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Cross-sectional Analysis of Health Related Quality of Life in Pediatric Liver Transplant Recipients

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Abstract

Objective—To investigate the distribution of health related quality of life in pediatric liver transplant recipients compared to a normative population.

Study design—Cross-sectional, multi-center study conducted at select SPLIT centers. Patients between 2-18 years of age, surviving liver transplantation by at least 12 months were eligible. Parent/guardian fluency in English or Spanish was required. Children 8 years and parents of all children completed the age appropriate versions of the PedsQL™ 4.0. Scores were compared to a

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healthy children sample (n=3911) matched by age group, gender, race/ethnicity and to a sample of pediatric cancer patients receiving chemotherapy and/or radiation.

Results—Participants included 65% (873/1339) of eligible patients. Mean age was 8.17 ± 4.43 years and 55% were female. The total and subscales scores of PedsQL™ 4.0 were lower than healthy children ($p < 0.001$) with effect sizes for self-report ranging from -0.25 for Emotional Functioning to -0.68 for School Functioning. Patients and their parents reported better physical functioning than cancer patients, but similar social and school functioning. Correlations between parent and self-reports were in the moderate agreement range.

Conclusion—Pediatric liver transplant recipients and their parents report lower HRQOL than controls with some domains equal to children receiving cancer therapy.

Keywords

outcomes; children; organ transplantation; liver disease; cognitive development

Liver transplantation is expected not only to prolong life and reverse the consequences of end-stage organ failure, but also to result in a health state that is desirable and a marked improvement from the pre-transplant condition. In considering all aspects of health, physicians must examine not only physical outcomes but also psychosocial outcomes including mental health, behavior and role function. Health related quality of life (HRQOL) is a multidimensional measurement of health outcomes that includes assessment of physical, psychosocial and functional status. HRQOL can be measured directly from the patient's perspective, or in situations in which the patient is unable to adequately respond, from the perspective of an involved proxy, such as a parent. Liver transplantation is typically performed in children as a treatment for life-threatening complications of liver disease with an expected improvement in HRQOL status as a secondary objective. However, a full understanding of HRQOL in children following liver transplantation will help to better define overall outcomes for this group, set expectations for health care providers and parents, and identify areas of functional deficits that might be improved with focused interventions.

The purpose of this study was to use a well-validated instrument to measure HRQOL in patients included in the Studies of Pediatric Liver Transplantation (SPLIT) Registry, the largest assembled cohort of pediatric liver transplant recipients in North America [1]. Previous reports have suggested that HRQOL in patients who have survived liver transplantation is not equal to healthy children, but these reports have not been large or comprehensive enough to truly define this population [2-7]. This report includes data from the majority of children that have survived liver transplantation at 22 North American transplant centers during the past ten years. As such, it provides the broadest perspective of health outcomes in this population yet described and renders a snap-shot of the pediatric liver transplant survivor experience in the current era.

Methods

Twenty-two centers elected to participate in this ancillary study to the SPLIT Registry. Patients between 2 and up to 18 years of age, recipients of liver transplantation, and survival of at least 12 months following transplant were eligible. Patients and parents/guardians were also required to be fluent in English or Spanish. Children who were not maintaining regular medical follow-up with their transplant center and recipients of combined organ transplants were also excluded. The study was approved by the Institutional Review Boards at participating centers and written informed consent was obtained from parents or guardians

prior to participation. Assent was obtained from children as required by individual institutions.

Measures

We used the 23-item PedsQL™ 4.0 Generic Core Scales which encompass: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), and 4) School Functioning (5 items), and were developed through focus groups, cognitive interviews, pre-testing, and field testing measurement development protocols. The instrument takes approximately 5 minutes to complete [8]. Participating families of children age 6 and older also completed the School Attendance and Performance Survey (SAPS) that is administered as part of the routine clinical data collected for the SPLIT registry.

Data Collection

Eligible patient and parent or guardian dyads were recruited during a routine follow-up visit at their transplant center between June 30, 2005 and June 30, 2008. The parent/guardian and patient (if age 8 or older) completed one of four age-specific versions of the PedsQL™ 4.0. Three of the 22 centers supplemented recruitment by mail. Overall, less than 50 patients included in the sample completed the survey by mail. Past as well as present demographic and clinical data for participating patients were extracted from the SPLIT database.

