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Outcomes of 5-Year Survivors of Pediatric Liver Transplantation: Report on 461 Children From a North American Multicenter Registry

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What's Known on This Subject

The success of liver transplantation in children is defined by more than just excellent survival rates. Better understanding of the long-term medical considerations is of critical importance in pediatric liver transplant recipients, who by nature of their young age face a greater cumulative burden of life-long immunosuppression.

What This Study Adds

Providing insight into the cumulative North American experience of long-term survivors after pediatric liver transplantation, this study emphasizes the need for a collaborative partnership between primary care practitioners and pediatric health care providers both beyond and within transplant centers to further improve outcomes for pediatric liver transplant recipients.

ABSTRACT

OBJECTIVES. Although liver transplantation has been the standard of care therapy for life-threatening liver diseases for >20 years, data on the long-term impact of liver transplantation in children have been primarily limited to single-center experiences. The objective of this study was to characterize and evaluate the clinical course of children who have survived ≥ 5 years after pediatric liver transplantation in multiple centers across North America.

PATIENTS AND METHODS. Patients enrolled in the Studies of Pediatric Liver Transplantation database registry who had undergone liver transplantation at 1 of 45 pediatric centers between 1996 and 2001 and survived >5 years from liver transplantation were identified and their clinical courses retrospectively reviewed.

RESULTS. The first graft survival for 461 five-year survivors was 88%, with 55 (12%) and 10 (2%) children undergoing a second and third liver transplantation. At the 5-year anniversary clinic visit, liver function was preserved in the majority with daily use of immunosuppression therapy, including a calcineurin inhibitor and oral prednisone, reported by 97% and 25% of children, respectively. The probability of an episode of acute cellular rejection occurring within 5 years after liver transplantation was 60%. Chronic rejection occurred in 5% patients. Posttransplant lymphoproliferative disease was diagnosed in 6% children. Calculated glomerular filtration rate was <90 mL/minute per 1.73 m² in 13% of 5-year survivors. Age- and gender-adjusted BMI >95th percentile was noted in 12%, with height below the 10th percentile in 29%.

CONCLUSIONS. Children who are 5-year survivors of liver transplantation have good graft function, but chronic medical conditions and posttransplantation complications affect extrahepatic organs. A comprehensive approach to the management of these patients' multiple unique needs requires the expertise and commitment of health care providers both beyond and within transplant centers to further optimize long-term outcomes for pediatric liver transplant recipients. *Pediatrics* 2008;122:e1128–e1135

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Key Words

liver transplantation, long-term outcome, renal function, school performance

Abbreviations

LT—liver transplantation
 SPLIT—Studies of Pediatric Liver Transplantation
 PTL—posttransplant lymphoproliferative disease
 EBV—Epstein-Barr virus
 cGFR—calculated glomerular filtration rate
 ADHD—attention-deficit/hyperactivity disorder
 LD—learning disability

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IN 1983, THE National Institutes of Health Consensus Conference declared liver transplantation (LT) to be a standard-of-care therapeutic modality for selected patients with life-threatening liver disease,¹ which, in children, is most commonly caused by diseases such as biliary atresia, fulminant liver failure, and metabolic diseases and less commonly by liver tumors and other rarer conditions.² Current 1-year patient survival rates are >90%, and 5-year

rates are >85% at experienced centers (The SPLIT Research Group, Annual Report, written communication, 2007).³⁻⁶ However, it is increasingly clear that the success of LT in children is defined by more than just excellent patient or graft survival rates, with a fatal disease being replaced by a chronic condition with its own associated extrahepatic comorbidities, as highlighted by multiple single-center studies assessing the long-term health and outcomes of children who have undergone LT.⁷⁻¹³ However, such single-center experiences may not be universally representative of long-term outcomes at all programs. Data available from a cumulative data set of pediatric LT recipients provided an opportunity to address this current gap in knowledge. Initiated in 1995, the Studies in Pediatric Liver Transplantation (SPLIT) registry is a prospective database following children under the age of 18 years who receive a LT in the United States and Canada.¹⁴ Herein, the objective of this study was to characterize the clinical outcomes and health status of children registered in an international multicenter consortium who were alive 5 years after LT.

