参考資料1

TRANSPLANTATION Vol. 70, 1283–1291, No. 9, November 15, 2000

IMPROVED GRAFT SURVIVAL OF PEDIATRIC LIVER RECIPIENTS TRANSPLANTED WITH PEDIATRIC-AGED LIVER DONORS

SUE V. MCDIARMID,1,3 DARCY B. DAVIES,2 AND ERICK B. EDWARDS

UCLA Medical Center, MDCC 12–383, Los Angeles, CA 90095 and United Network of Organ Sharing, Richmond, VA 23225

UNOS data 1992-1997の分析　(18歳未満を小児と定義)

小児ドナー中　35.6%が小児レシピエントに使用(1998年の小児、成人別登録後死亡率は小児7.4%、成人7.3%)

小児レシピ (n=2668)で、小児ドナーからと成人ドナーからの移植を比べると、３生率が81%対63%と有意に小児ドナーからの成績が良かった。成人レシピ (n=18525) で比べるとこのような差は見られなかった。

α-1,3-galactosyltransferase: expression cloning by gene transfer. Proc Natl Acad Sci USA 1989; 86: 8227.
9. Joziasse DH, Shaper NL, Kim D, Van den Eijinden DH, Shaper JH. Murine α1,3-galactosyltransferase. J Biol Chem 1992; 267: 5534.
10. Joziasse DH, Shaper JH, Van den Eijinden DH, Van Tunen AJ, Shaper NL. Bovine α1,3-galactosyltransferase: isolation and characterization of a cDNA clone. J Biol Chem 1989; 264: 14290.
11. Sandrin MS, Dekowski PL, Henning MM, Mouhtouris E, McKenzie IFC. Characterization of cDNA clones for porcine α(1,3)galactosyl transferase: the enzyme generating the GalαGal epitope. Xenotransplantation 1994; 1: 81.
12. Starahan K, Gu F, Preece AF, Gustavsson I, Andersson L, Gustafsson K. cDNA sequence and chromosome localization of pig α1,3 galactosyltransferase. Immunogenetics 1995; 41: 101.
13. Vanhove B, Goret F, Soulillou JP, Pourcel C. Porcine α1,3-galactosyltransferase: tissue-specific and regulated expression of splicing isoforms. Biochim Biophys Acta 1997; 1356: 1.
14. Katayama A, Ogawa H, Kadomatsu K, et al. Porcine α-1,3-galactosyltransferase; full length cDNA cloning, genomic organization, and analysis of splicing variants. Glycoconj J 1998; 16: 583.
15. Shapiro MB, Senapathy P. RNA splice junction of different classes of eukaryotes: sequence statics and functional implications in gene expression. Nucleic Acids Res 1987; 15: 7155.
16. Shaper NL, Harduin-Lepers A, Shaper JH. Male germ cell expression of murine β4-galactosyltransferase. J Biol Chem 1994; 269: 25165.
17. Yamamoto F, McNeill PD, Hakomori S. Genomic organization of human histo-blood group ABO genes. Glycobiology 1995; 5: 51.
18. Svensson EC, Soreghan B, Paulson JC. Organization of β4-galactoside α2,6-sialyltransferase gene. J Biol Chem 1990; 265: 20863.
19. Soejima M, Koda Y, Wang B, Kimura H. Functional analysis of the 5′-flanking region of FTA for expression of rat GDP-L-fucose:β-D-galactoside 2-α-L-fucosyltransferase. Eur J Biochem 1999; 266: 274.
20. Loa NW, Lau JTY. Transcription of b-galactoside α2,6-sialyltransferase gene in B lymphocytes is directed by a separate and distinct promoter. Glycobiology 1996; 6: 271.
21. Svensson EC, Conley P, Paulson JC. Regulated expression of α2,6-sialyltransferase by the liver-enriched transcription factors HNF-1, DBP, and LAP. J Biol Chem 1992; 267: 3466.
22. Jones PA. The DNA methylation paradox. Trends Genet 1999; 15 (1): 34.

Received 29 March 2000.
Accepted 24 July 2000.

