Psychological Determinants of Health-Related Quality of Life in Patients With Chronic Liver Disease

Jolie J. Gutteling, Ph.D., Hugo J. Duivenvoorden, Ph.D.
Jan J.V. Busschbach, Ph.D., Robert A. de Man, M.D., Ph.D.
Anne-Sophie E. Darlington, Ph.D.

Background: The negative impact of chronic liver disease on health-related quality of life (HRQoL) of patients with chronic liver disease (CLD) has long been established, and treatable physiological or psychological factors may potentially influence HRQoL. Objective: The authors assessed the interrelationships of multiple psychological factors and HRQoL in patients with CLD. Method: Both direct and indirect relationships among HRQoL, depression, anxiety, coping, and self-efficacy in 164 patients with CLD were assessed. Results: Depression, largely determined by low self-efficacy and, possibly, by use of maladaptive coping strategies, influenced HRQoL in three groups of liver patients. Conclusion: HRQoL in CLD patients may be positively affected by enhancing coping and self-efficacy skills, thus improving levels of depression.

(Tomorrow's Health) 2010; 51:157–165)

The negative impact of chronic liver disease (CLD) on health-related quality of life (HRQoL) has long been established. In daily clinical practice, knowledge of this negative association becomes particularly valuable with knowledge of treatable physiological or psychological factors that may potentially influence HRQoL. Recently, several studies have identified psychological factors that are related to HRQoL in patients with CLD: fatigue, anxiety, depression, and disease-related worries. Many published studies have tended to discuss a limited number of psychological variables at a time, without attempting to examine them in one integrated framework. This complicates the efforts to determine the variable with the strongest relationship with HRQoL. Furthermore, previous studies used multiple scores of HRQoL and therefore multiple outcome variables, which makes the interpretation of the results and the comparability between studies difficult. Finally, previous studies have, to the best of our knowledge, not taken into account two variables that are known to influence HRQoL, namely “coping” and “self-efficacy,” which have been shown to affect HRQoL, but never with regard to chronic liver disease.

Considering the size of the patient population that is affected by CLD, the severity of the disease, and the chronic nature of the symptoms, there is a need to examine the interaction between psychological variables more closely, as they can act as a target for interventions in order to improve HRQoL. Therefore, the aim of the present study was to investigate the relationship of several psychological variables with HRQoL simultaneously in a population of patients with CLD, with emphasis on establishing a detailed perspective on the direction of the interplay among the variables.

Received August 27, 2007; revised January 11, 2008; accepted January 28, 2008. From the Dept. of Gastroenterology and Hepatology, Erasmus MC, ’s Gravendijkwal 230, Rotterdam, the Netherlands; and the Dept. of Medical Psychology and Psychotherapy, Erasmus MC, Rotterdam, The Netherlands. Send correspondence and reprint requests to J.J. Gutteling, Dept. of Gastroenterology and Hepatology, CA 326, ’s Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands. e-mail: j.gutteling@dimence.nl

© 2010 The Academy of Psychosomatic Medicine

Psychosomatics 51:2, March-April 2010 http://psy.psychiatryonline.org 157
To that end, three hypotheses about the interrelationships of the psychological variables were integrated into one model. Since no such study has been conducted with patients having chronic liver disease before, the hypotheses were based on clinical practice as well as existing studies with other patient populations. The three hypotheses that were tested in the model are 1) that depression and anxiety affect HRQoL directly; 2) that maladaptive coping may affect HRQoL, either directly or indirectly, through elevated anxiety and depression scores; and 3) that low perceived self-efficacy may affect HRQoL through its associations with maladaptive coping strategies and elevated depression and anxiety scores.

METHOD

Participants

Questionnaire booklets were sent to 250 patients with the most common forms of chronic liver disease (cholestatic liver disease [N=80], hepatitis B [HBV; N=79], and hepatitis C [HCV; N=91]), who were selected from 15 consecutive consulting hours at the Department of Hepatology of the Erasmus Medical Center (Rotterdam, The Netherlands). Their medical data were obtained from the medical database. Patients had to be 18 years of age or older. Informed consent was given by returning the questionnaire booklet. The protocol was in accordance with the ethical guidelines of the Modified 1975 Declaration of Helsinki. Since the questionnaire booklets were only administered once and did not include invasive questions, ethical approval was not necessary under Dutch regulations.

