ORIGINAL ARTICLE

Pediatric Liver Transplantation for Urea Cycle Disorders and Organic Acidemias: United Network for Organ Sharing Data for 2002-2012

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Decision making concerning liver transplantation is unique for children with urea cycle disorders (UCDs) and organic acidemias (OAs) because of their immediate high priority on the waiting list, which is not related to the severity of their disease. There are limited national outcome data on which recommendations about liver transplantation for UCDs or OAs can be based. This study was a retrospective analysis of United Network for Organ Sharing data for liver recipients who underwent transplantation at an age < 18 years in 2002-2012. Repeat transplants were excluded. Among the pediatric liver transplants, 5.4% were liver-only for UCDs/OAs. The proportion of transplants for UCDs/OAs increased from 4.3% in 2002-2005 to 7.4% in 2010-2012 ($P < 0.001$). Ninety-six percent were deceased donor transplants, and 59% of these patients underwent transplantation at <2 years of age. Graft survival improved as the age at transplant increased ($P = 0.04$). Within 5 years after transplantation, the graft survival rate was 78% for children < 2 years old at transplant and 88% for children ≥ 2 years old at transplant ($P = 0.06$). Vascular thrombosis caused 44% of the graft losses, and 65% of these losses occurred in children < 2 years old. Patient survival also improved as the age at transplant increased: the 5-year patient survival rate was 88% for children with UCDs/OAs who were <2 years old at transplant and 99% for children who were ≥ 2 years old at transplant ($P = 0.006$). At the last-follow-up (54 ± 34.4 months), children who underwent transplantation for UCDs/OAs were more likely to have cognitive and motor delays than children who underwent transplantation for other indications. Cognitive and motor delays for children with UCDs/OAs were associated with metabolic disorders, but they were not predicted by age or weight at transplant, sex, ethnicity, liver graft type (split versus whole), or hospitalization at transplant in univariate and multivariate analyses. In conclusion, most liver transplants for UCDs/OAs occur in early childhood. Further research on the benefits of early transplantation for patients with UCDs/OAs is needed because a younger age may increase posttransplant morbidity. ***Liver Transpl 20:89-99, 2014***. **© 2013 AASLD.**

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Abbreviations: ALF, acute liver failure; HR, hazard ratio; IQR, interquartile range; LRLT, living related liver transplantation; MELD, Model for End-Stage Liver Disease; MMA, methylmalonic acidemia; MSUD, maple syrup urine disease; OA, organic acidemia; PA, propionic acidemia; PELD, Pediatric End-Stage Liver Disease; SRTR, Scientific Registry of Transplant Recipients; UCD, urea cycle disorder; UNOS, United Network for Organ Sharing.

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TABLE 1. Classification of UCDs and OAs

	UCDs (n = 186)	OAs (n = 137)
Mechanism	Defect in 1 of 6 urea cycle enzymes	Defect in an enzyme that metabolizes branched-chain amino acids or lysine or in another step of amino acid metabolism
Types		• MSUD
	• Carbamyl phosphate synthetase deficiency	• PA
	• *N*-Acetylglutamate synthetase deficiency	• MMA
	• Ornithine transcarbamylase deficiency (X-linked)	• Homocysteinuria/methylmalonic aciduria
		• Isovaleric acidemia
	• Argininosuccinic acid synthetase deficiency (citrullinemia)	• Biotin-unresponsive 3-methylcrotonyl coenzyme A carboxylase deficiency
	• Argininosuccinate lyase deficiency	• 3-hydroxy-3-methylglutaryl coenzyme A lyase deficiency
	• Arginase deficiency	• Ketothiolase deficiency
		• Glutaric acidemia type I

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Urea cycle disorders (UCDs) and organic acidemias (OAs) are inborn errors of protein metabolism, and their prevalences have been estimated to be 1:30,000 and 1:48,000 to 1:100,000, respectively.[1-3] Within these 2 categories are several disorders, each involving a single enzyme defect leading to the accumulation of toxic metabolites (primarily ammonia for UCDs and various amino acids for OAs; Table 1). Severe cases present in infancy with life-threatening metabolic decompensation, which is usually characterized by lethargy that progresses to coma, seizures, and multiorgan system failure. These disorders can be managed with dietary protein restriction and disorder-specific amino acid supplements. However, metabolic decompensation can recur episodically and be triggered by endogenous protein loads or exogenous protein catabolism during times of stress or illness. These episodes can be fatal or cause permanent neurological damage.

Liver transplantation was identified as an alternative option for treating UCDs and OAs in the late 1980s.[4] The transplanted liver provides sufficient enzymatic activity to correct the deficiency and removes the risk of metabolic decompensation and the need for dietary protein restriction.[5]

Because of their risk for sudden life-threatening decompensation, children with UCDs/OAs automatically receive a Model for End-Stage Liver Disease (MELD)/Pediatric End-Stage Liver Disease (PELD) score of 30 at listing for liver transplantation. They can be advanced to status 1B after 30 days. Neither requires a review by the regional review board. This priority status was established in 2005 after the initiation of the MELD/PELD scoring system in 2002.[6] It is based solely on the diagnosis rather than current life-threatening complications or the severity of illness, which applies to most other high-priority categories in the MELD/PELD system. This introduces unique factors into decision making about listing for transplantation and organ acceptance.[7]

There are limited national outcome data on which recommendations about liver transplantation for UCDs/OAs can be based. Because these disorders are rare, they are often grouped together with other metabolic diseases in outcome analyses.[8] There is a limited evidence base for guidelines about when these children should undergo transplantation to optimize long-term outcomes.[9]

The goals of this analysis were to describe US patterns of liver transplantation for children with UCDs/OAs, to evaluate regional and temporal variations, and to provide outcome data about posttransplant morbidity. Although there are important biochemical and clinical distinctions between UCDs and OAs, we considered both in this analysis because children with these disorders receive the same priority under current United Network for Organ Sharing (UNOS) policy. The analysis differentiates them as much as possible, but this differentiation was limited by the sample size and the diagnostic coding of the UNOS data. Because UNOS data from the Scientific Registry of Transplant Recipients (SRTR) are retrospective, data are variably missing, and there is limited information about cognitive and motor development, these data cannot definitively answer when children with UCDs or OAs should undergo liver transplantation. However, they do describe pediatric liver transplantation for UCDs/OAs in the United States and raise interesting questions for future research.

