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ACTA PÆDIATRICA NURTURING THE CHILD WILEY

ORIGINAL ARTICLE

Late nephrectomy in infants with congenital nephrotic syndrome of the Finnish type

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Abstract

Aim: Bilateral nephrectomy is commonly performed in patients with congenital nephrotic syndrome of the Finnish type. The optimal timing of nephrectomy is unclear.

Methods: Growth, thromboembolic events, infections, transplant-related complications and ability to eat were compared between infants with early (Group 1, $n=13$) and late (Group 2, $n=10$) nephrectomy. 'Early' was defined as nephrectomy at 7-kg body weight followed by peritoneal dialysis and 'late' as nephrectomy at ≥10 kg followed by 3–4 weeks of haemodialysis and kidney transplantation. Patients were followed until the end of the first post-transplant year.

Results: Dialysis time was significantly longer in group 1 than in group 2. Late nephrectomy did not increase the risk for thromboembolic events or septicaemia but decreased tube feeding dependency (group 1 69% vs. group 2 20%, $p=0.019$). Motor development at transplantation was considered normal in 80% of the infants with late nephrectomy compared to 31% in the early nephrectomy group ($p=0.019$); however, the difference between the groups disappeared by the end of the follow-up.

Conclusion: Infants with late nephrectomy have comparative outcome but less feeding tube dependency and better motor development during the first post-transplant months compared to infants with early nephrectomy.

KEYWORDS
congenital nephrosis, infant, nephrectomy, outcome, treatment, tube feeding

1 | INTRODUCTION

Congenital nephrotic syndrome (CNS) is a group of heterogeneous rare genetic kidney diseases characterised by severe proteinuria, hypoalbuminaemia and oedema that typically appear at or soon after birth.[1] The vast majority of CNS is caused by various mutations in podocyte structure or function-regulating genes.[2] Congenital nephrotic syndrome of Finnish type (CNF) is caused by a mutation in the *NPHS1* gene. The most common mutations leading to CNF, Fin-major (C.121_122delCT) and Fin-minor (C.3325C>T), are highly enriched in the Finnish population. These mutations severely damage the structures of the nephrin molecule, which is an important part of the podocyte slit diaphragm.[3] Patients with biallelic truncating mutations in the *NPHS1* gene have been considered poor prognosis

Abbreviations: CNS, congenital nephrotic syndrome; CNF, congenital nephrotic syndrome of Finnish type; CKD, chronic kidney disease; CVL, central venous line; EN, enteral tube feeding; G-tube, gastrostomy; KT, kidney transplantation; mGFR, measured glomerular filtration rate; NGT, nasogastric tube; NPHS1, nephrin gene.

patients requiring nephrectomy and eventually kidney transplantation.[1] However, with the development of gene sequencing methods, it has been found that some patients with biallelic mutations in the *NPHS1* gene can have a good response to conservative treatment and even spontaneous recovery of nephrotic syndrome.[4–7]

The treatment of nephrotic range proteinuria is based on the initiation of immunomodulatory and antiproteinuric medications, the avoidance of frequent albumin infusions and unilateral or bilateral nephrectomy.[8–10] The recent treatment guidelines encourage the adoption of a conservative approach; however, an individualised approach based on each patient's clinical needs is essential.[10] The majority of Finnish patients with CNF do not respond to conservative treatment, and in this distinct patient group, early bilateral nephrectomy and kidney transplantation (KT) is a commonly used treatment. This active approach was not possible before the beginning of the transplant era in the early 1980s, and infants with CNF died mostly due to infections or hemodynamic collapse, the mean survival being 7.6 months.[11] Initiation of daily albumin infusions and early bilateral nephrectomy followed by KT improved patient survival significantly and 10-year survival is currently over 95%.

In Finland, the treatment approach of the CNF infants remained the same until the 2010s. A bilateral nephrectomy has been performed when the child weighs approximately 7 kg, which is considered to enable safe peritoneal dialysis at home. Peritoneal dialysis has continued until KT at 10 kg from either a living or deceased donor. During the last decade, an alternative treatment option was developed consisting of late nephrectomy, which aims to shorten the time on dialysis and uraemia-related complications. In this approach, albumin infusions are continued either at the hospital or at home until the child weighs approximately 10 kg, followed by bilateral nephrectomy, a short 3–4-week period of haemodialysis and KT. If an infant is not able to consume a sufficient amount of feed, enteral tube feeding (EN) with a nasogastric tube (NGT) or a gastrostomy (G-tube) is promptly started to ensure adequate nutrition.[12]

The objective of this study was to evaluate whether late nephrectomy, prolonged nephrosis phase and shortened time on dialysis have an influence on the short-term outcome of CNF patients. The primary outcomes were patient survival, the number of thromboembolic events and infections before KT and the secondary outcomes were growth, motor development and the ability to eat before KT. We hypothesised that late nephrectomy would not worsen the outcomes of these patients.

