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Pediatric Living-Donor Liver Transplant Recipients without Transition After Reaching Adulthood

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Background: Transition to adult care can trigger certain problems for pediatric liver transplant recipients. At our institution, the same transplant team performs both adult and pediatric liver transplantation and post-transplant care; thus, pediatric liver transplant recipients do not have to be transferred. However, it is unclear whether this system affects the recipient's outcome during the transition period. Therefore, we retrospectively assessed pediatric liver transplant recipients who reached adulthood at our institution.

Material/Methods: This was a single-center, retrospective study involving consecutive pediatric living-donor liver transplant recipients who reached the age of 18 by October 2017. A total of 36 recipients, 20 females and 16 males, were included in the study.

Results: The 5- and 10-year patient survival after reaching the age of 18 was 100% and 93%, respectively. All of the 3 patients who died had been suffering from secondary biliary cirrhosis due to biliary stricture. In 5 patients (13.9%), biliary stricture became symptomatic or recurred after reaching the age of 18 years. Late-onset acute rejection and chronic rejection developed in 2 (5.6%) and 4 patients (11.1%), respectively. Only 4 (11.1%) patients were obviously noncompliant. We found no significant association between compliance and rejection or survival. Among the patients who are 18 years old and older, 5 (13.9%) had a psychiatric diagnosis.

Conclusions: Pediatric liver transplant recipients who underwent transplant surgery and received post-transplant care at our institution have good long-term outcomes. This suggests that having the same team perform both adult and pediatric transplantation and post-transplant care is beneficial for young adult recipients.

MeSH Keywords: Liver Transplantation • Living Donors • Pediatrics • Transition to Adult Care • Young Adult

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Background

Pediatric living-donor liver transplantation (LDLT) has improved the survival rate of children with liver disease. The 10-year patient survival rate of pediatric LDLT in Japan is 84.5% [1]. Therefore, an increasing number of pediatric liver transplant recipients are now reaching adulthood and need to be transferred to adult healthcare services. Although some researchers reported good outcomes after transferring to adult healthcare service [2–4], the psychological distress associated with the transfer may affect self-management, influence compliance, and result in graft loss [5]. Many post-transplant complications occur during adulthood, such as secondary biliary cirrhosis due to biliary complications, recurrent liver disease, *de novo* liver disease, and chronic rejection. Moreover, many comorbidities are diagnosed before and after reaching adulthood, including malignancy, cardiovascular disease, gastrointestinal disease, and neurological disease [2,3,6].

At some institutions in Japan, the same transplant team performs both adult and pediatric liver transplantation, and the same team also conducts recipient follow-up after discharge. At such institutions, pediatric liver transplant recipients need not be transferred. However, it is unclear whether this system affects the recipient's outcome during the transition period. Therefore, we retrospectively assessed pediatric LDLT recipients who reached adulthood, with the aim of clarifying the outcomes and identifying the issues associated with the transition period in this system.

Material and Methods

Between July 1991 and October 2017, 95 consecutive pediatric recipients underwent LDLT at the Tohoku University Hospital; of these 95, 36 recipients (20 females and 16 males) reached the age of 18 by October 2017, and these 36 recipients were included as subjects in the present study. At the Tohoku University Hospital, the same transplantation team performs both adult and pediatric liver transplantation, and both adult and pediatric recipients regularly visit the same post-transplant outpatient clinic. Therefore, they do not need to be transferred to another post-transplant service after reaching adulthood.

Data were acquired from databases and by reviewing medical records. The following characteristics were noted at the time of LDLT: age, sex, body weight, indications of transplant, donor age, donor sex, ABO compatibility, and result of lymphocyte crossmatch. The following data of the transplant surgery were recorded: graft type (left lateral lobe/left lobe/right lobe), graft weight, surgical duration, and blood loss during surgery. The immunosuppression regimen at the induction and at the age of 18 (date of first attendance at the outpatient clinic after reaching the age of 18), episode of rejection, recurrence of primary liver

disease, *de novo* liver disease, and cause of death were noted. A rejection episode was defined as biopsy-proven rejection.

