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ORIGINAL PAPER

Analysis of Graft Survival in Pediatric Patients Undergoing Kidney Transplantation

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ABSTRACT

Introduction: Kidney transplantation is the gold standard therapy for end-stage chronic kidney disease (CKD). However, aspects related to the characteristics of the donor and the recipient, the surgical technique, the immunosuppression protocol and comorbidities can impact graft survival. **Objectives:** To evaluate factors associated with graft survival in pediatric patients undergoing kidney transplantation. **Methods:** Descriptive, retrospective cohort study, which included all patients aged 1 to 18 years who underwent kidney transplantation at Unidade Renal Pediátrica of Instituto de Medicina Integral Prof. Fernando Figueira (IMIP), Recife, Brazil, from January 2017 to December 2021, with a minimum follow-up time of 10 months, totaling 51 patients. The IMIP ethics and research committee approved the study under CAAE: 52023921.1.0000.5201. **Results:** The median age of patients undergoing kidney transplantation was 12 years (9-13); 27 (52.9%) were male and eight (15.6%) were younger than 5 years of age. The main etiologies of CKD were congenital anomalies of the kidney and urinary tract (n = 25; 49%). As for kidney transplants, 49 (96.1%) were from a deceased donor and the median follow-up time was 32 (14-42) months. After transplantation, 58% of the population were hypertensive, while 80.4% had dyslipidemia. The 5-year graft and patient survival rates, assessed using the Kaplan Meier curve, were 86.3 and 90.2%, respectively. Seven (n = 5) patients lost the graft, the most common cause being renal vein thrombosis. Nonglomerular causes of CKD showed lower graft survival when compared to glomerular causes (log rank p = 0.035). **Conclusion:** Our sample's graft and patient survival rates are similar to national and global data. The most frequent causes of graft loss were thromboembolic events. Furthermore, we observed a high prevalence of hypertension and dyslipidemia. These results direct us to establish strategies to improve survival in pediatric kidney transplants.

Descriptors: Pediatrics; Kidney Transplant; Chronic Renal Failure; Survival Analysis.

Análise de Sobrevida do Enxerto em Pacientes Pediátricos Submetidos ao Transplante Renal

RESUMO

Introdução: O transplante renal é a terapia padrão ouro para doença renal crônica (DRC) em estágio final. Entretanto, aspectos relacionados às características do doador e do receptor, à técnica cirúrgica, ao protocolo de imunossupressão e comorbidade podem impactar a sobrevida do enxerto. **Objetivos:** Avaliar os fatores associados à sobrevida do enxerto em pacientes pediátricos submetidos ao transplante renal. **Métodos:** Estudo descritivo do tipo coorte retrospectivo que incluiu todos os pacientes de 1 a 18 anos submetidos ao transplante renal na Unidade Renal Pediátrica do Instituto de Medicina Integral Prof. Fernando Figueira (IMIP), Recife, Brasil, de janeiro de 2017 a dezembro de 2021, com tempo mínimo de seguimento de 10 meses, totalizando 51 pacientes. O estudo foi aprovado pelo Comitê de Ética e Pesquisa do IMIP sob o CAAE: 52023921.1.0000.5201. **Resultados:** A mediana de idade dos pacientes ao transplante renal foi de 12 anos (9-13), sendo 27 (52,9%) do sexo masculino e oito (15,6%) com menos de 5 anos. As principais etiologias da DRC foram as anomalias congênitas do rim e do trato urinário (n = 25; 49%). Quanto ao transplante renal, 49 (96,1%) foram de doador falecido e a mediana do tempo de seguimento foi de 32 (14-42) meses. Após o transplante, 58% da população eram hipertensos, enquanto 80,4% apresentavam dislipidemia. As taxas de sobrevida do enxerto e do paciente em 5 anos, avaliadas pela curva de Kaplan Meier, foram, respectivamente, 86,3 e 90,2%. Sete pacientes (n = 5) perderam o enxerto, sendo a causa mais frequente a trombose de veia renal. As causas não glomerulares de DRC mostraram menor sobrevida do enxerto quando comparadas às causas glomerulares (*log rank* p = 0,010). **Conclusão:** As taxas de sobrevida do enxerto e dos pacientes em nossa casuística assemelham-se aos dados nacionais e mundiais. As causas mais frequentes de perda do enxerto

foram os eventos tromboembólicos. Além disso, observamos elevada prevalência de hipertensão e dislipidemia. Esses resultados nos direcionam para estabelecer estratégias para melhorar a sobrevida nos transplantes renais pediátricos.