Outcomes

The primary outcomes measure was the total PedsQL™ 4.0 score from the child self report survey for children age 8-18 years. Secondary outcomes measures included the PedsQL™ 4.0 Total Score from the parental survey for children age 2 up to 18 years and the PedsQL™ 4.0 Summary Scores for Physical and Psychosocial Health from the parental and self-report survey. These outcomes were compared to a healthy children sample (n=3911) randomly matched by age group, gender, and race/ethnicity to the liver transplant sample utilizing the SPSS statistical software random sample case selection command [9]. The healthy children sample was derived from the PedsQL™ 4.0 Generic Core Scales initial field test (n = 329, 8.4%) [8], a State Children's Health Insurance Program (SCHIP) evaluation (n = 2199, 56.2%) [10], and from a school-based study within the San Diego Unified School District (n = 1383, 35.4%) [11].

We also compared the outcomes of the liver transplant group to a sample of children with cancer. The cancer group was chosen for this comparison because it represented a high level of medical disability that would be familiar to most pediatricians and provided a lower anchor to the spectrum of chronic disease in childhood. The pediatric cancer sample was derived from the PedsQL™ 3.0 Cancer Module field test [12] and included 183 patients, 105 with self-report and 180 with parent report results. The sample included pediatric cancer patients on cancer treatment (chemotherapy and radiation) with acute lymphocytic leukemia (n = 118, 64.5%), brain tumors (n = 8, 4.4%) non-Hodgkin's lymphoma (n = 9, 4.9%), Hodgkin's lymphoma (n = 6, 3.3%), Wilm's tumor (n = 7, 3.8%), and other cancers (n = 35, 19.1%). The size of the cancer sample precluded random matching to the liver transplant sample.

Statistical Analysis

The feasibility of the PedsQL™ 4.0 Generic Core Scales as an outcome measure for pediatric liver transplant patients was determined from the percentage of missing values for each item [13]. Scale internal consistency reliability was determined by calculating Cronbach's coefficient alpha [14]. Scales with reliabilities of 0.70 or greater are recommended for comparing patient groups, while a reliability criterion of 0.90 is

recommended for analyzing individual patient scale scores [15, 16]. Range of measurement was based on the percentage of scores at the extremes of the scaling range, that is, the maximum possible score (ceiling effect) and the minimum possible score (floor effect) [13]. Construct validity was determined utilizing the known-groups method [15]. In this study, independent samples *t*-tests were used to compare groups differing in known health status (pediatric liver transplant patients, the healthy children sample and the cancer patient sample) on the PedsQL™ 4.0 Generic Core Scales. The overall Type I error rate was maintained at 0.05 by the Hochberg adjustment for multiple comparisons [17]. This adjustment was made separately for child report and parent proxy report. Mann-Whitney U tests were performed to validate results obtained from parametric analyses. In order to determine the magnitude of the differences, effect sizes were calculated [18]. Effect sizes for differences in means are designated as small (.20), medium (.50), and large (.80) in magnitude [18]. Comparisons of the distribution and range of demographic and clinical variables between eligible participants and non-participants were conducted by chi-square and Kruskal-Wallis as appropriate. Agreement between child self-report and parent proxy-report was determined through Intraclass Correlations (ICC) [19, 20]. Intraclass Correlations are designated as 0.40 poor to fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 good agreement, and 0.81-1.00 excellent agreement [21, 22]. Statistical analyses were conducted using SAS version 8.02 and SPSS Version 15.0 for Windows [9].

