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ORIGINAL ARTICLE

Successful long-term outcome of pediatric liver–kidney transplantation: a single-center study

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Abstract

Introduction Liver–kidney transplantation is a rare procedure in children, with just ten to 30 cases performed annually worldwide. The main indications are autosomal recessive polycystic liver–kidney disease and primary hyperoxaluria. This study aimed to report outcomes of liver–kidney transplantation in a cohort of pediatric patients.
Methods We retrospectively analyzed all pediatric liver–kidney transplantations performed in our center between September 2000 and August 2015. Patient data were obtained by reviewing inpatient and outpatient medical records and our transplant database.
Results A total of 14 liver–kidney transplants were performed during the study period, with a median patient age and weight at transplant of 144.4 months (131.0–147.7) and 27.3 kg (12.0–45.1), respectively. The indications for liver–kidney transplants were autosomal recessive polycystic liver–kidney disease (8/14), primary hyperoxaluria −1 (5/14), and idiopathic portal hypertension with end-stage renal disease (1/14). Median time on waiting list was 8.5 months (5.7–17.3). All but two liver–kidney transplants were performed simultaneously. Patients with primary hyperoxaluria-1 tended to present a delayed recovery of renal function compared with patients transplanted for other indications (62.5 vs 6.5 days, respectively, P 0.076). Patients with liver–kidney transplants tended to present a lower risk of acute kidney rejection than patients transplanted with an isolated kidney transplant (7.2% vs 32.7%, respectively; $P < 0.07$). Patient and graft survival at 1, 3, and 5 years were 100%, 91.7%, 91.7%, and 91.7%, 83.3%, 83.3%, respectively. No other grafts were lost.
Conclusion Long-term results of liver–kidney transplants in children are encouraging, being comparable with those obtained in isolated liver transplantation.

Keywords Liver–kidney transplantation · Pediatrics · Highly sensitized patients · Allograft survival · Donor-specific antibodies

This article is part of the topical collection on "What's New in Renal Transplantation?"

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Introduction

In adults, combined liver–kidney transplantation (LKT) has become a standard procedure, with numbers increasing considerably in recent years [1–3]. Nevertheless, the procedure remains rare in the pediatric population, with only ten to 30 performed annually worldwide [4]. Despite the shortage of suitable organs and the longer waiting times compared with adults recipients [5], the number of transplants performed in children has increased gradually over the past decade [6].

The most common indications for LKT in children are end-stage renal disease (ESRD) due to congenital cystic or fibrous diseases [congenital hepatic fibrosis and autosomal recessive

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polycystic liver and kidney disease (ARPLKD)], and primary hyperoxaluria type 1 (PH-1). Other indications, such as atypical hemolytic uremic syndrome, methylmalonic acidemia, or alpha-1 antitrypsin deficiency have been reported [7].

The aim of this study was to assess the outcome of children undergoing LKT in our center and report indications and early and late complications of these patients.

Patients and methods

Data on all children who underwent LKT between September 2000 and August 2016 were retrospectively collected by reviewing inpatient and outpatient medical records and the prospective database of the pediatric liver (LT) and kidney (KT) transplant units. Patients were divided into two groups based on LKT indication: group 1, patients with PH-1; group 2, patients with other indications, mainly ARPKD) to compare pre- and post-LKT kidney function. Pre- and posttransplant estimated glomerular filtration rate (eGFR) was calculated using modified Schwartz formula [8] All documented episodes of rejection were biopsy proven. All biopsies were scored by pediatric histopathologists using the Banff schema [9]. No protocol biopsies were performed.

Primary hyperoxaluria diagnosis

PH-1 was confirmed by demonstrating reduction of alanine/ glyoxylate aminotransferase enzyme activity or gene mutation studies and elevated serum and urinary oxalate level.

Autosomal recessive polycystic liver and kidney disease diagnosis

ARPKD was diagnosed using imaging techniques (ultrasound or magnetic resonance imaging) and clinical presentation. In three cases, we performed direct sequencing of the entire coding region of the *PKHD1*.

Criteria for liver–kidney transplant

Patients with PH-1 were listed for LKT when presenting with ESRD and diagnosis was confirmed (enzymatically or genetically). In patients with ARPKD, LKT was performed when a patient with ESRD presented severe cholangitis despite prophylaxic antibiotics, or with life-threatening upper-gastrointestinal bleeding refractory to conventional preventive treatment. Each patient was evaluated and accepted for LKT by the liver and kidney transplant selection committee.

