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# Causes et déterminants du transfert en hémodialyse chez les patients traités par dialyse péritonéale : la survie technique

Antoine Lanot

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Normandie Université

## THÈSE

**Pour obtenir le diplôme de doctorat**

**Spécialité RECHERCHE CLINIQUE, INNOVATION TECHNOLOGIQUE, SANTE PUBLIQUE**

**Préparée au sein de l'Université de Caen Normandie**

### **Causes et déterminants du transfert en hémodialyse chez les patients traités par dialyse péritonéale - la survie technique**

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**Thèse soutenue le 14/12/2021  
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NORMANDIE



Normandie de Biologie Intégrative,  
Santé, Environnement







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## *Abréviations et acronymes*

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cs-HR :	Cause specific hazard-ratio
CCI:	Coefficient de corrélation intra-classe
DFG :	Débit de filtration glomérulaire
DPA :	Dialyse péritonéale automatisée
DPCA :	Dialyse péritonéale continue ambulatoire
IC <sub>95%</sub> :	Intervalle de confiance à 95%
IRCT :	Insuffisance rénale chronique terminale
ISPD :	International Society of Peritoneal Dialysis
OR :	Odds ratio
PROMS :	Patients-Reported Outcome Measures
PREMS :	Patient-Reported Experience Measures
REIN :	Registre Épidémiologique et Information en Néphrologie
RDPLF:	Registre de Diayse Péritonéale en Langue Française
sd-HR :	Subdistribution hazard-ratio
SNDS :	Système national des données de santé

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## ***I. INTRODUCTION***

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### **I.1. L'insuffisance rénale terminale**

L'insuffisance rénale chronique terminale (IRCT) est le dernier stade de la maladie rénale chronique, définie par un débit de filtration glomérulaire (DFG) inférieur à 15 ml/min/1,73m<sup>2</sup>. Les différentes fonctions physiologiques des reins sont alors défaillantes, au premier plan desquelles l'épuration de multiples toxines urémiques qui s'accumulent dans le secteur plasmatique. Les manifestations cliniques de la maladie apparaissent en général quand le DFG devient inférieur à 10 ml/min/1,73m<sup>2</sup> avec des variations inter individuelles importantes. C'est l'apparition de ces symptômes regroupés sous l'appellation de syndrome urémique qui indique la mise en place d'un traitement de suppléance de la fonction rénale [1]. Ces traitements de suppléance sont la transplantation rénale et deux techniques d'épuration extra-rénale : l'hémodialyse et la dialyse péritonéale.

### **I.2. Les traitements de suppléance de la fonction rénale**

La situation des patients atteints d'insuffisance rénale chronique terminale est singulière pour de multiples raisons. L'IRCT est la seule pathologie chronique pour laquelle des traitements de suppléance de la fonction d'organe défaillant sont largement disponibles. Chez les patients éligibles, la transplantation est le traitement qui offre la meilleure qualité de vie et la meilleure survie [2], [3]. Cependant, de nombreux patients ne

peuvent pas bénéficier d'une transplantation du fait de comorbidités qui contre-indiquent la chirurgie chez eux. Pour d'autres, la pénurie d'organes et des contraintes de compatibilité immunologique peuvent imposer des délais d'attente de plusieurs mois voire plusieurs années pendant lesquels la poursuite d'une technique d'épuration est nécessaire. Ainsi selon les données de l'année 2018 du Registre Épidémiologique et Information en Néphrologie (REIN), parmi les 89 692 patients prévalents traités pour une IRCT, 40 421 étaient porteurs d'un greffon fonctionnel tandis que 49 271 étaient traités par dialyse [4].

### **I.2.1. L'hémodialyse**

Les deux modalités de dialyse disponibles se différencient tout d'abord par leur accès au compartiment sanguin. L'hémodialyse met en jeu un abord sanguin direct : fistule artério-veineuse ou cathéter veineux central. Le sang est traité par un générateur et passe dans un dialyseur qui constitue le rein artificiel. Ce dialyseur est constitué d'une membrane semi-perméable qui délimite deux compartiments dans lesquels circulent à contre-courant le sang et le dialysat. Classiquement, les séances de dialyse sont réalisées trois fois par semaine, durant des séances de quatre heures [5]. L'équipement technologique complexe que requiert l'hémodialyse en a fait de manière prépondérante une technique développée au sein des hôpitaux ou de centres de soins dédiés. Cependant, il est possible d'adapter cette modalité au domicile.

### **I.2.2. La dialyse péritonéale**

La dialyse péritonéale mobilise la cavité péritonéale, délimitée par la membrane péritonéale. Cette membrane naturelle possède la propriété d'être semi-perméable et

richement vascularisée. Des échanges de soluté et d'eau ont lieu par diffusion et par convection entre le dialysat infusé dans la cavité péritonéale et le compartiment plasmatique. La dialyse péritonéale est une technique dite à l'équilibre, car les périodes de stase du dialysat dans la cavité péritonéale sont quasi constantes, entrecoupées de périodes de remplacement du dialysat dont la durée est d'environ 30 à 40 minutes. Ces échanges peuvent être effectués manuellement, en général 3 à 4 fois par jour. Cette modalité est appelée dialyse péritonéale continue ambulatoire (DPCA). Dans la modalité de dialyse péritonéale automatisée (DPA), un cycleur sur lequel sont disposées les poches de dialysat est connecté au cathéter chaque nuit pour réaliser les échanges de manière automatique pendant le sommeil [6].

### **I.3. Le fardeau de la maladie rénale chronique et les contraintes liées aux traitements**

La dialyse est un traitement lourd, extrêmement chronophage, et associé à un risque non négligeable d'évènements indésirables dont la gravité peut être variable. En plus du fardeau de la maladie, les patients doivent supporter les nombreuses contraintes de ce traitement sans lequel leur survie n'est pas possible. Ce fardeau de la maladie et de la charge de soins a également un retentissement négatif sur la qualité de vie des aidants [7]. Plusieurs études ont été réalisées dans le but de comparer le fardeau de différentes maladies chroniques et il a ainsi été montré que la qualité de vie des patients atteints d'insuffisance rénale terminale était altérée de manière similaire à celle des patients atteints de cancers à un stade avancé [8], [9]. Afin de limiter les contraintes liées aux soins et de les rendre plus tolérables, il est important de pouvoir proposer aux patients plusieurs options de traitement. Les processus de décisions partagées ont pour objectif de guider les

patients afin qu'ils hiérarchisent les options disponibles selon leurs préférences en bénéficiant de l'expérience de leur néphrologue et des données de la science [10].

#### **I.4. Les traitements par dialyse au domicile**

Quand un traitement par dialyse est nécessaire, les caractéristiques des différentes modalités de dialyse orientent le choix des patients. Si la dialyse péritonéale ne se pratique qu'à domicile, l'hémodialyse peut être proposée en centre de soins ou au domicile. On oppose souvent les techniques du domicile à l'hémodialyse en centre, tant le lieu du soin est un critère déterminant du choix de la technique. La sélection de la modalité de traitement de suppléance est un moment important pour les patients et il est primordial de pouvoir mettre en œuvre les moyens nécessaires au bon déroulement du traitement choisi ainsi que d'en assurer la pérennité. C'est particulièrement le cas lorsque le choix se porte sur une des modalités de dialyse à domicile, car ces traitements requièrent un investissement actif de la part des patients et de leurs aidants [11]. Il a bien été rapporté que le risque de transfert non souhaité vers l'hémodialyse en centre était une préoccupation centrale chez les patients traités par dialyse péritonéale [12], [13].

#### **I.5. Historique des techniques de dialyse**

L'histoire des découvertes ayant mené aux techniques de dialyse actuelles débute en 1827 avec le physiologiste français Dutrochet (1776-1847) qui a décrit le phénomène d'osmose. Le terme de dialyse fut ensuite inventé par l'écossais Thomas Graham (1805-1869) qui a découvert les propriétés des membranes semi-perméables. Il

faudra attendre 1924 pour la réalisation de la première dialyse chez l'homme par l'allemand Georges Haas (1886-1931), malheureusement sans réelle efficacité. En 1945, durant la deuxième guerre mondiale, le premier traitement efficace fut réalisé par Willem Kolf aux Pays-Bas. Une femme de 67 ans atteinte d'insuffisance rénale aiguë et de coma urémique put ainsi se réveiller après onze heures de traitement par hémodialyse [14]. Le procédé va se généraliser au traitement de l'insuffisance rénale chronique dans les années 1960 à Seattle grâce aux travaux de Scribner (1921-2003) et à ceux de James Cimino (1928-2010) à New-York qui développèrent des abords vasculaires pérennes.

Les propriétés de la membrane péritonéale ont été décrites en 1894 par Ernest Starling (1866-1927), et c'est en 1923 que Georges Ganter (1885-1940) utilisa pour la première fois la dialyse péritonéale chez l'Homme. L'utilisation de cette technique resta sporadique jusqu'aux années 1960. Henry Tenkhoff (1930-2017) breveta en 1968 le cathéter en silicone qui porte son nom et qui est encore utilisé actuellement. Cette avancée marque le début de l'utilisation de la dialyse péritonéale comme technique alternative à l'hémodialyse [15].

La dialyse péritonéale est une technique du domicile depuis ses débuts. Ce n'est pas le cas de l'hémodialyse qui a initialement été réservée à quelques grands hôpitaux en raison des équipements encombrants et coûteux qu'elle nécessitait. De manière remarquable, dès 1964 à Seattle, une machine d'hémodialyse fut développée spécifiquement pour le domicile sous l'impulsion de Scribner : la « mini-one » [16]. Les places à l'hôpital étaient alors très limitées et l'hémodialyse au domicile a connu un essor important dans ce contexte, mais qui s'est essoufflé au fil des ans avec la création dans le monde de centres d'hémodialyse de plus en plus nombreux. L'influence des politiques de santé publique a donc été indéniable sur l'offre de soins et en particulier sur l'essor de la dialyse en centre plutôt qu'au domicile.

