









Good outcomes after repeated pediatric liver retransplantations: A justified procedure even in times of organ shortage

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Abstract

Background: Pediatric liver transplantations generally represent advanced surgery for selected patients. In case of acute or chronic graft failure, biliary or vessel complications, a retransplantation (reLT) can be necessary. In these situations massive adhesions, critical patient condition or lack of good vessels for anastomosis often are problematic.

Methods: Between 2008 and 2021, 208 pediatric patients received a liver transplantation at our center. Retrospectively, all cases with at least one retransplantation were identified and stored in a database. Indication, intra- and postoperative course and overall survival (OS) were analyzed.

Results: Altogether 31 patients (14.9%) received a reLT. In 22 cases only one reLT was done, 8 patients received 2 reLTs and 1 patient needed a fourth graft. Median age for primary transplantation, first, second and third reLT was 14 (range: 1–192 months), 60.5 (range: 1–215 months), 58.5 (range: 14–131 months) and 67 months, respectively. Although biliary atresia (42%) and acute liver failure (23%) represented the main indications for the primary liver transplantation, acute and chronic graft failure (1st reLT: 36%, 2nd reLT: 38%), hepatic artery thrombosis (1st reLT: 29%, 2nd reLT: 25%, 3rd reLT: 100%) and biliary complications (1st reLT: 26%, 2nd reLT: 37%) were the most frequent indications for reLT. OS was 81.8% for patients with 1 reLT, 87.5% with 2 reLTs and 100% with 3 reLTs.

Conclusion: Pediatric liver retransplantation is possible with a good outcome even after multiple retransplantations in specialized centers. Nevertheless, careful patient and graft selection, as well as good preoperative conditioning, are essential.

Abbreviations: AKI, acute kidney injury; C.diff, clostridium difficile; CIT, cold ischemic time; cm, centimeter; CMV, cytomegalovirus; d, day; EC, red blood cell concentrate; FFP, fresh frozen plasma; Fig, figure; GI, gastrointestinal; GRWR, graft recipient weight ratio; HU, high urgency; ICU, intensive care unit; INR, international normalized ratio; kg, kilogram; LT, liver transplantation; MELD, model of end-stage liver disease; mg/dL, milligram per deciliter; min, minutes; OS, Overall survival; PELD, pediatric end-stage liver disease; PFIC, progressive familial intrahepatic cholestasis; reLT, liver retransplantation; Tab, table; TC, platelet concentrate; WIT, warm ischemia time.

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KEYWORDS

complications of liver transplantation, liver transplant, pediatric liver transplantation

1 | INTRODUCTION

Liver transplantation is the only curative option for pediatric recipients with end-stage liver disease; high technical skills and careful donor selection are critical.^{1–5} Reliver transplantation (reLT) is necessary in cases of primary nonfunction, acute or chronic rejection, chronic hepatic fibrosis and biliary or vessel complications.^{1–15} In previous studies, reLT for pediatric patients range from 9% to 29%.^{1–8} From a surgical perspective, reLT can be challenging due to massive adhesions, critical patient condition and lack of appropriate vessels for anastomosis.^{5–9} Given the shortage of donor organs and reportedly reduced survival rates for pediatric reLT, indications for pediatric reLT are discussed controversially.^{1,2,5–7} Indeed, because improved patient outcomes have been achieved by better perioperative management and modern immunosuppression regimens,^{1,7,8} multiple reLTs for one recipient are uncommon. As a result of donor organ shortages, and the ethical discussion of organ allocation, it is critical to better understand the problems that come along with reLT and outcomes for these critical patients.

We therefore analyzed in this single center study, despite all challenges, whether pediatric reLT is a safe procedure with good long-term outcomes for these complicated patients.

2 | METHODS

The University Children's Hospital Regensburg (KUNO) database for liver transplantation and liver re-transplantations for patients <18 years was retrospectively reviewed between 2008 and 2021. The study was approved by the Ethics Committee of the University Regensburg (Nr. 21–2536–104).

