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Effect of age and care organization on sources of variation in kidney transplant waiting-list registration

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Abbreviations

BLUP : Best Linear Unbiased Predictor

CK-EPI formula : Chronic Kidney Disease Epidemiology Collaboration formula to estimate eGFR

eGFR : estimated Glomerular Filtration Rate

ESKD : end-stage kidney disease

IQR : interquartile range

IRR : incidence rate ratios

REIN : Renal Epidemiology and Information Network

RRT : renal replacement therapy

SD : standard deviation

Abstract

Despite national guidelines, medical practices and kidney transplant waiting list registration policies may differ from one dialysis/transplant unit to another. Benefit risk assessment variations, especially for elderly patients, have also been described. The aim of this study was to identify sources of variation in early kidney transplant waiting list registration in France.

Among 16,842 incident patients during the period 2016-2017, 4,386 were registered on the kidney transplant waiting list at the start of, or during the first year after starting, dialysis (26%). We developed various log-linear mixed effect regression models on 3 levels: patients, dialysis networks and transplant centers. Variability was expressed as variance from the random intercepts (+/- standard error).

Although patient characteristics have an important impact on the likelihood of registration, the overall magnitude of variability in registration was low and shared by dialysis networks and transplant centers. Between-transplant center variability (0.23 +/- 0.08) was 1.8 higher than between-dialysis network variability (0.13 +/- 0.004). Older age was associated with a lower probability of registration and greater variability between networks (0.04, 0.20, 0.93 in the 18-64, 65-74 and 75-84 age groups).

Targeted interventions should focus on elderly patients and/or certain regions with greater variability in waiting list access.

Introduction

Despite national and international guidelines, many studies have shown variations in kidney transplant waiting list practices or policies between departments, regions or dialysis units (1–6). Regarding patients, the clinical characteristics of patients with end-stage kidney disease (ESKD) are associated with the likelihood of being registered on the waiting list for a kidney transplant (2,3,5,7–11). As expected, comorbid patients have less access, given the expected risk-benefit ratio (12). Other individual non-medical factors, such as living in a deprived or rural area, gender and marital status have also been discussed (4,13–17). A systematic review, based on fifteen guidelines for kidney transplant waitlisting published from 2001 to 2011, showed some inconsistency according to age criteria (18). Some guidelines define age limits whereas others say that patients should not be deemed ineligible based on their age. In 2018, an online survey distributed to all 71 renal centers in the UK showed that age was an exclusion criterion for waitlisting in 3 centers, all of which had a cutoff of 75 years (2). The French Guidelines, published in 2015, recommend the systematic evaluation of all patients aged under 85. For patients over 85, this evaluation should remain exceptional. Given this inconsistency, it is not surprising to observe variations in clinical practices according to age.

In the French context of a “universal healthcare system”, equal access to suitable care must be evaluated. Because sources of variation between patients, dialysis units and transplant units may be observed, choosing the right degree of granularity is crucial to the analysis. Studies focusing only on the effects of patient characteristics but ignoring the professional network or regional effect, have used statistical models which assume the independence of individual observations. This may result in a biased estimation of waiting-list registration predictors and limit the exploration of sources of variability, such as differences in professional practices or the characteristics of dialysis units. Therefore, many studies include another level of analysis. Certain US studies have explored the impact of the dialysis facility chain (11) or dialysis facility ownership (19). In the UK or Italy, the renal unit itself has been used as a level of granularity (1,2,6,20). In France, variability between regions has already been published (3,21). In France, the region represents the administrative level of healthcare organization under a regional health agency. However, this level of analysis does not allow a more in-depth analysis of variations in local practices. A center effect was found in a French pediatric cohort but not explained by the center’s characteristics (22). Another French study showed variability between renal units in terms of preemptive registration in a North-West French network (14).

Our hypothesis is that variability may occur on 3 levels. The aim of our study was to therefore to break down these levels to identify exactly how they effect the variations in renal transplantation waiting-list registration at onset or in the first year after starting dialysis.

Methods

Data source : the French REIN registry

The Renal Epidemiology and Information Network (REIN) is the French national registry of all patients being treated by renal replacement therapy (RRT) (23). Clinical, demographic, and laboratory data are collected at the start of RRT along with dialysis modalities and are updated annually. Events such as death, transfer, withdrawal from dialysis, placement on a transplant waiting-list and kidney transplantation (from living or deceased donors) are systematically reported in real time. Short-term transfers of less than 2 months are not recorded (i.e. hospital stay, vacation).

