

Safety and Risk of Using Pediatric Donor Livers in Adult Liver Transplantation

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成人レシピエントで、小児（13歳未満）から（70例）と 19歳以上の成人から移植を受けた患者（1051例）の成績を比較した。肝動脈血栓症発症の率が、小児からの移植で12.9%と成人の3.8%より有意に高かった。特に、移植肝がレシピエント推定肝容積の10%未満の患者で発症率が高かった。よって、小児肝を成人に移植するにしても、10%以上が望ましい。

Safety and Risk of Using Pediatric Donor Livers in Adult Liver Transplantation

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Pediatric donor (PD) livers have been allocated to adult transplant recipients in certain situations despite size discrepancies. We compared data on adults (age ≥ 19 years) who underwent primary liver transplantation using livers from either PDs (age < 13 years; $n = 70$) or adult donors (ADs; age ≥ 19 years; $n = 1,051$). We also investigated the risk factors and effect of prolonged cholestasis on survival in the PD group. In an attempt to determine the minimal graft volume requirement, we divided the PD group into 2 subgroups based on the ratio of donor liver weight (DLW) to estimated recipient liver weight (ERLW) at 2 different cutoff values: less than 0.4 ($n = 5$) versus 0.4 or greater ($n = 56$) and less than 0.5 ($n = 21$) versus 0.5 or greater ($n = 40$). The incidence of hepatic artery thrombosis (HAT) was significantly greater in the PD group (12.9%) compared with the AD group (3.8%; $P = .0003$). Multivariate analysis showed that preoperative prothrombin time of 16 seconds or greater (relative risk, 3.206; $P = .0115$) and absence of FK506 use as a primary immunosuppressant (relative risk, 4.477; $P = .0078$) were independent risk factors affecting 1-year graft survival in the PD group. In the PD group, transplant recipients who developed cholestasis (total bilirubin level ≥ 5 mg/dL on postoperative day 7) had longer warm (WITs) and cold ischemic times (CITs). Transplant recipients with a DLW/ERLW less than 0.4 had a trend toward a greater incidence of HAT (40%; $P < .06$), septicemia (60%), and decreased 1- and 5-year graft survival rates (40% and 20%; $P = .08$ and $.07$ v DLW/ERLW of 0.4 or greater, respectively). In conclusion, the use of PD livers for adult recipients was associated with a greater risk for developing HAT. The outcome of small-for-size grafts is more likely to be adversely affected by longer WITs and CITs. The safe limit of graft volume appeared to be a DLW/ERLW of 0.4 or greater. (*Liver Transpl* 2001;7:41-47)

Although pediatric donor (PD) livers are ideally used for pediatric recipients, they are occasionally allocated to adult recipients, e.g., when only a pediatric liver is available for a critically ill adult or when an adult patient is listed with the weight range for a PD. In these circumstances, it is important to know the risks of using a small-for-size liver in an adult.

The main risk with such grafts is that they will fail secondary to inadequate liver volume. Experience with living related liver transplantation (LT) in adults has shown that grafts as small as 25% to 30% of ideal liver volume can be tolerated.^{1,2} However, Emond et al³ reported early functional impairment with grafts less than 50% of the expected liver volume. In addition, Kiuchi et al⁴ reported that small-for-size grafts (<1% of

recipient body weight) were associated with lower graft survival, probably because of enhanced parenchymal cell injury and reduced metabolic and synthetic capacity. Thus, in living donor LT, it is now accepted that grafts must be greater than 0.8% of the recipient body weight (or >40% of expected liver volume).⁵

Similar data on small-for-size cadaveric liver grafts are not available. In this study, we reviewed our large experience with the transplantation of pediatric livers into adult recipients and attempted to identify risk factors for poor graft survival and determine minimal graft volume requirements.

