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Health-related quality of life after combined liver and kidney transplantation in children

Kaja Schmaeschke[1] | Susanne Lezius[2] | Enke Grabhorn[1] | Markus J. Kemper[3] |
Florian Brinkert[1] (iD)

[1]Pediatric Gastroenterology and Hepatology,
University Children's Hospital,
University Medical Center Hamburg-
Eppendorf, Hamburg, Germany

[2]Department of Medical Biometry and
Epidemiology, University Medical Center
Hamburg-Eppendorf, Hamburg, Germany

[3]Pediatric Nephrology, University Children's
Hospital, University Medical Center Hamburg-
Eppendorf, Hamburg, Germany

Correspondence
Florian Brinkert, Pediatric Gastroenterology
and Hepatology, University Medical Center
Hamburg-Eppendorf, Hamburg, Germany.
Email: f.brinkert@uke.de

Abstract

While reduced HRQOL following isolated organ transplantation has been previously reported, there are no data in the context of children following CLKT. Twenty-three children who underwent CLKT at our institution were included in the study. The indication for CLKT was PH1 in 13 patients and ARPKD in 10 patients. Quantification of HRQOL was facilitated through the use of the PedsQL 4.0 Generic Core Scale. The results of the study were compared to healthy children and published data of children who had undergone LTx or KTx. The CLKT samples' child self-report showed good HRQOL. No statistically significant difference was found between the patients with PH1 and patients with ARPKD (P=.4). Compared to healthy children, a significant difference in the total scale score, the physical health score, and the school functioning was reported. HRQOL did not differ significantly when compared to patients following isolated LTx or KTx. To improve HRQOL after CLKT, a focus on patients' physical health, educational performances, and overall quality of life is crucial. Thus, coordinated medical care across disciplines and psychological and social support is essential to achieve this goal.

KEYWORDS
children, combined liver-kidney transplantation, health-related quality of life, kidney transplantation, liver transplantation

1 | INTRODUCTION

In the past 40 years, advancement in transplantation medicine has been enormous. As a consequence, LTx and/or KTx in both pediatric and adult populations can be thought of as routine clinical practice.[1-3] CLKT can similarly be considered routine therapy in adults; however, CLKT in the pediatric population remains only possible in specialized centers where a highly trained multidisciplinary team is available.[4,5]

The diagnoses leading to this challenging procedure are often rare metabolic diseases leading to renal damage, including PH1, or diseases causing both renal and liver failure such as ARPKD.[6-8] In the United States, only 166 CLKT in children had been performed from 1988 to 2007.[9] In contrast, 600 LTx and 800 KTx are performed annually.[3,10,11]

In patients with PH1, if end-stage renal failure is present, a CLKT is the only curative therapeutic option and thus the clinical decision-making and therapeutic recommendation to the parents to perform a CLKT is reasonably straightforward.[6]

A more difficult scenario presents, however, for patients with ARPKD. Renal replacement therapy is often necessary due to the defective PKHD1 protein. The liver is also structurally affected demonstrating a defective remodeling of the ductal plate, abnormal portal

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veins, and progressive fibrosis of the portal tracts lead to severe portal hypertension. The metabolic function of the liver, however, is usually well preserved.[6] Consequently, a balanced assessment of conservative therapy options vs a CLKT is essential in the decision-making process.

Given the comparable immediate survivability, of growing interest is the broader question of functional patient outcome, including issues such as longer-term complications and QoL. Thinking prospectively, postoperative psychosocial performance (and impairment) could prove to be a significant factor when determining the best therapy option for these pediatric patients, specifically in the context of CLKT in children with ARPKD.

