ORIGINAL ARTICLE

Liver transplantation for congenital hepatic fibrosis

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SUMMARY

Congenital hepatic fibrosis (CHF) is a hereditary fibrocystic disease that can progress to portal hypertension and recurrent cholangitis requiring liver transplantation (LT). It can be associated with renal pathology and need for kidney transplantation (KT). We describe the clinical characteristics and outcomes of patients undergoing liver transplantation alone (LTA) and simultaneous liver–kidney transplantation (SLKT) for CHF using the Unites States Scientific Registry of Transplant Recipients. A total of 197 patients who received LT for CHF between 2002 and 2018 were identified – 87 (44.2%) received SLKT, 110 (55.8%) received LTA. The 1-, 3- and 5-year patient survival were 99.0%, 96.2% and 94.6%. The 1-, 3- and 5-year liver graft survival were 94.9%, 91.1% and 89.6%. No significant differences in patient or liver graft survival were observed between the SLKT and LTA groups, or between paediatric and adult recipients. 53.3% of patients with CHF necessitating LT also have significant renal disease requiring KT. Kidney graft survival for isolated KT prior to LT were poorer compared with KT performed simultaneously or after LT. Both LTA and SLKT for CHF are associated with excellent long-term outcomes in paediatric and adult patients.

Transplant International 2021; 34: 1281–1292

Key words
ciliopathy, hepatorenal fibrocystic disease, polycystic kidney disease, Scientific Registry of Transplant Recipients, simultaneous liver kidney transplantation

Received: 6 January 2021; Revision requested: 25 March 2021; Accepted: 12 April 2021; Published online: 30 May 2021

Introduction

Congenital hepatic fibrosis (CHF) is a developmental disorder characterized by ductal plate malformations and variable degrees of periportal fibrosis with a prevalence of 1/10 000–20 000 [1–3]. Clinical manifestations and timing of symptoms are highly heterogeneous, which makes diagnosis often challenging [4]. Presentation is most frequently during adolescence but can range from early childhood to the 5th or 6th decade of life [5–7]. Patients generally exhibit one of four recognized phenotypes of CHF – portal hypertensive (most common; manifesting as splenomegaly and variceal bleeding), cholangitic (manifesting as cholestasis and recurrent cholangitis), mixed (features of both), or latent (incidentally discovered during other workup, at surgical exploration, or at autopsy) [1,2,8]. Patients who develop serious complications of portal hypertension or cholangiopathy may require liver transplantation (LT) [2]. Approximately 2% of patients also develop cholangiocarcinoma [5].

Congenital hepatic fibrosis is rarely found in isolation and is most commonly associated with renal abnormalities in autosomal recessive conditions, such as autosomal recessive polycystic kidney disease (ARPKD) and nephronophthisis [9,10]. Patients with dual organ

doi:10.1111/tri.13884

failure may require both liver and kidney transplantation with variable timing and sequence [11]. Given the condition's heterogeneity and rarity, studies describing its treatment and outcomes are limited to primarily case reports, case series and small cohort studies [2,12–17]. Outcomes following liver transplantation alone (LTA) or SLKT in patients with CHF have not yet been investigated in a larger cohort. We aimed to examine the demographics, clinical characteristics and outcomes of patients undergoing LTA and SLKT for CHF using national registry data.

Patients and methods

Data source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, wait-listed candidates and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

Patient identification

We identified all patients undergoing a first LT for CHF in the Unites States between February 2002 and June 2018 in the September 2020 release of the SRTR Standard Analysis Files. The diagnosis of CHF was determined by the respective SRTR recipient primary and/or secondary diagnosis code ('4280'). Two comparison groups were generated, one comprised of patients undergoing SLKT and one comprised of patients undergoing LTA. One patient was listed for SLKT, but expired shortly after undergoing LTA, prior to receiving KT – this patient was excluded from our analysis.

For patients in the SLKT group or in the LTA group with a history of prior kidney transplant (KT), the indication for KT was determined to be polycystic kidney disease (PKD) by either the respective SRTR diagnosis code ('3008'), or by the free-text field if the diagnosis was coded as other('999'). For age-based subgroup analyses, comparison groups consisted of patients with age <18 years ('children') and ≥18 years ('adults') at the time of LT. Liver transplant records of the SLKT and LTA recipients who had received or waitlisted for a KT before, simultaneous to, or after LT were linked to the respective kidney transplant and/or waitlist SRTR datasets. All reported MELD/PELD scores were directly collected from the registry. Laboratory MELD/PELD scores represent calculated scores based on published algorithms. Allocation MELD/PELD scores represent adjusted scores after exception points were taken into consideration.

Statistical analysis

Continuous variables were summarized as medians with interquartile ranges (IQRs) and categorical variables as frequencies (%). Between-group comparisons of patient characteristics were performed using the Mann–Whitney *U* test for continuous variables, and the chi-square or Fisher's exact test for categorical variables. Patient survival was defined as the time period from the date of LT until the date of last patient contact or patient death. Liver and kidney graft survival were defined as the time period from the date of LT or KT until the date of liver or kidney graft failure, respectively. The median follow-up time after LT was calculated using the reverse Kaplan–Meier method [18]. The Kaplan–Meier method was used to determine the 1-, 3- and 5-year patient, liver graft and kidney graft survival rates. Between-group differences in patient and graft survival were assessed using the log-rank test. Cohort development and statistical analyses were performed using STATA IC 16.0 (StataCorp LLC, College Station, TX, USA).

