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ORIGINAL ARTICLE

Setting reasonable objectives for improving preemptive kidney transplantation rates in children

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Abstract

Background This study aims to develop a method to estimate the potential of preemptive kidney transplantation (PKT) by identifying patients who were transplanted after a dialysis period (non-preemptive kidney transplantation (NPKT)) despite being medically suitable for PKT.

Methods All children (< 18 years old) starting kidney replacement therapy (KRT) in France, between 2010 and 2016 and transplanted before December 31, 2017, were included. A propensity score (PS) of receiving PKT was estimated by multivariate logistic regression based on recipient medical characteristics. Healthcare use during the 24 months prior to KRT initiation was extracted from the French National Health Insurance database, and a pre-KRT follow-up of more than 18 months was considered sufficient to allow preemptive transplantation.

Results Among 643 patients who started KRT, 149 (23.2%) were preemptively transplanted. Using PS stratification, among 391 NPKT patients, we identified 145 patients (37%) suitable for PKT, according to clinical characteristics. Mean age was 12.3 years, 67% were males, and 56% had urological abnormalities. Among those 145 patients, we identified 79 NPKT patients who started on dialysis despite early referral to a nephrologist (more than 18 months prior to KRT initiation).

Conclusions This method estimates a potential of 228 (149 + 79) PKT (35%) among pediatric patients in France. A similar method could be used in adults or in other countries. Estimation of the rate of patients with CKD stage 5 medically suitable for PKT will be of interest for health policy makers when setting up objectives for improvement in preemptive kidney transplant access.

Keywords Children · Clinical epidemiology · CKD 5 · Preemptive kidney transplantation · Propensity score

Introduction

Kidney transplantation is nowadays recognized as the modality of choice for kidney replacement therapy (KRT) in children and has been associated with a better survival and an improved quality of life [1–3]. Preemptive kidney transplantation (PKT), defined as transplantation prior to the initiation of dialysis, is the optimal treatment for patients with stage 5 chronic kidney disease (CKD 5) [4–6]. In children, PKT prevents dialysis-related medical and psychosocial complications and is associated with better kidney transplantation outcomes and lower financial costs [7–9].

Despite the World Health Organization recommendations of equitable access to transplantation, disparities in preemptive transplantation have been reported in the adult and pediatric CKD 5 populations [10–12]. European countries differ widely in their overall rates of preemptive transplantation

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ranging from < 5 to > 60% of all pediatric kidney transplantations [13].

Geographical differences in the prevalence of the underlying diseases, which display various rate of progression, only partially explain the disparities in PKT rates. Those disparities may also be due to differences in the organization of KRT care, time to referral for transplantation, deceased donor allocation policies, and availability of living donors.

Indeed, early specialized nephrology care prior to KRT is associated with increased survival [14, 15], earlier access to the waitlist for kidney transplantation, and greater rates of transplantation [16–18].

Therefore, we hypothesize that clinical characteristics and early referral may allow the identification of pediatric patients suitable for PKT. The aim of this study is to develop a generalizable method to estimate the potential number of pediatric CKD 5 patients medically eligible for a preemptive transplantation.

Methods

Population

We considered for inclusion all children in the French CKD 5 National Registry, REIN, who started KRT: hemodialysis (HD), peritoneal dialysis (PD) or PKT, between 1 January 2010 and 31 December 2016, aged < 18 years at KRT onset. The organization, data collection, and quality control of the REIN registry have been described elsewhere [19]. Patients were followed until 31 December 2017 or until death so that all patients have at least 12 months of follow-up.

Patient characteristics

Relevant patient characteristics recorded in the REIN registry were the year and age at start of KRT, sex, primary kidney disease, country of birth, date of registration on the waiting list, immunological data (ABO and HLA groups, anti-HLA antibodies), height, weight, comorbidities, disabilities at baseline, and type of donor: deceased (DD) or living donor (LD). Comorbidities were summarized in one dichotomous variable: at least one comorbidity (yes/no). We determined growth retardation (for height and weight) according to international standards for chronological age (height or BMI < − 2 standard deviations).

The cause of CKD was classified according to seven primary kidney disease groups for children (vascular diseases, urological abnormalities, glomerulonephritis, interstitial nephritis, hereditary nephropathy, other, unknown). Using the immunological data (ABO group, HLA antigens, and antibodies), we calculated the FAGN (national ease of graft access) index for each child [20]. This score, used since July 2010 to allocate organs in France, rates from 0 to 60 the number of possible donors with the same ABO group, fewer than 3 HLA mismatches, and no donor-specific HLA antibodies during the previous 5 years.