Data were obtained from patient medical records and laboratory notes. For the analysis, patient demographics, indications for LT and reLT, graft type, operative times, WIT, CIT, and pre-op, early postoperative laboratory markers (post op day 3, 7), and laboratory markers at last follow-up (median follow-up 79 months) were obtained. Early reLT was defined as <1 month after the first transplantation, and considered a late reLT thereafter (>1 month). In some cases, primary transplantation was performed at another transplant center.

Post-operative complications were graded according to the Clavien–Dindo Classification with five severity grades, Grade I–V: I (any deviation from the normal), II (requiring pharmacological treatment), III (requiring surgical, endoscopic or radiological intervention), IV (life threatening complications), and V (death of the patient).¹⁶

In addition to the model for end stage liver disease (MELD) score, the pediatric end-stage liver disease (PELD) score for children with chronic liver disease was used to prioritize children awaiting liver

transplantation by Eurotransplant. The PELD score includes the patient's age, bilirubin, albumin and INR.¹⁷

The data were stored in an Excel database. The study results are only considered as descriptive, since a statistical analysis could not be given adequate power with this limited patient cohort. Graft and patient survival rates were calculated with Kaplan–Meier curves and expressed as a median value.

2.1 | Patients

Grafts from living and post mortal brain-dead donation were used, as well as full size organs and transplantation with technical variants (reduced size, split grafts, auxiliary transplantation). Immunosuppression after primary LT and most reLTs included basiliximab (d0 and d4), prednisolone and cyclosporine A; in some cases, cyclosporine was switched to tacrolimus after immunological graft rejection.

3 | RESULTS

3.1 | Patient characteristics

At our center, 31 of 208 (14.9%) pediatric patients received one or more reLTs. 22 (71%) received only one reLT, 8 (25.8%) patients received two reLT and 1 (3.2%) patient received three reLTs.

Median age at primary transplantation was 14 months with a median height of 72.5 cm and median weight of 9.2 kg. The first, second and third reLTs were performed at similar median ages of 60.5, 58.5 and 67 months, and a comparable median height (105.5, 104 and 104 cm) and weight (17.8, 20 and 20 kg). Furthermore, height adjusted weight percentile for recipients of the 1st, 2nd and 3rd reLT was in median 34.5, 54.4 and 94.7, respectively. The equivalent z-scores were –0.35, 0.15 and 1.6.

As expected, the urgency and critical condition increased with each LT as indicated by a median PELD score of 28 at first reLT and 36 at second reLT. High urgency status was assigned in 8 (25.8%) cases at primary transplantation, and 13 (41.9%) cases at first reLT, 4 (50%) cases at second reLT and 1 case at third reLT (Table 1).

3.2 | Indication for LT and reLT

Main indications for primary liver transplantation were biliary atresia (42%), acute liver failure (23%) and metabolic diseases (16%). Main indications changed for reLT, where chronic or acute graft failure (1st reLT: 36%, 2nd reLT: 38%), hepatic artery

TABLE 1 Patient characteristics.

	Primary LT		1. reLT		2. reLT		3. reLT ^a	
Age, months (median, range)	14 (1–192)		60.5 (1–215)		58.5 (14–131)		67	
Height, cm (median, range)	72.5 (49–161)		105.5 (49–177)		104 (70–160)		104	
Weight, kg (median, range)	9.1 (2.4–62)		17.8 (2.4–62)		20 (8–48)		20	
Weight [height adjusted]- Percentile (median, range)	39.4 (0.1–95.4)		34.5 (0.1–97.9)		54.4 (1.3–94.7)		94.7	
Weight [height adjusted]- z-score (median, range)	−0.3 (−3.1–1.7)		−0.35 (−3.1–2.0)		0.15 (−2.2–1.6)		1.6	
Meld-Score (median, range)	LAB	PED	LAB	PED	LAB	PED	LAB	PED
	18.5	30	12	29	16	36	30	40
	(6–38)	(22–40)	(6–26)	(22–40)	(10–30)	(20–40)		
HU-Status (%)	8 (25.8)		13 (41.9)		4 (50)		1	
Blood group (%)								
AB	2 (6.5)		2 (6.5)		0 (0)		0	
A	7 (22.5)		7 (22.5)		1 (12.5)		0	
B	8 (25.8)		8 (25.8)		3 (37.5)		0	
O	14 (45.2)		14 (45.2)		4 (50)		1	
Graft types (%)								
Whole	6 (19.4)		10 (32.3)		3 (37.5)		0	
Auxiliary	2 (6.5)		1 (3.2)		0 (0)		0	
Living donation	12 (38.7)		5 (16.1)		1 (12.5)		0	
Split	25 (80.6)		21 (67.7)		5 (62.5)		1	
GRWR, % (median, range)	3.9 (0.7–9.9)		2.8 (1.3–7.6)		2.7 (1.5–5.6)		1.8	

