Long Term Outcomes of Pediatric Liver Transplantation According to Age

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INTRODUCTION

Liver transplantation (LT) has been the key therapy for end stage liver diseases. However, LT in infancy is still understudied. From 1992 to 2010, 152 children had undergone LT in Seoul National University Hospital. Operations were performed on 43 patients aged less than 12 months (Group A) and 109 patients aged over 12 months (Group B). The mean age of the recipients was 7 months in Group A and 74 months in Group B. The patients’ survival rates and post-LT complications were analyzed. The mean Pediatric End-stage Liver Disease score was higher in Group A (21.8) than in Group B (13.4) \((P = 0.049)\). Fulminant hepatitis was less common in Group A (4.8%) than in Group B (13.8%) \((P = 0.021)\). The post-transplant lymphoproliferative disorder and portal vein complication were more common in Group A (14.0%, 18.6%) than in Group B (1.8%, 3.7%) \((P = 0.005)\). However, the 1, 5, and 10 yr patient survival rates were 93%, 93%, and 93%, in Group A and 92%, 90%, and 88%, in Group B \((P = 0.212)\). The survival outcome of pediatric LT is excellent and similar regardless of age. LTs in infancy are not riskier than those of children.

Keywords: Pediatrics; Liver Transplantation; Survival Rate; Fulminant Hepatitis; Living Donors; Liver Transplantation

MATERIALS AND METHODS

Data collection
Between 1992 and 2010, 152 pediatric recipients who had undergone their first ABO compatible LT in Seoul National University Hospital were retrospectively reviewed. Identification of 152 children (boys = 75, girls = 77) under 18 yr of age at LT was undertaken from medical records and electronic databases (Table 1). The mean body weight of the recipients was 17.9 ± 14.4 kg and 5 (3.3%) patients had a body weight of less than 6 kg. The mean height of all recipients was 104 cm. The most common underlying liver disease was biliary atresia (BA) \((n = 94, 59.9\%)\). The mean age of the recipients at the time of LT was 55 months (range, 0-210). The most common graft type was LDLT \((n = 118, 75.2\%)\) and left lateral section graft \((n = 52, 33.1\%)\). Mean graft versus weight ratio (GRWR) was 2.33%. A maintenance immunosuppressants 145 (95.4%) and 7 (5.6%) used tacrolimus and cyclosporine respectively. The mean postoperative hospital stay was 34.9 ± 21.6 days. We divided patients into two groups according to the age at the time of transplantation; Group A, age under 12 months (infant group, \(n = 43\)) and Group B, over 12 months (children group, \(n = 109\)).
Assessment of variables

We assessed pre-operative and peri-operative characteristics that are known to be related to survival outcomes of LT. The characteristics include the age, gender, and body weight of the recipients. Pre-operative conditions underlying liver disease include the Child-Turcotte-Pugh (CTP) score, Pediatric End-stage Liver Disease (PELD) score, and Korean Organ Network for Organ Sharing (KONOS) status. Peri-operative characteristics include year of transplant, donor source, and graft type. Post-operative complications include acute and chronic rejection, bacterial, fungal, and viral infection. Surgical complications were included. The PELD and CTP scores were calculated with the latest laboratory data before the surgery. KONOS status is the regulation for organ sharing in Korea, for which United Network
for Organ Sharing (UNOS) criteria was a model: Status 1, intensive care unit-bound with expected survival less than 7 days; Status 2, continuously hospitalized; and Status 3, at home, but requiring continuous medical care (7). Graft rejections were identified with histopathological diagnosis of graft biopsy via Baff-score. Post-transplant lymphoproliferative disease (PTLD) was confirmed by immunohistologic staining of tissue biopsy. Surgical complications were diagnosed with imaging modalities of computed tomography and Doppler ultrasound.

Statistical analysis
Statistical analyses were performed using the SPSS 19.0 statistical software program for Window. Descriptive data are reported using parameters such as frequency, mean, mode, and standard deviation. The cumulative survival rates and graphs were calculated using the Kaplan-Meier method and compared using a log-rank test. Continuous data are presented as mean with standard deviation and categorical data are presented as a number with percentage. The hazard ratios and multivariate analysis were performed with Cox’s proportional hazards model. The level of significance was set at 0.05.

Ethics statement
This study protocol was reviewed and approved by the institutional review board of the Seoul National University Hospital (H-1208-030-121). Informed consent was waived by the board.