Information about medications, hospitalizations, and outpatient visits was extracted from the exhaustive French National Health Insurance database (SNDS), which includes all reimbursed prescriptions and procedures delivered on an outpatient basis and all hospital discharges. We included all information from the SNDS within 24 months prior to KRT start in order to determine the date of first contact with a nephrologist or a pediatric nephrologist. It was defined as the date of the first nephrology specialist consultation, or the date of the first use of a chronic kidney disease (CKD)–specific drug, or the first hospitalization with a renal diagnostic. Since data from both databases are de-identified and no unique identifier or crosswalk between these databases is available, we performed a stepwise indirect linkage of these two databases, based on demographic data previously published elsewhere [21]. In total, 89.7% of our population could be linked.

Drugs were classified based on their Anatomical Therapeutic Chemical (ATC) classification codes, and the use of a drug was defined as having at least one reimbursement of this drug over the time period. Institutional review boards or independent ethics committees reviewed and approved the study (CNIL number 903188).

Estimation of the proportion of CKD 5 patients eligible for preemptive transplantation

First step: We selected pediatric patients who received a kidney transplant before the end of the follow-up, in order to identify patients clinically suitable for transplantation.
Second step: We performed a multivariable logistic regression model in order to estimate the probability to be transplanted preemptively versus non-preemptive kidney transplantation (NPKT) after a dialysis period (dichotomous outcome) based solely on recipients' medical characteristics, including demographics (age, sex, country of birth) and clinical characteristics (primary kidney disease). Since our goal was to evaluate medical suitability and not ease of access to preemptive transplantation, we purposefully did not include factors impacting access to a transplant once listed (e.g., blood type, HLA type frequency in the donor pool (summarized in the FAGN)). Potential availability of a living donor is not recorded in the registry. For each patient, the estimated propensity score (PS) was obtained from the fit of this previous multivariate logistic regression model. The PS estimates the likelihood of a recipient to receive a PKT.
Third step: We used a quartile stratification PS-based model [22] and selected the patients with a preemptive transplant probability within the two upper quartiles of

the PS distribution (patients with a high probability of PKT).

Fourth step: Among those patients with a good profile to be preemptively transplanted, we selected patients with a follow-up by a nephrologist of at least 18 months prior to KRT start. This cut-off of 18 months was chosen to allow enough time for pre-transplant workup, waitlisting, and kidney allocation based on previous reports from the French data [23, 24].

Assessment of additional barriers to preemptive kidney transplantation

Among patients deemed eligible for kidney transplant (good profile to be preemptively transplanted, and a follow-up by a nephrologist of at least 18 months prior to KRT start), we compared donor, immunological characteristics, and time on the waiting list between PKT and NPKT patients to assess whether these factors might explain the remaining difference observed.

Statistical analysis

For descriptive analysis, continuous variables are given as medians, interquartile ranges (IQR), and dichotomous variables in percentages. We used Chi-square and Wilcoxon tests to assess the difference between dichotomous and continuous variables respectively.

Quantitative variables were tested for linearity and were dichotomized in classes if the association was found to be non-linear. All variables with a p value less than 0.2 were included in the multivariable logistic model and presented with estimations of the odds ratio (OR) and confidence intervals (CIs). p values < 0.05 were considered statistically significant and statistical analysis was performed using SAS 9.4.

Complementary analysis

Some additional sensitivity analyses were performed.

The PS was estimated for all wait-listed pediatric patients (not only those transplanted before the end of the follow-up). We also assessed the effect of choosing different threshold of pre-CKD 5 nephrology follow-up (6 and 12 months), to define early referral compatible with preemptive transplantation.

Results

Patient and transplant characteristics

Table 1 describes patient characteristics at KRT start and transplant characteristics by first KRT modality. A total of 643 patients aged less than 18 years old started KRT in France between 2010 and 2016, 149 of whom received a PKT (23.1%). Patients were 58% male with a median age at KRT start of 13.2 (9.9–16.2) years. The primary cause of CKD was urological abnormalities in 31.6%, hereditary nephropathies in 25.8%, and glomerular diseases in 16.3% of the patients.

At the end of follow-up, 540 (84%) were transplanted (median follow-up after KRT start 3.0 years [IQR 1.3–5.0]) after a median waiting time on the national list of 7.6 months [IQR 3.8–15.2]. PKT patients had a higher NFAG (ease of graft access index) (15 [IQR 8–22] vs. 12 [IQR 6–19]) compared with NPKT. Moreover, they were transplanted more rapidly after registration (4.8 months [IQR 2.3–9.0] vs. 9.5 [4.6–16.2], $p < 0.001$) and more frequently with a LD (36.7% vs. 11.8, $p < 0.001$).