In general, short-term outcome after solid organ transplantation has reached survival rates of more than 90%. Thus, long-term complications are coming more and more into focus. Therefore, examination of HRQOL after solid organ transplantation has been addressed in the last 10-15 years. Currently, there exist data regarding HRQOL after almost all single solid organ transplantations.[3,12] Several studies did use the PedsQL questionnaire.[13-20]

After deceased donor liver transplantation in children, a significantly lower outcome in the overall, emotional, psychosocial, and school functioning score in comparison with a healthy control group has been published.[13,16] The same findings have been reported after living donor liver transplantation in children.[15]

It is well known that children with end-stage renal disease receiving dialysis report lower HRQOL compared to healthy controls and even compared to patients with a functioning kidney graft.[17] Haavisto et al. showed that there are no differences between heart-, liver-, and kidney-transplanted groups. But all of them scored significantly lower results for HRQOL in comparison with the control group, especially in the preadolescent (8-11 years) age group.[12]

Remarkably, CLKT patients were excluded from most of these studies.[12] This indicates that the authors expect different results in combined transplanted patients in comparison with single-organ-transplanted children. To this end, data regarding HRQOL following CLKT in pediatric populations are necessary. Overall, due to the complexity of the underlying congenital diseases and the required treatment, we assume that HRQOL of those patients is impaired compared to children after single-organ transplantation.

2 | PATIENTS AND METHODS

The PedsQL Generic Core Scale questionnaire, a well-proven and reliable measurement for HRQOL in children, was sent to all 25 families and their children, who had undergone CLKT in our center and survived at least 12 months between 1998 and 2014.[21-23] None of the CLKT patients were excluded from the study. The participants gave written informed consent and received an introduction on how to complete the questionnaire. The children were guided to complete the form as a self-report, and the parents were instructed to assess from the child's perspective. In cases where the patient was older than 18 years at the time of the survey, only the child's self-report questionnaire was completed.

2.1 | Measures

The 23-item measurement of the PedsQL Generic Core Scale 4.0 is divided in four subscales: (i) physical functioning (eight items), (ii) emotional functioning (five items), (iii) social functioning (five items), and (iv) school functioning (five items). The two formats of the questionnaire (one for the patient and one for the parents) were filled in separately. The items for both groups are identical; they simply differ in age-appropriate language and first- or third-person tense. The 23-item PedsQL child self-report is available for age groups 5-7, 8-12, 12-18, and 18-24 (young adult). Parent proxy-report asks the parents to assess the HRQOL of their children and is available for the age groups 2-4, 5-7, 8-12, and 12-18.

The participants were asked how much of a problem each of the different items has been during the last month (0=never, 1=almost never, 2=sometimes, 3=often, 4=almost always). Items are reverse-scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, and 4=0. Thus, a higher score indicates a better HRQOL.

The Psychosocial Score contains the items answered in the Emotional, Social, and School Function Scale. The Physical Health Summary Score contains the items answered in the Physical Function Scale. The Total Summary Health Score is the result of all edited items. The different mean scores were computed by taking the sum of the items divided by the number of items which were answered (this accounts for missing data).[22]

2.2 | Healthy controls

The sample of healthy children is extracted from a statewide State's children health insurance program (SCHIP) evaluation and the initial field test of the PedsQL 4.0.[21,22,24] Children and parents evaluated their HRQOL during general medical checkups at the physician's office or took part in a survey by mail or telephone. The total average age of the 4897 boys (51.1%) and 4668 girls (48.8%) was 7.84 years. For the child self-report, the average age of the 2810 boys (51.3%) and 2669 girls (48.7%) was 9.8 years.[24]

2.3 | Liver transplantation cohort

The LTx sample is based on a Study of Pediatric Liver Transplantation Registry (SPLIT).[13] Inclusion criteria were liver graft recipients between 2 and 18 years and a survival of at least 12 months after LTx. Child self-report was available for 363 participants and parent proxy-report for 869 participants. Both were available for 359 cases. For all participants, the average age of the 479 girls (54.9%) and 394 boys (45.1%) was 8.17 years. For child self-report, the average age of the 199 girls (54.8%) and 164 boys (45.2%) was 12.49 years. Median time from transplant to survey was 3.1 (1.68-5.32) years.

