Development and Validation of the Pediatric Liver Transplantation Quality of Life: A Disease-Specific Quality of Life Measure for Pediatric Liver Transplant Recipients

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Objectives To develop and validate a Pediatric Liver Transplantation Quality of Life (PeLTQL) questionnaire via an international multicenter collaboration.

Study design Item generation with 146 child and/or parent interviews (92 pediatric liver transplantation [LT] recipients) and 3 focus groups generated over 300 items. An item reduction questionnaire with 76 questions was completed by 320 participants (212 pediatric LT recipients).

Results Frequency-importance product ranking, questionnaire formatting, and pre-testing resulted in a 26-item PeLTQL questionnaire. Factor analysis identified 3 domains: future health, coping and adjustment, and social-emotional. The validation phase was completed by 133 (46% male) LT recipients (aged 8-18 years). Internal consistency (Cronbach α = 0.86) and test-retest reliability (intraclass correlation coefficient = 0.85) were excellent. Mean patient PeLTQL score was 69.54 $\pm$ 13.06. Construct validity with validated tools identified significant correlations between mean PeLTQL scores and (1) Pediatric Quality of Life Inventory generic (r = 0.64, $P < .001$); (2) Pediatric Quality of Life Inventory transplant (r = 0.73, $P < .001$); and (3) Screen for Child Anxiety Related Disorders (r = −0.57, $P < .001$) scores. Only 17/3458 (0.5%) questions were left blank. A Flesch-Kincaid grade level of 5.4 was calculated as a measure of the PeLTQL readability statistic.

Conclusions The PeLTQL is a valid and reliable novel 26-item disease-specific health related quality of life instrument for LT recipients aged 8-18 years. Low PeLTQL scores can identify patients at risk for childhood anxiety and depression. The tool is now ready for broad use in both clinical practice and clinical interventional trials. *(J Pediatr 2014;165:547-55)*.

Liver transplantation (LT) is life-saving, standard of care therapy for infants and children with a variety of primary liver conditions including biliary atresia, acute liver failure, metabolic liver diseases, and hepatic tumors.[1] Data from the United Network for Organ Sharing show 5-year patient survival rates ranging between 78% and 86% (deceased donor) and 86% and 90% (live donor).[2] Therefore, the focus of post-LT care in children has now shifted to encompass consequences related to the post-transplant course.

A key challenge for clinical care teams is identifying and addressing relevant issues affecting quality of life (QOL) years restored by LT.[3] The Studies of Pediatric Liver Transplantation registry, a multicenter North American database, report that one-third of 10-year survivors of pediatric LT in Canada and the US were maintained on immunosuppression monotherapy with normal growth velocity in the absence of immune suppression-induced complications such as post-transplant lymphoproliferative disease (PTLD), hypercholesterolemia, and renal dysfunction.[4] However, over 90% of these long-term LT survivors self-report decreased health-related QOL (HRQOL) utilizing the Pediatric Quality of Life Inventory (PedsQL) generic tool.[4]

CDI-S	Children's Depression Inventory Short Form	PedsQL	Pediatric Quality of Life Inventory
CSAS	Cantril Self-Anchoring Striving Scale	PeLTQL	Pediatric Liver Transplantation Quality of Life
FAS	Family Awareness Scale	PTLD	Post-transplant lymphoproliferative disease
HRQOL	Health-related quality of life	QOL	Quality of life
LT	Liver transplantation	SCARED	Screen for Child Anxiety Related Disorders
LTDS	Liver Transplant Disability Scale		
MTB	Medication-Taking Behavior		

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Supported by the Hospital for Sick Children (Pediatric Consultants' Creative Professional Activity grant 2004-2005), IWK Health Centre (Category A grant 2004-2005), Canadian Institutes of Health Research (Operating grant FRN-77626, 2005-2009). The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2014.05.024

The concept of HRQOL complements the World Health Organization definition of health as a "state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity."[5] Meaningful assessment of HRQOL in children relies on the ability to reliably and accurately assess well-being using psychometrically robust instruments.[6] To date, the published literature on HRQOL of pediatric LT recipients is primarily populated by results derived from utilization of validated generic HRQOL pediatric questionnaires. Generic instruments are comprised of questions broad enough to be applicable to a wide variety of populations and disease states, and major findings indicate that HRQOL in pediatric LT recipients is lower than healthy pediatric control populations, but similar to children with other chronic conditions.[7,8] However, generic measures of health status have less sensitivity to clinical change than disease-specific tools.[9] Targeted QOL instruments also have the advantage of including items focused on disease- and treatment-specific topics of particular interest to the patient population being assessed. The development of novel, validated disease-specific HRQOL tools for pediatric LT recipients has been flagged by others as a key priority.[3,6] Therefore, the aims of this study were to develop and validate the first disease-specific HRQOL questionnaire for use in children who have undergone isolated LT, using well-established tool development methodology.[10]