Results

Patient Characteristics

There were 1339 patients eligible during the study period and 873 (65%) children participated. At the time of this analysis, there were 331(25%) patients that were still eligible and could be subsequently enrolled and 135 (10%) that were closed out of the study. Proxy respondents included 706 mothers (80.9%), 132 fathers (15.1%), 31 guardians (3.6%). Parents of four children 8 years of age (0.5%) found they were unable to complete the questionnaire since they were not fluent in English or Spanish. Both child self-report and parent proxy-report were available for 359 cases. For all participants combined, the average age of the 479 girls (54.9%) and 394 boys (45.1%) was 8.17 ± 4.43 years. For child self-report, the average ages of the 199 girls (54.8%) and 164 boys (45.2%) were 12.49 ± 3.05 years. The median interval from transplant to survey was 3.10 (inter-quartile range 1.68-5.32) years. Demographic and clinical characteristics of the patient sample are included in Table 1.

There were no significant differences in gender, age at transplant, median interval from transplant or primary disease between participants and eligible non-participants. Participants were more likely to be white (60% vs. 49%) and less likely to be Hispanic (15% vs. 24%), $p < 0.0001$. The percent hospitalized during the follow-up interval was not different, 32% versus 30% for participants and non-participants, respectively. However, the median hospital days were different, 5.00 (inter-quartile range 3-12) for participants and 8.00 (inter-quartile range 4-16) for non-participants ($p = 0.022$).

The SAPS data were available for 449/534 (84%) participants and 165/349 (47%) non-participants in this age group. Two of the areas surveyed on this form are the primary caregiver's highest level of education and the patient's school attendance over the previous year. The education levels of the primary caregivers of the participants were significantly higher than those of non-participants, with some high school or less attended by 9% versus 16%, a high school diploma or GED achieved by 22% versus 17%, vocational school or some college attended by 30% versus 21%, a college degree achieved by 24% versus 21%, and a professional or graduate degree obtained by 11% versus 4%, missing data 3% versus 22%, $p = 0.004$. There was no significant difference between the groups in the number of

patients that attended school, 97% of participants and 89% of the non-participants. School days missed for medical reasons (illness or doctors visits) were also compared. The percentage of participants missing 10 days of school were similar; 65% of participants and 63% of non-participants. However, participants were more likely to have missed more than 31 days as compared to non-participants, 13% versus 8%, $p=0.005$, (Table 5; online).

Measurements Psychometrics

The overall percentage of missing item responses across the PedsQL™ 4.0 Generic Core Scales for patient self-report and parent proxy-report for the pediatric liver transplant sample was 0.0% and 0.0%, respectively. Internal consistency reliability alpha coefficients for the majority of the patient self-report scales and parent proxy-report scales met or exceeded the minimum reliability standard of 0.70, while the Generic Core Total Scale Score for both child self-report and parent proxy-report approached or exceeded the reliability criterion of 0.90. There were no significant floor effects and ceiling effects were minimal (e.g., ranged from 1.7% to 25.6% for child self-report and from 6.2% to 28.2% for parent proxy-report) and were consistent with the ceiling effects reported for this scale in healthy children [8].

Comparisons to healthy sample

Table 2 presents the means and standard deviations of the PedsQL™ 4.0 Generic Core Scales Scores for pediatric liver transplant patients and the matched healthy children sample. For each scale and summary score, pediatric liver transplant patients and their parents reported significantly lower HRQOL than healthy children. Most effect sizes were in the small to medium effect size range, with the largest effect sizes found in the comparison of the School Functioning Scale. Thirty-one percent of both the liver transplant child self-report and parent proxy report Total PedsQL™ 4.0 scores were more than 1 standard deviation below the mean score of the healthy sample. Table 3 includes a sub-analysis of the five items contributing to the School Function scale of the PedsQL™ 4.0 grouped by their relationship to cognitive function versus school absences. Questions related to missed school days had the largest impact on the scale score for School Functioning.

Comparison to cancer patients

Comparison of demographic variables between the liver transplant and cancer groups revealed that the cancer sample contained a significantly larger proportion of patients who were male (58.5% vs. 45.1%, $p<0.001$) and who were Hispanic (49.7% vs. 14.8% $p<0.001$). There was no difference in the mean age between the groups. Table 4 presents the means and standard deviations for the child self-report and parent proxy report of the liver transplant samples compared to the cancer sample. The mean Total and Physical health scores of the liver transplant sample were significantly higher than the cancer sample by both parent and self-report with moderate to large effect sizes. Parents, but not children, reported significantly better Psychosocial Health and Emotional function with moderate effect sizes.