PATIENTS AND METHODS

This research was registered with the committee on human research at the University of California San Francisco, but it was institutional review board–exempt because no patient identifiers were accessed by the investigators.

In the UNOS/SRTR database, children with UCDs/OAs were identified by diagnostic codes, and this was then confirmed by automated text searching of the

primary and secondary diagnosis text fields to capture all variants of these diseases. We were able to identify all children with maple syrup urine disease (MSUD) because there is a specific associated diagnostic code, and we were able to differentiate children with UCDs from children with OAs via text searching. However, because most of these children were coded as *metabolic disease–other* and variable levels of detail were provided about the specific diagnoses, we were not able to accurately classify the children further within these categories. Children with other indications for transplantation were categorized on the basis of the coded diagnoses. Children with acute liver failure (ALF) and children with tumors were combined because of their high wait-list priority (status 1A and status 1B, respectively).

Our retrospective cohort included all recipients of first liver transplants between 2002 and 2012 who were <18 years old at the time of transplantation and underwent transplantation after the MELD/PELD score was instituted. Children undergoing repeat transplantation were excluded.

Chi-square testing was used to compare categorical variables, and Kruskal-Wallis testing was used for comparisons of continuous variables. Spearman's rank correlation coefficient was used to examine relationships between percentages of regional transplants for UCDs/OAs, waiting-list mortality, and wait times. Nonparametric testing was chosen because of the skewed nature of several variables of interest (eg, age and weight at transplant), the small sample sizes for the children with UCDs/OAs, and the small number of regions. Kaplan-Meier analysis and Cox proportional hazards modeling were used to identify factors associated with graft and patient survival. No significant interactions were detected in a multivariate survival analysis. Logistic regression was used to evaluate risk factors for cognitive and motor delays during follow-up. Variables with $P < 0.15$ in the univariate analysis were retained for the multivariate analysis. Into the multivariate model of posttransplant patient survival, a UCD diagnosis versus an OA diagnosis was also forced. $P < 0.05$ was considered statistically significant. Stata 12 (StataCorp, College Station, TX) was used for all analyses.

The UNOS database includes information about the functional status at listing, transplant, and follow-up for children 1 year and older. Data about cognitive and motor delays are collected in UNOS follow-up data requests but not in listing/transplant questionnaires. For both cognitive and motor delays, the follow-up questionnaires ask whether there is definite, probable, questionable, or no delay/impairment. Information about functional status, cognitive delays, and motor delays was included in the analysis as available.

RESULTS

There were 5672 pediatric liver transplants in the United States between 2002 and 2012, and 323 of these transplants were for UCDs/OAs. This number includes 17 children who underwent liver-kidney transplantation for OAs. During the study period, 8 children with UCDs/OAs 2.4% (8/(323 transplanted + 8 waiting-list deaths) died on the liver transplant waiting list. Six of the 8 waiting-list deaths were for children who were <2 years old at listing; the causes of death were multiorgan system failure (n = 4) and unknown (n = 4). Four children who died on the waiting list had carbamyl phosphate synthetase deficiency, 2 had ornithine transcarbamylase deficiency, and 2 had MSUD. The median waiting-list time before death for these patients was 36 days [interquartile range (IQR) = 13-63 days].

The proportion of pediatric liver transplants performed for UCDs/OAs increased from 4.3% in 2002-2005 to 7.4% in 2010-2012 ($P < 0.001$). UNOS regions 2 (Delaware; Washington, DC; Maryland; New Jersey; Pennsylvania; Northern Virginia; and West Virginia) and 5 (Arizona, California, Nevada, New Mexico, and Utah) accounted for 45% of transplants for UCDs and OAs (87 and 59, respectively) but for only 33% of pediatric liver transplants overall. The number of UCD/OA transplants in other regions during the study period ranged from 9 to 32.

Overall, 79% of the children with UCDs/OAs underwent liver transplantation in their presumed home region (ie, the recipient's state of residency at listing was in the region in which the transplant was performed). Out-of-region liver transplants were most common in region 2 and accounted for 41% of all transplants for UCDs/OAs. In region 5, 17% of liver-only transplants for UCDs/OAs were for out-of-region residents, and this proportion was similar to the proportions in other regions. For the 17 liver-kidney transplant recipients, 9 transplants were performed in region 5; 78% were in-region transplants. Thus, the large number of transplants for UCDs/OAs in regions 2 and 5 may represent a combination of UCD/OA disease distribution and patient travel to specific centers.

Only 4% of children with UCDs/OAs underwent living donor liver transplantation, whereas 16% with biliary atresia, 8.5% with other metabolic/cholestatic liver diseases, and 12% with ALF or a tumor did ($P < 0.001$). The proportion of living donor liver transplant recipients with UCDs/OAs decreased slightly during the study period from 7% (6/84) in 2002-2005 to 2.8% (3/107) in 2010-2012, but the numbers were small ($P = 0.43$). The 13 living donor liver transplant recipients did not differ by age at transplant, sex, ethnicity, diagnosis, or days on the waiting list from deceased donor liver transplant recipients with UCDs/OAs. Six of the 13 underwent transplantation in region 2.