2.4 | Renal transplantation cohort

The KTx sample was achieved from a study comparing HRQOL in pediatric patients with end-stage renal disease.[13,14] Child self-report

TABLE 1 Baseline characteristics of the 23 CLKT patients

Pat ID	Sex	Diagnosis	Age at Tx	Weight at Tx	FU	GFR lfu	ReLKTx	ReLTx	Age at survey
P1	m	PH1	2.8	12.0	10.8	78			13
P2	f	PH1	8.2	22.0	9.2	105			17
P3	f	PH1	1.4	10.0	9.8	27			10
P4	m	ARPKD	15.9	53.0	7.4	45			23
P5	m	ARPKD	4	17.0	7.3	87			11
P6	m	PH1	1.6	9.0	7.6	33			8
P7	m	ARPKD	10.1	32.0	7.4	120			17
P8	f	PH1	8	17.0	6.9	D			14
P9	m	ARPKD	10.1	26.0	6.6	54			16
P10	m	PH1	1.5	9.0	6.0	53			7
P11	f	ARPKD	1.7	11.2	6.3	71			7
P12	f	ARPKD	6.5	17.0	5.6	57		2009	11
P13	m	PH1	1.4	12.6	4.2	D			5
P14	f	PH1	1.3	9.2	4.8	61			5
P15	m	PH1	13	30.0	4.0	74			17
P16	f	PH1	2.3	9.9	3.4	D	2011		5
P17	f	ARPKD	15	53.0	3.3	77			17
P18	m	PH1	12.5	52.0	2.3	74			14
P19	m	ARPKD	14.3	35.0	1.8	58		2013	15
P20	f	ARPKD	7.8	25.0	1.1	132			9
P21	m	ARPKD	9.8	28.3	1.6	92			10
P22	f	PH1	13.9	50.4	1.0	73			14
P23	m	PH1	14.2	51.9	1.0	56			14

FU: follow-up (years), GFR (mL/min/1.73 m^2), lfu: last follow-up value, Age at Tx (years), Weight at Tx (kg), Age at survey (years).

was available for 39 patients, and parent proxy-report was available for 45 patients. The average age of the children for child self-report was 14 years, and the average age for all participants was 12.8 years.

2.5 | Statistical analyses

The mean PedsQL 4.0 score was calculated for each subscale and for each patient sample. The mean scores of the CLKT sample were compared to the other three groups using independent-sample *t* test. For the primary outcome total scale score, the overall type I error rate was determined at the 0.016 level using the Bonferroni correction for multiple testing (separately for the child self- and parent proxy-report). The subscores were secondary outcomes, and therefore, no adjustment for multiple testing took place; α=0.05 was used. The effect size is a magnitude for the difference and was calculated by subtracting the mean scores and dividing through the pooled SD. Dimension for effect size is 0.2 as small, 0.5 as medium, and 0.8 as large.[13]

For analyzing the agreement of the child self- and parent proxy-report, the ICC was used. ICC is interpreted as ≤0.40 poor-to-fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 good agreement, and 0.81-1.00 excellent agreement.[18,25–27]

Scale internal consistency reliability was defined using the Cronbach's coefficient alpha.[22] Scales with a reliability of 0.70 or greater are recommended for comparing groups. A reliability of at least 0.90 is recommended for analyzing individual patient scale scores.[18] Statistical analyses were conducted using MS Excel (2010) and SPSS 22.0 for Windows.

3 | RESULTS

Two of the 27 patients transplanted at our institution died of infectious complications in the perioperative period and were not included in the study sample. Of the remaining 25 patients, 23 children and 22 parents/caregivers completed and returned the PedsQL 4.0 questionnaire resulting in capture rate of 92%. The patients were fairly evenly distributed for indication of transplant between PH1 and ARPKD. Slightly more males than females were enrolled in the study (Table 1). The median age of the children at the time of survey was 13.6 (5.6-23.3) years. Age groups are divided as follows: 5-7 (5); 8-12 (6); 13-18 (11); and 18-25 (1). The median time from transplantation to survey was 5.6 years with a range of 1-10.8 years. Three patients (two girls, one boy) were receiving dialysis again at the time of questionnaire completion. At last follow-up, the liver graft function was normal in

