参考資料１

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

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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。

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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-**

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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

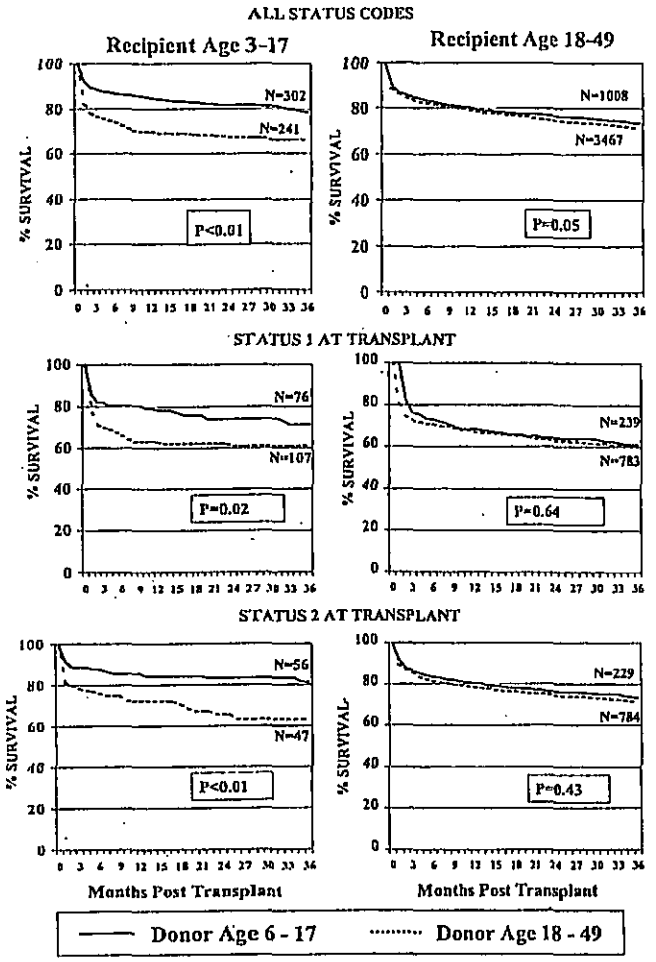

FIGURE 1. The unadjusted Kaplan-Meier 3-year survivals are shown for pediatric recipients (3–17 years) receiving livers from pediatric-aged donors (6–17 years) compared to adult donors (18–49 years) and adult recipients (18–49 years) receiving livers from pediatric aged donors (6–17 years). Results shown include retransplants, all UNOS statuses, and analyses for status 1 and status 2. Graphs on the left show the pediatric recipient data, graphs on the right show the adult recipient data.

exclude patients removed from the list because they became too ill to transplant. The percentage of patients dying was highest in the less than 1-year age range. Combining the <1 and 1- to 5-age groups, the percentage of patients dying is 10%, still higher than any other age range. From this data, the overall percent of children and adults dying in 1998 on the liver list was almost identical, 7.4%, the children (115 of 1541) and 7.3% adults.(1202 of 16,442)

We also analyzed the probability of death on the waiting list, divided by status at time of listing and adjusted for race, ABO match, and repeat listing. For adult and pediatric liver recipients added to the waiting list between 1/1/95 and 12/31/97, four possible events could occur: 1) the patient was removed from the waiting list for reasons other than death or transplant, 2) the patient continued to wait, 3) the patient received a cadaveric organ, (living related transplants excluded, reduced and split grafts included), 4) the patient died before transplantation. Patients removed from the list because they were too ill to receive a transplant were counted as pretransplant deaths. Table 4 shows the estimates for the probability of these four possible outcomes in the first 6 months after listing for patients added to the list between 1/1/95 and 12/31/97. Both adult and pediatric patients at status 1 and 3 had similar probabilities of dying on the list. A total of 31% of adults and 27% of children initially listed in status 1, died waiting. In status 2, pediatric patients had a lower probability of dying but a longer waiting time compared to adults. A total of 25.7% of adults at status 2 died compared with 12.4% of children, whereas 14.5% of adults originally listed were still waiting at the end of 6 months compared to 23.7% of children at status 2. In the second 6 months after listing the probability for all four outcomes was similar between adults and children (data not shown).

