Health-Related Quality of Life and Cognitive Functioning in Pediatric Liver Transplant Recipients

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The goal of this work was to examine the change in health-related quality of life (HRQOL) and cognitive functioning from early childhood to adolescence in pediatric liver transplantation (LT) recipients. Patients were recruited from 8 North American centers through the Studies of Pediatric Liver Transplantation consortium. A total of 79 participants, ages 11-18 years, previously tested at age 5-6 years in the Functional Outcomes Group study were identified as surviving most recent LT by 2 years and in stable medical follow-up. The Pediatric Quality of Life 4.0 Generic Core Scale, Pediatric Quality of Life Cognitive Function Scale, and PROMIS Pediatric Cognitive Function tool were distributed to families electronically. Data were analyzed using repeated measures and paired *t* tests. Predictive variables were analyzed using univariate regression analysis. Of the 69 families contacted, 65 (94.2%) parents and 61 (88.4%) children completed surveys. Median age of participants was 16.1 years (range, 12.9-18.0 years), 55.4% were female, 33.8% were nonwhite, and 84.0% of primary caregivers had received at least some college education. Median age at LT was 1.1 years (range, 0.1-4.8 years). The majority of participants (86.2%) were not hospitalized in the last year. According to parents, adolescents had worse HRQOL and cognitive functioning compared with healthy children in all domains. Adolescents reported HRQOL similar to healthy children in all domains except psychosocial, school, and cognitive functioning ($P = 0.02$; $P < 0.001$; $P = 0.04$). Participants showed no improvement in HRQOL or cognitive functioning over time. For cognitive and school functioning, 60.0% and 50.8% of parents reported "poor" functioning, respectively (>1 standard deviation below the healthy mean). Deficits in HRQOL seem to persist in adolescence. Over half of adolescent LT recipients appear to be at risk for poor school and cognitive functioning, likely reflecting attention and executive function deficits.

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Neurological injury early in life due to conditions such as perinatal complications, traumatic brain injury, and cancer has the potential to inflict significant, long-lasting developmental consequences. Hepatic encephalopathy and other neurological insults associated with end-stage liver disease may have a similar potential. The majority of pediatric liver transplantation (LT) recipients experience end-stage liver disease early in life, and in most large series, the median age at transplantation is <2 years.[1,2] Despite improvements in mortality and morbidity following pediatric LT, survivors continue to report lower health-related quality of life (HRQOL)

Abbreviations: BRIEF, Behavior Rating Inventory of Executive Function; CONSORT, Consolidated Standards of Reporting Trials; FOG, Functional Outcomes Group; FSIQ, full scale intelligence

and cognitive functioning than their healthy peers. These deficits appear to persist years after the immediate recovery period.[3-10] Early disease onset, poor nutritional status, growth deficits, and longer duration of illness prior to transplant have been implicated as factors associated with poorer outcomes.[11-13]

The Functional Outcomes Group (FOG), an ancillary study of the Studies of Pediatric Liver Transplantation (SPLIT) research collaborative, was the first multisite, longitudinal study to explore cognitive outcomes following LT in early childhood. This study of 144 LT recipients, age 5-6 years and at least 2 years beyond LT, demonstrated that LT recipients were twice more likely than expected to have mild to moderate or severe cognitive delay (intelligence quotient [IQ] ≤85). These children also had an increased prevalence of learning disabilities and impaired executive functioning compared with the normal population.[9] At 2-year follow-up, more patients than expected remained at increased risk for persistent cognitive and academic deficits, with deficits in IQ, executive function, and math achievement remaining stable.[10]

Although this initial set of FOG studies suggests that learning difficulties after transplantation may not improve in early childhood, it is unknown whether these cognitive and academic difficulties persist into adolescence. The present study builds upon the original FOG study. The current study aimed to determine longterm HRQOL and cognitive functioning in previous FOG participants via follow-up questionnaires administered between ages 11 up to 18 years. On the basis of prior studies suggesting that even longterm LT survivors have diminished HRQOL, we hypothesized HRQOL would improve as a function of time since transplantation but would not be equal to that of healthy peers. We expected delays in cognitive development observed in early childhood to persist or worsen in adolescence as cognitive and academic demands intensify, presenting increased challenges for patients with preexisting deficits in these domains. We also hypothesized pretransplantation, peritransplantation, and posttransplantation medical and demographic variables that have been found to be predictive of cognitive outcomes in early childhood, such as growth delay at LT, total bilirubin at LT, parent education, and household status, would remain predictive of functioning in adolescence.

quotient; GED, general educational development; HRQOL, health-related quality of life; ICU, intensive care unit; ID, identification number; IEP, individualized education program; IQ, intelligence quotient; LT, liver transplantation; NPV, negative predictive value; NS, nonsignificant; PedsPCF, PROMIS Pediatric Cognitive Function; PedsQL, Pediatric Quality of Life Inventory; PedsQL 4.0, Pediatric Quality of Life Inventory 4.0 Generic Core Scale; PELD, Pediatric End-Stage Liver Disease; PPV, positive predictive value; REDCap, Research Electronic Data Capture; SAAPS, School Attendance and Academic Performance Survey; SD, standard deviation; SPLIT, Studies of Pediatric Liver Transplantation; T1, time 1; T2, time 2; T3, time 3.