0041-1337/00/7009-1283/0
TRANSPLANTATION

Vol. 70, 1283–1291, No. 9, November 15, 2000
Printed in U.S.A.

IMPROVED GRAFT SURVIVAL OF PEDIATRIC LIVER RECIPIENTS TRANSPLANTED WITH PEDIATRIC-AGED LIVER DONORS

SUE V. MCDIARMID,[1,3] DARCY B. DAVIES,[2] AND ERICK B. EDWARDS

UCLA Medical Center, MDCC 12-383, Los Angeles, CA 90095 and United Network of Organ Sharing, Richmond, VA 23225

Background. **Improving graft survival after liver transplantation is an important goal for the transplant community, particularly given the increasing donor shortage. We have examined graft survivals of livers procured from pediatric donors compared to adult donors.**

Methods. **The effect of donor age (<18 years or ≥18 years) on graft survivals for both pediatric and adult liver recipients was analyzed using data reported to the UNOS Scientific Registry from January 1, 1992 through December 31, 1997. Graft survival, stratified by age, status at listing, and type of transplant was computed using the Kaplan-Meier method. In addition, odds ratios of graft failure at 3 months, 1 year, and 3 years posttransplant were calculated using a multivariate logistic regression analysis controlling for several donor and recipient factors. Modeling, using the UNOS Liver Allocation Model investigated the impact of a proposed policy giving pediatric patients preference to pediatric donors.**

Results. **Between 1992 and 1997 pediatric recipients received 35.6% of pediatric aged donor livers. In 1998 the percent of children dying on the list was 7.4%, compared with 7.3% of adults. Kaplan-Meier graft survivals showed that pediatric patients receiving livers from pediatric aged donors had an 81% 3-year graft survival compared with 63% if children received livers from donors ≥18 years ($P<0.001$). In contrast, adult recipients had similar 3-year graft survivals irrespective of donor age. In the multivariate analysis, the odds of graft failure were reduced to 0.66 if pediatric recipients received livers from pediatric aged donors ($P<0.01$). The odds of graft failure were not affected at any time point for adults whether they received an adult or pediatric- aged donor. The modeling results showed that the number of pediatric patients trans-**

[1] UCLA Medical Center.
[2] United Network of Organ Sharing.
[3] Address correspondence to: Sue V. McDiarmid, MD, Medical Center, 10833 Le Conte Avenue, MDCC 12–383, Los Angeles, CA 90095.

planted increased by at most 59 transplants per year. This had no significant effect on the probability of pretransplant death for adults on the waiting list. Waiting time for children at status 2B was reduced by as much as 160 days whereas adult waiting time at status 2B was increased by at most 20 days.

Conclusion. **A policy that would direct some livers procured from pediatric- aged donors to children improves the graft survival of children after liver transplantation. The effect of this policy does not increase mortality of adults waiting. Such a policy should increase the practice of split liver transplantation, which remains an important method to increase the cadaveric donor supply.**

The nationwide donor shortage has forced scrutiny of our practices of organ allocation. In particular, liver allocation policies have been the subject of intense debate extending beyond the medical profession to the pages of the lay press and the corridors of the federal government (*1–4*).The issues of waiting time and mortality while waiting are amplified for liver transplant candidates (*5*) (and heart transplant candidates) because unlike kidney transplant candidates, no sustainable form of artificial organ support exists. In such patients allocation policies therefore take on a new urgency. If there were unlimited numbers of organs the justice of the argument "sickest first" is undisputed. However, given the limited organ supply, consideration must also be given to the question of how a scarce resource should be best utilized (*6*). In effect, which patients are likely to have the best graft survival?

