Liver Transplantation in Children with Urea Cycle Disorders: The Importance of Minimizing Waiting Time

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Liver transplantation (LT) for children with urea cycle disorders (UCDs) is capable of correcting the enzymatic defect and preventing progressive neurologic injury. We describe the characteristics and outcomes of pediatric LT recipients with UCDs. We identified all pediatric (<18 years) LT candidates with UCDs in the United Network for Organ Sharing (UNOS) database (February 2002 to September 2020). Multivariable Cox and logistic regression were used to determine risk factors for graft loss and cognitive delay, respectively. Of 424 patients, 1.9% (8/424) experienced waitlist mortality and 95.0% underwent LT (403/424). The most frequently encountered UCDs in our cohort were ornithine transcarbamylase deficiency (46.2%), citrullinemia (20.3%), and argininosuccinic aciduria (ASA; 12.9%). The 1-, 3-, and 5-year graft survival rates were 90.4%, 86.3%, and 85.2%, respectively. Multivariable analysis showed a decreased risk of graft loss with increasing weight at LT (adjusted hazard ratio [aHR], 0.96; 95% confidence interval [CI], 0.94-0.99; $P = 0.02$), male sex (aHR, 0.49; 95% CI, 0.28-0.85; $P = 0.01$), and ASA diagnosis (aHR, 0.29; 95% CI, 0.09-0.98; $P = 0.047$), when adjusting for location (intensive care/hospital/home) and graft type (both $P \geq 0.65$). In multivariable logistic regression, waitlist time (adjusted odds ratio [aOR], 1.10; 95% CI, 1.02-1.17; $P = 0.009$) and male sex (aOR, 1.71; 95% CI, 1.02-2.88; $P = 0.04$) were associated with increased odds of long-term cognitive delay. Waitlist duration is associated with a long-term risk of cognitive delay. Given excellent long-term outcomes, early LT evaluation should be considered in all children with UCDs to prevent progressive neurologic injury and optimize cognitive outcomes.

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The urea cycle is the primary biochemical pathway for the detoxification of nitrogenous waste and the synthesis of arginine. Urea cycle disorders (UCDs) arise from defects in enzymes or transporters in this pathway and can present with life-threatening metabolic decompensation manifesting as cerebral edema, seizures, or multiorgan failure.[1] UCDs include deficiencies of the enzymes carbamoyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS; also known as citrullinemia), argininosuccinate lyase (also known as argininosuccinic aciduria [ASA]), and arginase (ARG), as well as deficiencies of *N*-acetylglutamate synthase and the mitochondrial ornithine/citrulline antiporter, causing the hyperornithinemia-hyperammonemia-homocitrullinuria syndrome.[1] The typical presentation is in early infancy with increased ammonia levels and encephalopathy, the severity of which ranges from minor symptomatology to fatal neonatal hyperammonemia.[2] The goal of medical management in patients with UCDs is to normalize ammonia levels by reducing protein intake, using alternate pathway ammonia scavenging therapies, and providing dialysis for refractory cases to minimize the risk of irreversible

Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; ARG, arginase; ASA, argininosuccinic aciduria; ASS, argininosuccinate synthetase; CI, confidence interval; CPS, carbamoyl phosphate synthetase; HR, hazard ratio; IQR, interquartile range; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NA, not applicable; OPTN, Organ Procurement and Transplantation Network; OR, odds ratio; OTC, ornithine transcarbamylase; PELD, Pediatric End-Stage Liver Disease; UCD, urea cycle disorder; UNOS, United Network for Organ Sharing.

neurologic injury.[3] Liver transplantation (LT) can effectively replace the deficient enzyme and has emerged as the only potential cure.

The primary indication for LT in patients with UCDs is to prevent neurocognitive impairment resulting from hyperammonemia. The limited number of LTs performed by any single center for UCDs has limited the opportunity to examine factors associated with post-LT survival and neurologic injury using a large contemporary sample. Thus, we aimed to describe the clinical characteristics, waitlist and post-LT survival, and developmental outcomes in children with UCDs using national transplant registry data.

Patients and Methods

DATA SOURCE, PATIENT IDENTIFICATION, DATA ENCODING

The United Network for Organ Sharing (UNOS) database administers the Organ Procurement and Transplantation Network (OPTN) under contract with the US Department of Health and Human Services. This database contains data on all transplant candidates undergoing listing for solid organ transplantation in the United States since October 1987.

Patient pretransplant, transplant, and follow-up data were obtained from the UNOS Standard Transplant Analysis and Research data file (released on September 4, 2020). In this retrospective cohort study, we included all pediatric (<18 years) patients with UCDs listed for a first isolated LT (not multiorgan) between February 27, 2002, and September 4, 2020 in the United States. To avoid bias by intrapatient correlation, when patients had multiple listings, only the most recent listing of each patient for a first isolated LT within the study period was used in the analysis. The diagnosis of any UCD was determined via free text searches in the free text diagnosis field of UNOS, looking for any of the following word fragments to avoid missing patients due to typographical errors: "ucd", "urea", "cycle", "ornith", "ornithine", "ornithine transcarbamylase deficiency", "omithine transcarbamylase deficiency", "transcarb", "otc", "oct", "cps", "csp", "carbamyl", "carabamyl", "carbamoyl", "carabamoyl", "citr", "cirt", "asa", "asl", "als", "acet", "arg", and "agr". In addition, we examined the free text diagnosis field of UNOS for each patient with a code of "4315 – LI: METDIS: OTHER SPECIFY" to identify potentially missed children with a UCD diagnosis.

Cognitive and motor delay/impairment are coded based on follow-up questionnaires as (1) definite, (2) probable, (3) questionable, and (4) no delay in UNOS (Supporting Information). We determined the cognitive and motor delay/impairment status of each patient at initial and last posttransplant follow-up according to the availability of data. Patients were considered to have a deteriorated versus same or improved cognitive or motor development status according to the change between initial and last posttransplant follow-up.