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Additional supporting information may be found in the online version of this article.

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Patients and Methods

FOG T1 AND T2

FOG was an independently funded ancillary study of the SPLIT research collaborative (R01 HD045694). During time 1 (T1), participants were recruited from 20 participating medical centers through the infrastructure of the SPLIT registry between June 1, 2005, and December 31, 2009. Eligible patients were single-organ LT recipients who were 5-6 years of age, fluent in English (patient and primary caregiver), and at least 2 years from most recent LT. Patients were required to pass a hearing screen before enrollment, and those with uncorrected vision loss or serious neurologic injury were excluded.

A neurocognitive assessment was performed at T1, with follow-up testing being performed when the patients are age 7-9 years old at time 2 (T2), which is 18-36 months later. The present study continues this longitudinal assessment of cognitive functioning, adding a third time point in adolescence (time 3; T3).

FOG T3

For logistical reasons, the present study (FOG T3) includes only sites that enrolled >6 participants during

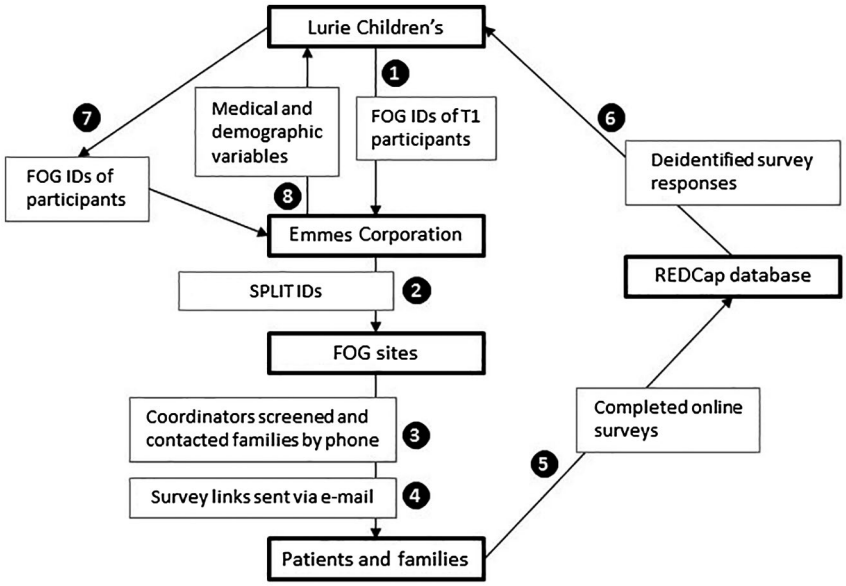

FIG. 1. Data collection.

T1 who remained active members in the SPLIT registry. These 8 sites, of the original 20, comprised 108 patients out of the 144 included in the original FOG T1 study.

The study was approved by institutional review boards at participating centers. Patients were identified using project identification numbers (IDs) from the original FOG study and participants' SPLIT IDs. Participating centers screened participants from T1 for inclusion in T3. Candidates were between 11 and 17 years 11 months 29 days of age; at least 1 year from the most recent transplant; were seen in the enrolling center's clinic at least once in the last 2 years; and were currently enrolled in the SPLIT registry. Those with unstable medical status (eg, currently hospitalized), combined organ transplant recipients, or those with current evidence of hepatic encephalopathy were excluded.

Eligible participants were recruited by the transplant center where they received medical follow-up (Fig. 1). Site coordinators approached eligible families by phone and distributed e-mail links to online surveys after receiving verbal consent and assent where applicable. Verbal assent was obtained from children as required by individual institutions. Families completed surveys using the Research Electronic Data Capture (REDCap) survey interface hosted at Northwestern University (CTSI UL1TR001422). REDCap is a secure, Web-based application designed to support data capture for research studies, providing an intuitive interface for validated data entry; audit trails for tracking data manipulation and export procedures; automated export procedures for seamless data downloads to common statistical packages; and procedures for importing data from external sources.[14] Demographic and medical data for participating patients were extracted from the SPLIT registry.