Patients and Methods

Study Population and Design

Between September 1988 and March 1999, 1,121 adults (age ≥ 19 years) underwent primary LT using full-size (whole) allografts from either PDs (age < 13 years; $n = 70$) or adult donors (ADs; age ≥ 19 years; $n = 1,051$). Patients who received primary transplants from donors aged between 13 and 18 years were excluded from analysis.

Mean post-LT follow-up was 1,830 days (median, 1,738 days; range, 78 to 3,664 days) in the PD group and 1,591 days (median, 1,477 days; range, 5 to 3,840 days) in the AD group. Donor liver weight (DLW) was measured at the end of the back-table procedure. Based on data from the first thousand LTs performed at our institution, estimated recipient liver weight (ERLW) was calculated using a formula developed at our center⁶:

$$\text{ERLW (cubic centimeters)} = 6 \times \text{weight (lb)} \\ + 4 \times \text{age (years)} + 350$$

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In this study, DLW/ERLW ratio was used as an indicator of graft size matching.

Part 1: Comparison of outcomes in PD and AD groups. We compared the following factors between groups: recipient and donor age and sex, DLW/ERLW ratio, indication for LT, United Network for Organ Sharing (UNOS) status, and preoperative values for total bilirubin (TBil), prothrombin time (PT), and creatinine. Surgical data analyzed included cold (CIT) and warm ischemic time (WIT), total operative time, bypass use, type of caval reconstruction, and use of packed red blood cells and fresh frozen plasma. CIT was defined as the period from donor cross-clamping to the start of anastomosis in the recipient, and WIT was defined as the period from the start of anastomosis to allograft reperfusion. One- and 5-year patient and graft survival were also compared between groups, as was the incidence of postoperative complications, including primary nonfunction (PNF), hepatic artery thrombosis (HAT), portal vein thrombosis, bile leak, intrahepatic and extrahepatic bile duct stricture, septicemia, acute rejection, and post-LT ascites.

Part 2: Univariate and multivariate analysis. Univariate and multivariate analyses were performed in the PD group to determine the independent risk factors that adversely affected 1- and 5-year patient and graft survival. Continuous variables were dichotomized at clinically established cutoff points and presented as categorical. Diagnoses at primary LT were categorized into acute or chronic for statistical convenience. Variables found to predict 1-year graft survival on univariate analysis were further entered into multivariate analysis.

Part 3: Risk factors for prolonged cholestasis. To identify factors that predict and/or increase the risk for prolonged cholestasis in adults who receive small-for-size cadaveric livers, we compared PD recipients with and without prolonged cholestasis (TBil \geq 5.0 mg/dL on postoperative day [POD] 7). Eighteen patients were excluded because of either graft loss within 7 days or inadequate data. Of the 52 patients remaining, TBil level was less than 5.0 mg/dL in 41 patients and 5.0 mg/dL or greater in 11 patients. Recipient and donor age, UNOS status, DLW/ERLW, CIT, WIT, use of packed red blood cells and fresh frozen plasma, and 1- and 5-year patient and graft survival were compared between the subgroups.

Part 4. To clarify minimal liver volume requirements, PD patients were divided on the basis of 2 different DLW/ERLW cutoff values (<0.4 or ≥ 0.4 and <0.5 or ≥ 0.5). Nine patients were excluded for lack of data on either DLW ($n = 4$) or recipient body weight (RBW) ($n = 5$); 61 patients were included in the analysis, as follows: DLW/ERLW less than 0.4 ($n = 5$) versus 0.4 or greater ($n = 56$) and DLW/ERLW less than 0.5 ($n = 21$) versus 0.5 or greater ($n = 40$).

Postoperative complications, including the incidence of PNF, HAT, portal vein thrombosis, bile leak, septicemia, and acute rejection, were compared at each cutoff point, as were 1- and 5-year patient and graft survival. TBil, glutamic-oxaloacetic transaminase, and PT values for PODs 2, 7, and 14 were also compared between the groups.