^aBecause only one patient received a third reLT no range specified.

thrombosis (1st reLT: 29%, 2nd reLT: 25%, 3rd reLT: 100%) and biliary complications (1st reLT: 26%, 2nd reLT: 37%) were most frequent (Figure 1).

Early (<1 months) reLT was performed in 42.5% patients with acute graft failure and hepatic artery thrombosis being the main indications. Additionally, HU-status was assigned more often in early (94.1%) versus late (8.7%) reLT.

3.3 | Grafts and operative items

The primary liver transplantation was done using a living related donor in 12 cases (38.7%), and in 19 cases (61.3%) by post-mortal donation (Table 1). In case of early or late reLT, living donations decreased to 5% (early reLT) and 10% (late reLT). Furthermore, whole liver grafts were used in 6 cases (19.4%) at primary LT, in 4 cases (10%) at early reLT and in 10 cases (25%) at late reLT. An auxiliary transplantation was done in 2 cases at primary LT, and 1 case at late reLT. The indication for auxiliary transplantation was a Crigler-Najjar-syndrome for one case of primary LT and a late reLT, as well as in the case of a small graft size in a critical patient with acute liver failure.

Complete median operation time was 306 min at primary LT and, as expected, the late 1st and late 2nd reLT had slightly longer median operative times (354 min and 327 min) due to more intrabdominal adhesions. In comparison, early reLT surgery was faster than primary LT, with 204 min for the 1st early reLT and 3rd reLT,

and 234 min for the 2nd early reLT. This might be due an easier hepatectomy and fewer adhesions. Cold ischemia time was longer at early and late 1st reLT as well as early 2nd reLT, compared to primary LT (Figure 2).

Although technical difficulties were reported in 10 cases (32.3%) at first reLT, 3 cases (37.5%) at second reLT and during the 1 third reLT, the median warm ischemia time (WIT) was similar for primary LT compared to early and late reLT (Figure 2). Technical difficulties consisted mostly of vessel-related difficulties such as artery interposition or revision of vessel anastomoses (Table 2). These data show that although technical difficulties occurred, implantation times did not appreciably differ. Intraoperative transfusion of blood products such as red blood cell concentrates (EC), platelet concentrates (TC) or fresh frozen plasma (FFP) were needed similarly with primary LT, 1st reLT or 2nd reLT. In detail, the transfusion of in median 3 EC's and 6.5 FFP's was necessary during the primary LT. In comparison, at 1st reLT 2.5 EC's and 4.5 FFP's and at 2nd reLT 2.5 EC's and 3 FFP's were needed. During the 3rd reLT, 2 EC's and 15 FFP's were transfused. Platelets were given only in a few cases during all transplants.