Parent/child agreement

For the 359 cases in which both child self-report and parent proxy-report are available for the pediatric liver transplant sample, Intraclass Correlations (ICC) between child self-report and parent proxy-report across the PedsQL™ 4.0 Generic Core Scales are as follows: Total Score = 0.55, Physical Health = 0.45, Psychosocial Health = 0.55, Emotional Functioning = 0.53, Social Functioning = 0.46, and School Functioning = 0.53. All ICCs are in the moderate agreement range. Across each of the PedsQL™ Scales, parents reported a lower mean score compared to their children.

Discussion

The results of this multi-center, cross-sectional study demonstrate that children who survive liver transplantation have moderately diminished HRQOL as compared to their healthy peers. The PedsQL™ 4.0 Generic Core Scales Total score functioned well to measure the spectrum of generic HRQOL in this transplant sample with only 1.7% of children and 6.2% of parents endorsing the highest health state and none the lowest. There was considerable variability in the transplant sample with nearly one third of the patients scoring more than one standard deviation below the mean of the healthy sample. Our results support the findings of other single center studies suggesting that HRQOL is impaired in pediatric liver transplant recipients even in long-term follow-up [2, 5, 23]. Both physical and psychosocial health are decreased to a similar degree with lower school functioning having the biggest impact on psychosocial health. These findings support the concept that survival after liver transplant is associated with a chronic health condition which distinguishes these children from their healthy peers.

Many factors may contribute to diminished physical health in these patients. The generic questions of the scale we used address energy level, physical stamina and chronic pain. Children who have survived transplant are required to take immunosuppressive medications that may alter their growth, physical appearance or energy level. These medications render them more susceptible to infection and they remain at risk for graft dysfunction and injury even many years after transplantation. In addition to these unavoidable factors that could diminish energy and physical stamina, studies have suggested that pediatric liver transplant recipients have decreased exercise tolerance which may be related to “de-conditioning” and may be improved with physical training and rehabilitation [24, 25]. Identifying the modifiable versus static (or fixed) determinants of physical function in these recipients will be an important next step in designing strategies to improve functional outcomes.

The largest differences noted in comparison to the healthy children were in the area of School Functioning, effect sizes for self-reported and parent-reported function were .68 and .62, respectively. As demonstrated in the initial field test of the PedsQL™ 4.0 Generic Core Scales [8], and subsequent investigations [26-28], two constructs are being measured by the School Functioning Scale (school-related cognitive functioning and school-related days missed). As such, we conducted a post-hoc analysis to determine the relative impact of school-related cognitive functioning and days missed from school for the present liver transplant sample. These data demonstrate the relatively large effect of days missed from school from the perspective of both patients and their parents. This finding is consistent with the magnitude of school absences reported to the SPLIT registry where 35% of the children in our sample missed more than 10 days in the previous 12 months. Although there is mounting evidence that pediatric liver recipients are more likely to have cognitive deficits and learning disabilities than their peers [29-31], our data would suggest that these families view school absence as a significant concern. Therefore, until subsequent studies can more fully examine these outcomes, we recommend that clinicians and educators focus on both issues and obtain information from both the child's and parent's perspectives when clinically assessing this area.

The comparison to the pediatric cancer sample was included to provide a framework in which to consider liver transplant patients within the spectrum of severe pediatric illness. The large reported differences in physical health were expected since these liver transplant patients had recovered from their last transplant by at least 12 months and the cancer patients were in the treatment phase of their illness. We were surprised to find comparable Social and School Function, suggesting that liver transplant patients share similar struggles

in these areas even years after transplantation. Again, difficulties related to missed days of school may be a key issue.

Our finding that pediatric liver transplant patients and their parents demonstrated only moderate agreement in reporting HRQOL is consistent with both the adult and pediatric literature, suggesting information provided by proxy-respondents is not equivalent to that reported by the patient [32, 33]. Imperfect agreement between self-report and proxy-report has been consistently documented in the HRQOL measurement of children with and without chronic illness [34], particularly for less observable or internal symptoms. Taken together, the evidence suggests that evaluating both children's and parents' perspectives regarding HRQOL should be the standard for routine assessment in clinical practice and clinical trials for pediatric liver transplant patients since their different perspectives potentially provide unique information.

