

Impact of Hepatitis C on Health Related Quality of Life: A Systematic Review and Quantitative Assessment

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Hepatitis C virus (HCV) diminishes health related quality of life (HRQOL), and it is now common to measure HRQOL in clinical trials. We sought to summarize the HRQOL data in HCV, and to establish the minimally clinically important difference (MCID) in HRQOL scores in HCV. We performed a systematic review to identify relevant studies, and converted HRQOL data from each study into clinically interpretable statistics. An expert panel used a modified Delphi technique to estimate the MCID in HCV. We found that patients with HCV scored lower than controls across all scales of the SF-36. Patients achieving sustained virological response (SVR) scored higher across all scales versus patients without SVR, especially in the physical health domains. HRQOL differences did not correspond with differences in liver histology or ALT levels. Based upon the published data, the expert panel concluded that the SF-36 vitality scale was most relevant in patients with HCV, and generated a mean MCID of 4.2 points on this scale. **In conclusion**, patients with HCV have a clinically significant decrement in HRQOL versus controls, and physical HRQOL improves in patients achieving SVR but not in those without SVR. The data further suggest that traditional outcomes fail to capture the full spectrum of illness related to chronic HCV. A difference of 4.2 points on the SF-36 vitality scale can be used as an estimate of the MCID in HCV, and this value may be used as the basis for power calculations in clinical trials evaluating HRQOL. *Supplementary material for this article can be found on the HEPATOLOGY website (<http://www.interscience.wiley.com/jpages/0270-9139/suppmat/index.html>).* (HEPATOLOGY 2005;41:790-800.)

Abbreviations: HCV, hepatitis C virus; HRQOL, health related quality of life; SVR, sustained virological response.

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Chronic hepatitis C virus (HCV) infection is a prevalent and expensive condition affecting 4 million people in the United States at a cost of over \$700 million annually.¹ HCV leads to cirrhosis in up to 20% of those chronically infected² and is the primary indication for liver transplantation worldwide.³ This economic burden is multiplied by the dramatic impact of HCV on health related quality of life (HRQOL) resulting from complications of advanced liver disease such as encephalopathy, variceal hemorrhage, ascites, and liver transplantation.⁴⁻⁶ However, these end-stage complications are relatively rare compared with the vast majority of patients with HCV in the absence of clinically significant liver disease. Despite the previous consensus that this majority of patients has asymptomatic seropositivity,⁷ evolving data now indicate that HCV itself may diminish HRQOL in the absence of advanced liver disease,⁸⁻²⁰ perhaps as a result of extrahepatic symptoms related to HCV, cognitive dysfunction related to HCV, or a negative synergy between HCV and comorbid psychosocial disorders.^{10,21}

As awareness grows of the HRQOL decrement from HCV and its clinical consequences, investigators have be-

Table 1. Systematic Review Search Strategy

Group	Search Terms	Significance of Grouping
1	MEDLINE + EMBASE	Targeted Bibliographic Databases
2	(Hepatitis C (MeSH—exploded) OR Hepatitis C (tw) OR Viral Hepatitis (tw))	Targeted Topic Focus
3	(Quality of life (MeSH—exploded) OR Health Status (MeSH—exploded) OR Level of health (tw) OR Health Level* (tw) OR Life Qualit* (tw) OR SF-36 (tw) OR Short Form 36 (tw) OR SIP (tw) OR Sickness Impact Profile (tw) OR Minimally important difference (tw) OR Responsiveness (tw))	Targeted Content Keywords
4	(Letter (pt) OR editorial (pt) OR review (pt) OR news (pt))	Excluded study types

NOTE. The asterisk (*) indicates keyword truncation. The five search groups were combined as follows: (1 AND 2 AND 3 NOT 4). (MeSH = medical subject heading; pt = publication type; tw = text word).

come progressively interested in measuring HRQOL in HCV clinical trials. This acknowledgment that the burden of HCV extends beyond its economic impact coincides with recommendations by the National Institutes of Health to conduct studies that measure not only traditional biological outcomes in HCV (*i.e.*, HCV RNA, liver enzyme levels, liver histology), but also patient-oriented outcomes.²² However, most clinicians are not versed in the interpretation of HRQOL in HCV, and patient-oriented outcomes such as HRQOL may fail to resonate with clinicians in the same way as traditional biological parameters. Failure to understand and interpret HRQOL data in HCV may lead to the myopic view that biological outcomes are of primary importance — a view that likely underestimates the true burden of illness engendered by HCV.

In light of the disconnection between the growing importance of measuring HRQOL in HCV and the inability of many clinicians to readily interpret HRQOL differences, it is imperative to establish the clinical significance (in contrast to the statistical significance) of HRQOL score differences by anchoring them to changes in clinically familiar outcomes. By knowing the clinically important differences in HRQOL, researchers, physicians, and patients can better understand not only the overall health burden of HCV, but also the optimal approach to managing HCV. Nonetheless, despite the increasing awareness of HRQOL in HCV, there has been no attempt to systematically review the HRQOL literature in HCV.

In light of this shortcoming we performed a systematic review and quantitative assessment with the following objectives: (1) to identify and summarize the published literature pertaining to HRQOL in HCV; (2) to compare the HRQOL in patients with HCV versus healthy controls; (3) to compare the HRQOL in HCV patients achieving sustained virologic response (SVR) versus those without SVR; (4) to stratify HRQOL data in HCV by clinically-relevant anchors, including liver disease severity anchors and neurological, psychological, and social anchors; and (5) to establish the minimally clinically impor-

tant HRQOL difference (MCID) in HCV. These data may provide the basis for appropriate sample size calculations in treatment trials, allow physicians to better monitor patient outcomes in clinical practice, and equip patients with the knowledge to better select between competing management strategies.

Materials and Methods

Systematic Review. We performed a systematic review of MEDLINE, EMBASE, and published abstracts to identify relevant English-language publications from January 1990 to June 2004. Refer to the Technical Appendix for a detailed description of our systematic review methodology, including the keywords, search strings, and inclusion/exclusion criteria applied (Table 1).

