

# Clinical Outcomes of Belgian Children Following Kidney Transplantation, Comparative Analysis from 2005 to 2022

Sidney Van Leynseele<sup>a</sup>, Brigitte Adams<sup>b,c</sup>, Benedetta Chiodini<sup>c</sup>, Laure Collard<sup>d</sup>, Nathalie Godefroid<sup>e</sup>, Ann Raes<sup>f</sup>, Koen Van Hoeck<sup>g</sup>, Elena Levtschenko<sup>h</sup>, Noël Knops<sup>i</sup>

<sup>a</sup> Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium

<sup>b</sup> University Hospitals Leuven, Department of Pediatric Nephrology, Leuven, Belgium

<sup>c</sup> Queen Fabiola Children's Hospital, Department of Paediatric Nephrology, Brussels, Belgium

<sup>d</sup> CHU de Liège, Department of Pediatric Nephrology, Liège, Belgium

<sup>e</sup> Cliniques Universitaires Saint-Luc, Department of Pediatric Nephrology, Brussels, Belgium

<sup>f</sup> Ghent University Hospital, Department of Pediatric Nephrology, Erknnet Center, Ghent, Belgium

<sup>g</sup> Antwerp University Hospital, Department of Pediatric Nephrology, Edegem, Belgium

<sup>h</sup> Emma Children's Hospital, Department of Pediatric Nephrology, Amsterdam University Medical Center, the Netherlands

<sup>i</sup> Groene Hart Ziekenhuis, Department of Pediatrics, Gouda, The Netherlands

noelknops2@gmail.com

## Keywords

End stage renal disease ; kidney transplantation ; renal replacement therapy ; hypertension ; growth stunting.

## Abstract

The aim of this study was to analyze the annual cross-sectional data on the outcome of all patients followed after pediatric kidney transplantation in Belgium, as collected for the Convention of Pediatric Nephrology from 2018-2022. During this period, a total of 569 entries of individual follow-up data were included in the registry with a mean of 113.8 entries annually, mean follow-up time was 5.6 years post-transplantation. Most patients were classified as having chronic kidney disease (CKD) stage 2 or 3 (36.4% and 41.3% respectively). The mean estimated glomerular filtration rate (eGFR) was lower compared to the 2005 cohort (61.8 + 25.4 ml/min/1.73 m<sup>2</sup> vs. 68.1 + 17 ml/min/1.73 m<sup>2</sup>, respectively (p<0.05)). eGFR decreased with the number of years of follow-up, which was particularly evident in boys but not in girls. We compared our findings to the Belgian registry cohort of 2005 and to the recently published data from North-American and European registries. Overall, we observed a positive evolution in growth and cardiovascular outcomes, with mean height and blood pressure standard deviation scores (SDS) significantly improving compared to both the 2005 and the international cohorts.

## Introduction

Chronic kidney disease affects approximately 9% of the global population and causes approximately 1,2 million deaths annually (1). The incidence of kidney failure (KF) in the general population is approximately 144 cases per million people (pmp) (2).

In contrast, KF affects only 5 to 15 per million children (pmc) annually, worldwide. However, it is associated with significant morbidity, including cardiovascular disease and growth stunting (3). Moreover, children with KF face a mortality risk 30 times higher than that of the general pediatric population (4, 5). Kidney transplantation (KTx) is the preferred kidney replacement therapy (KRT) for both adults and children with KF, offering a significant survival advantage over dialysis (6). In Europe, the median incidence rate of pediatric KTx is 5.7 pmc, while in Belgium, the incidence exceeds 10.5 pmc, with approximately 24 pediatric KTx performed annually (7). Over the last few decades, there have been significant improvements in patient and graft survival rates among

children receiving kidney transplants, largely due to advances in immunosuppressive therapy, surgical techniques, organ allocation policies and increased rates of living donor transplantation (6).

