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ORIGINAL ARTICLE

Association between kidney retransplantation and survival according to age in the French national cohort of dialysis patients

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The mean age of patients returning to dialysis after a first kidney transplantation (KT) has increased in the past decades. We aimed to assess the association between second KT (2KT) and survival according to age at the time of return to dialysis. Data of 5334 patients registered in the French Renal Epidemiology and Information Network (REIN) (mean age 56.6 ± 13.6 years) who returned to dialysis after a first KT were collected. The association of 2KT with death was assessed using a propensity score-based analysis taking into account baseline and follow-up variables. In relisted patients (3272 patients, 61.3%), retransplantation was associated with better overall survival in comparison with patients who remained in dialysis (adjusted HR 0.75 [0.63–0.89], $p = .0009$). The survival advantage conferred by retransplantation gradually declined with increasing age (adjusted HR 0.41 [0.24–0.70] in patients <50, HR 0.94 (0.69–1.27) in patients aged 70 or older, p for interaction 0.034 for age considered as a continuous variable). 2KT is associated with better survival as opposed to remaining on dialysis after a first kidney graft failure. Nevertheless, this survival benefit is age dependent and diminishes with increasing age. The risk/benefit ratio should be comprehensively assessed in the oldest patients when relisting is considered.

KEYWORDS
dialysis, kidney transplantation, second kidney transplantation, survival

1 | INTRODUCTION

In patients having returned to dialysis after a first kidney transplantation (KT), a second transplantation (2KT) has been reported to be associated with better survival in North American cohorts in the 2000s.[1,2] Nevertheless, the mean age of patients with end-stage renal disease receiving a first KT has significantly increased in the past decades and, as a result, the age of patients returning to dialysis or receiving a second preemptive KT is also increasing.[3] Moreover, patients receiving either a first KT or a 2KT nowadays have a greater number of comorbidities (diabetes, peripheral vascular disease, heart failure, history of cancer) than those included in the seminal studies showing a benefit of 2KT.[3] Such benefit may thus be altered/weakened in this older population because 2KT is likely to

Abbreviations: 2KT, second kidney transplantation; BMI, body mass index; CORR, Canadian Organ Replacement Register; CV, cardiovascular; HLA, human leukocyte antigen; HR, hazard ratio; IPTW, inverse probability treatment weighting; KT, kidney transplantation; REIN, French Renal Epidemiology and Information Network; USRDS, United States Renal Data System.

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be associated with more complications such as infections, neoplasia or cardiovascular (CV) events among older patients. However, the impact of dialysis return could also be more detrimental among the oldest patients given their higher CV risk.

In clinical practice, relisting is a challenging clinical endeavor given the seemingly higher risk of adverse events related to 2KT. Considering the current drastic organ shortage and subsequent increased waiting list times,[4] a better identification of patients most likely to benefit from 2KT would be useful. Moreover, having contemporary risk/benefit data to present to patients might furthermore facilitate the clinical discussion prior to relisting. Of note, relisting is of numerical importance since patients relisted for 2KT represent 14.9% of yearly inscriptions (and 23.7% of the total number of patients on the waiting list).[5] The proportion of patients relisted on a waiting list is steadily increasing in France,[5] as well as in the United States,[6] and in Australia-New Zealand.[4]

In the present study conducted in the French Renal Epidemiology and Information Network (REIN) registry of dialysis patients,[7] we aimed to assess the association between kidney retransplantation and survival according to age at the time of return to dialysis after a first graft failure.

2 | Methods

2.1 | Study population

Data were extracted from the REIN registry.[7] A total of 5363 patients returned to dialysis or received a second preemptive KT between January 2008 and December 2015 and followed up until July 2019. Patients with a second preemptive KT were excluded ($n = 29$) and the analysis was ultimately conducted among the 5334 patients who returned to dialysis after a first kidney graft failure. The REIN study was approved by the Commission Nationale Informatique et Libertés (CNIL) on May the 19th 2003 (Authorization number 903188).

2.2 | Study variables

Baseline characteristics (at the return to dialysis) included: (1) age and comorbidities: age, gender, smoking status (no/former/active), diabetes, chronic respiratory failure, coronary disease, heart failure, arrhythmia, peripheral vascular disease, history of stroke, cancer, or malignant hemopathy (undergoing treatment including chemotherapy, radiotherapy, surgery or palliative care, or with metastases), cirrhosis, hepatitis B virus, hepatitis C virus, and human immunodeficiency virus status; (2) renal history: causal nephropathy, date of first dialysis or first preemptive KT, date of first KT, type of donor of the first KT, date of return to dialysis, current dialysis modality (hemodialysis or peritoneal dialysis), type of current vascular access if appropriate (native arteriovenous fistula, prosthetic fistula, central catheter); (3) clinical status: body mass index (BMI), ability to walk, cognitive impairment, blindness, hemiplegia; and (4) biological data: Kt/V, hemoglobin (g/dL), albumin (g/L). A CV history was defined as a history of myocardial infarction, and/or a coronary disease, and/or a peripheral vascular disease, and/or heart failure, or arrhythmia.

The following durations were calculated: duration of the dialysis before the first KT, duration of the first KT, time to relisting on the waiting list, time to 2KT.

Two exposure variables were studied: (1) relisting on the waiting list during follow-up and (2) a second KT during follow-up.

2.3 | Outcome and follow-up

The outcome was death during follow-up. Follow-up was defined as the duration between the return to dialysis and death or the last follow-up. Patients were followed annually until July 2019.

2.4 | Statistical analysis

All analyses were performed using R software (the R Foundation for Statistical Computing). The two-tailed significance level was set at $p < .05$ except for the analyses of interactions. Given the low power of interaction tests, a significance level of 0.10 was used for interaction p-values.[8,9]

Categorical variables are described as frequencies (percentages), whereas continuous variables are described as median (percentile 25–75). Missing data were not taken into account in the calculation of percentages. Baseline characteristics according to groups defined by the relisting on the waiting list and the second KT were analyzed and compared using the non-parametric Kruskal–Wallis test for continuous variables and chi-square test or Fisher's exact test for categorical variables.

To assess the association between 2KT and death, time-to-event analyses were performed using Cox regression models. Proportional hazard assumption was thoroughly verified using the Schoenfeld residuals test. Hazard ratios (HRs) are presented with their 95% confidence intervals as HR (95% CI). The relisting on the waiting list (either before or after the return to dialysis) as well as the 2KT after the return to dialysis (preemptive 2KT being excluded from the present study) were considered as time-dependent variables in the models due to the nature of these exposure variables. Relisting on the waiting list for a second transplant is an exposure variable that can occur before return to dialysis (preemptive relisting) or during the follow-up after return to dialysis, and retransplantation is an exposure variable that necessarily occurs after return to dialysis and only after relisting on the waiting list. The association between relisting or retransplantation and death was also assessed according to age by including an interaction term between these time-dependent variables and age in Cox models.