Construction of Level 2 : The dialysis unit network

As French adult dialysis units are widespread throughout the country (over 1,150 dialysis units as of December 2018), with varying numbers of patients (median 25 patients, interquartile range : 11-59, up to 320), various providers (public, private for profit, private not-for-profit, university hospital) and various treatment arrangements offered (hospital-based, satellite unit, self-care unit or home dialysis), the level of dialysis unit is inappropriate for studying the question of access to waiting-lists in France. Also, patients may move from one unit to another (73 796 transfers between dialysis units during the period 2016 - 2018) and placement on waiting-lists requires careful coordination and teamwork. Therefore the complete network, including dialysis units that work together to be able to offer all the different treatment types in a given area, seems to be a more appropriate level. Our hypothesis was that, within one network, heterogeneity of practice would be small.

At the end of 2018 in France, end-stage renal disease care was being offered in 1,166 dialysis units owned by 326 different healthcare providers (6% public university hospitals, 12% public non-university hospitals, 54% private non-profit units, and 27% private for-profit units), and 34 university hospital centers that perform transplants. The dialysis activity was organized and regulated regionally and transplantation activities were organized and regulated on a supraregional level. On a regional level, a regional health agency (Agence Régionale de Santé) is in charge of planning ambulatory and hospital care via a regional

health project based on population needs. Different types of dialysis are offered, each characterized by the dialysis technique (hemodialysis or peritoneal dialysis), the extent of professional assistance and the treatment site (hospital-based, satellite unit or self-care unit, home dialysis), regardless of the provider (24). Home dialysis and self-care units are mainly provided by non-profit-making units. Patients are transferred to the different dialysis units according to their needs and choice. Indeed, patients are free to choose their physician and dialysis unit although the choice is made according to proximity to their homes. In mainland France (excluding overseas territories), the median time taken to get to a dialysis unit is 17 minutes.

All 1,114 French dialysis units in mainland France (excluding overseas territories), were classified into 167 networks using the Fast Greedy method (25), a hierarchical agglomeration algorithm for detecting community structures. The classification criterion was the number of transfers of patients between each unit declared in the REIN registry during the period 2016-2018 (72,968 transfers were observed). This algorithm determines optimal groupings in terms of modularity: within each network, the dialysis units are strongly interconnected so the number of transfers is high. Conversely, between networks, patient transfers are low. The results given by this method were validated by each regional level of the REIN registry (coordinating nephrologist and research assistants for the registry). During the study period, 95% of patients were treated in one network. Three networks with only one incident patient during the study period were not included, neither were 2 pediatric transplant centers.

Construction of Level 3 : Transplant reference center

Registration on the waiting-list also depends on the transplant center's policy (at least one transplant center in each region). The number of transfers from a dialysis unit to a kidney transplant center for transplantation during the period 2006-2018 was used to identify the reference transplant center for each network. If a network was collaborating with more than one transplant center, the one with the highest number of transfers for renal transplantation was chosen.

Study population

From 2016 to 2017, all incident patients starting dialysis treatment, aged 18-84 years in mainland France were included. The patients' trajectories were reconstructed and the contributions in terms of follow-up duration for each patient in each network during their trajectory was calculated. End of follow-up occurred at death, first registration on the waiting-list or 12 months after starting dialysis. Patients registered before the start of dialysis or soon after were included with a duration of participation in the denominator corresponding to the delay between dialysis start and the end of the 1st month. Patients

starting with a preemptive graft, patients treated in overseas territories or abroad and three networks with only one incident patient between 2016-2017 were excluded.

Outcome

The outcome of interest was the first placement on the waiting list for a kidney transplant (living or deceased donor) at the start of dialysis or in the first year after starting it.