The large percent of patients that were eligible but did not participate pose a potential threat to the generalizability of our results. Many of the children that lived long distances from their transplant centers were not recruited because they did not return to their transplant center for a follow-up visit during the study period. A patient's geographic distance from the transplant center could have affected the study findings in either direction. Children that returned to their center may have been receiving focused medical attention which could potentially improve their post-transplant health as compared to non-participants. Conversely, patients that returned to their center may have been "sicker" experiencing more chronic health problems than the non-participants who were receiving medical care in their community. We addressed this potential problem by inclusion of multiple transplant centers located in large urban communities that provide service to a more narrow geographic area and have more complete follow-up of their transplant populations. We also addressed this by comparing demographic and clinical characteristics between the two groups. We found that non-participants had primary care givers with lower levels of education and were more likely to be Hispanic. Although the study instrument was available in Spanish, some centers did not have Spanish speaking staff available to assist in recruiting patients which may have limited their participation. However, it is reassuring to note that the percentage of Hispanic patients in this cohort was similar to that of pediatric liver recipients listed in the UNOS registry for the calendar year of 2006, 15% versus 21%, respectively, www.unos.org. Similarly, we believe the distribution of education levels among participants, although higher than the non-participants, is representative of the US population with approximately 30% having a college degree or higher, www.census.gov/population/www/socdemo/education/cps2005.html. We also attempted to compare the level of chronic medical disability between the groups by assessing school attendance, missed school days due to illness and hospitalization during the follow-up interval. Hospitalization rates were similar between the two groups with the non-participants having higher median hospital days than participants, suggesting that the participants were not sicker. Interestingly, the participants were more likely to have missed greater than 31 days of school. Since missing school was the scale component that had the biggest impact on school function, this difference may have introduced bias toward lower school function in the participants. The factors that cause school absenteeism in this sub-set of transplant recipients clearly warrant a more detailed analysis.

In summary, we report the HRQOL of a large cross-section of pediatric liver transplant recipients. Liver recipients and their parents reported outcomes that were lower than a matched population of healthy children in all domains with the most significant differences observed in School Functioning. The differences reported in school function appeared to be driven by frequent school absences. These parents' ability to report on behalf of their children was moderate at best, emphasizing the need to assess qualitative outcomes directly

from the child's perspective whenever possible. Analyses of risk factors that are associated with lower HRQOL in these patients are ongoing and must be studied in multivariate analysis to separate the impact of confounding variables. These findings also support the need for further studies that focus on school attendance and cognitive function in this population, as we strive to develop interventions that will close gaps in HRQOL for this important and growing patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

HRQOL	Health related quality of life
SPLIT	Studies of Pediatric Liver Transplantation
SAPS	School Attendance and Performance Survey
SCHIP	State Children's Health Insurance Program
ICC	Intraclass Correlations

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Table 1

Patient Characteristics

Demographic and Clinical Variables	N	%
Total	873	100.0
Age at Transplant		
0-12 months	287	32.9
1-5 years	315	36.1
6-18 years	271	31.1
Gender		
Female	479	54.9
Race/Ethnicity		
White	527	60.4
Black	130	14.9
Hispanic	129	14.8
Other	84	9.6
Missing	3	0.3
Primary Disease		
Biliary Atresia	387	44.3
Other Cholestatic	108	12.4
Fulminant Liver Failure	110	12.6
Metabolic	134	15.3
Other	134	15.4
Health Insurance Status		
US federal or state funded services	272	31.2
Provincial Government (Canada)	68	7.8
HMO or managed care	194	22.2
Private insurance	242	27.7
Other	32	3.7
Missing	65	7.4
Hospitalized during follow-up interval	276	32.2
	Median	Inter-quartile Range
Hospital days	5.00	(3-12)