Conceptual Framework Overview. There are several methods to estimate the clinical significance of HRQOL score differences. The most clinically meaningful method is to anchor score differences to outcomes that are familiar to physicians and patients. This “anchor-based” approach can be classified as criterion-anchored or construct-anchored, as depicted in the conceptual framework in Fig. 1. Because HRQOL is a patient-oriented outcome, the criterion standard by which to anchor HRQOL is patient-reported change in overall health status. In contrast, “construct anchoring” refers to comparing HRQOL differences to disease-specific biological or clinical outcomes rather than patient-based reporting.²³ We performed our data abstraction and quantitative analyses according to this conceptual framework. Refer to the Technical Appendix (available at <http://interscience.wiley.com/jpages/0270-9139/suppmat/index.html>) for a detailed description of this framework and the related statistics, including mean HRQOL group differences, HRQOL group difference in differences (DID), and corresponding effect sizes (ES). The ES for between-group HRQOL differences is calculated using the following equation (SD = standard deviation):

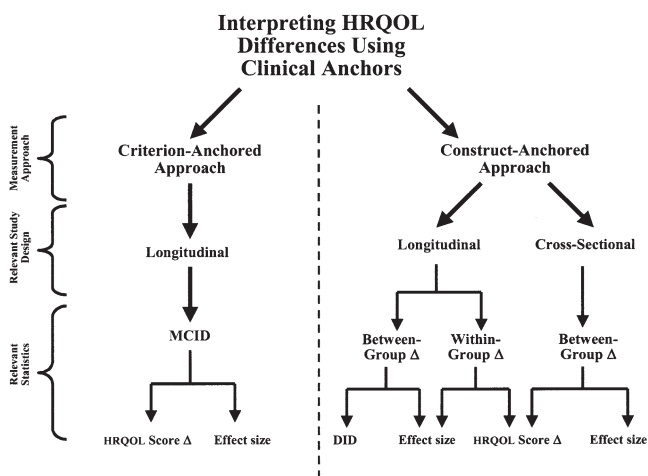


Fig. 1. Health Related Quality of Life (HRQOL) Conceptual Framework. Refer to text and Technical Appendix for description of terms. MCID, minimal clinically important difference; DID, difference in difference score.

$$ES = \frac{(HRQOL_{\text{group 1}} - HRQOL_{\text{group 2}})}{SD_{\text{group 1}}}$$

Cohen has standardized the interpretation of the ES by suggesting that a value of <0.2 represents a small clinical effect, 0.5 a moderate effect, and >0.8 a large effect.²⁴ The advantage of this interpretation scheme is that HRQOL outcomes in different interventions and health states can be compared using a standardized ES — a statistic with clinical relevance that serves as an “exchange currency” across disparate fields in medicine. Refer to the Technical Appendix (at the HEPATOLOGY website (<http://interscience.wiley.com/jpages/0270-9139/suppmat/index.html>)). for additional information about the ES.

Statistical Analysis. We classified each identified study according to the HRQOL conceptual framework in Fig. 1.

We converted the HRQOL from each study to one or more of the clinically interpretable statistics described above and listed in Fig. 1. Where necessary we converted standard errors into SDs prior to calculating the ES. We then constructed evidence tables to display the compiled HRQOL data stratified by clinical anchors, and present the weighted mean and median for each relevant statistic stratified by anchor.

Expert Panel to Estimate Minimally Clinically Important Difference (MCID). Because statistical significance does not always correlate with clinical relevance, it is important to determine whether a given HRQOL difference between groups is clinically important to patients themselves. The MCID is defined as the smallest change in HRQOL that is important to patients, and this value is essential for monitoring patient outcomes and calculating

appropriate sample sizes for clinical trials employing HRQOL as an outcome.²⁵ Refer to the Technical Appendix for a detailed description of the MCID.

Because few studies directly measure MCID, we convened an expert panel to indirectly estimate the MCID in HCV based upon the existing HRQOL data. The panel consisted of three board-certified hepatologists and two HRQOL methodologists with experience in chronic liver disease-specific HRQOL. All members of the panel have published extensively within the field of HRQOL in chronic liver diseases and have participated in the development and testing of HRQOL instruments in chronic liver diseases.

Using the results of the systematic review, the panel estimated the MCID in HCV by using the existing HRQOL data. This approach of combining existing data to derive the MCID is an accepted technique that has been employed in other areas of medicine.²⁶ To achieve this goal, we employed a modified Delphi technique²⁷ consisting of 5 steps: (1) the results of the systematic review were distributed to the panelists for independent review; (2) in light of the review, each panelist independently submitted his/her first-round estimate of the MCID; (3) the panelists then convened in-person to jointly discuss the systematic review findings; (4) the first-round estimates of the MCID were anonymously revealed and discussed; and (5) each panelist submitted his/her final estimate of the MCID. We present the final mean and range of MCID resulting from the evidence-driven expert panel assessments.

Results

Study Selection

The search strategy identified 259 titles, of which 32 met explicit inclusion criteria (Fig. 2). Of the 32 studies, all provided sufficient data to calculate either an HRQOL mean group difference or a DID, 20 provided sufficient distributional data to calculate an ES, and none provided criterion-anchored data to measure the MCID.

Results Stratified by Clinical Anchors

HRQOL in HCV Versus Healthy Controls. Although HCV may diminish HRQOL through complications of advanced cirrhosis, it may also diminish HRQOL in the absence of clinically significant liver disease.⁸⁻²⁰ The mechanism of HRQOL decrement in the absence of liver damage is unclear. Potential mechanisms include the development of extrahepatic somatic symptoms (*e.g.*, HCV-related arthralgia and myalgia), extrahepatic disorders (*e.g.*, HCV-related cryoglobulinemia, sicca syndrome, glomerulonephritis), or HCV-related subclinical cognitive dysfunction, among others.^{10,21}

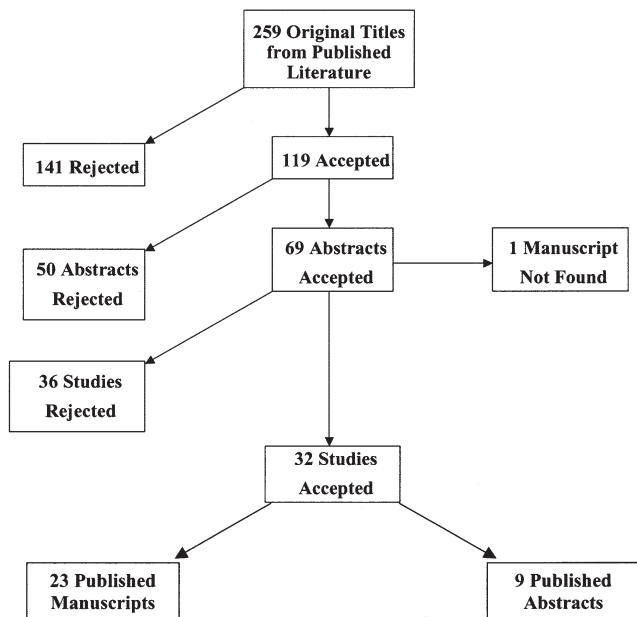


Fig. 2. Results of Literature Search. Of the 32 studies selected for inclusion in the review, 23 were published manuscripts, and 9 were published abstracts. Inter-rater agreement was high for each phase of selection (title phase $\kappa = 0.85$; abstract phase $\kappa = 0.92$; manuscript phase $\kappa = 0.98$).

