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Liver Transplantation in Children with Metabolic Disorders in the United States

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We studied pediatric liver transplantation for metabolic disease in a large national cohort to determine whether smaller studies suggesting a survival advantage for these recipients could be corroborated. We also hoped to determine whether higher survival rates in recipients with metabolic disease are associated with lack of structural liver disease, and to evaluate these recipients' risk factors for mortality. Data from the Scientific Registry of Transplant Recipients were used to analyze nationwide results (1990–99) of pediatric liver transplantation for patients with biliary atresia and metabolic disease. Adjusted patient survival rates for children with metabolic disease at 1 and 5 years were 94% and 92%, respectively, – significantly higher than for recipients with biliary atresia (90% and 86%) (p = 0.008). Cox regression models identified recipient black race [relative risk (RR) = 5.1] and simultaneous transplantation of other organs (RR = 3.2) as significant risk factors for mortality in the metabolic group. Adjusted survival rates for metabolic patients with structural and nonstructural liver diseases were similar to each other at both 1 and 5 years. Children with metabolic disease had significantly higher adjusted short- and long-term post-transplant survival rates than those with biliary atresia. Structural disease was not a risk factor for worse outcomes.

Key words: liver transplantation, metabolic disorders, outcomes, pediatric

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Introduction

After liver transplantation, the 5-year survival of pediatric patients is reported to be in the range of 70%–86% (1,2). Among children transplanted for metabolic disease, overall survival rates between 45% and 100% have been reported (3). Some reports have suggested improved outcomes in metabolic patients compared to those with cholestatic disease (3,4). The improved outcomes have been attributed to the healthier clinical status of patients with metabolic disease at the time of transplantation, many of whom do not have portal hypertension or other sequelae of long-term liver dysfunction (4–6). However, a recent single-center study that compared children transplanted for cirrhotic or noncirrhotic metabolic disease failed to find a survival difference (7).

The ability to study outcomes in pediatric liver transplant patients is limited, since even at the largest centers, the pediatric population is small and heterogeneous. In addition, the interpretation of single-center studies is more subject to biases introduced by center-specific factors and changes in patient care practices over time, and may not be applicable to the pediatric liver transplant population in general.

We had three major purposes in this study: (i) to analyze the results of pediatric liver transplantation for metabolic disease in a large national cohort to determine whether previous smaller studies suggesting a survival advantage in these patients could be corroborated; (ii) to determine whether higher survival rates in recipients with metabolic disease are associated with lack of structural liver disease; and (iii) to evaluate risk factors for mortality in children with metabolic disease.

Patients and Methods

The Scientific Registry of Transplant Recipients (SRTR) analyzes data collected by the Organ Procurement and Transplantation Network (OPTN) on all liver transplants performed in the United States. Data from all 76 US transplant centers that reported at least one case of pediatric (<18 years) liver transplant for a primary diagnosis of either biliary atresia or metabolic liver disease performed between January 1990 and December 1999 were included in the study.

Children with a primary diagnosis of metabolic disease were stratified by the presence or absence of structural liver damage. A tentative assignment to the structural or nonstructural group was made based on whether the natural history of the underlying metabolic disease results in parenchymal liver damage. Additional variables from the SRTR database indicative of structural liver disease, portal hypertension, or cirrhosis, including evidence of pretransplant ascites, encephalopathy (in cases where the metabolic disease does not in and of itself cause neurological impairment), portal venous thrombosis, and/or concomitant chronic infection with hepatitis B or C virus, were used to refine the assignments as necessary. Donor and

recipient demographics and other variables that could influence transplant outcome for pediatric liver transplant recipients were also assessed.

Cox proportional hazards regression models were created to analyze risk factors for mortality. Models were adjusted for the following categorical variables: donor and recipient sex (male vs. female) and race (black vs. non-black), recipient weight ($\leq$10 kg vs. $>$10 kg), hospitalization status at time of transplant [intensive care unit (ICU), hospitalized not in the ICU, outpatient, or unknown], previous liver transplantation (yes vs. no), ABO blood type matching (identical, compatible, or incompatible), simultaneous transplantations of nonhepatic organ(s) (yes vs. no), partial liver transplantation (yes vs. no), and year of transplant. Donor and recipient age and weight, as well as organ cold ischemia time, were analyzed as continuous variables. Additional binary covariates were analyzed within the metabolic group for the following diagnoses: α-1-antitrypsin deficiency, Wilson's disease, hereditary tyrosinemia type I, other structural liver disease, urea cycle disorders, hyperoxaluria type 1, and other nonstructural liver disease. Patient survival rates from first liver transplantation were estimated from the Cox models. Statistical analyses were performed using SAS software, version 8 (SAS Institute, Inc., Cary, NC, USA). Statistical significance was accepted at $p < 0.05$.

