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Long-term mortality in pediatric solid organ recipients—A nationwide study

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Abstract

Background: The present study aimed at investigating long-term mortality of patients who underwent solid organ transplantation during childhood and at identifying their causes of death.

Methods: A cohort of 233 pediatric solid organ transplant recipients who had a kidney, liver, or heart transplantation between 1982 and 2015 in Finland were studied. Year of birth-, sex-, and hometown-matched controls ($n = 1157$) were identified using the Population Register Center registry. The Causes of Death Registry was utilized to identify the causes of death.

Results: Among the transplant recipients, there were 60 (25.8%) deaths (median follow-up 18.0 years, interquartile range of 11.0–23.0 years). Transplant recipients' risk of death was nearly 130-fold higher than that of the controls (95% CI 51.9–1784.6). The 20-year survival rates for kidney, liver, and heart recipients were 86.1% (95% CI 79.9%–92.3%), 58.5% (95% CI 46.2%–74.1%), and 61.4% (95% CI 48.1%–78.4%), respectively. The most common causes of death were cardiovascular diseases (23%), infections (22%), and malignancies (17%). There were no significant differences in survival based on sex or transplantation era.

Conclusion: The late mortality is still significantly higher among pediatric solid organ recipients in comparison with controls. Cardiovascular complications, infections, and cancers are the main causes of late mortality for all studied transplant groups. These findings emphasize the cruciality of careful monitoring of pediatric transplant recipients in order to reduce long-term mortality.

KEYWORDS
cause of death, long-term, mortality, pediatric solid organ transplantation

Abbreviations: AZA, azathioprine; CsA, cyclosporin A; CNF, congenital nephrosis; CVD, cardiovascular disease; EBV, Epstein–Barr virus; HR, hazard ratio; HTx, heart transplant; KTx, kidney transplant; LTx, liver transplant; MP, methylprednisolone; NAPRTCS, North American Pediatric Renal Trials and Collaborative Studies; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplantation; Tx, transplantation.

1 | INTRODUCTION

Solid organ transplantation (SOT) has become the treatment of choice for kidney, liver, and heart failure with improved short- and long-term prognosis. The survival rates are now better due to improvements in surgical techniques, immunosuppressive therapy, and management of infections.[1–3] Since a growing number of pediatric transplant recipients reach adulthood, the long-term morbidity and the risk factors for late mortality are of great interest.

Previous studies have reported 10-year survival rates for kidney (KTx), liver (LTx), and heart transplant (HTx) recipients as 90%, 70%, and 50%, respectively.[3–5] Even though the short-term survival after transplantation is well documented, there are no data of survival after 20 years from pediatric solid organ transplantation.

Lifelong immunosuppressive regimen is a necessary treatment to prevent allograft rejection. In pediatric patients, the exposure to immunomodulative drugs may last over decades and the susceptibility to drug-induced side effects in pediatric population is still largely unknown.[2,6] Hypertension, dyslipidemia, impaired glucose metabolism, and weaker immune response are associated with immunosuppressive medication.[7,8] As a consequence, the SOT recipients have an increased risk for diabetes, osteoporosis, cardiovascular complications, and malignancies.[9–11]

More than 600 pediatric organ transplantations have been performed in Finland since the early 1980s. The kidney, liver, and heart are the most frequently transplanted organs, covering nearly 96% of all the pediatric transplantations performed in Finland.[12] All pediatric transplantations in Finland are centralized in the Helsinki University Hospital (HUS) since 1982. The patients had at least annual followed-up visit in the HUS until the patients were transferred to adult care at the age of 18–22 years. Other follow-ups were in the patient's own hospital. The Transplantation Registry, maintained by HUS Transplantation Office, records the data of transplanted patients and collects follow-up data annually.

The most common causes for pediatric SOT are on account of congenital disorders, which lead to severe organ failure despite conservative treatment or surgery. The primary indication for kidney transplantation is congenital nephrotic syndrome of Finnish type (CNF), covering 39% of kidney transplantations. Liver transplantations are most often performed due to biliary atresia (38%), whereas the main indications for heart transplantations are cardiomyopathy (40%) and congenital heart anomaly (60%).[13–15] Due to high incidence of CNF, on average kidney transplantations are performed for much younger patients in Finland compared with other countries.[16,17] Therefore, pediatric SOT recipients are exposed relatively early to immunosuppressive and other medical treatment.

