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Assessment of the Care for Children and Young Adults with End-Stage Renal Disease

Julien Hogan

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Par

Mr le Dr Julien Hogan

Assessment of the care for children and young adults with End-stage Renal Disease

Thèse présentée et soutenue au Kremlin Bicêtre le 17 mai 2017

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Titre : Evaluation de la prise en charge de l'insuffisance rénale chronique et terminale (IRCT) chez l'enfant et l'adulte jeune.

Mots clés : Insuffisance rénale chronique, transplantation rénale, dialyse, pédiatrie, épidémiologie.

La transplantation rénale est reconnue comme le traitement de choix de l'insuffisance rénale terminale chez l'enfant et l'adulte jeune et est associée à une augmentation de la survie et une amélioration de la qualité de vie des patients tout en étant le traitement le plus coûteux efficace à long terme. Néanmoins, il persiste de nombreuses questions sur la prise en charge des patients avant, pendant et après la transplantation. Le but de cette étude est d'analyser le parcours de soin des enfants présentant une maladie rénale chronique afin de mettre en évidence d'éventuelles disparités dans la prise en charge des patients et de fournir des outils d'aide à la décision afin d'améliorer la prise en charge et le traitement de ces patients.

Nous avons utilisé différentes sources de données : le registre français des patients avec traitement de suppléance rénale (registre REIN), le registre européen de traitement de suppléance rénale (ESPN/ERA-EDTA registry) et la base de données médico-administrative des hospitalisations (PMSI).

Tout d'abord, nous avons étudié les facteurs médicaux et non-médicaux pouvant induire des inégalités et avons mis en évidence que le sexe féminin est associé à un accès retardé à la transplantation rénale et particulièrement à la transplantation rénale préemptive. Ce désavantage pourrait être en partie expliqué par une progression plus rapide vers l'insuffisance rénale terminale même chez des patients présentant la même maladie. Nous avons également montré que les pratiques des centres de traitements impactaient de façon importante la trajectoire des patients. C'est un déterminant majeur du choix de la modalité de suppléance rénale initiale (hémodialyse ou dialyse péritonéale) et de l'accès à la transplantation rénale essentiellement par le biais de la rapidité d'inscription sur la liste d'attente.

Nous nous sommes focalisé sur le sous-groupe des patients les plus jeunes, débutant le traitement de suppléance avant l'âge de 2 ans, dont la prise en charge reste un challenge. Nous avons confirmé d'importants progrès dans la prise en charge de ces patients en montrant que seule la présence de comorbidités extra-rénales restait associée à une survie inférieure à celle des autres patients en insuffisance rénale terminale. Concernant la durée de vie des greffons, nous avons montré l'importance du matching de taille entre le donneur et le receveur avec un ratio de taille donneur/receveur optimal entre 1.4 et 1.8. De même, nous retrouvons l'importance du matching HLA classe 2 sur la survie du greffon. Nous allons combiner ces facteurs de risques dans un outil de prédiction pour aider les cliniciens dans le choix des greffons et allons réaliser une validation externe de cet outil sur une autre cohorte.

A partir des données d'hospitalisation, nous avons montré que les infections sont la première cause d'hospitalisation post-transplantation devant les rejets et les cancers.

Enfin, du fait de la durée de vie limitée des greffons rénaux et de l'amélioration importante de l'espérance de vie, ces jeunes patients ont la particularité de nécessiter fréquemment des transplantations répétées plus ou moins précédées de périodes de dialyse. De ce fait, il convient de considérer la trajectoire globale de ces patients afin de maximiser le temps passé avec un greffon fonctionnel et de minimiser le temps passé en dialyse. Nous avons développé un outil de simulation permettant de tester des modifications de stratégies de prise en charge (ex : augmentation du don vivant ou de la transplantation préemptive, modification des exigences de matching HLA) et leurs effets sur la trajectoire des patients. Cet outil sera développé afin de répondre à des questions plus complexes sur des sous-groupes de patients.

Title : Assessment of the care for children and young adults with End-stage Renal Disease

Keywords : End-stage renal disease, renal transplantation, dialysis, pediatrics, epidemiology.

Renal transplantation is nowadays recognized as the treatment of choice for end-stage renal disease in children and young adults. It is associated with improved survival, better quality of life and better long-term cost-effectiveness. However, many questions remain considering the optimal management of the patients before transplantation, during the transplantation process and after transplantation. We aim to analyze the care and treatment received by children with chronic kidney diseases, to detect potential disparities in patients' management and to provide useful tools to help decision-making and treatment planning.

We used several data sources including the French renal replacement therapy (RRT) registry (REIN), the European RRT registry (ESPN/ERA-EDTA) and the French National medico-administrative Hospital Discharge database (PMSI).

First, we focused on medical and non-medical factors that may induce disparity and found that besides medical factors, female gender was associated with a delayed access to renal transplantation and especially to preemptive transplantation. This might be partially explained by a faster decline of renal function in girls that remains to be explored. Aside from patients' characteristics, we found that centers' practices strongly impact patients' trajectories. It is a main factor both in the choice of the first modality of RRT (hemodialysis or peritoneal dialysis) and in the access to renal transplantation especially through a faster access to the renal transplant waiting list.

Then, we focused on the subgroup of the younger patients starting RRT before 2 years old, whose management is particularly challenging. We confirmed the great improvement in the care of those patients with only extrarenal comorbidities being still associated with a poorer survival. Considering renal transplant survival, we assess the importance of a matching in height between the donor and the recipient with an optimal donor/recipient height ratio between 1.4 and 1.8 and the importance of HLA matching especially in class 2. We aim to combine those risk factors in a prediction tool to help clinicians in their choices and will perform an external validation of this tool on another cohort.

Based on the hospital discharge data, we studied post-transplant complications requiring a hospitalization and found that infections are the main cause of hospitalization post-transplant, far more frequent than graft rejection or cancer.

Finally, given the longevity of children undergoing kidney transplantation, most pediatric recipients will inevitably develop graft failure, requiring a return to dialysis or a second transplant so that one should consider the complete trajectory of the patients and try to maximize the time spent with a functioning transplant and minimize the time spent on dialysis. We developed a simulation tool allowing us to test modifications of treatment strategies (e.i: increase in transplantation from living-donor kidney or in preemptive transplantation, better HLA-matching at first transplantation) and their effect on patients' trajectories. This tool will be further implemented to answer more complex questions on specific subgroups of patients.

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I. List of the publications and congress presentations

Publications

1. **J Hogan**, C Couchoud. Use of hierarchical models in nephrology. *Nephrol Ther.* 2014 April 29.
2. **J Hogan**, E Savoye, MA Macher, J Bachetta, F Garaix, A Lahoche, T Ulinski, J Harambat, C Couchoud. Rapid Access to Renal Transplant Waiting List in Children: Impact of Patient and Center Characteristics in France. *Nephrol Dial Transplant.* 2014 Jun 30.
3. **J Hogan**, B Audry, J Harambat, O Dunand, A Garnier, R Salomon, T Ulinski, MA Macher, C Couchoud. Are there good reasons for inequalities in access to renal transplantation in children? *Nephrol Dial Transplant.* 2014 Nov 23.
4. T Phirtskhalaishvili, F Bayer, S Edet, I Bongiovanni, **J Hogan**, C Couchoud. Spatial Analysis of Case-mix and Dialysis Modality Associations. *Perit Dial Int.* 2015 Oct 16.
5. **J Hogan**, C Couchoud, M Bonthuis, JW Groothoff, KJ Jager, F Schaefer, KJ Van Stralen; ESPN/ERA-EDTA Registry. Gender Disparities in Access to Pediatric Renal Transplantation in Europe: Data From the ESPN/ERA-EDTA Registry. *Am J Transplant.* 2016 Jul;16(7):2097-105.
6. **J Hogan**, B Ranchin, M Fila, J Harambat, S Krid, I Vrillon, G Roussey, M Fischbach, C Couchoud. Choice of First Dialysis Modality for Children and Young Adults in France. *Pediatr Nephrol.* 2016 Nov 14
7. **J Hogan**, C Pietrement, AL Sellier-Leclerc, F Louillet, R Salomon, MA Macher, E Berard, C Couchoud Infection-related Hospitalizations after Kidney Transplantation in Children: Incidence, Risk Factors and Cost. *Pediatr Nephrol.* 2017 Apr;32(4):659-667

Oral presentations in congresses :

Société française de néphrologie pédiatrique, Genova, november 2013

J Hogan, C Couchoud, MA Macher. Outcome in children starting renal replacement therapy (RRT) before 24 months of age in France.

J Hogan, E Savoye, MA Macher, J Bachetta, F Garaix, A Lahoche, T Ulinski, J Harambat, C Couchoud. Rapid Access to Renal Transplant Waiting List in Children: Impact of Patient and Center Characteristics in France.

J Hogan, B Audry, J Harambat, O Dunand, A Garnier, R Salomon, T Ulinski, MA Macher, C Couchoud. Are there good reasons for inequalities in access to renal transplantation in children?

Journée de Transplantation pédiatrique, Paris, June 2013

J Hogan, C Couchoud, MA Macher. Outcome in children starting renal replacement therapy (RRT) before 24 months of age in France.

European Society of Pediatric Nephrology (ESPN), Porto, 16-20 September 2014

J Hogan, C Couchoud, MA Macher. Outcome in children starting renal replacement therapy (RRT) before 24 months of age in France.

European Association-European Dialysis and Transplantation Association (ERA-EDTA) congress, London, May 2015

J Hogan, C Couchoud, M Bonthuis, J W. Groothoff, K J. Jager, F Schaefer, K J. Van Stralen. Why do girls with end-stage renal disease wait longer for transplantation than boys?

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J Hogan, C Couchoud, M Bonthuis, J W. Groothoff, K J. Jager, F Schaefer, K J. Van Stralen.
Why do girls with end-stage renal disease wait longer for transplantation than boys?

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J Hogan, C Pietrement, AL Sellier-Leclerc, F Louillet, R Salomon, MA Macher, E Berard , C Couchoud . Infection-related Hospitalizations after Kidney Transplantation in Children: Incidence, Risk Factors and Cost.

International Pediatric Nephrology Association Congress, Foz de Iguazu, September 2016

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Choice of First Dialysis modality for Children with End Stage Renal Disease

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Poster presentations in congresses:

International Pediatric Nephrology Association Congress, Shanghai, September 2013

J Hogan, E Savoye, MA Macher, J Bachetta, F Garaix, A Lahoche, T Ulinski, J Harambat, C Couchoud. Rapid Access to Renal Transplant Waiting List in Children: Impact of Patient and Center Characteristics in France

American Society of Nephrology, San Diego, 2015

J Hogan, B Ranchin, M Fila, J Harambat, S Krid, I Vrillon, G Roussey, M Fischbach, C Couchoud.
Choice of First Dialysis modality for Children with End Stage Renal Disease

International Pediatric Nephrology Association Congress, Foz de Iguazu, September 2016

Hogan J, Pietrement C, Sellier-Leclerc AL, Louillet F, Salomon R, Macher MA, Berard E, Couchoud C. Infection-related Hospitalizations after Kidney Transplantation in Children: Incidence, Risk Factors and Cost.

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III. Context

A. Epidemiology of End-stage Renal Disease in Children worldwide

End-stage renal disease (ESRD) is a leading cause of morbidity and mortality worldwide. Renal replacement therapy (RRT) either through dialysis or through renal transplantation is a life-saving treatment. However, the high cost of these treatments has become a challenge both in low income countries where offering RRT to an increasing number of patients has become a major public health issue and in high income countries where the burden of ESRD on the public health system is of major importance.

A recent review by Liyanage et al. published in the Lancet describes the access to RRT worldwide and highlights major disparities between countries (1). In 2010, 2.6 millions of people were receiving RRT when the need for RRT was estimated between 4.9 and 9.7 million with a major inadequacy between the needs and the treatment available in low income countries (Figure III.1).

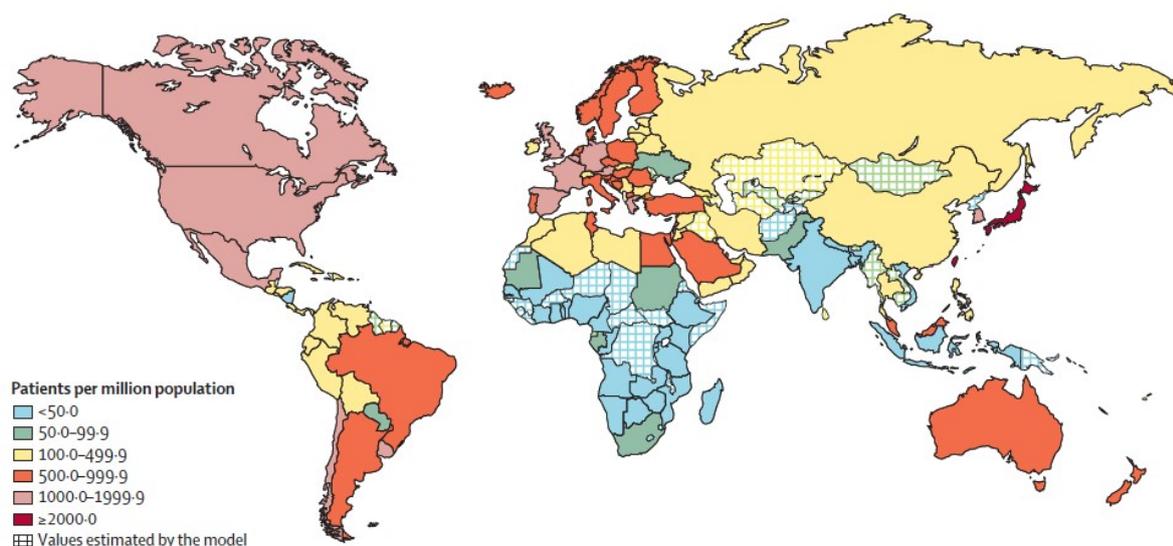


Figure III.1: Patients receiving renal replacement therapy in 2010.

Among children under 19 years old, the estimated prevalence of ESRD worldwide is 250 000 when only 20 000 of those patients have actually access to RRT so that less than 10% of the children needing RRT have access to it (2). This report also highlights major disparities between countries with over 80% of the treated patients living in high income countries.

When, focusing on European countries, incidence of RRT decreased from Western to Eastern Europe and increased from Southern to Northern Europe. Again, higher RRT treatment rates were found in

wealthier countries and among those that tend to spend more on healthcare and where patients pay less out-of-pocket for healthcare (3).

B. Epidemiology of End-stage Renal Disease in Children in France

1. The REIN registry

The French Renal Epidemiology and Information Network (REIN) registry began in 2002 to provide a tool for public health decision support, evaluation and research related to ESRD and its treatments (4). It relies on a network of nephrologists, epidemiologists, patients and public health representatives, coordinated regionally and nationally. Continuous registration covers all dialysis and transplanted patients. In its annual report, the REIN registry provides data on the epidemiology of ESRD in children.

2. Incidence and prevalence of ESRD in France

In the last report based on the data of 2014, 106 children and teenagers below 20 years old started on RRT including 7 children younger than one year old. Table III.1 presents the incidence of ESRD by age groups.

Age at RRT	n	%	Crude rate (pmi)	CI 95%
0-4 years old	21	19,8	5,2	[3,0-7,4]
5-9 years old	13	12,3	3,2	[1,5-4,9]
10-14 years old	28	26,4	6,9	[4,3-9,4]
15-17 years old	26	24,5	10,8	[6,7-15,0]
18-19 years old	18	17,0	11,4	[6,1-16,6]
Total	106	100,0	6,6	[5,3-7,8]

Table III.1: Incidence of ESRD by age groups

Among them 18 (17%) received a preemptive transplantation including 6 from a living donor when 55 (51.9%) and 33 (31.1%) started on hemodialysis and peritoneal dialysis respectively. The repartition of RRT modalities at start are presented in Table III.2.

First treatment modality	0-4 years		5-9 years		10-14 years		15-17 years		18-19 years		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Hemodialysis	6	28,6	4	30,8	19	67,9	15	57,7	11	61,1	55	51,9
Peritoneal dialysis	15	71,4	8	61,5	4	14,3	1	3,8	5	27,8	33	31,1
Transplantation			1	7,7	5	17,9	10	38,5	2	11,1	18	17,0
Living donor					1	3,6	4	15,4	1	5,6	6	5,7

Table III.2: Distribution of the incident patients according to the first modality of treatment

The crude incidence rate of treated ESRD in patients younger than 20 years old was 6.6 per million age-related inhabitants and the prevalence of RRT was 53 per million age-related inhabitants with an increase with age from 14 pmi in children below 5 years old to 122 pmi between 17 and 19 years old. The incidence and prevalence of ESRD remain stable over time.

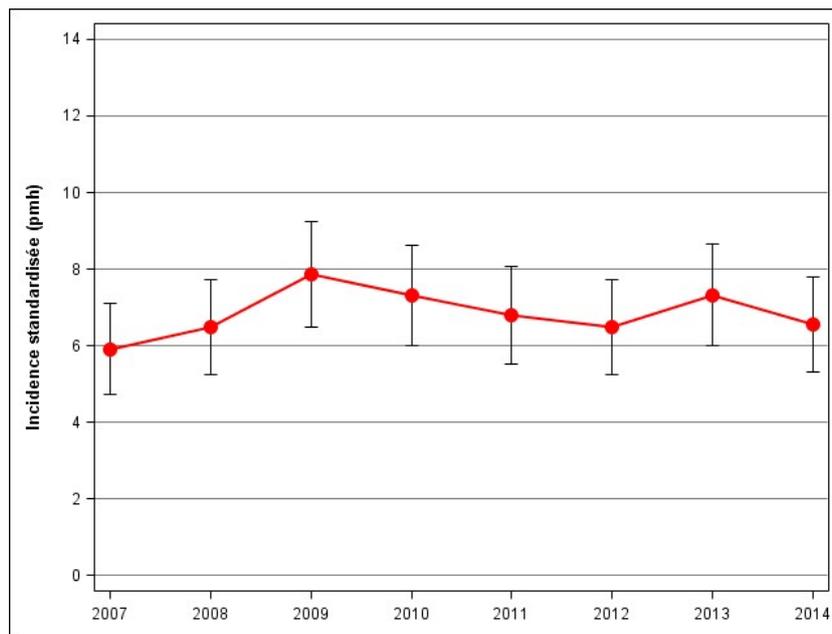


Figure III.2: Incidence of ESRD in patients younger than 20 years old over time

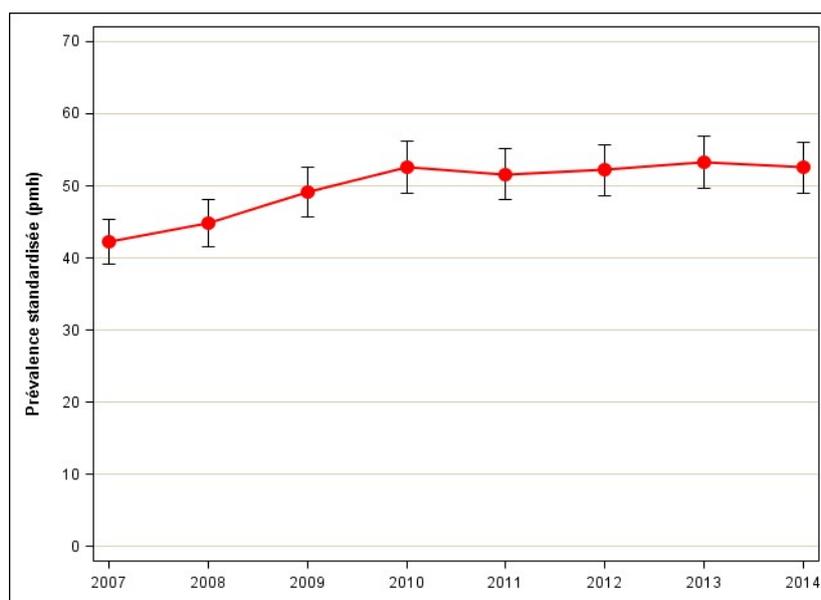


Figure III.3: Prevalence of ESRD in patients younger than 20 years old over time.

C. Classification and repartition of primary renal diseases leading to ESRD

1. Repartition of the primary renal diseases among incident patients in 2014

Median age at RRT was 13.8 years and 55.7% of the patients were male. Primary renal diseases are usually classified according to the classification of the French Society of Nephrology based on anatomopathology examination and genetic testing. Among children congenital nephropathy including Congenital Abnormalities of the Kidney and the Urinary Tracts (CAKUT) and other genetic diseases account for more than half of the cases (55.7%) when acquired glomerulonephritis account

for only 19.8% of the primary renal diseases. This repartition is similar to those reported in other European countries (ERA-EDTA annual report 2014) among children and is very different than the one found in adult patients. Table III-3 presents the repartition of the primary renal diseases among incident patients.

Primary renal diseases	0-4 years	5-10 years	10-14 years	15-17 years	18-19 years	Total
<u>Hereditary nephropathy</u>						
Congenital abnormalities of the kidney and the Urinary tracts (CAKUT)	5	6	5	8	3	27
Hypodysplasia	2	4	2	2	1	11
Reflux nephropathy	2	1	2	4	1	10
Interstitial nephritis associated with obstructive uropathies	1	1	1	2	1	6
Genetic diseases	13	4	10	4	1	32
Hereditary cystic nephropathy (excluding ADPKD and ARPKD)	4	2	4	1	0	11
Congenital nephrotic syndrome	6	1	0	0	0	7
Secondary tubule-interstitial nephritis	1	0	3	0	0	4
Cystinosis	0	0	0	1	1	2
Hereditary glomerulopathy	2	0	0	0	0	2
Alport syndrome	0	0	2	1	0	3
Medullary cystic nephropathy (including nephronophthisis)	0	0	0	1	0	1
Primary oxalosis	0	0	1	0	0	1
ADPKD	0	0	1	0	0	1
ARPKD	0	1	0	0	0	1
<u>Acquired nephropathy</u>						
Acquired glomerulonephritis	0	1	5	7	8	21
Idiopathic nephrotic syndrome (FSGS and MCD)	0	0	2	3	2	7
IgA nephropathy (excluding HSP)	0	0	1	1	3	5
Primary glomerulonephritis without histological assessment	0	1	0	1	1	3
Glomerulonephritis associated with systemic diseases, other	0	0	0	1	1	2
Lupus nephritis	0	0	1	0	1	2
Membranous nephropathy	0	0	1	0	0	1
Crescentic glomerulonephritis	0	0	0	1	0	1
Vascular nephropathy	1	1	1	0	3	6
Hemolytic and uremic syndrome	1	1	1	0	2	5
Nephroangiosclerosis	0	0	0	0	1	1
Acquired interstitial nephritis	1	0	2	1	1	5
Other	1	0	0	2	0	3
Miscellaneous	0	2	10	8	4	24
TOTAL	21	13	28	26	18	106

Table III.3: Distribution of the incident patients according to the primary renal disease in 2014.

2. Issues of the classification of primary renal diseases

Owing to the great variety of primary kidney diseases (132) in relation to the number of patients, grouping diseases is necessary in order to perform the analysis. The classical classification of primary renal diseases based on pathological abnormalities found in the kidney is not always relevant since it associates diseases with very different prognosis and management. For the purpose of our studies, we thus developed a systematic classification which aims at creating more homogeneous groups

considering the ease of transplantation. Specifically, diseases were characterized by their coordinate values in the system of axes defined by the principal components of a multiple correspondence analysis based on seven items (immune renal injury, possible other immune injury, extra-renal vascular injury, possible extra-renal injury of other causes, genetic diseases and congenital abnormalities of the kidney and the urinary tract, possible post-transplantation, recurrence of initial nephropathy and urological abnormality). An example of the graphical representation of 2 axes is presented in supplemental Figure 1.

Diseases were then grouped by an ascending hierarchical classification (5, 6), an iterative process, with an algorithm that starts with as many clusters as data items and builds up a tree by successively merging the two nearest clusters. The result of this classification is presented in supplemental Figure 2. The choice of the number of groups is based both on the number of patients with the need to choose a reasonable number of groups to have enough patients in each group and on the quality criteria. Criteria available are the pseudo-F statistic, the Cubic Clustering Criterion (CCC) and the pseudo-T squared. The pseudo-F statistic gives a measure of the difference between the groups with the aim to maximize this difference. CCC ($CCC = \ln[1 - E(R^2)/1 - R^2] * K$) tests the null hypothesis that the data present a uniform distribution (no groups can be made) with a CCC above 2 indicating an appropriate classification and an elevated pseudo T-squared indicates that two clusters should not be combined because their median vectors are different. The results of those statistics are presented in figure III.4.

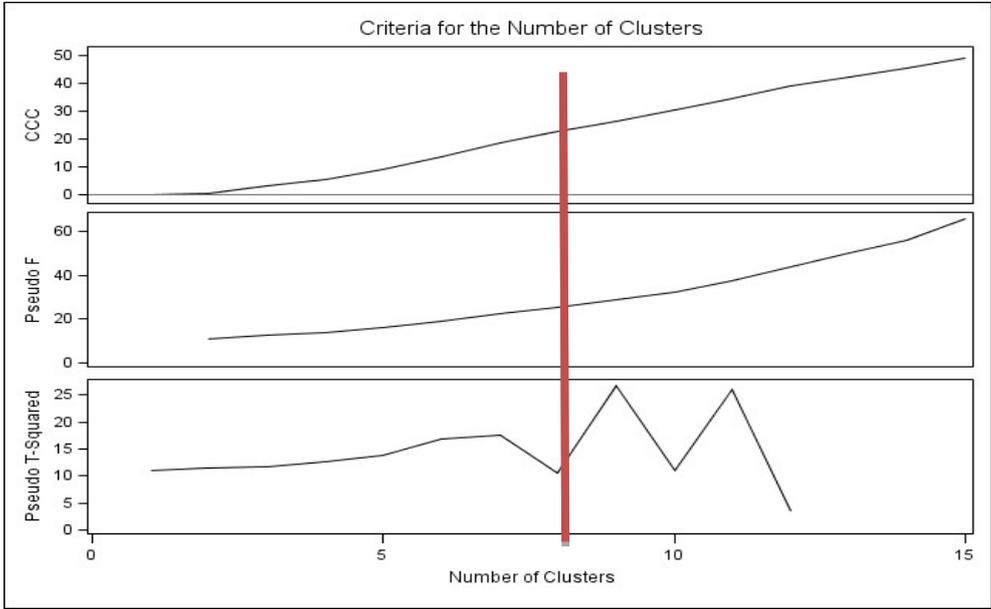


Figure III.4 : Graphical presentation of the quality criteria (CCC, Pseudo F et Pseudo T-squared)

We thus obtained six groups that we named after their main shared criteria (vascular diseases, nephropathies with possible extra-renal immune injury, urological abnormalities, genetic or toxic abnormalities, risk of post-transplantation recurrence and unknown). This classification is presented in annex 3 and has been used in the following studies on the access to the waiting list and to renal transplantation.

IV. Aim of our research

In this context, our objective is to analyze the care and treatment received by children with chronic kidney diseases, to detect potential disparities in patients' management and to provide useful tools to help decision-making and treatment planning.

V. Issues

A. Disparities in access to RRT in children: What about France?

As previously developed, the access to renal replacement therapy in France as in most developed countries is good. However, many studies and reports pointed out major inequalities in access to dialysis and transplantation. Although medical factors partially explain differences in access to dialysis and transplantation, such as the primary renal disease as recently demonstrated among patients with different types of glomerulonephritis in the United States (7) or the age at RRT initiation, many studies reported on the effect of socio-demographic and economic factors. In both European and American adults, female gender has been associated with lower access to transplantation, substantially lower registration on the transplant waiting list and a longer time from the start of dialysis to wait listing (8-11). Among children, racial inequalities have been reported in the choice of the dialysis modality (12), in dialysis adequacy (13), in access to the renal waiting list (14) and in the access to transplantation (15) and to preemptive transplantation (16, 17).

Several studies also investigate the effect of socioeconomic status on the access to the waiting list and to renal transplantation (18, 19).

In the US, implementation of the Share 35 has attenuated racial disparities in the time to and probability of children receiving a deceased-donor kidney transplant (20).

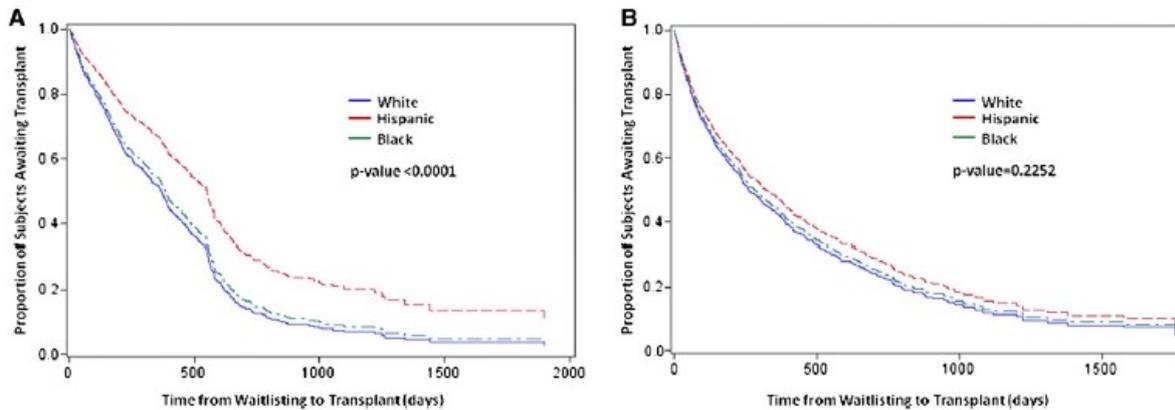


Figure V.1: Adjusted survival curves for time from wait-listing by race/ethnicity. (A) Pre-Share 35. (B) Share 35 era.

(Values are adjusted for age, etiology of ESRD, sex, OPO region, BLI, blood type, PPRA, insurance and neighborhood poverty)

Besides patients' characteristics, centers and physicians' practices are known factors of disparity in the care of adult patients with ESRD. Significant disparities have been reported depending on the characteristics of the center, such as its size (21-23), the ownership of dialysis facilities (e.g. for-profit or not-for-profit) (24) and the presence of a transplantation program (9, 10, 25, 26).

In France, the "Haute Autorité de Santé" (HAS) published guidelines on renal transplantation (27). In those guidelines they underline that disparities in access to the renal waiting list exist between regions (28) and that non-medical factors impact the access to the waiting-list among adults (8) and prompt the nephrologists to screen all patients for kidney transplantation, to speed the inscription on the renal waiting-list for eligible patients and to try to reduce disparities in access to renal transplantation.

Our first research objective is to assess the existence of disparities in access to renal replacement therapy and especially in access to renal transplantation among children in France. They are many steps between the recognition of the renal disease and transplantation including referral, choice of dialysis modality if needed, listing and organ receipt. We aim to study medical and non-medical factors that may arise at each step and induce disparity and especially factors related to centers' practices.

B. Optimal management of pediatric patients: Are we there yet?

Renal transplantation is nowadays recognized as the treatment of choice for end-stage renal disease (ESRD) in both adults and children. It is associated with improved survival: transplantation in children has been shown to increase life expectancy by 20–40 years, compared with patients who remained

on dialysis (29, 30). It is also associated with a better quality of life (31-33) and with better long-term cost-effectiveness (34, 35). However, many questions remain considering the optimal management of the patients before transplantation, during the transplantation process and after transplantation.

It is recognize that one should try to offer preemptive transplantation to patients in order to avoid dialysis and its complications. However, when this preemptive transplantation cannot be achieved, dialysis is required. Despite numerous studies that aim to assess the best modality of dialysis treatment, results remain conflicting (36). In adults, differences in survival found in observational studies have been attributed to the different methods of case-mix adjustment to overcome selection bias, the different methods used to take into account the non-proportional risk over time and treatment switches and the use of different subgroups (37). Several studies that appropriately address the issue of case-mix difference between peritoneal dialysis (PD) and hemodialysis (HD) patients did not found any patient survival differences (38, 39) or only an early benefit of PD that disappeared with time (40). Moreover, Molnar et al. did not find any impact of pre-transplant dialysis modality on graft loss and delayed graft function (41, 42).

When considering renal transplantation, several concerns specific to children and young adults arise. First, in the youngest ones, there is no guideline for the management of infants with ESRD and the optimal management of those patients remains debated. In 1998, a survey among pediatric nephrologists reported that only 41% would offer RRT for all patients younger than one month old and only 53% would offer RRT in all patients between one and 12 months old (43). Since then, several studies from the United States (44) and Europe (45) reported an improvement of the outcome of those patients but discrepancies in the care of those patients remain. In a survey that we performed among the 14 French centers of pediatric nephrology (unpublished data); several questions were asked with regard to the management of those patients:

- a) What is the minimal weight to be registered on the renal waiting-list?
- b) What is the minimal weight to be transplanted?
- c) Should those patients be registered on inactive status or wait for a registration on active status later?
- d) Considering a 26-months old receiver weighting 13kg for 85cm, would you accept a kidney from donor A (10 years-old, 30kg and 130cm), donor B (15 years-old, 45kg and 160cm), donor C (20 years-old, 55kg and 170cm), donor D (25 years-old, 75kg and 180cm)?

The answers are presented below, showing important discrepancies between centers.

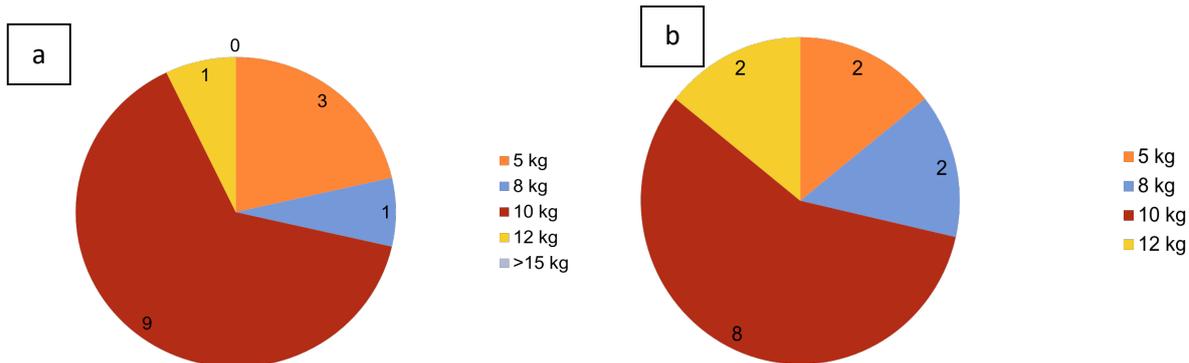


Figure V.2: Repartition of the centers' answers for the minimum weight required for (a) registration on the waiting-list, (b) transplantation.

c 4 centers registered the patients as soon as possible and put them on inactive status when 10 waited before registering them.

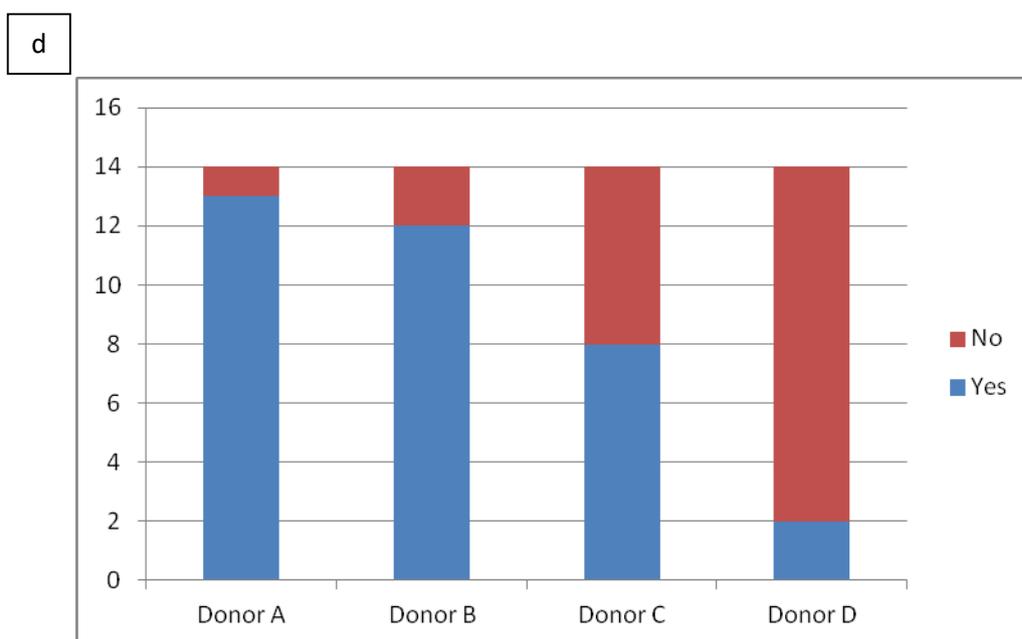


Figure V.3: Graphical presentation of the centers' acceptance rates for each donor.

Finally, because of the longevity of children undergoing kidney transplantation, most pediatric recipients will inevitably develop graft failure, requiring a return to dialysis or a second transplant. Thus, while adult studies mostly focus on the survival of the first transplantation, pediatric studies should take into account the high probability of repeated transplantation and the risk of immunization. When the importance of HLA matching is fading in adults in the era of more potent immunosuppressive drugs, several authors studied the impact of HLA mismatch on subsequent immunization. Poorer HLA matching at first transplant was associated with higher panel reactive antibodies (PRAs) at second transplant among adults and children (46, 47). Increased sensitization leads to longer waiting times for a second graft and a higher risk of loss of the second graft (46, 48,

49). Foster et al. reported on a significant benefit of a better HLA-matching at first transplant on life-time with graft function (50). Another specific question is the interest of performing deceased donor transplantation first despite a compatible living donor in order to keep the living donor for the second transplantation when waiting-time is often longer especially if the patient has lost in pediatric priority. Based on the data of the American Scientific Registry of Transplant Recipients, Van Arendonk et al. demonstrated that the cumulative graft life of two transplants was similar regardless of the order of deceased donor and living donor transplantation (51). However, a deceased-donor-first strategy was advantageous only for the most highly sensitized patients (PRA>80%), for all other patients (PRA<80%), a living-donor-first strategy was recommended (52).

Our second research objective was to answer questions on the optimal management of children and young adults especially considering renal transplantation in terms of donor/recipient morphological and immunological matching.

C. How to evaluate the outcome of our patients: a graft life versus a lifetime perspective.

Since the optimal management of children with ESRD remains debated, studies evaluating the outcome of the patients by strategy of treatment are needed. The survival of children and young adults with ESRD really improved in the last decades (53). In France the 5-year survival of pediatric patients after RRT initiation is 96.5% [95.4-97.7]. Thus, mortality cannot be our outcome of interest and most studies focused on the transplant's survival. However, given the the longevity of children undergoing kidney transplantation, most pediatric recipients will inevitably develop graft failure, requiring a return to dialysis or a second transplant so that one should considered the complete trajectory of the patients and try to maximize the time spent with a functioning transplant and minimize the time spent on dialysis on the widest period of time possible. A schematic presentation the trajectory of a patient is presented in Figure V.4.

