Health Status of Children Alive 10 Years after Pediatric Liver Transplantation Performed in the US and Canada: Report of the Studies of Pediatric Liver Transplantation Experience

Vicky L. Ng, MD, FRCP(C)[1], Estella M. Alonso, MD[2], John C. Bucuvalas, MD[3], Geoff Cohen, PhD[4], Christine A. Limbers, PhD[5], James W. Varni, PhD[6], George Mazariegos, MD[7], John Magee, MD[8], Susan V. McDiarmid, MD[9], and Ravinder Anand, PhD[4], for the Studies of Pediatric Liver Transplantation (SPLIT) Research Group*

Objectives To determine clinical and health-related quality of life outcomes, and to derive an "ideal" composite profile of children alive 10 years after pediatric liver transplantation (LT) performed in the US and Canada.

Study design This was a multicenter cross-sectional analysis characterizing patients enrolled in the Studies of Pediatric Liver Transplantation database registry who have survived >10 years from LT.

Results A total of 167 10-year survivors were identified, all of whom received daily immunosuppression therapy. Comorbidities associated with the post-LT course included post-transplantation lymphoproliferative disease (in 5% of patients), renal dysfunction (9%), and impaired linear growth (23%). Health-related quality of life, as assessed by the PedsQL 4.0 Generic Core Scales, revealed lower patient self-reported total scale scores for 10-year survivors compared with matched healthy children (77.2 ± 12.9 vs 84.9 ± 11.7; $P < .001$). At 10 years post-LT, only 32% of patients achieved an ideal profile of a first allograft stable on immunosuppression monotherapy, normal growth, and absence of common immunosuppression-induced sequelae.

Conclusion Success after pediatric LT has moved beyond patient survival. Availability of an ideal composite profile at follow-up provides opportunities for patients, families, and healthcare providers to identify broader sets of outcomes at earlier stages, ultimately contributing to improved outcomes after pediatric LT. *(J Pediatr 2012;160:820-6)*.

Liver transplantation (LT) is a well-established treatment for children with end-stage liver disease caused by biliary atresia, fulminant liver failure, metabolic liver conditions, hepatic tumors, and other rare cholestatic liver diseases.[1,2] The reported 5-year patient survival rate after pediatric LT performed in North America is >85%.[3] Although a recent study reported an overall life expectancy of 22.2 years for adult LT recipients, the true ceiling for patient survival and allograft longevity in children who have undergone LT remains unknown and is likely higher.[4,5] Thus, the focus of post-LT care in children has shifted to encompass consequences related to the post-transplant course. Current knowledge dictating lifelong treatment with immunosuppressive medications has particular impact for pediatric patients, given that many children will live long enough to potentially develop end-organ damage.[5-7]

Comprehensive descriptions of health status and analysis of factors that induce illness in the long-term follow-up of pediatric LT recipients are lacking. Consequently, the primary objective of this study was to address this gap in the literature by characterizing clinical outcomes, health status, and health-related quality of life (HRQOL) in children registered in a multicenter North American database registry, the Studies of Pediatric Liver Transplantation (SPLIT), who achieved 10-year survival. The secondary objective was to characterize the "ideal" long-term survivor of pediatric LT and to provide clinically relevant information to healthcare practitioners caring for recipients of LT performed in childhood.

ACR	Acute cellular rejection
BMI	Body mass index
EBV	Epstein-Barr virus
HRQOL	Health-related quality of life
LT	Liver transplantation
PTLD	Post-transplantation lymphoproliferative disease
SPLIT	Studies of Pediatric Liver Transplantation

From the [1]SickKids Transplant Center, The Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada; [2]Siragusa Transplant Center, Children's Memorial Hospital and Northwestern University Feinberg School of Medicine, Chicago, IL; [3]Pediatric Liver Care Center, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [4]The EMMES Corporation, Rockville, MD; [5]Department of Psychology and Neuroscience, Baylor University, Waco; [6]Departments of Pediatrics and Landscape Architecture and Urban Planning, Texas A&M University, College Station, TX; [7]Hillman Center for Pediatric Transplantation, Children's Hospital of Pittsburgh and Thomas E. Starzl Transplantation Institute, University of Pittsburgh Medical Center, Pittsburgh, PA; [8]Division of Transplantation, University of Michigan Health System, Ann Arbor, MI; and [9]Dumont–University of California Los Angeles Liver Transplant Center, UCLA School of Medicine and Mattel Children's Hospital, Los Angeles, CA

*A list of members of the SPLIT Research Group is available at www.jpeds.com (**Appendix**).

The SPLIT Research Group is supported by National Institute of Diabetes and Digestive and Kidney Diseases (grant U01-DK061693-01A1), unrestricted grants from Astellas Pharma US, Inc, and Roche Laboratories. An American Recovery and Reinvestment Act (ARRA) 2009 grant awarded to the SPLIT Research Group supported the current study design, data analysis, and interpretation, with writing and completion of the manuscript being entirely investigator-initiated. J.V. holds the copyright and the trademark for PedsQL and receives financial compensation from the Mapi Research Trust, a nonprofit research institute that charges distribution fees to for-profit companies that use the PedsQL. The authors declare no conflicts of interest.

 10.1016/j.jpeds.2011.10.038

Methods

Founded in 1995 as a prospective data repository for children undergoing LT in the United States and Canada, the SPLIT registry is the largest detailed database of pediatric LT recipients internationally. For the present study, a SPLIT 10-year survivor was defined as a pediatric recipient of LT before December 1999 who had a scheduled 10-year anniversary follow-up visit (defined as occurring 9.5-10.5 years after the date of first LT) recorded in the SPLIT database. We identified 632 children who underwent a first LT before December 1999. Patients who had died before their 10-year anniversary (n = 109) and patients from whom data for the 10-year follow-up visit was not available (n = 356) were excluded from the analysis. Identifiable reasons for missing 10-year anniversary clinic visit data included transfer of care to a non-SPLIT center (n = 46), official transfer to an adult LT center (n = 61), receipt of bone marrow transplantation at any time point after LT (n = 15), and missing data with no reason provided (n = 234). A total of 167 patients met our eligibility criteria and compose the study cohort for this cross-sectional study.

