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Development of a Disease-Specific Questionnaire to Measure Health-Related Quality of Life in Liver Transplant Recipients

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Currently, no disease-targeted instrument is available for measuring health-related quality of life (HRQOL) in liver transplant recipients. We developed and tested a post-liver transplant quality of life (pLTQ) instrument. Item selection for the pLTQ instrument was based on responses from liver transplant recipients, 12 liver experts, and a literature search. Impact scores were generated, and a factor analysis was conducted to organize the items into domains. Questions were constructed for each item, and redundant questions were removed. The pLTQ instrument was initially administered to 196 liver transplant patients and then was again administered to 77 patients 6 to 9 months later with a generic HRQOL survey [Medical Outcomes Study Short Form 36 (SF-36)]. Analysis of variance was used to compare the scores of patients at different times since transplantation and with various indications for transplantation. After redundancies were eliminated, the pLTQ instrument included 32 items in 8 domains: Emotional Function, Worry, Medications, Physical Function, Healthcare, Graft Rejection Concern, Financial, and Pain. We found stable pLTQ instrument and SF-36 instrument scores over time. Data 6 to 9 months after the initial assessment indicated stable quality of life outcomes. The pLTQ instrument is applicable to a variety of liver transplant recipients. The questionnaire was tested with a cross-sectional and longitudinal approach. *Liver Transpl* 17:567-579, 2011. © 2011 AASLD.

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Orthotopic liver transplantation provides a definitive therapeutic measure for patients with end-stage liver disease.¹ In the last few decades, there have been incremental improvements in patient and graft survival.² Currently, the 5-year patient survival rate is approximately 70%, and the 10-year survival rate is 60%.³⁻⁵ As a result, there has been a shift from the acute management of liver transplant patients to a more long-term approach as life expectancy after liver transplantation continues to improve. With this shift to a long-term approach, there has been a greater focus on health-related quality of life (HRQOL), which

includes not only the physical well-being of patients but also their emotional and social well-being.

Quality of life is defined by the World Health Organization as "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns."⁶⁻⁸ The concept of HRQOL is a more focused assessment determining the quality of life by health parameters such as psychological functioning, social functioning, and physical functioning.⁷ Several generic HRQOL questionnaires have been developed, but they do not identify

Additional Supporting Information may be found in the online version of this article.

Abbreviations: ANOVA, analysis of variance; GRC, global rating of change; HRQOL, health-related quality of life; NASH, nonalcoholic steatohepatitis; pLTQ, post-liver transplant quality of life; SF-36, Short Form 36.

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disease-specific domains for specific medical states. Disease-specific questionnaires provide greater specificity and sensitivity for patients of that population.⁷⁻⁹ Moreover, questionnaires that have been developed to assess quality of life in patients with chronic liver diseases also fail to capture unique components of liver transplant recipients, such as rejection, disease recurrence, side effects of immunosuppression, cardiovascular and cerebrovascular disease, infection, and de novo malignancies.^{1,10,11}

Several studies have assessed the quality of life in liver transplant recipients and have identified important items such as fatigue, physical function, psychosocial stress, medical complications, cognitive function, employment status, and sexual dysfunction.^{3,12-22} Such studies have shown that the quality of life improves after liver transplantation; this is demonstrated by improvements in a patient's self-image, functioning ability, and perception of healthy status, and these factors continue to improve over time.²³⁻²⁵ However, no disease-targeted instrument has been available to measure HRQOL after liver transplantation specifically in these patients.^{26,27} Thus, we sought to develop a disease-specific HRQOL instrument for liver transplant recipients, that is, a post-liver transplant quality of life (pLTQ) instrument.

PATIENTS AND METHODS

Instrument Development Phase

We developed an instrument for measuring longitudinal changes over time in HRQOL for individuals who have undergone liver transplantation. Our aim was to construct an instrument able to assess both physical and mental health, reflect areas of function that have been identified to be important to post-liver transplant recipients, and track changes that are clinically important over a narrow time range. We sought (1) to develop an instrument capable of producing summary scores that can be statistically analyzed, (2) to provide evidence of the reliability and validity of the instrument, and (3) to develop a cost-effective and efficient questionnaire that is easy to administer, widely applicable, and relatively quick to complete with the least number of questions possible (Fig. 1).

Patients

We selected patients from the post-liver transplant hepatology outpatient practice at the Pflieger Liver Institute of the University of California Los Angeles Medical Center. Patients evaluated at the post-liver transplant clinic were asked to participate in the study. The patients were recruited over a course of 6 months. Patients were included if they were liver transplant recipients and were older than 18 years. Both English-speaking and Spanish-speaking patients were included in the study. The project was approved by the investigational review board of the University of California Los Angeles Medical Center. Informed consent in writing was obtained from each patient. Participation in the study was strictly voluntary, and participants were not compensated.

Item Selection

The initial development of the pLTQ instrument involved the collection of items that were thought to be relevant to post-liver transplant patients with respect to their functional status and sense of well-being. Liver transplant recipients were interviewed in focus group discussion sessions led by a moderator, and items most pertinent to these patients were collected through the focus groups. In addition, 12 liver transplant experts were surveyed with open-ended questionnaires on which they listed items that have a significant impact on the quality of life of post-liver transplant patients, and the importance of each item was ranked on a 5-point Likert scale, with 1 being the least important and 5 being the most important. On the basis of the patient data, expert opinion, and a literature review of quality of life of post-liver transplant recipients, an initial pLTQ instrument containing 121 items was developed.

Item Reduction

For the item reduction phase, 92 liver transplant recipients (a separate sample) were surveyed with open-ended questionnaires containing the 121 items selected in the previous phase of the study, and they were asked to identify which items were of particular concern to them and to rate their importance. The importance of each item that was of concern to the patient was then ranked on a 5-point Likert scale, with 1 being the least important and 5 being the most important.

Only items endorsed as concerns by more than 50% of the patients were then considered. Impact scores were generated for these items. Each impact score was the product of the proportion of patients identifying an item as a concern and the mean importance attributed to that item. The impact scores could range from 0 to 5.

Forty items were identified as concerns by more than 50% of the patients. We then conducted a factor analysis of these items to help categorize the items into various domains. Eigenvalue criteria and a scree plot were used to determine the numbers of factors to be considered. Items with an eigenvalue greater than 1 were identified. The rise of an eigenvalue correlated with the increasing proportion of variance explained by a factor, so a cutoff of 1 was used to identify factors for consideration. A scree plot was also used to decide the number of possible domains. The scree plot presented the eigenvalues of each factor in descending order and determined where there was a drop in the proportion of variance. Varimax rotation was used to separate the factors with the optimal balance of variance explained by each factor. In our case, the scree plot identified a model of 10 domains.