The aims of the present study were to (1) evaluate late mortality in patients with a history of solid organ transplantation during childhood, (2) compare mortality between different transplant groups treated at the same center, (3) identify causes of death after SOT, and (4) compare mortality between pediatric solid organ transplant recipients and a group of year of birth-, sex-, and hometown-matched control subjects. We hypothesized that transplant recipients have increased mortality and shortened lifetime in comparison with controls.

2 | PATIENTS AND METHODS

2.1 | Study population

This retrospective register-based cohort study included all pediatric transplant patients who underwent solid organ (kidney, liver, and heart) transplantation between January 1982 and December 2015 in Finland. The criteria for transplant group selection were (1) age under 16 years at transplantation and (2) age over 18 at the time of last follow-up day.

Overall, 233 solid organ transplantation recipients fulfilled the inclusion criteria, including 137 (58.8%) kidney, 53 (22.7%) liver, and 43 (18.5%) heart transplant recipients. Transplantation patients were identified using the transplantation registry.

Each patient had three to five sex-, year of birth-, and hometown-matched controls ($n = 1157$). Patients for whom it was not possible to find five peers according to the above-mentioned criteria had three or four controls. The control group was identified from the Digital and Population Data Services Agency registry.

The survival for the cohort stratified by transplant organ, sex, age at transplantation, retransplantation, and transplantation years was analyzed. The impact of these covariates on survival was compared between transplant groups, KTx recipients being as reference group.

The Causes of Death Registry, maintained by Statistics Finland, contains data of the deceased, including the cause of death and age. The causes of death used in this study were based on the immediate cause of death, which we further divided into four main categories (infections, malignancies, cardiovascular diseases, and others). International Classification of Diseases, Ninth Revision (ICD-9), was used to identify the causes of death until 1996 and Tenth Revision (ICD-10) after that.

2.2 | Immunosuppression protocol

The maintenance immunosuppression protocol after LTx and HTx was triple medication consisting of cyclosporin A (CsA), azathioprine (AZA), and methylprednisolone (MP). For HTx patients, the primary immunosuppression consisted of CsA with AZA until 2010 and combination of tacrolimus and AZA or mycophenolic acid (MPA) after that.[18]

2.3 | Statistics

Statistical analyses were performed using R software version 4.0.3 (Foundation for Statistical Computing) and SPSS statistics 27 (SPSS, Inc.). Fisher's exact test was used to compare differences between categorized groups for categorical variables and Kruskal–Wallis test for continuous variables. Survival curves were plotted with the Kaplan–Meier method, and they were compared using the log-rank test. To investigate risk factors related to post-transplant death, Cox proportional-hazard models were used. The

TABLE 1 Clinical characteristics of the kidney, liver, and heart transplant recipients

Characteristic	All Tx	KTx	LTx	HTx	Controls
TOTAL, *n* (%)	233	137 (58.8%)	53 (22.7%)	43 (18.5%)	1157
Males, *n* (%)[a]	139 (59.7%)	92 (67.2%)	25 (47.2%)	22 (51.2%)	691 (59.7%)
Age at time of Tx, median (IQR)	7.9 (2.5–13.2)	7.9 (2.6–13.2)	4.9 (1.1–12.7)	10.3 (5.6–13.2)	-
Age at time of study (IQR)	24.6 (20.6–29.1)	25.5 (22.2–29.7)	23.3 (11.3–26.7)	21.5 (18.6–28.3)	26.4 (22.9–31.3)
Dead, *n* (%)[a]	60 (25.8%)	20 (14.6%)	23 (43.4%)	17 (39.5%)	2 (0.2%)
Dead males, *n* (%)	33 (23.7%)	15 (16.3%)	10 (40.0%)	8 (36.4%)	2 (0.3%)
Dead females, *n* (%)	27 (28.7%)	5 (11.1%)	13 (46.4%)	9 (42.9%)	0 (0.0%)
Age at death (IQR)	18.0 (6.3–23.2)	20.4 (17.9–26.1)	8.5 (1.8–20.5)	18.0 (7.3–21.2)	25.5 (22.1–28.8)
Time from Tx to death (IQR)	8.1 (1.2–12.8)	11.9 (8.7–19.2)	1.4 (0.8–10.9)	6.7 (2.5–9.0)	-