Table 2

Comparison to a Healthy Sample Matched for Gender, Race and Age

	Liver Transplant						Healthy			Adjusted Significance Level	Effect Size
Scale	n	Mean	SD	% Floor	% Ceiling	n	Mean	SD			
Child Self-Report											
Total Score	363	77.21	14.28	0.0	1.7	1844	83.68	12.26	<0.001	-0.51	
Physical Health	363	82.29	15.62	0.0	16.0	1843	88.07	12.30	<0.001	-0.45	
Psychosocial Health	363	74.51	15.83	0.0	1.9	1842	81.33	14.04	<0.001	-0.48	
Emotional Functioning	363	74.00	19.90	0.0	15.7	1845	78.56	18.29	<0.001	-0.25	
Social Functioning	363	80.95	19.09	0.0	25.6	1841	85.50	16.93	<0.001	-0.26	
School Functioning	361	68.53	18.56	0.0	5.0	1823	79.83	16.33	<0.001	-0.68	
Parent Proxy-Report											
Total Score	869	77.26	17.58	0.0	6.2	3869	84.12	13.74	<0.001	-0.47	
Physical Health	869	79.33	22.07	0.0	20.5	3869	86.87	17.05	<0.001	-0.42	
Psychosocial Health	869	75.72	17.33	0.0	9.3	3867	82.53	14.09	<0.001	-0.46	
Emotional Functioning	869	73.27	19.28	0.0	13.8	3868	81.02	15.93	<0.001	-0.47	
Social Functioning	869	78.99	20.63	0.2	28.2	3862	85.93	16.98	<0.001	-0.39	
School Functioning	746	67.42	22.43	0.0	10.5	3215	79.34	18.37	<0.001	-0.62	

The healthy children sample was matched to the pediatric liver transplant sample by age group, gender, and race/ethnicity. Effect sizes (liver transplant – healthy sample) are designated as small (–.20), medium (–.50), and large (–.80).

Table 3

School Functioning Scale Components

	Liver Transplant			Healthy			Significance Level	Effect Size
Scale	n	Mean	SD	n	Mean	SD		
Child Self-Report								
<u>School Functioning Scale (Total 5 items)</u>	361	68.53	18.56	1823	79.83	16.33	<0.001	0.68
<u>Cognitive School Sub-scale (3 items)</u>	361	70.89	24.13	1823	78.17	20.71	<0.001	0.34
<u>Missed School Sub-scale (2 items)</u>	361	64.98	21.85	1824	82.30	19.51	<0.001	0.87
Parent Proxy-Report								
<u>School Functioning Scale</u>	746	67.42	22.43	3215	79.34	18.37	<0.001	0.62
<u>Cognitive School Sub-scale</u>	746	67.24	27.10	2858	74.12	24.40	<0.001	0.28
<u>Missed School Sub-scale</u>	746	67.69	23.82	2861	84.02	17.79	<0.001	0.85

Table 4

Comparisons with Pediatric Cancer Patient Scores

	Liver Transplant			Cancer (On-Treatment)			Adjusted Significance Level	Effect Size
Scale	n	Mean	SD	n	Mean	SD		
Child Self-Report								
Total Score	363	77.21	14.28	105	68.92	15.97	<0.001	0.56
Physical Health	363	82.29	15.62	105	65.54	23.14	<0.001	0.95
Psychosocial Health	363	74.51	15.83	105	71.04	15.17	NS	0.22
Emotional Functioning	363	74.00	19.90	105	68.81	21.24	NS	0.26
Social Functioning	363	80.95	19.09	105	77.19	18.29	NS	0.20
School Functioning	361	68.53	18.56	92	66.22	19.60	NS	0.12
Parent Proxy-Report								
Total Score	869	77.26	17.58	180	66.95	19.85	<0.001	0.57
Physical Health	869	79.33	22.07	180	65.00	26.26	<0.001	0.63
Psychosocial Health	869	75.72	17.33	180	68.19	18.25	<0.001	0.43
Emotional Functioning	869	73.27	19.28	180	63.26	20.70	<0.001	0.51
Social Functioning	869	78.99	20.63	180	75.58	20.08	NS	0.17
School Functioning	746	67.42	22.43	120	63.61	24.03	NS	0.17

Effect sizes (liver transplant – cancer sample) are designated as small (.20), medium (.50), and large (.80)