Measurement Instruments

Health-Related Quality of Life  HRQoL was measured with the Short Form–6D (SF–6D), which is based on a subset of questions from the widely used Short Form–36, which has good reliability and validity. Recently, the SF–6D been validated to produce a “utility score,” which ranks health states on a scale with the value 0.00 representing death to 1.00 representing full health.

Depression  Depression was measured with the Dutch version of the Beck Depression Inventory (BDI–II, NL), a 21-item self-report rating inventory. The total score ranges between 0 and 63, with scores <14 considered normal, a score of 14–19 indicating mild-to-moderate depression, a score of 20–28 indicating moderate-to-severe depression, and scores >28 indicating severe depression. Validity and reliability of the BDI have been established.

Anxiety  Anxiety was measured with the State–Trait Anxiety Inventory (STAI), which is one of the most widely used instruments for measuring anxiety in adults. In this study, only Trait Anxiety was being measured; this refers to a general tendency to respond with anxiety to perceived threats in the environment. The Trait Anxiety scale consists of 20 statements assessing how respondents feel “generally.” Scores can vary between 20 and 80, with higher scores indicating more anxiety. Normative data are available. The STAI has proven to be valid and reliable.

Self-Efficacy  Self-efficacy (SE) which refers to the optimistic self-belief that one can perform difficult or new tasks or that one can cope adequately with adversity, was measured with the 10-item Self-Efficacy Scale. Scores vary between 10 and 40, with a higher score indicating more self-efficacy. High reliability and construct validity of the SES have been confirmed in earlier studies.

Maladaptive Coping  Maladaptive coping was derived from the short version of the Cognitive Operations Preference Enquiry, called the COPE–Easy, which is a validated questionnaire that assesses individuals’ coping responses when confronted with stressful situations and adversity. The items comprising Maladaptive Coping were selected on the basis of principal-component analysis with varimax rotation. Items mainly fell into two groups of coping reactions: adaptive and maladaptive coping, which is consistent with previous research. Preliminary analysis showed no or weak relationships of adaptive coping with the psychological variables (depression, anxiety, HRQoL, and SE) assessed in this study. Maladaptive Coping did show statistically significant relationships with these psychological variables and was therefore included in this study. Maladaptive Coping consists of four subscales considered detrimental to patients’ well being: 1) “getting upset;” 2) “denial;” 3) “behavioral disengagement,” which refers to giving up; and 4) “substance abuse,” which refers to alcohol, smoking, and non-prescribed medication.

Statistical Modeling

Structural Equation Modeling (SEM) is a statistical method that considers a confirmatory (i.e., hypothesis-testing) approach to the interdependency of variables. This interdependency distinguishes endogenous variables (i.e., outcome variables, dependent variables) from exogenous variables (determinants, predictor vari-
ables, independent variables). SEM enables us to identify, estimate, and test interdependency in terms of manifest and latent variables. SEM has several advantages over multivariate explorative procedures like regular factor analysis: it takes a strict confirmatory, rather than an exploratory, approach to data analysis by demanding that the relationships between variables be specified a-priori, and it is capable of assessing or correcting for measurement error. In this study, the interdependency of manifest variables was explored.

Path analysis is a special kind of SEM, which was used in this study. Path analysis was originally developed by Wright (1934). This technique was later introduced in the fields of econometrics and social sciences. Path analysis is tailored to assess the impact of one variable (i.e., an exogenous variable) on another (i.e., an endogenous variable) in a nonrandomized trial. Typically, in a path model, a variable might be both endogenous and exogenous simultaneously. SEM takes a hypothesis-testing (i.e., confirmatory) approach to the multivariate analysis of a structural theory bearing on some phenomenon. Typically, this theory represents causal processes that generate observations on multiple variables. Relationships between variables are specified a priori, and are one-way. However, since the data in this study were cross-sectional, it is not possible to draw decisive conclusions in terms of causality. SEM has several advantages over multivariate explorative procedures like typical factor analysis: it takes a strict confirmatory rather than an exploratory approach to data analysis by demanding that the relationships between variables be specified a priori; it is capable of assessing or correcting for measurement error; and it is able to test hypotheses of causality.