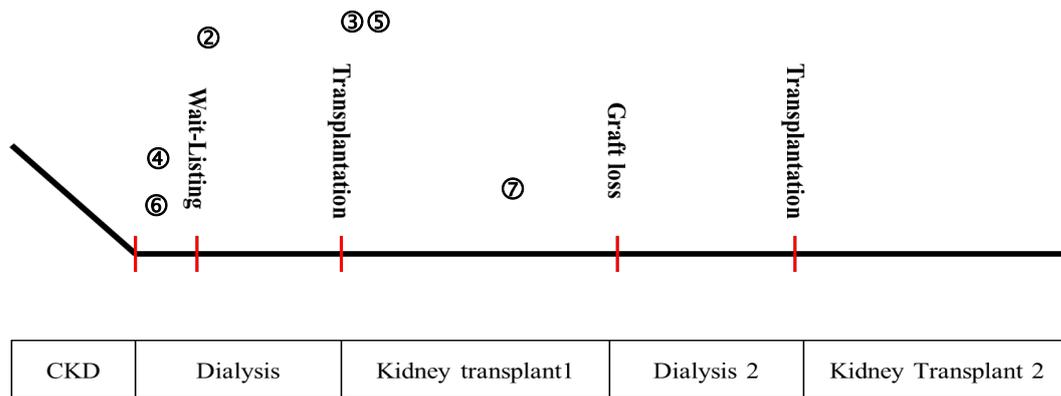


Figure V.4: Schematic presentation of the trajectory of children with ESRD. Numbers correspond to published articles as presented on page 7.

1. Limitations of the available data

The complete trajectory of a patient in ESRD, namely the succession of treatment modalities, starts with the initiation of RRT until death.

Based on the data from the REIN registry, it is not possible to capture the entire trajectory of the patients. The construction of the trajectories from the available data raises too major problems. First, most of the pediatric patients included in the registry are still alive so that their trajectories are “right-truncated” with some of them having only a short follow-up. Second, the REIN registry includes data on transplantation with data available since 1960 and data on dialysis exhaustively only since 2005. Thus, we miss data on the beginning of the trajectory for some patients who are considered “left-truncated”. Therefore, we need a model that is able to take into account the data of the “right-truncated” patients but also the data of the “left-truncated” patients that will allow us to predict trajectories on wide periods of time. This model includes data from both incident and prevalent (“late-entry”) patients by taking into account for prevalent patients the time since the first treatment.

2. A dynamic process: the need for a model

The simple observation of the number of patients in each treatment modality at different time-points is not sufficient. A statistic model able to capture the dynamic process would allow both the estimation of the trajectories formed from data from incident and prevalent patients and to simulate the modification of some of the parameters of the model (initial distribution of the patients, transition rates...) in order to test possible modifications of the current practices.

Our third research objective is to develop a simulation tool to be able to describe and predict the trajectory of the patients and simulate new strategy of care.

VI. Results

A. Evaluation of the disparities in access to renal replacement therapies: The burden of centers' practices

1. How to assess and quantify disparities in centers' practices: the use of hierarchical model.

This first article reviews the rationale for using hierarchical models in public health research and especially in nephrology research.

The use of hierarchical models in public health research is recently increasing in order to study all the factors explaining health outcomes. Thus, a better understanding of those models is needed first to identify questions that may be answered by using them and also to be aware of their limitations. On the one hand, hierarchical models managed to take into account the hierarchical structure of the data allowing a better estimation of the effects of the explanatory variables and the study of the impact of the "environment" (i.e.: neighborhood, treatment center, same clinical trial. . .) on health outcomes. They also allow the study of factors that may explain this impact of the "environment". On the other hand, they are more complex and a reflection on which determinant to include and how the environment is supposed to impact patients' health is much needed. We attempt to give a simple presentation of these models and to illustrate their results and potential use in the field of nephrology, as well as their limits.

Utilisation de modèles hiérarchiques en néphrologie

Use of hierarchical models in nephrology

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Nephrol Ther. 2014 Jul;10(4):216-20.

1. Introduction

Au cours des dernières années, sous l'impulsion d'autres domaines de recherche comme la sociologie, l'utilisation de modèles hiérarchiques s'est développée en recherche biomédicale.

Ce développement est dû, tout d'abord, à une volonté d'étudier l'ensemble des déterminants de santé, et non seulement ceux liés aux caractéristiques individuelles des patients, et également à la prise en compte des limites des modèles classiques dans l'étude de données hiérarchiques.

Cet article a pour objectif de présenter le rationnel pour l'utilisation de modèles hiérarchiques, de réaliser une présentation simple de ces modèles et de leurs résultats en illustrant leur application dans le champ de la néphrologie et d'en discuter les principales limites.

2. Intérêt de l'utilisation d'un modèle hiérarchique

En recherche biomédicale, les données hiérarchiques ou « nichées » sont extrêmement fréquentes. L'étude d'individus appartenant à différents groupes (même néphrologue référent, même centre de traitement, même région ou pays de résidence. . .), à différentes études cliniques dans le cadre de méta-analyses, mais également les mesures répétées chez un même individu, en sont autant d'exemples. Ne pas prendre en compte la structure hiérarchique des données conduit à une mauvaise évaluation des intervalles de confiance des coefficients de régression, odds ratio (OR) ou hazard ratio (HR), par les méthodes classiquement utilisées (régression linéaire, régression logistique ou modèle de Cox). En effet, une hypothèse majeure et commune à ces modèles classiques est l'indépendance des observations. Ainsi, chaque patient apporte une information unique et les informations des patients s'additionnent. C'est pourquoi la puissance des études calculées par ces modèles ainsi que la précision des estimations augmentent proportionnellement au nombre de patients. Dans le cas de données hiérarchiques (par exemple des patients dialysés traités par dialyse péritonéale dans différents départements), les observations sont corrélées, ce qui équivaut à dire qu'une partie de l'information apportée par un patient est redondante avec celle des patients du même groupe (le département, dans notre exemple). De ce fait, à nombre de patients égal, la puissance et la précision des estimations sont inférieures à celles suggérées à tort par les modèles classiques. Les modèles classiques peuvent ainsi potentiellement conclure à tort à la présence d'une association. Prendre en compte la structure hiérarchique des données offre la possibilité d'étudier spécifiquement l'existence de variations entre groupes (pourcentage de démarrage en dialyse péritonéale [DP] selon le département par exemple), de quantifier la part de l'effet observé à l'échelon individuel (démarrage en DP) lié aux groupes (département) et non seulement à chaque individu, et d'étudier les caractéristiques des groupes permettant d'expliquer cet effet.

1) Exemple proposé

Il a été démontré un lien entre l'âge et le statut diabétique d'un patient en insuffisance rénale chronique terminale (IRCT) et la probabilité de démarrer par une DP comme premier traitement de suppléance (54). À partir des patients incidents 2009/2010 du registre REIN, nous avons vérifié le fait qu'être diabétique diminue la probabilité d'être traité par DP avec un odds ratio de 0,79 (intervalle de confiance [IC] 95 % 0,72-0,88) associé au traitement initial par DP chez les patients diabétiques après ajustement sur l'âge.

Il est également bien connu que le pourcentage de recours à la DP comme première modalité de traitement est extrêmement disparate d'un département à un autre (55) (avec des variations de 0 à

32 %), et que la prévalence du diabète diffère entre les départements (56) (de 2,8 à 6,5 % de la population). Se pose alors deux questions :

- l'effet du statut diabétique sur la probabilité de démarrer en DP diffère-t-il d'un département à un autre ? Témoin d'une différence de pratiques par exemple ?
- l'hétérogénéité entre les départements est-elle due aux différences entre les patients traités dans ces départements (case-mix) ? Autrement dit, à patient égal cette hétérogénéité disparaît-elle ?

L'utilisation d'un modèle hiérarchique sur les patients incidents 2009/2010 du registre REIN permet de montrer les résultats suivants (Figure VI.1) :

- il existe une variabilité statistiquement significative entre départements en faveur d'un « effet département » sur la probabilité de démarrer en DP ;
- il existe une hétérogénéité entre départements qui n'est pas due au case-mix des patients : la variabilité reste statistiquement significative après introduction des facteurs patients (diabète et âge) ;
- l'association entre diabète et démarrage en DP diminue de façon importante lorsque que l'on tient compte de l'effet du département (OR 0,98 [IC 95 % 0,97-0,99] versus OR 0,79 [IC 95 % 0,72-0,88]). Le département étant un reflet des pratiques médicales dans le département, il agit comme médiateur dans la relation entre diabète et démarrage en DP ;
- l'effet du statut diabétique sur la probabilité de DP diffère d'un département à un autre : dans certains départements, le fait d'être diabétique n'est pas lié à la probabilité de démarrer en DP alors que dans d'autres départements, les diabétiques démarrent plus rarement en DP. Ayant mis en évidence des différences de pratiques importantes entre départements (un effet différentiel du diabète sur la probabilité de démarrer en DP), il est licite d'essayer d'expliquer ces pratiques par des caractéristiques des départements. Pour cela, des variables sont introduites dans le modèle au niveau département, comme, par exemple, la variable dichotomique « département à forte prévalence de diabète » ;
- aucune association significative n'est retrouvée entre le fait d'être traité dans un département à forte prévalence de diabète et la probabilité d'être traité initialement par DP ;
- « L'effet département » sur la mise en DP n'est pas lié à la prévalence du diabète dans le département.

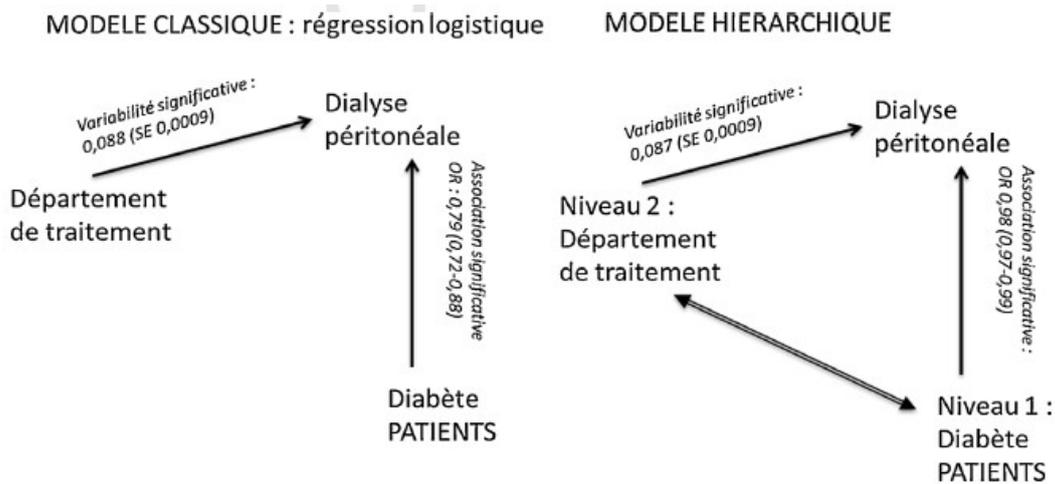


Figure VI.1: Représentation schématique des relations entre les caractéristiques des patients et de l'environnement sur la probabilité de bénéficier de dialyse péritonéale

3. Exemples d'utilisation dans la littérature

1) Facteurs influençant le devenir des patients

Un article publié par Dudley et al. (21) utilise un modèle de régression logistique hiérarchique afin d'étudier l'accès à la liste chez les adultes au Royaume-Unis. Ce modèle permet de mettre en évidence des variables individuelles (variables patients) associées à la probabilité d'être inscrit sur liste :

- âge du receveur ;
- maladie rénale initiale ;
- nombre de transplantations ;
- origine ethnique ;
- niveau social ;
- variables concernant les centres : taille du service (évalué en nombre de patients), importance du programme de donneur vivant et pourcentage de receveurs de donneur vivant inscrits sur liste.

Par ailleurs, un effet-centre non expliqué persistait après ajustement sur les variables patients et centre.

Il est également possible d'étudier l'effet du centre de traitement en appliquant un modèle hiérarchique dans une analyse de survie. Asrani et al. utilisent un tel modèle (modèle de survie à risque proportionnel hiérarchique) afin d'étudier l'effet du centre sur la survie des greffons hépatiques à un an aux États-Unis (57). Les variables individuelles significativement associées à la survie du greffon sont :

- l'âge du receveur ;
- le fait de présenter une hépatopathie alcoolique ou cholestatique ;

- la sévérité de la décompensation hépatique du receveur (score MELD) ;
- les caractéristiques du donneur représentées par le DonorRisk Index (DRI).

Par ailleurs, un effet significatif du centre de traitement est observé ($p < 0,001$), avec une déviation standard (DS) de l'HR à 0,29, indiquant que les centres se situant à 2 DS de la moyenne ont un risque de perte de greffon augmenté ou diminué de 58 %. La figure VI.2 permet de représenter l'importance de l'effet du centre en comparaison aux autres variables.

Enfin, les auteurs essaient d'expliquer cet effet du centre de traitement en introduisant le volume du centre dans le modèle, sans montrer de corrélation entre le volume du centre et la survie des greffons.

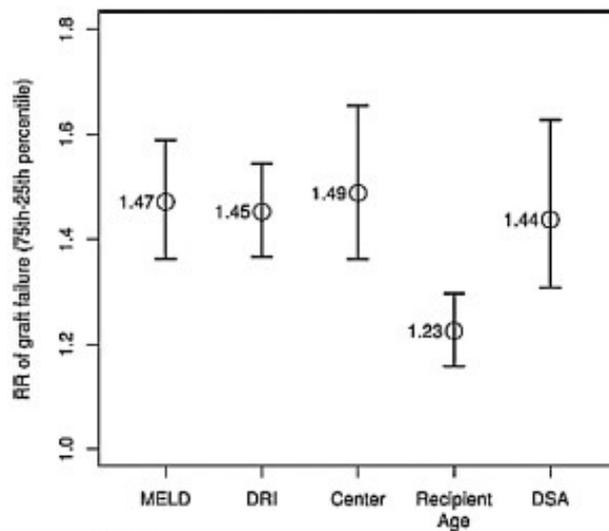


Figure VI.2: Risque relatif de perte de greffon des patients du 75^{ème} percentile versus 25^{ème} percentile des variables étudiées après ajustement sur les caractéristiques des donneurs, des receveurs et sur les conditions de la transplantation. D'après Asrani et al. (57).

2) Variabilité inter- et intra-individuelle des mesures biologiques

Agarwal et al. (58) ont étudié, grâce à un modèle hiérarchique, la variabilité des mesures de débit de filtration glomérulaire (DFG) chez des hommes avec une néphropathie diabétique ayant bénéficié de mesures successives du DFG, permettant de mettre en évidence une variabilité importante du DFG d'un mois à l'autre en tenant compte de la corrélation des mesures réalisées chez un même patient.

3) Modèle hiérarchique dans une méta-analyse

L'un des problèmes soulevés par la réalisation de méta-analyses est l'hétérogénéité potentielle entre les études utilisées. Cela est d'autant plus vrai lorsque l'on sort du cadre des méta-analyses d'essais thérapeutiques randomisés. En effet, il est alors nécessaire de prendre en compte la variabilité inter-études dans l'analyse, ce que permet l'utilisation de modèles hiérarchiques. La méta-analyse de

Haase et al. (59) portant sur les valeurs diagnostique et pronostique du dosage de Neutrophil Gelatinase-Associated Lipocalin (NGAL) dans l'insuffisance rénale aiguë (IRA) illustre l'utilisation de cette méthode. En effet, bien que compilant des études réalisées auprès de populations très différentes (portant tantôt sur une population pédiatrique, tantôt sur une population adulte, incluant ou non des patients ayant une insuffisance rénale chronique), avec des résultats en terme de qualité diagnostique différents (sensibilité variant de 44 à 100 % et spécificité variant de 38 à 100 %), et des valeurs limites de NGAL très variées (de 10 à 450 ng/ml), les auteurs parviennent à obtenir une estimation des sensibilité et spécificité de NGAL (respectivement 76,4 % et 85,1 %) et d'une région de confiance. Ils mettent également en évidence que la concentration de NGAL permettant les meilleures sensibilité et spécificité dépend de la cause de l'IRA et de l'âge du patient donnant néanmoins 150 ng/ml comme cut off consensuel.

Bien que non développée dans cet exemple, cette approche permet, outre une meilleure estimation de la valeur pronostique du test étudié, d'obtenir des informations sur l'origine de l'hétérogénéité inter-étude (par exemple si elle est due principalement aux différences de valeurs seuils ou non).

4. Limites des modèles hiérarchiques

En dehors de toute considération méthodologique, les difficultés principales de l'utilisation de modèles hiérarchiques sont la définition du niveau de regroupement et le choix des variables explicatives au niveau du groupe et du patient.

Le choix du niveau de regroupement doit être guidé par l'hypothèse a priori d'un impact de ceux-ci sur l'événement de santé étudié et non pas pour des raisons de simplicité. Pour cette raison, les groupes administratifs ne sont pas forcément les plus pertinents, dans notre exemple, le regroupement par territoire de santé, voire par équipe médicale, plutôt que par département aurait peut-être été préférable.

Les variables explicatives au niveau des regroupements (niveau 2) doivent réellement expliquer des caractéristiques du groupe et non pas seulement servir de proxies à des données manquantes au niveau individuel. Si cela est évident pour des variables n'ayant pas d'équivalent au niveau individuel (par exemple, la présence ou non d'un CHU dans le département), il faut être vigilant dans le cas des variables agrégées. Dans notre exemple, l'effet du pourcentage de diabétiques dans le département et l'effet de la variable individuelle « être diabétique » sont différents et tous deux pourraient être importants dans l'explication du recourt initial à la DP au niveau individuel¹.

Enfin, tout comme les modèles classiques, les modèles hiérarchiques supposent l'indépendance entre les variables à chaque niveau.

L'une des critiques faites sur les modèles hiérarchiques est que l'effet du niveau de regroupement pourrait simplement refléter l'absence de certaines variables explicatives individuelles dans le modèle. C'est pour cela qu'il est important, d'une part, de disposer des variables individuelles pertinentes afin de les inclure dans le modèle et, d'autre part, d'avoir une hypothèse sur la façon dont les caractéristiques des niveaux de regroupement peuvent impacter l'événement de santé étudié (des pratiques différentes entre équipes médicales, par exemple).

Enfin, cette méthode permettant de modéliser des phénomènes plus complexes, elle est de fait plus compliquée à utiliser que les modèles classiques (60). Par exemple, le calcul du nombre de sujets nécessaires et de la puissance de l'étude est particulièrement compliqué. La puissance dépend à la fois du nombre de groupes et du nombre de sujets par groupe. À noter que les études de simulations estiment entre 30 et 50 le nombre minimal de regroupements pour obtenir des estimations précises des coefficients et de la variance résiduelle, alors que le nombre de sujets par groupe peut être faible (certaines études portent sur des paires de jumeaux avec donc seulement deux sujets par groupe). De plus, plus le modèle est complexe (ajout d'effets aléatoires, modèles non linéaires), plus l'interprétation des variances et leur explication par différentes variables deviennent compliquées.

Malgré ces limites, et même en l'absence de variables permettant d'expliquer l'effet observé au niveau 2, l'utilisation de modèles hiérarchiques permet une estimation plus exacte des coefficients de régression par la prise en compte de la structure hiérarchique des données et donc de la probable corrélation entre patients d'un même groupe. En mettant en évidence un effet du niveau 2 (« effet centre de traitement », par exemple), les résultats de telles études permettent d'orienter les futures analyses vers la description des pratiques par exemple. À l'inverse, si la variance est majoritairement liée au niveau 1, les futures études seront plus ciblées sur les caractéristiques des patients.

5. Conclusion

Les modèles hiérarchiques présentent de très nombreuses applications en médecine (recherche clinique, épidémiologie, méta-analyses...). Ils permettent à la fois de prendre en compte des déterminants impactant la santé à différents niveaux (individuel, groupe), mais aussi de tenir compte de la structure très souvent hiérarchique des données utilisées. Ces modèles sont particulièrement utiles pour l'évaluation des pratiques médicales qui est aujourd'hui une question d'actualité. Encore assez peu employés en néphrologie, l'utilisation de ces modèles pourrait permettre un éclairage nouveau sur les déterminants de la prise en charge et du devenir des patients souffrant de maladies rénales.

6. Pour en savoir plus

Le modèle en bref

Dans ce genre de modèle, un niveau 1 est défini, celui des individus (par exemple les patients) sur lesquels sont mesurés l'événement d'intérêt, et un niveau 2, qui représente le groupe (le département de traitement, par exemple). Un niveau 3 peut également être envisagé, par exemple la région de traitement.

Les modèles hiérarchiques ont été initialement développés pour l'étude de variables continues, l'équation 1 de base est donc similaire à une régression linéaire classique. Néanmoins, ils peuvent être généralisés à d'autres modèles (régression logistique, modèle de survie), en faisant l'hypothèse d'une distribution particulière de l'effet aléatoire au 1^{er} niveau (modèle logistique pour l'équation 2, par exemple).

$$\text{Équation 1. } Y_{ij} = \beta_{0j} + \beta_{1j}X_{ij} + \varepsilon_{ij}, \varepsilon_{ij} \sim N(0, \sigma^2)$$

$$\text{Équation 2. } \text{Logit}P_{ij} = \text{Log}(P_{ij}/1-P_{ij}) = \beta_{0j} + \beta_{1j}X_{ij}$$

Avec Y_{ij} , la valeur de la variable à expliquer pour le patient i du groupe j , et X_{ij} la valeur de la variable patient explicative du patient i du groupe j .

On suppose que les erreurs au niveau patient (ε_{ij}) au sein de chaque groupe sont indépendantes et réparties selon une distribution normale de moyenne 0 et de variance σ^2 .

Dans l'équation 2, modèle logistique, ε_{ij} n'apparaît pas car la variance au 1^{er} niveau est fixée par le modèle à $\pi^2/3$.

La particularité du modèle hiérarchique est que l'intercept (β_{0j}) et les coefficients (dans notre exemple β_{1j}) peuvent varier d'un groupe à un autre, comme en témoignent les équations ci-dessous :

$$\beta_{0j} = \gamma_{00} + \gamma_{01}C_j + u_{0j}, u_{0j} \sim N(0, \tau_{00})$$

$$\beta_{1j} = \gamma_{10} + \gamma_{11}C_j + u_{1j}, u_{1j} \sim N(0, \tau_{11})$$

Avec C_j la valeur de la variable groupe (C) du groupe j .

On suppose que les erreurs au niveau groupe (u_{0j} et u_{1j}) sont de distribution normale et de variance τ_{00} et τ_{11} .

En pratique :

- β_{0j} représente la valeur moyenne des patients du groupe j (après prise en compte des variables explicatives individuelles X) ;
- γ_{00} représente la valeur moyenne de l'ensemble des groupes (après prise en compte des variables explicatives groupe C) ;
- u_{0j} est l'écart du groupe j à la moyenne des groupes persistant après introduction des variables explicatives individuelles et groupes (et donc non expliquée). Tester l'existence d'une variabilité résiduelle entre les groupes consiste à tester l'hypothèse $H_0 : \tau_{00} = 0$.

De la même façon :

- β_{1j} représente le coefficient moyen associé à la variable individuelle X des patients du groupe j ;
- γ_{10} représente la valeur moyenne du coefficient sur l'ensemble des groupes ;
- u_{1j} est l'écart entre la valeur du coefficient β_{1j} du groupe j et la moyenne des coefficients des groupes persistant après introduction des variables explicatives individuelles et groupes. Tester si l'effet de la variable individuelle X diffère entre les groupes consiste à tester l'hypothèse $H_0 : \tau_{11} = 0$.

Au total :

- on conclut à un « effet groupe » si $\tau_{00} \neq 0$ dans un modèle vide (sans variables explicatives) ;
- afin de tester si cet effet groupe est expliqué par le case-mix du groupe, l'on estime δ_{00} dans un modèle ajusté sur les variables individuelles (exemple : X) : si $\tau_{00} \neq 0$, alors il existe un « effet-groupe » non expliqué par les caractéristiques individuelles des patients ;
- pour essayer d'expliquer cet « effet groupe », des variables explicatives groupes sont introduites. Si $\tau_{00} \neq 0$ dans ce modèle, c'est qu'il persiste une variabilité entre les groupes non expliquée par les variables individuelles et groupes inclus dans le modèle.

Deux indices d'intérêt sont :

- le coefficient de corrélation intra-classe (CCI), qui mesure le degré de ressemblance des individus d'un même groupe ou la proportion de la variance expliquée au 2e niveau (niveau groupe) : $CCI = \tau_{00} / (\sigma^2 + \tau_{00})$,
- les pourcentages de modification de variance (PMV), qui quantifient la réduction de la variance après ajustement sur les variables individuelles (comparaison τ_{00} du modèle vide et τ_{00} du modèle ajusté sur les variables individuelles), puis après ajustement sur les variables groupes (comparaison entre τ_{00} du modèle ajusté sur les variables individuelles et τ_{00} du modèle ajusté sur les variables individuelles et centres).

L'exemple de la dialyse péritonéale

Tout d'abord, voyons si l'hétérogénéité inter-département est expliquée par les caractéristiques des départements. La variance au niveau département du modèle vide ($\tau_{00}(1)$) = 0,088 (SE 0,0009) est significativement différente de 0, il existe donc un « effet département » sur la probabilité de démarrer en DP. La variance du modèle après introduction des facteurs patients (diabète et âge) est de ($\tau_{00}(2)$) = 0,087 (SE 0,0009) et reste donc très significative. Le pourcentage de variance expliquée par ces facteurs patients est de 0,6 %. Il existe donc une hétérogénéité entre département qui n'est pas due au case-mix des patients.

Le deuxième constat est la modification de l'odds ratio associé au fait d'être diabétique. En effet, dans un modèle de régression logistique classique, les diabétiques ont une probabilité de mise en DP inférieure aux autres (OR 0,79 ; IC 95 % 0,72-0,88 après ajustement sur l'âge des patients). Cette association diminue de façon importante lorsque que l'on tient compte de l'effet du département (OR 0,98 ; IC 95 % 0,97-0,99). L'« effet département » agit comme un facteur de confusion dans la relation entre diabète et démarrage en DP.

La seconde question est donc de savoir si l'effet du diabète sur la probabilité d'être en DP varie d'un département à un autre. Pour cela, un modèle où le coefficient associé au diabète (β_{1j}) peut varier d'un département à un autre est testé (ces modèles sont dits « pentes aléatoires » car une erreur u_{1j} est ajoutée dans l'expression de β_{1j}). La variance du coefficient du diabète au niveau département (τ_{11}) = 0,090 (SE 0,0009) est significative, l'effet du statut diabétique sur la probabilité de DP diffère donc d'un département à un autre. Afin d'illustrer ce fait, l'OR du statut diabétique dans l'Allier est de 2,32 [0,90-5,95], alors qu'il est de 0,10 [0,01-0,80] en Haute-Garonne.

Ayant mis en évidence des différences de pratiques importantes entre départements (un effet différentiel du diabète sur la probabilité de démarrer en DP), il est licite d'essayer d'expliquer ces pratiques par des caractéristiques des départements. Pour cela, des variables sont introduites dans le modèle au niveau département (niveau 2), comme par exemple la variable dichotomique « département à forte prévalence de diabète » (taux standardisé de prévalence $\geq 4,51$ %). Aucune association significative n'est retrouvée entre le fait d'être traité dans un département à forte prévalence de diabète et la probabilité d'être traité initialement par DP (OR 1,02 ; IC 95 % 0,99-1,06). De même, la variance au niveau département reste inchangée ($\tau_{00} = 0,087$). « L'effet département » sur la mise en DP n'est donc pas lié à la prévalence du diabète dans le département.

Mise en œuvre

- Dans SAS, peuvent être utilisés les PROC NMIXED et PROC GLIMIX.
- Dans R, le package Linear and Nonlinear Mixed Effects Models (nlme) peut être utilisé.
- Dans STATA, la commande .MIXED peut être utilisée.

2. Disparities in access to renal replacement therapies: The choice of the first dialysis modality

Effect of center practices on the choice of the first dialysis modality for children and young adults.

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Introduction

Despite the numerous studies that aim to assess the best modality of dialysis treatment, results remain conflicting (36). In adults, differences in survival found in observational studies have been attributed to the different methods of case-mix adjustment to overcome selection bias, the different methods used to take into account the non-proportional risk over time and treatment switches and the use of different subgroups (37). Several studies that appropriately address the issue of case-mix difference between peritoneal dialysis (PD) and hemodialysis (HD) patients did not find any patient survival differences (38, 39) or only an early benefit of PD that disappeared with time (40). Moreover, Molnar et al. did not find any impact of pre-transplant dialysis modality on the risk of graft loss and delayed graft function (41, 42). This lack of strong medical evidence leads many commentators to emphasize the importance of patients' choice in the decision process considering the profound impact of this decision on patient's daily life (61, 62). However, several studies report an important discrepancy between the patients' wishes and the first modality used. Maaroufi et al, found that among patients choosing PD, only 50% actually received PD and that the cause of this mismatch was in half of the cases related to non-medical factors (63). Moreover, nephrologists' attitude is known to potentially influence the patient's choice since predialysis care and accurate information on the dialysis modalities is associated with an increased probability to choose PD (64).

Among children, PD has been widely considered as the modality of choice especially in the youngest ones mainly because of vascular access issues, better residual renal function preservation (65) and the lack of adequate HD devices. However, there is no clear evidence to support a better outcome in children treated with PD. Data from both USRDS and ANZDATA registries did not find any significant difference in patients' survival between HD and PD (53, 66). However, when focusing on younger children under 5 years old, Mitsnefes et al. found a decreased risk of death with PD that was not found in older patients (67). However, indication bias cannot be ruled out and a recent study from

the ESPN/ERA-EDTA registry did not find any difference in survival between HD and PD among children under one year old (45). Furthermore, there have been major technical improvements in HD for children, although not available everywhere yet, with the development of miniaturized circuit and high precision devices that allow higher dialysis clearances and more precise ultrafiltration control than PD without the need for blood priming (68, 69). Thus, as in adults, no strong evidence supports the choice of one modality rather than the other in children so that patient and family choices based on fair information and an adequate education should be pursued. Moreover, since 2002, all treatment centers are required to offer all renal replacement therapy (RRT) modalities either on their own or by developing cooperation with other centers (70). However, PD rate in France remains low when compared with other European countries and major geographical disparities has been reported among adults (71). Although variations in ESRD epidemiology between countries or regions might explain some of these differences, we hypothesize that non-medical factors and especially centers' practices may impact the choice of the dialysis modality. In this study, we try to assess factors that impact the choice of dialysis modality in children and young adults and sought to determine the respective roles of medical factors and center practices.

Material and Methods

We considered for inclusion all incident patients < 20 years at start of RRT, recorded in the French RRT Registry: "The Renal Epidemiology and Information Network" (REIN) between January 1, 2002 and December 31, 2013. Organization, data collection, and quality control of the REIN registry have been described elsewhere (4). The French Advisory Committee on Information Processing in Material Research in the Field of Health (CCTIRS) and the National Commission for Information Technology and Privacy (Commission Nationale de l'Informatique et des Libertés) approved in 2003 the data collection and the analysis conducted by the REIN registry.

Relevant patient characteristics recorded in the REIN registry were gender, primary renal disease (PRD), the year and age at start of RRT, starting RRT in an emergency setting (defined as an immediate RRT start for life-threatening condition), height, weight, place of residence (municipality and geographic location) and treatment center. Comorbidities (high blood pressure, heart failure, neurological impairment, chronic respiratory insufficiency and cancer) were also recorded at baseline.

We used the Network Analyst module from ARCGIS (72) to calculate the distance between the home address and the center of treatment. Because the registry does not include relevant socioeconomic data for children and their family, we used the municipality of residence as a proxy and crossed our database with unemployment, median income and educational level data from the French National

Institute of Statistics and Economic Studies (INSEE) to investigate possible associations with social factors.

Missing data were handled by using multiple imputations with a Markov chain Monte Carlo (MCMC) method (73).

The center's characteristics studied were: pediatric specialization, kidney transplantation provided (3 categories: no transplantation at all, transplantation following dialysis only, both preemptive and post-dialysis transplantation available) and the rate of patients treated with PD in the center.

Univariable association between explanatory variables and the probability of starting with PD was studied by Chi-square test and Student-t test for qualitative and quantitative variables respectively. Quantitative variables were tested for linearity and were dichotomized in classes if the association was found to be nonlinear. All variables with a p-value less than 0.2 were included in the multivariable analysis. We used multivariate hierarchical logistic regression models (60) to study patient and center characteristics associated with the probability of starting with PD. The effect of the centers was assessed by including centers as a random effect. When appropriate we tested some patient characteristics as random slope in order to study whether the effect of those variables may be different from one center to another. We studied three models: Model 1 is an empty model (not adjusted for the characteristics of patients or centers), while model 2 studied the centers' effect after adjustment for patients' characteristics. Finally, we tried to explain the variability between centers by further including center fixed effects in the models (Model 3). Center effect was assessed by studying the second level residual variance (τ_{00}) in the three models. We also evaluated the proportion of the variance in outcome between centers by calculating the intraclass correlation coefficient [$ICC = \tau_{00} / ((\pi^2/3) + \tau_{00})$].

In order to test the robustness of our results, we performed several sensitivity analyses: the first including only patients older than 15 years old, the second excluding centers that only perform hemodialysis, the third only including patients under 18 years, the fourth one excluding patients who started their treatment in emergency, and the last one only including specialized pediatric centers.

All tests were performed at an α -risk of 0.05. Statistical analysis was performed using SAS 9.2.

Results

The study included 806 patients younger than 20 years old who started RRT in 177 centers. Among them, 601 (74.6%) started with HD while 205 (25.4%) started with PD. Table VI.1 describes the patients' characteristics at start of RRT. The univariable analysis found the following patients' characteristics to be associated with a higher probability to start with PD: younger age, congenital

abnormalities of the kidney and the urinary tract (CAKUT) or hereditary nephropathy as PRD, short stature (height $<-2SD$), and living far away from a dialysis center (travel time > 20 minutes). Hypertension as well as starting RRT in emergency was associated with a decreased probability of PD whereas patients with a history of neurological impairment had an increased probability of being treated with PD. We also found a negative correlation between the local unemployment rate and the probability of being treated with PD. Patients with missing data did not differ from the others considering the compulsory data (age, gender and primary renal disease, data not shown).

Among the 177 centers, 23 (13%) were specialized pediatric centers in which 62% of patients in our cohort were treated. There were 48 centers (27.1%) that performed renal transplantation (18 pediatric centers (78%) and 30 adult centers (20%)) and 65 centers (36.7%) that performed PD. Centers' characteristics are summarized in Table VI.2.

The hierarchical model (model 1) showed significant variability between centers (residual variance 2.46 [0.41-4.52]) that accounted for 43% of the total variability (ICC). Because this variability persisted after adjustment for patient level variables (Model 2: residual variance 3.28 [1.20-5.72]), patient characteristics did not explain the variability between centers in the probability to perform PD as first treatment modality. However, after including center variables (Model 3), variance decreased and was no longer significantly different from 0 meaning that the remaining center effect was fully explained by the center characteristics included in the model.

In this final model, we found a higher probability of PD as first RRT modality in younger children (OR 45.8 [12.2-171.6] in patients under 4 years old and 6.2 [2.5-15.5] in patients between 5 and 9 when compared to patients aged 15 to 19 years old). Among 88 patients younger than 2 years old, only 18 (20%) were treated with HD. Starting the treatment in emergency remained strongly associated with a low use of PD (OR 0.3 [0.2-0.6]) and this effect seemed to be consistent among centers. Considering the time to travel to the treatment center, there was a significant interaction with the age of the patients ($p<0.001$). The probability of PD significantly increased with travel time to the treatment center among patients over 15 years. On the contrary, we found a negative association between the probability of PD and travel time to the treatment center in younger patients. Among socio-economic factors, educational level in the hometown (high school completion rate) was the only one associated with the probability of starting with PD mostly driven by an increased probability of PD in the second quartile (OR 2.0 [1.1-3.8]). Being treated in a specialized pediatric center was significantly associated with a decreased probability of starting dialysis with PD (OR 0.2 [0.1-0.6]), while the probability of PD was proportional to the rate of PD in the center (OR per 10% increase in PD rate 2.3 [2.0-2.6]). The presence of a transplantation unit in the center did not significantly impact the choice of the dialysis

modality although there was a trend towards a higher use of PD in centers providing kidney transplantation (Table VI.3).

The results from the five sensitivity analyses were consistent with those of the main analysis considering both patients' characteristics associated with PD and the effect of the center of treatment. Among the 23 specialized pediatric centers the median percentage of PD was 23.1% [12.5-50.0%]. In patients older than 15 years old, being treated in a pediatric center remained strongly associated with a decreased probability of PD and the travel time was found significantly correlated to the probability of PD. The results of these analyses are presented as Supplemental data.

Discussion

In this study we confirm that, besides patients' medical characteristics, the centers' practices play a major role in the choice of dialysis modality among children in France.

Despite conflicting results on the long-term outcome of PD versus HD treatment and recent technological development in pediatric HD (67), PD remains the preferred treatment in the youngest children. These results are consistent with the data from the NAPRTC study showing that 96% of the patients below two years old started with PD when this number was decreasing to 59% in adolescents (74). A possible explanation is the difficulty to create arteriovenous (AV) access in young children so that a percutaneous catheter is needed to perform HD. Vascular access sparing in children that will probably need HD and renal transplantation later in life and the risk of catheter infection may lead nephrologists to favor PD in this age group (75). Starting treatment in an emergency was associated with a decreased probability to start with PD. Our results corroborate the conclusion of a recent meta-analysis that found that PD uptake was twice as common in patients referred earlier to a nephrologist (76). However, recent guidelines stated that PD is a suitable treatment of acute kidney injury (AKI) in children (77). Observational studies have shown no difference in mortality between children treated with PD and those receiving CVVH for AKI (78, 79). This underlines the fact that PD can be used to treat unprepared patients reaching ESRD.

Socio-economic factors have been found related to dialysis modality use in the literature. Among adult patients in the US, the use of home dialysis modalities, especially PD, decreases with the travel distance to the closest in-center dialysis facility (80). In our study, we similarly found an increased probability of PD therapy with the travel time between home and treatment center in the oldest patients aged over 15 years old. However, this effect was not found in the younger patients and

especially in the youngest ones who displayed an inverse correlation between travel time and the probability of PD. Although unexpected, this result may reflect the fact that in the youngest patients the possibility to quickly go from home to the treatment center in case of problem helps deciding to undergo home PD. Considering social factors, we found a tendency towards a decreased probability of PD in patients living in towns with both the highest and the lowest education level rates. Data on the relationship between socio-economic status and dialysis modalities vary greatly between countries. In the US, the type of insurance and the type of employment was associated with the probability of being treated with PD but not the education level (81). In Australia and New Zealand a lower socio-economic status was associated with an increased probability of PD therapy (82) whereas in India PD patients had higher annual income and rate of university graduation (83). The lower rates of PD in patients with a lower socio-economic status may be related to both the lack of a home compatible with PD treatment, to a more demanding training of those patients in order to assure a good understanding of the treatment and to a higher rate of peritonitis. However, in France, specialized nurses paid by the national health care system can assist patients. This has been shown to allow the use of PD at home in the elderly (84). A greater resort to specialized nurses in pediatric patients may allow a greater use of PD that actually mainly rely on the parents' ability and will to perform this treatment.

An important finding of this study was the major role of the center of treatment in the choice of the dialysis modality, which accounted for almost half of the decision (ICC=43%). Unexpectedly, among patients older than 15 years, pediatric centers tended to favor HD when compared with adult centers with only 6% of those treated in pediatric centers undergoing PD compared with 17.5% of those treated in adult centers. Our findings are in opposition to those published by Furth et al., who found that the use of PD increases with the pediatric expertise of the facility (85). This underlines the major variability in dialysis practices between countries and centers (86). In our study, the probability of starting RRT with PD was directly proportional to the rate of PD performed in the center. This clearly shows that the attitude of the doctors towards PD is almost as important as the patient's medical condition and wish in the decision process. A survey among French nephrologists found that although factors like the lack of specialized nurses to promote home assisted PD, limited training or low reimbursement of PD participate in the overall low PD rate in France, regional discrepancies were strongly associated with the nephrologists' opinion on PD (87).

