Introduction

Liver transplantation (LT) is an effective therapy for patients with end-stage liver disease. Pediatric living donor LT (LDLT) has become the main choice in many countries of Asia. Along with the development of organ donation after death of people in China, pediatric deceased donor has become an important supplement to the graft pool. Some of the clinical applications of adult donor livers from deceased donor have achieved remarkable results in China. However, the outcome of pediatric deceased donor livers, especially when transplanted into adult recipients, has not been well studied.\(^1\)\(^{-}\)\(^2\) This may be because children’s liver volume cannot meet the needs of adult recipients and the higher incidence of vascular and biliary tract complications.

We conducted a retrospective study of LT, in which grafts were obtained from pediatric deceased donors. We investigated the prognosis of pediatric deceased donor livers used in pediatric and adult LT and compared the outcomes. We also analyzed the risk factors for early vascular complications (VCs) in pediatric LT and evaluated the effect of donors’ serum sodium levels on the prognosis of LT.
**Methods**

**Ethical approval**

There were ten cases of organs that were procured in the Beijing Friendship Hospital, and the remaining cases were allocated to this hospital through the China Organ Transplant Response System (COTRS) because of a lack of a compatible recipient in the local hospital. The child transplant waiting list from the registration center was checked twice in the COTRS. When there were no compatible pediatric candidates, a donor liver was applied to adult recipients. The donation procedure was initiated according to the China Guidelines for DCD. Written consent was provided by the pediatric donors’ parents. Written informed consent was obtained from all of the patients before their surgery. All LTs were approved by the Human Organ Transplantation and Ethics Committee of the Beijing Friendship Hospital. All of the study protocols were in accordance with the ethical principles of the Ethics Committee of the Beijing Friendship Hospital, and the ethics committee had given a priori approval for this study.

**Study design**

The donors’ age was below 14 years, and the recipients, according to their ages, were divided into the pediatric-to-pediatric LT group (recipients’ age ≤13 years) and the pediatric-to-adult LT group (recipients’ age ≥19 years). From June 2013 to August 2016, we performed 102 LTs using grafts from pediatric deceased donors including 83 pediatric-to-pediatric LTs and 19 pediatric-to-adult LTs. Data were collected including characteristics of donors, recipients, and transplantations, early VC, and survival of grafts and patients. The occurrence of VC within 3 months after transplantation was defined as early VC. Early VC included hepatic artery thrombosis (HAT), hepatic artery stenosis, portal vein thrombosis (PVT), and portal vein stenosis (PVS) in this study. We performed a retrospective analysis to compare outcomes between the two groups and analyzed the risk factors for early VC in pediatric LT and the effect of donor hypernatremia (serum sodium levels ≥150 mmol/L) on liver function, early VC, and graft and patient survival.

**Organ procurement procedure**

After arrival in the operating room, the life support system was gradually withdrawn. Five minutes later, after we ensured that cardiac arrest and autoresuscitation did not occur, death was declared and organ procurement was initiated. The abdominal aorta and mesenteric vein were catheterized. Liver and kidneys were jointly procured. The University of Wisconsin solution was sequentially used for perfusion, and the inferior vena cava was also catheterized for drainage. The actual warm ischemia time was recorded as the duration from withdrawn of the life support system to abdominal aorta perfusion. The cold ischemia time was recorded as the duration from perfusion to blood reperfusion during transplantation surgery.

**Intraoperative and postoperative treatment**

Orthotopic LT was the standard operative technique in all cases. All LTs were performed by the same surgical team. Portal vein anastomosis was performed using 6-0 polypropylene sutures in a running fashion with a growth factor. An interposition portal venous graft, which was obtained from the deceased donor iliac vein, was needed in recipients whose diameter of the portal vein was smaller than 5 mm. Hepatic artery anastomosis was performed using interrupted 8-0 polypropylene sutures. Doppler ultrasound was performed intraoperatively after vascular anastomosis. Biliary drainage was established by duct-to-duct or by a duct-to-Roux-en-Y small bowel loop.

The immunosuppressive treatment protocols included tacrolimus and methylprednisolone, and tacrolimus, mycophenolate mofetil, and methylprednisolone. The protocol containing mycophenolate mofetil was used in children older than 2 years and that containing no mycophenolate mofetil was used in children aged 2 years or younger. Trough level of tacrolimus was adjusted to 8–10 ng/ml.