## I.6. Épidémiologie de la dialyse dans le monde et en France

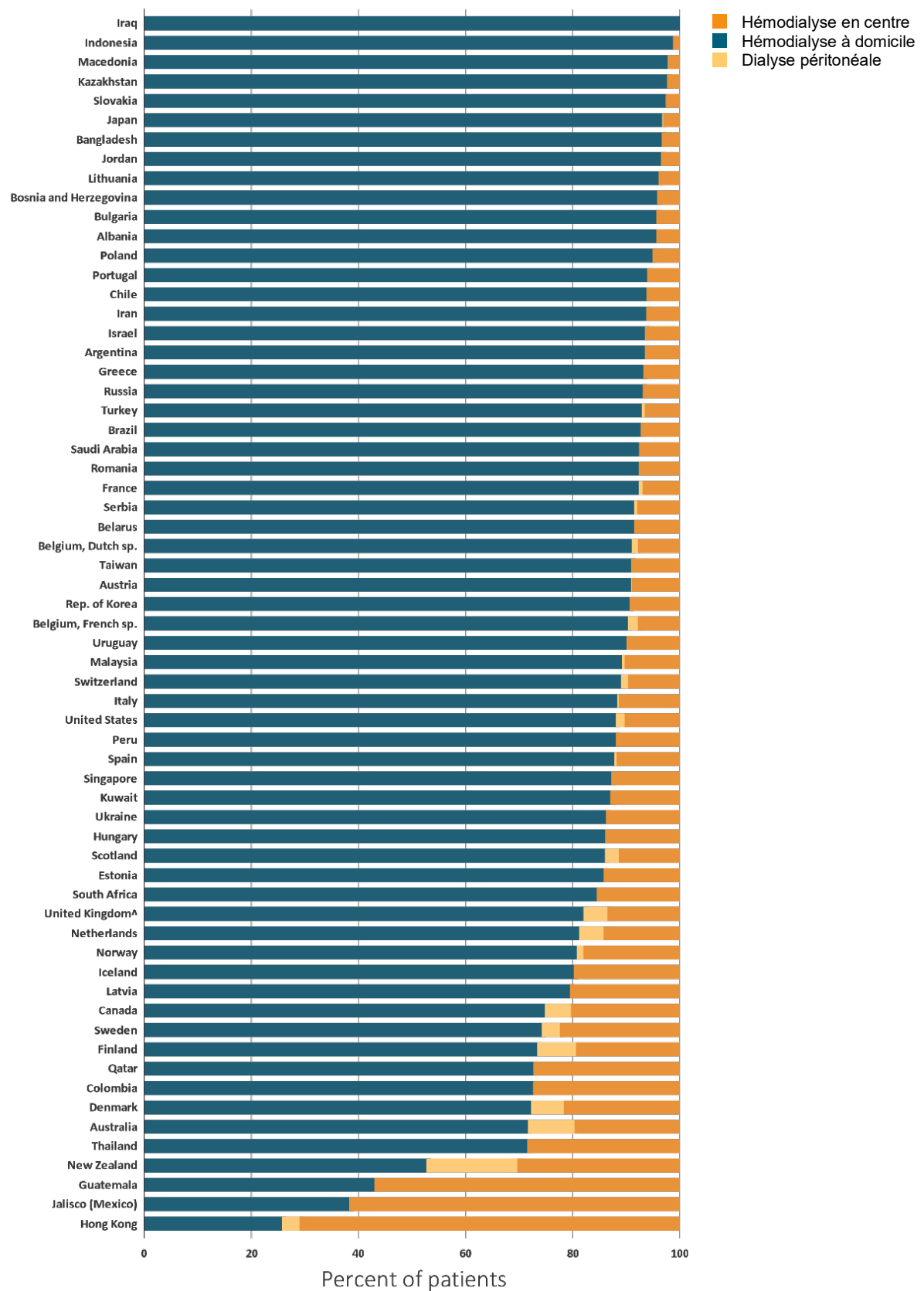
L'accès au traitement de suppléance de la fonction rénale connaît de larges variations dans le monde. Le nombre de patients atteints d'IRCT est en constante augmentation. Selon des projections faites pour 2030, ce nombre de patients devrait être multiplié par 2 à 4 avec les taux de croissance les plus importants dans les pays en voie de développement. L'accès aux soins est déjà un défi de santé publique majeur notamment en Asie et en Afrique où l'IRCT est la cause de plusieurs millions de décès prématurés. A l'échelle mondiale, le nombre de personnes atteintes d'IRCT est estimé à dix millions chaque année, alors que seuls 2,5 millions de patients reçoivent un traitement [17]. En 2016, l'IRCT tenait le 16<sup>ème</sup> rang au classement des causes de décès dans le monde. Les projections pour 2040 la placent au cinquième rang [18]. Actuellement, l'hémodialyse en centre est le traitement d'épuration extra-rénale largement majoritaire dans le monde. Dans quatre pays sur cinq elle représente le traitement de plus de 80 % des patients prévalents traités par dialyse. De larges variations existent dans l'utilisation de la dialyse péritonéale, dont la prévalence est comprise entre 10 et 20 % dans la majorité des États. L'utilisation de l'hémodialyse à domicile est quant à elle plus marginale, avec moins de 3 % des patients traités globalement. Quelques pays ont mis en place des programmes actifs d'incitation à la dialyse au domicile avec des résultats très encourageants. C'est le cas par exemple à Hong-Kong où 71% des patients traités par dialyse en 2016 l'étaient par dialyse péritonéale, ou dans la région de Jalisco au Mexique où ce chiffre s'élève à 61 % (figure 1) [19]. Les Etats-Unis ont lancé l'« Advancing American Kidney health Initiative » en 2019, projet dont le but est de réduire les coûts du traitement pour les patients porteurs d'IRCT, en faisant la promotion active de la transplantation rénale mais également des modalités de dialyse à domicile par rapport à l'hémodialyse en centre [20].



En France, 6% des patients prévalents en dialyse sont traités par dialyse péritonéale, ce pourcentage variant de façon importantes selon les régions, allant de moins de 5 % en Picardie, Ile de France, Aquitaine, Midi-Pyrénées, Provence-Alpes-Côte d'Azur, Guadeloupe, Guyane et la Réunion, jusqu'à plus de 10 % en Alsace, Auvergne, Basse Normandie, Bourgogne et Franche-Comté. Seulement 1 % des patients sont traités par hémodialyse à domicile globalement, et au maximum ce pourcentage s'élève à 4,3 % en Basse-Normandie [4].

Figure 1. Répartition des prévalences des modalités de dialyse dans le monde.

Rapport 19 [19].



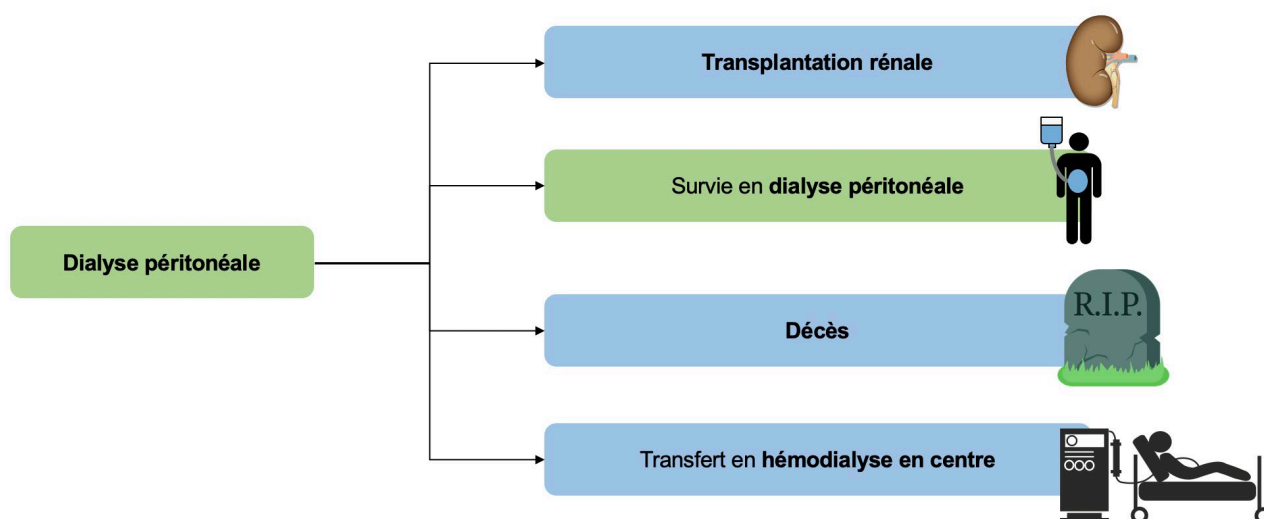
## I.7. L'échec technique, un évènement d'intérêt

La notion d'échec technique ne fait pas l'objet de consensus. Une revue de littérature parue en 2021 a répertorié les essais randomisés dans lesquels la survie technique était un évènement d'intérêt. Dans les 25 essais inclus, 17 définitions différentes étaient utilisées [21]. L'équipe australienne du registre ANZDATA a proposé en 2016 de définir l'échec technique en dialyse péritonéale comme l'évènement composite : décès ou transfert en hémodialyse [22]. Plusieurs points méritent d'être discutés concernant cette définition. Le premier est le fait de considérer la survenue du décès comme étant un échec de la technique. Envisageons par exemple le cas des patients traités par dialyse à domicile et non éligibles à une transplantation rénale. Chez ces patients, la dialyse est nécessaire au long cours. Le décès peut survenir pour de multiples causes n'ayant aucun rapport avec la dialyse, et on peut dans ce cas questionner la pertinence de qualifier d'échec le maintien jusqu'au décès d'une technique à domicile qui a été choisie par le patient. Le deuxième point concerne la nomenclature. L'utilisation du terme même *d'échec* doit être remis en cause en raison de ses connotations péjoratives. Ainsi, l'usage de terminologies positives est un des objectifs qui a été retenu par les groupes de patients traités par dialyse péritonéale au cours du projet SONG-PD [23]. Le terme de *survie de la technique* a été suggéré en remplacement ou celui de *transfert de modalité*, avec la nécessité d'être clair et précis dans les termes employés, car les raisons pour lesquelles une personne arrête la dialyse péritonéale peuvent être très différentes. Pour ces raisons, nous avons choisi de nous intéresser principalement aux transferts de la dialyse péritonéale vers l'hémodialyse en centre. Une durée de deux mois au moins était jugée nécessaire pour considérer un transfert vers l'hémodialyse en centre comme étant définitif.

## I.8. Le transfert en hémodialyse en centre, un évènement compétitif

La situation d'un patient traité par dialyse péritonéale peut évoluer au cours du temps selon la survenue de plusieurs évènements. Les évènements potentiellement observables sont : le décès, l'arrêt de la dialyse après une transplantation rénale, et le transfert de la dialyse péritonéale vers l'hémodialyse en centre. Ces évolutions sont représentées sur la figure 2 (figure 2).

**Figure 2. Parcours de soins des patients porteurs d'insuffisance rénale chronique terminale.**



La survenue de certains de ces évènements implique que les autres évènements ne seront plus observables par la suite. Ainsi, si un patient bénéficie d'une transplantation rénale ou décède alors qu'il est traité par dialyse péritonéale, l'évènement d'intérêt : « transferts de la dialyse péritonéale vers l'hémodialyse en centre » ne sera plus observable. On parle dans ce cas d'évènements compétitifs dont le traitement statistique nécessite des techniques particulières qui ont été utilisées dans nos travaux.

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## **II. OBJECTIFS DU TRAVAIL DE THESE**

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Les résultats d'un travail de recherche translationnelle sont profitables au clinicien s'ils lui permettent d'améliorer le devenir des patients. L'objectif de cette thèse est de définir à partir de données de registres français les caractéristiques associées à un risque de transfert vers l'hémodialyse en centre.

Nous avons pour cela mis en œuvre des méthodes épidémiologiques robustes afin de nous adapter aux spécificités du devenir des patients atteints d'IRCT. Ces spécificités nécessitent la prise en compte de nombreux facteurs de confusion liés à la complexité des traitements par dialyse, à la diversité des pratiques de soins, et à la sélection des patients dans les différentes modalités de traitement. Il convient également de tenir compte de la compétition qui existe entre les événements d'intérêts qui jalonnent le parcours de soins des patients atteints d'IRCT, et qui nécessitent des traitements statistiques particuliers.

Le service de néphrologie du CHU de Caen possède une expertise reconnue dans les traitements par dialyse à domicile. Nos travaux réalisés pendant les trois années de thèses prennent leur ancrage dans ce cadre et sont la suite logique de deux études débutées au cours des deux années précédentes. Nous avons choisi de présenter également ici ces deux études afin que le lecteur puisse bien appréhender le fil logique qui a dirigé l'ensemble de nos recherches sur la survie technique en dialyse péritonéale.

Notre premier travail mené avant l'inscription en thèse portait sur une pratique unique de soins liés au cathéter. Nous avons observé l'existence d'un effet centre qui modifiait de manière notable l'influence de l'administration d'une antibioprofylaxie administrée à la pose du cathéter sur le risque d'infection péritonéale. Ce résultat nous a conduit à interroger l'homogénéité des pratiques de soins des différents centres. Nous

avons alors cherché à identifier des groupes de centres ayant des pratiques homogènes, et une fois ces groupes constitués, nous avons étudié les différences de survie technique entre ces groupes de centres. Chez les patients autonomes pour la réalisation de la dialyse péritonéale, nous avons étudié l'effet des pratiques éducatives sur le risque d'infection péritonéale. Enfin, nous avons cherché à comprendre l'effet de l'assistance pour la réalisation de la dialyse péritonéale sur le risque de transfert en hémodialyse en centre et comment cet effet pouvait varier selon les causes spécifiques du transfert.

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## **III. Effet centre et prévention des infections péritonéales**

*(Travail hors période d'inscription en thèse)*

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### **III.1. Introduction**

Les pratiques des soins sont des variables modifiables, et peuvent donc être adaptées par les cliniciens selon les preuves d'efficacité obtenues dans les travaux de recherche. Parmi les multiples pratiques de soins liées à la dialyse péritonéale, peu ont fait l'objet de recommandations formelles, car peu d'études ayant un bon niveau de preuves sont disponibles. L'administration d'une antibioprophylaxie est au contraire une pratique dont l'efficacité a été prouvée dans quatre essais randomisés et à ce titre son usage est préconisé dans les guidelines de l'ISPD [24]. Cependant, les quatre essais en question étaient tous monocentriques. Cet aspect du design des études en est une limitation. Les données de registre sont observationnelles donc soumises à des biais de sélection mais elles sont disponibles à une grande échelle et permettent à ce titre d'évaluer les différences entre différentes unités de traitements.