For estimating the causal effect of relisting or retransplantation exposure on the occurrence of death, stabilized inverse probability weights (IPWs) were used in Cox models to correct for

time-dependent confounding. Patient follow-up can be divided into two periods depending on exposure to relisting or retransplantation. The first consisted of the period between the return to dialysis and the relisting on the waiting list or the last follow-up if the patient was not relisted (exposure to relisting), whereas the second consisted of the period between the relisting on the waiting list and the 2KT or the last follow-up if the patient was not retransplanted (exposure to retransplantation) (Figure 1). Of note, patients who were not relisted during the follow-up were considered only for the first period, whereas the patients preemptively relisted were considered only for the second period. Stabilized IPW at each time-point were estimated over each period by modeling the relationship between exposure (relisting in the first period, retransplantation in the second period) and confounders using a Cox model with time-dependent variables using ipwtm function from the package R ipw.[10,11] The time-dependent variables included in the PS model were diabetes, CV history, active neoplasia, serum albumin less than 35 g/L, moderate or severe anemia (hemoglobin level less than 11 g/L), and BMI in 4 classes. The non-time-dependent variables included in the PS model were age, gender, and causal nephropathy in three classes. A missing indicator approach was used in the estimation of the PS for categorical variables in order to preserve the maximum of data completeness.

3 | RESULTS

3.1 | Characteristics of the study population

A total of 5334 patients who returned to dialysis after a first kidney graft failure were included in the analysis. Patients were aged 56.6 ± 13.6 years old at the time of dialysis return (after a mean first KT duration of 8.6 ± 7.4 years), 62.1% of whom were male. Of the included patients, 21.2% had an end-stage renal disease related to hypertension or diabetes, whereas 46.4% suffered from chronic glomerulonephritis, polycystic disease, or urological disorder (Table 1).

At return to dialysis, 25.3% of the patients were diabetic, 34.6% had a CV history and 7.5% had a cancer or malignant hemopathy. Half (53.9%) of the patients had an albumin level <35 g/L and 2/3 (70.3%) had a hemoglobin level <11 g/dL.

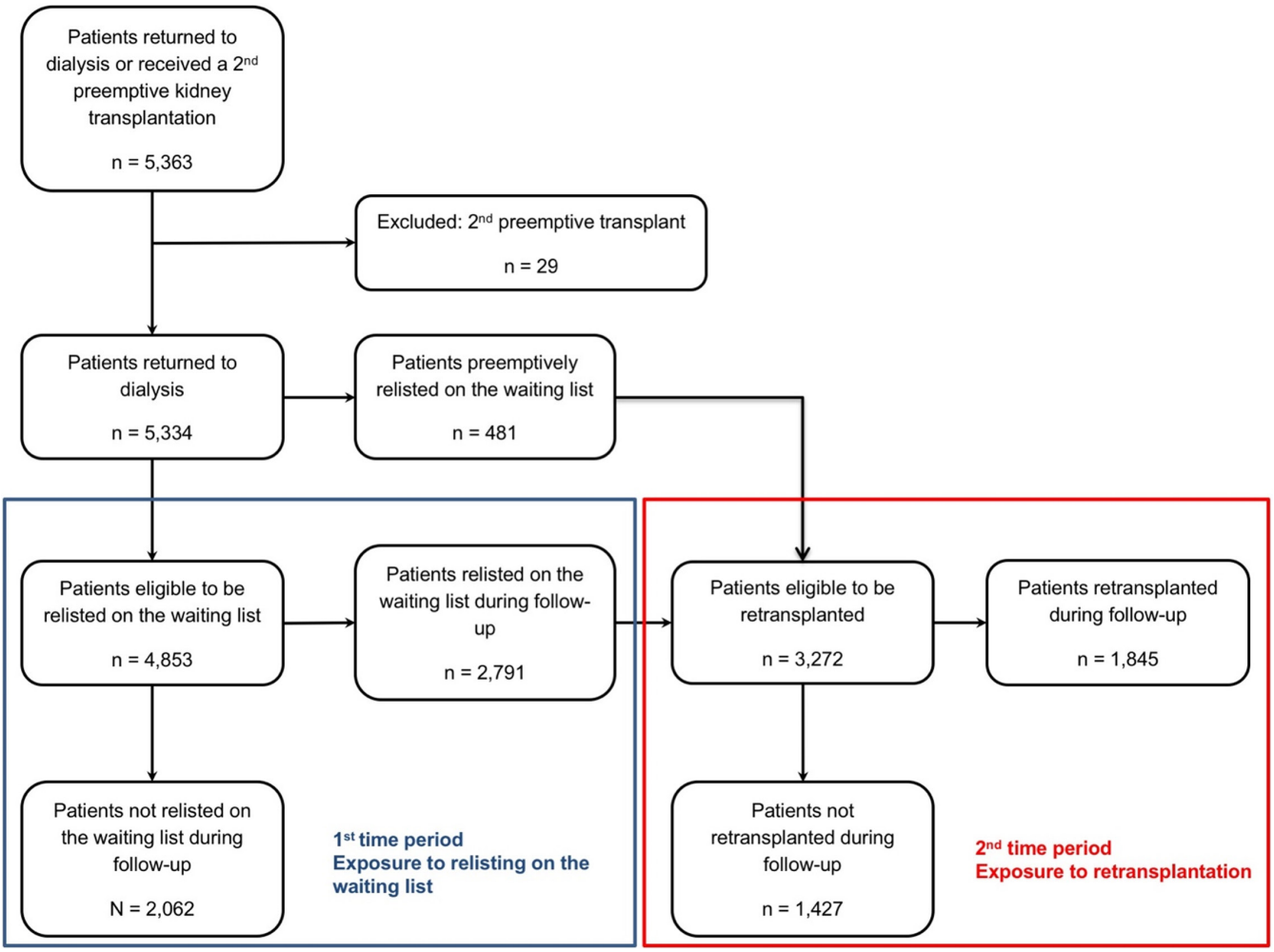


FIGURE 1 Flow-chart [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Description of the study population ($N = 5334$ patients)