**Statistical analysis**

Continuous data are expressed as median (range). Categorical data are expressed as counts and percentages. Categorical variables were analyzed using the Chi-square test and Fisher’s exact tests. Continuous variables were analyzed using the Student’s t-test. A value of $P < 0.05$ was considered statistically significant. The differences in variables between VC group and non-VC group were analyzed using the univariate analysis, and variables significant at a $P < 0.20$ in the univariate analyses were used in the multivariate logistic regression model. Next, a backward elimination procedure was performed. Survival of grafts and recipients was determined by Kaplan-Meier curves. Differences in survival between the two groups were compared with the log-rank test. All statistical analysis was performed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA).

**Results**

**Pediatric-to-pediatric liver transplantation versus pediatric-to-adult liver transplantation**

Donor characteristics of the pediatric-to-pediatric LT compared with the pediatric-to-adult LT groups are shown in Table 1. There was no significant difference in sex, cause of death, levels of alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, albumin, creatinine, serum sodium, warm ischemia time (WIT), and cold ischemia time (CIT) between the two groups. The median value of age, body weight, and graft weight were significantly higher in the pediatric-to-adult LT group than those in the pediatric-to-pediatric LT group (all $P < 0.05$).

Recipient and transplantation characteristics are shown in Table 2. There was no significant difference in sex, INR, bilirubin levels, albumin levels, ABO compatibility, operation time, and anhepatic phase between the two groups. Age was significantly older and body weight of recipients was higher in the pediatric-to-adult LT group than in the pediatric-to-pediatric LT group (both $P < 0.05$), and blood loss, concentrated red blood cell transfusion, and plasma transfusion were less in the pediatric-to-pediatric LT
The graft-to-recipient weight ratio (GRWR) was larger in the pediatric-to-pediatric LT group than that in the pediatric-to-adult LT group \((P < 0.05)\).

The incidence of VC was similar between the pediatric-to-pediatric LT and pediatric-to-adult LT groups \((19.3\% \text{ vs. } 10.6\%, P = 0.514)\). In pediatric-to-pediatric LT, early VC occurred in 16 patients. Eight patients developed HAT. One of these patients underwent embolectomy, one had an endovascular intervention and died of serious infection 7 months later, one received retransplantation, and the others underwent thrombolytic therapy. Two patients developed HAT combined with PVT. Both of these patients died as a direct result of VC, even though they underwent embolectomy. One patient developed PVT and underwent thrombolytic therapy. Five patients developed PVS, which occurred at the anastomotic site interposed between the
native and donor portal veins. All of these patients underwent balloon dilatation through endovascular intervention. In pediatric-to-adult LT, there was one case of HAT 4 days after the operation, and embolectomy was performed. In this patient, biliary strictures occurred secondary to HAT, and liver function gradually improved after treatment by endoscopic nasobiliary drainage. There was one case of PVS which improved after balloon dilatation [Table 3].

Kaplan-Meier analysis showed that recipients had similar graft and patient survivals in the two groups \( (P = 0.872 \text{ and } P = 0.652, \text{ respectively}) \) [Figure 1]. The 1-year cumulative survival rates of grafts and recipients were 89.16% and 91.57% in the pediatric-to-pediatric LT and 89.47% and 94.74% in the pediatric-to-adult LT, respectively.

**Risk factors of early vascular complication in pediatric liver transplantation**

VC occurred in 16 patients in pediatric LT. The differences in variables between the VC group and non-VC group were analyzed using the univariate analysis. Factors significant at a \( P < 0.20 \) in the univariate analyses were used in the multivariate logistic regression model. These variables included the donors’ characteristics (age, body weight, and serum sodium levels) and recipients’ characteristics (age, body weight, primary disease, albumin levels, and PELD) [Table 4]. Logistic regression using the backward method showed that low recipients’ body weight was an independent risk factor for early VC in pediatric LT (odds ratio: 0.856, 95% confidence interval: 0.752–0.975, \( P = 0.019 \)).