Study variables

Patient characteristics

The following patient baseline characteristics at the time of starting dialysis were used : age, gender, diabetes, heart failure (Stage I to IV, New York Heart Association classification), peripheral vascular disease (Stage I to IV, Leriche classification), cerebrovascular disease (stroke or transitory ischemic event), arrhythmia (specific treatment with anti-arrhythmics or pacemaker or implantable defibrillator), coronary heart disease (history of angioplasty or bypass surgery, or coronary artery disease documented by stress electrocardiogram, coronary angiography, or thallium scintigraphy), active malignancy (cancer or malignant hemopathy, undergoing treatment (chemotherapy, radiotherapy, surgery or palliative care) or with metastases), pulmonary disease (in stable state PaO₂ <60 mmHg or a cough with permanent or recurrent expectoration, 3 months / year for 2 consecutive years), liver disease (chronic hepatitis B or C, cirrhosis Child-Pugh score A to C), ability to walk alone, severe obesity (body mass index ≥ 35 kg/m²), behavioral disorders (include dementia, psychosis, severe neurosis which significantly limits the patient's autonomy or compliance with treatment), emergency start of dialysis first dialysis session performed within 24 hours due to a vital risk) and estimated Glomerular Filtration Rate (eGFR) at initiation <8 ml/min (median value on the overall study cohort, CK-EPI formula). The patient's refusal to be listed was considered at any time during their follow-up, even after the first year.

Customer characteristics

The 'customer' characteristics (case-mix) were calculated as the mean of the patient characteristics in each network: age, gender, diabetes, heart failure, peripheral vascular disease, cerebrovascular disease, arrhythmia, coronary heart disease, active malignancy, pulmonary disease, liver disease, ability to walk alone, severe obesity (body mass index ≥ 35 kg:m²), behavioral disorder, emergency dialysis initiation, eGFR < 8 ml/min and patient's refusal to be listed.

Network characteristics

The two following network characteristics were used : arrangements for treatment - the proportion of patients treated with in-center hemodialysis, out-center hemodialysis, hemodialysis in self-care units, home dialysis (hemodialysis or peritoneal dialysis) - and legal status - the proportion of patients treated in private-for-profit, private-not-for-profit, public and university units.

Statistical analysis

Different mixed effect log-linear regression models were built to explore sources of variations in registration rates (Figure 1). Successive analyses were made on complete data due to the low level of missing data and the complexity of our model.

The dataset has a hierarchical structure on three levels, each of which might be a source of variability in registration: patient (Level 1), dialysis unit network (Level 2) and renal transplantation center (Level 3). To study the contribution of variability associated with each level on total variability we used a multi-level analysis (Supplementary Figure 1).

In order to take into account the overdispersion of the registration rate at patient level, a negative binomial regression was used, corresponding to a log-linear model with a supplementary parameter modelling the overdispersion. The total number of days spent in each network was introduced as an offset. The likelihood ratio test was used to compare different nested models.

This mixed model makes it possible to introduce a random effect on network (Level 2) or renal transplantation center level (Level 3). For a given network or a given transplantation center, the random effect corresponds to the difference in the logarithm for the registration rate with regard to the mean value. The random effects are predicted in linear mixed models as Best Linear Unbiased Prediction (BLUP).

The estimated variance of the random effects at network (U_j) and transplant center level (U_k) quantifies the variability of the logarithm of registration rate between networks (Level2) and between transplant centers respectively (Level3). By introducing random effects it is possible to take into account the correlation with the outcome of patients within the same network and the same transplantat center.

In a first stage, two-level models including a random network effect were used, Model 0 (empty model) and Model 1 based on the characteristics of patients, customers and networks. In a second stage, a three-level model, adding the transplant center was used (Model 2). To take into account the risk of endogeneity, patient characteristics (Level 1, X_1) were centered around their corresponding network mean (Group-Mean Centering, i.e “patient effect”) and the mean of the network (Level 2, X_2) was added to the model (compositional effect, case-mix, “customer effect”)(26,27). Finally, additional items for each

network's characteristics (Model 1b, **X3**) were entered at Level 2. To visualize the customer effect, scatter plots representing the effect on the registration rate of the mean of patient characteristics at network level, were generated.

The analysis was also performed on three age groups: 18-64, 65-74 and 75-84 years.

A sensitivity analysis excluding networks with extreme values, i.e. absolute value of the random effect >1 , was made. This concerned five networks in the Nord-Pas de Calais region among eleven networks in this region and three networks in the Île-de-France among the twenty networks in this region. Another sensitivity analysis was made according to the time of registration, before or after the start of dialysis.

Fixed effects on the registration rate were expressed as incidence rate ratios (IRR) with 95% confidence intervals (95% CI). The median rate ratio and interquartile range (IQR) were used to quantify the variability between networks on the incidence rate ratio (IRR) scale. The median rate ratio is defined as the median of the set of IRR that could be obtained by comparing two patients with identical characteristics from two randomly-chosen different networks. The distribution of the Best Linear Unbiased Predictors (U_j) is presented using boxplots.