	Missing data *n* (%)	Mean ± SD/*n* (%)	Median (Q1–Q3)
Age at return to dialysis after a first transplantation (years)	—	56.6 ± 13.6	58.4 (47.4–66.8)
Age at the onset of end-stage renal disease (first dialysis or first preemptive transplantation) (years)	—	45.1 ± 14.7	46.0 (33.5–56.8)
Gender			
Women		2022 (37.9%)	
Men		3312 (62.1%)	
Causal nephropathy (eight classes)			
Other		1072 (20.1%)	
Glomerulonephritis		1507 (28.3%)	
Hypertension		571 (10.7%)	
Unknown		657 (12.3%)	
Diabetic nephropathy		537 (10.1%)	
Polycystic disease		590 (11.1%)	
Malformative uropathy		376 (7.0%)	
Vascular nephropathy		24 (0.4%)	
Causal nephropathy (three classes)			
Glomerulonephritis/polycystic disease/malformative uropathy		2473 (46.4%)	
Hypertension/diabetic nephropathy/vascular nephropathy		1132 (21.2%)	
Other/unknown		1729 (32.4%)	
Characteristics of the first transplantation			
Age at the first transplantation (years)	—	48.0 ± 14.6	49.1 (36.5–59.7)
First preemptive transplantation	—	217 (4.1%)	
Donor type for the first transplantation	633 (11.9%)		
Donor after cardiac death		67 (1.4%)	
Brain dead donor		4412 (93.9%)	
Living donor		222 (4.7%)	
Time between the first dialysis and the first transplantation (months)	—	35 ± 37	24 (12–45)
Duration of the first transplantation (years)	—	8.6 ± 7.4	7.1 (2.5–13.2)
Comorbidities at inclusion (at the return to dialysis after a first transplantation)			
Smoking	1206 (22.6%)		
Former smoker		1012 (24.5%)	
Active smoker		654 (15.8%)	
Non smoker		2462 (59.6%)	
Diabetes	570 (10.7%)	1204 (25.3%)	
Chronic respiratory disease	665 (12.5%)	294 (6.3%)	
Chronic oxygen therapy	669 (12.5%)	82 (1.8%)	
Myocardial infarction	668 (12.5%)	346 (7.4%)	
Coronary disease	664 (12.4%)	781 (16.7%)	
Myocardial infarction and/or coronary disease	668 (12.5%)	841 (18.0%)	
Heart failure	662 (12.4%)	745 (15.9%)	
Heart rhythm disorder	673 (12.6%)	694 (14.9%)	
Cardiovascular history	677 (12.7%)	1610 (34.6%)	

(Continues)

TABLE 1 (Continued)

	Missing data *n* (%)	Mean ± SD/*n* (%)	Median (Q1–Q3)
Peripheral artery disease	661 (12.4%)	560 (12.0%)	
Stroke	746 (14.0%)	321 (7.0%)	
Cancer not in remission	657 (12.3%)	351 (7.5%)	
HIV/AIDS	683 (12.8%)	35 (0.8%)	
Liver cirrhosis	664 (12.4%)	82 (1.8%)	
Chronic hepatitis B	662 (12.4%)	85 (1.8%)	
Chronic hepatitis C	678 (12.7%)	160 (3.4%)	
Clinical and biological parameters at inclusion (at the return to dialysis)			
Albumin (g/L)	2298 (43.1%)	33.8 ± 6.3	34.0 (30.0–38.0)
Albumin <35 g/L	2298 (43.1%)	1637 (53.9%)	
Hemoglobin (g/dL)	1746 (32.7%)	10.1 ± 1.7	10.0 (9.0–11.2)
Anemia	1746 (32.7%)	3281 (91.4%)	
Moderate or severe anemia	1746 (32.7%)	2522 (70.3%)	
BMI (kg/m^2)	1768 (33.1%)	24.1 ± 5.2	23.3 (20.5–26.8)
BMI (4 classes)	1768 (33.1%)		
<18.5		356 (10.0%)	
18.5–24.9		1927 (54.0%)	
25.0–29.9		852 (23.9%)	
>=30		431 (12.1%)	
Ability to walk	1081 (20.3%)		
Incapacity		96 (2.3%)	
Normal		3965 (93.2%)	
Necessity to be helped by someone		192 (4.5%)	
Paraplegia/hemiplegia	769 (14.4%)	59 (1.3%)	
Blindness	754 (14.1%)	128 (2.8%)	
Cognitive impairment	765 (14.3%)	88 (1.9%)	
Therapeutic modalities at inclusion (at the return to dialysis)			
Type of dialysis	452 (8.5%)		
Peritoneal dialysis		236 (4.8%)	
Hemodialysis		4646 (95.2%)	
Vascular access	1212 (22.7%)		
Other		151 (3.7%)	
Tunneled central catheter		910 (22.1%)	
Native arteriovenous fistula		2990 (72.5%)	
Prosthetic fistula		71 (1.7%)	
Follow-up			
Follow-up (years)	—	4.9 ± 2.9	4.7 (2.9–7.0)
Relisting on the waiting list and/or retransplantation during follow-up	—		
Not relisted		2062 (38.7%)	
Relisted but not retransplanted		1427 (26.8%)	
Retransplanted		1845 (34.6%)	

TABLE 1 (Continued)

	Missing data *n* (%)	Mean ± SD/*n* (%)	Median (Q1–Q3)
Relisting on the waiting list during follow-up for a second transplantation	–	3272 (61.3%)	
Time between inclusion and relisting (months)	–	11 ± 19	8 (2–17)
Preemptive relisting (before inclusion in the study)	–	481 (14.7%)	
Second transplantation during follow-up	–	1845 (34.6%)	
Donor type for the second transplantation	1 (0.1%)		
Donor after cardiac death		1 (0.1%)	
Brain dead donor		1695 (91.9%)	
Living donor		148 (8.0%)	
Time between inclusion and the second transplantation (months)	–	33 ± 22	28 (17–45)
Death during follow-up	–	2001 (37.5%)	

Abbreviations: AIDS, acquired immunodeficiency syndrome; BMI, body mass index; HIV, human immunodeficiency virus; Q1, first quartile; Q3, third quartile; SD, standard deviation.

3.2 | Comparison between patients according to relisting and retransplantation status

In total, 3272 patients (61.3%) were registered for a 2KT, either before (14.7%) or after (85.3%) the return to dialysis. For patients relisted after the return to dialysis, the mean time before registration was 11 ± 19 months. Of the latter, 1845 patients (34.6%) received a 2KT during follow-up after a mean duration of 33 ± 22 months, 8% from a living donor (Table 2 and Figure 1).