Key notes

- Current guidelines recommend conservative treatment for infants with congenital nephrotic syndrome; however, bilateral nephrectomy and kidney transplantation are the appropriate treatments in selected patients with severe disease.
- Infants with early versus late nephrectomy had similar outcomes before and 12 months after kidney transplantation.
- Nephrectomy can be postponed in infants with severe forms of congenital nephrosis of the Finnish type.

2 | PATIENTS AND METHODS

2.1 | Data acquisition

The study consists of 23 patients with CNF, who were treated and followed up at the study centre between January 1, 2013 and December 31, 2023. The data were retrospectively collected from the electronic medical databases. The patients were divided into two groups based on their treatment protocol: The patients in group 1 ($n = 13$) were treated according to our traditional protocol, including: (1) daily albumin infusions of 1–4 g/kg/day until nephrectomy; (2) bilateral nephrectomy at the average body weight of 7 kg, (3) preferably peritoneal dialysis until body weight of approximately 10 kg, followed by (4) KT. All patients had a tunnelled central venous line (CVL) inserted at the age of 3–4 weeks. The principles of the treatment of congenital nephrosis are described in more detail in a review by Hölttä and Jalanko.[12] Patient group 2 ($n = 10$) consisted of patients treated with an alternative protocol, including: (1) daily albumin infusions of 1–4 g/kg/day until nephrectomy at a body weight of approximately 10 kg; (2) bilateral nephrectomy; (3) a short 3- to 4-week period on haemodialysis (one patient on peritoneal dialysis) and (4) KT from a living donor. The treatment protocol was decided case by case taking into consideration parental opinion, the possibility of living donation, growth, the presence of infectious problems and thromboembolic events during the nephrosis phase. No exclusion criteria were used in patient selection.

The data collected from databases included the following parameters: gestational age, birth weight, type of the nephrin mutation (homozygous Fin-major or Fin-major, compound heterozygous Fin-minor/Fin-major/point mutation), age at CNF diagnosis, number of thromboembolic events and infectious episodes during nephrosis, age, weight and height at nephrectomy and at KT, plasma albumin at nephrectomy, surgical complications (lymphocele, ureter stenosis and vascular complications), wound-related problems (success of primary closure, need for artificial surface material in wound closure and wound infection), need for reoperation before discharge, measured glomerular filtration rate (mGFR) at discharge and 3, 6 and, 12 months after the KT, and weight, height and graft function one year after the KT.

Patients' motor development and ability to eat before and 1, 3, 6 and 12 months after the KT were assessed. The infants' ability to eat was categorised into three groups: (1) the patient eats and drinks everything orally; (2) the patient eats partially orally and receives partial EN via G-tube or NGT and (3) the patient does not eat or drink orally. The assessment was made using patient records from dietitian appointments. The motor development was assessed to be either normal or abnormal using the patient records from neurological and occupational therapy appointments.

2.2 | Statistical analysis

Data are presented as the number of subjects and percentages, mean ± standard deviation (SD) or median and range, as appropriate. We used the Chi-squared test to compare qualitative variables and the *T*-test for comparing continuous variables. Statistics were performed with SPSS 28.0 (SPSS, Inc., Chicago, IL, USA), and the level of statistical significance was set at 0.05 for all analyses.

3 | RESULTS

3.1 | Patient demographics

The key patient characteristics are presented in Table 1. There were no statistically significant differences between the groups in terms of baseline patient demographics. All patients had a mutation in the *NPHS1* gene, with the majority having homozygous Fin-major mutation (Table 1). Five patients had a compound heterozygous C.121_122delCT mutation in one allele and a non-Finnish point mutation in the other allele. These five patients received either captopril ($n=2$), captopril or enalapril in combination with losartan ($n=1$), or captopril, losartan and indomethacin ($n=2$) according to our treatment protocol. In one patient, proteinuria reduced after initiation of antiproteinuric medication; however, he underwent nephrectomy at the age of 13 months because of uraemia and continuing nephrotic range proteinuria.