Liver and kidney function

Recovery of kidney function was defined as eGFR > 60 ml/ min/1.73/m^2 without need of dialysis during the 3 days prior to eGFR determination. Recuperation of liver function was defined as International Normalized Ratio (INR) < 1.5 without administration of fresh–frozen plasma for at least 24 h. Patient survival was defined as the time from transplantation to death or last follow-up. Liver graft survival was defined as the time from transplantation to death, last follow-up, or retransplantation. Kidney graft survival was defined as the time from transplantation to death, last follow-up, or return to dialysis. In patients transplanted because of PH-1, we used continuous venovenous hemodiafiltration during the first 3 days after transplantation to decrease the burden of plasma oxalate released by tissues. No other measures to manage hyperoxalemia were used.

Pretransplant immunological monitoring

To perform an immunological assessment, a panel reactive antibody (PRA) was performed every 6 months during the pretransplant period. When PRA was > 10%, single antigen class I and II (One Lambda Inc., CA, USA) beads were used to detect donor-specific antibodies (DSA). These were read on a Luminex ® (One Lambda Inc.) platform, as described elsewhere [10]. DSA levels are reported as mean fluorescence index (MFI). If a PRA was > 10%, then the patient was considered sensitized. If the PRA was > 80% and DSA levels were ≥ 6000 MFI, then patients were considered as highly sensitized. In sensitized patients, pretransplant immunological status was checked every 3 months. A routine baseline flow cytometric cross-match and T-cell-complement-dependent cytotoxicity were done in all recipients, as previously described [11].

Desensitization strategies

Patients with PRA DSA levels < 6000 MFI received desensitization treatment with a high dose of, nonspecific immunoglobulin (1–2 g/kg body weight) monthly until transplant or desensitization. Patients considered highly sensitized received five sessions of plasmapheresis/ immunoadsorption (TheraSorb-LIFE 18; Miltenyi Biotec) with a low-dose of nonspecific immunoglobulin [100–400 g/kg body weight plus one dose of rituximab (375 mg/m^2)] after the fifth session of plasmapheresis/ immunoadsorption. Immunological status was then rechecked and if patients still fulfilled the highly sensitized criteria, they received another course of five plasmapheresis/immunoadsorption therapy and a low dose of immunoglobulin. In highly sensitized patients, five peritransplant sessions of plasmapheresis/immunoadsorption and a low dose of immunoglobulin were administered (one session just before transplant and four posttransplant) [12].

Immunosuppression

Nonsensitized patients

In all patients, induction therapy consisted of 10 mg/kg of methylprednisolone i.v. before hepatic revascularization, followed by 2.5 mg/kg twice daily, tapering to 1 mg/kg per day over 6 days. Basiliximab was administered i.v. on the 1st and 5th postoperative days at 10 or 20 mg, depending on patient weight (less or more than 30 kg, respectively). Tacrolimus at 0.075 mg/kg twice daily was started in the pediatric intensive care unit via a nasogastric tube until oral intake was tolerated to achieve a trough level of 8–12 ng/ml over the first 2 weeks. Mycophenolic acid was started at 20 mg/kg twice daily.

Sensitized patients

In sensitized patients, basiliximab was replaced by thymoglobulin (3 mg/kg on the 1st, 3rd, and 5th postoperative days, respectively, maximum dose 12 mg/kg). Drug tolerability was checked after each administration to assess the possibility of administering the next dose. Methylprednisolone, tacrolimus, and mycophenolic acid were started as is usual in LKT.

Immunological monitoring and immunosuppression in isolated KT and LT

In KT patients, immunological monitoring, desensitization strategies, and immunosuppression were the same as those in LKT. However, in LT only cross-match and T-cell-complement-dependent cytotoxicity were done before transplant, and transplantation was performed regardless of result. As no LT patient was considered as sensitized, basiliximab was always use as induction therapy followed by tacrolimus and methylprednisolone as in LKT.

Postrransplant immunological monitoring

Since 2002, in patients not highly sensitized, DSA levels posttransplant have been monitored once a year. In highly sensitized patients, DSA levels are monitored at 1, 3, 6, and 12 months posttransplant and yearly thereafter.