L'objectif de l'antibioprophylaxie administrée à la pose du cathéter est de limiter le risque infectieux et notamment celui des infections péritonéales précoces, cause fréquente d'arrêt de la dialyse péritonéale. Nous avons donc cherché à évaluer si l'administration d'un antibiotique à la pose du cathéter était associée à un plus faible risque d'infection péritonéale précoce, et si ce résultat était consistant quand on introduisait un effet centre dans les modèles d'études.

## III.2. Outils statistiques et méthodologie

L'évènement d'intérêt était la survenue d'une infection péritonéale précoce, définie comme survenant dans les trois premiers mois après le début de la dialyse péritonéale. S'agissant d'une variable binaire nous avons utilisé un modèle de régression logistique qui permet l'estimation du risque lié à l'occurrence de l'évènement à un temps donné. Nous avons utilisé une modélisation multiniveaux pour créer trois modèles.

Un modèle 0 ou modèle vide dans lequel le centre de traitement était inclus comme effet aléatoire, et qui ne contient pas de variable explicative :

$$\text{Modèle 0 : } \textit{logit} [p(Y_{i,j} = 1 | X)] = \alpha + u_j$$

Un modèle de niveau 1, dans lequel les variables liées aux patients (niveau 1) étaient ajoutées :

$$\text{Modèle 1 : } \textit{logit} [p(Y_{i,j} = 1 | X)] = \alpha + u_j + X_1.A_1$$

Un modèle de niveau 2, dans lequel les variables liées aux patients (niveau 1) et les variables liées aux centres (niveau 2) étaient incluses

$$\text{Modèle 2 : } \textit{logit} [p(Y_{i,j} = 1 | X)] = \alpha + u_j + X_1.A_1 + X_2.A_2$$

Avec :

$Y_{i,j}$  : la variable aléatoire binaire indiquant la survenue d'une péritonite précoce chez le patient  $i$  traité dans le centre  $j$

$\alpha$  : le logarithme du risque moyen de péritonite précoce

$u_j$  : la variance



$X_1$  : le vecteur des caractéristiques patients

$A_1$  : le vecteur des effets fixes liés aux variables patients

$X_1$  : le vecteur des caractéristiques centres

$A_1$  : le vecteur des effets fixes liés aux variables centres

Cette stratégie de modélisation permet d'estimer l'hétérogénéité entre les centres de traitement grâce au calcul du coefficient de corrélation intra-classe (CCI). Le CCI représente la proportion de la variance totale de l'évènement qui est liée aux différences entre les centres. Il est calculé suivant :

$$ICC = \frac{\sigma_A^2}{\sigma_A^2 + \frac{\pi^2}{3}}$$

Avec  $\sigma_A^2$  la variance de l'effet aléatoire, et le terme  $\pi^2/3$  qui est la variance de l'erreur logistique standard [25].

### III.3. Article

(Hors période d'inscription en thèse)

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*Efficacy of prophylactic antibiotics at peritoneal catheter insertion on early peritonitis. Data from the catheter section of the RDPLF*

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# Efficacy of Prophylactic Antibiotics at Peritoneal Catheter Insertion on Early Peritonitis: Data from the Catheter Section of the French Language Peritoneal Dialysis Registry

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## Key Words

Peritoneal dialysis · Peritonitis · Prophylactic antibiotics · Catheter

## Abstract

**Background:** International guidelines recommend the use of a prophylactic antibiotic before the peritoneal dialysis (PD) catheter can be inserted. The main objective of this study was to assess whether this practice is associated with a lower risk of early peritonitis and to estimate the magnitude of the centre effect. **Methods:** A retrospective, multi-centric study was conducted, in which data from the French Language Peritoneal Dialysis Registry was analysed. Patients were separated into 2 groups based on whether or not prophylactic antibiotics were used prior to catheter placement. **Results:** Out of the 2,014 patients who had a PD catheter placed between February 1, 2012 and December 31, 2014, 1,105 were given a prophylactic antibiotic. In a classical logit model, the use of prophylactic antibiotics was found to protect the individual against the risk of early peritonitis (OR 0.67, 95% CI 0.49-0.92). However, this association lost significance in a mixed logistic regression model with centre as a random effect: OR 0.73 (95% CI 0.48-1.09). Covariates

associated with the risk of developing early peritonitis were age over 65: OR 0.73 (95% CI 0.39-0.85), body mass index over 35 kg/m<sup>2</sup>: OR 1.99 (95% CI 1.13-3.47), transfer to PD due to graft failure: OR 2.24 (95% CI 1.22-4.11), assisted PD: OR 1.96 (95% CI 1.31-2.93), and the use of the Moncrief technique: OR 3.07 (95% CI 1.85-5.11). **Conclusion:** There is a beneficial effect of prophylactic antibiotic used prior to peritoneal catheter placement, on the occurrence of early peritonitis. However, the beneficial effect could be masked by a centre effect.

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## Introduction

Peritoneal infection – which can cause technique failure – remains a frequent complication that occurs during the course of the peritoneal dialysis (PD) process, in spite of tremendous efforts taken to prevent this infection from occurring. It has been documented that early peritonitis is associated with an increased risk of early PD failure [1]. Therefore, the prevention of early peritoneal infection could also increase technique survival. Bacterial contamination of the peritoneal cavity may occur during peritoneal catheter placement.

In an attempt to prevent peritonitis, the use of prophylactic antibiotics at catheter insertion has been recommended. European Renal Best Practice guidelines recommended the infusion of cephalosporin or vancomycin at the time of catheter insertion [2]. International Society for Peritoneal Dialysis (ISPD) guidelines suggest the use of prophylactic antibiotics based on the local microbial ecology [3], as well as present an assessment of the efficacy of vancomycin for the prevention of peritonitis [4]. More recently, the Kidney Health Australia-Caring for Australasians with Renal Impairment guidelines have also recommended antibiotics prophylaxis at the time of catheter insertion [5].

These recommendations are based on the results of a systematic review, published in 2004 [6]. Nevertheless, the 4 randomised control trials that were included in the meta-analysis were all monocentric studies. The use of monocentric trials raises the question of the generalisability of the results, as centre practice could influence the occurrence of peritonitis. Peritonitis incidence may differ from one centre to another, so that the magnitude of the effect of prophylactic antibiotics can vary between centres. To our knowledge, the effect of prophylactic antibiotic on the rate of early peritonitis (occurring during the first 3 months of PD) has not yet been evaluated.

Although this is only an observation, it is found that data from registries allows large-scale studies to be carried out, which can provide information at the population level. Furthermore, the centre effect on the outcome can be taken into account in studies based on registries, and this can help nephrologists to assess whether measures other than antibiotic prophylaxis should be implemented at the centre level to decrease the incidence of early peritonitis [7, 8].

The aim of this study was to assess whether the use of prophylactic antibiotics at the time of PD catheter placement was associated with a lower risk of peritonitis within the first 3 months of PD at the population level and if there was a centre effect on the occurrence of early peritonitis.

### Patients and Methods

This was a retrospective study that was conducted using data from the 'catheter' section of the French Language Peritoneal Dialysis Registry (RDPLF); this registry has already been described in a previous publication [9]. Of the 144 French PD centres participating in the registry, 78 also provide data for the optional catheter section of the registry. The peritonitis diagnosis criteria were those specified by the ISPD guidelines [4]. Of the French PD patients registered in the RDPLF, the peritonitis rate during the first month of PD was 0.04 per patient (95% CI

0.03–0.05), whereas peritonitis rate within the first 3 months of PD was 0.09 per patient (95% CI 0.08–0.11). Early peritonitis was defined as any peritonitis episode occurring within the first 3 months of PD.

Patients older than 18 years starting dialysis between February 1, 2012 and December 31, 2014 were included in the study. Patients treated in the French overseas territories were not included. During the study period, there were 2,061 incident PD patients. Of these 2,061 patients, 47 were excluded, 2 had a percutaneously inserted catheter, 2 had a catheter of unknown type, and data on prophylaxis antibiotics were missing for 43 patients. There were 59 inconsistent items of data regarding the body mass index (BMI), and these were imputed by the mean BMI value. Within the first 3 months following PD, 113 (5.61%) died, 152 (7.54%) were transferred to hemodialysis, and 66 (3.28%) underwent transplantation. Eventually, 2,014 patients were analysed.

The covariates extracted from the registry were antibiotics prophylaxis at catheter insertion, age, gender, BMI, comorbidities, underlying nephropathy, presence of diabetes mellitus, treatments used prior to PD, PD modality at dialysis initiation (automated PD or continuous ambulatory PD), assistance for PD (self-PD, family assistance, nurse assistance), type of PD catheter, surgery technique (laparoscopy or laparotomy), Moncrief method, type of structure in which the patient was treated, and the centre size (number of new patients per year and per centre). Comorbidities were assessed by calculating a modified Charlson Comorbidity Index (CCI) and subtracting the age subscore from the CCI, in order to evaluate the role of the comorbidities independently of the patient's age.

### Statistical Analysis

The event of significance was the occurrence of peritonitis within the first 3 months of being on PD. PD patients were separated in 2 groups based on whether or not prophylactic antibiotics were used at the time of PD catheter insertion. No statistical test was performed to compare the 2 groups in order to avoid multiple testing issues. Categorical variables were described by proportion and percentage and continuous variables were described by the median value and the first and third tertile values.

Renal transplantation and death during the first 3 months on PD were censored. Estimation of the random effect using a Cox model is controversial. The logistic regression model enables the possibility of estimating risk at a specific time point. Therefore, a mixed logistic model, which provides a robust estimation of the centre effect, was used for the statistical analysis. To investigate the centre effect on the occurrence of early peritonitis, an empty logistic regression model was compared with a mixed logistic model with centre as a random effect. There was significant heterogeneity between centres, and this remained the case after adjustment for the use of prophylactic antibiotics. A logistic regression model and a mixed logistic regression model with centre as a random effect were therefore used for the statistical analysis. A level 1 model with individual covariates was elaborated to investigate whether centre heterogeneity could be explained by the patient composition of the centre. Centre-specific covariates were then included in a level 2 model, to detect the extent to which the centre effect was influenced by available centre characteristics. Intraclass correlation coefficient and proportional change in variance were presented with this aim. The link between each covariate and the event of interest

was assessed by univariate analysis with a logistic regression model. For the multivariate analysis, the use of prophylactic antibiotics was entered into the model a priori, since it was the explanatory covariate. Covariates were otherwise included in the multivariate analysis when the p value was <0.20 in the univariate analysis. The multi-level modeling was also tested in a sensitivity analysis, after exclusion of the centres in which the rate of prophylactic antibiotics use was 0 or 100%. The uncertainty of the OR was expressed by their 95% CI, estimated via a bootstrapping procedure.

Statistical analyses were performed with R 3.1.1 (R foundation for statistical computing) including the lme4 package.

The RDPLF has the approval of the French National Ethics Committee (Commission nationale de l'informatique et des libertés). This study took place within the framework of this authorisation.

## Results

### *Characteristics of Patients According to the Group of Treatment*

The median age was 67.04 (interquartile range 52.38–78.9), and 1,204 patients (59.78%) belonged to the male gender. Patients' characteristics are displayed in table 1.

Of the 2,014 patients included, 1,105 had received prophylactic antibiotics (vancomycin: 373, other antibiotics: 732) at the time of PD catheter placement. There were 185 episodes of early peritonitis, 99 (10.89%) of which occurred in the group that was not given prophylactic antibiotics, and 86 (7.78%) in the prophylactic antibiotics group. The rate of early peritonitis was higher in the group of patients who had received prophylactic antibiotics, according to chi-square test ( $p = 0.02$ ). The class of microorganism responsible for early peritonitis was Gram positive cocci: 45 (45.45%) in the group that was not given prophylactic antibiotics and 41 (47.67%) in the group that was given prophylactic antibiotics. Seventeen (21.79%) centres never used prophylactic antibiotics, whereas 18 (23.08%) centres always did. The remaining 43 (55.13%) centres used antibiotics in variable frequencies.

### *Univariate Analysis*

According to the logit model, prophylactic antibiotherapy protected against the risk of early peritonitis (OR 0.69, 95% CI 0.51–0.93; table 2).

Patient-specific covariates that were significantly associated with early peritonitis were male gender (OR 0.69, 95% CI 0.51–0.93), BMI between 35 and 40 kg/m<sup>2</sup> (OR 2.44, 95% CI 1.33–4.27), polycystic kidney disease (OR 0.41, 95% CI 0.16–0.88), failed transplant (OR 1.93, 95% CI 1.07–3.3) and family assistance for dialysis

(OR 1.81, 95% CI 1.12–2.85; table 2). Centre-specific covariates associated with early peritonitis were the catheter type (OR 1.56, 95% CI 1.05–2.32 for swan neck and coiled intra-peritoneal segment catheters) and the use of the Moncrief technique (OR 2.45, 95% CI 1.61–3.64; table 3).