We identified 15 studies that compared HRQOL in patients with compensated HCV seropositivity versus healthy control subjects without HCV (Table 2 and Table 3).^{5,8-20,28} All 15 studies measured HRQOL with the SF-36 Health Survey (refer to the Technical Appendix for information regarding the SF-36).

HRQOL Score Differences: All 15 studies provided cross-sectional group mean HRQOL differences stratified by HCV status — the clinical anchor in this circumstance. Table 1 presents the data across the 8 SF-36 scales and provides the weighted mean and median for each scale. The largest impact of HCV was in the role-physical scale (HCV vs. healthy control weighted mean cross-sectional difference = -15.8 points), followed by the role-emotional scale (-13.0) and the general health scale (-12.6). Three studies measured differences in the Mental Component Score (MCS) and Physical Component Score (PCS).^{9,11,17} The weighted mean differences in MCS and PCS were -12.8 and -9.1, respectively. Although there is no established minimally important difference in SF-36 scale scores in HCV, a review of SF-36 data in other diseases revealed that a 3-5 point difference in scale scores may represent a clinically important difference.²⁹ Although these thresholds are potentially arbitrary and fail to account for the underlying variation in HRQOL scores,³⁰ they suggest that the 7-15 point differences observed in compensated HCV versus healthy controls represent a clinically important difference across all SF-36 scales.

Effect Sizes: Ten studies provided sufficient data to calculate cross-sectional ES for HRQOL in compensated HCV versus healthy non-HCV controls (Table 3).^{5,8,12-20} The largest ES for HCV was in the social function and general health scales (both weighted mean ES = -0.7), followed by the vitality and role-physical scales (both -0.6). Two studies measured ES in the MCS and PCS

Table 2. Studies Comparing HRQOL in Patients With HCV Versus Healthy Controls—Cross-Sectional Mean Differences Between Groups

Author	Ref #	N	SF-36 Scales									
			Physical Function	Role Physical	Bodily Pain	General Health	Vitality	Social Function	Role Emotional	Mental Health	MCS	PCS
Cordoba	5	160	-9	-22	-16	-17	-10	-5	0	1	-	-
McHutchison	8	912	-1.5	-3.8	-0.8	-4.1	-4.5	-2.1	-0.6	-0.6	-	-
Hussain	9	220	-10	-18	-14	-20	-11	-9	-14	-15	-5	-5
Kramer	10	200	-7	-19	-7	-9	-11	-15	-16	-12	-	-
Gifford	11	462	-	-	-	-	-	-	-	-	-20.3	-12.7
Bini	12	260	-24.6	-46	-30.2	-25	-22	-39	-44.8	-11.3	-	-
Foster	13	116	-13.2	-34.5	-13.7	-26	-15.7	-25.8	-26.1	-16	-	-
Bayliss	14	157	-9.6	-23.7	-10.9	-19.1	-17.5	-7.6	-11	-4.3	-	-
Gallegos-Orozco	15	157	-14.2	-15.6	-3.5	-27.2	-14.6	-3.0	-10.0	-2.3	-	-
Dalgard	16	199	-14	-30	-29	-32	-24	-48	-61	-34	-	-
Fleming	17	299	-4.5	-23.6	-16.3	-15.2	-17.9	-11.1	-19.4	-12.9	-7	-6.6
Pojoga	18	102	-8.4	-1.7	-	-8.7	-5.3	-3	-1.8	-8.6	-	-
Hunt	19	31	-10	-25	-22	-25	-15	-12	0	-8	-	-
Miller	20	95	-5.1	-17.3	-8.2	-22.5	-14.2	-62	-32	-13.7	-	-
Paterson	28	163	-5	-2	0	-1.8	-2	0	-1	-2	-	-
Weighted Mean →			-7.0	-15.8	-9.0	-12.6	-10.1	-11.9	-13.0	-7.2	-12.8	-9.11
Median →			-9.3	-20.5	-13.7	-19.6	-14.4	-10.0	-12.5	-10.0	-7	-6.6

NOTE. The data are presented across the 8 SF-36 scales and the 2 SF-36 component scales—the Mental Component Score (MCS) and Physical Component Score (PCS). The weighted mean and median are presented for the cumulative data (bottom rows).

Table 3. Studies Comparing HRQOL in Patients With HCV Versus Healthy Controls—Cross-Sectional Effect Sizes Between Groups

Author	Ref #	N	SF-36 Scales									
			Physical Function	Role Physical	Bodily Pain	General Health	Vitality	Social Function	Role Emotional	Mental Health	MCS	PCS
Cordoba	5	160	-0.6	-0.7	-0.7	-0.8	-0.4	-0.2	0	0.04	-	-
McHutchison	8	912	-0.16	-0.34	-0.08	-0.4	-0.4	-0.2	-0.06	-0.06	-	-
Kramer	10	200	-0.6	-0.5	-0.3	-0.4	-0.5	-0.6	-0.4	-0.6	-	-
Bini	12	260	-0.9	-1.2	-1.1	-1	-0.9	-2.9	-1.2	-0.9	-	-
Foster	13	116	-1	-1.5	-0.7	-1.6	-0.8	-1.6	-0.9	-1	-	-
Bayliss	14	157	-0.5	-1.4	-0.5	-1	-0.7	-0.3	-0.3	-0.1	-	-
Gallegos-Orozco	15	157	-1.6	-1.0	-0.2	-1.7	-1.2	-0.2	-0.3	-0.2	-1.5	-1.05
Fleming	17	299	-0.16	-0.5	-0.5	-0.6	-0.7	-0.4	-0.5	-0.5	-0.7	-0.6
Pojoga	18	102	-0.7	-0.4	-	-	-	-	-	-	-	-
Miller	20	95	-0.2	-0.4	-0.3	-0.8	-0.5	-2.1	-0.7	-0.6	-	-
Weighted Mean →			-0.45	-0.6	-0.4	-0.7	-0.6	-0.7	-0.35	-0.3	-1.0	-0.75
Median →			-0.6	-0.6	-0.5	-0.8	-0.7	-0.4	-0.4	-0.5	-	-

NOTE. The data are presented across the 8 SF-36 scales and the 2 SF-36 component scales. The weighted mean and median are presented for the cumulative data (bottom two rows).

scores. The weighted mean estimates were -1.0 and -0.75 for MCS and PCS, respectively. Although there is no established ES corresponding with a minimally important difference in HCV, the conventional benchmark for a “small” ES is <0.2 .³⁰ By this standard the 0.3 to 1.0 range in ES (using absolute values) observed in compensated HCV versus healthy controls likely represents a clinically meaningful impact on HRQOL.

