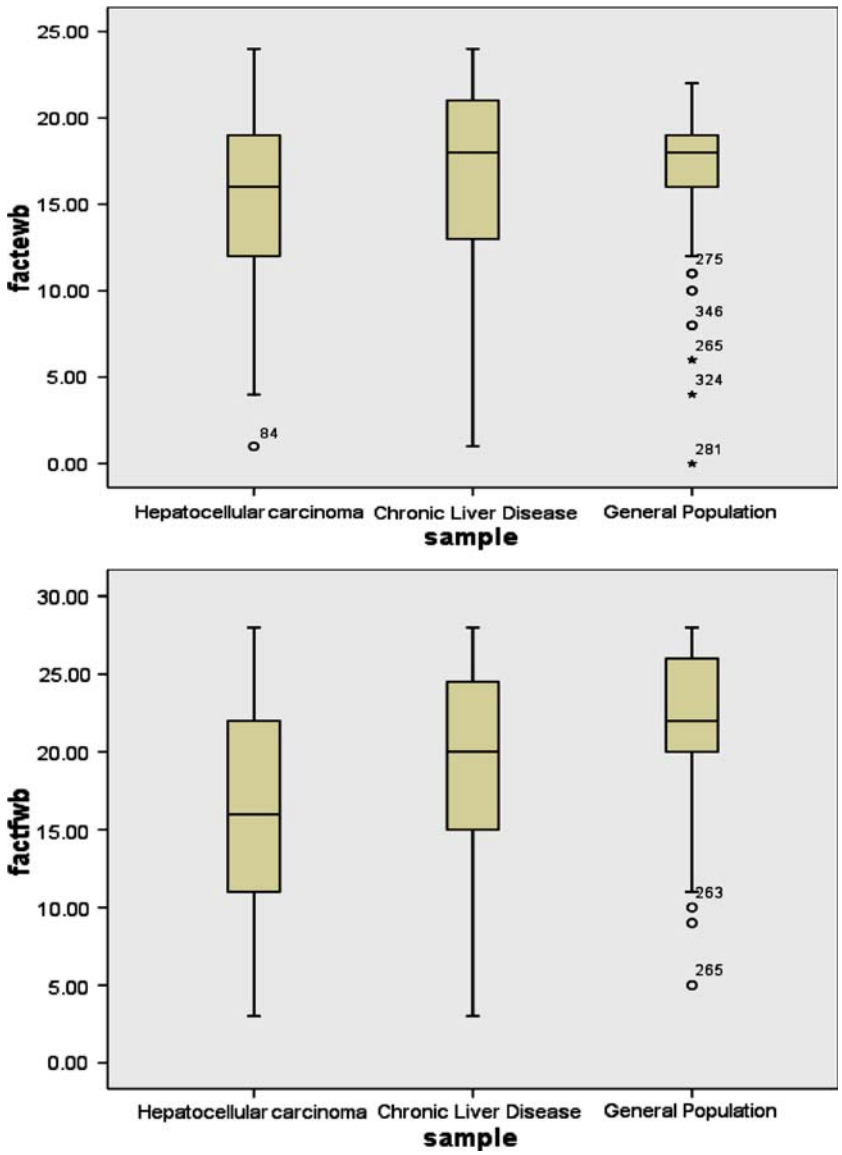

Figure 1. contd

of cancer, and possible neuroendocrine and immune changes that may occur with such a diagnosis, could result in higher rates of depression and anxiety which may be reflected in the EWB subscale of the FACT. Furthermore, EWB of the HCC group was lower than the CLD sample and the norms for other cancer types [26]. These results are consistent with previous research which has found that people diagnosed with liver cancer often have higher levels of psychological distress than people diagnosed with other chronic diseases and cancer types, with the exception of lung and pancreatic cancer [30].