Results

Cohort characteristics

The study cohort consisted of 197 patients who received LT for CHF, of whom 87 were SLKT recipients and 110 were LTA recipients. The median follow-up was 76.3 months (95% CI: 61.3–93.6) for the entire cohort, 76.3 months (95% CI: 55.5–88.2) for the SLKT group and 85.2 months (95% CI: 62.3–98.0) for the LTA group. Baseline cohort and transplant characteristics are shown in Table 1. The median age at the time of LT was 19 years in the SLKT group and 18 years in the LTA group ($P = 0.74$). Compared with the LTA group, the SLKT group had a greater proportion of patients on dialysis the week prior to LT (59.3% vs. 2.8%; $P < 0.001$), higher creatinine (median: 3.8 vs. 0.8, $P < 0.001$), lower INR (median: 1.2 vs. 1.3; $P = 0.02$), and lower bilirubin (median: 1.0 vs. 1.9, $P < 0.001$). No statistically significant differences were observed between

Table 1. Cohort characteristics.

Variables*	SLKT (n = 87)	LTA (n = 110)	P-value	Total (n = 197)
General demographics				
Sex				
Female	40 (46.0%)	48 (43.6%)	0.74	88 (44.7%)
Male	47 (54.0%)	62 (56.4%)		109 (55.3%)
Race				
White	75 (86.2%)	94 (85.5%)	1.00	169 (85.8%)
Black	8 (9.2%)	10 (9.1%)		18 (9.1%)
Asian	2 (2.3%)	3 (2.7%)		5 (2.5%)
Native	2 (2.3%)	2 (1.8%)		4 (2.0%)
Multi	0 (0.0%)	1 (0.9%)		1 (0.5%)
At the time of listing				
Age (years)	17.0 (8.0–36.0)	17.0 (8.0–38.0)	0.80	17.0 (8.0–36.0)
Laboratory MELD/PELD score	15.0 (2.0–22.0)	8.0 (4.0–16.0)	**0.03**	10.0 (3.0–19.0)
Waitlist time (days)	267.0 (101.0–516.0)	118.5 (45.0–351.0)	**0.002**	184.0 (63.0–419.0)
At the time of transplant				
Age (years)	19.0 (8.0–37.0)	18.0 (9.0–39.0)	0.74	19.0 (9.0–37.0)
Height (cm) (n = 189)	154.9 (117.3–170.2)	160.0 (124.5–172.7)	0.33	157.5 (122.0–172.2)
Weight (kg) (n = 193)	50.1 (23.6–68.2)	57.6 (27.9–79.4)	0.12	53.1 (24.2–75.3)
BMI (kg/m^2) (n = 188)	20.4 (18.1–24.1)	21.9 (18.1–26.2)	0.28	20.9 (18.1–25.3)
Laboratory MELD/PELD score	20.0 (2.0–24.0)	11.0 (7.0–21.0)	0.10	14.0 (6.0–23.0)
Albumin (g/dl)	3.5 (3.0–4.0)	3.3 (2.9–3.9)	0.14	3.4 (2.9–3.9)
Bilirubin (mg/dl)	1.0 (0.6–2.0)	1.9 (0.8–5.3)	**<0.001**	1.4 (0.7–3.1)
INR	1.2 (1.1–1.4)	1.3 (1.1–1.9)	**0.02**	1.3 (1.1–1.6)
Serum creatinine (mg/dl) (n = 196)	3.8 (2.6–5.9)	0.8 (0.6–1.1)	**<0.001**	1.4 (0.7–3.7)
Serum sodium (mEq/L) (n = 178)	139.5 (137.0–142.0)	139.0 (137.0–141.0)	0.14	139.0 (137.0–141.0)
Exception MELD/PELD score				
No	41 (47.1%)	58 (52.7%)	0.44	99 (50.3%)
Yes	46 (52.9%)	52 (47.3%)		98 (49.8%)
Allocation MELD/PELD score (n = 195)	29.0 (22.0–35.0)	23.0 (16.0–30.0)	**0.003**	24.0 (20.0–33.0)
Location				
ICU	6 (6.9%)	7 (6.4%)	0.98	13 (6.6%)
Hospitalized, not in ICU	10 (11.5%)	12 (10.9%)		22 (11.2%)
Not hospitalized	71 (81.6%)	91 (82.7%)		162 (82.2%)
Ascites (n = 183)				
Absent	47 (58.8%)	46 (44.7%)	0.13	93 (50.8%)
Slight	24 (30.0%)	37 (35.9%)		61 (33.3%)
Moderate	9 (11.3%)	20 (19.4%)		29 (15.9%)
Encephalopathy (n = 183)				
None	59 (73.8%)	72 (69.9%)	0.81	131 (71.6%)
Grade 1–2	17 (21.3%)	24 (23.3%)		41 (22.4%)
Grade 3–4	4 (5.0%)	7 (6.8%)		11 (6.0%)
Portal vein thrombosis (n = 193)				
No	78 (90.7%)	90 (84.1%)	0.20	168 (87.1%)
Yes	8 (9.3%)	17 (15.9%)		25 (13.0%)
Dialysis within prior week (n = 193)				
No	35 (40.7%)	104 (97.2%)	**<0.001**	139 (72.0%)
Yes	51 (59.3%)	3 (2.8%)		54 (28.0%)
Mechanically assisted				
No	82 (94.3%)	106 (96.4%)	0.51	188 (95.4%)
Yes	5 (5.8%)	4 (3.6%)		9 (4.6%)
Donor type				
Deceased	86 (98.9%)	96 (87.3%)	**0.002**	182 (92.4%)
Living	1 (1.2%)	14 (12.7%)		15 (7.6%)

Table 1. Continued.

