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Access to preemptive registration on the waiting list for renal transplantation: a hierarchical modeling approach

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Summary

Preemptive kidney transplantation is associated with both longer patient and graft survival. This study was carried out to estimate the association between the renal units and preemptive registration on the waiting list for first deceased donor renal transplantation in a French network of care. From 2008 to 2012, 1529 adult patients followed in 48 units of the French North-West network and registered on the waiting list for a first deceased donor renal allograft were included. We used a mixed logistic regression with renal units as random-effects term for statistical analysis. Of the 1529 patients included, 407 were placed on the waiting list preemptively. There was a significant variability across renal units (variance 0.452). In multivariate analysis, factors independently associated with preemptive registration were cardiovascular disease (odds ratio (OR) 0.57, [95% CI: 0.42–0.79]), social deprivation (OR 0.73, [95% CI 0.57–0.94]), and renal units' characteristics (ownership of the facility: academic hospital, reference—community hospital, OR 0.44, [95% CI 0.24–0.80]—private hospital, OR 0.35, [95% CI 0.18–0.69] and transplant center; $P < 0.10$]. Variability between renal units was reduced after taking into account their characteristics but was not influenced by patient characteristics. Preemptive registration is associated with renal units, transplant centers, and social deprivation and can be partly explained by disparities in practices.

Introduction

It is well established that preemptive kidney transplantation is associated with both longer patient and graft survival compared with transplantation performed after dialysis onset [1,2]. In the international guidelines, preemptive transplantation is recommended whenever feasible [3,4]. In France, as in others countries, patients must be registered on the national waiting list, which is under the responsibility of the Agence de Biomédecine, to receive a deceased donor renal transplantation. Numerous studies have identified comparable barriers to access to the waiting list across national lines [5]. However, most of these studies have focused on registration after dialysis initiation. Several factors that could influence registration on the waiting list have been identified, such as diabetes and other comorbidities, patient age, gender, race/ethnicity, income, type of insurance, and level of education [2,6–14]. Furthermore, there are significant differences between renal units in the time taken to register patients on the waiting list that cannot be explained by differences in patient characteristics [7,10,15–17]. To our knowledge, this variability between geographical areas and centers regarding registration on the waiting list has remained unexplained, especially for preemptive registration. Understanding which factors play a role in preemptive registration may provide an opportunity to improve equity of access to preemptive transplantation.

This study was carried out to estimate the association between renal units and preemptive registration on the waiting list for first deceased donor kidney transplantation in a French care network.

Study population and methods

Study population

This was a retrospective study using data from the national waiting list. The French waiting list for renal transplantation is divided in seven geographical areas (called ZIPR). The North-West ZIPR corresponds to an area of four regions with a population of 4 486 035 inhabitants according to the 2010 census. Each of the four regions has one academic hospital, which is the only transplant center of the region, but also provides care to patients with chronic kidney disease (CKD), including dialysis. To be registered, patients from community and private hospitals have to be directed to the affiliated academic hospital of their region.

A subset of the data corresponding to the North-West ZIPR was extracted from the database. We included in the study patients older than 18 years registered on the waiting list for a first renal transplantation and treated for CKD in one of the 48 renal units of the North-West ZIPR between January 01, 2008, and December 31, 2012. The 48 renal units of the North-West ZIPR consisted of 27 community hospitals, 17 private hospitals, and the 4 academic hospitals. We excluded patients who had already received a transplantation of any type, and/or who were registered for a living donor. In addition, patients treated in a center outside of the North-West ZIPR were not included in the study. Finally, 1529 patients were included (Table 1).

Data collection

We analyzed patient- and renal unit-specific variables that influenced access to the waiting list. Individual predictors (level 1) included the following: age, gender, diabetes, hypertension, dyslipidemia, smoking status, cardiovascular disease (coronary artery disease, peripheral vascular disease, congestive heart failure, and cerebrovascular disease), respiratory disease, neuropathic disease, hepatic disease, HIV, body mass index (BMI) (categorized as 20, 20.1–25, and >25 kg/m^2), and blood type. The European Deprivation Index (EDI), an ecologic proxy for individual-level socioeconomic status, was calculated for every patient [18].