Kaplan-Meier patient and graft survivals: effect of donor age on outcome of pediatric and adult liver recipients. Our first analysis attempted to answer this question by subdividing donor and recipient ages into several age ranges. However, the numbers in each subgroup became too small to allow for a meaningful statistical analysis. It was decided to eliminate several subdivisions of age ranges as well as extremes of donor and recipient age that might bias the results. Therefore, for the first analysis, the 0–5 age range for donors and the 0–2 age range for recipients was eliminated and the 3- to 5-year and 6- to 17-year age range for recipients was combined into one group, i.e., 3–17 years. It was also reasoned that pediatric recipients less than 3 years generally received whole organs from similar age donors based on size considerations. The upper limit of donor and recipient age was set at less than 50 years to exclude the possible negative effects of older donors and recipients. Figure 1, shows the unadjusted Kaplan-Meier 3-year graft survivals for pediatric recipients (3–17 years) receiving livers from pediatric-aged donors (6–17 years) compared to adult donors (18–49 years), and adult recipients receiving livers from pediatric aged donors. Results shown include retransplants, all UNOS statuses and a further analysis for status 1 and status 2. Excluded are reduced, split or living donor transplants. Pediatric recipients receiving livers from younger donors had a significantly improved graft survival, 81% compared with

TABLE 5. The odds of graft survival compared for adult and pediatric donors and recipient: whole grafts only

Recip age (yr)	Donor age (yr)	Num txd	Time points					
			3 Mo post-Tx		1-Yr post-Tx		3 Yr post-Tx	
			Odds ratio	P	Odds ratio	P	Odds ratio	P
3–17	6–17	496	0.62	0.02	0.50	<0.01	0.58	0.03
3–17	18–49	362	1.00	Ref.	1.00	Ref.	1.00	Ref.
18–49	6–17	1699	0.82	0.20	0.77	0.07	0.84	0.36
18–49	18–49	5879	0.78	0.08	0.77	.05	0.84	0.26

TABLE 6. Transplants performed 4/1/94–12/31/97, numbers of whole, reduced, split, and living donors by year 1994–1997

Yr	Type of transplant				
	Whole	Reduced	Split	Live	Total
1994	2669	108	26	45	2848
1995	3771	87	21	45	3924
1996	3865	84	62	46	4057
1997	3935	79	84	60	4158
Total	14240	358	193	196	14987

TABLE 7. Numbers of whole, reduced, split and living donors by age of recipient: 1994–1997

Age	Type of transplant				
	Whole	Reduced	Split	Live	Total
<1	254	131	39	106	530
1–2	304	102	35	47	488
3–5	192	42	13	15	262
6–10	223	35	13	14	285
11–17	375	21	13	7	416
18+	12892	27	80	7	13006
Total	14240	358	193	196	14987

63%, $P<0.001$. In contrast, adult recipients had similar graft survivals irrespective of donor age. These differences remained significant when status at time of listing was considered.

Multivariate analyses: effect of donor age or outcome of pediatric and adult liver recipients. The Kaplan-Meier survival curves were unadjusted for risk. Therefore a further multivariate regression analysis was performed to determine if placing younger donor livers into younger recipients reduced the odds of graft failure. As before, this analysis excluded living related donors and split and reduced grafts. Donor and recipient risk factors controlled for were: donor and recipient race, donor cause of death, recipient diagnosis at transplant, medical condition (UNOS status) at transplant, cold ischemia time, ABO match, donor creatinine level, and year of transplant. The odds of graft failure at three months, 1 and 3 years posttransplant were determined (Table 5). At all three time points, the odds of graft failure were significantly less if pediatric recipients (3–17 years) received livers from younger donors (6–17 years). In contrast the odds of graft failure at each time point for adult recipients were similar whether or not the donor was younger or older.

The same multivariate regression analysis was repeated but now applied to all pediatric and adult recipients, with no age exclusions and inclusive of split and reduced grafts. Table 6 shows the number of reduced and split organ transplants performed during the period of this analysis, and Table 7 the type of transplant according to age. During this time period 66 pediatric-aged donors were split, of which 24 segments were placed in adults.

The results of the unrestricted analysis (Table 8) remained very similar to the restricted analysis: pediatric patients have significantly reduced odds of graft failure if receiving a graft from a pediatric-aged donor whereas the age of the donor had little impact on the odds of graft failure to adult recipients.