KF is a rare condition in children compared to adults, making evidence-based conclusions about optimal treatment and outcome parameters more challenging. To gather valuable data on pediatric KTx, several (inter)national retrospective data registries have been established, such as the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) and the Cooperative European Pediatric Renal Transplant Initiative Registry (CERTAIN) (8, 9). However, the CERTAIN registry does not include data from all six centers currently involved in pediatric KTx in Belgium.

In 2001, the Belgian Pediatric Nephrology Registry (BPNR) was established to collect comprehensive data on all children diagnosed with chronic kidney disease (CKD) in Belgium. The goal was to monitor and analyze outcomes before and after the diagnosis of pediatric KF in Belgium, as described by Hiep et al.

in 2010 (10). Unfortunately, this registry has not been continued. In 2009 the "Convention for Pediatric Nephrology" was introduced as a collaboration between the government, health insurance companies and pediatric nephrology centers (11). This convention aims to enable children with severe kidney diseases to live "as normal as possible" and "in the best feasible health condition" by offering additional financial support to the centers, enabling them to deliver tailored multidisciplinary care. To comply with the convention, each center is required to conduct regular face-to-face contact, provide individual medical reports to healthcare workers and provide outcome parameters for children receiving care under the convention. An interim analysis of the data was performed by Knops et al. (12).

This study aimed to analyze the data collected for the Convention of Pediatric Nephrology and provide information on the outcomes of all patients who underwent pediatric KTx in Belgium between 2018-2022. This study will report their clinical characteristics and outcomes and compare them with previously gathered data from 2005, as well as data from larger international registries.

## Materials and Methods

In this multicenter, retrospective cross-sectional study, data were collected from the six academic centers in Belgium that perform KTx in children: CHU (Liege), HUDERF and UCL (Brussels), UZ Antwerp, UZ Ghent and UZ Leuven. The study included patients with CKD under 19 years of age who underwent KTx between January 1, 2018, and December 31, 2022, as described in the registry (the Convention of Pediatric Nephrology). According to national protocol, children under 19 years of age should receive a kidney transplant in pediatric and not adult centers. Each pediatric nephrology department was represented by at least one local investigator responsible for the patient inclusion and annual follow-up data. The principal investigator conducted a general audit to ensure data completeness. The following information was collected annually: sex, age, date of transplant, time since transplant, length, weight, systolic and diastolic blood pressure and serum creatinine levels. This assembly took place by circulating the same request to provide these data on the individual patients in current follow-up to all centers by the principal investigator at the same time of the year in relation to an annual convention meeting. Informed consent was not required given the anonymity of the data. Estimated glomerular filtration rate (eGFR) was calculated using the Schwartz equation (13). Creatinine was, depending on the center, measured by either the photometric or enzymatic method and has its known limitations in estimating the eGFR such as dependency on age and muscle mass (14). CKD stages were defined according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) (15).