Results

A total of 2728 pediatric liver transplant recipients was examined. Biliary atresia accounted for 2176 cases (1260 females; 916 males; minimum age 5 months) and metabolic disease for 551 cases (225 females; 326 males; minimum age 5 months). Structural disease was present in 68% (n = 378) of the metabolic cases and included patients with α-1-antitrypsin deficiency (n = 261), Wilson's disease (n = 67), glycogen storage disease types III and IV (n = 15), hereditary tyrosinemia type I (n = 9), and other (n = 26) (Table 1). The remaining 32% (n = 173) had nonstructural metabolic disease consisting of urea cycle disorders (n = 42), hyperoxaluria type 1 (n = 54), hereditary tyrosinemia type I (n = 46), Crigler–Najjar syndrome (n = 12), glycogen storage disease type I (n = 10), disorders of organic acid metabolism (n = 6), and other (n = 3) (Table 1).

Recipient information is summarized in Table 2. Compared to the metabolic group, patients transplanted for biliary atresia were significantly younger (3.1 ± 3.8 vs. 7 ± 5.4 years; $p < 0.0001$) and of lower weight (13.2 ± 11.4 vs. 26.1 ± 19.2 kg; $p < 0.0001$). There was also a significantly greater proportion of females (58% vs. 41%; $p < 0.0001$), recipients of black race (24% vs. 5%; $p < 0.0001$), retransplantations (21% vs. 15%; $p = 0.0003$) and partial liver transplantations (30% vs. 20%; $p < 0.0001$) in the group with biliary atresia. More metabolic patients received simultaneous kidney allografts (7% vs. 0.4%; $p < 0.0001$). The simultaneously transplanted organs in the metabolic group were all kidneys, while patients with biliary atresia received a variety of simultaneous organs including: kidney (n = 1), heart (n = 1), heart-lung (n = 1), intestine (n = 3), pancreas-intestine (n = 2), and kidney-pancreas-intestine transplants (n = 1).

Within the metabolic group, patients with structural disease were similar to those without structural disease, except that all but one of the simultaneous kidney transplants were performed in the nonstructural group ($< 1\%$ vs. 29%; $p < 0.0001$) (Table 2). Indications for combined kidney and liver transplantation included primary hyperoxaluria (n = 35), methylmalonic acidosis (n = 2), glycogen storage disease type I (n = 1), protein C deficiency (n = 1), and α-1-antitrypsin deficiency (n = 1).

Donor demographics are summarized in Table 3. More patients with biliary atresia received cadaveric organs (91% vs. 88%; $p = 0.01$), organs from donors of black race (17% vs. 12%; $p = 0.01$), and organs from lower weight donors (mean weight 31.9 ± 24.4 vs. 39.2 ± 25.9 kg; $p < 0.0001$). Among the cohort with metabolic disease, only donor age differed significantly in the structural and nonstructural subgroups (mean age 16 ± 15 vs. 12.4 ± 12.9 kg; $p < 0.0041$).

Figure 1 depicts overall patient survival from the Cox proportional hazards regression model. Adjusted patient survival rates for children with metabolic disease at 1 and 5 years were 94% and 92%, respectively, which were significantly higher than for patients transplanted for biliary atresia (90% and 86%, respectively) ($p = 0.008$). Adjusted patient survival rates among metabolic patients with structural disease were not significantly different at 1 and 5 years post transplant (94% and 92%, respectively) compared to patients with structurally normal livers (94% and 93%, respectively) (p = ns). Patients with α-1-antitrypsin deficiency demonstrated significantly better survival at 1 and 5 years (96% and 94%, respectively) ($p = 0.006$) compared to those with biliary atresia, while survival rates among the other metabolic cohorts (Wilson's disease, hereditary tyrosinemia type I, other structural liver disease, urea cycle disorders, hyperoxaluria type 1, and other nonstructural liver diseases) were not significantly different (data not shown).

