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ORIGINAL ARTICLE

# Sustained linear growth and preserved renal function in 10-year survivors of pediatric liver transplantation

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**Keywords**
growth, liver transplantation, long term, pediatric, renal function.

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## Summary

The aim of this study was to characterize the clinical outcomes of children and adolescents who achieved survival of more than 10 years following liver transplantation (LT) in a single center in Korea. From June 1996 to October 2003, 57 pediatric LTs were performed. The medical records of 44 patients who had survived more than 10 years were reviewed retrospectively. Median age of patients at LT was 0.8 years. Forty-one patients received living donor LT, and three patients received deceased donor LT. Biliary atresia was the most common indication (65.9%). Thirty-five patients were on tacrolimus monotherapy at 10 years post-LT with a mean trough level of 2.73 ng/ml, and five patients were maintaining stable graft function without any immunosuppression. There were no patients receiving antihypertensive medication and one case of diabetes mellitus. Renal dysfunction was seen in two patients (4.5%), while none required renal replacement therapy. Mean height *z*-score prior to LT was −1.35 and at 10 years post-transplant was 0.05. Good linear growth was sustained in this cohort throughout the 10 years, approaching the 50th percentile. Also, there were remarkably low incidences of renal dysfunction and patients requiring medications for glycemic or hypertensive control, all hallmarks of continued use of immunosuppressive agents.

## Introduction

Liver transplantation (LT) has proven to be a life-saving treatment for infants and children with end-stage liver disease of various etiologies. Analyses of large registry data sets from different parts of the world have shown graft and patient survival above 80% at 5–10 years post-transplant [1–4]. However, with longer expectancy of patient survival following pediatric LT, the focus has now shifted toward minimizing potential complications of sustained immunosuppression and quality-of-life issues. These recent areas of interest are of great importance to pediatric recipients, because many of these patients will now survive long enough to potentially acquire serious complications pertaining to their post-transplant status [5].

The aim of this study was to characterize the clinical outcomes of children and adolescents who achieved more than 10 years' survival following LT at a single center in Korea. Our goal was to portray how the transplant and the inevitable long-term immunosuppression impacted these children in their daily lives.

## Patients and methods

From June 1996 to October 2003, 56 pediatric LTs (recipient age ≤18 years) were performed at Samsung Medical Center (Seoul, Korea). Forty-four patients who are presently alive and being followed up at 10 years post-transplant were included in the study. The other 12 patients were excluded from the analysis due to patient death prior

 

to the 10-year follow-up visit. The medical records of 44 patients in the cohort were retrospectively reviewed.

Immunosuppression was given according to the following protocol. No induction therapy using antibody agents was used. A bolus of steroids was given intra-operatively (methylprednisolone 20 mg/kg) and was tapered to 0.3 mg/kg/day as oral prednisone by post-transplant day 8. This maintenance dose of prednisone was continued for 3 more weeks and was completely withdrawn at 1 month post-transplant. Maintenance immunosuppression was tacrolimus monotherapy beginning on the first post-transplant day with an initial target trough level of 10–12 ng/ml in the first week. Then, the target trough level was lowered to 8–10 ng/ml until 3 months and then 5–8 ng/ml for the rest of the first post-transplant year. For patients showing evidence of renal dysfunction, mycophenolate mofetil (MMF) was added to the regimen with a decrease in tacrolimus dosage.

Prophylaxis against Epstein–Barr virus (EBV) infection was provided for patients with a high risk of *de novo* EBV infection: an EBV IgG-positive donor/EBV naïve recipient combination or any recipient under the age of 12 months at LT. The prophylactic regimen consisted of ganciclovir given intravenously for 2 weeks, which was then switched to oral acyclovir for 24 months.

Standardized *z*-scores for height for age and weight for age were calculated based on age- and gender-specific growth charts for the normal Korean pediatric population [6]. Renal function was determined by calculated glomerular filtration rates (cGFR) using the Schwartz formula [7]. The values of $k$ in the equation were 0.45 for infants 1–52 weeks old, 0.55 for children 1–13 years old, 0.55 for adolescent girls 13–18 years old, and 0.7 for adolescent boys 13–18 years old, respectively.

## Results

Patient demographics are presented in Table 1. Median age of patients at LT was 0.8 years (range 2 months to 14 years). There were 20 boys and 24 girls. The most common etiology for LT was biliary atresia in 29 cases (65.9%), followed by neonatal hepatitis in five cases (11.4%), and acute liver failure in two cases (6.8%). Median pediatric end-stage liver disease (PELD) score at the time of LT was 17. The majority of cases were living donor LTs (93.2%), and the remaining three cases were deceased donor split LTs using left lateral section grafts.