Three groups of patients were studied: (1) patients ($N = 2062$) not relisted, (2) patients ($N = 1427$) relisted and not retransplanted, and (3) patients ($N = 1845$) retransplanted during follow-up. Patients who were not relisted differed significantly from relisted patients: they were 10+ years older on returning to dialysis (median age 65.7 years vs. 55.1 for relisted but not retransplanted and 52.1 for retransplanted patients, $p < .0001$) and had a higher likelihood of having diabetes (33.9% vs. 22.3% and 17.6%, respectively, $p < .001$) or CV history (50.8% vs. 27.8% and 21.2%, respectively, $p < .0001$). The proportion of patients with an albumin level <35g/L was higher (62.7% vs. 49.4% and 47.4%, respectively, $p < .0001$), as well as the proportion of patients with malnutrition defined by a BMI <18.5 (12.1% vs. 9.3% and 8%, respectively), or severe obesity defined by a BMI ≥30 (14.6% vs. 13.2% and 8.4%, respectively). Lastly, the proportion of patients with walking difficulties was higher (13.6% vs. 2.7% and 2.2%, respectively). The clinical profile of patients relisted but not retransplanted was relatively similar to patients relisted and retransplanted. Age at 2KT according to the donor type (i.e., deceased or living) is presented in Table S1. Of note, among the 1845 patients retransplanted during follow-up, only 148 patients (8.0%) were retransplanted with a living donor.

3.3 | Association between relisting/retransplantation and survival

A total of 2001 patients (37.5%) died (1771/3489 patients without 2KT; 230/1845 in patients with 2KT) during the follow-up period (mean follow-up time 4.9 ± 2.9 years). A PS-based analysis was performed in order to assess the association between 2KT and survival (Figures 2 and 3, Table 3). The weighting used for IPTW is presented in Supplementary Figure 1.

Among the subgroup of patients who were not retransplanted during follow-up (i.e., patients not relisted or relisted and not retransplanted), relisting was associated with decreased mortality (IPTW HR for relisting = 0.39 [0.35–0.44]) $p < .0001$). Among patients who were relisted during follow-up, 2KT (vs. no retransplantation) was associated with decreased mortality (HR 0.75 [0.63–0.89], $p = .0009$). (Figure 2).

We then further considered the timing of mortality after 2KT. Of the 1845 patients retransplanted during follow-up, 230 patients died, 35 of them within 3 months of retransplantation. Compared with patients relisted but not retransplanted, the risk of mortality was significantly higher in patients retransplanted since ≤3 months (HR = 1.64 [1.16–2.33], $p = .005$), whereas 2KT was associated with better outcome after 3 months (Table 3).

3.4 | Interaction of relisting and retransplantation with age

In this population, 1614 patients were aged <50 years, 896 were 50–59 years, 1266 were 60–69 years, and 1558 were 70 years or older. The number of patients relisted and retransplanted according to predefined age classes (<50 years, 50–59 years, 60–69 years, ≥70 years) is presented in Table S2. The association between relisting and survival was homogeneous according to age (p for interaction 0.94) (Figure 2). In contrast, retransplantation was associated with a lower risk for death that was dependent on age (p for interaction 0.055) (Figure 2). A significant survival advantage was observed in patients under 70 (HR 0.41 [0.24–0.70] in patients <50, HR 0.64 (0.44–0.94) in patients 50 to 59, and HR 0.72 (0.55–0.94) in 60 to 69), but not for patients aged 70 or older (HR 0.94 [0.69–1.27], $p = .68$).

TABLE 2 Comparison of patients according to relisting on the waiting list and retransplantation during follow-up

Variables	Not relisted on the waiting list during follow-up ($n = 2062$)		Relisted but not retransplanted during follow-up ($n = 1427$)		Relisted and retransplanted during follow-up ($n = 1845$)		p-value[a]
	N	Median (Q1–Q3)/*n* (%)	*N*	Median (Q1–Q3)/*n* (%)	*N*	Median (Q1–Q3)/*n* (%)	
Age at return to dialysis after a first transplantation (years)	2062	65.7 (57.6–72.3)	1427	55.1 (44.7–63.1)	1845	52.1 (42.5–61.3)	<0.0001
Age at the onset of end-stage renal disease (first dialysis or first preemptive transplantation) (years)	2062	53.7 (43.5–61.9)	1427	42.6 (31.6–52.6)	1845	39.6 (28.2–50.5)	<0.0001
Gender	2062		1427		1845		0.39
Women		803 (38.9%)		540 (37.8%)		679 (36.8%)	
Men		1259 (61.1%)		887 (62.2%)		1166 (63.2%)	
Causal nephropathy (eight classes)	2062		1427		1845		<0.0001
Other		397 (19.3%)		261 (18.3%)		414 (22.4%)	
Glomerulonephritis		472 (22.9%)		419 (29.4%)		616 (33.4%)	
Hypertension		264 (12.8%)		167 (11.7%)		140 (7.6%)	
Unknown		258 (12.5%)		177 (12.4%)		222 (12.0%)	
Diabetic nephropathy		289 (14.0%)		136 (9.5%)		112 (6.1%)	
Polycystic disease		260 (12.6%)		154 (10.8%)		176 (9.5%)	
Malformative uropathy		114 (5.5%)		103 (7.2%)		159 (8.6%)	
Vascular nephropathy		8 (0.4%)		10 (0.7%)		6 (0.3%)	
Causal nephropathy (three classes)	2062		1427		1845		<0.0001
Glomerulonephritis/polycystic disease/malformative uropathy		846 (41.0%)		676 (47.4%)		951 (51.5%)	
Hypertension/diabetic nephropathy/vascular nephropathy		561 (27.2%)		313 (21.9%)		258 (14.0%)	
Other/unknown		655 (31.8%)		438 (30.7%)		636 (34.5%)	
Characteristics of the first transplantation							
Age at the first transplantation (years)	2062	57.2 (47.2–64.9)	1427	45.8 (34.8–55.4)	1845	41.7 (30.5–52.4)	<0.0001
First preemptive transplantation	2062	53 (2.6%)	1427	63 (4.4%)	1845	101 (5.5%)	<0.0001
Donor type for the first transplantation	1834		1280		1587		<0.0001
Donor after cardiac death		7 (0.4%)		25 (2.0%)		35 (2.2%)	
Brain dead donor		1790 (97.6%)		1177 (92.0%)		1445 (91.1%)	
Living donor		37 (2.0%)		78 (6.1%)		107 (6.7%)	
Time between the first dialysis and the first transplantation (months)	2062	29 (16–54)	1427	26 (12–48)	1845	18 (8–33)	<0.0001
Duration of the first transplantation (years)	2062	6.6 (2.2–12.9)	1427	6.5 (2.1–12.4)	1845	8.3 (3.2–14.2)	<0.0001
Comorbidities at inclusion (at the return to dialysis after a first transplantation)							
Smoking	1605		1139		1384		<0.0001
Former smoker		455 (28.3%)		245 (21.5%)		312 (22.5%)	
Active smoker		205 (12.8%)		213 (18.7%)		236 (17.1%)	
Non smoker		945 (58.9%)		681 (59.8%)		836 (60.4%)	
Diabetes	1873	635 (33.9%)	1275	284 (22.3%)	1616	285 (17.6%)	<0.0001
Chronic respiratory disease	1838	172 (9.4%)	1256	68 (5.4%)	1575	54 (3.4%)	<0.0001
Chronic oxygen therapy	1837	52 (2.8%)	1256	23 (1.8%)	1572	7 (0.4%)	<0.0001
Myocardial infarction	1829	203 (11.1%)	1256	80 (6.4%)	1581	63 (4.0%)	<0.0001
Coronary disease	1835	459 (25.0%)	1256	167 (13.3%)	1579	155 (9.8%)	<0.0001