Based on the findings from previous studies [2, 22], we had hypothesized that persons diagnosed with CLD, in comparison with those in the GP, would report lower emotional functioning as a result of being diagnosed with a chronic illness such as liver disease. This hypothesis was not supported. It is possible that previous studies reporting emotional/psychological well-being were based on samples of patients with CLD who were

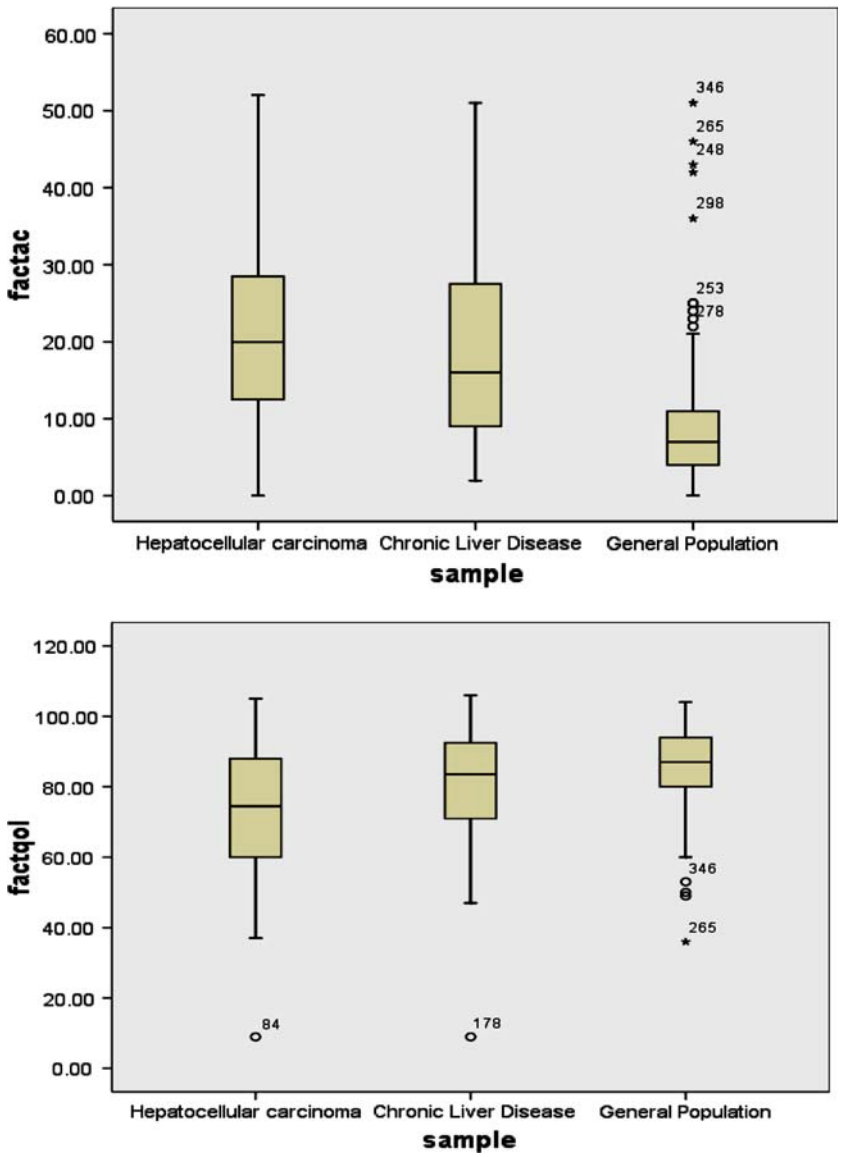

Figure 1. contd

undergoing treatment with interferon [31] and that psychiatric symptoms resulting from treatment with interferon in these patients had led to lowered EWB. In the current study, no patients with CLD were receiving interferon.