The mixed multi-level models were fitted using the SAS[®] GLIMMIX procedure.

Results

Patients and networks

During the period 2016-2017, 16,842 incident patients were treated by dialysis, in at least one of the 164 networks for a total of 152,369 months (Supplementary Figure 2). Among them, 4,386 were registered on the waiting-list for a kidney transplant at the start of, or during the first year after starting dialysis (26%) in one of the 32 transplant centers. Among them 1,963 were preemptive registrations. The mean age of patients was 67.6 (SD 13.5). In the younger group aged 18-64 years, 51% of the patients were registered at one year, in the group 65-74 years it was 23% and in the oldest group, 75-84 years, only 5% (Supplementary Table 1) . As expected, the patients registered were younger with fewer comorbidities (Table 1). Patients registered before starting dialysis were younger with fewer comorbidities (Supplementary Table 2).

The median number of dialysis units in a network was 5.0 (IQR 3.5-9.0) and the median number of incident patients was 87.5 (IQR 56-114.5). In the majority of the networks, patients were treated with in-center hemodialysis in a public structure. The median number of registered patients was 18 (IQR 10-33). The overall registration rate was 28.8 (95%CI 25.8-32.1) registrations/1000 months of dialysis. This registration rate ratio decreased with age : 68.2 (95%CI 61.2-76.1), 24.2 (95%CI 21.4-27.4) and 5.0 (95%CI 4.2-5.9) registrations/1000 months of dialysis , respectively in patients 18-64, 65-74 and 75-84 years old at the start of dialysis.

Inter-network variability

In Model 0 with no explanatory factors, the variance between networks (U_j random network intercept) was 0.41 with a standard error (SE) of 0.07 (Table 2). In Model 1, after introducing patient effects X_1 and customer effects X_2 , the variance decreased by 17% to 0.34 (SE 0.06). The median rate ratio was 1.7 (i.e. in 50% of cases, with equal patient characteristics, the registration rate for a network with a higher rate did not exceed 170% of the registration rate of a network with a lower rate). The sensitivity analysis excluding the 5 lower registration rate networks and the 3 higher registration rate networks led to a reduction in variance between networks of 0.26 (SE 0.05) in Model 1. When transplant centers were entered as a random effect (Model 2), variance in the random network effect (U_j) decreased to 0.13 (SE 0.04) and variance in the random transplant center effect (U_k) was equal to 0.23 (SE 0.08). The distribution of the Best Linear Unbiased Predictors according to the different models is represented in Figure 2.

Subgroup analysis according to age showed an important increase in the variance with age for the network random effect and, to a lesser extent, for the transplant center random effect. These results are in favor of greater variability in registration practices between networks than between transplant centers for elderly patients, not explained by patient characteristics (Table 2, Figure 3).

Results were similar for the overall cohort and in the subgroup without preemptive registration patients. Variability between networks was more pronounced for early registration practices, before starting dialysis (Supplementary Table 3).

Patient and customer characteristics and waiting-list registration

For patients, the fact of being younger, with an absence of comorbidities and capable of walking alone was associated with a higher registration rate on the waiting-list (Table 3). The IRR of age was 0.43 (95%CI 0.40-0.46) indicating that, for each increase of one standard deviation for age, the probability of being registered on the waiting-list decreases by 57%. Being able to walk without help, a proxy for global good health, increased the probability of being listed by 6.5 (95% CI 4.7-9.1). If a patient started dialysis in an

emergency manner, or refused at one point to be listed or had an initial eGFR above 8 ml/min, this was associated with a lower registration rate. Gender was not associated with the registration rate (Table 1).

At customer level, whatever the patient's characteristics, being treated in a network with a younger patient population with less diabetes or heart failure, or with more patients starting with a eGFR below 8ml/min, was associated with a higher rate of registration (Table3, Supplementary Figure 3, Supplementary Figure 4).

The effects of patients' characteristics on registration varied according to the age subgroups. In younger people, the initial eGFR was not associated with the registration rate (Supplementary Table 1). In 65-74 year-old patients, results tend to be similar to those of younger patients. In elderly patients, a lower age and the absence of comorbidities had a major effect. However, due to the small proportion of patients registered on the waiting list, these results should be interpreted with caution.