Moreover, on the one hand, the rate of PD among patients under 20 years is only 25% in our cohort which is lower than what is found in other countries (for instance in the UK, about 60% of the pediatric dialysis patients start on PD) (88), despite a trend to an increased use of PD in children in

France (30). On the other hand, studies focusing on patient preferences found that patients approve by a large majority home-based dialysis modalities. In the UK, Little et al. demonstrated in adults that 45% of patients chose PD and that the probability of choosing PD increased with pre-dialysis counseling (89, 90). Furthermore, Wuerth et al. found that among 40 patients interviewed, all those treated with PD reported choosing their treatment modality while only 8 patients over the 20 treated with HD did so. 83% of the patients reported that their physician was important in influencing their choice (91). Several pediatric studies focused on the Quality of Life (QOL) of the patients and their parents; however no modality showed a clear benefit over the other in term of QOL (92, 93). In a recent study from Brazil, no difference was found in QOL between pediatric patients treated with PD compared to those treated with HD but PD was associated with a higher QOL in the patients' parents (94). However, there is to date no study on parents' choice regarding dialysis modality for their children, on factors influencing this choice and on the adequacy with the treatment finally provided.

The main strength of our study is its use of a hierarchical logistic model that allowed to demonstrate the effect of centers on the decision process and to quantify this effect. Moreover this model takes into account the correlation between patients treated at the same center and thus allows more accurate estimation of ORs and their confidence intervals than models usually used to study hierarchical data. Another advantage of this model is that it enables us to study several center characteristics to explain the variability between centers.

We acknowledge that this study has several limitations including the missing data in patients' characteristics and the lack of reliable individual socioeconomic data. However we used geographical proxies to assess these factors, which is now a widely used method. We studied the initial dialysis modality as the endpoint and did not study the changes in dialysis modality over time, however data from the REIN registry show that in patients younger than 20 years old less than 5% will be switched to PD so that the initial modality of treatment can reasonably be used as treatment modality. Modality failure is the main reason for switching from PD to HD (10% of the patients who started with PD after 6 months) so that non-medical factors should not play a major role in the decision (30). Considering centers' characteristics, we only had 3 variables (pediatric specialization, transplantation center and PD rate), the latest being derived from patients' data. The REIN registry is a registry of patients and does not collect data on the centers of treatment. Several characteristics such as the number of medical and paramedical employees, the presence of a nurse dedicated to PD or the number of HD generators would have been of interest to test whether centers' practices are affected by resources and not only by doctors' beliefs. We are also lacking data on patient and parent choices,

which precludes our assessing for certain how doctor and center practices may modify or take over these choices.

Conclusions:

Although little evidence exists to favor a dialysis modality over the other in children, HD remains the predominant modality in France. As previously described, PD is still mostly offered to the youngest children while it remains underused in patients starting RRT in emergency. However, we demonstrate that besides medical factors, center practices are a major factor in the choice of dialysis modality. This raises concerns about the place left to patient and family choices and to what extent doctors may influence the final decision. Further pediatric studies focusing on children and parents' wishes are needed in order to provide care as close as possible to patient and family expectations.

	Missing data	Pediatric centers N (%PD)	Adult centers N (%PD)	Total N=806	% PD in each class	p-value
Age (years)	0					<0,001
[0-4]		141 (67,4)	3 (100,0)	144	68.1	
[5-9]		89 (22,5)	5 (60,0)	94	24.5	
[10-14]		170 (15,3)	12 (16,7)	182	15.4	
[15-19]		100 (6)	286 (17,5)	386	14.5	
Gender	0					0.84
Male		279 (31,9)	184 (16,3)	463	25.7	
Female		221 (26,2)	122 (23,0)	343	25.1	
Primary renal disease	0					0.002
Glomerulonephritis		109 (19,3)	104 (15,4)	213	17.4	
Hereditary nephropathy		142 (38,0)	58 (27,6)	200	35	
CAKUT		117 (33,3)	35 (17,1)	152	29.6	
Vascular diseases		45 (28,9)	31 (12,9)	76	22.4	
Acute interstitial nephritis		29 (10,3)	21 (28,6)	50	18	
Miscellaneous		29 (27,6)	6 (33,3)	35	28.6	
Unknown		29 (31,0)	51 (15,7)	80	21.3	
Statural growth impairment	115					0.16
Absent		361 (27,9)	207 (20,4)	552	25.2	
Moderate (-2 to -3SD)		64 (31,3)	21 (19,1)	85	28.2	
Severe (<-3SD)		47 (36,2)	7 (42,9)	54	37	
Low BMI	132					0.88
Normal		395 (29,6)	189 (20,0)	584	26.5	
Moderate (-2 to -3SD)		44 (27,3)	19 (26,3)	63	27	
Severe (<-3SD)		21 (28,6)	6 (0,0)	27	22.2	
Hypertension	130					0.002
Yes		75 (20,0)	135 (16,3)	210	17.6	
No		327 (33,0)	147 (20,4)	474	29.1	
Heart failure	118					0.50
Yes		11 (54,6)	14 (14,3)	25	32	
No		394 (30,7)	269 (19)	663	25.9	
Neurological impairment	133					0.03
Yes		7 (71,4)	4 (25,0)	11	54.6	
No		388 (30,2)	274 (18,6)	662	25.4	
Chronic respiratory insufficiency	127					0.39
Yes		4 (25,0)	4 (0,0)	8	12.5	
No		393 (30,8)	278 (19,1)	671	25.9	
Cancer	123					0.22
Yes		10 (10,0)	6 (16,7)	16	12.5	
No		390 (31,3)	277 (18,8)	667	26.1	
Unemployment rate (in quartiles)	0					0.002
<8,6%		125 (36,0)	76 (32,9)	201	34.8	
[8,6%-12,0%]		125 (23,2)	74 (23,0)	199	23.1	
]12,0%-15,3%]		124 (27,4)	78 (5,1)	202	18.8	
>15,3%		126 (31,0)	78 (15,4)	204	25.0	
Emergency treatment	52					0.005
Yes		134 (21,0)	115 (12,2)	249	16.9	
No		337 (28,8)	168 (20,8)	505	26.1	
Travel time between home and treatment center (minutes)	0					0.03
< 20		158 (29,8)	172 (13,4)	330	21.2	
[20-40[128 (25,8)	78 (24,4)	206	25.2	
≥40		214 (31,3)	56 (28,6)	270	30.7	
Rate of inhabitants that completed high school (in quartiles)	0					0.13
≤ 32%		135 (25,9)	81 (24,7)	216	25.5	
]32%-39%]		121 (38,0)	78 (23,1)	199	32.2	
]39%-48%]		123 (31,7)	76 (13,2)	199	24.6	
>48%		121 (22,3)	71 (14,1)	192	19.3	
Median income of municipality of residence per year (in quartiles)	0					0.80
≤15594€		128 (28,1)	74 (14,9)	202	23.3	
]15594€-17431€]		110 (34,6)	92 (19,6)	202	27.7	
]17431€-19775€]		132 (25,8)	69 (14,5)	201	21.9	
>19775€		130 (30,0)	71 (26,8)	201	28.9	

Table VI.1 Patients' characteristics at RRT start and rate of PD by subgroup and type of center.

BMI: Body Mass Index

CAKUT: Congenital Abnormalities of the Kidneys and the Urinary Tracts

PD: Peritoneal Dialysis

Centers' characteristics	Pediatric centers (N=23)		Adult centers (N=154)	
	N	Column percent	N	Column percent
Transplantation				
No transplantation	5	21,7	124	80,5
No preemptive transplantation	9	39,1	17	11,0
Preemptive and post-dialysis transplantation	9	39,1	13	8,4
Peritoneal dialysis				
None	3	13,0	109	70,8
< 25% of the patients starting with PD	12	52,2	9	5,8
> 25% of the patients starting with PD	8	34,8	36	23,4

Table VI.2: Centers' characteristics

PD: Peritoneal Dialysis

Patients' and Centers' characteristics	Model 2		Model 3	
	OR	95% Confidence Limits	OR	95% Confidence Limits
Age (years)				
[0-4]	33,36	[11,12-100,11]	45,78	[12,21-171,58]
[5-9]	4,36	[1,99-9,59]	6,21	[2,48-15,53]
[10-14]	1,55	[0,73-3,28]	2,27	[0,85-6,05]
[15-19]	1,00		1,00	
Gender				
Male	1,1	[0,66-1,83]	1,10	[0,64-1,89]
Female	1,00		1,00	
Primary renal disease				
Glomerulonephritis	0,70	[0,27-1,77]	0,93	[0,44-1,94]
Hereditary nephropathy	0,87	[0,36-2,14]	1,07	[0,58-1,97]
Unknown	0,69	[0,27-1,76]	1,54	[0,55-4,26]
Vascular diseases	0,49	[0,16-1,49]	0,71	[0,22-2,25]
Acute interstitial nephritis	0,67	[0,22-1,99]	0,55	[0,14-2,14]
Miscellaneous	0,54	[0,17-1,68]	0,70	[0,35-1,38]
CAKUT	1,00		1,00	
Statural growth impairment				
Absent	0,84	[0,33-2,17]	0,89	[0,35-2,23]
Moderate (-2 to -3SD)	0,82	[0,25-2,68]	0,74	[0,24-2,26]
Severe (<-3SD)	1,00		1,00	
Hypertension	0,62	[0,33-1,15]	0,69	[0,35-1,38]
Neurological impairment	4,17	[0,91-19,10]	3,29	[0,62-20,79]
Unemployment rate (in quartiles)				
<8,6%	3,49	[0,85-14,39]	1,41	[0,43-4,59]
[8,6%-12,0%]	1,27	[0,47-3,40]	0,80	[0,33-1,96]
]12,0%-15,3%]	1,11	[0,41-2,95]	0,86	[0,34-2,22]
>15,3%	1,00		1,00	
Emergency treatment	0,32	[0,19-0,54]	0,31	[0,17-0,56]
Travel time between home and treatment center (minutes)				
[0-4]ans				
< 20	2,96	[1,04-8,41]	4,57	[1,43-14,58]
[20-40[1,12	[0,44-2,85]	1,53	[0,58-4,08]
≥40	1,00		1,00	
[5-14]ans				
< 20	0,27	[0,10-0,72]	0,21	[0,01-12,2]
[20-40[0,53	[0,18-1,62]	0,50	[0,19-1,33]
≥40	1,00		1,00	
[15-19]ans				
< 20	0,44	[0,09-2,10]	0,18	[0,03-0,99]
[20-40[0,41	[0,10-1,69]	0,2	[0,05-0,91]
≥40	1,00		1,00	
Rate of inhabitants that completed high school (in quartiles)				
≤ 32%	1,13	[0,44-2,87]	1,05	[0,42-2,62]
]32%-39%]	1,98	[1,00-3,89]	2,02	[1,07-3,82]
]39%-48%]	1,24	[0,65-2,34]	1,39	[0,76-2,53]
>48%	1,00		1,00	
Type of center				
Pediatric center			0,23	[0,09-0,58]
Adult center			1,00	
Transplantation center				
No transplantation			0,57	[0,31-1,05]
No preemptive transplantation			0,70	[0,42-1,16]
Preemptive and post-dialysis transplantation			1,00	
Rate of peritoneal dialysis in the center (per 10% increase in DP rate)			2,32	[2,03-2,64]

Table VI.3: Odds ratio of starting with PD as first treatment associated to patient and center characteristics.

CAKUT: Congenital Abnormalities of the Kidneys and the Urinary Tracts

3. Disparities in access to renal transplantation

Many disparities in access to renal transplantation have been reported based on patients' medical and non-medical characteristics and also between countries. Two steps are necessary in order to get a renal transplantation; the first one is the registration on the renal transplant waiting-list depending on the time to assess the patient suitability for transplantation and to perform the pre-transplant check-up. The second one is the procurement of a transplant that also depends on the policies of kidney allocation. Those policies vary from one country to another. Harambat et al. reported on the different policies of kidney allocation within Europe (Table VI.4) (95).

Organization (countries)	Allocation of kidneys to children
Eurotransplant (Austria, Belgium, Croatia, Germany, the Netherlands, Slovenia)	Recipients <16 years receive waiting time extra points Since 2010: Recipients older than 16 years old are also granted the pediatric bonus if growth potential still exists and donors <16 years are preferentially offered to pediatric recipients <16
Scandiartplant (Denmark, Finland, Norway, Sweden, Iceland)	Donors <40 years are offered to recipients <16 years as long as there is DR compatibility and no more than 2 HLA-A or-B mismatches. Additional national priorities are available in some countries
Agence de la Biomédecine—ABM (France)	Recipients <18 years have national priority for donors <18 years and regional priority for donors <30 years. If RRT has started <18 years, pediatric priority is prolonged after 18
Autoridade dos Serviços de Sangue e Transplantação—ASST (Portugal)	Recipients <18 years have national priority (points score) for donors <18 years
Centro Nazionale Trapianti—CNT (Italy)	Donors <15 years are offered to recipients <18 years
National Transplant Coordinating Centre—KST (Czech Republic)	Recipients <19 years have national priority for pediatric and adult donors (after full HLA matching and urgent KTx)
Direction for Biomedicine (Serbia)	Recipients <21 years have regional priority for donors <30 years
Hellenic Transplant Organization (Greece)	Recipients <16 years double their points score
Hungarian National Blood Transfusion Service (Hungary)	Recipients <18 years have national priority (points score) for donors <30 years
National Organ and Tissue Transplantation Coordination System (Turkey)	Since 2008: Recipients <11 years double their points score (based on HLA matching). Score multiplied by 1.5 in recipients aged 11–18 years
National Organ Transplant Bureau (Lithuania)	Recipients <18 years have national priority (extra points)
NHS Blood and Transplant (UK)	Recipients <18 years have national priority (points score) for HLA well-matched kidneys (no DR and no more than 1 HLA-A or -B mismatches) for donors <50 years Since 2009: pediatric priority is prolonged after 18 years if RRT has started <18 years
Organizacion Nacional de Trasplantes—ONT (Spain)	Recipients <15 years have national priority for donors <15 years, specific algorithms vary by regions (several regions give pediatric priority for donors <40 years)
Poltransplant (Poland)	Recipients <18 years have national priority (points score) for donors <16 years
Slovak Centre for Organ Transplantation (Slovakia)	Recipients <19 years have national priority for pediatric and adult donors (after full HLA matching and urgent KTx)
Swisstransplant (Switzerland)	Recipients <20 years have national priority for donors <60 years (after urgent transplantation)
Tartu University Hospital (Estonia)	Donors <30 years are preferentially offered to recipients <16 years

Table VI.4: Pediatric kidney allocation schemes in Europe (From Harambat et al)

In France, recipients younger than 18 years old have national priority to receive from donors younger than 18 years old and regional priority from donors younger than 30 years old. If RRT has started before 18 years old, pediatric priority can be prolonged until procurement of the first transplant if requested.

Access to the renal transplant waiting-list in France

Rapid Access to Renal Transplant Waiting List in Children: Impact of Patient and Center Characteristics in France

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Introduction

Renal transplantation is nowadays recognized as the treatment of choice for end-stage renal disease (ESRD) in both adults and children. It is associated with improved survival: transplantation in children has been shown to increase life expectancy by 20 to 40 years, compared with patients who remained on dialysis (29, 30). It is also associated with a better quality of life (31-33) and with better long-term cost effectiveness (34, 35).

Despite the World Health Organization recommendations of equitable access to transplantation, studies demonstrate important inequalities in access to the cadaveric donor waiting list for adult patients in both the United States and Europe. Although some medical conditions explain a portion of these inequalities, non-medical factors also influence the probabilities of being listed and transplanted. Among these factors, some are patient characteristics such as gender (8, 9, 14, 96-98), race (10, 14, 97-99), educational level (100), and place of residence (municipality). Other factors are characteristics of the hospital center, such as its size (21-23), ownership of dialysis facilities (eg, for profit or not-for-profit) (24), and the presence of a transplantation program (9, 10, 25, 26).

Studies of children in the United States and in the United Kingdom report similar results: girls and non-white patients have a lower probability of being listed (10, 96, 98, 101). Few studies, however, have investigated characteristics of both patients and centers simultaneously in children.

In France, despite a very high rate of transplantation among children and an overall rapid access to transplantation in this population (median waiting-time during the 2008-2012 period: 7.3 months)(102) because of a strong pediatric priority (95), public health decisions' makers are still promoting faster access to renal transplantation mainly because of the association between dialysis duration and long term cardiovascular events (103). Moreover, because of the repartition of

transplant at a national level, the time it takes to register on the waiting list is most likely the explanation for the variation from one center to another.

In this nationwide study, we sought to ascertain the influence of patient and center characteristics on rapid access to the renal transplant waiting list for pediatric patients (younger than 18 years).

Subjects and Methods

Population study

We considered for inclusion all children in the French ESRD National Registry, REIN, who started renal replacement therapy (RRT: hemodialysis, peritoneal dialysis, or preemptive transplantation) between 1 January 2002 and 31 December 2011, aged < 18 years at RRT onset. The organization, data collection, and quality control of the REIN registry have been described elsewhere (4).

Since in France all patients awaiting a transplant have to be registered on the renal waiting list, patients planned to receive a transplant from a living donor (LD) were also included in the study (10-15% of transplantation per year are from LD). Patients undergoing preemptive transplantation were also included in the analysis as our aim was to evaluate practices of early inscription on the waiting list and rapid transplantation. Patients were followed through 30 June 2012 or until death, so that all surviving patients have at least 6 months of follow-up. Some of those patients may have reached 18 years during the follow-up

Information collected

Patients' characteristics

Relevant patient characteristics recorded in the REIN registry were the year of and age at start of RRT, gender, primary kidney disease, height, comorbidities, disabilities (4), whether RRT began as an emergency, place of residence, center, and country of birth. From comorbidities and disabilities, we created the binary variables: has at least one comorbidity and has at least one disability. We determined growth retardation at RRT onset (for height) according to international standards for chronological age (104). We calculated the distance between the home address and the treatment center and between the home and the closest pediatric transplantation center with the ARCGIS module *Network Analyst*. Since the registry does not include relevant socio-economic data for children, we used the place of residence as a proxy and crossed our database with unemployment and median income data from the French National Institute of Statistics and Economic Studies (INSEE) to investigate the possibility that social factors influenced our results (105, 106).

Due to the great variety of primary kidney diseases in relation to the number of patients in our study, we grouped them in categories. Specifically, diseases were characterized by their coordinate values in the system of axes defined by the principal components of a multiple correspondence analysis based on seven items (immune renal injury, possible other immune injury, extrarenal vascular injury, possible extrarenal injury of other causes, genetic diseases and congenital abnormalities of the kidney and the urinary tract, possible post-transplantation recurrence of initial nephropathy, and urological abnormality). Diseases were then grouped by an ascending hierarchical classification (AHC) (5, 6), an iterative process, with an algorithm that starts with as many clusters as data items and builds up a tree by successively merging the two nearest clusters. We used pseudo F statistics to choose the threshold for stopping the classification, so that we created groups homogenous for the difficulty of transplantation. We thus obtained six groups that we named after their main shared criteria (vascular diseases, nephropathies with possible extrarenal immune injury, urological abnormalities, genetic or toxic abnormalities, risk of post-transplantation recurrence, and unknown).

Centers' characteristics

The center characteristics we considered were pediatric specialization (some adult center take care of 15-18 years old patients, especially in area where there is no pediatric centers), the proportion of patients on the waiting list placed on inactive status during the first month after listing, and the proportion of preemptive transplantations, categorized into two separate groups: one with the median proportion as the cut-off point, and the other categorized into two groups according to center size, with the third quartile as the cut-off point (based on the number of new patients treated in 2010/2011).

Statistical analysis

Rapid access to the waiting list was defined as being listed within 6 months after dialysis start or starting with a preemptive graft. The primary outcome was the probability of being listed within 6 months after starting RRT (start of dialysis or preemptive graft). We chose a binary outcome with a cut-off at 6 months in order to be able to give clinical guidelines to harmonize registration if any inequalities between centers were shown.

Logistic regression models were used to study the association between the patients' characteristics and the outcome. We first performed univariable logistic regressions on all the patient characteristics to determine which ones to include in our final models. All variables with a p-value greater than 0.2 were included in the multivariable logistic regression models. All continuous variables were tested

for linearity with the SAS macro LGTPHCURV9 (107); the age at start of RRT was included in the models as a restricted cubic spline (no linear relation).

We then assessed the center effect by a hierarchical multivariate regression that included the centers as a random effect. We studied three models: *Model 1* is an empty model (not adjusted for the characteristics of patients or centers), while *model 2* studied the center effect after adjustment for patients' characteristics. Afterwards, we tested patients' characteristics of interest as random effects to determine whether some associations varied among centers. Finally, we examined the variability between centers by including center fixed effects in the models (*Model 3*). Center effect was assessed by studying the second level residual variance (τ_{00}) in the three models. We also evaluated the proportion of the variance in outcome between centers by calculating the intraclass correlation coefficient [$ICC = \tau_{00} / ((\pi^2/3) + \tau_{00})$]. When we suspected an interaction between a center characteristic and a patient characteristic, we tested for cross-level interaction. Fifty-nine patients with missing data for variables selected in the multivariate analysis were not included in the analysis. We compared those patients to the 555 included in the multivariable analysis and found no significant difference on the variable included (age, primary kidney disease, year of RRT onset and starting treatment in emergency) except for gender with a higher proportion of girls in the group excluded (53% vs. 39%, $p < 0.05$).

We used the Kaplan-Meier method to plot the cumulative incidence curve, and the funnel plots method to present crude and adjusted variability between centers (108, 109). To assess the reliability of our findings, we performed two sensitivity analyses using the same model to predict inscription on the waiting list at 3 and 12 months after RRT, and a third that excluded patients treated by preemptive transplantation. We also tested our models only on the patients treated in pediatric centers to verify the reliability of our results. All tests were performed at an α -risk of 0.05. Statistical analysis was performed with SAS 9.2.

Results

Patient population

The study included 614 incident patients younger than 18 years who had started RRT in 54 centers; 421 (68.6%) were listed within 6 months after starting RRT (among whose 195 (31.8%) were registered and 119 (19.2%) were transplanted pre-emptively) and 556 (90.5%) were listed during the study period. The median time to registration was 3 months (Figure VI.3).

Access to the transplant waiting list

Table VI.5 summarizes the patients' characteristics when they started RRT.

The univariable analysis found the following patient characteristics associated with inclusion on the waiting list: age when RRT started, gender, primary renal disease, comorbidity factors, disabilities, emergency treatment onset, the distance between home and the treatment center and between home and the closest pediatric transplantation center, non-French birth, the year treatment started, and the median income of the place of residence. We did not find any association between the probability of listing and either growth retardation or the unemployment rate in the town of residence (Table VI.6).

Hierarchical multivariate logistic regression showed a higher risk of not being listed within 6 months after RRT in patients younger than 2 years, or with a renal disease included in a group with a high risk of recurrence after transplantation (OR 2.61; 95% CI [1.37-4.97]), or with possible extrarenal immune injuries (OR 4.33; 95% CI [1.30-14.41]). Interestingly, the risk for the group with vascular primary renal disease became non-significant after adding the variable of emergency RRT initiation (OR 2.58; 95% CI [1.46-4.56]). We also found a significant vintage effect: the probability of not being listed decreased over time (OR per 1 year +0.83, 95% CI [0.74-0.94]) (Table VI.6).

The association between gender and the probability of not being listed within 6 months after RRT did not remain statistically significant, but the trend toward disfavoring girls persisted.

Among the 54 treatment centers, the median rate of reaching the waiting list within 6 months after RRT was 61.5% IQ [31-80%]. Centers' characteristics are presented in Table VI.7.

The hierarchical model (*model 1*) showed significant variability between centers (residual variance: 0.623, SE 0.269) that accounted for 15.9% of the total variability (ICC). Because this variability persisted after adjustment for patient level variables (*Model 2*: residual variance: 1.012, SE 0.474), patient characteristics do not explain the variability between centers. Crude and adjusted funnel plots (Figure VI.4 and VI.5) that show outliers (centers outside the 99% confidence interval) present this variability. We found no significant difference between centers in the effects of gender, age, primary renal disease, and emergency RRT initiation on the probability of being listed within 6 months.

Finally, none of the centers' characteristics were significantly associated with the probability of the child's inscription on the waiting list within 6 months after ESRD began (Table VI.8). A significant center disparity remained after adjustment for all patient and center characteristics (*model 3*) (variance 1.288, SE 0.593). The results of the sensitivity analysis that considered the proportion of children reaching the waiting list within 3 months of starting RRT were similar for age, primary renal disease, emergency RRT start, and vintage effect.

At 12 months after the first RRT, 76.2% of patients were listed. The condition still associated with a lower probability of being listed was younger age (less than 2 years). In this model the probability of

being listed was no longer significantly associated with renal disease, nor was the risk of post-transplantation recurrence. The association with uropathies appeared to be significant (OR 2.73; 95% CI [1.09-6.83]). The same results were found for all patient characteristics when considering only patients with dialysis as the first RRT (n=496). The results found for pediatric centers alone were similar to those previously described (data not shown).

Discussion

In this nationwide, longitudinal study, we found that centers varied significantly in their speed of access to the renal waiting list for children, even after we took patients' characteristics, socio-economic factors, and some center specificities into account. We confirmed that younger age, starting RRT in emergency, and having renal diseases at risk of post-transplantation recurrence are associated with a lower probability of reaching the renal waiting list within 6 months of ESRD. We also observed a significant improvement in the rate of registration over time in France; it suggests that efforts to promote early wait-listing are effective and that it is now widely recognized as a good practice (the rate of unlisted patients at 6 months remained around 50% between 2002 and 2005 and then decreased regularly, reaching 31.5% in 2011). However, considering the short waiting-time among children in France, efforts to promote pre-emptive listing and transplantation are still to be made in order to avoid as much as possible dialysis in children.

The association between younger age and a decreased probability of being listed is mainly explained by the increased risk of thrombosis that motivates pediatric nephrologists to wait until patients weigh at least 9 to 10 kg.

Although there was a trend, we did not find a significant negative association between female gender and the probability of placement on the waiting list. This association has been known for a long time in adults (8, 9, 97) without real agreement on the reasons that produce this inequity and remains controversial in children.

A recent report by Garg et al. (96) studying a large cohort of patients younger than 20 years in the United States found a significant negative association between female gender and the probability of inscription on the waiting list. Some argue that this gender effect may be due to the difference in primary renal diseases between boys and girls.

Most of the previous studies used adult classifications to adjust for the initial renal disease (including diabetes, hypertension, lupus, and HIV-related illness), which might not be totally relevant for assessing the effect of child-specific diseases. To address this issue, we used a pediatric classification designed to be as predictive as possible of the ease of transplantation and of the need for additional

time for check-ups before transplantation. This might explain the absence of any significant effect of gender in our study.

Another interesting point is the absence of association between presenting a comorbidity or a disability and the registration on the waiting-list. One could imagine that some transplantation teams may hesitate to transplant patients with heavy comorbidity or deep mental retardation. Firstly, the absence of statistical association does not rule out this possibility because the little number of patients with such condition may decrease statistical power, secondly, comorbidities and disabilities are, in children, mainly related to their primary renal disease. The effect of the renal disease may be difficult to separate from associated pathological conditions.

Our sensitivity analyses for the primary renal diseases showed that although the result at three months after RRT were the same, at 12 months the uropathy group was significantly associated with wait-list status. This difference may be due to patients requiring complex urological surgery before transplantation.

Finally, in view of the clear benefits of rapid access to transplantation, our showing of a significant center effect for access to the waiting list, which is the first step towards transplantation, may enable improvement in our practices. Ravanan et al. (10), studying all the centers participating in the UK Renal Registry, found a significant inter-center variability in the time taken to register patients. According to the literature, center characteristics associated with a higher probability of listing are (larger) center size (21, 23), presence of a transplantation unit in the center (9, 10, 25, 26), and non-profit ownership of dialysis facilities (24). A recent study by Nguyen et al. (23) found similar results in the US pediatric population; the probability of listing was higher in high-volume (>6.76 transplants per year) compared to low-volume centers (<2.25 transplants per year).

Our study did not find a center size effect, but we considered the number of patients treated for ESRD in the center whereas Nguyen et al. considered the number of transplants performed. This may explain the different results. As nearly all centers in France were non-profit dialysis and transplantation centers, we could not evaluate the impact of the presence of a transplantation unit in the center or of the ownership of dialysis facilities. We also studied two other centers' characteristics: the proportion of patients on the waiting list placed on inactive status during the first month after listing and the proportion of preemptive transplantations. We did so because these are two characteristics that greatly vary between centers in France. In a descriptive study of centers' practices we showed that 29% of the centers declared registering the patient immediately, even if he is not eligible for transplantation, in order to gain priority on the list, whereas 71% declared not doing so (personal communication). This is mainly due to the fact that the priority rules in France

take into account the time spent on the waiting-list and not the time spent on dialysis. The same is true for the rate of preemptive transplantation that greatly varies from a center to another. However, none of these centers' characteristics were found to explain inter-center variability. Of note is the high rate of preemptive registration among children in France (31.8% vs. 14% in the Eurotransplant community) that still needs to be improved since preemptive transplantation showed a decreased of acute rejection and a trend towards a better graft survival (110).

The inter-center variability we observed in the time to wait-listing children was not fully explained by their characteristics. The main strength of our study is to demonstrate this inter-center variability among pediatric centers with a hierarchical logistic model. This model is more accurate for studying hierarchical data since it takes into account the correlation between patients at the same center and thus allows better estimation of the confidence intervals of odds ratios and of the residual inter-center variance. This model is also highly interesting because we can study several center characteristics to investigate the variability between centers.

We also created a systematic pediatric classification of the primary renal diseases to extract as much information as possible from this major factor. Another strength of our study is the high rate of transplantation among children in France, which augments the frequency of our primary outcome and thus increases our statistical power.

The limitations of our study are the lack of reliable socio-economic data for children, although the universal medical care system in France is likely to decrease inequalities in France, and the absence of evaluation of racial disparities, because such statistics cannot be kept in France. To take into account socio-economic status in our analysis we used pooled socio-economic data from the place of residence. Although, this is nowadays a common method it is important to remember that drawing conclusion at an individual level from pooled data is at risk of ecological fallacy.

We may also have omitted some characteristics of interest of some centers that may explain part of the center effect, such as a systematic organization for pre-transplant check-ups and inscription on the waiting list. Although all French centers are included in this study, there is a limited number of centers treating patients under 18 years in France; this affects the statistical power of our study to find significant center characteristics, as simulation studies suggest that at least 30 to 50 groups are needed to obtain precise estimates and that the variance components tend to be underestimated when the number of level 2 units (centers) is small (111, 112).

Conclusion

Although overall access to renal transplantation for children is good in France, this study confirms inequalities among children in rapid access to the renal transplant waiting list. We demonstrate that

both the patients' and the centers' characteristics may play a role in these inequalities. Further studies focusing on the centers' organization and practices of the centers are needed to explain the remaining variability. Pediatric studies recording the families' preferences and medical justifications for not listing are also needed.

Finally, this study should motivate us to standardize practices better nationally to offer care as evidence-based and as equitable as possible.

	Population description	
	N (Tot=614)	% non-listed within 6 months
Age		
[0-2 years-old[72	72.2
[2-5 years-old[59	18.8
[5-10 years-old[110	31.8
[10-15 years-old[194	36.6
>=15 years-old	179	42.5
Gender		
Male	365	37.0
Female	249	46.6
Primary renal disease		
Vascular diseases	54	63.0
Nephropathies with possible immune extra-renal injury	32	62.5
Urological abnormalities	78	34.6
Congenital or toxic abnormalities	230	25.2
Unknown	68	47.1
Risk of post-transplantation recurrence	152	52.6
Growth retardation	<i>(Missing=152)</i>	
No	365	45.5
Yes (Z-score<-2DS)	97	51.6
Presenting at least 1 comorbidity		
No	426	35.9
Yes	188	52.1
Presenting at least 1 handicap		
No	400	51.8
Yes	214	20.6
Emergency treatment	<i>(Missing=22)</i>	
No	435	34.5
Yes	157	59.2
Being born overseas	<i>(Missing=19)</i>	
No	523	38.6
Yes	72	52.8
	Médian	IQ
Hometown median income (euros) <i>(Missing=21)</i>	17894	[15677;20765]
Distance between home and treatment's center (km)	26	[7;67]
Distance between home and the closest pediatric transplantation center (km)	44.5	[13;92]
Hometown unemployment rate (%)	450.0%	[3,3;5,9]

Table VI.5: Patients' characteristics at renal replacement therapy onset and rate of non-listed patient within 6 months after RRT onset.

	Univariate analysis			Multivariate analysis	
	OR	CI 95%	p	OR	CI 95%
Age at ESRD			<0,0001	Φ	<0,0001
Gender			0.018		
Male	1				
Female	1.49	[1,07- 2,06]		1.41	[0,84; 2,35]
Primary renal disease			<0,001		
Vascular diseases	5.04	[2,69- 9,44]		2.24	[0,91; 5,52]
Nephropathies with possible immune extra-renal injury	4.94	[2,28- 10,73]		4.33	[1,30; 14,41]
Urological abnormalities	1.57	[0,90- 2,73]		2.14	[0,95; 4,82]
Congenital or toxic abnormalities	1			1	
Unknown	2.64	[1,50- 4,62]		1.85	[0,68; 5,05]
Risk of post-transplantation recurrence	3.30	[2,13- 5,10]		2.61	[1,37; 4,97]
Growth retardation			0.288		
No	1				
Yes (Z-score<-2DS)	1.28	[0,82- 2,00]			
Presenting at least 1 comorbidity			0.000		
No	1				
Yes	1.94	[1,37- 2,75]		1.42	[0,81; 2,49]
Presenting at least 1 handicap			<0,0001		
No	1				
Yes	0.24	[0,16- 0,36]		0.57	[0,30; 1,08]
Emergency treatment			<0,0001		
No	1				
Yes	2.76	[1,90- 4,02]		2.58	[1,46; 4,56]
Distance between home and treatment's center			0.0001		
OR per 1km increase	0.99	[0,989; 0,997]		1.00	[0,99; 1,01]
Distance between home and the closest pediatric transplantation center			0.005		
OR per 1km increase	0.99	[0,992; 0,999]		1.00	[0,99; 1,01]
Being born overseas			0.023		
No	1				
Yes	1.78	[1,08- 2,91]		1.27	[0,64; 2,54]
Vintage effect			0.0002		
OR per 1 year increase	0.88	[0,82- 0,94]		0.83	[0,74; 0,94]
Hometown median income			0.07		
OR per 100 euros increase	1.00	[1,00; 1,00]		1.00	[1,00; 1,00]
Hometown unemployment rate			0.32		
OR per 1% increase	1.04	[0,97; 1,11]			

Table VI.6: Odds-ratio of non-registration on the renal waiting list within 6 months after RRT onset associated to patients' characteristics.

Φ No OR is given for the age at start of RRT since it was included in the model as a restricted cubic spline.

Centers	Number of centers	Number of patients
Adultes	38	136 (22,2%)
Pediatrics	16	478 (77,8%)
	Médian	IQ
% preemptive transplantation	0%	[0;26,3%]
% patients inactivated on the waiting-list	25%	[0%;54,6%]
Number of new cases (2010-2011)	1	[0;3]

Table VI.7: Centers' characteristics

	OR	CI95%
Type of center		
<i>pediatrics</i>	1	
<i>adults</i>	0.43	[0,11; 1,74]
Preemptive transplantation		
<i>yes</i>	1	
<i>no</i>	2.1	[0,75; 5,87]
% patients inactivated on the waiting-list		
<i><25%</i>	1	
<i>>=25%</i>	1.2	[0,51; 2,84]
Center size (2009-10)		
<i>high volume (>3 new patients)</i>	1	
<i>low volume (<=3 new patients)</i>	1.3	[0,34; 4,97]

Table VI.8: Odds-ratio of non-registration on the renal waiting list within 6 months after RRT onset associated to centers' characteristics.