An expected outcome of a policy that would direct more livers from pediatric donors to pediatric recipients would be an increased number of relatively large organs being directed to smaller recipients. This would encourage split liver transplantation whereby two recipients benefit from one organ. As well, reduced size transplantation, where part of the liver is discarded, might also occur. Therefore, we investigated the graft survivals of reduced and split size livers. For the time period 4/1/94–12/31/97 the Kaplan-Meier 3-year graft survival estimates for pediatric recipients of primary liver transplants subdivided by the type of organ received are shown (Fig. 2). It can be seen that reduced size grafts had a significantly lower 3-year graft survival compared to all other graft types. In comparison, split liver grafts had an overall 70% 3-year graft survival, not significantly different from either whole or living donor grafts. We were also interested in whether a split liver from a pediatric donor had a different patient and graft survival compared to that from an adult donor. Although the numbers were small, Kaplan-Meier three year adjusted patient survivals for split livers were not different if the liver was from an adult donor (n=51, patient survival 87%) or a pediatric donor (n=32, patient survival 89%). However, in comparison, the 3-year Kaplan-Meier graft survival was worse if the split liver was from an adult donor, 62%, as compared to a pediatric donor, 83%.

For all the above analyses of graft survivals, patient survivals were also examined (data not shown), and similar results were observed. Because of the complexity of the analyses derived from data accrued over several years, we did attempt to detect any possible center effects.

UNOS liver allocation model (ULAM) results. ULAM was used to investigate whether the proposal to allocate livers from pediatric donors preferentially to pediatric recipients, within urgency status and geographic areas, would have a detrimental impact on adult patients waiting on the list. In particular we believed it was important to investigate whether the number of adults dying either pretransplant or posttransplant would be effected by the proposed new policy. The proposed allocation sequence used in the model is shown in Table 9.

Two models were developed; the first defined a pediatric

TABLE 8. Odds of graft survival compared for pediatric and adult aged donors and recipients; including reduced and split grafts

Recip age (yr)	Donor age (yr)	Num txd	Time points					
			3 Mo post-Tx		1 Yr post-Tx		3 Yr post-Tx	
			Odds ratio	P	Odds ratio	P	Odds ratio	P
0–17	0 –17	1786	0.66	<0.01	0.62	<0.01	0.65	<0.01
0–17	18+	882	1.00	Ref.	1.00	Ref.	1.00	Ref.
18+	0 –17	3225	0.62	<0.01	0.84	0.29	1.06	0.75
18+	18+	15300	0.66	<0.01	0.86	0.33	1.06	0.75

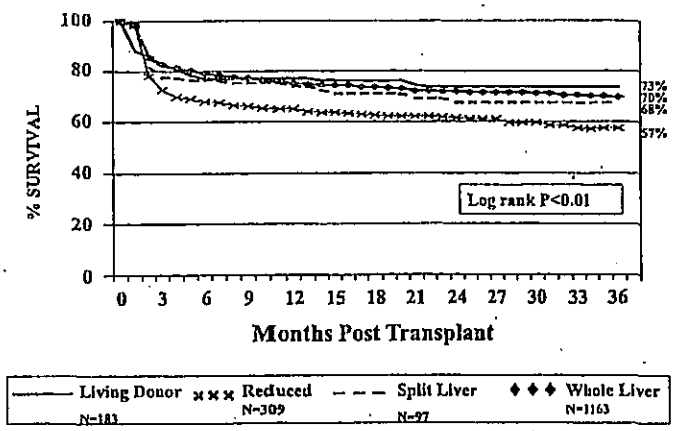

FIGURE 2. The Kaplan-Meier 3-year graft survivals are shown for pediatric recipients of primary liver transplants subdivided by type of organ received.

donor as <18 years, and the second defined a pediatric donor as <18 years and less than a specified weight range. Three weight ranges were investigated, <40, <45, and <50 kg. The second model was developed in response to concerns that small adult recipients might be disadvantaged by the proposed pediatric definition of <18 years without weight restrictions.

Neither model takes into account the data presented above which shows improved patient and graft survivals for children receiving livers from pediatric aged donors. Further, split liver transplant and outcomes were not considered.

Table 10 summarizes the most relevent data from the simulations comparing the current allocation policy to the four proposed pediatric donor definitions: 1) <18 years, 2) <18 years and <40 kg, 3) <18 years and <45 kg, 4) <18 years and <50 kg (Table 11).

The data presented in Table 12 represents the average of each measure for 5 years (1999–2003) and over four simulation runs. The data address: 1) the number of pediatric and adult patients transplanted by age (pediatric recipients divided 0 to 5 years, 6–11 years, 11–17 years) and by status, 2) median waiting time by status, and 3) probability of pretransplant death within 6 months of listing. The number of repeat transplants, and patient life years under the different proposals is not shown because the model did not account for expected improvements in pediatric graft survival should pediatrics recipients receive livers from pediatric aged donors.