Abbreviations: HTx, heart transplant; KTx, kidney transplant; LTx, liver transplant; Tx, transplantation.
[a]% within group.

proportionality assumption was verified for each variable explored based on Schoenfeld residuals. Hazard ratios (HR) with 95% confidential intervals were used as effect measure. For all analyses, event was defined as all-cause death and time interval was from transplantation to death or end of follow-up. All tests were two-tailed, and $p <$ value under .05 was considered statistically significant.

2.4 | Ethical considerations

An approval from The Research Ethics Committee of Helsinki University Hospital, the Finnish Institute for National Health and Welfare, and the Office of the Data Protection Ombudsman has been granted for this study protocol.

3 | RESULTS

3.1 | Characteristics of study population

The median follow-up time of the study population was 18.0 (IQR 11.0–23.0 years) years, and the median age at the time of the study was 24.6 (IQR 20.6–29.1) years. The median age at the time of transplantation was 7.9 years (IQR 2.5–13.2). Among transplant recipients, 139 (59.7%) were men. (Table 1) There were 27 patients (11.6%), who underwent retransplantation.

Of the 1157 controls, median age was 26.4 years (IQR 22.9–31.3) and 691 (60%) were males.

3.2 | All-cause mortality

A total of 25.8% ($n = 60$) transplant recipients and 0.2% ($n = 2$) controls died during the follow-up. The median age of death for transplant recipients was 18.0 years, and the median time from transplant to death was 12.8 years. Transplant recipients' risk of death was nearly 130-fold higher than that of the controls during our follow-up (95% CI 51.9–1784.6). The survival for all transplant recipients after 10 years from transplantation was 84.3% (95% CI 79.7%–89.1%).

Figure 1 shows the differences in patient survival between the transplant groups. Both LTx and HTx recipients had significantly higher HR for death compared with KTx recipients (HR = 3.86, 95% CI 2.11–7.04 and HR = 3.77, 95% CI 1.96–7.28, respectively). Ten-year patient survival rates for KTx, LTx, and HTx recipients were 95.5% (95% CI 92.1%–99.1%), 67.7% (95% CI 56.2%–81.6%), and 69.5% (95% CI 56.9%–84.8%), respectively. The corresponding rates 20 years after transplantations were 86.1% (95% CI 79.9%–92.3%), 58.5% (95% CI 46.2%–74.1%), and 61.4% (95% CI 48.1%–78.4%). No statistically significant difference in survival was observed in terms of sex, but the survival of female tended to be better in our study cohort (HR = 1.33, 95% CI 0.80–2.22).

Twenty-seven patients (11.6%) were retransplanted, and 33% of these patients died after retransplantation during follow-up (HR = 1.1, 95% CI 0.53–2.23). Lowest survival of retransplanted was among LTx patients (the 10-year survival 50.0%), while for KTx and HTx patients, the survival was 100% 10-years post-transplant. Every fifth liver recipients underwent retransplantation, whereas only a tenth of the kidney and heart patients had a new organ. There was no significant difference in survival between retransplanted patients and patients with primary transplant (log-rank $p = .82$). Neither was the difference statistically significant among KTx ($p = .99$), LTx ($p = .4$) and HTx ($p = .12$) recipients.

When analyzing the effect of the risk factors on survival, transplanted organ and age at transplantation had statistically significant impact on survival (Table 2). Patients transplanted under the age of 1 year had the highest hazard ratio for death, compared to those transplanted later ($p < .001$). There were no significant differences in survival based on sex or transplantation era (Figure 2).