Descritores: Pediatria; Transplante de Rim; Insuficiência Renal Crônica; Análise de Sobrevida.

INTRODUCTION

In children with chronic kidney disease, kidney transplantation demonstrates a significant improvement in survival and quality of life compared to dialysis[1]. Despite the number of kidney transplants in pediatrics and their consolidation as the gold standard for advanced stages of chronic kidney disease, there are still many obstacles to be faced, including maintaining graft survival. Graft failure is a significant factor in post-transplant morbidity and mortality, deserving special attention in clinical practices. The age of the donor and, graft recipient, the surgical technique used, the immunosuppression protocol, and the characteristics of the donor can impact long-term renal graft survival[2]. Furthermore, it is understood that obesity, hypertension, diabetes and dyslipidemia are factors involved in morbidity and mortality. Therefore, understanding these issues is essential to ensure more efficient conduct, mainly aimed at preventing rejection and graft loss in the long term[3].

Medical literature still needs to be more comprehensive regarding pediatric patients, especially in the regional scenario. Therefore, our study aims to evaluate the factors associated with graft survival in children and adolescents undergoing kidney transplantation in a reference center in the northeast of the country.

METHODS

A retrospective cohort study evaluated children aged 1 to 18 years who underwent pediatric kidney transplantation at the Pediatric Renal Unit of the Instituto de Medicina Integral Prof. Fernando Figueira (IMIP), Recife, Brasil, from January 2017 to December 2021, with a minimum follow-up period of ten months. The exclusion criteria were impossibility of collection due to lack of data in the medical records, patient refusal, and failure to sign the consent form.

Service routine

IMIP's pediatric kidney transplant service is a reference in the northeast and has performed an average of 12 kidney transplants per year over the last 10 years. Currently, it only performs transplants from deceased donors in patients aged up to 18 years and weighing at least 10 kg. Until 2021, induction of immunosuppression was performed preferably using basiliximab in patients with usual immunological risk, reserving thymoglobulin as a therapeutic option for patients with high immunological risk. Given the greater availability of the medication in the Unified Health System (Sistema Único de Saúde-SUS), we opted for induction with thymoglobulin for all patients. Initial maintenance immunosuppression is performed through triple therapy with the combination of tacrolimus, sodium mycophenolate, and prednisone. Anticoagulant therapy in the postoperative period is not universally performed, only in patients with a previous history of thrombosis after evaluation and indication by hematology. In the first days after transplantation, patients are admitted to the pediatric intensive care unit (ICU), followed by the pediatric nephrology ward, with an average length of stay of 9 days. Outpatient consultations are weekly during the first three months after transplantation and individualized according to the patient's needs.

Data Collection Instrument

Data collection included demographic variables, anthropometric, clinical, and laboratory data of the recipient, such as age at the time of kidney transplantation, gender, etiology of chronic kidney disease, and time on dialysis before transplantation. Donor and transplant data were also collected, such as kidney transplant time, whether the donor was alive or deceased, donor age and cold ischemia time, reactive antibody panel, and use of immunosuppressive drugs. Body mass index (BMI), renal function, creatinine levels, lipid profile, presence of dyslipidemia, and arterial hypertension after kidney transplantation were also recorded.