Questionnaire Construction and Pretesting

Appropriate questions were then constructed for each item identified after the item reduction phase, and the responses were based on how often the particular item was of concern to the patient in the past 4

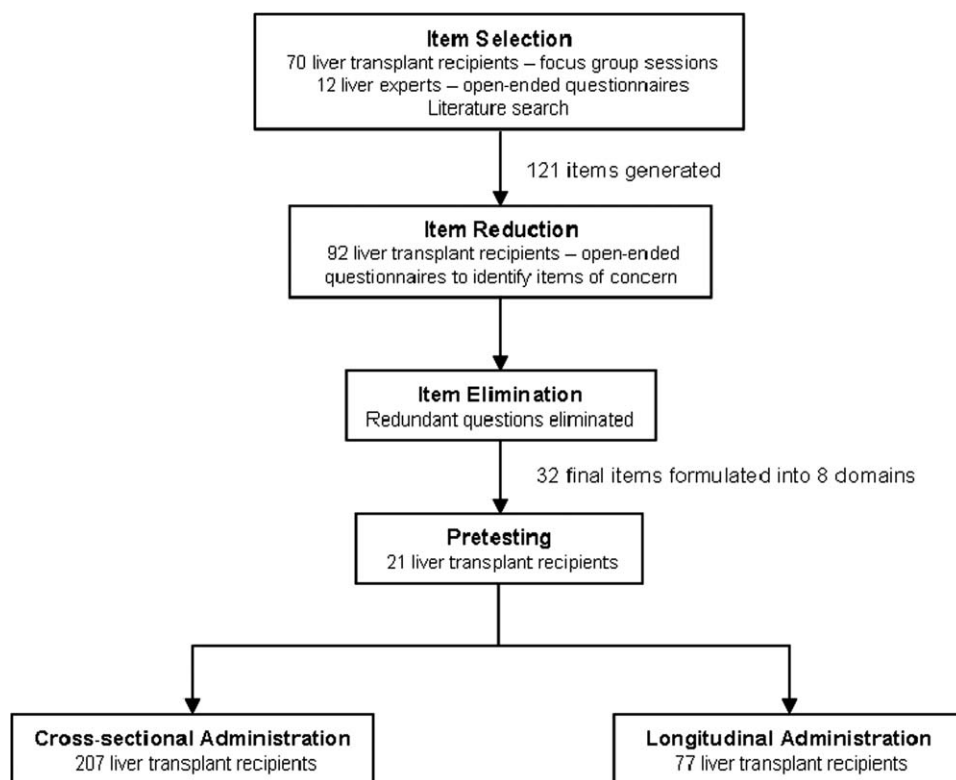


Figure 1. Development of the pLTQ instrument.

weeks. A 7-point Likert scale was designed for the responses, which ranged from being concerned all of the time (Likert value 1) to not being affected at all (Likert value 7). The 7-point Likert scale was chosen on the basis of previously developed questionnaires examining the quality of life in patients with chronic liver diseases. The number of question items was reduced from 40 to 32 to eliminate redundancies and reduce responder fatigue. Twenty-one patients completed the self-administered pLTQ instrument for pretesting, and they commented on questions that they found to be unnecessary or whose wording was unclear. Changes were then made to the questionnaire on the basis of the pretesting comments. A Spanish version of the instrument was then developed via the translation of the English instrument. Patients were also timed in taking the questionnaire.

Measures

Based on the item reduction and pretesting phase, the final pLTQ instrument consisted of 32 items. The 32 items were grouped into 8 domains, and each had a mean score ranging from 1 to 7 that was based on a Likert scale. A higher score indicated a better quality of life for each domain. The survey's reliability was tested by test-retest methods, and Cronbach's alpha statistic is provided as a measure of the internal reliability of the instrument. All 8 domains were found to have satisfactory internal reliability, and they are categorized as follows: (1) Emotional Function (4 items; Cronbach's

alpha = 0.78), (2) Worry (7 items; Cronbach's alpha = 0.85), (3) Medications (4 items; Cronbach's alpha = 0.70), (4) Physical Function (6 items; Cronbach's alpha = 0.79), (5) Healthcare (4 items; Cronbach's alpha = 0.66), (6) Graft Rejection Concern (2 items; Cronbach's alpha = 0.72), (7) Financial (2 items; Cronbach's alpha = 0.64), and (8) Pain (3 items; Cronbach's alpha = 0.60). In addition, the overall pLTQ instrument score across the 32 items had satisfactory internal reliability (Cronbach's alpha = 0.93).

The Medical Outcomes Study Short Form 36 (SF-36) instrument consisted of the following domains: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotion, and Mental Health.²⁸ In addition, the Mental Component Summary score and the Physical Component Summary score are reported.

In order to track whether patients remained clinically and physically stable or had changes in their status over this time between the initial pLTQ instrument completion and the completion of the instrument 6 to 9 months later, an additional global rating of change (GRC) questionnaire, a short 4-question survey, was created and administered. A 7-point scale was used for the responses for this 4-question survey; the scale was related to the patient's view of how his or her health had changed in the last 6 to 9 months and ranged from "much worse" (3) to "no change" (0) to "much better" (+3). Therefore, patients with an average score of -3 to -1 were noted to have an overall deterioration in their health status, patients with a

score of 0 experienced no change, and patients with an average score of +1 to +3 experienced an overall improvement in their health status over time.

Assessment of HRQOL With the pLTQ Instrument

Cross-Sectional Administration of the pLTQ Instrument

We administered the final 32-item pLTQ instrument and SF-36 to post-liver transplant patients with a wide variety of indications for transplantation and at various times since transplantation; demographic and clinical data were recorded at the time of questionnaire administration. The target sample size was 200; we hoped that recruiting patients with a wide variety of disease types at different times from transplantation would allow us to detect differences in a wide range of groups.

Longitudinal Administration of the pLTQ Instrument

The pLTQ and SF-36 instruments were once again administered to the patients 6 to 9 months after the original administration of the instruments. The GRC questionnaire, a short 4-question survey, was also administered at this time. Patients who did not return the questionnaire were called, and a repeat questionnaire was mailed to those who stated that they did not receive the first mailed questionnaire to improve the response rates.