### *Multivariate Analysis*

Prophylactic antibiotics had a protective effect against early peritonitis in the multivariate logit model (OR 0.67, 95% CI 0.49–0.92). However, when the centre effect was taken into account by performing mixed logistic regression, prophylactic antibiotics were not shown to reduce the risk of early peritonitis (OR 0.73, 95% CI 0.48–1.09). Age (OR 0.57, 95% CI 0.39–0.85), BMI (OR 1.99, 95% CI 1.13–3.47), failed transplant (OR 2.24, 95% CI 1.22–4.11), family-assisted PD (OR 1.96, 95% CI 1.31–2.93), and use of the Moncrief technique (OR 3.07, 95% CI 1.85–5.11) were associated with the occurrence of early peritonitis in the mixed logistics multivariate analysis (table 4). In the sensitivity analysis, after exclusion of the centres in which the rate of use of prophylactic antibiotics were 0 or 100%, we found that the use of prophylactic antibiotics was not significantly associated with the risk of early peritonitis (OR 0.72, 95% CI 0.48–1.08).

## Discussion

Guidelines exist regarding the use of prophylactic antibiotics before surgery in general. Antimicrobial prophylaxis is recommended for most procedures, but not for what are known as "clean surgical procedures". However, there is lack of evidence regarding the efficacy of prophylactic antibiotics due to the difficulty in establishing significant differences in efficacy between prophylactic antimicrobial agents and the effect of the study per se [10]. In a study published in 2000, 221 participants were randomised to receive prophylactic intravenous vancomycin 12 h prior to PD catheter placement, or cefazolin 3 h before the procedure or no antibiotics at all. In this study, peritonitis was defined as any episode of peritoneal infection occurring within the first 14 days following catheter placement. A single peritonitis episode occurred in one patient (1%) of the vancomycin group, in 6 patients (7%) of the cefazolin group, and in 10 patients (12%) of the control group. When vancomycin prophylaxis was chosen as the reference, the OR of peritonitis was 11.64 (95% CI 1.456–93.14) for the control group, and 6.45 (95% CI 0.76–54.8) for the cefazolin group [11].

**Table 1.** Patient characteristics according to prophylactic antibiotic at catheter insertion

Covariates	No prophylactic antibiotics (n = 909)	Prophylactic antibiotics (n = 1,105)
Age at PD initiation, years, median (IQR)	68.15 (52.70–79.95)	65.87 (52.20–78.25)
Modified CCI, median (IQR)	4 (2–5)	4 (2–5)
Number of new patients per year per centre, median (IQR)	11.2 (6.64–13.89)	9.81 (7.55–18.26)
Gender, male, n (%)	553 (60.84)	651 (58.82)
BMI, kg/m <sup>2</sup> , n (%)		
<18	35 (3.85)	42 (3.80)
18–25	387 (42.57)	486 (43.98)
25–30	296 (32.56)	372 (33.67)
30–35	119 (13.09)	164 (14.84)
35–40	60 (6.60)	30 (2.71)
>40	12 (1.32)	11 (1.00)
Diabetes, n (%)	326 (35.86)	387 (35.02)
Nephropathy, n (%)		
Diabetic	184 (20.24)	200 (18.10)
Unknown	75 (8.25)	120 (10.86)
Interstitial nephritis	60 (6.60)	55 (4.98)
Glomerulonephritis	143 (15.73)	162 (14.66)
PKD	73 (8.03)	81 (7.33)
Uropathy	45 (4.95)	53 (4.80)
Vascular	248 (27.28)	292 (26.43)
Systemic disease	24 (2.64)	40 (3.62)
Other cause	57 (6.27)	102 (9.23)
Treatment before PD, n (%)		
No dialysis	719 (79.10)	822 (74.39)
Hemodialysis	145 (15.95)	222 (20.09)
Transplantation	45 (4.95)	61 (5.52)
PD modality (CAPD), n (%)	720 (79.21)	758 (68.6)
Assisted PD, n (%)	472 (51.93)	544 (49.23)
Modality of PD assistance, n (%)		
Self PD	427 (46.97)	561 (50.77)
Family-assisted PD	89 (9.79)	110 (9.95)
Nurse-assisted PD	393 (43.23)	434 (39.28)
Exit site antibioprophyllaxy, n (%)		
Unknown	22 (2.42)	33 (2.99)
None	719 (79.10)	838 (75.84)
Present	168 (18.48)	234 (21.18)
Catheter type, n (%)		
Straight neck, straight IPS	284 (31.24)	197 (17.83)
Swan neck, straight IPS	301 (33.11)	420 (38)
Straight neck, coiled IPS	166 (18.26)	222 (20.09)
Swan neck, coiled IPS	158 (17.38)	266 (24.07)
Surgery technique, n (%)		
Laparotomy	668 (73.49)	847 (76.65)
Laparoscopy	241 (26.51)	258 (23.35)
Moncrief technique, n (%)	88 (9.68)	100 (9.05)

IQR = Interquartile range; PKD = polycystic disease; CAPD = continuous ambulatory PD; IPS = intra peritoneal segment.

**Table 2.** Univariate analysis for the risk of early peritonitis (logistic regression): patient-specific covariates

Covariates	Logistic regression	
	unadjusted OR (95%CI)	p value
Antibioprophylaxy	0.69 (0.51–0.93)	<0.05
Age at PD initiation, years	0.99 (0.99–1.00)	0.18
Modified CCI	1.01 (0.96–1.06)	0.72
Gender, male	0.69 (0.51–0.93)	<0.05
BMI, kg/m <sup>2</sup>		
<18	1.39 (0.63–2.76)	0.38
18–25	Ref.	
25–30	0.98 (0.68–1.40)	0.90
30–35	0.97 (0.59–1.55)	0.91
35–40	2.44 (1.33–4.27)	<0.01
>40	1 (0.16–3.49)	0.10
Diabetes	1.24 (0.91–1.69)	0.17
Nephropathy		
Unknown	0.77 (0.41–1.39)	0.40
Interstitial nephritis	0.91 (0.43–1.78)	0.79
Glomerulonephritis	0.80 (0.47–1.34)	0.40
Diabetic PKD	Ref.	–
PKD	0.41 (0.16–0.88)	<0.05
Uropathy	1.32 (0.65–2.51)	0.42
Vascular	0.80 (0.51–1.25)	0.33
Systemic disease	1.23 (0.51–2.64)	0.62
Other cause	1.10 (0.60–1.95)	0.76
Treatment before PD		
No dialysis	Ref.	
Hemodialysis	1.29 (0.87–1.87)	0.19
Transplantation	1.93 (1.07–3.30)	<0.05
Number of new patients per year per center	1 (0.96–1.05)	0.85
Type of structure		
Non profit	1.04 (0.45–2.20)	0.93
Community hospital	Ref.	
Academic hospital	0.75 (0.31–1.62)	0.48
Private	0.89 (0.25–2.40)	0.83
PD modality (CAPD)	1.33 (0.98–1.80)	0.28
Assisted PD	1.35 (1.00–1.83)	0.07
Modality of PD assistance		
Self PD	Ref.	
Family-assisted PD	1.81 (1.12–2.85)	<0.01
Nurse-assisted PD	1.22 (0.88–1.69)	0.24

In a randomised trial published in 1997, 18 patients received cefuroxime intravenously at catheter insertion, and 250 mg intraperitoneally in the first dialysis bag, whereas in the control group, 20 patients received no prophylactic antibiotics at all. No peritonitis episode occurred within the first 10 days following catheter

**Table 3.** Univariate analysis for the risk of early peritonitis (logistic regression): centre-specific covariates

Covariates	Logistic model	
	unadjusted OR (95%CI)	p value
Antibioprophylaxy	0.69 (0.51–0.93)	<0.05
Type of structure		
Non profit	1.04 (0.45–2.20)	0.93
Community hospital	Ref.	
Academic hospital	0.75 (0.31–1.62)	0.48
Private	0.89 (0.25–2.40)	0.83
Exit site antibioprophyllaxy	1.16 (0.79–1.66)	0.43
Catheter type		
Straight neck, straight IPS	1.24 (0.82–1.85)	0.30
Swan neck, straight IPS	Ref.	
Straight neck, coiled IPS	0.92 (0.57–1.46)	0.74
Swan neck, coiled IPS	1.56 (1.05–2.32)	<0.05
Surgery technique		
Laparotomy	Ref.	
Laparoscopy	1.01 (0.70–1.42)	0.98
Moncrief technique	2.45 (1.61–3.64)	<0.001
Referent surgeon	0.73 (0.44–1.26)	0.23
Use of local antiseptis	0.83 (0.51–1.43)	0.48
Nasal staphylococcus seeking	1.06 (0.78–1.44)	0.69

IPS = Intra-peritoneal segment.

implantation in the cefuroxime group, while 4 patients in the control group contracted a peritoneal infection [12].

In a double-blind trial performed in 1988, 27 patients were randomised in a 1:1 design to receive either intravenous gentamicin at the time of catheter insertion or no antibiotic at all. In the first 4 post-operative weeks, 6 cases of peritonitis occurred in the control group and one in the gentamicin group [13].

In 1992, 50 participants were enrolled in a randomised trial that aimed to compare the effect of a single dose of cefazolin and gentamicin in the intervention group with no antibiotics in the control group. There was no significant difference between the 2 groups in terms of the occurrence of peritonitis and/or exit site infection [14].

Three out of the 4 randomised controlled trials concluded that the use of prophylactic antibiotics at catheter insertion has a beneficial effect. However, it has to be underlined that in one study, peritonitis was defined by microbial growth in the dialysis fluid [12] and that in 2 studies infection was defined by the incidence of exit site infection and/or peritonitis [13, 14].

The meta-analysis published in 2004 analysed the data from the 335 patients included in the 4 previously

**Table 4.** Multivariate logistic regression, and mixed logistic regression with center as random effect of factors associated with early peritonitis risk

Covariates	Logistic regression	Hierarchical modeling		
		empty model	model 1	model 2
Random effects				
Variance (SD)	–	0.35 (0.60)	0.30 (0.56)	0.27 (0.52)
ICC, %	–	9.74	8.47	7.53
PCV, %	–	Ref.	14.17	24.49
Level 1: patients, OR (95% CI)				
Antibioprophylaxy	0.67 (0.49–0.92)	–	0.73 (0.48–1.11)	0.73 (0.48–1.09)
Age >65 years	0.65 (0.44–0.95)	–	0.6 (0.41–0.88)	0.57 (0.39–0.85)
Gender, male	1.15 (0.84–1.6)	–	1.19 (0.85–1.65)	1.16 (0.83–1.61)
BMI >35 kg/m <sup>2</sup>	1.93 (1.09–3.28)	–	1.88 (1.05–3.25)	1.99 (1.13–3.47)
Diabetes	1.07 (0.76–1.5)	–	1.07 (0.76–1.52)	1.11 (0.78–1.56)
Nephropathy (PKD)	0.5 (0.21–1.05)	–	0.53 (0.21–1.10)	0.50 (0.23–1.12)
Treatment before PD (transplantation)	2.24 (1.21–3.95)	–	2.16 (1.15–3.87)	2.24 (1.22–4.11)
Assisted PD	1.69 (1.16–2.47)	–	1.84 (1.23–2.76)	1.96 (1.31–2.93)
Level 2: centres, OR (95% CI)				
Catheter type (swan neck and coiled IPS)	1.56 (1.09–2.2)	–	–	1.33 (0.84–2.11)
Moncrief technique	2.68 (1.74–4.02)	–	–	3.07 (1.85–5.11)

ICC = Intraclass correlation coefficient; PCV = proportional change in variance; PKD = polycystic disease; IPS = intra-peritoneal segment.

quoted randomised trials [11–14]. The results were in favour of the efficacy of prophylactic antibiotics in the prevention of early peritonitis (RR 0.35, 95% CI 0.15–0.8) [6]. Nevertheless, since only monocentric studies were included in the multivariate analysis, the centre effect was not taken into account. In addition, these studies were conducted over a decade ago, and it has been documented that the incidence of peritonitis has declined over the last 10 years. Furthermore, these trials focused on infections that set in very early, which are not as common.