Statistical analysis

Data were collected using a standardized form, with closed and pre-coded questions for entry into the computer, recorded in a table built in Excel for Windows, and subsequently analyzed using the Statistical Package for the Social Sciences version 29. Continuous data and semi-continuous were analyzed using the Shapiro-Wilk test to determine normality. Continuous variables were expressed as mean ± standard deviation (SD) or median and percentiles (25; 75). Survival was analyzed using the Kaplan-Meier curve with log rank. A risk of $\alpha \leq 0.05$ for type I error was considered for the entire study.

Ethical aspects

The research followed CNS Resolution 466/12 for research on human beings and was approved by the ethics committee under number CAAE: 52023921.1.0000.5201.

RESULTS

From January 2017 to December 2021, 51 kidney transplants were performed at the IMIP Pediatric Renal Unit, with all patients included in the sample. The median age of patients at the time of kidney transplantation was 12 years (9-13); 27 (52.9%) were male, and eight (15.6%) were less than 5 years old. Regarding the etiology of chronic kidney disease (CKD), 25 (49.1%) were patients with congenital anomalies of the kidney and urinary tract, while 23 (45.1%) had glomerulopathies and three (5.8%) had other causes. The median time on dialysis before kidney transplantation was 29 (12-60) months, with hemodialysis being the most frequent modality (n = 29, 56.8%). These data are presented in Table 1.

Table 1. Demographic profile of patients.

Variable	
Age at transplant (years)	12 (9-13)
< 5	8 (15,6)
Gender	
Male	27 (52,9)
Female	24 (47,1)
Etiology of CKD	
Congenital anomaly	25 (49,1)
Glomerulopathy	23 (45,1)
Others	3 (5,8)
Dialysis modality	
No dialysis	2 (3,9)
Hemodialysis	29 (56,8)
Peritoneal	14 (27,4)
Hemodialysis + peritoneal	6 (11,7)
Dialysis time (months)	29 (12-60)

Source: Elaborated by the authors

Data are presented as n (%), mean, standard deviation, and median (25-75).

Regarding kidney transplant data, the median transplant time was 32 (14-42) months, with the majority (n = 49; 96.1%) coming from deceased donors. Fifty patients showed a reactive antibody panel of 0, with a median cold ischemia time of 15 (11-18) hours. Seven (17.6%) patients lost the graft, and five (9.8%) died. In our sample, no patient used prophylactic anticoagulation. Furthermore, none were prioritized, underwent retransplantation or presented anti-donor antibodies. Kidney transplant data are shown in Table 2.

Table 2. Kidney transplant data.

Variable	
Kidney transplant time (months)	32 (14-42)
Type of donor	
Deceased	49 (96,1)
Alive	2 (3,9)
Donor age (years)	11 (7-17)
< 5 years	9 (17,6)
Antibody Reactivity Panel	
0%	50 (98,0)
94%	1 (2,0)
Cold ischemia time (hours)	15 (11-18)
Induction drug	
None	9 (17,6)
Basiliximab	20 (39,2)
Thymoglobulin	22 (43,1)
Maintenance drug	
Tacrolimus	42 (82,4)
Sirolimus	9 (17,6)
Mycophenolate	45 (88,2)
Prednisone	50 (98,0)

Source: Elaborated by the authors

Data are presented as n (%), mean, standard deviation, and median (25-75).

Regarding clinical and laboratory data after transplantation, five patients (9.8%) were overweight/obese, 30 (58.8%) had hypertension, and 41 (80.4%) were dyslipidemic (Table 3).