Network characteristics and waiting-list registration

Entering in Model 1, the network characteristics (Level 2, **X2c**) describing the arrangements for treatment and legal status did not decrease the variability between networks (0.36, SE 0.06). The fact of being treated in a network with a higher proportion of patients in a self-care unit (IRR 1.5, 95%CI 1.2-1.9) or at home (IRR 2.4, 95%CI 1.9-2.9) was associated with a higher registration rate. Being treated in a network with a higher proportion of patients in a private-for-profit unit (0.8, 95%CI 0.6-0.97) or private not-for-profit unit (0.7, 95%CI 0.6-0.9) was associated with a lower registration rate in the first year after the start of dialysis, after taking treatment arrangements into account.

Discussion

Our multi-level approach shows that variability between dialysis networks in terms of registration on the waiting-list can be explained by patient and customer characteristics, network characteristics and the transplant center. The fact of being younger, with an absence of comorbidities and able to walk alone was associated with a higher registration rate on the waiting list. The magnitude of between-dialysis-unit network variability was lower than the effect of patient characteristics. However, variability in registration practices was higher for older patients on dialysis.

To our knowledge, this is the first use of a model using a patient level, a second level based on networking between dialysis units and a third level corresponding to the transplant center. We used a functional

definition of “network” based on the number of transfers between dialysis units. Our hypothesis was that, within one network, heterogeneity of practice would be small. This does not correspond to a fixed organization. It is of smaller granularity than the US ESKD Network Organizations defined geographically by the number and concentration of ESKD beneficiaries in each area (19). Some US Networks represent one state, others multiple states. Our network does not correspond to chain organizations either (11). Our hierarchical classification method was not restricted by volume or distance. Therefore, the volume of patients in each network was very different. In rural areas, the number of dialysis units and patients are lower than in large urban areas.

In accordance with other studies, within one network, patients had a lower rate of registration on the waiting-list with increasing age, in the presence of comorbidities or inability to walk, if dialysis had been started in an emergency or if the patient had once refused to be listed (2,5,11).

Even after taking several comorbidities into account, the age-effect was still significant. According to French guidelines, up to the age of 85, age alone should not be a barrier to waitlisting. However, with elderly patients, the risk-benefit ratio should be carefully discussed (12,28). This implies an additional procedure to identify risk factors such as silent cancer, cardiovascular disease or infection. This pre-registration assessment may take time. Our study, limited to one year may have been unfavorable to elderly patients for whom the preregistration assessment may take longer. However, for these elderly patients, the longer we wait, the more the possibility of being transplanted decreases. A cutoff of one year has been determined in accordance with the French guidelines in favor of early registration.

In our study, we estimated the effect of patient characteristics on an individual level and on a network level (customer effect, case-mix) separately. Being treated in a network with a population of younger patients, less diabetes or heart failure, or with more patients starting with an eGFR below 8ml/min was associated with a higher registration rate, illustrating either the influence of the medical environment on medical practice, or common selection strategies between units rather than personalized patient-specific decisions for registration.

The fact of being treated in a network with a higher proportion of patients in a self-care unit or at home was associated with a higher registration rate, even after taking the patients’ age and comorbidities into account. Certain patients’ characteristics like involvement or autonomy, not available in the REIN registry, may explain these results. Being treated in a network with a higher proportion of patients in a private unit (profit or non-profit) was associated with a lower registration rate, after taking into account the arrangements for treatment knowing that, in France, the majority of patients treated at home or in self-

care units depend on a non-profit private unit. In a US study, patients from for-profit facilities were less likely to be waitlisted compared to non-profit facilities. However, comparisons between countries should be made with caution given the different arrangements for healthcare and financing.

Throughout this study, we analyzed the evolution of the variance of the network random effect to study variability between networks. This allowed us to explore factors associated with deviations from the mean registration rate. In Model 1, after introducing patient and customer effects, the between-network variability decreased slightly compared with Model 0 without fixed effects. After adding a transplant center random effect, between-network variability was very low (0.15), illustrating a certain homogeneity in practices, probably due to the influence of the transplant center. In fact, the between-transplant center variability was 1.8 higher than the between-network variability. However, the magnitude of the between-transplant center variability was lower than the effect of patient characteristics. Some residual variability could also be due to patient characteristics not collected in our registry or some risk factors at the discretion of clinicians.