Patients in group 1 were significantly younger at nephrectomy compared to patients in group 2 correspondingly, the median time on dialysis was longer (Table 1). The majority of the patients in group 2 were on haemodialysis, while patients in group 1 were mainly on peritoneal dialysis. The median age at transplant did not differ statistically significantly between the groups (Table 1).

Patients with late nephrectomy had significantly higher median plasma creatinine concentrations at nephrectomy than patients with early nephrectomy. Plasma urea or albumin concentrations did not differ between the groups. Four patients in late nephrectomy groups developed chronic kidney disease (CKD) stage 4 and two patients stage 3b CKD before nephrectomy.

3.2 | Complications before KT

There was no statistical difference in thromboembolic events between the groups (Table 2). In group 1, two patients had thrombosis in the internal jugular vein, and the other one was also in the right

TABLE 1 Patients with congenital nephrotic syndrome divided into two groups based on timing of nephrectomy. The key clinical parameters presented in patients with early and late nephrectomy.

	Group 1	Group 2	
	Early nephrectomy ($n=13$)	Late nephrectomy ($n=10$)	*p*-Value
Male gender, *n* (%)	7.0 (53.9)	6.0 (60.0)	>0.99
Gestational age, weeks, median	34.9 (31.7–39.0)	36.7 (33.3–38.4)	0.092
Birth weight, g, median	2120.0 (1700.0–3264.0)	2490.0 (1745.0–3175.0)	0.237
Nephrin mutation, *n* (%)			
Fin-major, homozygote	8.0 (61.5)	7.0 (70.0)	0.831
Fin-major, fin-minor	3.0 (23.1)		
Fin-major, point mutation	2.0 (15.4)	3.0 (30.0)	
Age at diagnosis, under two weeks, *n* (%)	12.0 (92.3)	9.0 (90.0)	>0.99
Age at nephrectomy, months, median	9.3 (6.8–14.9)	13.6 (8.9–25.6)	0.019
Age at KT, months, median	18.1 (12.7–27.5)	14.8 (10.4–27.6)	0.263
Dialysis modality, *n* (%)			
Peritoneal dialysis	8.0 (61.5)	1.0 (10.0)	0.029
Haemodialysis	5.0 (38.5)	9.0 (90.0)	
Days on dialysis, median	261.0 (103.0–503.0)	35.5 (10.0–59.0)	<0.001
Weight at nephrectomy, *Z*-score, median	−1	7	0.142
Weight at KT, *Z*-score, median	15	6	0.236
Height at nephrectomy, *Z*-score, median	−3	−2	0.083
Height at KT, *Z*-score, median	−2	−2	0.592
Plasma creatinine at nephrectomy, μmol/L, median	13.0 (9.0–33.0)	71.0 (9.0–221.0)	0.005
Plasma urea at nephrectomy, mmol/L, median	7.8 (5.3–19.2)	13.1 (3.6–13.2)	0.393
Plasma albumin at nephrectomy, g/L, median	18.6 (8.0–49.0)	21.0 (11.0–36.0)	0.329

Abbreviation: KT, kidney transplantation.

TABLE 2 Key clinical outcome variables presented in patients with early nephrectomy and patients with late nephrectomy.

	Early nephrectomy ($n = 13$)	Late nephrectomy ($n = 10$)	p-Value
Patients alive, *n* (%)	13.0 (100.0)	10.0 (100.0)	
Thromboembolic events during nephrosis, *n* (%)			
Patients with verified thrombosis, *n* (%)	4.0 (40.0)	4.0 (30.8)	0.645
Thrombosis per patient year	0.19	0.29	0.93
Sepsis/bacteraemia before KT			
Total number	12.0	8.0	0.97
Sepsis/bacteraemia per patient year	0.53	0.60	0.96
Patients with peritonitis, *n* (%)	4.0 (31.0)	0.0	
Peritonitis per patient year	0.15	0.00	
Mean number of CVLs before nephrectomy per patient	1.38 (1.00–3.00)	1.38 (1.00–2.00)	>0.99
Surgical complications, *n* (%)			
Vascular complication	0.0	0.0	
Ureter stenosis	1.0 (7.7)	2.0 (20.0)	0.560
Lymphocele	0.0	0.0	
Wound-related problems, *n* (%)			
Primary closure	11.0 (84.6)	9.0 (90.0)	>0.99
Skin closed, fascia open	2.0 (15.4)	1.0 (10.0)	
Wound infection	0.0	0.0	
Reoperation before discharge, *n* (%)	4.0 (31)	5.0 (50)	0.434
Total hospital days (KT), median	21.0 (14.0–46.0)	22.0 (18.0–59.0)	0.103
Glomerular filtration rate, mL/min/1.73 m^2, median			
At discharge	73.0 (47.0–114.0)	80.5 (24.0–144.0)	0.899
3 months after KT	63.5 (38.0–111.0)	80.0 (56.0–104.0)	0.127
6 months after KT	69.5 (41.0–114.0)	64.5 (49.0–107.0)	0.973
12 months after KT	62.0 (43.0–105.0)	67.0 (49.0–96.0)	0.777