Variables*	SLKT (n = 87)	LTA (n = 110)	P-value	Total (n = 197)
Graft type				
Whole	79 (90.8%)	87 (79.1%)	**0.02**	166 (84.3%)
Partial	3 (3.5%)	17 (15.5%)		20 (10.2%)
Split	5 (5.8%)	6 (5.5%)		11 (5.6%)
Previous kidney transplantation				
No	59 (67.8%)	92 (83.6%)	**0.008**	151 (76.7%)
Yes	28 (32.2%)	18 (16.4%)		46 (23.4%)
Indication for kidney transplantation (n = 105)				
PKD	63 (72.4%)	16 (88.9%)	0.23	79 (75.2%)
Other/unknown	24 (27.6%)	2 (11.1%)		26 (24.8%)

ICU, intensive care unit; INR, international normalized ratio; LTA, liver transplantation alone; MELD, Model for End-stage Liver Disease; PELD, Paediatric End-stage Liver Disease; PKD, polycystic kidney disease; SLKT, simultaneous liver–kidney transplantation.

Data are presented as frequencies (%) or as median (IQR).
P values < 0.05 were considered significant and are bolded.

*The data are available for the whole cohort of 198 patients, unless otherwise specified.

the two groups with regards to laboratory MELD/PELD scores at time of LT (median: 20 vs. 11; $P = 0.10$) and the proportions of patients receiving LT with MELD/PELD exception points (52.9% vs. 47.3%; $P = 0.44$). Compared with LTA recipients, SLKT recipients had longer waitlist time (median: 267 vs. 118.5 days; $P = 0.002$), more often received a deceased donor LT (98.9% vs. 87.3%, $P = 0.002$), and more often received a whole-liver graft (90.8% vs. 79.1%, $P = 0.02$). A greater proportion of SLKT recipients had a history of a prior KT (32.2% vs. 16.4%, $P = 0.008$). Eight (9.3%) of SLKT patients and seventeen (15.9%) of LTA patients had preoperative portal vein thrombosis (PVT) at the time of LT ($P = 0.20$).

We next examined the characteristics of the paediatric and adult subgroups, which are presented in Table 2. Notably, in the adult subgroup, SLKT patients had higher allocation MELD scores than LTA patients (median: 28.0 vs. 23; $P = 0.006$). Thirty-one of 43 (72.1%) paediatric SLKT patients and 31 of 55 (56.4%) paediatric LTA patients received LT with exception points, compared to 15 of 44 (34.1%) adult SLKT and 21 of 55 (38.2%) adult LTA patients.

Patient and liver graft survival

The 1-, 3- and 5-year patient survival rates were 99.0%, 96.2% and 94.6% (Fig. 1a). The 1-, 3- and 5-year liver graft survival rates were 94.9%, 91.1% and 89.6% (Fig. 1b). No significant difference was observed in patient ($P = 0.45$) or liver graft ($P = 0.29$) survival between SLKT and LTA groups, with 5-year patient survival rates of 96.3% vs. 93.3%, respectively (Fig. 1c), and 5-year liver graft survival rates of 91.6% vs. 88.1%, respectively (Fig. 1d). After sub-stratification by age, no significant difference was found in patient or liver graft survival between paediatric and adult recipients of SLKT and LTA (Fig. 1e,f). One-, 3- and 5-year patient and liver graft survival rates for subgroups are shown in Table 3.

Renal disease and kidney graft outcomes

Of the 197 patients included in the study, 105 patients (53.3%) underwent a prior or simultaneous KT. Forty-eight KTs were performed in 46 patients prior to their LT (one patient had 2 KTs before SLKT and one patient had 2 KTs before LTA). After LT, 16 patients underwent KT and another nine patients were wait listed for KT (Fig. 2). The impact of kidney transplant sequence on kidney graft survival is shown in Fig. 3. No significant difference was observed in kidney graft survival between KT performed simultaneous to LT (SKLT) and KT performed after LT ($P = 0.83$). However, KT performed before LT was associated with significantly poorer kidney graft survival compared to SLKT ($P < 0.001$).

Indications for first-time KT in children and adults are listed in Table 4. PKD was the most common aetiology of renal disease in patients who underwent upfront KT (37 of 46; 80.4%) as well as in those who underwent upfront SLKT (44 of 59; 74.6%). Of 92

Table 2. Cohort characteristics by age subgroups.