Liver and kidney transplantation

In all patients, transplantation procedure followed standard techniques, with liver graft preceding renal graft implantation. Hepatectomy with vena cava preservation was performed whenever possible. Technical details for LT have been described in detail by our group [13, 14]. After laparotomy closure and hemodynamic stability was achieved, KT was performed. Children were managed postoperatively within a multidisciplinary team.

Statistical analysis

Survival curves were computed using Kaplan–Meyer methods. Continuous variables are presented as median, with range and categorical variables as value with percentage. Dichotomous variables were obtained using the chi-square or Fisher's exact test. Mean comparisons were performed using Student's t test. The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 18.0 was used for analyses, and significance level was set at 0.05.

Results

A total of 174 LT and 181 KT were performed: 14 were LKT (8.0% of LT and 7.7% of KT). Indications for LKT were ARPLKD (8/14) and PH-1 (5/14). The remaining patient was a Chinese teenager with an ESRD and multiple hepatic adenomas with intratumor bleeding. Patient characteristics and characteristics of LT, KT, and LKT are shown in Tables 1 and 2, respectively.

All LKT allografts were from ABO-compatible heart-beating deceased donors. Two patients received a nonsimultaneous LKT from different donors. The first nonsimultaneous LKT patient was initially planned to be simultaneous; due to hemodynamic instability during the hepatic surgery, the KT had to be postponed. The kidney graft was successfully transplanted to another pediatric recipient. Ten months later, a solitary KT was performed without any technical complications. The second patient was scheduled as a nonsimultaneous LKT because of her low weight (7 kg). She was a PH-1 patient who first received an LT to prevent oxalosis progression; 2 months later, when the patient weighted >10 kg, the KT was successfully performed.

The average time in intensive care unit and of hospitalization was 11 (range 5.5–13.5) and 28 (range 19.7–74.5) days, respectively. Median follow-up was 106.9 months (30.3–195.9).

Indication for LKT in ARPKD patients

Among the 27 patients diagnosed with ARPKD during the study period, 15 received a solid organ transplant (two isolated LT, five KT, eight LKT). Five patients received an LKT as first-line therapy. Indication for LT in those patients was portal hypertension with variceal bleeding. Eight patients presented kidney dysfunction without major liver involvement, so they initially received an isolated KT. Three of them presented severe cholangitis after the KT, leading to an LKT a mean of 4.21 years (0.43–7.31) after the KT. All episodes of cholangitis were observed as chronic infections requiring

Table 1 Patient characteristics

	Indication	Age (months)	Pre-LKT DSA	LKT type	Liver graft	Indication for LT	Previous KT	Complications
Patient 1	PH-1	105.93	Not available	Simultaneous	Whole liver	Metabolic	No	
Patient 2	ARPKD	152.23	Not available	Simultaneous	Whole liver	Portal hypertension	No	
Patient 3	ARPKD	142.40	Nonsensitized	Simultaneous	Whole liver	Portal hypertension	No	Acute kidney rejection
Patient 4	ARPKD	119.50	Nonsensitized	Simultaneous	Whole liver	Portal hypertension	No	
Patient 5	PH-1	91.17	Sensitized	Simultaneous	Split	Metabolic	No	Renal retransplantation post-LKT Hepatic artery thrombosis, Acute Lliver rejection
Patient 6	PH-1	112.17	Nonsensitized	Simultaneous	Whole liver	Metabolic	No	
Patient 7	ARPKD	31.30	Sensitized	Simultaneous	Whole liver	Portal hypertension	No	Exitus (adenovirus infection). Acute liver rejection
Patient 8	ARPKD	109.50	Nonsensitized	Simultaneous	Whole liver	Portal hypertension	No	BK virus infection (resolution)
Patient 9	PH-1	40.13	Nonsensitized	Simultaneous	Whole liver	Metabolic	No	Renal retransplantation post-LKT
Patient 10	ARPKD	184.67	Highly sensitized	Simultaneous	Whole liver	Cholangitis	Yes	Portal hypertension
Patient 11	PH-1	20.97	Nonsensitized	Nonsimultaneous	Whole liver	Metabolic	No	
Patient 12	ESRD + PHT	159.40	Nonsensitized	Nonsimultaneous	Whole liver	Intratumoral bleeding	No	Intraoperative arrhythmia
Patient 13	ARPKD	197.77	Highly sensitized	Simultaneous	Whole liver	Cholangitis	Yes	BK virus infection (waiting list for KT). Acute liver rejection
Patient 14	ARPKD	47.97	Highly sensitized	Simultaneous	Whole liver	Cholangitis Portal hypertension	Yes	Acute liver rejection DSA transient positivization