**Table 3: Comparison of the incidence of early vascular complications between pediatric-to-pediatric liver transplantation and pediatric-to-adult liver transplantation groups**

| Vascular complications | Pediatric-to-pediatric \( (n = 83), n (%) \) | Pediatric-to-adult \( (n = 19), n (%) \) | \( P \) |
|------------------------|---------------------------------------------|------------------------------------------|------|
| HAT                    | 8 (9.6)                                    | 1 (5.3)                                  |      |
| PVT                    | 1 (1.2)                                    |                                          |      |
| HAT and PVT            | 2 (2.4)                                    |                                          |      |
| PVS                    | 5 (6.1)                                    | 1 (5.3)                                  |      |
| Overall                | 16 (19.3)                                  | 2 (10.6)                                 | 0.514* |

*Fisher’s exact tests. HAT: Hepatic artery thrombosis; PVT: Portal vein thrombosis; PVS: Portal vein stenosis.

**Effect of serum sodium levels on prognosis**

All recipients were divided into two groups according to donor’s serum sodium levels: Group A (serum sodium levels \(<150 \text{ mmol/L, } n = 68\) ) and Group B (serum sodium levels \(\geq 150 \text{ mmol/L, } n = 34\) ). Liver function was defined based on liver enzymes (ALT + AST)/2 on postoperative day 2 as follows: good function, \(< 285 \text{ U/L}; \) average function, 285–986 U/L; and initial poor function (IPF), \(> 986 \text{ U/L}.\) There were no significant differences in early liver function after LT and the incidence of early VC between the two groups [Table 5]. There was no significant difference in the patients’ survival rate between the two groups \( (P = 0.290) \) while the graft survival rate was worse in the Group B than that in the Group A \( (P = 0.037, \text{ Figure 2}) \). The 1-year survival rates of grafts and recipients were 92.11% and 93.63% in Group A and 82.09% and 88.06% in Group B, respectively.

**Discussion**

Community-based organ donation has become the only legitimate source of transplantable organs in China since January 1, 2015. The COTRS is the only legitimate official organ allocation computer system in China. According to the COTRS, there were 2766 community-based deceased organ donations between January 1, 2015 and December 31, 2015, which accounted for 2150 livers.\(^8\) Organ donation and LT have rapidly developed in China in recent years,\(^9\) but pediatric LT developed lately in China, and the lack of donor is one of the important obstacles in its development. Donor source is one of the risk factors that affect the prognosis of liver transplantation. Austin et al.\(^7\) reported that graft and patient survival rates in the LDLT were better than those of patients who underwent deceased donor LT (DDLT), while the study of Khalaf\(^8\) showed that overall graft survival was significantly worse in the LDLT group than that in the DDLT group. Mateo et al.\(^9\) analyzed data of the United Network for Organ Sharing and found that a donor liver WIT of >30 min and CIT of >10 h have a negative effect on graft survival. The study showed that LT using pediatric deceased donor livers had an excellent outcome, and the donor livers used in pediatric and adult patients had similar rates of graft and patient survival. Patients who used donors with hyponatremia had a worse graft survival.

The incidence of VC as reported in the pediatric LT literature is variable and can be up to 25–33%.\(^10\text{-}12\) HAT is the most
2 weeks after transplantation. This study showed a similar incidence of early VC between pediatric-to-pediatric LT group and pediatric-to-adult LT group, and a low body weight of the recipient was an independent risk factor of VC in pediatric LT. A low body weight of the recipient likely indicates the presence of smaller vasculature, and a size mismatch between the graft and the small abdominal cavity of the recipient.

Recipients with a low body weight may benefit from arterial reconstruction with a conduit to decrease the risk of vascular thrombosis.

We consider that recipients with a low body weight should receive strict posttransplant management to monitor them for development of VC. This management could help prevent VC, such as by providing stronger anticoagulation treatment and frequent Doppler ultrasonography examinations.

The graft weight is estimated according to the donor’s height and body weight before organ procurement, and the size of the blood vessels and bile duct is evaluated by imaging examinations. Pediatric-to-adult LT has shown a real benefit because of a decreased waiting time and avoiding organ waste. For application of pediatric deceased donor liver in adult LT, whether liver volume can meet the needs of the recipient is an important factor for determining the outcome of treatment. Emre et al. reported that when the recipient’s serum sodium levels <150 mmol/L, Group B: Donor’s serum sodium levels ≥150 mmol/L. For the graft survival, \( \chi^2 = 4.330, P = 0.037 \); and for the patient survival, \( \chi^2 = 1.122, P = 0.290 \).