Variables*	Children (<18 years)			Adult (≥18 years)		
	SLKT (*n* = 43)	LTA (*n* = 55)	*P*-value	SLKT (*n* = 44)	LTA (*n* = 55)	*P*-value
General demographics						
Sex						
Female	20 (46.5%)	26 (47.3%)	0.94	20 (45.5%)	22 (40.0%)	0.59
Male	23 (53.5%)	29 (52.7%)		24 (54.6%)	33 (60.0%)	
Race						
White	33 (76.7%)	41 (74.6%)	0.80	42 (95.5%)	53 (96.4%)	0.77
Black	8 (18.6%)	9 (16.4%)		0 (0.0%)	1 (1.8%)	
Asian	0 (0.0%)	2 (3.6%)		2 (4.6%)	1 (1.8%)	
Native	2 (4.7%)	2 (3.6%)		0 (0.0%)	0 (0.0%)	
Multi	0 (0.0%)	1 (1.8%)		0 (0.0%)	0 (0.0%)	
At the time of listing						
Age (years)	8.0 (4.0–14.0)	8.0 (5.0–12.0)	0.84	35.0 (23.0–43.5)	36.0 (26.0–46.0)	0.26
Laboratory MELD/PELD score	2.0 (−2.0–7.0)	4.0 (−6.0–12.0)	1.00	21.0 (18.0–23.5)	12.0 (7.0–18.0)	**<0.001**
Waitlist time (days)	230.0 (63.0–449.0)	92.0 (31.0–280.0)	**0.02**	297.5 (158.5–895.5)	143.0 (71.0–491.0)	0.06
At the time of transplant						
Age (years)	8.0 (5.0–15.0)	9.0 (7.0–13.0)	0.93	35.5 (25.5–45.5)	39.0 (29.0–50.0)	0.23
Height (cm) (*n* = 189)	115.7 (98.0–148.5)	125.8 (103.0–148.0)	0.36	169.6 (160.0–177.8)	172.2 (166.0–177.8)	0.19
Weight (kg) (*n* = 193)	23.6 (16.5–39.1)	28.0 (19.6–46.5)	0.32	68.2 (58.5–81.6)	78.6 (69.4–85.7)	**0.01**
BMI (kg/m^2) (*n* = 188)	18.2 (16.3–20.1)	18.3 (16.2–19.8)	0.88	23.7 (20.7–27.2)	25.7 (23.4–28.2)	0.054
Laboratory MELD/PELD score	2.0 (−2.0–14.0)	8.0 (−1.0–15.0)	0.42	23.0 (21.0–27.5)	16.0 (10.0–23.0)	**<0.001**
Albumin (g/dl)	3.6 (3.2–4.1)	3.3 (2.9–3.9)	0.10	3.4 (2.8–3.9)	3.3 (2.5–3.9)	0.64
Bilirubin (mg/dl)	0.8 (0.5–1.6)	1.3 (0.6–5.2)	**0.02**	1.2 (0.7–2.5)	2.4 (1.1–7.1)	**0.009**
INR	1.2 (1.1–1.3)	1.3 (1.2–1.6)	**0.02**	1.3 (1.1–1.5)	1.3 (1.1–2.0)	0.29
Serum creatinine (mg/dl) (*n* = 196)	3.6 (2.3–5.5)	0.6 (0.3–0.9)	**<0.001**	4.2 (2.9–6.0)	0.9 (0.7–1.3)	**<0.001**
Serum sodium (mEq/l) (*n* = 178)	140.0 (137.0–142.0)	139.0 (137.0–141.0)	0.26	139.0 (136.0–142.0)	139.0 (136.0–140.5)	0.27
Exception MELD/PELD score						
No	12 (27.9%)	24 (43.6%)	0.11	29 (65.9%)	34 (61.8%)	0.67
Yes	31 (72.1%)	31 (56.4%)		15 (34.1%)	21 (38.2%)	
Allocation MELD/PELD score (*n* = 195)	30.0 (20.0–35.0)	20.0 (11.0–32.0)	0.11	28.0 (23.0–33.0)	23.0 (17.0–30.0)	**0.006**
Location						
ICU	4 (9.3%)	2 (3.6%)	0.45	2 (4.6%)	5 (9.1%)	0.48
Hospitalized, not in ICU	4 (9.3%)	8 (14.6%)		6 (13.6%)	4 (7.3%)	
Not hospitalized	35 (81.4%)	45 (81.8%)		36 (81.8%)	46 (83.6%)	
Ascites (*n* = 183)						
Absent	23 (63.9%)	27 (56.3%)	0.40	24 (54.6%)	19 (34.6%)	0.14
Slight	10 (27.8%)	12 (25.0%)		14 (31.8%)	25 (45.5%)	
Moderate	3 (8.3%)	9 (18.8%)		6 (13.6%)	11 (20.0%)	

Table 2. Continued.