Statistical Analysis

We compared the pLTQ instrument scores and SF-36 domains by the time since liver transplantation. The time since transplantation was categorized as follows: 1 to less than 6 months, 6 to 12 months, and greater than 12 months. Comparisons of the pLTQ instrument scores and SF-36 scores by the time since transplantation were conducted by analysis of variance (ANOVA). Similarly, we used ANOVA to compare pLTQ instrument scores by GRC scores. We also compared the pLTQ instrument scores and SF-36 scores by the hepatitis C status of patients. These comparisons were made with *t* test statistics. We report the *F* test statistic for ANOVA and the *t* test statistic for the *t* test. The ages were compared with the *t* test. Demographic proportions were compared with Fisher's exact test. *P* values less than 0.05 are considered to be statistically significant. All analyses were conducted with SAS 9.2 (SAS, Inc., Cary, NC).

RESULTS

Instrument Development Phase

Item Selection

We interviewed 70 liver transplant recipients for the initial item selection phase; 44% were female. The

mean age of the patients was 53.8 ± 11.5 years. Twenty-nine of the patients had hepatitis C, 8 had hepatitis B, 9 had alcoholic cirrhosis, 14 had hepatocellular carcinoma, 9 had cryptogenic cirrhosis or nonalcoholic steatohepatitis (NASH), 3 had primary biliary cirrhosis, 4 had primary sclerosing cholangitis, 5 had fulminant hepatic failure, and 4 had other types of liver disease. Fifteen patients had more than one indication for transplantation (eg, both hepatitis C and hepatocellular carcinoma). In addition, 12 liver experts, who included liver transplant surgeons, transplant coordinators, and hepatologists, were surveyed with open-ended questionnaires on which they listed items that have a significant impact on the quality of life of post-liver transplant recipients. Initially, 121 items were identified.

Patients for Item Reduction

For the item reduction phase, 92 post-liver transplant patients (a separate sample) were surveyed with open-ended questionnaires containing the 121 items from the initial pLTQ instrument. Of the 92 patients surveyed, 48% were female. The mean age of the patients was 52.5 ± 13.0 years. Thirty-six of the patients had hepatitis C, 12 had hepatitis B, 13 had alcoholic cirrhosis, 20 had hepatocellular carcinoma, 11 had cryptogenic cirrhosis or NASH, 3 had primary biliary cirrhosis, 4 had primary sclerosing cholangitis, 7 had fulminant hepatic failure, and 10 had other types of liver disease. Twenty-three recipients had more than one indication for transplantation (eg, both hepatitis C and hepatocellular carcinoma).

Item Reduction and Factor Analysis

Forty items were identified as concerns by more than 50% of the patients. Principal component analysis and a scree plot suggested a 10-factor model. A factor analysis was performed, and each item was assigned to 1 of the 10 factors (Table 1). Redundant questions were eliminated, and the final questionnaire was formulated with 32 items. Eight final domains were identified for the 32 items after the redundant items were eliminated.

Pretesting of the Questionnaire

The 32-item questionnaire was pretested with 21 patients. These patients were also timed and took 8 minutes on average to complete the questionnaire. Thirteen of the 21 timed patients completed the English questionnaire, and 8 patients completed the Spanish questionnaire; on average, 6.6 minutes was needed to complete the English version of the questionnaire, and 10.3 minutes was needed for the Spanish version of the questionnaire. The pLTQ instrument is summarized in the supporting information.

TABLE 1. pLTQ Item Impact Scores and Factor Loadings

pLTQ Item	Proportion With Concern	Importance	Impact	Factor Loading
Factor 1				
Q83. Memory loss	0.64	3.03	1.95	0.67
Q84. Depression	0.54	3.34	1.82	0.75
Q85. Getting upset easily	0.51	3.57	1.83	0.80
Q86. Mood swings	0.51	3.19	1.63	0.79
Q87. Increased worry	0.53	3.55	1.89	0.62
Q89. Anxiety	0.52	3.52	1.84	0.73
Factor 2				
Q12. Instructions for medication	0.53	4.14	2.19	0.55
Q14. Multiple doctor visits	0.54	3.72	2.00	0.80
Q15. Multiple blood draws	0.54	3.74	2.03	0.78
Q18. Need to clarify everything with doctor	0.51	3.66	1.87	0.68
Q67. Having to take too many medications	0.62	3.67	2.27	0.43
Factor 3				
Q26. Limitations in activities	0.70	3.67	2.58	0.57
Q51. Decreased energy	0.72	3.83	2.75	0.79
Q54. Loss in strength	0.77	3.72	2.87	0.80
Q93. Change in sleep patterns	0.67	3.56	2.40	0.60
Q99. Being dependent on others	0.66	3.70	2.46	0.52
Factor 4				
Q7. Length of recovery	0.73	4.04	2.93	0.54
Q36. Fear of recurrent disease	0.61	3.96	2.41	0.63
Q38. Unaware underlying disease may remain	0.57	3.94	2.23	0.79
Q120. Question lifespan	0.55	4.17	2.31	0.35
Factor 5				
Q68. Cost of medications	0.63	3.95	2.49	0.77
Q116. Many bills	0.60	4.12	2.48	0.83
Q117. Trouble with billing	0.51	3.90	2.00	0.73
Factor 6				
Q6. Joint/back pain	0.54	3.72	2.00	0.51
Q27. Learning to walk after surgery	0.64	3.74	2.38	0.57
Q28. Decreased physical activity	0.75	3.57	2.67	0.64
Q29. Ability to drive	0.60	3.65	2.19	0.64
Q98. Family members worry about illness	0.73	3.84	2.79	0.48
Q100. Being burden on family members	0.63	3.78	2.38	0.38
Factor 7				
Q34. Taking better care of health	0.66	4.00	2.65	0.73
Q111. New appreciation for life	0.63	4.17	2.63	0.71
Factor 8				
Q35. Fear of rejection	0.75	4.10	3.08	0.65
Q37. Worry about infection due to immunosuppression	0.78	3.75	2.93	0.53
Q82. Fear complications if forgot to take medicine	0.57	4.10	2.32	0.62
Q112. Difficulty returning to work	0.52	3.88	2.04	0.71
Factor 9				
Q3. Postoperative pain	0.67	3.47	2.34	0.54
Q4. Recurring abdominal pain	0.52	3.54	1.85	0.71
Q71. Side effects	0.64	3.56	2.28	0.57
Factor 10				
Q16. Long waits for appointments	0.59	3.57	2.10	0.48
Q61. Numbness/tingling	0.51	2.98	1.52	0.76

NOTE: The proportions of variance were as follows: factor 1, 0.2988; factor 2, 0.0852; factor 3, 0.0490; factor 4, 0.0477; factor 5, 0.0452; factor 6, 0.0426; factor 7, 0.0372; factor 8, 0.0312; factor 9, 0.0303; and factor 10, 0.0256.

