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Outcome-dependent geographic and individual variations in the access to renal transplantation in incident dialysed patients: a French nationwide cohort study

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Abbreviations:
ABM: Agence de la Biomédecine (Biomedecine Agency)
CI: Confidence Interval
ESRD: End Stage Renal Disease
HR: Hazard Ratio
REIN: Renal Epidemiology and Information Network
RRT: Renal Replacement Therapy

Conflict of interest: The authors declare that they have no conflict of interests.

Abstract

This study investigated geographic variations of access to renal transplantation using three outcomes (access to the transplant waiting list, access to renal transplantation after waitlisting and access to renal transplantation after dialysis start). Associations of patient-related and regional variables with the studied outcomes were assessed using a Cox shared frailty model and a Fine and Gray model. At the study endpoint (December 31, 2015), 26.3% of all 18-90-year-old patients who started dialysis in the 22 mainland and 4 overseas French regions in 2012 (n=9312) were waitlisted and 15.1% received a kidney transplant. The geographic disparities of access to renal transplantation varied according to the studied outcome. Patients from the Ile-de-France region had the highest probability of being waitlisted, but were less likely to receive a kidney transplant. Two regional factors were associated with the access to the waiting list and to renal transplantation from dialysis start: the incidence of preemptive kidney transplantation and of ESRD. The use of different outcomes to evaluate access to kidney transplantation could help healthcare policy-makers to select the most appropriate interventions for each region in order to reduce treatment disparities.

Introduction

The progressively increasing number of patients with chronic kidney disease, particularly due to aging and type 2 diabetes, is becoming a public health burden in France [1] as worldwide [2]. Patients with End Stage Renal Disease (ESRD) are treated by Renal Replacement Therapy (RRT) to increase their life expectancy. RRT includes kidney transplantation and dialysis (hemodialysis and peritoneal dialysis). For medically eligible patients, kidney transplantation is considered to be the most effective ESRD treatment in terms of survival [3-6], quality of life [7-9], and costs [6, 10-12]. However, organ supply currently does not cover the increasing demand worldwide. Indeed each year, around 56% of all patients with ESRD treated by dialysis are waiting for a kidney transplant, but only 25% will receive it [13].

Increasing the number of renal grafts is an important issue for both patients and health policy makers. Access to renal transplantation includes two steps: placement on the transplant waiting list and allocation of an organ. Therefore, it can be studied using different outcomes of interest, such as access to the transplant waiting list after dialysis start [14-19], access to renal transplantation after placement on the waiting list [15, 17, 19], and access to renal transplantation after dialysis start [15, 18]. As equity of access to kidney transplantation is a sensitive issue, the choice of outcome/methodology to evaluate the access to renal transplantation is a crucial topic.

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In France, registration in the national kidney transplant waiting list is mandatory even for people receiving a living-donor kidney transplant. The waiting list management and the organ allocation policy are regulated by the Agence de la Biomédecine (ABM) [20]. The decision to place a patient on the waiting list depends is taken by the nephrologist and ideally based on medical determinants. However, some non-medical factors might be related to access to the waiting list and some patients could refuse to be waitlisted and transplanted. Generally, it is taken by the transplant center nephrologists to whom patients are referred by the dialysis center nephrologists. Consequently, it may be subject to variations in practices. Our group previously reported geographic variations in the access to the renal transplant waiting list and showed that both patient-related and regional factors influence the placement on the list [14]. However, these observations could not be generalized to the entire country because the study included only 11 French regions and did not consider the biggest region of France (Ile-de-France: 18% of all French inhabitants). Another study showed that access to the waiting list is easier for patients living in Ile-de-France compared with patients from the Bretagne region who were 23% less likely to be placed on the list [15]. This study also showed that despite the easier access to the waiting list, the likelihood of renal transplantation was lower in Ile-de-France than in Bretagne. Therefore, easy access to the renal transplant waiting list is not necessarily associated with a better access to renal transplantation. This could be partly explained by the fact that access to renal transplantation depends on a national organ allocation score and on organ availability. The allocation score is developed by ABM and takes into account the time passed on the waiting list and on dialysis, the age difference between donor and recipient, and the donor-recipient immunological and blood group compatibility (see Table S1 for more details). Moreover, for kidney, each donor gives two organs where one of them is necessarily allocated to the transplantation team close to the donor reanimation team. Organ availability is then dependent to the donor activity and might differ between regions.

Therefore, the objectives of this study were to assess geographic variations in the access to renal transplantation in all French regions and to identify individual and regional determinants of access to renal transplantation using three outcomes of interest: placement on the renal transplant waiting list, access to renal transplantation after being waitlisted, access to renal transplantation after dialysis start.

Patients and Methods

REIN registry

The French Renal Epidemiology and Information Network (REIN) registry was established in 2002 and since 2011 it covers all French regions. The REIN registry includes all patients with ESRD undergoing RRT (dialysis or kidney transplantation) and living in France [21].

Study population

All patients aged between 18 and 90 years who started dialysis in France in 2012 were extracted from the REIN registry. To evaluate the access to the renal waiting list after dialysis start, patients were followed until December 31, 2015 (endpoint). The included patients lived in mainland France or in the overseas regions. Patients who received a preemptive kidney transplant were excluded because the comorbidities were not available for these patients.

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Collected data

For this study, patient-related and regional data were collected.

Patient-related data were extracted from the REIN registry. Three categories of variables were collected. The first concerned sociodemographic data: sex, age group (18-39, 40-59, 60-69, 70-79, 80-89 years), activity status (inactive: student, retired, at home; active: unemployed, full-time and part-time employed) and French region of residence at first dialysis.

The second individual category covered clinical data at dialysis start: primary kidney disease (glomerulonephritis, pyelonephritis, diabetic nephropathy, hypertensive and vascular nephropathy, polycystic kidney disease and other or unknown causes); comorbidities, such as respiratory disease, active malignancy, liver disease, diabetes, cardiovascular disease (coronary artery disease, peripheral vascular disease, congestive heart failure, arrhythmia, aortic aneurism and cerebrovascular disease), physical disabilities (physical impairment of ambulation, para- or hemi-plegia, blindness, member amputation) and psychiatric disorders; albumin (<30, ≥30 g/dl) and hemoglobin concentration (<10, 10-12, >12 g/dl); body mass index (BMI; <18.5, 18.5-23, 23-25, ≥25 kg/m²); and smoking status (never smoker, current/former smoker). Blood group (A, O, B and AB) and panel reactive antibody levels (<80%, ≥80%) were available for all waitlisted patients.

The third individual category included factors related to ESRD management in nephrology centers: nephrology facility ownership (public non-university center, public university center, private for-profit center and private not-for-profit center), center performing renal transplantation, emergency first dialysis, first dialysis with catheter, autonomous first dialysis session (home and out-center hemodialysis, non-assisted peritoneal dialysis), date of first dialysis, placement on the waiting list, renal transplantation and death.