Several investigators have identified factors that affect outcome after pediatric liver transplantation. Not surprisingly, as in adult liver recipients, the most important predictor is medical urgency (*7*). Although the technical challenges are considerable, young age itself is not a predictor of poor outcome in experienced centers (*8–11*). To date, donor factors considered have focused on whether the use of partial liver grafts affects the outcome of pediatric liver recipients. The use of split livers (one cadaveric donor divided to provide two transplantable segments), reduced livers (a cadaveric donor liver reduced in size to produce one transplantable segment), and living donor grafts, have already been shown to decrease the mortality of pediatric patients awaiting liver transplantation without decreasing patient and graft survivals (*12–14*). However, the effect of pediatric versus adult donor age on outcome has not been well studied. Our preliminary data showed that the majority of livers procured from pediatric-aged donors (<18 years of age) were transplanted into adults, although proportionately the same number of children die on the list as adults. This information caused to us question whether the outcome of pediatric or adult recipients was affected by the age of the donor. We postulated that if the results of this investigation showed that pediatric liver recipients benefited from receiving a donor of a pediatric age, as measured by improved graft and patient survival, without causing a negative impact on the adult population, then both utility and justice would suggest that pediatric recipients should receive at least some preference in receiving organs from pediatric donors.

METHODS

These analyses of posttransplant outcome were based on liver transplants reported to UNOS Scientific registry from January 1, 1992 through December 31, 1997. Odds ratios were calculated using a multivariate logistic regression analysis. This analysis controlled for several donor and recipient risk factors (e.g. donor race, donor cause of death, recipient race, diagnosis at time of transplant, previous transplant, medical condition at time of transplant, cold ischemia time, serum creatinine level and year of transplant). The outcome of interest was the odds of graft failure within 3 months, 1 year and 3 years posttransplant. PROC LOGISTIC, SAS version 6.3, was used to perform the logistic regression analysis. A stepwise regression technique, was used to determine the factors to be included in the final logistic regression model. Missing values for continuous variables were set to the mean, and for categorical variables, were set to the baseline value.

Acturial graft survival was computed using Kaplan-Meier method. These survival curves were stratified by age, status at transplant, type of transplant, and ICU group. A log-rank statistic was used to test the hypothesis of no difference in survival between groups.

For the median waiting times analyses, the cohort of patients included all registrations added to the UNOS Liver Waiting List between January 1, 1995 and December 31, 1997. Kaplan-Meier waiting times where calculated using PROC LIFETEST, SAS version 6.3. The actual probabilities on the waiting list of death, transplant, removed (not for reason of death or transplant), and still waiting, were computed using a competing risk method.

In April 1994 the UNOS liver data collection forms were amended. Among the information added to the forms was whether the transplanted liver was split or otherwise reduced in size. Therefore any information that specifies whole or split livers covers only the time period from April 1994 through December 31, 1997.

Modeling methods. Modeling results were generated by ULAM, the UNOS Liver Allocation Model. ULAM is a PC-based software package that simulates the current national and alternative liver allocation policies. Details of the construction of ULAM have been

TABLE 1. Distribution of pediatric and adult donor livers into pediatric and adult recipients, divided by age ranges: 1/1/92–12/31/97

Recipient age (yr)	Donor age (yr)				Total
	0–17		18+		
0–17	1786		882		2668
18+	3225		15300		18525
Total	5011		16182		21193
Recipient age	0–5	6–17	18–49	50+	
0–2	531	459	324	25	1339
3–17	263	533	449	84	1329
18–49	15	1712	5917	1989	9633
50+	13	1485	5224	2170	8892
Total	822	4189	11914	4268	21193

TABLE 2. Median waiting times for liver transplantation: by age and UNOS status: 1/1/92–12/31/97

Age group	Num Added	Status 1 95%			Status 2 95%			Status 3,4,7 95%	
		MWT	Conf limits	Num added	MWT	Conf limits	Num added	MWT	Conf limits
0–2 yr	295	23	(12,50)	178	51	(29,73)	815	189	(173,213)
3–5	75	10	(5,47)	36	35	(17,130)	211	231	(207,300)
6–10 yr	74	12	(5,40)	57	53	(22,246)	241	328	(235,428)
11–17 yr	153	10	(7,16)	77	46	(18,80)	382	409	(347,520)
18–49 yr	1236	9	(8,11)	834	28	(22,34)	8929	495	(472,517)
50+ yr	753	10	(8,12)	690	27	(22,32)	8757	460	(434,486)