STATISTICAL ANALYSIS

Continuous variables were presented as medians with interquartile ranges (IQRs) and categorical variables as frequencies and percentages. Between-group differences were determined using the Mann-Whitney U or Kruskal-Wallis test for continuous variables and the chi-square or Fisher's exact test for categorical variables, as appropriate. For the waitlist outcomes analysis, there are 2 competing risks/outcomes: (1) death/delisting due to being too sick, which was

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defined as waitlist mortality and was the main risk/outcome of interest; (2) LT, which was the competing risk/outcome. Patients who were removed from the waiting list for other reasons or who were still on the waiting list by the date of the last follow-up were censored. Survival was measured from the date of listing for LT until the date of removal from the waiting list for any reason or until the date of the last follow-up.[4] Posttransplant patient and graft survival were defined as the duration from the date of LT to the date of last patient contact or patient death/graft loss, respectively. The Kaplan-Meier method was used to determine the 1-, 3-, and 5-year patient and graft survival rates. The log-rank test was used to assess differences in posttransplant patient/graft survival. Age groups (<1, ≥1-5, ≥5-12, and ≥12 years) and weight groups (<10, ≥10-20, and ≥20 kg) were generated with cutoffs based on clinical practice for univariable comparisons of patient/graft survival. Retransplantation rate was defined as the number of retransplants divided by the number of graft losses. Cox proportional hazards regression models were also fitted to estimate the hazard ratio (HR) and 95% confidence interval (CI) and to identify risk factors of patient mortality and graft loss. Multivariable logistic regression models were also fitted to identify risk factors of definite cognitive and motor impairment at the last posttransplant follow-up. The variables incorporated in the multivariable models were prespecified to avoid the inferential limitations around selecting covariates for multivariable analysis based on stepwise procedures or univariable comparisons.[5] Cohort development and statistical analyses were performed using Stata/IC (version 16.0; StataCorp., College Station, TX).

Results

WAITLIST COHORT

A total of 424 patients with UCDs listed for a first LT were identified. The crude waitlist mortality rate was 1.9% (8/424). The majority of children underwent LT (403/424, 95.0%) after a median waitlist time of 71 (IQR, 36-152.5) days. The median age was less than 1 (IQR, 0-4) years, and the median laboratory Model for End-Stage Liver Disease/Pediatric End-Stage Liver Disease (MELD/PELD) score was −3.5 (IQR, −6 to 1). The majority of children were male (64.2%), and the most common diagnosis was OTC (46.5%), followed by ASS/citrullinemia (20.1%). No patient underwent LT for *N*-acetylglutamate synthase or for hyperornithinemia-hyperammonemia-homocitrullinuria syndrome. Encephalopathy was present in 20.0%, and preoperative mechanical assistance was required in 2.6%. All characteristics for the waitlisted patients are presented in Table 1.

TRANSPLANT COHORT

Between February 27, 2002, and September 4, 2020, 8384 isolated first LTs (not multiorgan) were performed in children (age < 18 years) in the United States, of which 403 (4.8%) were performed for UCDs. The median age at LT was 1 (IQR, 0-4) year. Children with OTC, CPS, ASS, or UCD not otherwise specified were transplanted at a younger age compared with those with ASA or ARG ($P < 0.001$). A greater proportion of patients transplanted for OTC and ARG were male, while the proportion of males to females was similar for other UCDs ($P < 0.001$). The median laboratory MELD/PELD score at LT was −2 (IQR, −6 to 3) without any statistically significant between-group differences. Status 1 exception was assigned to 35 (8.7%) and Status 1b exception to 250 (62.0%) recipients. All characteristics of the transplanted patients are presented in Table 2.

POSTTRANSPLANT OUTCOMES

The 1-, 3-, and 5-year benchmark point estimates of unadjusted cumulative patient and graft survival after LT for all 403 children with UCDs were 97.3%, 95.9%, 94.7%, and 90.4%, 86.3%, 85.2%, respectively (Table 3). No difference in unadjusted patient and graft survival was identified between the 4 age groups (no deaths for children aged ≥ 5 years; Fig. 1A,B). Children in the highest weight group demonstrated superior patient and graft survival compared with those in the lower weight groups (no deaths for children weighing ≥20 kg; Fig. 1C,D). A total of 64 of the 403 LT recipients experienced graft loss, resulting in 24 deaths and 40 retransplants. No differences between weight groups were identified in terms of retransplantation rates (<10 kg: 21/35 [60.0%] versus ≥10-20 kg: 12/22 [54.5%] versus ≥20 kg: 7/7 [100.0%]; $P = 0.08$). Univariable and multivariable Cox regression analyses of risk factors for patient mortality and graft loss are presented in Table 4. Age was not included in the multivariable models due to collinearity with weight. In multivariable analysis, increasing weight at LT was