In the Cox proportional hazards model, significant risk factors for mortality in the metabolic group were black race [relative risk (RR) = 5.1; 95% confidence interval (CI) = 1.6–16.2] and simultaneous transplantation of other organs (RR = 3.2; CI = 1.2–8.8).

Discussion

This SRTR analysis of pediatric liver transplant recipients between 1990 and 1999 demonstrates significantly better 1- and 5-year survival rates in children transplanted for metabolic disease compared to those with biliary atresia. By multivariate analysis, black recipient race and simultaneous transplantation of other organs were significant independent risk factors for mortality in the metabolic group. The presence of structural disease in liver recipients with metabolic disease did not appear to be a risk factor for significantly worse outcomes.

While the effects of race and ethnicity on the outcome of transplantation have been well established for renal graft

Table 1: Structural and nonstructural metabolic liver diseases as primary diagnosis for pediatric liver transplants, January 1990 – December 1999

Inborn errors of metabolism	Number of transplants
Metabolic diseases that cause or were associated with evidence of structural liver disease (total)	**378**
α-1-Antitrypsin deficiency	261
Wilson's disease	67
Glycogen storage diseases types III, IV	15
Tyrosinemia type I	9
Neonatal hemochromatosis	4
Crigler–Najjar syndrome type I	4
Homozygous hyperlipidemia	4
Erythropoietic protoporphyria	4
Niemann-Pick disease II (C)	3
Disorders of fatty acid metabolism	2
Adrenal leukodystrophy	1
Cholesterol ester storage	1
Factor VII deficiency	1
Protein C deficiency	1
Mucopolysaccharidosis	1
Metabolic diseases that do not cause and were not associated with structural liver disease	**173**
Primary hyperoxaluria type 1	54
Tyrosinemia type I	46
Inborn errors of urea synthesis (total)	42
Ornithine transcarbamylase deficiency	25
Carbamyl phosphate synthetase deficiency	7
Argininosuccinate synthetase deficiency (citrullinemia)	3
Argininosuccinase deficiency	3
Inborn errors of urea synthesis, not specified	4
Crigler–Najjar syndrome type I	12
Glycogen storage diseases type I	10
Inborn errors of organic acid metabolism	6
Factor VII deficiency	1
Protein C deficiency	1
Fructosemia	1

Source: Scientific Registry of Transplant Recipients.

recipients (8–10), reports in the setting of liver transplantation have been conflicting (11–18) and have not previously been reported in a cohort of patients undergoing liver transplantation for metabolic disorders. In renal transplantation, data from both American and European registries have demonstrated poorer long-term allograft survival in black recipients (8–10). In liver transplantation, multiple studies have found similar patient (11–14) and graft survival (12,13) by race in adults (13–15) and children (13,15), while other reports have demonstrated worse outcomes in black liver transplant recipients (16–18). There is no obvious explanation for the lower survival rate among black recipients in the current study.

Our finding that simultaneous extrahepatic organ transplantation is a risk factor for death among children with metabolic disease was not surprising. Previously reported analyses demonstrated that impaired renal function is an independent risk factor for children undergoing liver transplantation (19), particularly for patients requiring dialysis or who receive combined liver-kidney transplantation (20). Among the combined kidney-liver transplants in the current analysis, 88% had primary hyperoxaluria. Lower patient survival rates in this subgroup have previously been noted. A study from the European primary hyperoxaluria transplant registry of 87 pediatric liver transplants (most in combination with a renal transplant) found worse survival rates in patients who had been on dialysis for more than 2 years and in those who had worse general medical condition (21). In our analysis, which was not controlled for duration of dialysis or general health, patients with primary hyperoxaluria did have a higher mortality risk when compared to those with biliary atresia, but this difference was not statistically significant (RR = 1.48; 95% CI = 0.4–5.8; p = 0.57).