The EDI has been constructed from a European survey specifically designed to study deprivation. It is based on ecological variables that reflect the individual experience of deprivation and are available in the 2007 French census. The EDI provides a score which is available for each one of the smallest geographical census units of the entire French mainland. Each census unit includes approximately 2000 individuals with relatively homogeneous social characteristics. In our study, the availability of an exact address allowed us to derive the EDI for each patient. The EDI was first categorized in national quintiles with quintile 1 representing the least deprived and quintile 5 the most deprived areas, and then used as a binary variable for statistical analysis (quintile 5 versus all other quintiles).

Renal unit factors (level 2) included the type of ownership of the facility and the affiliated transplant center (four transplant centers representing the four regions of the North-West ZIPR as described above). The private nonprofit facilities of the North-West ZIPR, as in most French regions, provide care to patients at the dialysis stage and do not follow CKD patients before dialysis onset. These patients come principally from public facilities (academic or community hospitals) and so are linked to these public facilities. Therefore, patients from each private nonprofit facility were grouped with the public facility associated with it, and the facility variable was divided into three categories: academic hospital, community hospital, and private (for-profit) hospital.

The year of registration on the waiting list (2008, or >2008) was also considered as an adjustment variable at each level, as a recommendation of the Transplantation Committee of the French Society of Nephrology published in 2008 may have influenced practices toward preemptive registration [19].

Statistical analysis

Results were expressed as frequencies and percentages, or mean and standard deviation (SD), when appropriate. Bivariate analyses were performed by traditional logistic regression. Crude odds ratios (ORs) with their 95% confidence intervals (95% CIs) were estimated. Covariates were selected for multivariate analysis when their *P*-value was lower than 0.20 by bivariate analysis, and according to their clinical relevance. To avoid introducing highly correlated variables into the models, variance inflation factor was assessed and did not detect any collinearity.

Because multilevel models are particularly well suited to investigations of hierarchical data, we adopted a modeling strategy that consists in increasing model complexity at each step, using a mixed logistic model with renal unit as a random-effects variable [20], and patients (level 1) nested in renal units (level 2).

We first used an empty model (including no covariates) to investigate heterogeneity between renal units. This model provided estimates of the proportion of total variance in preemptive registration that was due to differences between renal units, as measured by the intraclass correlation coefficient (ICC). In a multilevel logistic regression, the ICC is calculated according to the latent variable

Table 1. Bivariate analysis of factors associated with preemptive registration on the waiting list by traditional logistic regression.