TABLE 2 (Continued)

Variables	Not relisted on the waiting list during follow-up (n = 2062)		Relisted but not retransplanted during follow-up (n = 1427)		Relisted and retransplanted during follow-up (n = 1845)		p-value[a]
	N	Median (Q1–Q3)/*n* (%)	*N*	Median (Q1–Q3)/*n* (%)	*N*	Median (Q1–Q3)/*n* (%)	
Myocardial infarction and/or coronary disease	1833	494 (27.0%)	1255	185 (14.7%)	1578	162 (10.3%)	<0.0001
Heart failure	1837	463 (25.2%)	1258	146 (11.6%)	1577	136 (8.6%)	<0.0001
Heart rhythm disorder	1828	441 (24.1%)	1256	124 (9.9%)	1577	129 (8.2%)	<0.0001
Cardiovascular history	1830	929 (50.8%)	1254	348 (27.8%)	1573	333 (21.2%)	<0.0001
Peripheral artery disease	1840	359 (19.5%)	1256	101 (8.0%)	1577	100 (6.3%)	<0.0001
Stroke	1804	194 (10.8%)	1228	63 (5.1%)	1556	64 (4.1%)	<0.0001
Cancer not in remission	1837	207 (11.3%)	1255	61 (4.9%)	1585	83 (5.2%)	<0.0001
HIV/AIDS	1818	8 (0.4%)	1259	15 (1.2%)	1574	12 (0.8%)	0.061
Liver cirrhosis	1831	46 (2.5%)	1260	18 (1.4%)	1579	18 (1.1%)	0.007
Chronic hepatitis B	1834	32 (1.7%)	1262	29 (2.3%)	1576	24 (1.5%)	0.30
Chronic hepatitis C	1829	61 (3.3%)	1260	49 (3.9%)	1567	50 (3.2%)	0.56
Clinical and biological parameters at inclusion (at the return to dialysis)							
Albumin (g/L)	1189	32.4 (28.0–37.0)	783	35.0 (31.0–38.0)	1064	35.0 (31.7–39.0)	<0.0001
Albumin <35 g/L	1189	746 (62.7%)	783	387 (49.4%)	1064	504 (47.4%)	<0.0001
Hemoglobin (g/dL)	1406	10.0 (9.0–11.1)	929	10.0 (8.9–11.1)	1253	10.0 (9.0–11.3)	0.31
Anemia	1406	1292 (91.9%)	929	853 (91.8%)	1253	1136 (90.7%)	0.48
Moderate or severe anemia	1406	1013 (72.0%)	929	662 (71.3%)	1253	847 (67.6%)	0.033
BMI (kg/m^2)	1402	23.3 (20.3–27.0)	932	23.4 (20.7–27.1)	1232	23.2 (20.7–26.3)	0.44
BMI (4 classes)	1402		932		1232		<0.0001
<18.5		170 (12.1%)		87 (9.3%)		99 (8.0%)	
18.5–24.9		720 (51.4%)		494 (53.0%)		713 (57.9%)	
25.0–29.9		307 (21.9%)		228 (24.5%)		317 (25.7%)	
>=30		205 (14.6%)		123 (13.2%)		103 (8.4%)	
Ability to walk	1655		1142		1456		<0.0001
Incapacity		83 (5.0%)		9 (0.8%)		4 (0.3%)	
Normal		1430 (86.4%)		1111 (97.3%)		1424 (97.8%)	
Necessity to be helped by someone		142 (8.6%)		22 (1.9%)		28 (1.9%)	
Paraplegia/hemiplegia	1771	39 (2.2%)	1239	5 (0.4%)	1555	15 (1.0%)	<0.0001
Blindness	1777	64 (3.6%)	1242	28 (2.3%)	1561	36 (2.3%)	0.036
Cognitive impairment	1771	49 (2.8%)	1240	20 (1.6%)	1558	19 (1.2%)	0.004
Therapeutic modalities at study inclusion							
Type of dialysis	1916		1298		1668		<0.0001
Peritoneal dialysis		62 (3.2%)		67 (5.2%)		107 (6.4%)	
Hemodialysis		1854 (96.8%)		1231 (94.8%)		1561 (93.6%)	
Vascular access	1654		1110		1358		0.0001
Other		78 (4.7%)		30 (2.7%)		43 (3.2%)	
Tunneled central catheter		413 (25.0%)		211 (19.0%)		286 (21.1%)	
Native arteriovenous fistula		1133 (68.5%)		848 (76.4%)		1009 (74.3%)	
Prosthetic fistula		30 (1.8%)		21 (1.9%)		20 (1.5%)	
Follow-up							
Follow-up (months)	2062	36 (10–61)	1427	57 (41–83)	1845	75 (54–100)	<0.0001

(Continues)

TABLE 2 (Continued)

Variables	Not relisted on the waiting list during follow-up (*n* = 2062)		Relisted but not retransplanted during follow-up (*n* = 1427)		Relisted and retransplanted during follow-up (*n* = 1845)		*p*-value[a]
	N	Median (Q1–Q3)/*n* (%)	*N*	Median (Q1–Q3)/*n* (%)	*N*	Median (Q1–Q3)/*n* (%)	
Follow-up (years)	2062	3.0 (0.8–5.1)	1427	4.8 (3.4–6.9)	1845	6.2 (4.5–8.3)	<0.0001
Death during follow-up	2062	1380 (66.9%)	1427	391 (27.4%)	1845	230 (12.5%)	<0.0001

Abbreviations: AIDS, acquired immunodeficiency syndrome; BMI, body mass index; HIV, human immunodeficiency virus; *N*, number of non-missing data; Q1, first quartile; Q3, third quartile.