DSA donor-specific antibody, *LKT* liver–kidney transplant, *ARPKD* autosomal recessive polycystic kidney disease, *PH-1* primary hyperoxaluria type 1, *LT* liver transplant, *KT* kidney transplant

Table 2 Transplant characteristics

	KT	LT	LKT	KT vs LKT	LT vs LKT
Median age (months)	109.4 (9.6–288.0)	37.5 (2.5–112.7)	144.4 (31.0–147.7)	$p < 0.91$	$p < 0.002$
Gender (% male/female)	54.0/46.0	54.2/45.8	50.0/50.0		
Weight (kg)	30.1 (16.2–46.2)	8.5 (2.7–49.3)	27.3 (12.0–45.1)	$p < 0.52$	$p < 0.051$
Time on waiting list (months)	7.1 (4.9–9.1)	4.6 (2.2–7.5)	8.5 (5.7–17.3)	$p < 0.67$	$p < 0.05$
Liver cold ischemia time (min)		310 (240–435)	293 (156–468)		$p < 0.778$
Kidney cold ischemia time (min)	720 (603–912)		615 (565–770)	$p < 0.64$	

KT kidney transplant, *LT* liver transplant, *LKT* liver–kidney transplant

antibiotic treatment i.v. for a mean of 10.77 months (4.57–17.8). The other five isolated KT patients present a normal liver function without any episode of cholangitis or variceal bleeding due to portal hypertension during the follow-up. No cholangitis episodes were observed in LKT recipients without a previous KT. No differences were observed in age at LKT between LKT performed as a first-line therapy or after cholangitis (110.83 months; 31.03–152.23 vs 143.46 months; 47.97–197.77, respectively; $P = 0.56$). Recipients of an isolated LT presented normal kidney function at the end of follow-up.

Pretransplant renal function

Median pretransplant eGFR was 11.8 ml/min/1.73 m^2 (range 9.6–17). All patients were on hemodialysis support before transplant (median 6.2 months; range 4.1–8.8). Only one patient needed dialysis from birth (patient 14). There were no statistically significant differences in eGFR values or median hemodialysis time depending on different causes of LKT. All patients presented hypertension before transplant using two or more antihypertensive drugs in all but three cases. Two patients used more than four drugs.

Pretransplant liver function

All patients presented good liver function. Only one case presented mild hepatic synthetic dysfunction, which was not the indication for liver transplant.

Sensitized patients

Five patients were considered sensitized, and basiliximab was replaced with thymoglobulin, as described. Three were highly sensitized: The first received plasmapheresis plus a high dose of immunoglobulin and rituximab pretransplant. In the remaining two, plasmapheresis was replaced with immunoadsorption. All highly sensitized patients had ARPKD with previous KT and their negative DSA pretransplant remained negative at the end of follow-up.

One highly sensitized patient pretransplant was positive for de novo DSA types 1 and 2, 1 month after LKT. Nevertheless, there was neither kidney nor hepatic graft dysfunction. Two months later, DSA was negative and remained so at the end of the follow-up period. The remaining LKT recipients presented no DSA positivity.
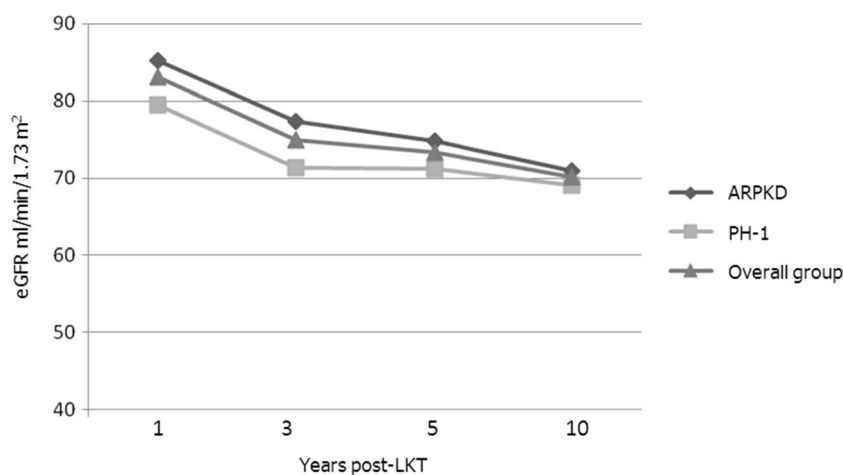
Posttransplant renal function