**TABLE 1:** general characteristics of the study population

Characteristic	Study population
Sex (N (%))	Male: 349 (61.3%) Female: 220 (38.7%)
Age at follow-up (mean + SD) - Male population - Female population	12.8 ± 4.2 years - 13.0 ± 4.3 years - 12.7 ± 4.0 years
Age at transplant (mean + SD) - Male population - Female population Age categories (N (%))	7.4 ± 4.6 years - 7.4 ± 4.6 years - 7.5 ± 4.6 years 0-1 years: 27 (4.7%) 2-5 years: 244 (42.9%) 6-12 years: 193 (33.9%) 13-17 years: 104 (18.3%) > 18 years: 1 (0.2%)
Years of follow-up after transplant (mean + SD) - Male population - Female population	5.6 ± 4.3 years - 5.7 ± 4.3 years - 5.4 ± 4.3 years
Center of follow-up (N (%))	HUDERF: 133 (23.4%) UZL: 99 (17.4%) UZGent: 115 (20.2%) UZA: 104 (18.3%) Liege: 57 (10.0%) UCL: 61 (10.7%)
Entries per year of report (N (%))	2018: 121 (21.3%) 2019: 117 (20.6%) 2020: 116 (20.4%) 2021: 109 (19.2%) 2022: 106 (18.6%)
BMI SDS (mean + SD) - Male population - Female population	0.0 ± 1.2 - 0.1 ± 1.3 - -0.1 ± 1.0
Height SDS (mean + SD) - Male population - Female population	-1.2 ± 1.4 - -1.2 ± 1.5 - -1.2 ± 1.4
eGFR (mean + SD) - Male population - Female population	61.8 ± 25.4 mL/min/1.73m <sup>2</sup> - 57.6 ± 25.7 mL/min/1.73m <sup>2</sup> - 68.6 ± 23.5 mL/min/1.73m <sup>2</sup>
CKD stage (N (%))	1: 77 (13.5 %) 2: 207 (36.4 %) 3: 235 (41.3%) 4: 27 (4.7%) 5: 23 (4.0%)
Systolic blood pressure SDS (mean + SD) - Male population - Female population	0.7 ± 0.9 - 0.7 ± 0.9 - 0.7 ± 0.9
Diastolic blood pressure SDS (mean + SD) - Male population - Female population	0.6 ± 0.8 - 0.7 ± 0.8 - 0.5 ± 0.8

Hypertension was determined based on the clinical guidelines by Flynn et al., with hypertension defined as systolic or diastolic blood pressure above the 95th percentile for the patients' age, sex and height (16). Stunting was defined as a height standard deviation below -1,96 according to age and sex (17). Statistical significance was defined as a two-sided p-value <0.05. Data analysis was performed using SPSS version 29.0 for Windows (SPSS, Chicago, IL) and the results were compared with the previously published data by Hiep et al. (10).

## Results

### Demographics of study population

The characteristics of the study population are shown in Table 1. Between 2018 and 2022, 569 entries of individual follow-up data were recorded in the registry, with an average of 113.8 annually. Of these, 61.3% were male. The children were aged 2 - 18 years, with a mean of 12.8 years at the last follow-up visit. The mean age at the time of transplant was 7.4 years, with no significant differences between the centers included in the registry. Only 4.7% of the population underwent transplantation before the age of 2 years. The mean follow-up time after transplant was 5.6 years. The

**TABLE 2:** number of patients in follow-up per center, listed per year of report

	CHU (Liege)	HUDERF (Brussels)	UCL (Brussels)	UZ Antwerp	UZ Ghent	UZ Leuven	Total
2018	13	34	9	22	24	19	121
2019	12	28	10	23	23	21	117
2020	12	26	14	20	24	20	116
2021	12	21	13	21	23	19	109
2022	8	24	15	18	21	20	106

number of patients in follow-up at each center remained stable over the years, although with a slight annual decrease, as shown in Figure 1 and Table 2, with HUDERF following the largest number of patients overall.