	Preemptive registration (n = 407) N (%)	Non preemptive registration (n = 1122) N (%)	OR (95% CI)	P-value
Age				
18–45 years	131 (32.2)	320 (28.5)	Ref.	<0.10
45.1–60 years	174 (42.7)	474 (42.2)	0.90 (0.69–1.17)	
≥60.1 years	102 (25.1)	328 (29.2)	0.76 (0.56–1.03)	
BMI*				
20.1–25 kg/m²	178 (43.9)	432 (38.7)	Ref.	<0.10
≤20 kg/m²	25 (6.2)	102 (9.1)	0.59 (0.36–0.94)	
>25 kg/m²	202 (49.9)	582 (52.2)	0.84 (0.66–1.07)	
Males	258 (63.4)	704 (62.8)	1.03 (0.81–1.30)	0.82
Diabetes*	50 (12.4)	195 (17.6)	0.66 (0.47–0.92)	<0.05
Hypertension*	273 (69.1)	734 (68.7)	1.02 (0.80–1.31)	0.87
Dyslipidemia*	206 (53.2)	498 (47.0)	1.28 (1.02–1.62)	<0.05
Smoking*				
Non smoker	68 (17.5)	181 (16.9)	Ref.	0.92
Stopped	125 (32.1)	338 (31.5)	1.04 (0.80–1.35)	
Active	196 (50.6)	553 (51.6)	1.06 (0.76–1.46)	
Cardiovascular disease†	64 (16.6)	263 (24.8)	0.60 (0.44–0.81)	<0.01
Respiratory disease*	11 (2.7)	30 (2.7)	1.01 (0.48–1.97)	0.98
Neuropathy*	20 (5.0)	71 (6.4)	0.76 (0.45–1.24)	0.31
Hepatic disease*	5 (1.2)	16 (1.5)	0.84 (0.27–2.17)	0.75
HIV*	2 (0.5)	8 (0.7)	0.68 (0.10–2.74)	0.65
Blood type				
A	173 (42.2)	485 (43.2)	Ref.	0.34
B	34 (8.4)	124 (11.1)	0.77 (0.50–1.16)	
O	184 (42.5)	479 (42.7)	1.08 (0.84–1.37)	
AB	16 (3.9)	34 (3.0)	1.32 (0.69–2.41)	
EDI*				
Quintile 1–4 (least deprived)	227 (56.7)	528 (48.1)	Ref.	<0.01
Quintile 5 (most deprived)	173 (43.3)	569 (51.9)	0.71 (0.56–0.89)	
Transplant center				
A	70 (17.2)	283 (25.2)	Ref.	<0.001
B	101 (24.8)	154 (13.7)	2.65 (1.85–3.82)	
C	146 (35.9)	455 (40.6)	1.30 (0.94– 1.80)	
D	90 (22.1)	230 (20.5)	1.58 (1.11–2.27)	
Ownership of the facility				
Academic hospital	154 (37.8)	226 (20.1)	Ref.	<0.001
Community hospital	182 (44.7)	608 (54.2)	0.44 (0.34–0.57)	
Private hospital	71 (17.5)	288 (25.7)	0.36 (0.26–0.50)	
Year of registration				
2008	50 (12.3)	229 (20.4)	Ref.	<0.001
>2008	357 (87.7)	893 (79.6)	1.83 (1.33–2.57)	

Missing values were not imputed for bivariate analysis: *<5% of missing values, †<10% of missing values.

method as: ICC = $V_A/(V_A + (\text{pi}^2/3))$, where V_A is the level 2 variance [21]. The significance of the variance estimates was determined using the likelihood ratio test, or deviance difference.

Secondly, we entered patient variables into the model (model 1). Thirdly, renal unit variables were added to model 1 (model 2: final model). The final multivariate model was selected for optimal parsimony by minimizing the deviance criterion evaluated by the likelihood ratio test. The criterion for statistical significance was $P < 0.05$.

The contribution to the variance of the stepwise introduction of the different variables in the models was determined by the proportional change in variance (PCV) at different levels: $((V_1–V_2)/V_1) \times 100$, where V_1 is the level 2 variance of the multilevel model with M1 variables, and V_2, the level 2 variance of the multilevel-adjusted model M2 with M1+ additional variables [22].

Statistical analysis were conducted using R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) including the lme4 and mice packages.

Results

Patient characteristics

Among the 1529 patients included in the study, 407 (26.6%) were placed on the waiting list preemptively (Table 1). Their mean age was 51.2 years (SD 13.1), and 964 (62.8%) were male. The underlying renal diseases were primary glomerular disease (26.8%), polycystic kidney disease (19.9%), diabetic nephropathy (8.9%), uropathy disease (7.7%), renovascular nephropathy (7.4%), chronic interstitial nephritis (6.4%), systemic nephropathy (0.9%), unknown (14.4%), and miscellaneous (7.6%).