Five of 14 patients (35.7%) required continued postoperative hemodialysis after kidney transplant (media duration of posttransplant dialysis 12.5 days, range 6.5–19.5). Among these five patients, four had PH-1. During the first 3 days, those four patients were under continuous venovenous hemodiafiltration to decrease oxalate overload, then switched to intermittent hemodialysis until renal function recovery. Only one of eight patients with ARPKD needed hemodialysis after KT. Overall, patients achieved normalization of renal function at postoperative day 10.5 (range 4–32). Patients with PH-1 showed a delayed recovery of renal function compared with those with ARPKD. However, no statistically significant differences were observed, possibly due to the small sample size: 6.5 days (r 4–13.8) vs 22.5 days (r 4.8–56) in ARPKD and PH-1 patients, respectively (P 0,076). The long-term eGFR of LKT recipients were excellent, with a median filtration rate of 83.1 ± 12.5, 75.0 ± 15.1, 73.4 ±11.2 and 70.2 ± 7.4 ml/min/1.73 m^2 at 1, 3, 5, and 10 years, respectively. No differences were observed between the indication of LKT and posttransplant evolution of eGFR (Fig. 1).

Posttransplant hepatic function

One patient presented chronic liver rejection with a severe ductopenia 1 year after rapamycin at 1 mg/m^2/day once a day was started, with an improved liver function after 6 months. At the end of the follow-up, the patient presented normal blood test and biopsy with normal portal/biliary duct ratio.

Fig. 1 Glomerular filtration rate evolution. *LKT* liver–kidney transplant, *PH-1* primary hyperoxaluria type 1, *eGFR* estimated glomerular filtration, *ARPKD* autosomal polycystic kidney disease

Posttransplant morbidity

Renal post-LKT morbidity

One PH-1 patient presented thrombosis of a renal artery branch and developed severe hypertension and kidney dysfunction that led to renal retransplantation 12 months after the first transplant. Another patient presented chronic rejection of the renal graft requiring renal retransplantation 10 years after the LKT. Two patients presented BK virus primoinfection; both were treated with cidofovir, and immunosuppression was changed to rapamycin-based therapy. One patient presented viral clearance with total renal function recovery. The other presented progressive renal dysfunction with severe tubulopathy and is on the waiting list for kidney retransplantation. Patients with LKT tended to present a lower risk of acute kidney rejection than those who received an isolated KT (7.2% vs 30.4% respectively; $P < 0.07$).

Hepatic post-LKT morbidity

One of 14 (7.1%) patients presented early hepatic thrombosis in the postoperative period, which resolved with interventional radiology. Four of 14 (28.6%) patients presented biopsy-proven hepatic acute cellular rejection, all of whom were treated successfully with corticoid overload and immunosuppression optimization. There were no statistically significant differences regarding acute liver rejection episodes between patients who underwent LKT and isolated LT (28.5% vs 25.7%, respectively; $p < 0.76$). All patients with liver rejection were pre-LKT sensitized (two highly sensitized).

Hepatic and kidney graft survival

Kidney graft survival at 1, 3, and 5 years were 92.9%, 85.7%, 85.7%, respectively. Causes of the renal failure were thrombosis of the renal artery and chronic rejection, respectively. No significant differences were observed between disease groups. No patient required hepatic retrasplantation due to graft lost during the follow-up.

Mortality

One patient died due to sepsis secondary to adenovirus infection at 265 days post-LKT. Patient survival was 92.9% at 1, 3, and 5 years after LKT.

Discussion

We report the long-term outcome of 14 LKT performed in our center over 16 years. LKT forms a small proportion of all LT (8.0%) and KT (7.7%) performed during this time in our center. Overall patient survival rate of 92.9% at 1, 3, and 5 years are better than those reported in adults [15]. This excellent short- and long-term survival is comparable with that in patients who underwent single LT or KT in our institution.