Abbreviations: CVL, central venous line; KT, kidney transplantation.

ventricle. One patient had inferior vena cava thrombosis, and another had thrombosis in the pulmonary artery. Four (40%) patients in the late nephrectomy group had verified thrombosis before KT. In three cases, thrombosis was either in the internal jugular vein or in the subclavian vein. One patient had sinus sagittalis thrombosis. None of the patients with thrombosis had a genetic predisposition to thromboembolic events.

All patients had CVL, which was typically inserted at the age of 3–4 weeks. The mean number of CVLs was 1.38 in both groups (Table 2). In the early nephrectomy group, three patients required CVL reinstallation: two patients due to malfunction of the catheter and thrombosis, and one patient due to infection. In the late nephrectomy group, CVL was changed in four patients. Two of them had recurrent infections and two had thrombosis.

A total of 20 bacteraemia/sepsis episodes in 12 patients were identified during the nephrosis phase (Table 2). There was no statistically significant difference between the two groups.

A total of 7 patients (30%) experienced severe bacterial infection after nephrectomy. One patient in each group had bacterial pneumonia after nephrectomy, four had peritonitis and one patient had haemodialysis catheter-related bacteraemia.

3.3 | Complications and patient outcome after KT

All patients in both groups were alive after the 12-month post-KT follow-up time. Graft function did not differ between the groups approximately 1, 3, 6 and 12 months after the KT (Table 2). The number of KT-related surgical complications, such as vascular complications, ureter-related problems, wound infections, the presence of lymphocele or the need for re-operations did not differ between the groups (Table 2).

3.4 | Growth and motor development before and after KT

The supine length/height of the patients, either before or after KT, did not differ between the groups. The median weight *z*-score at nephrectomy did not differ statistically significantly between the groups (Table 1). There was no difference in median weight and height between the groups 12 months after KT (Table 3).

Motor development before KT was better in patients with late nephrectomy, however, the number of patients with significant

TABLE 3 Development, eating habits and growth data after kidney transplant in patients with early and late nephrectomy.

	Group 1 Early nephrectomy ($n = 13$)	Group 2 Late nephrectomy ($n = 10$)	*p*-Value
Neurological development before transplant, *n* (%)			
Normal	4.0 (30.8)	8 (80.0)	0.039
Mild delay	8.0 (61.6)	1 (10.0)	
Significant delay	1.0 (7.7)	1 (10.0)	
Neurological development after KT, *n* (%)			
Normal	11.0 (84.6)	9.0 (90.0)	0.441
Mild delay	1.0 (7.7)		
Significant delay	1.0 (7.7)	1.0 (10.0)	
Feeding before KT, *n* (%)			
All orally		5.0 (50.0)	0.015
Complementary EN	7.0 (53.9)	3.0 (30.0)	
All EN	6.0 (46.2)	2.0 (20.0)	
Feeding after KT, *n* (%)			
All orally		1.0 (10.0)	0.369
Complementary EN	8.0 (61.5)	7.0 (70.0)	
All EN	5.0 (38.5)	2.0 (20.0)	
Feeding 3 months after KT, *n* (%)			
All orally	1.0 (7.7)	5.0 (50.0)	0.046
Complementary EN	10.0 (76.9)	3.0 (30.0)	
All EN	2.0 (15.4)	2.0 (20.0)	
Feeding 6 months after KT, *n* (%)			
All orally	4.0 (30.8)	8.0 (80.0)	0.039
Complementary EN	8.0 (61.5)	1.0 (10.0)	
All EN	1.0 (7.7)	1.0 (10.0)	
Feeding 12 months after KT, *n* (%)			
All orally	9.0 (69.2)	8.0 (80.0)	0.285
Complementary EN	4.0 (30.7)	1.0 (10.0)	
All EN		1.0 (10.0)	
Weight at latest FO, kg, median	11.3 (10.0–13.0)	11.9 (10.6–13.3)	0.606
Height at latest FO, cm, median	85.2 (81.2–92.4)	84.9 (80.9–92.7)	0.751