Statistical Analysis

Survival analysis was performed using the Kaplan-Meier method, and the groups were compared by means of the log-rank test. Continuous variables were compared using a 2-tailed, unpaired *t*-test for independent samples. Categorical data were compared using chi-squared test. For survival analysis, continuous variables were dichotomized at a clinically relevant cutoff point. Variables found to impact significantly on 1-year graft survival were analyzed by multivariate analysis. Multivariate analysis was performed using stepwise forward and backward Cox proportional-hazards models. *P* less than .05 is considered significant. All statistical analyses were performed with the StarView7 4.5 software for Macintosh (Abacus Concepts Inc, Berkeley, CA).

Results

Part 1

Groups were similar in terms of recipient age, cause of liver disease, UNOS status, and pre-LT liver function test results. There was also no difference between groups in terms of WIT or total ischemic time, bypass use, arterial anastomosis technique, blood product use, and initial immunosuppression. Preoperative demographics and surgical data, including initial immunosuppressive therapy, are listed in Table 1.

One- and 5-year patient survival rates were 82.9% and 70.0% in the PD group and 82.5% and 73.2% in the AD group (*P* = not significant). One- and 5-year graft survival rates tended to be less in the PD group than the AD group (68.6% *v* 75.0% for 1-year survival; *P* = .17; 52.6% *v* 65.8% for 5-year survival; *P* = .051), but did not reach statistical significance (Fig. 1).

Table 2 lists the incidence of postoperative complications and length of hospital and intensive care unit stays. The rate of HAT was 12.9% in the PD group compared with 3.8% in the AD group (*P* = .0003).

Figure 2 shows the causes of graft loss in the 2 groups. Thirty-five grafts were lost in the PD group and 361 grafts were lost in the AD group. Overall, causes of graft loss were similar between the groups.

Part 2

On univariate analysis, diagnosis at primary LT (*P* = .01), UNOS status (*P* < .05), pre-LT PT (*P* = .005), creatinine level (*P* = .01), DLW/RBW (*P* = .01), and primary immunosuppressive therapy (*P* = .03) reached statistical significance regarding 1-year graft survival in PD recipients. These variables were further evaluated in forward and backward stepwise Cox regression models. Independent risk factors were a high pre-LT PT and not using FK506 as primary immunosuppressive therapy (Table 3).

Variables	Group		P
	PD (n = 70)	AD (n = 1,051)	
Recipient variables			
Sex (% female)	78.6	39.8	<.0001
RBW (kg)	65.3 ± 14.3	75.6 ± 16.9	<.0001
ERLW (g)	1,346 ± 319	1,511 ± 319	<.0001
Donor variables			
Donor age (yr)	8.9 ± 2.1	45.3 ± 17.3	<.0001
Sex (% female)	35.7	41.3	NS
Donor body weight (kg)	33.4 ± 11.7	72.9 ± 15.4	<.0001
DLW (g)	865 ± 267	1,477 ± 308	<.0001
DLW/ERLW	0.69 ± 0.44	1.05 ± 0.50	<.0001
CIT (h)	10.9 ± 3.4	10.0 ± 3.3	.04
Piggyback (%)	51.4	4.6	<.0001
Bile duct reconstruction (%)			
Duct-to-duet with T-tube	49.3	44.5	
Duct-to-duet without T-tube	24.0	42.7	
Roux-en-Y	26.7	12.8	
ICU stay (d)	10.0 ± 11.7	8.9 ± 13.4	NS
Hospital stay (d)	36.7 ± 33.9	35.5 ± 32.8	NS

NOTE. Values expressed as mean ± SD unless otherwise noted. Abbreviations: ICU, intensive care unit; NS, not significant.

Part 3

Table 4 shows the effect of post-LT cholestasis on patient and graft survival. One- and 5-year patient and graft survival were significantly worse in patients with a TBil level ≥5.0 mg/dL on POD 7. In these patients, WIT and CIT were significantly longer than those in patients with TBil levels less than 5 mg/dL on POD 7 (57.2 ± 13.0 v 45.5 ± 9.0 minutes; 13.1 ± 4.3 v 10.5 ± 3.0 hours, respectively).