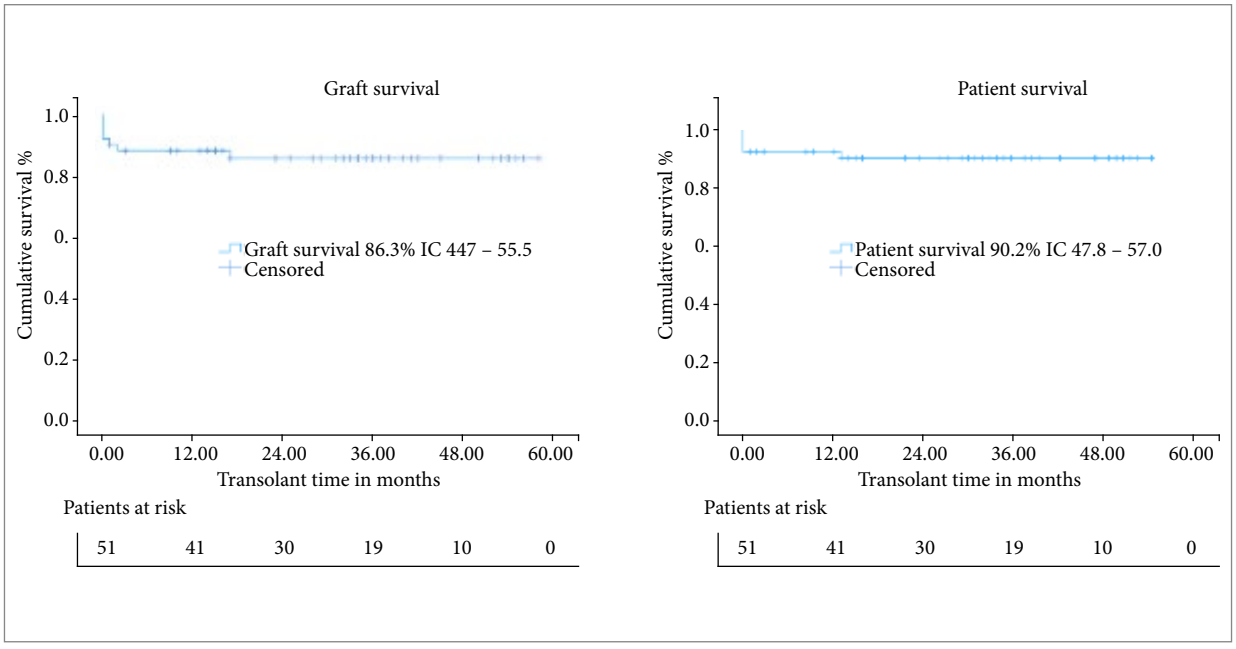
Table 3. Clinical and laboratory data of patients after kidney transplantation (n = 51).

Variable	
BMI	18,1 (16,7-21,4)
z score BMI	0,38 (-1,4-1,0)
Obesity/overweight	5 (9,8)
Hypertension	30 (58,8)
Triglycerides	111 (88-159)
Total cholesterol	164 (140-195)
LDL colesterol	102 (87-125)
HDL cholesterol	47,8 ± 15,0
Dyslipidemia	41 (80,4)
Creatinine	0,8 (0,7-0,9)

Source: Elaborated by the authors

Data are presented as n (%), mean, standard deviation, and median (25-75).

Evaluation using the Kaplan-Meier curve showed that graft and patient survival rates at 60 months were 86.3 and 90.2%, respectively (Fig. 1).



Source: Elaborated by the authors.

Figure 1. Graft and patient survival.

When analyzing graft survival concerning the etiology of CKD, we observed that glomerulopathies showed more remarkable survival than non-glomerular causes. The analysis of the other variables showed no difference in the graft survival rate (Table 4).

Of the seven patients who lost the graft, five were due to renal vein thrombosis, one due to acute cellular rejection due to poor adherence to treatment and the other due to humoral rejection. Of the 51 children evaluated in this study, five (9.8%) died. Deaths occurred within a period of up to 2 years after transplantation, with four patients suffering kidney graft loss due to associated venous thrombosis and one patient dying with a functioning graft. Regarding the cause of death, two patients had sepsis, one due to sclerosing cholangitis and the other due to complications from lymphoproliferative disease; one patient died from cardiovascular disease, one from fluid and electrolyte disorders and another from hemorrhagic shock. These data are presented in Table 5.

Table 4. Graft survival analysis according to clinical and demographic variables.