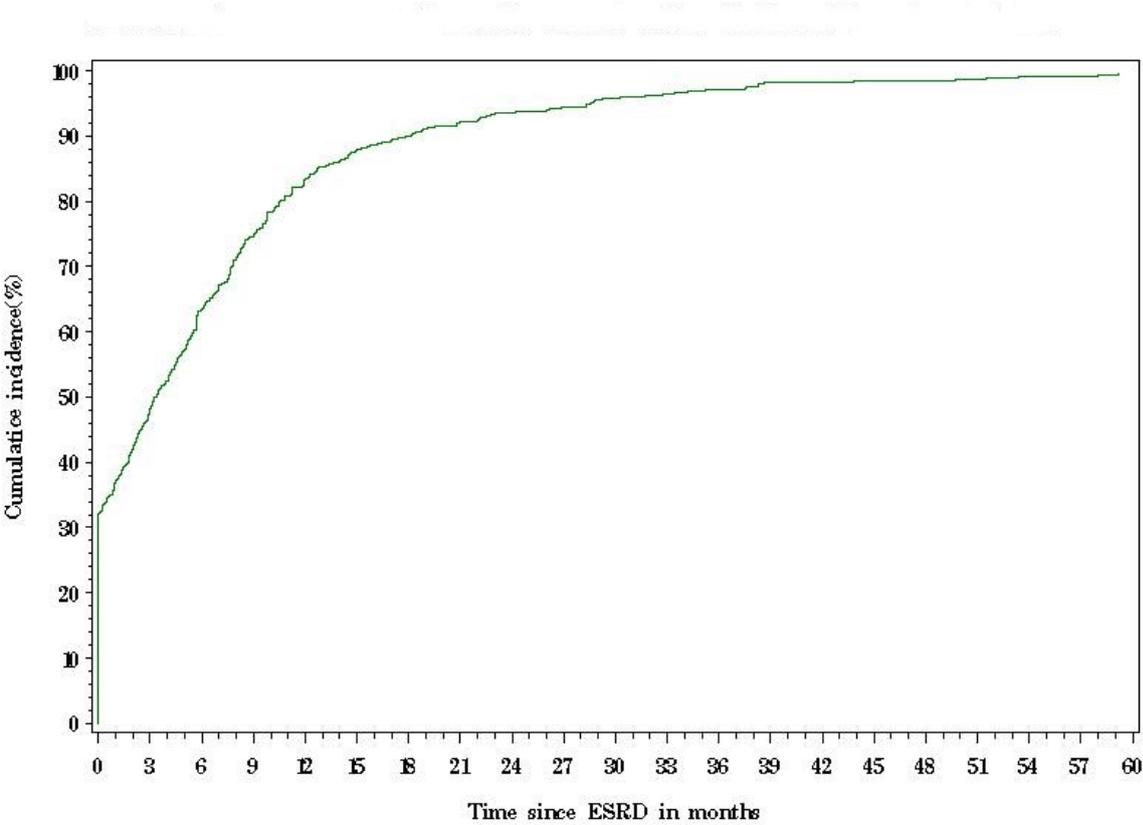


Figure VI.3: Cumulative rate of registration on the renal waiting list

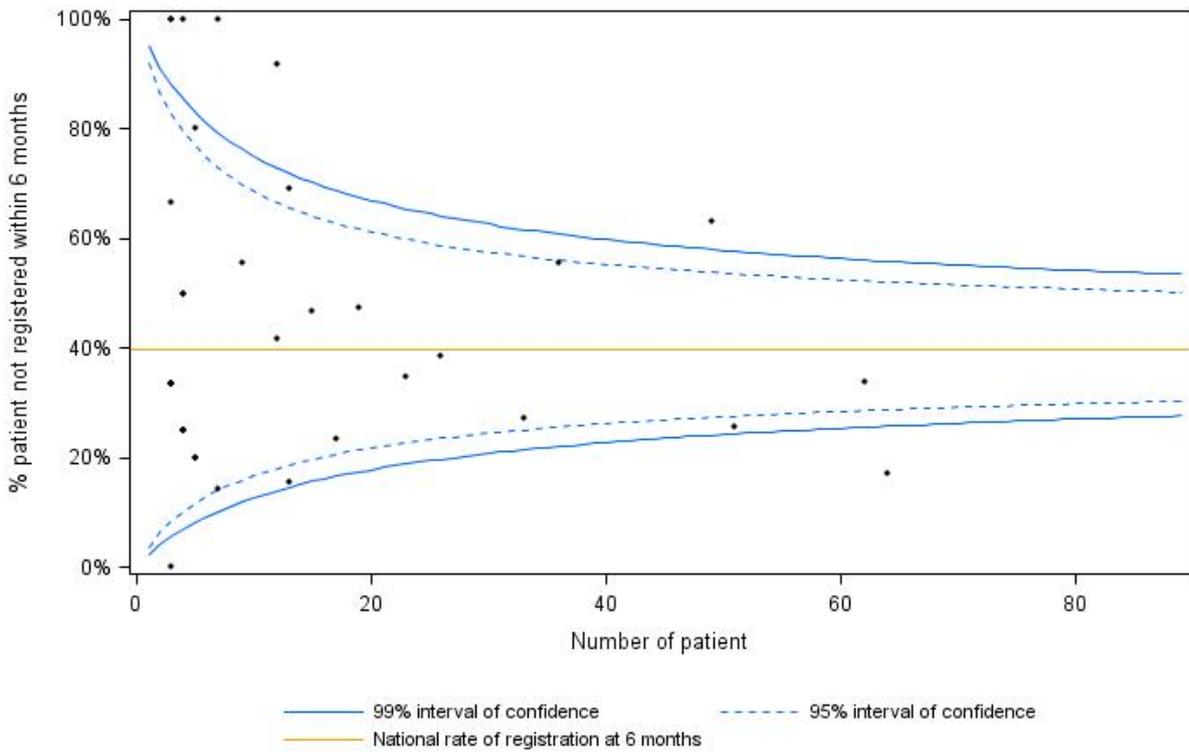


Figure VI.4: Funnel plot of crude centers' rate of non-inscription on the waiting list at 6 months

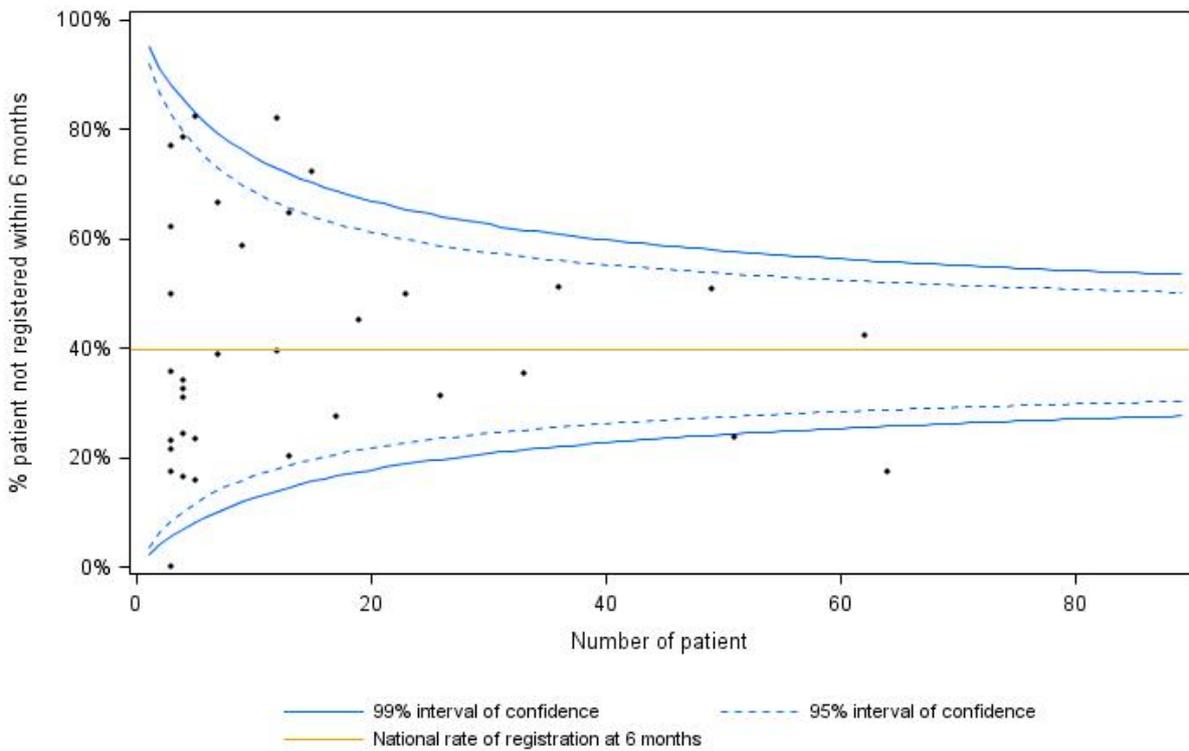


Figure VI.5: Funnel plot of adjusted centers' rate of non-inscription on the waiting list at 6 months

Are there good reasons for inequalities in access to renal transplantation in children?

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Introduction

Renal transplantation is recognized today as the first-choice treatment for both adults and children with end-stage renal disease (ESRD). It is associated with improved survival and has been shown to increase life expectancy by 20 to 40 years for children receiving kidney grafts, compared with those who continue to be treated by dialysis (30). It is also associated with a better quality of life (31-33) and with the best long-term cost-effectiveness ratio (34, 113).

Important inequalities in access to transplantation after acceptance on the waiting list exist for adults in both the United States and Europe. Although medical conditions explain some of these inequalities, nonmedical factors also affect the probability of receiving a transplant. Some of these are patient characteristics, including gender (9, 98, 99, 101), race (10, 97-99, 101), educational level (100), and place of residence (municipality) (9). Others are characteristics of the center, such as ownership of dialysis facilities (e.g., profit or non-profit status) (24) and the presence of a transplantation unit (9). No study has simultaneously investigated the impact of patient and center characteristics on children's access to renal transplantation. Accordingly, we conducted a nationwide study in France to evaluate the effect of these characteristics on wait-listed children's access to renal transplantation, as well as to distinguish valid medical reasons, from unfounded medical or organizational reasons, that aimed to be address.

Methods

Population study

We considered for inclusion all incident pediatric patients (< 18 years at commencement of RRT), recorded in the French REIN ESRD National Registry and registered on the renal transplantation waiting list between January 1, 2002, and June 30, 2011. Important French specificities are that all patients are registered on the waiting list even though a living donor transplantation is planned and that all patients starting RRT before 18 years old are eligible for pediatric priority for graft allocation, even if the registration occurs after 18 years. Organization, data collection, and quality control of the

REIN registry have been described elsewhere (4). Patients were followed until June 30, 2012, or until death so that all patients have at least 12 months of follow-up.

Information collected

Patients' characteristics

Relevant patient characteristics recorded in the REIN registry were the year and age at start of renal replacement therapy (RRT), gender, primary renal disease, emergency RRT start (defined as a immediate RRT start), place of residence (municipality and geographic location), treatment center, country of birth, date of registration on the waiting list, time on inactive status on the waiting list during the first year following listing, and immunological data (ABO and HLA groups, anti-HLA antibodies). Height and weight, comorbidities, and disabilities at baseline were also recorded.

From comorbidities and disabilities, we created two dichotomous variables: at least one comorbidity (yes/no) and at least one disability (yes/no). We determined growth retardation (for height and weight) according to international standards for chronological age (cut-off $-2DS$) (104). We used the *Network Analyst* module from ARCGIS to calculate the distance between the home address and the center of treatment and between the home and the closest pediatric transplantation center. Because the registry does not include relevant socioeconomic data for children, we used the municipality of residence as a proxy and crossed our database with unemployment and median income data from the French National Institute of Statistics and Economic Studies (INSEE) to investigate possible associations with social factors (105, 106).

Given the great variety of primary renal diseases relative to the number of patients in our study, we grouped these into categories. Diseases were characterized by their coordinate values in the system of axes defined by the principal components of a multiple correspondence analysis (108) based on seven items: immune renal injury, possible immune extrarenal injury, extrarenal vascular injury, possible extrarenal injury of other causes, genetic diseases and congenital abnormalities of the kidney and the urinary tract, possible post-transplantation recurrence of nephropathy, and urological abnormality. The diseases were then grouped by an ascendant hierarchical classification (AHC) (5, 6), an iterative process in which the algorithm starts with as many clusters as there are data items and builds up a tree by successively merging the two nearest clusters. We used pseudo F statistics to choose the threshold at which classification stopped, so that we could create groups homogenous for the difficulty of transplantation. We thus obtained seven groups that we named after their principal shared criteria: vascular diseases, nephropathies with possible immune extrarenal injury, urological abnormalities, congenital or toxic abnormalities, risk of post-transplantation recurrence, and others.

From the immunological data (ABO group, HLA antigens, and antibodies), we retrospectively calculated the FAGN (national ease of graft access) index (114) for each child. This score, used since July 2010 to allocate organs in France, rates from 0 to 60 the number of possible donors with the same ABO group, fewer than 3 HLA mismatches, and no donor-specific antibodies during the previous 5 years.

Center characteristics

The center characteristics we considered were its pediatric specialization (only treating patients under 18 years and with pediatrician as medical staff), the proportion of patients on inactive status on the waiting list during the first month following listing, and the proportion of preemptive transplantations, categorized in two dichotomous groups, one with the median as the cutoff and the other by the size of the renal unit, with the third quartile as the cutoff (based on the number of new patients treated in 2010/2011).

Statistical analysis

The primary outcome was the probability for a patient on the waiting list of receiving a transplant within 12 months after listing.

The association between the patients' characteristics and the outcome was studied with logistic regression models. We performed univariable logistic regressions on all the patient characteristics to determine those to include in our final models. All variables with a p-value less than 0.2 were included in the multivariable logistic regression. All continuous variables were tested for linearity with the SAS macro LGTPHCURV9 (107). Gender, year of first treatment, and primary renal disease were included (forced) in the model regardless of their significance in the univariable analysis.

Then we assessed the center effect by performing a hierarchical multivariable regression and including centers as a random effect. We studied three models. *Model 1* was an empty model (not adjusted for patient or center characteristics), and *Model 2* studied the center effect after adjustment for patient characteristics. Afterwards, we tested some patient characteristics as random effects to determine whether or not some associations varied between centers. Finally, we sought to explain part of the variability between centers by including center fixed effects in the models (*Model 3*). The center effect was assessed by studying the second-level residual variance (τ_{00}) in the three models; this step allowed us to calculate the intraclass correlation coefficient [$ICC = \tau_{00} / ((\pi^2/3) + \tau_{00})$], which evaluates the proportion of variance in the outcome between centers. We also studied the change in the residual variance between models 1 and 2 [$CRV = ((\tau_{00(1)} - \tau_{00(2)}) / \tau_{00(1)}) * 100$], which evaluates the proportion of variance in the outcome between centers that is explained by patient

characteristics (case mix). When an interaction between a center and a patient characteristic was suspected, we tested for cross-level interaction.

We used the Kaplan-Meier method to plot the cumulative incidence curves and the funnel plot method to present crude and adjusted variability between centers (108, 109). To assess the reliability of our findings, we performed two sensitivity analyses with the same model: one to predict transplantation after excluding patients treated by preemptive transplantation and the second assessing only those patients treated in pediatric centers. All tests were performed with the α -risk set at 0.05. Statistical analysis was performed with SAS 9.2.

Complementary analysis

To describe center practices that might explain the remaining difference observed between pediatric and adult centers after adjustment on the items available in the registry, we surveyed transplantation practice and policies by asking one nephrologist per center to complete a questionnaire.

To outline additional possible differences in HLA compatibility requirements, we analyzed the patients from the French Renal Transplantation database (115) to examine whether the type of center affected HLA matching between donors and receivers. We performed a linear regression with the number of matches for DR, B, and A as outcome and adjusted it for age at and year of placement on the waiting list and the FAGN score.

Results

Patient population

We identified 556 patients treated at 54 different centers who were added to the waiting list during the study period. Among them, 450 (80.9%) received transplants during the year after their listing and 498 (89.6%) had received a graft by the end of the study period. The median time to transplantation was 4.2 months.

Access to transplantation

Table VI.9 summarizes the patients' characteristics at inclusion on the waiting list.

Relevant patient characteristics found in the univariable analysis to be associated with a renal transplantation during the first 12 months after listing at a p-value of 0.2 were higher age at inclusion on the waiting list, absence of comorbidities and disabilities, preemptive listing (listed before starting

dialysis), lower distance to the treatment center, lower time of inactive status on the waiting list during the first year after listing, higher FAGN score, and both lower unemployment rate and higher median income in the municipality of residence. We found no relation between the probability of transplantation and gender, primary renal disease, growth retardation, distance to the closest pediatric transplantation center, or birth outside France (Table VI.10). Hierarchical multivariable logistic regression showed that the risk of no transplantation 12 months after inclusion on the waiting list increased with time of inactive status during the year ($p < 0.0001$). As expected, this risk was negatively associated with the FAGN index ($p = 0.02$). The risk of not receiving a graft 12 months after wait-listing was higher for patients who were first listed after their 18th birthdays (OR 6.57, 95%CI [1.78-24.27]) and those with preemptive registration (OR 3.46, 95%CI [1.64-7.33]). We also found an almost significant vintage effect resulting in a decreased probability over time of not receiving a graft (OR per 1 year increase 0.89, 95%CI [0.78-1.00]) (Table VI.10).

The median rate of transplantation within 12 months after listing for all centers was 75% (IQR: 50-100%). The hierarchical model showed significant variability between centers (*Model 1*: residual variance: 0.746, SE 0.299) (Figure VI.6), which accounted for 18.5% of the total variability (ICC). This difference decreased after adjustment for patient-level variables (*Model 2*: residual variance: 0.140, SE 0.165) and did not remain significant (Figure VI.7). Patient characteristics explained 56% of the variability between centers. None of the effects of the patients' characteristics differed significantly between centers. However, after including center variables (*Model 3*), variance decreased to 0.039 (SE 0.110); 72% of the variance that remained after taking case mix into account was explained by center characteristics. Center characteristics that were significantly associated with an increased risk of no transplantation 12 months after wait-listing were: (1) no preemptive transplantations (OR 3.06, 95%CI [1.34-6.99]), (2) a high rate of patients on inactive status on the waiting list during the first month following inscription (OR 1.91, 95%CI [1.03-3.54]) and (3) a pediatric center (OR 4.18, 95%CI [1.53-11.39]) (Table VI.11). The test for cross-level interaction between the patient characteristic "time of inactive status on the waiting list during the first year" and the center characteristic "percentage of patients on inactive status during the first month after listing" was not significant ($p = 0.77$).

The sensitivity analysis of patients with dialysis as their first RRT showed similar results even for the patient variable "preemptive listing" (OR 2.99, 95%CI [1.48-6.06]) and the center variable "no preemptive transplantations" (OR 2.44, 95%CI [1.03-5.80]).

When we tested the model on patients treated in pediatric centers only, we found a significant center effect (*Model 1*: variance 1.02, SE 0.50), explained mainly by patient characteristics (*Model 2*: variance 0.24, SE 0.25). No preemptive transplantations remained significantly associated with the

risk of not being transplanted 12 months after listing (OR 3.07, 95%CI [1.04-9.14]) and a high rate of patients on inactive status on the waiting list during the first month after listing remained close to significant (OR 1.99, 95%CI [0.94-4.22]).

Complementary analysis

Descriptive survey of center practices

Twenty-seven centers participated in the descriptive survey of center practices, 14 pediatric centers and 13 adult centers that accounted for 85% of the patients in our study. Among the interesting findings were substantial differences in policies for wait-listing: four pediatric centers reported that they list patients as soon as possible even if they have temporary medical contraindications to transplantation, while 10 reported that patients are only placed on the waiting list when immediate transplantation is possible. Another interesting result concerned the substantial differences between pediatric and adult centers for HLA matching policies. Five of 14 pediatric centers (36%) reported that they excluded donors with frequent non-shared HLA groups (i.e., Group A2), but only one adult center of 13 (8%) did so. Moreover, eight of 13 adult centers (62%) stated — but no pediatric center did — that they did not require any HLA compatibility between the recipient and the donor. On the contrary, 11 pediatric centers (79%) required at least 2 compatibilities in HLA B and/or DR.

Analysis of observed donor-recipient HLA matching

We included 2058 patients, aged 15 to 21 years old at registration on the waiting list, who received grafts from deceased donors between January 1, 1993, and December 31, 2012. Treatment in a pediatric center was associated with better HLA matching ($p=0.005$) after adjustment for age at inclusion on the waiting list ($p=0.07$), year of transplantation ($p<0.0001$), and the FAGN index ($p<0.0001$).

Discussion

In this nationwide, longitudinal study, we confirm that patients' and centers' characteristics both impact the time to access a renal transplantation among children. Thus, it is justified to question which characteristics are legitimate in lengthening this time and which are not and should be addressed.

Considering patients' characteristics, we found that, as expected, immunological factors were the main predictors of time to renal transplantation, precisely because they are essential for the safe

allocation of grafts. As far as that goes, the time on inactive waiting-list status during the first year was strongly associated with the probability of no transplantation. If this finding seems logical, we noted that some patients spend the entire year on inactive status, a finding that suggests, as the descriptive survey confirmed, that centers have various strategies of early listing without intent to transplant. The major reason for this strategy may well be that allocation rules in France take into account the time spent on the waiting list. However this practice induces inequalities among patients that could be reduced by using the time spent on RRT rather than on the waiting list in the allocation policy.

If the above findings did not surprise us, we also found an association between the age at inclusion on the waiting list and the probability of transplantation within 12 months after listing: patients put on the waiting list after their 18th birthdays had a higher risk than those younger than 18 of not receiving a graft (OR 6.57, 95%CI [1.78-24.27]). This finding not only underlines the major impact of the pediatric priority rules in France that have resulted in one of Europe's shorter waiting times for renal transplantation in children (95), but also shows that centers have different attitudes towards this priority. Because all our patients started RRT before 18, they were eligible for pediatric priority either immediately or at the center's request if they were not wait-listed until after 18. Our results show that some centers do not request pediatric priority for their patients who are eligible, which results in a loss-of-chance for these patients.

Considering the effect of centers, we found a significant variation between centers in children's access to renal transplantation that accounted for 18.5% of the total variability, consistent with the 22% found by Schold et al. for adults in the United States (116).

However, after adjustment for patients' characteristics, intercenter variability in the probability of transplantation 12 months after inscription was no longer significant. This result suggests that on the whole the national allocation rules in France allow an equitable allocation of kidneys for children. However, we found that, although the variance was not statistically different from 0, it decreased after the centers' characteristics were added to the model. It thus remains possible that intercenter variability remains after adjustment for patients' characteristics but that we lacked statistical power to demonstrate it.

Moreover, we observed that patients treated in centers with a high percentage of patients on inactive status during the first month after inclusion on the waiting list also had a higher risk of no transplantation within 12 months after listing, even after taking individual inactive time into account. Patients treated in centers without preemptive transplantation programs also had a higher risk of not receiving a graft. Although it is possible that the time between inclusion on the waiting list and

transplantation varies according to whether or not the patient had preemptive transplantation, the association remains significant after excluding those with preemptive transplantation. These findings indicate that the center's practice has a true effect on the probability of transplantation and that efforts have to be made in promoting preemptive transplantation as much as possible.

Finally, treatment in a pediatric center was associated with a higher risk of no transplantation within 12 months after inclusion; this finding is probably due to the higher requirements for accepting transplants in those centers. This explanation is corroborated by the descriptive survey of centers' practices, which showed that 79% of pediatric centers required at least two compatibilities in B and/or DR and that 36% exclude donors with a high-frequency HLA group that the patient does not share, compared to 30% and 8% respectively in adult centers. Moreover, we showed that patients receiving grafts in pediatric centers have a higher degree of donor-recipient HLA matching. Although questions have been raised about the importance of HLA matching in view of the improvement in immunosuppression (117), there is growing evidence that HLA matching in children is associated with graft survival (118) and has a strong impact on the probability of retransplantation and on waiting time to retransplantation (47) in patients who will need several transplantations during their life. Moreover, even if improved immunosuppression does allow better graft survival despite poor HLA matching, the side effects of these treatments must not be overlooked: the incidence of non-Hodgkin lymphoma has increased in children with a poor HLA-matching (119, 120). Pediatric centers appear to optimize HLA compatibility and thus improve transplant survival and decrease the risk of immunization for a second transplantation.

The main strength of our study is its use of a hierarchical logistic model that makes it possible to demonstrate this intercenter variability. This model is more accurate than the models usually used to study hierarchical data because it takes into account the correlation between patients treated at the same center and thus allows more accurate estimation of ORs, their confidence intervals, and the estimation of the residual intercenter variance. Another advantage of this model is that it enables us to study several center characteristics to explain the variability between centers.

The primary limitations of our study are the lack of reliable individual socioeconomic data, even though the universal health care insurance system might decrease inequalities in France, at least in comparison with some other countries.

We also have a limited number of centers that treat patients younger than 18 years. The center effect is no longer significant after adjustment for patients' characteristics. We cannot, however, conclude from these results that the variables included in the model enable us to explain in full the variability between centers in access to transplantation after wait-listing; but rather that we might

lack power. Simulation studies have suggested that at least 30 to 50 groups are needed to obtain precise estimates and that variance components tend to be underestimated when the number of level 2 units (centers) is small (111, 112)

Conclusion

Although overall access to renal transplantation in France is good, this study confirms the existence of inequalities among children in access to transplantation after placement on the waiting list. We found that characteristics of both patients and centers may play a role in these inequalities.

Although some medical characteristics such as immunological factors, rationally impact access to transplantation, information about the appropriate use of the pediatric priority and the inactivated status on the waiting-list is needed to address those unjustified sources of inequality. We also demonstrated a difference in policies between adult and pediatric centers, especially for HLA matching. Further studies are needed to evaluate the impact of these policies, not only on the time needed to access a first transplantation and on survival of the first transplant, but also on access to a second transplantation later in life, on the survival of both the graft and the patient, and on the occurrence of complications. Such studies will enable us to harmonize practices according to evidence based data and thus reduce inequalities in access to renal transplantation while providing patients with the best present and future graft and personal survival chances.

	Population Description	
	N (Tot=556)	% not transplanted within 12 months
Age at registration on the waiting-list		
< 18 years	525	28.0
>= 18 years	31	54.8
Gender		
Male	328	20.1
Female	228	17.5
Primary renal disease		
Vascular diseases	42	19.1
Nephropathies with possible immune extra-renal injury	25	16
Urological abnormalities	74	21.6
Congenital or toxic abnormalities	221	19.5
Unknown	58	17.2
Risk of post-transplantation recurrence	136	18.4
Growth retardation	<i>(Missing 94)</i>	
No	340	22.1
Yes (Z-score<-2DS)	85	12.9
BMI < -2DS	<i>(Missing 113)</i>	
No	361	21.3
Yes	59	10.2
Presenting at least 1 comorbidity		
No	392	16.8
Yes	164	24.4
Presenting at least 1 handicap		
No	358	19.8
Yes	198	17.7
Emergency treatment	<i>(Missing 19)</i>	
No	393	16.8
Yes	144	22.2
Being born overseas	<i>(Missing 14)</i>	
No	477	19.5
Yes	65	16.9
	Mediane	IQ
Duration of inactive status on waiting-list during the first year (in days)	0	[0-42]
FAGN score	16	[8-25]
Year of first RRT (Vintage effect)	2008	[2006-2010]
Median income (Euros) of municipality of residence <i>(Missing=19)</i>	17894	[15736-20659]
Distance between home and the closest pediatric transplantation center (km)	46	[14-94]
Distance between home and treatment's center (km)	28	[8-68]
Unemployment rate (%), municipality of residence <i>(Missing 19)</i>	4.5%	[3.3%-5.8%]

Table VI.9: Patients' characteristics at inclusion on the waiting list and rate of non-listed patient within 6 months after RRT onset.

	Univariable analysis			Multivariable analysis	
	OR	IC 95%	p	OR	IC 95%
Age at registration on the waiting-list			0.002		
<18 years-old	1.00				
>= 18 years-old	3.12	[1.50- 6.50]		6.57	[1.78- 24.27]
Gender			0.960		
Male	1				
Female	0.99	[0.68- 1.44]		0.81	[0.47- 1.42]
Primary renal disease			0.177		
Vascular diseases	1.42	[0.69- 2.93]		1.60	[0.53- 4.86]
Nephropathies with possible immune extra-renal injury	1.49	[0.61- 3.65]		1.49	[0.39- 5.69]
Urological abnormalities	1.43	[0.80- 2.56]		1.04	[0.40- 2.68]
Congenital or toxic abnormalities	1			1	
Unknown	1.21	[0.63- 2.32]		2.20	[0.82- 5.90]
Risk of post-transplantation recurrence	1.90	[1.20- 3.03]		1.95	[0.97- 3.89]
FAGN score			0.0002		
	0.97	[0.95- 0.98]		0.96	[0.93- 0.98]
Growth retardation			0.757		
No	1				
Yes (Z-score<-2DS)	0.92	[0.56- 1.54]			
BMI<-2DS			0.476		
No	1				
Yes	0.8	[0.44- 1.47]			
At least one comorbidity			0.018		
No	1				
Yes	1.60	[1.08- 2.36]		0.81	[0.45- 1.47]
At least one disability			0.002		
No	1				
Yes	0.52	[0.35- 0.78]		0.65	[0.32- 1.32]
Preemptive listing			<0.0001		
No	1				
Yes	2.91	[1.78- 4.75]		3.46	[1.64- 7.33]
Distance between home and treatment center			0.114		
OR per 1km increase	0.99	[0.994- 1.001]		1.00	[0.99- 1.01]
Distance between home and the closest pediatric transplantation center			0.225		
OR per 1km increase	1.00	[0.99- 1.00]			
Birth outside France			0.957		
No	1				
Yes	1.78	[0.56- 1.74]			
Vintage effect			0.243		
OR per 1 year increase	1.05	[0.97- 1.13]		0.89	[0.78- 1.00]
Median income, municipality of residence			0.0002		
OR per 100 euros increase	1.00	[1.00- 1.00]		1.00	[1.00- 1.00]
Unemployment rate, Municipality of residence			<0.0001		
OR per 1% increase	1.24	[1.14- 1.35]		1.08	[0.87- 1.33]

Table VI.10: Odds-ratio of not being transplanted within 12 months after registration on the waiting-list associated to patients' characteristics.

	N	OR	CI95%
Center type			
<i>adult</i>	38	1	
<i>pediatric</i>	16	4.18	[1.53- 11.39]
Preemptive transplantation			
<i>yes</i>	23	1	
<i>no</i>	31	3.06	[1.34- 6.99]
% patients on inactive status on the waitig list			
<25%	26	1	
≥25%	28	1.91	[1.03- 3.54]
Number of new cases (2009-2010)			
>3	12	1	
≤3	42	1.58	[0.66- 3.78]

Table VI.11: Odds-ratio of not being transplanted within 12 months after registration on the waiting-list associated to centers' characteristics.

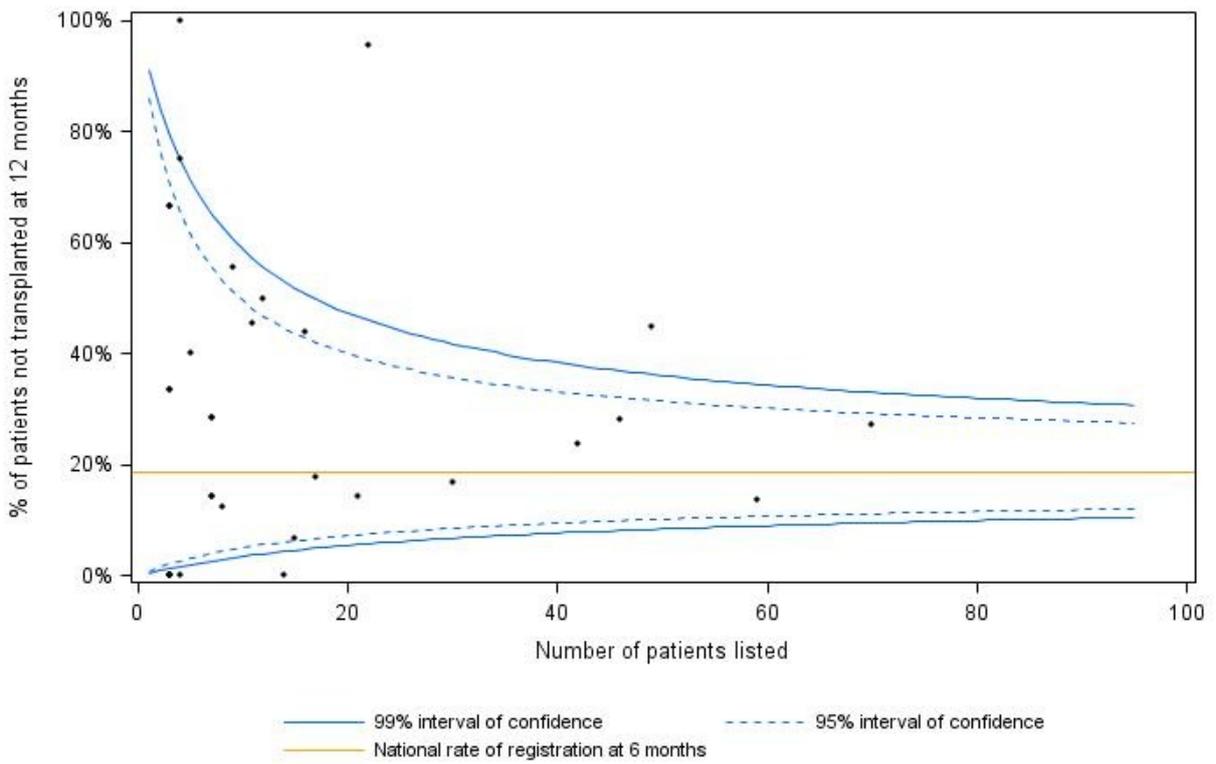


Figure VI.6: Funnel plot of crude centers' rate of patients not transplanted at 12 months

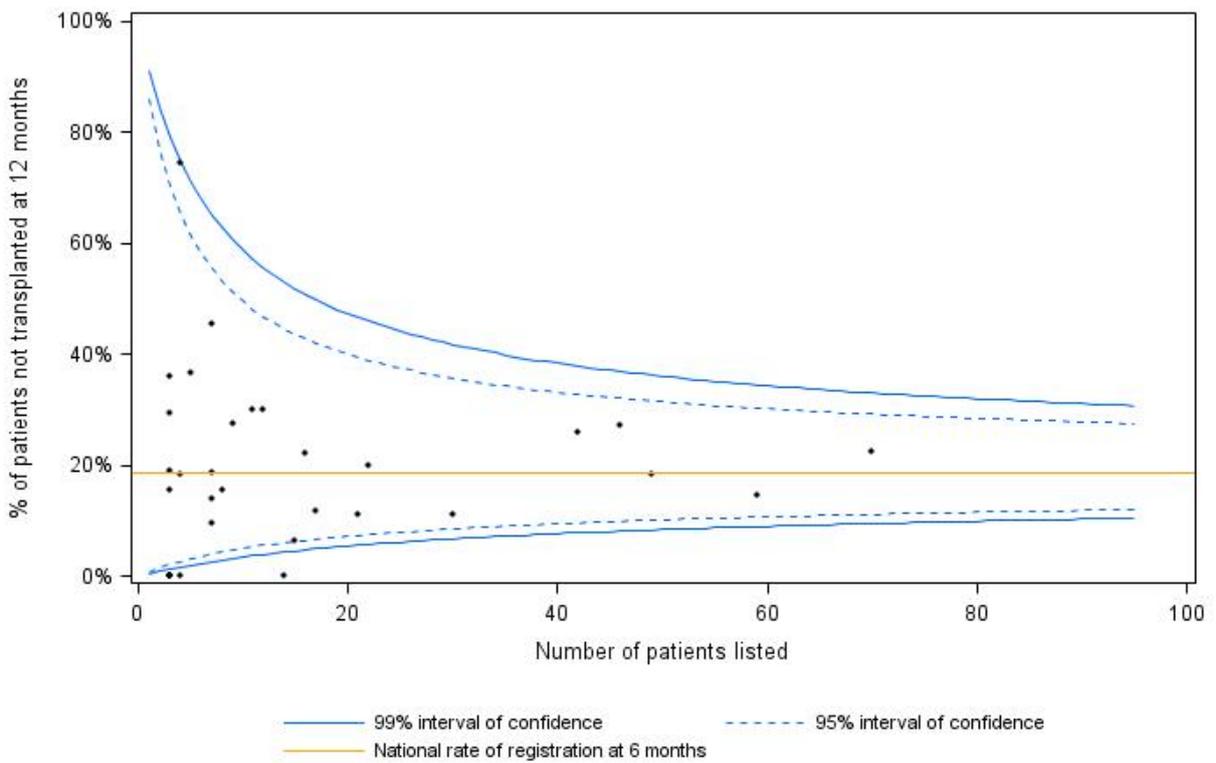


Figure VI.7: Funnel plot of adjusted centers' rate of patients not transplanted at 12 months

B. Disparities in access to renal transplantation based on patients' characteristics

1. Gender effect in access to renal transplantation

Gender inequity in access to renal transplantation waiting lists, in favor of men, has long since been demonstrated in a number of studies among adults (8). While studying the access to the renal transplant waiting-list among children in France, we found an association between female gender and a lower probability of being registered 6 months after RRT initiation. Although, this association was not statistically significant after multivariate adjustment, the trend remained. We hypothesize that, in children, female gender was associated with a poorer access to renal transplantation and that we were lacking statistical power to demonstrate it. Therefore, we requested the access to the data of the ERA-EDTA/ESPN registry including data from many countries within Europe in order to validate this hypothesis and I went to Amsterdam (AMC University) to perform the study on this database.

Gender Disparities in Access to Pediatric Renal Transplantation in Europe : Data from the ESPN/ERA-EDTA Registry

Julien Hogan, Cécile Couchoud, Marjolein Bonthuis, Jaap W. Groothoff, Kitty J. Jager, Franz Schaefer, Karlijn J. Van Stralen, on behalf of the ESPN/ERA-EDTA registry
Am J Transplant. 2016 Jul;16(7):2097-105.

Introduction

Renal transplantation is widely recognized as the treatment of choice for end-stage renal disease (ESRD) in both children and adults. It is associated with improved survival, better quality of life (31-33) and superior long-term cost effectiveness (34, 35) compared to patients who remain on dialysis (29, 30). Despite the World Health Organization recommendations regarding fair access to transplantation, studies in adults have demonstrated important inequalities between women and men. In both Europe and the United States female gender has been associated with lower access to transplantation, substantially lower registration on the transplant waiting list and a longer time from the start of dialysis to wait listing (8-11).(8-11)

Factors contributing to these differences include a longer transplantation work-up in women as compared to men (121) potentially resulting from a lower willingness of women to undergo transplantation (122), as well as a higher level of Donor Specific Antibodies (DSA) secondary to pregnancies. However, in children the influence of such factors should be negligible as transplantation work-up is usually guided by the parents, whereas pregnancies and transfusions are

rare. Still Nguyen et al. also found that, in US children, girls have a 22% lower access to being waitlisted (23). However, in that study findings could not be explained, possibly due to limitations in data collection and poor adjustment for confounding factors.

The ESPN/ERA-EDTA Registry combines detailed data on children and adolescents with ESRD from renal registries in 35 European countries and therefore provides an opportunity to validate this gender inequality in a large European population and to investigate its underlying causes.

Material and Methods

Study population

All children starting renal replacement therapy (RRT: haemodialysis, peritoneal dialysis, or pre-emptive transplantation) between 1 January 2000 and 31 December 2012 at an age of 18 years or younger were included. The organization, data collection, and quality control within the ESPN/ERA-EDTA Registry have been described elsewhere (123). The inclusion period varied per country to ensure a complete follow-up of all patients. Patients were followed till the 31st of December 2012, renal transplantation, recovery of renal failure, or death whichever came first.

Data collected

Relevant characteristics recorded in the registry included date of birth, gender, cause of renal failure, date of RRT start, date of first transplantation, type of donor (living, deceased or not reported), country of treatment and status at last follow-up (transplanted, on dialysis, dead or recovery of renal function). We categorized the age at start of RRT in 6 groups (0<1, 1<2, 2<6, 6<10, 10<14 and 14 years and older) based on a spline modelling procedure yielding classes with homogeneous likelihood of transplantation. The cause of renal failure was classified according to the 11 ERA-EDTA primary renal disease (PRD) groups for children (Congenital Abnormalities of the Kidney and the Urinary Tract (CAKUT), Glomerulonephritis, Cystic kidney disease, Hereditary nephropathy, Ischemic renal failure, Haemolytic and Uremic syndrome (HUS), Metabolic disorders, Vasculitis, Neurogenic bladder, Miscellaneous and Missing). Three primary renal diseases occur almost exclusively in boys and their corresponding codes were as follows: Prune Belly syndrome (99% males), Alport syndrome (82% males) and Congenital obstructive uropathy which included posterior urethral valves (87% males). These disease groups were therefore excluded from some of the analyses.

In a subset of patients for whom data were available, the eGFR at first visit to a nephrologist as well as the eGFR at start of RRT were calculated using simplified Schwartz formula based on creatinine serum levels.

Statistical analysis

For descriptive analysis, continuous variables are given as medians and interquartile ranges and dichotomous variables in percentages. We used Chi-square and student t-test to test the difference between boys and girls for dichotomous and continuous variables respectively.

Gender effect on time between start of RRT and transplantation

We used the cumulative incidence competing risk (CICR) method to account for the competing risks of death or recovery of renal failure and the Gray method to compare CICR curves, with the time between the start of RRT and transplantation as primary outcome and with gender as independent variable. For patients with a pre-emptive transplantation, the time between the start of RRT and transplantation was set to 0. A proportional hazards frailty model was used to study the association between gender and the probability to receive a transplant with adjustment for confounding factors. This model is a generalization of Cox model in case of hierarchical data (in our case, patients clustered within countries) and gives more accurate and valid estimations of HR and confidence intervals. Proportional hazards assumption of the model was assessed by graphical methods.

Gender effect on the probability of pre-emptive transplantation

We applied a hierarchical logistic model to study the association between gender and the probability of receiving a pre-emptive transplant using a random intercept and slope for countries and gender. The country effect was assessed by studying the second level residual variance. This allowed us to take into account the variation across countries in the access to pre-emptive transplantation and to test whether the potential effect of gender was homogeneous among European countries. We stratified by cause of renal failure to see if any effect was specific for certain categories.

Effect of the time of follow-up by a nephrologist prior to RRT on the probability of pre-emptive transplantation

When studying, in a subgroup of patients for whom the data were available, the time between first visit to a nephrologist and the start of RRT, eGFR at start and the rate of decline in eGFR, we used T-tests to compare the groups, and linear regression analyses to adjust for age at the first visit and cause of renal failure. Values were log-transformed in case of non-normal distributions.

All tests were performed at a p-value of 0.05. Statistical analysis was performed with SAS 9.3.

