ORIGINAL ARTICLE

Preemptive second kidney transplantation is associated with better graft survival compared with non-preemptive second transplantation: a multicenter French 2000–2014 cohort study

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SUMMARY

The impact of preemptive second kidney transplantation (2KT) on graft and patient survival is poorly established. The association between preemptive 2KT (p2KT, $N = 93$) and outcomes was estimated in a multicenter French cohort of 2KT ($N = 1314$) recipients using propensity score methods. During the follow-up, there were 274 returns to dialysis and 134 deaths. p2KT was associated with lower death-censored graft loss (HR = 0.39 [0.18–0.88], $P = 0.024$) and graft failure from any cause including death (HR = 0.42 [0.22–0.80], $P = 0.008$). Similar associations were observed for death with a functioning graft, although not reaching statistical significance (HR = 0.47 [0.17–1.26], $P = 0.13$). There was a significant interaction between donor type and p2KT (P for interaction = 0.016). Indeed, p2KT was not significantly associated with the risk of graft failure from any cause including death in living donor 2KT ($P = 0.39$), whereas the association was substantial in the deceased donor subset (HR = 0.30 [0.14–0.64], $P = 0.002$). Of note, the adjusted graft survival of p2KT with deceased donor paralleled that of 2KT with living donor, either preemptive or not (93.8% vs. 88.6% at 4 years and 76.1% vs. 70.5% at 8 years, $P = 0.13$). This large French multicenter study analyzed using propensity scores suggests that p2KT is associated with better graft prognosis.

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Key words
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Introduction

The number of patients waiting for a second kidney transplantation (2KT) is steadily growing [1,2], given the increased life expectancy of first kidney transplantation (1KT) recipients [3] and a better prognosis of retransplantation in comparison with the return to dialysis [4,5]. Moreover, access to kidney transplantation has generally improved, irrespective of the rank of the graft, with more frequent transplantation of older recipients [3,4] or recipients with comorbidities. Considering the poorer graft survival of 2KT [6,7], and the more difficult access to 2KT than 1KT due to HLA sensitization and organ shortage [3,4], it is therefore critical to elucidate the optimal therapeutic strategy for retransplantation. In particular, little is known regarding the impact of preemptive 2KT on graft and patient prognosis.

The beneficial impact of first preemptive renal transplantation on graft and patient survival is well established [8–11], particularly in the case of living donor transplantations [12–14]. While dialysis duration has been proven to be associated with poorer graft prognosis [8,10], only sparse studies have assessed the impact of a preemptive second kidney transplantation (p2KT) on graft and patient survival [7,15–17] or on pre-retransplant dialysis duration [7,15,18,19] with conflicting results.

Deleterious effects of dialysis after graft failure may differ in comparison with transplant-naive incident dialysis patients, leading to a differential impact of preemptive transplantation in instances of 1KT or 2KT. Indeed, patients with severe graft dysfunction are under immunosuppressive therapy [20] and frequently present a chronic inflammatory state [21] as well as a poorer nutritional status [22] than transplant-naive patients. Moreover, the optimal glomerular filtration rate for initiating dialysis is uncertain [23], *a fortiori* in case of return to dialysis after graft failure [24,25].

The objective of this study was hence to assess the impact of p2KT on graft survival and patient outcomes.

Methods

Study population

A total of 1314 patients were extracted from the prospective French multicenter database of transplanted patients DIVAT (computerized and VAlidated data in Transplantation) [26], which includes the University Hospitals of Nantes, Nancy, Montpellier, Toulouse, Necker (Paris), Lyon, Saint-Louis (Paris), and Nice. The "Comité National de l'Informatique et des Libertés" approved the study (CNIL no. 891735), and written informed consent was obtained from the participants. All patients fulfilling the following inclusion criteria were studied: adult recipients who received a 2KT performed between January 2000 and December 2014 from deceased or living donors. Data were prospectively entered in a computerized database on day 0, 3 months, and 12 months of 2KT and were updated annually thereafter. Patients were followed annually until February 2015. A preemptive 2KT was defined by the absence of dialysis between the two transplantations or dialysis duration of <7 days prior to 2KT, as usually defined in the literature.

Data collection

Baseline characteristics collected at 2KT included gender, age, body mass index, comorbidities (diabetes, hypertension, cardiac and/or vascular disease, dyslipidemia), causal nephropathy, dialysis method (peritoneal dialysis or hemodialysis) and time on dialysis prior to 2KT (in case of non-preemptive 2KT (np2KT)), duration on waiting list, and duration of the first graft. Immunological data (blood group, historical anti-HLA sensitization) were also collected.

Second kidney transplantation parameters included preemptive status, donor type (living donors; standard criteria donors (SCD); expanded criteria donors (ECD): donors aged 60 years and older, and those aged over 50–59 years with at least two of the following three conditions: cerebrovascular cause of death, serum creatinine greater than 1.5 mg/dl (132.6 μmol/l), or a history of hypertension), HLA A-B-DR incompatibilities, cold ischemia time, induction therapy (antithymocyte globulin or antilymphocyte globulins; anti-IL-2 receptor monoclonal antibodies; none), and maintenance immunosuppressive regimen.

Second kidney transplantation follow-up included delayed graft function, defined by the necessity of one or more dialysis sessions in the first week after 2KT, acute rejection, creatinemia, and estimated glomerular filtration rate (eGFR) at 3, 6, 12 months, and once yearly thereafter. eGFR was estimated using the MDRD formula [27]. Return to dialysis and death before return to dialysis were collected.

French policy for graft allocation

During the study period, pretransplant immunological status was assessed using various assays over time

(CDC, ELISA, or Luminex Bead Array). In addition, the French graft allocation scoring system also changed during this period in part by taking into account these modifications. Thus, sensitization against HLA antigen class I and/or class II was considered regardless of the method used. Of note, in July 2009, the policy for graft allocation was modified, aiming to prioritize access to transplantation for highly sensitized patients.

Statistical analysis

All analyses were performed using R software (the R Foundation for Statistical Computing). The two-tailed significance level was set at $P < 0.05$. Categorical variables are described as frequencies (percentages), while continuous variables are described as mean ± standard deviation if normally distributed or as median (percentile 25–75) if distribution was skewed. Hazard ratios are presented with their 95% confidence intervals as HR (CI 95%). Comparisons of baseline characteristics according to preemptive and non-preemptive 2KT were made using Welch's *t*-test or nonparametric Mann–Whitney test for continuous variables as appropriate, and chi-square or Fisher's exact test for categorical variables.

To assess the associations between p2KT and outcomes (return to dialysis or preemptive third kidney transplantation (p3KT), death before return to dialysis or p3KT, return to dialysis or death before return to dialysis or p3KT), time-to-event analyses were performed using Cox regression models. Proportional hazard assumption was thoroughly verified using the Schoenfeld residuals test.

As previously used by our team [28], in order to correct for potential bias in the selection of patients, a propensity score (PS)-based analysis was performed in order to calculate the probability of having a p2KT status. The PS representing the likelihood of receiving a p2KT was calculated for each patient using a logistic regression model [29]. There were some missing variable values in the data: 1.5% of patients had at least one missing value among continuous variables, 21.6% at least one missing value among categorical variables and 22.4% at least one missing value among all variables. Furthermore, the number of patients with p2KT ($n = 93$) was smaller than that of those without p2KT ($n = 1221$). A missing indicator approach was used in the estimation of the PS for categorical variables in order to preserve the maximum of data completeness [30,31]. Furthermore, the variables were introduced in the PS using an iterative forward procedure [29,32]. This process is detailed in Appendix S1.