To fully apply the advantages of SEM models, they should be built on substantive grounds and, also, be as simple as possible. To test the adequacy of the models, chi-square tests were used to determine the model-fit. We examined the value of $\chi^2$, its p value, and the number of degrees of freedom (df). A nonsignificant p value ($p > 0.05$) and the ratio of $\chi^2/df < 1.5$ represent a good model fit. Four other goodness-of-fit indices were also used: the Comparative Fit Index (CFI) and the Tucker-Lewis Index (TLI), the Root Mean Square Error of Approximation (RMSEA), and the Standardized Root Mean Square Residual (SRMR). For the model to fit, the CFI and TLI must be above 0.95, and the RMSEA as well as the SRMR, preferably lower than 0.05. In this study, the interrelationships of the different variables in the model were expressed in terms of standardized regression weights. The regression weights represent the strength of a relationship, while taking into account the other relationships supposed in the model. The direction of the relationship is always one way. The regression weights can be interpreted as follows: for each point-increase in z-score of the determining variable, the outcome variable will increase or decrease by the standardized regression weight.

### Statistical Analysis

First, we described the mean scores and standard deviations (SD) on HRQoL, depression, anxiety, coping, and perceived self-efficacy of patients with HBV, HCV, and cholestatic liver disease.

Figure 1 shows the hypothesized model that estimated the likelihood that HRQoL is influenced by treatable psychological factors. Our data-analysis strategy was the following: The interrelationships of the variables HRQoL, depression, anxiety, coping, and self-efficacy, as represented in Figure 1, were analyzed in M-plus, Version 5, for
all CLD patients. The exogenous variable was Self-Efficacy, and the endogenous variable was HRQoL. The other variables in the model were both endogenous and exogenous. In order to assess the influence of disease-severity on HRQoL, the model was tested again with a dummy variable representing the presence or absence (value: 0) of (de)compensated cirrhosis (value: 1). The hypothesized model was explored for differences in diagnosis (HBV, HCV, and cholestatic liver disease) by simultaneously adding these as subgroups in the analysis.
We explored which relationships between the parameters were the same for all subgroups, and which relationships differed, by fixing as many relationships as possible, while maintaining adequate model fit.

In order to test the hypothesized model, the goodness-of-fit of this model was compared with the goodness-of-fit of several “competing models.” These competing models are shown in Figure 2; they were constructed by varying the interrelationships of the component variables. Since findings from the literature and clinical experience were already incorporated in the original model (Figure 1), the competing models could only be based on common sense, and may therefore be less convincing, but, nevertheless, plausible. Models 2A and 2B reflect the hypothesis that Depression and Anxiety influence Self-Efficacy instead of vice versa, as in the original model. In Model 2C, we hypothesize that Maladaptive Coping influences Self-Efficacy. Model 2D reflects the hypothesis that Depression and Anxiety influence HRQoL only indirectly, via Maladaptive Coping, instead of directly, which was hypothesized in the original model. Model 2E states that, contrary to the original model, Depression and Anxiety influence Maladaptive Coping, rather than vice versa.

RESULTS

Patient Characteristics

Of the 250 patients who were sent a questionnaire booklet, 175 responded (response rate: 70%). The nonrespondents were mostly male (68%), with an average age of 47.2 years. Of these, 13 were diagnosed with cholestatic liver disease, 22 with HBV, and 40 HCV (Table 1). Respondents used interferon, which can induce a temporary state of depression, and were therefore excluded from the analyses. A group of 164 patients were included in the analyses (89 [54%] men, 75 [46%] women). Of these, 55 had HBV, 43 had HCV, and 66 had cholestatic liver disease. Their mean age was 45.8 years (Table 1). Differences on the variables Age, Gender, and Diagnosis between respondents and nonrespondents were assessed by means of chi-square tests or a t-test. Respondents and nonrespondents differed significantly on the variable Diagnosis, with a significantly larger percentage of HCV nonrespondents differed significantly on the variable Diagnoses on the variables Age, Gender, and Diagnosis between respondents and nonrespondents were assessed by means of chi-square tests or a t-test.