Results

A total of 6454 patients starting RRT in 35 countries were included in the study. Of those 57.3% were male, median age was 10.7 years (interquartile range 4.6 to 14.4). By the end of the follow-up, a similar proportion of boys (N=2647; 71.6%) and girls (N=1942 girls; 70.5%) had received a transplant; whereas 126 boys (3.4%) and 110 girls (4.0%) died ($p=0.30$). Table VI.12 describes the patient characteristics by gender. At the start of RRT, boys were significantly younger than girls and boys were overrepresented in the CAKUT group, whereas significantly more girls than boys had vasculitis as cause of renal failure. The type of donor did not differ between boys and girls even in the subgroup of patients with pre-emptive transplantation ($p=0.19$).

Time to Access to renal transplantation

Female gender was associated with a slower access to transplantation when compared to males (HR 0.88, 95%CI 0.83-0.94) after adjustment for age (Table VI.13). The median time to transplantation from start of RRT was 14.2 months in boys and 16.5 months in girls (Figure VI.8) and the cumulative incidence of transplantation over time was significantly lower in girls than in boys ($p=0.006$). After additional adjustment for PRD the hazard ratio of transplantation for females as compared to males became 0.94 (95% CI: 0.89-1.00). The reduced access of females was largely similar in all patient subgroups (Table VI.13).

Access to pre-emptive renal transplantation

Pre-emptive transplantation rate was 22.5% in boys vs. 16.7% in girls, corresponding to a 23% lower chance of females to receive a transplant pre-emptively as compared to males (OR adjusted for age and cause of renal failure 0.77, 95%CI 0.66-0.88) (Table VI.14). The slower access to renal transplantation in girls was completely explained by a lower rate of pre-emptive transplantation. Indeed, after adjustment for pre-emptive transplantation, there were no longer differences with respect to time to transplantation (HR girls vs boys: 0.99, 95%CI: 0.92-1.06, $p=0.80$).

Although European countries differed widely in their overall rates of pre-emptive transplantation ranging from less than 5% to over 60% of all renal transplantations (95), we observed the same decrease in the likelihood of pre-emptive transplantation in girls in all European countries (second level residual variance for gender non significantly different from 0).

The effect of gender was also consistent across all age groups with exception of the infant age group, in which a negligible percentage of patients underwent pre-emptive transplantation. We found a

significant effect of the primary renal disease; the effect of gender was the greatest in patients with CAKUT, even after excluding male-limited diseases (OR 0.76 95%CI 0.59-0.97), in the ischemic renal failure group (OR 0.22, 95%CI 0.07-0.74) and in the 'miscellaneous' group (OR 0.51, 95%CI 0.31-0.82).

In a sub-group of 1024 patients from 15 countries, the date of first appointment with a pediatric nephrologist, the eGFRs at first appointment as well as the one at start of RRT were known. Those patients did not differ significantly from the others with regards to age and primary renal diseases (data not shown). The distribution of genders according to the time between first visit to a nephrologist and start of RRT and eGFR decline per year during this period is shown in Figure VI.9. Two time periods during which patients started RRT were identified, namely quite acute starters, and those with a longer time to start RRT. As shown in Figure VI.9, girls tended to start RRT more rapidly after first appointment than boys. As a result, the median time between the first visit to a pediatric nephrologist and the start of RRT, was significantly longer in boys (23.0 months [IQR: 2.4-68.6]) than in girls (14.4 months [IQR: 0.6-53.6]), $p=0.009$ (Table VI.15).

The eGFR at first appointment differed slightly between the genders ($p=0.04$ after adjustment for age) (Table VI.15). eGFR did not differ between genders at the start of RRT. As a result, we found a non-significant difference in the rate of eGFR decline between males (-10.3 95%CI -15.5 to -6.4 ml/min/1.73m² per year) and females -15.1 95%CI -19.6 to - 10.5 ml/min/1.73m² per year), $p=0.08$ after adjustment for age. However, as shown in figure VI.9, boys tended to have a slower yearly eGFR decline, while girls often presented a more rapid decline. This difference was stronger in children younger than 12 years at start of RRT ($p=0.02$) and in patients with CAKUT ($p= 0.005$, adjusted for age $p=0.02$). As expected, a longer time between first visit and start of RRT was associated with a higher chance of receiving a pre-emptive transplant (OR 1.19 95%CI 1.15-1.24 per year increase in pre-ESRD care). Therefore, when adjusting for age, diagnosis and pre-RRT follow-up time, the OR of boys to receive a pre-emptive transplant as compared to girls decreased from 1.56 [95%CI 1.13-2.16] to 1.36 [95%CI 0.95-1.95]. There was no significant modification after further adjustment for eGFR at first visit (OR 1.37 95% 0.95-1.96). Hence, the difference in pre-RRT follow-up time explains part of the gender effect on the access to pre-emptive transplantation.

Mediation analyses

In order to get insight in the potential mechanisms underlying the reduced access to pre-emptive transplantation in female patients, we performed mediation analyses among a subgroup of patients for whom data on eGFR at first appointment with a pediatric nephrologist, as well as eGFR at start of RRT were available (N=1024). Results of the mediation analyses are shown in Table VI.16. After

adjustment for age, the OR of pre-emptive transplantation for females as compared to males was 0.57 (95%CI 0.41-0.80). After additional adjustment for PRD (OR 0.70) and time between first visit by a nephrologist and start of RRT the OR became 0.81 (95%CI 0.56-1.18). Similar associations were found after excluding patients with male-limited diseases (e.g. posterior urethral valves, prune belly syndrome, and Alport syndrome) (Table VI.16). We found similar trends after excluding patients with a follow-up shorter than one month (results not shown). This suggest that although we were able to explain about 70% of the difference between boys and girls in access to a pre-emptive transplantation, there still remains a 19% difference in access to pre-emptive transplantation between the genders.

Discussion

In this longitudinal study including over 6000 pediatric patients throughout Europe, we found that female gender was associated with a delay in access to renal transplantation in children. While studies in the United States previously found important disparities in access to the renal transplant waiting list between boys and girls (14, 23, 96), no study to date assessed in detail the potential reasons for this gender difference.

A major finding of this study is that the gender difference in time to access to transplantation was entirely explained by a lower rate of pre-emptive transplantation in girls. Europe-wide, girls were 23% less likely to receive a pre-emptive transplant than boys. This finding is consistent with data from the NAPRTCS registry, which reported a similar difference in the rate of pre-emptive transplantation between boys and girls (28% vs. 20%, $p < 0.0001$) (124). We thus investigated medical factors that may cause this gender difference in access to pre-emptive transplantation.

Patient age has a major impact on the probability of pre-emptive transplantation since young infants are usually not considered suitable for renal transplantation until they reach a weight of about ten kilograms. However, we found the gender effect to be consistent across all age groups; hence, the difference in age distribution between boys and girls cannot explain the difference in access to pre-emptive kidney transplantation.

In children, since comorbidities are rare, the underlying renal disease is the major predictor of the time needed to access transplantation. For instance, rapid transplantation is often not considered appropriate for medical reasons in patients with glomerulonephritis, HUS or vasculitis, whereas this is usually not the case for patients with CAKUT. Thus, it has been argued that previous findings on the

gender difference in transplant access might have been related to insufficient adjustment for primary renal diseases. However, in our analysis a significant gender difference still remained after careful adjustment for PRDs and age. Furthermore, the gender effect tended to be present in most diagnosis groups.

Since some time is needed for the medical work-up for transplantation, we hypothesized that the duration of specialist care prior to start of renal replacement therapy may impact the probability of undergoing pre-emptive transplantation. We found that the time between first referral to a pediatric nephrologist and ESRD was almost one year longer in boys than in girls. We then tested two hypotheses to explain this difference, the first being that girls were systematically referred or diagnosed later in the course of disease. We therefore analysed the difference of eGFRs at time of diagnosis. As the gender difference was most prominent among patients with CAKUT, probably explained by the fact that uropathic CAKUT manifesting in early childhood is more common in boys or even limited to the male gender (posterior urethral valves), we speculated that this might lead to an earlier diagnosis and subsequently a more timely referral for transplantation work-up in boys than in girls. However, when adjusting for age and cause of renal failure we found no significant gender difference in eGFR at first visit to a specialist, whereas the lower rate of pre-emptive transplantation in girls persisted. Hence, delayed diagnosis or referral does not fully explain the lower access of girls to pre-emptive transplantation.

The other hypothesis that we tested was that the gender difference would be explained by difference in time of progression towards end-stage renal disease. A more rapid progression of renal failure in girls would give less time to prepare them for pre-emptive transplantation. We indeed found a trend towards faster rate of eGFR decline in females. Studies in adults have found opposite results with a more rapid deterioration of the renal function in men than in women (125). Experimental models on rats suggested that hormonal factors may slow down renal function loss in women (126). However, endocrine factors may be less relevant in pediatric CKD, supported by the fact that the largest gender difference in access to pre-emptive transplantation was observed in the pre-pubertal period. It should also be considered that many studies on disease progression are done among patients with CKD, while we have only those patients ending up on RRT. Adjustment for age, PRD and the slope of the eGFR decline indeed showed that the differences between boys and girls were in part mediated through these factors.

Since medical factors only partially explain the gender difference in access to renal transplantation, other explanations need to be considered. In several adult studies, women have been found to

refuse more frequently to be listed because of the perception of a greater risk and adverse effects of surgery and immunosuppressive treatment (8, 122). While it might be speculated that such considerations might impact on the willingness for early transplantation in adolescent girls, they do not seem relevant to explain the gender effect found in younger children.

When it comes to children, the decision of transplantation is mainly guided by the parents and the pediatric nephrologist in charge. Living donor transplantation generally allows a shorter waiting time before transplantation; Bloembergen et al. found that women were 10% less likely to receive a living donor transplantation than men (127). This difference remained significant even when considering only pediatric patients aged 0 to 19 years. Thus, one could hypothesize that parents more often give their kidney to their sons than to their daughters. Unfortunately, no published information on gender-specific attitudes in parental decision-making in children with chronic and life-threatening diseases is available to support or refute this hypothesis. Some of the explanation may also lie with health care professionals. A national random survey of 271 nephrologists in the USA showed that female gender was associated with a reduced likelihood that nephrologists would recommend transplantation (128). However, this study did not really explore the reasons for this difference and was performed among adult nephrologists, so that its generalizability in children is far from certain. A main concern when considering transplantation is the risk of noncompliance. Although among adults males seem to be at greater risk of non-adherence (129), non-adherence in adolescents is considered more prevalent among females likely due the adverse aesthetic effects of steroids (e.g. stretch marks, weight gain) and calcineurin inhibitors (e.g. hypertrichosis). This notion, which is indirectly supported by the increased rate of graft loss in adolescent girls as compared both to their male peers and to younger girls and adult women (130) may prompt physicians to delay transplantation and argue against pre-emptive donation. However, this phenomenon does not explain the gender difference in transplant access at the younger ages.

Finally, several studies found a centre effect on the time to register on the renal waiting list (131) and to access transplantation (132) even after adjusting for patient case-mix. However, although we don't have the data to completely rule out the possibility of a centre effect with regards to the gender difference in access to pre-emptive transplantation, there is no evidence to support this hypothesis. Moreover, the gender difference was found to be consistent across countries.

To our knowledge, this is the largest study to date exploring gender differences in access to renal transplantation in children. An important strength of our study lies in the inclusion of patients from 35 countries, supporting the generalizability of the observed results in the Western world. Moreover,

because of the important number of data collected in the ESPN/ERA-EDTA registry, we were able to study in more detail the reasons of this gender disparity considering the access to kidney transplantation.

Our study also has several limitations. Data on eGFR and the date of the first visit to a specialist were not available in all patients. We also do not have data on patient race and immigrant status. However, although racial inequalities have been found in access to renal transplantation (14), we do not see a clear reason why this would explain the gender differences. The pre-RRT follow-up time was quite short and first reported eGFR was low, limiting the accuracy of GFR loss calculations and we used reported estimated GFR since most children do not have their GFR measured. However, a recent study from the CKiD cohort also found a significantly faster decline of eGFR in girls but did not investigate its causes (133). We thus required those data and will investigate the causes of the difference in chronic kidney disease progression between boys and girls. Differences between countries and centres may occur in serum creatinine measurement and eGFR formulas used. Although a similar gender effect has been found in other studies, our study is based on an European population and might need validation in other populations. Finally, our study does not assess whether the longer time spent on dialysis by girls impacts long-term graft and patient outcome. Further study following patients throughout childhood and adulthood is still needed to evaluate the long-term outcome.

Conclusion

This large European study demonstrates substantial gender inequalities with regards to the access of children to renal transplantation. Girls with ESRD are waiting longer to receive an allograft, an effect explained by a lower pre-emptive renal transplantation rate which was only partially explained by patients' age, underlying kidney disease, timing of referral and rate of loss of residual GFR.

Non-medical factors such as patient motivation and parental and physician attitude towards living donor transplantation may participate in this inequality between genders and need to be studied in detail. Our study should raise awareness for the management of girls with renal diseases and prompt all caregivers to avoid any undue delays in pre-transplant workup.

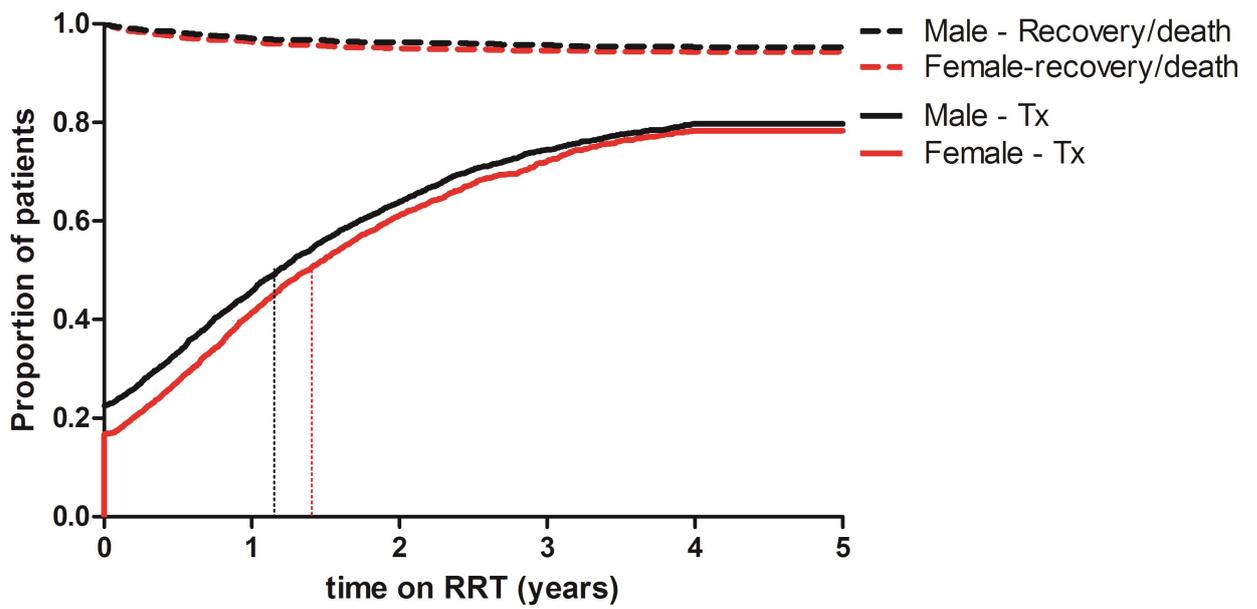


Figure VI.8: Cumulative incidence of transplantation by gender with death or recovery of renal function as competing risks (with reference lines stated median time to transplantation: 14.2 months in boys and 16.5 months in girls).

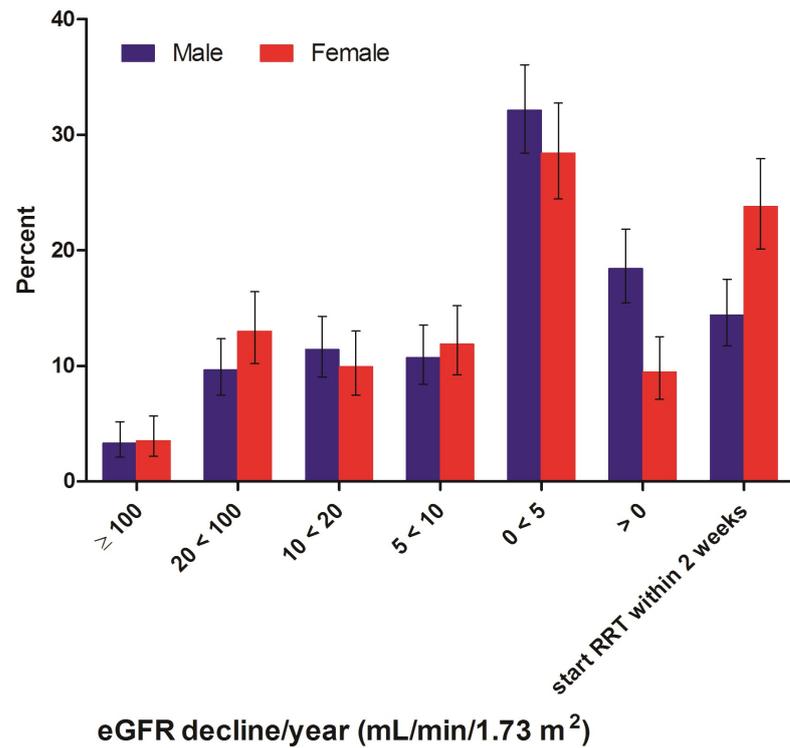
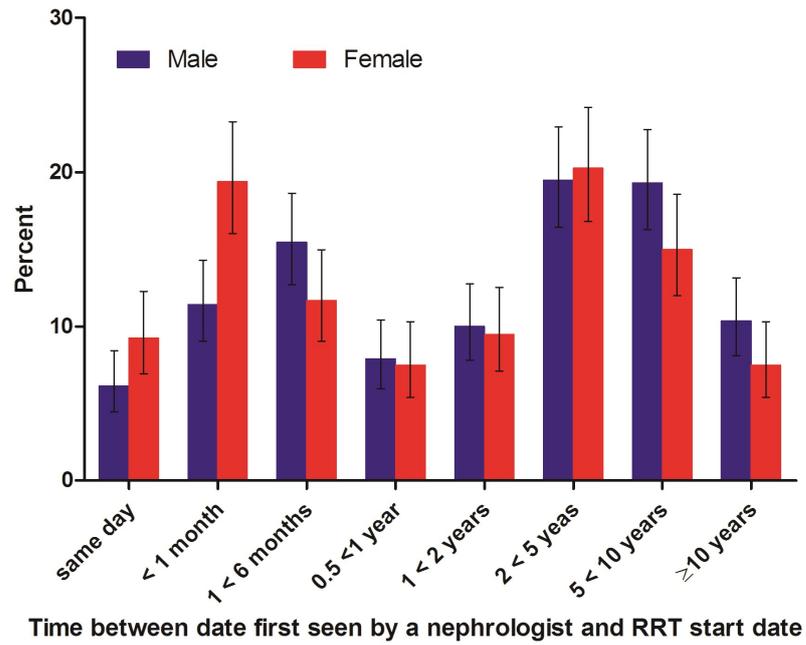


Figure VI.9: Distribution of patients by gender (454 girls and 570 boys) according to time between first visit to a nephrologist and RRT start date (A) and eGFR decline per year between first visit and RRT start date (B).

	Boys (N=3699)		Girls (N=2755)		P
	N	%	N	%	
Age at RRT					
0<1 years	442	12.0	232	8.4	<0.0001
1<2 years	207	5.6	128	4.7	
2<6 years	563	15.2	370	13.4	
6<10 years	614	16.6	443	16.1	
10<14 years	818	22.1	787	28.5	
≥14 years	1055	28.5	795	28.9	
Primary renal diseases					
CAKUT ¹	1654	44.7	743	27.0	<0.0001
Glomerulonephritis	499	13.5	505	18.3	
Cystic kidney disease	331	9.0	334	12.1	
Hereditary nephropathy	281	7.6	193	7.0	
Ischaemic renal failure	71	1.9	49	1.8	
HUS ²	117	3.2	157	5.7	
Metabolic disorders	111	3.0	91	3.3	
Vasculitis	34	0.9	93	3.4	
Neurogenic bladder	37	1.0	74	2.7	
Miscellaneous	308	8.3	250	9.0	
Missing	256	6.9	266	9.7	
Donor type					
Deceased donor	1183	32.0	927	33.7	0.09
Living donor	816	22.1	590	21.4	
Unknown	648	17.5	425	15.4	
No Transplant	1052	28.4	813	29.5	

¹CAKUT: Congenital Abnormalities of the Kidney and the Urinary Tracts; ²HUS: Hemolytic and Uremic Syndrome

Table VI.12: Patient characteristics by gender

Patient characteristics	Univariate analysis HR (95% CI)	Multivariate analysis I HR (95% CI) ¹	Multivariate analysis II HR (95% CI) ²
Overall population	0.93 (0.88-0.99)	0.88 (0.83-0.94)	0.94 (0.89-1.00)
Age at RRT³			
0<1 years	0.79 (0.62-1.01)	-	0.79 (0.60-1.02)
1<2 years	0.77 (0.57-1.03)	-	0.85 (0.61-1.17)
2<6 years	0.80 (0.68-0.94)	-	0.87 (0.73-1.03)
6<10 years	0.77 (0.67-0.89)	-	0.86 (0.74-1.00)
10<14 years	0.88 (0.79-0.99)	-	0.92 (0.82-1.03)
≥14 years	1.03 (0.92-1.15)	-	1.08 (0.96-1.21)
Type of donor			
Deceased donor	0.88 (0.81-0.96)	0.84 (0.77-0.92)	0.89 (0.81-0.98)
Living donor	0.88 (0.79-0.98)	0.84 (0.76-0.94)	0.88 (0.79-0.98)
Unknown	0.95 (0.83-1.07)	0.88 (0.77-0.99)	0.92 (0.81-1.06)
Primary renal disease			
CAKUT ⁴	1.00 (0.90-1.11)	0.90 (0.81-1.00)	-
Glomerulonephritis	1.13 (0.97-1.31)	1.14 (0.98-1.33)	-
Cystic kidney disease	0.97 (0.80-1.16)	0.98 (0.81-1.17)	-
Hereditary nephropathy	0.99 (0.80-1.24)	1.05 (0.83-1.32)	-
Ischaemic renal failure	0.84 (0.52-1.34)	0.61 (0.36-1.03)	-
HUS ⁵	0.97 (0.69-1.34)	0.95 (0.68-1.33)	-
Metabolic disorders	0.97 (0.69-1.36)	0.89 (0.63-1.25)	-
Vasculitis	0.66 (0.39-1.10)	0.69 (0.41-1.16)	-
Neurogenic bladder	1.25 (0.70-2.26)	1.23 (0.69-2.23)	-
Miscellaneous	0.78 (0.63-0.97)	0.77 (0.62-0.95)	-
Missing	0.95 (0.76-1.19)	0.93 (0.74-1.16)	-

¹ Adjusted for age at RRT; ² Adjusted for age at RRT and PRD; ³RRT: Renal Replacement Therapy;

⁴CAKUT: Congenital Abnormalities of the Kidney and the Urinary Tracts; ⁵HUS: Hemolytic and Uremic Syndrome

Table VI.13 : Time to transplantation by patient subgroups: females as compared to males (proportional hazards frailty model)

	Boys N=570	Girls N=454	P-value
Median time from first visit to RRT start (IQR)(months)	23.0 (2.4-68.6)	14.4 (0.6-53.6)	0.009
Median (IQR) eGFR at first visit	15.9 (7.9-30.1)	16.7 (8.5-37.2)	0.04
Median (IQR) eGFR at start RRT	9.0 (6.7-11.6)	8.5 (6.4-11.4)	0.19
Rate of eGFR decline (mL/min/1.73m ² /year)	-10.3 (-15.5 to -6.4)	-15.1 (-19.6 to -10)	0.08

Table VI.14 : Time between first visit and start of RRT, eGFR at first visit, and eGFR at start of RRT by gender

Model	All patients OR (95% CI)	Excluding patients with male-limited diseases OR (95% CI)
Gender	0.77 (0.55-1.08)	0.76 (0.53-1.09)
Gender+ age at RRT	0.57 (0.41-0.80)	0.68 (0.47-0.97)
Gender+age at RRT+PRD	0.70 (0.49-0.99)	0.74 (0.50-1.08)
Gender+age at RRT+PRD+eGFR first seen by a nephrologist	0.70 (0.49-1.00)	0.74 (0.51-1.09)
Gender+age at RRT+PRD+eGFR at start RRT	0.77 (0.53-1.11)	0.83 (0.56-1.23)
Gender+age at RRT+PRD+eGFR decline per year	0.70 (0.49-1.01)	0.72 (0.49-1.05)
Gender+age at RRT+ PRD+ time between first visit and start	0.81 (0.56-1.18)	0.80 (0.54-1.20)
Gender+age at RRT + time between first visit and start	0.66 (0.47-0.94)	0.70 (0.48-1.03)
Gender+age at RRT+ eGFR decline per year	0.60 (0.43-0.85)	0.66 (0.46-0.96)

Table VI.15 : Mediation analysis: Odds ratio of pre-emptive transplantation in females as compared to males among those for whom all information is available (N=1024)

2. Effect of the age at ESRD on the access to renal transplantation: The issue of RRT in infants.

INTRODUCTION

End-stage renal disease (ESRD) is a rare condition in infants and young children. The incidence of ESRD in children younger than 4 years old is 5.2 per million age-related inhabitants in France (30) and 6.5 per million age-related inhabitants in Europe (134). Despite major technical improvement in the care of children requiring renal replacement therapy before two years of age, the management of those patients remains challenging (68, 69). Renal transplantation is generally delayed until the child weighs 10 kg or is 2 years old exposing the youngest patients to prolonged period of dialysis and major issues in term of nutrition, statural growth and psychomotor development. Moreover, extra-renal comorbidities are frequent in this group because more than half of the primary renal diseases in this group are genetic diseases (30) with potential extra-renal involvement and because prenatal renal failure potentially complicated by oligamnios or anamnios exposes some of those patients to pulmonary hypoplasia and premature birth and its complications.

However, major improvement in the survival of those patients has been reported over the last decades. Mitsfenes et al. reported a decrease of the mortality rate from 11.2% in the early 90s to 8.3% between 2005 and 2010 in the US (67) and McDonald et al., based on the data of the ANZDATA registry, reported a decrease in the risk ratio of death from 116 to 32 when compared with the age-related mortality of the general population between the 60s and the 90s (53). Despite the progresses made, initiating RRT especially in the younger children remains controversial. Geary et al. performed two surveys, one in 1998 and one in 2010 and found that clinical management perspectives have not significantly changed since renal replacement therapy was offered by 41% of the nephrologists to all infants <1 month old and by 53% to all infants between 1 and 12 months in 1998 and to 30% and 50.2% respectively in 2010 (43, 135).

Considering renal transplantation, graft survival has been consistently reported to be worse in the youngest children when compared with the oldest ones (30). Although many studies investigated the impact of morphological (136-138), and immunological matching (50, 139) on graft survival, major discrepancies on the minimal recipient weight for renal transplantation, the choice of deceased versus living donor and minimal HLA-matching have been reported between centers and countries

(140). Moreover, no study investigated the impact of those factors together to help clinicians in their decisions.

Thus, we aim to study patients' and grafts' survivals in children starting RRT before two years old to help clinicians and parents to make decisions on RRT initiation and transplantation programming.

MATERIAL AND METHODS

Study population and data

We aimed to include all patients that started RRT before 24 months old in France between January 1st 1992 and December 31st 2012. In order to be exhaustive, three complementary ways of detecting patients were used: through the National Transplant Database (CRISTAL) that records data on all the patients registered on the waiting list, through the National ESRD registry (REIN) that records data on all patients on RRT and is exhaustive in children since 2005 and through all individual hospitals' databases.

Patients' characteristics recorded were patients' age at RRT initiation and at renal transplant, gender, primary renal diseases (PRD) that were classified in four groups (Congenital Abnormalities of the Kidney and the Urinary Tracts (CAKUT), Genetic diseases, Vascular diseases and others), first renal replacement therapy modality (peritoneal dialysis, hemodialysis and preemptive transplantation), comorbidities (from which we created the binary variables at least one comorbidity) and date of death if applicable.

Data on the transplantation included age at renal transplant, weight and height of the donor and the receiver, type of donor (living or deceased), HLA matching and ischemia time.

Statistical analysis

For descriptive analysis, continuous variables are given as medians and interquartile ranges and dichotomous variables in percentages.

Patients' survival and access to renal transplantation

We present the cumulative incidence of death and transplantation overall and stratified by risk

factors. In order to assess the factors associated with the risk of death on dialysis, we used univariate and multivariate proportional hazard Cox regression, with the time between the start of RRT and death as primary outcome and with renal transplantation as censoring event. Patients that received preemptive transplantation (N=6) were excluded from the analysis. All variables significant at a p-value of 0.20 in the univariate analysis were included in the multivariate analysis. We tested for the presence of a cohort effect by testing the association between the year at RRT initiation and death with the SAS macro RCS-REG that test both the linearity and the significance of the association using spline modeling.

Renal transplant survival

The primary outcome was a composite outcome defined as graft loss or death. We used univariate Cox regression to assess the association between each variable and the outcome. Proportional hazards assumption of the models was assessed by graphical methods. All continuous variables were tested for linearity with the SAS macro RCS-REG. We used Kaplan Meier modeling to present the survival curve. Multivariate cox regression was used to assess factors independently associated with graft loss. We used the HR from this model to create the predicted survival curves for every combination of risk factors.

RESULTS

We included 244 patients who started RRT before 24 months old. Among them 141 (62.9%) were male, the median age at RRT start was 10.4 [5.8-15.6] months and the most prevalent primary renal diseases were CAKUTs and genetic diseases. Patients' characteristics at RRT start are presented in Table VI.16.

The median follow-up time was 78 [36-147] months. During follow-up 174 renal transplant were performed in 159 patients and 29 patients died (18 before renal transplantation and 11 after renal transplantation) with the two main causes of death being infections and cardiovascular events (Table VI.17). Only 10 transplantations were from a living donor. None of the patients was withdrawn from dialysis to palliative care. Overall patients' 5 and 10 years-survivals were 87% [82%-91%] and 84% [77%-89%] respectively.

Determinants of patients' survival on dialysis and access to transplantation

Patients' characteristics found to be associated with an increased risk of death by univariate analysis were to present a genetic disease as PRD (HR 5.6 [1.3-25.0] compared to patients with CAKUT) and to suffer from extra-renal comorbidities (HR 7.7 [2.4-24.5]). There was a trend towards a decreased risk of death with age although it did not reach statistical significance. Starting RRT on PD or HD did not significantly impact patients' survival (Table VI.18).

To suffer from extra-renal comorbidities was the only factor significantly associated with the hazard of death by multivariate analysis (HR 5.9, 95%IC [1.8-19.3]). Figure VI.10 and VI.11 present the cumulative incidence of death and renal transplantation stratified on the presence of comorbidity and on the groups of age respectively.

Determinants of graft survival

The 10 years graft survival was 74% [67%-81%]. Figure VI.12 presents the graft survival curve.

Over the 159 first renal transplantations performed in our patients, median age at transplantation was 30.2 [21.8-40.7] months with median recipient weight and height being 12.0 [10.4-13.6] kg and 85.0[80.5-92.5] cm respectively. Overall, our population of recipients was very homogeneous with only 5% of the recipients aged less than 1 year old. They were very close in terms of weight and height. This homogeneity precluded us from studying the impact of those variables on renal survival. Variables found associated with transplant survival by univariate analysis were the donor/recipient height ratio ($p=0.05$) and the number of mismatch in HLA group DR ($p=0.02$) (Table VI.19).

In order to make our results potentially useful in clinical practice, we dichotomized donor/recipient height ratio in 5 groups ($\text{ratio} \leq 1$, $1 < \text{ratio} < 1.4$, $1.4 \leq \text{ratio} \leq 1.8$, $1.8 < \text{ratio} < 2.2$, $\text{ratio} \geq 2.2$). Figure VI.13 presents the evolution of the HR of graft loss with donor/recipient height ratio.

There was a tendency towards an improved graft outcome with time since the HR of graft lost was 2.1 in the older period when compared to the most recent one (HR of graft lost by year 0.95, $p=0.13$).

The two factors found significantly associated with graft loss by multivariate analysis were donor/recipient height ratio and presenting 2 HLA DR mismatches (Table VI.20). In order to help clinicians to transpose those results in clinical practice, we created a predictive model using those two main risk factors. The discrimination of this model is shown in figure VI.14. The AUC of this model was 0.63.

Discussion

In this national cohort of patients starting RRT before the age of two years old, we confirmed the overall good patients' survival with a 5-years patient survival of 87% [82%-91%] close to survival reported in the US in patients aged 0 to 4 years old (84%) (141).

As reported in many previous studies (53, 67, 142, 143), we found a trend towards an increased risk of death in the youngest children, although age at RRT initiation did not reach statistical significance. Carey et al, did not find a significant difference of survival between patients starting RRT before 1 month old and those starting between 1 and 24 months old (144), however because NAPRTCS only includes patients who started dialysis in centers willing to participate in the registry, selection bias of the youngest patients with the most favorable prognosis might explain the absence of effect of the age at initiation of RRT in this study. In our study, the only factor significantly associated with patients' survival on dialysis was the presence of extra-renal comorbidities with a cumulative incidence of death ranking from 4% in patients without extra-renal comorbidities to 30% in patients with at least one comorbidity. This is consistent with the data published in the Netherlands in patients aged 0-14 years old treated between 1972 and 1992 (145). Similarly, a study focusing on patients with CAKUT demonstrated that the major risk factor of death was to present CAKUT associated with extra-renal abnormalities (146).

Considering the access to renal transplantation, many studies emphasized the issues raised by renal transplantation in this population. Should we favor living kidney donation usually from adults with major morphological differences? Is HLA matching still important in children? However, mixing all those results together to guide clinical decision remains challenging so that there is a great heterogeneity of practices. In our study, morphological matching especially in height was highly associated with graft survival and a donor/recipient height ratio between 1.4 and 1.8 was found to be associated with the best graft survival. One of the main causes of graft loss in patients younger than 2 years old is thrombosis (147) and many studies reported worse graft outcome when using size-matched donors. Moreover, Dick et al. found a decreased renal survival among adolescent's recipients who received a kidney from a donor smaller than them (Donor/recipient body surface area ratio < 0.9) confirming the risk associated with smaller donors (136). Although, Pape et al. studying children under 10 years old questioned the use of kidneys from adult donors because they found that three to five years after transplantation the corrected GFR was significantly higher in children who had received a pediatric graft, with grafts also doubling in size whereas no increase in size was

noted in adult grafts (148), our study confirms that in the youngest patients the use of size-matched kidneys increases the risk of graft loss and should be avoided. Moreover, the scarcity of small pediatric kidney donors would lead to unacceptable waiting time on dialysis (138).

The other factor found significantly associated with the graft's survival in our patients was HLA-matching for class 2 antigen DR. Recently, many authors questioned the importance of HLA-matching (149) and emphasized the importance of other factors such as prioritizing kidney from young adults for pediatric recipients (139) and minimizing cold ischemia time. Moreover, not waiting for HLA-matched kidney could favor rapid access to transplantation and allow preemptive transplantation in some children. However, a poorer HLA matching harbors the risk of panel reactive antibodies (PRA) development that could hamper both the ability to receive subsequent transplantation and the survival of the graft. This is a major concern in young children receiving renal transplantation since they will require further transplantation in their lifetime. Moreover, results on this question remain unclear since Gritsch et al. did not find any difference in PRA level between well-matched and unmatched patients (139). Recently, Tinckam et al. also reported on the risk of repeated HLA-mismatch and showed that the presence of HLA class 2 mismatches especially if PRA were present before the second transplantation decreases graft survival. This effect was even stronger in patients who underwent a nephrectomy of the first transplant (150).

Finally, the major issue faced by clinicians when deciding the optimal strategy of transplantation is to combine all those data together to take evidence-based decisions. Among adults, several authors created clinical scores aiming to predict renal transplantation outcome based on pre-transplant (151) and post-transplant data (152-155). Among children, a study aiming at defining groups of patients by risk of graft loss has been recently published based on the data from the ESPN/ERA-EDTA registry (156) and identified age, duration of dialysis prior to transplantation and eGFR post-transplantation as major factors associated with graft survival. However, the specificity of the patients starting RRT before 2 years old requires specific studies focusing on this population. Based on the results of the analysis of graft survival, we present the predicted risks of graft failure for every combination of risk factors. This will allow us to display the risk of graft failure based on donor and recipient height at transplantation and HLA DR matching. In order to be able to include in our predictive tool the type of donor and to give prediction with the higher precision possible, we will try to repeat this analysis on a larger European cohort.

Based on the data of this national cohort, we were able to confirm and identify risk factors of patients' and transplants' survivals in the youngest children starting RRT and to develop tools to help

the choice of the transplant. Our study also has some limitations. First, the retrospective design of the study and the absence of registry of termination of pregnancy and of conservative treatments does not allow us to study the survival of all patients with ESRD but only those who started RRT. Moreover, practices of RRT initiation are different between countries and centers. Due to the scarcity of the patients starting RRT before 2 years old, we included patients on a 20-years period of study. Although we did not find any statistically significant cohort effect, modifications of practices happened that could modify the association reported. Finally, the scarcity of transplantation from living donors precluded us to compare graft survival by type of donor and to include this parameter in our predictive model.

Conclusion

In this national retrospective cohort study, we confirm the overall good overcome of children starting RRT before two years old. Considering the choice of starting RRT, extrarenal comorbidity should be the main factor considered since patients' survival in the absence of those comorbidities is excellent. Thus, the main question in infants with ESRD remains when and how to transplant them. Our study provides data on the optimal morphological and immunological matching in order to help clinicians in their decisions. By extending this analysis to other cohorts, we aim to develop a tool able to predict graft loss and help clinicians when choosing the optimal kidney for their patients.