The variables included in the PS model were gender, age, comorbidities, blood group, HLA sensitization anticlass I, HLA sensitization anticlass II, duration on waiting list, time since 1KT, year of 2KT, renal transplant center, CMV status, HLA incompatibilities, cold ischemia time, and type of donor.

Among observational studies, the use of PS-based methodology ensures the closest design to a clinical trial [33]. Among PS-based techniques, an inverse probability treatment weighting (IPTW) was performed herein using stabilized weights [26]. These probabilities correspond to the inverse of the PS calculated from the logistic regression. Stabilized weights were obtained by multiplying IPTW by the marginal probability. Of note, this IPTW technique has been shown in simulation studies to provide the least biased results in survival analysis [26]. In contrast with PS matching, IPTW avoids discarding patients from the analysis; every patient is analyzed, being attributed with an individualized weight, which is never set to 0.

The balance between the two groups (p2KT vs. np2KT) was assessed using two methods. The absolute standardized mean difference (ASMD) was first calculated before and after weighting. For each variable, the ASMD represents the absolute difference between the mean values in the two groups divided by the common standard deviation. For each categorical variable with more than two levels, the ASMD was calculated for each level. As there is no clear consensus determining the threshold value indicating variable balance [31,34], variable balance was considered to be obtained when ASMD was <25%. In a second step, group imbalance was also verified with weighted Welch's *t*-test for continuous variables and weighted chi-square test for binary variables.

Weighted Cox regression models were also performed using stabilized weights. Survival rates are illustrated using weighted Kaplan–Meier analyses using the *survfit* function in the R *survival* package. Differences between survival curves were analyzed using the robust log-rank test.

Interactions between p2KT and a set of variables selected for their clinical relevance (namely year of transplantation, age at second transplant, donor type (living or deceased), HLA sensitization positive anticlass I and II) were evaluated in weighted Cox models.

The dose effect due to duration of dialysis among patients without p2KT was also studied in comparison with patients with p2KT.

A sensitivity analysis was performed on a subset of patients to compare patients with p2KT and patients with np2KT but preemptively re-enrolled before dialysis initiation.

Table 1. Baseline characteristics of patients at second kidney transplantation according to preemptive or non-preemptive status.

	Missing data	np2KT (*N* = 1221)	p2KT (*N* = 93)	*P*-value
Demographics				
Male	–	757 (62.0%)	54 (58.1%)	0.45
Age at second transplant	–	47.1 ± 13.4	45.7 ± 13.8	0.35
Body mass index (kg/m²)	13 (1.0%)	23.0 ± 3.9	23.2 ± 3.9	0.59
Comorbidities at second transplant				
Diabetes	–	69 (5.7%)	10 (10.8%)	0.046
Hypertension		963 (78.9%)	78 (83.9%)	0.25
Vascular disease		165 (13.5%)	10 (10.8%)	0.45
Cardiac disease		426 (34.9%)	20 (21.5%)	0.009
Cardiovascular disease		509 (41.7%)	28 (30.1%)	0.029
Dyslipidemia		330 (27.0%)	39 (41.9%)	0.002
Viral hepatitis B or C		154 (12.6%)	6 (6.5%)	0.080
Neoplasia		197 (16.1%)	19 (20.4%)	0.28
Tuberculosis		1 (0.1%)	1 (1.1%)	0.14
Blood group				
A	1 (0.1%)	563 (46.1%)	52 (55.9%)	0.29
O		495 (40.6%)	29 (31.2%)	
B		110 (9.0%)	8 (8.6%)	
AB		52 (4.3%)	4 (4.3%)	
HLA immunization				
Positive anticlass I	103 (7.8%)	802 (71.0%)	33 (40.7%)	<0.0001
Positive anticlass II	159 (12.1%)	778 (72.4%)	40 (49.4%)	<0.0001
Positive anticlass I and II	155 (11.8%)	611 (56.7%)	24 (29.3%)	<0.0001
Causal nephropathy				
Chronic glomerulonephritis	–	536 (43.9%)	43 (46.2%)	0.51
Diabetic nephropathy		12 (1.0%)	0 (0.0%)	
Vascular nephropathy		43 (3.5%)	3 (3.2%)	
Chronic tubulointerstitial		483 (39.6%)	41 (44.1%)	
Unknown		147 (12.0%)	6 (6.5%)	
Time on waiting list (in months)	–	25.2 (9.5–48.8)	8.0 (3.6–20.5)	<0.0001
Duration of first graft (in years)	70 (5.3%)	7.5 (2.5–13.4)	13.6 (9.3–19.6)	<0.0001
Pretransplant dialysis time (in months)	4 (0.3%)	39.2 (19.5–74.7)		–
Dialysis method				
Peritoneal dialysis	–	48 (3.9%)	–	–
Hemodialysis		1173 (96.1%)	–	
Second renal transplant				
Year of second transplant				
2000–2004	–	309 (25.3%)	9 (9.7%)	0.003
2005–2009		527 (43.2%)	46 (49.5%)	
2010–2014		385 (31.5%)	38 (40.9%)	
Living donor	6 (0.5%)	85 (7.0%)	27 (29.0%)	<0.0001
Type of donor				
Living donor	6 (0.5%)	85 (7.0%)	27 (29.0%)	<0.0001
Standard criteria donor		765 (63.0%)	45 (48.4%)	
Expanded criteria donor		365 (30.0%)	21 (22.6%)	
Viral status CMV donor/recipient				
Donor + / recipient +	15 (1.1%)	440 (36.5%)	40 (43.0%)	0.24
Donor + / recipient −		170 (14.1%)	11 (11.8%)	
Donor − / recipient +		414 (34.3%)	24 (25.8%)	
Donor − / recipient −		182 (15.1%)	18 (19.4%)	
HLA A-B-DR incompatibilities				
0	27 (2.1%)	97 (8.1%)	7 (7.5%)	0.044
1–2		465 (38.9%)	30 (32.3%)	
3–4		547 (45.8%)	42 (45.2%)	
5–6		85 (7.1%)	14 (15.1%)	

Table 1. Continued.

	Missing data	np2KT (*N* = 1221)	p2KT (*N* = 93)	*P*-value
Cold ischemia time (h)	7 (0.5%)	20.7 ± 8.9	14.4 ± 9.9	<0.0001
Cold ischemia time (h)				
Living donor	13 (1.0%)	2.4 ± 1.9	1.9 ± 1.1	0.087
Deceased donor		22.0 ± 7.7	19.5 ± 6.7	0.005
Immunosuppressive regimen				
Cyclosporin	2 (0.2%)	142 (11.6%)	15 (16.1%)	0.20
Tacrolimus		1050 (86.1%)	79 (84.9%)	0.75
mTOR inhibitors		22 (1.8%)	1 (1.1%)	1.00
Mycophenolate mofetil		1185 (97.2%)	91 (97.8%)	1.00
Azathioprin		18 (1.5%)	2 (2.2%)	0.65
Corticosteroid		1192 (97.8%)	90 (96.8%)	0.47
Induction treatment		1182 (97%)	87 (93.5%)	0.12
Lymphocyte-depletive agent		933 (76.5%)	58 (62.4%)	0.002

np2KT, non-preemptive second kidney transplant; p2KT, preemptive second kidney transplant.