TABLE 2 Results for the PedsQL 4.0 child self-report and parent proxy-report of all four samples (CLKT, LTx, KTx, and healthy) divided for each subscale

	CLKT sample		LTx sample[13]		KTx sample[13,14]		Healthy sample[21-23]	
	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD	N
Child self-report								
Total score	77.81±13.81	23	77.21±14.28	363	78.94±14.24	39	83.84±12.65	5480
Physical	77.45±23.37	23	82.29±15.62	363	80.76±20.53	39	87.53±13.50	5470
Psychosocial	77.97±11.77	23	74.51±15.82	363	77.86±13.46	39	81.87±14.09	5469
Emotion	77.83±15.94	23	74.00±19.90	363	79.04±18.70	39	79.33±18.15	5468
Social	84.78±16.55	23	80.95±19.09	363	82.31±17.54	39	85.15±16.76	5455
School	71.25±18.36	23	68.53±18.56	363	72.31±16.13	39	81.12±16.45	5412
Parent proxy-report								
Total score	73.01±14.81	22	77.26±17.58	869	75.57±17.75	45	82.70±15.40	9430
Physical	72.71±23.65	22	79.33±22.07	869	78.38±24.65	45	84.48±19.51	9413
Psychosocial	73.18±13.6	22	75.72±17.33	869	74.14±17.50	45	81.65±15.22	9431
Emotion	72.5±19.56	22	73.27±19.28	869	75.67±18.36	45	81.31±16.50	9410
Social	80.91±20.39	22	78.99±20.63	869	78.56±22.20	45	83.70±19.43	9406
School	66.14±15.73	22	67.42±22.43	869	66.06±18.53	41	78.38±19.59	7898

N, number.

nearly all cases with a median aspartate aminotransferase of 27 (11-103) U/L. Only one patient was listed for a liver retransplant due to chronic cholangitis. The median eGFR (excluding the three patients on dialysis) according to the new Schwartz formula was 72 (27-132) mL/min/1.73 m^2.[28] Patients' characteristics of the CLKT sample are summarized in Table 1.

The results indicated as mean±SD, for the CLKT samples' child self-report and for the parent proxy-report, are given in Table 2. The total scale score was 77.8±13.8 for child self-report and 73.0±14.8 for parent proxy-report.

The lowest subscale mean was calculated for CLKT child self- and parent proxy-report in the school functioning scale (71.3 and 66.1). The three patients, requiring dialysis, scored lower than the other 20 CLKT children over all domains of the survey in both reports. Mean difference for the total scale is 16 for child self-report and 17 for parent proxy-report. A significant difference was shown in physical health for parent proxy- and child self-report with P=.003 and P=.01.

Furthermore, in both reports (children and parents) no statistically significant difference was found between the patients with PH1 and patients with ARPKD by comparison of the mean scores in all areas.

The majority of the internal correlation coefficient alpha comes very close to or exceeded the accepted standard of 0.7 for the child self- and parent proxy-report. In detail, the internal correlation coefficient alpha for parent proxy-report is 0.89 for the total scale, 0.90 for physical functioning, 0.80 for emotional functioning, 0.86 for social functioning, 0.60 for school functioning, and 0.82 for the psychosocial score. For child self-report, it is 0.85 for the total scale score, 0.89 for physical functioning, 0.55 for emotional functioning, 0.70 for social functioning, 0.70 for school functioning, and 0.71 for psychosocial functioning.[22]

3.1 | Parent/child agreement

For those 22 CLKT cases where both the child self-report and the parent proxy-report are available, an intraclass correlation coefficient was calculated across the PedsQL 4.0 Generic Core Scale resulting as follows: total scale score: 0.899; physical health score: 0.934; psychosocial health score: 0.842; emotion functioning: 0.902; social functioning: 0.866; and school functioning: 0.806. All intraclass correlation coefficients are in the excellent agreement range. However, across all scales and subscales of the PedsQL 4.0 the parents reported lower mean scores than their children.