Patient survival was calculated after reaching the age of 18, using the Kaplan-Meier method. Statistical analysis was performed using JMP®13 (SAS Institute Inc., Cary, NC, USA). Continuous variables were compared using the Mann-Whitney test. Fisher's exact test was used for comparing categorical data. $P < 0.05$ was considered statistically significant.

Results

Characteristics of patients and immunosuppression

Patient age at the last visit to our outpatient clinic until October 2017 was 18–36 years (median 21.5 years). The median follow-up after transplantation was 218 months (range 92–313 months). The median age at LDLT was 4 years (0–17)/55.5 months (6–212). The most common indication for LDLT was biliary atresia (78%, 28 cases). The living donors consisted of one of the parents of each patient, with a median age of 35.5 years (24–50). Three patients received grafts from ABO blood type-incompatible donors and 2 from lymphocyte cross-match-positive donors. Only 3 patients (3.3%) received right lobe grafts. The mean graft recipient weight ratio was 2.00.

Five (13.9%) patients received induction therapy using basiliximab. The primary immunosuppression regimen consisted of a calcineurin inhibitor (tacrolimus in 28 patients and cyclosporine in 8 patients) and methylprednisolone. Azathioprine was administered to 10 (27.8%) patients, whereas mycophenolate mofetil was administered to 1 patient for primary immunosuppression. By the time the patients reached the age of 18, the immunosuppression regimen consisted of tacrolimus monotherapy (18 patients, 50%), cyclosporine monotherapy (10 patients, 27.8%), tacrolimus combined with mycophenolate or methylprednisolone (2 patients, 5.6%), and cyclosporine combined with methylprednisolone or prednisolone with or without mycophenolate (2 patients, 5.6%). A total of 4 (11.1%) patients did not receive immunosuppression therapy. Patient characteristics and data regarding transplant surgery and immunosuppression are presented in Table 1.

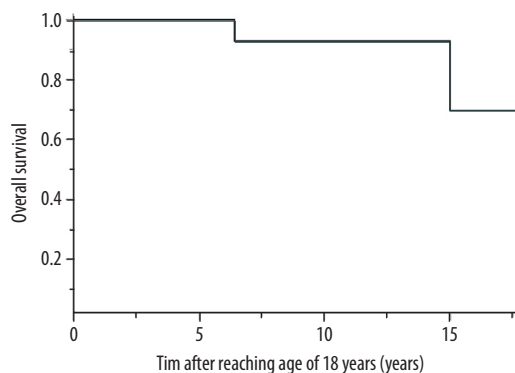
Survival after reaching the age of 18

The 5- and 10-year actual patient survival after reaching the age of 18 were 100% and 93%, respectively (Figure 1). There were no recipients who underwent re-transplantation. All of the 3 patients who died after reaching the age of 18 had been suffering from repeated cholangitis and biliary strictures, which resulted in secondary biliary cirrhosis. One patient died before being enlisted on the waiting list for re-transplantation at the age of 33

Table 1. Patient's characteristics, data of surgery and immunosuppression.