Study Design and Data Collection

This cross-sectional study is a component of the larger SPLIT prospective database, which has been approved by the Institutional Review Board or Research Ethics Board of each involved institution. Individual informed consent was obtained from each parent/guardian, and assent was obtained from each child as required by the individual institutions. Deidentified information, including clinical, laboratory, operative, medical treatment, complications, and outcome data fields, was submitted to the SPLIT data coordinating center via a standardized Web-based data entry system starting at the time of listing for LT. The data were analyzed to determine the number of participants that were ideal 10-year survivors. This analysis was based on 13 medical variables characterizing allograft health and representing consequences of long-term immunosuppression.

Previous data from a cross-sectional ancillary study conducted at 22 of the SPLIT centers investigating HRQOL in 1000 pediatric LT recipients[8,9] also were included in this analysis. PedsQL 4.0 Generic Core Scales data were available from parent proxy reports for 80 of the 167 10-year survivors at a median interval from first LT to survey of 8.97 years (IQR, 1.65 years), and pediatric patient self-reports were available for 73 of these 80 patients. These outcomes were compared with outcomes in a group of healthy children matched by age group, sex, and race/ethnicity to the subcohort of 10-year survivors using the SPSS statistical software (SPSS Inc, Chicago, Illinois) random sample case selection command.[10,11] The sample of healthy children was obtained from the PedsQL initial field test and a State Children's Health Insurance Program evaluation.[10,11]

Statistical Analyses

Statistical analyses were performed using SAS 9.2 for Windows (SAS Institute, Cary, North Carolina) and SPSS 15.0 for Windows (SPSS Inc, Chicago, Illinois). Differences were tested using the χ^2 test, Student t test, and Wilcoxon log-rank test. Standardized height-for-age, weight-for-age, and body mass index (BMI) z-scores were calculated based on age- and sex-specific growth charts for the normal population (Centers for Disease Control and Prevention; www.cdc.gov/growthcharts). Kaplan-Meier curves were used to depict patient survival, graft survival, and acute cellular rejection (ACR). For the study cohort of 10-year survivors, independent-sample t tests[12] were used to compare PedsQL 4.0 Generic Core Scales scores across the 10-year pediatric LT survivors and the matched healthy children, as reported previously.[8] Effect sizes were calculated to determine the magnitude of the differences between LT survivors and healthy children.[15] Effect sizes for differences in means were classified as small (0.20), medium (0.50), and large (0.80) in magnitude.[13]

Results

Figure 1 (available at www.jpeds.com) illustrates the Kaplan-Meier probability of patient survival for SPLIT patients who underwent LT before December 1999. Table I summarizes patient characteristics of the 167 SPLIT 10-year survivors; the data demonstrate that, with the exception of recipient age at time of LT, our study cohort is representative of the population of SPLIT patients who underwent LT before December 1999. SPLIT 10-year survivors were younger at the time of LT compared with excluded patients (2.6 years vs 5.1 years; $P < .0001$). The distribution of recipient age at LT differs significantly different, with only 7.8% of SPLIT 10-year survivors aged ≥8 years at time of LT, compared with 28.8% of excluded patients ($P < .0001$).

Graft Outcome and Immunosuppression Practices

Among the 10-year survivors, first allograft survival rates were 94% at 1 year, 91% at 5 years, and 88% at 10 years. Retransplantation occurred in 20 (12%) 10-year survivors, for indications including hepatic artery thrombosis (n = 7), chronic rejection (n = 5), and primary graft dysfunction (n = 2). Two patients (1%) underwent a third LT. Within the first 10-year period after primary LT, 111 patients (66%) had 1 or more documented episodes of ACR. Figure 2 (available at www.jpeds.com) shows the cumulative incidence of ACR in the first 10 years after LT. More than 80% of cases of ACR occurred in the first year after LT. Histologically confirmed chronic rejection was diagnosed in 15 patients (9%) within the first 10 years after LT. Median time to diagnosis of chronic rejection was 2.2 years (range, 0.03-9.2 years). Table II presents clinical and biochemical findings from the 10-year follow-up visit. No association between BMI and elevated serum liver transaminase levels was noted at the 10-year follow-up visit.

All patients were receiving immunosuppression therapy at the 10-year anniversary visit, including calcineurin inhibitor agents (tacrolimus in 68% of patients; cyclosporine in 23%)

Table I. Characteristics of study cohort of 167 10-year survivors and excluded patients