The main indications for LKT in children are variants of PH-1 and polycystic disease associated with end-stage organ failure [7]. PH-1 is a rare disorder of oxalate metabolism, of autosomal recessive inheritance, caused by liver microsomal deficiency of alanine glycoxilate transaminase. This leads to overproduction of oxalate, which must be excreted by kidneys. Hyperoxaluria results in nephrocalcinosis and urolithiasis, which causes renal insufficiency [16]. Apart from the isolated metabolic defect, liver function was normal, but KT alone fails because of recurrent disease in the kidney allograft [17]. In theory, in PH-1 patients, pre-emptive LT is the appropriate therapy [18] but is rarely possible because patients are usually diagnosed or referred once renal failure develops. Moreover, in severe forms of the disease, when eGFR falls < 40 ml/min/m^2, systemic deposition of oxalate crystals may occur, especially in heart, cornea, and brain. Therefore, LKT should be considered when eGFR falls between 20 and 40 ml/min/m^2 [16]. In the series

reported here, this could not be achieved, and children had severe, advanced renal disease at the time of transplant (eGFR < 15 ml/min/m^2), and all patients were under hemodialysis prior to LKT. Perera et al. [17] demonstrated that patients with PH-1 presented a significantly slower recovery of eGFR after LKT than patients transplanted for other reasons. They observed in renal biopsies that increased oxalate excretion in the early posttransplant period tends to deposit oxalate crystals, and this may have an impact on eventual graft function. That could explain the slow rate of posttransplant renal function improvement (6.5 days in patients with ARPKD and 22.5 days in patients with PH-1) despite of the use of continuous venovenous hemodiafiltration systems the first 3 days after transplantation. Although differences are apparently huge, they may not have reached statistical significance due to the small sample size.

Taking into account that the low weight of one PH-1 patient (7 kg) advised against LKT, a nonsimultaneous first-recipient LT was carried out . Complications associated with the accumulation of oxalic acid in heart and cornea were thus avoided. Two months later, a KT was successfully performed. To date, due to limited experience, there is no evidence that supports this approach, but there is a strong biochemical rationale [19]. We also changed posttransplant management in this patient, and, to ensure removal of oxalic acid, implemented aggressive fluid management, with fluid intake 3 L/m^2 per day plus high-volume hemodiafiltration in combination with citrate orally was started [17].

We also report a significantly lower rate of acute kidney cellular rejection episodes in recipients of LKT vs isolated KT during the study period. Similar findings were reported by Fong et al. [20], supporting the theory that the liver provides immunologic protection to the kidney. Some authors suggest that liver allograft provides renal graft immunoprotection if both organs are transplanted simultaneously but not for kidneys transplanted subsequently [21]. This approach has not been assessed in our population because of the small sample size.

The rate of liver rejection was similar of that observed in isolated LT in our center. However, it is important to highlight that four of six pre-LKT-sensitized patient presented acute liver but not kidney rejection. In no hepatic rejection episode was posttransplant DSA detected. One patient presented chronic rejection without response to conventional immunosuppression (tacrolimus, mycophenolate mofetil, and methylprednisolone). Although studies in pediatric solid-organ recipients using rapamycin are rare, they contain valuable data regarding treatment for chronic allograft rejection in the adult population [22]. Following that data, rapamycin at a dose of 1 mg/m^2/day once a day was started, and the patient experienced good hepatic evolution, with blood tests and histological normalization until the last follow-up.

Only one patient developed posttransplant DSA without any signs of graft dysfunction. Nevertheless, DSA was again negative 1 month later and continued so after 24 months. This relatively short follow-up after DSA positivity prevents determination of the real impact of autoantibodies. In all sensitized and highly sensitized patients, pretransplant DSA showed a negative value at the end of the follow-up. In terms of ARPKD, early results of isolated KT were dominated by high morbidity, mainly because of severe recurrent cholangitis [23, 24]. LKT should be a reasonable approach, but outcome data are scarce, especially in children [25]. The decision to perform a KT is relatively clear. Renal phenotype is easy to follow-up, and renal replacement therapy was often initiated before renal transplant. Nevertheless, there is no consensus regarding optimal LT strategy for ARPKD [26, 27]. In most cases, liver disease is mild, with preserved synthetic function. Thus, isolated KT is usually performed in the setting of ESRD. However, Davis et al. reported a higher incidence of sepsis-related mortality in recipients of an isolated KT with hepatorenal fibrocystic diseases [28]. In our series, three patients with ESRD and initially with minor liver disease received a previous single kidney transplant. These patients were followed for liver behavior. Sepsis due to ascending cholangitis and portal hypertension with ESRD led to LKT at 1, 6, and 8 years after the first single transplant. Among the 27 patients followed in our hospital with an ARPKD, five received an isolated KT and experienced no infectious complications.