At the regional level, four categories of variables were collected. The first one included socioeconomic indicators extracted from the National Institute of Statistics and Economic Studies (INSEE): gross domestic product per capita in € (per habitant/year), and disposable household income per capita in 2012.

The second regional category comprised healthcare offer indicators: density of general practitioners and specialists per 100 000 inhabitants in 2012 provided by the Department of Research, Studies, Evaluation and Statistics (DREES) of the French Health Ministry, and the density of nephrologists per 100 000 inhabitants in 2012 from the National College of Physicians. The number of dialysis and transplantation centers per million population (pmp) in 2012 was provided by ABM.

The third regional category concerned factors related to the healthcare needs: mean prevalence and mean incidence of dialyzed patients with ESRD for the 2011-2013 period per million population. Factors that could influence ESRD incidence also were collected from the French National Institute of Health and Medical Research (INSERM) Statistics: cardiovascular and diabetes mortality rates per 100 000 inhabitants during the 2012-2014 period.

The fourth regional category included the mean rate of living-donor renal transplants for the 2011-2013 period. As mentioned above, we couldn't include the preemptive kidney transplanted patients. However, we took into account this variable at the regional level with the mean incidence of preemptive renal transplants for the 2011-2013 period. For each French region, a linear regression

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model was used to study the annual number of patients who underwent kidney transplantation, of patients who were withdrawn from the list and of patients on the waiting list, on January 1 of each year, from 2011 to 2013.

Statistical analyses

The outcomes of interest were: (i) placement on the renal transplant waiting list; patients pre-emptively placed on the waiting list were considered as waitlisted at dialysis start. Time to outcome was assessed from dialysis start to waitlisting, death, or the endpoint (December 31, 2015); (ii) deceased-donor renal transplant after being waitlisted. Time to outcome was measured from waitlisting to renal transplantation, death or the endpoint; and (iii) deceased- donor renal transplant after dialysis start. Time to outcome was measured from dialysis start to renal transplantation, death or the endpoint.

Missing data in our database were missing completely at random. So, before the implementation of the survival models for each outcome, missing data were handled by using multiple imputation by chained equations (MICE) with ten imputations and five cycles [22].

The association between patient-related data and the three outcomes of interest was assessed by using univariate and multivariable Cox proportional hazard model. To analyze the association between both the patient level (demographic and bio-clinical characteristics of patients) and regional level (regions socioeconomics, health care need…) variables with the outcomes of interest, a multilevel model with the region as the frailty factor (Cox shared frailty model) was used [23].

Moreover, death before placement on the waiting list could be considered as a competing event with waitlisting. Death before transplantation and living donor transplantation could be considered as competing events with deceased donor transplantation. So, Fine and Gray univariate and multivariable models, taking into account these competing events, were also used to analyze the associations between patient level factors and the outcomes of interest [24]. Results are presented in Tables S2, S3, S4 (supplementary material).

Variables with a p-value <0.20 in univariate models were included in the multivariable models. A p-value <0.05 was considered statistically significant. Results were reported as hazard ratios (HR) for Cox analyses and subdistribution hazard ratios (SHR) for Fine and Gray analyses with 95% confidence intervals (95% CI). All statistical analyses were performed with the STATA 13.1 software.

Results

In 2012, 9312 patients from 18 to 90 years of age started dialysis in the 22 mainland France regions and 4 overseas territories (289 preemptively transplanted patients and 1 patient transplanted abroad were excluded). The patients' mean age was 68 ±14.9 years at dialysis start (Tables 1 and 2).

Patients' characteristics

Among all incident patients, 63.9% were men; 48% of patients had low hemoglobin (<10 g/dl) and 18.3% low albumin (<30 g/dl) levels. Patients presented several comorbidities: 47% had at least one cardiovascular disease, 13.8% respiratory insufficiency, 41.8% diabetes and 11.4% an active malignancy. Moreover, 30% of patients were dialyzed in a private for-profit center and 30% in a

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public non-university center. Only 18.5% started dialysis in a center performing also renal transplantation. Finally, 15% of patients were on autonomous dialysis and 29.1% started dialysis in emergency (Table 1).

Geographic variations of access to renal transplantation

By the end of 2015, 2448 (26.3%) patients had been placed on the kidney transplant waiting list. Cumulative incidence of waitlisting one, two and three years after dialysis start was respectively 18%, 23% and 25.5%. The percentage of waitlisted patients at the endpoint varied among regions, from 3.2% in the four overseas territories to 40.1% in the Ile-de-France region of mainland France (Table 2). Cumulative incidence of waitlisting three years after dialysis start by region are figured out in the Figure 1.

Among these waitlisted patients, 1402 (57.3%) underwent kidney transplantation. In Ile-de-France, only 43.5% of all waitlisted patients had received a kidney graft by the end of the follow-up, despite having the highest waitlisting rate. Conversely, in several French regions where the percentage of waitlisted patients was lower than in Ile-de-France (<30%), almost all of them (80 to 90%) underwent kidney transplantation. For instance, in Basse-Normandie 24.2% of all incident patients were waitlisted and 90% of waitlisted patients received a kidney transplant.

Among all incident dialyzed patients (n=9312), 1402 (15.1%) underwent kidney transplantation by the end of 2015. Cumulative incidence of transplantation from dialysis start one, two and three years after dialysis start was respectively 2.3%, 6.8% and 11.5%. The percentage of transplanted patients varied from <10% in the overseas territories, Lorraine and Nord-Pas-de-Calais to 20-25% in Corse, Basse-Normandie, Bretagne and Provence-Alpes-Côte-d'Azur. Cumulative incidence of transplantation three years after dialysis start by region are presented in the Figure 2.

Factors associated with access to the waiting list

Adjusted Cox proportional hazards and Cox shared frailty models were used to determine the associations between patient-related and regional factors and placement on the waiting list, respectively (Table 3). Concerning the patient-related variables, the adjusted Cox model showed that being a woman, age >39 years, presence of comorbidities, all nephropathies (*vs* polycystic disease), hemoglobin <10g/dl, albumin <30g/dl, BMI <23kg/m² or ≥25kg/m² (*vs* 23-25 kg/m²), inactivity, and starting dialysis in emergency, in a non-autonomous way or with a catheter were significantly associated with a lower probability of being waitlisted. Moreover, in 14 French regions and the four overseas territories, access to the waiting list was lower than in Ile-de-France. The results of Fine & Gray models were similar to those of Cox models (Supplemental Table S2).

The results of the shared frailty Cox model that included patient-related and regional factors highlighted that an increase in the mean ESRD incidence during the 2011-2013 period was associated with a lower probability of being placed on the waiting list (HR=0.993; 95%CI: 0.987-0.998). Conversely, an increase in the mean incidence rate of preemptive renal transplantation was associated with a higher probability of being waitlisted (HR=1.09; 95%CI: 1.03-1.15).