Summary of HRQOL in HCV vs. Healthy Controls.

The data consistently reveal that patients with compensated HCV seropositivity have a diminished HRQOL compared with healthy controls. Moreover, the impact of HCV on HRQOL is moderate to large across all SF-36 scales. The impact of HCV is most dramatic in social and physical function, general health, and vitality.

HRQOL Stratified by Sustained Virological Response (SVR) Status. The traditional short-term goal of treatment in HCV is to achieve SVR. Although SVR is a biochemical rather than clinical outcome measure, it is considered to be a surrogate marker for clinically relevant outcomes including progression to cirrhosis and survival. Therefore, SVR is a relevant clinical anchor for HRQOL data. We identified 9 studies that measured HRQOL stratified by SVR (Table 4).^{8,31-38}

HRQOL Score Differences: Seven studies measured HRQOL DID scores (see equation [2] in Technical Appendix) stratified by SVR status (Table 3).^{8,31-35,38} The largest DID score was in the role-physical scale (weighted mean = 10.4), followed by role-emotional (7.5), general health (7.1), and vitality (6.6). The weighted mean DID scores in the MCS and PCS were 2.7 and 2.6, respectively. Only 2 studies reported cross-sectional mean HRQOL score differences stratified by SVR.^{36,37} The largest mean difference was in the physical function scale

(11.1), followed by mental health (7.7) and social functioning (7.5).

Effect Sizes: Six studies provided sufficient data to calculate an ES for HRQOL in patients achieving SVR following antiviral therapy versus nonresponders.^{32-36,38} Two studies presented cross-sectional ES data^{36,37} and 4 presented longitudinal data.³²⁻³⁵ Consistent with the DID scores, the impact of SVR was most pronounced on the role-physical and general health scales (mean weighed ES = 0.4), followed by vitality, physical function, and social function (0.3 for latter 3 scales).

Summary of HRQOL Stratified by SVR. The data indicate that HRQOL is consistently worse in patients that fail to achieve SVR versus patients that develop viral clearance following treatment for HCV. The impact of SVR is most pronounced in the role-physical and general health scales. The data suggest that patients achieving SVR may have clinically significant improvements in these HRQOL domains compared to patients with an unsuccessful treatment course.

HRQOL Stratified by Neuropsychosocial Anchors.

HRQOL Score Differences. Data indicate that HCV not only impacts biological functioning, but also neurological, psychological and social functioning. These “neuropsychosocial” effects of HCV adversely impact HRQOL. We identified 6 studies that measured HRQOL stratified by a neuropsychosocial anchor.^{9,10,15,39-41} One study measured a strictly neurological anchor (subclinical cognitive dysfunction determined by evoked potentials),¹⁰ 4 measured psychological anchors (including depression, “psychiatric comorbidity,” and “emotional distress”),^{9,15,39,40} and one measured a social anchor (“stigmatization”).⁴¹ Five of the 6 studies measured HRQOL with the SF-36 (Table 5),^{9,10,15,39,40} and one used the Sickness Impact

Table 4. HRQOL Stratified by SVR Status

Author	Ref #	N	SF-36 Scales									
			Physical Function	Role Physical	Bodily Pain	General Health	Vitality	Social Function	Role Emotional	Mental Health	MCS	PCS
HRQOL Score Difference in Differences – SVR versus No SVR												
McHutchison	8	912	2.3	4.5	1.6	5	4.8	3	3	2.3	–	–
Hassanein	38	1121	5.5	5.7	4.1	7.4	6.3	5.8	9.3	5	2.6	2.2
Neary	31	257	6	10	4.1	6.2	6	9	2.9	0.7	–	–
Bernstein	32	1441	4.6	9.8	2.9	9.1	9.6	6.2	8.4	4.6	3	2.8
Bonkovsky	33	1392	5.5	22	–1	8	8	9	12	4	–	–
Raseneck	34	531	5.0	13.9	5.2	12.3	9.4	5.8	8.4	5.3	2.2	2.9
Ware	35	324	3.4	3.1	1.6	5.5	2.7	4.3	1.1	0.6	–	–
Weighted Mean/Median →			4.3/5.0	9.8	2.0/2.9	7.4	6.3	5.8/5.8	7.5/8.4	3.5/4.0	2.7/2.6	2.6/2.8
HRQOL Cross-Sectional Mean Difference – SVR versus No SVR												
Coughlan	36	93	14	1.1	4.8	9.6	4.0	9.4	–3.4	9.3	–	–
Hassanein	37	36	3.7	0.9	3.4	0.6	–	2.6	9.7	3.7	0.9	3.4
Weighted Mean →			11.1	1.0	4.4	7.1	4.0	7.5	2.4	7.7	0.9	3.4
HRQOL Effect Size Results – SVR versus No SVR												
Bernstein	32	1441	0.3	0.3	0.2	0.5	0.4	0.3	0.2	0.3	0.3	0.3
Bonkovsky	33	1392	0.3	0.7	–0.05	0.4	0.4	0.4	0.4	0.25	–	–
Raseneck	34	531	0.2	0.2	0.2	0.4	0.3	0.2	0.2	0.2	0.3	0.25
Ware	35	324	0.4	0.3	0.2	0.4	0.3	0.4	0.1	0.1	–	–
Coughlan	36	93	0.5	0.05	0.2	0.4	0.2	0.3	–0.1	0.4	–	–
Hassanein	37	36	0.1	0.02	0.1	0.02	–	0.1	0.2	–	–	–
Weighted Mean/Median →			0.3/0.3	0.25	0.1/0.2	0.4	0.3	0.3/0.3	0.2/0.2	0.25	0.3/–	0.3/–

NOTE. Three types of data are presented: (1) HRQOL difference in difference scores stratified by SVR status; (2) HRQOL cross-sectional mean difference scores stratified by SVR status; and (3) HRQOL effect sizes stratified by SVR status. The data are presented across the 8 SF-36 scales and the 2 SF-36 component scales. The weighted mean and median are presented for each set of data (bottom row of each section).