Methods

Inclusion criteria were English-speaking parents and patients <18 years old, at least 1 year post-LT. Comorbidities were recorded but did not exclude participation. Participants were drawn from the same population for both Pediatric Liver Transplantation Quality of Life (PeLTQL) development and psychometric testing phases. An accompanying parent was asked to participate in each phase. If the patient was unable to provide self-report (typically if under 5 years of age, too ill, or developmentally delayed), the parent alone was asked to participate. Study sites included pediatric LT programs in Canada (4), US (1), Australia (2), and the United Kingdom (1). This study was approved by the institutional ethics review board at each study site and informed consent was obtained from all participants.

A flow chart outlining PeLTQL development is presented in Figure 1.

Development of PeLTQL

Item Generation. Item generation comprised 1:1 interviews with patients and parents, focus groups, and extensive literature review with content analysis by NVivo 2.0 data analysis software (QSR International Pty Ltd, 2002) software for thematic extraction. Qualitative HRQOL elements important to pediatric LT participants and their health care providers have been published previously.[11] Using a semi-structured protocol, interviews with patients and parents continued until saturation of items was achieved. Items from the literature review were synthesized with primary findings to yield 76 items in the final item reduction questionnaire.

Item Reduction. Patients were stratified by age (5-7, 8-12, and 13-17 years). For patients between 1 and 4 years of age, only parents completed the item reduction questionnaire. For patients between 5 and 7 years of age because of concerns of respondent burden, the questionnaire was 'broken' into 4 parts so that individual participants did not have to rank each of the 76 items. In addition, for this 5- to 7-year age group, a research assistant read the questions and instructed the children on the ranking process. All item reduction participants were asked to rank both the frequency and importance of concern for each of the 76 items on a 5-point Likert scale, with higher scores representing degree and frequency of worry. An impact score for each item was derived from the product of the frequency and importance ratings. Final items chosen for the PeLTQL were those that had the highest average impact scores across patients 8- to 17-years-old. In developing the PeLTQL, the primary goal was to derive a tool that could describe key HRQOL issues for children and teens post-LT. Thus, it was the perspective of the children and teens deemed critical in determining which items would be retained in the final instrument. Although proxy reporting by parents (parents respond from the perspective of their child, and not themselves) provides a valuable perspective on HRQOL,[12] item reduction rankings by parents were not used in determining items included on the PeLTQL.

Testing the Psychometric Properties of PeLTQL

Questionnaire formatting mirrored earlier pediatric questionnaire development studies.[13-15] Following item reduction, the questionnaire was formatted and pre-tested. Items were modified to maximize readability and comprehension through a systematic peer-adjudicated process. This was an iterative process carried out with health care professionals who had expertise and experience caring for post-LT children. Feedback from patients involved in item reduction was also incorporated into the final changes of the PeLTQL questionnaire.

Psychometric evaluation (validity, reliability, and sensibility) of the PeLTQL involved patients and parents, who completed the PeLTQL and the following self-administered questionnaires: (1) PedsQL 4.0 (generic HRQOL, 23 items)[16,17]; (2) PedsQL 4.0 cognitive functioning module (memory, attention, processing speed, 6 items)[18]; (3) PedsQL 4.0 transplant module (nonorgan specific solid organ transplant scale, 46 items)[14]; (4) "Your Present Life" subscale from Cantril Self-Anchoring Striving Scale (CSAS) (global QOL visual analogue scale)[19]; (5) Screen for Child Anxiety Related Disorders (SCARED) (anxiety, 41 items)[20]; (6) Children Depression Inventory Short Form (CDI-S) (depression, 10 items)[21,22]; (7) Medication-Taking Behavior (MTB) (medication adherence, 9 items) adapted from Morisky et al[23]; and (8) Family Awareness Scale (FAS) (family competence as described in the Beavers-Timberlawn Model of Family Competence, 14 items).[24] The FAS was completed by participants aged 13-17 years, based on