[a]Kruskal-Wallis test for continuous variables, chi-square test or Fisher's exact test for categorical variables.

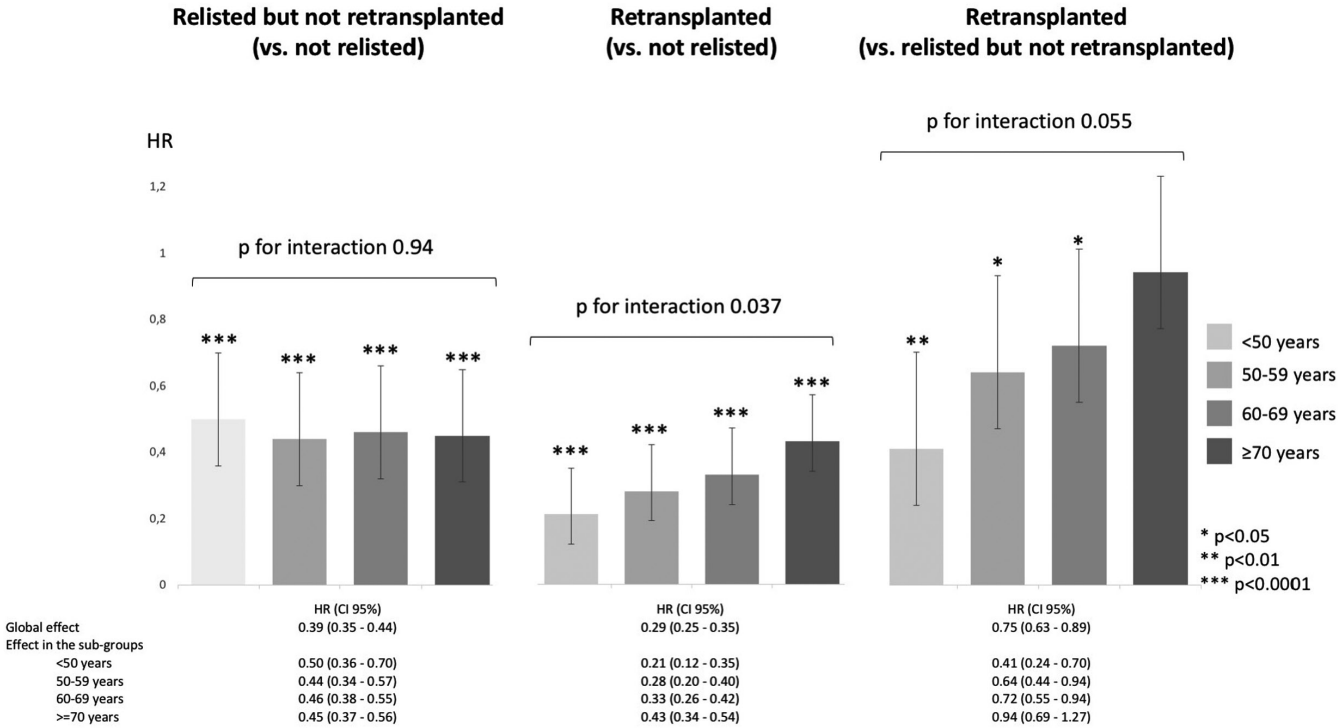


FIGURE 2 Association between relisting or retransplantation and mortality according to age (weighted Cox models)

Figure 3 shows the association between retransplantation and survival according to age when considered as a linear variable (*p* for interaction 0.034). As presented in the table, the survival benefit of retransplantation was not significantly different after 72 years of age.

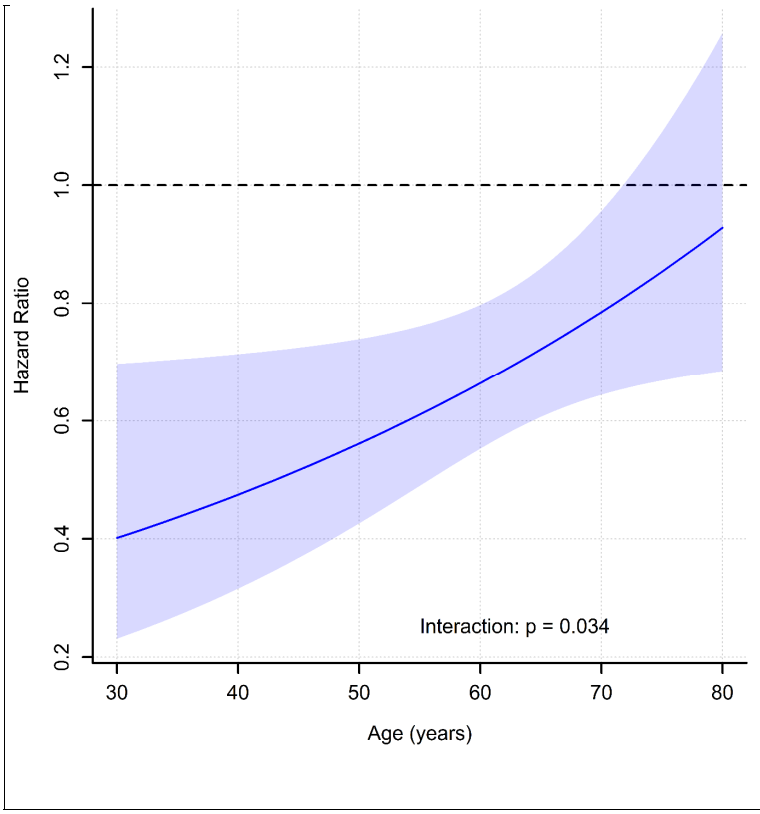
The excess of mortality observed during the 3-month postoperative period among patients receiving a 2KT in comparison with relisted patients was not significantly different according to age (interaction *p*-value =0.78). Moreover, the absence of significant survival benefit of 2KT persists among the oldest recipients aged ≥70 years even when we restricted the analysis to >3 months postoperative period (0.86 [0.63–1.18], *p* = .36) (Table 3).

3.5 | Association of age with rates of death and graft loss

In a supplementary analysis, we evaluated the association of age with death and graft loss (return to dialysis of third preemptive transplant) individually. Age was significantly associated with death (HR = 10.77 [6.72–17.27], *p* < .0001 for ≥70 vs. <50 years) but not graft loss (HR = 1.28 [0.82–1.99], *p* = .27). (Table 3).