In the patient with portal hypertension and liver fibrosis in combination with ESRD, a portosystemic shunt prior to KT or LKT was discussed as an alternative, but the literature is controversial [29]. Among our patients, a splenorenal shunt was performed prior to LT in one case, because the patient presented a severe portal hypertension with bleeding of esophageal varices. After the shunt, no other episodes of variceal bleeding occurred, and the patient was successfully transplanted.

At our institution, we now perform LKT in cases of severe portal hypertension or repeated cholangitis and ESRD, but the optimal approach has not been evaluated in a systematic manner. In conclusion, long-term results of LKT in children are encouraging, being comparable with those obtained with isolated LT. The Results are excellent, especially if patients are evaluated and listed before they become critically ill or present systemic manifestation of subsequent metabolic disease. In our study, patients with PH-1 tended to experience slower eGFR recovery than patients with ARPKD.

References

1. Davis CL, Feng S, Sung R, Wong F, Goodrich NP, Melton LB, Reddy KR, Guidinger MK, Wilkinson A, Lake J (2007) Simultaneous liver–kidney transplantation: evaluation to decision making. Am J Transplant 7(7):1702–1709

2. Eason JD, Gonwa TA, Davis CL, Sung RS, Gerber D, Bloom RD (2008) Proceedings of consensus conference on simultaneous liver kidney transplantation (SLK). Am J Transplant 8(11):2243–2251

3. Freeman RB, Wiesner RH, Harper A, SV MD, Lake J, Edwards E, Merion R, Wolfe R, Turcotte J, Teperman L, UNOS/OPTN Liver Disease Severity Score, UNOS/OPTN Liver and Intestine, and UNOS/OPTN (2002) The new liver allocation system: moving toward evidence-based transplantation policy. Liver Transpl 8(9):851–858

4. Jalanko H, Pakarinen M (2014) Combined liver and kidney transplantation in children. Pediatr Nephrol 29(5):805–814 **quiz 812**

5. Otte JB (2002) History of pediatric liver transplantation. Where are we coming from? Where do we stand? Pediatr Transplant 6(5):378–387

6. Burdelski M, Nolkemper D, Ganschow R, Sturm E, Malago M, Rogiers X, Brölsch CE (1999) Liver transplantation in children: long-term outcome and quality of life. Eur J Pediatr 58(Suppl 2):S34–S42

7. Chava SP, Singh B, Pal S, Dhawan A, Heaton ND (2009) Indications for combined liver and kidney transplantation in children. Pediatr Transplant 13(6):661–669

8. Gao A, Cachat F, Faouzi M, Bardy D, Mosig D, Meyrat BJ, Girardin E, Chehade H (2013) Comparison of the glomerular filtration rate in children by the new revised Schwartz formula and a new generalized formula. Kidney Int 83(3):524–530

9. Demetris A, Adams D, Bellamy C, Blakolmer K, Clouston A, Dhillon AP, Fung J, Gouw A, Gustafsson B, Haga H, Harrison D, Hart J, Hubscher S, Jaffe R, Khettry U, Lassman C, Lewin K, Martinez O, Nakazawa Y, Neil D, Pappo O, Parizhskaya M, Randhawa P, Rasoul-Rockenschaub S, Reinholt F, Reynes M, Robert M, Tsamandas A, Wanless I, Wiesner R, Wernerson A, Wrba F, Wyatt J, Yamabe H (2000) Update of the international Banff schema for liver allograft rejection: working recommendations for the histopathologic staging and reporting of chronic rejection. An international panel. Hepatology 31(3):792–799

10. Taner T, Gandhi MJ, Sanderson SO, Poterucha CR, De Goey SR, Stegall MD, Heimbach JK (2012) Prevalence, course and impact of HLA donor-specific antibodies in liver transplantation in the first year. Am J Transplant 12(6):1504–1510

11. Gloor JM, DeGoey S, Ploeger N, Gebel H, Bray R, Moore SB, Dean PG, Stegall MD (2004) Persistence of low levels of alloantibody after desensitization in crossmatch-positive living-donor kidney transplantation. Transplantation 78(2):221–227

12. Marfo K, Lu A, Ling M, Akalin E (2011) Desensitization protocols and their outcome. Clin J Am Soc Nephrol 6(4):922–936