STUDY MEASURES

FOG T1

At T1, patients completed the Wechsler Preschool and Primary Scale of Intelligence, 3rd edition[15]; the Word Reading and Math Computation subtests of the Wide Range Achievement Test, 4th edition[16]; and the School Readiness Composite of the Bracken Basic Concept Scale, Revised (Supporting Table 1).[17] The Wechsler Preschool and Primary Scale of Intelligence, 3rd edition, provides a measure of full scale intelligence quotient (FSIQ) with Verbal IQ/Verbal Comprehension, Performance IQ/Perceptual Reasoning, and Processing Speed subscores. The Wide Range Achievement Test serves as a screener of basic academic skills in reading and math. The normative population mean is 100 ± 15 for both the Wechsler Preschool and Primary Scale of Intelligence and the Wide Range Achievement Test.

Parents and teachers completed the Behavior Rating Inventory of Executive Function (BRIEF), a survey of executive function tapping real-life situations.[18] The normative population mean is 50 ± 10, with higher scores indicating greater difficulties.

Measurements of HRQOL and cognitive function were gathered via the parent-reported Pediatric Quality of Life Inventory 4.0 Generic Core Scale[19,20] (PedsQL 4.0) and Pediatric Quality of Life Inventory (PedsQL) Cognitive Functioning Scale.[21-24] The PedsQL 4.0 was selected to provide an overall assessment of HRQOL, including physical, emotional, social, and school functioning. The 6-item PedsQL Cognitive Functioning Scale, which was originally developed as a measure of cognitive fatigue within the PedsQL Multidimensional Fatigue Scale, was selected because it was demonstrated to have excellent reliability and validity and was shown to correlate highly with the BRIEF in the pediatric LT population.[25,26] Scores for the PedsQL tools are reported as scaled scores ranging from 0 to 100, with higher scores reflecting better functioning.

Information regarding the use of special educational resources and school attendance was obtained via a parent-completed School Attendance and Academic Performance Survey (SAAPS). Special education was defined as additional educational services recommended by an individualized education program (IEP), which typically includes formal support provided in small groups by teachers with advanced training in cognitive and/or learning issues.

FOG T2

At T2, patients completed the Wechsler Intelligence Scales for Children, 4th edition,[27] and repeated the Wide Range Achievement Test, 4th edition, Word Reading and Math Computation subtests. Parents again completed the BRIEF, the PedsQL 4.0, the PedsQL Cognitive Functioning Scale, and SAAPS, with patients age 8 years and older completing the respective self-reported versions of the BRIEF and PedsQL measures.

FOG T3

Because of logistical and cost considerations, formal cognitive testing was not repeated at T3. Patients and parents instead completed online questionnaires distributed via the REDCap Web application. Both parents and patients again completed the PedsQL 4.0 and the PedsQL Cognitive Functioning Scale. Although the BRIEF was not repeated at T3, the PedsQL was considered an acceptable surrogate given its relative brevity and established correlation with the BRIEF in the pediatric LT population.[25,26] Parents and patients also completed the PROMIS Pediatric Cognitive Function (PedsPCF) tool, a 43-item parent- and self-reported survey that has been shown to be useful in identifying cognitive dysfunction in children with neurological insults or disorders.[28-30] The PedsPCF yields T scores, with a normative population mean of 50 ± 10. Higher scores reflect better functioning. Information regarding use of educational resources and school attendance was again queried via the SAAPS.

To determine whether optimal health status predicts cognitive functioning in adolescents, patients meeting ideal posttransplant health parameters, originally outlined by Ng et al.[31] and modified by Feldman et al.,[32] were classified as "ideal survivors." Ideal survivors were defined by absence of specific complications (no retransplantation, posttransplant lymphoproliferative disease, or chronic rejection; no cholangitis or gastrointestinal bleeding in the last 12 months), normal laboratory values at last follow-up visit (alanine aminotransferase <100 IU/L, total bilirubin <2.0 mg/dL, albumin >3.0 g/dL, gamma-glutamyltransferase <200 IU/L, and platelet count >80,000/mm^3), adequate growth (>−2 standard deviations [SDs] for the healthy population), and no ongoing use of insulin, prednisone, or antihypertensives.[31,32] Failure to meet any 1 of these criteria disqualified participants from being classified as an ideal survivor, such that patients were dichotomized either as ideal survivors or not.

STATISTICAL ANALYSIS

Descriptive statistics were generated for demographic and clinical patient variables and are reported as medians and ranges for continuous variables and frequencies/proportions for categorical variables. Participants and nonparticipants were compared using χ^2 statistics to ensure similarity between groups. Comparisons on the PedsQL 4.0 and PedsQL Cognitive Functioning Scale between LT recipients and the controls were made using previously published data from nonmatched, healthy pediatric samples.[19,21] Means were compared using independent samples *t* tests. The type I error rate was maintained at 0.05 by the Hochberg adjustment for multiple comparisons.[33] To determine the magnitude of the differences, effect sizes were calculated.[34] Effect sizes for differences in means were

designated as small (0.20), medium (0.50), and large (0.80) in magnitude.