TABLE 1. Characteristics of the Waitlisted Patients

Variable*	n	Censored (n = 13)	Death/Delisting for Being Too Sick (n = 8)	Liver Transplantation (n = 403)	Total (n = 424)	*P* Value
Age, years	424	4.0 (1.0-15.0)	0.0 (0.0-1.0)	0.0 (0.0-4.0)	0.0 (0.0-4.0)	0.03
Waitlist time, days	424	378.0 (77.0-625.0)	225.0 (124.0-390.0)	68.0 (36.0-137.0)	71.0 (36.0-152.5)	<0.001
Sex	424					0.10
Female		5 (38.5)	0 (0.0)	147 (36.5)	152 (35.9)	
Male		8 (61.5)	8 (100.0)	256 (63.5)	272 (64.2)	
Diagnosis	424					0.02
OTC		9 (69.2)	2 (25.0)	186 (46.2)	197 (46.5)	
CPS		0 (0.0)	3 (37.5)	36 (8.9)	39 (9.2)	
ASS/citrullinemia		3 (23.1)	0 (0.0)	82 (20.4)	85 (20.1)	
ASA		0 (0.0)	0 (0.0)	52 (12.9)	52 (12.3)	
ARG		1 (7.7)	0 (0.0)	8 (2.0)	9 (2.1)	
Not otherwise specified		0 (0.0)	3 (37.5)	39 (9.7)	42 (9.9)	
Ethnicity	424					0.10
White		7 (53.9)	2 (25.0)	247 (61.3)	256 (60.4)	
Black		1 (7.7)	4 (50.0)	40 (9.9)	45 (10.6)	
Hispanic		3 (23.1)	2 (25.0)	75 (18.6)	80 (18.9)	
Asian		1 (7.7)	0 (0.0)	32 (7.9)	33 (7.8)	
American Indian/Alaska Native		0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	
Native Hawaiian/Other Pacific Islander		0 (0.0)	0 (0.0)	2 (0.5)	2 (0.5)	
Multiracial		1 (7.7)	0 (0.0)	6 (1.5)	7 (1.7)	
Blood group	424					0.66
A		2 (15.4)	3 (37.5)	143 (35.5)	148 (34.9)	
AB		0 (0.0)	0 (0.0)	17 (4.2)	17 (4.0)	
B		1 (7.7)	1 (12.5)	50 (12.4)	52 (12.3)	
O		10 (76.9)	4 (50.0)	193 (47.9)	207 (48.8)	
Height, cm	424	102.6 (75.4-152.5)	70.2 (60.0-79.2)	73.1 (61.0-99.1)	73.6 (61.0-99.6)	0.04
Weight, kg	424	16.4 (11.3-45.0)	7.7 (6.4-9.3)	9.7 (6.4-17.0)	9.7 (6.5-17.1)	0.01
Body mass index, kg/m^2	423	19.0 (16.5-20.6)	17.3 (14.9-19.5)	17.6 (16.0-19.5)	17.6 (16.0-19.5)	0.41
Laboratory MELD/PELD score	424	6.0 (–5.0 to 10.0)	–3.0 (–4.0 to –1.5)	–4.0 (–6.0 to 1.0)	–3.5 (–6.0 to 1.0)	0.24
Albumin, g/dL	424	3.9 (3.7-4.0)	3.2 (2.9-3.8)	3.6 (3.1-4.0)	3.6 (3.1-4.0)	0.17
Total bilirubin, mg/dL	424	0.3 (0.2-0.4)	0.3 (0.2-0.3)	0.3 (0.2-0.5)	0.3 (0.2-0.5)	0.76
International normalized ratio	424	1.0 (1.0-1.2)	1.0 (0.9-1.1)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	0.25
Serum creatinine, mg/dL	394	0.3 (0.2-0.5)	0.2 (0.2-0.3)	0.3 (0.2-0.4)	0.3 (0.2-0.4)	0.40
Serum sodium, mEq/L	377	140.0 (138.5-141.5)	137.5 (136.0-143.0)	140.0 (138.0-141.0)	140.0 (138.0-141.0)	0.65
Ascites	265					0.40
No		11 (91.7)	4 (100.0)	242 (97.2)	257 (97.0)	
Yes		1 (8.3)	0 (0.0)	7 (2.8)	8 (3.0)	
Encephalopathy	265					0.03
No		9 (75.0)	1 (25.0)	202 (81.1)	212 (80.0)	
Yes		3 (25.0)	3 (75.0)	47 (18.9)	53 (20.0)	
Portal vein thrombosis	417					0.14
No		12 (92.3)	8 (100.0)	394 (99.5)	414 (99.3)	
Yes		1 (7.7)	0 (0.0)	2 (0.5)	3 (0.7)	
Dialysis within prior week	387					>0.99
No		13 (100.0)	8 (100.0)	361 (98.6)	382 (98.7)	
Yes		0 (0.0)	0 (0.0)	5 (1.4)	5 (1.3)	

TABLE 1. *Continued*

Variable*	n	Censored (n = 13)	Death/Delisting for Being Too Sick (n = 8)	Liver Transplantation (n = 403)	Total (n = 424)	*P* Value
Mechanically assisted	424					>0.99
No		13 (100.0)	8 (100.0)	392 (97.3)	413 (97.4)	
Yes		0 (0.0)	0 (0.0)	11 (2.7)	11 (2.6)	

*All variables refer to values at the time of listing for liver transplantation. Presented as median (IQR) for continuous variables and frequency (percentage) for categorical variables.

associated with a decreased risk of patient mortality (adjusted HR [aHR], 0.90; 95% CI, 0.81-0.99; $P = 0.03$) when adjusting for sex, UCD diagnosis, location at LT, and graft type (all $P \geq 0.06$). Increasing weight at LT (aHR, 0.96; 95% CI, 0.94-0.99; $P = 0.02$), male sex (aHR, 0.49; 95% CI, 0.28-0.85; $P = 0.01$), and ASA diagnosis (aHR, 0.29; 95% CI, 0.09-0.98; $P = 0.047$) were associated with a decreased risk of graft loss when adjusting for hospitalization at the time of LT and graft type (both $P \geq 0.65$). Repeat analyses including age instead of weight in the multivariable models led to similar results and conclusions.

COGNITIVE AND MOTOR DELAY/IMPAIRMENT

At a median initial post-LT follow-up of 6.2 (IQR, 5.6-7.5) months, 27.8% (70/252) of children had definite cognitive delay, while at last post-LT follow-up (median, 83.7; IQR, 40.1-132.6 months) 39.3% (125/318) of children had cognitive delay (Fig. 2A). A total of 233 children had available cognitive development data at both initial and last post-LT follow-up (median interval, 56.2; IQR, 22.0-95.4 months). The post-LT cognitive status deteriorated over time in 60 (25.8%) children, whereas it remained the same or improved in 173 (74.2%) (Fig. 2A). Children whose cognitive status deteriorated were younger at the time of LT compared with those whose cognitive status remained the same or improved (median, 1 year [IQR, 0-2] versus 1 year [IQR, 0-5]; $P = 0.006$).