	10-year survivors (n = 167)	Excluded patients (n = 465)	*P* value
Patient age at LT, years			
Mean ± SD	2.6 ± 3.3	5.1 ± 5.6	<.0001
Median (IQR)	1.0 (0.6-3.6)	1.8 (0.8-9.3)	
Recipient age at LT, years, n (%)			
<1	85 (50.9)	171 (36.8)	<.0001
1-7.9	69 (41.3)	160 (34.4)	
8-12.9	9 (5.4)	60 (12.9)	
≥13	4 (2.4)	74 (15.9)	
Male sex, n (%)	75 (44.9)	211 (45.4)	.92
Ethnicity, n (%)			.69
White	104 (62.3)	288 (61.9)	
Black	28 (16.8)	74 (15.9)	
Hispanic	15 (9.0)	56 (12.0)	
Other	20 (11.9)	47 (10.1)	
Primary diagnosis, n (%)			.05
Biliary atresia	92 (55.1)	200 (43.0)	
Acute liver failure	18 (10.8)	74 (15.9)	
Metabolic liver disease	23 (13.8)	58 (12.5)	
Tumor	6 (3.6)	22 (4.7)	
Other cholestatic conditions	17 (10.2)	50 (10.8)	
Other	11 (6.6)	61 (13.1)	
Graft type, n (%)			.06
Deceased donor whole	76 (45.8)	230 (49.7)	
Deceased donor reduced	52 (31.3)	101 (21.8)	
Deceased donor split	9 (5.4)	42 (9.1)	
Live donor graft	25 (15.1)	79 (17.1)	
ABO-incompatible graft n (%)	7 (4.2)	14 (3.0)	.47
Retransplantation, n (%)	20 (12.0)	78 (16.8)	.14
Chronic rejection, n (%)	15 (9.0)	18 (3.9)	.01
ACR in first 6 months, n (%)	83 (49.7)	200 (43.0)	.14
Duration of ICU stay in first 30 days, median (range)	5 (0-30)	5 (0-30)	
Dialysis required before LT, n (%)	1 (0.6)	9 (2.0)	.22

ABO, hemolytic disease of the newborn; *ICU*, intensive care unit.

and newer agents (in 5%). Regimens included 2 daily immunosuppressant agents in 26% of patients and 3 daily immunosuppressant agents in 11%. In the patients taking 2 immunosuppressants daily, the second agents included prednisone (n = 14), mycophenolate mofetil (n = 13), and azathioprine (n = 5). None of the 32 patients receiving prednisone therapy took prednisone alone. Oral steroid therapy was combined with tacrolimus (n = 23), cyclosporine, (n = 7), or sirolimus (n = 1). In addition, 2 patients were taking prednisone with both sirolimus and a calcineurin inhibitor. The median daily prednisone dosage was 5 mg (range, 0.5-60 mg). Possible indications for steroid therapy included an episode of ACR in the preceding 12 months (n = 5), a diagnosis of histologically confirmed chronic rejection (n = 2), a primary condition of primary sclerosing cholangitis with a comorbidity of inflammatory bowel disease (n = 2), and a primary baseline diagnosis of autoimmune hepatitis (n = 1). An additional 2 patients had a serum total bilirubin level ≥17.1 μmol/L. In 20 patients, the reason for prednisone therapy was not apparent from database information.

Post-Transplantation Lymphoproliferative Disease and Epstein-Barr Virus Disease

At 10 years after LT, 46 (47%) of 97 patients who were Epstein-Barr virus (EBV) seronegative at time of transplantation had seroconverted. Nine (9%) did so during the first year after LT. Symptomatic EBV disease was reported in 25 patients (15%) by the 10-year follow-up visit. Tissue-confirmed post-transplantation lymphoproliferative disease (PTLD) was diagnosed in 9 patients (5.3%), with all diagnoses made within the first 4 years after LT. Four of these 9 patients were EBV-negative before LT, and 8 of the 9 patients were aged <2 years at the time of LT. Two of these children had previously received lymphocyte-depleting therapy for steroid-resistant ACR.

Post-Transplantation Renal Dysfunction

Calculated glomerular filtration rate was determined using the Schwartz formula[14] for 118 10-year survivors. Stage 2 chronic kidney disease, defined as calculated glomerular filtration rate <90,[15] was identified in 11 patients (9%) (Table II). One patient had undergone renal transplantation.

Cardiovascular Risk Factors

Among participants with available fasting values, 20% had hypercholesterolemia and 26% had hypertriglyceridemia (Table II). There was no association between the presence of fasting hypertriglyceridemia or hypercholesterolemia and abnormal aspartate aminotransferase and alanine aminotransferase levels at the 10-year anniversary clinic visit. A patient who answered positively to queries of diabetes, glucose intolerance, or insulin use was considered to have diabetes. Fifteen of 167 10-year survivors (9%) had diabetes presenting beyond 30 days post-LT. Two of these

Table II. Results of clinical outcomes at the 10-year anniversary clinic visit

Test	n	Mean ± SD	Normal test value, n (%)
Graft outcomes			
TB, umol/L	165	10.4 ± 7.0	161 (98)
Albumin, g/L	162	41 ± 4	160 (99)
ALT, IU/L	166	39 ± 45	148 (89)
GGT, IU/L	149	49 ± 78	126 (85)
Renal function			
Serum creatinine, umol/L	162	71 ± 96	151 (93)
cGFR, mL/min/1.73 m^2	118	137 ± 42	107 (91)
Cardiovascular risks			
Cholesterol, mmol/L	97	3.81 ± 0.83	58 (60)
Triglycerides, mmol/L	93	1.04 ± 0.85	69 (74)
Growth			
Height/age, *z*-score	121	−0.51 ± 1.11	
>25th percentile			71 (59)
>10th percentile			93 (77)
>3rd percentile			108 (89)
Weight/age, *z*-score	121	−0.06 ± 1.32	
>25th percentile			87 (72)
>10th percentile			111 (92)
>3rd percentile			114 (94)

ALT, alanine aminotransferase; *cGFR*, calculated glomerular filtration rate; *GGT*, gamma-glutamyl transpeptidase; *TB*, total bilirubin.
Normal ranges: TB, <26 umol/L, serum albumin, >30 g/L; ALT, <60 IU/L; GGT, <75 IU/L; serum creatinine, <106 μmol/; hemoglobin, 130-160 g/L (males), <120 g/L (females); cGFR, >90 mL/min/1.73 m^2; cholesterol, 3.2-4.4 μmol/L; triglycerides, 0.4-1.3 mmol/L; linear height, >−2 SD; weight, >−2 SD.