Recipient		GRWR	
Gender (Female)	20 (55.6%)		2.00±1.02
Age at LDLT (years)	4 (0–17)	Biliary reconstruction	
Age at LDLT (months)	55.5 (6–212)	Hepaticojejunostomy	34 (94.4%)
Age at last visit (years)	21.5 (18–36)	Duct to duct	2 (5.6%)
Median follow up since LDLT (months)	218(92–313)	Surgical duration (min)	878±298
Body weight at LDLT (kg)	22.4±18.6	Blood loss/body weight (ml/kg)	200±184
Etiology of liver disease		Immunosuppression at first	
Biliary atresia	28	CNI	
Metabolic disease	3	Tacrolimus	28 (77.8%)
Cryptogenic cirrhosis	2	Cyclosporine	8 (22.2%)
NASH	1	Azathioprine	10 (28%)
Alagille syndrome	1	MMF	1 (2.8%)
Patent ductus venosus	1	mPSL	36 (100%)
Donor		Basiliximab induction	5 (13.9%)
Donor age (years)	35.5 (24–50)	Immunosuppression at 18 years old	
Donor gender (Female)	20 (55.6%)	Tacrolimus monotherapy	18 (50%)
Donor relationship (parent)	36 (100%)	Cyclosporine monotherapy	10 (28%)
ABO-incompatible	3 (8.3%)	Tacrolimus/MMF	1 (2.8%)
LCM positive	2 (5.6%)	Tacrolimus/mPSL	1 (2.8%)
Surgery		Cyclosporine/PSL	1 (2.8%)
Graft (right lobe)	3 (8.3%)	Cyclosporine/mPSL/MMF	1 (2.8%)
		Free	4 (11.1%)

Values expressed as number (percent), median (range) and mean ±S.D. where appropriate. LDLT – living-donor liver transplantation; NASH – nonalcoholic steatohepatitis; LCM – lymphocyte cross-matched; GRWR – graft recipient weight ratio; CNI – calcineurin inhibitor; MMF – mycophenolate mofetil; mPSL – methylprednisolone; PSL – prednisolone.

**Figure 1.** Kaplan-Meier curves of patient survival.

because of gastrointestinal bleeding related to portal hypertension 15.3 years following transplantation. The second patient died while on the waiting list for re-transplantation at the age of 24, 23.3 years following transplantation. The third patient who developed portal thrombosis refused re-transplantation and died at the age of 36, 20 years after transplantation; she had been suffering from diffuse developmental disability. The liver biopsy of the 3 patients showed graft fibrosis; however, a diagnosis of chronic rejection was suspected only in the third patient. A summary of the data of these 3 patients is shown in Table 2.

Rejection and compliance (Table 3)

A total of 25 patients (69%) had neither late-onset acute cellular (occurring more than 6 months after LDLT) nor chronic

Table 2. Summary of three cases who died after reaching adulthood.

Gender	Etiology of liver disease	Age at LDLT (years)	Age of death (years)	Cause of death	* Complications after reaching 18 years old
Male	Biliary atresia	17	33	GI bleeding	Late-onset acute cellular rejection
Male	Biliary atresia	1	24	Graft failure	Intrahepatic lithiasis
Female	Biliary atresia	17	36	Graft failure	Portal vein thrombosis, chronic rejection suspected, appendicitis, asthma, hemorrhage, herpes encephalitis, diffuse development disability

* All of three patients has been suffering from repeated cholangitis due to biliary strictures, and had resulted in secondary biliary cirrhosis. LDLT – living-donor liver transplantation; GI – gastrointestinal.

Table 3. Rejection and compliance.

Rejection episode after 6 months	<18 y.o.	≥18 y.o.	Episode of medication non-compliance for more than one months	p
Non		25	2 (8%)	0.6
LAR or CR		11	2 (18%)	
LAR	6	2	2 (25%)	
CR	0	4	1 (25%)	

One patient, who had a episode of medication non-compliance, had suffering from both of LAR and chronic rejection. LAR – late-onset acute cellular rejection; CR – chronic rejection.

rejection, whereas 8 patients (22.2%) had an episode of late-onset acute cellular rejection and 4 patients (11.1%) developed chronic rejection (including otherwise unexplained graft fibrosis). Two patients experienced late-onset acute rejection after reaching the age of 18, and all of the 4 chronic rejection cases occurred after the patients reached 18 years. There has been no graft loss due to chronic rejection to date, and rejection episodes were found to have no significant effect on patient survival.

In the cohort, 2 patients admitted that they did not take medicine for more than 1 month when they were below age 18 years; one of them developed late-onset acute rejection. Two patients did not take medicine for more than 1 month after reaching 18 years old; one of them developed repeated late-onset acute rejection and chronic rejection. There were no significant differences in terms of demographic data and rejection episodes between the noncompliant and compliant groups.