Tables 2 and 3 show the CLKT sample in comparison with each sample group. A negative effect size means a higher average for the concerning scale in the comparison group than in the CLKT sample. The mean scores of all groups for child self-report are portrayed in Figure 1 and for parent proxy-report in Figure 2.

3.2 | Comparison to healthy controls

In comparison with the sample of healthy children, there is a significant difference in the child self-report in the total scale score with P=.020 (effect size=−0.5), the physical health score with P<.001 (effect size=−0.7), and the school functioning with P=.004 (effect size=−0.6). The total scale score is only significant at the 0.05 level, not at the Bonferroni correction. The other subscales do not show a significant difference. From the CLKT sample, 17.4% of the total scale, 8.7% of the psychosocial scale, 26.1% of the physical health scale, 17.4% of the emotional function scale, 13% of the social function scale, and 30.4% of the school function scale for child self-report scored at least 1 SD below the mean score of the sample of healthy children.

TABLE 3 Tabular listing of the respective P-values, effect sizes, and mean differences for each subscale and each sample compared to the CLKT sample

	LTx sample[13]			KTx sample[13,14]			Healthy sample[21-23]		
	P	Mean Δ	es	P	Mean Δ	es	P	Mean Δ	es
Child self-report									
Total score	.845	0.6	0.04	.761	−1.1	−0.08	.023	−6.0	−0.48
Physical	.165	−4.8	−0.30	.562	−3.3	−0.15	.000	−10.1	−0.74
Psychosocial	.303	3.5	0.22	.974	0.1	0.01	.185	−3.9	−0.28
Emotion	.366	3.8	0.19	.796	−1.2	−0.07	.692	−1.5	−0.08
Social	.348	3.8	0.20	.587	2.5	0.14	.916	−0.4	−0.02
School	.496	2.7	0.15	.813	−1.1	−0.06	.004	−9.9	−0.60
Parent proxy-report									
Total score	.261	−4.3	−0.24	.561	−2.6	−0.15	.003	−9.7	−0.63
Physical	.166	−6.6	−0.30	.374	−5.7	−0.23	.005	−11.8	−0.60
Psychosocial	.495	−2.5	−0.15	.822	−1.0	−0.06	.009	−8.5	−0.56
Emotion	.853	−0.8	−0.04	.518	−3.2	−0.17	.012	−8.8	−0.53
Social	.666	1.9	0.09	.678	2.3	0.11	.501	−2.8	−0.14
School	.790	−1.3	−0.06	.986	0.1	0.00	.003	−12.2	−0.63

P, P-value; es, effect size; mean Δ, mean difference.

FIGURE 1 Child self-report PedsQL 4.0 of all four (CLKT, LTx, KTx, and healthy) groups. Mean scores for each subscale and each sample for the child self-report; $P<.01$*, $P<.05$+; significant difference indicates the comparison between the CLKT sample and the selected group
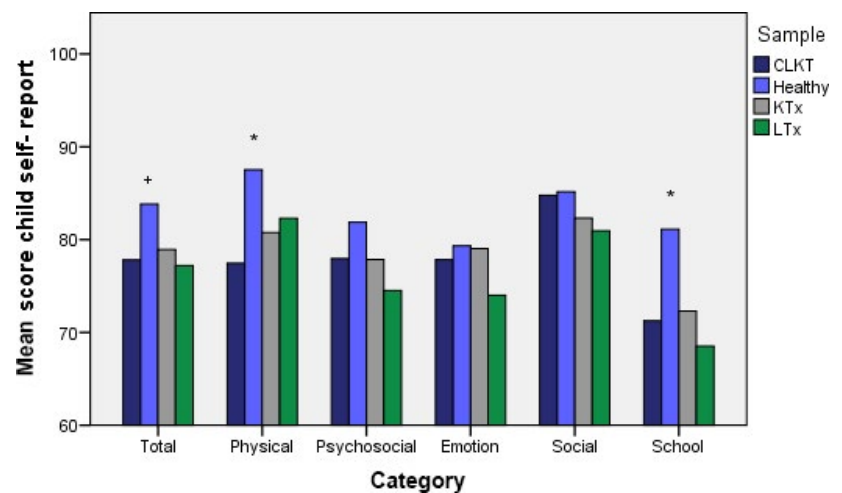
In contrast to their children, the parents reported a significant difference in all domains besides the social functioning scale; for the total scale score $P=.003$ (effect size=−0.6), for the physical health score $P=.005$ (effect size=−0.6), for psychosocial health $P=.009$ (effect size=−0.6), for the emotional function scale $P=.012$ (effect size=−0.5), and for school function $P=.003$ (effect size=−0.6). The mean difference for the social function scale is lower by −2.8 for the CLKT with no significant P-value. The evaluation of the parent proxy-report has shown that 27.3% of the total scale, 22.7% of the physical health score, 18.2% of the psychosocial health score, 22.7% of the emotional function scale, 18.2% of the social function scale, and 31.8% of the school function scale from the CLKT sample were at least 1 SD below the mean of the sample of healthy children.