The results of the present study were generally consistent with previous research which has found that patients with CLD have lower HRQL when compared to healthy controls [32]. Park and colleagues concluded that decrements in HRQL mental domains were evident early in the disease process (patients with Child's Pugh score A) while physical decrements became evident as the disease progressed (patients with Child's Pugh score C; 28). Park and colleagues reported weak but significant relationships were found between age, albumin, prothrombin time, and bilirubin and HRQL. Severity of liver disease, as assessed with the Child's Pugh score, was positively associated with HRQL but no other disease-specific factors were associated with HRQL in the present study.

Table 5 Mean, standard deviations, and standardized canonical discriminant function coefficient for each subscale of the FACT-Hep

Subscale	Mean (S.D.) by sample			Standardized canonical discriminant function coefficient	
	HCC	CLD	GP	HCC	CLD
PWB***	20 (7)	21 (7)	24 (7)	−0.25	−0.83
SFWB^	22 (6)	24 (8)	21 (5)	0.42	0.21
EWB*	15 (5)	17 (6)	17 (4)	0.22	0.65
FWB***	16 (7)	19 (7)	22 (4)	−0.45	0.90
AC***	21 (13)	19 (13)	9 (9)	0.56	0.19
QoL***	74 (18)	80 (18)	86 (12)	–	–

^$p < 0.10$; $p < 0.05$; $p < 0.01$; $p < 0.001$.
PWB = Physical Well-Being; SFWB = Social and Family Well-Being; EWB = Emotional Well-Being; FWB = Functional Well-Being; AC = Additional Concerns module; QOL = Overall health related quality of life.

The study has several limitations. The most important of these relates to the differences across the groups in regard to sampling procedures. The current study was not originally designed to include the comparison across different samples and therefore the patients in the CLD and HCC groups were consecutive patients who were included in a prospective study regarding HRQL while the GP sample was a randomly selected group of people from a national database of all US residents. Related to this issue is the difference in the percent of non-responders in each of the samples. Eighty-six percent of the GP sample did not respond to our request to complete questionnaires whereas the nonresponse rate for the CLD (20%) and HCC (7%) samples was much lower. It is likely that the mailed versus face to face recruitment influenced the response to participating in the study. The high rate of nonresponse in the GP sample could result in under reporting of symptoms, particularly psychological symptoms that may be reflected in the SFWB or EWB subscales. Theoretically, this sample could also have CLD or HCC that may or may not be diagnosed as this question was not posed to these participants. The U.S. normative sample [26] was likely bias secondary to the compensation participants received (access to WebTV) and possibly the lack of representativeness in regard to level of literacy needed to complete the FACT-G online. The GP sample collected as part of the present study was also likely biased due to the low response rate (14% versus 80% for the U.S. norm sample).

Other limitations include the lack of information regarding medical comorbidities which has been found to be associated with decreased HRQL [23] and the ethnic composition of the sample. Although information regarding medical comorbidities and ethnicity is available for the two medical population samples, the information is not available for the general population sample. Although there are limitations, the comparison of HRQL across samples begins to elucidate differences in HRQL across two similar medical samples and further study of the discriminant value of HRQL in disease progression. However, the potential for confounding effects with respect to these participant characteristics cannot be discounted. The internal consistency for the AC subscale, although adequate for both samples, was higher in the GP than the HCC sample. It is likely that the consistency across the sample in the lack of symptoms contributed to the higher Cronbach's alpha that was found in the GP group versus the HCC sample.

Acknowledgement

We would like to thank the American Cancer Society for their support of this research

References

1. Harrison TJ. Viral hepatitis and primary liver cancer. In: Arrand JR, Harper DR (eds.Viruses and Human Cancer. Oxford: BIOS Scientific Publishers Limited, 1998.
2. Bonkovsky HL, Woolley JM, and the Concsensus Interferon Study Group (1999) Reduction of health related quality of life in chronic hepatitis C and improvement with interferon therapy. Hepatology 29(1):264–270.