3.4 | Postoperative course and follow up

As postoperative (days 3 and 7) liver function parameters including serum bilirubin levels, factor V and INR were measured preoperatively, as well as kidney function by creatinine. Here,

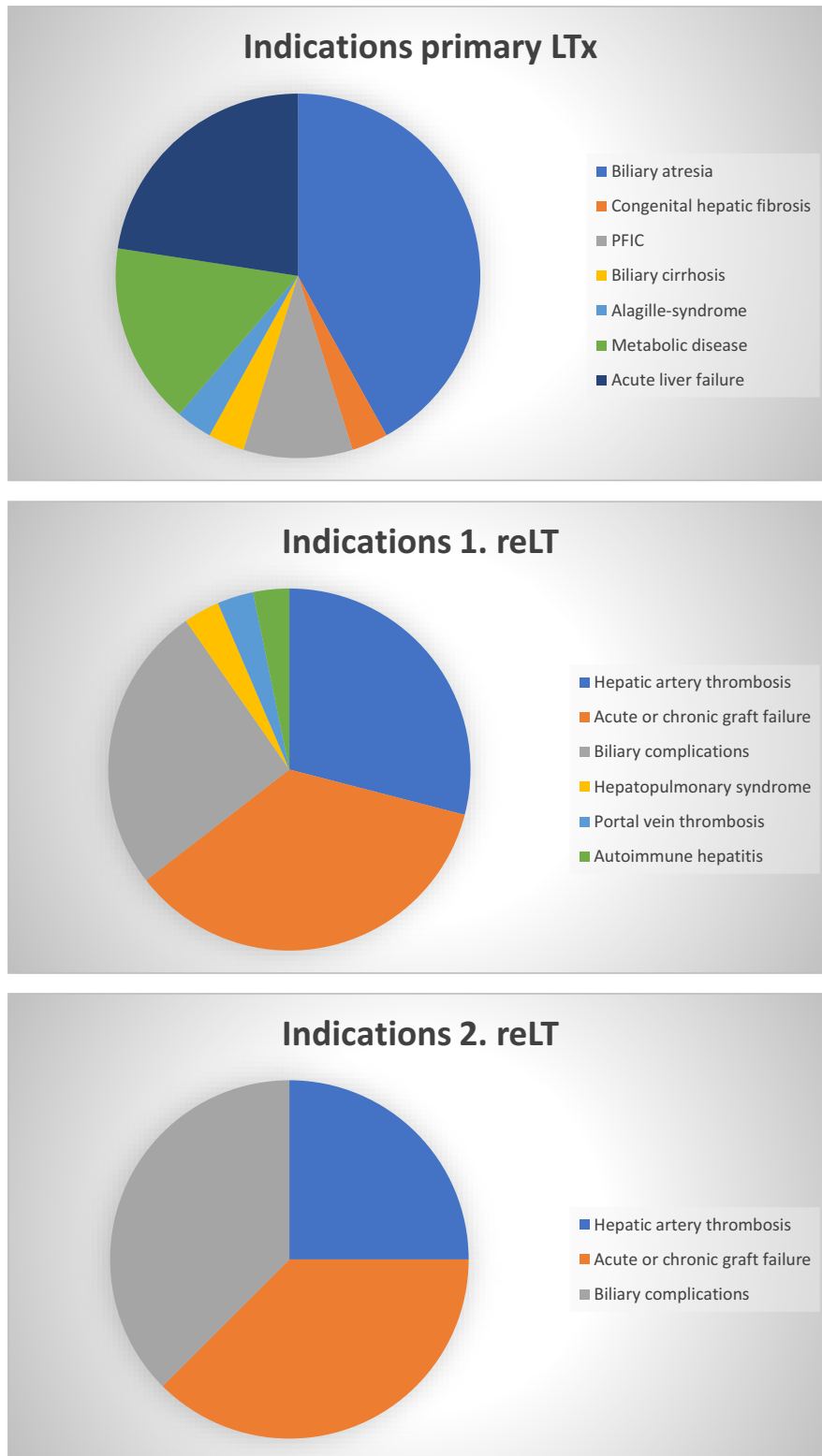


FIGURE 1 Shown are the indications for primary LT, first reLT and second reLT. Biliary atresia, acute liver failure and metabolic diseases were the most frequent indications for primary LT. Hepatic artery thrombosis, acute or chronic graft failure and biliary complications for first and second reLT.

decreasing bilirubin and INR values, as well as rising factor V serum levels, generally indicate good liver function after reLT, and no differences were found comparing first, second and third reLT. Furthermore, no differences in renal function were observed. At present, almost all patients have normal bilirubin, renal and INR values (Figure 3).