METHODS

Subjects of the Study

As of June 1, 2006, the SPLIT registry database contained data on 2291 children who had undergone a first liver-only transplantation at 1 of 45 SPLIT centers. A 5-year survivor was defined as any pediatric recipient of a LT between March 1991 and June 2001 who had his or her 5-year anniversary clinic visit at a SPLIT center between 57 and 65 months after the date of first transplant surgery. Therefore, excluded from further study were patients who had died <57 months after LT ($n = 268$), were not reported to have died and had <57 months of follow-up data in the SPLIT database ($n = 1543$), or had survived >57 months but did not have a 60-month visit recorded in the SPLIT registry ($n = 19$). Hence, the final study cohort was composed of a total of 461 five-year survivors. As described previously, all of the participating SPLIT centers had institutional review board and/or research ethics board approval for data collection and analysis.¹⁵ Individual informed consent was obtained from parents and/or guardians.

Data Collection

After LT, follow-up data were submitted by each participating center to the SPLIT data coordinating center every 6 months for 2 years and annually thereafter until the subject's 18th birthday. These regular follow-up forms requested data elements on demographics, blood chemistry, hospitalizations, school status and performance, infections, posttransplant complications, immunosuppression, and other medication regimens, with events such as death, retransplantation, allograft rejection, and posttransplant lymphoproliferative disease (PTLD) reported on separate forms. For data analysis in this study, all of the SPLIT 5-year follow-up and accompanying event forms were reviewed. Collection of detailed data on school performance began in 2002.

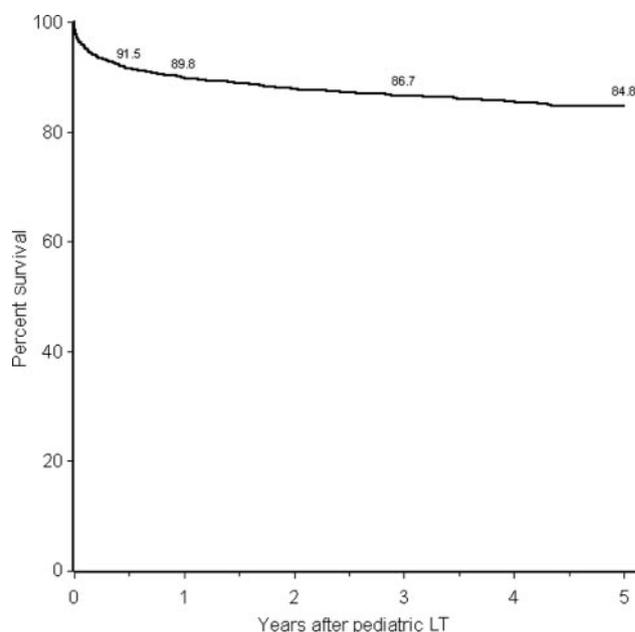


FIGURE 1
Kaplan-Meier probability of patient survival after pediatric LT.

Statistical Methods

Statistical analyses were performed using the SAS System for Windows 8.02 (SAS Institute, Inc, Cary, NC), and differences were tested using χ^2 , Student's *t*, Wilcoxon, and log-rank tests. Standardized height-for-age, weight-for-age, and BMI *z* scores were calculated by reference to age- and gender-specific charts for the normal population (Centers for Disease Control and Prevention, please see www.cdc.gov/growthcharts). Kaplan-Meier curves were used to plot the probabilities of patient survival for all of the patients enrolled within the SPLIT registry, as well as graft survival and acute cellular rejection against time since LT for the study cohort of 5-year survivors.

RESULTS

Overall 1- and 5-year Kaplan-Meier estimates of patient survival after pediatric LT for all of the SPLIT registry participants are 89.8% and 84.8% (Fig 1). The clinical and demographic details of this study cohort's 461 five-year survivors of pediatric LT are provided in Table 1. Twenty percent ($n = 91$) of children received live donor grafts. Deceased donor organs were used as whole ($n = 233$ [51%]), reduced ($n = 97$ [21%]), and split ($n = 36$ [8%]) grafts. Graft type was unrecorded in 4 deceased donor cases.