At a median initial post-LT follow-up of 6.2 (IQR, 5.6-7.4) months, 22.5% (58/258) of children had definite motor delay, whereas at last post-LT follow-up (median, 83.2; IQR, 40.1-130.8 months), 20.4% (65/318) of children had motor delay (Fig. 2B). A total of 235 children had available motor development data at both initial and last post-LT follow-up (median interval, 56.2; IQR, 21.2-95.4 months). The motor status deteriorated in 32 (13.6%) children, whereas it remained the same or improved in 203 (86.4%; Fig. 2B). Children whose motor status deteriorated were transplanted younger than those whose motor status remained the same or improved (median, 0.5 year [IQR, 0-1.5] versus 1 year [IQR, 0-5]; $P = 0.049$).

In multivariable logistic regression for cognitive delay (Table 5), increasing waitlist time (adjusted odds ratio [aOR], 1.10; 95% CI, 1.02-1.17; $P = 0.009$) and male sex (aOR, 1.71; 95% CI, 1.02-2.88; $P = 0.04$) were associated with increased odds of having cognitive delay at last post-LT follow-up. Recipient weight, UCD diagnosis, location at LT, and post-LT length of hospital stay were not independently associated with cognitive delay at last post-LT follow-up (all $P \geq 0.20$). In multivariable logistic regression for motor delay (Table 5), none of the parameters included in the model were independently associated with motor delay at last post-LT follow-up (all $P \geq 0.11$).

Discussion

LT for UCDs constitutes <5% of all pediatric LTs performed in the United States. In this population, the goal of LT is to minimize the risks of recurrent hyperammonemic crises and progressive neurologic injury. Although LT can correct the hepatic enzyme defect and prevent post-LT hyperammonemia,[6] the historical morbidity and mortality risks associated with LT and long-term immunosuppression have often led to a preference for medical management.[7] However, improvements in both surgical technique and immunosuppression management have resulted in excellent long-term survival after pediatric LT,[8] thus raising the question of whether LT should be considered earlier in the treatment of patients with UCDs. In this study, we examined waitlist mortality and post-LT survival and neurologic development in children with different

TABLE 2. Characteristics for the Transplanted Patients

Variable*	n	OTC (n = 186)	CPS (n = 36)	ASS/citrullinemia (n = 82)	ASA (n = 52)	ARG (n = 8)	Not otherwise specified (n = 39)	All UCD (n = 403)	*P* Value
Age, years	403	0.0 (0.0-4.0)	0.0 (0.0-1.0)	1.0 (0.0-4.0)	2.0 (1.0-6.0)	5.0 (1.5-13.0)	1.0 (0.0-4.0)	1.0 (0.0-4.0)	<0.001
Waitlist time, days	403	67.0 (36.0-121.0)	65.5 (32.5-161.0)	81.5 (35.0-157.0)	79.5 (37.5-173.0)	75.5 (31.5-112.0)	69.0 (32.0-151.0)	68.0 (36.0-137.0)	0.95
Sex	403								<0.001
Female		44 (23.7)	17 (47.2)	41 (50.0)	26 (50.0)	2 (25.0)	17 (43.6)	147 (36.5)	
Male		142 (76.3)	19 (52.8)	41 (50.0)	26 (50.0)	6 (75.0)	22 (56.4)	256 (63.5)	
Ethnicity	403								0.001
White		106 (57.0)	20 (55.6)	54 (65.9)	40 (76.9)	2 (25.0)	25 (64.1)	247 (61.3)	
Black		22 (11.8)	4 (11.1)	6 (7.3)	1 (1.9)	0 (0.0)	7 (18.0)	40 (9.9)	
Hispanic		44 (23.7)	6 (16.7)	11 (13.4)	3 (5.8)	6 (75.0)	5 (12.8)	75 (18.6)	
Asian		10 (5.4)	4 (11.1)	9 (11.0)	7 (13.5)	0 (0.0)	2 (5.1)	32 (7.9)	
American Indian/ Alaska Native		0 (0.0)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	
Native Hawaiian/ Other Pacific Islander		0 (0.0)	1 (2.8)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	
Multiracial		4 (2.2)	0 (0.0)	1 (1.2)	1 (1.9)	0 (0.0)	0 (0.0)	6 (1.5)	
Blood group	403								0.61
A		65 (35.0)	12 (33.3)	28 (34.2)	24 (46.2)	2 (25.0)	12 (30.8)	143 (35.5)	
AB		4 (2.2)	1 (2.8)	6 (7.3)	3 (5.8)	1 (12.5)	2 (5.1)	17 (4.2)	
B		24 (12.9)	7 (19.4)	9 (11.0)	4 (7.7)	0 (0.0)	6 (15.4)	50 (12.4)	
O		93 (50.0)	16 (44.4)	39 (47.6)	21 (40.4)	5 (62.5)	19 (48.7)	193 (47.9)	
Height, cm	403	73.6 (67.0-97.0)	71.5 (63.3-82.3)	78.0 (68.5-99.0)	89.8 (81.1-105.2)	105.5 (81.7-148.8)	80.0 (66.5-101.0)	78.0 (67.5-101.0)	0.001
Weight, kg	403	10.4 (8.2-16.8)	9.9 (7.1-13.2)	10.7 (8.2-17.8)	14.6 (11.3-20.6)	21.8 (12.4-42.5)	11.8 (8.2-17.4)	11.3 (8.4-17.5)	0.001
Body mass index, kg/m^2	403	18.3 (16.6-20.7)	18.8 (16.7-20.4)	17.9 (16.4-20.0)	18.2 (17.0-19.3)	18.9 (17.2-20.8)	17.8 (16.8-20.3)	18.2 (16.7-20.3)	0.76
Laboratory MELD/PELD score	403	–2.0 (–5.0 to 3.0)	–1.5 (–5.0 to 6.0)	–2.0 (–5.0 to 3.0)	–3.0 (–6.5 to 5.0)	–5.0 (–8.5 to 4.5)	–3.0 (–6.0 to 2.0)	–2.0 (–6.0 to 3.0)	0.86
Allocation MELD/PELD score	118	30.0 (30.0-30.0)	30.0 (30.0-30.0)	30.0 (29.0-30.0)	30.0 (27.0-30.0)	30.0 (30.0-30.0)	30.0 (29.5-30.0)	30.0 (30.0-30.0)	0.72
Status 1	35	17 (9.1)	5 (13.9)	10 (12.2)	2 (3.9)	0 (0.0)	1 (2.6)	35 (8.7)	0.35
Status 1B	250	116 (62.4)	22 (61.1)	52 (63.4)	28 (53.9)	6 (75.0)	26 (66.7)	250 (62.0)	
Albumin, g/dL	403	3.7 (3.3-4.2)	3.7 (3.3-4.4)	3.6 (3.0-3.9)	3.9 (3.6-4.2)	3.8 (3.6-4.1)	3.8 (3.4-4.2)	3.7 (3.3-4.1)	0.11
Total bilirubin, mg/dL	403	0.3 (0.2-0.5)	0.3 (0.2-0.6)	0.3 (0.2-0.5)	0.5 (0.3-0.7)	0.4 (0.4-0.5)	0.4 (0.2-0.6)	0.3 (0.2-0.5)	0.003
International normalized ratio	403	1.1 (1.0-1.2)	1.1 (1.0-1.3)	1.1 (1.0-1.3)	1.2 (1.1-1.3)	1.1 (1.0-1.4)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	0.006
Serum creatinine, mg/dL	389	0.3 (0.2-0.4)	0.2 (0.2-0.3)	0.3 (0.2-0.4)	0.3 (0.2-0.4)	0.4 (0.3-0.8)	0.3 (0.2-0.3)	0.3 (0.2-0.4)	0.003