3.3 | Cause-specific mortality

The main causes of death with a functioning graft were cardiovascular diseases (23%), infections (22%), and malignancy (17%), covering 62% of all deaths (Figure 3). Cardiovascular deaths were mainly caused by cerebral hemorrhage ($n = 2$, 13%), heart attack ($n = 2$, 13%), and arterial thrombosis ($n = 2$, 13%). Vast majority of the infections leading to death after Tx were consequences of sepsis ($n = 7$,

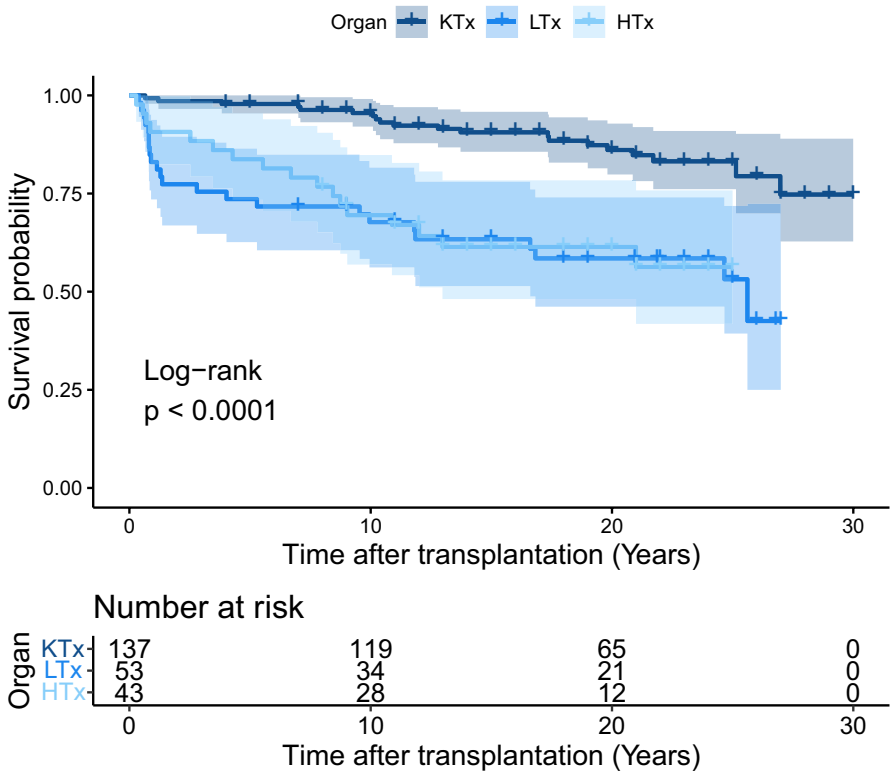

FIGURE 1 Kaplan–Meier survival curve for kidney (KTx), liver (LTx), and heart (HTx) transplant recipients

TABLE 2 Cox regression model indicating factors significant for survival

	Univariate			Multivariate		
Variable	**HR**	**95% CI**	***p*-Value**	**HR**	**95% CI**	***p*-Value**
Organ						
Kidney	Ref.	–	–	Ref.	–	–
Liver	3.86	2.11–7.04	<.001*	3.37	1.74–6.52	<.001*
Heart	3.77	1.96–7.28	<.001*	3.72	1.88–7.33	<.001*
Sex						
Male	Ref.	–	–	Ref.	–	–
Female	1.33	0.80–2.22	.300	1.04	0.62–1.76	.870
Tx age (years)						
<1	Ref.	–	–	Ref.	–	–
1–10	0.27	0.11–0.66	.004*	0.54	0.21–1.41	.210
>10	0.34	0.14–0.83	.018*	0.57	0.21–1.52	.260
Retransplantation						
No	Ref.	–	–	Ref.	–	–
Yes	1.09	0.53–2.23	.800	1.00	0.48–2.08	1.000
Transplantation era						
1982–1995	Ref.	–	–	Ref.	–	–
1996–2010	1.00	0.57–1.75	>.900	0.99	0.56–1.77	.980

Statistically significant *p*-values are marked with an asterisk.

50%) or pneumonia (n = 3, 21%), and most of the cancer-related deaths were due to post-transplant lymphoproliferative disorder (PTLD) (n = 6, 86%).