Profile.⁴¹ The largest impact on HRQOL was in the SF-36 role–emotional scale, with cross-sectional HRQOL differences ranging from –4.0 (subclinical cognitive dysfunction) to –39.0 (emotional distress). Perhaps more surprising, all of the somatic scales (physical function, role-physical, bodily pain) also demonstrated large group mean differences. Zickmund et al. found similarly large effects on Sickness Impact Profile scores stratified by patient-reported “stigmatization.”⁴¹ Compared with HCV patients who did not feel stigmatized by their disease, those who felt “severely stigmatized” scored 8 points lower on average on the total Sickness Impact Profile score.

Effect Sizes: Our review failed to identify any study presenting sufficient distributional data to calculate an ES across a neurological, psychological, or social anchor.

Summary of HRQOL Stratified by Neuropsychosocial Anchors. The data indicate that there are large HRQOL differences in HCV across neurological, psychological, and social anchors. These results are not unexpected since each of these anchors, when present, may independently diminish HRQOL. It is difficult to determine whether the large impact on HRQOL observed in

these studies is primarily related to the specific anchors, or whether there is a negative synergistic effect between these anchors and HCV.

HRQOL Stratified by Liver Disease Severity Anchors. HCV is associated with a wide-range of extrahepatic manifestations. Nonetheless, its primary biological impact is on the liver. Although liver damage does not always correspond with patient symptoms and overall health status, liver disease severity is an important surrogate outcome in the management of HCV. Traditional markers of liver disease severity include histological activity (e.g., Knodell scores), biochemical activity (e.g., ALT levels), and clinical activity (e.g., Child’s class, MELD score). We identified 5 studies that measured HRQOL stratified by one or more liver disease severity anchor(s) (Table 6).^{5,8,15,36,42}

Histological Activity Anchors: Two studies stratified HRQOL by histological anchors.^{8,36} McHutchison et al. found no significant difference in HRQOL in patients with a >5 point change in Knodell score (a histologically important change in disease activity) versus no change in Knodell score.⁸ The HRQOL DID scores ranged from 0.5 in physical function to 2.4 in vitality. Similarly, Coughlan et al. detected no significant HRQOL differ-

Table 5. HRQOL Stratified by “Neuropsychosocial” Anchors

Author	Ref #	Anchor	SF-36 Scales									
			Physical Function	Role Physical	Bodily Pain	General Health	Vitality	Social Function	Role Emotional	Mental Health	MCS	PCS
HRQOL Cross-Sectional Mean Difference Stratified by Anchor												
Hussain	9	Psychiatric comorbidity versus no comorbidity*	-30	-35	-22	-25	-15	-22	-25	-9	-5	-11
Kramer	10	Subclinical cognitive dysfunction versus no cognitive dysfunction**	-17	-7	-21	-15	-5	-10	-4	-2	-	-
Gallegos-Orozco	15	Comorbid depression versus no depression	-16.7	-31.4	-15.3	-9.8	-17.6	-23	-26	-18	-20	-17
Fontana	39	Psychiatric comorbidity versus no depression***	-3	-20	-13	-3	-5	-5	-20	-9	-	-
Fontana	40	Emotional distress versus no emotional distress***	-22	-38	-22	-25	-17	-30	-39	-12	-10	-10
HRQOL Effect Size Stratified by Neuropsychosocial Factor												
Gallegos-Orozco	15	Comorbid depression versus no depression	-0.6	-0.7	-0.5	-0.4	-0.7	-0.8	-0.6	-0.8	-0.9	-1

* Defined as carrying at least one psychiatric diagnosis.

** As measured by P300 event-related evoked potentials.

*** Defined as being in the top 10 percentile of the global severity index (GSI).

ence in patients with a <3 Knodell score versus >4 Knodell score following treatment for HCV.³⁶ The cross-sectional mean HRQOL differences ranged from -1.8 in role-physical (suggesting a unexpectedly higher HRQOL in patients with worse histological activity) to 2.2 in vitality.

Biochemical Activity Anchors: Two studies stratified HRQOL by ALT levels.^{8,42} McHutchison et al. found no significant difference in HRQOL in patients with a >3 times improvement in the ALT ratio (a clinically important change in biochemical activity) versus no change in the ALT ratio.⁸ Similarly, Miller et al. detected no difference in either the MCS or PCS in patients with high versus normal ALT levels.⁴² In fact, there was a trend towards lower HRQOL in those with normal levels (cross section mean difference for MCS = -0.1 , PCS = -3.3).

Clinical Activity Anchors: Two studies compared HRQOL in patients with HCV-related Child's class B cirrhosis versus noncirrhotic chronic HCV.^{5,15} Both studies revealed large differences in HRQOL across all scales. The cross-sectional mean differences ranged from -7.0 for general health to -44.0 for role-physical and PCS, and the ES ranged from -0.3 for general health to -1.4 for physical function and PCS.

Summary of HRQOL Stratified by Liver Disease Severity Anchors. The data suggest that subtle histological or biochemical changes are not perceived as clinically

important by patients, thereby suggesting that these traditional biological outcomes may fail to capture the full spectrum of illness related to chronic HCV. In contrast, there are large and clinically significant differences in HRQOL in patients with versus without cirrhosis. The large differences in HRQOL stratified by cirrhosis are not unexpected given the well-documented negative impact that cirrhosis itself exerts on HRQOL, independent of concurrent HCV.

Expert Panel Estimate of MCID in HCV

Based upon *a priori* hypotheses and data from the systematic review, the expert panel concluded that the SF-36 vitality scale (Table 7) captures the HRQOL domain of the SF-36 that is most relevant to patients with HCV. Specifically, because HCV and its treatment are associated with a range of devitalizing symptoms such as tiredness, lack of energy, and lassitude, the SF-36 vitality scale is pertinent in HCV. Moreover, our systematic review revealed that vitality was one of the key domains most affected by HCV. Of the 8 SF-36 scales, the vitality scale ranked in the top 3 for size of HCV impact on HRQOL across all clinical anchors.