Variable	n	Events(n)	Log-rank p-value
Gender			0,515
Male	27	4	
Female	24	3	
Etiology of CKD			0,010
Glomerulopathy	23	0	
Non-glomerulopathy	28	7	
Receiver's age (years)			0,936
> 5	43	6	
< 5	8	1	
Donor age (years)			0,826
> 5	42	6	
< 5	9	1	
Cold ischemia time (hours)			0,624
> 12	32	5	
< 12	19	2	
Induction drug			0,932
Basiliximab	20	3	
Thymoglobulin	22	3	
Did not perform	9	1	
Arterial hypertension			0,479
Yes	30	5	
No	21	2	
Dyslipidemia			0,624
Yes	40	6	
No	11	1	

Source: Elaborated by the authors.

Table 5. Data on patients who died.

Patient	Age (years)	Transplant time	Graft loss	Cause of death
1	14	22 months	No	Sepsis, post-transplant lymphoproliferative disease
2	4	46 days	Yes (venous thrombosis)	Sepsis, sclerosing cholangitis
3	5	11 months	Yes (arterial thrombosis)	Seizures, fluid and electrolyte disturbance
4	12	2 days	Yes (venous thrombosis)	Intra-abdominal hemorrhage secondary to graft rupture
5	13	12 months	Yes (venous thrombosis)	Cardiac insufficiency

Source: Elaborated by the authors

DISCUSSION

In the present study, renal graft and patient survival were, respectively, 86.3 and 90.2%. These data are similar to those from the North American Pediatric Renal Trials and Collaborative Studies[4] (NARPTCS), which included 12,189 pediatric patients and observed, from 2005 to 2013, a 5-year graft survival of 83%. Data from the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA)[5], with 322 children under 5 years of age, showed graft survival at 1, 5 and 10 years, respectively, of 93, 87 and 77%. A similar study carried out in Brazil, Collaborative Brazilian Pediatric Renal Transplant Registry (CoBrazPed-RTx)[6], which evaluated 2,744 patients from 2014 to 2018, obtained graft survival of 87% when the transplant was performed with a living donor and 78% when it was with a deceased donor. Patient survival in this study was 95 and 94% for living and deceased donors, respectively. These studies[4,6] compared patients who received grafts from living and deceased donors and showed more remarkable survival in the living donor transplant group. This can be justified by the harmful effects of prolonged cold ischemia and/ischemia-reperfusion injury present in allografts from deceased donors, unlike the controlled environment with minimal ischemic injury in kidneys from living donors, capable of enabling a prolonged half-life in this type of graft. However, our study found this analysis impossible because most donors were deceased.

In both living and deceased donor transplants, studies show that one of the most frequent causes of graft loss is renal thrombosisl[7-10]. This data was confirmed in our observation, with the losses being early in the first month post-transplant.

The CoBrazPed-RTx study[6] also observed renal thrombosis as the primary etiology (20%), followed by graft dysfunction (17%) and death with a functioning graft (15%). Such findings differ from the NAPRTCS report[4], which found chronic rejection as the leading cause of graft loss (35.8%), followed by acute rejection (13%) and vascular thrombosis (9.6%), in addition to death with a functioning graft in 9.1% of cases.

Renal graft thromboses may be related to the characteristics of the donor, the recipient and preoperative variables, such as ischemia time, surgical technique and management in the immediate postoperative period[9-12]. In Brazil, a retrospective study carried out by Avilez et al.[13], at the State University of Campinas, São Paulo, showed that graft loss due to thrombosis was mainly associated with those patients undergoing a second transplant (22.7% vs. 8.2% in the first transplant) and donors with a high BMI (with mean BMI of 29.11 in the group with thrombosis vs. 22.47 in the group without thrombosis).

Currently, there is a much discussion about forms of prophylaxis, whether medicinal or not, to reduce the incidence of thrombosis and other vascular events that can lead to kidney graft loss. However, despite the severe consequences of renal thrombosis in these patients, there is still no consensus on the use of drug thromboprophylaxis in pediatric kidney transplantation. Some centers already use low molecular weight heparin, unfractionated heparin or even antiplatelet agents for this purpose[9,10,14,15]. Our center still does not perform routine prophylaxis on these patients.