Of the 164 patients who participated in the study, 161 patients (98%) completed the BDI–II, NL, and 160 (98%) completed the STAI and the Self-Efficacy questionnaire. The COPE–Easy was completed by 157 (96%), and the

<table>
<thead>
<tr>
<th>TABLE 1. Demographic Characteristics of the Respondents Included in the Analyses, and Non-Respondents</th>
<th>Respondents (N=164)</th>
<th>Non-Respondents (N=75)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>89 (54)</td>
<td>51 (68)</td>
<td>0.05</td>
</tr>
<tr>
<td>Women</td>
<td>75 (46)</td>
<td>24 (32)</td>
<td></td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>45.8 (12.9)</td>
<td>47.2 (12.3)</td>
<td>0.18</td>
</tr>
<tr>
<td>Diagnosis, N (%)</td>
<td></td>
<td></td>
<td>0.00</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>55 (34)</td>
<td>22 (43)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>43 (26)</td>
<td>40 (53)</td>
<td></td>
</tr>
<tr>
<td>Cholestatic liver disease</td>
<td>66 (40)</td>
<td>13 (17)</td>
<td></td>
</tr>
</tbody>
</table>

SD: standard deviation.

| TABLE 2. Mean Scores of Patients With HBV, HCV, and Cholestatic Liver Disease on HRQoL, Depression, Anxiety, Self-Efficacy, and Maladaptive Coping |
|------------------------------------------------------------------------------------------------|-------------------|----------------------|-------------------|-------------------|-------------------|-------------------|
|                                                                                              | HBV (N=55)        | HCV (N=43)           | Cholestatic Liver Disease (N=66) |
| HRQoL                                                                                         | 0.77 (0.14)       | 0.66 (0.14)          | 0.75 (0.13)       |
| Depression                                                                                     | 11.68 (11.24)     | 18.87 (13.51)        | 10.00 (7.63)      |
| Anxiety                                                                                        | 40.94 (13.47)     | 45.80 (14.10)        | 38.57 (11.49)     |
| Self-Efficacy                                                                                  | 30.80 (6.24)      | 29.28 (7.06)         | 31.85 (5.65)      |
| Maladaptive Coping                                                                            | 1.75 (0.65)       | 1.83 (0.62)          | 1.58 (0.52)       |

Values are mean (standard deviation). HRQoL: health-related quality of life; HBV: hepatitis B virus; HCV: hepatitis C virus.

The hypothesized model showed good model fit (Figure 1: X² [1]=0.63; p=0.43; CFI=1.00; TLI=1.00; RMSEA=0.00; SRMR=0.00). The standardized regression weight that accompanies each arrow in the models represents the strength of the relationship between the variables. Statistically significant relationships (p<0.05) between variables are in bold. Depression had the strongest direct relationship with HRQoL (β=−0.68). Self-Efficacy was related to Depression (β=−0.50), as was Maladaptive

SF–36 by 154 patients (94%). The mean scores of patients with HBV, HCV, and cholestatic liver disease on HRQoL, Depression, Anxiety, Self-Efficacy, and Maladaptive Coping dimensions are presented in Table 2. Correlations between HRQoL, Depression, Anxiety, Self-Efficacy, and Maladaptive Coping are shown in Table 3. The mean reliability coefficients of the variables were the following: BDI–II, NL: α=0.94; STAI: α=0.33; Maladaptive Coping: α=0.83; HRQoL: α=0.81.

Structural Equation Modeling

The hypothesized model showed good model fit (Figure 1: X² [1]=0.63; p=0.43; CFI=1.00; TLI=1.00; RMSEA=0.00; SRMR=0.00). The standardized regression weight that accompanies each arrow in the models represents the strength of the relationship between the variables. Statistically significant relationships (p<0.05) between variables are in bold. Depression had the strongest direct relationship with HRQoL (β=−0.68). Self-Efficacy was related to Depression (β=−0.50), as was Maladaptive
Coping \((\beta=0.38)\). The model-testing was rerun including a variable representing Disease Severity (absence [value: 0] or presence of (de)compensated cirrhosis [value: 1]). Disease Severity had a modest but statistically nonsignificant relationship with HRQoL \((r=0.08; p=0.05)\). Subsequently, the model was tested for patients with cholestatic liver disease, HBV, and HCV separately by adding these as subgroups in the analysis. We fixed the relationships between Self-Efficacy and Depression, Self-Efficacy and Maladaptive Coping, Self-Efficacy and Anxiety, Anxiety and HRQoL, and Depression and HRQoL. Adequate model fit was maintained \((\chi^2 = 19.32; p=0.11; CFI=0.97; RMSEA=0.10; SRMR=0.11)\). The path coefficients in the model were similar for all three subgroups of patients except for the relationships between Maladaptive Coping and HRQoL (range of \(\beta\): −0.01 to 0.17), Maladaptive Coping and Depression (range of \(\beta\): −0.48 to 0.68), and Maladaptive Coping and Anxiety (range of \(\beta\): 0.23 to 0.42). Depression showed the strongest direct relationship with HRQoL \((\beta=−0.68)\) The final model (Figure 1) was compared with five competing models (Figure 2 [A] to [E]). Four of these had bad model fit (Table 4). However, one competing model (Figure 2, Model 2e) had adequate model fit \((\chi^2 = 32; p=0.57; CFI=1.0; TLI=1.01; RMSEA=0.00; SRMR=0.01)\) and is shown in more detail in Figure 3. This model was largely similar to the hypothesized model.\(^5\)^\(^6\) The difference lies herein: that the relationships between Maladaptive Coping and Depression and Anxiety were inversed.