Varni et al.[20] identified significant cutoff points for those at risk for impaired quality of life, determining in a large pediatric population that 1 SD below the mean of the total sample was a clinically meaningful measure of impaired quality of life. Scores below this cutoff were comparable with patients who had a severe chronic health condition. Therefore, we categorized a school or cognitive functioning score as "poor" if the scores were more than 1 SD below the mean for the healthy population. Perfect scores of 100 on the PedsQL or those more than 1 SD above the healthy mean were considered "excellent."

Stability of HRQOL and cognitive function over time on parent-reported PedsQL 4.0 and PedsQL Cognitive Functioning Scale were examined using repeated measures, and paired samples *t* tests were used on self-reported scores available at T2 and T3 (participants were too young to self-report at T1).

Predictive value of early childhood assessment was determined by calculating the positive predictive value (PPV) of scores more than 1 SD below the healthy mean on PedsQL measures at T1. A univariate regression analysis was conducted to identify whether the BRIEF scores at T1 predicted PedsQL Cognitive Functioning Scale scores at T3.

Contribution of pretransplantation, peritransplantation, and posttransplantation factors to cognitive function was examined by univariate analysis with PedsQL Cognitive Functioning Scale and PedsPCF scores at T3. Variables chosen for univariate analysis were available through the SPLIT registry and included height and weight *z* scores at transplant, total bilirubin at transplant, current household status, and current parent education. With the exception of the height *z* score, these variables had previously predicted FSIQ ≤85 at T2.[10] Although height *z* score was not one of the original predictors, it was included due to the high prevalence of growth failure in LT patients and evidence suggesting height is predictive of reported HRQOL in a larger sample of pediatric LT recipients.[35] Ideal survivorship was also explored as a possible predictor. Statistical analyses were conducted using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

Results

Of the 108 patients enrolled at the 8 participating centers during T1, 79 were eligible for enrollment during the T3 study period. Reasons for exclusion at T3 included the participant being age ≥18 years at screening, the patient being deceased or no longer in stable medical follow-up at their enrolling center, or the patient not currently enrolled in the SPLIT registry (Fig. 2). Of the eligible families, 69 were successfully contacted at T3. In total, 65 (94.2%) parents and 61 (88.4%) patients completed online study surveys. Participants and nonparticipants did not differ on basic demographic or medical variables. Median age at survey completion was 16.1 (12.9-18.0) years, and the median age at transplant was 1.1 (0.1-4.8) years. Over half of the patients (58.5%) underwent transplantation for biliary atresia. Six patients were completely off immunosuppression. Of those currently receiving immunosuppression, 86.4% (51/59) were taking tacrolimus. Median FSIQ of T3 participants, as measured at T1,

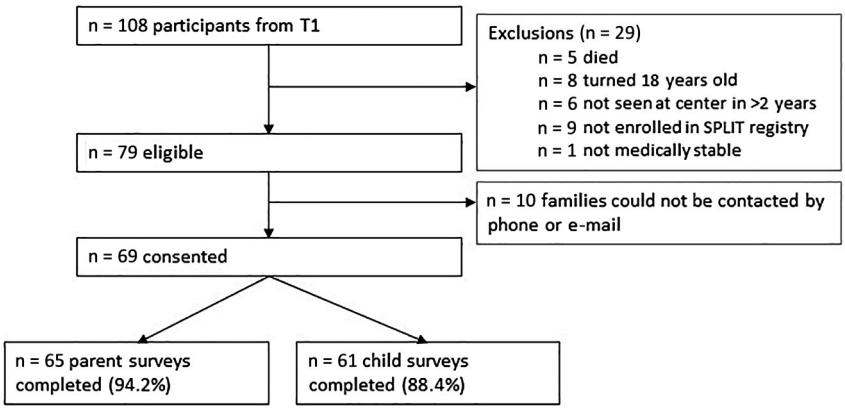

FIG. 2. CONSORT diagram.

was 96.5 (range 56-125) with 32.8% of participants scoring more than 1 SD below the population mean (IQ ≤85). Demographic and clinical characteristics of the patient sample are summarized in Table 1.

SCHOOL ATTENDANCE AND ACADEMIC PERFORMANCE SURVEY

At T3, 44.6% (n = 29) of respondents reported that their child had received special educational services as recommended by an IEP and 21.5% (n = 14) reported that their child had been described or diagnosed as having attention-deficit/hyperactivity disorder. Most participants (64.6%, n = 42) reported missing no school days in the past month due to physical or mental health. Only 7.7% (n = 5) reported missing 8 or more school days in the past 30 days.