Variables*	Children (<18 years)			Adult (≥18 years)		
	SLKT (*n* = 43)	LTA (*n* = 55)	*P*-value	SLKT (*n* = 44)	LTA (*n* = 55)	*P*-value
Encephalopathy (*n* = 183)						
None	34 (94.4%)	45 (93.8%)	1.00	25 (56.8%)	27 (49.1%)	0.75
Grade 1–2	2 (5.6%)	2 (4.2%)		15 (34.1%)	22 (40.0%)	
Grade 3–4	0 (0.0%)	1 (2.1%)		4 (9.1%)	6 (10.9%)	
Portal vein thrombosis (*n* = 193)						
No	41 (95.4%)	47 (88.7%)	0.29	37 (86.1%)	43 (79.6%)	0.41
Yes	2 (4.7%)	6 (11.3%)		6 (14.0%)	11 (20.4%)	
Dialysis within prior week (*n* = 193)						
No	20 (47.6%)	50 (96.2%)	**<0.001**	15 (34.1%)	54 (98.2%)	**<0.001**
Yes	22 (52.4%)	2 (3.9%)		29 (65.9%)	1 (1.8%)	
Mechanically assisted						
No	40 (93.0%)	55 (100.0%)	0.08	42 (95.5%)	51 (92.7%)	0.69
Yes	3 (7.0%)	0 (0.0%)		2 (4.6%)	4 (7.3%)	
Donor type						
Deceased	42 (97.7%)	48 (87.3%)	0.08	44 (100.0%)	48 (87.3%)	**0.02**
Living	1 (2.3%)	7 (12.7%)		0 (0.0%)	7 (12.7%)	
Graft type						
Whole	35 (81.4%)	37 (67.3%)	0.13	44 (100.0%)	50 (90.9%)	0.06
Partial	3 (7.0%)	12 (21.8%)		0 (0.0%)	5 (9.1%)	
Split	5 (11.6%)	6 (10.9%)		0 (0.0%)	0 (0.0%)	
Previous kidney transplantation						
No	31 (72.1%)	39 (70.9%)	0.90	28 (63.6%)	53 (96.4%)	**<0.001**
Yes	12 (27.9%)	16 (29.1%)		16 (36.3%)	2 (3.6%)	
Indication for kidney transplantation (*n* = 105)						
PKD	35 (81.4%)	14 (87.5%)	0.71	28 (63.6%)	2 (100.0%)	0.54
Other/unknown	8 (18.6%)	2 (12.5%)		16 (36.4%)	0 (0.0%)	

ICU, intensive care unit; INR, international normalized ratio; LTA, liver transplantation alone; MELD, Model for End-stage Liver Disease; PELD, Paediatric End-stage Liver Disease; PKD, polycystic kidney disease; SLKT, simultaneous liver–kidney transplantation.

Data are presented as frequencies (%) or as median (IQR).
P values < 0.05 were considered significant and are bolded.

*The data are available for the whole cohort of 198 patients, unless otherwise specified.

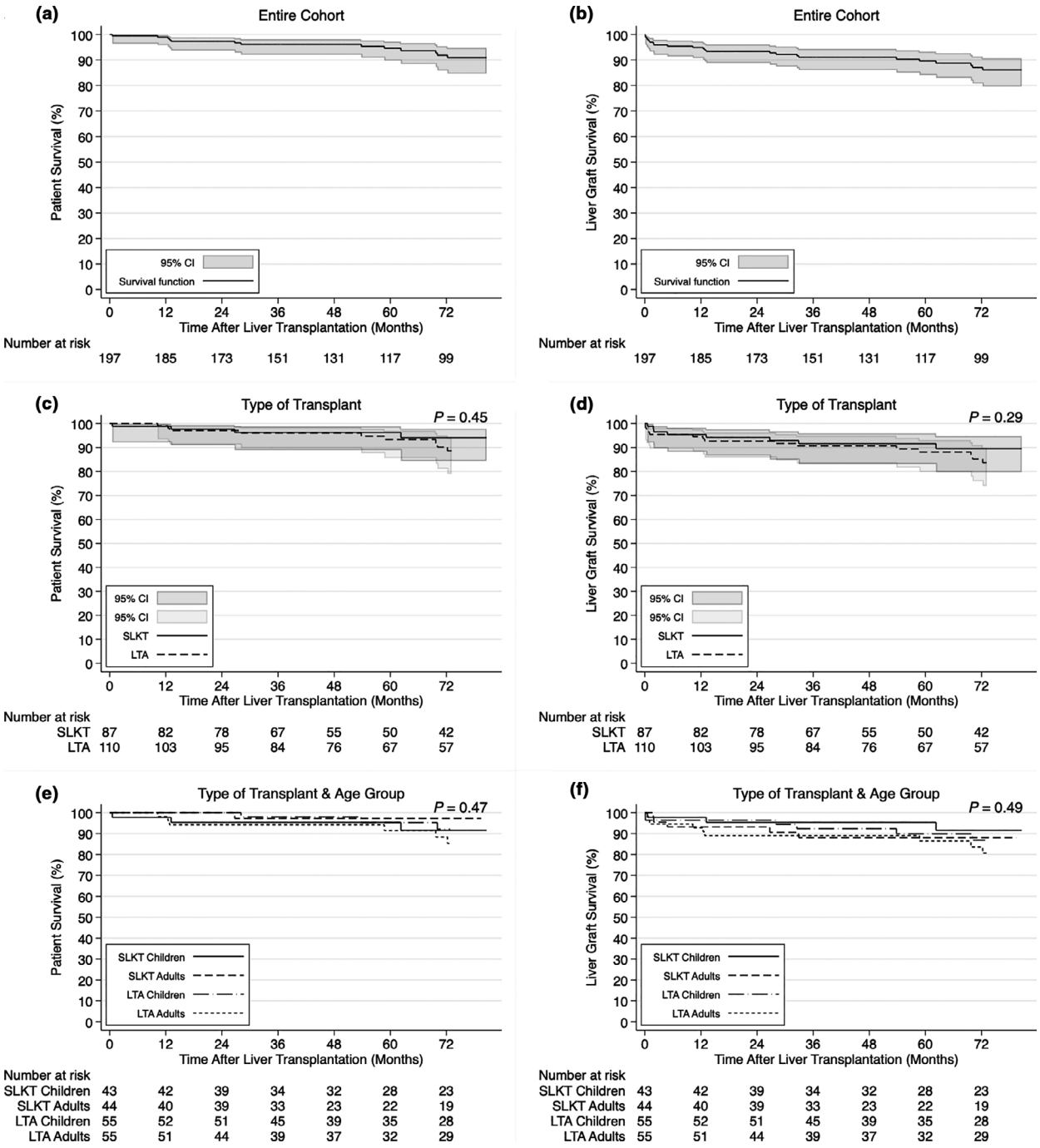

Figure 1 Kaplan–Meier curves demonstrating overall (a) patient and (b) liver graft survival in our cohort, (c) patient and (d) liver graft survival by transplant type, and (e) patient and (f) liver graft survival by transplant type and age group. LTA, liver transplantation alone; SLKT, simultaneous liver–kidney transplantation.

patients who underwent LTA without a prior KT, 12 patients subsequently either listed for or underwent KT, with the most common indication being calcineurin inhibitor toxicity (6 of 12 patients). Four of these 12 patients, all paediatric, were listed or transplanted for an indication of PKD.