4 | DISCUSSION

In this nationwide multicenter study conducted in the most recent era in France, we confirmed that 2KT was associated with better survival among patients who returned to dialysis between 2008 and 2015 after a first KT, even when the analysis was restricted to patients having been relisted on the waiting list during follow-up. Of note, the statistical methods used herein allowed taking into account not only the comorbidities of patients at return to dialysis, but also the evolution of these parameters during follow-up until relisting and subsequent 2KT. Nevertheless, the beneficial impact of a second KT on survival was not homogeneous across



Age	HR (CI 95%)	p-value	Age	HR (CI 95%)	p-value
30	0.40 (0.23 - 0.70)	0.001	56	0.62 (0.50 - 0.77)	<0.0001
31	0.41 (0.24 - 0.70)	0.001	57	0.63 (0.52 - 0.77)	<0.0001
32	0.42 (0.25 - 0.70)	0.0010	58	0.64 (0.53 - 0.78)	<0.0001
33	0.42 (0.25 - 0.70)	0.0009	59	0.65 (0.54 - 0.79)	<0.0001
34	0.43 (0.26 - 0.70)	0.0008	60	0.66 (0.55 - 0.80)	<0.0001
35	0.44 (0.27 - 0.70)	0.0007	61	0.67 (0.56 - 0.81)	<0.0001
36	0.44 (0.28 - 0.71)	0.0006	62	0.69 (0.58 - 0.82)	<0.0001
37	0.45 (0.29 - 0.71)	0.0005	63	0.70 (0.59 - 0.83)	<0.0001
38	0.46 (0.30 - 0.71)	0.0005	64	0.71 (0.60 - 0.84)	0.0001
39	0.47 (0.31 - 0.71)	0.0004	65	0.72 (0.61 - 0.86)	0.0002
40	0.47 (0.32 - 0.71)	0.0003	66	0.73 (0.62 - 0.88)	0.0006
41	0.48 (0.33 - 0.72)	0.0003	67	0.75 (0.62 - 0.89)	0.001
42	0.49 (0.34 - 0.72)	0.0002	68	0.76 (0.63 - 0.91)	0.003
43	0.50 (0.35 - 0.72)	0.0002	69	0.77 (0.64 - 0.93)	0.008
44	0.51 (0.36 - 0.72)	0.0002	70	0.78 (0.64 - 0.96)	0.016
45	0.52 (0.37 - 0.72)	0.0001	71	0.80 (0.65 - 0.98)	0.031
46	0.52 (0.38 - 0.73)	0.0001	72	0.81 (0.66 - 1.01)	0.056
47	0.53 (0.39 - 0.73)	<0.0001	73	0.83 (0.66 - 1.03)	0.093
48	0.54 (0.40 - 0.73)	<0.0001	74	0.84 (0.66 - 1.06)	0.14
49	0.55 (0.41 - 0.74)	<0.0001	75	0.85 (0.67 - 1.09)	0.20
50	0.56 (0.43 - 0.74)	<0.0001	76	0.87 (0.67 - 1.12)	0.28
51	0.57 (0.44 - 0.74)	<0.0001	77	0.88 (0.68 - 1.15)	0.36
52	0.58 (0.45 - 0.75)	<0.0001	78	0.90 (0.68 - 1.19)	0.45
53	0.59 (0.46 - 0.75)	<0.0001	79	0.91 (0.68 - 1.22)	0.54
54	0.60 (0.48 - 0.76)	<0.0001	80	0.93 (0.68 - 1.26)	0.63
55	0.61 (0.49 - 0.76)	<0.0001			

FIGURE 3 Association between retransplantation and mortality according to age (HR for comparison between patients retransplanted versus patients relisted but not retransplanted) [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Association between relisting or retransplantation since ≤3 months or >3 months and death according to age (weighted Cox models)

	Not relisted (versus relisted but not retransplanted)		Retransplanted since ≤3 months (versus relisted but not retransplanted)		Retransplanted since >3 months (versus relisted but not retransplanted)		
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	Overall *p*-value
Overall effect	2.54 (2.26–2.86)	<0.0001	1.64 (1.16–2.33)	0.005	0.67 (0.56–0.80)	<0.0001	<0.0001
Effect according to age							
<50 years	2.00 (1.44–2.79)	<0.0001	1.37 (0.55–3.42)	0.50	0.32 (0.17–0.58)	0.0002	<0.0001
50–59 years	2.29 (1.76–2.98)	<0.0001	1.32 (0.58–3.04)	0.51	0.58 (0.39–0.87)	0.008	<0.0001
60–69 years	2.18 (1.82–2.61)	<0.0001	1.69 (0.99–2.88)	0.054	0.64 (0.48–0.84)	0.001	<0.0001
≥70 years	2.21 (1.79–2.74)	<0.0001	2.19 (1.10–4.33)	0.025	0.86 (0.63–1.18)	0.36	<0.0001
Interaction		0.94		0.78		0.030	0.23

the various age classes and was no longer beneficial for patients aged 72 years or older.

The beneficial impact of 2KT on survival was previously reported in a few limited studies conducted among patients who returned to dialysis after a first KT in the 1990s. In a study by Ojo et al. analyzing data from the United States Renal Data System (USRDS) among 19208 patients with a first graft failure between 1985 and 1995, the authors observed that the survival conferred by 2KT varied according to diabetic status and was particularly significant among type 1 diabetic patients (RR 0.55 after 90 days). Among non-diabetic patients, the benefit of 2KT was also substantial (RR 0.77 after 90 days). Perioperative mortality was very high in both groups. The number of relisted type 2 diabetic patients was too low to interpret the data in this particular subgroup. Rao et al. reported data from the Canadian Organ Replacement Register (CORR) among 3067 patients who returned to dialysis between 1981 and 1998. Overall, they observed that retransplantation was associated with a 50% reduction in mortality in comparison with dialysis.

Data evaluating the interaction between age and the survival benefit following KT are scarce, even more so following a 2KT. The most recent meta-analysis evaluating the survival benefit associated with a first KT in comparison with dialysis[12] present a subgroup

analysis according to age (<60 years and ≥60 years). Among patients of the ≥60 years group, HR for mortality after KT was 0.42 (0.34 to 0.53) and was similar to the HR observed for patients ages less than 60 years (0.47 [0.38 to 0.59]). Most importantly, to the best of our knowledge, there is no contemporary data exploring the effect of 2KT on outcome according to age. In the study of Rao et al., the benefit of 2KT was not significant among patients over 60 years of age, but the number of patients in this subgroup was very low.[2] Moreover, the authors did not compare patients retransplanted with patients relisted but not retransplanted.