### Table 4: Baseline risk factors for vascular complications that were included in the multivariate logistic regression model

| Variables                      | Non-VC (n = 67) | VC (n = 16) | \( \chi^2/t \) | P  |
|--------------------------------|-----------------|-------------|----------------|----|
| **Donor factors**              |                 |             |                |    |
| Age (months), median (range)   | 45 (2–156)      | 13 (2–156)  | 1.80*          | 0.075 |
| Body weight (kg), median (range)| 15 (5–45)      | 10 (5–35)   | 2.14*          | 0.035 |
| Serum sodium (mmol/L), median (range) | 143.0 (119.0–175.0) | 140.0 (131.9–151.0) | 1.97* | 0.054 |
| **Recipient factors**          |                 |             |                |    |
| Age (months), median (range)   | 35.0 (5.0–148.0) | 11.5 (4.0–115.0) | 2.88* | 0.007 |
| Body weight (kg), median (range)| 14.0 (6.0–50.0) | 7.8 (5.0–23.0) | 2.51* | 0.014 |
| Primary disease, n (%)         |                 |             |                |    |
| Biliary atresia                | 34 (50.8)       | 14 (87.5)   | 7.51*          | 0.038 |
| Metabolic diseases             | 16 (23.9)       | 0           |                |    |
| Retransplantation              | 9 (13.4)        | 1 (6.3)    |                |    |
| Others                         | 8 (11.9)        | 1 (6.3)    |                |    |
| Albumin (g/L), median (range)  | 34.6 (11.7–45.5) | 32.4 (19.0–41.5) | 1.69* | 0.095 |
| PELD, median (range)           | 5.7 (−17.1–38.2) | 13.1 (−3.1–33.7) | 1.39* | 0.168 |

* \( t \) values; \( \chi^2 \) values. VC: Vascular complication; PELD: Pediatric end-stage liver disease.

### Table 5: Comparison of liver function and vascular complications between liver transplantation patients using pediatric deceased donor liver with different serum sodium levels

| Items                              | Group A (n = 68) | Group B (n = 34) | \( \chi^2 \) | P  |
|------------------------------------|-----------------|-----------------|--------------|----|
| Liver function, n (%)              |                 |                 |              |    |
| Good function                      | 41 (60.4)       | 14 (41.2)       | 5.02         | 0.076 |
| Average function                   | 22 (32.3)       | 13 (38.2)       |              |    |
| IPF                                | 5 (7.3)         | 7 (20.6)        |              |    |
| VC, n (%)                          |                 |                 |              |    |
| Yes                                | 15 (22.1)       | 3 (8.8)         | 2.73         | 0.167 |
| No                                 | 53 (77.9)       | 31 (91.2)       |              |    |

Group A: Donor’s serum sodium levels <150 mmol/L; Group B: Donor’s serum sodium levels ≥150 mmol/L. IPF: Initial poor function; VC: Vascular complication.

2 serious complication after LT, and early HAT is the main cause of graft loss in pediatric LT. Duffy et al. reported that the rates of HAT in pediatric and adult patients were 8% and 3.9%, respectively. There are two outcomes of HAT, including acute liver necrosis and ischemic biliary complications, and they usually lead to primary nonfunction of grafts or death of the recipient. Early HAT usually occurs within the first 2 weeks after transplantation. This study showed a similar incidence of early VC between pediatric-to-pediatric LT group and pediatric-to-adult LT group, and a low body weight of the recipient was an independent risk factor of VC in pediatric LT. A low body weight of the recipient likely indicates the presence of smaller vasculature, and a size mismatch between the graft and the small abdominal cavity of the recipient. Recipients with a low body weight may benefit from arterial reconstruction with a conduit to decrease the risk of vascular thrombosis. We consider that recipients with a low body weight should receive strict posttransplant management to monitor them for development of VC. This management could help prevent VC, such as by providing stronger anticoagulation treatment and frequent Doppler ultrasonography examinations.