15 patients reported diabetes at the 10-year anniversary visit, with 1 of these 2 receiving prednisone.

Growth

At 10 years after LT, the mean *z*-score for linear height was significantly below that expected in the normal population, with 69% of patients below the 50th percentile and 23% below the 10th percentile. There was a strong association between low *z*-score for height at the 10-year follow-up and ongoing steroid therapy, with patients <10th percentile for height >3 times more likely to still be receiving steroid therapy compared with those >10th percentile (43% vs 11%; $P = .0007$; relative risk, 3.56). Weight distribution was similar in the 10-year survivors and the normal population, with no weight deficit observed. Ten percent of the patients were obese (defined as BMI >95th percentile). The probability of being obese at 10 years after LT was not associated with steroid therapy (5% rate of obesity in those on prednisone vs 11% in those not on prednisone; $P = .70$).

School Performance

Approximately 23% (32/137) of the participants had either repeated a grade or been held back at least 1 school year, with 28% currently in grades 7-12. Parents reported established diagnosis of attention deficit-hyperactivity disorder in 9% of participants and that of learning disability in 26% of participants. Nine of 87 participants (∼10%) had missed at least 20 school days in the preceding year.

HRQOL

There were no statistically significant differences in age at LT, sex, race/ethnicity, or primary diagnosis of participants who participated in the ancillary HRQOL study at the designated centers and those who did not. Table III compares mean PedsQL 4.0 Generic Core Scales scores for 10-year LT survivors versus the sample of matched healthy children. Participants and their parents reported significantly lower HRQOL scores for all scales and summary scores compared with healthy children. Most effect sizes were in the medium to large range (0.50-0.80). The largest effect sizes were found in the comparison of the Emotional Functioning and School Functioning Scales. A subanalysis of the 5 items contributing to the PedsQL School Functioning Scale grouped by their relationship to cognitive functioning items versus missed school items revealed that questions

Table III. HRQOL of 10-year survivors of pediatric LT: comparison with a healthy sample matched for age group, sex, and race/ethnicity

	10–year survivor LT			Healthy				
PedsQL 4.0 scales	n	Mean	SD	n	Mean	SD	Difference	Effect size
Child self-report								
Total score	73	77.16	12.93	686	84.91	11.73	7.75*	0.66
Physical health	73	84.25	14.61	686	89.26	11.87	5.02†	0.42
Psychosocial health	73	73.31	13.61	686	82.59	13.45	9.28*	0.69
Emotional functioning	73	70.75	18.55	686	80.44	18.04	9.68*	0.54
Social functioning	73	81.44	18.62	686	85.96	16.47	4.52‡	0.27
School functioning	71	67.96	15.67	686	81.26	15.54	13.30*	0.86
Parent proxy report								
Total score	80	73.07	16.51	870	84.02	13.51	10.95*	0.79
Physical health	80	78.45	21.76	870	87.60	16.63	9.14*	0.53
Psychosocial health	80	70.24	15.80	870	82.05	14.16	11.81*	0.83
Emotional functioning	80	68.31	17.89	870	81.09	16.51	12.78*	0.77
Social functioning	80	77.00	22.83	870	85.76	17.19	8.76*	0.49
School functioning	77	65.58	20.37	870	79.07	18.01	13.49*	0.74

Effect sizes are designated as small (<0.20), medium (0.20-0.80), and large (>0.80).
*$P < .001$ based on independent-samples *t* tests.
†$P < .05$ based on independent-samples *t* tests.
‡$P < .01$ based on independent-samples *t* tests.

Table IV. The ideal SPLIT 10-year survivor of pediatric LT

Medical variable: result reported at 10-year visit	Patient data available, n	Patients who answered "yes" to variable as phrased, n (%)	Patients missing data, n (%)
Sustainability of allograft			
1 No retransplantation	167	147 (88%)	0
2 No chronic rejection; confirmed diagnosis previously/presently	167	152 (91%)	0
3 Serum ALT normal	166	148 (89%)	1 (1%)
4 Serum TB normal	165	161 (98%)	2 (2%)
5 Serum albumin normal	162	160 (99%)	5 (3%)
6 Serum GGT normal	149	126 (85%)	18 (11%)
Absence of immunosuppression-induced comorbid conditions			
7 No PTLD; previous diagnosis of tissue-confirmed PTLD	167	158 (94%)	0
8 No renal dysfunction; cGFR <90 mL/min/1.73 m^2	118	107 (91%)	49 (29%)
9 Acceptable linear growth; >−2 SD for healthy population	121	112 (93%)	46 (27%)
10 No diabetes	167	165 (99%)	0
Absence of need for additional medications			
11 No ongoing use of prednisone	167	135 (81%)	0
12 No use of antihypertensive agent	167	146 (87%)	0
13 No use of antiseizure medication	167	167 (100%)	0

related to missed school days had the largest impact on the School Functioning Scale score. Fourteen percent of 10-year survivors had a PedsQL Total Scale Score >2 SDs below the mean score of the healthy children.

Composite Profile of the "Ideal" 10-Year Survivor of Pediatric LT

Table IV lists 13 historically, clinically, and biochemically obtainable variables typically assessed at follow-up visits for LT recipients. These variables were phrased to facilitate a "yes" or "no" answer on review by the health care provider, and were grouped into 3 categories: allograft stability, absence of immunosuppression-induced comorbid conditions, and absence of the need for additional medications. A total of 106 10-year survivors had complete data at their SPLIT 10-year anniversary visit for these variables, with 53 10-year survivors answering "yes" to all 13 elements and thus meeting the criteria for what we consider an "ideal" 10-year survivor. The presence of 1 or more missing data elements (61 patients) and answering "no" to 1 or more variables (53 patients) contributed to the remaining 114 10-year survivors (68%) who did not meet the criteria for the ideal 10-year survivor (Table V; available at www.jpeds.com).