The strength of this study is its large population basis, the use of a methodology making it possible to explore different levels of variability. However, this study does have certain limitations. Our method of network classification was restricted by the fact that one unit could only be classified in one network and only in a network of its own region. This was decided due to the regional organization of healthcare. However, the final validation by regions only revealed minor remarks on this automatic classification. The variations observed could be affected by variations in coding comorbidities. However, coding rules are published in the REIN registry protocol and in each region: research assistants help the nephrologists collect the data and do the post hoc quality control analysis (23). Finally, we cannot exclude unmeasured confounders which might explain additional variations.

This study is a first step towards a more ambitious project to improve access to kidney transplant waiting lists in France. Following the publication of a national guideline to encourage early registration for patients aged up to 85 if appropriate, our analysis shows that the variability of practices is greater in patients over 65 years of age, but not explained by the presence of comorbidities. Given the fact that organ shortages are relatively lower for this age group and in addition to the benefits of a transplant on improving the quality of life, preserving autonomy, and reducing the medico-economic impact of patients with ESKD, all elderly patients should benefit from a systematic evaluation for transplant eligibility and all eligible patients should be informed about the possibility of a kidney transplant (12). A prognosis tool

could be used to help nephrologists select those individuals who, despite their age, might be suitable candidates for a kidney transplant (29).

On an individual level, further analysis should be made to understand the barriers to registration. In a previous French survey on patients aged under 80, on dialysis but not registered, the nephrologists declared that, in 14% of cases, the patient refused to be registered, with proportionately more women in this category (30). This high refusal rate should be more thoroughly investigated, particularly from the patient's viewpoint and with the help of patient associations.

One concrete consequence of this study will be the possibility for regional networks to compare themselves with each other and to readjust their policies for access to the waiting list. Within dialysis unit networks, care should be taken to ensure that patient registration is not slowed down by transfers from one unit to another. The gateway to the network has a crucial role. Each region will have access to infraregional results so that variability within networks in their area can be analyzed, especially for elderly patients. In some areas of France, reference transplant centers have organized tele-expertise with dialysis units to discuss complicated cases.

On a national level, this report will be made available to scientific Societies and the French transplant Agency (Agence de la Biomédecine) so that practices between transplant centers can be harmonized.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

Figure Legends

Table 1. Clinical characteristics of incident patients according to transplant waiting list registration at the start of dialysis or during the first year after starting it.

Table 2. Estimation of variability in the network random effect according to adjustment characteristics and an estimation of variability in the waiting list registration random effect for the whole cohort and for the three age groups.

Table 3. Incidence rate ratios estimating the effect of patient characteristics (individual and customer effect) on the waiting list registration rate (per 1,000 months of dialysis): results of Model 2 with a network random effect and transplant center random effect).

Figure 1. Simplified representation of the models used to explore variability sources (successive additions are indicated in bold).

Figure 2. Distribution of the Best Linear Unbiased Predictors of the network random intercept according to the different models.

Figure 3. Distribution of the Best Linear Unbiased Predictors of the network random intercept and transplant center random intercept according to age in Model 2 with fixed effects from Level 1 (patient characteristics) and Level 2 (customer characteristics).

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table 1. Clinical characteristics of incident patients according to transplant waiting list registration at the start of dialysis or during the first year after starting it.

	Overall cohort			Not registered	Registered
	N= 16 842	% among non-missing data	% missing data	N = 12456	N = 4386
Age (years)			0		
18-44	1 341	8.0		3.4	21.0
45-64	4 303	25.6		18.8	44.7
65-74	5 336	31.7		33.2	27.5
75-84	5 862	34.8		44.7	6.8
Male	10 953	65.03	0	65.1	64.9
Diabetes	7 981	47.6	0.43	53.7	30.4
Heart failure	4 218	25.48	1.7	31.2	9.3
Cardiovascular disease	4 559	27.61	1.95	32.8	12.9
Arrhythmia	3 861	23.3	1.6	28.8	7.8
Cerebrovascular disease	1 925	11.61	1.53	13.6	5.9
Peripheral vascular disease	3 699	22.57	2.67	27.4	8.9
Pulmonary disease	3 089	18.71	1.96	22.5	8.1
Active malignancy	2 036	12.27	1.5	15.4	3.4
Liver disease	832	5.11	3.24	5.5	4.0
Behavioural disorder	555	3.52	6.28	4.4	1.2
Walk without help	13 307	84.31	6.29	79.6	97.5
Denutrition	8 130	53.83	10.32	56.8	45.1
Obesity	1 494	9.84	9.84	11.3	5.6
EGFR<8 ml/min	7 624	50.23	9.89	47.6	57.7
Emergency initiation	4 590	28.33	3.81	32.0	18.0
Patient's refusal to be listed	833	4.95	0	6.4	0.9

eGFR*: estimated Glomerular Filtration Rate (ml/min), with 8 as a median value on the overall study cohort, CK-EPI formula

Table 2. Estimation of variability in the network random effect according to adjustment characteristics and estimation of variability in the waiting list registration random effect for the whole cohort and for the three age groups.