Children who underwent deceased donor liver transplantation for UCDs/OAs were more likely to be male and Caucasian than children who underwent transplantation for other indications, and the majority were <2 years of age at transplant (Table 2). Among the children undergoing transplantation for UCDs, 34%

TABLE 2. Demographics of Pediatric Deceased Donor Liver Transplant Recipients by Diagnosis: UNOS Data for 2002-2012

	UCD/OA (n = 293)	Biliary Atresia (n = 1571)	Other Cholestatic/ Metabolic Diseases (n = 1983)*	ALF/Tumor (n = 1036)	*P* Value†
Male sex [n (%)]	181 (62)	625 (40)	1004 (51)	581 (56)	<0.001
Ethnicity [n (%)]					
White	191 (65)	728 (46)	1116 (57)	496 (48)	<0.001
Black	24 (8)	335 (21)	342 (17)	172 (17)	
Hispanic	49 (17)	329 (21)	399 (20)	290 (28)	
Asian	25 (9)	113 (7)	66 (3)	48 (4)	
Other‡	4 (1)	66 (4)	60 (3)	30 (3)	
Age at transplant [n (%)]					
<1 year	97 (33)	759 (48)	391 (20)	128 (12)	<0.001
1-2 years	77 (26)	492 (31)	492 (25)	265 (26)	
3-6 years	52 (18)	113 (7)	244 (12)	217 (21)	
7-11 years	41 (14)	118 (8)	293 (15)	159 (15)	
12-18 years	26 (9)	89 (6)	563 (28)	267 (26)	
Status at transplant [n (%)]					
MELD/PELD score	151 (52)	1394 (89)	1590 (80)	263 (25)	<0.001
Status 1B	142 (48)	65 (4)	133 (7)	151 (15)	
Status 1A	0	112 (7)	260 (13)	622 (60)	
MELD/PELD laboratory score at transplant	−3 (−7 to 3)	16 (8-23)	20 (1-31)	15 (7-24)	<0.001
Transplant type [n (%)]					
Whole liver	250 (85)	1208 (77)	1787 (90)	829 (80)	<0.001
Split liver	43 (15)	363 (23)	196 (10)	207 (20)	
Posttransplant follow-up (months)§	36.3 (12.1-72.6)	43.1 (12.2-83.6)	43.3 (12.3-79.1)	34.1 (10.9-70.3)	<0.001

*Other metabolic conditions include alpha-1-antitrypsin deficiency, Crigler-Najjar syndrome, cystic fibrosis, inborn errors in bile acid metabolism, neonatal hemochromatosis, primary hyperoxaluria, tyrosinemia, Wilson's disease (nonfulminant failure), mitochondrial diseases, familial hypercholesterolemia, cholesterol ester storage defects, Niemann-Pick disease, and glycogen storage disease. Other cholestatic conditions include Alagille syndrome, progressive intrahepatic cholestatic syndromes (including Byler's disease), total parenteral nutrition cholestasis, sclerosing cholangitis, and idiopathic cholestasis.
†The *P* values were determined by chi-square testing for categorical variables and by Kruskal-Wallis testing for continuous variables.
‡Other ethnicity includes Native American, Alaskan, Pacific Islander, Hawaiian, multiracial, and unknown.
§The data are presented as medians and IQRs.

were female. During the study period, there were no significant temporal trends in the proportions of transplants for UCDs/OAs at an age < 2 years ($P = 0.38$) or in the median age at transplant (1 year, IQR = 0-6 years, $P = 0.35$). The proportion of UCD/OA children who underwent transplantation before the age of 1 year did vary substantially by region (from 14% in region 3 to 56.5% in region 4). In region 2, 18% of children with UCDs/OAs underwent transplantation before the age of 1 year, whereas 46% did in region 5 [$P = 0.03$ (all regions included)].

For deceased donor liver transplant recipients with UCDs/OAs, the median weight at transplant was 12.6 kg [IQR = 8.6-21.1 kg (weight data were available for 273 recipients)], and there were no significant changes over time ($P = 0.14$). Only 3% of the recipients with UCDs/OAs underwent transplantation with a weight <5 kg, 33% underwent transplantation with a weight of ≥5 – <10 kg, and 38% underwent transplantation with a weight of ≥10 – <20 kg. There was some variation in the median weight at transplant between regions: it ranged from 8.5 kg (IQR = 7.1-18.6 kg) in region 6 to 17.4 kg (IQR = 10.4-24.0 kg) in region 3 ($P = 0.03$). The median weight in region 2 was 14.8 kg (IQR = 9.5-26.1 kg), and in region 5, it was 10.5 kg (IQR = 8.4-15.4 kg).

One hundred sixteen children received deceased donor transplants for OAs, and 59% of these transplants were for MSUD. Children with MSUD were older than other UCD/OA children at transplant, with 28% being <2 years old at transplant and 46% being 7 to 17 years old at transplant. They consequently had a higher median weight at transplant (22.4 kg, IQR = 14.4-43.3 kg) than children with UCDs (7.5 kg, IQR = 7.5-16.8 kg) and other OAs (13.6 kg, IQR = 10.3-20.7 kg, $P < 0.001$). There was no significant difference in sex distributions between children with MSUD and children with UCDs or other OAs ($P = 0.20$). Children

with MSUD were more likely to be Caucasian (69% versus 67% for children with UCDs and 54% for children with other OAs) and were less likely to be Hispanic or Asian ($P = 0.02$). Sixty-three percent of all transplants for MSUD were performed in region 2.