Most children with hepatic-based metabolic disorders undergo liver transplantation to treat symptoms and sequelae of chronic end-stage liver disease or for fulminant hepatic failure. In some of these patients, liver

Table 2: Recipient demographics

Parameter	Biliary atresia (n = 2176)	Metabolic disease (n = 551)	p-value	Metabolic disease: Structural disease (n = 378)	Metabolic disease: Nonstructural disease (n = 173)	p-value
Male	916 (42%)	326 (59%)	<0.0001	225 (60%)	101 (58%)	NS
Female	1260 (58%)	225 (41%)		153 (40%)	72 (42%)	
Race: Non-black	1644 (76%)	523 (95%)	<0.0001	351 (94%)	166 (96%)	NS
Race: Black	523 (24%)	28 (5%)		21 (6%)	7 (4%)	
Weight ⩽ 10 kg	1275 (59%)	94 (17%)	<0.0001	57 (15%)	37 (21%)	NS
Weight >10 kg	788 (36%)	428 (78%)		301 (80%)	127 (73%)	
Missing weight	113 (5%)	29 (5%)		20 (5%)	9 (5%)	
ABO identical or compatible	2088 (96%)	533 (97%)	NS	367 (97%)	167 (97%)	NS
ABO incompatible	87 (4%)	17 (3%)		11 (3%)	6 (3%)	
Previous liver transplant	469 (22%)	81 (15%)	0.0003	55 (15%)	26 (15%)	NS
First liver transplant	1707 (78%)	470 (85%)		323 (85%)	147 (85%)	
Simultaneous transplants	9 (0.4%)	40 (7%)	<0.0001	2 (<1%)	38 (22%)	<0.0001
Pretransplant condition			NS			NS
Hospitalized ICU	474 (22%)	112 (20%)		87 (23%)	25 (14%)	
Hospitalized ICU	474 (22%)	114 (21%)		74 (20%)	40 (23%)	
Outpatient	1207 (55%)	321 (58%)		214 (57%)	107 (62%)	
Unknown	21 (<1%)	4 (<1%)		3 (<1%)	1 (<1%)	
Partial liver transplant	638 (30%)	112 (20%)	<0.0001	70 (19%)	42 (24%)	NS
Whole liver transplant	1538 (70%)	439 (80%)		308 (81%)	131 (76%)	
Mean age (years) ± SD	3.1 ± 3.8	7.0 ± 5.4	<0.0001	7.6 ± 5.4	5.8 ± 5.3	0.0004
Range (months–years)	(5–18.0)	(5–17.9)		(5.3–18.0)	(5.0–17.9)	
Mean weight ±SD	13.2 ± 11.4	26.1 ± 19.2	<0.0001	28.5 ± 20.5	20.9 ± 14.9	<0.0001
Range (kg)	(3.1–98.3)	(3.1–98.3)		(4.0–97.2)	(3.4–72)	
Cold ischemia time (h)	10.4 ± 5.0	9.8 ± 5.2	0.03	9.8 ± 5.2	10.0 ± 5.1	NS
Range (h)	(1–45.1)	(1–41.9)		(1.0–41.9)	(3.4–39.8)	

Source: Scientific Registry of Transplant Recipients.

replacement also serves to cure an enzymatic or protein deficiency, reverse or stabilize peripheral organ damage, or remove the risk of developing hepatocellular carcinoma (22). Smaller populations of metabolic patients do not develop structural disease and undergo liver transplantation solely to improve quality of life (by providing a missing protein or enzyme). Severe dietary restrictions are required in patients with glycogen storage disease type 1 (23), familial hypercholesterolemia (24), urea cycle defects (25), and disorders of organic acid metabolism (26,27). As a result, many of these patients suffer from frequent episodes of infection and growth impairment (28). Phototherapy and exchange transfusions are needed in children with Crigler–Najjar syndrome (29). Plasmapheresis is

Table 3: Donor demographics

Parameter	Biliary atresia (n = 2176)	Metabolic disease (n = 551)	p-value	Metabolic disease: Structural disease (n = 378)	Metabolic disease: Nonstructural disease (n = 173)	p-value
Male gender	1215 (56%)	311 (56%)	NS	210 (56%)	101 (58%)	NS
Female gender	961 (44%)	240 (44%)		168 (44%)	72 (42%)	
Non-black race	1782 (82%)	478 (87%)	0.01	327 (87%)	151 (87%)	NS
Black race	360 (16%)	67 (12%)		46 (12%)	21 (12%)	
Missing race	34 (<2%)	6 (1%)		5 (1%)	1 (<1%)	
Deceased donor	1907 (88%)	504 (91%)	0.01	345 (91%)	159 (92%)	NS
Living donor	269 (12%)	47 (9%)		33 (9%)	14 (8%)	
Mean age (years) ± SD	12.3 ± 13.4	14.8 ± 14.5	0.0002	16.0 ± 15.0	12.4 ± 12.9	0.0041
Range (months-years)	(3.6–89.3)	(3.6–70.1)		(4.0–70.1)	(3.6–59.9)	
Mean weight ±SD	31.9 ± 24.4	39.2 ± 25.9	<0.0001	40.6 ± 26.0	36.7 ± 25.4	NS
Range (kg)	(5.4–101.8)	(5.9–99.8)		(5.9–99.8)	(7.0–94.0)	

Source: Scientific Registry of Transplant Recipients.