Factors associated with access to renal transplantation after being waitlisted

In the multivariable Cox model (Table 4), patients in the 40-59 years age group had a lower access to renal transplantation after waitlisting in comparison with the 18-39 years group (HR= 0.78, 95%CI: 0.67-0.90). Moreover, active malignancy, diabetes, the B and O blood groups (*vs* A group) were

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associated with a lower probability of receiving a kidney transplant. Conversely, old age (70-79 vs 18-39 years; HR=1.48, 95%CI: 1.18-1.85) and starting dialysis with a catheter (HR= 1.19, 95%CI: 1.05-1.35) were associated with higher access to renal transplantation. Compared with the Ile-de-France residents, people living in the other French regions (but not for Champagne-Ardenne, Lorraine, Midi-Pyrénées and overseas territories) were more likely to undergo kidney transplantation (univariate analyses in Supplemental Table 3). Panel reactive antibody level was not significantly associated with access to renal transplantation after being waitlisted. The results of the multivariable Fine & Gray model were similar to those obtained with the Cox model, but for the 40-59 years age group and starting dialysis with a catheter variables that were not associated with higher access to renal transplantation (Supplemental Table S3).

The results of the shared frailty Cox model showed at regional level that an increase in the mean ESRD incidence during the 2011-2013 period and an increase in the number of patients on the list (slope of number of patients still on the list on January 1 from 2011 to 2013) were associated with a lower probability of receiving a renal transplant after being waitlisted (Table 4).

Factors associated with access to renal transplantation from dialysis start

For the patient-related variables, the multivariable Cox analyses (Table 5, left panel) showed that female sex, age, presence of comorbidities, hypertensive and vascular nephropathy, diabetic nephropathy and unknown nephropathies (vs polycystic disease), albumin <30g/dl, BMI <18.5kg/m² or ≥25kg/m² (vs 23-25 kg/m²), and starting dialysis in emergency, in a non-autonomous way or with a catheter were significantly associated with a lower probability of being transplanted. Conversely, compared with patients dialyzed in public non-university centers, those dialyzed in a not-for-profit center were more likely to undergo kidney transplantation (HR=1.21, 95%CI: 1.03-1.42). The results of the adjusted Fine and Gray model were not different from those of the Cox model, but for the absence of association between nephrology facility and renal transplantation (Supplemental Table S4).

The results of the Cox shared frailty model that included patient-related and regional factors showed that regionally, an increase of the mean incidence rate of preemptive renal transplantation was associated with a higher access to renal transplantation (HR=1.11; 95%CI: 1.03-1.18; Table 5, right panel). Conversely, an increase in the mean ESRD incidence was associated with a lower probability of receiving a kidney transplant (HR=0.991; 95%CI: 0.98-0.997).

Discussion

This is the first study that assessed the geographic variations of access to renal transplantation in the entire France (mainland France and overseas territories) using three outcomes of interest (placement on the waiting list, access to renal transplantation after being waitlisted and after dialysis start). The association of different patient-related and regional variables with access to renal transplantation depended on the chosen outcome. Some variables (for instance, comorbid diabetes) were associated with a lower access to renal transplantation, whatever the outcome of interest. On the other hand, being a woman was associated with a lower access to the waiting list and to transplantation after dialysis start, but not with access to transplantation after waitlisting. Similarly, older age was associated with a lower probability of access to the waiting list and to transplantation after dialysis start, but with a better access to transplantation after being waitlisted.

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Our study also showed that regional disparities in the access to renal transplantation in France varied in function of the chosen outcome. For example, after adjustment to the patients' characteristics, patients living in the Languedoc-Roussillon region were 38% less likely to be waitlisted than those living in Ile-de-France. Nevertheless, the likelihood of renal transplantation after being waitlisted and after dialysis start was respectively 2.4 times (95%CI: 1.8-3.3) and 1.4 times (95%CI: 1.1-1.9) higher in the Languedoc-Roussillon region than in Ile-de-France. These results confirm that the better access to the renal transplant waiting list in Ile-de-France does not mean a better access to renal transplantation [15]. Moreover, in the model that analyzed access to renal transplantation after being waitlisted, the probability of access to renal transplantation was higher in almost all the other French regions than in Ile-de-France. However, in the model that assessed access to renal transplantation after dialysis start, only 10 of the 22 French regions had a better access to renal transplantation compared with Ile-de-France.

Importantly, patients from the French overseas territories had the worst access to the waiting list and to renal transplantation. This population presents specific characteristics that distinguish them from patients living in mainland France. They are younger, with more comorbidities (for instance, diabetes) and more often living in precarious situations compared with people living in mainland France [25]. The age- and sex-adjusted ESRD incidence is more than twice higher in the overseas territories than in mainland France [25]. Moreover, the healthcare offer is limited, with only two transplant centers (Guadeloupe, La Réunion) for all the overseas territories [26]. Consequently, patients from these territories, eligible for renal transplantation, might have to come to mainland France for kidney transplantation. This travel could be very expensive and not totally reimbursed by social security. Moreover, the patients would be away from their family for a long period. These facts could discourage some of them.

Our study confirmed previous results on the association between female sex, older age, presence of comorbidities and lower access to the waiting list [14-19] and to renal transplantation after dialysis start [15]. Moreover, differently from previous studies [3, 18, 19] but in agreement with others [16, 19], female sex was not associated with access to renal transplantation after being waitlisted. In addition, patients in the 70-79 years age group (compared with the 18-39 years age group) were 48% more likely to undergo kidney transplantation after being waitlisted. This could be explained by the "old for old" approach described by previous studies [5, 27, 28]. In France, because of aging of organ donors and donor-recipient age-matching, waitlisted older patients might have a higher probability of receiving a kidney transplant. After being waitlisted, the panel reactive antibody level was not significantly associated with renal transplantation. Conversely, patients with the O and B blood groups had a lower probability of being transplanted than patients with the A group, as previously reported [15]. Whatever the outcome of interest, diabetes and active malignancy were associated with a lower access to renal transplantation. Starting dialysis in a center performing transplantation was not associated with higher access to renal transplantation. However, patients dialyzed in a private not-for-profit center were 21% more likely to have access to the list and to transplantation after dialysis start in comparison with patients treated in public non-university centers (adjusted Cox model). This confirmed the findings of a previous study on the access to the kidney transplant waiting list in 11 French regions [14]. In the United States of America (USA), Patzer et al found that at dialysis facility level, for profit centers were associated with a lower standardized transplant ratio [29].