Therefore, rather than develop individual MCID estimates for each of the 8 SF-36 scales, the panel focused its estimates on the vitality scale. Based upon independent

Table 6. HRQOL Stratified by Liver Disease Severity Anchors

Author	Ref #	Anchor	SF-36 Scales									
			Physical Function	Role Physical	Bodily Pain	General Health	Vitality	Social Function	Role Emotional	Mental Health	MCS	PCS
HRQOL Score Difference in Differences Stratified by Anchor												
McHutchison	8	HAI score improvement versus no improvement	0.5	3	0.5	2.3	2.4	0.8	2.1	1.8	—	—
McHutchison	8	ALT level improvement versus no improvement	0.5	3.0	0.5	2.3	2.4	0.8	2.1	1.8	—	—
HRQOL Cross-Sectional Mean Difference Stratified by Anchor												
Cordoba	5	Child's Class B versus non-cirrhotic chronic HCV	-25	-44	-10	-23	-23	-20	-16	-12	-25	-44
Gallegos-Orozco	15	Child's Class B versus non-cirrhotic chronic HCV	-15	-22	-13	-7	-10	-12	-22	-6	-15	-22
Coughlan	36	HAI score improvement versus no improvement	2.1	-1.8	3.4	1.2	2.2	0.4	0.2	0.3	—	—
Miller	42	High ALT level versus normal ALT level	—	—	—	—	—	—	—	—	-0.1	-3.3
HRQOL Effect Size Stratified by Anchor												
Cordoba	5	Child's Class B versus non-cirrhotic chronic HCV	-1.4	-1.1	-0.3	-1.1	-0.9	-0.8	-0.4	-0.6	-1.4	-1.1
Gallegos-Orozco	15	Child's Class B versus non-cirrhotic chronic HCV	-0.6	-0.5	-0.5	-0.3	-0.4	-0.4	-0.5	-0.3	-0.6	-0.5
Coughlan	36	HAI score improvement versus no improvement	0.1	0.1	0.1	0.03	0.1	0.01	0.01	0.01	—	—

Abbreviations: HAI, Histological Activity Index—aka Knodell score; ALT, Alanine Transaminase.

review of the systematic review, the panel initially generated a mean MCID of 4.9 points (range, 2-6) on the SF-36 vitality scale. After convening in-person and completing the remaining steps of modified Delphi procedure, the expert panel generated a mean MCID of 4.2 points (range, 3-5) on the SF-36 vitality scale, with a corresponding ES of 0.2 (range, 0.15-0.25).

Discussion

The burden of disease engendered by chronic HCV extends beyond its impact on traditional biological outcomes to include a negative impact on patient-oriented outcomes such as HRQOL. It is now common practice to include HRQOL as a primary outcome in clinical trials,

Table 7. SF-36 Vitality Scale

These questions are about how you feel and how things have been with you during the past four weeks. For each question, please give the one answer that comes closest to the way that you have been feeling. How much of the time during the past four weeks—

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
1. Did you feel full of pep? . . .	1	2	3	4	5	6
2. Did you have a lot of energy? . . .	1	2	3	4	5	6
3. Did you feel worn out? . . .	1	2	3	4	5	6
4. Do you feel tired? . . .	1	2	3	4	5	6

$$\text{Transformed Scale} = \frac{(\text{Raw Score} - 4)}{20} \times 100$$

→ For example, if a patient scores “3” on all 4 questions, then the raw score is 12. The transformed scale score is then = (12 - 4)/20 × 100 = 40. NOTE. The scale is scored using the provided equation⁴³ (see example below).

to incorporate HRQOL in cost-effectiveness analyses, and to monitor HRQOL in everyday clinical practice in HCV. In light of these trends, we performed a comprehensive systematic review to quantify the impact of chronic HCV on HRQOL. Our analysis has five key findings: First, patients with HCV have consistently diminished HRQOL compared with matched controls without HCV. Second, patients with HCV achieving SVR have an improved HRQOL compared with those without SVR. Third, the impact of HCV is most pronounced on the vitality, general health, physical function, and social function scales of the SF-36 Health Survey, thereby indicating an impact across a wide range of HRQOL domains. Fourth, the impact of HCV on HRQOL is likely to be clinically important as measured by proposed criteria for determining the significance of HRQOL effect sizes.²⁴ Last, traditional outcomes in both clinical management and treatment trials, such as ALT levels and early histological changes, fail to correlate with HRQOL, thereby suggesting that traditional outcomes may fail to capture the full spectrum of illness related to chronic HCV.

The insight that HCV diminishes HRQOL is a necessary first step to understand why it is important to measure HRQOL in clinical practice. However, knowing that HCV diminishes HRQOL is insufficient for knowing *how* to use this information in clinical practice. This practical challenge can be met by establishing the minimal change in HRQOL that patients with HCV perceive to be important. We therefore convened an expert panel to establish the MCID in HCV using a modified Delphi technique.²⁷ The panel relied upon existing construct-anchored HRQOL data in HCV to estimate the MCID for the vitality scale of the SF-36, and generated a value of 4.2 with an ES of 0.2. This value can be used in everyday clinical practice and in clinical trials. For example, in clinical practice physicians can measure patient outcomes by routinely administering the 4-item SF-36 vitality scale (Table 7) during office visits. If a patient fails to achieve an increase of 4.2 points over time (corresponding ES = 0.2), then it implies that the ongoing care has failed to perceptively improve the patient's HRQOL. In clinical trials, the MCID can be used as a yardstick to determine whether patients have benefited from the study intervention. Specifically, patients may be defined as responders if they achieve or exceed the MCID of 4.2 or an ES of 0.2 on the vitality scale. This can be used as the basis for power calculations. Table 8 provides the estimated sample sizes needed to detect a difference of 5%, 10%, 15%, 20% and 25% between 2 groups at a power of 80% and 90%.

Our analysis has several strengths. First, we performed an explicit and reproducible (Table 1) systematic review

Table 8. Estimated Sample Sizes Needed for Clinical Trials Using a Dichotomous Primary Outcome

% Difference Between Group	p(B) in Control Group	Estimated Sample Size Requirement Per Group
Assuming $\alpha = 0.05$, Power = 80%		
5	10	724
	20	1133
	30	1415
10	10	219
	20	313
	30	376
15	10	112
	20	151
	30	175
20	10	72
	20	91
	30	103
25	10	51
	20	62
	30	68
Assuming $\alpha = 0.05$, Power = 90%		
5	10	958
	20	1504
	30	1883
10	10	286
	20	412
	30	496
15	10	146
	20	197
	30	230
20	10	92
	20	118
	30	134
25	10	65
	20	80
	30	88

NOTE. In studies using HRQOL as the primary outcome, patients either achieve the MCID over the course of a clinical trial, or they do not. This metric can be used to calculate the percentage benefiting, or p(B), in each arm of a trial (defined as the percentage achieving the MCID).²³ The projected difference in p(B) between arms can then be used as the basis for powering clinical trials.²³ For example, if an investigator hopes to find a 20% difference in the p(B) on the vitality scale between two groups (where "benefit" defined as ≥ 4.2 point improvement on vitality scale), then 72 patients will be required per arm assuming an α of 0.05, power of 80%, and anticipated p(B) of 10% in the control arm.

to identify relevant data across several sources, including published manuscripts from two bibliographic databases and published abstracts from 4 subspecialty journals. Second, we relied upon a pre-specified conceptual model to guide our data abstraction (Fig. 1). Third, in recognition that different clinical anchors have variable impacts on HRQOL, we stratified our analysis across a comprehensive range of neurological, psychological, social, and liver disease severity anchors. Fourth, in accordance with recommendations for interpreting HRQOL, we selected quantitative summary estimates that emphasize clinical relevance over statistical significance.²³ Last, our analysis systematically estimates the MCID in HCV – data that may have important clinical usefulness as described above.