Discussion

This North American multicenter cross-sectional study provides a comprehensive assessment of the health status of patients who are alive 10 years after undergoing LT during childhood. We have demonstrated that the current practice of long-term immunosuppressive therapy mandates attention to specific post-LT care-induced complications, including post-transplantation renal dysfunction, PTLD, hypertriglyderidemia, and hypercholesterolemia. Moreover, less than one-third of the 10-year survivors met the criteria for the ideal survivor with a first allograft stable on immunosuppression monotherapy, normal growth, and absence of the most common sequelae of long-term immunosuppression therapy. In addition, the LT survivors reported diminished HRQOL, with 14% reporting a generic HRQOL value of >2 SDs below that of a matched healthy population. These results serve to confirm the long-term survivorship benefit of LT in children, and to remind all healthcare providers of the challenges requiring their attention.

In this study, survival rates for first allograft were 94% at 1 year and 88% at 10 years. A previous analysis of the SPLIT database found that late graft losses were caused by acute and chronic rejection and by chronic effects of hepatic arterial thrombosis and biliary strictures.[16] Other factors linked to compromised long-term graft status include chronic post-transplantation hepatitis, de novo steatosis, and alloimmune-mediated reactions, each with varying potential for progression to fibrosis[17] (although the significance of longer-term allograft fibrosis also has also been attributed to the physiological growth of the graft with the growth of the pediatric recipient over time[18]). Indeed, our analysis revealed elevated serum alanine aminotransferase in 11% of 10-year LT survivors and elevated gamma glutamyl transpeptidase in 15% of survivors. BMI did not differ significantly between participants with elevated liver biochemical results and those with normal values at 10-year follow-up, suggesting contribution of an inflammatory process rather than benign steatosis. Our study was limited by the lack of serial platelet count and histological data. Fibrosis has been reported in up to 69% of 10-year survivors who underwent liver biopsy by protocol, despite ideal post-LT clinical outcomes.[19] A single-center series reported that the prevalence of fibrosis associated with chronic hepatitis increased with time to 91% at 10 years after pediatric LT.[20] The potential for progressive (and insidiously) worsening fibrosis in the graft in apparently healthy patients, despite serially normal liver biochemical values and ultrasonography findings, raises the question of the true contributions of protocol liver biopsy in optimizing outcomes for long-term survivors of pediatric LT.[19] Moving forward, an evidence-based practice for optimal monitoring of long-term allograft status is needed. In

the interim, long-term follow-up care remains essential, with a regimen of regular blood studies, continued surveillance with noninvasive modalities such as serial ultrasound, and prompt "for cause" liver biopsy or cholangiography to identify any intervenable or treatable etiologies.

Effective immunosuppression is touted as the key to the success of pediatric LT, with success defined as minimal rejection risk with concomitant minimal drug toxicities. Our study confirms that daily immunosuppression with calcineurin inhibitor agents and newer options such as sirolimus remains the present clinical practice for long-term survivors of pediatric LT in North America. The use of prednisone by 19% of children at the 10-year anniversary clinic visit is of concern, especially given that participants with height <10th percentile were more than 3 times more likely to be still receiving steroids compared with those with height >10th percentile. A previous analysis of SPLIT data found that longer duration of steroid exposure was associated with both growth impairment and limited catch-up growth after the second and third post-LT years.[21] A recent meta-analysis showed that steroid-free protocols with calcineurin inhibitor therapy did not increase the risk of rejection and was associated with improved catch-up growth and decreased linear growth impairment.[22]

Our study also confirms the relatively low prevalence of specific immune and nonimmune complications associated with long-term immunosuppression use, including tissue-confirmed PTLD, post-transplantation renal dysfunction, and post-transplantation diabetes mellitus. Previous SPLIT analyses have provided detailed information on these post-LT treatment-induced comorbidities.[21,23,24] (Michael Narkewicz personal communication, September 2011). Given the healthcare complexities involved, an overall framework for outcome assessment based on an hierarchy of outcome measures might be applicable to pediatric LT,[25] in contrast to the current focus on the risk of individual complications when counseling families. In this study, we attempted to derive an ideal outcomes composite for a child undergoing LT. Our finding that less than one-third of 10-year survivors met the criteria for an ideal 10-year survivor, with sustained health of the first graft and freedom from the most common sequelae of immunosuppression use in the first decade after LT, underscores the importance of all health care providers encountering these children to be attentive to the broader determinants of "success" after pediatric LT. Ideally, the presence of histopathological and imaging data (eg, ultrasound) would further enhance assessment and make such a composite more robust, but regardless, this composite lays the foundation for future initiatives.