### DISCUSSION

The main objective of this study was to test the hypothesis that various potentially-treatable psychological variables are related in a causal way to HRQoL in patients with chronic liver disease. The hypothesized model, tested for patients with HBV, HCV, and cholestatic liver disease, showed good model-fit, meaning that the a-priori hypothesized relationships between the variables are plausible: depression had a direct effect on HRQoL in all patients with chronic liver disease. Self-Efficacy and Maladaptive Coping had an indirect effect on HRQoL, through depression. Direct relationships between HRQoL and anxiety and coping were present in the model, but they were very weak, indicating a negligible direct contribution of these factors to HRQoL. Disease-severity was of modest influence on HRQoL while not significantly altering the proposed model. This is in line with previous research, which has also shown a relationship between disease-severity and HRQoL in this specific patient population.\(^4\) The model did not differ between patients with different diagnoses (HBV, HCV, or cholestatic liver disease). Path coefficients generally were similar, with depression showing the strongest relationship with HRQoL. Relationships of maladaptive coping with HRQoL, depression, and anxiety did differ. This suggests that Maladaptive Coping has a different influence on these variables for these subgroups of patients. This finding of an unclear role of coping in the model also emerges from the competing model. Further research is needed to explore these findings.

These findings are in accordance with previous studies using different patient populations, which showed direct re-
relationships between depression and HRQoL$^{24,33,34,61}$ and indirect relationships between HRQoL and negative/maladaptive coping and self-efficacy through depression.$^{33,34}$ This previous finding of a direct relationship between maladaptive coping and depression suggests that maladaptive coping affects depression, and not vice versa, as our alternative model proposed. A direct relationship between anxiety and HRQoL, which was found in one previous study in patients with coronary artery disease,$^{61}$ was not replicated in our study with CLD patients. The acute nature of a stroke or heart attack, as compared with the more chronic nature of liver failure, may explain this finding. The finding of a previous study of a direct effect of HRQoL on depression (instead of vice versa) in patients with psoriasis$^{62}$ was not tested in the current study, in which HRQoL was the outcome measure, and can therefore be neither confirmed nor rejected. The possibility of such a relationship existing in patients with CLD is one that needs further exploration in future studies.

A limitation of SEM, and, therefore, of the present study, is that not all models imaginable can be tested, since one has to choose which models to test, often on the basis of theory and/or clinical experience. As a result, the finding of a plausible model (with good model-fit) does not mean that no other models are plausible. Suggesting and testing several so-called “competing models” can rule out or identify other plausible models. In the current study, we tested several competing models and found that besides the hypothesized model, competing model 2E was plausible. Future studies should be conducted to determine which of these models provides the best fit to the data in other samples. A limitation of this cross-sectional study is that no conclusions can be drawn in terms of causality. In order to actually test causality, a study comparing several data-points should be conducted. Another limitation is the fact that only patients with CLD were included, which limits generalization of the results to other patient populations. However, the results of the present study are in accordance with previous studies with other patient populations, and therefore strengthen the hypothesis that depression is the most important determinant of HRQoL and that self-efficacy and maladaptive coping affect HRQoL through depression. Since depression scores of the patients in the study did not reflect clinical levels of depression, but rather depressive symptomatology, focusing treatment solely on depression seems unadvisable. Instead, the relationship between coping and depression should be observed. Improved HRQoL may be obtained by improving levels of coping and self-efficacy, which will, in turn, reduce levels of depression.

References
Quality of Life and Liver Disease

51. Carver CS: You want to measure coping but your protocol’s too long: consider The Brief Cope. Int J Behav Med 1997; 4:92–100