Our analysis has potential limitations. First, we estimated the MCID in HCV indirectly by using the results of existing data rather than directly measuring the MCID according to a standard protocol. Therefore, our data should not be confused with a direct measurement of the MCID. However, the indirect approach has been used in other areas of medicine²⁶ and, in the absence of a directly measured MCID, is an acceptable strategy for estimating this clinically useful value. Future research should aim to directly measure the MCID using the accepted patient-based methods,²³ not only for the SF-36, but also for a disease-targeted measure such as the Hepatitis Quality of Life Questionnaire (HQLQ).^{14,35} Second, our estimate of the MCID only applies to the vitality scale of the SF-36. Although the vitality scale in has *a priori* and clinical data to support its usefulness in HCV, relying on the vitality scale alone does not capture all of the key aspects of HRQOL in HCV. We have therefore made efforts in our systematic review to abstract data across all 8 scales, and believe that a balanced understanding of the relationship between HCV and HRQOL ultimately requires information from all areas of biological, psychological, and social health, and not just one scale alone. Third, the nature of the HRQOL literature in HCV is itself limited by several factors. For example, most of the studies included patients from tertiary care referral centers, and the resulting data may not be generalizable to community-based cohorts with HCV. However, although the degree of HRQOL decrement may be smaller in community versus referral cohorts, there is no reason to expect that the negative impact of HCV on HRQOL will disappear in community-based cohorts. In addition, most of the studies employed the SF-36 Health Survey, a generic measure of HRQOL, and only one used a disease-targeted measure of HRQOL — the HQLQ.^{14,35} Because the SF-36 may fail to capture the full range of HRQOL decrements from HCV, it is important to develop and employ disease-targeted instrument such as the HQLQ in addition to generic measures like the SF-36.

In conclusion, chronic HCV diminishes HRQOL across a wide range of clinical anchors. The impact on HRQOL is highly clinically significant and affects physical, social, and mental health domains. Sustained virological response is associated with improvement in HRQOL, thereby indicating that treatment of HCV may improve patient-oriented outcomes in addition to established biological outcomes. We estimate that a change of 4.2 points on the vitality scale of the SF-36 may represent the minimally important difference in HRQOL in HCV. This value may be used to monitor patient outcomes in clinical practice as well as clinical trials.

References

- Kim WR, Brown RS, Tarrault NA, El-Serag H. Burden of liver disease in the United States: summary of a workshop. *HEPATOLOGY* 2002;36:227-242.
- Poynard T, Bedossa P, Opolon P for the OBSVIRC, METAVIR, CLINIVIR and DOSVIRC groups. Natural history of liver fibrosis progression in patients with chronic hepatitis C. *Lancet* 1997;349:825-32.
- United Network of Organ Sharing. Available at: www.unos.org. Accessed June 1, 2004.
- Chong CA, Gulamhussein A, Heathcote EJ, Lilly L, Sherman M, Naglie G, et al. Health-state utilities and quality of life in hepatitis C patients. *Am J Gastroenterol* 2003;98:630-638.
- Cordoba J, Flavia M, Jacas C, Sauleda S, Esteban JI, Vargas V, et al. Quality of life and cognitive function in hepatitis C at different stages of liver disease. *J Hepatol* 2003;39:231-8.
- Siebert U, Sieberer R, Greiner W, et al. Patient-based health-related quality of life in different stages of chronic hepatitis C [Abstract]. *HEPATOLOGY* 2001;34(Pt 2): AB222A.
- National Institutes of Health Consensus Development Panel Statement. Management of hepatitis C. *HEPATOLOGY* 1997;26(Suppl 1):2S-10S.
- McHutchison JG, Ware JE Jr, Bayliss MS, Pianko S, Albrecht JK, Cort S, et al. The effects of interferon alpha-2b in combination with ribavirin on health related quality of life and work productivity. *J Hepatol* 2001;34: 140-147.
- Hussain KB, Fontana RJ, Moyer CA, Su GL, Sneed-Pee N, Lok AS. Comorbid illness is an important determinant of health-related quality of life in patients with chronic hepatitis C. *Am J Gastroenterol* 2001;96: 2737-2744.
- Kramer L, Bauer E, Funk G, Hofer H, Jessner W, Steindl-Munda P, Wrba F, Madl, et al. Subclinical impairment of brain function in chronic hepatitis C infection. *J Hepatol* 2002;37:349-54
- Gifford SM, O'Brien ML, Bammer G, Banwell C, Stooze M. Australian women's experiences of living with hepatitis C virus: results from a cross-sectional survey. *J Gastroenterol Hepatol* 2003;18:841-850.
- Bini EJ, Baskies MA, Achkar JM, Maslow MJ. Impact of HIV infection on health-related quality of life in patients with chronic hepatitis C: an unexpected finding [Abstract]. *HEPATOLOGY* 2000;32(Pt 2):AB486.
- Foster GR, Goldin RD, Thomas HC. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. *HEPATOLOGY* 1998;27:209-212.
- Bayliss MS, Gandek B, Bungay KM, Sugano D, Hsu MA, Ware JE Jr. A questionnaire to assess the generic and disease-specific health outcomes of patients with chronic hepatitis C. *Qual Life Res* 1998;7:39-55.
- Gallegos-Orozco JF, Fuentes AP, Gerardo Argueta J, Perez-Pruna C, Hinojosa-Becerril C, Sixtos-Alonso MS, et al. Health-related quality of life and depression in patients with chronic hepatitis C. *Arch Med Res* 2003; 34:124-129.
- Dalgard O, Egeland A, Skaug K, Vilimas K, Steen T. Health-related quality of life in active injecting drug users with and without chronic hepatitis C virus infection. *HEPATOLOGY* 2004;39:74-80.
- Fleming CA, Christiansen D, Nuñez D, Heeren T, Thornton D, Horsburgh CR Jr, et al. Health-related quality of life of patients with HIV disease: impact of hepatitis C coinfection. *Clin Infect Dis*. 2004;38:572-578.
- Pojoga C, Dumitrascu DL, Pascu O, Grigorescu M, Radu C, Damian D. Impaired health-related quality of life in Romanian patients with chronic viral hepatitis before antiviral therapy. *Eur J Gastroenterol Hepatol* 2004; 16:27-31.
- Hunt CM, Dominitz JA, Bute BP, Waters B, Blasi U, Williams DM. Effect of interferon-alpha treatment of chronic hepatitis C on health-related quality of life. *Dig Dis Sci* 1997;42:2482-2486.
- Miller ER, Hiller JE, Shaw DR. Quality of life in HCV-infection: lack of association with ALT levels. *Aust N Z J Public Health* 2001;25:355-361.
- Nocente R, Ceccanti M, Bertazzoni G, Cammarota G, Silveri NG, Gusbarrini G. HCV infection and extrahepatic manifestations. *Hepatogastroenterology* 2003;50:1149-1154.