Complications of grade 3 or higher, according to the Clavien-Dindo classification, occurred in 82.4% of cases after early, and 75% after late, reLT with a cumulative occurrence of 78.1% over all cases (Table 3). Acute cellular rejection occurred in 38.5% of the cases after primary LT, 51.6% after 1st reLT, 37.5% after 2nd reLT; acute rejection also occurred in the 3rd reLT.

FIGURE 2 Shown are warm ischemia times, cold ischemia times and complete operation times for primary LT, as well as first, second and third reLTs. Early and late reLTs are listed separately. WIT was very similar between primary LT and all reLTs. Although primary LT and late reLTs showed no relevant difference in complete operation time, early reLTs were significantly shorter procedures.

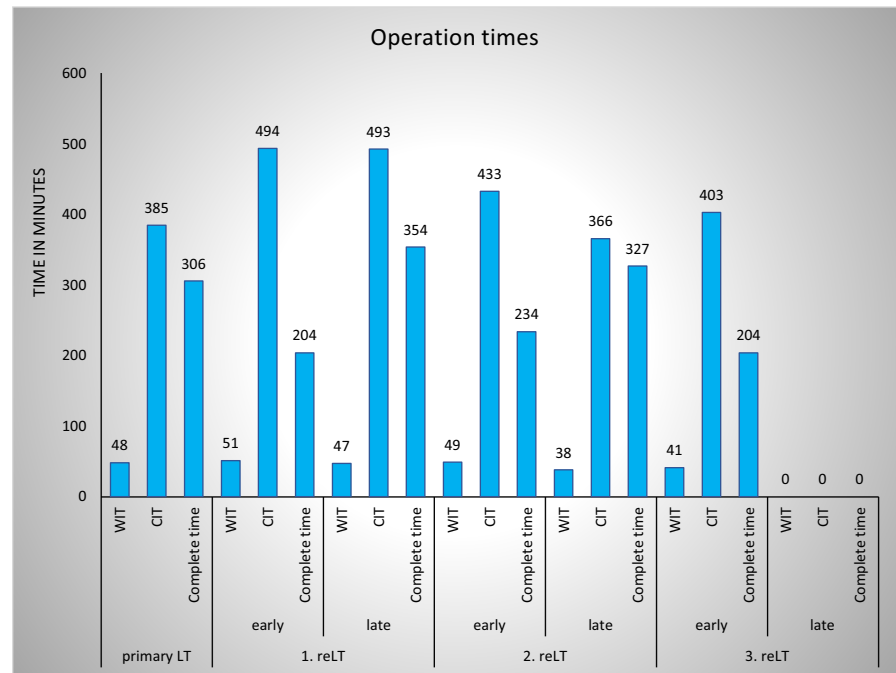


TABLE 2 Technical problems.

	1. reLT	2. reLT	3. reLT
Artery interposition	3	3	1
Revision artery anastomosis	2	-	-
Portal vein thrombosis	1	-	-
Revision cava anastomosis	3	-	-
Large-for-size graft	1	-	-

All patients had ICU stays in median of 33 days after first reLT, 26 days after the second reLT and 43 days after the third reLT. Complete hospital stay until discharge was 78 days (median) after the first reLT, 74 days after the second reLT and 83 days after the third reLT. Interestingly, patients with an early reLT had a longer median ICU and complete hospital stay compared to late reLT; this showed a similar pattern for first and second reLT patients (first reLT: ICU: 37.5 vs. 18 days, complete: 109 vs. 69 days; second reLT: ICU: 26 vs. 12 days, complete: 98.5 vs. 74 days).