Results

Characteristics at the time of the second transplantation

Between 2000 and 2014, a total of 1314 2KT were performed, including 93 preemptive p2KT (Table 1). The proportion of p2KT increased over time (2.8% during the 2000–2004 period, 8.0% during the 2005–2009 period, 9.0% during the 2010–2014 period, $P = 0.003$). Moreover, the proportion of living donor 2KT was greater than in the p2KT group (29% vs. 7% in the np2KT group, $P < 0.0001$).

Recipients of a p2KT had a shorter waiting list time (16.7 ± 24.2 months vs. 35.1 ± 34.4 months, $P < 0.001$), along with a longer duration of their first graft (14.6 ± 7.4 vs. 8.6 ± 7.1 years, $P < 0.0001$). They did not differ from the other patients with regard to gender, age, BMI, or causal nephropathy. There were more diabetic patients in the p2KT group, whereas cardiovascular comorbidities were less frequent. The percentage of patients with anti-HLA sensitization was much lower in the p2KT group whether for class I (40.7% vs. 71%) or class II (49.4% vs. 72.4%). Despite the higher proportion of living donors in the p2KT group, more patients had poor HLA matching in the p2KT group comparatively to the np2KT group (5 or 6 A-B-DR incompatibilities: 15.1% vs. 7.1%). Fewer patients received a lymphocyte-depleting agent as induction therapy in the p2KT group (62.4% vs. 76.5%). The use of mycophenolate mofetil and tacrolimus was similar in both groups. Cold ischemia time was shorter in the p2KT group in the case of transplantation with deceased donors (19.5 ± 6.7 vs. 22.0 ± 7.7 h, $P = 0.005$), but similar in the case of living donors.

As shown in Table 2, propensity score analysis and use of ITPW analysis enabled to correctly balance baseline characteristics between patients with preemptive or non-preemptive 2KT. Only the time interval of 2KT performed between 2000 and 2004 and renal transplant center remained unbalanced after this process, and survival analyses were therefore adjusted for these two remaining factors.

Short- and long-term outcomes of second kidney transplantation

Patients with p2KT experienced less delayed graft function (2.2% vs. 36.6%, $P < 0.0001$; Tables 3 and 4). Post-transplant cardiovascular complications were similar in both groups. In contrast, cellular and/or humoral rejections were more frequently observed in np2KT than in p2KT ($P = 0.005$). eGFR was higher in the p2KT group during the entire follow-up, although statistically significant only until 1 year after the 2KT (at 1 year 58.7 ± 16.9 vs. 53.2 ± 19.7 ml/min/1.73 m^2, $P = 0.011$), with the number of patients decreasing over time.

During the follow-up, 274 patients lost their graft and 134 died with a functioning graft. Weighted Kaplan–Meier survival curves for return to dialysis (or p3KT), death, death or return to dialysis in patients with a preemptive and non-preemptive 2KT are presented in Fig. 1a–c. In unweighted Cox models, p2KT was associated with better graft survival (HR for death-censored graft loss = 0.51 [0.26–0.99], $P = 0.048$; HR for graft failure from any cause including death = 0.58 [0.35–0.97], $P = 0.039$). After taking into account baseline factors using PS methods, p2KT was associated with significant better graft survival (HR for death-

Table 2. Balance of patient characteristics at second kidney transplantation according to preemptive or non-preemptive status before and after weighting.

	Before weighting (*N* = 1314)				After weighting (*N* = 1306)			
	np2KT (*N* = 1221)	p2KT (*N* = 93)	ASMD (%)	*P*-value	np2KT (*N* = 1213)	p2KT (*N* = 93)	ASMD (%)	*P*-value
Sum of weights	1221	93	–	–	1214.1	83.7	–	–
Demographics								
Male	757 (62.0)	54 (58.1)	8.0	0.45	750.9 (61.8)	49.0 (58.5)	6.8	0.55
Age at second transplant	47.1 ± 13.4	45.7 ± 13.8	10.3	0.35	47.0 ± 13.4	48.4 ± 12.8	10.6	0.31
Body mass index (kg/m²)	23.0 ± 3.9	23.2 ± 3.9	5.9	0.59	23.0 ± 3.9	22.5 ± 3.7	11.5	0.29
Comorbidities at second transplant								
Diabetes	69 (5.7)	10 (10.8)	18.7	0.046	71.5 (5.9)	2.8 (3.3)	12.1	0.47
Hypertension	963 (78.9)	78 (83.9)	12.9	0.25	962.7 (79.3)	63.9 (76.4)	7.0	0.53
Vascular disease	165 (13.5)	10 (10.8)	8.5	0.45	160.5 (13.2)	5.3 (6.3)	23.4	0.068
Cardiac disease	426 (34.9)	20 (21.5)	**30.1**	**0.009**	413.0 (34.0)	31.4 (37.6)	7.4	0.51
Cardiovascular	509 (41.7)	28 (30.1)	24.3	**0.029**	495.5 (40.8)	36.1 (43.1)	4.7	0.68
Dyslipidemia	330 (27.0)	39 (41.9)	**31.8**	**0.002**	338.2 (27.9)	21.4 (25.6)	5.1	0.66
Viral hepatitis B or C	154 (12.6)	6 (6.5)	21.1	0.080	147.0 (12.1)	4.8 (5.7)	22.5	0.080
Neoplasia	197 (16.1)	19 (20.4)	11.1	0.28	197.4 (16.3)	18.4 (22.0)	14.5	0.18
Blood group								
A	563 (46.1)	52 (55.9)	19.7	0.068	569.4 (46.9)	40.7 (48.6)	3.4	0.76
O	495 (40.5)	29 (31.2)	19.6	0.076	486.6 (40.1)	34.6 (41.4)	2.7	0.81
B	110 (9.0)	8 (8.6)	1.4	0.89	107.9 (8.9)	7.3 (8.7)	0.7	0.95
AB	52 (4.3)	4 (4.3)	0.2	1.00	49.3 (4.1)	1.1 (1.3)	16.9	0.34
Missing	1 (0.1)	0 (0.0)	4.0	1.00	1.0 (0.1)	0.0 (0.0)	4.0	1.00
HLA immunization anticlass I								
Yes	802 (65.7)	33 (35.5)	**63.4**	**<0.0001**	771.2 (63.5)	50.0 (59.7)	7.8	0.49
No	328 (26.9)	48 (51.6)	**52.4**	**<0.0001**	349.4 (28.8)	26.0 (31.1)	5.0	0.65
Missing	91 (7.5)	12 (12.9)	18.1	0.059	93.6 (7.7)	7.7 (9.2)	5.3	0.63
HLA immunization anticlass II								
Yes	778 (63.7)	40 (43.0)	**42.4**	**<0.0001**	757.9 (62.4)	54.4 (65.0)	5.4	0.63
No	296 (24.2)	41 (44.1)	**42.8**	**<0.0001**	311.1 (25.6)	19.3 (23.1)	5.9	0.60
Missing	147 (12.0)	12 (12.9)	2.6	0.81	145.1 (12.0)	10.0 (11.9)	0.1	0.99
Causal nephropathy								
Chronic glomerulonephritis	536 (43.9)	43 (46.2)	4.7	0.66	532.8 (43.9)	34.7 (41.5)	4.8	0.67
Diabetic nephropathy	12 (1.0)	0 (0.0)	14.1	0.69	12.4 (1.0)	0.0 (0.0)	14.3	0.73
Vascular nephropathy	43 (3.5)	3 (3.2)	1.6	1.00	41.7 (3.4)	1.9 (2.3)	6.8	0.81
Chronic tubulointerstitial	483 (39.6)	41 (44.1)	9.2	0.39	480.1 (39.5)	40.4 (48.2)	17.6	0.12
Unknown	147 (12.0)	6 (6.5)	19.4	0.11	147.1 (12.1)	6.7 (8.0)	13.8	0.26
Duration on waiting list (in month)	35.1 ± 34.4	16.7 ± 24.2	**62.1**	**<0.0001**	33.9 ± 34.2	28.4 ± 31.7	17.0	0.10
Time since first graft (year)	12.9 ± 7.0	14.6 ± 7.4	23.5	**0.034**	13.1 ± 7.1	13.9 ± 8.0	12.5	0.27

Table 2. Continued.