TABLE 2. Demographic Characteristics of the Primary and Follow-Up Cohorts of Liver Transplant Recipients

Characteristic	Initial Cohort	Follow-Up Cohort		P Value*
		Responders	Nonresponders	
Total patients (n)	196	77	119	
Age (years)*	53.1 ± 12.6	55.6 ± 11.7	51.8 ± 13.1	0.134
Gender: male/female (n/n)	117/79	49/28	68/51	0.584
Time since transplantation at initial survey [n (%)]				
0 to <6 months	57 (29.1)	22 (28.6)	35 (29.4)	0.710
6 to 12 months	22 (11.2)	14 (18.2)	8 (6.7)	0.163
>12 months	117 (59.7)	41 (53.2)	76 (63.9)	0.343
Indication for transplantation [n (%)]				
Hepatitis C	79 (40.3)	29 (37.6)	50 (42.0)	0.552
Hepatitis B	29 (14.8)	15 (19.5)	14 (11.8)	0.153
Hepatocellular carcinoma	51 (26)	22 (28.5)	29 (24.4)	0.511
Alcoholic cirrhosis	28 (14.3)	13 (16.8)	15 (12.6)	0.411
Cryptogenic cirrhosis and NASH	25 (12.8)	12 (15.6)	11 (9)	0.081
Primary sclerosing cholangitis or primary biliary sclerosis	17 (8.7)	10 (13)	7 (5.9)	0.118
Fulminant hepatic failure	13 (6.6)	2 (2.6)	11 (9.2)	0.082
Other	19 (9.69)	5 (6.5)	14 (11.8)	0.323
More than 1 indication [†]	59 (30.1)	32 (41.6)	27 (22.7)	0.007

*Patient ages are presented as means and standard deviations.

[†]For example, some patients had both hepatitis C and hepatocellular carcinoma.

Assessment of HRQOL With the pLTQ Instrument

Cross-Sectional Administration of the pLTQ Instrument

Of the 196 post-liver transplant patients who completed the pLTQ instrument in the next phase of the study, 40.3% were women, and the mean age was 53.1 ± 12.6 years. In all, 209 surveys were administered, but data from 13 patients were not included because of incomplete questionnaires. Of these patients, 79 had hepatitis C, 29 patients had hepatitis B, 51 had hepatocellular carcinoma, 28 had alcoholic cirrhosis, 25 had cryptogenic cirrhosis or NASH, 17 had primary sclerosing cholangitis or primary biliary sclerosis, 13 had fulminant hepatic failure, and 19 had other causes of liver failure requiring transplantation. Notably, there were 59 patients with more than 1 diagnosis for transplantation (eg, both hepatitis C and hepatocellular carcinoma; Table 2).

The 196 patients completing this phase of the study were also divided according to the time since liver transplantation: 0 to 90 days for 29 patients (14.8%), 91 to 180 days for 28 patients (14.3%), 181 days to less than 1 year for 22 patients (11.2%), 1 to less than 2 years for 25 patients (12.8%), 2 to less than 5 years for 36 patients (18.4%), 5 to less than 10 years for 26 patients (13.2%), and more than 10 years for 30 patients (15.3%).

The patients were stratified according to 3 time points since transplantation: 1 to 6 months, 6 to 12 months, and greater than 12 months (Table 3). In general, the overall pLTQ instrument score corresponds to the time since transplantation. Among all patients, we

observed an overall improvement across time in the pLTQ instrument Physical Function ($F = 4.39$, $P = 0.014$) and Healthcare domains ($F = 5.25$, $P = 0.006$). When the pLTQ instrument scores were stratified according to the indication for transplantation, we observed that the overall pLTQ instrument score for patients with hepatitis C at the time of transplantation was lower than the score for patients with other causes of liver transplantation. We observed a similar gradient across each of the 8 domains. In fact, when we examined the pLTQ instrument domains across time among patients without hepatitis C, we found a significant improvement in overall pLTQ instrument scores ($F = 3.23$, $P = 0.043$) and in the Physical Function ($F = 5.84$, $P = 0.004$), Healthcare ($F = 5.41$, $P = 0.006$), and Pain domains ($F = 3.80$, $P = 0.025$). However, this improvement was not seen in patients with hepatitis C.

The patients were also asked to complete the SF-36 along with the pLTQ instrument (Table 4). For analysis, the results were stratified into 3 time points since liver transplantation: 1 to less than 6 months, 6 to 12 months, and greater than 12 months. Among all patients, we observed significant improvements over time in the Physical Functioning ($F = 10.47$, $P < 0.001$), Role-Physical ($F = 19.72$, $P < 0.001$), and General Health domains ($F = 3.08$, $P = 0.048$) and in the Physical Component Summary score ($F = 10.87$, $P < 0.001$). When the results were stratified according to the indication for transplantation, patients without hepatitis C were noted to have improvements in the Physical Functioning ($F = 12.59$, $P < 0.001$) and Role-Physical domains ($F = 11.60$, $P < 0.001$) and in the Physical Component Summary score ($F = 8.95$, $P = 0.003$). However, in patients with hepatitis C, an improvement was noted only in the Role-Physical domain ($F = 7.62$, $P = 0.001$) over time.