Discussion

Congenital hepatic fibrosis is the most common hepatic manifestation of a heterogeneous group of disorders resulting from cilia abnormalities [3]. Cilia are cellular projections that function as sensory organelles and

Table 3. Benchmark point estimates of unadjusted cumulative patient and liver graft survival after liver transplantation.

Benchmark post-transplant time point	Total (n = 197)	SLKT			LTA		
		All SLKT (n = 87)	Children (n = 43)	Adults (n = 44)	All LTA (n = 110)	Children (n = 55)	Adults (n = 55)
Patient survival							
1 year	99.0 (0.5)	98.9 (1.1)	97.7 (2.3)	100.0 (-)	99.0 (1.0)	100.0 (-)	98.1 (1.9)
3 years	96.2 (1.4)	96.3 (2.1)	95.4 (3.2)	97.2 (2.7)	96.0 (1.9)	97.9 (2.1)	94.2 (3.3)
5 years	94.6 (1.8)	96.3 (2.1)	95.3 (3.2)	97.2 (2.7)	93.3 (2.7)	95.3 (3.3)	91.4 (4.2)
Liver graft survival							
1 year	94.9 (1.6)	95.4 (2.3)	97.7 (2.3)	93.2 (3.8)	94.5 (2.2)	96.4 (2.5)	92.7 (3.5)
3 years	91.1 (2.1)	91.6 (3.1)	95.4 (3.2)	88.0 (5.1)	90.7 (2.8)	92.4 (3.7)	89.0 (4.2)
5 years	89.6 (2.3)	91.6 (3.1)	95.4 (3.2)	88.0 (5.1)	88.1 (3.3)	89.9 (4.4)	86.4 (4.9)

LTA, liver transplantation alone; SLKT, simultaneous liver–kidney transplantation.
Tables entries are estimates of cumulative patient and liver graft survival percentages (standard errors).

signal transducers in many polarized cells, including cholangiocytes and renal tubular epithelium. Its ubiquity is responsible for the variable and multi-organ clinical features seen in ciliopathies [19]. In the liver, mutations in ciliary proteins during embryogenesis lead to abnormal biliary development and incomplete ductal plate remodelling. This results in the formation of abnormal bile ducts surrounded by dense extracellular matrix seen in CHF [20]. Clinically, CHF presents as firm hepatomegaly with progressive portal hypertension or cholangitis [5,11,21]. Medical therapy consists of managing the associated complications but LT remains the only definitive treatment [22]. When dual-organ involvement is present, renal and hepatic pathologies are thought to progress independently of one another [3]. In the event of concurrent hepatic deterioration and ESRD, SLKT has been described in cases and small series with good long-term outcomes [2].

In this study, we present the largest, national database-derived cohort of LTA and SLKT recipients for CHF, to synthesize the available evidence on the clinical characteristics and outcomes in this patient population. Over half of patients undergoing LT for CHF also had renal disease with either previous or simultaneous KT. The nonuniform sequence of KT and LT highlight the independent and variable progression of renal and liver disease in CHF-associated ciliopathies. No difference was observed in patient or liver graft survival between LTA and SLKT when a kidney transplant was indicated. However, kidney graft survival for isolated KT *prior to* LT was significantly poorer compared with kidney grafts transplanted simultaneously or subsequently to liver grafts.

The mechanism for this difference is unclear, but may be related to the long-established immune privilege conferred by LT when transplanted concurrently with other organs [23,24]. Taner *et al.* have previously demonstrated that simultaneous LT was associated with reduced immunologic injury and slowed renal function decline in KT recipients [25,26]. With more than 20% of our cohort having received or listed for 2 or more KT, the majority of whom belong in the group that received initial isolated KT prior to LT, this finding supports a simultaneous as opposed to sequential KT followed by LT approach for patients with progressive CHF and concomitant renal failure when possible.

The LTA and SLKT cohorts received LT at median ages of 18 and 19, respectively, comparable to the age at LT for this condition reported in prior studies [15].