Part 4

Table 5 lists postoperative complication rates and 1- and 5-year patient and graft survival rates, with special reference to DLW/ERLW. There was no statistical difference in diagnosis, UNOS status, or surgical variables (data not shown). Patients with a DLW/ERLW less than 0.4 had a trend toward a greater rate of HAT (40% v 10.7%; P < .06) and septicemia (60% v 25.0%). Furthermore, 1- and 5-year graft survival rates in this

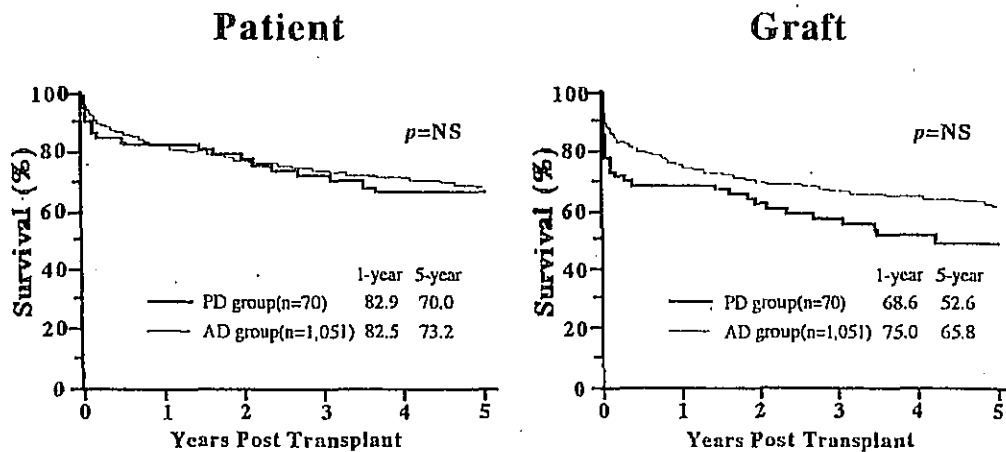


Figure 1. Comparison of patient and graft survival between the PD (n = 70) and AD groups (n = 1,051).

Table 2. Postoperative Complications

Variables	PD (n = 70)	AD (n = 1,051)	P
PNF (%)	7.1	6.3	NS
HAT (%)	12.9	3.8	.0003
Portal vein thrombosis (%)	2.1	1.5	NS
Bile leak (%)	5.7	3.8	NS
Bile duct stricture (%) [*]	5.7	5.8	NS
Septicemia (%)	28.6	19.8	NS
Acute rejection (%)	42.9	50.1	NS
Posttransplantation ascites (%)	7.1	10.5	NS

Abbreviation: NS, not significant.
^{*} Intrahepatic and extrahepatic stricture.

Table 3. Independent Predictors of Inferior 1-Year Graft Survival in Recipients of PD Livers

Variables	Graft Survival (%)	Coefficient	Relative Risk	P
PT (s)				
<16	80.5	1		
≥16	51.7	1.165	3.206	.0115
FK506 use				
Yes	86.2	1		
No	57.5	1.499	4.477	.0078

group were only 40% and 20% compared with 73.2% and 57.1% in patients with a DLW/ERLW of 0.4 or greater. Although there was no statistical significance, probably because of the small sample size, diminished graft survival in this group of patients should be noted. When divided at a cutoff value of 0.5 for DLW/ERLW, postoperative complications and patient and graft survival were similar between the groups, except for a greater incidence of bile leak in patients with a DLW/ERLW less than 0.5.

Regarding chronological changes in serum TBil, glutamic-oxaloacetic transaminase, and PT values early after LT, we found that serum bilirubin levels tended to be greater in the group with a DLW/ERLW less than 0.4 at all points, but this did not reach statistical significance. PT POD 2 was significantly greater in the

group with a DLW/ERLW less than 0.4 compared with the group with a DLW/ERLW of 0.4 or greater ($P < .05$).