Considering the importance of thromboembolic events as the main complication that leads to early graft loss, a questionnaire carried out in 80 pediatric kidney transplant centers by the European Society for Pediatric Nephrology from 2019 to 2020 and a systematic review carried out in Germany on antithrombotic prophylaxis in pediatric kidney transplantation showed that this practice appears to reduce the number of thrombotic complications. However, the risks of bleeding remain unknown. These centers also highlight that the best medication, the time to start and the population of patients who should use thromboprophylaxis remain uncertain, varying between the transplant centers studied[11,15]. In Brazil, a study conducted at the Hospital das Clínicas of the University of São Paulo by Beatrice et al.[10] reported 10 years of experience carrying out antithrombotic prophylaxis. It reduced the thrombosis rate without increasing the risk of bleeding.

Other factors that may be associated with graft loss are the etiology of CKD, cold ischemia time, age of the donor and recipient, hypertension and dyslipidemia. In our series, we observed that patients whose CKD etiology was not glomerulopathies, mostly congenital anomalies of the kidney and urinary tract, presented lower graft survival. These data differ from the NARPTCS study[4], which showed that graft survival in glomerulopathic patients was lower than ours results. This study showed that patients undergoing deceased donor kidney transplantation had a 5-year graft survival rate of 63% for those patients whose disease etiology was glomerulonephritis; for those with focal segmental glomerulosclerosis (FSGS), the rate was 67%. The CoBrazPed-RTx study[6] showed that the graft survival rate, according to the etiology in 5 years, was 84% for patients who did not have FSGS and 68% for those who did. Patients with FSGS had 26.7% graft loss due to primary disease recurrence, and this group had 1.5 times the risk of graft loss compared to recipients whose etiology was not FSGS. Analyzing the difference between our results compared to the literature is challenging, and any statement may be speculative. However, the predominance of graft loss due to thrombosis in our sample, which is a cause of early loss, may have contributed to the difference in results.

Regarding cold ischemia time, similar to the NAPTRCS study[4], we did not observe an association of this factor with graft survival. Likewise, we found no association between the donor's age and the recipient's graft survival. Moudgil's studies et al.[16], who analyzed North American children undergoing kidney transplantation, also did not identify a difference in graft survival between donors aged 6 to 35 years and those aged less than 5 years. In another study[17], it was observed that the use of grafts from older donors was associated with worse graft survival, especially when the donor was deceased, with those over 55 years of age having a worse prognosis. Regarding the recipient's age, eight children (15.6%) were under 5 years old in our study. Although with a tiny sample, we did not observe differences in the survival analysis regarding the recipient's age, more or less than 5 years, or gender. Our results are similar to those of NAPRTCS[4]. The ANZDATA data[5] showed little difference in 5-year graft survival for children who received a transplant before age 2 compared to those aged 6 or older – 81 and 83%, respectively. However, another similar Brazilian study noted a trend toward worse survival in those whose transplants occurred in recipients under 5 years of age[18].

In the present study, 58.8% of patients had high blood pressure after transplantation, which is close to data in the literature[19], in which 50 to 65% of recipients present hypertension 1 year after transplantation. This is likely due to a combination of rapid weight gain, medication side effects, and kidney damage20.In our series, most patients had an appropriate BMI for their age, and although no association was observed between this variable and hypertension with the graft survival rate in the period analyzed, controlling weight and hypertension is a goal that must be pursued.[21,22].

In a study that looked at post-transplant hypertension, it was seen that children with systolic hypertension had a significantly higher graft failure rate, regardless of donor type, cause of renal failure, presence or absence of acute rejection, and 1-year allograft function after transplantation. For every 10% increase in systolic blood pressure one year after kidney transplantation, there is a doubled risk of subsequent graft failure. A negative effect of elevated systolic blood pressure on long-term outcome was seen even

in "low-risk" children with living donor transplantation, no acute rejection, and a relatively good allograft (glomerular filtration rate > 50 mL/min per 1 .73 m^2)1 year after transplant[23]. This is important to note, as some previous studies have argued that increased blood pressure would not be the cause but simply a marker of chronic allograft dysfunction that may develop due to the previously described risk factors[24].