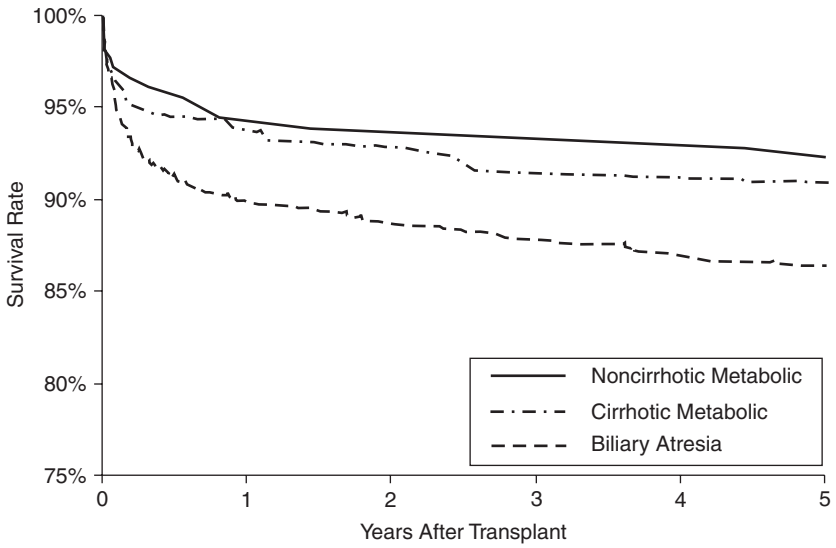

Figure 1: Patient survival after pediatric liver transplantation, by primary diagnosis. Source: Scientific Registry of Transplant Recipients (1990–1999).

required in familial hypercholesterolemia (30). These treatments can take a toll on general health. In many patients, enzymatic deficiency in an otherwise normal liver leads to damage in other organs, such as the central nervous system, kidneys, and heart. Ongoing neurological injury commonly occurs among patients with urea synthesis defects (31,32), Crigler–Najjar syndrome (29), and metabolic acidosis (26). Renal insufficiency may develop in patients with metabolic acidosis (33) and glycogen storage disease type I (23) and is usually present in patients with hyperoxaluria undergoing liver transplantation (34). Children with familial hypercholesterolemia develop skin xanthomata, generalized atheromatous lesions and cardiac disease (24).

Our data demonstrated similar overall mortality rates in children with metabolic disease associated with structural disease compared to those without. Since pretransplant health status affects post-transplant survival, our hypothesis was that children with nonstructural metabolic disease would have better outcomes after liver transplantation than metabolic patients whose livers were structurally abnormal. However, our findings of similar survival in the two groups may be explained by the presence of medical risk factors in the nonstructural patients not controlled for in our data. These children may develop complications that are risk factors for post-transplant death aside from those directly associated with structural liver disease (22–28). In addition, we found that some patients, such as those with α-1-antitrypsin deficiency (which is always associated with major structural liver disease), had significantly lower mortality than biliary atresia patients, thus contributing to the overall favorable survival in the structural subgroup.

In summary, this study demonstrated adjusted 1- and 5-year survival rates of 94% and 92%, respectively, in children transplanted for metabolic diseases. These outcomes were significantly better than for children with biliary atresia, who in general have more severe pretransplant morbidity. Interestingly, the best 1- and 5-year survival rates were seen in children with α-1-antitrypsin deficiency (96% and 94%, respectively). These results may reflect the healthier status of these patients compared to both those with biliary atresia or other metabolic diseases. While the presence of structural liver disease did not appear to be a risk factor for significantly worse outcomes among liver recipients with metabolic disease, recipient black race and simultaneous organ transplantation were found to be independent risk factors for mortality. Further studies are needed to elucidate whether risk factors among black recipients can be identified and ameliorated. Finally, liver transplantation performed before the onset of advanced systemic disease or the need for other organ transplants may significantly improve survival rates among patients with nonstructurally based metabolic disorders amenable to hepatic replacement therapy.

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