	Before weighting (*N* = 1314)				After weighting (*N* = 1306)			
	np2KT (*N* = 1221)	p2KT (*N* = 93)	ASMD (%)	*P*-value	np2KT (*N* = 1213)	p2KT (*N* = 93)	ASMD (%)	*P*-value
Second renal transplant								
Year of second transplant								
2000–2004	309 (25.3)	9 (9.7)	**42.0**	**0.0007**	293.0 (24.1)	11.6 (13.9)	**26.3**	**0.033**
2005–2009	527 (43.2)	46 (49.5)	12.7	0.24	530.9 (43.7)	38.8 (46.3)	5.3	0.64
2010–2014	385 (31.5)	38 (40.9)	19.5	0.063	390.1 (32.1)	33.3 (39.7)	15.9	0.15
Renal transplant center	143 (11.7)	15 (16.1)	12.8	0.21	146.2 (12.0)	19.2 (22.9)	**28.9**	**0.004**
Type of donor								
Living donor	85 (7.0)	27 (29.0)	**60.0**	**<0.0001**	104.3 (8.6)	9.7 (11.5)	9.8	0.36
Standard criteria donor	765 (62.7)	45 (48.4)	**29.0**	**0.006**	745.5 (61.4)	50.4 (60.3)	2.3	0.84
Expanded criteria donor	365 (29.9)	21 (22.6)	16.7	0.14	358.5 (29.5)	23.6 (28.2)	2.9	0.80
Missing	6 (0.5)	0 (0.0)	9.9	1.00	5.8 (0.5)	0.0 (0.0)	9.8	1.00
Positive CMV serology recipient								
Yes	858 (70.3)	64 (68.8)	3.2	0.77	856.2 (70.5)	61.0 (72.9)	5.4	0.64
No	356 (29.2)	29 (31.2)	4.4	0.68	352.9 (29.1)	22.6 (27.1)	4.5	0.69
Missing	7 (0.6)	0 (0.0)	10.7	1.00	4.9 (0.4)	0.0 (0.0)	9.0	1.00
Positive CMV serology donor								
Yes	614 (50.3)	51 (54.8)	9.1	0.40	617.6 (50.9)	40.2 (48.0)	5.8	0.61
No	598 (49.0)	42 (45.2)	7.6	0.48	588.3 (48.5)	43.5 (52.0)	7.1	0.53
Missing	9 (0.7)	0 (0.0)	12.2	0.86	8.2 (0.7)	0.0 (0.0)	11.7	0.97
HLA A-B-DR incompatibilities								
0	97 (7.9)	7 (7.5)	1.6	0.89	97.0 (8.0)	8.5 (10.1)	7.4	0.49
1–2	465 (38.1)	30 (32.3)	12.2	0.26	458.4 (37.8)	31.8 (37.9)	0.4	0.97
3–4	547 (44.8)	42 (45.2)	0.7	0.95	541.4 (44.6)	38.8 (46.3)	3.5	0.76
5–6	85 (7.0)	14 (15.1)	**26.1**	**0.004**	91.8 (7.6)	4.7 (5.6)	7.9	0.51
Missing	27 (2.2)	0 (0.0)	21.3	0.28	25.5 (2.1)	0.0 (0.0)	20.7	0.35
Cold ischemia time (hours)	20.7 ± 8.9	14.4 ± 9.9	**66.8**	**<0.0001**	20.2 ± 9.2	19.3 ± 9.0	9.7	0.37

ASMD, absolute standardized mean difference; np2KT, non-preemptive second kidney transplant; p2KT, preemptive second kidney transplant.

Balance of variables before and after weighting was assessed using ASMD and statistical tests (unweighted and weighted Welch's *t*-test for continuous variables, unweighted and weighted chi-square test for categorical variables). Results with p value less than 5% were emphasized using bold letters.

Table 3. Early graft events of second kidney transplantation according to preemptive or non-preemptive status.

	Missing data	np2KT (*N* = 1221)	p2KT (*N* = 93)	*P*-value
Pre-transplantation events				
Delayed graft function	43 (3.3%)	432 (36.6%)	2 (2.2%)	<0.0001
Graft recovery (days)	16 (1.2%)	4.7 ± 6.4	1.5 ± 1.7	<0.0001
Post-transplantation events				
Death-censored graft failure	–	265 (21.7%)	9 (9.7%)	0.006
Death	–	128 (10.5%)	6 (6.5%)	0.22
Graft failure and death with a functioning graft	–	393 (32.2%)	15 (16.1%)	0.001
Acute rejection	–	321 (26.3%)	18 (19.4%)	0.14
Type of acute rejection				
Borderline	–	92 (28.7%)	11 (61.1%)	0.07
Cellular		118 (36.8%)	4 (22.2%)	0.31
Humoral		101 (31.5%)	3 (16.7%)	0.29
Cellular and humoral		10 (3.1%)	0 (0%)	–
Humoral or cellular and humoral		111 (34.6%)	3 (16.7%)	0.13
Cellular and/or humoral		229 (18.8%)	7 (7.5%)	0.005
Post-transplantation biology				
Number of patients with study visit at 3 months		*N* = 1046	*N* = 79	
eGFR (ml/min/1.73 m²)	35 (3.1%)	52.4 ± 20.2	58.2 ± 16.0	0.004
Number of patients with study visit at 1 year		*N* = 972	*N* = 75	
eGFR (ml/min/1.73 m²)	59 (5.6%)	53.2 ± 19.7	58.7 ± 16.9	0.011
Number of patients with study visit at 5 years		*N* = 493	*N* = 31	
eGFR (ml/min/1.73 m²)	45 (8.6%)	51.7 ± 20.7	57.2 ± 16.9	0.11

np2KT, non-preemptive second kidney transplant; p2KT, preemptive second kidney transplant; eGFR, estimated glomerular filtration rate, according to MDRD formula.

Table 4. Unweighted and weighted survival analysis.

	Unweighted Cox model		IPTW-weighted Cox model		IPTW-weighted and adjusted* Cox model	
	HR (CI 95%)	*P*-value	HR (CI 95%)	*P*-value	HR (CI 95%)	*P*-value
Return to dialysis						
np2KT	1.00	–	1.00	–	1.00	–
p2KT	0.51 (0.26–0.99)	**0.048**	0.36 (0.16–0.81)	**0.014**	0.39 (0.18–0.88)	**0.024**
Death						
np2KT	1.00	–	1.00	–	1.00	–
p2KT	0.73 (0.32–1.66)	0.45	0.44 (0.16–1.20)	0.11	0.47 (0.17–1.26)	0.13
Death or return to dialysis						
np2KT	1.00	–	1.00	–	1.00	–
p2KT	0.58 (0.35–0.97)	**0.039**	0.39 (0.20–0.76)	**0.006**	0.42 (0.22–0.80)	**0.008**
Vascular complication						
np2KT	1.00	–	1.00	–	1.00	–
p2KT	0.88 (0.41–1.88)	0.73	0.94 (0.33–2.67)	0.91	0.77 (0.26–2.26)	0.64

np2KT, non-preemptive second kidney transplant; p2KT, preemptive second kidney transplant.