Estimation of the proportion of CKD 5 patients eligible for preemptive transplantation

One hundred three patients were not transplanted and were removed from the analysis as described at the first step of the methods to exclude patients not suitable for transplantation (Fig. 1). Indeed, those 103 patients had a specific profile, younger at KRT initiation with a median age of 4.0 years [IQR 1.1–13.5] and with a shorter follow-up 1.1 years [IQR 0.6–2.4] after KRT start (Table 1). 39/103 (37.8%) were still not registered on the waiting list at the end of the follow-up.

In univariable analysis, PKT patients were significantly older with only 1.3% of patients aged 0–3 years old compared with 12.5% in NPKT patients, more likely to be born in France ($p = 0.001$) and to present urological abnormalities (59% vs. 24%), as primary kidney disease ($p < 0.0001$). Patients with PKT tended to be less often girls with 35% vs. 41% for NPKT ($p = 0.18$) (Table 2). Finally, we found no association between the probability of PKT and underweight, growth retardation, or comorbidity.

In multivariable analysis, the following patient characteristics remained significantly associated with a lower probability to receive a PKT (Table 2): age < 3 years (OR 0.08 [95% CI 0.02–0.35] compared with 6–10 years old), vascular diseases or glomerular diseases (OR 0.05 [95% CI 0.01–0.25] and 0.05 [95% CI 0.02–0.14] respectively compared with urological abnormalities), birth abroad (OR 0.23 [95% CI 0.11–0.49]).

As mentioned in step 2 of the methods, we calculated the propensity score (PS) of PKT for each transplanted patient. The median PS value of the study population was 0.27 [IQR 0.08–0.42]. As expected, NPKT patients had a lower PS 0.15 [IQR 0.08–0.29] than PKT patients 0.42 [IQR 0.27–0.60].

Following step 3, we then selected 265 patients with a high probability of PKT defined as patients with PS > 0.27 (two uppers quartiles), with respectively 120 PKT patients (45%) and 145 NPKT (55%) who presented clinical characteristics compatible with PKT (Fig. 1). In this group, there was no patient under 3 years, with vascular disease or glomerulonephritis.

Table 1 Patient characteristics at KRT start and transplant characteristics by first KRT modality

Patient characteristics	**All population (*N* = 643)**	**PKT (*N* = 149)**	**NPKT (*N* = 391)**	**no transplantation (*N* = 103)**
Follow-up (years) (median-IQR)	3.0 [1.3–5.0]	3.0 [1.0–5.1]	3.6 [1.9–5.3]	1.1 [0.6–2.4]
	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**
Preemptive transplantation	149 (23.1)	149 (100)	-	-
Hemodialysis	340 (53)	-	278 (71.0)	62 (61.2)
Peritoneal dialysis	154 (23.9)	-	113 (29.0)	41 (39.8)
Gender				
Female	270 (42)	52 (35)	161 (41)	57 (55.4)
Male	373 (58)	97 (65)	230 (59)	46 (44.6)
Age at start of KRT (median-IQR)	11.7 [4.9–15.5]	13.2 [10.0–16.2]	12.0 [5.1–15.5]	4.0 [1.1–13.5]
Age at start of KRT (years)				
0–2 years	88 (13.7)	2 (1.3)	49 (12.5)	37 (36)
3–5 years	79 (12.3)	12 (8)	46 (11.8)	21 (20.4)
6–10 years	93 (14.5)	24 (16.1)	58 (14.8)	11 (10.7)
11–15 years	199 (31)	59 (39.6)	125 (32)	15 (14.6)
16–17 years	184 (28.5)	52 (35)	113 (28.9)	19 (18.3)
Renal diseases				
Urological abnormalities	203 (31.6)	88 (59)	94 (24)	21 (20.4)
Vascular diseases	49 (7.6)	3 (2)	31 (7.9)	15 (14.6)
Hereditary nephropathy	166 (25.8)	26 (17.4)	120 (30.7)	20 (19.4)
Glomerulonephritis	105 (16.3)	5 (3.4)	77 (19.7)	23 (22.3)
Interstitial nephritis	39 (6.1)	11 (7.4)	21 (5.4)	7 (6.8)
Unknown	60 (9.3)	11 (7.4)	39 (10)	10 (9.7)
Other	21 (3.3)	5 (3.4)	9 (2.3)	7 (6.8)
Country of birth	***Missing = 14***			
France	532 (84.6)	134 (93)	313 (81.5)	85 (84.2)
Other	97 (15.4)	10 (7)	71 (18.5)	16 (15.8)
underweight	***Missing = 50***			
No	527 (88.9)	123 (91.2)	321 (89)	81 (85.3)
Moderate (− 2 < z-score ≤ -3SD)	49 (8.2)	9 (6.6)	31 (8.5)	9 (9.5)
Severe (z-score < -3SD)	17 (2.9)	3 (2.2)	9 (2.5)	5 (5.3)
Growth retardation	***Missing = 40***			
No	457 (75.8)	105 (76.6)	290 (78.1)	62 (65.3)
Moderate (−2 < z-score ≤ -3SD)	97 (16.1)	23 (16.8)	56 (15.1)	18 (18.9)
Severe (z-score < -3SD)	49 (8.1)	9 (6.6)	25 (6.8)	15 (15.8)
At least one comorbidity	***Missing = 58***			
No	533 (91)	126 (92)	330 (93.2)	77 (82)
Yes	52 (9)	11 (8)	24 (6.8)	17 (18)
Transplant characteristics				
Waiting time on the list (months) (median-IQR)	7.6 [3.8–15.2]	4.8 [2.3–9.0]	9.5 [4.6–16.2]	–
Donor type	***Missing = 4***			
Living	100 (18.7)	54 (36.7)	46 (11.8)	–
Dead	436 (81.3)	93 (63.3)	343 (88.2)	–
NFAG	12 [6–20]	15 [8–22]	12 [6–19]	–