Only two regional factors were associated with the access to the waiting list and to renal transplantation from dialysis start: the incidence of preemptive kidney transplantation and of ESRD. An increased mean incidence of preemptive renal transplantation during the study period was associated with a higher probability of access to the waiting list and to renal transplantation. This

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suggests that changes in the preemptive renal transplantation rates are an indicator of a dynamic renal transplantation activity. Conversely, an increased mean ESRD incidence was associated with a lower probability of waitlisting and renal transplantation. In USA, geographic variations in the access to renal transplantation have been associated with ESRD incidence [30]. The authors explained that high ESRD incidence leads to saturation of transplant resources and increases the time on dialysis, which restricts the access to renal transplantation. Mathur et al, didn't analyze preemptive kidney transplantation incidence at area level, nevertheless they observed that, transplant rates increased with increasing donation rates [30]. Consistently with the previous study in 11 French regions [14], the gross domestic product per capita, disposable household income per capita and healthcare offers indicators were not associated with the placement on the list. Moreover, the number of dialysis and transplantation center per region was not associated with access to the waiting list or renal transplantation. Coversely, in the USA, Patzer et al observed that an additional transplant center per 10 000 patients increases the standardized transplant ratio at network level [29].

This study has some limitations. It only took into account the first transplant and did not consider candidates for a new kidney transplant after graft rejection. In addition, it did not analyze the reasons of non-placement in the kidney transplant waiting list because they are not recorded in the REIN registry. Individual socio-economics factors (like level of income or education) are not available in REIN, so we couldn't include these individual variables in our analyses but only regional socio-economic indicators. In addition, data about race, ethnicity or referral to a transplant center are not available in the REIN registry.

For public health policy makers and patients associations, it is important to determine the existence of discrepancies in kidney transplant access rates, which are traditionally measured on the basis of the mean or median waiting times, in order to raise concerns about the equity of the allocation policies and/or disparities in the access to the national waiting list. Here, we analyzed regional disparities in access to renal transplantation in France by taking into account both patient-related and regional variables and using different outcomes of interest. This comprehensive approach is very useful for informing public health interventions. Indeed, on the basis of the present results, healthcare policy makers could further promote the placement on the waiting list in some regions or organ procurement in other regions in order to reduce regional disparities in the access to renal transplantation.

The establishment of national recommendations by the Haute Autorité de Santé (French national health agency) in 2015 for the placement on the waiting list should homogenize the clinical practices in France. Future studies should evaluate the impact of these recommendations in all French regions.

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Table 1. Characteristics of incident dialyzed patients at baseline.

	Incident dialyzed patients n (column %)	Percentage of waitlisted patients (row %)	Percentage of transplanted patients (row %)
	n=9312	**26.3%**	**15.1%**
	Sociodemographic data		
Sex			
Men*	5953 (63.9)	26.8	15.4
Women	3359 (36.1)	25.4	14.5
Age (years)			
18-39	537 (5.8)	83.4	54.9
40-59	1863 (20)	60.2	33.0
60-69	2058 (22.1)	33.2	17.8
70-79	2610 (28)	7.4	4.8
80-90	2244 (24.1)	0.2	0.1
Activity status			
Inactive	7131 (76.6)	15.7	9.1
Active	1395 (15)	64.5	38.1
Missing data	786 (8.4)	54.2	28.2
	Clinical data		
Hemoglobin (g/dl)			
<10	4470 (48)	23.2	12.8
[10-12]	2811 (30.2)	27.5	16.4
>12	1387 (14.9)	31.5	18.5
Missing data	644 (6.9)	31.5	17.1
Albumin (g/dl)			
<30	1707 (18.3)	14.9	7.6
≥30	5773 (62)	29.2	17.0
Missing data	1832 (19.7)	27.7	15.8
BMI (kg/m²)			
<18.5	379 (4)	24.8	12.9
[18.5-23[	1730 (18.6)	28.2	18.2
[23-25[	1150 (12.4)	27.7	17.7
≥25	3947 (42.4)	24.8	13.8
Missing data	2106 (22.6)	27.1	13.8
Smoking status			
Current/former smoker	3157 (33.9)	26.2	14.7
Never smoker	4563 (49)	28.9	16.6
Missing data	1592 (17.1)	18.9	11.3
Number of cardiovascular diseases			
0	4365 (46.9)	42.1	25.2
1	2219 (23.8)	19.2	9.8
2	1450 (15.6)	8.5	3.7
≥3	1278 (13.7)	4.8	2.4
Respiratory disease			
Yes	1238 (13.8)	10.0	4.6
No	7699 (86.2)	29.2	16.9
Missing data	375 (4)	19.5	12.5
Active malignancy			
Yes	1062 (11.4)	7.1	2.4
No	7933 (85.2)	29.1	16.8
Missing data	317 (3.4)	21.5	13.6
Liver disease			
Yes	190 (2)	6.8	3.7
No	8794 (94.5)	26.9	15.4

Missing data	328 (3.5)	20.7	12.1
Diabetes			
Yes	3891 (41.8)	15.4	21.1
No	5370 (57.7)	34.1	6.5
Missing data	51 (0.5)	37.3	33.3

(continued)	**Incident dialyzed patients n (column %)**	**Percentage of waitlisted patients (row %)**	**Percentage of transplanted patients (row %)**
Psychiatric disorder			
Yes	247 (2.7)	10.1	3.2
No	8447 (90.7)	27.4	15.8
Missing data	618 (6.6)	17.2	10.0
Number of physical disabilities			
0	8804 (94.5)	27.2	15.6
≥1	508 (5.5)	11.2	5.5
Primary kidney disease			
Polycystic disease	518 (5.6)	66.6	43.8
Hypertensive and vascular nephropathy	2566 (27.6)	15.0	7.3
Diabetic nephropathy	2094 (22.5)	16.3	6.9
Glomerulonephritis	1002 (10.8)	54.0	34.9
Pyelonephritis	406 (4.4)	29.8	18.7
Others	2726 (29.3)	26.2	15.3
	ESRD management		
Ownership of nephrology facility			
Private for-profit center	2802 (30.1)	24.4	13.2
Private not-for-profit center	1586 (17)	32.6	21.0
Public university center	2098 (22.5)	28.9	14.4
Public non-university center	2826 (30.4)	22.7	14.1
Center performing kidney transplantation			
Yes	1718 (18.5)	28.9	14.3
No	7594 (81.5)	25.7	15.2
First dialysis session			
Non-autonomous	7914 (85)	25.6	14.3
Autonomous	1398 (15)	32.2	21.4
Emergency start			
Yes	2709 (29.1)	20.6	10.5
No	6101 (65.5)	29.2	17.2
Missing data	502 (5.4)	21.1	13.4
First dialysis with catheter			
Yes	4570 (49)	20.2	10.6
No	3945 (42.4)	33.7	20.0
Missing data	797 (8.6)	24.6	16.4

BMI: Body Mass Index; Cardiovascular diseases: coronary artery disease, peripheral vascular disease, congestive heart failure, arrhythmia, aortic aneurism and cerebrovascular disease; Physical disabilities: physical impairment of ambulation, para- or hemi-plegia, blindness, member amputation.