We included a measure of fundtional outcomes to better describe the health status of 10-year survivors of pediatric LT. Because a subset of our study cohort had participated in an ancillary cross-sectional study of HRQOL,[8] we had the opportunity to compare outcomes to a matched healthy population. For some of the participants, HRQOL had been measured at an annual visit before the tenth anniversary of LT; however, at the time of the survey, all patients had achieved at least 5-year survival, and because SPLIT data collection began in the mid-1990s, none had survived longer than 15 years. In the larger study from which these data were drawn, pediatric LT recipients reported significantly lower HRQOL than matched controls across all domains, but HRQOL measures did not vary with interval from LT.[8] The lower individual scale scores of our participants displayed a similar pattern, with the lowest scores in the Emotional and School Functioning Scales. Interestingly, the effect sizes were somewhat larger in these longer-term survivors than in the full cohort, which included patients with post-LT survival as short as 1 year. This observation supports the concept that HRQOL does not consistently improve with increasing time from LT. Assessment of disease-specific aspects of HRQOL after pediatric transplantation has identified treatment anxiety and issues surrounding adherence with chronic medications as key factors impairing HRQOL.[26] These factors would not be expected to diminish over time; in fact, their impact may increase as pediatric LT survivors reach adolescence, even if their overall health status is essentially unchanged. Finally, school absences might be expected to become less common with increasing interval from LT, given the low risk of opportunistic infection and infrequency of medical visits. Surprisingly, 10% of these children had missed more than 20 days in the preceding school year, and missing school days had a significant impact on HRQOL. This finding suggests that chronic medication exposure may adversely impact health status by increasing the risk of community-acquired infections that cause lost school days. As increasing numbers of pediatric LT recipients enter adolescence and young adulthood, all healthcare providers need to recognize nonadherence, provide tools for transition to adulthood, and collaborate between pediatric and adult care centers to prevent the trend of graft failure as children transition to adult care centers.[27]

Potential limitations and biases of this study relate to database registry research. This study relies on the analysis of historical data collected from participating SPLIT centers in North America. It is possible that the higher proportion of children who were aged >8 years at time of LT within the group of excluded patients group might have turned age 18 years before the 10-year anniversary and were less likely to have remained within a SPLIT site. Despite rigorous data quality controls, missing and incomplete data were common for variables due to institutional differences in standard of care. This is seen particularly in our analysis of the ideal 10-year outcome, with 61 patients failing to meet ideal criteria simply because of missing data. SPLIT data collection did not include histological or routine radiographic assessments, although documented vascular abnormalities were reported; thus, assessment of our ideal criteria could not include these parameters. In addition, the SPLIT database does not routinely collect data that might be important indicators of graft injury or chronic infection, such as serum conjugated bilirubin levels, international normalized ratio values, serum immunoglobulin levels, serum autoantibody titers, and EBV DNA by polymerase chain reaction. Regardless of these

limitations, our study underscores the urgent need for individualized patient-specific immunosuppression and monitoring that can guide optimal recommendations over the long term, as well as serial HRQOL assessments as points for intervention from the healthcare team. ■

We thank Diane C. Blonski for her assistance.

Submitted for publication Jun 1, 2011; last revision received Aug 12, 2011; accepted Oct 27, 2011.

Reprint requests: Ravinder Anand, PhD, The EMMES Corporation, 401 N Washington Street, Suite 700, Rockville, MD 20850. E-mail: ranand@emmes.com

References

1. Thuluvath PJ, Guidinger MK, Fung JJ, Johnson LB, Rayhill SC, Pelletier SJ. Liver transplantation in the United States, 1999-2008. Am J Transplant 2010;10:1003-19.
2. Kamath BM, Olthoff KM. Liver transplantation in children: update 2010. Pediatr Clin North Am 2010;57:401-14.
3. Ng VL, Fecteau A, Shepherd R, Magee J, Bucuvalas J, Alonso E, et al. Outcomes of 5-year survivors of pediatric liver transplantation: report on 461 children from a North American multicenter registry. Pediatrics 2008;122:1128-35.
4. Barber K, Blackwell J, Collett D, Neuberger J. Life expectancy of adult liver allograft recipients in the UK. Gut 2007;56:279-82.
5. Duffy JPK, Kao K, Ko CY, Farmer DG, McDiarmid SV, Hong JC, et al. Long-term patient outcome and quality of life after liver transplantation: analysis of 20-year survivors. Ann Surg 2010;252:652-61.
6. Bucuvalas JC, Alonso E, Magee JC, Talwalkar J, Hanto D, Doo E. Improving long-term outcomes after liver transplantation in children. Am J Transplant 2008;8:2506-13.
7. Choquette M, Goebel JW, Campbell KM. Nonimmune complications after transplantation. Pediatr Clin North Am 2010;57:505-21.
8. Alonso EM, Limbers CA, Neighbors K, Martz K, Bucuvalas JC, Webb T, et al. Cross-sectional analysis of health-related quality of life in pediatric liver transplant recipients. J Pediatr 2010;156:270-6.
9. Limbers CA, Neighbors K, Martz K, Bucuvalas JC, Webb T, Varni JW, et al. Health-related quality of life in pediatric liver transplant recipients compared with other chronic disease groups. Pediatr Transplant 2011;15:245-53.
10. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambul Pediatr 2003;3:329-41.
11. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care 2001;39:800-12.
12. Nunnally JC, Bernstein IR. Psychometric therory. 3rd ed. New York: McGraw-Hill; 1994.
13. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Erlbaum; 1988.
14. Schwartz GJ, Haycock GB, Edelmann CM Jr., Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 1976;58:259-63.
15. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 2003;139:137-47.
16. Soltys KA, Mazariegos GV, Squires RH, Sindhi RK, Anand R, Group SR. Late graft loss or death in pediatric liver transplantation: an analysis of the SPLIT database. Am J Transplant 2007;7:2165-71.
17. Nobili V, Candusso M, Torre G, de Ville de Goyet J. Steatosis and fibrosis in pediatric liver transplant: insidious graft's enemies. A call for clinical studies and research. Pediatr Transplant 2010;14:441-4.
18. Magee JC. Graft fibrosis in stable pediatric liver transplant recipients: what does it mean? Hepatology 2009;49:726-8.
19. Scheenstra R, Peeters PM, Verkade HJ, Gouw AS. Graft fibrosis after pediatric liver transplantation: ten years of follow-up. Hepatology 2009;49:880-6.
20. Evans HM, Kelly DA, McKiernan PJ, Hubscher S. Progressive histological damage in liver allografts following pediatric liver transplantation. Hepatology 2006;43:1109-17.
21. Alonso EM, Shepherd R, Martz KL, Yin W, Anand R, Group SR. Linear growth patterns in prepubertal children following liver transplantation. Am J Transplant 2009;9:1389-97.
22. Sgourakis G, Radtke A, Fouzas I, Mylona S, Goumas K, Gockel I, et al. Corticosteroid-free immunosuppression in liver transplantation: a meta-analysis and meta-regression of outcomes. Transpl Int 2009;22:892-905.
23. Campbell K, Ng V, Martin S, Magee J, Goebel J, Anand R, et al. Glomerular filtration rate following pediatric liver transplantation: the SPLIT experience. Am J Transplant 2010;10:2673-82.
24. Hathout E, Alonso E, Anand R, Martz K, Imseis E, Johnston J, et al. Post-transplant diabetes mellitus in pediatric liver transplantation. Pediatr Transplant 2009;13:599-605.
25. Porter ME. What is value in health care? N Engl J Med 2010;363:2477-81.
26. Nicholas DB, Otley AR, Taylor R, Dhawan A, Gilmour S, Ng VL. Experiences and barriers to health-related quality of life following liver transplantation: a qualitative analysis of the perspectives of pediatric patients and their parents. Health Qual Life Outcomes 2010;8:150-7.
27. Bell LE, Bartosh SM, Davis CL, Dobbels F, Al-Uzri A, Lotstein D, et al. Adolescent transition to adult care in solid organ transplantation: a consensus conference report. Am J Transplant 2008;8:2230-42.