3. Martin LM, Sheriddan MJ, Younossi ZM The impact of liver disease on health related quality of life:A review of the literature. Current Gasteroenterol Rep 2002; 4(1): 79–83.
4. Earlam S, Glover C, Fordy C, Burke D, Allen-Mersh TG Relation between tumor size, quality of life, and survival in patient with colorectal liver metastases. J Clin Oncol 1996; 14(1): 171–175.
5. Pistevou-Gombaki K, Eleftheriadis N, Plataniotic GA, Sofroniadid I, Kouloulias VE Octreotide for palliative treatment of hepatic metastases from non-neuroendrocine primary tumours:Evaluation of quality of life using the EORTC QLQ-30 questionnaire. Palliat Med 2003; 17(3): 257–262.
6. Poon RTP, Fan ST, Yu WC, Lam BKY, Wong J A prospective longitudinal study of quality of life after resection of hepatocellular carcinoma. Arch Surg 2001; 136(6): 693–699.
7. Ueno S, Tanabe G, Nuruki K, Yoshidome S, Kubo F, Kihara K, Aoki D, Aikou T. Quality of life after hepatectomy in patients with hepatocellular carcinoma:Implications of change in hepatic protein synthesis. Hepato-Gastroenterology 2002; 49(44): 492–496.
8. Steel J.L., Geller D.A., Carr B.I. Proxy Ratings of Health Related Quality of Life in Patients with Hepatocellular Carcinoma. Qual Life Res 2005; 14: 1025–1033.
9. Steel J.L., Carr B.I., Baum A. Quality of life in patients diagnosed with primary hepatocellular carcinoma:Hepatic arterial infusion of Cisplatin versus 90-Yttrium microspheres (Therasphere®). Psycho-Oncol 2004; 13(2): 73–79.
10. Steel JL, Eton DT, Cella D, Olek MC, Carr BI. Clinically meaningful changes in health related quality of life in patients diagnosed with hepatobiliary carcinoma. Ann Oncol, in press.
11. Hefferman S, Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J The Functional Assessment of Cancer Therapy scale:Development and validation of the general measure. J Clin Oncol 1993; 11(3): 570–579.
12. Blazeby JM, Currie E, Zee BCY, Chie W-C, Poon RT, Garen OJ, on behalf of the EORTC Quality of Life Group. Development of a questionnaire module to supplement the EORTC QLQ-C30 to assess quality of life in patients with hepatocellular carcinoma, the EORTC QLQ-HCC18. Eur J Cancer 2004; 40(16): 2439–2444.
13. Pokros PJ, Shiffman ML, Schoff ER, Sulkowski MS, Younossi Z, Dieterich DT, Wright TL, Mody SH, Tang KL, Goon BL, Bowers PJ, Leitz G, Afdhal NH Epoetin alfa improves quality of life in anemic HCV-infected patients receiving combination therapy. Hepatogology 2004; 40(6): 1450–1458.
14. Casanovas T, Vallejo G, Herdman M, Casado A, Ribas S, Rodriquez FE, Tremosa G, Menchon JM, Figueras J, Casais LA Validation of the Spanish version of the Liver Disease Quality of Life questionnaire in transplant patients. Transplant Proc 2003; 35(5): 1803–1805.
15. Plas SMvan der, Hansen BE, deBoer JB, Stijnen T, Passchier J, Man RAde, Schalm SW The Liver Disease Symptom Index 2.0:Validation of a disease specific questionnaire. Qual Life Res 2004; 13(8): 1469–1481.
16. Hauser W, Schnur M, Steder-Neukamm U, Muthny FA, Grandt D Validation of the German version of the Chronic Liver Disease Questionnaire. Eur J Gastroenterol Hepatol 2004; 16(6): 599–606.
17. Gralnek IM, Hays RD, Kilbourne A, Rosen HR, Artinian L, Kim S, Lazarovici D, Jensen DM, Busuttil RW, Martin P Development and evaluation of the liver disease quality of life instrument in persons with advanced, chronic liver disease-the LDQOL 1.0. Am J Gasteroenterol 2000; 95(12): 3552–3365.