In our study, we made the hypothesis that prophylactic antibiotic could decrease the rate of exit site infection and this in turn could decrease the rate of peritonitis occurring during the first 3 months of PD. Supporting this hypothesis, it has recently been shown that exit site infection is an independent risk factor for early peritonitis, defined as occurring within 3 months following PD initiation [15]. Exit-site infection was not assessed, as the criteria of diagnosis were not standardised between centres. Our report shows that prophylactic antibiotic was associated with a lower risk of peritoneal infection within the first 3 months of PD.

Surprisingly, our study revealed a link between the Moncrief procedure and early peritonitis. However, few centres used this procedure, and it has been well documented that the Moncrief procedure is associated with a lower risk of exit-site infection [16]. Our result on this point should therefore be interpreted very cautiously.

The risk of early peritonitis was influenced by the patients' BMI, which is in line with the results of a study from the ANZDATA registry, revealing obesity to be a risk factor for peritonitis [17].

Transplant failure patients had a higher risk of early peritonitis compared to other patients. Continuation of immunosuppressive therapy during the early phase of PD may explain this finding.

Due to the retrospective nature of our study, one must be careful not to draw any definitive conclusion from its finding. Nevertheless, our results raise questions regarding the 'centre effect' on the occurrence of early peritonitis. Lack of statistical data could also explain the negative result observed in our study, although more than 2,000 patients were included in the analysis. Furthermore, the effect of prophylactic antibiotics on exit-site infection was not assessed in our study.



The results of our multivariate logistic regression were in favour of a protective effect of the use of prophylactic antibiotics on early peritonitis. However, the hierarchical modelling approach showed that the centre residual confounder may also affect early peritonitis occurrence. This is consistent with the findings of a recent study, which identified centre-specific characteristics associated with the variation in peritonitis risk [7]. In our study, no centre-specific confounders were identified (table 3). Many covariates depending on centres policy can be hypothesized. A multi-centric international prospective cohort study has begun to identify modifiable and measurable PD practices associated with improved outcomes for patients. In this study, practices indicators or processes of care will be analysed at the patient level and at the centre level [18].

It can be concluded that prophylactic antibiotics can be used to decrease the risk of early peritonitis. Neverthe-

less, our study also emphasises the fact that other measures should be implemented at the centre level. Training programs and education may be part of these important measures. Guidelines on teaching PD recently published by the ISPD indicate the interest on evaluating the effect of training on infection rate and longevity of the technique [19].

### Acknowledgement

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### Disclosure Statement

The authors have no conflicts of interest to declare.

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### III.4. Discussion

Conformément aux résultats des essais randomisés monocentriques réalisés par le passé, nous avons montré que l'administration d'une antibioprophylaxie à la pose du cathéter de dialyse péritonéale avait un effet protecteur contre le risque d'infection péritonéale précoce (OR 0,69 ; IC<sub>95%</sub> 0,51 – 0,93). Cependant, la prise en compte des variations liées aux centres de traitement annulait la significativité de ce résultat. Ainsi, 9,8 % de la variabilité de l'incidence d'infection péritonéale précoce était expliquée par cet effet centre. Après ajustement sur les variables individuelles (niveau 1) et centres (niveau 2) disponibles, la variabilité de l'incidence était encore de 7,5 %.

Ce résultat interroge sur les recommandations qui se basent sur quatre essais randomisés monocentriques. En termes de niveau de preuve, les résultats d'essais randomisés sont supérieurs à ceux d'études rétrospectives, notamment car la randomisation élimine les biais de sélection inhérents aux design rétrospectifs. En revanche, les essais prospectifs monocentriques ne permettent pas de prendre en compte les variations qui peuvent exister entre différentes unités de traitement. C'est cet aspect que nous avons mis en exergue à partir de données certes rétrospectives, mais robustes en raison de l'effectif important analysé.

A partir de l'étude d'une pratique de soins, la modélisation multiniveaux utilisée rend compte de l'impact du centre de traitement et des covariables non mesurées qui en sont dépendantes. C'est donc naturellement que suite à ces résultats, nous avons voulu nous intéresser aux autres pratiques de soins. Ces pratiques étant très nombreuses, nous avons cherché une alternative à l'étude « classique » de l'effet des pratiques considérées une à une. Nous nous sommes posé la question de l'homogénéité des groupes de pratiques de

soins appliquées par les différents centres et avons donc cherché si des groupements pouvaient être faits. Cette question a fait l'objet du travail suivant.

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## ***IV. CLUSTERS DE PRATIQUES ET TRANSFERT VERS L'HEMODIALYSE CHEZ LES PATIENTS TRAITES PAR DIALYSE PERITONEALE***

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### **IV.1. Introduction**

A la suite de notre travail sur l'effet de l'administration d'une antibioprophylaxie à la pose du cathéter nous avons cherché à étudier plus en détail les liens entre les pratiques de soins à l'échelle des centres de traitement.

Les traitements d'épuration extra-rénale ont la particularité d'avoir une composante technique importante, avec la possibilité de mettre en œuvre des matériels divers et des manipulations variées. Dans le cas de la dialyse péritonéale, on peut lister de manière non exhaustive : le type de cathéter choisi, la procédure opératoire pour le poser, les mesures préventives des infections à la pose du cathéter et par la suite les soins régulièrement apportés au cathéter, le type de dialysat utilisé, son volume, la modalité de réalisation des échanges de dialysat et le nombre de ces échanges, le recours à une tierce personne pour la réalisation de la dialyse. L'ensemble de ces pratiques fait l'objet de peu de recommandations car peu d'études de bon niveau de preuve sont disponibles qui ont montré la supériorité d'une pratique en particulier.

Parmi les variables incluses dans les modèles d'inférences statistiques pour l'analyse de données cliniques des patients atteints d'IRCT, on peut distinguer des variables non modifiables et des variables modifiables. Les variables non modifiables sont principalement les variables individuelles : âge, sexe, poids, taille, néphropathie, diabète et autres comorbidités. Les variables modifiables sont quant à elles toutes les variables liées aux pratiques de soins et au centre de traitement. La mise en évidence d'un effet protecteur

ou délétère d'une variable non modifiable n'a pas de portée clinique directe pour le néphrologue en considérant un patient donné en cours de traitement. Ces données sont néanmoins intéressantes car elles permettent de définir des caractéristiques individuelles associées à un meilleur pronostic pour une technique d'épuration par rapport à une autre, et de conseiller au mieux les patients lors du choix de la technique. L'impact clinique est plus direct concernant les variables modifiables, car un effet associé à la survenue d'un évènement d'intérêt comme le transfert en hémodialyse en centre incite à questionner cette variable et dans notre cas à remettre en cause les pratiques de soins définies par cette variable.

Nous avons donc souhaité réaliser une analyse de l'effet des pratiques de soins en dialyse péritonéale sur le risque de transfert en hémodialyse en centre. Une dizaine de variables associés à des pratiques de soins ont été répertoriées dans la base de données du RDPLF. Chacune de ces pratiques de soins comprenait deux à cinq modalités, avec un total de combinaisons potentielle dénombrées à plus de  $2.10^6$ . Nous avons formulé l'hypothèse que les interactions entre pratiques de soins pouvaient être synergiques. Si l'effet d'une pratique prise isolément n'est pas toujours bénéfique, il est possible que l'association de certaines pratiques de soins ait un effet bénéfique sur les évènements cliniques observés.

Nous présentons ici les deux articles qui ont été rédigés au sur la thématique des groupes de centres. Le premier travail a été réalisé avant la période d'inscription en thèse et a constitué la base de nos travaux lors de la thèse.

## IV.2. Outils statistiques et méthodologie

Les données de la base du RDPLF ont été mises à profit lors de cette étude. Une des forces de ce registre est sa forte granularité. Il y existe des modules satellites dans lesquels sont recueillies les données individuelles sur de nombreux aspects du traitement des patients inclus. Le module « cathéter » notamment dont nous avons extrait les données comporte une vingtaine de variables associées aux soins portés aux cathéters de dialyse péritonéale.

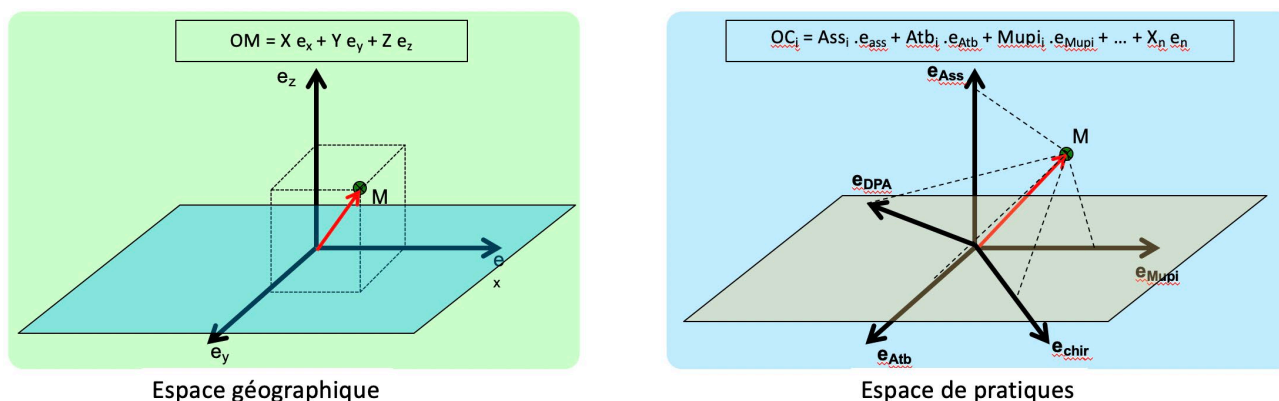
### IV.2.1. Classification ascendante hiérarchique

Nous avons souhaité analyser l'impact d'une dizaine de pratiques de soins et de leurs éventuelles interactions sur le transfert vers l'hémodialyse en centre. Une analyse classique aurait pu consister en la réalisation de test de l'effet de chacune des variables, des interactions de variables 2 à 2 puis éventuellement 3 par 3 et ainsi de suite, au prix de la réalisation d'un grand nombre de tests statistiques et d'une inflation du risque de première espèce alpha, c'est-à-dire du risque de conclure à tort à l'existence d'un effet statistiquement significatif. Nous avons donc opté pour une approche différente dans laquelle nous ne formulons pas d'hypothèse a priori, mais selon laquelle nous cherchions à déterminer des groupes de centres de dialyse dans lesquelles les pratiques de soins présentaient une homogénéité. La classification ascendante hiérarchique est une technique statistique qui vise à créer des partitions dans une population donnée. Cette méthode s'appuie sur les lois de l'algèbre linéaire au sein d'espaces vectoriels normés.

Au sein de chaque centre, les pratiques standards ont été définies par l'utilisation d'une même pratique dans plus de 75 % des cas répertoriés du centre. Les modalités de

chacune des pratiques de soins ont été codées numériquement, et on a ainsi créé un espace vectoriel dont la dimension était le nombre N de variables analysées. Dans cet espace vectoriel, la position de chaque centre était donc définie par ses N coordonnées, et une distance centrée et normée a été créée afin de calculer la proximité des centres entre eux relativement à l'homogénéité de leurs pratiques de soins proposés (Figure 3). Les distances entre chaque centres pris deux à deux ont pu être calculées et agencées sous forme d'une matrice des distances. Nous avons choisi d'utiliser une distance euclidienne sur notre espace vectoriel de pratiques de soins.

**Figure 3 : Représentation schématique de l'espace vectoriel des pratiques de soins.**



Cadre vert de gauche : espace géographique à 3 dimensions :  $e_x$ ,  $e_y$ ,  $e_z$ . Cadre bleu de droite : représentation d'un espace de pratiques à n dimensions parmi lesquelles les dimensions  $e_{ass}$  (recours à l'assistance d'une tierce personne),  $e_{atcb}$  (antibioprophylaxie à la pose du cathéter),  $e_{mupi}$  (application en routine de mupirocine à l'émergence du cathéter),  $e_{chir}$  (technique chirurgicale),  $e_{DPA}$  (Modalité de dialyse péritonéale).

La méthode de classification passe ensuite par l'établissement d'un objet graphique : le dendrogramme. L'algorithme de création de ce dendrogramme peut être énoncé ainsi :

Dans un espace vectoriel E.

Soient  $C_i$  (pour i allant de 1 à k) les différents centres considérés appartenant à E.

Soit une application  $d : E^2 \rightarrow R_+$  répondant à la définition de distance.