RESULTS
Post-operative complications
Post-operative complications of the recipients are summarized in Table 2. The post-operative complication rate was 72.4%. The most common complication was acute cellular rejection in 49 cases (32.2%). Bile duct complication was most common in surgical aspect (17.1%). Epstein-Barr virus (EBV) infection was diagnosed in 8 cases (5.3%). PTLD was diagnosed in 8 cases (5.3%).

Within 15 hepatic arterial complication cases, 8 had re-operations, 1 had angi-intervention, and 6 had conservative managements. Within 18 hepatic vein complication cases, 4 had re-operations, 4 had stent insertions, 7 had balloon dilatations, and 3 had conservative managements. Within 14 portal vein complication cases, 3 had re-operations, 4 had stent insertions, 3 had balloon dilatations, and 4 had conservative managements. Within 26 bile duct complication cases, 5 had re-operations, 15 had percutaneous transhepatic biliary drainage (PTBD) insertions, 3 had endoscopic retrograde biliary drainage (ERBD) insertions, and 2 had both PTBD and ERBD insertions. There were 27 (17.8%) cases of immediate post-operative complications that needed operative interventions under general anesthesia. The most common cause of grade IIIb complication was post-operative bleeding which was in 9 (5.9%) cases. Other causes of grade IIIb complications were 6 (3.9%) bile duct complications, 3 (2.0%) portal vein complications, 2 (1.3%) hepatic arterial thrombosis, 2 (1.3%) hepatic arterial stenosis, 2 (1.3%) hepatic vein complications, and 1 (0.7%) graft liver torsion, ileal perforation, adhesive ileus. There were 2 cases (1.3%) of re-operation cases for post-transplant lymphomas.

Post-operative complications according to graft types
Post-operative complications according to graft types are presented in Table 2B. There were no statistical differences of surgical complication within left lateral section graft and other grafts.

Survival outcome
The patient survival rate and the graft survival rate were calculated using the Kaplan-Meier method (Fig. 1). Six cases (3.9%) of re-LTs were performed. Three were re-transplanted due to acute rejection. Others were owing to hepatic artery thrombosis, hepatic vein stenosis, and recurled Allagile syndrome. The overall mean graft survival was 177 months and mean patient survival was 179 months. The 1, 5, and 10 yr graft survival rates were 92%, 88%, and 86%, respectively; and the 1, 5, and 10 yr patient survival rates were 93%, 90%, and 87%, respectively.

Patient characteristics between the two age groups; Group A and B
We analyzed the characteristics of the two groups as shown in

Table 2A. Post-operative complications

| Post-operative complications | Total (n = 152) | Age < 12 mo (n = 43) | Age ≥ 12 mo (n = 109) | P value |
|------------------------------|----------------|---------------------|---------------------|--------|
| Surgical complications       |                |                     |                     |        |
| Hepatic artery               | 15 (9.9%)      | 4 (9.3%)            | 11 (10.1%)          | 0.883  |
| Hepatic vein                 | 18 (11.8%)     | 2 (4.7%)            | 16 (14.7%)          | 0.085  |
| Portal vein                  | 14 (9.2%)      | 6 (18.6%)           | 8 (5.5%)            | 0.012  |
| Bile duct                    | 26 (17.1%)     | 7 (16.3%)           | 19 (17.4%)          | 0.865  |
| Allergy                      | 5 (3.3%)       | 0 (0.0%)            | 5 (4.6%)            | 0.322  |
| Infections                   |                |                     |                     |        |
| EBV                          | 45 (29.6%)     | 20 (46.5%)          | 25 (22.9%)          | 0.006  |
| CMV                          | 8 (5.3%)       | 3 (7.0%)            | 5 (4.6%)            | 0.688  |
| PTLD                         | 8 (5.3%)       | 6 (14.0%)           | 2 (1.8%)            | 0.003  |
| De novo hepatitis            | 9 (5.9%)       | 0 (0.0%)            | 9 (8.3%)            | 0.061  |
| Rejection                    |                |                     |                     |        |
| Acute                        | 49 (32.2%)     | 13 (30.2%)          | 36 (33.0%)          | 0.848  |
| Chronic                      | 3 (2.0%)       | 0 (0.0%)            | 3 (2.8%)            | 0.559  |
| LLS, Left lateral section.   |                |                     |                     |        |