*For example: 63.9% of incident dialyzed patients were men; 26.8% of incident male patients were waitlisted; 15.4% of incident male patients received a kidney transplant.

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Table 2. Geographic variations of access to renal transplantation in France.

Region of residence	Population 31/12/2012	Incident patients (2012)	Placement on the waiting-list (31/12/2015) (n=2448)		Access to renal transplantation after waitlisting (31/12/2015) (n=1402)		Access to renal transplantation after dialysis start (31/12/2015) (n=1402)	
	Number	Number (%)	% of incident patients	Median time in months (IQR)[1]	% of waitlisted patients	Median time in months (IQR)[2]	% of incident patients	Median time in months (IQR)[3]
Alsace	1 859 869	283 (3)	18.0	10.8 (5.0-17.3)	56.9	16.3 (10.0-24.3)	10.3	28.6 (18.6-34.2)
Aquitaine	3 285 970	489 (5.3)	25.8	6.2 (0.8-11.4)	69	15.6 (9.7-26.5)	17.8	22.7 (14.9-29.5)
Auvergne	1 354 104	219 (2.4)	25.1	6.4 (2.6-14.5)	58.2	12.2 (2.2-24.6)	14.6	20.8 (11.9-29.5)
Basse-Normandie	1 477 209	178 (1.9)	24.2	4.5 (0.1-9.3)	90.7	15.5 (6.9-24.4)	21.9	18.6 (13.5-22.7)
Bourgogne	1 641 130	219 (2.4)	16.4	7.4 (1.1-12.7)	61	17.7 (9.1-31.6)	10.1	20.3 (13.6-27.1)
Bretagne	3 237 097	381 (4.1)	27.8	5.1 (0.7-12.2)	77.4	10.5 (3.6-17.9)	21.5	13.1 (8.4-23.7)
Centre	2 563 586	363 (3.9)	26.7	12.4 (4.6-22.2)	59.8	9.3 (5.1-21.5)	16	23.0 (15.1-31.0)
Champagne-Ardenne	1 339 270	200 (2.2)	26.0	5.6 (1.6-15.3)	53.8	12.8 (9.0-20.5)	14	21.3 (10.6-29.7)
Corse	316 257	37 (0.4)	27	7.3 (0.1-10.9)	90	10.5 (7.3-19.6)	24.3	20.8 (16.3-28.5)
Franche-Comté	1 175 684	144 (1.6)	30.6	4.4 (0.1-10.3)	63.6	13.5 (4.9-24.9)	19.4	19.7 (7.7-29.8)
Haute-Normandie	1 845 547	234 (2.5)	21.8	5.5 (0.1-12.0)	68.6	16.3 (8.5-24.2)	15	21.7 (14.3-28.4)
Ile-de-France	11 898 502	1623 (17.4)	40.1	5.3 (0.1-11.6)	43.5	21.3 (10.1-31.1)	17.4	22.6 (13.4-32.8)
Languedoc-Roussillon	2 700 266	466 (5)	18.5	8.3 (0.1-15.0)	67.4	10.9 (5.3-21.6)	12.5	20.8 (12.2-30.1)
Limousin	738 633	92 (1)	23.9	9.6 (3.7-12.9)	72.7	14.2 (7.7-23.3)	17.4	22.8 (14.0-31.6)
Lorraine	2 349 816	363 (3.9)	20.4	7.8 (0.1-15.4)	48.6	15.8 (8.1-23.9)	9.9	19.7 (8.8-32.4)
Midi-Pyrénées	2 926 592	393 (4.2)	28	4.4 (0.1-13.6)	50.9	16.9 (8.3-34.8)	14.3	20.3 (10.5-29.6)
Nord-Pas-de-Calais	4 050 756	688 (7.4)	17.7	14.2 (1.9-22.1)	54.9	17.8 (10.2-28.3)	9.7	26.7 (23.1-33.3)
Pays de la Loire	3 632 614	370 (4)	30.8	5.6 (0.1-13.2)	64	13.3 (8.1-21.4)	19.7	19.1 (8.2-27.1)
Picardie	1 922 342	280 (3)	22.1	6.0 (0.1-11.3)	61.3	21.0 (12.6-29.1)	13.6	23.2 (16.9-31.6)
Poitou-Charentes	1 783 991	209 (2.2)	27.3	8.9 (2.3-19.8)	80.7	10.3 (5.9-19.2)	22	18.4 (7.8-29.7)
Provence-Alpes-Côte-d'Azur	4 935 576	793 (8.5)	19.4	9.9 (3.7-18.6)	76.6	7.5 (2.5-18.2)	14.9	20.3 (12.6-28.9)
Rhône-Alpes	6 341 160	849 (9)	29.1	7.2 (0.1-12.6)	56.3	14.9 (7.9-30.3)	16.4	21.7 (13.1-32.1)
Overseas territories	1 865 270	439 (4.7)	3.2	17.0 (7.2-24.3)	29.5	18.8 (7.1-35.4)	1.6	35.8 (19.4-40.7)
Total	**65 241 241**	**9312**	**26.3**	**6.8 (0.2-14.6)**	**57.3**	**14.7 (7.2-26.2)**	**15.1**	**21.4 (12.8-30.9)**

*population recorded by the National Institute of Statistics and Economic Studies at the end of 2012; std: standard derivation; IQR: interquartile range; [1]median time from dialysis start to waitlisting; [2]median time from placement on the waiting list to kidney transplantation; [3]median time from dialysis start to kidney transplantation.

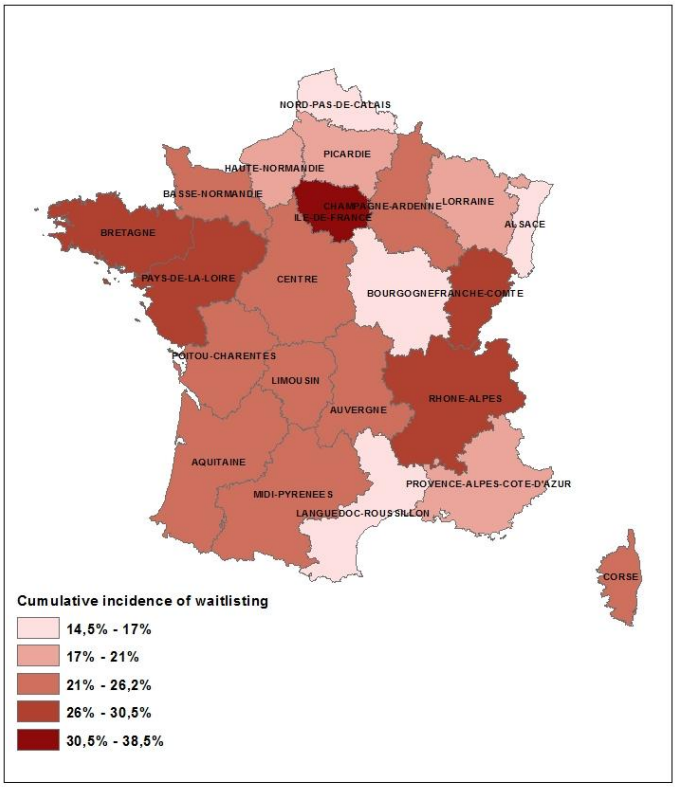

Figure 1. Cumulative incidence of waitlisting three years after dialysis start, by mainland French regions.
(Cumulative incidence of overseas territories are not showed in this graph).