Notably, all children receiving liver-kidney transplants had methylmalonic acidemia (MMA; n = 17) and underwent transplantation when they were older than 3 years, with 53% being 12 to 17 years old at transplant. Eighty-eight percent received whole liver transplants. The median posttransplant follow-up time was 2.9 years (IQR = 0.9-5.2 years).

UNOS policy changed in 2005 to allow children with UCDs/OAs to be listed as status 1B after 30 days on the waiting list. Subsequently, the proportion of children with UCDs/OAs who underwent transplantation with status 1B increased over time from 35% in 2006-2009 to 63% in 2010-2012 ($P < 0.001$). There was no change in the median number of days on the waiting list for children with UCDs/OAs over this time period: 69 days (IQR = 26-180 days) in 2002-2005, 68 days (IQR = 32-212 days) in 2006-2009, and 60 days (IQR = 36-131 days) in 2010-2012 ($P = 0.91$). Notably, region 2 had significantly longer wait-list times for children undergoing transplantation by the MELD/PELD score (285 days, IQR = 161-453 days, n = 36) in comparison with other regions (25 days, IQR = 13-122 days, n = 75), although the waiting times for children undergoing transplantation with status 1B were similar (87 days in region 2, IQR = 52-130 days, n = 23; 66 days in all other regions, IQR = 45-101 days, n = 81). Eighty percent of the 34 children in region 2 who waited for more than 30 days and underwent transplantation by the MELD/PELD score had MSUD. They all received whole liver transplants.

In the multivariate logistic regression of deceased donor liver transplant recipients with UCDs/OAs (with the exclusion of region 2), an age < 1 year increased the odds of undergoing transplantation with status 1B (odds ratio = 4.3, 95% confidence interval = 1.8-10.1, $P < 0.0001$) after we controlled for the year of transplantation, diagnosis, sex, ethnicity, weight at transplant, and median regional waiting time. Other variables were not significant. Including children from region 2 did not substantially change the odds ratio associated with an age < 1 year.

The percentage of regional pediatric liver transplants performed for UCDs/OAs did not correlate with the regional death rate on the waiting list ($r = 0.31$, $P = 0.36$) or the regional ratio of deaths to transplants ($r = 0.44$, $P = 0.18$) for non-UCD/OA children. By region, the median days on the waiting list for non-UCD/OA children did increase as the percentage of pediatric transplants for UCDs/OAs increased ($r = 0.76$, $P = 0.007$). Children with UCDs/OAs who received deceased donor transplants overall spent less time on the waiting list (median = 67 days, IQR = 32-175 days) than children with biliary atresia (83 days, IQR = 32-195 days) or other metabolic/cholestatic diseases (73 days, IQR = 22-196 days, $P = 0.02$). Among children who underwent transplantation with status 1B, children with UCDs/OAs waited longer (median = 60 days, IQR = 39-107 days) than children with ALF or a tumor (44 days, IQR = 29-106 days) and children with other metabolic diseases (49 days, IQR = 17-102 days), but they waited approximately the same time as children undergoing transplantation for biliary atresia (62 days, IQR = 24-136 days, $P = 0.001$).

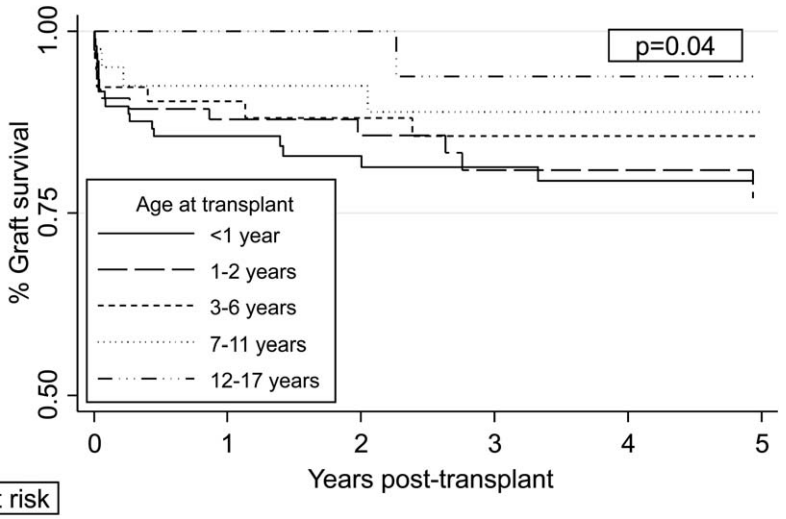
Among children who received a deceased donor liver, children with UCDs/OAs were more likely to get a whole liver than children with biliary atresia or a tumor but were less likely to get one than children with other metabolic/cholestatic diseases (Table 2). The pattern was the same for those who were transplanted by assigned MELD/PELD score and with Status 1b. The status at transplant was not associated with receiving a whole liver in the univariate or multivariate analysis (data not shown).

Graft Survival for Deceased Donor Liver Transplant Recipients With UCDs/OAs

The median total patient follow-up time for deceased donor liver transplant recipients with UCDs/OAs was 36.3 months (IQR = 12.1-72.6 months). For children with UCDs/OAs, the graft survival rates were 92% at 30 days, 89% at 1 year, and 83% at 5 years. These rates were similar to those for children with biliary atresia (91% at 30 days, 88% at 1 year, and 83% at 5 years) and were better than those for children with other metabolic/cholestatic conditions (95% at 30 days, 86% at 1 year, and 75% at 5 years; $P < 0.001$).