3.5 | Patient and graft survival

Median follow-up was 79 months (range: 0–180 months), with a median graft survival of 4 months after primary LT, 52 months after 1st reLT, 86.5 months after 2nd reLT and 123 months after 3rd reLT. OS was 81.8% for patients with 1 reLT, 87.5% with 2 reLTs and 100% for the patient with 3 reLTs. OS of all pediatric LT recipients at our center was 91% (Figure 4). Comparing the early reLT and late reLT groups, OS was 82.3% and 91.3%, respectively. In case of split grafts, OS was 80.8% compared to 100% after a whole liver transplantation.

4 | DISCUSSION

In this single center study, we investigated whether pediatric reLT is a safe procedure with good outcomes for these complicated patients. Our results show, despite all challenges in pediatric reLT, that patients receiving multiple reLT have excellent patients survival and have normal long-term liver and renal functions. We performed 31 reLT and observed survival rates over 80%, which indicates a clear outcome improvement over the last decade, compared to previous reported pediatric reLT patient survival of 60% in earlier times.^{1,5,6,11,13} The improved outcomes in pediatric LT are related to better perioperative treatment, a modern immunosuppression regimen and stricter patient selection. Furthermore, once patients are discharged from the hospital, a strict follow-up regime with monthly site visits initially following transplantation, and 6–12 month interval visits thereafter supporting excellent long-term liver and renal function for multiple reLT patients.

However, our data suggest that technical challenges do increase with repeated LT in pediatric patients. Arterial interponates and non-standard venous anastomosis were necessary in over 30% of our cases. Even with these complications at our center, we observed no differences in complete surgical procedure duration and WIT between the initial transplantation, first, second or third reLT. These results indicate that specialized high volume centers can perform reLT with a high surgical and technical standard, resulting good patient outcomes even after multiple reLTs. These findings are contrary to previous reported data where 2nd reLTs were associated with increased operative times.¹⁸

Early reLT, technical variant grafts and a PELD score >20 have been described as risk factors for reduced graft and patient survival.^{6–8} In case of early reLT and a high PELD score, a poorer patient condition and more urgent transplant indication can explain worse