The type of transplant showed no significant effect on the cause of death (p = .40) (Table 3). However, malignancies were slightly more common among kidney transplant recipients (25.0%) in comparison with LTx (4.5%) (p = .19) and HTx (5.9%) (p = .37) patients. There was no statistically significant difference in the causes of death in terms of sex (p = .39). However, the cancer-related mortality was more common among males since 6 males and 1 female died

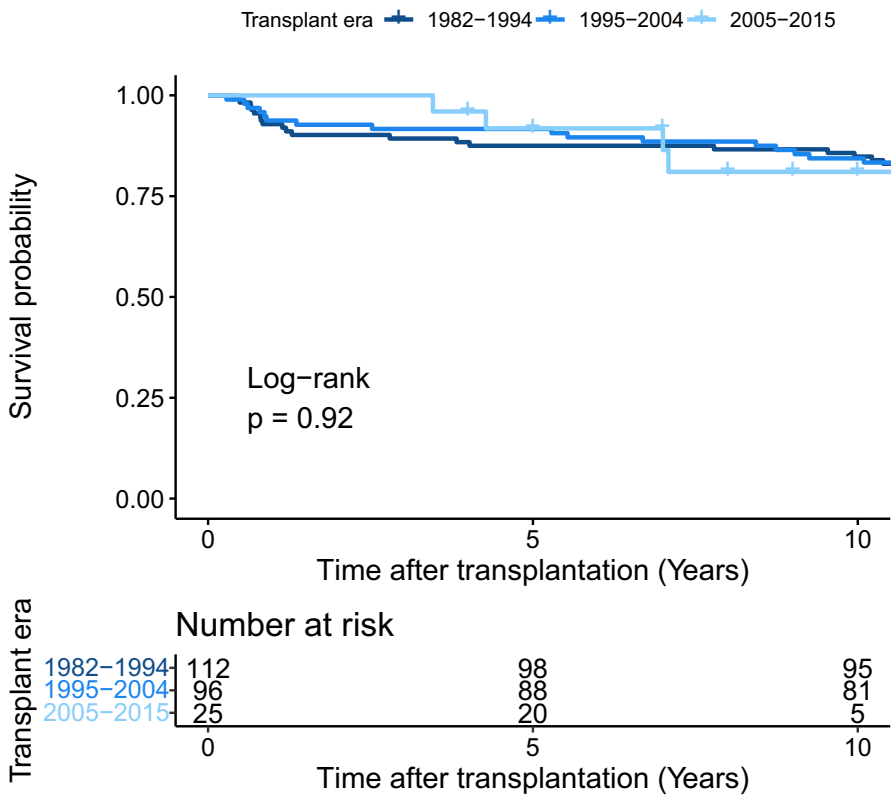

FIGURE 2 Kaplan–Meier survival curve in terms of transplant era

of cancer (OR = 5.64, 95% CI 0.62–275.4). Retransplantation showed no significant impact on cause of death ($p = .42$).

The causes of death tended to depend on the duration of follow-up, however, not statistically significantly ($p = .53$). Table 3 shows the relationship between the cause of death and the post-transplant time. The infection-related mortality was highest <1-year post-transplant, while the first cancer-related death was reported 6.5 years post-transplant (mean time interval from Tx to cancer death was 14.8 years). Most of the cardiovascular diseases leading to death occurred 10 years after transplantation (range 0.5–27.0 years, median 1.4 year).

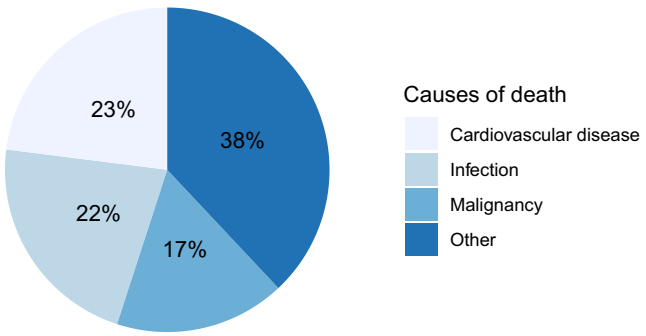

FIGURE 3 Causes of death among transplant recipients. *The causes of death classified as "other" comprised (including controls, $n = 2$): 10 complications of the treatment, 3 gastrointestinal complications, 2 poisonings, 2 suicide, 1 respiratory failure, 1 missing death certificate, and 7 unknown reasons. One transplant recipient (0.4%), and one control (0.1%) committed suicides.