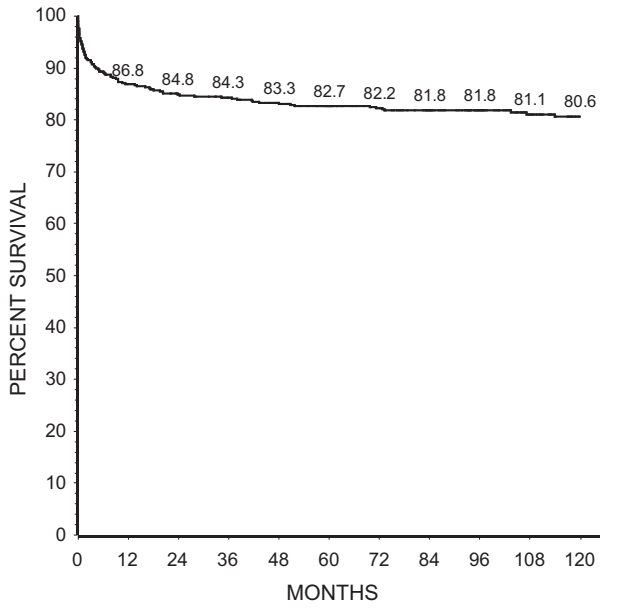

Figure 1. Kaplan-Meier probability of patient survival, 10-year and non–10-year survivors (n = 632).

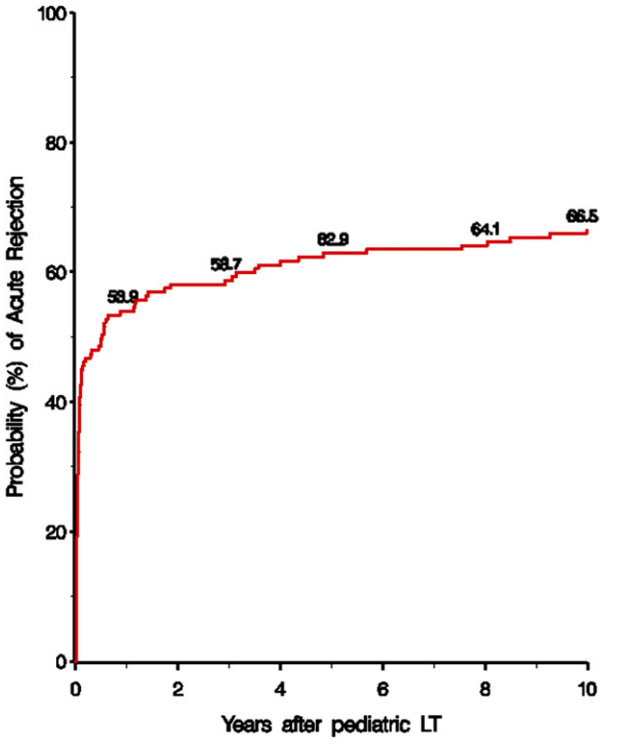

Figure 2. Kaplan-Meier probability of acute rejection after LT in children.

Table V. Presence of one or more medical variable excluding 53 patients with complete data from being an ideal survivor

Number of Failures	Retx	Chronic Rejection	Abnormal ALT	Abnormal Total Bilirubin	Abnormal Albumin	Abnormal GGT	PTLD	Renal Dysfunction	Growth Deficit	Diabetes	Ongoing Prednisone	Anti-hypertensive agent	Anti-seizure medication	Frequency
1	■													2
		■												3
			■											1
				■										1
						■								2
								■						4
									■					2
											■			5
												■		6
2	■	■												2
		■						■						1
			■			■								2
				■		■								1
						■					■			1
								■				■		1
											■	■		3
3	■	■					■							1
	■	■				■								1
	■		■									■		1
	■					■		■						1
	■					■					■			1
		■	■			■								1
		■									■	■		1
			■				■				■			1
			■						■		■			1
			■						■			■		1
									■		■	■		1
4	■					■					■	■		1
		■	■			■	■							1
			■			■		■			■			1
						■		■			■	■		1
8	■				■	■		■	■	■	■	■		1
														53

Each shaded cell represents the presence of a post-transplantation complication and thereby the reason for failure to achieve an ideal survivor composite profile. Patients with <13 completed medical variables (n = 61) were ineligible for ideal survivor status, and thus are not represented in this **Table**.