(1). Pour  $i \in [1 ; k]$  et  $j \in [1 ; k]$  tels que  $i < j$ , Calculer  $d(C_i, C_j)$

(Calculer les distances entre tous les centres pris deux à deux)

(2). Pour  $i$  et  $j$  tels que  $d(C_i, C_j)$  est minimum, placer  $C_i$  et  $C_j$  côte à côte sur une horizontale et les relier en un point de hauteur proportionnelle  $d(C_i, C_j)$ . Le groupement de ces deux centres définit un cluster.

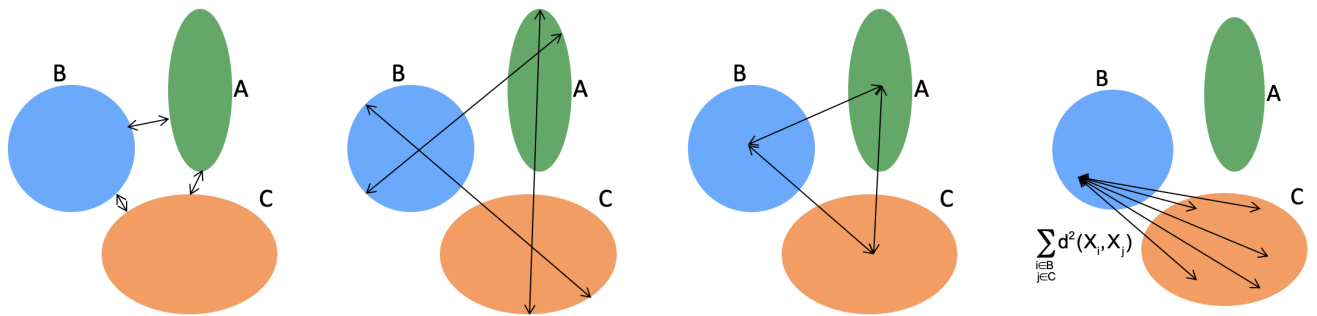
(3). Calculer les distances des centres / clusters pris deux à deux.

(4). Recommencer à l'étape 2 jusqu'à l'obtention d'un cluster unique contenant tous les  $C_i$ .

Dans cet algorithme, l'étape (3) impose de définir une méthode d'agrégation, c'est à dire la façon de calculer la distance entre les clusters de centres. Plusieurs méthodes d'agrégation ont été proposées (Figure 4). La méthode du *single linkage* va regrouper les deux clusters pour lesquels la distance entre leurs deux éléments les plus proches est minimale. A l'opposé dans la méthode du *maximum linkage*, on regroupe les deux clusters pour lesquels la distance entre leurs deux éléments les plus éloignés est maximale. Selon la méthode *average linkage*, on regroupe les deux clusters pour lesquels la moyenne des distances entre l'ensemble de leurs éléments est minimale. D'autres méthodes ont été décrites, mais c'est la méthode de Ward qui est la plus largement utilisée. Dans cette méthode pas à pas, les regroupements sont effectués après calcul de toutes les variances intra-classes des clusters potentiels, et en conservant le cluster qui minimise cette variance intra-classe [26], [27].



**Figure 4 : choix d'une méthode d'agrégation des clusters**



**Single linkage:**

Regroupement selon la distance minimale entre les éléments de chaque groupes.

$$D(A, B) = \min_{\substack{i \in A \\ j \in B}} d(i, j)$$

**Maximum linkage:**

Regroupement selon la distance maximale entre les éléments de chaque groupes.

$$D(A, B) = \max_{\substack{i \in A \\ j \in B}} d(i, j)$$

**Average linkage:**

Regroupement selon la distance moyenne entre les éléments de chaque groupes.

$$D(A, B) = \frac{1}{n_A \cdot n_B} \sum_{\substack{i \in A \\ j \in B}} d(i, j)$$

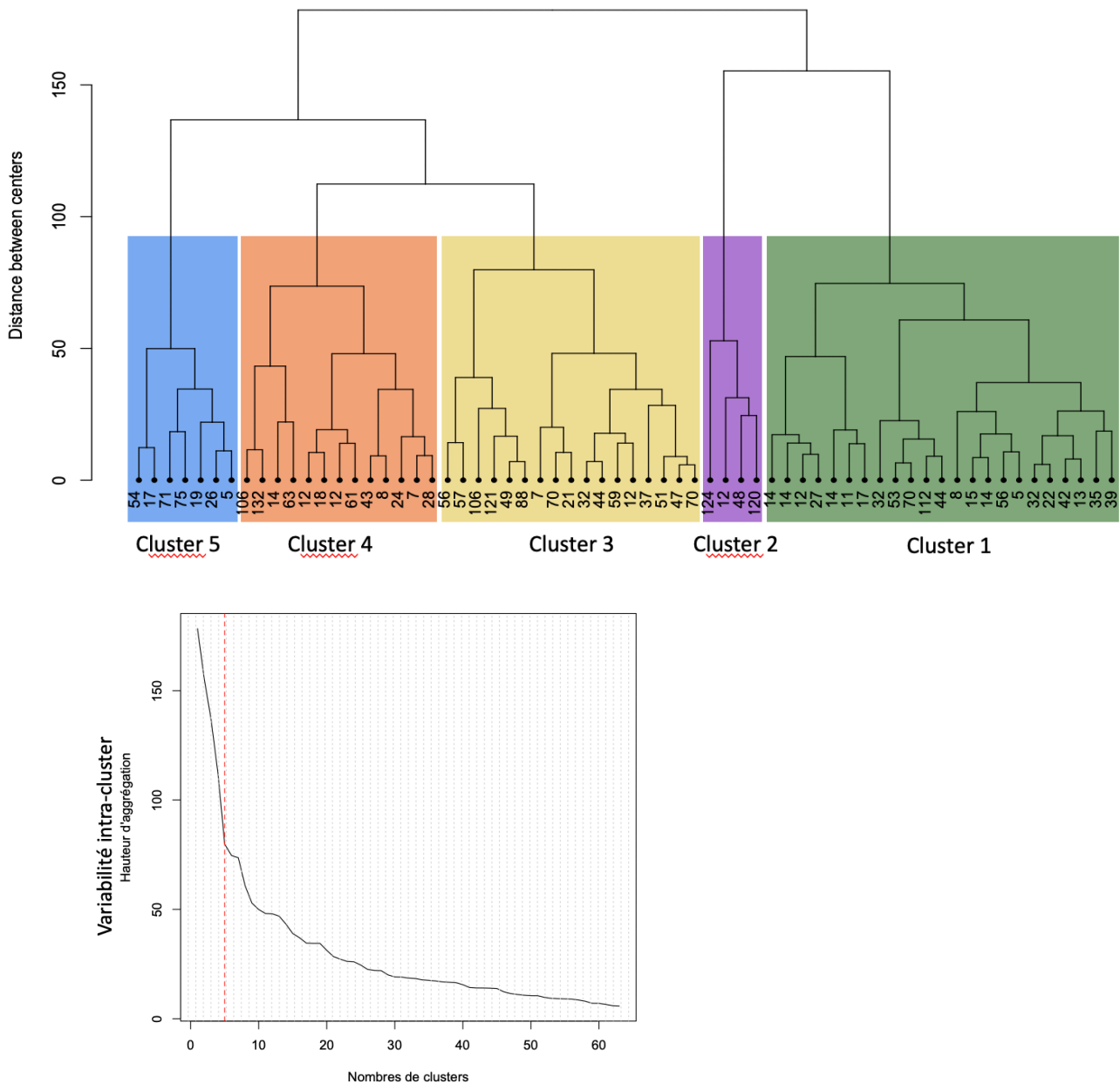
**Méthode de Ward:**

Calcul de la variance intra-classe pour chaque nouveau groupe. Regroupement pour minimiser la variance intra-classe.

Une fois le dendrogramme créé, le choix de la partition peut être fait. Il n'existe pas de méthode consensuelle et des solutions plus ou moins complexes à ce problème ont été proposées [28]. La méthode graphique et souvent préconisée, par analyse visuelle de la forme globale du dendrogramme et de la courbe représentant la variabilité intra-cluster selon le nombre de regroupements effectués. Cette méthode permet d'estimer le nombre de clusters avec lequel on minimise la complexité de la partition tout en optimisant la variabilité inter-clusters (Figure 5).

Cinq clusters de centres ayant des pratiques de soins homogènes ont ainsi été définis, et les analyses inférentielles ultérieures ont été réalisées en comparant les associations statistiques entre l'appartenance à un des clusters et le risque de survenue des évènements d'intérêts.

Figure 5 : Dendrogramme et partition retenue selon la méthode “du coude”

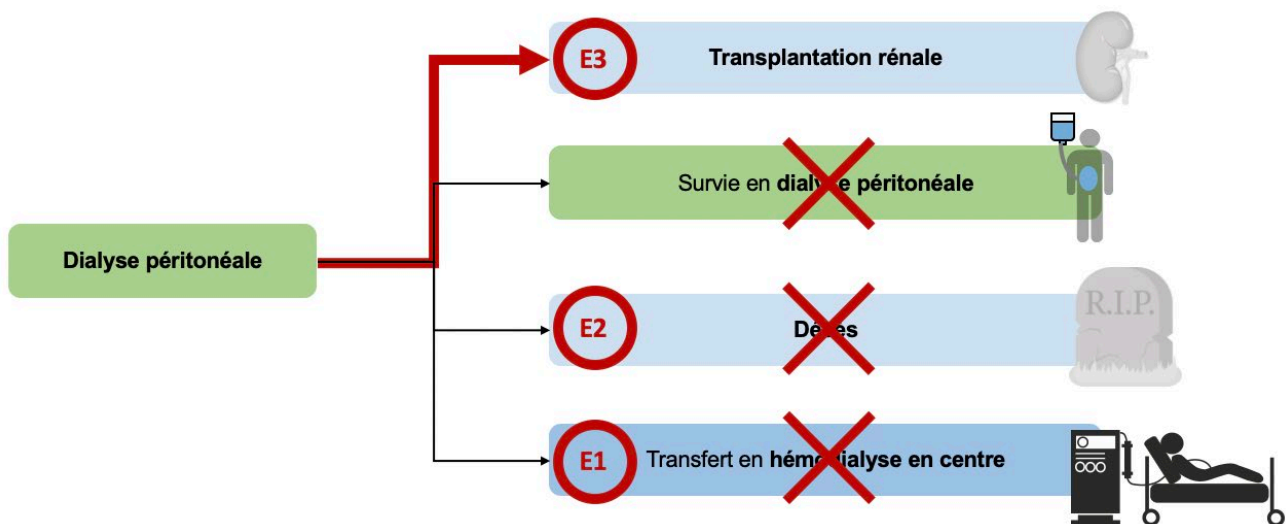


Partie haute : dendrogramme représentant les centres et leurs effectifs en abscisse, au sein des 5 clusters retenus. Partie basse : courbe des hauteurs d'agrégation en fonction du nombre de cluster retenu. Le choix de 5 clusters permet un gain important de variabilité intra-cluster par rapport à 3 ou 4. Peu de bénéfice en revanche à en retenir 6 ou 7 car la courbe des hauteurs d'agrégation reste alors quasiment constante.

## IV.2.2. Évènements compétitifs dans les modèles de survie

Les évènements susceptibles de mener à l'arrêt de la dialyse péritonéale sont le transfert en hémodialyse ( $E_1$ ), le décès ( $E_2$ ), et la transplantation rénale ( $E_3$ ). Les évènements  $E_2$  ou  $E_3$  sont compétitifs puisque la survenue de l'un d'eux empêche l'observation de l'évènement d'intérêt  $E_1$  (figure 6).

Figure 6 : évènements compétitifs



Dans une analyse de survie standard, tout patient qui n'a pas présenté l'évènement d'intérêt durant la période d'observation est censuré à la fin de la période de suivi, qu'il ait été perdu de vue, ou qu'il ait présenté un évènement compétitif. Dans le contexte de l'analyse de données de survie avec évènements compétitifs, l'approche classique ne permet pas une analyse complète des taux d'incidence des évènements. Deux approches sont utilisées dans ce cadre.