Graft Outcome

Among the 5-year survivors, first allograft survival rates at 1, 3, and 5 years were 93%, 90%, and 88%, respectively (Fig 2), with no statistically significant difference in graft survival rate by type of donor graft (log rank $P = .1558$; Fig 3). Retransplantation was required in 55 (12%) 5-year survivors and occurred more frequently in children receiving primary LT before January 1, 2000

TABLE 1 Five-Year Survivor Characteristics (n = 461)

Characteristic	Measurement
Recipient age at liver transplant, y	
Median (quartiles)	1.6 (0.7, 6.5)
<1 y of age, n (%)	177 (38.4)
<2 y of age, n (%)	249 (54)
>13 y of age, n (%)	30 (6.5)
Gender, % male	48.6
Ethnicity, n (%)	
White	303 (65.7)
Black	76 (16.5)
Hispanic	56 (12.1)
Other	26 (5.7)
Primary diagnosis, n (%)	
Biliary atresia	220 (47.7)
Metabolic liver disease ^a	59 (12.8)
Acute liver failure	51 (11.1)
Tumor	19 (4.1)
Other cholestatic conditions ^b	68 (14.8)
Other ^c	44 (9.5)
Follow-up time, median (range), y	6.0 (4.8–15.0)

^a Data include α -1-antitrypsin deficiency, Crigler-Najjar syndrome, cystic fibrosis, glycogen storage disease, inborn errors in bile acid metabolism, neonatal hemochromatosis, primary hyperoxaluria, tyrosinemia, urea cycle defects, and Wilson's disease.

^b Data include Alagille syndrome, Byler disease, progressive intrahepatic cholestatic syndromes, total parenteral nutrition cholestasis, sclerosing cholangitis, and idiopathic cholestasis.

^c Data include congenital hepatic fibrosis, Budd-Chiari syndrome, autoimmune hepatitis cirrhosis, drug toxicity, hepatitis C cirrhosis, and unknown cirrhosis.

(*n* = 43 [13.9%]), than in patients transplanted after January 1, 2000 (*n* = 12 [7.9%]; log rank *P* = .0804). Indications for pediatric liver retransplantation included hepatic artery thrombosis (*n* = 16), chronic rejection (*n* = 8), primary graft dysfunction (*n* = 7), biliary complications (*n* = 6), and miscellaneous (*n* = 13). In 5 patients, the reason for LT was missing. Ten 5-year survivors (2%) underwent a third LT.

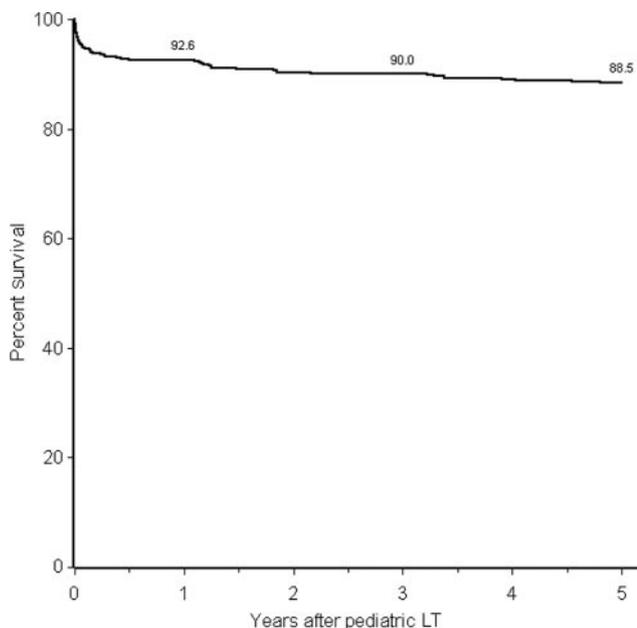


FIGURE 2 Kaplan-Meier probability of first allograft survival of 5-year survivors of pediatric LT.

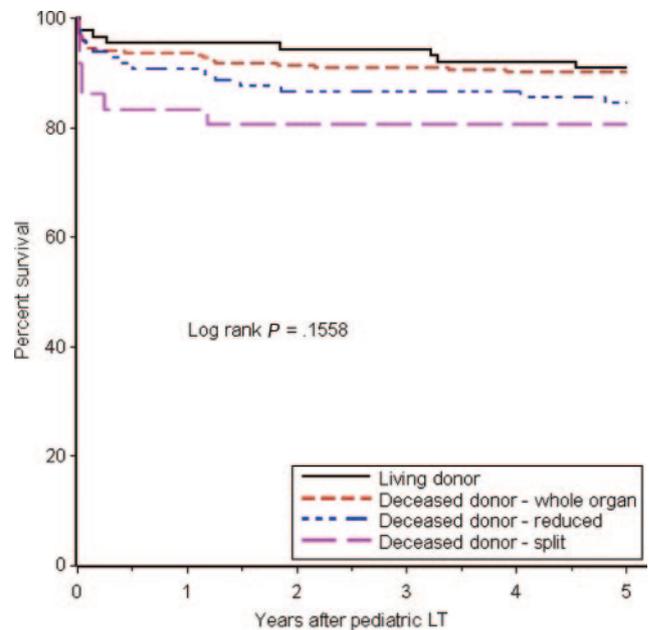


FIGURE 3 Kaplan-Meier probability of first allograft survival by graft type among 5-year survivors of pediatric LT.