KRT, kidney replacement therapy; *PKT*, preemptive kidney transplantation; *NPKT*, non-preemptive kidney transplantation; *SD*, standard deviation; *FAGN*, national ease of graft access

To be sure that patients with a high probability based on their medical characteristic profile of PKT could have been really preemptively transplanted, we restricted our sample to those with an early referral defined as a nephrology follow-up of over

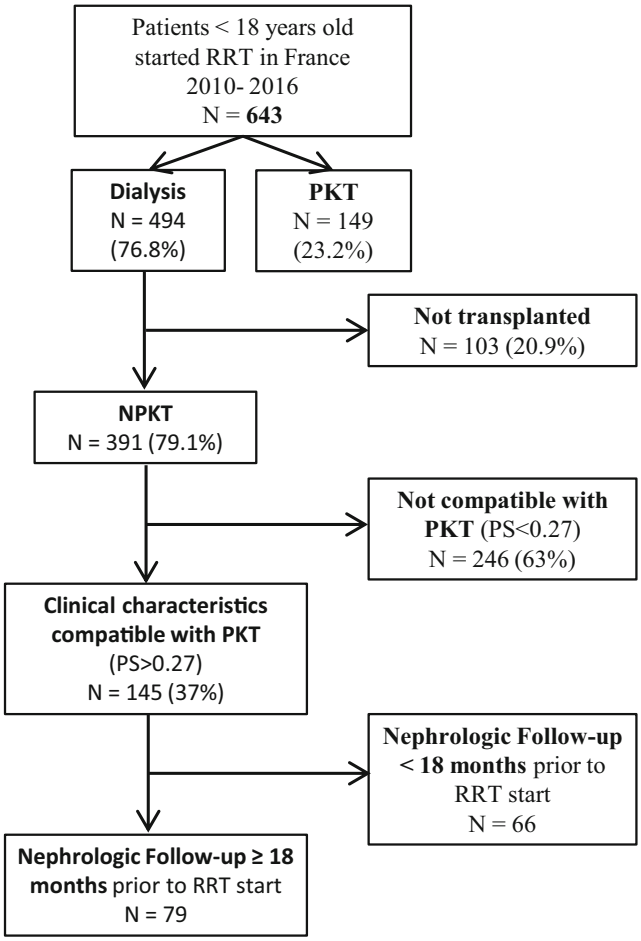

Fig. 1 Selection of the proportion of CKD 5 patients eligible for preemptive transplantation. KRT, renal replacement therapy; PKT, preemptive kidney transplantation; NPKT, non-preemptive kidney transplantation; PS, propensity score

18 months before dialysis start. Finally, 79 NPKT (among 391, i.e., 20%) patients could have potentially benefited from a PKT in view of their clinical and demographic characteristics (PS > 0.27) and their prolonged nephrology pre-KRT follow-up.