4 | DISCUSSION

Despite significantly improved patient survival among solid organ transplant recipients, both morbidity and mortality have remained higher than in general population.[19,20] The present study confirms this previous finding showing almost 130-fold higher mortality among transplant recipients in comparison with matched controls. The most significant causes of death were cardiovascular causes, infections, and malignancies, which suggest the adverse effects of the prolonged exposure to immunosuppressants.[21–24] The number of long-term survivors after pediatric transplantation has increased only recently, and therefore, understanding of late morbidity has remained scant. In addition, there are no previous studies comparing mortality between different transplant groups at the same transplant center.

Transplanted organ and primary diagnosis leading to transplantation have a great impact on survival.[25] Kim et al.[3] found the survival of different transplant groups to be 92% (KTx), 77% (LTx), and 58% (HTx) after 10-year post-transplant. Our findings in terms of survival rates of Tx patients are broadly similar to the reported ones, despite a slightly better outcome of HTx patients. However, in contrast to previous studies, all the transplantations of different transplant groups were performed at the same hospital in our study. This means that we were able to exclude the cofounding factors caused by different centers. Patients treated in the same unit have very identical treatment protocols and follow-ups. These matters might have had an impact of mortality across transplant groups in previous studies.

TABLE 3 Causes of death according to the time elapsed after transplantation

Post-transplant time	Infection ($n = 14$)	CVD ($n = 15$)	Malignancy ($n = 7$)	Other ($n = 24$)
≤1 year	**9 (64.3%)**	**4 (26.7%)**	**0 (0.0%)**	**6 (25.0%)**
Kidney	2	1	0	0
Liver	6	3	0	3
Heart	1	0	0	3
1–10 years	**3 (21.4%)**	**5 (33.3%)**	**1 (14.3%)**	**9 (37.5%)**
Kidney	0	2	0	2
Liver	2	1	0	2
Heart	1	2	1	5
≥10 years	**2 (14.3%)**	**6 (40.0%)**	**6 (85.7%)**	**9 (37.5%)**
Kidney	2	2	5	4
Liver	0	1	1	4
Heart	0	3	0	1

Note: Total number of deaths (column percentage of patients at risk). All transplantation patients marked in bold.

Abbreviation: CVD, cardiovascular disease.

Francis et al.[26] showed that kidney patients transplanted between 2005 and 2015 have 72% lower mortality risk compared with patients transplanted in 1970–1985 (median follow-up 13.4 years). Similar improvement has been shown in Nordic pediatric kidney transplant population, especially among the youngest recipients.[27] Surprisingly, the transplant era showed no statistically significant impact in survival in our study. However, it should be considered that before the 1980s, prior to the use cyclosporin, the outcomes of transplanted patients were modest. In our study, the patients were followed up since 1982. Other possible explanation for this finding may be patients' selection. Along with increased experience in the field, SOTs are currently performed on patients with complex diseases and comorbidities, which may have influence on mortality. Along with remote transplant era, the male sex has been found to be an independent prognostic factor for poorer graft survival.[28] Despite these reported superior survival rates of females, in our study, the mortality of men was lower than women as far as 25 years after transplantation. This may be explained by the fact that, in our study, the incidence of cancer-related deaths of men was sixfold higher than in women.