Overall, graft survival for children with UCDs/OAs improved as their age at transplant increased ($P = 0.04$; Fig. 1). There was no difference in graft survival between children < 1 year old at transplant and children ≥1 and <2 years old at transplant ($P = 0.93$ for overall survival difference). Within 5 years of transplantation, the graft survival rate was 78% for children < 2 years old at transplant and 88% for those ≥ 2 years old ($P = 0.06$ for overall survival difference). Children with MSUD had lower rates of graft loss (6%) than children with UCDs (18%) or other OAs (15%, $P = 0.05$).

Forty-three deceased donor liver transplant recipients experienced graft loss, and the reported causes included vascular thrombosis (n = 19), primary graft nonfunction (n = 7), infection (n = 2), biliary complications (n = 3), and acute rejection (n = 2). 46% (20 of 43) of the graft losses occurred within 2 weeks of transplantation. 42% (8 of 19) of the 19 children with vascular thromboses were less than 1 year old at transplant, and another 26% (5 of 19) were ≥1 and <2 years old. 79% (15 of 19) had received a whole liver. Vascular thrombosis accounted for 41% of the graft losses in children with UCDs and for 55% in children with OAs. Sixty percent of the 10 patients with no reported cause of graft loss lost their graft 1 to 6 months after transplantation.



Number at risk						
<1 year at transplant	97	71	53	48	39	29
1-2 years	77	54	39	31	25	20
3-6 years	52	41	38	30	24	21
7-11 years	41	34	30	24	19	15
12-17 years	26	18	16	12	10	8

Figure 1. Graft survival for children who received liver transplants for UCDs or OAs by the recipient age at transplant ($P = 0.04$ according to a Cox proportional hazards regression analysis). Only recipients of deceased donor livers are included.

In the multivariate analysis of graft survival for children who underwent deceased donor liver transplantation for UCDs/OAs, females and Hispanics had a higher risk of graft loss. A younger age and a lower weight increased the risk of graft loss in the univariate analysis but not in the multivariate analysis. Although children with MSUD had better graft survival than both children with UCDs and children with OAs in the univariate analysis, there were no significant differences after we controlled for the age at transplant and other factors in the multivariate analysis (Table 3). The inclusion of children with UCDs/OAs who underwent living donor liver transplantation did not change the significant predictors of graft survival.

Among the 17 liver-kidney recipients, all of whom had MMA, only 1 patient (6%) lost the liver graft during follow-up. The cause was hepatic artery thrombosis, and the patient underwent retransplantation 15 days after the initial liver-kidney transplant. Ten other children with MMA received liver-only transplants; 80% were <2 years of age at transplant. In this group, 1 patient lost the graft 13 days after transplantation to vascular thrombosis and underwent retransplantation. There were no deaths during follow-up. None of the 27 children with MMA had undergone kidney transplantation before their liver or liver-kidney transplant.

Patient Survival for Deceased Donor Liver Transplant Recipients With UCDs/OAs

For deceased donor liver transplant recipients with UCDs/OAs, the patient survival rates were 99% at 30 days, 96% at 1 year, and 95% at 5 years. These rates were similar to those for biliary atresia recipients (97% at 30 days, 95% at 1 year, and 93% at 5 years) and better than those for children undergoing transplantation for other metabolic/cholestatic conditions (96% at 30 days, 89% at 1 year, and 81% at 5 years; $P < 0.001$).

Overall, patient survival improved as the age at transplant increased, with no posttransplant deaths occurring in children > 4 years old at transplant ($P = 0.008$ for the trend). The 5-year patient survival rates were 88% for deceased donor liver transplant recipients with UCDs/OAs who were <2 years old at transplant and 99% for children who were ≥2 years old ($P = 0.006$). Fifty-seven percent of the 14 posttransplant deaths occurred within 6 months of transplantation. The reported causes of death included multiorgan system failure (n = 5), sepsis/infection (n = 4), primary graft nonfunction (n = 2), respiratory failure/cardiac arrest (n = 1), posttransplant lymphoproliferative disease (n = 1), and metabolic crisis (n = 1).

In the univariate analysis, an age < 2 years at transplant, a split liver, and Hispanic ethnicity increased the risk of posttransplant death (Table 4). OAs were not associated with a higher risk of graft loss or mortality in comparison with UCDs in the univariate or multivariate analysis. No children with MSUD died during the posttransplant follow-up; thus, we considered only UCDs versus OAs for the mortality analysis. A higher weight at transplant was protective against death in the univariate analysis (Table 4), but the risk was not significantly different between those weighing ≥5 – 10 kg, and those weighing ≥10 – 20 kg at

TABLE 3. Risk Factors for Posttransplant Graft Loss in Deceased Donor Liver Transplant Recipients With UCDs/OAs

	Univariate HR	*P* Value*	Multivariate HR	*P* Value*
Age < 2 years at transplant	1.77 (0.95-3.3)	0.07	1.10 (0.45-2.71)	0.84
Female sex	1.54 (0.84-2.81)	0.15	1.97 (1.01-3.85)	0.05
Ethnicity				
White	Reference		Reference	
Black	2.04 (0.76-5.44)	0.15	2.07 (0.76-5.64)	0.15
Hispanic	3.35 (1.68-6.64)	0.001	3.63 (1.74-7.56)	0.001
Asian	1.22 (0.36-4.11)	0.75	0.99 (0.29-3.45)	0.99
Other†	2.59 (0.34-19.35)	0.35	1.68 (0.21-13.4)	0.31
Weight at transplant (kg)	0.97 (0.94-1)	0.06	0.98 (0.94-1.02)	0.31
Diagnosis				
UCD	Reference		Reference	
MSUD	0.31 (0.11-0.89)	0.03	0.44 (0.14-1.34)	0.15
OA (non-MSUD)	0.88 (0.39-2.01)	0.77	0.73 (0.30-1.75)	0.48
Split liver (versus whole liver)	1.86 (0.91-3.77)	0.09	1.31 (0.62-2.79)	0.48
Cold ischemia time (hours)	1.00 (0.91-1.1)	0.92		
Year of transplant				
2002-2005	Reference			
2006-2009	0.75 (0.37-1.52)	0.43		
2010-2012	0.93 (0.42-2.06)	0.87		
Hospitalized at transplant	1.53 (0.73-3.18)	0.26		
Status at transplant				
MELD/PELD score of 30	Reference			
Status 1B	1.00 (0.55-1.83)	0.98		