TABLE 3. Mortality of patients on the UNOS liver waiting list for 1998 (Source UNOS OPTN Waiting List and Removal Files as of 9/7/1999)

Age (yr)	<1	1–5	6–10	11–17	18–34	35–49	50–64	65+
Patients	286	549	295	411	1143	6358	7411	1530
Deaths	50	34	15	16	84	445	556	117
Rate[a]	827.5	119.6	87.2	70.9	131.8	123.2	128.8	123.7
%	17.5	6.2	5.1	3.9	7.3	7.0	7.5	7.6

[a] Annual death rate per 1000 patient years at risk.

published elsewhere (*15*). In brief, ULAM is a discrete event simulation that matches individual donors and recipients using the same general algorithm as the UNOS match system. All statistical components of ULAM were derived from historical OPTN/SR data and the model has been validated against actual data from 1998–1999.

In our analysis, ULAM results were generated for the current national policy and the proposed policy giving pediatric patients preference to pediatric donors. For each policy, four independent simulations of 1998–2003 were generated with statistics collected from 1999–2003. A 1-year transition period allows the effects of the current policy to dissipate so that the impact of the proposed policy can be assessed more accurately. Output measures from the model represent the average of the four simulations of 1999–2003.

RESULTS

Current allocation of livers procured from donors <18 years. The first analysis determined how many livers procured from donors less than 18 years of age were transplanted into children (<18 years) compared to adults (18+ years). As seen in Table 1, which includes all cadaveric organs procured between 1/1/92 and 12/31/97 (including reduced and split grafts) pediatric recipients received 1786 of the total of 5011 (35.6% of pediatric-aged donor livers).

Analyzing these data further by dividing recipient and donor ages into subgroups, it can be seen that it is predominantly donors in the 6–17 age group that are transplanted into adults. Of donors aged 6–17 years, 1712 were transplanted into recipients aged 18–49, and 1485 into recipients aged greater than 50 years. Taken together, 3197 of 4189 (76.3%) 6- to 17-year-old donors were placed into adult recipients of which 46.4% were older than 50 years of age. In contrast, children received 882 of 16,182 adult liver donors (5.4%); this includes split and reduced size grafts (Table 2).

Current pediatric and adult mortality and waiting times on liver transplant list. The next questions examined were whether waiting time and mortality on the list differed between children and adults. Table 2 shows median waiting times for cadaveric liver transplants for pediatric and adult patients added to the liver waiting list between 1/1/95 to 12/31/97, divided according to age and UNOS status at time of listing. (Summary of Definitions of UNOS status codes: Up to and including 1997: status 1=In intensive care unit (ICU); status 2=hospitalized not in ICU; status 3=at home. 1998: status 1 adults=acute liver failure and in ICU; status 1 pediatrics=in ICU; status 2A (adults only)=chronic liver failure in ICU; status 2B=moderately urgent, defined by specific criteria; status 3=least urgent. Full definitions of status codes used can be found in the 1996 and 1998 UNOS Annual Reports.)

It can be seen that children 0–2 years waited longer in status 1 and status 2 than any other age range apart from status 2, 6- to 10-year-olds with an initial listing of status 2. At status 3, 4, and 7, adults waited longer than children. When this analysis was divided into years before and after split and reduced graft data were collected, i.e., 1/1/92 to 12/31/94 compared to 1/1/95 to 12/31/97 the same trends persisted (data not shown).

Mortality on the liver waiting list was also considered for different age ranges. For all patients on the liver waiting list during calendar year 1998 the number and percentage of patients dying is shown in Table 3. Note these numbers

TABLE 4. Patients listed on the liver waiting list between 1/1/95–12/31/97 (first 6 months after listing: probability of events)

Group	Initial status	Removed	Waiting	Transplanted	Died
Adult	1	0.151	0.082	0.448	0.319
	2	0.088	0.145	0.510	0.257
	3	0.032	0.690	0.197	0.082
Pediatric	1	0.179	0.118	0.433	0.270
	2	0.152	0.237	0.488	0.124
	3	0.088	0.573	0.283	0.056