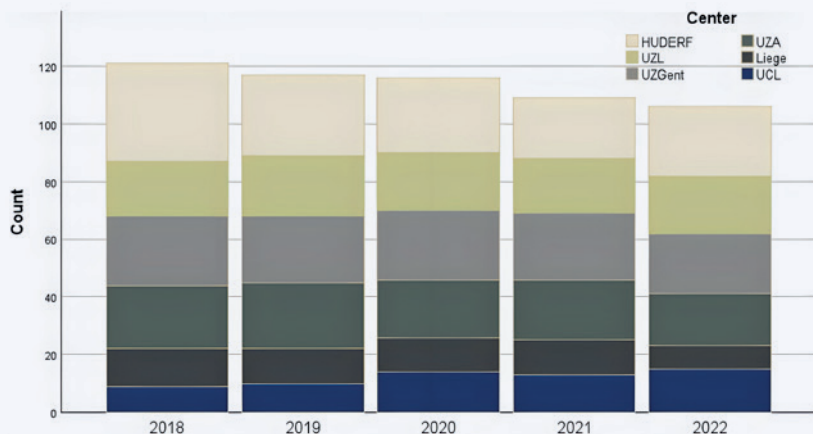
### Height and weight

The mean height SDS was  $-1.2 \text{ SDS} \pm 1.4 \text{ SD}$ . More than a quarter (27.4%) of the study population demonstrated growth stunting, but the mean height SDS was significantly better compared to the population in 2005:  $-1.9 \text{ SDS} \pm 1.5 \text{ SD}$  ( $p < 0.01$ ) (Figure 2). The entire population had a normal BMI ( $0.0 \text{ SDS} \pm 1.2 \text{ SD}$ ), with 3.1% of the population having a BMI SDS of 2.0 or higher, and 4.4% having a BMI SDS of -2.0 or lower. Overall height and weight SDS scores were not significantly correlated with the number of years of follow-up after transplantation. However, in female patients, there was a significant negative correlation between age at follow-up and height or weight SDS (Pearson correlation coefficient respectively -0.138 and -0.220 ( $p < 0.05$ )).

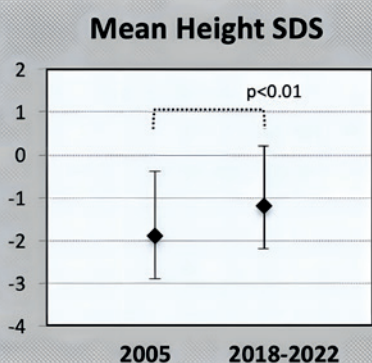
### Blood pressure

Mean reported BP measurements were slightly higher than reference values for normal children with a mean systolic score of  $0.7 \text{ SDS} \pm 0.9$  and

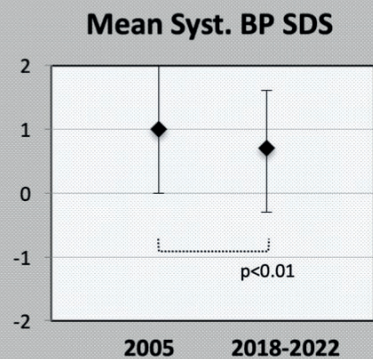
**FIGURE 1:** number of patients in follow-up per center, listed per year of report



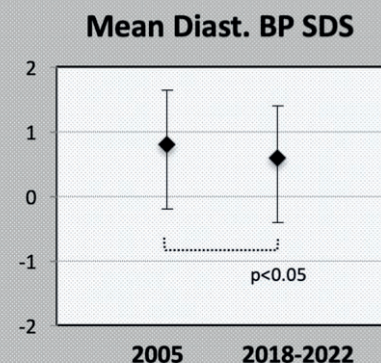
**FIGURE 2:** comparison of mean height SDS between 2005 and 2018-2022



**FIGURE 3:** comparison of mean systolic blood pressure SDS between 2005 and 2018-2022



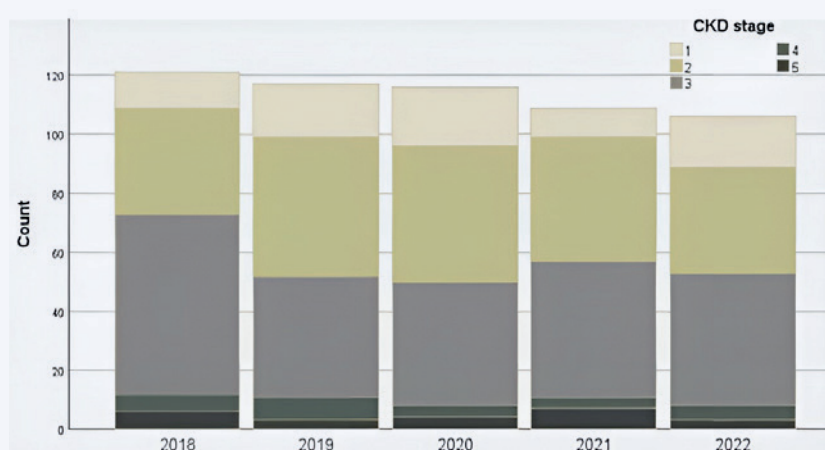
**FIGURE 4:** comparison of mean diastolic blood pressure SDS between 2005 and 2018-2022