Dyslipidemia is a common complication after kidney transplantation and a significant risk factor for cardiovascular diseases, which also contribute to kidney dysfunction. The pathogenesis is multifactorial, but there is an essential association with the use of immunosuppressants, especially cyclosporine. Our study showed that 80.4% of patients had dyslipidemia after transplantation, but there was no difference in the graft survival rate compared to those who did not present this change. The fact that we did not find this association does not exempt us from caring about the treatment of these patients, given the high cardiovascular risk and the possibility of chronic rejection in the long term. Therefore, controlling dyslipidemia should be a goal to be achieved[19,25,26].

In our series, death occurred in five (9.8%) patients. Of these, two were secondary to sepsis, one due to cardiovascular disease, one due to water and electrolyte disorders and the other due to hemorrhagic shock. In the CoBrazPed-RTx study[6], Death occurred in 5.4% of patients, with the main etiologies being infection (47%) and cardiovascular disease (19%). ANZDATA data[27], on the other hand, show higher mortality from cardiovascular causes (40%), followed by infectious causes (17%) and cancer (12%). This report also points out the 1st year after transplantation as the period with the highest risk of death, with approximately double the incidence per patient/year compared to subsequent years. Infection was the most common cause of death during this period. These data corroborate the findings of our study, in which all deaths occurred within 2 years after transplantation. Our results are also close to the NAPRTCS report[4], which showed a mortality rate of 5.3%, with infection being the leading cause (28.4%), followed by cardiopulmonary disease (14.6%), causes of malignancy (11.5%) and complications related to dialysis (3%).

Over time, a significant improvement in post-transplant mortality has been observed in the literature due to improvements in immunosuppression protocols, prevention and treatment of infections, and greater attention to cardiovascular risks. Regarding post-transplant lymphoproliferative disorders (PTLD), there was no improvement in mortality, which remains stable[28]. It is known that PTLD is associated with primary Epstein-Barr virus (EBV) infection, and improvements in therapeutic strategies are related to better knowledge about the biology of PTLD, the role of EBV infection, and the application of molecular genomic techniques[29].

Despite improvements in the overall survival of patients undergoing kidney transplantation, cardiovascular disease remains the cause of a third of deaths in those who receive a transplant before the age of 21, and the life expectancy of these patients is approximately 15 to 20 years shorter than the general population[19,28]. Efforts need to be made to optimize the long-term function of the graft, identify risks early, and improve therapeutic interventions.

When preparing this study, we identified limitations that must be considered. As it was a retrospective study, the analysis of other variables associated with kidney graft loss, in addition to those mentioned, was restricted by the lack of data in the medical records. Another obstacle was that it was a single-center study, with a small sample size and few transplants from living donors, making it difficult to generalize the results. On the other hand, the relevant aspects of the research were knowing the survival outcomes of pediatric kidney transplants performed at the reference center in the area, IMIP, identifying the risk factors associated with these results, and, in this way, being able to contribute to proposing improvements in management. of the pediatric kidney transplant patient.

CONCLUSION

In this study, we observed that the survival characteristics of the graft and patients are similar to data in the literature. Renal thrombosis, demonstrated here as the predominant cause of graft loss directs us to plan a protocol for prevention measures. Furthermore, investigating the high prevalence of non-immunological factors, such as hypertension and dyslipidemia, which contribute to chronic rejection and cardiovascular mortality, requires an individualized approach for control based on a standardized, structured and standardized care routine.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Soeiro EMD, Lopes DSG; **Conception and design:** Soeiro EMD; **Data analysis and interpretation:** Soeiro EMD, Lopes DSG; **Article writing:** Soeiro LG, Silva APV, Lima ACM, Araújo MEC; **Critical revision:** Soeiro EMD; **Final approval:** Soeiro EMD, Lopes DSG, Araújo IO.

DATA AVAILABILITY STATEMENT

Data will be available upon request.

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