There were 12 deaths before 10 years in our cohort. Seven cases were early mortalities (death within 90 days) including primary nonfunction and sepsis-related events. Late mortalities ranged from 14 months to 8 years post-transplant and were due to infection (three cases), post-transplant lymphoproliferative disease (PTLD, one case), and biliary complication (one case).

**Table 1.** Patient demographics.

| | $n = 44$ |
|---|---|
| Age at LT, median years (range) | 0.8 (2 months to 14 years) |
| Male:Female | 20:24 |
| Diagnosis, *n* (%) | |
| Biliary atresia | 29 (65.9) |
| Neonatal hepatitis | 5 (11.4) |
| Acute liver failure | 3 (6.8) |
| HBV-LC & HCC | 2 (4.5) |
| Wilson's disease | 1 (2.3) |
| Alagille syndrome | 1 (2.3) |
| Hemangioendothelioma | 1 (2.3) |
| Congenital hepatic fibrosis | 1 (2.3) |
| Cryptogenic LC | 1 (2.3) |
| PELD score, median (range) | 17 (−10 to 53) |
| Donor type, *n* (%) | |
| Living donor | 41 (93.2) |
| Deceased donor split | 3 (6.8) |
| Length of ICU stay, median days (range) | 8 (6 to 59) |
| Length of hospital stay, median days (range) | 38 (21 to 118) |

LT, liver transplantation; HBV, hepatitis B virus; LC, liver cirrhosis; HCC, hepatocellular carcinoma; PELD, pediatric end-stage liver disease; ICU, intensive care unit.

### Graft and patient outcome

Median follow-up time was 150 months after the first LT. Forty-three children had functioning grafts from the initial LT, and one patient received a second LT 15 years after the first LT. There were 248 cases of hospitalization during the 10 years of follow-up after initially being discharged after LT (0.56 readmission/person-year). Most cases of hospitalization were observed in the first post-transplant year (Fig. 1a). Patient conditions leading to these hospitalizations were infectious in 81 cases, vascular complication-related in 74 cases, and acute rejection in 34 cases (Fig. 1b).

Twenty children (45.5%) had at least one episode of biopsy-proven acute rejection (BPAR), and three children had more than three rejection episodes. A total of 32 BPARs were diagnosed in these children, with 17 cases (53.1%) occurring in the first post-transplant year. All cases of BPAR were effectively controlled with steroid pulse therapy or increments of tacrolimus. There were no cases diagnosed as chronic rejection.

### Renal function and other chronic medical conditions

Mean serum creatinine was 0.66 mg/dl (±0.18 SD), and mean cGFR was 103.28 ml/min/1.73 $m^2$ (±12.94 SD) at 10 years post-transplant. Forty-three patients had cGFR above 100 ml/min/1.73 $m^2$, while one patient (2.3%)


 

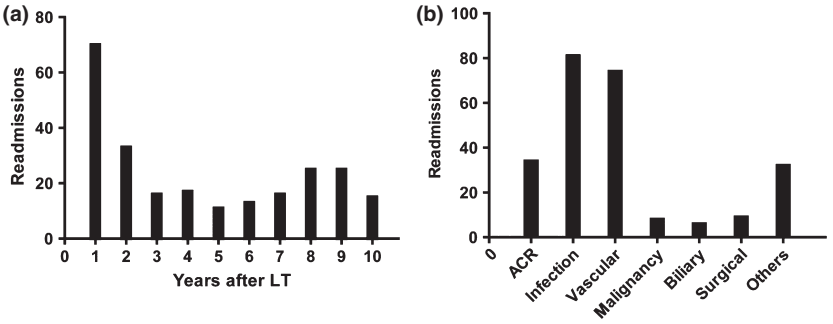


**Figure 1** (a) Hospital readmissions by years after liver transplantation and (b) causes of hospital readmissions in 10 year survivors of pediatric liver transplantation.

displayed mild renal dysfunction (cGFR <90 ml/min/1.73 $m^2$) at post-transplant 10 years. The patient was a 14-year-old girl with acute liver failure of unknown etiology and no renal dysfunction prior to transplant. Her serum creatinine was 1.2 mg/dl, and cGFR was 55.2 ml/min/1.73 $m^2$ at 10 years post-transplant. Her cGFR is currently 69.2 ml/min/1.73 $m^2$ at 14.5 years post-transplant with a tacrolimus trough level of 2.7 ng/ml. However, none were on dialysis or received kidney transplants. Serum creatinine and cGFR levels of 10-year survivors are shown in detail in Fig. 2.