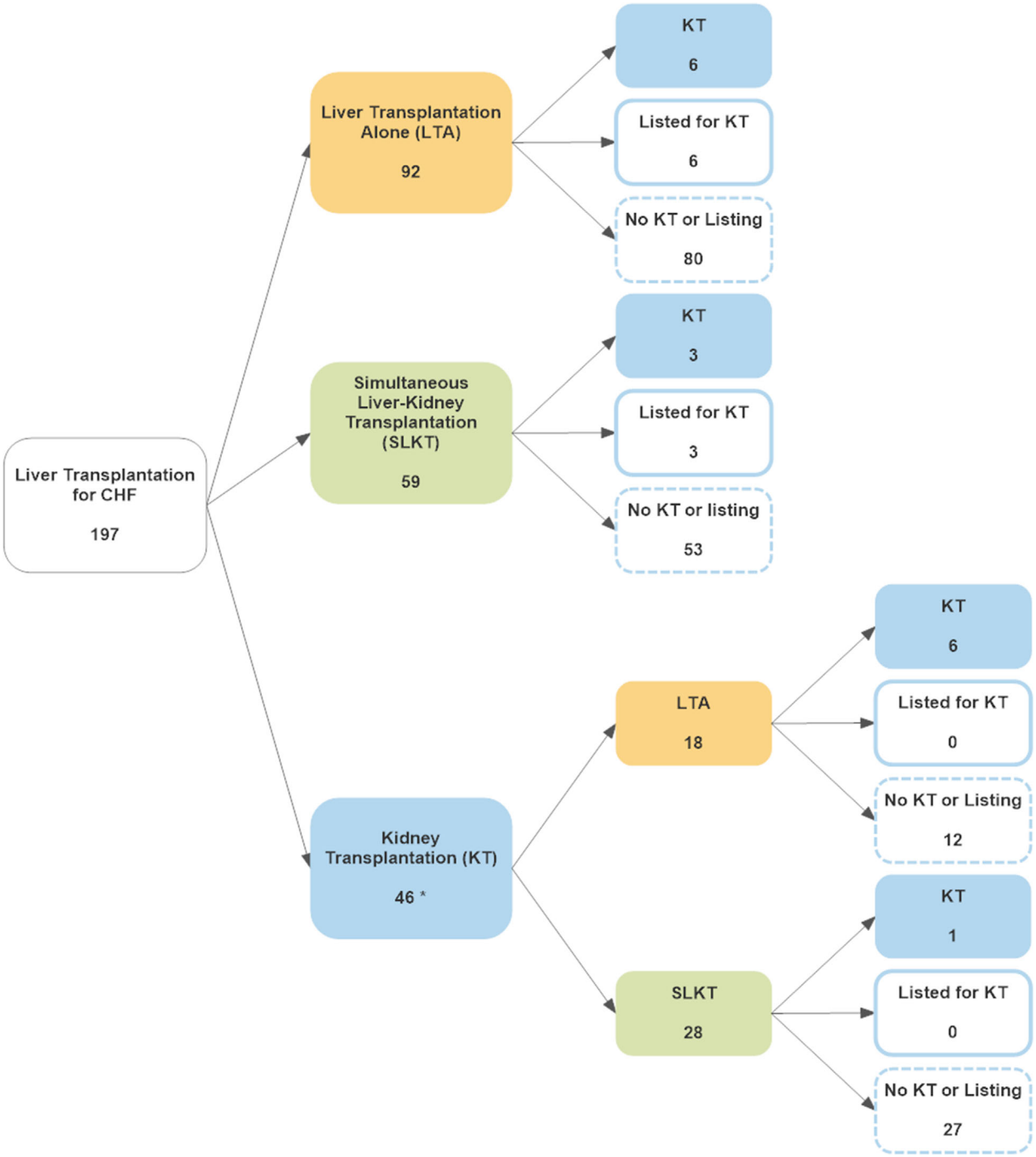

Figure 2 Flow diagram of transplantation sequences in our cohort. *Two recipients each underwent 2 kidney transplants prior to subsequent liver transplantation (1 SLKT, 1 LTA). KT, kidney transplantation; LTA, liver transplantation alone; SLKT, simultaneous liver–kidney transplantation.

The majority of paediatric SLKT and LTA recipients were transplanted with exception points, emphasizing again that the mechanism of hepatic decompensation is not primary synthetic insufficiency captured by our current MELD/PELD scoring system. Paediatric patients with renal dysfunction also do not benefit from allocation advantage resulting from elevated creatinine because of the exclusion of serum creatinine from calculation of the laboratory PELD score. This highlights the importance of exception points allotment in bridging this gap and ensuring access to transplantation for paediatric CHF patients. To a lesser degree, a substantial proportion of adult patients were also transplanted with exception points.

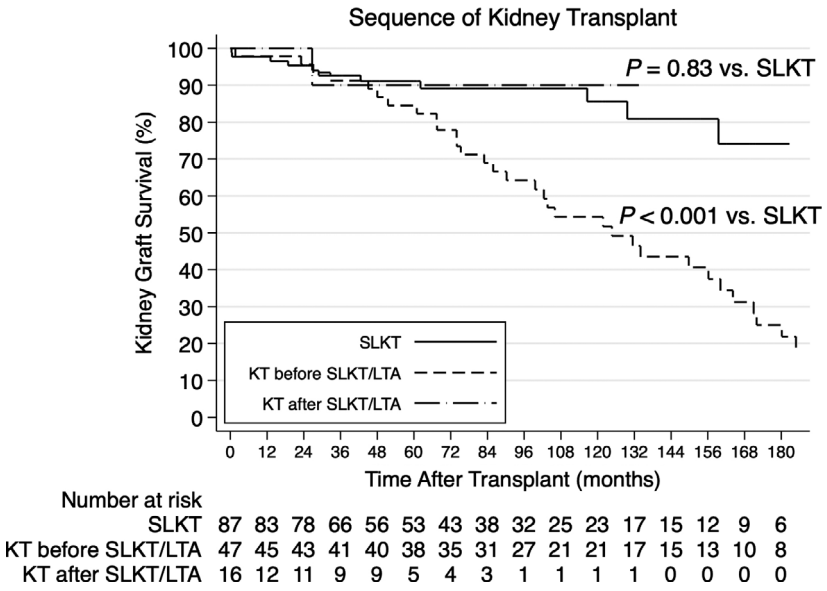

Figure 3 Kaplan–Meier curves demonstrating overall kidney graft survival by sequence of kidney transplantation. KT, kidney transplantation; LTA, liver transplantation alone; SLKT, simultaneous liver–kidney transplantation.