TABLE 3. pLTQ Scores Compared by the Time Since Transplantation and Stratified by the Hepatitis C Status (n = 196)

pLTQ Domain	All Patients (n = 196)			Non-Hepatitis C Patients (n = 116)			Hepatitis C Patients (n = 80)					
	Mean	1-<6 Months (n = 57)	6-12 Months (n = 22)	1-<6 Months (n = 117)	6-12 Months (n = 14)	6-12 Months (n = 31)	1-<6 Months (n = 71)	6-12 Months (n = 26)	6-12 Months (n = 8)	> 12 Months (n = 46)	P Value	
				P Value			P Value					
Overall	5.09 (1.00)	4.89 (1.00)	5.05 (1.00)	0.144	4.75 (1.05)	5.25 (1.04)	5.30 (1.00)	0.043	5.04 (0.93)	4.71 (0.88)	5.05 (0.97)	0.645
pLTQ												
Emotional Function	4.90 (1.30)	5.06 (1.39)	4.67 (1.09)	0.453	5.05 (1.61)	4.88 (1.22)	4.96 (1.35)	0.928	5.06 (1.10)	4.31 (0.75)	4.70 (1.18)	0.197
Worry	4.84 (1.30)	4.62 (1.33)	4.63 (1.32)	0.156	4.44 (1.44)	4.91 (1.37)	5.11 (1.24)	0.064	4.83 (1.17)	4.15 (1.15)	4.79 (1.31)	0.371
Medications	5.49 (1.20)	5.38 (1.05)	5.51 (1.29)	0.701	5.42 (1.10)	5.86 (1.01)	5.58 (1.28)	0.526	5.34 (1.00)	4.91 (1.56)	5.48 (1.23)	0.446
Physical Function	5.15 (1.26)	4.75 (1.21)	5.14 (1.17)	0.014	4.62 (1.25)	5.22 (1.28)	5.56 (1.28)	0.004	4.89 (1.18)	5.00 (1.02)	5.01 (1.18)	0.925
Healthcare Graft	5.44 (1.12)	5.04 (1.05)	5.66 (1.03)	0.006	4.94 (1.03)	5.93 (0.97)	5.63 (1.16)	0.006	5.16 (1.08)	5.19 (1.02)	5.52 (1.07)	0.345
Rejection Concern	4.95 (1.56)	4.88 (1.68)	4.69 (1.43)	0.580	4.50 (1.63)	4.75 (1.58)	4.85 (1.63)	0.603	5.33 (1.64)	4.57 (1.17)	5.34 (1.32)	0.404
Financial Pain	5.11 (1.61)	5.06 (1.60)	5.30 (1.31)	0.837	4.79 (1.44)	5.46 (1.35)	5.05 (1.64)	0.402	5.38 (1.74)	5.00 (1.25)	5.12 (1.75)	0.801
	4.93 (1.39)	4.62 (1.46)	5.06 (1.48)	0.135	4.46 (1.47)	5.02 (1.66)	5.27 (1.23)	0.025	4.81 (1.46)	5.13 (1.19)	4.73 (1.42)	0.768

NOTE: The pLTQ domains were scored on a scale of 1 to 7. The data are presented as means (with standard deviations in parentheses).

TABLE 4. SF-36 Scores Compared by the Time Since Transplantation and Stratified by the Hepatitis C Status (n = 190)

SF-36 Domain	All Patients (n = 190)			Non-Hepatitis C Patients (n = 111)			Hepatitis C Patients (n = 79)					
	Mean	1-<6 Months (n = 56)	6-12 Months (n = 21)	1-<6 Months (n = 113)	6-12 Months (n = 13)	6-12 Months (n = 30)	1-<6 Months (n = 68)	6-12 Months (n = 26)	6-12 Months (n = 8)	> 12 Months (n = 45)	P Value	
				P Value			P Value					
Physical Functioning	54.48 (29.9)	41.25 (26.8)	49.32 (20.0)	62.18 (30.6)	<0.001	36.33 (27.4)	50.71 (17.2)	66.14 (28.9)	<0.001	46.92 (25.3)	56.14 (32.4)	0.397
Role-Physical	41.07 (41.9)	16.52 (26.2)	31.82 (41.0)	55.17 (42.6)	<0.001	18.33 (26.2)	33.93 (45.6)	58.71 (42.5)	<0.001	14.42 (26.6)	28.13 (33.9)	0.001
Bodily Pain	59.22 (25.8)	53.75 (25.2)	60.10 (25.8)	61.77 (25.9)	0.162	55.17 (23.8)	63.85 (27.2)	63.60 (24.9)	0.285	52.12 (27.0)	54.00 (23.8)	0.570
General Health	57.43 (22.0)	62.81 (21.3)	49.89 (20.8)	56.01 (22.2)	0.048	61.40 (20.9)	49.36 (25.2)	57.09 (20.9)	0.273	64.43 (21.9)	50.63 (14.5)	0.142
Vitality	48.02 (22.0)	47.94 (22.1)	42.92 (16.6)	48.94 (22.8)	0.529	45.23 (22.5)	45.28 (15.1)	51.18 (22.3)	0.386	50.96 (21.7)	39.38 (19.2)	0.388
Social Functioning	65.28 (28.1)	59.82 (27.9)	66.67 (24.5)	67.71 (28.7)	0.222	58.33 (27.1)	69.23 (27.3)	71.38 (29.4)	0.116	61.54 (29.1)	62.50 (20.0)	0.995
Role-Emotion	65.44 (41.9)	58.93 (41.7)	69.70 (42.3)	67.85 (42.0)	0.380	58.89 (42.6)	73.81 (41.7)	69.61 (41.0)	0.413	58.98 (41.4)	62.50 (45.2)	0.844
Mental Health	68.61 (21.3)	69.79 (21.2)	71.05 (16.3)	67.60 (22.3)	0.711	68.80 (22.2)	73.75 (19.1)	69.56 (22.4)	0.797	70.92 (20.3)	67.00 (10.6)	0.463
Mental Component	47.67 (11.8)	48.80 (12.4)	49.17 (9.8)	46.81 (11.9)	0.511	48.20 (11.6)	50.60 (11.2)	47.71 (12.1)	0.757	49.46 (13.4)	47.21 (7.5)	0.415
Summary score	37.72 (11.3)	33.08 (9.3)	33.87 (9.9)	40.85 (11.5)	<0.001	32.53 (9.3)	33.95 (10.9)	41.93 (11.0)	0.003	33.70 (9.4)	33.77 (9.2)	0.101
Physical Component												
Summary score												

NOTE: The data are presented as means (with standard deviations in parentheses).

Longitudinal Administration of the pLTQ and SF-36 Instruments

The 196 patients who completed the pLTQ instrument in the previous phase were all mailed the pLTQ instrument to complete again within 6 to 9 months of completing the initial questionnaire. Of the 196 patients, 77 patients (39.3%) returned the questionnaire. On follow-up, 8 of the initially recruited patients (4.08%) died before requestioning. There were no statistical differences between the 77 people who returned the survey and those patients who did not return the survey (Table 2). Of the 77 patients completing the pLTQ instrument in this phase of the study, 28 patients (36.4%) were female, and the mean age of the patients was 55.6 ± 11.7 years. Of these patients, 29 had hepatitis C, 15 had hepatitis B, 22 had hepatocellular carcinoma, 13 had alcoholic cirrhosis, 14 had cryptogenic cirrhosis or NASH, 10 had primary sclerosing cholangitis or primary biliary sclerosis, 2 had fulminant hepatic failure, and 5 had other causes of liver failure requiring transplantation. Notably, there were 32 patients with more than 1 diagnosis for transplantation (eg, both hepatitis C and hepatocellular carcinoma).