Serum levels of total bilirubin and albumin at the 5-year anniversary visit were normal in 91% and 94% of patients, respectively (Table 2). Serum aspartate aminotransferase and alanine aminotransferase levels were within reference ranges in 67% and 69% of patients. Serum γ -glutamyltransferase levels, corrected for age and gender, were normal in 54% of children.¹⁶

Graft Rejection and Immune Suppression

Within the first 5-year period after primary LT, 276 patients (60%) had ≥ 1 documented episode of acute

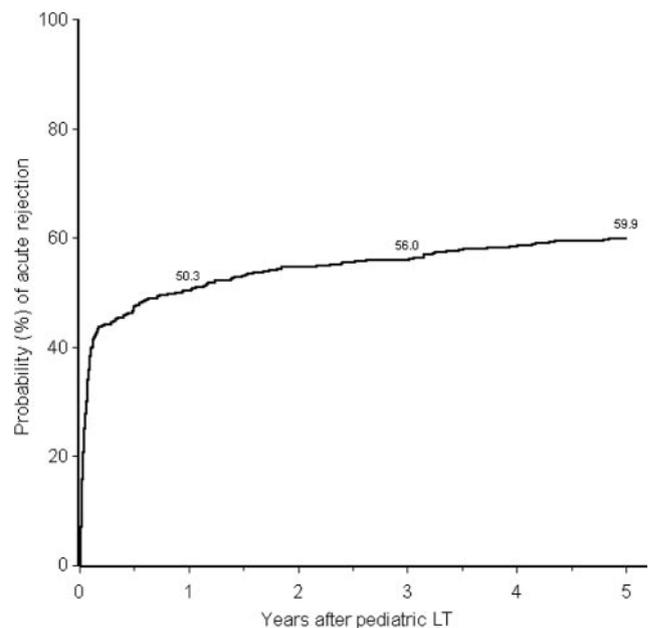


FIGURE 4 Kaplan-Meier probability of acute rejection after LT in children.

TABLE 2 Liver Tests, Biochemistry Results, and Outcomes 5 Years After LN

Test	N	Mean ± SD	% With Abnormal Test ^a
Alanine aminotransferase, IU/L	424	44 ± 61	31
Aspartate aminotransferase, IU/L	424	47 ± 38	33
γ-Glutamyltransferase, IU/L	380	65 ± 130	46
Total bilirubin, μmol/L	448	11.8 ± 27.8	9
Albumin, g/L	435	43 ± 30	6
Serum creatinine, μmol/L	440	58 ± 76	5
cGFR, mL/min per 1.73 m ²	352	135 ± 61	13
Cholesterol, mmol/L ^b	173	3.60 ± 0.98	47
Triglycerides, mmol/L ^b	167	1.01 ± 0.56	25
Hemoglobin, g/L ^b	74	130 ± 16	38
Height/age, z score	361	-0.72 ± 1.43	
<25th percentile	—	—	47
<10th percentile	—	—	29
<3rd percentile	—	—	18
Weight/age, z score	364	-0.16 ± 1.38	
<25th percentile	—	—	29
<10th percentile	—	—	18
<3rd percentile	—	—	10

^a Reference ranges are as follows: alanine aminotransferase, <40 IU/L; aspartate aminotransferase, <45 IU/L; γ-glutamyltransferase, <15 years: <45 IU/L, ≥15 years: male subjects, <75 IU/L, female subjects, <55 IU/L; total bilirubin, <17.2 μmol/L; albumin, 33–58 g/L; creatinine, <106 μmol/L; cGFR, ≥90 mL/minute per 1.73 m²; total cholesterol, 3.21–4.40 mmol/L; triglycerides, 0.40–1.30 mmol/L; hemoglobin: male subjects, 130–160 g/L, female subjects, 120–160 g/L.