Diabetes mellitus was diagnosed in one patient, who is currently using insulin for glucose control. No patients were on antihypertensive medications.

### Growth and social adjustment

Trends in linear growth and weight gain are shown in Fig. 3. Linear growth showed a steady rise from a mean *z*-score of −1.35 at pretransplant to −0.10 at 5 years post-transplant. The normalization in height observed in these patients was maintained at 10 years with a mean *z*-score of 0.05. A quick rise in weight *z*-score was observed at 1 year post-transplant from −1.18 to −0.34. From the third post-transplant year on, mean body weight of patients was near the 50th percentile of children of their gender and age.

Forty-four children and adolescents are either currently attending school at their age-appropriate grades or have completed their education. None has had to repeat a school year. Four patients (9.1%) currently hold full-time jobs after finishing their education.

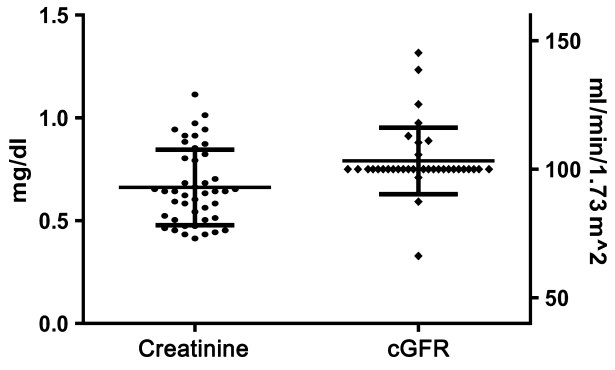


**Figure 2** Scatter plot of patients' creatinine and calculated glomerular filtration rate (cGFR) values at 10 years post-transplant showing mean and standard deviation.

### Immunosuppression and operational tolerance

Maintenance immunosuppression regimen at the last clinic visit is described in Table 2. Thirty-five patients (79.5%) were on tacrolimus monotherapy, and five patients were receiving both tacrolimus and MMF. No patient was receiving any form of corticosteroids at 10 years following LT. Mean tacrolimus trough levels across the 10 years following LT are shown in Fig. 4. Minimal dosages of tacrolimus were given to maintain trough levels below 3–4 ng/ml beyond the first post-transplant year. At post-transplant 10 years, 20 patients were maintaining stable graft function with tacrolimus trough levels <2.0 ng/ml, including four patients entirely off immunosuppression.

Five patients were off all immunosuppression medication at 10 years post-transplant (Table 3). Cumulative time off immunosuppression was 4–14 years. Reasons for discontinuing immunosuppression were noncompliance in four cases and management of PTLD in one case. All but one patient had normal liver function test results at 10 years. Three patients had protocol liver biopsies at post-transplant 10 years, which revealed no histological abnormality in one case and nonspecific minimal portal infiltrates in two cases.

### Post-transplant lymphoproliferative disease

Twenty-five patients (56.8%) were categorized as EBV high-risk and received prophylactic antiviral treatment. Six

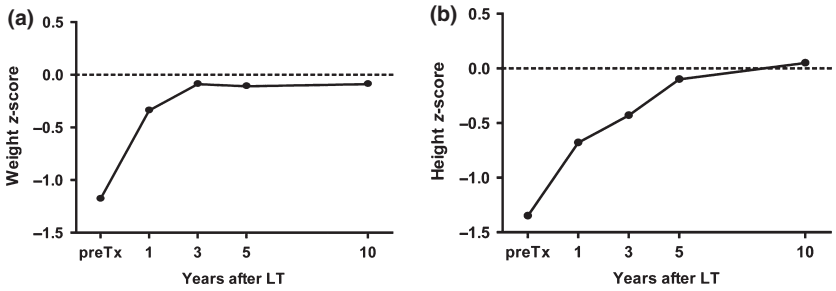


**Figure 3** (a) Mean height *z*-score of patients and (b) mean weight *z*-score of patients, from pretransplant to 10 years post-transplant.

**Table 2.** Current immunosuppression regimen.

| | *n* = 44 |
|---|---|
| Tacrolimus monotherapy | 35 |
| Tacrolimus + MMF | 4 |
| No immunosuppression | 5 |
| For PTLD treatment | 1 |
| Noncompliance | 4 |

MMF, mycophenolate mofetil; PTLD, post-transplant lymphoproliferative disease.