Bivariate analysis

In bivariate analysis (Table 1), preemptive registration was significantly lower in patients with diabetes and cardiovascular disease, in those with BMI =<20 kg/m² compared with intermediate BMIs (20.1–25 kg/m²), in those from community and private hospitals compared to academic hospitals, and in most deprived patients. Preemptive registration was significantly higher in patients with dyslipidemia, and after 2008. Preemptive registration also varied significantly according to the transplant center ($P < 0.001$). A trend toward a negative association between preemptive registration and age was observed ($P < 0.10$).

Multivariate mixed logistic regression (Table 2)

Factors associated with preemptive registration: fixed effects

In respect of the change in the deviance evaluated by the likelihood ratio test statistic for nested models, BMI, diabetes, and dyslipidemia were not included for further analysis as they were nonsignificant patient factors. At the patient level, factors independently associated with preemptive registration on the waiting list were cardiovascular disease (OR, 0.57; 95% CI, 0.42–0.79) and social deprivation (OR, 0.73; 95% CI, 0.57–0.94) (model 2). There still was a trend toward a negative association between preemptive registration and age ($P = 0.11$). At the renal unit level, community and private hospitals, compared to academic hospital, were associated with a lower odds of preemptive registration (respectively, OR, 0.44; 95% CI, 0.24–0.80; and OR, 0.35; 95% CI, 0.18–0.69). Moreover, patients were more likely to be preemptively wait-listed when referred to transplant center B compared to transplant center A. There were no other differences between transplant centers. There was also a time period effect when comparing 2009–2012 with 2008 (OR, 1.85; 95% CI, 1.31–2.62).

Thus, as an illustrative example of the most extreme possibilities, the probability of being registered preemptively for a patient older than 60 years, with a past history of cardiovascular disease, living in a deprived area, and followed in a community hospital of region A was 8.6% vs. 60.8% for a patient younger than 45 years, with no cardiovascular disease, living in one of the least deprived areas, and followed in the academic center of region B.

Variability across renal units: random effects

The empty model showed significant variability across renal units ($P < 0.001$). Overall, 12.1% of the variation in preemptive registration (i.e. ICC = 0.121) was attributable to variability between renal units. The remainder of the variation existed within units (at the patient level). In other words, although the majority of variation occurred at the patient level, renal units differed significantly in the proportion of preemptive patients they referred for registration on the waiting list.

Adjustment for level 1 variables increased differences between renal units by 1.5% (model 1B), suggesting that these findings were not due to differing patient populations across renal units. The addition of the level 2 variables (model 2), that is, ownership of the facility and affiliated transplant center, reduced the variability across renal units by 46%, signifying that characteristics of the units accounted for almost half of the disparities between units. Both ownership of the facility and the transplant center were significant factors on the center effect (PCV, 29% and 19.6%, respectively).

Discussion

This study showed that there was wide variation in preemptive registration rates on the waiting list for first deceased donor kidney transplantation between renal units in the French North-West ZIPR.

Overall, 12.1% of the variation in preemptive registration was attributable to variability between renal units. These differences could not be explained by the patient case mix, that is to say by the possible differences due to systematic variation in patient factors between sites. Nevertheless, renal unit factors accounted for almost half the variability between renal units, which probably reflects differences in practices and/or organization.

Preemptive registration rates were significantly different between transplant centers of affiliation. In other words,

Table 2. Multivariate mixed logistic regression of factors associated with preemptive registration.