La première approche consiste à utiliser un modèle semi-paramétrique classique de Cox avec censure à droite des risques compétitifs [30]. Ces modèles permettent l'estimation de *cause-specific hazard ratio* (cs-HR), représentatif du rapport des risques

instantanés de survenue de l'évènement d'intérêt parmi les sujets chez qui aucun évènement (d'intérêt ou compétitif) n'est survenu. Si  $T$  est le temps écoulé entre le début des observations et la survenue de l'évènement d'intérêt, alors le risque instantané *cause-specific* de survenue de l'évènement  $E_i$  est :

$$h_i^{cs}(t) = \lim_{\Delta t \rightarrow 0} \frac{P(t \leq T < t + \Delta t, E = E_i | T \geq t)}{\Delta t}$$

C'est-à-dire le taux instantané d'occurrence de  $E_i$  à l'instant  $t$  parmi les sujets n'ayant encore présenté aucun évènement. Il s'ensuit que pour la variable étudiée  $Z$  :

$$cs - HR = \frac{h_i^{cs}(t, Z = 1)}{h_i^{cs}(t, Z = 0)}$$

Si une covariable est associée à une augmentation du risque d'un évènement compétitif  $E_i$ , alors, indirectement elle sera associée à une réduction du risque de l'évènement d'intérêt. Ainsi, l'approche par cs-HR ne permet pas d'établir de lien direct avec le risque de survenue de l'évènement d'intérêt [31].

La deuxième approche proposée en 1999 par Fine et Gray consiste à estimer le risque de survenue de l'évènement d'intérêt parmi les personnes qui n'ont pas encore présenté cet évènement (donc également parmi ceux qui ont expérimenté un des évènements compétitifs) [32]. Dans cette approche, le risque instantané de sous-distribution est :

$$h_i^{sd}(t) = \lim_{\Delta t \rightarrow 0} \frac{P(t \leq T < t + \Delta t, E = E_i | T \geq t \cup (T < t \cap E \neq E_i))}{\Delta t}$$

C'est-à-dire le taux instantané d'occurrence de  $E_i$  à l'instant  $t$  parmi les sujets qui n'ont pas présenté l'évènement  $E_i$  auparavant, qu'ils soient indemnes de tout évènement ou aient présenté un évènement compétitif. Dans cette approche, les sujets qui ont présenté avant l'instant  $t$  un évènement compétitif sont pris en compte dans la population qui reste à risque de présenter l'évènement d'intérêt. Le modèle de Fine Gray a l'avantage de permettre l'estimation directe de l'incidence de l'évènement d'intérêt et la fonction d'incidence cumulée.

L'évaluation des risques selon les deux approches diffère par la population considérée comme étant toujours à risque à l'instant  $t$  ou *riskset* (figure 7) [33].

**Figure 7 : Exemple de calcul des risques cause-spécifiques et de sous-distribution en temps discret.**

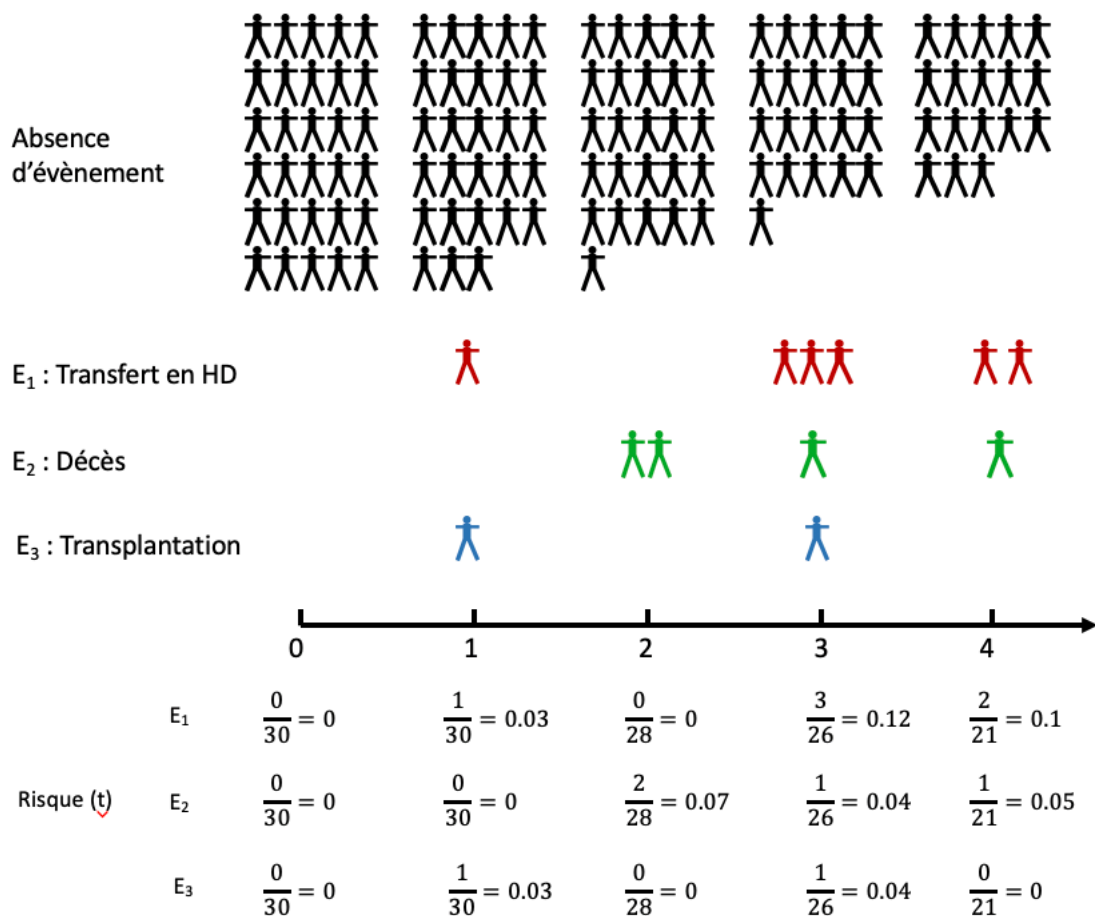


Figure 7a : Risques cause-spécifique. Évaluation en temps discret.

Trente patients constituent la population initiale. Les individus qui présentent un risque compétitif ( $E_2$  ou  $E_3$ ) à l'instant  $t$  ne sont plus considérés comme susceptibles de présenter l'évènement d'intérêt  $E_1$  aux temps ultérieurs.

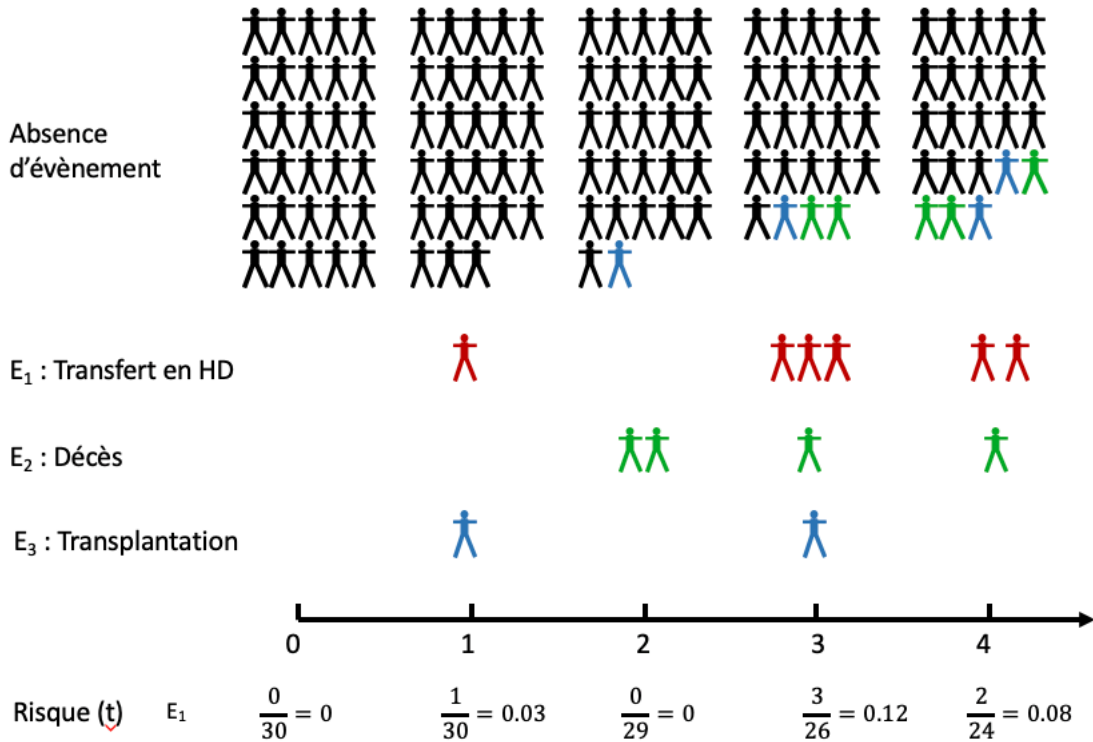


Figure 7b : Risques de sous-distribution. Évaluation en temps discret.

Trente patients constituent la population initiale. Les individus qui présentent un risque compétitif ( $E_2$  ou  $E_3$ ) à l'instant  $t$  sont toujours considéré à risque de présenter l'évènement d'intérêt  $E_1$  aux temps ultérieurs. Le risque de sous-distribution est ainsi toujours inférieur ou égal au risque cause-spécifique.

En pratique, le cs-HR évalué par modèle de Cox avec censure à droite des évènements compétitifs devrait être privilégié lorsque l'objectif de recherche est l'estimation de l'association entre des covariables et l'évènement d'intérêt. Si l'objectif de l'étude est en revanche d'estimer la fonction d'incidence cumulée ou d'élaborer un modèle prédictif, alors c'est le calcul des sd-HR grâce à un modèle de Fine Gray qui est à privilégier. Afin d'apporter une information complète, plusieurs auteurs recommandent de faire figurer les

cs-HR ainsi que les sd-HR dans les résultats d'analyse de survie avec risque compétitifs [29].

#### **IV.2.3. Prise en compte de l'effet centre : modèles de survie multiniveaux**

Dans les premières parties de nos analyses, nous avons considéré les patients à l'échelle des variables individuelles. Nous avons affecté à chaque sujet des covariables correspondantes à leur centre de traitement, ou au cluster de centre auquel ils appartenaient. Cependant, cette modélisation ne tient pas compte de la structure hiérarchique des données. On peut en effet classer les données des patients traités par dialyse selon une structure hiérarchisée, en considérant le fait que les patients sont inclus dans un centre de traitement, ce qui constitue un facteur contextuel important. La prise en compte de cette structuration des données est importante pour au moins deux raisons : premièrement, il est probable que les sujets traités au sein d'un centre donné partagent des caractéristiques individuelles communes (par exemple exposition à des toxiques environnementaux, similitudes de régime alimentaire, phototype...). Deuxièmement les pratiques de soins appliquées au sein d'un centre donné sont souvent homogènes. La structure hiérarchisée des données entraîne donc une violation de l'hypothèse d'indépendance des observations, ce qui peut conduire à des évaluations faussées des estimateurs statistiques dans les modèles de régression classique [34]. Les modèles multiniveaux (également appelés modèles hiérarchiques) ont l'avantage de prendre en compte la structure hiérarchique des données lors de l'estimation des paramètres. La stratégie de modélisation consiste à tester un modèle vide, puis dans un second temps à

introduire dans le modèle les variables individuelles dites de niveau 1, et enfin dans un dernier temps les variables à l'échelle du centre, dites de niveau 2 [35].

Le cas des modèles linéaires et logistiques mixtes a été décrit en détail. Cependant, l'évaluation des paramètres des modèles de survie multiniveaux est plus délicate [36]. Pour preuve, le package *coxme* qui permet l'implémentation de ces modèles dans R n'est disponible que depuis 2015 [37]. Un terme d'effet aléatoire est ajouté au modèle de Cox classique afin de prendre en compte l'homogénéité intra-centre lors de l'évaluation des évènements. Ces effets aléatoires incluent la variabilité du risque selon les différents centres.

$$h_i(t) = h_0(t) \cdot e^{X_i \cdot \beta + \alpha_j}$$

Avec  $h_0(t)$  le risque de base,  $X_i$  les covariables explicatives,  $\beta$  le vecteur des coefficients des effets fixes, et  $\alpha_j$  le vecteur des effets aléatoires associés au  $j^{\text{ème}}$  centre. La stratégie de construction du modèle de survie de Cox multiniveaux s'articule en trois étapes, de manière similaire au cas de la régression linéaire. Premièrement, un modèle vide (modèle 0) est créé ne contenant pas de variable explicative mais dans lequel on définit un effet aléatoire qui dépend des centres de traitement. Dans ce modèle vide, l'exponentielle de l'écart-type de l'effet aléatoire est une estimation du risque relatif lié au centre. Deuxièmement, on inclut les variables individuelles de niveau 1 en plus de l'effet aléatoire lié au centre (modèle 1). Enfin, la variable contextuelle d'appartenance à un cluster de centre donné est introduite dans un dernier modèle (modèle 2). L'examen de l'évolution des variances des effets aléatoires dans les trois modèles permet d'estimer en quelle mesure les variables individuelles (niveau 1) puis la variable cluster (niveau 2) expliquent l'effet centre mesuré [38].