TABLE 2. *Continued*

Variable*	n	OTC (n = 186)	CPS (n = 36)	ASS/citrullinemia (n = 82)	ASA (n = 52)	ARG (n = 8)	Not otherwise specified (n = 39)	All UCD (n = 403)	*P* Value
Serum sodium, mEq/L	364	139.0 (138.0-142.0)	140.0 (138.0-143.0)	141.0 (139.0-143.0)	140.0 (138.0-143.0)	140.0 (138.0-141.0)	139.0 (138.0-141.0)	140.0 (138.0-142.0)	0.03
Ascites	264								0.66
No		110 (94.0)	19 (90.5)	57 (98.3)	36 (94.7)	7 (100.0)	22 (95.7)	251 (95.1)	
Yes		7 (6.0)	2 (9.5)	1 (1.7)	2 (5.3)	0 (0.0)	1 (4.4)	13 (4.9)	
Encephalopathy	268								0.18
No		89 (74.2)	15 (68.2)	48 (82.8)	34 (89.5)	4 (57.1)	17 (73.9)	207 (77.2)	
Yes		31 (25.8)	7 (31.8)	10 (17.2)	4 (10.5)	3 (42.9)	6 (26.1)	61 (22.8)	
Portal vein thrombosis	395								0.78
No		181 (98.9)	35 (100.0)	80 (97.6)	51 (98.1)	7 (100.0)	36 (100.0)	390 (98.7)	
Yes		2 (1.1)	0 (0.0)	2 (2.4)	1 (1.9)	0 (0.0)	0 (0.0)	5 (1.3)	
Dialysis within prior week	389								0.37
No		173 (98.9)	36 (100.0)	79 (98.8)	52 (100.0)	8 (100.0)	36 (94.7)	384 (98.7)	
Yes		2 (1.1)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	2 (5.3)	5 (1.3)	
Mechanically assisted	399								0.24
No		180 (98.4)	35 (97.2)	81 (98.8)	50 (96.2)	7 (100.0)	36 (92.3)	389 (97.5)	
Yes		3 (1.6)	1 (2.8)	1 (1.2)	2 (3.9)	0 (0.0)	3 (7.7)	10 (2.5)	
Location	399								0.002
Intensive care unit		16 (8.7)	1 (2.8)	4 (4.9)	3 (5.8)	0 (0.0)	8 (20.5)	32 (8.0)	
Hospitalized, not in intensive care unit		23 (12.6)	10 (27.8)	8 (9.8)	1 (1.9)	0 (0.0)	4 (10.3)	46 (11.5)	
Not hospitalized		144 (78.7)	25 (69.4)	70 (85.4)	48 (92.3)	7 (100.0)	27 (69.2)	321 (80.5)	
Graft type	403								0.96
Deceased donor whole graft		120 (64.5)	24 (66.7)	55 (67.1)	34 (65.4)	6 (75.0)	22 (56.4)	261 (64.8)	
Deceased donor partial/split graft		60 (32.3)	10 (27.8)	24 (29.3)	16 (30.8)	2 (25.0)	14 (35.9)	126 (31.3)	
Living donor graft		6 (3.2)	2 (5.6)	3 (3.7)	2 (3.9)	0 (0.0)	3 (7.7)	16 (4.0)	
Length of hospital stay, days	392	17.0 (11.0-30.0)	22.5 (13.0-33.5)	17.0 (12.0-26.0)	14.0 (10.0-23.0)	8.0 (6.0-13.0)	17.0 (14.0-27.0)	17.0 (11.0-18.0)	0.04

*All variables refer to values at the time of liver transplantation. Presented as median (IQR) for continuous variables and frequency (percentage) for categorical variables.