Abbreviations: EN, Enteral tube feeding; FO, follow-up visit; KT, Kidney transplantation.

motor delay did not differ between the groups (Table 3). One year after KT, there was no significant difference in motor development between the two groups (Table 3).

3.5 | Ability to eat

Enteral tube feeding was required less frequently in group 2 (Table 3). Before transplantation, 50% of the patients in group 2 received no EN, while in group 1, all patients required feeding via NGT or G-tube (Table 3). The number of patients requiring EN was significantly higher at the time of KT, three, and six months after KT in group 1. After 12 months of KT, no significant difference was found between the groups (Table 3).

4 | DISCUSSION

Congenital nephrotic syndrome of the Finnish type is caused by two truncating mutations in the *NPHS1* gene, leading to massive proteinuria that is unresponsive to conservative treatment. In Finland, the treatment modality has traditionally been daily albumin infusions until bilateral nephrectomy at a body weight of about 7 kg, followed by peritoneal dialysis and kidney transplantation when the body weight has reached 10 kg. Increasing the number of living kidney donors and the possibility of albumin infusions at home have made it possible to revise our treatment protocol, aiming for shorter dialysis time and a better quality of life. The present study compares the outcome and prevalence of disease- and treatment-related complications in infants treated with the traditional method and those

treated with late nephrectomy, a short period of haemodialysis and KT. Patients with late nephrectomy had better motor development, and they required enteral tube feeding less frequently during the first post-transplant months than infants with early nephrectomy. We found no difference in the number of infection episodes, thromboembolic events, surgical complications or growth between the two groups. These findings suggest that a protocol with late bilateral nephrectomy and short dialysis time offers better quality of life and favours late nephrectomy in Finnish patients with biallelic truncating mutations.

Congenital nephrotic syndrome is, in most cases, genetic disease, the severity of the symptoms depending on the mutation that causes the disease.[4,10,13] The current treatment recommendation encourages the initiation of antiproteinuric medication, including renin-angiotensin-aldosterone system inhibitors with or without prostaglandin inhibitors and the avoidance of frequent albumin infusions and nephrectomy.[10] Using this approach, the length of hospitalisation and the number of CVL-related thromboembolic events and infections have decreased, especially in children with non-*NPHS1* gene mutations or patients with a mild CNF phenotype.[13–15] However, this appears not to be the case in patients with homozygous truncating mutations in the *NPHS1* gene.[16]

Massive proteinuria and nephrotic syndrome are known to increase the risk for infections and thromboembolic events.[17,18] These complications have been connected to urinary loss of immunoglobulins and factors involved in the coagulation system, especially antithrombins, and the presence of a central venous line.[10] The reported prevalence of infections and thrombotic complications among nephrotic infants is around 13%–54%, depending on the patient cohort.[10,13,17–19] In the present study, thrombosis was diagnosed in four patients in each group (0.19 and 0.29 per patient year). The relatively low prevalence of thrombosis complications may be partly explained by the routine use of warfarin as an antithrombotic prophylaxis and omega-3 fish oil both during nephrosis and dialysis. The latter is used predominantly to lower triglyceride levels; however, it has been shown to affect the coagulation system and, in that way, reduce the risk of thrombosis.[20]

Peritoneal dialysis has previously been recommended as the primary dialysis modality after nephrectomy as it preserves central venous access and is thought to decrease the number of infections and thrombosis compared to haemodialysis.[13] Hölttä et al.[21] have reported the largest CNS cohort so far, showing 68.3% of PD in non-Finnish-type patients and 100% in infants with CNS of the Finnish type. In the present study, haemodialysis was successfully used in almost all the patients in group 2. Our protocol was planned to include only a short period of dialysis, which probably explains the low number of dialysis-related complications. Despite our encouraging results, if delayed access to KT is expected, for example due to a lack of potential living donors, we would still recommend peritoneal dialysis as the primary dialysis modality.