^b Data were not collected routinely at all SPLIT centers. Collection of hemoglobin began in October 2005.

cellular rejection, with 19 of these children subsequently receiving augmentative immunosuppression therapy with OKT3 (a monoclonal lymphocyte-depleting agent; *n* = 18) or thymoglobulin (a polyclonal lymphocyte-depleting agent; *n* = 1) because of nonresponse to conventional pulse methylprednisone therapy. Figure 4 shows the cumulative incidence of acute rejection in the first 5 years after LT.

Histologically confirmed chronic rejection was diagnosed in 21 patients (5%) during the first 5 years after LT, with mean serum total bilirubin levels at the time of diagnosis of 78 μmol/L (SD: 103 μmol/L). Median time to first evidence of chronic rejection was 1.4 years (range: 0.1–5.0 years). Eight (38%) of these 21 patients underwent a liver retransplantation, including 1 patient who subsequently received a third allograft because of chronic rejection.

Ninety-eight percent of 5-year survivors remained on a calcineurin inhibitor-based immunosuppression regimen of either tacrolimus (74%) or cyclosporine (24%) taken twice daily. Calcineurin inhibitor immunosuppression was used more often as monotherapy (tacrolimus 48.0% or cyclosporine 15.0%) than in combination therapy with additional immunosuppression agents such as sirolimus (3.6%) or mycophenolate mofetil (14.0%; Table 3). Mean tacrolimus trough levels were significantly lower for children on tacrolimus monotherapy compared with children taking tacrolimus in combination with additional immune suppression agents (*P* < .0001). Mycophenolate mofetil was never used as monotherapy, whereas sirolimus was used as mono-

TABLE 3 Immunosuppression Medications Taken by Survivors at the 5-Year Anniversary Visit

Drug	Patients Receiving the Drug, <i>n</i> (%)	Daily Dose, Mean ± SD, mg
Cyclosporine	107 (24)	128.9 ± 81.5
Tacrolimus	332 (74)	3.4 ± 2.6
Prednisone	114 (26)	6.5 ± 8.1
Mycophenolate mofetil	63 (14)	782.5 ± 562.8
Azathioprine	16 (4)	45.8 ± 44.5
Sirolimus	17 (4)	2.4 ± 3.1
Single-drug therapy	285 (64)	—
Double-drug therapy	111 (25)	—
Triple-drug therapy	51 (11)	—

Data are for 447 out of 461 five-year survivors; information regarding immunosuppression at 60-month visit was missing for 14 survivors.

therapy in 2 children. Two children (0.4%) were reported to be off all of the immune suppression therapy at their 5-year anniversary visit.

Twenty-five percent (*n* = 114) of patients were still on prednisone at the 5-year anniversary visit, with a median daily dosage of 5 mg (range: 1–60 mg). The probability of remaining on prednisone after 5 years did not differ between patients transplanted before or after June 1, 2000 (25% and 23%, respectively). Possible explanations for steroid requirement at 5 years after LT included a primary baseline disease of autoimmune hepatitis (*n* = 9); treatment for an acute cellular rejection episode within the preceding 12 months (*n* = 27, of whom 4 had baseline autoimmune hepatitis); and histologically confirmed chronic rejection (*n* = 8, of whom 1 had a late acute cellular rejection). Hence, there remained 75 children for whom the reason for prednisone usage at the 5-year anniversary clinic visit could not be determined.

Epstein-Barr Virus and PTLD

Five years after LT, 165 (59%) of 281 patients who were Epstein-Barr virus (EBV) seronegative at time of transplant surgery had not seroconverted. Of those who did seroconvert, 94 did so during the first year after LT. Symptomatic EBV disease was reported in 70 patients by the 5-year follow-up visit. Tissue-confirmed PTLD was diagnosed in 28 (6%) of 5-year survivors, with 23 of these children under the age of 2 years at the time of LT and 2 children receiving treatment with a lymphocyte-depleting agent for steroid-resistant acute cellular rejection. Seven (25%) of these 28 patients had never had a previous episode of either acute cellular or chronic rejection. Nine of the patients previously diagnosed with PTLD were still receiving prednisone at the 5-year anniversary clinic visit.