TABLE 3. Benchmark Point Estimates of Unadjusted Cumulative Patient and Graft Survival After Liver Transplantation

Benchmark Posttransplant Time Point	OTC (n = 186)	CPS (n = 36)	ASS/citrullinemia (n = 82)	ASA (n = 52)	ARG (n = 8)	Not otherwise specified (n = 39)	All UCD (n = 403)
Patient Survival							
1 year	97.7 (1.2)	96.9 (3.1)	96.0 (2.3)	100.0 (NA)	100.0 (NA)	94.1 (4.0)	97.3 (0.9)
3 years	96.1 (1.6)	96.9 (3.1)	96.0 (2.3)	100.0 (NA)	100.0 (NA)	88.2 (5.5)	95.9 (1.1)
5 years	93.4 (2.2)	96.9 (3.1)	96.0 (2.3)	100.0 (NA)	100.0 (NA)	88.2 (5.5)	94.7 (1.3)
Graft Survival							
1 year	92.3 (2.0)	83.3 (6.2)	88.7 (3.6)	98.1 (1.9)	72.9 (16.5)	84.5 (5.8)	90.4 (1.5)
3 years	87.4 (2.6)	79.4 (7.1)	85.8 (4.0)	95.6 (3.1)	72.9 (16.5)	79.2 (6.6)	86.3 (1.8)
5 years	84.9 (2.9)	79.4 (7.1)	85.8 (4.0)	95.6 (3.1)	72.9 (16.5)	79.2 (6.6)	85.2 (1.9)

NOTE: Table entries are estimates of cumulative patient and graft survival percentages (standard errors).

types of UCDs (proximal or distal pathway blocks) and of different age and weight groups.

Waitlist mortality was extremely rare for patients with UCDs listed for LT. Post-LT survival was uniformly excellent across UCD diagnoses, with increasing recipient weight being associated with modestly improved patient and graft survival on multivariable analysis. We specifically chose to utilize recipient weight rather than age in our analyses to objectively assess the effect of patient size on outcomes. Smaller recipients have a decreased pool of size-appropriate donors resulting in both the more frequent use of technical variant allografts and increased LT operative complexity. Recipients weighing <10 kg have higher complication and mortality rates compared with larger recipients.[9,10] In our study, 41% of recipients weighed <10 kg with a 94.6% 3-year patient survival, 38% of recipients weighed ≥10-20 kg with a 94.9% 3-year patient survival, and 21% weighed ≥20 kg with a 100% 3-year patient survival.

Similar to prior reports, we found that nearly 40% of the children undergoing LT for UCDs had definite cognitive delay post-LT.[6,11] This high incidence of neurologic injury is related to the exposure to high pre-LT ammonia concentrations that normalize following LT and prevent further neurologic injury.[6,12] Although our study cannot account for either the duration or the severity of metabolic decompensation prior to LT due to registry limitations, we utilized time on the waiting list as a surrogate indicator for the duration of ongoing neurologic injury secondary to hyperammonemia. When controlling for other factors, we found that every month spent on the waiting list increased a child's adjusted odds of long-term cognitive delay at last post-LT follow-up by 10% (95% CI, 2%-17%). Recipient male sex was also independently associated with an increased risk of definite cognitive delay, which may result from sex-related differences in the incidence of OTC. The location of the *OTC* gene on the X chromosome results in the increased incidence of OTC disease in hemizygous males.[13,14] In comparison to heterozygous females, significant loss of function mutations in the *OTC* gene result in severe neonatal hyperammonemia and increased neurological injury in males.[15] Controlling hyperammonemia is especially challenging in neonatal UCDs such as OTC, where amino acid catabolism for the purpose of gluconeogenesis must be minimized while meeting the child's daily nutritional requirement of amino acids. These children often sustain significant neurological