		Model 1(A)		Model 1(B)		Model 2 (final)	
Fixed effects	Empty model	OR (95% CI)	*P*-value†	OR (95% CI)	*P*-value†	OR (95% CI)	*P*-value†
Level 1: patients							
Age							
18–45 years		Ref.	<0.10	Ref.	0.10	Ref.	0.11
45.1–60 years		0.87 (0.65–1.17)		0.92 (0.69–1.23)		0.93 (0.70–1.23)	
≥60.1 years		0.72 (0.51–1.01)		0.76 (0.55–1.05)		0.76 (0.55–1.06)	
BMI*							
20.1–25 kg/m²		Ref.	0.12	–	–	–	–
≤20 kg/m²		0.62 (0.37–1.00)		–	–	–	–
>25 kg/m²		0.89 (0.69–1.16)		–	–	–	–
Diabetes*		0.89 (0.61–1.28)	0.52	–	–	–	–
Dyslipidemia*		1.21 (0.92–1.59)	0.17	–	–	–	–
Cardiovascular disease*		0.57 (0.41–0.79)	<0.001	0.57 (0.41–0.78)	<0.001	0.57 (0.42–0.79)	<0.001
EDI*							
Quintile 1–4 (least deprived)		Ref.	<0.01	Ref.	<0.01	Ref.	<0.05
Quintile 5 (most deprived)		0.72 (0.55–0.92)		0.70 (0.54–0.90)		0.73 (0.57–0.94)	
Year of registration							
2008		Ref.	<0.001	Ref.	<0.001	Ref.	<0.001
>2008		1.84 (1.30–2.63)		1.87 (1.33–2.67)		1.85 (1.31–2.62)	
Level 2: renal units							
Transplant center							
A						Ref.	<0.10
B						2.35 (1.25–4.41)	
C						1.40 (0.85–2.31)	
D						1.70 (0.92–3.14)	
Ownership of the facility							
Academic hospital						Ref.	<0.01
Community hospital						0.44 (0.24–0.80)	
Private hospital						0.35 (0.18–0.69)	
Random effects							
Level 2 variance	0.452	0.445		0.459		0.248	
P (LRT χ^2)	<0.001	<0.001		<0.001		<0.001	
PCV	–	1.6%		−1.5%		46.0%	

LRT, Likelihood Ratio Test, test of random intercept = D_0–D_1. Under H0, the statistics of LRT follows a distribution of χ^2 in one degree of freedom. D_1, deviance of multilevel model with random intercept; D_0, deviance of logistic model without random effect.
PCV, Proportional change in variance.
*A multiple imputation by chained equations was performed for missing data.
†p trend, probability for linear tendency (categorical variables); *P* heterogeneity, probability for heterogeneity (non-ordering variables).

there was a regional variability in preemptive access to the waiting list. Furthermore, a significant part of the random center effect was explained by this regional variability. These results suggest that renal units implicitly share common practices toward preemptive referral and registration inside a single region, perhaps under the influence of the regional transplant center, as we also found that patients were more likely to be preemptively wait-listed in academic hospitals.

Indeed, preemptive registration rates were at least twofold higher when the renal unit was an academic hospital, that is, a hospital also performing transplantation, compared to public community and private hospitals. In the USA, it has been demonstrated that for-profit ownership of dialysis facilities, as compared with nonprofit ownership, was associated with decreased rates of placement on the waiting list, but no differences were detected with public facilities [23]. On the contrary, in France, placement on the waiting list, before or after dialysis initiation, was not associated with the type of ownership of the facility but with the medical follow-up in the department performing transplantation [11]. Our results are in concordance with the past French study conducted in the Lorraine region. We did not find any differences between community hospitals and private hospitals regarding preemptive registration, indicating that, more than the type of ownership of the facility, the medical follow-up in a transplant center may influence the placement on the waiting list. However, given the pattern for CKD care in the North-West ZIPR, we made the decision to group patients from non-for-profit facilities with patients from the related academic or community hospitals. This categorization may have negatively impacted the preemptive registration rate of the community hospitals. It is also noteworthy that no patient followed in a for-profit facility was registered before dialysis start in the study of Bayat *et al.* [11]. Furthermore, we did not evaluate the effect of the size of the renal unit which could have been an adjustment variable. Indeed, the center size has been associated with rate of registration in previous studies [10,12,24].