*Adjusted for the two variables which remained unbalanced after weighting: renal transplant center and year of second transplant between 2000 and 2004. Results with p value less than 5% were emphasized using bold letters.

censored graft loss = 0.36 [0.16–0.81], $P = 0.014$; HR for graft failure from any cause including death = 0.39 [0.20–0.76], $P = 0.006$). Finally, adjusted weighted Cox models (adjusted for year of 2KT between 2000 and 2004 and the renal transplant center) yielded similar results (respectively, HR 0.39 [0.18–0.88], $P = 0.024$, and HR = 0.42 [0.22–0.80], $P = 0.008$). Similar associations were observed for death, although it failed to reach statistical significance (HR = 0.47 [0.17–1.26], $P = 0.13$).

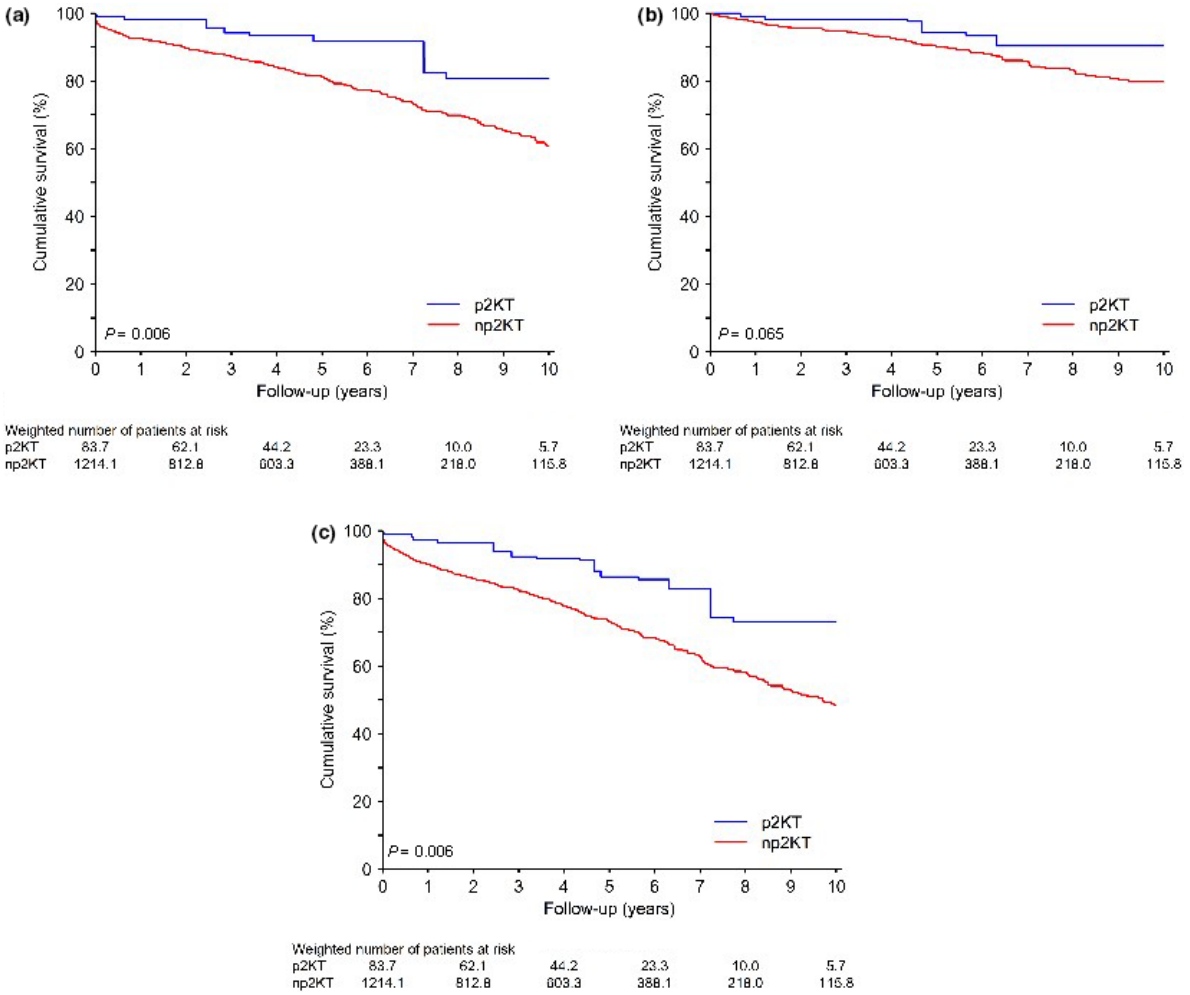

Figure 1 Weighted Kaplan–Meier survival curves in patients with preemptive and non-preemptive second kidney transplant for (a) return to dialysis, (b) death, and (c) death or return to dialysis. p2KT, preemptive second kidney transplant; np2KT, non-preemptive second kidney transplant.

Exploration of interactions

Among the tested interactions, a significant interaction was only observed between donor type and p2KT (P for interaction = 0.016, Table 5 and Fig. 2). Indeed, p2KT was not significantly associated with the risk of graft failure in living donor 2KT (P = 0.39), whereas the association was substantial in the deceased donor 2KT subset (HR for return to dialysis or death before return to dialysis = 0.30 [0.14–0.64], P = 0.002). In order to further explore this interaction, the weighted Kaplan–Meier survival curves for graft failure according to preemptive status and donor type are presented in Fig. 3a–d. Of note, the adjusted graft survival of p2KT with deceased donor paralleled that of 2KT with living donor, whether preemptive or not (93.8% vs. 88.6% at 4 years and 76.1% vs. 70.5% at 8 years, P = 0.13).

Dose effect of time on dialysis before 2KT

The increasing detrimental impact of dialysis duration before 2KT on graft survival is presented in Table 6. Dialysis duration longer than 2 years before 2KT appeared to be particularly detrimental for graft survival (in weighted-adjusted Cox models, for a duration of dialysis 2–4 years: HR = 2.45 [1.26–4.77], P = 0.008; for a duration of dialysis >4 years: HR = 2.83 [1.47–5.47], P = 0.002).

Comparison between patients with PSK and patients with np2KT but who were preemptively relisted

As a sensitivity analysis, we compared patients with a p2KT with patients who received a np2KT, but were relisted before return to dialysis (n = 223; Appendix S2). Patients did not differ in terms of

Table 5. Association of p2KT with graft failure (return to dialysis or death before return to dialysis) according to different subgroups in weighted Cox models.