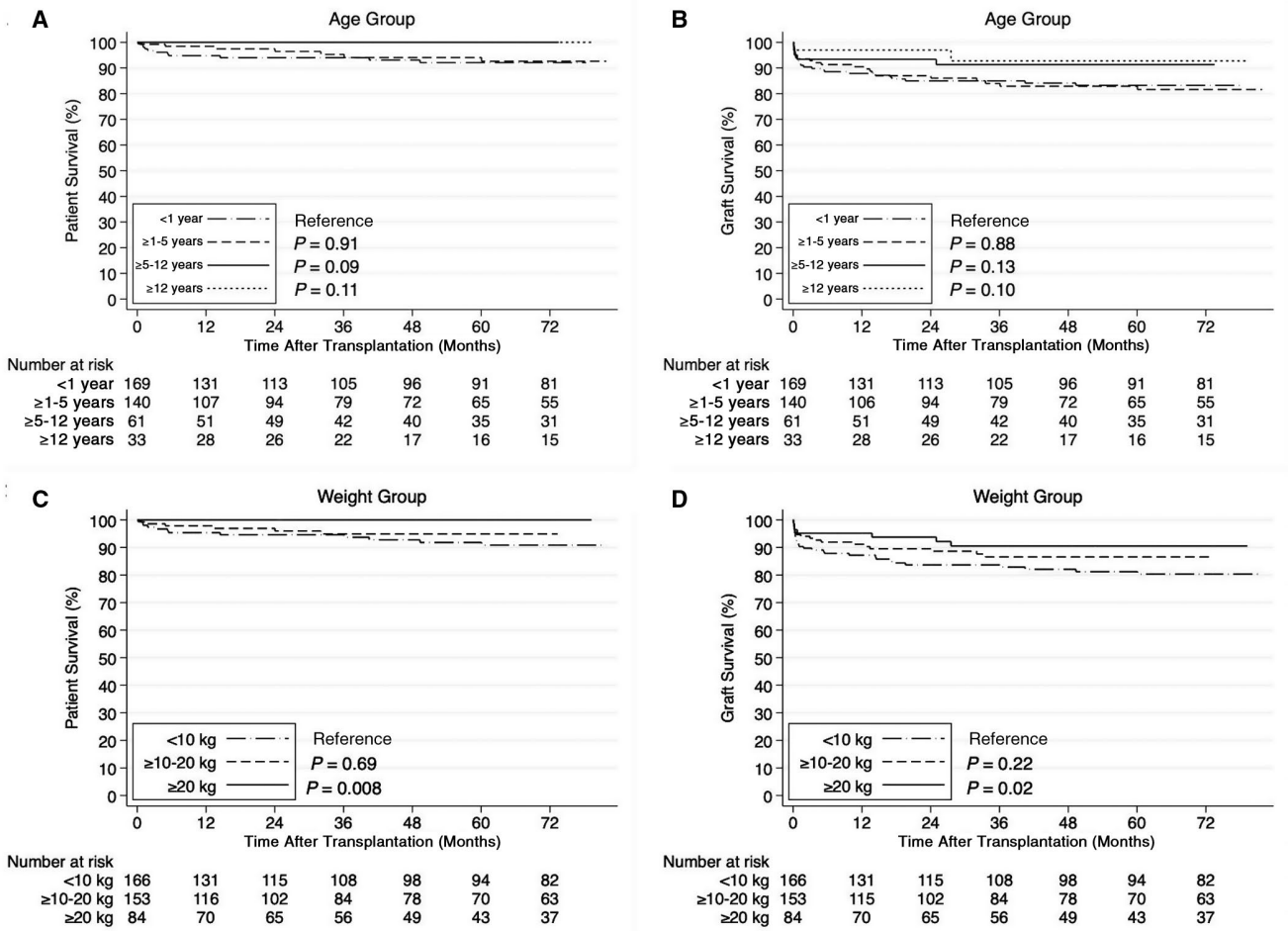

FIG. 1. Kaplan-Meier curves demonstrating (A) patient and (B) graft survival by age group and patient (C) and graft (D) survival by weight group.

injury and are referred for early LT,[6,12] thus explaining our finding that children with post-LT cognitive deterioration were younger at the time of LT. In our study, 35% of all LT recipients were male with a diagnosis of OTC.

There are certain limitations to this study. Because of its retrospective nature, the present study imparts a degree of bias in patient selection and management that we cannot account for. The registry does not include specific diagnosis codes for each UCD, so the groups were identified using a search strategy formulated by the authors to best capture all UCD diagnoses in the free text entry field. Missed patients could have resulted from diagnoses that were simply not entered or entered with misspellings that we had not included in the search strategy. Moreover, there is a lack of reporting for parameters that may influence outcomes (eg, ammonia levels, tools or scales used to assess cognitive and motor development, neurologic status at the time of listing, other neurologic or developmental manifestations). The method by which cognitive or motor delay was captured in the registry does not represent measures from a standardized and validated assessment tool; thus, we cannot exclude the presence of intercenter and interpatient variability in the use of cognitive and motor assessment instruments. In addition, the cognitive and motor delay variables in the UNOS database are fully populated for only 58% of patients transplanted for UCDs, which introduces potential observer and reporting bias. Future studies should include granular and longitudinal data to capture long-term cognitive and motor development outcomes using validated and uniform tools across centers, while taking into account the presence of competing

TABLE 4. Univariable and Multivariable Cox Regression to Identify Risk Factors of Patient Mortality and Graft Loss

	Patient Mortality				Graft Loss			
	Univariable Analysis		Multivariable Analysis (n = 399)		Univariable Analysis		Multivariable Analysis (n = 399)	
Variable*	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, years†	0.80 (0.65-0.99)	0.04	—	—	0.93 (0.86-0.99)	0.04	—	—
Male sex (reference: female sex)	1.27 (0.54-3.07)	0.59	0.75 (0.27-2.07)	0.58	0.65 (0.40-1.06)	0.09	0.49 (0.28-0.85)	0.01
Diagnosis (reference: OTC)	—	—	—	—	—	—	—	—
CPS	0.84 (0.19-3.68)	0.81	0.84 (0.18-3.83)	0.82	1.56 (0.71-3.42)	0.27	1.20 (0.53-2.72)	0.66
ASS/citrullinemia	0.46 (0.13-1.61)	0.23	0.42 (0.12-1.53)	0.19	0.92 (0.47-1.80)	0.81	0.72 (0.36-1.46)	0.37
ASA	0.23 (0.03-1.78)	0.16	0.26 (0.03-2.09)	0.20	0.35 (0.11-1.14)	0.08	0.29 (0.09-0.98)	0.047
ARG	—‡	—‡	—‡	—‡	2.49 (0.59-10.52)	0.21	3.43 (0.80-14.67)	0.10
Not otherwise specified	1.41 (0.46-4.29)	0.55	1.65 (0.50-5.37)	0.41	1.67 (0.81-3.42)	0.17	1.45 (0.69-3.05)	0.33
Laboratory MELD/PELD score†	1.01 (0.96-1.06)	0.75	—	—	0.99 (0.96-1.03)	0.66	—	—
Weight, kg†	0.92 (0.85-0.99)	0.03	0.90 (0.81-0.99)	0.03	0.97 (0.94-0.99)	0.03	0.96 (0.94-0.99)	0.02
Albumin, g/dL†	0.76 (0.46-1.26)	0.29	—	—	0.95 (0.68-1.32)	0.74	—	—
Total bilirubin, mg/dL†	0.70 (0.28-1.76)	0.45	—	—	0.66 (0.36-1.23)	0.19	—	—
International normalized ratio†	0.73 (0.27-1.96)	0.53	—	—	0.91 (0.59-1.41)	0.68	—	—
Serum creatinine, mg/dL†	0.24 (0.01-7.61)	0.42	—	—	0.79 (0.25-2.53)	0.69	—	—
Serum sodium, mEq/L†	0.97 (0.85-1.11)	0.67	—	—	0.99 (0.92-1.08)	0.98	—	—
Ascites (reference: no)	—‡	—‡	—	—	2.95 (1.04-8.41)	0.04	—	—
Encephalopathy (reference: no)	0.88 (0.19-4.13)	0.87	—	—	1.31 (0.61-2.82)	0.49	—	—
Portal vein thrombosis (reference: no)	—‡	—‡	—	—	—‡	—‡	—	—
Dialysis within prior week (reference: no)	2.61 (0.34-19.71)	0.35	—	—	1.07 (0.15-7.76)	0.95	—	—
Mechanically assisted (reference: no)	4.98 (1.17-21.22)	0.03	—	—	1.60 (0.39-6.55)	0.51	—	—
Intensive care unit/hospitalized (reference: Not hospitalized)	0.54 (0.16-1.81)	0.32	0.29 (0.08-1.05)	0.06	1.24 (0.70-2.22)	0.46	1.02 (0.55-1.88)	0.95
Graft type (reference: Deceased donor whole graft)	—	—	—	—	—	—	—	—
Deceased donor partial/split graft	1.37 (0.58-3.20)	0.47	1.22 (0.52-2.89)	0.65	1.01 (0.59-1.73)	0.97	0.88 (0.51-1.53)	0.65
Living donor graft	2.16 (0.48-9.61)	0.31	1.22 (0.26-5.82)	0.80	1.50 (0.54-4.20)	0.44	1.09 (0.38-3.13)	0.87

*All variables refer to values at the time of liver transplantation.
†Continuous variables (representing a trend or change in the factor, not a minimum or maximum value).
‡No events occurred.