Complications after the age of 18

Complications that occurred during adulthood (≥18 years old) are shown in Table 4. There were various post-transplant complications, including gastrointestinal tract disorder, cardiovascular disease, gynecological disease, and psychiatric disorders. Two patients (5.6%) developed portal thrombosis more

than 15 years after LDLT because of graft cirrhosis; one was a case of chronic rejection and the other had repeated cholangitis due to hepaticojejunostomy stricture. A total of 5 patients (13.9%) developed hepaticojejunostomy stricture during adulthood. Moreover, the strictures found in 2 patients were a recurrence of the strictures that had been treated with percutaneous transhepatic biliary drainage (PTBD) followed by balloon dilation and placement of an internal drainage tube before the patients turned 18 years old; one of the patients was treated successfully with the PTBD approach, but the other patient had several treatment failures, developed secondary biliary cirrhosis, and died. Two patients who developed biliary stricture ≥15 years after LDLT were successfully treated using an endoscopic approach through laparotomy after failed PTBD and endoscopic approach. The last patient who underwent LDLT at the age of 17 developed biliary stricture within 1 year after LDLT. He underwent surgical revision following PTBD and prolonged placement of a drainage tube and developed secondary biliary cirrhosis resulting in death 15.3 years after transplantation. Biliary stricture was significantly more frequent in the group of patients who died.

Five patients (13.9%) had a psychiatric diagnosis after reaching 18 years old. These included schizophrenia, personality disorder, depression, diffuse developmental disability, and psychogenic reaction. One patient who was diagnosed with compulsive

Table 4. Complications occurred after adulthood.

Complications	All cases N=36	Dead cases N=3	Survival cases N=33	p
ACR	2	1	1	0.2
Chronic rejection	4	0	4	1
PV thrombosis	2	1	1	0.2
Biliary stricture	5	2	3	0.04
GI tract disorders	3	1	2	0.2
Cardiovascular diseases	2	0	2	1
Asthma	1	1	0	0.08
NODAT with insulin	1	0	1	1
Ovarian cyst	2	0	2	1
Marfan syndrome	1	0	1	1
Neurological disease	2	1	1	0.2
Psychiatric disorders	5	1	4	0.4

GI tract disorders consist of gastric varices (1), crohn disease (1), appendicitis (1) and bleeding hemorrhage (1). Cardiovascular diseases consist of pulmonary hypertension (1) and angina (1). Neurological disease consist of autoimmune cerebritis (1) and herpes encephalitis (1). Psychiatric disorders consist of schizophrenia (1), personal disorder (1), depression (1), diffuse development disability (1) and psychogenic reaction (1). ACR – acute cellular rejection; PV – portal vein; GI – gastrointestinal; NODAT – new onset diabetes after transplantation.

and dependent personality disorder did not take medicine for more than 6 months and slit her wrist. Another patient was diagnosed as having psychogenic reaction to violence by her partner; she is suffering from the consequences of severe leukoencephalopathy resulting in noncompliance and chronic rejection. No patient experienced harmful alcohol consumption or illicit drug use. Furthermore, there were no significant differences in terms of demographic data and rejection episode between patients with and without psychiatric disorders.

Circumstance of study or employment

In the study cohort, 27 (75%) patients were either employed or studying as of October 2017. Among the remaining 9 patients, the 3 patients who died before October 2017 had had a regular job until their general health conditions worsened. Two patients were full-time homemakers. The remaining 4 patients were neither employed nor studying; 2 had a psychiatric diagnosis, one of which is suffering from the consequences of cerebral infarction, and one is suffering from several complications.