Table 2B. Post-operative complications according to graft types

| Post-operative complications | Total (n = 152) | LLS (n = 52) | Others (n = 100) | P value |
|------------------------------|----------------|-------------|-----------------|--------|
| Surgical complications       |                |             |                 |        |
| Hepatic artery               | 14 (9.2%)      | 4 (7.7%)    | 10 (10.0%)      | 0.602  |
| Hepatic vein                 | 18 (11.8%)     | 4 (7.7%)    | 14 (14.0%)      | 0.229  |
| Portal vein                  | 14 (9.2%)      | 3 (6.2%)    | 11 (11.0%)      | 0.267  |
| Bile duct                    | 26 (17.1%)     | 9 (17.3%)   | 17 (17.0%)      | 0.973  |
Table 1. The gender proportion was almost equal in the two groups (boys/girls 51.2%/48.8% in Group A, and 48.6%/51.4% in Group B). BA was more common in Group A (76.7%) than in Group B (54.1%) \((P = 0.021)\). Fulminant hepatitis (FH) was 4.7% in Group A and 13.8% in Group B \((P = 0.021)\) which was significantly different. The percentage of recipients with a body weight under 6 kg was 7.0% in group A and 1.8% in group B \((P = 0.128)\). The year of LT did not significantly differ. The percentage of recipients with a CTP score of over 7 was 95.1% in Group A and 71.7% in Group B \((P = 0.001)\). The mean PELD score was higher in Group A \((13.4 \pm 11.6)\) \((P = 0.049)\). This indicates that the worse pre-operative condition of patients was that of Group A. The proportion of deceased donors was 16.3% in Group A and 24.8% in Group B \((P = 0.181)\). The donor type of the left lateral section was 47.6% in Group A and 29.9% in Group B \((P = 0.231)\).

In post-operative condition, the acute rejection rate was 30.2% in Group A and 33.0% in Group B \((P = 0.848)\). Chronic rejection was not found in Group A but 2.8% was found in Group B \((P = 0.559)\). Hepatic artery complication was 9.3% in Group A and 8.3% in Group B \((P = 1.000)\). Hepatic vein complication was 4.7% in Group A and 11.9% in Group B \((P = 0.235)\). Portal vein complication was 18.6% in Group A and 3.7% in Group B, with a statistical difference \((P = 0.005)\). Bile duct complication was 34.9% in Group A and 22.9% in Group B \((P = 0.154)\). The re-transplantation rate was 2.3% in Group A and 4.6% in Group B \((P = 1.000)\). Portal vein complications were more common in Group A than in Group B, but others were not significant.

Survival outcomes between the two age groups

Fig. 2A shows the patient and graft survival outcomes of the two groups using the Kaplan-Meier method. The 1, 5, and 10 yr graft survival rates were 93%, 89%, and 89% in Group A and 91%, 89%, and 87% in Group B \((P = 0.555)\). The 1, 5, and 10 yr patient survival rates were 93%, 93%, and 93%, in Group A and 92%, 90%, and 88% in Group B \((P = 0.212)\).

Analysis of prognostic factors affecting patient and graft survival according to age

On univariate risk analysis for patient and graft survival of Group A (Table 3), hepatic artery complication was the only significant prognostic factor \((P = 0.037)\) for graft survival, and there was no significant factor for patient survival. In multivariate analysis of Group A, there was no statistically significant factor for either patient or graft survival.

On univariate risk analysis for graft survival of Group B (Table 4), FH \((P = 0.003)\), re-transplantation \((P = 0.014)\), and deceased donor \((P = 0.044)\) were significant prognostic factors; and on patient survival, FH \((P < 0.001)\), and re-transplantation \((P = 0.018)\) were significant prognostic factors. On multivariate analysis for graft and patient survival of Group B, FH \((P = 0.001)\) for graft, hazard ratio = 0.12, and \(P < 0.001\) for patient, hazard ratio = 0.10, and re-transplantation \((P = 0.021)\) for graft, hazard ratio = 0.13, and \(P = 0.025\) for patient, hazard ratio = 0.14) were significant prognostic factors.

DISCUSSION

Although LT has been a key therapy for end stage liver diseases in children, the LT of infants has conventionally been avoided due to technical difficulties and poor survival outcome (8-12). This study describes a single center, long term data analysis of LT recipients under the age of one year old. Several articles have
been published analyzing recipients in this age group; however, most of the previous data were obtained from DDLT based centers of western countries. Since our center’s data has more than 75% of LDLT dominancy, the purpose of this study was to evaluate our data in detail, and to compare the outcome of recipients under 12 months of age and associated factors with other age groups in a LDLT based study group.