4.1 | Hypotheses regarding the lack of survival benefit of a second transplantation with aging

One can hypothesize that the cumulative deleterious impact of immunosuppressive therapy in the context of 2KT may be more sizeable among the oldest patients, in particular for cancers. In a study conducted in the Scientific Registry of Transplant Recipients, Yanik et al. evaluated how the incidence of cancers varied among candidates and recipients either for a first graft or a retransplantation,[13] according to intervals with a transplant in comparison with intervals on dialysis (either before the first KT or after the return to dialysis). The incidence of infection-related and immune-related cancers was higher during the intervals with a functioning graft than during intervals on dialysis. On the contrary, the incidence of cancers related to end-stage renal disease (e.g., kidney cancer) was lower during intervals with a functioning graft. In general, the incidence of cancer increases with aging. One can hypothesize that the deleterious impact of immunosuppressive therapy (for infection-related and immune-related cancers in particular) increases with aging. Moreover, cancer therapy options are likely more limited for the oldest patients. This may contribute to the interaction between age and survival benefit of retransplantation.

In the context of first KT for patients aged 70 years or older, an increased risk of event has been reported within 3 months of KT, whereas a survival advantage was only observed after 36 months of KT.[14] Therefore, one could speculate that the lack of survival benefit of 2KT among the oldest patients may be related to a particular excess of postoperative mortality. However, in the present study, the excess of mortality observed during the 2KT postoperative period was not significantly different across age categories. Moreover, the absence of significant survival benefit of 2KT persists among the oldest recipients aged ≥70 years even when the analysis was restricted to the period >3 months after surgery. This result is of particular importance because it suggests that the absence of survival benefit of retransplantation among the oldest patients is not related to an excess in perioperative mortality. One can speculate that, even if the oldest patients carefully selected in order to limit perioperative mortality, they nonetheless did not experience long-term benefit.

Higher age was associated with the risk of death but not with graft loss. This suggest that the differential impact of 2KT on survival we observed was rather related to competing risk arising from underlying conditions related to age/frailty than intrinsically worse graft outcome (i.e., recipients factors rather than graft factors).

4.2 | Study limitations

HLA sensitization data were unavailable in the present study. Considering the potential impact of HLA sensitization on the access to retransplantation, it would have been of interest to adjust the analyses based on these data. Nevertheless, such adjustment would unlikely have modified the interaction between age and survival for retransplantation. Moreover, the causes of death were not available and we were unable to assess whether the oldest patients were at increased risk of cancer, infections or CV complications after 2KT in comparison with dialysis. Evolution of biological and clinical data is not collected after 2KT in this registry. Nevertheless, the clinical objective of this study for future clinical implication is to evaluate whether patients should be candidates or not for a 2KT (i.e., to help decide if they should be relisted or not), considering their clinical and biological characteristics on return to dialysis and during the dialysis period preceding the 2KT. Our analysis considered both deceased-donor and living donor transplant. We cannot ascertain that our results are homogeneous across donor types (i.e., deceased/living), as interaction analysis require very large samples because of statistical power constrains. Preemptive 2KT is associated with better survival[15]; however, the number of patients who underwent preemptive 2KT was too low to perform a dedicated analysis. 2KT outcomes (i.e., the presence or absence of delayed graft function, non-primary function, rejections) were also not available for this study. Finally, in the present study, periods during which patients were on the waiting list but had a temporary contra-indication for KT were not taken into account.

4.3 | Clinical implications

The present study could help clinicians to better disclose the risk and benefits of a second transplantation to their patients who have returned to dialysis. Although there is no doubt that retransplantation is beneficial for the majority of the youngest patients with no contraindication for transplantation, such benefit still remains uncertain for older patients. The decision to wait-list a patient or not for a 2KT is frequently difficult, in particular for the oldest patients with an uncertain benefit/risk ratio. It represents a clinical challenge for the frailest patients. The overall benefit of transplantation, as well as retransplantation, may be considered as homogenous by patients and some physicians—whereas, it is not in light of our results.

Considering that the mean age of recipients of a first kidney graft is increasing, the question of retransplantation for older patients will be of increasing significance over the next decades. This should be considered as a growing issue, even more so in the context of organ shortage. Moreover, it is vital to have clinical tools to rapidly decide

if patients should be relisted or not, in order to ascertain whether immunosuppressive therapy should be continued even after the return to dialysis so as to avoid HLA sensitization. Considering the high risk of infections and/or cancers among the oldest patients, this is of particular importance in these patients.

4.4 | Ethical concerns

Considering the current organ shortage, the absence of survival benefit of a second KT among patients aged 72 years and older raises ethical questions regarding graft allocation policies. Nevertheless, in France, it should be mentioned that there is a relative adequacy between the age of the donors and the age of the recipients. Consequently, with the current policies, the allocation of kidneys to old second graft recipients does not preclude the allocation of these grafts to younger patients. Nevertheless, this study raises the question of the most accurate allocation of the grafts from old donor to old recipients between first and second kidney graft recipients. This study was not designed to compare the graft survival between first and second kidney graft recipients. A Swedish study previously reported that patient survival of patients aged 65 year or older receiving either a first KT or a second KT was similar.[16] Notwithstanding, it should be emphasized that the proportion of patients with diabetes or coronary heart disease was significantly lower among 2KT recipients relative to first KT recipients, reflecting the fact that patients may be more severely selected for a 2KT than for a first KT and contributing to a similar survival.

Finally, it should be highlighted that patient survival is only one aspect of the complex issue of the interest of retransplantation. Quality of life is also of crucial importance, with clinicians being acutely aware of the psychological consequences of the return to dialysis for patients after a first KT. Clinicians and policies should also take into account these aspects, along with the typically better quality of life observed in KT recipients versus patients undergoing hemodialysis. In addition, an integrative frailty evaluation[17] of patients >75 years could be useful to guide clinical decision-making.

5 | CONCLUSION

In this large multicenter French study of patients who returned to dialysis between 2008 and 2015 after a first KT, we confirmed that a second KT is associated with better survival as opposed to remaining on dialysis, even when restricting the analysis to patients having been relisted on the waiting list. Nevertheless, the beneficial effect of retransplantation is mainly observed in younger patients. The risk/benefit ratio should be thoroughly conveyed to the oldest patients when relisting is discussed.

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DISCLOSURE

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. SG, KD, CC, EL, CC, MK, and LF has no disclosure to declare. MB report speaker fees from Baxter. NG report honoraria from Novartis, AstraZeneca, Servier, Vifor, Bayer, Boehringer Ingelheim, and Lilly and is supported by public grants overseen by the European Commission (EUFP7) and the French National Research Agency (ANR) as part of the second 'Investissements d'Avenir' programme FIGHT-HF (ANR-15-RHU-0004).

DATA AVAILABILITY STATEMENT

Study data can be made available through a formal proposal to the REIN registry

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SUPPORTING INFORMATION

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