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ratio of the donor liver weight and standard liver weight of the recipient was >0.4, there was no significant difference in the incidence of donor liver complications and graft survival between pediatric-to-pediatric and adult-to-adult LT. The function and survival time of the graft were dependent not only on the graft size but also on the quality and severity of primary disease of the recipient. The relatively large portal venous flow and portal venous pressure of the adult enables small-for-size syndrome to easily occur.[16] Pediatric-to-adult liver mismatch not only leads to a high perfusion risk but also causes portal hepatic blood flow to decrease, resulting in thrombosis.[17] Therefore, postoperative prophylactic anticoagulation is necessary. Postoperative somatostatin is administered to reduce portal vein blood perfusion. In the current study, if portal vein pressure was >20 mmHg (1 mmHg = 0.133 kPa) or portal vein flow was >250 ml·min⁻¹·100 g⁻¹ liver tissue,[18,19] we performed ligation of the splenic artery. Splenectomy was considered in case of no significant improvement after ligation. However, strictly controlling the indications for this procedure is necessary because splenectomy may also increase the chance of infection.[20]

Hyponatremia is an important cause of graft dysfunction after LT. Physicians have avoided using organs from hyponatremic donors in LT for fear of poor postoperative outcomes. However, the data supporting this assumption are currently limited, conflicting, and mainly address the adult population. Cywinski et al.[21] found no relationship between hyponatremia in donors and poor outcomes following LT. In our study, hyponatremia (serum sodium levels ≥150 mmol/L) was a risk factor of graft survival; however, there were no relationships with early VC, early liver function, and patient survival. A potential explanation for this finding is a rapid change in intracellular and extracellular osmotic pressure before and after procurement, resulting in cellular swelling and damage.[22] We consider that donors with hyponatremia can be actively treated by continuous renal replacement therapy, and the organs can be carefully used a few days later.

In summary, LT using grafts from pediatric deceased donors show a real benefit because of a decreased waiting time and better outcome. We believe that pediatric deceased donor graft injury can be minimized with rational intensive care unit management. We also believe that preoperative evaluation of the donor liver and recipient, and proper surgical techniques and anastomotic techniques in pediatric-to-adult LT are feasible. However, because of the small number of cases in this study, some problems still need to be further addressed.

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Conflicts of interest
There are no conflicts of interest.

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儿童死亡器官捐献供肝肝移植：单中心102例供体分析

摘要

背景：儿童死亡器官捐献供肝移植的效果目前研究较少，特别是儿童供肝用于成人肝移植。本研究旨在评估使用儿童死亡器官捐献供肝的肝移植的疗效，并比较儿童供肝用于儿童和成人的临床效果。

方法：对2013年6月至2016年8月期间我院使用儿童死亡器官捐献供肝的肝移植患者进行回顾性分析。根据接受者的年龄不同分为儿童-儿童肝移植组和儿童-成人肝移植组。观察两组早期血管并发症的生存率和生存率。分析儿童肝移植早期血管并发症发生的危险因素以及供体高钠血症对受者预后的影响。

结果：自2013年6月至2016年8月，我院共实施儿童死亡器官捐献供肝移植102例，其中儿童-儿童肝移植组83例(受者年龄≤13岁)，儿童-成人肝移植组19例(受者年龄≥19岁)。两组早期血管并发症发生率相似(19.3% vs. 10.6%，P=0.514)。在儿童肝移植中，受体低体重是早期血管并发症发生的独立危险因素(OR: 0.856, 95% CI: 0.752–0.975, P=0.019)。两组移植物及受者生存率差异无统计学意义(χ²=0.026, P=0.872 and χ²=0.204, P=0.652)。儿童-儿童肝移植组移植物和受者的1年生存率为89.16%，91.57%，而儿童-成人肝移植组分别为89.47%，94.74%(均为P>0.05)。供者高钠血症会导致受者的移植物存活率降低(χ²=4.330, P=0.037)。

结论：儿童死亡器官捐献供肝用于儿童和成人肝移植有相似的移植物和受者生存率。受体低体重是儿童肝移植早期血管并发症发生的独立危险因素。高钠血症供者可影响受者移植物的生存率。