The acceptable outcome of long term graft survival rates for children less than 12 months have been reported to be as low as 50%-69% and patient survival rates have been reported to be 74%-80% (13-16). Recently, Venick et al. (17) reported that the 1, 5, and 10 yr graft survival rates under 12 months of age were 75%, 72%, and the patient survival rates 68% and 79%, 77%, and 75%, respectively. Their report concluded that, compared to older recipients, small infants showed poorer survival outcome. Infants historically had the highest wait-list mortality owing to lack of small size donors in DDLT dominant societies (22, 23). Compared to older children, infants tend to have a greater survival with LDLT grafts because of the shorter waiting time and shorter ischemic time compared to DDLT graft (24). A number of reports have been published showing equal survival outcome for small infants, but the study size were small to get a clinical significances (18, 19).

The option of LDLT for infant recipients allowed for a reduc-
ed wait-list mortality with minimal ischemia time (17). Even though a few reports have been presented that did not show survival advantages with LDLT (20, 21), other large single center long term analysis reported better survival outcome. The Japanese Liver Transplantation Society (28) recently reported the 20 yr survival outcomes of 2,200 cases of pediatric LT; the 1-, 5-, 10- and 20-yr patient survival rates were 88.3%, 85.4%, 82.8%, and 79.6%, respectively. The recipient ages of less than 6 months (n = 106, 4.8%) and over 10 yr (n = 396, 17.8%) showed lower survival outcomes. The Korean multicenter studies of pediatric LT (29) recently showed the survival outcome; 1-, 5-, and 10-yr patient survival rates were 87.8%, 82.2%, and 78.1%, respectively. The survival outcome did not differ according to the recipient age of less than 12 months (n = 187, 35.0%). However these reports did not show the associated prognostic factors according to the age group. Analyzing factors according to age has relevance because the general conditions and underlying liver disease differed somewhat according to the age at the time of the transplant.

In the present study, the number of recipients less than 6 months was small (n = 8, 5.3%), which may lead to type II errors. Therefore, we merely divided the patient group according to infants and children within 12 months of age. Furthermore to ensure that small infants do not have inferior survival rate, we additionally evaluated survival outcome of recipients less than 6 months as well as in Fig. 2B. Although no significant survival difference was observed, we analyzed the factors associated with survival outcome according to the age group. The overall survival outcomes of our study including both age groups were acceptable compared to other previously reported papers (4-6); the 1, 5, and 10 yr graft survival rates were 92%, 88%, and 86%, and the patient survival rates were 93%, 90%, and 87%, respectively.

The infants (Group A) had poorer pre-operative conditions i.e., higher PELD and higher CTP score and had worse post-operative complications. Since our center has 76% of LDLT dominance, the waitlist mortality rates were relatively low. Similar findings have also been documented in other studies (17, 25). Due to the small size of vessels, small infants are known to be related with higher vascular complication rates (10, 26). In our data, the portal vein complications in Group A were statistically higher than in Group B. In Group A, a total of 8 cases of portal vein stenosis were treated with stent insertion, and none of these

### Table 3. Factors affecting survival outcome on univariate analysis in Group A (infant)

| Variables               | Risk factor | Reference | Graft loss | Death | P value | P value |
|-------------------------|-------------|-----------|------------|-------|---------|---------|
| Sex                     | Boys        | Girls     | 0.670      | 1.000 |         |         |
| Weight (kg)             | < 6         | ≥ 6       | 1.000      | 1.000 |         |         |
| Disease                 | Fulminant hepatitis | Others | 1.000 | 0.108 |         |         |
| CTP score               | ≥ 7         | < 7       | 0.524      | 0.188 |         |         |
| PELD score              | ≥ 20        | < 20      | 1.000      | 1.000 |         |         |
| Year of transplant      | < 2005      | ≥ 2005    | 1.000      | 0.635 |         |         |
| Re-transplantation      | Yes         | No        | 0.572      | 0.153 |         |         |
| PTLD                    | Present     | Absent    | 1.000      | 1.000 |         |         |
| Acute rejection         | Present     | Absent    | 0.037      | 0.060 |         |         |
| Surgical complications  | Hepatic vein | Absent | 1.000      | 1.000 |         |         |
|                         | Portal vein  | Absent    | 1.000      | 0.565 |         |         |
|                         | Bile duct    | Absent    | 1.000      | 0.643 |         |         |

CTP, Child-Turcotte-Pugh; PELD, pediatric end-stage liver disease; PTLD, post-transplant lympho-proliferative disease.