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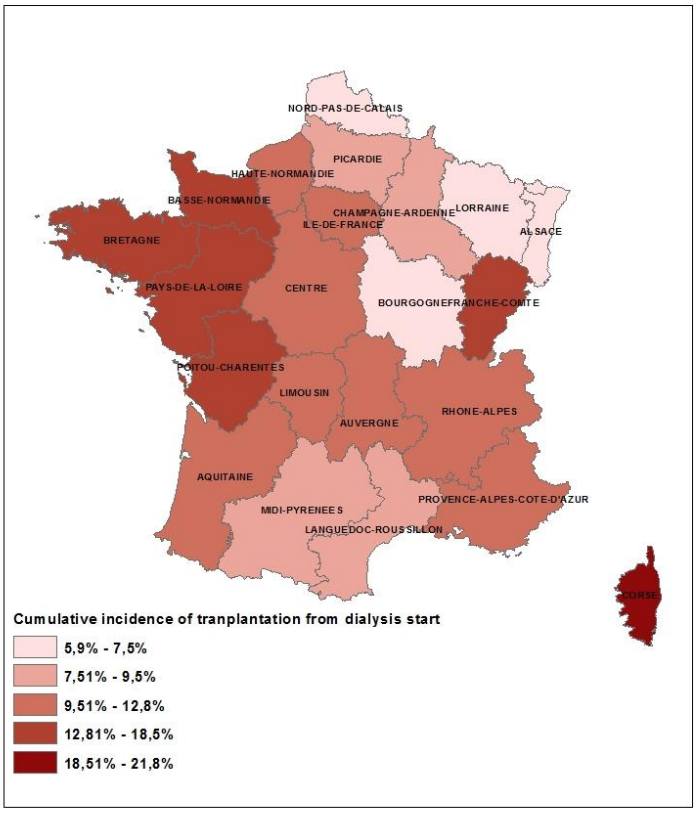

Figure 2. Cumulative incidence of renal transplantation three years after dialysis start, by mainland French regions. (Cumulative incidence of overseas territories are not showed in this graph).

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Table 3. Association of patient-related and regional variables with placement on the waiting list (Multivariable Cox and Cox shared frailty models; n=9312 incident patients. Among them, 2448 patients were waitlisted).

	Multivariable Cox model		Multivariable Cox shared frailty model	
	HR (95%CI)	**p**	**HR (95%CI)**	**p**
	Sociodemographic data			
Region of residence				
Alsace	0.39 (0.29-0.53)	**<0.001**		
Aquitaine	0.88 (0.72-1.07)	0.204		
Auvergne	0.55 (0.41-0.73)	**<0.001**		
Basse-Normandie	0.77 (0.56-1.06)	0.107		
Bourgogne	0.55 (0.39-0.78)	**0.001**		
Bretagne	0.67 (0.54-0.83)	**<0.001**		
Centre	0.91 (0.73-1.13)	0.378		
Champagne-Ardenne	0.66 (0.49-0.88)	**0.004**		
Corse	0.50 (0.27-0.95)	**0.034**		
Franche-Comté	0.86 (0.63-1.19)	0.376		
Haute-Normandie	0.80 (0.60-1.07)	0.139		
Ile-de-France	1		n/a	
Languedoc-Roussillon	0.62 (0.49-0.77)	**<0.001**		
Limousin	0.54 (0.35-0.84)	**0.005**		
Lorraine	0.55 (0.43-0.71)	**<0.001**		
Midi-Pyrénées	1.1 (0.89-1.35)	0.384		
Nord-Pas-de-Calais	0.37 (0.31-0.46)	**<0.001**		
Pays de la Loire	0.94 (0.76-1.15)	0.531		
Picardie	0.57 (0.44-0.75)	**<0.001**		
Poitou-Charentes	0.84 (0.63-1.11)	0.219		
Provence-Alpes-Côte-d'Azur	0.59 (0.49-0.70)	**<0.001**		
Rhône-Alpes	0.76 (0.65-0.88)	**<0.001**		
Overseas territories	0.27 (0.21-0.34)	**<0.001**		
Sex				
Men	1		1	
Women	0.86 (0.79-0.94)	**0.001**	0.86 (0.79-0.94)	**<0.001**
Age (years)				
18-39	1		1	
40-59	0.70 (0.62-0.78)	**<0.001**	0.69 (0.61-0.78)	**<0.001**
60-69	0.47 (0.40-0.54)	**<0.001**	0.47 (0.40-0.54)	**<0.001**
70-79	0.09 (0.07-0.11)	**<0.001**	0.09 (0.07-0.11)	**<0.001**
80-90	0.002 (0.001-0.006)	**<0.001**	0.002 (0.001-0.006)	**<0.001**
Activity status				
Inactive	0.80 (0.72-0.89)	**<0.001**	0.80 (0.72-0.89)	**<0.001**
Active	1		1	
	Clinical data			
Hemoglobin (g/dl)				
<10	0.83 (0.76-0.92)	**<0.001**	0.83 (0.75-0.91)	**<0.001**
[10-12]	1		1	
>12	0.99 (0.88-1.12)	0.896	0.99 (0.88-1.12)	0.912
Albumin (g/dl)				
<30	0.76 (0.67-0.86)	**<0.001**	0.76 (0.68-0.86)	**<0.001**
≥30	1		1	
BMI (kg/m²)				
<18.5	0.78 (0.64-0.96)	**0.019**	0.78 (0.64-0.96)	**0.020**
[18.5-23[	0.86 (0.74-0.99)	**0.034**	0.86 (0.75-0.99)	**0.042**
[23-25[	1		1	
≥25	0.87 (0.77-0.98)	**0.026**	0.87 (0.77-0.99)	**0.029**

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Number of cardiovascular diseases				
0	1		1	
1	0.77 (0.69-0.87)	**<0.001**	0.77 (0.69-0.87)	**<0.001**
2	0.48 (0.40-0.59)	**<0.001**	0.48 (0.40-0.58)	**<0.001**
≥3	0.39 (0.30-0.51)	**<0.001**	0.38 (0.29-0.50)	**<0.001**