HEALTH-RELATED QUALITY OF LIFE

Parent-reported HRQOL on the PedsQL 4.0 was worse than that of healthy peers in all domains, including physical health, emotional functioning, social functioning, and school functioning (Table 2). The largest differences were apparent in school functioning ($P < 0.001$). Differences in social and emotional functioning had medium effect sizes ($P < 0.001$; $P < 0.001$).

On self-report, patients rated their HRQOL as equal to healthy peers in all domains except psychosocial and school functioning ($P = 0.02$; $P < 0.001$). Although reported differences in these domains were significant, effect sizes were smaller than those seen on the parent reports.

On parent-reported PedsQL 4.0 total scores, 44.6% of parents rated their teens as having poor overall HRQOL compared with 29.2% at T1 (Table 3). For school functioning, 50.8% of parents noted poor function compared with 35.0% in early childhood (T1). Although the proportion of parents reporting poor overall HRQOL and school functioning was not statistically different from T1 to T3, there was a trend toward an increased percentage in adolescence (Fig. 3). On self-reported measures at T3, 23.3% endorsed poor total scores, whereas 30.0% endorsed poor school functioning. PedsQL 4.0 mean scores, including both parent- and self-reports for all subscales, did not differ between male and female participants.

COGNITIVE FUNCTIONING

Both parent- and self-reported cognitive functioning on the PedsQL Cognitive Functioning Scale was significantly below the healthy population at T3 ($P < 0.001$; $P = 0.04$; Table 2).

A large proportion of both parents and children reported poor cognitive functioning on the PedsQL Cognitive Functioning Scale, with 60.0% of parents and 40.7% of children endorsing poor cognitive functioning (Table 3). This percentage was unchanged compared with T1. However, there was a trend toward an increase in participants reporting excellent cognitive functioning at T3, with 24.6% of parents (compared with 11.8% at T1) and 20.2% of children (compared with 7.7% at T2) endorsing excellent function at T3 (Fig. 3).

On the PedsPCF, median scores on both parent- and self-reports fell within the normal range for the healthy population (50.0 ± 10.0, with higher scores indicating better functioning). Median parent-reported scores were 48.1 (interquartile range, 42.0-59.3). Self-reported median scores were 48.9 (interquartile range, 43.8-57.5). Of parent respondents, 17.5% indicated their child had poor cognitive functioning, whereas 10.0% of children endorsed poor cognitive functioning on this measure. Reported cognitive functioning on the PedsQL Cognitive Functioning Scale and PedsPCF did not differ between male and female participants.

STABILITY OF FUNCTIONING OVER TIME

There were no significant differences from T1 to T2 to T3 for parent-reported scores on the PedsQL 4.0 or PedsQL Cognitive Functioning Scale (Table 4). There were no differences from T2 to T3 on self-reported measures.

PREDICTIVE VALUE OF EARLY CHILDHOOD ASSESSMENT

Parent-reported PedsQL measures completed at T1 showed excellent predictive value for parent-reported scores at T3. For the PedsQL 4.0 total scores, the PPV was 73.7% (Table 5). For the PedsQL School Functioning Scale, the PPV was 85.7%. For the PedsQL Cognitive Functioning Scale, the PPV was 71.0%. Negative predictive values (NPVs) were 67.4%, 74.4%, and 50.0%, respectively.

TABLE 1. Participant Demographic and Medical Characteristics at T3

	Value (n = 65)
Age at survey completion, years	16.1 (12.9-18.0)
Age at LT, years	1.1 (0.1-4.8)
Interval from LT, years	14.5 (10.7-17.5)
PELD score at LT (4 missing)	14.5 (–9.7 to 46.6)
Height *z* score at LT	–1.7 (–7.0 to 3.4)
Weight *z* score at LT (9 missing)	–1.2 (–8.9 to 1.4)
Total bilirubin at LT, mg/dL	11.8 (0.1-58)
FSIQ at T1	96.5 (56-125)
Sex, female	36 (55.4)
Race	
White	43 (66.2)
Black	9 (13.8)
Hispanic	6 (9.2)
Other	7 (10.8)
Primary diagnosis (6 missing)	
Biliary atresia	38 (64.4)
Acute liver failure	2 (3.4)
Other cholestatic etiologies	10 (16.9)
Metabolic	8 (13.6)
Other	1 (1.7)
Household status	
2-person household	56 (86.2)
1-person household	9 (13.9)
Education of primary caregiver (15 missing)	
Some high school or less	3 (6.0)
High school diploma/GED	5 (10.0)
Some college or more	42 (84.0)
Status at transplantation	
ICU, intubated	5 (7.7)
ICU, not intubated	5 (7.7)
Hospitalized/no ICU	13 (20.0)
Not hospitalized	42 (64.6)
Number of LTs	
1	62 (95.4)
>1	3 (4.6)
Donor graft	
Living donor	18 (27.7)
Whole	26 (40.0)
Technical variant	21 (32.3)
Type of immunosuppression	
Currently not receiving immunosuppression	6 (9.2)
Currently receiving immunosuppression	59 (90.8)
Tacrolimus	51 (86.4)
Sirolimus	12 (20.3)
Mycophenolic acid/mycophenolate mofetil	9 (15.3)
Corticosteroids	5 (8.5)
Other	5 (8.5)
Primary insurance at transplant (10 missing)	
Private	17 (30.9)
US federal or state-funded	17 (30.9)
Provincial government (Canada)	7 (12.7)
Other	14 (25.5)

NOTE: Data are given as median (range) or n (%).