Conversely, 60 PKT (40%) had a PS < 0.27 and/or a nephrology pre-KRT follow-up < 18 months. Adding those 79 eligible patients to the 149 PKT patients would increase the proportion of patients with the possibly of PKT in France from 23 to 35% of all CKD 5 pediatric patients starting KRT (Fig. 1).

In comparison, if the selected cut-offs had been 12 or 6 months prior to KRT (instead of 18), the number of dialysis patients considered eligible for PKT would have been 88 and 94 (vs. 79) respectively, and thus an estimated 36.9% and 37.8% (vs. 35%) of PKT.

Assessment of additional barriers to preemptive kidney transplantation

The median waiting time to transplant after registration on the national waiting list for the 79 NPKT patients was longer compared with the 149 PKT: 9.9 [IQR 5.4–17.9] months vs. 4.8 [IQR 2.3–8.9] ($p < 0.001$). Among those 79 NPKT patients, 28 (35.4%) were waitlisted after the start of dialysis and 51 (64.6%) were waitlisted before dialysis start (median time from waitlisting to dialysis 3.9 months [IQR 1.6–8.0] vs. 4.8 [IQR 2.3–9.0] in PKT patients). Living donor transplantation was more frequent in the PKT group with 36.9% vs. 11.9% in the NPKT group ($p < 0.001$). No difference was found in the immunological characteristics (NFAG) of the two groups.

Discussion

In this nationwide study, we developed a systematic method to estimate the potential increase in PKT rates. This method, based on the linkage of the REIN registry to the National Health Insurance database, combines clinical characteristics at KRT and pre-CKD 5 follow-up data to identify patients medically eligible for a PKT. This methodology could be extended in adults and to other countries based on data availability. In France, we found that PKT rates could be improved by 50% from 23 to 35% in children, based on patient characteristics and pre-KRT follow-up time.

The aim of this study was to assess medical suitability for PKT; therefore, we only included clinical characteristics in the PS. Major characteristics found associated with PKT were age and primary kidney disease. Indeed, most pediatric transplant centers require a minimum weight for transplantation (usually between 10 and 15 kg). Therefore, children reaching CKD 5 before 3 years of age were usually transplanted after a dialysis period (NPKT). Given the low prevalence of extra-renal comorbidities in children, the primary kidney disease is a major predictor of the time needed to access transplantation. For example, preemptive transplantation is usually difficult to achieve in rapidly progressive glomerulonephritis, in specific diseases with systemic involvement such as lupus, or in diseases requiring pre-transplant nephrectomy.

The target of 35% PKT appears reasonable in comparison with the other European countries [13], but remains lower than United Kingdom (UK) (around 45%) or Scandinavian countries (more than 50%). The probability of receiving a preemptive transplantation also depends on factors affecting the access to transplant. We therefore compared these factors, among patients deemed eligible for PKT, between patients who did or did not receive a PKT. This approach can provide indications on the main barriers to PKT and guide modification of health policies. In France, we found that the low rate of living donation may be the main barrier to increasing PKT rate. Indeed, the proportion of living donor transplantation in France (16% in 2016 [23]) is much lower than those in the UK and Scandinavian countries, with rates of LD higher than 40 and 80%, respectively [25].

Table 2 Rate of PKT, univariate and multivariable logistic regression analysis of factors associated with PKT among transplanted children (PKT versus NPKT)

Transplanted patient characteristics *N* = 540	% of PKT %	Univariable analysis *p*	Multivariable Analysis OR [95% CI]
Gender			
Female	24.4	0.18	1
Male	29.6		1.06 [0.67–1.68]
Age at KRT (years)			
0–2 years	3.9	< 0.001	0.08 [0.02–0.35]
3–5 years	20.7		0.64 [0.27–1.52]
6–10 years	29.3		1
11–15 years	32.1		1.35 [0.71–2.55]
16–17 years	31.5		1.38 [0.73–2.66]
Kidney diseases			
Urological abnormalities	48.3	< 0.001	1
Vascular diseases	8.9		0.05 [0.01–0.25]
Hereditary nephropathy	17.8		0.23 [0.13–0.40]
Glomerulonephritis	6.1		0.05 [0.02–0.14]
Interstitial nephritis	34.4		0.44 [0.19–1.01]
Unknown	22.0		0.27 [0.12–0.58]
Other	35.7		0.59 [0.17–1.97]
Country of birth	Missing = 12		
France	30.0	0.001	1
Other	12.3		0.23 [0.11–0.49]