The patients completing this phase of the study were also divided according to the time since liver transplantation and according to the time since the initial completion of the first pLTQ instrument in the previous phase of the study. Among the 77 patients, 7 patients (9%) were 0 to 90 days from transplantation, 15 patients (19.5%) were 91 to 180 days from transplantation, 14 patients (18.2%) were 181 days to 12 months from transplantation, 7 patients (9%) were 1 to less than 2 years from transplantation, 15 patients (19.5%) were 2 to less than 5 years from transplantation, 8 patients (10.4%) were 5 to less than 10 years from transplantation, and 11 patients (14.3%) were more than 10 years from liver transplantation.

For validation of the pLTQ instrument and SF-36 scores, the data were stratified by the hepatitis C status (Table 5). Among the 77 who completed the follow-up assessment, 72 patients had complete baseline and follow-up data. Across all patients who completed both assessments, we observed that patients remained physically and clinically stable over time; this was reflected in both pLTQ instrument and SF-36 scores. We observed a significant improvement in the SF-36 Physical Functioning domain after 6 to 9 months ($t = 2.18$, $P = 0.031$). Among patients without hepatitis C, we observed a significant improvement in the pLTQ instrument Healthcare domain ($t = 2.33$, $P = 0.022$) and the SF-36 Physical Functioning domain ($t = 2.27$, $P = 0.026$).

To further determine whether the pLTQ instrument scores and SF-36 scores remained stable over time, we examined the pLTQ instrument and SF-36 associations with the GRC scores, which were categorized as follows: got worse, no change, or improved (Table 6). We observed a general improvement in the pLTQ instrument and SF-36 scores across GRC scores.

Among all patients, we observed a significant positive association between the GRC score and the SF-36 General Health domain score ($F = 6.34$, $P = 0.003$), Vitality domain score ($F = 4.85$, $P = 0.011$), and the Physical Component Summary score ($F = 4.36$, $P = 0.017$). Among patients without hepatitis C, we observed a significant positive association between the GRC score and the SF-36 Role-Emotion domain ($F = 4.13$, $P = 0.023$). Among patients with hepatitis C, we observed a significant positive association between the GRC score and the SF-36 Role-Physical ($F = 4.20$, $P = 0.027$), General Health ($F = 6.14$, $P = 0.007$), and Vitality domains ($F = 5.82$, $P = 0.009$) and the Physical Component Summary score ($F = 4.24$, $P = 0.027$).

DISCUSSION

Using a framework previously used for the development of other disease-specific HRQOL instruments, we have developed the first disease-targeted HRQOL instrument for patients who have undergone liver transplantation: the pLTQ instrument.²⁹⁻³¹ Previously, the absence of a disease-specific instrument for assessing HRQOL in this specific patient population has been a significant drawback for adequately assessing the quality of life after liver transplantation. Although the SF-36 has become the most frequently used HRQOL instrument, it has many disadvantages, such as the lack of assessment of cognitive function and the lack of validation of changes in patient responses over time.³²

Additionally, there are concerns specific to the post-liver transplant population that may affect patients' quality of life and simply cannot be addressed in a generic quality of life instrument, such as adverse effects of immunosuppressive medications, rejection, and the ability to pay for follow-up care. In our study, a wide variety of sources, including patients with a variety of indications for liver transplantation and a panel of liver experts, were used to develop the initial items to ensure that the most pertinent items were captured. The use of factor analysis allowed categorization of the different items into appropriate domains representing specific components of HRQOL pertaining to post-liver transplant patients. The pLTQ instrument is unique because there are several domains in our study designed to be specific to our population that are not measured in the SF-36 or other generic questionnaires, such as the Worry, Medications, Healthcare, and Financial domains. The rest of the domains in the instrument were designed to be comparable to the SF-36 domains for purposes of cross-comparison and validation, although the questions within each domain were intended to be specific to liver transplant recipients. The pretesting found that the pLTQ instrument is clear, is easy to administer, and can be completed fairly quickly. Our instrument is able to capture factors specific to liver transplant recipients that are generally not addressed by general questionnaires.

TABLE 5. Validation Data for the pLTQ and SF-36 Scores Stratified According to the Hepatitis C Status (n = 72)