	Overall study cohort 18-84 years	18-64	65-74	75-84
Between-network variability : Variance of the random intercept U_j (Standard error)				
Model 0 random network effect and no fixed effects	0.41 (0.07)	0.22 (0.05)	0.47 (0.13)	0.40 (0.37)
Model 1 random network effect and fixed effects from Level 1 (patient characteristics) and Level 2 (customer characteristics)	0.34 (0.06)	0.15 (0.05)	0.35 (0.12)	1.14 (0.47)
Model 2 random network effect and random transplant center effect and fixed effects from Level 1 (patient characteristics) and Level 2 (customer characteristics)	0.13 (0.04)	0.04 (0.04)	0.20 (0.11)	0.93 (0.50)
Between-transplant center variability : Variance of the random intercept U_k (Standard error)				
Model 2 random network effect and random transplant center effect and fixed effects from Level 1 (patient characteristics) and Level 2 (customer characteristics)	0.23 (0.08)	0.08 (0.04)	0.19 (0.11)	0.32 (0.39)

Reading key : the higher the random intercept variance, the more the networks or transplant centers differ from each other.

Table 3. Incidence rate ratios estimating the effect of patient characteristics (individual and customer effect) on the waiting list registration rate (per 1,000 months of dialysis): results of Model 2 with network random effect and transplant center random effect)

	Individual effect			Customer effect		
	Incidence Rate Ratio			Incidence Rate Ratio		
	95%CI			95%CI		
Age	0.43*	0.40	0.46	0.90**	0.85	0.95
No Obesity	2.47	1.92	3.19	1.32	0.99	1.75
No Heart failure	2.06	1.68	2.53	1.21	1.05	1.39
No Peripheral vascular disease	1.99	1.62	2.44	0.95	0.82	1.09
No Cerebrovascular disease	1.40	1.10	1.78	1.11	0.82	1.49
No Arrhythmia	1.56	1.27	1.92	1.12	0.93	1.35
No Cardiovascular disease	1.28	1.07	1.54	0.90	0.74	1.09
No Diabetes	1.50°	1.30	1.74	1.24°°	1.01	1.52
Walk without help	6.54	4.69	9.11	1.14	0.96	1.37
No Active malignancy	4.86	3.70	6.38	1.28	0.99	1.66
No Pulmonary disease	1.61	1.32	1.98	0.91	0.74	1.11
No Behavioural disorder	3.45	2.09	5.69	1.07	0.68	1.70
Emergency initiation	0.29	0.25	0.34	1.00	0.89	1.13
Patient's refusal to be listed	0.07	0.04	0.11	0.89	0.63	1.26
No Denutrition	1.60	1.40	1.83	1.01	0.92	1.11
No Liver disease	1.52	1.08	2.14	0.79	0.54	1.17
eGFR<8 ml/min	1.18	1.03	1.35	1.10	1.01	1.21

Reading key :

Cells are in gray when the effect is not significant.

*The registration rate decreases by 57% when the patient's age increases by one standard-deviation.

** The registration rate decreases by 10% when the mean age of the network increases by one standard-deviation.

° The registration rate for a patient without diabetes is 50% higher compared to a patient with diabetes.

°° The registration rate increases by 24% when the proportion of diabetic patients in the network decreases by 10%.

Figure 1. Simplified representation of the models used to explore variability sources (successive additions are indicated in **bold type**).

$$\text{Model 0 : } \log(\tilde{Y}_{ij}) = a + u_j$$

no fixed effects, **random network effect**

$$\text{Model 1 : } \log(\tilde{Y}_{ijk}) = a + u_j + X_1 B_1 + X_2 B_2$$

fixed effects from level1 (**patient characteristics**) and 2 (**customer characteristics**),
random network effect

$$\text{Model 1b : } \log(\tilde{Y}_{ijk}) = a + u_j + X_1 B_1 + X_2 B_2 + X_3 B_3$$

fixed effects from Level 1 (patient characteristics) and Level 2 (customer and **network characteristics**), random network effect

$$\text{Model 2 : } \log(\tilde{Y}_{ijk}) = a + u_j + u_k + X_1 B_1 + X_2 B_2$$

fixed effects from Level 1 (patient characteristics) and Level 2 (customer characteristics), random network effect and **random renal transplant center effect**