Parent-reported BRIEF scores from T1, specifically the Metacognition Index and Working Memory subscore, predicted parent-reported PedsQL Cognitive Functioning Scale scores at T3 (Supporting Table 2). These BRIEF subscores were previously shown to correlate highly with the PedsQL Cognitive Functioning Scale on concurrent assessment.[25]

FACTORS PREDICTING COGNITIVE OUTCOMES

PedsQL Cognitive Functioning Scale scores were not predicted by any of the examined medical or demographic variables. Parent-reported PedsPCF scores were not predicted by total bilirubin at transplant, height and weight *z* scores at transplant, or parent education. However, living in a single-parent household compared with a 2-person household predicted worse reported functioning on the PedsPCF ($P = 0.03$; estimate = –8.3; 95% confidence interval –15.9 to –0.6).

In this sample, 53.8% of patients (n = 35) met the classification as ideal survivors. Although the original ideal survivor parameters outlined by Ng et al. included estimated glomerular filtration rate criteria,[31] these data were not included due to the high frequency of missing values. Participants with missing data in any other category (n = 11) were excluded from consideration as ideal survivors. Of those who did not meet the ideal survivor categorization, 3 had undergone retransplant; 1 had a history of posttransplant lymphoproliferative disease; 5 were currently receiving corticosteroids; 5 were receiving antihypertensives; 1 was on seizure medication; 3 had elevated alanine aminotransferase levels; 6 had elevated total bilirubin; 2 had elevated gamma-glutamyltransferase; and 6 had growth delay. There was no significant difference between mean reported cognitive functioning in adolescence for ideal survivors compared

TABLE 2. PedsQL Comparisons With Healthy Sample

Scale	LT Recipients at T3			Healthy Sample			Adjusted Significance Level	Effect Size
	n	Mean	SD	n	Mean	SD		
Parent-reported PedsQL								
Total score	65	77.5	16.3	717	87.6	12.3	<0.001	0.79
Physical health	65	84.7	19.0	717	89.3	16.4	0.03	0.28
Psychosocial functioning	65	73.7	18.0	717	86.6	12.8	<0.001	0.97
Emotional functioning	65	71.6	22.0	718	82.6	17.5	<0.001	0.62
Social functioning	65	82.9	19.8	716	91.6	14.2	<0.001	0.59
School functioning	65	66.4	22.0	611	85.5	17.6	<0.001	1.05
Cognitive functioning	65	69.2	26.6	102	90.7	15.2	<0.001	1.06
Self-reported PedsQL								
Total score	60	78.6	15.9	401	83.0	14.8	NS	
Physical health	60	83.6	17.0	400	84.4	17.3	NS	
Psychosocial functioning	60	75.9	17.8	399	82.4	15.5	0.02	0.41
Emotional functioning	60	75.4	21.9	400	80.9	19.6	NS	
Social functioning	60	84.5	17.6	399	87.4	17.2	NS	
School functioning	60	67.8	21.6	386	78.6	20.5	<0.001	0.53
Cognitive functioning	59	70.8	22.4	52	81.1	17.4	0.04	0.51

NOTE: Effect sizes designated as small (0.20), medium (0.50), and large (0.80).

with nonideal survivors on both parent- and self-reported measures.

Ideal survivors differed from nonideal survivors in utilization of special educational resources. Ideal survivors were less likely than nonideal survivors to have participated in a Head Start or Early Intervention program (25.7% versus 63.2%; $P < 0.01$), to have had testing to develop an IEP (40.0% versus 83.3%; $P < 0.01$), or to have received special educational services as recommended by an IEP (28.6% versus 72.2%; $P < 0.01$). There was no difference between ideal and nonideal survivors in ever having received a diagnosis of attention-deficit/hyperactivity disorder.

Discussion

This is the first prospective multicenter longitudinal evaluation of HRQOL and neurocognitive functioning in pediatric LT recipients from early childhood through adolescence. Overall means of parent- and self-reported HRQOL and cognitive functioning at T3 were similar to T1 and T2 means. Reported functioning remained significantly below that of a nonmatched sample of healthy children. This suggests that impairments in quality of life and cognitive functioning persist into adolescence, even more than a decade following transplantation in the first 2 years of life.