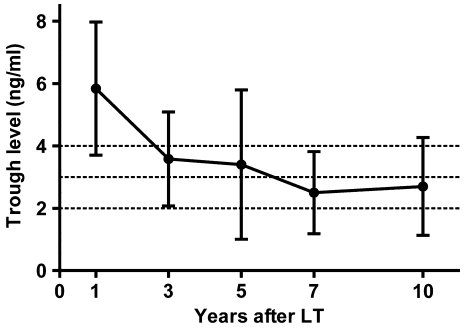


**Figure 4** Mean 12-h trough level of tacrolimus in patients taking tacrolimus by years after liver transplantation.

cases (6/44, 13.6%) of PTLD with positive tissue biopsies were diagnosed (Table 4). All patients with tissue-confirmed PTLD were EBV high-risk. PTLD was diagnosed between 4 and 18 months, with biopsies from the colon and rectum in four cases and tonsils in two cases. All cases were managed with minimization or discontinuation of immunosuppression.

### Vascular and biliary complications

Nine patients were diagnosed with stenosis or obstruction of the portal vein requiring intervention. Median time from transplantation to initiation of portal vein intervention was 107.3 months (range 5–190 months). Indications for portal vein intervention were abnormal liver function tests with concomitant signs of portal hypertension such as ascites, splenomegaly, or thrombocytopenia. Seven patients received percutaneous portal vein balloon angioplasty, and successful treatment of the stenosis was seen in five cases. Two patients had complete obstruction of the extrahepatic portal vein and were managed with splenorenal shunt surgery at 9 and 10 years post-transplant, respectively. Two patients were diagnosed with subhepatic inferior vena cava obstruction. These patients display well-developed collateral vessels and are being followed up without treatment. There were no complications related to the hepatic artery or the hepatic vein.

Biliary anastomosis leakage was seen in three cases during the immediate postoperative period. In two cases, hepaticojejunostomy revision was performed, while one case was conservatively managed with percutaneous drainage. There were two cases of biliary stricture that were detected at 1 month and 12 years post-transplant, respectively. Both cases required percutaneous transhepatic biliary drainage and serial balloon dilatations.

## Discussion

After the initial challenge of acute rejection was more or less overcome with stronger and more effective immunosuppression, attention in pediatric LT has shifted toward a new goal of maintaining allograft function while minimizing the long-term adverse effects of immunosuppressive agents in these children. Heightened interest in recent years on long-term outcomes, including immunosuppression complications and health-related quality-of-life issues in pediatric LT recipients is proof of this trend in the pediatric transplant community [4,8–11]. In this study, we analyzed the outcome of 44 patients who received their first LT during childhood, and who survived longer than a decade. We have observed good linear growth and weight gain which were sustained throughout the 10 years to approach the 50th percentile for their age and gender. Also, there were remarkably low incidences of renal dysfunction and patients requiring medications for glycemic or hypertensive

**Table 3.** Characteristics of recipients who are off immunosuppression at 10 years after liver transplantation.

| Case # | Age at LT | Donor | Etiology | BPAR | Years off IS | Reason for stopping IS | Liver function | 10-year protocol biopsy |
|---|---|---|---|---|---|---|---|---|
| 1 | 19 months | Father | BA | 1 | 10 | Noncompliance | Normal | Minimal portal infiltrates |
| 2 | 13 months | Mother | NH | 0 | 14 | PTLD | Abnormal | Not done |
| 3 | 3 years | Father | BA | 1 | 6 | Noncompliance | Normal | Well-preserved hepatic architecture |
| 4 | 8 years | Deceased donor | HCC-B | 0 | 9 | Noncompliance | Normal | Not done |
| 5 | 8 months | Mother | BA | 0 | 4 | Noncompliance | Normal | Minimal portal infiltrates |

LT, liver transplantation; BPAR, biopsy-proven acute rejection; IS, immunosuppression; BA, biliary atresia; NH, neonatal hepatitis; PTLD, post-transplant lymphoproliferative disease; HCC-B, hepatocellular carcinoma with chronic hepatitis B.

**Table 4.** Characteristics of patients with post-transplant lymphoproliferative disease.

| Case # | Age at LT (months) | Diagnosis (post-LT, months) | Biopsy site | EBV risk | Treatment |
|---|---|---|---|---|---|
| 1 | 12 | 12 | GIT | High | Stop IS |
| 2 | 12 | 12 | GIT | High | Minimize IS |
| 3 | 18 | 12 | Tonsil | High | Minimize IS |
| 4 | 9 | 6 | Tonsil | High | Minimize IS |
| 5 | 10 | 4 | GIT | High | Minimize IS |
| 6 | 5 | 18 | GIT | High | Minimize IS |

LT, liver transplantation; EBV, Epstein–Barr virus; GIT gastrointestinal tract; IS, immunosuppression.

control, all hallmarks of the continued use of immunosuppressive agents.