\tilde{Y}_{ij} = predicted rate for patient i in network j

a = logarithm of the mean rate

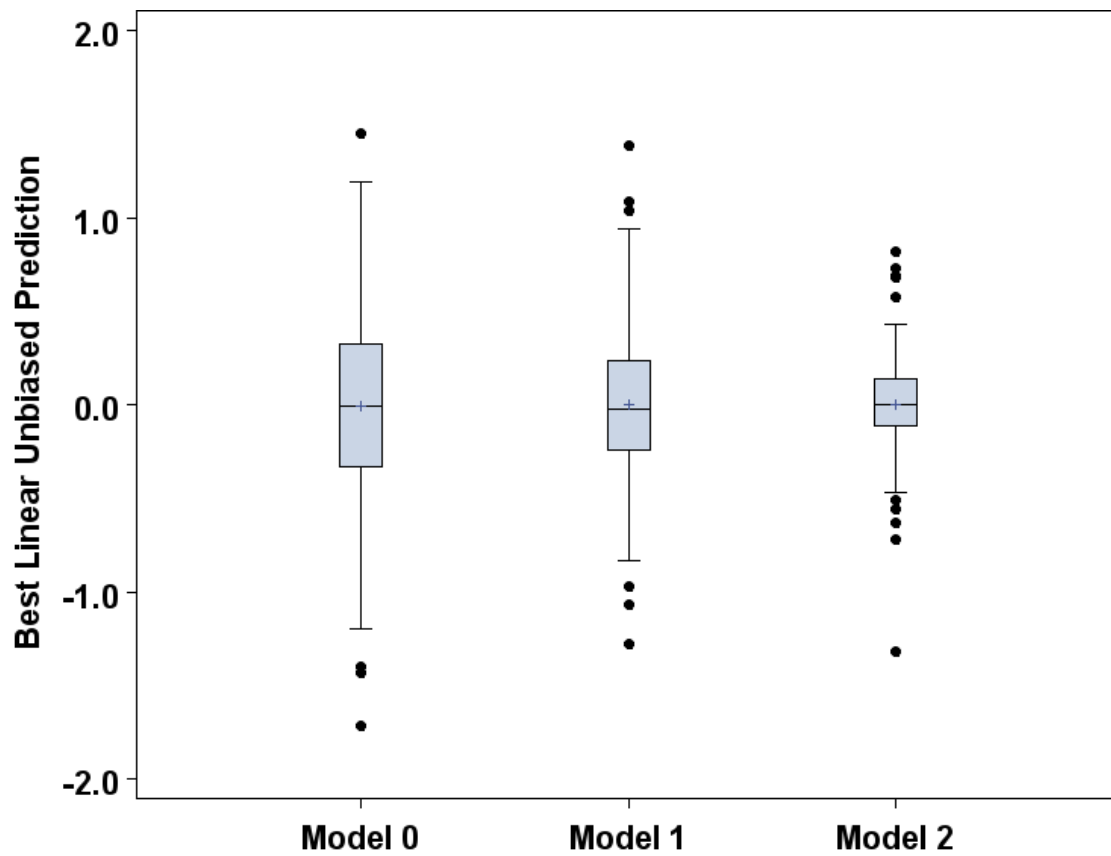
u_j = deviation from the logarithm of the mean rate of the network j

u_k = deviation from the logarithm of the mean rate of the transplant center k

X_1 : vector of patient characteristics

B_1 : vector of fixed effects for the patient characteristics

Figure 2 Distribution of the Best Linear Unbiased Predictors of the network random intercept according to the different models



Model 0: random network effect and no fixed effect

Model 1: random network effect and fixed effects from Level 1 (patient characteristics) and Level 2 (customer characteristics).

Model 2: random network effect and random transplant center effect and fixed effects from Level 1 (patient characteristics) and Level 2 (customer characteristics).

Figure 3. Distribution of the Best Linear Unbiased Predictors of the network random intercept and transplant center random intercept according to age in Model 2 with fixed effects from Level 1 (patient characteristics) and Level 2 (customer characteristics).