Patients' characteristics		
	n = 244	N (%)
Gender	Boys	141 (62.9)
Age at RRT start (months)	(mean and IQ)	10,4 [5.8-15.6]
Primary renal disease	CAKUT	76 (34.1)
	Genetic diseases	85 (35.1)
	Vascular diseases	33 (14.8)
	Others	29 (13.0)
Comorbidities	None	96 (42.9)
	At least one	45 (20.1)
	Unknown	83 (37.1)
Initial Treatment modality	Peritoneal dialysis	144 (64.3)
	Hemodialysis	61 (27.2)
	Dialysis NS	12 (5.4)
	Preemptive Transplantation	7 (3.1)
Time spent on dialysis (months)	(mean and IQ)	22,1 [10,1-33,4]

CAKUT: Congenital Abnormalities of the Kidney and the Urinary Tracts

IQ: Interquartiles

Table VI.16: Patients characteristics at renal replacement therapy initiation

Causes of death		
N = 29	N	%
Infections	6	21%
Cardiovascular	9	31%
Treatment withdrawal	0	0%
Neoplasia	2	7%
Liver failure	2	7%
Multiple organ failure	3	10%
Unknown	7	24%

Table VI.17: Number and Causes of death

		Univariate Analysis		Multivariate Analysis	
Patients' characteristics	N=217	HR	95%IC	HR	95%IC
Age at RRT start (months)	[0-6]	6,1	[0,8-48,8]	7,7	[0,9-63,1]
]6-12]	3,0	[0,4-25,0]	3,8	[0,4-31,9]
]12-18]	1,8	[0,2-20,0]	2,2	[0,2-24,6]
]18-24]	1		1	
Gender	Boys	1		1	
	Girls	1,6	[0,6-3,9]	0,8	[0,3-2,2]
Primary renal disease	CAKUT	1		1	
	Genetic diseases	5,6	[1,3-25,0]	3,9	[0,8-18,8]
	Vascular diseases	1,0	[0,1-11,7]	0,9	[0,1-9,9]
	Others	3,9	[0,7-22,7]	3,9	[0,6-26,5]
Comorbidities	None	1		1	
	At least one	7,7	[2,4-24,5]	6,2	[1,9-20,1]
	Unknown	1,8	[0,4-8,3]	1,5	[0,3-6,8]
Initial Treatment modality	Hemodialysis	2,2	[0,9-5,6]		
	Peritoneal dialysis	1			
	Dialysis NS	1,3	[0,2-10,5]		
Time spent on dialysis (months) ^ψ			NS		

^ψ Spline modelling

CAKUT: Congenital Abnormalities of the Kidney and the Urinary Tracts

Table VI.18: Cause-specific hazards of death on dialysis

Recipients characteristics			
		Univariate Analysis	
	Description	HR	p-value
Female gender	55 (34,6%)	1,20	0,62
Primary renal disease			0,93
CAKUT	50	1,00	
Genetic diseases	61	0,64	
Vascular diseases	27	0,90	
Others	24	0,95	
Comorbidities			0,28
None	101	1,00	
At least one	26	2,00	
Unknown	44	1,00	
Initial treatment type			0,91
HD	43	1,00	
DP	111	0,74	
Dialyse NS	11	0,83	
Tx	6	0,83	
Donor Characteristics			
Age (in years)	11,9 [6-15]	0,99	0,78
Weight (in kg)	38,2 [20,0-52,0]	1	0,85
Height (in cm)	139,7 [120-162]	1	0,82
Donor-Recipient matching			
Donor/Recipient Body weight ratio	3,82 [1,71-4,17]	ψ	0,33
Donor/Recipient Body height ratio	1,62 [1,33-1,87]	ψ	0,05
DR Mismatch number			0,02
2	25	1,00	
1	104	0,32	
0	30	0,48	
B Mismatch number			0,58
2		1,00	
1		1,49	
0		0,00	
A Mismatch number			0,19
2		1,00	
1		0,56	
0		0,80	
Year of transplantation		0,95	0,13

ψSpline modelling

Table VI.19: Hazard ratios of graft failure or death in transplanted patients (univariate analysis)

	HR	p-value
Donor/Recipient Body height ratio		
≤1	4	0,03
1 < ratio < 1,4	1,6	0,21
1,4 ≤ ratio ≤ 1,8	1	
1,8 < ratio < 2,2	1,4	0,64
≥ 2,2	7,6	0,03
Number of HLA DR Mismatches		
0 to 1	1	
2	2,34	0,03

Table VI.20: Hazard ratios of graft failure or death in transplanted patients (Multivariate Analysis)

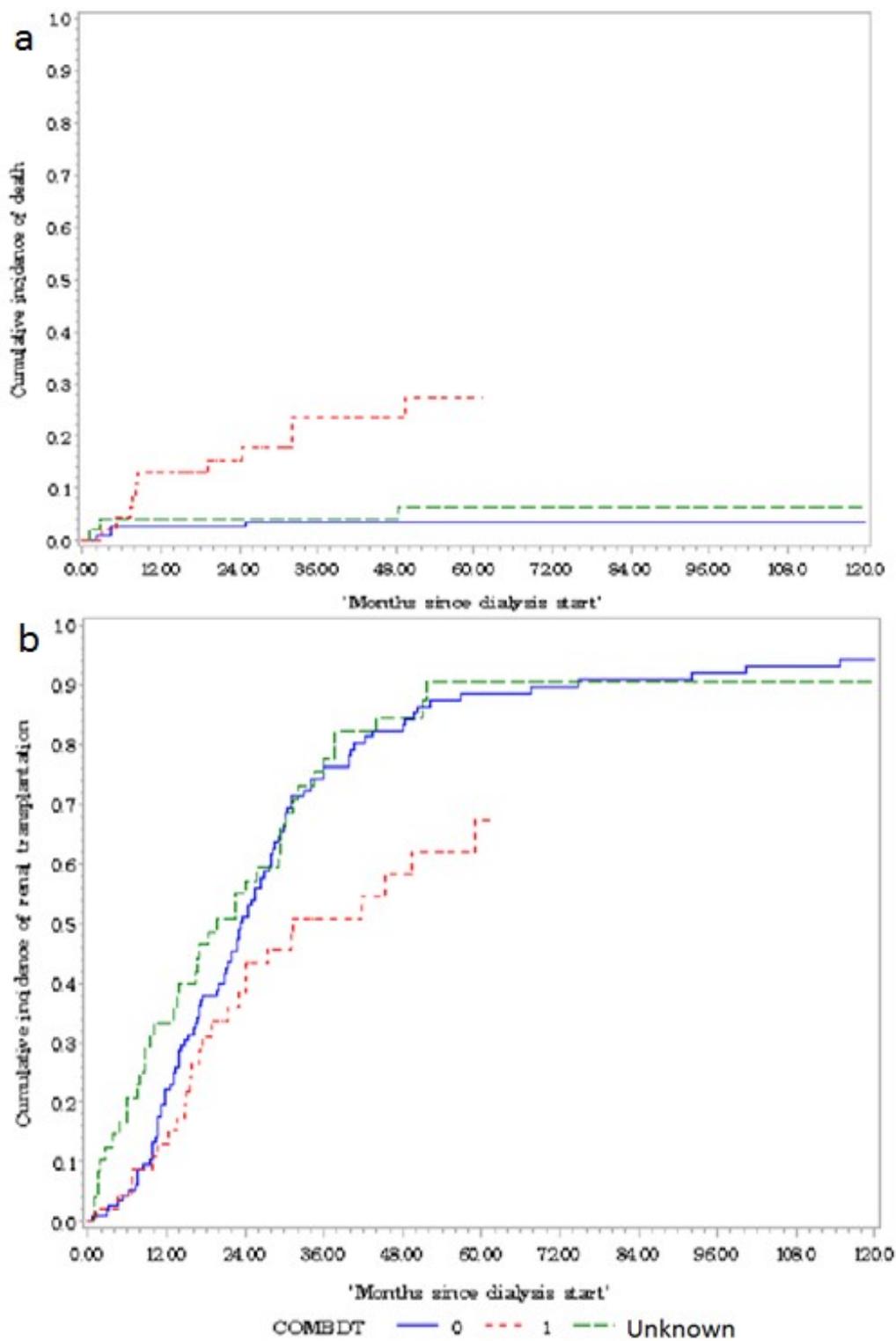


Figure VI.10: Cumulative incidence of death (a) and transplantation (b) stratified on comorbidities

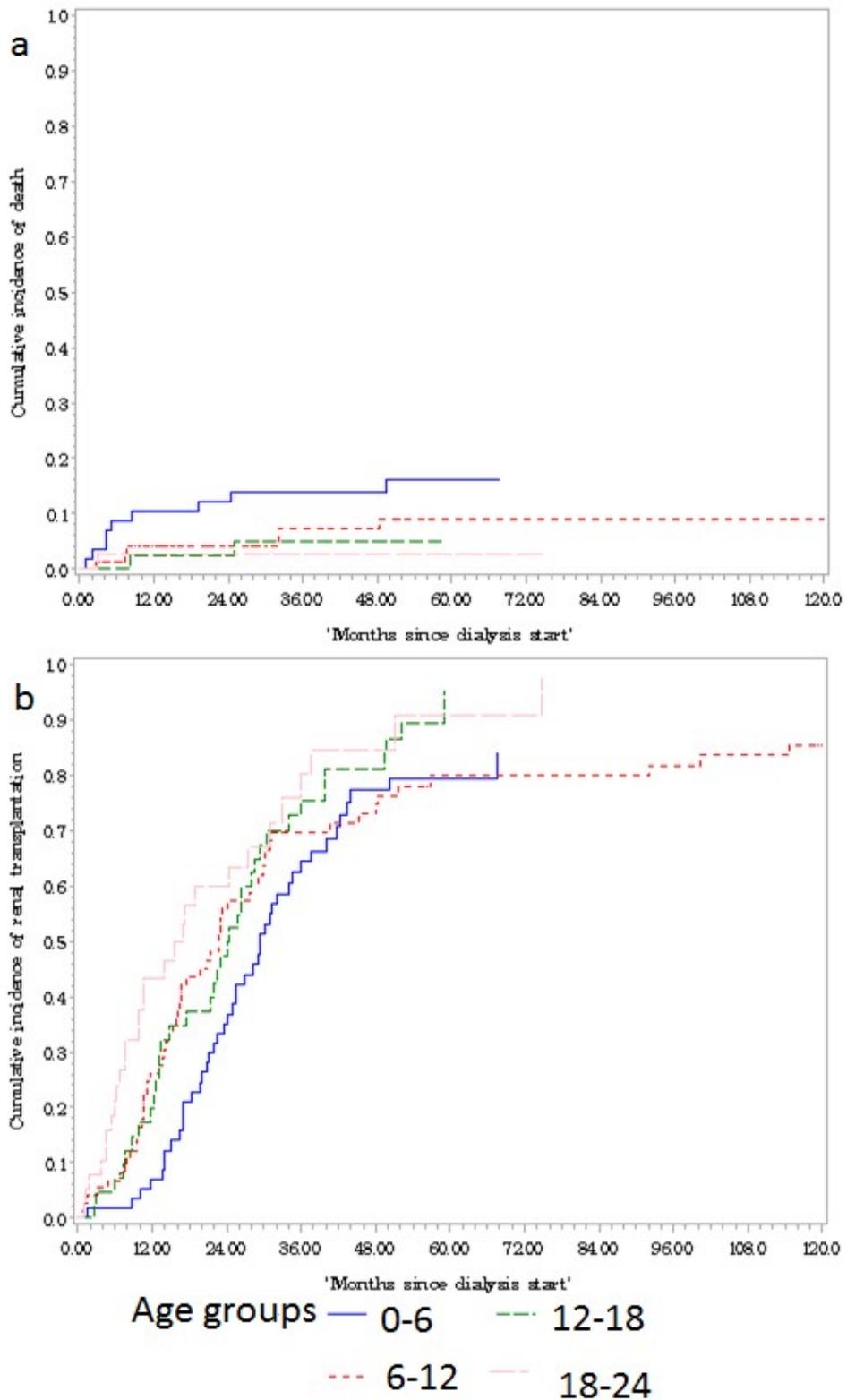


Figure VI.11: Cumulative incidence of death (a) and transplantation (b) stratified by age

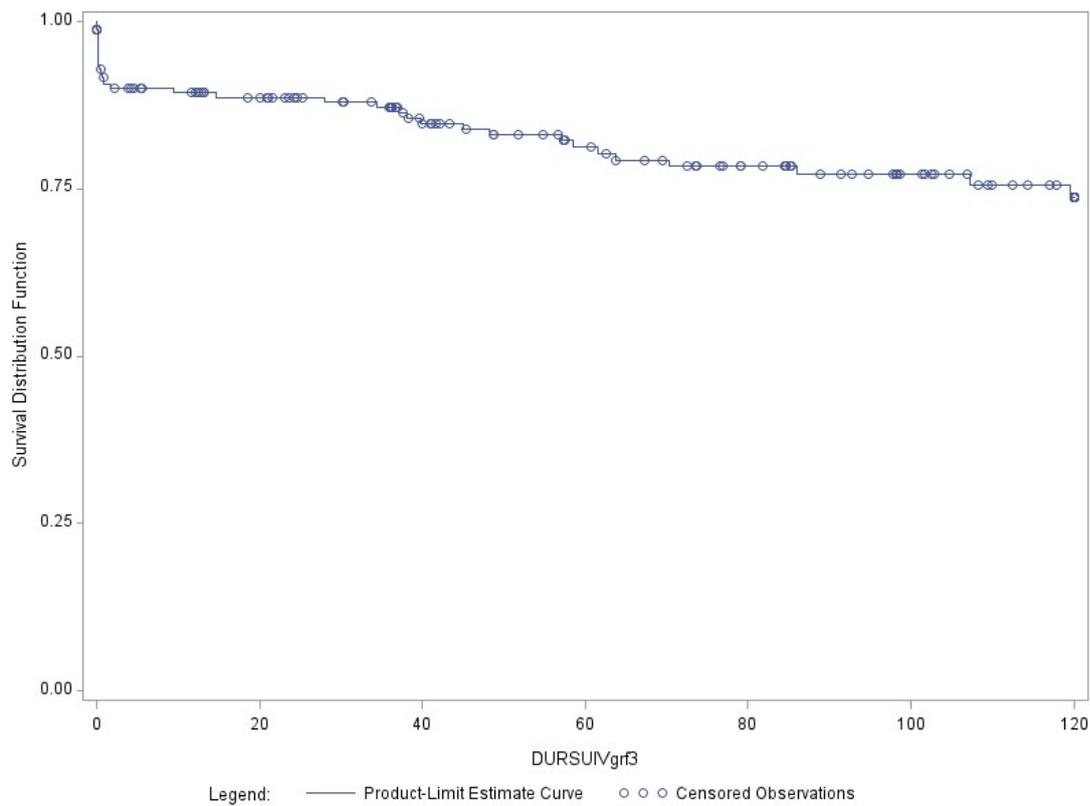


Figure VI.12: Kaplan Meier curve of graft survival over a 10 years follow-up.

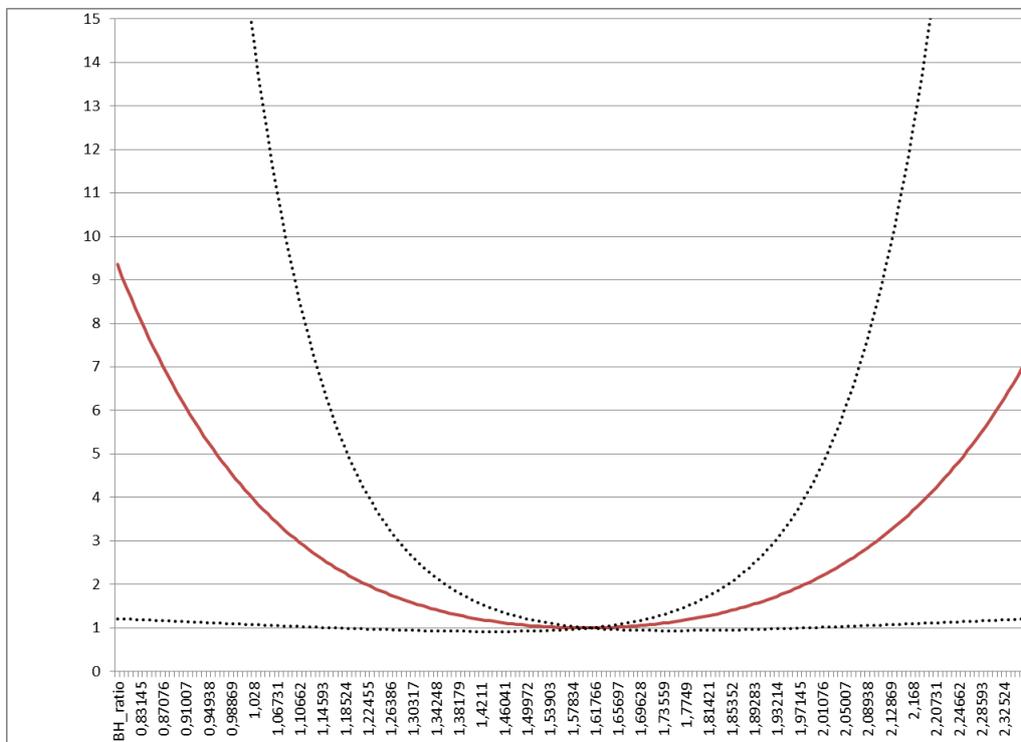
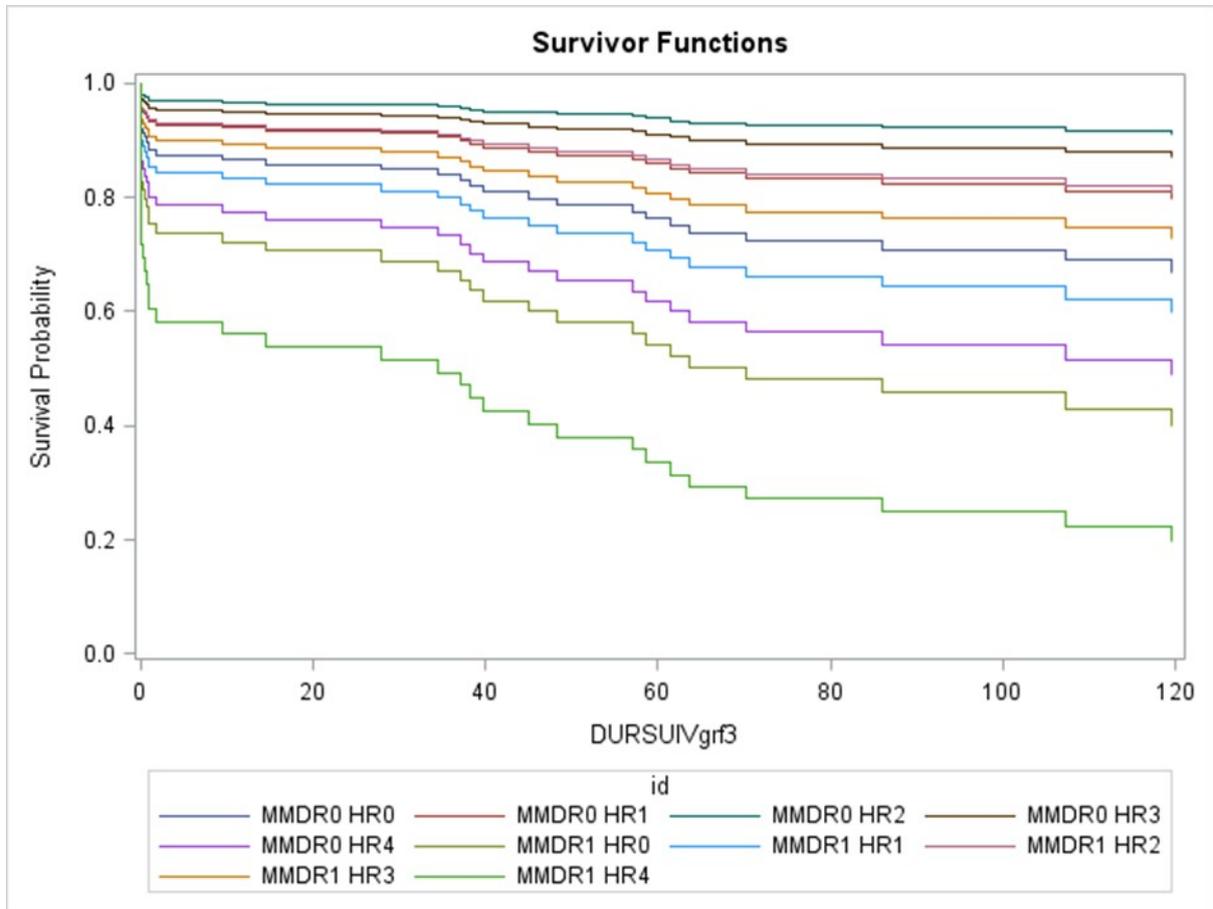


Figure VI.13: Evolution of the HR of graft loss or death with donor/recipient height ratio



Donor/recipient height ratio	≤ 1	$]1-1,4[$	$[1,4-1,8]$	$]1,8-2,2[$	$\geq 2,2$
0 or 1 DR Mismatch					
2 DR Mismatches					

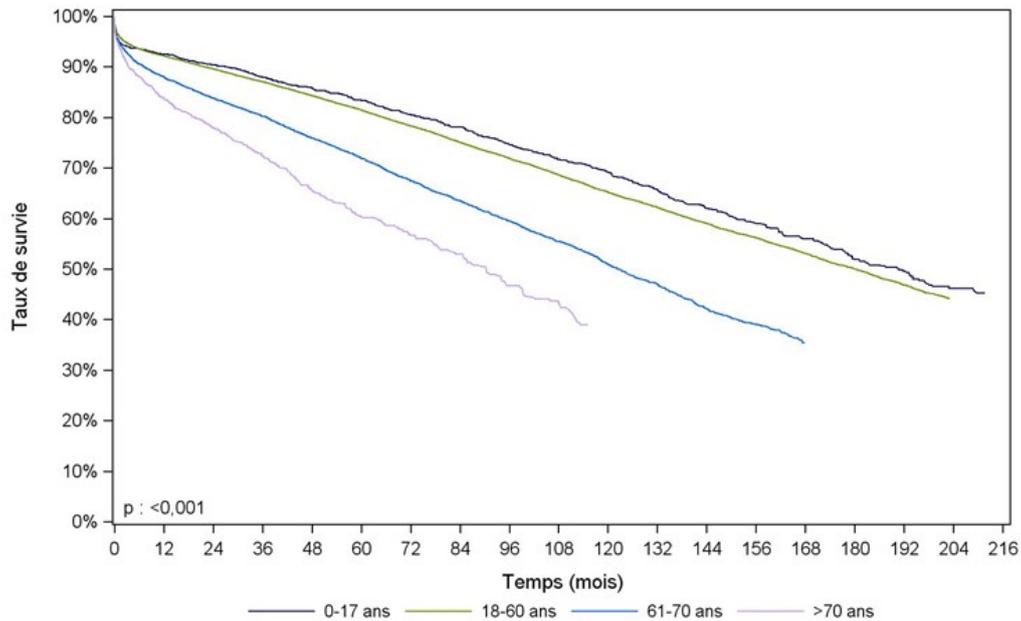
Figure VI.14: Predicted survivals based on HLA DR mismatch number and Donor/recipient height ratio.

C. Transplantation outcome and complications

1. Study of patients and graft survival

Patients' and transplants' survivals are reported every year in the Annual Report of the French Biomedecine Agency (102). Figure 4.15 presents graft survivals by recipients' age-groups.

Figure R8. Survie du greffon rénal selon l'âge du receveur (1993-2012)



Age du receveur	N	Survie à 1 mois	Survie à 1 an	Survie à 5 ans	Survie à 10 ans	Survie à 15 ans	Médiane de survie (mois)
0-17 ans	1942	95,3% [94,2% - 96,1%]	92,5% [91,2% - 93,6%]	83,4% [81,6% - 85,1%]	69,2% [66,7% - 71,6%]	52,0% [48,6% - 55,2%]	190,8 [177,8 - 202,8]
nombre de sujets à risque*		1832	1744	1214	655	247	
18-60 ans	34649	96,2% [96,0% - 96,4%]	92,2% [91,9% - 92,5%]	81,5% [81,0% - 81,9%]	65,2% [64,6% - 65,9%]	50,0% [49,2% - 50,9%]	180,2 [176,4 - 183,4]
nombre de sujets à risque*		33007	30685	20378	9345	3151	
61-70 ans	7671	95,0% [94,5% - 95,5%]	88,0% [87,2% - 88,7%]	72,0% [70,8% - 73,1%]	50,9% [49,3% - 52,5%]	NO	122,4 [118,5 - 126,8]
nombre de sujets à risque*		7188	6331	3260	1132	261	
>70 ans	1493	94,2% [92,9% - 95,3%]	83,8% [81,8% - 85,6%]	60,4% [57,2% - 63,5%]	NO	NO	90,4 [81,3 - 99,2]
nombre de sujets à risque*		1377	1127	363	56	4	

□ : Intervalle de confiance

NO : non observable

* : Nombre de malades restant à observer pour chaque temps et pour lesquels aucun évènement ni censure n'est survenu

Figure VI.15: Graft survival by recipients' age-groups.

Moreover, Kabore et al. studied the effect of age on the probability of graft loss and identified an increased risk in teenager and young adults that remains beyond the period of transition between pediatric and adult nephrology units (157).

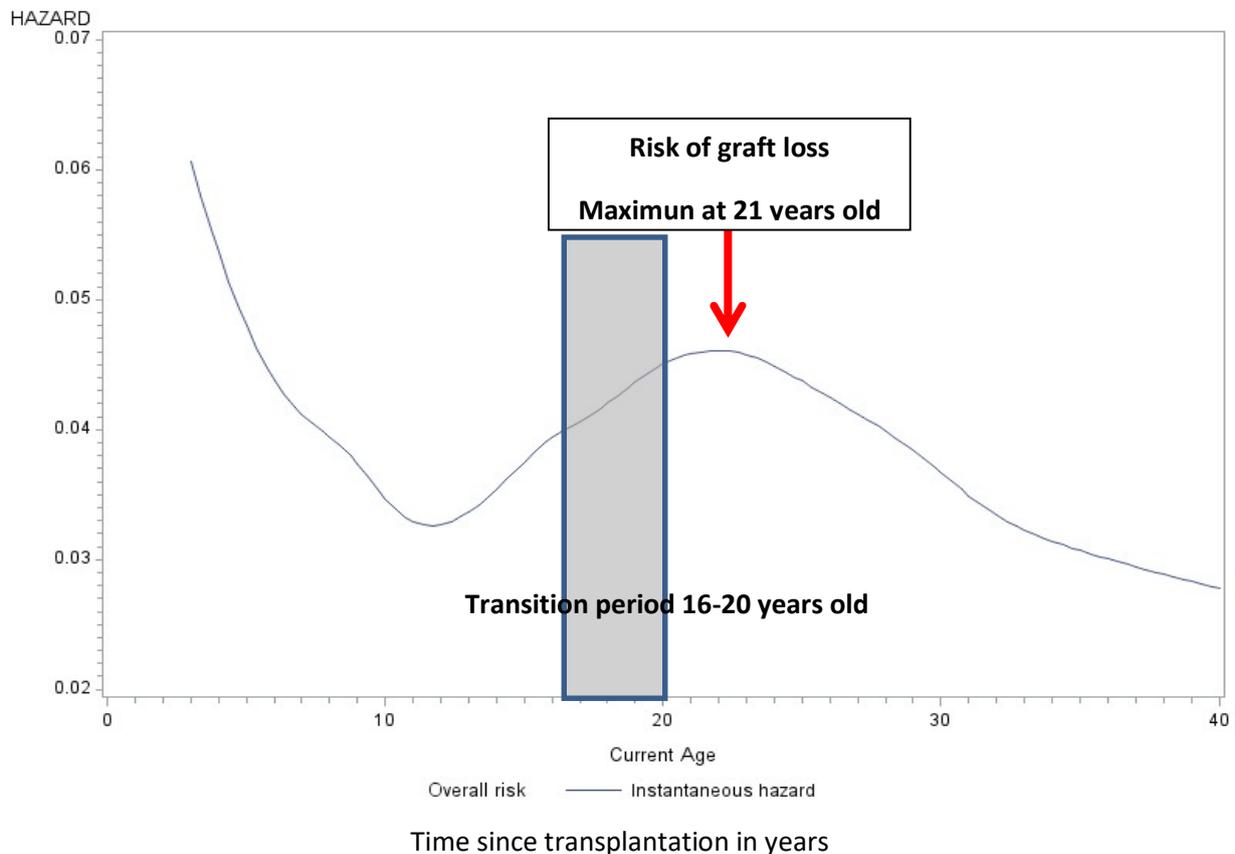


Figure VI.16: Hazard ratio of graft loss function of current age (157)

Therefore, we did not study graft survival and will use already published data to feed our model.

2. Study of post-transplant complications

As we were studying the trajectories of the children and the young adults reaching ESRD, we realized that the trajectories of the patients were not only the succession of the RRT modalities but could also take into consideration the occurrence of complications such as infections or neoplasia. Those complications are poorly captured in the registry so we decided to match using indirect matching the data of the registry with the data of the French Medico-administrative database (PMSI). We present here the study we performed on the infection-related hospitalizations after renal transplantation.

Infection-related Hospitalizations after Kidney Transplantation in Children: Incidence, Risk Factors and Cost.

Julien Hogan, Christine Pietrement, Anne-Laure Sellier-Leclerc, PhD, Ferialle Louillet, Rémi Salomon, Marie-Alice Macher, Etienne Berard, Cécile Couchoud

Pediatr Nephrol. 2017 Apr;32(4):659-667.

Introduction:

Renal transplantation is nowadays recognized as the modality of choice for renal replacement therapy in children and has been associated with a better survival (29, 30) and an improved quality of life (31). However, transplanted patients are at risk of graft rejection, primary renal disease recurrence and infections that can impair graft and patient survival and patient's quality of life through multiple hospitalizations. Over the last decade, infection has become the first cause of death in pediatric patients living with a renal transplant above cardiovascular death (158). In the US, while the number of hospitalization is decreasing, the number of infection-related hospitalizations among adult patients remains stable (141). Among children, infection-related hospitalizations has become the first cause of hospitalization after transplantation in the US (159) and a recent study from a Dutch cohort reported an increase in infections requiring hospitalization over time in pediatric transplant recipients (160).

Moreover, renal transplantation is considered as the renal replacement therapy (RRT) modality with the best long-term cost-effectiveness (34, 35). However, infection-related hospitalizations induce additional costs that need to be evaluated.

In this study we attempt to describe post-transplant infections requiring hospitalization in a French national cohort of pediatric renal transplant recipients, to study the risk factors of infections and to evaluate the cost of those infection-related hospitalizations.

Material and Methods:

The National medico-administrative Hospital Discharge database (PMSI) registers all hospitalizations of the French population with data on the medical conditions that justified the hospitalization, medical procedures during the stay, date and duration of the stay. All patients under 20 years old who received a kidney transplant in France between 2008 and 2013 were extracted from this database. We extracted all their hospitalizations following transplantation between 1st January 2008 and 31st December 2013 and classified them according to their causes namely infections, graft rejection and neoplasia based on the first ten main diagnosis and the first ten related diagnosis

reported. Infection-related hospitalizations were further divided according to the type of pathogen (virus, bacteria, fungus or parasite and unknown) and the localization of the infection (urinary, respiratory, digestive, sexually transmitted, neurological, bacteremia, others and unknown). Among viral infections we were able to isolate CMV infections, EBV infections and other herpes virus infections from the other viral infections. The cost evaluation was made using the 2009 Public Health Care Tariff Calculations (161).

In order to get detailed data on the patients' pre-transplant condition and on the transplant, we performed a probabilistic matching with the National Renal Transplant Database (CRISTAL) based on patients' age, gender, month and year of transplantation and district of treatment. Data extracted from the Transplant database were date of birth, date of transplantation, gender, previous RRT modality (hemodialysis, peritoneal dialysis or none for patients with pre-emptive transplantation), primary renal disease, presence of comorbidity such as uropathies or diabetes, HLA matching (considering HLA A, B and DR), cold ischemia time, pre-transplant CMV and EBV status (both in the donor and the recipient) and the initial immunosuppressive treatment.

For descriptive analysis, continuous variables are given as medians and interquartile ranges and dichotomous variables in percentages. We used Chi-square and student t-test to test the difference between dichotomous and continuous variables respectively. We used univariate and multivariate Cox regressions to study the risk factors of being hospitalized for infection and Kaplan-Meier method to present the cumulative incidences of hospitalization stratified by risk factors. In order to assess the evolution of the risk with time, we calculated the crude infection-related hospitalization rate by 1-month interval for all infections and by type of infection and plotted the evolution of the risks with time. Patients were censored at death or graft failure.

The French Advisory Committee on Information Processing in Material Research in the Field of Health (CCTIRS) and the National Commission for Information Technology and Privacy (Commission Nationale de l'Informatique et des Libertés) approved in 2003 the data collection and the analysis conducted by the REIN registry.

Results:

Study population

In the PMSI database, 632 patients aged less than 20 years old who received a first renal transplantation were found. Among them, 593 (94%) were matched with recipients from the national transplant database (Figure VI.17). There was 59% male with a median age at renal transplantation at 14.1 [8.9-17.1] years. The most prevalent causes of ESRD were Congenital Abnormalities of the

Kidney and the Urinary Tracts (CAKUT) for 33.2% and glomerular diseases for 22.6% of them. Considering viral serologies, 62.4% and 34.4% were negative for CMV and EBV respectively. Initial immunosuppressive regimen consisted in Tacrolimus (67.4%), Mycophenolate (91.3%) and steroids (99.3%) and median number of mismatches was 3[3-4]. The median follow-up time was 34.7 [14.7-53.2] months.

Risk of infection-related hospitalization

During the five year period, 660 infection-related hospitalizations were identified in 260 patients. Table VI.21 describes the hospitalizations by type of infection and reports the number of stays and their median duration, the number of patients infected, the incidence rate of hospitalization by patient year, the delay between transplantation and hospitalization and the cost by type of infection (total and by patient-year). The first cause of infection-related hospitalization was urinary-tract infections with 283 hospitalizations and an incidence rate of 16.6 per 100 patient-years. UTI recurrence was frequent with half of the 118 patients undergoing two or more UTI-related hospitalizations and 25% of them presenting at least 3 hospitalizations. Among patients with UTI, 11 (9.3%) needed a surgical management of a vesico-ureteral reflux on the transplant. Other bacterial infections were responsible for 95 hospitalizations (incidence rate 5.6 per 100 patient-years): 42 respiratory tract infections, eight digestive infections (including three Clostridium Difficile infections), 35 bacteremia (15 gram negative bacteria, five cocci gram positive, one anaerobic bacteria and 14 from unspecified bacteria) and 10 other bacterial infections. The incidence of hospitalization for viral infection was 15.6 per 100 patient-years. In our cohort, the first virus-related hospitalization cause was digestive infections (128 hospitalizations in 50 patients, incidence rate 7.5/ 100py) and upper and lower respiratory tract infections (70 hospitalizations in 50 patients, incidence rate 4.1/100py). There were 47 hospitalizations related to herpes viruses' infections: 22 due to CMV infections, only 2 to EBV infections and 23 to HSV or VZV infections. Only 15 hospitalizations related to fungal or parasitic infections were observed including 4 cryptosporidiosis and 4 pneumocystosis.

Change in risk over time

The monthly rate of infection-related hospitalization decreased with time from about 8% per month in the first six months post-transplantation to about 1% at five years post-transplantation (Figure VI.18). Such a decrease was found for all type of infections except for CMV infections that showed a peak around 6 months post-transplantation corresponding to the withdrawal of the prophylactic

treatment. At any time, infection-related hospitalization remained the first cause of hospitalization in our population (Figure VI.19). The risk of hospitalization remained stable over the five year period of the study.

Risk factors for hospitalization

Patients' characteristics overall and by type of infection and in the group of patients without any infection-related hospitalization during the follow-up are reported in Table VI.22 and VI.23. When comparing patients with or without infection-related hospitalizations, the risk factors of hospitalization were a younger age at renal transplantation (HR 0.95 [0.92-0.97] per year of age), a higher number of HLA mismatch (HR 1.14 [1.01-1.28] per mismatch) and the use of Cyclosporine A rather than Tacrolimus as first anticalcineurin treatment (HR 1.40 [1.05-1.88]). In our cohort, induction treatment consisted of Basilixumab in 82.1% and antithymocyte globulin in 17.9% of the patients. There was no statistically significant relation between the type of induction and the risk of infection-related hospitalization. Because the use of antithymocyte globulin decreased with time and has been replaced by basiliximab in low risk patients, while the use of Tacrolimus and mycophenolate was increasing, we performed two sensitivity analyses including either the type of induction or the type of antiproliferative agent to explore potential confounding effects. However, the association with the use of Cyclosporine remained unchanged (HR 1.47 [1.09-1.98] when including the induction treatment; HR 1.49 [1.10-2.03] when including the type of antiproliferative agent) (Table VI.24). Cumulative incidence curves of hospitalization by age and by type of anticalcineurin inhibitors are presented in Figures VI.20 and VI.21. The overall rate of hospitalization ranged from 52% in children less than five years old to 27% in patients older than 15 years old. There was a trend toward a higher risk of hospitalization in patients with pre-transplant urological comorbidities (HR 1.34 [0.89-2.02]).

We performed sensitivity analysis to determine if some risk factors were specifically associated with a certain type of infection. Female gender (HR 2.10 [1.40-3.10]), the presence of an uropathy (HR 2.0 [1.14-3.7]), prolonged cold ischemia time (HR 1.03 [1.01-1.06] per hour) and cyclosporine as first anticalcineurin treatment (HR 1.80 [1.20-2.70]) were associated with an increased risk of urinary tract infection. We did not find any effect of age at transplantation on the risk of urinary tract infection. However, age was found inversely correlated with the risk of other bacterial infections (HR 0.95 [0.91-0.99]). A trend towards a higher risk of hospitalization for bacterial infections in patients treated with cyclosporine remained but did not reach statistical significance (HR 1.5 [0.90-2.60]).

Age at renal transplantation was the only risk factor inversely correlated with the risk of hospitalization for diarrhea of viral or unknown origin (HR 0.90 [0.87-0.94] per year), the risk of hospitalization for viral respiratory tracts infections (HR 0.88 [0.84-0.93]) and the risk of herpes-related hospitalization (HR 0.89 [0.82-0.97]). Initial immunosuppressive regimen did not affect the risk of hospitalization related to these infections.

Cost of hospitalizations

The total cost of infection-related hospitalizations was 1 600k€ (933€/py) for 3529 days of hospitalization. Hospitalizations because of bacterial infections other than urinary tract infections were the most expensive with a median cost by stay of 2443 [1611-6330] euros. This cost was partly explain by a higher rate of patients requiring admission in an intensive care unit (16.8% vs 5.7%, $p>0.001$). Considering the total financial burden of infection related hospitalizations, urinary tract infections and viral digestive infections were the two other main contributors because of the high prevalence of those infections in transplant recipients.

Discussion:

In this unbiased national study focusing on recent data, we confirmed the high incidence of infection-related hospitalizations after renal transplantation in pediatric recipients. The overall hospital admission rate (HAR) of 38.7 per 100py found in our population is consistent with previous reports such as the HAR of 34.1 per 100py found in the first year post-transplantation in a Dutch cohort (160). Our results also underline that, although the risk of hospitalization is decreasing with time from transplantation, infection-related hospitalizations remain a burden several years after transplantation.

An interesting finding of this study is the increased burden of infection-related hospitalization in younger children since 52% of children younger than five years old experienced at least one infection-related hospitalization at one year post transplantation when only 27% of the patients older than 15 years old did. This result is consistent with previous report from the US showing that among kidney transplant recipients the rate of infection-related hospitalization for pediatric patients was twice that of their adult counterparts and was increased when compared with children on dialysis (162). Puliyananda et al. also reported a higher rate of infection-related hospitalization in children younger than one year old compared to children older than 12 years old at transplantation

(163). This higher rate of hospitalization is mainly driven by viral infections since a younger age is not a risk factor of UTI unlike in adults among which the risk of UTI increases with age (164). The higher probability of other bacterial infections in younger patients was mostly induced by bacteremia. The increased risk of viral infections in the younger patients is consistent with findings in other immunocompromised patients (165) probably due to both a lower level of immunization against viruses in general and to medical practices with increased precautions taken in younger children.