Although females accounted for 39.8% of AD recipients, 78.6% of PD recipients were female. Primary biliary cirrhosis (21.4%) was a relatively frequent indication in the PD group compared with AD group (10.4%).

Table 1 lists surgical data. Mean CIT was significantly longer in PD recipients ($P < .04$). A piggyback procedure was used in 51.4% of PD recipients in contrast to only 4.6% of AD recipients ($P < .0001$). Patients in the PD group were significantly more likely to require Roux-en-Y hepaticojejunostomy than patients in the AD group because of the size discrepancy between donor and recipient ducts (26.7% v 12.7%).

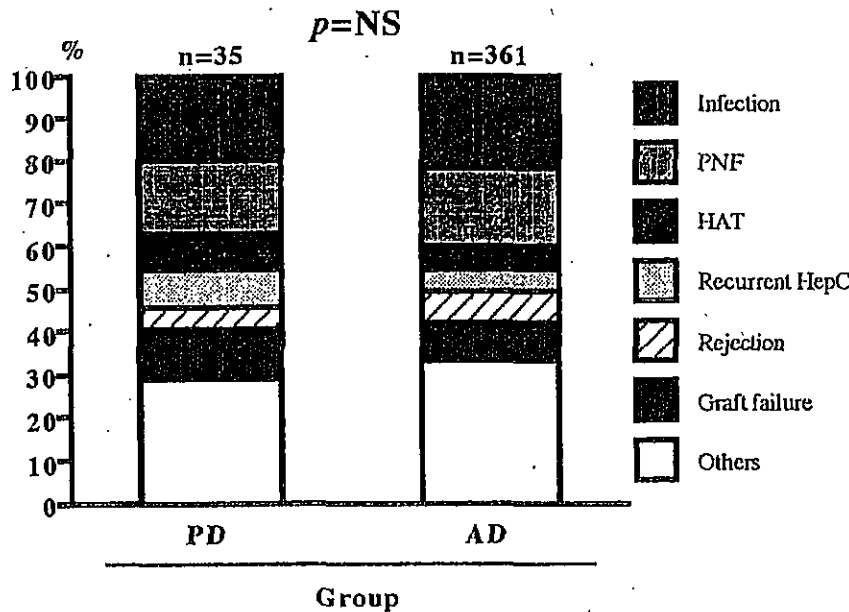


Figure 2. Comparison of causes of graft loss between the PD (n = 70) and AD groups (n = 1,051). (HepC, hepatitis C; NS, not significant.)

Variables	TBil (mg/dL) POD 7		P
	<5.0 (n = 41)	≥5.0 (n = 11)	
Recipient age (yr)	51.1 ± 14.3	51.0 ± 14.5	NS
UNOS status (%)			NS
1	11.1	27.2	
2	36.1	18.2	
3	52.8	54.6	
Donor age (yr)	8.7 ± 2.1	9.7 ± 1.3	NS
DLW (kg)	855 ± 385	784 ± 147	NS
DLW/ERLW	0.63 ± 0.23	0.67 ± 0.49	NS
CIT (h)	10.5 ± 3.0	13.1 ± 4.3	.02
WIT (min)	45.5 ± 9.0	57.2 ± 13.0	.001
Intraoperative transfusions			
PRBCs (units)	10.9 ± 7.2	15.7 ± 14.9	NS
FFP (units)	17.9 ± 14.3	11.8 ± 8.7	NS
Patient/graft survival (%)			
1-yr	92.7*/80.5†	54.5*/36.4†	*†<.001
5-yr	80.5‡/65.9§	36.4‡/18.2§	‡§<.0001

NOTE. Values expressed as mean ± SD unless noted otherwise.
 Abbreviations: PRBC, packed red blood cells; FFP, fresh frozen plasma; NS, not significant.
 * 1-year patient survival.
 † 1-year graft survival.
 ‡ 5-year patient survival.
 § 5-year graft survival.