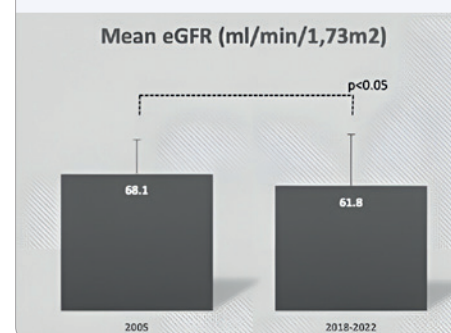
**TABLE 3:** CKD stages per year of report

	CKD stage 1 N (% of total)	CKD stage 2 N (% of total)	CKD stage 3 N (% of total)	CKD stage 4 N (% of total)	CKD stage 5 N (% of total)	Total
<b>2018</b>	12 (9.9%)	36 (29.8%)	61 (50.4%)	6 (5.0%)	6 (5.0%)	121
<b>2019</b>	18 (15.4%)	47 (40.2%)	41 (35.0%)	8 (6.8%)	3 (2.6%)	117
<b>2020</b>	20 (17.2%)	46 (39.7%)	42 (36.2%)	4 (3.4%)	4 (3.4%)	116
<b>2021</b>	10 (9.2%)	42 (38.5%)	46 (42.2%)	4 (3.7%)	7 (6.4%)	109
<b>2022</b>	17 (16.0%)	36 (34.0%)	45 (42.5%)	5 (4.7%)	3 (2.8%)	106

**FIGURE 5:** CKD stages per year of report



**FIGURE 6:** comparison of mean eGFR between 2005 and 2018-2022



a mean diastolic score of  $0.6 \text{ SDS} \pm 0.9$ . In this population 9.1% had systolic hypertension and 7.7% had diastolic hypertension. However, the mean systolic and diastolic blood pressures were significantly lower compared to those recorded in 2005 ( $+1.0 \text{ SDS}$  ( $p < 0.01$ ) for systolic and  $+0.8 \text{ SDS}$  ( $p < 0.05$ ) for diastolic blood pressure) (Figures 3 and 4). Additionally, there was a significant difference in the mean diastolic SDS between boys and girls ( $+0.7$  versus  $+0.5 \text{ SDS}$  ( $p < 0.01$ )), while the mean systolic pressure SDS did not differ significantly between the sexes. Blood pressure SDS was not significantly correlated with the number of years of follow-up after transplantation. However, both systolic and diastolic blood pressure SDS scores were negatively correlated with age at follow-up (Pearson correlation coefficient respectively  $-0.142$  and  $-0.107$  ( $p < 0.01$ )). When analyzed by sex, this negative correlation remained significant for male subjects but not for females. Additionally, systolic blood pressure SDS, but not diastolic blood pressure SDS, was significantly correlated with BMI SDS (Pearson correlation coefficient  $0.108$  ( $p < 0.05$ )). 17.8% and 17.6% of the population had systolic and diastolic pressure SDS  $< 0.0$ , respectively.

### Glomerular filtration rate and CKD stages

Mean eGFR was  $61.8 \pm 25.4 \text{ ml/min/1.73 m}^2$ . Most patients were classified as having CKD stage 2 or 3 (36.4% and 41.3%, respectively), and this distribution remained stable over the follow-up period, as shown in Figure 5 and Table 3. Only 12.8% of the

population had an eGFR of  $90 \text{ ml/min/1.73 m}^2$  or higher. The eGFR was significantly lower in males compared to females ( $p < 0.01$ ). At one year post-transplantation, the mean eGFR was higher ( $71.2 \pm 27.3 \text{ ml/min/1.73 m}^2$ ). The mean eGFR in the years 2018-2022 was significantly lower than in 2005 ( $68.1 \pm 17 \text{ ml/min/1.73 m}^2$  ( $p < 0.05$ )) (Figure 6).