In all of the proposed policies, slightly more pediatric patients were transplanted over the 5-year period. The increase over the current policy ranged from 151 over 5 years (30 per year) for the most restrictive policy with donors defined as <18 years and <40 kg, to 297 over 5 years (59 per year) the least restrictive policy defining a pediatric donor as <18 years. Consequently, each of the policies resulted in a corresponding decrease in the number of adult patients receiving transplants.

Investigating the change in the number of transplants by age and status showed that among pediatric patients fewer were transplanted in status 1 under the proposed policies. This is because more pediatric patients were transplanted at less urgent statuses under the proposed policies. In contrast about the same or slightly higher numbers of adult patients

TABLE 9. Proposed order of allocation for a liver from a pediatric donor

1. Local
Pediatric status 1
Adult status 1
2. Regional
Pediatric status 1
Adult status 1
3. Local
Adult status 2a
Pediatric status 2b
Adult status 2b
Pediatric status 3
Adult status 3
4. Regional
Adult status 2a
Pediatric status 2b
5. National
Pediatric status 1
Adult status 1
Adult status 2a
Adult status 2b
Pediatric status 3
Adult status 3

were transplanted in status 1 because there were fewer pediatric patients competing for organs while in status 1. This is reflected in the increased numbers of children transplanted at status 2B. This was most evident in the policy defining pediatric donors <18 years without weight restriction. The increase in pediatric status 2B patients transplanted was 304 over 5 years compared to current policies. This benefit was diluted as the more restrictive pediatric donor definitions by weight were applied. In contrast, the more stable pediatric patients at status 3 showed only a modest increase, approximately 4–10 more children per year. In examining the data by status for adults, it is also important to note that all of the proposed policies slightly increased the number of adult patients transplanted at status 2A. This effect ranged among 18 to 78 patients over 5 years.

Of all pediatric donor livers, the percent that went into adults was 68.8% under the current policy. Under the least restrictive proposed policy the percentage of adults still receiving pediatric donors was 59.2%, and ranged between 63–64% under the other pediatric donor proposals divided by weight. There was also a decrease in the percentage of adult livers that were transplanted into pediatric patients. This was most pronounced, 3.9%, in the policy defining pediatric donors <18 years, without weight restriction. Only a negligible increase in the percentage of adult livers that were transplanted into adults was demonstrated.

The percentage of local, regional, and national transplants was essentially unchanged as was the average and median distance the organ traveled. The percentage of organs that traveled greater than 1000 miles increased from 1.6 to 1.7%.

Deaths pretransplant and posttransplant and total deaths for the proposed policies was examined and no significant changes were noted with all four policies proposed as compared to the current policy.

When the probability of pre transplant death within 6 months of listing was analyzed, there were minimal differences, none of which was statistically significant, between

TABLE 10. ULAM comparison of current liver allocation policy to four proposed pediatric donor definitions: <18 yr and <40 kg; <18 yr and <50 kg; the model simulates 5 yr of transplant activity under the various definitions

	Current policy	<18 Yr	<40 kg	<45 kg	<50 kg
No. ped. txs	2132	2429	2283	2299	2307
Change from current policy		+297	+151	+167	+175
No. ped. txs by age					
0–5	1238	1417	1336	1339	1353
6–11	367	413	387	391	397
11–17	528	600	560	569	558
Txs by age and status					
Adult 1	4061	4085	4056	4100	4087
Adults 2A	4713	4731	4729	4733	4781
Ped 1	764	711	755	733	731
Ped 2B	1069	1372	1206	1246	1256
% of total/ped donor to adult recipient					
	69%	59%	64%	64%	63%
Med wait time					
Ped. 2B:2B	340.8	179.0	264.5	252.3	243.0
Ped. 3:2B	776.5	624.3	685.5	699.5	674.0
Adult 2A:2A	11.3	12.3	11.3	11.3	11.5
Adult 2B:2B	553.0	573.0	550.8	572.3	569.0
Adult 3:2B	947.5	968.5	958.5	963.0	965.5
Probability of pre-Tx death w/in 6 mo of listing					
Adult 1	11.8%	11.4%	11.7%	11.9%	11.6%
Ped 1	16.4%	15.5%	15.3%	15.4%	15.1%
Adult 2A	23.4%	22.2%	22.0%	21.9%	22.9%
Adult 2B	13.7%	14.0%	13.9%	13.6%	13.6%
Ped 2B	13.5%	12.3%	12.8%	12.0%	12.5%