	IPTW-weighted Cox model		IPTW-weighted and adjusted* Cox model	
	HR (CI 95%)	*P*-value	HR (CI 95%)	*P*-value
Overall	0.39 (0.20–0.76)	**0.006**	0.42 (0.22–0.80)	**0.008**
Type of donor				
Living donor	1.68 (0.52–5.47)	0.39	1.56 (0.45–5.37)	0.48
Deceased donor	0.30 (0.14–0.64)	0.002	0.33 (0.16–0.68)	0.003
Interaction		**0.016**		**0.033**
Year of second transplantation				
2000–2004	0.39 (0.09–1.75)	0.22	0.50 (0.12–2.14)	0.35
2005–2009	0.42 (0.18–0.98)	0.046	0.47 (0.21–1.05)	0.064
2010–2014	0.23 (0.05–1.01)	0.052	0.22 (0.05–0.97)	0.045
Interaction		0.78		0.64
Age at second transplant				
18–50 years	0.48 (0.20–1.17)	0.11	0.47 (0.19–1.13)	0.092
>50 years	0.30 (0.11–0.80)	0.015	0.36 (0.14–0.92)	0.032
Interaction		0.48		0.71
HLA immunization I				
No	0.65 (0.29–1.47)	0.30	0.70 (0.33–1.50)	0.36
Yes	0.35 (0.12–0.99)	0.049	0.36 (0.13–1.01)	0.052
Interaction		0.36		0.30
HLA immunization II				
No	0.80 (0.38–1.69)	0.55	0.79 (0.38–1.64)	0.52
Yes	0.34 (0.12–0.97)	0.044	0.36 (0.13–1.01)	0.052
Interaction		0.19		0.23

p2KT, preemptive second kidney transplant.

In this table, the effect of p2KT on each subgroup and *P*-value associated with interaction are reported.

*Adjusted for the two variables which remained unbalanced after weighting: renal transplant center and year of second transplant between 2000 and 2004. Results with p value less than 5% were emphasized using bold letters.

gender, age, and comorbidities, except for diabetes (Table S1). Of note, the proportion of O blood group was higher in the group of patients preemptively relisted but not preemptively retransplanted, as well as the proportion of HLA-sensitized patients. The proportion of living donor 2KT was higher in the p2KT group. In weighted Cox model, the beneficial effect of p2KT persisted in this subgroup of patients (for graft failure from any cause including death HR = 0.45 [0.23–0.89], $P = 0.021$; Table S2).

Discussion

This is the first large multicenter European study assessing the impact of p2KT on graft and patient survival. In addition, to the best of our knowledge, this is the first study to assess the interaction between donor type and the impact of p2KT on these outcomes. Our main finding is that p2KT is associated with better graft survival, whether assessed with death-censored graft loss or graft failure from any cause including death, using extensive PS methods aimed at decreasing the attribution bias for p2KT treatment. The other important findings of our analysis are: (i) the detrimental dose effect of time on dialysis on graft survival, and (ii) the more pronounced beneficial effect of p2KT in the deceased donor subset compared with the living donor 2KT subset.

p2KT, a rare but increasingly frequent entity

This study confirms that p2KT still remains a rare option (7.1% of 2KT in this cohort), although increasingly frequent over time, and thus necessitates careful evaluation. The proportion of living donors is much higher in the case of p2KT as opposed to np2KT (29.0% vs. 7.0% in this cohort). The proportion of living donor transplantation is moreover globally on the rise in France (15.9% of all kidney transplantations in 2014 vs. 7.9% in 2009 according to the French national registry data [4], as well as the proportion of

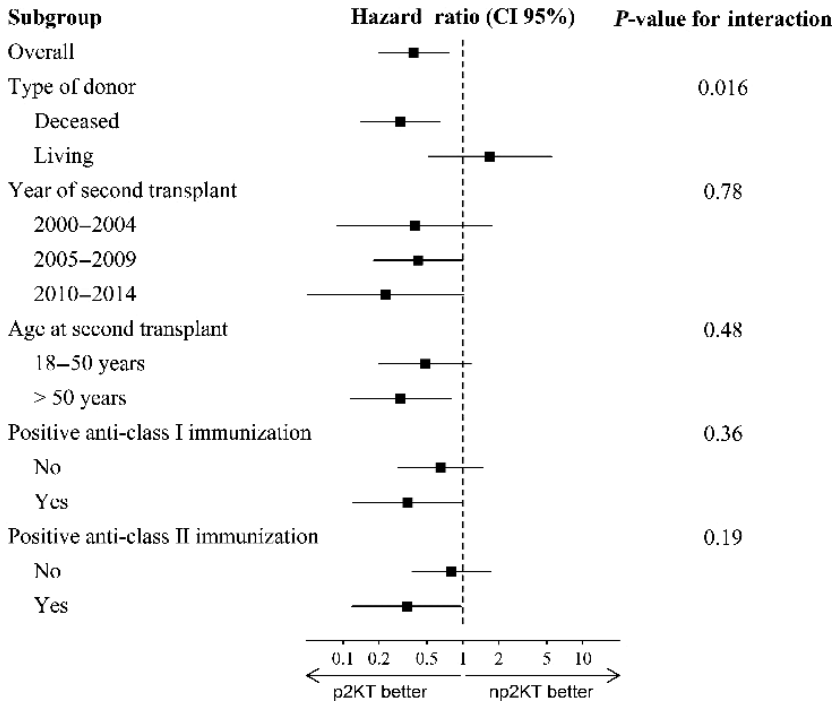

Figure 2 Forest plot: Association of p2KT with graft failure (return to dialysis or death before return to dialysis) according to the different subgroups in weighted Cox models. p2KT, preemptive second kidney transplant; np2KT, non-preemptive second kidney transplant.

preemptive 1KT (15.9% in 2014 vs. 12.3% in 2009)) [4]. In the United States, the proportion of p2KT is also higher and equally on the rise (13.7% of p2KT in 1990–2000 [7], 15.1% in 1995–1998, and 29.6% in 2003–2007 [15]), whereas the ANZDATA registry reported similar proportions of p2KT as in the present cohort (4.5% in the 1997–2009 period) [19]. Of note, transplantation guidelines for 2KT appear to be fairly concurrent in the United States and in Europe, indicating relisting in patients with eGFR <20 ml/min/1.73 m^2 [35].

p2KT is inconsistently associated with graft or patient survival in the literature

Few studies have assessed the impact of p2KT [7,15–17] or pre-retransplant dialysis duration [7,15,19] on graft and patient survival, with conflicting results. A large American study including retransplantation between 1990 and 1999 reported a deleterious effect of p2KT on death-censored graft failure [7], but also, intriguingly, a deleterious effect of long pre-retransplant dialysis duration. A more recent American study including 17 584 2KT (3509 p2KT) performed between 1995 and 2007 observed a neutral effect on death-censored graft loss of p2KT [15]. The pre-retransplant dialysis duration was also found to be associated with a neutral effect on death-censored graft failure of 2KT performed between 1997 and 2009 in the ANZDATA registry (n = 911) [19]. In contrast, other studies [7,15,19] have reported that p2KT was associated with better patient survival, either evaluated by death with a functioning graft (HR = 0.76 [0.66–0.87]) [15] or by death with or without a functioning graft (HR = 0.83 [0.69–0.99]) [7]. Similarly, Wong *et al.* [19]. also observed a detrimental effect of pre-retransplant dialysis duration on patient survival (for every 1-year increase in waiting time before 2KT, HR = 1.13 [1.07–1.19]).

Factors possibly explaining the beneficial impact of p2KT on graft survival

It is unclear whether the general advantage associated with preemptive transplantation holds true for patients with prior kidney transplantation. Indeed, the deleterious vascular impact of dialysis duration would most likely be similar in the case of 1KT or 2KT. In contrast, the immunological factors are of predominant importance in 2KT and can be modified by a return to dialysis. Moreover, the impact of dialysis on nutritional and inflammatory status may vary in 1KT and 2KT settings.