18. Chow PK, Tai BC, Tan CK, Machin D, Win KM, Johnson PJ, Soo KC, and the Asian-Pacific Hepatocellular Carcinoma Trials Group. High dose tamoxifen in the treatment of inoperable hepatocellular carcinoma:A multicenter randomized controlled trial. Hepatology 2002; 36(5): 122–1226.
19. Brans B, Lambert B, DeNeule E, De Winter F, Van Belle S, Van Vlierberghe H, Hemptinne Bde, Dierckz RA Quality of life assessment in radionuclide therapy:A feasibility study of the EORTC QLQ-C30 questionnaire in palliative (131) I-lipiodol therapy. Eur J Nucl Med Mol Imaging 2002; 29(1): 1374–1379.
20. Hauser W, Holtmann G, Grandt D Determinants of health-related quality of life in patients with chronic liver disease. Clin Gasteroenterol Hepatol 2004; 2(2): 157–163.
21. Younossi ZM, Guyatt G, Kiwi M, Boparai N, King D Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. Gut 1999; 45(2): 295–300.
22. Younossi ZM, Boparai N, Price LL, Kiwi ML, McComrmick M, Guyatt G Health related quality life in chronic liver disease:the impact of the type and severity of disease. Am J Gastroenteronol 2001; 96(7): 199–205.
23. Bianchi G, Loguercio C, Sgarbi D, Abbiati R, Brunetti N, DeSimone T, Zoli , M , Marchesini G Reduced quality of life of patients with hepatocellular carcinoma. Dig Liver Dis 2003; 35(1): 46–54.
24. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J The Functional Assessment of Cancer Therapy scale: Development and validation of the general measure. J Clinl Oncol 1993; 11(3): 570–579.
25. Webster K, Cella D, Yost , K The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System:properties, applications, and interpretation. Health Qual Life Outcomes 2003; 1: 11–18.
26. Brucker PS, Yost K, Cashy J, Webster K, Cella D General population and cancer patient norms for the Functional Assessment of Cancer Therapy-General (FACT-G). Eval Health Prof 2005; 28(2): 192–211.
27. Steel JL, Eton D, Cella D, Olek M, Carr BI. Measuring health related quality of life in patients with hepatobiliary carcinoma. Annals of Oncology 2005, in press.
28. Cronbach LJ Coefficient alpha and the internal structure of tests. Psychometrika 1951; 16: 297–333.
29. Arguedas MR, DeLawrence TG, Mc Guire BM Influence of hepatic encephalopathy on health related quality of life in patients with cirrhosis. Dig Dis Sci 2003; 48(8): 1622–1626.

30. Zabora J., Brintzenhofeszoc K., Curbow B., Hooker C., Piantadosi S. The prevalence of psychological distress by cancer site. Psycho-Oncol 2001; 20: 19–28.
31. Scalori A, Pozzi M, Bellia V, Apale P, Santamaria G, Bordoni T, Redaelli A, Avolio A, Parravicini P, Pioltelli P, Roffi L Interferon-induced depression:prevalence and management. Dig Liver Dis 2005; 37(2): 102–107.
32. Park CK, Park SY, Kim ES, Park JH, Hyun DW, Yun YM, Jo CM, Tak WY, Kweon YO, Kim SK, CHoi YH, Park SG Assessment of quality of life and associated factors in patients with chronic viral liver disease. Korean J Hepatol 2003; 9(3): 212–221.

Address for correspondence: Jennifer L. Steel, University of Pittsburgh, School of Medicine; Starlz Transplantation Institute, 3459 Fifth Avenue; Montefiore 7 S, Pittsburgh, PA 15213, USA
Phone: +412-692-2041; Fax: +412-692-2002
E-mail: steeljl@msx.upmc.edu