The regimen and doses of both induction and maintenance immunosuppression have much variability among transplant centers around the world. However, the basic concept in immunosuppression is the same: to provide the least possible amount of immunosuppression without compromising graft function. We use an intra-operative steroid bolus with no monoclonal or polyclonal antibody agents for induction therapy. Tacrolimus is maintained at trough levels of 5–8 ng/ml during the first year. Beyond the first year post-transplant, tacrolimus is gradually decreased while carefully monitoring changes in liver function tests. This results in mean tacrolimus trough levels maintained below 4 ng/ml from the third year post-transplant. Bourdeaux *et al.* in their report of 171 pediatric LT recipients, described 79 patients with tacrolimus trough levels <4 ng/ml as being in a state of *prope* tolerance, a term previously coined by Sir Roy Calne [12,13]. At the 10-year time point, 36 (81.8%) of our patients are *prope* tolerant by this definition while exhibiting normal graft function. Twenty-one (47.7%) patients show tacrolimus trough levels <2.0 ng/ml, with five patients completely off all immunosuppression. Mean dose of tacrolimus per body weight was 0.05 mg/kg/day in the 39 patients on tacrolimus at 10 years post-transplant. Twenty-two (22/39, 56.4%) patients satisfied the criteria of minimal maintenance immunosuppression suggested by Ohe *et al.* [14] Another key aspect of our immunosuppressive regimen is the minimal use and early withdrawal of steroids. Our protocol called for discontinuation of all steroids within 1 month of LT. When steroid bolus was given as antirejection therapy, we also tapered off steroids within 1–2 months after the initial steroid bolus. We were stringent in our efforts to minimize the use of steroids, and none of the patients in this cohort were on steroids at the 10-year mark.

The low level of maintenance immunosuppression and absence of steroids did not lead to higher rates of acute rejection in this cohort. A report by Ng *et al.* [4] analyzing the outcome of 10-year survivors of pediatric LT found the incidence of acute rejection to be 66% and initial graft survival 88% at 10 years. Our study showed comparable results with a 45.5% acute rejection rate and 97.7% initial graft survival at 10 years. Also, among the children that did develop BPAR, there were no cases of steroid-resistant acute rejection and the presence of multiple episodes of BPAR did not compromise long-term graft function. There were three children with more than three episodes of BPAR (two children with three episodes and one with five episodes). All three patients still have functioning first grafts and display normal liver function. However, despite our

efforts to minimize immunosuppression and EBV prophylaxis in high-risk recipients (which is uncommon practice in other transplant centers), our incidence of PTLD was not lower than that of other centers at approximately 13% overall.

We believe the encouraging outcomes related to linear growth and renal function observed in this cohort are the composite end result of our immunosuppression practices, both in terms of steroid withdrawal and tacrolimus minimization. A large study evaluating the Studies of Pediatric Liver Transplantation (SPLIT) registry growth data showed that catch-up growth slowed and was incomplete after the second and third post-transplant years [9]. The authors proposed the elimination of steroids as an important modifiable factor for linear growth in these children. We have observed continued growth beyond the third post-transplant year and arrival at the 50th percentile at 10 years in our patients, which differed from the SPLIT data. Also, our cohort showed a remarkably low prevalence of renal dysfunction. Renal dysfunction in pediatric LT recipients has been associated with immunosuppressive agents, age at transplant, GFR at transplant, and growth failure in another series analyzing the SPLIT registry data [15]. Several authors have pointed out the beneficial effects of steroid withdrawal and calcineurin inhibitor minimization on post-transplant renal function [16].

Potential limitations and biases of this study are related to its retrospective design. Despite vigorous efforts at quality control, incomplete or missing data were present, especially in the earlier cases. Also all of the data are from 10-year survivors of pediatric LT, so great caution should be exercised in the interpretation of these results, to avoid overgeneralization to the overall pediatric LT recipient population.

In conclusion, good linear growth was sustained in our pediatric LT recipient cohort throughout the 10 years, to approach the 50th percentile. As the years spent post-transplant increase to decades in these recipients, more emphasis should be placed on ensuring quality of life, as well as longevity of the graft and patient.

## Authorship

Y-HC, J-WJ, S-KL: designed the study. SL, J-MK, G-SC, CHDK: collected the data. SL, J-MK: analyzed the data. SL, S-KL: wrote the paper.

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