PKT, preemptive kidney transplantation; *NPKT*, non-preemptive kidney transplantation; *OR*, odds ratio; 95% CI, confidence interval

Those differences may be explained by differences in the allocation systems. In France, patients on dialysis are being given priority over patients preemptively listed. However, the strong pediatric priority and the little benefit conferred by the time on dialysis in the French allocation system maintain a relatively good access to DD transplantation in preemptively listed patients. In the USA, the implementation of a new allocation system for pediatric recipients (SHARE 35) that preferentially offers kidneys from young deceased donors to pediatric recipients, has resulted in shorter waiting times for DD transplantation, but in a decrease in the rate of LD transplantation [26]. Similarly, the good access to DD transplantation in pediatric recipients preemptively waitlisted may disincentivize patients and families to pursue living donation. Thus, incentives to favor living donation in this population are needed. Moreover, the development of incompatible ABO transplants and of a paired-exchange kidney program may facilitate the increase in living donation and PKT in the years to come. Therefore, increasing the rate of PKT in France beyond 35% may require achieving a significant increase in living donation and is currently a major focus of the French regulatory agency.

HLA type frequency in the donor pool (summarized in the FAGN) was no different in the two groups, but of course, individual immunological factors can influence the waiting time for a transplant. Many studies prove that HLA mismatch significantly increases the risk of graft failure for both LD and DD recipients, and the waiting time on the list may therefore increase in the case of an unfavorable ABO or a lower ease of graft access [27, 28]. Data from the registry do not include donor selection policies or HLA mismatch for every patient. In the future, a qualitative study asking nephrologists why each potentially eligible patient did not get a PKT would be very interesting and will provide further information to develop interventions aimed at increasing PKT rates.

However, our approach may underestimate the potential of PKT due to a conservative approach by selecting only patients with a follow-up by a nephrologist of at least 18 months prior to KRT start. This cut-off is superior to other definitions of the late referral ranging from 1 to 6 months [14, 29, 30], but reflect current practices in France with a median time of 5 months from CKD 5 to registration on the kidney transplant waiting list [24] and then a 5-month median waiting time on the list during the 2002–2016 period [23]. Lowering our threshold from 18 to 6 months would slightly increase the proportion of potential PKT.

A recent European study [17] analyzed late referral using a glomerular filtration rate (GFR)–based definition of late

referral. In our study, due to the lack of GFR data at presentation to a nephrologist, timing of referral was based on actual time prior to KRT rather than based on GFR. Moreover, there are no standardized criteria to guide transplant referral and evaluation practices in children, creating practice variation with subjective interpretation of GFR cut-offs for waitlisting and medical and psychosocial "readiness."

Although this study, based on patients' characteristics and follow-up pre-KRT, clearly demonstrated a potential for increasing PKT rate in children in France, there are several limitations to be considered. First, we selected only children finally transplanted before the end of the follow-up. In fact, 90% of these non-transplanted patients had a PS less than 0.27 and therefore did not have the eligible medical profile for PKT, mainly due to their young age.

Furthermore, besides medical factors and follow-up time, other factors are known to impact access to PKT. In North America, and Europe, several patient-level factors including ethnicity, socioeconomic status, and residence location have been associated with access to pediatric kidney transplantation and were not available in this study [11, 12, 24].

Given the small size of most of pediatric transplant centers, we could not investigate potential center effects among the patients eligible for PKT, although center characteristics are known to play a role in disparities in access to the kidney transplant waiting list in France [24], which is the first step towards preemptive transplantation. Furthermore, this is a population-based statistical approach and there are patients with low PS who have had access to a preemptive transplantation. Finally, the aim of the study is not to give French guidelines but to identify room for improvement in PKT rate in children.

In conclusion, in this study we report on a simple generalizable method to estimate the potential increase in PKT. This method can be replicated for other countries by recalculating a specific PS. When applying this method to the French pediatric CKD 5 population, we estimate that 12% (79/643) additional CKD 5 pediatrics patients could have been transplanted preemptively. Although overall access to transplantation for children in France is good, with one of Europe's highest rates of transplantation and shortest waiting times thanks to a strong pediatric priority, efforts should be made to promote preemptive listing and living donor transplantation and avoid, as much as possible, exposure to dialysis in children. Further studies are now needed to check the applicability and usefulness of our approach in other countries with other practices.

Compliance with ethical standards

Institutional review boards or independent ethics committees reviewed and approved the study (CNIL number 903188).

Conflict of interest The authors declare that they have no conflicts of interest.

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