the current and proposed policies among adult and pediatric recipients. Among pediatric patients, death rates decreased for patients listed initially in status 2B and status 3. Waiting time as measured by Kaplan-Meier estimates for most categories were reduced for pediatric patients and increased slightly for adult patients. Of importance, both pediatric and adult patients at status 1 had essentially no change in waiting time at status 1 although on average pediatric patients waited 2 days longer for transplant at status regardless of the policy. Of importance, children in status 2B had the most benefit from the policy defining pediatric <18 years without weight restriction, with median waiting time reduced by 160 days. In that same simulation adult waiting time at 2B was increased by only 20 days. When pediatric donors were further restricted by weight, the beneficial effect of decreased waiting time at status 2B for children continued to be evident but much less important ranging between 76 and 97 days, whereas the waiting time for adults was effected only slightly 2–16 days. Among adults waiting times increased the most for patients listed initially in status 3 with an ending status of 2B from 947 to 966 days and under the least restrictive policy.

DISCUSSION

We have shown that there is a significant beneficial effect on liver graft survival if pediatric recipients receive livers from pediatric-aged donors, whereas graft survival of adult recipients is not advantaged or disadvantaged by the age of the liver donor. This effect is seen at 3 months after liver transplantation, when donor factors are likely to have the strongest influence on outcome, but also persists at 3 years posttransplant. These findings hold true whether using a univariate or multivariate method of analysis or unadjusted Kaplan-Meier estimates of graft survival. Importantly, whether the analysis is performed on a restricted population of donor and recipients to decrease the potential impact of the extremes of donor and recipient age, and the possible influence of partial liver grafts, or the entire population of adult and pediatric recipients and donors, including partial liver grafts, the same benefit to pediatric patients receiving livers from younger donors persists. The improvement in graft survival for pediatric patients who receive younger donors compared to adults receiving younger donors, will have the greatest impact on the most medically urgent children, who we have shown wait longer to receive a donor, especially if aged less than 5 years, compared with adults of equivalent status.

We can only postulate why pediatric recipients have an improved survival if they receive a liver from a pediatric-aged donor. Donor quality, which is usually excellent in pediatric-aged donors, is a likely explanation. The recent research impetus studying the process of senescence at the cellular level, may provide new insights in the future.

Should these results be utilized to change allocation policies to give children awaiting liver transplantation some preference in receiving younger donors? To answer this important question several related issues must first be considered. 1) Do children already hold an advantage over adults waiting liver transplantation, reflected either by shorter waiting times or a decreased mortality on the list? 2) Would redirecting some pediatric donors away from adults awaiting liver transplantation have a significant negative effect on the outcome of adults undergoing liver transplantation? 3) Could directing some adolescent donor livers to small children encourage split liver transplantation, which would increase the donor supply?

It has been argued that children already have an advantage over adult candidates awaiting liver transplantation because they have three possible options for receiving a liver:

a whole cadaveric graft, a partial cadaveric graft or a living donor organ (*16*). Despite this, an analysis of the last 3 years of the UNOS database show that children have similar mortalities and waiting times compared to adults on the transplant list. In fact, it is children less than 2 years of age at status 1 who waited significantly longer than any other age group. As well, in 1998, children less than 1 year had the highest mortality rate waiting for any age group, followed only by children in the 1- to 5-year age range. Therefore the data suggest that the availability of living related donors and partial liver grafts, which would most likely have benefited small children on the list, has not yet had a significant impact on pediatric mortality or waiting time as compared with adults. Furthermore, given that the results of liver transplantation in small pediatric patients in experienced centers are comparable to those of older children, there can be no justification for not providing young children with at least equal access to liver donors.

Although living related donation for children has been properly advocated as one means of alleviating the donor shortage for children (*17*), this modality should not be viewed as an excuse to divert cadaveric donors away from children (*18*). Because of the risk to the otherwise healthy donor, most often a parent (*18*), the ethically correct position is that living related donation should continue to be seen as last resort to try and alleviate the donor supply problem. Conversely, the split liver donor technique should become the first consideration for every suitable donor (*19*). The most recent reported results are comparable to whole graft transplantation (*20*). As well, a recent report suggests graft survival is better in infants who receive a split compared to a whole graft (*21*). However, reduced graft transplantation should be actively discouraged: not only are the results inferior, but a whole liver is diverted away from a more appropriately sized recipient.