13. Margarit C, Lázaro JL, Hidalgo E, Balsells J, Murio E, Charco R, Revhaug A, Mora A, Cortés C (1998) Cross-clamping of the three hepatic veins in the piggyback technique is a safe and well tolerated procedure. Transpl Int 11(Suppl 1):S248–S250

14. Bueno J, Escartín A, Balsells J, Margarit C (2007) Intraoperative flow measurement of native liver and allograft during orthotopic liver transplantation in children. Transplant Proc 39(7):2278–2279

15. Chava SP, Singh B, Stangou A, , Battula N, Bowles M, O'Grady J, Rela M, Heaton ND (2010) Simultaneous combined liver and kidney transplantation: a single center experience. Clin Transpl 24(3):E62-E68

16. Cochat P, Groothoff J (2013) Primary hyperoxaluria type 1: practical and ethical issues. Pediatr Nephrol 28(12):2273–2281

17. Perera MT, McKiernan PJ, Sharif K, Milford DV, Lloyd C, Mayer DA, Kelly DA, Mirza DF (2009) Renal function recovery in children undergoing combined liver kidney transplants. Transplantation 87(10):1584–1589

18. Shapiro R, Weismann I, Mandel H, Eisenstein B, Ben-Ari Z, Bar-Nathan N, Zehavi I, Dinari G, Mor E (2001) Primary hyperoxaluria type 1: improved outcome with timely liver transplantation: a single-center report of 36 children. Transplantation 72(3):428–432

19. Cochat P, Liutkus A, Fargue S, Basmaison O, Ranchin B, Rolland M-O (2006) Primary hyperoxaluria type 1: still challenging! Pediatr Nephrol 21(8):1075–1081

20. Fong T-L, Bunnapradist S, Jordan SC, Selby RR, Cho YW (2003) Analysis of the united network for organ sharing database comparing renal allografts and patient survival in combined liver–kidney transplantation with the contralateral allografts in kidney alone or kidney-pancreas transplantation. Transplantation 76(2):348–353

21. Simpson N, Cho YW, Cicciarelli JC, Selby RR, Fong T-L (2006) Comparison of renal allograft outcomes in combined liver–kidney transplantation versus subsequent kidney transplantation in liver transplant recipients: analysis of UNOS database. Transplantation 82(10):1298–1303

22. Kniepiess D, Iberer F, Grasser B, Schaffellner S, Tscheliessnigg KH (2003) Sirolimus and mycophenolate mofetil after liver transplantation. Transpl Int 16:504–509

23. Chapal M, Debout A, Dufay A, Salomon R, Roussey G, Burtey S, Launay EA, Vigneau C, Blancho G, Loirat C, Hourmant M, Fakhouri F (2012) Kidney and liver transplantation in patients with autosomal recessive polycystic kidney disease: a multicentric study. Nephrol Dial Transplant 27(5):2083–2038

24. Khan K, Schwarzenberg SJ, Sharp HL, Matas AJ, Chavers BM (2002) Morbidity from congenital hepatic fibrosis after renal transplantation for autosomal recessive polycystic kidney disease. Am J Transplant 2(4):360–365

25. Ueno T, Barri YM, Netto GJ, Martin A, Onaca N, Sanchez EQ, Chinnakotla S, Randall HB, Dawson S, Levy MF, Goldstein RM, Klintmalm GB (2006) Liver and kidney transplantation for polycystic liver and kidney-renal function and outcome. Transplantation 82(4):501–507

26. Srinath A, Shneider BL (2012) Congenital hepatic fibrosis and autosomal recessive polycystic kidney disease. J Pediatr Gastroenterol Nutr 54(5):580–587

27. Shneider BL, Magid MS (2005) Liver disease in autosomal recessive polycystic kidney disease. Pediatr Transplant 9(5):634–639

28. Davis ID, Ho M, Hupertz V, Avner ED (2003) Survival of childhood polycystic kidney disease following renal transplantation: the impact of advanced hepatobiliary disease. Pediatr Transplant 7(5):364–369

29. Brinkert F, Lehnhardt A, Montoya C, Helmke K, Schaefer H, Fischer L, Nashan B, Bergmann C, Ganschow R, Kemper MJ (2013) Combined liver–kidney transplantation for children with autosomal recessive polycystic kidney disease (ARPKD): indication and outcome. Transpl Int 26(6s):640–650