Renal Dysfunction

The median serum creatinine level for 440 five-year survivors was 44 μmol/L. The use of a nondiuretic antihypertensive medication was reported by 41 children at the 5-year visit, with 20 (49%) concurrently on prednisone. Median calculated glomerular filtration rate (cGFR) using the Schwartz formula¹⁷ for 352 patients

was 128 mL/minute per 1.73 m² (range: 12–301 mL/minute per 1.73 m²). Stage 2 chronic kidney disease, defined as cGFR <90,¹⁸ was identified in 45 children (13%; Table 2). Ten patients had a cGFR <70 mL/minute per 1.73 m², whereas 138 patients (39%) had a cGFR >140 mL/minute per 1.73 m². Mean cGFR at the time of primary LT did not differ significantly between children with 5 year cGFR ≥90 and those with 5 year cGFR <90. There was a significant association between having cGFR <90 at transplant and still having a cGFR <90 at the 60-month visit (*P* = .02). No patients had undergone renal transplantation.

Growth

At 5-years after LT, height was significantly below that expected in the normal population, with 73% below average height, 47% below the lower quartile, and 29% below the 10th percentile. There was a strong association between low height at 60 months and still being on steroids at 60 months, with children under the 10th height percentile twice as likely to still be on steroids as compared with children above the 10th height percentile (36% vs 18%; *P* = .0004). Weight distribution of 5-year survivors was similar to the normal population, with no weight deficit observed. Twelve percent of 5-year survivors were overweight, with body weights exceeding the 95th percentile. The probability of being overweight 5 years after LT was not associated with being on corticosteroids (15% overweight among those on prednisone vs 11% overweight among those not on steroids; *P* = .32).

Cardiovascular Risk Factors

The mean total serum cholesterol level for 173 five-year survivors was 3.59 mmol/L, and the median total serum triglyceride level for 167 patients was 1.0 mmol/L (Table 2). Of available fasting serum cholesterol and triglyceride levels, 7% and 10%, respectively, of 5-year survivors were reported in the hypercholesterolemia and hypertriglyceridemia range.

Sixty-two (13%) of 461 five-year survivors had evidence of diabetes mellitus after LT, with 53 patients (of 62 [85%]) on a tacrolimus-based immunosuppression regimen at the 5-year visit. Twenty-four patients (5%) were receiving either insulin or antihyperglycemic medications.

School Performance

Information on school performance in the year preceding the 5-year anniversary clinic visit was available for 103 survivors, of whom 31% were in grades 7 through 12. In this group, 17% survivors reported missing ≥20 school days in the preceding year. Approximately 18% of 5-year survivors had either repeated a grade or been held back ≥1 school year. Information regarding attention-deficit/hyperactivity disorder (ADHD) and learning disability (LD) was only available for 5-year visits made after August 2005. In this small subset of 47 survivors, an established diagnosis of ADHD or LD was reported by parents in 5 (11%) and 10 (21%) of 5-year survivors,

respectively. Prednisone use at the 5-year visit was reported for 1 (20%) and 2 (20%) of these patients with ADHD and LD, respectively.

DISCUSSION

The present findings demonstrate that children who have undergone LT require ongoing medical attention for multiple comorbid conditions. The primary physician and the general pediatrician, because of their longitudinal knowledge of and unique relationship with patients and their families, are in an advantageous position to screen for and detect the early signs of such medical complications, as well as to recognize risks or clues of noncompliance with immunosuppressive therapy that may jeopardize the long-term health of the transplanted graft, particularly as patients enter adolescence. Prompt bidirectional communication between primary physicians and transplant centers about such important observations will facilitate involvement, set expectations, and provide guidance for both families and all health care professionals toward the goal of maximizing the successes attainable by this ever-growing population of patients.

The overall 5-year graft survival rate was 88%, with no statistical difference in graft outcomes between the graft types used at LT surgery. Although a recent analysis of a larger SPLIT cohort found that technical variant (reduced and split) grafts were associated with increased morbidity and decreased overall survival,¹⁹ the lack of difference was likely attributable to the fact that this present study considered graft survival specifically for 5-year survivors, with all graft failures later than 65 months after LT censored. We have previously reported a multicenter pediatric liver retransplantation rate of 11.2%.²⁰

Although tests of graft function were preserved in 90% of 5-year survivors, one third of children did not have completely normalized liver enzymes. This suggests some level of ongoing graft inflammation. The diagnosis of chronic hepatitis with accompanying liver fibrosis on liver histopathology described in 43% of otherwise asymptomatic 5-year survivors has speculated that the use of standard liver biochemistry tests without accompanying histopathological information from a liver biopsy may be inadequate in the monitoring or prognostication of long-term allograft status.²¹ Whether pediatric recipients can expect long-standing normal graft function as currently hoped or whether there will be a gradual decline and eventual graft loss in certain circumstances can only be answered by properly designed prospective longitudinal studies.^{22,23}