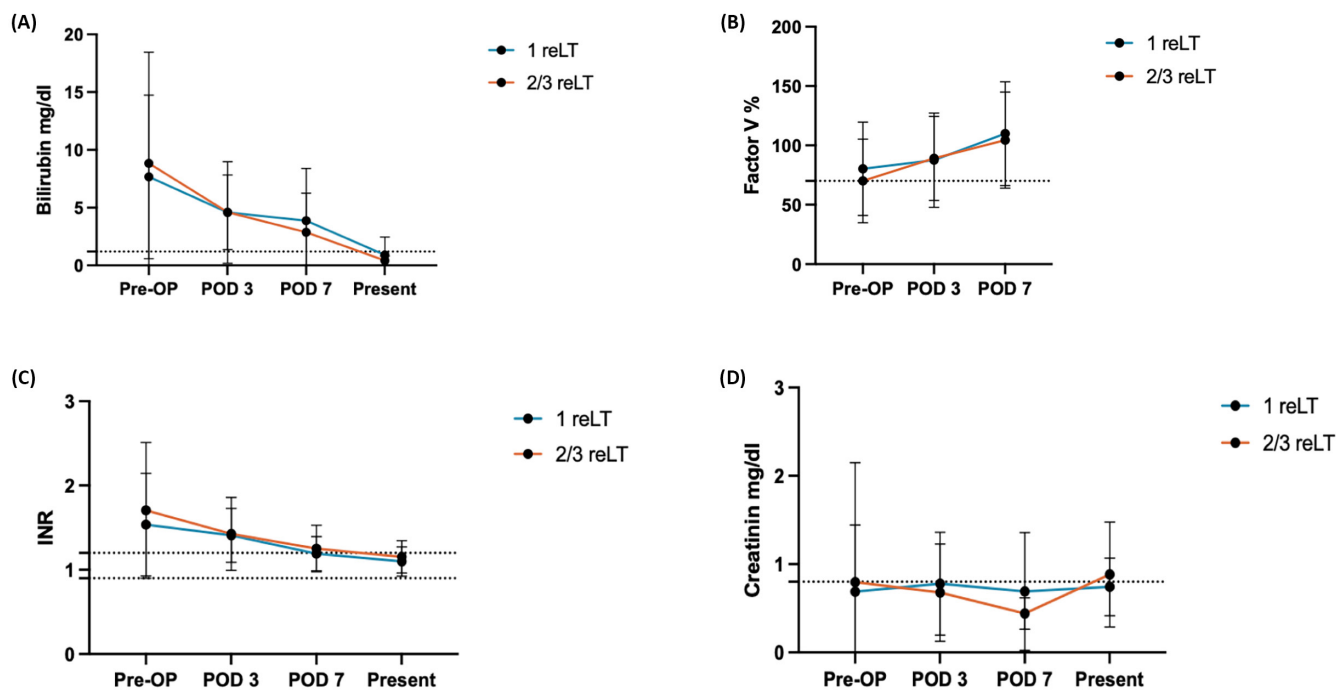


FIGURE 3 Shown are the values (norm marked with dotted line) for bilirubin (A), factor V (B), INR (C) and creatinine (D) preoperatively, at POD 3, POD 7 and present. Increasing factor V levels as well as decreasing INR and bilirubin values and normal creatinine levels over the first 7 days post-transplant indicate adequate graft function; this remains stable in the long-term follow-up. Factor V was only measured shortly after LT and not in the regular follow-up.

TABLE 3 Postoperative complications.

(A) Overview	
Secondary bleeding (<i>requiring transfusion</i>)	8 (19.5%)
Intraabdominal hematoma (<i>no transfusion</i>)	8 (19.5%)
GI-bleeding	6 (14.6%)
AKI with dialysis	5 (12.2%)
AKI without dialysis	6 (14.6%)
Acute rejection	14 (34.1%)
Delirium	4 (9.8%)
Cerebral seizure	4 (9.8%)
Cholangitis	9 (22%)
Biliary leakage	7 (17.1%)
Bile duct stenosis	5 (12.2%)
Small bowel perforation	5 (12.2%)
Gastroenteritis	1 (2.4%)
C. diff. Colititis	1 (2.4%)
Ileus	2 (4.8%)
Pancreatitis	2 (4.8%)
Portal vein thrombosis	3 (7.3%)
Stenosis/thrombosis of the hepatic artery	8 (19.5%)
Abdominal compartment syndrome	1 (2.4%)
Pneumonia	5 (12.2%)
Pleural effusion	8 (19.5%)
Pneumothorax	1 (2.4%)

Diaphragmatic hernia	1 (2.4%)	
Sepsis	6 (14.6%)	
CMV infection	10 (24.4%)	
Wound infection	5 (12.2%)	
Urinary tract infection	1 (2.4%)	
Seroma	2 (4.8%)	
Perihepatic abscess	2 (4.8%)	
Fascial dehiscence	1 (2.4%)	
Hemophagocytosis	1 (2.4%)	
(B) Clavien-Dindo Classification		
Grade I	4 (9.8%)	
Grade II	5 (12.2%)	
Grade IIIa	5 (12.2%)	
Grade IIIb	17 (41.5%)	
Grade IVa	4 (9.8%)	
Grade IVb	1 (2.4%)	
Grade V	5 (12.2%)	
	Early (n = 17)	
	Late (n = 24)	
(C) Complications early/late reLT		
Clavien-Dindo ≥ 3	14 (82.4%)	18 (75%)
Operative revision	9 (53%)	15 (62.5%)