Analogous to patterns observed during the previous 2 time points, a larger proportion of patients and parents than expected reported "poor" functioning at T3, which was defined as scores more than 1 SD below the healthy mean. Notably, there was a trend toward an increase in the percentage of parents reporting poor functioning at T3 compared with T1 for both total scores and school functioning.

In the context of relative stability of overall means, the trend toward an increased proportion of those with poor overall HRQOL and school functioning reflects an increase in variability from T1 to T3. Although more parents reported impaired functioning in adolescence compared with early childhood, there was also a trend toward an increase in those reporting "excellent" functioning (more than 1 SD above the healthy mean or a perfect score of 100). Therefore, some patients do seem to improve over time, whereas others appear to experience worse HRQOL or function in adolescence. Perhaps this is reflective of the inability to meet increasing demands at school, home, and in social relationships.

The changes in variability are also prominent within the domain of cognitive functioning. Although not statistically significant due to the small sample size,

TABLE 3. PedsQL and PedsPCF Score Distribution

	FOG T1		FOG T3		
	n (Total Responses)	%	n (Total Responses)	%	Significance
Parent-reported PedsQL					
Total score					
Poor functioning	19 (65)	29.2	29 (65)	44.6	NS
Excellent functioning	1 (65)	1.5	2 (65)	3.1	NS
School functioning					
Poor functioning	21 (60)	35.0	33 (65)	50.8	NS
Excellent functioning	5 (60)	8.3	6 (65)	9.2	NS
Cognitive functioning					
Poor functioning	31 (51)	60.8	39 (65)	60.0	NS
Excellent functioning	6 (51)	11.8	16 (65)	24.6	NS
Self-reported PedsQL					
Total score					
Poor functioning			14 (60)	23.3	
Excellent functioning			7 (60)	11.7	
School functioning					
Poor functioning			18 (60)	30.0	
Excellent functioning			6 (60)	10.0	
Cognitive functioning					
Poor functioning			24 (59)	40.7	
Excellent functioning			12 (59)	20.3	
Parent-reported PedsPCF					
Poor functioning			11 (63)	17.5	
Excellent functioning			15 (63)	23.8	
Self-reported PedsPCF					
Poor functioning			6 (60)	10.0	
Excellent functioning			11 (60)	18.3	

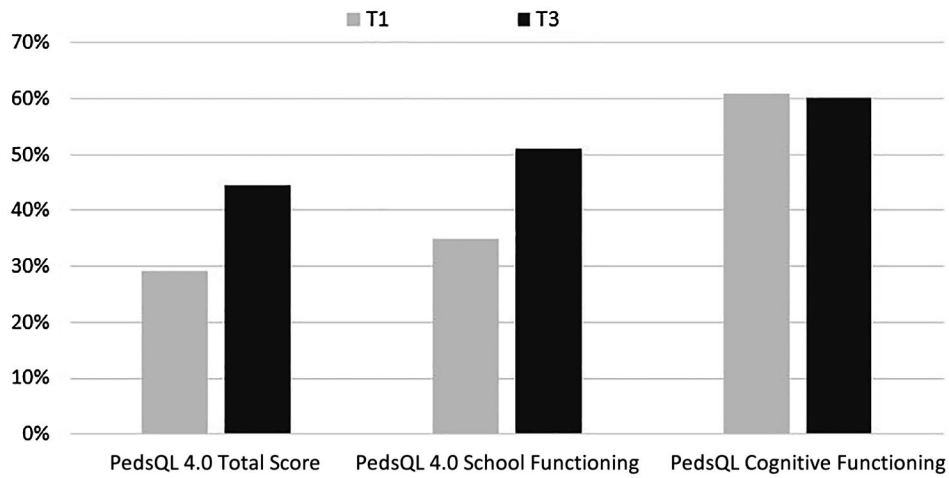

FIG. 3. Percentage of participants reporting poor functioning on parent-reported PedsQL (>1 SD below the healthy population mean).

TABLE 4. PedsQL Longitudinal Comparison

	n	T1	T2	T3	*P* Value
Parent-reported PedsQL*					
Total score	49	78.7 ± 14.0	76.7 ± 14.7	78.5 ± 16.1	NS
Physical health	49	83.4 ± 16.8	80.9 ± 21.1	86.2 ± 15.8	NS
Psychosocial functioning	49	76.3 ± 14.7	74.4 ± 15.0	74.3 ± 19.0	NS
Emotional functioning	49	73.1 ± 15.4	73.8 ± 15.7	71.3 ± 23.0	NS
Social functioning	49	83.7 ± 17.8	79.6 ± 17.5	84.2 ± 18.5	NS
School functioning	39	70.7 ± 20.1	67.3 ± 19.4	67.1 ± 23.8	NS
Cognitive functioning	35	70.8 ± 20.6	68.1 ± 23.1	66.3 ± 27.5	NS
Self-reported PedsQL†					
Total score	24		79.2 ± 13.3	77.3 ± 15.3	NS
Physical health	24		81.8 ± 15.0	84.4 ± 15.7	NS
Psychosocial functioning	24		77.7 ± 15.0	73.5 ± 17.7	NS
Emotional functioning	24		71.9 ± 22.8	72.7 ± 25.4	NS
Social functioning	24		83.3 ± 16.7	83.0 ± 15.2	NS
School functioning	18		77.8 ± 14.0	64.4 ± 18.0	NS
Cognitive functioning	23		69.6 ± 20.0	67.2 ± 22.5	NS