### Table 4. Factors affecting survival outcome in Group B (children)

| Variables               | Risk factor | Reference | Graft loss | Death | P value | P value | HR    | 95% CI | P value | HR    | 95% CI | P value |
|-------------------------|-------------|-----------|------------|-------|---------|---------|-------|--------|---------|-------|--------|---------|
| Sex                     | Boys        | Girls     | 0.256      | 0.166 |         |         |       |        |         |       |        |         |
| Weight (kg)             | < 6         | ≥ 6       | 0.229      | 0.246 |         |         |       |        |         |       |        |         |
| Disease                 | Fulminant hepatitis | Others | 0.003 | 0.000 | 0.12 | 0.03-0.43 | 0.001 | 0.10 | 0.03-0.37 | 0.000 | 0.000 | 0.000 |
| CTP score               | ≥ 7         | < 7       | 0.502      | 0.755 |         |         |       |        |         |       |        |         |
| PELD score              | ≥ 20        | < 20      | 0.087      | 0.181 |         |         |       |        |         |       |        |         |
| LT era                  | < 2005      | ≥ 2005    | 0.759      | 1.000 |         |         |       |        |         |       |        |         |
| Re-transplantation      | Yes         | No        | 0.014      | 0.018 | 0.13 | 0.002-0.73 | 0.021 | 0.14 | 0.03-0.78 | 0.025 | 0.025 | 0.025 |
| Donor source            | Deceased    | Living    | 0.044      | 0.057 | 1.62 | 0.42-6.33 | 0.487 | 1.41 | 0.37-5.36 | 0.613 | 0.613 | 0.613 |
| Graft type              | Left lateral section | Others | 0.199 | 0.346 |       |         |       |        |         |       |        |         |
| Acute rejection         | Present     | Absent    | 1.000      | 1.000 |         |         |       |        |         |       |        |         |
| Chronic rejection       | Present     | Absent    | 0.319      | 0.341 |         |         |       |        |         |       |        |         |
| PTLD                    | Present     | Absent    | 0.225      | 0.241 |         |         |       |        |         |       |        |         |
| Surgical complications  | Hepatic artery | Absent | 1.000      | 0.325 |       |         |       |        |         |       |        |         |
|                         | Hepatic vein  | Absent    | 0.358      | 0.212 |       |         |       |        |         |       |        |         |
|                         | Portal vein   | Absent    | 0.403      | 0.428 |       |         |       |        |         |       |        |         |
|                         | Bile duct     | Absent    | 0.490      | 0.734 |       |         |       |        |         |       |        |         |

CTP, Child-Turcotte-Pugh; PELD, pediatric end-stage liver disease; PTLD, post-transplant lymphoproliferative disease; HR, hazard ratio; CI, confidence interval.
directly affected patient survivals. Hepatic artery thrombosis is also known to occur frequently in small children, but in our analysis, it was not. This was also noticed in other previous studies using surgical microscopes (18, 19, 27).

It has been reported that there are relatively high incidence of PTLD in younger recipients (30, 31). In our study, PTLD was also significantly higher in the infant group. Six patients were diagnosed with PTLD in the infant group and two died of lymphoma. Since four infants are still on conservative management, the PTLD was not a significant prognostic factor for survival outcome.

There were 6 re-transplantation cases. Only one of Group A had a second LT due to portal vein complications. In addition, similar to other previous studies, re-transplantation in older children seems to carry an increased risk of death (17). The rates of acute and chronic rejection did not differ significantly. Because the two age groups significantly differed in pre-operative characteristics and post-operative complications, it is important to evaluate the prognostic factors differently for the different age groups in order to manage the patient properly and determine whether or not to perform LT. In the infant group, only hepatic artery complication was a significant prognostic factor in univariate analysis. On multivariate analysis, no factor proved to be significant in the infant group. In the children group, FH and retransplantation was a significant prognostic factor in multivariate analysis.

The limitation of our study is that it was retrospectively reviewed. Long term growth and development of the recipients were not analyzed in our study. However, since our study was detailed, long-term, and a LDLT dominant single center study, it may aid clinicians and surgeons in their medical decisions. Survival outcome was not inferior in infants (≤ 12 months) compared to children, although the pre-transplant medical condition was more critical and post-transplant complication was more common in the infants. Age alone should not be regarded as a contraindication for LT. LT in small infant is a safe procedure. Careful treatment is recommended over fulminant hepatitis patients, which is the only preoperative prognostic factor on the survival outcome, especially for children (> 12 months).

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DISCLOSURE

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