The ranges in parentheses are 95% confidence intervals for the hazard ratios.
**P* values were taken from Cox proportional hazards models.
†Other ethnicity includes Native American, Alaskan, Pacific Islander, Hawaiian, multiracial, and unknown.

transplant [hazard ratio (HR) = 0.46, 0.15-1.3, $P = 0.19$, n = 194]. In the multivariate analysis, only Hispanic ethnicity increased the mortality risk. The power was limited because of the small number of deaths.

Hispanic children had a higher overall prevalence of OAs (57%) than children of other ethnicities (38% for whites, 25% for blacks, and 36% for Asians; $P = 0.02$) and a lower prevalence of MSUD. However, Hispanic ethnicity remained a predictor of mortality even after we controlled for the diagnosis (Table 4). There was no difference in the age distribution at transplant by ethnicity ($P = 0.16$). The region and the insurance type were not associated with graft loss or survival; adjusting for them did not attenuate the association between Hispanic ethnicity and poor outcomes. When we considered deceased donor pediatric recipients who underwent transplantation for all indications, Hispanic ethnicity did not increase the graft loss or mortality risk in the univariate or multivariate analysis (data not shown).

Cognitive and Motor Delays After Transplantation

In the UNOS database, data about cognitive and motor delays are collected in posttransplant records but not in pretransplant records. Information from follow-up records less than 7 months after transplantation was used as our best available indication of the pretransplant status. Children who underwent transplantation for UCDs/OAs were significantly more likely to have definite or probable cognitive and motor delays at both the first posttransplant follow-up and the last posttransplant follow-up than children who underwent transplantation for other indications (Table 5). The reported prevalence of cognitive and motor delays was significantly lower for children with MSUD and higher for children with other OAs at all time points in comparison with children with UCDs (Table 5).

At the last follow-up, the prevalence of cognitive delays in children with UCDs/OAs did not differ by the age at transplant. A definite or probable cognitive delay was reported for 43% of the children undergoing transplantation at <2 years of age (n = 114) and for 41% of the children undergoing transplantation at ≥2 years of age (n = 121, $P = 0.70$). A motor delay was slightly more likely to persist at the last follow-up in children with UCDs/OAs who underwent transplantation at <2 years (35%, n = 117) versus children who underwent transplantation at ≥2 years (24%, n = 122, $P = 0.06$).

In the multivariate analysis, MSUD was associated with a decreased risk of cognitive delays (HR = 0.29, 0.12-0.69, $P = 0.005$) and motor delays (HR = 0.33, 0.13-0.89, $P = 0.03$), and other OAs were associated with an increased risk of cognitive delays (HR = 6.09, 2.40-15.4, $P < 0.001$) and motor delays (HR = 3.26, 1.36-7.76, $P = 0.008$) in comparison with UCDs.

TABLE 4. Risk Factors for Posttransplant Mortality in Deceased Donor Liver Transplant Recipients With UCDs/OAs

	Univariate HR	*P* Value*	Multivariate HR	*P* Value*
Age < 2 years at transplant	6.34 (1.42-28.39)	0.02	0.97 (0.12-7.98)	0.97
Female sex	0.72 (0.22-2.32)	0.59		
Ethnicity				
White	Reference		Reference	
Black	3.43 (0.66-17.72)	0.14	3.79 (0.72-19.95)	0.12
Hispanic	5.91 (1.79-19.48)	0.004	4.73 (1.35-16.54)	0.02
Asian	1.6 (0.18-13.72)	0.67	1.36 (0.15-12.03)	0.78
Other[†,‡]				
Weight at transplant (kg)	0.87 (0.77-0.98)	0.02	0.86 (0.71-1.05)	0.14
Diagnosis				
UCD	Reference		Reference	
OA[†]	0.41 (0.11-1.46)	0.17	0.69 (0.16-2.97)	0.62
Split liver (versus whole liver)	3.62 (1.21-10.82)	0.02	2.25 (0.72-7.03)	0.17
Cold ischemia time (hours)	0.96 (0.8-1.16)	0.72		
Year of transplant				
2002-2005				
2006-2009	0.89 (0.27-2.96)	0.86		
2010-2012	0.77 (0.17-3.45)	0.74		
Hospitalized at transplant	0.93 (0.21-4.19)	0.94		
Status at transplant				
MELD/PELD score of 30	Reference			
Status 1B	0.88 (0.3-2.54)	0.82		

The ranges in parentheses are 95% confidence intervals for the hazard ratios.
**P* values were taken from Cox proportional hazards models.
[†]Other ethnicity includes Native American, Alaskan, Pacific Islander, Hawaiian, multiracial, and unknown.
[‡]Unable to calculate HR because of low numbers in this category.
[§]There were no deaths among MSUD patients after transplantation, so this diagnostic category was not considered separately for the mortality analysis.