Variables	DLW/ERLW		P	DLW/ERLW		P
	<0.4 (n = 5)	≥0.4 (n = 56)		<0.5 (n = 21)	≥0.5 (n = 40)	
Mean preoperative variables						
Recipient age (yr)	51.4	50.7	NS	51.5	50.4	NS
RBW (kg)	78.0	64.2	.04	69.0	63.4	NS
Donor age (yr)	8.6	8.7	NS	8.0	9.1	.06
Donor body weight (kg)	26.0	32.9	NS	26.6	35.2	.003
DLW (g)	555.6	883.2	.007	619.4	980.8	<.0001
DLW/ERLW	0.35	0.63	.001	0.42	0.71	NS
Postoperative complications						
PNF (%)	20.0	7.1	NS	5.8	10.0	NS
HAT (%)	40.0	10.7	.06	14.3	12.5	NS
Portal vein thrombosis (%)	0.0	3.6	NS	0.0	5.0	NS
Bile leak (%)	0.0	7.1	NS	19.0	0.0	.004
Septicemia (%)	60.0	25.0	NS	38.1	22.5	NS
Acute rejection (%)	40.0	44.6	NS	47.6	42.5	NS
Patient/graft survival (%)						
1-yr	80.0/40.0	85.7/73.2	NS	85.7/71.4	85.0/70.0	NS
5-yr	60.0/20.0	73.2/57.1	NS	66.7/52.4	75.0/55.0	NS

Abbreviation: NS, not significant.

Discussion

Currently, more than 14,000 patients are on the waiting list for liver transplants in the United States, with an expected supply of 4,500 donors per year.⁷ The gap between the demand and supply of donor organs has been constantly increasing. As a result, centers have been expanding their donor acceptance criteria, including the use of small-for-size livers under certain conditions.

The use and allocation of pediatric livers in adult recipients is controversial. According to UNOS data,⁷ approximately 20% of liver donors in the United States in 1997 were aged younger than 18 years, and 8.7% were aged younger than 10 years. Approximately 150 livers per year procured from PDs (defined as age < 13 years) were transplanted into adults (≥ 19 years; UNOS data request, 1999). According to Wight,⁸ 28 pediatric livers were transplanted into adults in the United Kingdom in 1989, whereas 64 pediatric livers were transplanted into pediatric patients.

Because there was no UNOS policy for allocating PD livers to pediatric recipients during this study period, the use of pediatric livers in adult recipients was justified under certain urgent conditions. Recently, UNOS adopted a policy to allocate PD livers preferentially to pediatric recipients in the same region.

Our study showed that results with the use of pediatric livers in adults was similar to results with adult-to-adult combinations, although graft survival tended to be less in the former group. Of note, the incidence of HAT was significantly greater in the PD group compared with the AD group (12.9% *v* 3.8%). The incidence of HAT after primary LT varies from 1.6% to 8% in adults⁹⁻¹³ and 5% to 38% in children.¹⁴⁻¹⁶ Numerous factors have been implicated in HAT, including a prolonged CIT.^{13,17-19} Not surprisingly, an increased incidence has been reported in pediatric recipients, in whom vessels are small.¹⁴ It is also reported that size mismatching in vascular components could be problematic in LT using small-for-size grafts.²⁰ In our present study, CIT was longer in the PDs, and this may partly explain the high incidence of HAT. Furthermore, we believe the small size of the donor artery and inevitable size discrepancy between donor and recipient arteries might facilitate development of HAT. It is our policy to administer anticoagulation therapy with heparin to the recipient in this setting to prevent HAT.