In this study, we also find a significantly increased risk of infection in patients treated with cyclosporine. This effect is independent from the other immunosuppressive drugs as shown by the sensitivity analyses performed including the type of induction treatment and the type of antimetabolite treatment. The development of Tacrolimus at the end of the 90s, has been a major event in kidney transplantation since it demonstrates the ability to lower the risk of rejection and to improve graft survival (166, 167) and more recently the ability to avoid Donor Specific Antibody (DSA) production (168). Despite its more potent immunosuppressive ability, Tacrolimus was associated in our study with a lower probability of being hospitalized because of infection with the difference being mainly found in the group of bacterial infections. We did not find any effect of the type of anticalcineurin inhibitor on the risk of viral infection. However, Trompeter et al. found, in a randomized trial comparing the use of Tacrolimus versus Cyclosporine, a higher risk of flu syndrome in the cyclosporine group (169) and Gaber et al. found an increased risk of herpes virus infection with Tacrolimus in a randomized trial evaluating the use of Sirolimus associated with either Cyclosporine or Tacrolimus (170). To further explore the association between the type of anticalcineurin inhibitor and the risk of infection, we tested for a potential interaction between the type anticalcineurin and the age of the patient that was not significant. However, this increased risk of infection in patient treated with cyclosporine should be interpreted carefully. The risk of infection is not only determined by the type of drug used but also by the use of higher dosage. Moreover, we only have data on the initial treatment and we cannot exclude that some patients may have been switched from one therapy to another by the time an infectious event occurs. Considering induction therapy, it has been reported that it increases the risk of infection-related hospitalization when compared with no induction (163). However, we did not find a difference in the risk of infection between patients treated with antithymocyte globulin and those who received basiliximab. In a meta-analysis, Liu et al found a decreased risk of infection with basiliximab (RR 0.87 [0.78-0.97]) in adults (171). However, most of the studies included in this analysis focused on the risk of CMV infection. Only one study reported an increased risk of UTI in patients treated with antithymocyte globulin (172). Thus, although the increased risk of CMV infection, especially CMV reactivation in seropositive recipients, has been reported in several studies in adults (173, 174) and in children (175), the impact of the type

of induction on other types of infection remains uncertain. In our study the effect of steroids did not reach statistical significance because almost all patients were on steroids. Again some patients may be treated by steroids for only a short period of time but we do not have the data to differentiate them from patients remaining on steroids on a long-term basis.

In the literature and in our cohort, UTI remains the most frequent infectious complication after renal transplantation. Aside for the effect of age and immunosuppression, risk factors found in our study are consistent with those already reported: female gender and increased cold ischemia time (164, 176). We did not have data on surgical procedures especially the type of ureter reimplantation technique (Lich-Gregoire or ureteroureterostomy) and the use of ureteral stent and evidence are lacking to favor one technique over another (177, 178). However, since about 2% of the patients needed a surgical management of a vesico-ureteral reflux on the transplant, studies focusing on those modifiable risk factors are needed. Such studies should also search for low urinary tract disorders before and after transplantation. Herthelius et al. evaluated bladder function in 68 pediatric renal transplant recipients. Among them, only 23 had pre-transplant urological abnormalities. However, 49 patients (72%) had abnormal bladder function with similar prevalence in patients with and without pre-transplant urological abnormalities (179). Those results were confirmed by other pediatric studies, one in a group of patients transplanted for glomerular diseases (180, 181) and one assessing the high prevalence of bladder dysfunction in children with chronic kidney disease on dialysis before kidney transplantation (182).

Considering the timing of infection occurrence, the incidence of infection-related hospitalization decreased with time, except for CMV infections that display a spike around 6 months post-transplantation which classically correspond to prophylactic treatment withdrawal. This increased rate of late CMV infection is consistent with numerous reports of the literature (183).

The major strength of our study is the cross-analysis of two national unbiased databases allowing nearly the exhaustivity of the cases. This allowed us to evaluate both the incidence of infection-related hospitalization after transplantation in a large and recent pediatric cohort, to further study the risk factors of hospitalization by type of infection and to calculate the global cost of these complications. The availability of the type of infection both for the site of infection and the specific organism involved is also one of the strength of our study.

However, our study is based on the hospitalization database so that infections that did not required hospitalization cannot be captured and that benign infections occurring during a hospitalization for another cause might be underreported. Thus, our results may in part reflect the practices of the

transplant centers regarding post-transplant infection management especially for benign infections in younger children. This also leads to an underestimation of EBV and CMV infections since all asymptomatic viral replications do not require hospitalization. We also acknowledge the lack of data on intermittent catheterization and anti-bacterial prophylaxis that would have been relevant when studying risk factors of UTI. Because no data on immunosuppressive treatment modification was available, results on treatment effect should be analyzed carefully. The decreasing risk of hospitalization with time may be due to a decreasing intensity of immunosuppression; however, we do not have the data to demonstrate this association. We were also limited to study the possible link between rejection, treatment modification and the risk of infection. Finally, since we only had the costs associated with the hospitalizations but not the cost of all the payments for all healthcare services, we cannot calculate marginal costs but only cost directly associated with the infection-related hospitalizations. Although, comparing costs between countries with different practices is difficult, this may explain why the costs reported in our study are much lower than marginal costs recently reported in the US (184).

Conclusion

In this national recent cohort study, we confirm the high burden of infection-related hospitalization after renal transplantation in children. The higher rate of hospitalization in younger children, mostly for viral infections, should be taken into account both for pre-transplantation information towards the children and their families and for designing procedures aiming to decrease the rate of avoidable hospitalization. As UTI remains the first cause of infection-related hospitalization further studies focusing on modifiable risk factors such as pre-transplant assessment of low urinary tract disorders, cold ischemia time, ureteral reimplantation techniques and ureteral stenting are still needed. Finally, studies investigating the impact of immunosuppressive regimens on each type of infection are needed in order to provide data to tailor treatments to patients' individual risk.

Infections' characteristics	CMV	EBV	Other Herpes Viruses	Viral digestive infections	Viral respiratory infections	Other viral infections	UTI	Other bacterial infections	Parasite and fungal infections
Number of hospital stay	22	2	23	128	70	22	283	95	15
Number of patients infected	19	2	19	94	50	15	118	66	11
Mean number of stay by infected patients	1.2	1,0	1.2	1.4	1.4	1.5	2.4	1.4	1.4
Median time between Tx and first infection (months)	6.2 [4.8-8.7]	12.5 [11.7-13.3]	22.7 [6.5-29.8]	9.9 [4.1-21.3]	14.8 [4.5-23.3]	5.3 [2.8-22.3]	5.3 [2.2-16.8]	9.9 [3.2-20.6]	9.8 [5.5-31.5]
Total days of hospitalisation	166	3	125	585	347	111	1236	863	93
Median time of hospitalisation (days)	6 [2-11]	1.5 [0-3]	5 [3-7]	1 [2-5]	2 [1-4]	3 [0-4]	2 [3-5]	4 [2-12]	3 [0-8]
Total cost (euros)	53929	3921	42314	259532	134710	40357	562305	460506	34958
Median cost by stay (euros)	1778 [994-3100]	1961 [927-2994]	1055 [808-2256]	1441 [618-3024]	1611 [669-2276]	1055 [808-2256]	1658 [678-2702]	2443 [1611-6330]	1294 [511-4912]
Incidence rate of hospitalization by type of infection (/100 py)	1.3	0.1	1.3	7.5	4.1	1.3	16.6	5.6	0.9
Cost by type of infection (/py)	31.6	2.3	24.8	152.0	78.9	23.6	329.4	269.8	20.5

Table VI.21: Description of infection-related hospitalizations

UTI : Urinary tract infection, py : patient year

		Infection	No infection	All patients
Patients' characteristics	N	260	333	593
Median age at Tx		11.8 [5,4-16.0]	15.4 [11.5-17.7]	14.1 [8.9-17.1]
Gender (Male)		55.8	61.9	59.2
Primary renal diseases	Other	10.4	4.8	7.3
	Glomerulonephritis	18.9	25.5	22.6
	Unknown	6.2	11.1	8.9
	Hereditary diseases	15.4	16.5	16.0
	Vascular diseases	7.3	5.1	6.1
	Acute interstitial nephritis	5.8	6,0	5.9
	CAKUT	36.2	30.9	33.2
Uropathy		28.2	20.6	24.1
Diabetes		2.4	1.9	2.1
RRT treatment before Tx	PD	16.2	13.8	14.8
	HD	44.2	48.1	46.4
	NONE	39.6	38.1	38.8
MM		4 [3-4]	3 [2-4]	3 [3-4]
Cold Ischemia time (min)		930 [720-1185]	844 [621.5-1080]	900 [666-1104]
CMV sero-negative		63.5	60.3	61.7
CMV matching	D-/R-	28.6	31.2	30.0
	D+/R-	30.8	23.1	26.5
	D-/R+ or D+/R+	40.6	45.8	43.5
EBV sero-negative		37.0	31.0	33.6
EBV matching	D-/R-	6.2	4.2	5.1
	D+/R-	27.2	23.1	24.9
	D-/R+ or D+/R+	66.7	72.8	70.1
Cyclosporine		39.0	30.2	34.1
Tacrolimus		61.0	69.8	65.9
Steroids		99.6	99.1	99.3
Azathioprine		10.5	8.7	9.8
MMF		90.4	87.1	90.2
ATG		18.4	17.5	17.9

Table VI.22: Patients' characteristics at transplantation

		CMV	EBV	Other Herpes Viruses	Viral or non identified digestive infections	Viral respiratory infections	Other viral infections	UTI	Other bacterial infections	Parasite and fungal infections
Patients' characteristics	N	19	2	19	94	50	15	118	66	11
Median age at Tx		14.4 [10.5-16.9]	5.6 [2.3-9.0]	6.6 [4.8-14.1]	10.3 [5.0-14.6]	9.2 [4.6-13.7]	5.0 [1.8-10.6]	12.2 [5.0-16.4]	13.0 [5.3-15.6]	16.6 [9.9-19.1]
Gender (Male)		73.7	0.0	73.7	61.7	70.0	80.0	45.8	54.6	81.8
Primary renal diseases	Other	10.5	0.0	15.8	11.7	12.0	13.3	10.2	6.1	0.0
	Glomerulonephritis	10.5	0.0	10.5	18.1	20.0	6.7	22.9	24.2	9.1
	Unknown	15.8	0.0	5.3	3.2	8.0	0.0	5.1	6.1	18.2
	Hereditary diseases	10.5	100.0	15.8	19.2	18.0	13.3	7.6	16.7	18.2
	Vascular diseases	10.5	0.0	0.0	8.5	6.0	13.3	5.9	6.1	18.2
	Acute interstitial nephritis	5.3	0.0	5.3	4.3	4.0	6.7	7.6	3.0	0.0
	CAKUT	36.8	0.0	47.4	35.1	32.0	46.7	40.7	37.9	36.4
Uropathy		21.1	0.0	31.6	30.7	22.9	40.0	32.1	29.7	36.4
Diabetes		15.8	0.0	0.0	2.3	4.3	0.0	1.8	1.6	0.0
RRT treatment before Tx	PD	10.5	0.0	36.8	18.1	24.0	33.3	19.5	12.1	18.2
	HD	42.1	50.0	42.1	38.3	48.0	33.3	45.8	37.9	72.7
	NONE	47.4	50.0	21.1	43.6	28.0	33.3	34.8	50.0	9.1
MM		3 [3.0-4.0]	2 [2-2]	4 [3-4]	3 [3-4]	4 [3-5]	3 [3-4]	4 [3-4]	4 [3-4]	4 [3-4]
Cold Ischemia time (min)		929 [301.8-1213]	1087.5 [1005-1170]	908 [720-1243]	936 [775-1151]	921 [720-1060]	923.5 [756-1151]	961.5 [749-1195]	900 [652.5-1057.5]	848 [695-1040]
CMV sero-negative		79.0	50.0	68.4	58.5	62	53.3	67.8	57.6	72.7
CMV matching	D-/R-	0.0	50.0	55.6	16.5	31.9	33.3	32.4	28.1	54.5
	D+/R-	71.4	0.0	11.1	37.7	27.7	20.0	31.4	22.8	18.2
	D-/R+ or D+/R+	28.6	50.0	33.3	45.9	40.4	46.7	36.2	49.1	27.3
EBV sero-negative		26.3	100.0	36.8	38.7	32.7	66.7	33.1	44.6	45.5
EBV matching	D-/R-	0.0	0.0	10.5	3.5	4.4	13.3	7.9	8.6	9.1
	D+/R-	12.5	100.0	26.3	31	23.9	53.3	22.8	29.3	36.4
	D-/R+ or D+/R+	87.5	0.0	63.2	65.5	71.7	33.3	69.3	62.1	54.6
Cyclosporine		22.2	50.0	50.0	30.8	39.6	71.4	48.3	41.5	40.0
Tacrolimus		77.8	50.0	50.0	65.9	60.4	28.6	50.8	50.8	60.0
Steroids		100.0	100.0	100.0	100.0	100.0	100.0	99.1	98.5	100.0
Azathioprine		16.7	0.0	16.7	9.0	4.2	0.0	10.1	9.2	0.0
MMF		83.3	100.0	83.3	91.0	91.7	92.9	88.1	90.1	90.0
ATG		16.7	0.0	5.6	20.7	27.1	7.1	15.0	21.9	20.0

Table VI.23: Patients' characteristics at baseline (transplantation) by type of infection

Tx: Transplantation, UTI: Urinary tract infection, CAKUT: Congenital Abnormalities of the Kidney and the Urinary Tract, MMF: Mycophenolate Mofetil, ATG: antithymocyte globulin

		Missing	Univariate analysis			Multivariate analysis	
			HR	95%IC	p	HR	95%IC
Age at renal transplantation		0	0.92	[0.90-0.94]	<0.0001	0.95	[0.92-0.97]
MM		0	1.12	[1.02-1.25]	0.02	1.14	[1.01-1.28]
ISCF (H)		0	1.02	[1.01-1.04]	0.01	1.02	[1.00-1.04]
Gender	Female	0	1.09	[0.85-1.39]	0.5	1.16	[0.88-1.53]
Primary renal diseases	Others	0	1.29	[0.84-1.97]	0.02	1.63	[0.96-2.77]
	Glomerulonephritis		0.69	[0.49-0.97]		0.7	[0.43-1.12]
	Unknown		0.49	[0.29-0.83]		0.56	[0.30-1.05]
	Hereditary nephropathy		0.79	[0.55-1.14]		1.04	[0.65-1.68]
	Vascular diseases		1.01	[0.62-1.65]		1.16	[0.63-2.13]
	Acute interstitial nephritis		0.95	[0.55-1.64]		0.93	[0.50-1.75]
CAKUT		1			1		
Uropathy	Yes	28	1.46	[1.11-1.93]	0.007	1.34	[0.89-2.02]
	No		1			1	
Diabetes		26	1.04	[0.46-2.34]	0.92		
RRT treatment before Tx	PD	0	0.97	[0.68-1.39]	0.58		
	HD		0.87	[0.67-1.14]			
	NONE		1				
Negative CMV serology		3	1.14	[0.88-1.46]	0.32		
CMV matching	D-/R-	73	1.06	[0.77-1.44]	0.09		
	D+/R-		1.4	[1.03-1.90]			
	D-/R+ or D+/R+		1				
Negative EBV serology		7	1.25	[0.97-1.62]	0.08		
EBV matching	D-/R-	38	1.27	[0.75-2.16]	0.18		
	D+/R-		1.29	[0.97-1.72]			
	D-/R+ or D+/R+		1				
Anticalcineurin inhibitor	Cyclosporine	61	1.5	[1.16-1.95]	0.003	1.4	[1.05-1.88]
	Tacrolimus		1			1	
Steroids		29	2.1	[0.30-15.00]	0.46		
Azathioprine		29	1.22	[0.81-1.83]	0.34		
MMF		29	0.75	[0.49-1.14]	0.18		
ATL		39	1.06	[0.77-1.47]	0.72		
Rejection		0	0.84	[0.59-1.21]	0.34	0.95	[0.63-1.43]
Year of transplantation		0	1.05	[0.96-1.13]	0.29	1.04	[0.95-1.14]

Table VI.24: Risk factors for all types of infections

CAKUT: Congenital Abnormalities of the Kidney and the Urinary Tract, MMF: Mycophenolate Mofetil, ATG: antithymocyte globulin

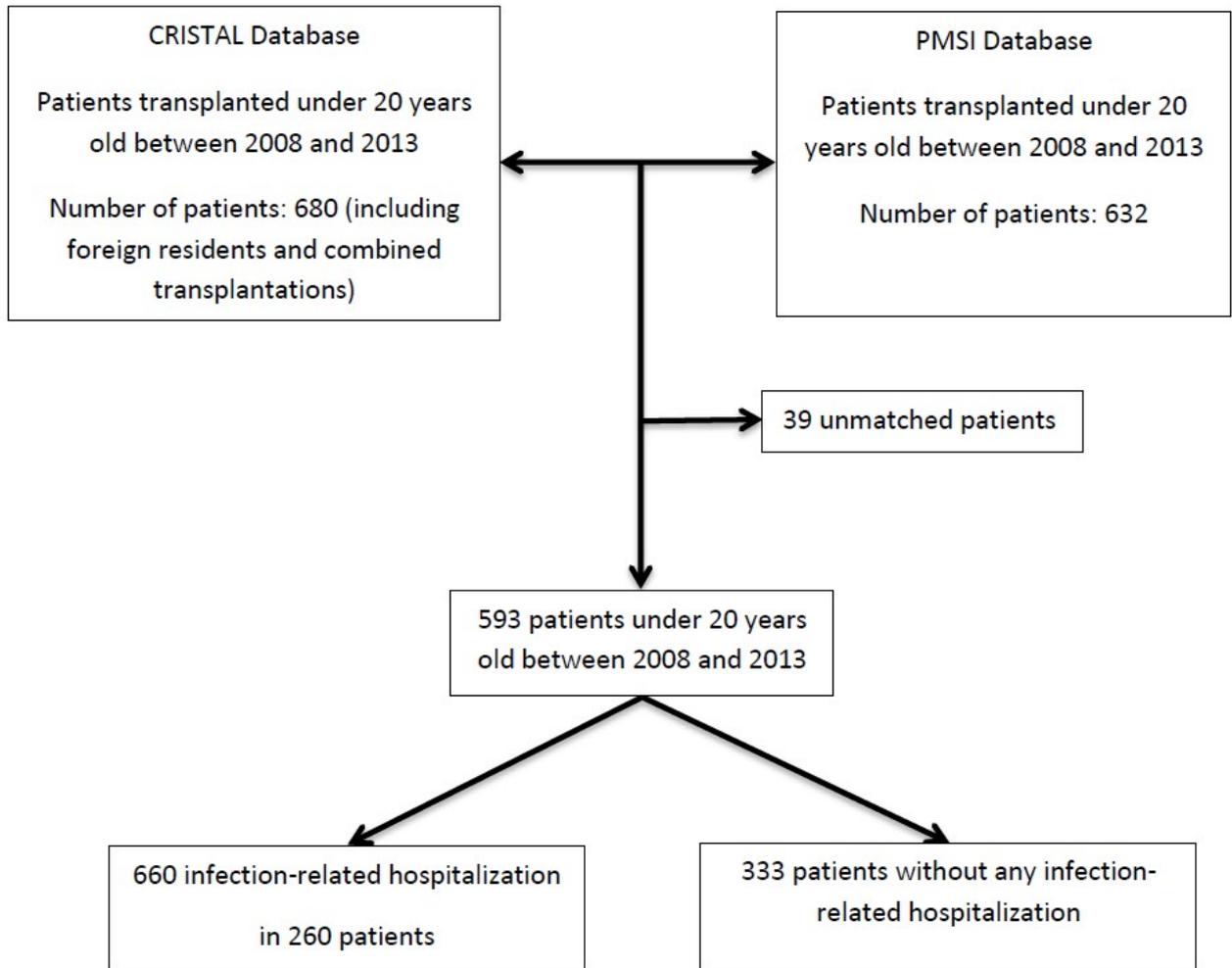


Figure VI.17: Patients' flow chart

Crude infection-related hospitalization rate

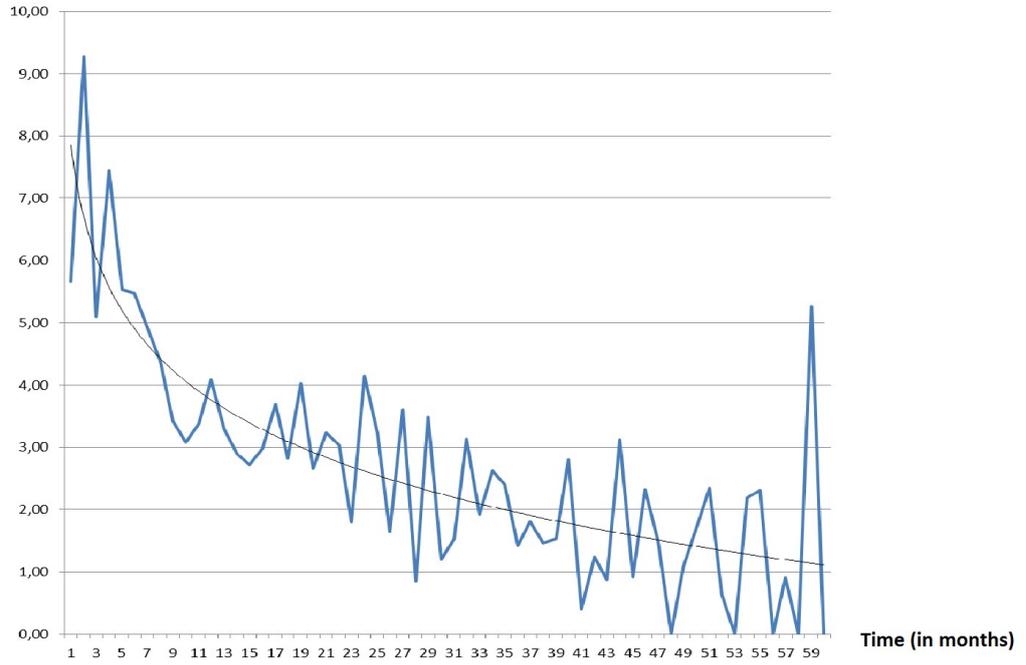


Figure VI.18: Crude infection-related hospitalization rate by 1-month interval

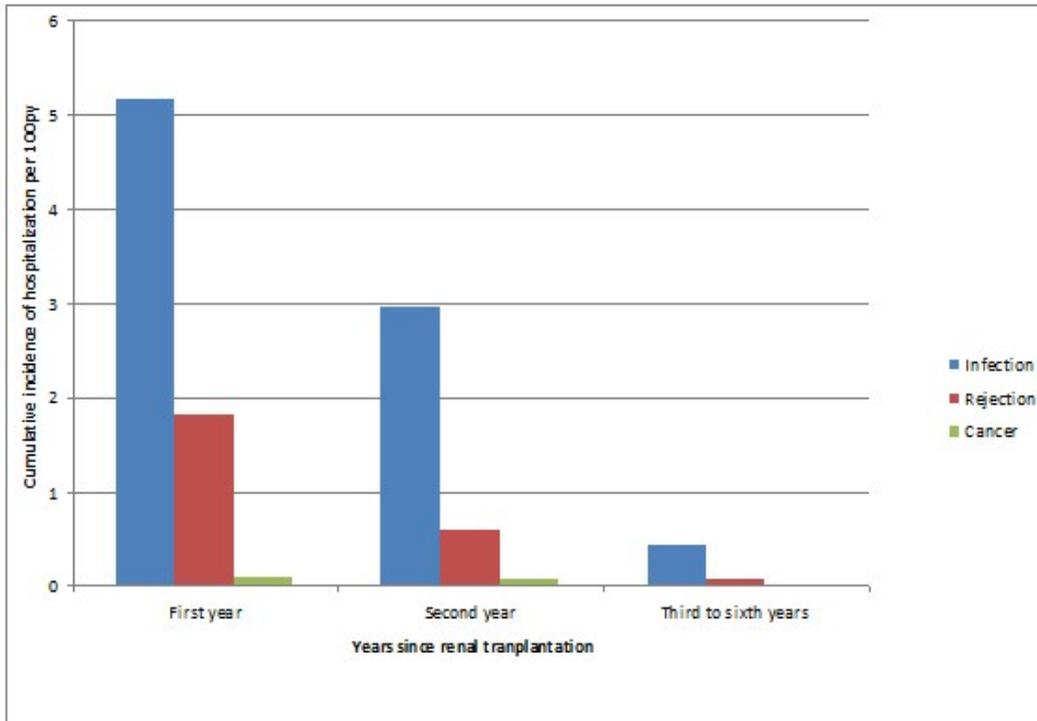


Figure VI.19: Cumulative incidence of hospitalization by cause

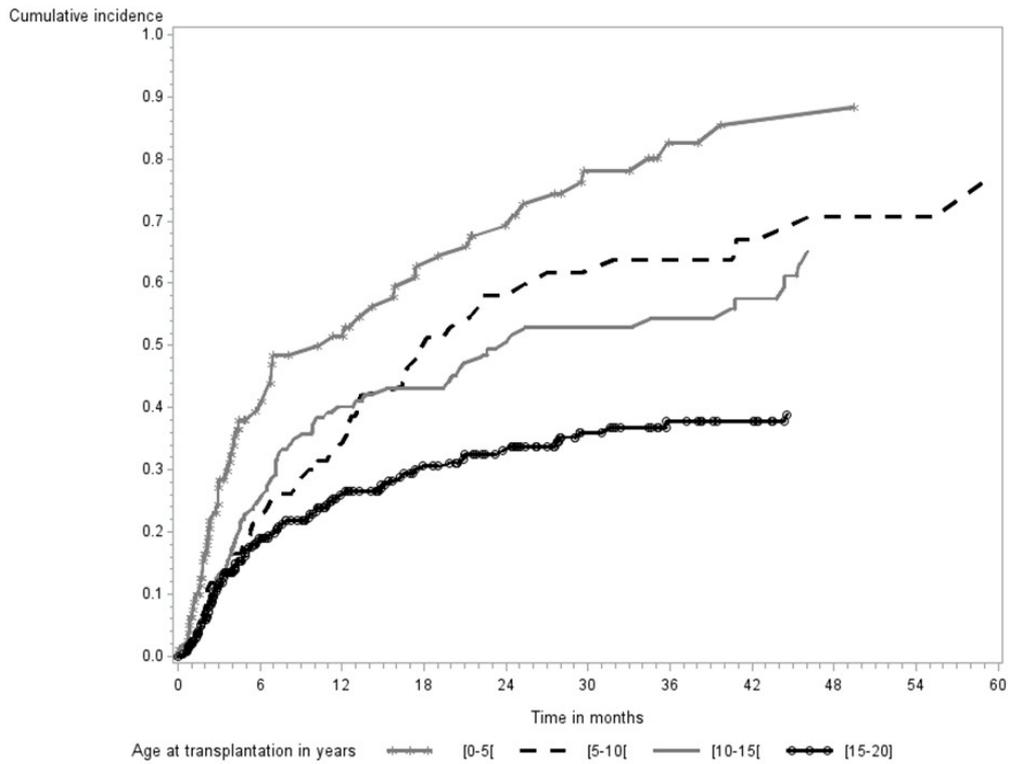


Figure VI.20: Cumulative incidence of infection-related hospitalization by age group (unadjusted)

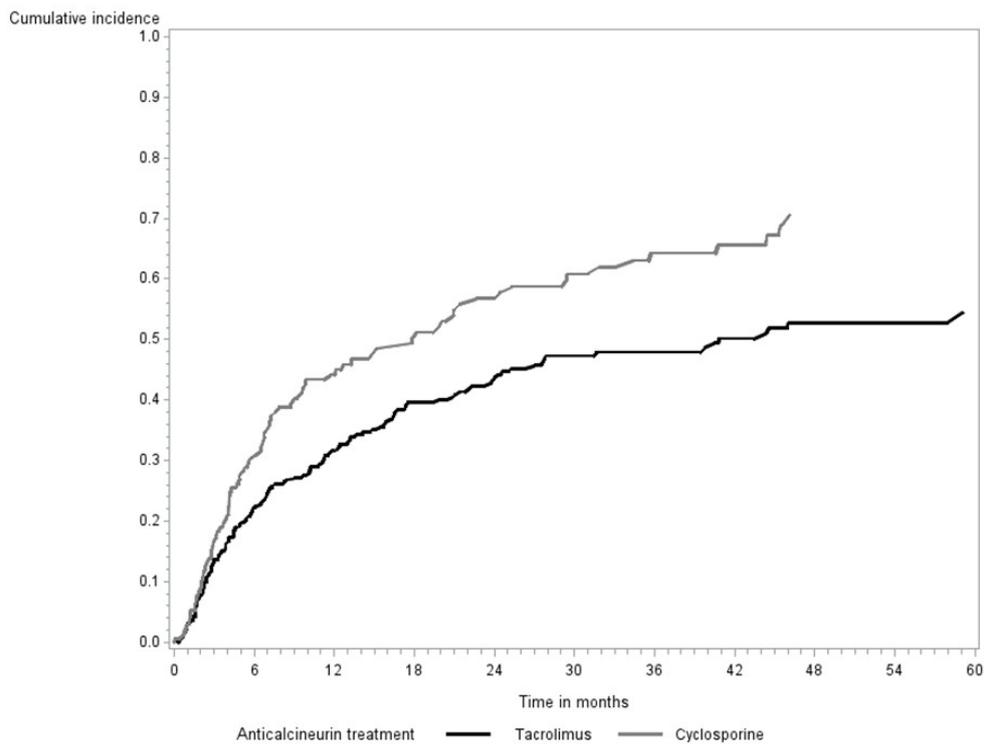


Figure VI.21: Cumulative incidence of infection-related hospitalization by type of anticalcineurin inhibitor (unadjusted)

VII. Modeling of the trajectories of children and young adults with ESRD

Since the optimal management of children with ESRD remains debated, studies evaluating the outcome of the patients by strategy of treatment are needed. Moreover, given the longevity of children undergoing kidney transplantation, most pediatric recipients will inevitably develop graft failure, requiring a return to dialysis or a second transplant so that one should consider the complete trajectory of the patients and try to maximize the time spent with a functioning transplant and minimize the time spent on dialysis on the widest period of time possible. Thus, we first aimed to describe and analyze the trajectories of children and young adults with ESRD. Our second aim was to simulate modifications of those strategies (e.i: increase in transplantation from living-donor kidney or in preemptive transplantation) to evaluate their impact on the time spent with a functional transplant or on dialysis over a 20-year period.

Material and Methods

Patients and data

In this pilot study, we included all patients registered in the REIN registry between 1995 and 2015 starting RRT before the age of 30 years old. Since the registry provides exhaustive data since 2005, we included both incident patients since 2005 for whom we have the complete trajectory but on a short period (right-truncated) and prevalent patients for whom the trajectory before the inclusion in the registry is not known (left-truncated) but who will help us study the end of the trajectories. Data collected were the dates of birth, RRT initiation, transplantation, loss of transplant's function and death, demographics data such as gender, primary renal disease, center of treatment, patients' height and weight and immunological data such as ABO group, HLA antigens, and antibodies (PRA). From HLA antigens and antibodies, we can calculate the FAGN (national ease of graft access) index (114) for each child. This score, used since July 2010 to allocate organs in France, rates from 0 to 60 the number of possible donors with the same ABO group, fewer than 3 HLA mismatches, and no donor-specific antibodies during the previous 5 years. We can also calculate the rate of incompatible transplant (TGI) which is the rate of transplant offered over the past year against which the patient presents at least one PRA. A TGI > 85% defines sensitized patients. We finally collected data on the donors: type of donor, age, HLA matching, weight and height.

Description of patients' trajectories

Dates of first RRT and of registration on the waiting-list are known for all patients who are followed until death or the end of the study. We considered four events of interest: RRT initiation, renal transplantation, graft failure and return to dialysis, and death and defined 14 states: Transplantation defined by its rank (1 to 4) and the type of donor (living (TXDV) or deceased (TXDD)), dialysis periods (DIAL) defined by their ranks (1 to 5) and death (DCD). The trajectory of a patient is defined as the succession of states and the time spent in each one.

Transition rates' calculation

We divided each trajectory by one-month periods to determine the state of each patient at any time and the presence of a transition from one state to another. Transition rates were considered stable over 3-months periods during the first year, then over 6-months periods between 1 and 10 years and over one-year periods after 10 years. The transition rates were calculated based on the number of patient at risk in each state and the number of transition observed.

Simulation

We then programmed, using SAS software, a statistical tool able to simulate the outcome of a cohort of ESRD patients over a 20-years period. The number of patient in the cohort, the initial distribution of the modality of RRT and the transition rates can be modified. The results obtain are a graphical presentation of the repartition of the patients over time, the average percent of time spent in each treatment category by the patients and the number of transplant needed by type of donor for each simulation.

Preliminary results

Figure 5.1 shows the trajectory of a cohort of 100 patients based on the observed initial repartition and transition rates.

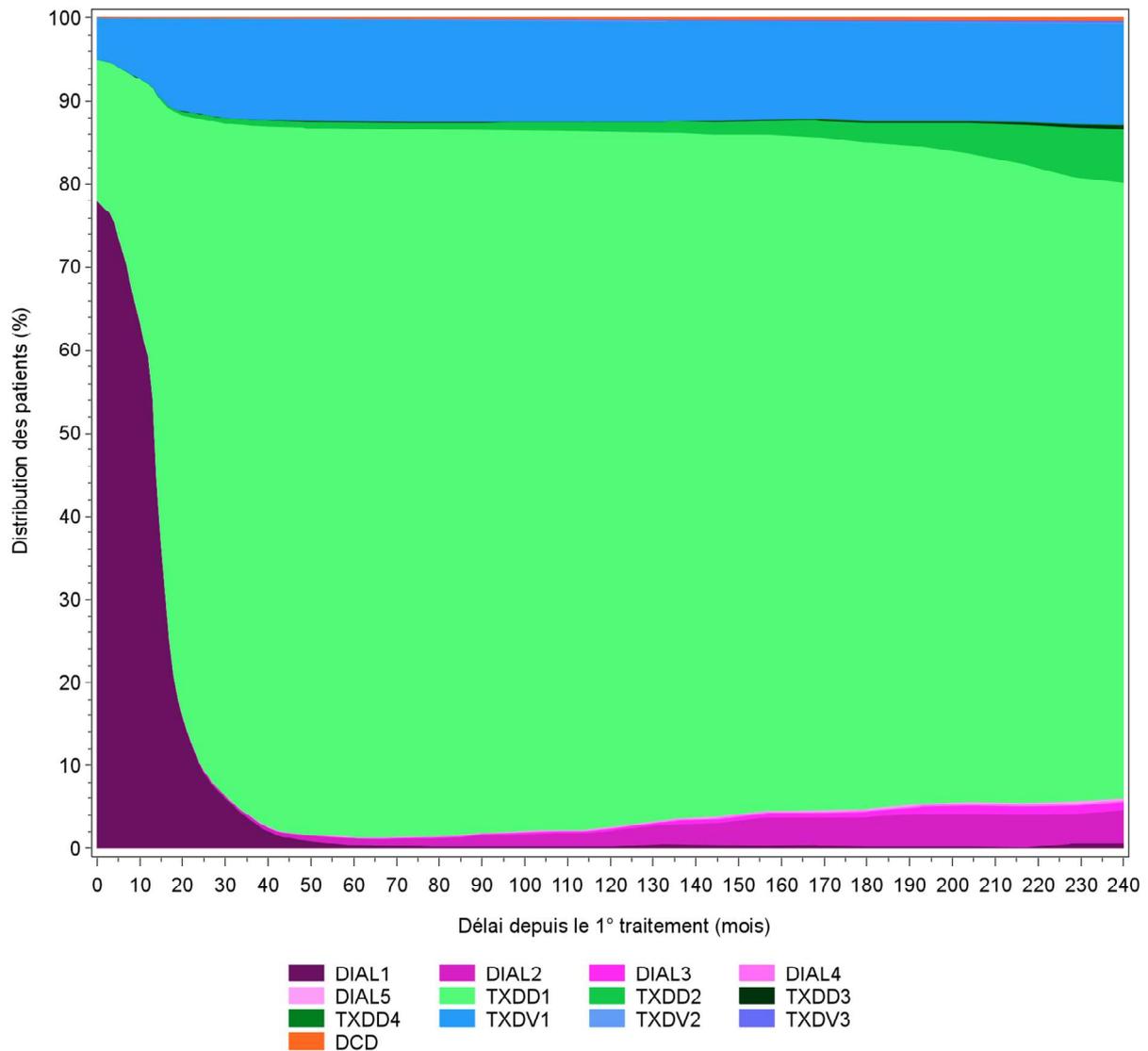


Figure VII.1: Patients' repartition between the modality of treatment by months since renal replacement therapy initiation. (Prediction based on observed data)

This graphical presentation clearly shows that only 22% of the patients receive a preemptive transplantation as first RRT modality with only 23% of them getting a transplant from a living donor. Over the 20-years period, the patients spent on average 8.4% of the time on dialysis and 81.2% of the time with a functioning graft. Thus, the average time spent on dialysis was 20 months and the restricted life expectancy was 239.7 months. Finally, in this simulation, 115 kidneys were used including 17 from living donors.

In France, both health authorities and patients' organizations underline the need to increase the rate of preemptive transplantation and living donation. We simulated the outcome of a cohort of 100 patients if interventions were made to reach the level of 32 % of preemptive transplantation including 47% from living donors as observed in the United Kingdom (88). We did not modify

transition rates. The result of this simulation is presented in Figure 5.2. Over the 20-years period, the patients spent on average 7.7% of the time on dialysis. Thus, the average time spent on dialysis was 18.4 months and the restricted life expectancy remained stable at 239.7 months. In this simulation, 114 kidneys were used including 26 from living donors.

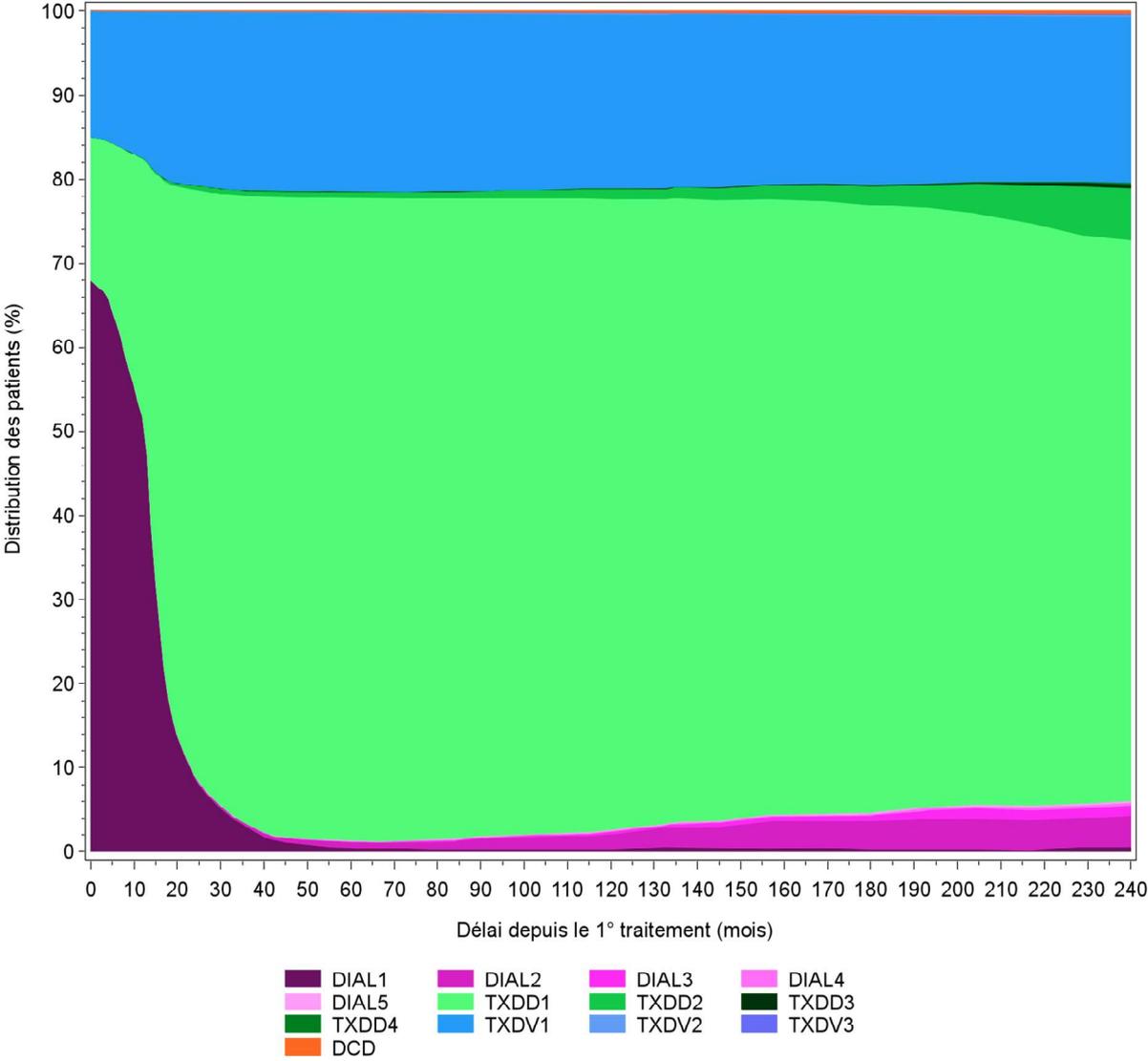


Figure VII.2: Patients’ repartition between the modality of treatment by months since renal replacement therapy initiation. (Simulation with the initial repartition of treatment observed in the United Kingdom)

Recently, Murray et al. presented at the International Pediatric Association congress the result of a study performed in the pediatric nephrology department of the Great Ormond Street Hospital in London where they reviewed all the medical records to assess if patients would have been eligible for preemptive transplantation. By doing so, they estimated that 48% of the patients were eligible to preemptive transplantation. We then performed another simulation based on those results and

considering the rate of preemptive transplantation to be stable in this center (58% of the preemptive transplantation) and the transition rates to be unchanged. The results of this simulation are presented in Figure 5.3. Over the 20-years period, the patients spent on average 6.6% of the time on dialysis. Thus, the average time spent on dialysis was 15.8 months and the restricted life expectancy remained stable at 239.7 months. In this simulation, 114 kidneys were used including 37 from living donors.