There was a strong negative correlation between eGFR and both age at follow-up and number of years post-transplantation (Pearson correlation coefficient respectively  $-0.135$  and  $-0.211$ ,  $p < 0.01$ ). When corrected for sex, this strong negative correlation persisted for male patients (Pearson correlation coefficient respectively  $-0.165$  and  $-0.282$  ( $p < 0.01$ )), but not for females. There was a positive, but not statistically significant correlation between age at transplant and eGFR (Pearson correlation coefficient  $0.078$ ,  $p = 0.062$ ). The eGFR was significantly negatively correlated with both systolic and diastolic blood pressure SDS (Pearson correlation coefficient respectively  $-0.120$  and  $-0.127$  ( $p < 0.01$ )).

### Discussion

In this multicenter, retrospective cross-sectional study, we collected data from the Belgian Convention of Pediatric Nephrology, which contains all patients followed after pediatric KTx in Belgium during the years 2018-2022. In the following, we compared our results with the Belgian 2005 cohort, as well as data from two major

registries: the 2018 North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) publication, who followed 11870 pediatric patients post-transplantation between 1987 and 2017, and the 2019 CERTAIN (European) registry publication, which followed 336 children transplanted between 1996 and 2012 (3, 10, 18). The mean age at transplant was lower in our cohort (mean age at transplantation  $7.4 \pm 4.6$  years in our cohort versus  $10.1 \pm 5.2$  years in the CERTAIN study), with the largest proportion of Belgian patients transplanted in the age categories of 2-5 years (42.9%), whereas the most common age at transplantation in the NAPRTCS study was 13-17 years (38.8%). The difference in age may be due to differences in protocols for KRT treatment, experience and availability of donor organs (living versus deceased donor) concerning young children between different countries and centers. Sex distribution was very similar in all three cohorts (male-to-female ratio 61.7/38.3 in our cohort, 60/40 in the NAPRTCS cohort, 62/38 in the CERTAIN cohort).

## Height and weight

Although we still reported growth stunting in more than a quarter of our patients, the mean height SDS was significantly higher than that in the 2005 cohort. This improvement is probably due to changes in post-transplantation immunosuppressive therapy over the decades, particularly the decreased use of systemic glucocorticoids (3, 6, 19). Difference in practices regarding the use of growth hormone before and after transplantation might have contributed to this positive trend, although our registry data lacked detailed information regarding the use of both treatments. Overall, growth outcomes in Belgian children with renal transplants appear to be better than those reported in other registries. Our reported mean height SDS ( $-1.2 \text{ SDS} \pm 1.4 \text{ SD}$ ) was higher compared to the 2018 NAPRTCS population (mean deficit of  $-1.62$ , SD not reported) and the 2019 CERTAIN study ( $-1.5 \text{ SDS} \pm 1.8 \text{ SD}$ ), although it is important to mention that the NAPRTCS reported at time of transplant and CERTAIN at discharge within 30 days of transplantation (3, 18). In our female patients, we observed a significant negative correlation between height SDS and age at follow-up, indicating that younger children in our cohort had a higher mean height SDS. This aligns with previous reports suggesting that younger children with CKD who experience growth stunting tend to show greater growth recovery post-transplantation (6). Similarly, the NAPRTCS registry reported the most significant improvement in height post-transplantation among the youngest children in their cohort (3). The observed correlation between height SDS and age at follow-up in our female population might be related to the earlier onset of adolescent growth spurt in girls, providing a shorter window for catch-up growth post-transplantation. We have no data indicating differences in growth hormone or corticosteroid treatments between the sexes. Although obesity and overweight are commonly reported after kidney transplantation in children, our population showed a median BMI SDS of 0.0, with only a small proportion classified as overweight or underweight (19). This could be attributed to improved multidisciplinary care with better nutritional practices and, as mentioned previously, reduced use of systemic glucocorticoids. In comparison, the European registry reported a mean BMI SDS of  $-0.11 \pm 1.31$  at discharge within 30 days post-transplantation, while the NAPRTCS registry did not provide a mean BMI SDS (3, 18).