Discussion

Liver transplantation is the standard of care for end-stage liver disease. Young adult recipients who underwent liver transplantation during childhood sometimes experience problems different from those experienced by recipients who undergo liver transplantation during adulthood. Some young adult recipients cannot fully accept their situation and behave in a problematic manner. For example, they experiment with illegal drugs and alcohol, skip healthcare visits, and stop taking immunosuppressive drugs without the physician's approval, thus increasing the risk of graft loss [7]. Moreover, psychosocial outcomes are worse for pediatric transplant recipients than for their age-matched healthy peers [8]. Additionally, surgical complications similar to those seen in adults can occur during adolescence or young adulthood. These complications include hepatic artery thrombosis, portal vein thrombosis, biliary complications, and outflow problems caused by remodeling of graft size. Concomitant medical problems, including chronic kidney disease, post-transplant lymphoproliferative disease, primary disease recurrence, *de novo* liver disease, malignant tumor, and cardiopulmonary disease, may also persist [6]. Therefore, transfer from a pediatric to an adult healthcare service requires great attention from the medical staff [9]. A small retrospective study conducted in the USA reported that 4 of 14 patients

died after transition to an adult program (a mortality rate of 29%) [10]. One patient died 2 years after the transition because of infection, and 3 patients died after 2 years from infection (1 patient) or chronic rejection (2 patients). Moreover, transition patients exhibited poor medical adherence. Therefore, they have changed the transfer program by redesigning the transfer process, addressing health care management support for patients prior to transfer, and adopting a long-term care approach to transition [11]. Careful transition programs might improve outcomes after transition. Sager et al. reported that the post-transfer 10-year patient and graft survival rates were 89.9% and 86.2%, respectively [2]. Transition may also influence psychosocial outcomes [8]. In addition, a service combining pediatric and adult healthcare in a single pediatric – young adult joint transition clinic reportedly improved adherence and outcomes [12]. In the present study, the same transplantation team performed both adult and pediatric liver transplantation, and both adult and pediatric recipients regularly visited the same post-transplant outpatient clinic. Therefore, pediatric recipients do not need to be transferred to another post-transplant service after reaching adulthood. The long-term outcomes of the patients in our cohort have been good – the 10-year patient survival rate was 93% after reaching age 18, in the context of median follow-up since transplantation, which was nearly 20 years. Although it has been suggested that a careful transition to adult healthcare services is useful to minimize graft loss [2], the strategy of having the same team perform both adult and pediatric transplantation and post-transplant care is similarly beneficial for adolescents and young adults with transplanted liver grafts during childhood.

Biliary stricture is one of the main biliary complications, leading to liver cirrhosis or graft failure without proper and timely treatment [13]. Percutaneous biliary intervention, endoscopic double-balloon techniques, and surgical revision are the primary treatment options [14]. Although several treatment methods had been used, 3 patients with biliary strictures (which developed before adulthood in 1 patient and after reaching adulthood in 2) in this study developed secondary biliary cirrhosis and died. Moreover, biliary stricture was significantly more frequent in the group of patients who died. It is considered that re-transplantation was necessary to prevent graft failure and improve patient survival. However, none of these 3 patients had related living-donor candidates, and it was very difficult to acquire deceased donor livers because of the donor shortage in Japan.

Although no patients were re-transplanted or died because of late-onset acute rejection or chronic rejection, late-onset acute rejection and chronic rejection developed in 2 (5.6%) and 4 (11.1%) patients in this study, respectively. Sagar et al. [2] reported that 2.9% of all transferred patients required re-transplantation or died from chronic rejection, and suggested that

nonadherence may have influenced the outcomes. Another researcher also suggested that poor medication compliance was correlated with increases in rejection and graft loss [10]. Additionally, a self-reported study reported that only 55% of pediatric liver transplant recipients who reached adulthood had good compliance with medications [8]. We found that only 11.1% of patients were obviously noncompliant in our cohort, with only 5.6% of the patients being noncompliant after reaching 18 years old. Although our study showed no significant association between medication compliance and rejection or survival, good medication compliance may be one of the contributing factors to good patient and graft survival in this cohort. Furthermore, it has been reported that patients who were noncompliant following transition were more predisposed to have psychological problems [4]. In the present study, 5 patients (13.9%) had a psychiatric diagnosis after reaching 18 years old. Although there was no significant association between noncompliance or rejection and psychiatric disorders, 2 of the 4 noncompliant patients were diagnosed with a psychiatric disorder after episodes of noncompliance.