3.3 | Comparison to liver- or kidney-transplanted children

In comparison with the isolated liver-transplanted children, neither the patients nor the parents reported a significant difference in any domain for HRQOL. For both reports, the largest mean difference occurred in physical health. In both cases, lower physical health mean scores were reported from the CLKT sample. The least difference of the mean scores occurred in the total score for child self-report and in the emotional score for parent proxy-report (Tables 2 and 3). Similar to the LTx sample, there were no significant differences comparing the mean scores of the kidney-transplanted cohort. Again the largest mean difference occurred in physical health and the lower score is related from the CLKT sample. The smallest mean score difference
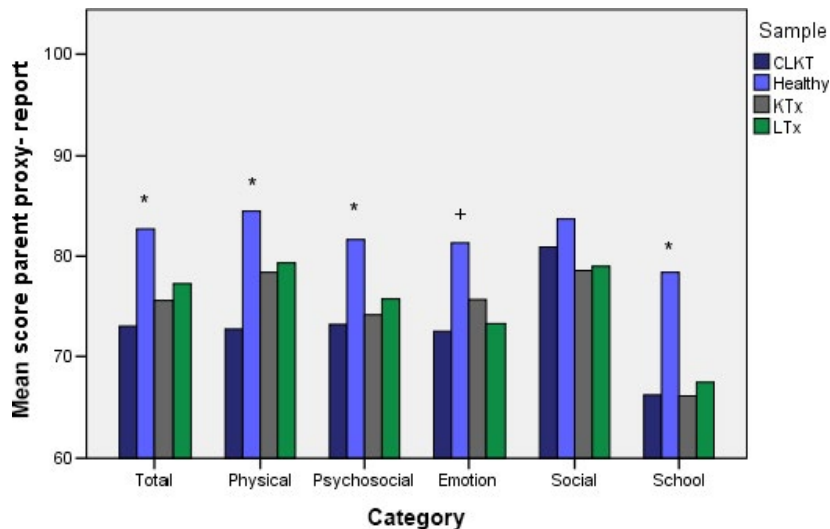
FIGURE 2 Parent proxy-report PedsQL 4.0 of all four (CLKT, LTx, KTx, and healthy) groups. Mean scores for each subscale and each sample for the parent proxy-report; $P < .01^*$, $P < .05^+$; significant difference indicates the comparison between the CLKT sample and the selected group

occurred for child self-report in the psychosocial health score and for parent proxy-report in the school function score (Tables 2 and 3).

4 | DISCUSSION

This is the first study to examine HRQOL following pediatric CLKT. There is no statistical difference in impairment of HRQOL when compared to isolated liver- or kidney-transplanted pediatric patient populations. Of interesting note is that despite the usually complicated past medical history, complexity, and severity of the underlying disease and associated long-term hospitalization, the pediatric CLKT patients did not demonstrate inferior HRQOL scores (from both the parent's and child's perspectives).