Adam et al²¹ reviewed their use of small donor livers in adult recipients and found that a very small graft size (<600 g), DRW ratio less than 0.5, and preservation time exceeding 12 hours were risk factors for complications. We did not confirm these findings in our patients

(data not shown). Our multivariate analysis showed 2 independent risk factors for poor graft survival: preoperative PT greater than 16 seconds and no use of FK506 for primary immunosuppression. Patients with a preoperative PT less than 16 seconds who were administered FK506 had a 1-year graft survival rate of 94.1% (*n* = 17) versus a 37.5% (*n* = 16) 1-year graft survival rate in patients with a PT greater than 16 seconds preoperatively who were not administered FK506. The effect of a high preoperative PT on negative outcome can be explained by poor pre-LT patient condition and intraoperative blood loss (data not shown). These results suggest that restricting the use of small PD livers to relatively healthy adults may be the key to better graft and patient survivals. However, possibly because a cyclosporine-based immunosuppressive regimen was used earlier in our program, the improved graft survival in the FK506 era may reflect our learning curve related to increased surgical experience.

It is important to know the expected (or ideal) recipient liver weight before accepting a donor liver, especially when there is a size discrepancy between the donor and recipient. Urata et al²² proposed a simple formula for predicting standard (or ideal) liver volume:

$$\text{Liver volume (milliliters)} = 706.2$$

$$\times \text{body surface area (square meters)} + 2.4$$

Since it was published in 1995, this formula has been widely used. However, we found that this formula tended to underestimate liver volume when we applied it to our donor population (data not shown). Heineemann et al²³ recently reported the same observation. The reason is not clear but is probably caused by the racial difference on which the formula was based. Thus, we adopted the formula developed at our institution:

$$\text{ERLW (grams)} = 6 \times \text{weight (lb)} + 4$$

$$\times \text{age (years)} + 350$$

Among 5 grafts with a DLW/ERLW less than 0.4, 1 graft (DLW/ERLW = 0.35) was lost to PNF, which was attributed to a small-for-size graft. The 2 smallest grafts (0.29 and 0.34) developed HAT on PODs 12 and 1. One graft (DLW/ERLW = 0.39) was lost to an unknown cause on POD 982. Thus, the 3 smallest of these 5 grafts were lost to causes attributable to the graft itself. Considering the high incidence of complications, including HAT (40%) and septicemia (60%), and the low graft survival, we currently believe we should not use grafts with a DLW/ERLW less than 0.4 in cadaveric LT.

In living related LT, small-for-size grafts are report-

edly associated with impaired graft function, indicated by prolonged hyperbilirubinemia, profuse ascites, and high PTs.³ In our study, TBil levels in patients with a DLW/ERLW less than 0.4 tended to be greater, but the difference did not reach statistical significance. PT on POD 2 was significantly higher in patients with a DLW/ERLW less than 0.4. The incidence of post-LT ascites was similar between the PD and AD groups. In living related donor LTs, the development of increased ascites related to small-for-size livers may be caused by the large cut surface on the donor liver. This theory may explain why increased ascites was not seen in our transplant recipients, in whom the small-for-size livers were whole organs.

When we divided the PD liver recipients into 2 groups based on TBil level on POD 7, we found that graft volume (DLW/ERLW) was not associated with prolonged cholestasis (defined as TBil \geq 5 mg/dL on POD 7). Conversely, grafts with long WITs and CITs developed cholestasis, suggesting that small-for-size livers were more vulnerable to ischemic insult. Furthermore, we found that graft and patient survival in patients who developed prolonged cholestasis were markedly inferior to those who did not.

In conclusion, the use of PD livers in adults was associated with a greater incidence of HAT, probably attributable to smaller donor vessel size and the inadequate capacity of the donor vessel for accommodating high arterial flow velocity in the recipient. Post-LT anticoagulation therapy is warranted when using PD livers in adults. The outcome of small-for-size grafts is more likely to be adversely affected by longer WITs and CITs. Grafts with a DLW/ERLW of 0.4 or greater (or \geq 40% of ideal liver volume) can be used safely.

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