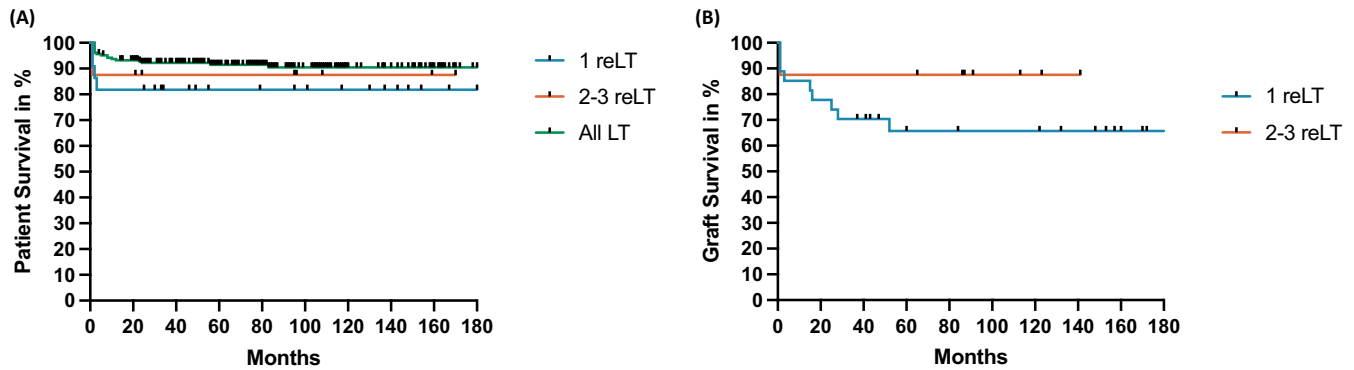


FIGURE 4 Shown are overall patient survival of all LT recipients, 1 reLT and 2–3 reLT (A) and graft survival (B). Excellent patient and graft survival was observed after 1 reLT, as well as after 2–3 reLTs.

patient outcomes.⁶ Critical patient condition in early reLTs in our study resulted in a longer ICU and complete hospital stay, compared to late reLTs. Furthermore, patients with critically urgent conditions showed a reduced overall survival (early 82.3% vs. late 91.3%), as well as recipients of a split liver graft (split 80.8% vs. full-size 100%).

Given the shortage of donor organs and reported reduced survival rates for pediatric reLT,^{5–9} indications for pediatric reLT are discussed controversially.^{1,2,5–7} Here we report long-term survival rates of >80%; despite critical patient situations, this survival rate reLT for pediatric recipients is similar to survival rates for adult recipients (76%–82%),¹⁹ which suggests justifiable use of organs even in this time of severe organ shortages. This is in accordance with a study from MR Couper et al., where 2nd reLT had similar 5-year survival rates to primary and 1st reLT.¹⁸ Indeed, in our study we show that pediatric liver reLT can be done safely and with good patient outcomes in a specialized center. Careful patient and graft selection, as well as good preoperative preparation, are essential for success.

In summary, our single center study shows that even after multiple reLT in critical pediatric patients, excellent long-term survival rates and normal liver and renal functions can be achieved. Therefore, we propose that a further discussion over prioritization of patients needing a first liver transplantation is in our opinion ethically debatable.

4.1 | Limitations

Our study shares the limitations common to all retrospective analyses. Biases like preoperative patient selection, different experience levels of performing surgeons and technical developments over the study period are possible. The experience of only one center is presented in this study. Furthermore, the study group was too small to perform a more rigorous statistical analysis.

AUTHOR CONTRIBUTIONS

Henrik Junger: participated in research design, data collection, data analysis, writing of the paper. Birgit Knoppke: participated in writing of the paper. Leonhard Schurr: participated in data analysis and writing of

the paper. Frank W. Brennfleck: participated in research design. Dirk Grothues: participated in patient information. Michael Melter: participated in writing of the paper. Edward K. Geissler: participated in writing of the paper. Hans J. Schlitt: participated in writing of the paper. Stefan M. Brunner: participated in research design, writing of the paper, contributed pictures. Markus Goetz: participated in research design, data collection, data analysis, writing of the paper.

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CONFLICT OF INTEREST STATEMENT

Author Birgit Knoppke is a member of the pediatric liver transplant working group (Germany), the authors Henrik Junger, Leonhard A. Schurr, Frank W. Brennfleck, Dirk Grothues, Michael Melter, Edward K. Geissler, Hans J. Schlitt, Stefan M. Brunner and Markus Goetz declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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