Immunological factors

In the present study, the detrimental impact of dialysis increased with dialysis duration prior to 2KT. Wong *et al.* [19]. observed that waiting time in dialysis before 2KT was associated with a greater risk of graft failure from any cause including death and all-cause mortality,

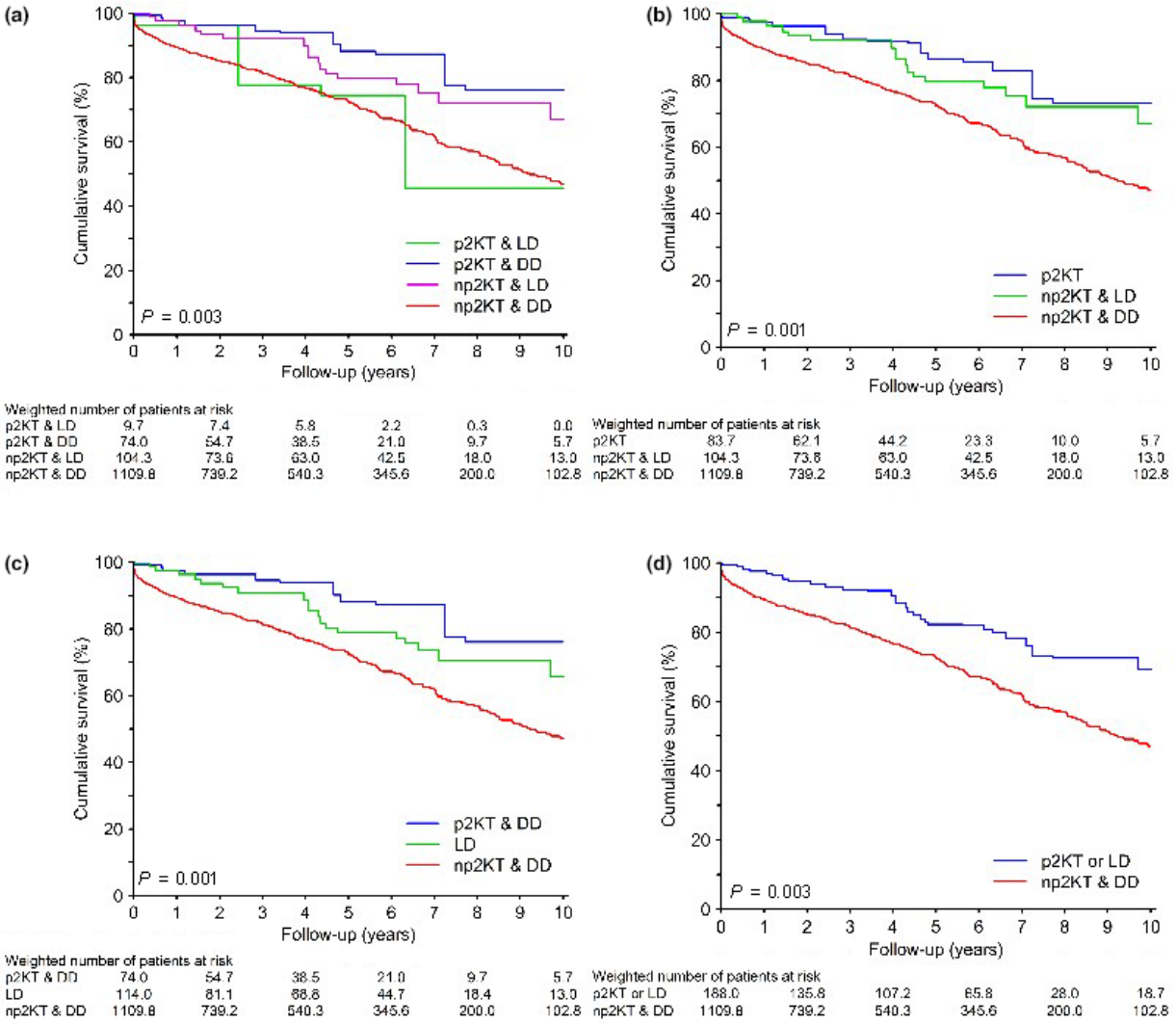

Figure 3 Weighted Kaplan–Meier survival curves for graft failure (death or return to dialysis) in patients according to preemptive status and/or donor type. p2KT: preemptive second kidney transplant; np2KT, non-preemptive second kidney transplant; LD, living donor; DD, deceased donor.

but not with death-censored graft loss, which suggested that waiting time before 2KT was primarily related to nonimmunological outcomes. In contrast, in the present cohort, we observed a lower risk of death-censored graft failure and graft failure from any cause, but not a lower risk of death with a functioning graft. p2KT may positively impact graft survival by the absence of a decrease or discontinuation of immunosuppressive therapy, which favors the development of anti-HLA antibodies [36], in particular when transplant nephrectomy is required [37]. The development of anti-HLA antibodies exposes patients to an increased risk of DSA (donor-specific antibodies) development and graft rejection. Concurrently, p2KT recipients herein were less sensitized at the time of the 2KT. Nevertheless, they also had longer 1KT duration, suggesting a lower level of sensitization regardless of the return to dialysis prior to 2KT. A longer duration of 1KT has previously been described among patients with p2KT [15] and was also associated with better 2KT survival [15] or with better patient and 2KT survival [19]. Of note, p2KT recipients also less frequently received well HLA-matched 2KT (due to the French policy of graft allocation in case of severe HLA sensitization) and less induction immunosuppression. All of the above confounding factors (which potentially have an impact on the attribution of p2KT treatment) were included in the PS analysis. Importantly, the association was somewhat strengthened when weighting on PS, which may be the consequence of the higher proportion of diabetes (twofold), dyslipidemia, and 5 HLA incompatibilities or higher in the p2KT group.

Table 6. Unweighted and weighted survival analysis: dose effect due to duration of dialysis before second kidney transplantation.

	Unweighted Cox model		IPTW-weighted Cox model		IPTW-weighted and adjusted* Cox model	
	HR (CI 95%)	*P*-value	HR (CI 95%)	*P*-value	HR (CI 95%)	*P*-value
Return to dialysis						
		0.040		**0.010**		**0.023**
p2KT	1.00	–	1.00	–	1.00	–
Dialysis 0–1 year	1.61 (0.76–3.40)	0.21	2.23 (0.91–5.47)	0.079	2.07 (0.86–4.99)	0.11
Dialysis 1–2 years	1.61 (0.78–3.32)	0.20	2.28 (0.96–5.45)	0.063	2.10 (0.89–4.94)	0.090
Dialysis 2–4 years	1.87 (0.93–3.75)	0.080	2.68 (1.15–6.27)	**0.023**	2.47 (1.07–5.67)	**0.033**
Dialysis >4 years	2.29 (1.16–4.50)	**0.016**	3.34 (1.45–7.68)	**0.005**	3.02 (1.33–6.86)	**0.008**
Death						
		0.33		0.068		0.087
p2KT	1.00	–	1.00	–	1.00	–
Dialysis 0–1 year	0.90 (0.33–2.44)	0.84	1.37 (0.44–4.30)	0.59	1.34 (0.42–4.20)	0.62
Dialysis 1–2 years	1.08 (0.43–2.73)	0.87	1.66 (0.56–4.93)	0.36	1.58 (0.53–4.71)	0.41
Dialysis 2–4 years	1.55 (0.65–3.67)	0.32	2.56 (0.91–7.16)	0.074	2.44 (0.87–6.81)	0.090
Dialysis >4 years	1.51 (0.65–3.49)	0.34	2.61 (0.95–7.17)	0.062	2.51 (0.91–6.97)	0.077
Death or return to dialysis						
		0.010		**0.0006**		**0.001**
p2KT						
Dialysis 0–1 year	1.32 (0.73–2.40)	0.35	1.91 (0.91–4.00)	0.085	1.80 (0.88–3.67)	0.11
Dialysis 1–2 years	1.40 (0.79–2.47)	0.25	2.05 (1.00–4.19)	**0.049**	1.91 (0.96–3.79)	0.066
Dialysis 2–4 years	1.74 (1.01–3.00)	0.045	2.64 (1.32–5.28)	**0.006**	2.45 (1.26–4.77)	**0.008**
Dialysis >4 years	1.98 (1.17–3.34)	0.011	3.07 (1.55–6.07)	**0.001**	2.83 (1.47–5.47)	**0.002**

p2KT, preemptive second kidney transplant.