NOTE: Data are given as mean ± SD.
*Repeated measures for *P* value.
†Paired *t* test for *P* value.

TABLE 5. Predictive Value of Early Childhood Assessment for Identifying Patients With Poor Functioning in Adolescence

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PedsQL 4.0 total score	48.0	86.0	73.7	67.4
PedsQL School Functioning Scale	64.0	91.0	85.7	74.4
PedsQL Cognitive Functioning Scale	69.0	53.0	71.0	50.0

the proportion of participants reporting excellent function on both parent- and self-reports more than doubled from T1 or T2 to T3. Although the overall sample mean and proportion of participants with poor function were similar at T1 and T3, the mean score for the poor cognitive functioning group dropped nearly 10 points from T1 to T3. This suggests that those who struggled in early childhood may face subjectively worsened functioning in adolescence as demands on executive functioning intensify.

Parents tended to report more significant impairments than adolescents, as observed in both overall mean scores compared with the healthy population and in the proportion of participants reporting poor functioning. It is unclear what underlies this difference. Parents may be better able to objectively compare their child's functioning relative to healthy siblings or peers. Alternatively, parents may overestimate the burden of their child's illness on their overall quality of life and cognitive function.

The early childhood assessment using PedsQL measures appears to be relatively predictive of functioning during adolescence in this population. The assessment was most useful for those who reported poor function at T1 because >70% of those children continue to report poor function in adolescence. However, given that a significant proportion of children join the poor functioning group sometime between early childhood and adolescence, repeat assessment at various time points throughout childhood may be necessary to maximize sensitivity.

In this relatively small sample, the only demographic variable predictive of cognitive functioning in adolescence was household status. Although this effect was not present for the PedsQL Cognitive Functioning Scale, those living in a 1-parent household status scored an average of 8 points lower on the parent-reported PedsPCF. This may reflect the increased time and/or socioeconomic burdens associated with caring for a pediatric transplant recipient, which could be less impactful in a 2-parent household.

None of the examined medical variables were predictive of cognitive functioning, perhaps because the most informative predictors were not successfully

captured or as in the case of immunosuppressive regimens were not varied enough to assess any potential cognitive impact. It is also possible that our sample, which was relatively healthy with few posttransplant complications, did not exhibit sufficient variability in health status for effects to be apparent. Alternatively, our outcome measures likely did not capture the existing variability.

The primary limitation of this study was that only a subset of T1 centers were included due to cost and logistical considerations. However, attrition for participation at the 8 centers was low, with 88.4% of eligible families consenting for T3 and 94.2% of enrolled families completing at least parent-reported surveys. Nonetheless, when accounting for excluded sites, patients who were no longer eligible for participation, and families who could not be contacted, only 45.1% of the original T1 population was studied at T3. Additionally, T3 relied exclusively on indirect measures. Formal IQ and achievement testing were not repeated. However, perceived functioning as measured by the PedsQL scales is an important outcome because it reflects how parents and patients experience their quality of life and cognitive function. The BRIEF, which was administered at T1 and T2 as a measure of executive function, was also not repeated at T3. However, the PedsQL Cognitive Functioning Scale has been previously shown to be highly correlated with the BRIEF in the LT population[25] and, therefore, can be considered a useful surrogate measure for attention and executive function.

Finally, although comparisons to healthy children were performed, these samples were not matched to our T3 participants. Notably, there were large age differences between the healthy and LT samples. The healthy children ranged in age from 2 to 18 years with an average age of approximately 9 years overall and 11 years on self-reported measures.[19,21] Median age of our LT sample was 16.1 years. Some of the differences between the LT sample and healthy controls may be attributable to the effects of age because certain quality-of-life elements worsen in adolescence even for healthy children. However, the differences in this study are consistent with previously reported comparisons of LT recipients and healthy peers.[3]

This study highlights persistent deficits in HRQOL and cognitive functioning after LT in adolescence. Potential future directions include development and implementation of targeted resources for children who are found to have poor functioning at time of school entry. Additionally, further understanding of the root causes of impaired functioning and modifiable presurgical and perisurgical risk factors could assist in maximizing longterm outcomes for transplant candidates and recipients.

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