Neither cognitive nor motor delays at last follow-up were predicted by the age or weight at transplant, sex, ethnicity, graft type (split liver versus whole liver), or hospitalization at transplant in the univariate or multivariate analysis before or after we controlled for the diagnosis (UCD versus MSUD versus other OA; data not shown). Children who underwent transplantation with status 1B were more likely to have motor delays (36% of 113) at the last follow-up than children who underwent transplantation with a MELD/PELD score of 30 (22% of 125) in the univariate ($P = 0.02$) and multivariate analyses (odds ratio = 1.89, 0.99-3.56, $P = 0.05$). The status at transplant was not associated with cognitive delays at the last follow-up.

Functional Status Before and After Transplantation

For children 1 year and older, data on age-adjusted functional limitations and the need for assistance with activities of daily living were recorded at transplant and during follow-up. Data were available at transplant for 2562 children, and those who underwent transplantation for UCDs/OAs were less likely to have significant functional limitations or assistance needs (8.5% of 153) than those with biliary atresia (16% of 626), other metabolic/cholestatic diseases (21% of 1176), or ALF or a tumor (42% of 607, $P < 0.001$). At the last follow-up (n = 3861), children with UCDs/OAs had a higher risk of significant functional limitations/assistance needs (6.5% of 232) than those with biliary atresia (1.9% of 1374), but the risk was comparable to that for children with other metabolic/cholestatic diseases (7.0% of 1465) and children with ALF or a tumor (5.3% of 790, $P < 0.001$).

DISCUSSION

UCDs and OAs are growing indications for pediatric liver transplantation in the United States. Most children who undergo liver transplantation for these disorders do so before the age of 2 years, but the median age at transplant varies by region and by diagnosis. Graft and patient survival rates are generally excellent; they match or exceed those for children undergoing transplantation for other indications.[8,10,11] The majority of posttransplant morbidity and mortality occurs within the first few months after transplantation. The youngest children are at the highest risk for posttransplant graft loss and mortality; this is likely related to their age and size and not to the transplant indication. After we controlled for the age and weight at transplant, the graft and patient outcomes did not differ by diagnosis within the UCD/OA cohort, although the prevalence of developmental delays did vary considerably.

TABLE 5. Cognitive and Motor Delays After Pediatric Liver Transplantation by Diagnosis

	Months After Transplantation*	UCD/OA [% (n)]	Biliary Atresia [% (n)]	Other Metabolic/ Cholestatic Diseases [% (n)]†	ALF/ Tumor [% (n)]	*P* Value‡
Cognitive delay§						
First posttransplant follow-up	5.8 ± 0.9‖	40.2 (102) UCD: 42.6 (61) OA: 71.4 (14) MSUD: 18.5 (27)	7.2 (501)	10.9 (559)	8.2 (331)	<0.001 0.004
Last posttransplant follow-up	54 ± 34.4‖	42.0 (235) UCD: 40.7 (140) OA: 77.8 (36) MSUD: 22.0 (59)	5.9 (1419)	13.6 (1571)	8.9 (836)	<0.001 <0.001
Motor delay§						
First posttransplant follow-up	5.8 ± 0.9‖	35.9 (103) UCD: 37.1 (62) OA: 85.7 (14) MSUD: 7.4 (27)	10.9 (510)	13.4 (568)	6.7 (330)	<0.001 <0.001
Last posttransplant follow-up	54 ± 34.4‖	29.3 (236) UCD: 29.9 (144) OA: 55.9 (34) MSUD: 12.1 (58)	4.0 (1459)	9.4 (1606)	6.1 (842)	<0.001 <0.001

NOTE: Living and deceased donor liver transplant recipients who were <18 years of age at transplant are included. The UNOS/SRTR database includes information on cognitive and motor delays only during posttransplant follow-up. The n-values are the total numbers of patients with the various conditions who have data available in the time period of interest.

*The data are presented as means and standard deviations.

†Other metabolic conditions include alpha-1-antitrypsin deficiency, Crigler-Najjar syndrome, cystic fibrosis, inborn errors in bile acid metabolism, neonatal hemochromatosis, primary hyperoxaluria, tyrosinemia, Wilson's disease (nonfulminant failure), mitochondrial diseases, familial hypercholesterolemia, cholesterol ester storage defects, Niemann-Pick disease, and glycogen storage disease. Other cholestatic conditions include Alagille syndrome, progressive intrahepatic cholestatic syndromes (including Byler's disease), total parenteral nutrition cholestasis, sclerosing cholangitis, and idiopathic cholestasis.

‡*P* values for differences in the prevalence of cognitive and motor delays were determined with chi-square testing.

§Children identified as having probable or definite delays are included.

‖There were no significant differences in the months after transplantation for UCDs versus OAs or MSUD within the UCD/OA category for any follow-up period.

The very low prevalence of living related liver transplantation (LRLT) for UCDs/OAs in our cohort (with the lowest prevalence occurring after 2005) was likely related to the high-priority status automatically received by these children. LRLT is more commonly used for UCDs/OAs in other countries. Most reports on LRLT for UCDs/OAs come from Japan because deceased donors are not used there. Satisfactory outcomes have been reported in case series of donations from both parents and known heterozygous donors. Most LRLT procedures are performed in children who are 1 to 5 years old and weigh 10 to 20 kg, and the patient survival data are similar to the UNOS data presented here.[12-14] To assess the safety of living related donors, these reports have recommended liver biopsy or other testing to prove the normal activity of the affected enzyme in potential donors and particularly in parents who are presumed to be heterozygous carriers.[13,15]

LRLT could be a reasonable option for more US children with UCDs/OAs in need of liver-only transplantation. Considering LRLT for those patients who do have feasible living donors would still allow early transplantation to prevent future decompensation episodes or neurocognitive delays while increasing overall organ availability. If LRLT is considered for these children, the enzymatic activity of the donors must be assessed; this is particularly true for presumably heterozygous parents and for disorders with significant enzyme activity outside the liver [eg, MMA and propionic acidemia (PA)].