*Adjusted for the two variables which remained unbalanced after weighting: renal transplant center and year of second transplant between 2000 and 2004. Results with p value less than 5% were emphasized using bold letters.

General factors

In the setting of 1KT, it is well established that dialysis vintage prior to KT is associated with accelerated vascular calcifications, poor nutritional status, and a chronic inflammatory state. In a similar manner, p2KT should positively impact both graft and patient survival as a result of the beneficial impact of dialysis avoidance. The deleterious consequences of dialysis duration prior to transplantation may even be more pronounced in 2KT, that is, in patients at higher risk of dialysis complications, than in 1KT. Indeed, in dialysis, anemia has been found to be more frequent in failed-graft patients than in transplant-naive patients [22,38–40], with a lower albuminemia level [22,41]. Moreover, the renal residual function may decline faster in failed-transplant patients [42].

Nevertheless, certain patients in the p2KT group may have benefited from a short dialysis period, leading to an underestimation of the beneficial effect of p2KT on patient survival in this study, and thereby explaining the nonsignificant effect of p2KT on patient survival. Indeed, transplanted patients are reluctant to return to dialysis, and it is sometimes difficult to undertake dialysis preparation and 2KT re-inscription sufficiently early. Although less frequently than in transplant-naive patients, some transplanted patients initiate dialysis in emergency with a very poor general status [22] and, in a similar manner, some p2KT patients receive their graft preemptively while being in a fragile state, whereas they could have benefited from a short time period in dialysis. This was also suggested by the large American study including retransplantation between 1990 and 1999, which reported a deleterious effect of p2KT on graft failure, and a beneficial effect of short pre-retransplant dialysis duration [7], which putatively suggest a potential benefit from a short dialysis period prior to 2KT.

Interaction of the impact of p2KT with donor type

The benefit from p2KT may be more obvious in living donor transplantation [12–14] than with deceased donors [43]. The impact of p2KT may be more pronounced in the deceased donor setting due to the

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overall poorer prognosis of these grafts. Surprisingly, in our cohort, p2KT prognosis with deceased donor was similar to that of 2KT with living donor, whether preemptive or not. This result suggests that, while living donor donation obviously remains preferable, a preemptive re-inscription should particularly be encouraged when no living donor is available.

Limitations

In this large multicenter cohort study, survival analyses were adjusted on numerous variables known to be associated with graft and patient survival using robust statistical methods (IPTW). Nevertheless, some residual confounding may remain. Only a randomized controlled trial (RCT) can adequately address the question of p2KT, although such a study is not feasible in clinical practice for ethical and methodological reasons as organ shortage and allocation policies preclude a RCT. Yet, the PS analysis provided herein is the closest possible to a RCT in the setting of an observational study, by specifically addressing attribution bias for treatment. Of note, less than one hundred patients had p2KT in our cohort (who experienced only 15 events of interest), most with deceased donor. Nevertheless, despite this moderate statistical power, both the association between p2KT with outcome and interaction between living donor status and p2KT was statistically significant despite proper adjustment strategies. In addition, data regarding the cause of first graft failure were lacking, as well as panel-reactive antibodies (PRA), residual kidney function at the time of 2KT, and DSA data during the follow-up. However, HLA sensitizations were thoroughly addressed and rejection episodes were prospectively collected.

Clinical implications

In patients with severe first graft dysfunction, p2KT appears to be the best therapeutic option. Consequently, clinicians should attempt to preemptively relist patients on the waiting list. Obviously, because of organ shortage, as in 1KT, a living donor should be searched early, when GFR is significantly declining. Given that second living donors may be more difficult to find than for 1KT (primarily because of HLA sensitization), early conveyance of information to patients and their relatives is required. p2KT with deceased donor appears to have similar good results as with living donor 2KT and should be particularly encouraged for patients in the absence of candidates for living donation. Nevertheless, given the organ shortage worldwide, preemptive retransplantation raises ethical considerations, which are at least as important of those raised by preemptive 1KT.

This study provides additional data supporting preemptive KT, even in the specific case of second transplantation. However, preemptive 2KT raises ethical concerns in the context of organ shortage as it could increase the risk of grafts allocation inequalities between 1KT and 2KT recipients. However, in France, the allocation policy limits the theoretical advantage of excessive—and possibly abusive—early referral on the waiting list. The scoring system includes waiting time on list without dialysis only up to 1 year (i.e., 1 year and 3 years on the waiting list without dialysis result in similar scoring). Consequently, early referral of patients can contribute to minimizing the risk of long-term duration on dialysis, without significantly limiting access for patients already on dialysis as the allocation scoring is capped. However, regardless of the healthcare system, it should remain a constant concern of the transplantation community to avoid significant inequalities if preemptive 2KT is further favored. Moreover, preemptively relisting will obviously not allow all highly immunized patients to be preemptively retransplanted because of the difficulty in finding a matched graft. Nevertheless, initiating the process of relisting early is likely to decrease the overall duration of graft waiting. Relisting patients with a failing first KT should consequently be a clinical concern.

Conclusion

This large French multicenter provides additional data supporting that p2KT is associated with better graft prognosis, even after the use of propensity score, which takes into account confounding factors possibly leading to better access to this therapeutic option, but with similar patient survival. However, p2KT raises ethical concerns in the context of organ shortage as it could increase the risk of grafts allocation inequalities between 1KT and 2KT recipients.

Authorship

SG: collected data, designed the study, analyzed and interpreted data, and wrote the manuscript. NG: designed the study, analyzed and interpreted data, and wrote the manuscript. KD: analyzed data and wrote the manuscript. MG, CL, GM, VG, EM, FB, NK, ADB, and ML: collected data and revised the manuscript. MK: collected data, interpreted data, and wrote the manuscript. LF: collected

data, interpreted data and revised the manuscript. All authors: approved the final version of the manuscript.

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Since its inception, the DIVAT cohort has been sustained by an industrial charity-type sponsor to store and secure the data, and to organize the running of the network.

Conflict of interest

M. Giral has been paid a consulting fee by Chiesi. The other authors declare no conflicts of interest.

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Since its inception, the DIVAT cohort has been sustained by an industrial charity-type sponsor to store and secure the data, and to organize the running of the network. We also wish to thank the DIVAT assistants in clinical research: C. Kerandel, S. Le Floch, C. Guillot-Gueguen, L. Faucher, C. Scellier, V. Eschbach, P. Przednowed, V. Godel, K. Zurbonsen, X. Longy, C. Dagot, F. M'Raiagh, PE. Imbert, J. Posson, and C. Coëlle.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Appendix S1. Details of the iterative forward process for including variables in the propensity score (PS).

Appendix S2.

Table S1. Sensitivity analysis – Balance of patients characteristics at second kidney transplantation according to preemptive or non-preemptive status before and after weighting.

Table S2. Sensitivity analysis – Unweighted and weighted survival analysis

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