Domain	All Patients (n = 72)			Non-Hepatitis C Patients (n = 45)			Hepatitis C Patients (n = 27)		
	Baseline	6-9 Months	P Value	Baseline	6-9 Months	P Value	Baseline	6-9 Months	P Value
pLTQ									
Overall pLTQ	5.35 (1.0)	5.50 (1.0)	0.352	5.41 (0.9)	5.66 (0.8)	0.158	5.27 (1.1)	5.24 (1.2)	0.931
Emotional Function	5.22 (1.2)	5.31 (1.2)	0.666	5.23 (1.3)	5.48 (1.1)	0.325	5.23 (1.1)	5.04 (1.2)	0.545
Worry	5.09 (1.2)	5.26 (1.3)	0.412	5.25 (1.2)	5.41 (1.1)	0.498	4.83 (1.3)	5.01 (1.5)	0.631
Medications	5.75 (1.1)	5.86 (1.1)	0.544	5.79 (1.0)	5.96 (0.9)	0.406	5.68 (1.3)	5.69 (1.4)	0.959
Physical Function	5.31 (1.2)	5.68 (1.1)	0.062	5.43 (1.2)	5.86 (0.9)	0.054	5.11 (1.4)	5.37 (1.3)	0.474
Healthcare	5.80 (1.0)	6.07 (1.0)	0.103	5.86 (0.9)	6.29 (0.8)	0.022	5.69 (1.1)	5.69 (1.2)	0.976
Graft Rejection Concern	5.07 (1.6)	5.17 (1.4)	0.692	4.89 (1.6)	5.21 (1.5)	0.323	5.37 (1.6)	5.09 (1.4)	0.507
Financial	5.44 (1.4)	5.15 (1.6)	0.252	5.53 (1.2)	5.38 (1.4)	0.574	5.30 (1.7)	4.78 (1.9)	0.299
Pain	5.19 (1.4)	5.22 (1.2)	0.491	5.10 (1.4)	5.36 (1.1)	0.340	5.32 (1.2)	4.98 (1.4)	0.338
SF-36									
Physical Functioning	57.25 (27.7)	66.90 (24.8)	0.031	58.49 (26.6)	70.11 (21.2)	0.026	55.19 (29.7)	61.35 (29.7)	0.458
Role-Physical	46.38 (44.0)	55.28 (41.8)	0.222	45.93 (45.0)	56.11 (39.9)	0.264	47.11 (43.2)	53.85 (45.7)	0.588
Bodily Pain	63.94 (26.3)	64.81 (25.1)	0.841	64.91 (24.6)	64.59 (22.9)	0.950	62.27 (29.4)	65.19 (28.8)	0.719
General Health	59.21 (20.9)	60.96 (22.5)	0.638	58.90 (21.6)	60.49 (21.5)	0.730	59.73 (20.3)	61.83 (24.8)	0.743
Vitality	48.38 (21.6)	52.10 (21.4)	0.309	49.70 (22.0)	53.41 (20.5)	0.416	46.15 (21.2)	49.80 (23.0)	0.558
Social Functioning	70.07 (25.5)	74.65 (21.6)	0.251	73.61 (25.0)	77.22 (20.7)	0.456	63.94 (25.6)	70.19 (22.9)	0.358
Role-Emotion	71.50 (39.3)	80.28 (35.0)	0.165	73.64 (37.5)	84.44 (30.7)	0.142	67.95 (42.7)	73.08 (41.1)	0.661
Mental Health	73.01 (18.4)	75.53 (18.5)	0.421	74.16 (18.8)	78.4 (16.1)	0.263	71.08 (17.7)	70.56 (21.7)	0.926
Mental Component	49.60 (10.6)	51.16 (9.9)	0.377	50.60 (10.6)	52.79 (8.7)	0.300	48.02 (10.5)	48.17 (11.3)	0.961
Summary score									
Physical Component	38.75 (11.7)	41.67 (11.1)	0.139	38.72 (11.3)	41.45 (10.1)	0.244	38.78 (12.4)	42.07 (13.0)	0.367
Summary score									

NOTE: The pLTQ domains were scored on a scale of 1 to 7. The data are presented as means (with standard deviations in parentheses).

TABLE 6. Follow-Up GRC for the pLTQ and SF-36 Scores Stratified According to the Hepatitis C Status (n = 72)

Domain	All Patients (n = 72)				Non-Hepatitis C Patients (n = 45)				Hepatitis C Patients (n = 27)			
	Got Worse	No Change	Improved	P Value	Got Worse	No Change	Improved	P Value	Got Worse	No Change	Improved	P Value
pLTQ												
Overall pLTQ	5.45 (0.9)	5.31 (1.2)	5.53 (0.9)	0.784	5.51 (1.0)	5.58 (1.1)	5.64 (0.6)	0.912	5.37 (0.9)	4.50 (1.4)	5.35 (1.2)	0.478
Emotional Function	5.05 (1.0)	5.44 (1.3)	5.30 (1.2)	0.708	5.10 (1.3)	5.48 (1.5)	5.58 (1.1)	0.635	5.00 (0.7)	5.33 (1.0)	4.93 (1.4)	0.876
Worry	5.12 (0.9)	4.88 (1.7)	5.34 (13.2)	0.482	5.27 (1.1)	5.35 (1.3)	5.42 (1.1)	0.946	4.95 (0.8)	3.48 (2.2)	5.25 (1.3)	0.124
Medications	6.22 (1.1)	5.83 (1.1)	5.72 (1.1)	0.363	6.11 (1.2)	5.78 (1.3)	5.83 (0.8)	0.774	6.36 (1.1)	6.00 (0.5)	5.56 (1.5)	0.436
Physical Function	5.45 (1.0)	5.51 (1.3)	5.75 (1.1)	0.612	5.71 (1.0)	5.88 (1.0)	5.86 (0.9)	0.922	5.14 (1.1)	4.39 (1.7)	5.59 (1.3)	0.288
Healthcare	5.87 (1.3)	6.04 (1.2)	6.15 (0.9)	0.669	5.93 (1.4)	6.25 (0.9)	6.40 (0.6)	0.408	5.79 (1.2)	5.42 (1.9)	5.81 (1.1)	0.871
Graft Rejection Concern	5.42 (1.2)	4.71 (1.5)	5.11 (1.5)	0.470	5.00 (1.3)	4.78 (1.8)	5.17 (1.5)	0.801	5.92 (0.9)	4.50 (0.9)	5.03 (1.5)	0.265
Financial	5.62 (1.2)	4.46 (2.1)	5.11 (1.6)	0.214	5.29 (1.2)	4.94 (1.8)	5.28 (1.4)	0.834	6.00 (1.1)	3.00 (2.6)	4.88 (1.8)	0.079
Pain	5.15 (1.2)	5.17 (1.6)	5.21 (1.2)	0.989	5.38 (1.0)	5.56 (1.3)	5.19 (1.0)	0.666	4.89 (1.5)	4.00 (2.1)	5.23 (1.3)	0.381
SF-36												
Physical Functioning	56.54 (29.1)	63.93 (20.8)	69.35 (24.2)	0.248	60.00 (28.7)	65.80 (19.4)	71.85 (20.6)	0.408	52.50 (31.7)	58.33 (28.4)	65.80 (28.8)	0.615
Role-Physical	36.54 (46.3)	43.75 (46.6)	62.50 (36.8)	0.080	57.14 (53.5)	47.22 (45.8)	60.19 (32.7)	0.695	12.50 (20.9)	33.33 (57.7)	65.79 (42.7)	0.027
Bodily Pain	54.08 (23.9)	55.50 (32.7)	68.51 (21.2)	0.077	56.57 (23.8)	59.89 (32.2)	64.38 (18.1)	0.683	51.17 (26.0)	42.33 (37.3)	74.16 (24.2)	0.058
General Health	46.08 (16.5)	50.86 (28.4)	66.96 (20.2)	0.003	50.00 (17.4)	55.28 (26.8)	65.12 (19.6)	0.176	41.50 (15.5)	31.00 (36.8)	69.72 (21.2)	0.007
Vitality	36.92 (19.6)	54.58 (29.3)	57.39 (18.5)	0.011	44.29 (20.5)	61.11 (30.2)	57.12 (17.1)	0.259	28.33 (16.0)	35.00 (18.0)	57.78 (20.9)	0.009
Social Functioning	66.35 (26.7)	68.75 (24.7)	77.99 (18.9)	0.146	73.2 (22.1)	69.44 (21.8)	80.09 (20.0)	0.371	58.33 (31.3)	66.67 (38.2)	75.0 (17.2)	0.303
Role-Emotion	79.49 (32.0)	61.11 (48.9)	83.33 (32.8)	0.167	85.71 (26.2)	59.26 (49.4)	91.36 (19.8)	0.023	72.23 (39.0)	66.67 (57.7)	71.93 (43.4)	0.980
Mental Health	72.31 (17.2)	73.00 (21.5)	77.54 (18.9)	0.591	76.57 (16.1)	72.89 (24.1)	82.31 (13.1)	0.304	67.33 (18.7)	73.33 (15.1)	70.67 (23.8)	0.920
Mental Component Summary score	49.81 (9.7)	48.05 (13.6)	52.49 (9.8)	0.392	52.20 (7.7)	48.78 (14.7)	55.31 (6.2)	0.163	47.03 (11.7)	44.78 (10.2)	48.42 (12.5)	0.909
Physical Component Summary score	34.20 (11.9)	39.84 (11.3)	43.72 (9.7)	0.017	36.99 (13.1)	40.37 (10.9)	42.67 (8.6)	0.470	30.93 (10.4)	37.45 (18.0)	45.97 (10.9)	0.027