In addition, various physical and psychological complications developed after reaching age 18, and some patients were not employed or studying, which may have resulted from physical or psychiatric complications. Therefore, a team approach with individual members belonging to various professions seems to be essential. These approaches may help provide better services to young adult recipients and sooner identify those with physical or psychiatric problems, thus preventing school dropout and job loss.

This study has some limitations. First, this was a single-center retrospective study with a small number of patients; therefore, the study results may not be generalizable. Second, the assessment of medication compliance was based on self-report only, which may underestimate the number of patients with medication noncompliance. Finally, we did not perform standard protocol biopsy until a few years ago, which may have underestimated the number of cases with rejection. Therefore, a multi-center prospective study is warranted to confirm our results.

Conclusions

Pediatric LDLT recipients who underwent transplantation surgery and post-transplant care at our institution have good long-term outcomes after reaching adulthood. This is probably due to having the same team for adult and pediatric transplantation and post-transplant care, which appears to be beneficial for young adult recipients.

References:

1. Inomata Y, Eguchi S, Umeshita K et al: Liver transplantation in Japan Registry by the Japanese Liver Transplantation Society. *Ishoku*, 2017; 52: 134–47
2. Sagar N, Leithead JA, Liyod C et al: Pediatric liver transplant recipients who undergo transfer to adult healthcare service have good long-term outcomes. *Am J Transplant*, 2015; 15: 1864–73
3. Rajchert J, Rosa M, Pawtowska J et al: Follow-up of pediatric liver transplant patients after reaching adulthood. *Ann Transplant*, 2016; 21: 644–48
4. Mitchell T, Gooding H, Mews C et al: Transition to adult care for pediatric liver transplant recipients: The western Australian experience. *Pediatr Transplant*, 2017; 21: e12820
5. Shemesh E, Annunziato RA, Arnon R et al: Adherence to medical recommendations and transition to adult services in pediatric transplant recipients. *Curr Opin Organ Transplant*, 2010; 15: 288–92
6. Nq VL, Alonso EM, Bucuvalas JC et al: 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. *J Pediatr*, 2012; 160: 820–26
7. Burra P, Germani G, Gnoato F et al: Adherence in liver transplant recipient. *Liver Transpl*, 2011; 17: 760–70
8. Dommergues JP, Letierce A, Gravereau L et al: Current lifestyle of young adults after liver transplantation during childhood. *Am J Transplant*, 2010; 10: 1634–42
9. Bell LE, Sawyer SM: Transition of care to adult services for pediatric solid organ transplant recipients. *Pediatric Clin North Am*, 2010; 57: 593–610
10. Annunziato RA, Emre S, Shneider B et al: Adherence and medical outcomes in pediatric liver transplant recipients who transition to adult service. *Pediatric Transplant*, 2007; 11: 608–14
11. Annunziato RA, Hogan B, Barton C et al: A transition and systemic approach to transferring liver transplant recipients from pediatric to adult-oriented care settings. *Pediatric Transplant*, 2010; 14: 823–29
12. Harden PN, Walsh G, Bandler N et al: Bridging the gap: An integrated paediatric to adult clinical service for young adults with kidney failure. *BMJ*, 2012; 344: e3718
13. Imamine R, Shibata T, Yabuta M et al: long-term outcome of percutaneous biliary interventions for biliary anastomotic stricture in pediatric patients after living donor liver transplantation with Roux-en-Y hepaticojejunostomy. *J Vasc Interv Radiol*, 2015; 26: 1852–59
14. Tokodai K, Kawagishi N, Miyagi S et al: Indications and outcomes of an endoscopic approach under laparotomy for the treatment of bilioenteric anastomosis strictures. *Pediatr Transplant*, 2016; 20: 316–20