Geographical and center differences in listing and transplantation practice have been reported in adult patients receiving dialysis or not, mainly in the UK [10,15] and in the USA [7,16,17]. As in our study, these differences could not be explained by patient-specific socio-demographic variables, insurance or disease state or, in contrast with us, by the center characteristics [10]. In a study from the UK [10], center characteristics included whether the renal unit also performed renal transplantation, which is the same as the academic hospital modality in our study. Therefore, whether the renal unit also performs renal transplantation might be an important determinant of the between-center variability in preemptive registration but not in registration after the dialysis initiation. One may hypothesize that nephrologists not working in academic hospitals, that is, in hospitals which also owns a transplant unit, are well informed about the benefits of kidney transplantation but not about the positive impact of preemptive transplantation. This assumption should be interpreted with caution and needs to be confirmed by additional studies. Indeed, there was no association between the transplant center and the center effect in the UK study [10], which could be linked to the fact that the transplant center was not associated with registration on the waiting list. These findings differed from those observed in previous studies [9,11].

Recently, Mohan *et al.* [25] found significant association between kidney transplantation and the poverty across geographical regions and hypothesized that poverty contributes to variations in rates of kidney transplantation in the USA. Reduced access to the deceased donor waiting list has been reported for the less educated and poorest patients and for Black people and South-East Asians in the USA [2,8,12,26], where the availability of private health insurance could have influenced access to the waiting list. In the UK, it has been shown that, despite a universal healthcare system, socially deprived patients also have reduced access to the deceased donor kidney transplantation enlistment [9,27]. There were no longer ethnic differences in access to the waiting list once results were controlled for patient characteristics and deprivation [27]. In our study, we found that the likelihood of preemptive placement on the waiting list was lower in case of socioeconomic deprivation but, because we did not have the data to elucidate this specific question, we were not able to identify the underlying causes. Further studies are needed to explore the hypothesis of the interplay of socioeconomic status, patients' preferences, providers' perceptions of deprived patients, and social support network with preemptive registration, which has previously been formulated to explain racial disparities in kidney transplantation [24,28–31]. It is otherwise important to notice that deprivation did not account for the center effect which meant that deprivation did not contribute to variability in preemptive registration rates between renal units. This result underlines the interest of a hierarchical modeling approach, rather than a conventional approach, to study this particular issue [25].

A past medical history of cardiovascular disease was the patient-level factor with the strongest negative association with preemptive registration. A history of diabetes and other comorbidities have been previously documented as being factors related to the timing and likelihood of being placed on the waiting list [2,7,10,11]. In our study, patients with diabetes were more likely to have a past history of cardiovascular disease, which could explain why diabetes did not reach significance in multivariate analysis.

Patient age has been associated with a reduced probability of being listed for transplantation [2,7,10,11]. This was not the case in our study although we could observe a trend toward association. However, this result may suffer from a selection bias as we exclusively included patients who were already registered on the waiting list.

There are some limitations in our study, which was a retrospective study. The process of registration is time-dependent, so that an approach that enables taking into account the delay for registration would have been more appropriate. Another limitation is that we only have few candidate explanatory variables at the renal unit level.

In conclusion, there was an effect of the renal unit on preemptive access to the national waiting list for kidney transplantation that cannot be explained by patient characteristics and is incompletely explained by center characteristics. Additional studies are needed to determine whether this effect is due to variations in availability of resources, or in practices. Moreover, deprivation is associated with a lower chance of being preemptively registered on the waiting list. It underlines the fact that efforts should be made to improve patient access to the waiting list. In an attempt to launch a health program devoted to deprived people, further studies are needed to fully understand the link between deprivation and registration.

Authorship

NR: participated in the research design, the data analysis, and drafted the manuscript. TL and BHL: participated in the research design and are the major reviewers of the manuscript. MH, DB, PFW and NB: participated in the data collection and reviewed the manuscript. GL: participated in the research design and reviewed the manuscript. ID: participated in the research design and the data collection. BHL: is the principal investigator for this project.

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