A

Variable	Initial posttransplant follow-up		Last posttransplant follow-up	
	Months	n (%)	Months	n (%)
Cognitive Delay/Impairment	6.2 (5.6-7.5)	n = 252	83.7 (40.1-132.6)	n = 318
Definite		70 (27.8)		125 (39.3)
Probable		23 (9.1)		17 (5.4)
Questionable		41 (16.3)		22 (6.9)
No		118 (46.8)		154 (48.4)

B

Variable	Initial posttransplant follow-up		Last posttransplant follow-up	
	Months	n (%)	Months	n (%)
Motor Delay/Impairment	6.2 (5.6-7.4)	n = 258	83.2 (40.1-130.8)	n = 318
Definite		58 (22.5)		65 (20.4)
Probable		19 (7.4)		18 (5.7)
Questionable		35 (13.6)		24 (7.6)
No		146 (56.6)		211 (66.4)

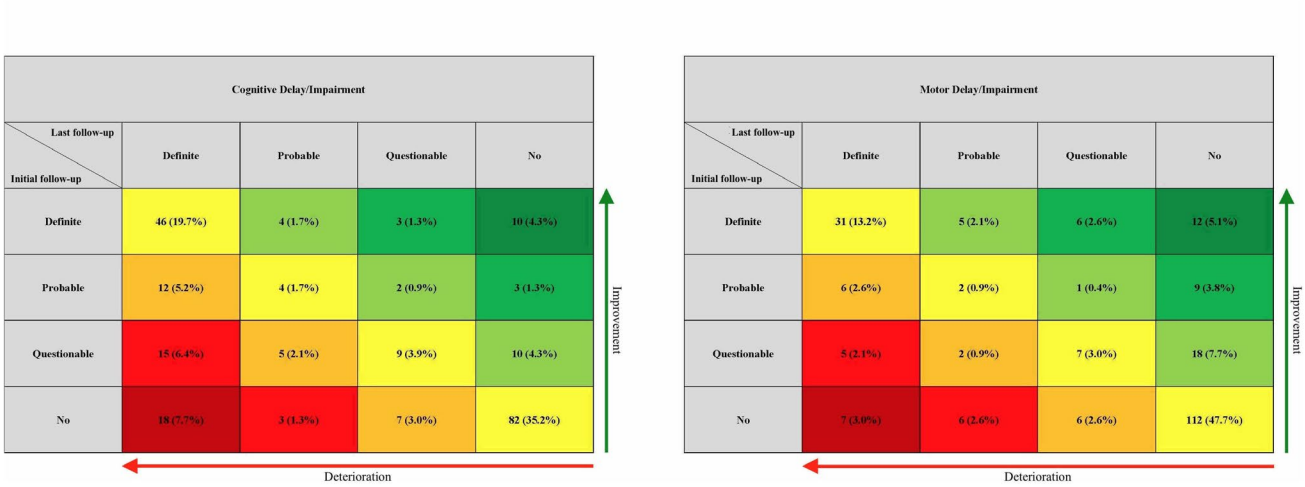

FIG. 2. (A) Cognitive and (B) motor developmental status at initial and last posttransplant follow-up. Months shown in median and IQR.

TABLE 5. Multivariable Logistic Regression to Identify Risk Factors of Cognitive and Motor Delay/Impairment at Last Posttransplant Follow-up

	Multivariable Analysis			
	Cognitive Delay/Impairment (n = 317)		Motor Delay/Impairment (n = 317)	
Variable*	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Weight, kg†	0.99 (0.98-1.01)	0.56	0.98 (0.95-1.00)	0.11
Waitlist time, months†	1.10 (1.02-1.17)	0.009	1.04 (0.96-1.12)	0.37
Male sex (reference: female sex)	1.71 (1.02-2.88)	0.04	1.27 (0.66-2.43)	0.47
Diagnosis (reference: OTC)	—	—	—	—
CPS	0.91 (0.38-2.19)	0.84	0.72 (0.25-2.09)	0.55
ASS/citrullinemia	0.78 (0.41-1.50)	0.46	0.63 (0.28-1.42)	0.27
ASA	1.48 (0.70-3.11)	0.30	0.70 (0.27-1.82)	0.47
ARG	0.38 (0.04-3.63)	0.40	1.04 (0.11-10.06)	0.98
Not otherwise specified	0.99 (0.44-2.26)	0.99	1.02 (0.39-2.64)	0.97
Intensive care unit/hospital (reference: Not hospitalized)	0.76 (0.40-1.46)	0.41	0.83 (0.39-1.76)	0.63
Length of hospital stay, days†	1.01 (0.99-1.02)	0.20	1.01 (0.99-1.02)	0.15

*All variables refer to values at the time of liver transplantation.
†Continuous variables (representing a trend or change in the factor, not a minimum or maximum value).

risks (ie, death from transplanting too early versus progressive neurologic injury).

In conclusion, excellent long-term outcomes are achievable for patients with UCDs undergoing LT. The marginal improvement in survival that may result from waiting for a recipient to achieve a weight >10 kg should be carefully balanced against the risk of ongoing neurological injury. Our finding that waitlist duration

is directly associated with the long-term risk of cognitive delay strongly supports early LT evaluation in patients with UCDs irrespective of age.

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