## Kidney function

We found a lower mean eGFR in our cohort than in the population of 2005. One possible explanation is that over recent decades, improvements in care have enabled the transplantation of more complex patients, including younger patients with more comorbidities, as suggested by other authors (20, 21). Consistent with this, our cohort included patients transplanted at a younger

age than those in the CERTAIN and NAPRTCS cohorts, with nearly 5% of our population being transplanted before the age of 2 years. Younger recipients in the NAPRTCS cohort experienced greater absolute decline in eGFR over time (3). In our patients, eGFR decreased with both older age at follow-up and longer time since transplantation, although we did not find a statistically significant correlation between eGFR and age at transplantation. Poor medication adherence is a common problem among adolescents and young adults and may contribute to this decline (6). Moreover, the underlying disease could play a role: glomerulopathy, which is more prevalent in older age groups, is associated with a faster decline in eGFR compared to patients with congenital anomalies of the kidney and urinary tract (CAKUT), although our data lacked information on CKD etiology (22). The mean eGFR at one year post-transplantation was also lower in our cohort compared to the CERTAIN study (mean eGFR respectively  $71.2 \pm 27.3 \text{ mL/min/1.73 m}^2$  versus  $80.6 \pm 29.0 \text{ mL/min/1.73 m}^2$ ) although the CERTAIN study measured eGFR at 30 days post-transplantation (18). Donor characteristics were not collected in this registry, but differences in donor criteria between Belgian and international pediatric nephrology centers, such as living versus deceased donor, age, size and HLA mismatch, could provide useful insight for future studies.

## Blood pressure

We observed significantly better systolic and diastolic blood pressure SDS than the 2005 cohort. Only 9.1% and 7.7% of our patient population had systolic and diastolic hypertension, respectively. In comparison, Belgian children performed better than those in the CERTAIN registry, where 77% of children were diagnosed with hypertension at three years post-transplant (18). We hypothesize that this improvement may also be due to improved multidisciplinary care within the convention, better therapy compliance and reduced use of systemic glucocorticoids. They observed higher systolic blood pressure (SBP) SDS in younger patients with a shorter time since transplantation, and in male patients with higher BMI and non-CAKUT cause of CKD. We also found a higher SBP SDS in younger patients and patients with higher BMI. Only the diastolic blood pressure (DBP) SDS was significantly higher in males compared to females. Arterial hypertension contributes to progression of kidney dysfunction and negatively affects graft survival and studies have shown that improved blood pressure control can slow CKD progression (23, 24). Undiagnosed hypertension in infants and young children is a common problem and other studies have also highlighted the undertreatment of hypertension in younger children undergoing KRT (25, 26). Given the correlation between higher BMI and hypertension, increased focus on healthy diet and exercise in patients with CKD could further optimize blood pressure control.

Limitations to this study include the cross-sectional nature of the data and the lack of data on CKD etiology, medication use, type of transplantation and donor characteristics. Methodology in creatinine assay differed between the centers. The number of entries gradually declined each year, without provided reasons, and patient mortality was not recorded. All individual entries were collected per year and merged; therefore, it is possible that a patient with multiple records had a greater influence on the population average.

## Conclusion

In conclusion, this study offers insights into the clinical outcomes of pediatric patients at follow-up after kidney transplantation in Belgium. Compared to the 2005 Belgian cohort and larger

European and American registries, we observed better growth and cardiovascular outcomes, which could be the result of improved post-transplant care made possible by a special funding program for multidisciplinary follow-up. However, the mean eGFR has not benefitted, particularly in older male patients, and efforts should be made to tackle eGFR decline during longer follow-up periods. All centers in the registry will continue to collect follow-up information as of 2023 and beyond.

## Conflicts of Interest

The authors declare no conflicts of interest.

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