NOTE: The pLTQ domains were scored on a scale of 1 to 7. The data are presented as means (with standard deviations in parentheses).

We administered the pLTQ instrument to a fairly large cohort of patients with a variety of indications for liver transplantation, and we captured the patients at a variety of time points since liver transplantation. Our data demonstrate that the patients' overall HRQOL and their HRQOL in various domains improved with time after transplantation. This is consistent with previous studies using the SF-36: both mental and physical components of life improved within 1 month after transplantation, and there was continued improvement 3 and 6 months after liver transplantation. Such changes in the SF-36 scores were also reflected by our cohort of patients over time.^{33,34}

In our study, we were able to show that patients with hepatitis C as an indication for liver transplantation had lower pLTQ instrument scores in comparison with patients who underwent liver transplantation for causes other than hepatitis C. We also noted that the pLTQ instrument scores generally did not improve over time as significantly as they did for patients with other indications for transplantation. This is consistent with findings from multiple studies looking at SF-36 HRQOL scores after liver transplantation for hepatitis C patients: lower scores were noted in comparison with scores for those undergoing transplantation for causes not related to hepatitis C. Scores were prominently lower for the Bodily Pain and Social Functioning domains. Both the physical and mental components of the SF-36 scores were also lower. This may have been due to the psychological stress of being concerned with disease recurrence and the sequelae associated with disease recurrence and progression.^{8,16,35-41}

Our validation data, which were obtained 6 to 9 months after the administration of the initial pLTQ and SF-36 instruments, indicated stable scores over time. In fact, we found significant improvements in several pLTQ instrument and SF-36 domains 6 to 9 months after the initial assessment. We were also able to demonstrate positive associations between the GRC scores and the pLTQ instrument scores and SF-36 scores 6 to 9 months after the initial assessment. The small number of patients studied after subgroup analyses may explain why significance was not seen in these domains with positive associations. Our findings underscore the utility of the pLTQ instrument for a variety of liver transplant recipients.

Our pLTQ instrument may play a role in unique liver transplant populations such as recipients of organs from living related donors. Indeed, recipients of living donor transplants experience psychosocial declines in their quality of life after transplantation.^{19,42} Because the pLTQ instrument is designed to track the psychological, social, and physical changes in the quality of life over time specifically in liver transplant recipients, future studies are required to assess the utility of our instrument in other populations.

The limitations of our study include the use of a single tertiary-care medical center in the construction and testing of our pLTQ instrument. Although we sampled patients who represented a large variety of indications for liver transplantation, a selection bias is

still possible. However, a large difference across populations seems unlikely because quality of life concerns are apparent across most populations. Furthermore, the next step in our study is to administer the pLTQ instrument at other liver transplant centers nationally to allow for a separate sample for further validation. Although a large sample size was chosen for the initial cohort of patients completing the pLTQ instrument, at 6 to 9 months, the sample size was smaller with a 39.3% response rate. However, this is reflective of the change in the way in which the pLTQ instrument was administered at the second time point because the patients were asked to respond by mail. The initial recruitment of the patients was conducted in the clinic setting; patients were asked to fill out a survey while they were waiting for their scheduled appointment in the posttransplant clinic, and they were subsequently mailed a follow-up pLTQ instrument at 6 to 9 months. It would not have been possible to re-administer the pLTQ instrument during a clinic visit because the follow-up intervals of these patients were not the same, and some of the patients were followed only yearly. Clinical study response rates vary widely.⁴³⁻⁴⁵ We believe that our response rate of approximately 40% is consistent with response rates observed in previous studies. We maximized our response rate by calling participants who did not return the questionnaire to remind them to return the survey, and we provided second mailings to those who did not receive the questionnaires initially. Comparing those who returned the follow-up questionnaire to those who did not, we found that the demographic characteristics were comparable, and this suggested that a response bias was unlikely in our sample (Table 2).

However, because of the smaller sample for the longitudinal data, we found that even though several domains of the study had positive associations in comparison with the SF-36 instrument, the associations did not reach significance because of the even smaller populations in subgroup analysis. Furthermore, because of limitations in the data collection and a lack of available pathological data, we were unable to correlate HRQOL with the stage of recurrent disease and instead used the time from liver transplantation for those with hepatitis C. Additionally, although a Spanish version of the questionnaire was developed and tested, significant recruitment of primarily Spanish-speaking patients did not occur. We plan additional studies in a Spanish-speaking population in the future.

In summary, the pLTQ instrument is the first disease-specific HRQOL instrument that has been developed with methodological rigor for patients who have undergone liver transplantation. As a population, liver transplant recipients are generally at risk from many conditions in comparison with the general population, and their HRQOL is typically affected most in the immediate postoperative period. Understanding how their HRQOL changes over time is important in tracking these patients over various studies. The pLTQ instrument can be useful in subsequent clinical research involving liver transplant patients.

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