In the previous studies, the most common causes of death with functioning graft among transplant recipients were noted as infections, cardiovascular diseases, and malignancies.[26] Our findings were in accordance with these results since the majority of deaths in our study were due to cardiovascular diseases (23%) and infections (22%). By contrast, the risk of cardiovascular-related death has been reported higher (30%–60%).[1,26,29] The lower proportion of CVD-related mortality may be partly explained by the underlying disease leading to SOT. We have previously shown in a long-term follow-up study, that in patients with CNF, which accounts majority of the KTx recipients in Finland, the incidence of CVD is relatively low.[30]

As in earlier studies, the distributions of causes of death changed according to the time after transplantation in our study. Rejection and infection play major part in post-transplant mortality <1 year after Tx. Subsequently, the proportions of cardiovascular- and malignancy-related deaths increased after 10 years of transplantation.[31–33] In the present study, the infections were most common ≤1-year post-transplant, whereas no more than one cancer-related death emerged before 10 years after transplantation. According to the NAPRTCS Annual Report and the NPRTSC report, the incidence of rejections has decreased dramatically along transplant era among pediatric kidney transplant recipients. Simultaneously, infections and malignancies remain significant causes of morbidity and mortality. The initial immunosuppression protocol in Finland has traditionally based on triple immunosuppression (CsA, AZA, and MP) unlike in many other centers, where tacrolimus, mycophenolate mofetil, and prednisone are the most common maintenance regimen.[34] Therefore, we found it noticeable that infections and malignancies played a significant role in causes of death (together covering 39% of the deaths), which indicate the adverse effects of immunosuppression agents. However, the differences in length of follow-up periods between earlier studies and the present study may contribute to the different distributions of causes of death.

Causes of death after Tx also vary depending on the transplanted organ. The most commonly reported late causes of death for KTx, LTx, and HTx patients were cardiovascular complications (25%), infection (12%), and infection (15%), respectively.[15,35,36] Pediatric renal and heart recipients have been reported to have the highest risk for cardiovascular complications with 30%–36% mortality rate after 10 years post-transplant.[37] Among pediatric liver recipients, Martin et al.[25] found the cardiac-related death rate to be 17% (follow-up of 7 years). Although our findings are broadly compatible with these observations, there was no significant difference in causes of death between transplanted organs in our study. However, death from cancer among KTx patients was much more common than in previous studies[38] and was nearly 2.5-fold

higher compared with other transplant groups. Again, due to high incidence of CNF in Finland, more than 30% of the KTx recipients were transplanted before the age of 2 years, leading to long-lasting exposure to immunosuppressive medication, whereas early mortality due to surgical complication and infections among liver and heart transplant recipients tend to be higher compared with KTx recipients. It is also of note that most of the patients were Epstein–Barr virus (EBV) naïve before transplantation, which increases their risk for EBV viremia and PTLD.

The long follow-up period across three largest transplant groups was the main strength of the present study. Since all pediatric transplantations are centralized in the Helsinki University Hospital since 1982, all the SOT patients in Finland could be searched. Therefore, to our knowledge, this is the first study to compare mortality between transplant groups without the cofounding factors caused by different centers. The study based on register data enabled the analysis of an extensive cohort with no participation or self-reported bias. According to the Finnish law, it is obligatory to write death certificates for deceased with immediate and underlying causes of death. Thus, data of causes of death were available.

Our study had some limitations. First, the sample size was small due to limited number of pediatric transplant recipients. Second, as this was a retrospective study of over 20 years, the classifications of diseases had been changed once. Therefore, the definition of immediate cause of death was not unambiguous with two different International Classification of Diseases (ICD-9 and ICD-10).

In conclusion, although SOT is a lifesaving treatment in organ failure, the long-term mortality of pediatric transplant patients is still remarkably higher than controls. Infections, cardiovascular diseases, and cancer are the most common causes of death in all transplant groups. These findings emphasize the cruciality of careful screening of comorbidities in this high-risk population. Also, further studies to evaluate the impact of medication other than immunosuppressants on long-term survival are worth considering.

AUTHOR CONTRIBUTIONS

Rebekka Salonen contributed to research design, data analysis, writing, statistical analysis, and editing figures. Timo Jahnukainen contributed to research design and writing, editing, and review of manuscript. Atte Nikkilä contributed to supervision on statistical analyses and writing, editing, and review of manuscript. Kira Endén contributed to research design, data collection and writing, editing, and review of manuscript.

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DATA AVAILABILITY STATEMENT

Unfortunately, we are unable to share these data due to the General Data Protection Regulation (GDPR) and lack of license.

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