22. Seeff LB, Hoofnagle JH. National Institutes of Health Consensus Development Conference: management of hepatitis C: 2002. *HEPATOLOGY* 2002;36(Pt 2):S1-S2.
23. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR, Clinical Significance Consensus Meeting Group. Methods to explain the clinical significance of health status measures. *Mayo Clin Proc* 2002;77:371-383.
24. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. London: Academic Press, 1969.
25. Jaeschke R, Singer J, Guyatt GH. Measurement of health status: ascertaining the minimal clinically important difference. *Control Clin Trials* 1989; 10:407-415.
26. Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *J Pain Symptom Manage* 2002;24:547-561.
27. Fink A, Kosecoff J, Chassin M, Brook RH. Consensus methods: characteristics and guidelines for use. *Am J Public Health* 1984;74:979-983.
28. Paterson DL, Gayowski T, Wannstedt CF, Wagener MM, Marino IR, Vargas H, et al. Quality of life in long-term survivors after liver transplantation: impact of recurrent viral hepatitis C virus hepatitis. *Clin Transplant* 2000;14:48-54.
29. Samsa G, Edelman D, Rothman ML, Williams GR, Lipscomb J, Matchar D. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. *Pharmacoeconomics* 1999;15:141-155.
30. Hays RD, Woolley JM. The concept of clinically meaningful difference in health related quality of life research: how meaningful is it? *Pharmacoeconomics* 2000;18:419-423.
31. Neary MP, Cort S, Bayliss MS, Ware JE Jr. Sustained virologic response is associated with improved health-related quality of life in relapsed chronic hepatitis C patients. *Semin Liver Dis* 1999;19(Suppl 1):77-85.
32. Bernstein D, Kleinman L, Barker CM, Revicki DA, Green J. Relationship of health-related quality of life to treatment adherence and sustained response in chronic hepatitis C patients. *HEPATOLOGY* 2002;35:704-708.
33. Bonkovsky HL, Woolley JM. Reduction of health-related quality of life in chronic hepatitis C and improvement with interferon therapy. The Consensus Interferon Study Group. *HEPATOLOGY* 1999;29:264-720.
34. Rasenack J, Zeuzem S, Feinman SV, Heathcote EJ, Manns M, Yoshida EM, et al. Peginterferon alpha-2a (40kD) [Pegasys] improves HR-QOL outcomes compared with unmodified interferon alpha-2a [Roferon-A]: in patients with chronic hepatitis C. *Pharmacoeconomics* 2003;21:341-349.
35. Ware JE Jr, Bayliss MS, Mannocchia M, Davis GL. Health-related quality of life in chronic hepatitis C: impact of disease and treatment response. The Interventional Therapy Group. *HEPATOLOGY* 1999;30:550-555.
36. Coughlan B, Sheehan J, Hickey A, Crowe J. Psychological well-being and quality of life in women with an iatrogenic hepatitis C virus infection. *Br J Health Psycho*. 2002;7:105-116.
37. Hassanein TI, Hilsabeck RC, Hwang S, Medley K, Ziegler BA. Assessment of quality of life in sustained responders [Abstract]. *HEPATOLOGY* 2001; AB1712.
38. Hassanein T, Cooksley G, Sulkowski M, Smith C, Marinos G, Lai MY, et al. The impact of peginterferon alpha-2a plus ribavirin combination therapy on health-related quality of life in chronic hepatitis C. *J Hepatol* 2004;40: 675-681.
39. Fontana RJ, Moyer CA, Sonnad S, Lok ASF, Sneed-Pee N, Walsh J, et al. Comorbidities and quality of life in patients with interferon-refractory chronic hepatitis C. *Am J Gastroenterol* 2001;96:170-178.
40. Fontana RJ, Hussain KB, Schwartz SM, Moyer CA, Su GL, Lok AS. Emotional distress in chronic hepatitis C patients not receiving antiviral therapy. *J Hepatol* 2002;36:401-407.
41. Zickmund S, Ho EY, Masuda M, Ippolito L, LaBrecque DR. "They treated me like a leper". Stigmatization and the quality of life of patients with hepatitis C. *J Gen Intern Med* 2003;18:835-844.
42. Miller ER, Hiller JE, Shaw DR. Quality of life in HCV-infection: lack of association with ALT levels. *Aust N Z J Public Health* 2001;25:355-361.
43. Ware JE, Snow KK, Kosinski MK, Gadnek B. Scoring the SF-36. In: *SF-36 Health Survey: Manual and Interpretation Guide*. Boston, MA: Nimrod Press, 1992.
44. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159-174.
45. De La Loge C, Trudeau E, Marquis P, Revicki DA, Rentz AM, Stanghellini V, et al. Responsiveness and interpretation of a quality of life questionnaire specific to upper gastrointestinal disorders. *Clin Gastroenterol Hepatol* 2004;2:778-786.
46. Galnek IM, Hays RD, Kilbourne A, Naliboff B, Mayer EA. The impact of irritable bowel syndrome on health-related quality of life. *Gastroenterology* 2000;119:654-660.
47. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003;41:582-592.
48. Farivar SF, Lieu H, Hays RD. Half standard deviation estimate of the minimally important difference in HRQOL scores. *Expert Rev Pharmacoeconomics Outcomes Res* 2004;4:515-523.
49. Ware JE, Sherbourne CD. A 36-item short-form health survey (SF-36): conceptual framework and item selection. *Med Care* 1992;30:473-483.