Lifelong immunosuppression, with reduction over time, remains the present practice recommended by the vast majority of pediatric LT programs. Currently, most programs strive to achieve just enough immunosuppression to preserve graft function and maximize graft life, ever mindful of the many adverse effects. The occurrence of tissue-confirmed PTLD in 6% in this study cohort undergoing primary LT before 2001 reemphasizes the need for careful attention to immunosuppression practices alongside surveillance and treatment strategies

to further decrease its prevalence.^{7,12} As newer immunosuppressive agents become available to LT teams, the late use of steroids in almost one quarter of our 5-year survivors for indications such as recent acute cellular rejection therapy may lessen with time,²⁴ because the concerns of steroid effects on posttransplant catch-up linear growth are long standing.^{25–27} The fact that 2 children were off immunosuppression all together at their 5-year anniversary clinic visit sustains the hope that stable organ engraftment with very low dependence or complete freedom from long-term immunosuppression therapy may become more widely achievable.²⁸

Cyclosporine and tacrolimus are known to cause significant nephrotoxicity,²⁹ with adult LT recipients identified to have a 5-year cumulative incidence of 18%.³⁰ The prevalence of stage 2 chronic kidney disease in 13% of our 5-year survivors may be an underestimate, given the known limitations of cGFR overestimating true glomerular filtration rate values in children.^{31,32} Indeed, when the “gold standard” of measured glomerular filtration rate with a radiolabeled nucleotide, such as technetium-labeled diethylene triamine pentaacetic acid, was used, renal insufficiency was identified in 33% and 77% of 3-year survivors³³ and 10-year survivors¹³ of pediatric LT, respectively. Research is currently underway within SPLIT to identify those at risk for the development of posttransplant nephrotoxicity and to define contributing factors,³⁴ with the ultimate goals being to prevent renal disease, prevent progression of renal disease, and salvage renal function. Questions yet to be answered include understanding the implications of a hyperfiltrating cGFR, whether renal impairment after pediatric LT is progressive,^{35,36} when or if it becomes irreversible, and the long-term projected incidence.³⁷

The long-term need for antirejection therapies places children surviving LT at increased risk for the accelerated onset of traditionally viewed adult cardiovascular conditions, such as heart disease and stroke.³⁸ The prevalence of cardiovascular risk factors such as hypercholesterolemia, hypertriglyceridemia, glucose intolerance, and increased BMI in 13% of 5-year survivors highlights the importance of surveillance, recognition, and early referral for strategies geared at early prevention, lifestyle modification, and treatment.^{39,40}

Re-establishing normal growth and development is an important sign of effective rehabilitation after pediatric LT. In our study cohort, height remained well below that expected in the standard population. The beneficial effect of steroid withdrawal on linear growth in children after LT has been well demonstrated.^{41,42} Indeed, 5-year survivors with height below the 10th percentile were twice as likely to still be on steroids compared with those with height above the 10th percentile. The lack of a weight deficit can be interpreted as evidence of effective rehabilitation given that the probability of a 5-year survivor being overweight was not significantly associated with a prednisone requirement. Additional longitudinal follow-up is warranted to assess for the risk of developing childhood obesity, particularly with associated morbidities such as nonalcoholic fatty

liver disease on allograft longevity and cardiovascular risk factors.⁴³

Potential limitations and biases of this study relate to database registry research. Despite rigorous data quality procedures and routine site visits to the majority of SPLIT centers, missing and incomplete data are unfortunately common for many variables. This can be partially attributed to the fact that approval of SPLIT protocols by local institutional research boards is predicated on individual SPLIT centers reporting only data collected as part of that particular institution’s standard of care for patients after pediatric LT. 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, serum immunoglobulin levels, serum autoantibody titers, or EBV DNA by polymerase chain reaction values. Nonetheless, despite these limitations and biases, our results are important, because they provide insight into the cumulative North American experience of long-term survivors of pediatric LT, contributing to the generation of hypotheses for future research and the foundation for clinical trials aimed at reducing the incidence of observed complications.

CONCLUSIONS

The success of pediatric LT is defined by more than just patient or graft survival rates. An ever-increasing population of long-term survivors after pediatric LT requires the skill set, expertise, and commitment of pediatric health care providers both beyond and within pediatric transplant centers.

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