(continued)	**Multivariable proportional Cox model**		**Multivariable Cox shared frailty model**	
	HR (95%CI)	**p**	**HR (95%CI)**	**p**
Respiratory disease				
Yes	0.55 (0.46-0.67)	**<0.001**	0.55 (0.46-0.67)	**<0.001**
No	1		1	
Active malignancy				
Yes	0.28 (0.22-0.35)	**<0.001**	0.28 (0.22-0.35)	**<0.001**
No	1		1	
Liver disease				
Yes	0.20 (0.12-0.35)	**<0.001**	0.20 (0.12-0.35)	**<0.001**
No	1		1	
Diabetes				
Yes	0.72 (0.62-0.82)	**<0.001**	0.71 (0.62-0.82)	**<0.001**
No	1		1	
Psychiatric disorder				
Yes	0.37 (0.25-0.55)	**<0.001**	0.37 (0.25-0.54)	**<0.001**
No	1		1	
Number of physical disabilities				
0	1		1	
≥1	0.61 (0.46-0.80)	**<0.001**	0.60 (0.46-0.79)	**<0.001**
Primary kidney disease				
Polycystic disease	1		1	
Hypertensive and vascular nephropathy	0.50 (0.43-0.59)	**<0.001**	0.51 (0.43-0.59)	**<0.001**
Diabetic nephropathy	0.47 (0.38-0.57)	**<0.001**	0.47 (0.39-0.58)	**<0.001**
Glomerulonephritis	0.79 (0.68-0.90)	**0.001**	0.78 (0.68-0.90)	**0.001**
Pyelonephritis	0.61 (0.49-0.75)	**<0.001**	0.61 (0.49-0.75)	**<0.001**
Others	0.57 (0.50-0.66)	**<0.001**	0.57 (0.50-0.65)	**<0.001**
	ESRD management			
Ownership of nephrology facility				
Private for-profit center	0.95 (0.84-1.07)	0.368	0.98 (0.87-1.10)	0.688
Private not-for-profit center	1.21 (1.06-1.38)	**0.004**	1.20 (1.06-1.37)	**0.005**
Public university center	1.05 (0.94-1.19)	0.386	1.07 (0.95-1.21)	0.242
Public non-university center	1		1	
First dialysis session				
Non-autonomous	0.85 (0.76-0.95)	**0.006**	0.86 (0.77-0.96)	**0.009**
Autonomous	1		1	
Emergency start				
Yes	0.87 (0.78-0.98)	**0.021**	0.87 (0.78-0.98)	**0.022**
No	1		1	
First dialysis with catheter				
Yes	0.69 (0.62-0.77)	**<0.001**	0.69 (0.62-0.77)	**<0.001**
No	1		1	
	Region level indicators			
Mean rate of preemptive Ktx (pmp)	n/a		1.09 (1.03-1.15)	**0.002**
Mean ESRD incidence	n/a		0.993 (0.987-0.998)	**0.008**

BMI: Body Mass Index; Cardiovascular diseases: coronary artery disease, peripheral vascular disease, congestive heart failure, arrhythmia, aortic aneurism and cerebrovascular disease; Physical disabilities: physical impairment of ambulation, para- or hemi-plegia, blindness, member amputation; Ktx: Kidney transplantation; pmp: per million population; ESRD: End Stage Renal Disease; HR: Hazard Ratio; CI: Confidence Interval.

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Table 4. Association between patients' characteristics and access to renal transplantation after being waitlisted (Multivariable Cox and Cox shared frailty models; n=2448 waitlisted patients. Among them, 1402 patients were transplanted).

	Multivariable Proportional Cox model		Multivariable Cox shared frailty model	
	HR (95%CI)	**p**	**HR (95%CI)**	**p**
	Sociodemographic data			
Region of residence				
Alsace	1.84 (1.25-2.72)	**0.002**		
Aquitaine	2.10 (1.64-2.70)	**<0.001**		
Auvergne	1.77 (1.22-2.58)	**0.003**		
Basse-Normandie	4.07 (2.90-5.73)	**<0.001**		
Bourgogne	1.82 (1.16-2.86)	**0.009**		
Bretagne	3.54 (2.73-4.59)	**<0.001**		
Centre	2.17 (1.62-2.91)	**<0.001**		
Champagne-Ardenne	1.41 (0.95-2.09)	0.086		
Corse	3.66 (1.87-7.16)	**<0.001**		
Franche-Comté	1.96 (1.32-2.89)	**0.001**		
Haute-Normandie	2.31 (1.61-2.33)	**<0.001**		
Ile-de-France	1		n/a	
Languedoc-Roussillon	2.44 (1.81-3.29)	**<0.001**		
Limousin	2.55 (1.53-4.26)	**<0.001**		
Lorraine	1.14 (0.79-1.63)	0.486		
Midi-Pyrénées	1.21 (0.91-1.62)	0.194		
Nord-Pas-de-Calais	1.91 (1.44-2.53)	**<0.001**		
Pays de la Loire	2.08 (1.59-2.71)	**<0.001**		
Picardie	1.56 (1.11-2.20)	**0.011**		
Poitou-Charentes	3.87 (2.81-5.33)	**<0.001**		
Provence-Alpes-Côte-d'Azur	3.75 (3.0-4.67)	**<0.001**		
Rhône-Alpes	1.50 (1.22-1.84)	**<0.001**		
Overseas territories	0.81 (0.53-1.26)	0.352		
Sex				
Men	1		1	
Women	0.95 (0.85-1.06)	0.343	0.95 (0.85-1.06)	0.352
Age (years)				
18-39	1		1	
40-59	0.78 (0.67-0.90)	**0.001**	0.78 (0.68-0.91)	**0.001**
60-69	0.93 (0.79-1.11)	0.426	0.95 (0.80-1.12)	0.512
70-79	1.48 (1.18-1.85)	**0.001**	1.50 (1.20-1.87)	**<0.001**
80-90	0.72 (0.16-3.24)	0.671	0.75 (0.17-3.34)	0.702
	Clinical data			
Active malignancy				
Yes	0.47 (0.31-0.73)	**0.001**	0.48 (0.31-0.74)	**0.001**
No	1		1	
Diabetes				
Yes	0.75 (0.64-0.87)	**<0.001**	0.74 (0.64-0.86)	**<0.001**
No	1			
Blood group				
A	1		1	
AB	1.12 (0.66-1.91)	0.627	1.12 (0.67-1.89)	0.626
B	0.61 (0.47-0.80)	**0.001**	0.62 (0.47-0.81)	**0.001**
O	0.57 (0.44-0.72)	**0.001**	0.57 (0.45-0.72)	**0.001**
	ESRD management			
First dialysis with catheter				
Yes	1.19 (1.05-1.35)	**0.008**	1.18 (1.04-1.34)	**0.010**
No	1		1	
	Region level indicators			

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Mean ESRD incidence	n/a	0.99 (0.98-0.999)	**0.045**
Slope of number of patients on the list on January 1 (2011-2013)	n/a	0.9998 (0.9996-0.9999)	**0.030**

HR: Hazard Ratio; SHR: Subdistribution Hazard Ratio; CI: Confidence Interval;

Table 5. Association of patient-related and regional variables with access to renal transplantation after dialysis start (Multivariable Cox and Cox shared frailty models; n=9312 incident patients. Among them, 1402 patients were transplanted).