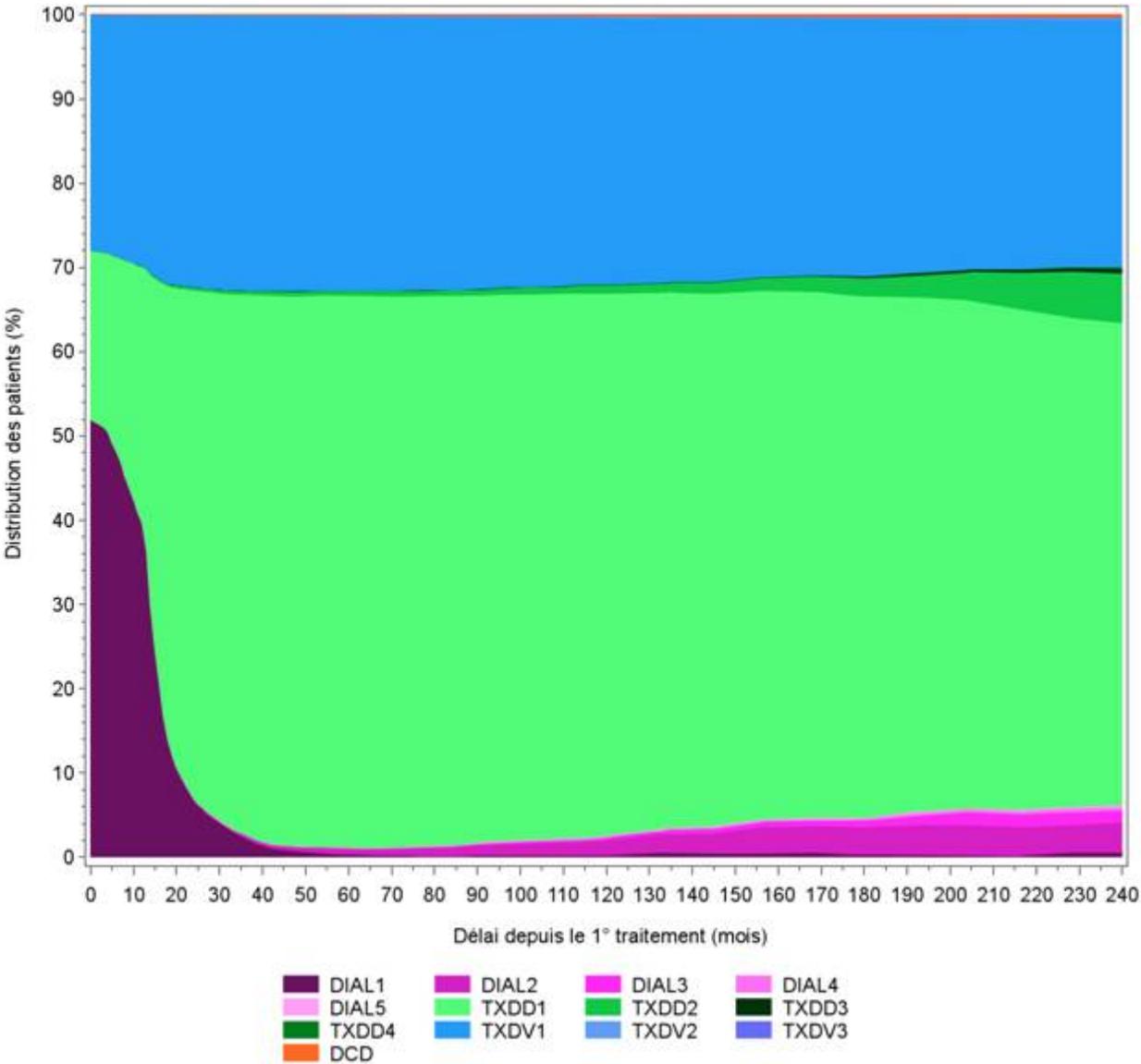


Figure VII.3: Patients’ repartition between the modality of treatment by months since renal replacement therapy initiation. (Simulation with the potential initial repartition of treatment reported by Murray et al. from the Great Ormond Street Hospital in London).

Discussion

Several lessons can be learned from those simulations. First of all, it confirms that transplantation is by far the most prevalent RRT modality in children and young adults in France. It also clearly shows the overall good and rapid access to kidney transplantation as we previously published (131, 132). When we compare our results with those of other countries it is clear that efforts can be made to promote preemptive transplantation and transplantation from living donors. However, our simulations show that major efforts such as raising our rate of preemptive transplantation from 22% to 48% and performing twice as many transplantation from living donors (58% vs 23%) will have moderate impact when considering the global trajectories of the patients by decreasing the average time spent on dialysis from 20 months to 15.8 months over a 20 years period. This benefit has to be weighed against the major efforts in terms of living donation with 37 versus 17 donations per year and the potential risk of decreasing graft survival if this increase in living donation is associated with less stringent selection of the donors.

Perspectives

As previously shown, the overall good outcome of the patients and the good access to renal transplantation hide major disparities that can be based on patients' characteristics such as age, gender, level of HLA sensitization or on other factors such as the characteristics of the center of treatment. Thus, also the simulations on the complete population are showing little possibility of improvement; major improvement might be possible when focusing on disadvantaged subgroups.

Therefore, we aim to develop our simulation tool to be able to describe the trajectories of children and young adults with ESRD and to describe the different strategies of treatment by subgroups. Then, we aim to simulate modifications of those strategies not only by modifying the initial repartition of treatment modalities but also by studying and implementing the effect of different practices such as HLA matching requirement or type of dialysis on the rates of transition.

Thus, three major implementations will be made. First, we will describe more precisely the trajectories of the patients by considering five events of interest: RRT initiation, renal transplantation, graft failure and return to dialysis, death and registration on the waiting-list and increasing the number of states from 14 to 20: Transplantation defined by its rank (1 to 3) and the type of donor (living or deceased), dialysis periods defined by their ranks (1 to 3), their modality (hemodialysis or peritoneal dialysis) and their status on the waiting-list, a state of preemptive registration and death (DCD).

Secondly, the rates of transition will be estimated using a multistate model by maximizing probabilities of Poisson taking into account the concurrent risks of transition to the other states (185). To study the impact of characteristics such as age or level of HLA sensitization, two methods will be used. First, we will perform analysis stratified by age groups or level of HLA sensitization to study the particularity of the trajectories of those patients. Then, we will include those factors as parameters in the model to analyze their impact on the rates of transition and to control the reliability of our results by computing confidence intervals of the parameters.

Finally, we will be able to simulate the strategies of treatment and to compare them based on the average time spent with a functional transplant or on dialysis over a 20-year period. We will also evaluate for each strategy the number of transplants needed by type of donor and the cost of the strategy.

This project will be performed during my post-doctoral years starting in September 2017.

VIII. Conclusions

All the studies performed confirm the overall good access to renal replacement therapy in children and young adults in France and the high quality of the care given to patients with end-stage renal diseases. However, as previously reported by the “Haute Autorité de Santé” disparities in access to those treatments exist in France, not only in adult but also in children, as shown in this work. To assess those disparities is of major importance and is the first step to design actions to reduce them. Considering our finding of a decreased access to renal transplantation in girls, no clear explanation was found to explain it. Both our study and recent studies on cohorts of patients with chronic kidney diseases reported a faster decline of renal function in girls. This gender effect remains to be confirmed and reasons for it to be explored. We attempt to pursue this work based on the data from the CKiD cohort, a prospective national cohort of American children following children from the early stages of chronic kidney disease until ESRD. We are in the process of obtaining the approval for this study.

Considering major variations in centers’ practices in France, our study on the access to the waiting list underlines differences in the timing of the registration on the list. This finding may induce reflections at a national level to harmonize the practices. Moreover, we also observed that some adult centers fail to request pediatric priority for young adult waiting for renal transplantation although they started dialysis before 18 years old which qualifies them for this priority. This finding may have rapid and concrete effect on the reduction of disparities in this population by better informing nephrologist on this issue.

Considering the care of the younger patients starting RRT before 2 years old, although several studies aimed at assessing factors associated with the best graft survival, tools able to help clinician in their everyday decision making are lacking. We report the importance of both morphological matching, with an optimal donor/recipient height ratio between 1.4 and 1.8, and immunological matching, especially in HLA class 2. In order to help clinicians to combine those predictive factors, we report predicted survivals associated with each combination of risk factors. This is the first step towards the creation of a predictive tool able to help clinicians in the choice of the optimal kidney transplant. We plan to further develop this tool and to perform an external validation on another large cohort of patients.

Finally, to combine all those results in one and to study the trajectories of the children with ESRD as a whole, we developed a simulation tool that is able to present the trajectories of the patients over a 20-years long period under current practices, and to simulate the effect of potential modifications in those practices. These simulations will be based on the different practices observed in France or in

other countries or designed in a pilot group of the French National Society of Pediatric Nephrology. The results may help harmonizing practices based on evidence-based data and support the development of pragmatic trials when practices' changes are considered.

This thesis provided many data on the trajectories of children and young adults with ESRD. Based on those results we are in the process of creating statistical tools to assist clinical decision. We initiated a reflection on how to promote those results. This will be done through scientific presentations in congresses and by supporting medical reflection within the French Society of pediatric nephrology which supports this work.

IX. Résumé substantiel en français

Introduction

La transplantation rénale est reconnue comme le traitement de choix de l'insuffisance rénale terminale chez l'enfant et l'adulte jeune et est associée à une augmentation de la survie et à une amélioration de la qualité de vie des patients tout en étant le traitement le plus coûteux efficace à long terme. Il existe d'importantes disparités d'accès aux traitements de l'insuffisance rénale entre les pays notamment du fait du coût élevé de ces traitements. En France l'accès à la dialyse et à la greffe rénale est globalement satisfaisant. En 2014, 852 enfants vivaient en France avec un traitement de suppléance rénale dont 78.2% avec un greffe rénale fonctionnelle. Néanmoins, ces résultats globaux satisfaisants peuvent masquer des différences de prise en charge importantes et le peu d'étude sur le sujet rend difficile la comparaison de ces prises en charges. Ainsi, il persiste de nombreuses questions sur la prise en charge des patients avant, pendant et après la transplantation. Le but de cette thèse est d'analyser le parcours de soin des enfants présentant une maladie rénale chronique afin de mettre en évidence d'éventuelles disparités dans la prise en charge des patients et de fournir des outils d'aide à la décision afin d'améliorer la prise en charge et le traitement de ces patients.

Objectifs de la thèse

La trajectoire des patients débute par un stade d'insuffisance rénale chronique avec une évolution plus ou moins rapide vers l'insuffisance rénale terminale et l'initiation d'un traitement de suppléance qui peut-être soit la dialyse soit une transplantation rénale dite préemptive. Du fait de la survenue précoce de l'insuffisance rénale chronique terminale et de la durée de vie limitée d'une transplantation rénale, ces patients vont alterner des périodes de dialyses et des périodes de transplantations avec donc le besoin de multiples transplantations.

Nous avons donc, dans un premier temps étudié chaque transition séparément en s'intéressant à la fois à l'impact des caractéristiques des patients mais également des pratiques médicales estimés sur la base de l'effet du centre de traitement. Afin de pouvoir différencier l'effet des caractéristiques des patients de celui des pratiques du centre de traitement, nous avons utilisé des modèles hiérarchiques. Ces modèles se sont développés en recherche biomédicale afin d'étudier l'ensemble des déterminants de santé, et non seulement ceux liés aux caractéristiques individuelles des patients. Nous avons publié un article méthodologique sur ce sujet afin de montrer les possibilités offertes par ces modèles. En effet, ils permettent de prendre en compte la structure hiérarchique des

données entraînant une meilleure estimation de l'effet des variables explicatives ainsi que la mise en évidence d'un effet de « l'environnement » (voisinage, centre de traitement, même essai thérapeutique par exemple) sur les événements de santé. Ils donnent également la possibilité d'étudier les facteurs expliquant cet effet de « l'environnement ». En revanche, ils sont plus complexes à mettre en œuvre et, surtout, ils nécessitent une réflexion approfondie sur les variables à inclure dans le modèle et sur la manière dont l'environnement étudié est supposé impacter l'état de santé des patients.

Dans un second temps, nous avons cherché à répondre à des questions encore débattues au sein de la communauté des néphrologues pédiatres notamment sur le choix du greffon optimal pour la transplantation.

Enfin, nous avons intégré ces données dans un outil de simulation afin de pouvoir décrire et prédire les trajectoires des patients. Le but de cet outil est de pouvoir comparer des stratégies de prise en charge existantes ou de tester de nouvelles stratégies de prises en charge.

Données utilisées

La plupart des données utilisées dans le cadre de cette thèse proviennent du registre REIN. Le Réseau Epidémiologie et Information en Néphrologie (REIN) a pour objectif général de décrire l'incidence et la prévalence des traitements de suppléance de l'insuffisance rénale chronique, les caractéristiques de la population traitée, les modalités de prise en charge et la qualité du traitement en dialyse, l'accès à la liste d'attente et à la greffe ainsi que la survie des malades. Sa finalité est de contribuer à l'élaboration et à l'évaluation de stratégies sanitaires visant à améliorer la prévention et la prise en charge de l'insuffisance rénale chronique et de favoriser la recherche clinique et épidémiologique. Il rassemble les données des patients traités en dialyse (DIADEM) et les données relatives à la transplantation rénale (CRISTAL). Depuis 2002, le Réseau Epidémiologie et Information en Néphrologie s'est développé progressivement sur l'ensemble du territoire français. Fin 2010, les 26 régions françaises ont intégré le Réseau, l'ensemble des centres de néphrologies pédiatriques ont intégré le réseau au plus tard en 2005. La qualité et l'exhaustivité des données sont contrôlées régulièrement.

Le registre REIN, comme l'ensemble des registres européens, transmet un certain nombre de données au registre européen ESPN / ERA-EDTA basé à Amsterdam afin de permettre des études collaboratives à l'échelle européenne tel que celle réalisée dans le cadre de cette thèse sur l'impact du sexe sur l'accès à la transplantation rénale.

Enfin, nous avons utilisés les données du Programme de Médicalisation des Systèmes d'Information (PMSI) qui regroupe les données sur l'ensemble des hospitalisations des patients en France.

Résultats

Dans un premier article publié dans « Pediatric Nephrology », nous nous sommes intéressés à l'impact du centre de traitement sur le choix de la modalité de suppléance rénale chez l'enfant et l'adulte jeune en France. La dialyse péritonéale (DP) reste la modalité de suppléance rénale de choix chez l'enfant, mais il n'existe pas de preuve évidente pour favoriser une modalité sur l'autre. Nous avons cherché à évaluer les facteurs qui influent sur le choix de la modalité de dialyse chez les enfants et les jeunes adultes en France et avons cherché à déterminer les rôles respectifs des facteurs médicaux et des pratiques médicales. Tous les patients âgés de moins de 20 ans à l'initiation de la suppléance rénale entre 2002 et 2013 ont été inclus. Des modèles de régression logistique hiérarchique ont été utilisés pour étudier l'association entre les caractéristiques des patients et des centres et la probabilité d'être traité par DP. Sur 806 patients ayant commencé un traitement de suppléance dans 177 centres, dont 23 centres spécialisés en pédiatrie, 601 patients (74,6%) ont commencé en hémodialyse (HD), alors que 205 (25,4%) ont commencé en DP. Une plus grande probabilité de DP a été trouvée chez les enfants les plus jeunes, alors que le démarrage du traitement dans un contexte d'urgence était associé à une faible utilisation de la DP. Nous avons constaté une grande variabilité entre les centres qui représente 43% de la variabilité totale observée. La probabilité de DP était plus élevée dans les centres adultes et est proportionnelle au taux de DP dans le centre. Ainsi, les pratiques des centres sont un facteur important dans le choix de la modalité de dialyse. Cela pose la question de la participation des patients et de leurs familles au choix de la modalité de dialyse et de l'influence des médecins sur la décision finale. D'autres études pédiatriques portant sur le souhait des enfants et des parents sont nécessaires afin de pouvoir adapter les pratiques aux attentes des patients et de leurs familles.

Nous avons par la suite étudié l'accès à la transplantation rénale en séparant deux périodes distinctes, l'accès à la liste d'attente à partir de l'initiation du traitement de suppléance et l'accès à la transplantation rénale une fois sur liste d'attente. En effet, de grandes inégalités d'accès à la transplantation rénale existent chez l'adulte. Notre objectif est d'évaluer l'existence d'inégalités, leurs déterminants et particulièrement l'impact du centre de traitement en pédiatrie. L'ensemble des patients pédiatriques incidents du Registre français de l'insuffisance rénale terminale REIN ayant débuté un traitement de suppléance rénale entre le 01/01/2002 et le 31/12/2011 ont été inclus. Nous avons utilisé des modèles de régression logistique hiérarchique pour évaluer l'existence d'un

effet centre et l'impact des caractéristiques des patients et des centres sur la probabilité d'inscription sur liste dans les 6 mois après le début de l'IRCT et sur la probabilité d'obtenir un greffon dans les 12 mois suivant l'inscription. Afin de mesurer au mieux l'impact de la pathologie rénale initiale sur l'accès à la transplantation, nous avons reclassé les diagnostics initiaux, à l'aide d'une analyse en composante multiple couplée à une classification hiérarchique, non pas selon la classification classique basée essentiellement sur des critères anatomopathologiques mais en fonction de critères susceptibles d'impacter le délais d'accès à la transplantation tels que la présence d'anomalies urologiques nécessitant une préparation chirurgicale préalable ou de plus amples explorations pré-transplantation ou le risque de récurrence post-transplantation. 614 patients traités dans 54 centres ont été inclus. Le jeune âge, l'initiation du traitement en urgence et les maladies à risque de récurrence post-transplantation sont associés à une probabilité diminuée d'inscription sur liste à 6 mois. Le taux d'inscription national moyen à 6 mois est de 60.1% avec une grande variabilité inter-centre (médiane 61.5% [IQ 30.8-80.0]) persistant après ajustement sur les caractéristiques des patients et non expliquée par les variables centres disponibles.

Présenter des groupes HLA rares (score FAGN), le temps passé en contre-indication temporaire (CIT), un âge à l'inscription supérieur à 18ans et avoir bénéficié d'une inscription préemptive sont associés à une probabilité diminuée de transplantation dans les 12 mois après l'inscription sur liste. Si les caractéristiques immunologiques du patient sont des facteurs attendus impactant l'accès à la transplantation, l'âge à l'inscription ne devrait pas avoir d'impact puisque l'ensemble des patients inclus dans l'étude, ayant débuté la dialyse avant l'âge de 18 ans, bénéficient de la même priorité pédiatrique à condition que le médecin suivant le patient en fasse la demande. Dans notre cohorte, 81% des inscrits sont transplantés dans l'année avec une variabilité entre les centres (médiane 75% [IQ 50-100]) en grande partie (56%) expliquée par les caractéristiques des patients. Néanmoins, les patients traités dans des centres pédiatriques présentent une probabilité de transplantation dans l'année diminuée du fait d'exigences supérieures en termes de compatibilité HLA. Ainsi, nous démontrons l'existence de disparités d'accès à l'inscription sur liste d'attente et d'accès à la transplantation une fois inscrit parmi les enfants en France. Les caractéristiques des patients mais également de leurs centres de traitement participant à ces disparités, une harmonisation des pratiques permettrait d'améliorer l'équité d'accès à la transplantation rénale en pédiatrie. Ces résultats ont fait l'objet de 2 publications dans « Nephrology, Dialysis and Transplantation ».

En étudiant l'accès à la transplantation rénale pédiatrique en France, nous avons été surpris par l'existence d'une tendance à une inscription retardée sur liste d'attente chez les filles. Chez les adultes, d'importantes inégalités d'accès à la transplantation entre les sexes ont été démontrées.

Nous avons donc décidé d'étudier l'effet du sexe sur l'accès à la transplantation rénale chez l'enfant et de rechercher les causes de cette inégalité.

Afin d'obtenir le pouvoir statistique nécessaire à cette étude, nous avons inclus 6454 patients ayant débuté un traitement de suppléance rénal avant 18 ans, dans 35 pays participant au registre ESPN / ERA-EDTA. Afin d'étudier les facteurs associés au temps nécessaire pour obtenir une transplantation, nous avons utilisé des modèles de survie à risque proportionnel avec prise en compte des risques concurrents de décès et de récupération de la fonction rénale. Une régression logistique hiérarchique a été utilisée pour étudier la probabilité d'accès à la transplantation préemptive.

Cette analyse confirme que les filles ont un accès retardé à la transplantation rénale en raison d'une probabilité 23% plus faible de recevoir une transplantation préemptive. Nous avons constaté que le temps de suivi avant l'initiation du traitement de suppléance était plus long chez les garçons que chez les filles en dépit d'un débit de filtration glomérulaire semblable au premier rendez-vous avec un néphrologue. Les filles ont tendance à progresser plus rapidement vers l'insuffisance rénale terminale que les garçons, ce qui peut rendre difficile la réalisation du bilan pré-transplantation avant l'initiation de la dialyse. Au total, les facteurs médicaux n'expliquent que 70% de la différence entre les sexes. Ainsi, en Europe, les filles ont un moins bon accès à la transplantation rénale préemptive pour des raisons qui ne sont que partiellement liées à des facteurs médicaux. La progression plus rapide de l'insuffisance rénale chez les filles même à pathologie rénale initiale égale est également retrouvé par d'autres auteurs ayant étudié l'évolution de la maladie rénale chronique chez l'enfant à partir de données de cohortes prospectives tel que la cohorte américaine CKiD. Nous envisageons d'explorer prochainement plus précisément l'impact du sexe sur la progression de la maladie rénale chronique chez l'enfant à partir des données de cette cohorte. Enfin, des facteurs non médicaux tels que la motivation du patient et l'attitude des parents et des médecins envers la transplantation et le don d'organes peuvent également contribuer à l'inégalité d'accès à la transplantation rénale entre les sexes.

Lorsque l'on étudie l'épidémiologie et la prise en charge de l'insuffisance rénale chronique terminale chez l'enfant, il apparaît rapidement que le groupe des plus jeunes enfants constitue un groupe à part avec des problématiques propres. De plus le faible nombre de patients concernés (21 patients incidents en 2014 âgés de 0 à 4 ans soit une incidence standardisée sur l'âge de 5.2 patients par million d'habitant) rend difficile la réalisation d'étude de qualité permettant de définir des prises en charges supportées par des preuves scientifiques. Cela explique la grande variabilité des pratiques observées en France dans le cadre d'un sondage réalisé auprès des centres de néphrologie. Par exemple, le poids minimal au delà duquel une transplantation rénale est jugée possible varie de 5 à 12 kg en fonction des équipes. De même, lorsque l'on propose des couples donneurs receveurs en

demandant de juger de l'acceptabilité de ce couple en termes de compatibilité HLA et de compatibilité morphologique on observe d'importante divergence d'avis. Afin d'aider à répondre à ces questions, nous avons étudié spécifiquement le devenir des patients ayant débuté un traitement de suppléance rénal avant l'âge de 2 ans en France. Nous avons inclus tous les patients ayant initié un traitement de suppléance rénal avant l'âge de 24 mois en France entre le 1er janvier 1992 et le 31 décembre 2012. Afin d'être exhaustif, trois méthodes complémentaires de détection des patients ont été utilisées : à travers la base de données nationale de transplantation (CRISTAL) qui enregistre les données sur tous les patients inscrits sur liste d'attente, par le biais du Registre REIN et dans les bases de données des différents hôpitaux. L'étude de la survie des patients et des greffons ainsi que des facteurs de risques associés à ces survies a été réalisée à l'aide de modèles de Cox. 244 patients ont été inclus avec un âge médian à l'initiation du traitement de suppléance de 10,4 mois. Au cours du suivi, 174 transplantations rénales ont été réalisées chez 159 patients et 29 patients sont décédés (18 avant transplantation rénale et 11 après transplantation rénale), les deux principales causes de décès étant des infections et des événements cardiovasculaires. Seulement 10 transplantations proviennent d'un donneur vivant. Les survies des patients à 5 et 10 ans étaient respectivement de 87% [82% -91%] et 84% [77% -89%]. Le fait de présenter des comorbidités extra-rénales était le seul facteur significativement associé au risque de décès, le type de dialyse initial n'avait pas d'impact sur la survie. On observe également une tendance à une diminution du risque de décès avec l'âge.

La survie des greffons à 10 ans était de 74% [67% -81%]. Sur les 159 premières transplantations rénales réalisées, l'âge médian à la transplantation était de 30,2 [21,8-40,7] mois, le poids et la taille médiane du receveur étant de 12,0 [10,4-13,6] kg et 85,0 [80,5-92,5] cm respectivement. Dans l'ensemble, nos patients étaient très homogènes, avec seulement 5% de receveurs âgés de moins de 1 an. Ils étaient très proches en termes de poids et de taille. Cette homogénéité nous a empêchés d'étudier l'impact de ces variables sur la survie rénale. Les deux facteurs trouvés significativement associés à la perte de greffon sont le ratio de taille donneur/receveur et le nombre de mismatch DR. Il y avait une tendance à amélioration de la survie des greffons avec le temps. Afin d'aider les cliniciens à transposer ces résultats dans la pratique clinique, nous avons créé un modèle prédictif utilisant ces deux principaux facteurs de risque. Afin de pouvoir inclure dans notre modèle d'autres données tels que le type de donneur et de pouvoir généré des estimations plus précises, nous envisageons de répéter cette étude sur une population plus large en colligeant les patients français et britanniques. Ainsi, dans cette étude de cohorte rétrospective nationale, nous confirmons le devenir favorable des enfants ayant débuté un traitement de suppléance rénal avant l'âge de deux ans. Les discussions sur l'opportunité de débuté un traitement de suppléance devrait essentiellement prendre en compte les comorbidités extrarénales car la survie des patients en l'absence de ces

comorbidités est excellente. La principale question chez les nourrissons en IRCT reste donc quand et comment les transplanter. Notre étude fournit des données sur l'impact du matching morphologique et immunologique afin d'aider les cliniciens dans leurs décisions. En étendant cette analyse à d'autres cohortes, notre but est de développer un outil capable de prédire la perte de greffon et d'aider les cliniciens à choisir le greffon optimal pour leurs patients.

L'étude de la survie des greffons sur l'ensemble de la population des enfants et des jeunes adultes en France est rapportée annuellement dans le rapport d'activité de l'Agence de la biomédecine et n'a donc pas été réétudié dans le cadre de cette thèse. Une étude spécifique sur le lien entre âge et risque de perte de greffon a été réalisée par d'autres auteurs. Néanmoins, ces résultats seront importants pour alimenter notre outil de simulation.

Nous nous sommes donc intéressés aux complications post-transplantations en étudiant les causes d'hospitalisations post-transplantation. Les hospitalisations pour causes infectieuses sont de loin les plus fréquentes, devant les rejets et les cancers. L'objectif de cette étude est de décrire ces hospitalisations dans une cohorte de transplantés rénaux pédiatriques, d'étudier les facteurs de risque d'infections et d'évaluer le coût supplémentaire de ces hospitalisations.

Les patients de moins de 20 ans transplantés en France entre 2008 et 2013 ont été inclus à partir de la base de données médico-administrative du PMSI et un appariement indirect a été effectué avec les données du registre REIN. Le calcul des coûts était basé sur le coût des remboursements en 2009 dans une perspective assurance maladie. Nous avons utilisé un modèle de Cox pour étudier les facteurs de risque d'hospitalisation. Pour évaluer l'évolution du risque avec le temps, nous avons calculé le taux mensuel d'hospitalisation pour toutes les infections et par type d'infection.

Parmi 593 patients, 660 hospitalisations chez 260 patients ont été identifiées. Le temps médian de suivi était de 34,7 [14,7-53,2] mois. La première cause d'hospitalisation était les infections urinaires avec une incidence de 16,6 pour 100 patient-année (pa) suivi des infections virales (15,6/100 pa) incluant 128 infections digestives, 70 infections des voies respiratoires et 47 hospitalisations liées aux herpès virus. Les facteurs de risque d'hospitalisation étaient le jeune âge, le nombre de mismatch HLA et l'utilisation de Cyclosporine plutôt que de Tacrolimus. Le sexe féminin, un antécédent d'uropathie et la durée d'ischémie froide étaient des facteurs de risque spécifiques d'infection urinaire. Le risque instantané d'infection diminue avec le temps, sauf pour l'infection à CMV qui présente un pic d'incidence vers 6 mois post-transplantation à la fin de la prophylaxie. Le coût total des hospitalisations liées à l'infection était de 1600k € (933 €/pa) pour 3529 jours d'hospitalisation. Ces résultats soulignent l'importance des complications infectieuses chez les transplantés rénaux pédiatriques, en particulier les plus jeunes en termes de qualité de vie et de coût de la santé.

La dernière partie de cette thèse consiste à réunir l'ensemble des résultats obtenus dans une étude globale de la trajectoire des enfants et adultes jeunes présentant une insuffisance rénale terminale. Ainsi, le premier objectif de notre étude est de décrire et d'analyser les trajectoires des enfants et des adultes jeunes en IRCT et de décrire les différentes stratégies de prise en charge globalement et par sous-groupe. Le second est de simuler la généralisation de certaines stratégies de prise en charge observées ou la modification de ces stratégies afin d'évaluer l'impact sur le temps total passé avec un greffon fonctionnel ou en dialyse sur une période de 20 ans. Ces simulations permettront également de mettre en perspective le bénéfice attendu pour les patients (temps passé avec un greffon, espérance de vie restreinte) avec les ressources nécessaires tant en termes de nombre de greffons nécessaires à chaque stratégie qu'en terme de coût.

Dans une étude pilote, nous avons inclus tous les patients inclus dans le registre REIN entre 1995 et 2015 ayant débuté un traitement de suppléance avant l'âge de 30 ans. Pour décrire les trajectoires des patients, nous avons tenu compte de quatre événements d'intérêt: l'initiation du traitement de suppléance, la transplantation rénale, l'échec de la greffe et le retour à la dialyse et le décès. Cela permet de définir 14 états : Transplantation définie par son rang (1 à 4) et le type de donneur (vivant ou décédé), les périodes de dialyse définies par leurs rangs (1 à 5) et le décès. La trajectoire d'un patient est définie comme la succession d'états et le temps passé dans chacun d'eux. Nous avons divisé chaque trajectoire par périodes de un mois pour déterminer l'état de chaque patient à tout moment et la présence d'une transition d'un état à l'autre. Les taux de transition ont été considérés comme stables par périodes de 3 mois au cours de la première année, puis par périodes de 6 mois entre 1 et 10 ans et par période d'un an après 10 ans. Les taux de transition ont été calculés en fonction du nombre de patients à risque dans chaque état et du nombre de transition observé. Nous avons ensuite programmé, en utilisant le logiciel SAS, un outil statistique capable de simuler le devenir d'une cohorte de patients en IRCT sur une période de 20 ans. Le nombre de patients dans la cohorte, la distribution initiale des modalités de suppléance et les taux de transition peuvent être modifiés. Les résultats obtenus sont une représentation graphique de la répartition des patients en fonction du temps, le pourcentage moyen de temps passé dans chaque état par les patients et le nombre de greffon nécessaire dans chaque simulation. L'étude des trajectoires observées montre que seulement 22% des patients reçoivent une transplantation préemptive comme première modalité de suppléance avec seulement 23% d'entre eux recevant une transplantation d'un donneur vivant. Sur une période de 20 ans, les patients passent en moyenne 8,4% du temps en dialyse et 81,2% du temps avec un greffon fonctionnel. Ainsi, le temps moyen passé en dialyse est de 20 mois

et l'espérance de vie restreinte était de 239,7 mois. Enfin, dans cette simulation, 115 greffons ont été utilisés, dont 17 provenant de donneurs vivants.

En France, les autorités sanitaires et les organisations de patients soulignent la nécessité d'augmenter le taux de transplantation préemptive et de dons vivants. Nous avons simulé le résultat d'une cohorte de 100 patients si des interventions étaient mise en œuvre pour atteindre le niveau de 32% de transplantation préemptive, dont 47% à partir de donneurs vivants comme observés au Royaume-Uni. Nous n'avons pas modifié les taux de transition. Dans cette simulation, sur 20 ans, les patients passent en moyenne 7,7% du temps en dialyse. Ainsi, le temps moyen passé en dialyse est de 18,4 mois et l'espérance de vie restreinte est restée stable à 239,7 mois. Dans cette simulation, 114 greffons ont été utilisés, dont 26 provenant de donneurs vivants. Nous avons répété cette simulation en considérant une répartition initiale avec 48% des patients avec transplantation préemptive dont 58% à partir de donneur vivant ce qui correspond aux taux de patients considérés comme éligible à une transplantation préemptive dans une récente étude rétrospective du service de néphrologie pédiatrique du Great Ormond Street Hospital. Sur une période de 20 ans, les patients passent alors en moyenne 6,6% de temps en dialyse. Ainsi, le temps moyen passé en dialyse est de 15,8 mois et l'espérance de vie restreinte est restée stable à 239,7 mois. Dans cette simulation, 114 greffons ont été utilisés, dont 37 provenant de donneurs vivants. Ainsi, lorsque nous comparons nos résultats avec ceux d'autres pays, il est clair que des efforts peuvent être faits pour promouvoir la transplantation préemptive et la transplantation à partir de donneurs vivants. Cependant, nos simulations montrent que des efforts majeurs tels que l'augmentation du taux de transplantation préemptive de 22% à 48% et la multiplication par 2 du nombre de transplantation de donneurs vivants auront un impact modéré sur les trajectoires globales des patients, diminuant le temps moyen passé en dialyse de 20 mois à 15,8 mois sur une période de 20 ans. Ce bénéfice doit être mis en rapport avec l'importance des efforts nécessaires à ces modifications.

Perspectives

Néanmoins, comme indiqué précédemment, il existe des disparités majeures pour l'accès à la transplantation rénale basées sur les caractéristiques des patients telles que l'âge, le sexe, le niveau de sensibilisation à l'HLA ou sur d'autres facteurs tels que les caractéristiques du centre de traitement. Ainsi, bien que les simulations en population générale montrent peu de possibilités d'amélioration, des améliorations majeures pourraient être possible en mettant l'accent sur les sous-groupes défavorisés. Par conséquent, nous souhaitons développer notre outil de simulation pour pouvoir décrire les trajectoires des enfants et des adultes jeunes en IRCT et pouvoir décrire les

différentes stratégies de traitement par sous-groupes. Ensuite, nous simulerons des modifications de ces stratégies non seulement en modifiant la répartition initiale des modalités de traitement, mais aussi en étudiant et en simulant l'effet de différentes pratiques telles que les exigences de matching HLA ou le type de dialyse sur les taux de transition. Pour cela, trois grandes implémentations seront nécessaires. Tout d'abord, nous décrirons plus précisément les trajectoires des patients en tenant compte de cinq événements d'intérêt : l'initiation du traitement de suppléance, la transplantation rénale, l'échec de greffe et le retour à la dialyse, le décès et l'inscription sur la liste d'attente. De ce fait, le nombre d'états augmentera de 14 à 20 : Transplantation définie par son rang (1 à 3) et le type de donneur (vivant ou décédé), les périodes de dialyse définies par leurs rangs (1 à 3), leur modalité (hémodialyse ou dialyse péritonéale) et leur statut sur la liste d'attente, un état « inscription préemptive et le décès. Deuxièmement, les taux de transition seront estimés en utilisant un modèle multi-état par maximisation de probabilités de Poisson en tenant compte des risques concurrents de transition vers les autres états. Pour étudier l'impact de caractéristiques telles que l'âge ou le niveau d'immunisation anti-HLA, deux méthodes seront utilisées. Tout d'abord, nous effectuerons une analyse stratifiée par groupes d'âge ou par niveau d'immunisation anti-HLA pour étudier les particularités des trajectoires de ces patients. Ensuite, nous inclurons ces facteurs comme paramètres dans le modèle pour analyser leur impact sur les taux de transition et pour contrôler la fiabilité de nos résultats en calculant les intervalles de confiance des paramètres. Enfin, nous pourrions simuler différentes stratégies de traitement et les comparer en fonction du temps moyen passé avec un greffon fonctionnel ou en dialyse sur une période de 20 ans. Nous évaluerons également pour chaque stratégie le nombre de transplantations nécessaires par type de donneur et le coût de la stratégie.

Conclusions

Toutes les études réalisées dans le cadre de cette thèse confirment que l'accès aux traitements de suppléance de l'insuffisance rénale chez les enfants et les jeunes adultes en France est globalement satisfaisant. Cependant, comme indiqué précédemment par la Haute Autorité de Santé, des disparités d'accès à ces traitements existent en France, non seulement chez les adultes mais aussi chez les enfants, comme le montre ce travail. L'évaluation de ces disparités est d'une importance majeure et constitue la première étape pour mettre en œuvre des actions visant à les réduire.

Enfin, du fait de la durée de vie limitée des greffons rénaux et de l'amélioration importante de l'espérance de vie, ces jeunes patients ont la particularité de nécessiter fréquemment des transplantations répétées plus ou moins précédées de périodes de dialyse. De ce fait, il convient de considérer la trajectoire globale de ces patients avec un horizon « vie entière » afin de maximiser le

temps passé avec un greffon fonctionnel et de minimiser le temps passé en dialyse. Nous avons développé un outil de simulation permettant de tester des modifications de stratégies de prise en charges et leurs effets sur la trajectoire des patients. Cet outil sera développé afin de répondre à des questions plus complexes sur des sous-groupes de patients.

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xii. Annexe 2

Résultat de la classification hiérarchique