Eating difficulties are a well-known problem among children with chronic kidney disease in all age groups, but the influence of uraemia-induced nausea and vomiting on growth and development is most detrimental during infancy.[22] In the present study, we found that the need for enteral tube feeding was more common in the group with early nephrectomy, which suggests that the reason for poor eating is prolonged dialysis and uraemia rather than other CNS-related factors. Although the infants with late nephrectomy had significantly higher P-Crea at nephrectomy, none of them had developed stage 5 CKD despite prolonged massive proteinuria. This may at least partly explain their better ability to eat without enteral tube support when compared to group 1. Many oral motor skills that are necessary for the development of normal feeding skills mature during the first year of life.[22] Disturbances in this developmental process may lead to long-lasting problems and delays in the development of eating skills.[23] We did not find any differences in physical growth between the groups up to one year after KT, since the hypercaloric diet and the use of NGT or G-tube tubes ensured the growth of the infants. However, the need for NGT or G-tube feeding has a great influence on quality of life and parental coping.

We have previously reported delayed motor development in 26.6% of CNF patients during their early childhood.[24] Possible factors affecting early motor development include long-lasting hypoproteinaemia and altered muscle structure with regard to CKD. In the present study, motor development was assessed to be better in the group with a late nephrectomy. This finding suggests that the delay in motor development and possible impaired physical performance capacity may be more affected by a long dialysis period and CKD than nephrosis.

All treatment protocols should be adjusted based on each patient's clinical demands and the abilities of the local health care providers. However, it is also important that parents receive at least an estimate of future treatment procedures and their timing. Our protocol aims to ensure normal growth, development and long-term prognosis with treatment that can be done safely at home whenever possible. Based on our experience, home PD is safe for infants weighing about 7 kg, that is approximately at the age of 0.6 years.[25] Many centres perform kidney transplantation from weights of 7–8 kg, but since the risk for surgical complications is relatively high, we have preferred minimum body weight of 9–10 kg.[26,27] Based on our experience, in most cases, albumin infusions can be given at home either by home nursing care or by parents from about 6–8 weeks of age. Based on our current results, late bilateral nephrectomy and a short period of haemodialysis before KT are safe treatment options for infants with severe form of CNS, such as congenital nephrosis of the Finnish type. Late nephrectomy also offers a good possibility for relatively short hospitalisation, which is likely to improve quality of life.

A clear caveat of the study is its retrospective nature and the small number of patients. The strength of the study, however, is that a single-centre study enables adherence to uniform protocols. Previous retrospective studies in larger patient materials have shown comparable long-term outcomes in CNS patients treated with early nephrectomy compared to patients with conservative treatment or late nephrectomy.[10,21] The studies have compared infectious

complications, growth during dialysis and overall survival. However, they have mainly compared infants with Finnish and non-Finnish *NPHS1* gene mutations. Although genotype-phenotype correlation among NPHS1 mutations has remained unproven, all patients in the present had either Fin-major or Fin-minor mutation in the *NPHS1* gene and therefore we presume that the patient outcome is mainly affected by the given treatment.

In conclusion, according to the present results, CNF patients treated with late nephrectomy and short dialysis prior to KT preserve their ability to eat and have a shorter dependence on NGT/G-tube-assisted feeding. A longer period of nephrosis did not increase the risk for thromboembolic events, infections, or growth problems compared to patients with early nephrectomy. These findings should be interpreted with caution due to the relatively small study population.

AUTHOR CONTRIBUTIONS

Aino Suihko: Investigation; writing – original draft; formal analysis. **Juuso Tainio:** Writing – review and editing; investigation; formal analysis. **Jetta Tuokkola:** Writing – review and editing; conceptualization; methodology. **Elisa Ylinen:** Investigation; writing – review and editing. **Tuula Hölttä:** Conceptualization; investigation; writing – original draft; supervision. **Timo Jahnukainen:** Conceptualization; funding acquisition; writing – original draft; supervision; resources.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest relevant to this article to disclose.

ETHICAL STATEMENT

The study protocol was approved by the Research Ethics Committee of Helsinki and Uusimaa Hospital District as part of the research project entitled 'Development of Pediatric Solid Organ Transplantation Program' (HUS 939/2018). According to current regulations, no informed written consent from study subjects or their caregivers is required in the case of a retrospective register-based study.

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