	Multivariable Cox model		**Multivariable Cox shared frailty model**	
	HR (95%CI)	**p**	**HR (95%CI)**	**P**
	Sociodemographic data			
Region of residence				
Alsace	0.74 (0.50-1.09)	0.129		
Aquitaine	1.50 (1.17-1.92)	**0.001**		
Auvergne	0.90 (0.62-1.31)	0.578		
Basse-Normandie	2.42 (1.71-3.42)	**<0.001**		
Bourgogne	1.02 (0.66-1.60)	0.920		
Bretagne	1.83 (1.40-2.38)	**<0.001**		
Centre	1.56 (1.17-2.08)	**0.002**		
Champagne-Ardenne	0.95 (0.64-1.41)	0.814		
Corse	1.67 (0.84-3.30)	0.142		
Franche-Comté	1.52 (1.01-2.26)	**0.042**		
Haute-Normandie	1.51 (1.06-2.15)	**0.024**		
Ile-de-France	1		n/a	
Languedoc-Roussillon	1.43 (1.07-1.90)	**0.016**		
Limousin	1.39 (0.84-2.32)	0.204		
Lorraine	0.79 (0.55-1.12)	0.187		
Midi-Pyrénées	1.19 (0.89-1.60)	0.238		
Nord-Pas-de-Calais	0.71 (0.54-0.94)	**0.018**		
Pays de la Loire	1.60 (1.22-2.10)	**0.001**		
Picardie	0.93 (0.66-1.32)	0.698		
Poitou-Charentes	2.35 (1.69-3.26)	**<0.001**		
Provence-Alpes-Côte-d'Azur	1.64 (1.31-2.04)	**<0.001**		
Rhône-Alpes	1.14 (0.92-1.41)	0.242		
Overseas territories	0.29 (0.19-0.44)	**<0.001**		
Sex				
Men	1		1	
Women	0.84 (0.75-0.95)	**0.003**	0.84 (0.75-0.94)	**0.003**
Age (years)				
18-39	1		1	
40-59	0.68 (0.59-0.79)	**<0.001**	0.68 (0.59-0.79)	**<0.001**
60-69	0.56 (0.47-0.66)	**<0.001**	0.56 (0.48-0.67)	**<0.001**
70-79	0.16 (0.12-0.20)	**<0.001**	0.16 (0.13-0.20)	**<0.001**
80-90	0.003 (0.001-0.012)	**<0.001**	0.003 (0.001-0.01)	**<0.001**
	Clinical data			
Albumin (g/dl)				
<30	0.76 (0.61-0.95)	**0.019**	0.76 (0.63-0.90)	**0.002**
≥30	1		1	
BMI (kg/m²)				
<18.5	0.73 (0.53-0.99)	**0.040**	0.69 (0.53-0.89)	**0.005**
[18.5-23[	0.92 (0.76-1.12)	0.404	0.92 (0.77-1.11)	0.388
[23-25[	1		1	

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≥25	0.81 (0.69-0.94)	**0.007**	0.81 (0.69-0.94)	**0.006**
Number of cardiovascular diseases				
0	1		1	
1	0.76 (0.66-0.89)	**0.001**	0.77 (0.66-0.90)	**0.001**
2	0.43 (0.32-0.57)	**<0.001**	0.43 (0.33-0.58)	**<0.001**
≥3	0.41 (0.28-0.59)	**<0.001**	0.41 (0.28-0.60)	**<0.001**
Respiratory disease				
Yes	0.55 (0.42-0.72)	**<0.001**	0.56 (0.43-0.74)	**<0.001**
No	1		1	
Active malignancy				
Yes	0.18 (0.12-0.27)	**<0.001**	0.18 (0.12-0.27)	**<0.001**
No	1		1	

(continued)	**Multivariable Cox model**		**Multivariable Cox shared frailty model**	
	HR (95%CI)	**p**	**HR (95%CI)**	**P**
Liver disease				
Yes	0.25 (0.12-0.54)	**<0.001**	0.26 (0.12-0.55)	**<0.001**
No	1		1	
Diabetes				
Yes	0.55 (0.45-0.68)	**<0.001**	0.54 (0.44-0.67)	**<0.001**
No	1		1	
Psychiatric disorder				
Yes	0.25 (0.12-0.54)	**0.001**	0.25 (0.12-0.50)	**<0.001**
No	1		1	
Number of physical disabilities				
0	1		1	
≥1	0.57 (0.39-0.84)	**0.004**	0.59 (0.40-0.87)	**0.008**
Primary kidney disease				
Polycystic disease	1		1	
Hypertensive and vascular nephropathy	0.55 (0.45-0.68)	**<0.001**	0.55 (0.45-0.68)	**<0.001**
Diabetic nephropathy	0.64 (0.48-0.85)	**0.002**	0.64 (0.48-0.86)	**0.003**
Glomerulonephritis	0.92 (0.76-1.10)	0.373	0.93 (0.78-1.11)	0.427
Pyelonephritis	0.84 (0.64-1.10)	0.203	0.84 (0.65-1.10)	0.214
Others	0.74 (0.62-0.87)	**<0.001**	0.74 (0.62-0.87)	**<0.001**
	ESRD management			
Ownership of nephrology facility				
Private for-profit center	0.92 (0.79-1.08)	0.322	0.92 (0.79-1.07)	0.292
Private not-for-profit center	1.21 (1.03-1.42)	**0.018**	1.19 (1.01-1.39)	**0.032**
Public university center	0.93 (0.79-1.09)	0.351	0.92 (0.78-1.08)	0.303
Public non-university center	1		1	
Emergency start				
Yes	0.81 (0.69-0.95)	**0.010**	0.81 (0.69-0.96)	**0.014**
No	1		1	
First dialysis with catheter				
Yes	0.82 (0.71-0.93)	**0.003**	0.81 (0.70-0.92)	**0.002**
No	1		1	
	Region level indicators			
Mean incidence rate of preemptive Ktx (pmp)	n/a		1.11 (1.03-1.18)	**0.003**
Mean ESRD incidence	n/a		0.991 (0.98-0.997)	**0.004**

BMI: Body Mass Index; Cardiovascular diseases: coronary artery disease, peripheral vascular disease, congestive heart failure, arrhythmia, aortic aneurism and cerebrovascular disease; Physical disabilities: physical impairment of ambulation, para- or hemi-plegia, blindness, member amputation; Ktx: Kidney transplantation; pmp: per million population; ESRD: End Stage Renal Disease; HR: Hazard Ratio; CI: Confidence Interval.

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