Deceased donor liver transplant recipients with UCDs/OAs are more likely to receive whole livers than children with biliary atresia. Unfortunately, we did not have information on transplant offers to evaluate whether centers turn down split liver offers for children with UCDs/OAs because they have high wait-list priority but tend to be medically stable while they are waiting. Our data showed no increased risk of graft loss or mortality for children with UCDs/OAs who received split livers, and this parallels a recent UNOS analysis of all pediatric liver transplant recipients.[16]

Thus, the increased use of split livers in children with UCDs/OAs may be another way of optimizing the utilization of deceased donor organs without delaying liver transplantation for these children.

Proponents of liver transplantation for UCDs and OAs have generally recommended transplantation in early childhood to prevent morbidity and mortality from further metabolic decompensation episodes.[17-19] Eight children in our analysis did die while they were waiting for transplantation, and this reinforces the potentially lethal nature of these disorders. Recent expert consensus guidelines recommend liver transplantation between 3 and 12 months of age once the child weighs more than 5 kg.[5] Our data suggest that children undergoing transplantation at the youngest ages have the highest risk of graft loss, and this is often related to technically difficult vessel anastomoses with subsequent thrombosis in small children. Posttransplant mortality was low, but the risk of death was higher in younger children. This risk is not unique to children with UCDs/OAs, but it raises interesting questions about the optimal timing for transplantation in this group. This finding may also represent a selection bias because those children with significant neurological injury or other systemic impairments that became evident with age may not have received liver transplants.

Interestingly, age and weight at transplant and diagnosis within the UCD/OA group (UCD versus OA versus MSUD) were not significant predictors of posttransplant graft loss or mortality in the multivariate analysis. This suggests that transplant centers may be successfully balancing age, size, and diagnosis considerations in decisions about when to perform transplantation for children with UCDs/OAs. For example, we found that children with MSUD generally underwent transplantation much later than children with other OAs or UCDs, but their prevalence of developmental delays was much lower during long-term follow-up. Interestingly, after we controlled for age and other variables, MSUD was not associated with better graft or patient survival. UNOS prioritization does not currently differentiate between MSUD and other OAs, but our analysis suggests that decision making about the optimal age for transplantation differs regionally. Further research and discussion are needed to optimize prioritization policies for these related but biochemically and clinically distinct disorders.

Hispanic ethnicity was the only significant predictor of both graft loss and mortality in the multivariate analysis. We were not able to identify why Hispanic deceased donor liver transplant recipients with UCDs/OAs were at increased risk for graft loss and mortality. Differences in UCD diagnosis versus OA diagnosis by ethnicity, age at transplant, region, insurance type, and other variables included in the multivariate analysis did not explain this association.

Our analysis echoes previous single-center studies demonstrating that developmental delays are common in liver transplant recipients with UCDs/OAs and that liver transplantation halts but does not reverse associated cognitive and motor delays.[14,20,21] One justification for early liver transplantation for UCDs/OAs is the prevention of developmental delays. Developmental delays during follow-up differed significantly within the UCD/OA cohort, with children with MSUD being at the lowest risk and children with other OAs being at the highest risk. However, after we controlled for diagnosis, our data showed that a younger age at transplant did not decrease the prevalence of cognitive or motor delays during long-term follow-up.

Unfortunately, the UNOS database does not include information on the pretransplant severity of UCDs/OAs or factors associated with developmental delay risks (eg, the peak ammonia level or the number of decompensation episodes/hospitalizations). We lacked baseline data for younger children, and further data were missing among the available follow-up data. Thus, we could not assess whether early transplantation was chosen for the most severely affected children and may have prevented worse long-term outcomes. Questions on developmental delays in the UNOS baseline and follow-up surveys are fairly subjective; evaluation is not rigorously standardized across all reporting centers.

Further prospective research with more standardized testing would be helpful for assessing neurocognitive benefits of early liver transplantation. Comparing a posttransplant cohort to current children with UCDs/OAs who do not undergo liver transplantation would also improve our understanding of the neuroprotective potential of liver transplantation, although we acknowledge that controlling for disease severity would be very difficult. More detailed neurocognitive follow-up might also help to determine whether early liver transplantation for UCDs/OAs could decrease the long-term prevalence of developmental delays and functional limitations instead of stabilizing them as observed in our analysis.

Other limitations of this analysis were also due to the retrospective nature of our study. The sample size was relatively small with few posttransplant deaths. We were limited to risk factors and outcomes assessed in the UNOS database. Because of diagnostic coding within the database, we could not separately analyze outcomes for each disorder within the UCD/OA cohort. It remains difficult to objectively assess donor quality for pediatric liver transplant recipients on the basis of UNOS data because there is no pediatric-specific donor risk index.[22] We did not have data about wait-list offers for these children. Thus, we can offer limited insight into whether decision making about organ acceptance differs for children undergoing transplantation for UCDs/OAs versus other indications. Our analysis also did not control for transplant center volumes and specific experiences with UCD/OA liver transplants, which did vary across regions as described.

This analysis does represent the largest and most comprehensive cohort of children who underwent transplantation for UCDs/OAs. It confirms that

posttransplant graft and patient survival for these children is excellent, but further research is needed to clarify the risks and benefits associated with early transplantation. Early liver transplantation for children with UCDs/OAs ideally minimizes their mortality risk and maximizes their neurodevelopmental potential, but a consideration of transplant-associated risks is also important for optimal decision making for this population.

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