The next question was more complex: would adults be disadvantaged by diversion of some pediatric donors to pediatric recipients? Fairness and balancing the conflicting notions of transplanting the most urgent first regardless of age versus best utilization of a scarce resource, would require that pediatric-aged donors should not always be placed in pediatric recipients. For example, it would seem inappropriate and unjust, either on a local or regional level that a status 1 adult should be bypassed for a status 2B child. For this reason, ULAM was programed to assign priority so that within each medical urgency status and within each geographic distribution level (local, regional, and national) pediatric candidates are prioritized.

The most important result of the modeling was that none of the proposed policies allocating livers from pediatric donors to pediatric recipients increased the probability of death for adults waiting on the transplant list. Although more children were transplanted per year (at most 59, less than 1 additional child per pediatric transplant center), and therefore proportionately less adults, the impact for the adults was on waiting time at the less urgent statuses, 2B and 3. Even then, the average wait was at most increased by 20 days. Importantly, the waiting time for the most medically urgent adults at status 2A and 1 was not affected by any of the proposed policies. In fact adults waited an average of 2 days less at status 1 compared to children, because more children were transplanted at status 2B. As well slightly more status 1 adult patients were transplanted under the proposed policies.

The decrease in waiting time for children at 2B was as much as 160 days. Clinically this is important as one of the most common criteria for listing children at status 2B is a growth failure, i.e., weight or height less than 5th percentile. The impact of decreasing waiting time by as much as half a year for the young, cholestatic, malnourished child is clinically highly relevant to the unique issues of growth and development in chronically ill children (*22, 23*). It has already been shown that malnutrition has a negative effect on both pre- and posttransplant survival (*24, 25*), and that age at transplant of <2 years in children is an important independent predictor of improved growth after transplantation (*26*). It should still be noted that even under the most liberal of the proposed policies, the majority of livers procured from pediatric aged donors will still be transplanted into adult recipients. As well, the percentage of transplants performed locally, regionally, and nationally would be affected only minimally.

The third question to be considered is how might a proposal to direct some livers from pediatric donors best encourage split liver transplantation. Our data show that split liver graft survival is significantly improved if the donor is in the pediatric age range. This result is most likely a reflection of the usually excellent quality of the adolescent donor and highlights the need for very careful donor selection if the split procedure is performed on adult-aged donors.

In comparing the four pediatric allocation proposals, with the least restrictive being any pediatric donor <18 years, and the most restrictive being <18 years as well as <40 kg, the data showed that the most positive effect occurred for the pediatric patients when the pediatric donor was defined <18 years. When the pediatric donor was further subdivided by weight, the potential benefit to pediatric patient was diminished without a substantial increase in benefit to adult patients. If the definition of the pediatric donor was restricted to weight <40 kg, the advantage of directing some of the larger pediatric donors to smaller pediatric recipients, which would promote split liver transplantation, would be lost. As can be seen from the data, most pediatric donor livers exported to adult recipients are in the donor age range of 11–17 years, are generally of excellent quality and ideal for splitting. In fact, UNOS recently approved a proposal that requires all participating centers to split suitable donor livers. If adolescent liver donors are preferentially offered to children waiting, many of whom would be too small to accept a whole graft, the center accepting such a liver should split the graft so that an adult patient would not be deprived of an organ. If the center was unwilling to split the donor liver, it should be returned to the donor pool for reassignment to the next eligible recipient. Such a policy could then be seen as a reason to improve the utilization of these excellent quality younger donors. The success of this concept will depend on centers being prepared to "share" split grafts. A recent report shows that "shipped" segments have an equivalent graft survival compared to locally procured segments (*27*). Given the demonstrated excellent results achievable both for the right and left split liver grafts (*28*), and the ongoing organ shortage, urgent priority should be assigned to any allocation policy that will encourage split liver transplantation (*29*). The onus will lie on the surgical transplant community to not

accept such livers for reduced size transplantation, a technique now in disrepute given the proven success of split livers, and the increasing donor shortage.

We have shown that an allocation policy giving some priority to children to receive livers from pediatric donors can improve the outcomes after liver transplantation, without a negative impact on adults. As well, such a policy would encourage split transplantation, the only method currently available to increase the cadaveric donor supply. Furthermore, this proposal strikes a balance between justice and utility; the sickest patients, whether adult or pediatric are still transplanted first, more grafts are made available by encouraging split transplantation, and patient and graft survival for children are improved without detriment to adult recipients outcome. As such this proposal is worthy of serious consideration by the community of transplant physicians, surgeons, and their patients.

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