Table 4. Aetiologies of renal insufficiency in patients undergoing or listed for a first KT.

	Children	Adults
KT prior to LTA/SLKT	Polycystic kidney disease (24) Tubulointerstitial disease Renal hypoplasia, dysplasia, or dysgenesis Nephronophthisis (2)	Polycystic kidney disease (13) Congenital cause, unspecified Medullary cystic disease Hypertensive nephrosclerosis Nephritis
SLKT	Polycystic kidney disease (27) Renal hypoplasia, dysplasia, or dysgenesis Jeune syndrome Focal glomerular sclerosis Nephritis	Polycystic kidney disease (17) Hypertensive nephrosclerosis Diabetic nephropathy Medullary sponge kidney Hepatorenal syndrome Unspecified glomerulosclerosis Unspecified nephrosclerosis
KT or listed for KT after LTA	Polycystic kidney disease (4) Calcineurin inhibitory toxicity (2)	Calcineurin inhibitor toxicity (4) Hypertensive nephrosclerosis (2)

KT, kidney transplantation; LTA, liver transplantation alone; SLKT, simultaneous liver–kidney transplantation.

Data in parentheses are number of patients. One paediatric patient who underwent KT prior to SLKT and 5 adult patients who underwent SLKT had missing or unknown aetiologies of renal disease.

Predictably, adult patients undergoing SLKT had evidence of poorer renal function at the time of transplant: elevated creatinine and greater proportion of patients on dialysis. This renal dysfunction drives the MELD score – and thereby allocation – in the adult SLKT group, while sequelae of portal hypertension and cholangiopathy drive MELD exception and allocation in the adult LTA group. Despite being transplanted at higher laboratory MELD scores and experiencing longer waitlist times, adult patients in the SLKT group did not experience significantly different survival outcomes compared with the LTA group.

Autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive ARPKD are the most common ciliopathies and were the most common indications for KT in our cohort. Phenotypes associated with these two hereditary conditions have been well-established as being highly variable in penetrance, which

may be partially responsible for the heterogeneity in renal disease seen in CHF patients and in our cohort [27,28]. Non-PKD indications in the paediatric group included other ciliopathies, compared with more universally prevalent aetiologies of chronic kidney disease in the adult group. In patients who developed renal failure after LTA (without prior KT), calcineurin inhibitor toxicity was the cause in 50% of cases, indicating a fundamentally different pathophysiology of renal disease in a subset of these patients compared with those who underwent upfront KT or SLKT.

Our study has limitations, mostly inherent to the nature of retrospective registry data. These include potential miscoding leading to under-identification of CHF patients undergoing LT in the United States, as well as lack of granularity in documentation around the chronicity of dialysis, immunosuppressive regimen, and reason for MELD/PELD exception points. Future studies investigating the specific indications for exception will help elucidate the mechanisms by which CHF patients decompensate (i.e. capture presence of variceal bleeding, recurrent cholangitis and other characteristic complications) and their impact on post-transplant outcomes. In addition, coding for certain rare but relevant conditions for this study, such as ADPKD or ARPKD, is nonspecific (i.e. coded as 'polycystic kidney disease' in transplant registries), or relies on accurate entry into a free-text field, limiting a more granular analysis of the renal pathology in this cohort of patients. Furthermore, many outcomes other than survival (such as quality of life, degree of liver or renal function) are often poorly captured in registry data – thus limiting the ability to analyse these secondary but important measures.

Conclusion

A significant proportion of patients with CHF requiring LT have concomitant renal dysfunction necessitating dual organ transplantation which may be sequential or SLKT. Equivalent and excellent long-term patient and liver graft outcomes are achievable for adult and paediatric patients with CHF undergoing LTA or SLKT. However, kidney graft survival for patients with dual organ involvement undergoing a KT first approach was inferior to that of patients undergoing SLKT or KT after LT. When feasible, SLKT should be considered in CHF patients being evaluated for LT or KT with underlying dual organ dysfunction.

Authorship

WKW and IAZ: involved in project conception/design, performance of the research, analysis and interpretation of data, drafting manuscript and critical revisions, final approval. MI, AKP, ETH and LKM: involved in analysis and interpretation of data, critical revision and final approval. SPA: involved in project conception/design, analysis and interpretation of data, critical revisions and final approval.

Funding

The authors have declared no funding.

Conflict of interest

The authors have no conflicts of interest to disclose.

Ethical approval

All data were de-identified and derived from a national registry. Data use was approved by the U.S. Health Resources and Services Administration. Thus, no Institutional Review Board approval was required.

Disclaimer

As a condition of the Scientific Registry of Transplant Recipients (SRTR) data use agreement for Standard Analysis Files, we note the following. The data reported here have been supplied by the Hennepin Healthcare Research Institute (HHRI) as the contractor for the SRTR. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government.

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