Appendix

The SPLIT Research Group is composed of the following centers, investigators, and coordinators: Alfred I. Dupont Hospital for Children, Wilmington, DE (S. Dunn, J. Menendez, V. Gopalareddy); Boston Children's Hospital, Boston, MA (M. Jonas, L. Krawczuk); Cardinal Glennon Children's Hospital, St Louis University, St Louis, MO (R. Kane, H. Solomon, E. Phillips); Children's Healthcare of Atlanta, Atlanta, GA (T. Heffron, J. DePaolo, T. Pillen, G. Smallwood, L. Davis, D. Welch); Children's Hospital Cincinnati, Cincinnati, OH (J. Bucuvalas, W. Balistreri, F. Ryckman, A. Howkins, S. Krug, G. Arya); Children's Hospital, University of Colorado School of Medicine, Aurora, CO (M. Narkewicz, R. Sokol, F. Karrer, K. Orban-Eller); Children's Hospital of Philadelphia, Philadelphia, PA (E. Rand, C. Goodsell); Children's Hospital of Pittsburgh, Pittsburgh, PA (G. Mazariegos, L. Chien, A. Smith); Children's Hospital Western Ontario, London, Ontario, Canada (P. Atkinson); Children's Hospital of Wisconsin, Wauwatosa, WI (G. Telega, S. Lerret, J. Nebel); Children's Medical Center of Dallas, Dallas, TX (J. Roden, N. Mittal, B. Friedman, L. Arnott, D. Cross, L. Cutright, E. Faye); Children's Memorial Medical Center, Chicago, IL (E. Alonso, R. Superina, P. Whitington, J. Lokar, K. Neighbors, S. Kelly); Children's Mercy Hospital, Kansas City, MO (W. Andrews, J. Daniel, V. Fioravanti, A. Tendick); Duke University School of Medicine, Durham, NC (D. Desai, S. Jarvis); Hospital for Sick Children Toronto, Toronto, Ontario, Canada (E. DeLuca, A. Fecteau, V. Ng); Indiana University Medical Center, Indianapolis, IN (J. Tector, J. Lim, J. Molleston, J. Pearson); Johns Hopkins Hospital, Baltimore, MD (P. DeRusso, P. Colombani, M. Alford, C. Bhave, L. Wilson, R. Jurao); Le Bonheur Children's Medical Center, Memphis, TN (H. Shokough-Amiri, H.Grewal, S. Powell); Mayo Medical School, Rochester, MN (D. Freese, J. Weckwerth, J. Greseth, L. Pearson, L. Young); Medical College of Virginia, Richmond, VA (R. Fisher, M. Akyeampong, M. Benka, A. Lassiter); Mount Sinai Medical Center, New York, NY (S. Emre, B. Shneider, S. Cuellar, R. Gagliardi); New York Presbyterian Hospital, New York, NY (S. Lobritto, L. Smith, P. Harren, K. Ventura); Primary Children's Medical Center, Salt Lake City, UT (L. Book, M. O'Gorman, C. Kawai, L. Bruschke, J. Kraus, R. Thorson); Sainte-Justine Hospital, Montreal, QC, Canada (F. Alvarez, S. Martin, C. Viau); St Christopher's, Philadelphia, PA (H. Soriano, K. Falkenstein); St Louis Children's Hospital, St Louis, MO (R. Shepherd, J. Lowell, M. Nadler); Stanford University Medical Center, Palo Alto, CA (K. Cox, W. Berquist, M. Kreisl, S. Alvarez, R. Berquist); Texas Children's Hospital, Houston, TX (S. Karpen, J. Mayo, J. Goss, B. Carter, D. Ybarra); University of California Los Angeles Medical Center, Los Angeles, CA (S. McDiarmid, S. Fiest); University of Alberta, Edmonton, AB, Canada (S. Gilmour, L. Greet, N. Kneteman); University of California, San Diego, CA (J. Lavine, A. Khanna, R. Clawson); University of California, San Francisco, CA (P. Rosenthal, D. Filipowski, J. Roberts); University of Chicago, Chicago, IL (J. Millis, P. Boone); University of Florida-Shands, Gainesville, FL (R. Gonza′ lez-Peralta, M. Hodik, M. Langham); University of Miami, Jackson Memorial Hospital, Miami, FL (A. Tzakis, T. Kato, D. Weppler, L. Cooper, M. Gonzalez, A. Santiago); University of Michigan, Ann Arbor, MI (J. Lopez, J. Magee, V. Shieck); University of Minnesota, Minneapolis, MN (A. Humar, B. Durand); University of Nebraska, Omaha, NE (A. Langnas, D. Antonson, J. Botha, W. Grant, D. Sundan, D. Andersen, B. Fleckten, K. Seipel, B. Shaw, C. Torres); University of North Carolina, Chapel Hill, NC (J. Fair, J. Prinzhorn, P. McIver, J. Young, A. Raizada); University of Rochester, Strong Memorial Hospital, Rochester, NY (T. Shisler, M. Orloff, T. Rossi, C. Hill- Sober); University of Texas, HSC San Antonio, San Antonio, TX (G. Halff, J. Silva); University of Washington, Seattle, WA (S. Horslen, K. Larocque); and University of Wisconsin, Madison, WI (M. Kalayoglu, A. D'Alessandro, N. Erickson, R. Judd, S. Knechtle, E. Spaith).