In comparison with healthy children, the overall HRQOL is impaired and again makes clear that the transplanted community requires, in addition to the physical care, specialized psychosocial support. A measurement of HRQOL after organ transplantation, especially in children, should be considered in routine clinical practice before and frequently after CLKT, allowing the opportunity to implement specific support for each individual patient and their family if it is required.

An example of an integrated multidisciplinary management and education program, implemented in the context of a lifelong complex medical diagnosis, could be the post-diagnosis system developed for children with DMT1. In a previous study, LTx patients' QoL was compared to those suffering from DMT1. The results demonstrated that patients with DMT1 had a significantly better HRQOL than the LTx sample despite similar daily challenges—including medication administration, learning to live with a lifelong illness, and regular clinical check-ups. A program, such as the coping skills training (CST), developed for patients with DMT1 could be an orientation adjusted to the transplantation patients to improve their QoL.[29] After diagnosis, patients will be included into a program for a certain time, where they learn how to deal with their disease, what it means to live with a chronic illness, how important regular drug use is, and how to handle social issues with peers through role-plays.[13,29-34]

In our study, the lowest scores recorded (from both children and parents) were in the school function domain. Cognitive impairment related to the transplant procedure itself is one consideration in determining causality of these scores. Similarly, current medical treatment side effects or missing days from school because of hospitalization or clinical visits could play a further role in this poor performance.[35] A previous trial with a major sample size regarding school function in pediatric liver-transplanted patients demonstrated a similar effect on school function and the need for arrangements to improve school outcomes following transplantation.[36] Parents and the transplant team should focus on encouraging their children's academic support, which could be a key point in the development of the improvement of HRQOL.[13] Furthermore, especially relevant for CLKT patients, attention should be drawn toward simplifying the medium-term postoperative outpatient management plan, helping families negotiate follow-up between the two clinical disciplines necessary following CLKT. An improved communication between physicians, both among each other and with patients and parents, could avoid misunderstandings and therefore increasing compliance. The numbers of missing school days are known risk factors for diminished HRQOL.

Our finding that the accordance between child self- and parent proxy-report is on an excellent level does not correspond to earlier results.[18,37,38] In these earlier studies, the correlation ranged in a moderate agreement. Grounds for the excellent agreement of our patients and parents report could certainly be sample-size-dependent. A further approach could be the gravity of the illness and related to the intensive support these children need, and the deep knowledge of the parents about their children's daily problems and cares.

Even if the results of our study seem to be consistent between parents and children, parents continuously scored a lower mean score over all scales. Should HRQOL measurement enter regular clinical practice, a separate measurement of the children and parents would provide the most comprehensive results about QoL of children and young adults.[18]

A number of limitations for the present study are conceivable. One of these is the small sample size of the pediatric CLKT population,

caused by the low prevalence of the underlying diseases. Due to this same reason, it was not possible for us to provide a comparison group for the patients with ARPKD who were treated conservatively. A comparison to those children would strengthen the significance and provide important findings regarding decision-making for a CLKT. Additionally, the use of the PedsQL 4.0 generic core scale limits the breadth of identified items resulting in impaired HRQOL. To more accurately detect the exact causes of impairment, the use of the PedsQL transplant module could be beneficial.[39] Furthermore, a multicenter study in the future would be beneficial to extend the sample size and provide representative findings.

In conclusion, children following CLKT, independent of the underlying medical diagnosis, have comparably impaired HRQOL when tested against isolated organ-transplanted children, despite the complexity and severity of the illness and procedure. Compared to a pediatric healthy population, the results of the present study illustrate the importance and need for multidisciplinary long-term intervention to improve QoL following organ transplantation in childhood and a regular assessment of the HRQOL of those patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

Kaja Schmaeschke: Participated in study design, data analysis, and writing of the manuscript; Susanne Lezius: Participated in data analysis and writing of the manuscript; Enke F. Grabhorn: Participated in design of the study and writing of the manuscript; Markus J. Kemper: Participated in design of the study and writing of the manuscript; and Florian Brinkert: Participated in study design, data analysis, and writing of the manuscript. All authors approved the final version of the article to be published.

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