## IV.3. Article

(Hors période d'inscription en thèse)

Lanot A, Bechade C, Verger C, Fabre E, Vernier I, Lobbedez T.

*Clusters of practice in peritoneal dialysis in France: data from the catheter section of the RDPLF.*

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## ORIGINAL ARTICLES

### CLUSTERS OF PRACTICE IN PERITONEAL DIALYSIS IN FRANCE: DATA FROM THE CATHETER SECTION OF THE RDPLF

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◆ **Background:** Peritonitis is a major cause of peritoneal dialysis (PD) failure. Recommendations for the prevention of peritonitis are available, but wide variations exist in the peritonitis rate among countries and PD units. The objective of this study was to describe the different pattern of practices in France.

◆ **Methods:** This was a retrospective, multicenter study based on data from the French Language Peritoneal Dialysis Registry. Center practices were described and mapped. Clusters of practices were sought in a hierarchical analysis and centers belonging to the same clusters of practices were mapped.

◆ **Results:** Data from 2,770 catheters placed in 64 centers in France between 1 February 2012 and 31 December 2016 were considered. A median of 34 (ranging from 5 to 133) catheters was reported in each center. Twenty-eight (43.8%) centers routinely administered a prophylactic antibiotic prior to catheter placement, and 8 (12.5%) centers applied a local prophylactic antibiotic at the exit site, as recommended by International guidelines. The presence of a PD nurse specialized in PD or PD referent nephrologist was not associated with better adherence to guidelines. Practices were heterogeneous across centers. We identified 5 clusters of centers according to practice. Geographical proximity was not associated with homogeneity in practices.

◆ **Conclusion:** Peritoneal dialysis practices are heterogeneous in France, even those that are subject to International guidelines. Studies to identify associations between center-specific practices and PD patient outcomes remain mandatory. Efforts should be made to standardize the PD standards of care in France.

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KEY WORDS: Peritoneal dialysis; peritoneal catheter; center effect; peritonitis; ascendant hierarchical clustering method.

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**P**eritonitis remains a major concern for the nephrologist involved in peritoneal dialysis (PD) and for patients treated with PD. Peritoneal infection is associated with an increased risk of technique failure (1). Furthermore, approximately 16% of deaths in PD patients occur in connection with peritonitis (2,3,4).

Guidelines are available for the prevention and treatment of peritonitis. Several measures are recommended to prevent peritonitis, such as the use of systemic prophylactic antibiotics prior to PD catheter insertion or daily topical application of antibiotic cream or ointment to the catheter exit site (5).

One study from our group has demonstrated that the protective effect of prophylactic antibiotics before catheter insertion could be masked by the existence of a center effect (6). Furthermore, in 1 recent study, 35% of the center effect on peritonitis risk was explained by center-specific covariates, and the risk of peritonitis could be decreased by home visits before dialysis initiation and by a nurse specialized in PD (7). There is wide variation in peritonitis rates across countries and across centers from the same country, without a clear explanation (3,8,9). Although recent evidence-based guidelines exist, several studies suggest that the adherence to recommendations varied by PD unit and was often insufficient (10,11). The PD training program is important and affects the risk of peritonitis. The International Society for Peritoneal Dialysis (ISPD) established a syllabus to train patients and their PD caregivers because the training method is known to influence the risk of peritonitis (12,13). Differences in practice between centers and the implementation of evidence-based recommendations could partially explain the center effect on peritonitis risk. As center practices are modifiable factors, it leads to practical questions: Are practices standardized in French PD units? What are the center-specific PD practices that could be protective against peritonitis? The identified practices could then be implemented at the center level to enhance the care given to PD patients.

The aim of this study was to assess the differences in PD catheter care among French PD units and to evaluate adherence to existing guidelines. This study was also performed to identify separate clusters of practice between the PD units.

## MATERIALS AND METHODS

### STUDY POPULATION

This was a retrospective study using data from the “catheter” section of the French Language Peritoneal Dialysis Registry (RDPLF) that has been described in a previous publication (15). Of the 144 French PD centers participating in the registry, 87 also provided data for the optional catheter section. All catheters inserted in these 87 centers were therefore required to be in the database.

Only incident catheters were considered, and we excluded centers for which less than 5 catheters were listed for the whole duration of the study. Patients older than 18 years old starting PD in France between 1 January 2012 and 31 December 2016 were included in the study. Patients treated in the French overseas territories were not included.

### DESCRIPTION OF VARIABLES

Variables describing the centers’ practices were extracted from the registry: type of PD catheter, surgery technique, use of Moncrief method, administration of antibiotic prophylaxis prior to catheter insertion, screening for nasal carriage of *Staphylococcus aureus* (*S. aureus*), use of local anti-staphylococcal cream or ointment on the catheter emerging site, duration between catheter insertion and first dressing of the exit site, type of antiseptic for dressing refection, anesthesia technique, PD modality 3 months after dialysis initiation or last modality used (automated peritoneal dialysis [APD] or continuous ambulatory peritoneal dialysis [CAPD]), assistance for PD (self-PD, family assistance, nurse assistance), type of administrative structure in which the patient was treated, center size (number of new patients per year), presence of a nurse specialized in PD in the center (meaning dedicated only to PD care), and presence of a PD referent nephrologist in the center (defined as a nephrologist having specific skills in PD but not only involved in PD).

### STATISTICAL ANALYSIS

Categorical variables were described by their frequencies and percentages, and continuous variables were described by their median and interquartile ranges. Fisher’s exact test was used to compare the distribution of categorical variables. A logistic regression model was used to assess the link between categorical variables. *P* values less than 0.05 were considered significant. We examined for collinearity by assessing the generalized variance inflation factor.

Statistical analyses for this study were mainly descriptive and were performed with R 3.1.1 (R foundation for statistical

computing, Vienna, Austria) using the maps, the hclust and the Hmisc package.

We performed a hierarchical cluster analysis using Ward’s method, with a Euclidian distance defined between the centers according to the similarity of their practices (14). Levels of practices were coded as factors. Then we computed distances between all the centers and distances between all the practices. These distances represent a measurement of similarities rather than geographical proximity. The number of clusters was determined graphically according to the semi-partial R-squared graph, to optimize the variability between clusters while minimizing complexity. Two hierarchical clustering analyses were produced. The first analysis was proposed to explore the existence of clusters of practices, and the second was proposed to determine clusters of centers that had similar practices.

For each center, whenever a practice was applied in 75% or more of the listed cases, it was defined as being the center standard practice during the follow-up period of the study. We established mapping of the center-specific practices. Given that some of these practices are the object of International guidelines (5), we tried to avoid pointing an accusing finger at anyone. To this end, we constructed a virtual map, and a hidden mathematical transformation was applied to the geographical coordinates of the centers and projected on the virtual map. Thereby, distances between centers on the virtual map are no longer preserved, but the neighbourhood was preserved.

The RDPLF has the approval of the French national ethics committee (*Commission nationale de l’informatique et des libertés*). This study occurred within the framework of this authorisation.

## RESULTS

### CENTER CHARACTERISTICS

Data concerning 2,770 PD catheters were included from 64 centers in France contributing to the “catheter modulus” of the RDPLF. Of the 64 centers, 7 were academic hospitals, 36 were community hospitals, 12 were non-profit centers, and 9 were private centers (Figure 1A). A median number of 34 (first and third quartiles = 14.8 – 61) catheters were placed and listed in each center. Of these, 2,543 catheters (91.8%) were naïve, 109 (3.9%) were second catheters placed, 17 (0.6%) were third catheters, and 1 (0.04%) was the fourth catheter placed. Forty-four centers had a nurse specialized in PD in their program, and there was a PD referent nephrologist in 41 centers. Twenty-eight centers benefited from the presence of a nurse specialized in PD together with a PD referent nephrologist (Figures 1B and 1C). The number of centers using each technique as a reference practice (meaning that it is used in greater than 75% of the cases) is presented in Table 1.

### SURGICAL PRACTICES FOR CATHETER IMPLANTATION

Specialized surgeons were in charge of PD catheter placement in 61 centers (95.3%). Little variation was noted across

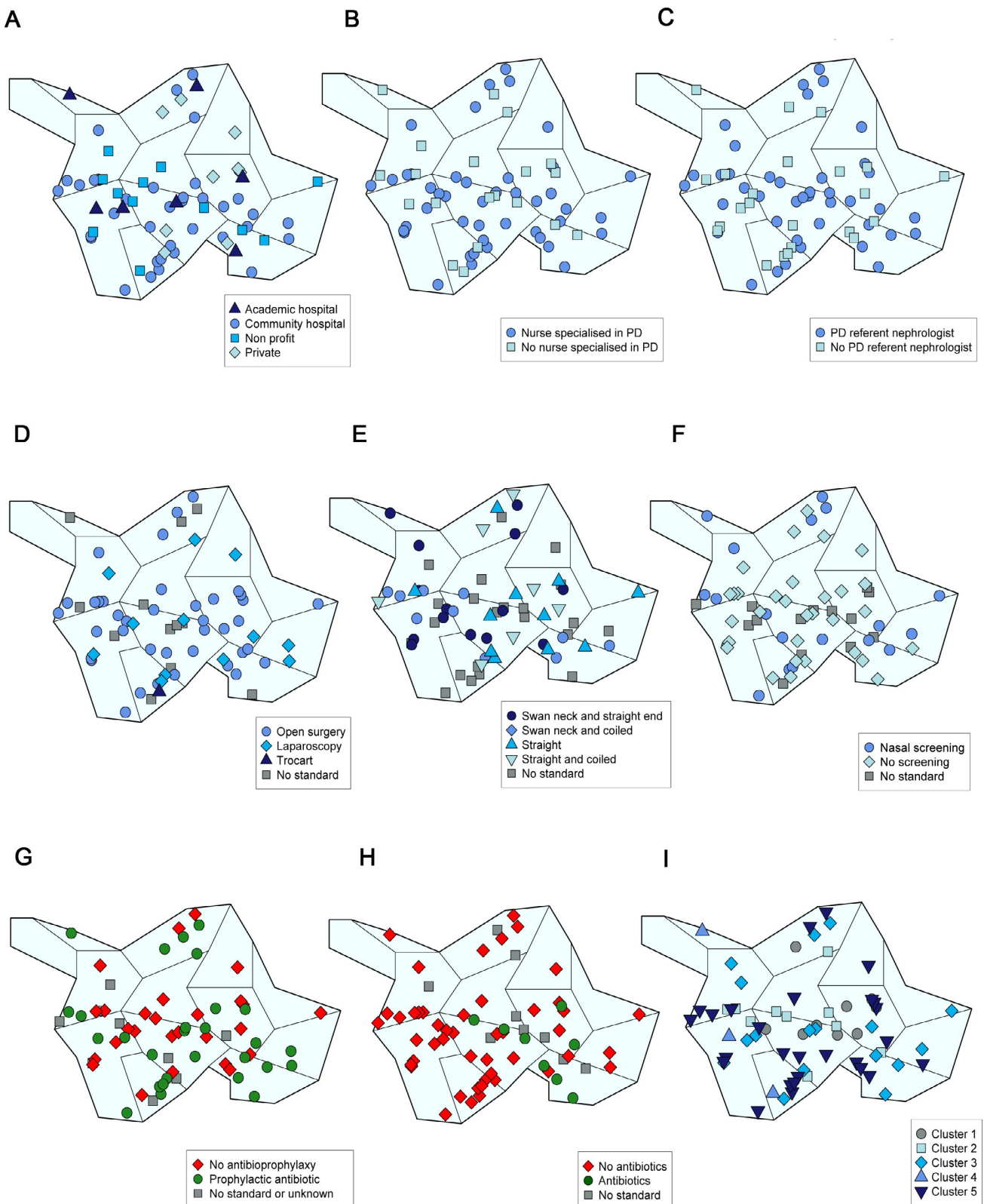


Figure 1 — Practices across PD units projected on the virtual maps. A: Type of administrative structure. B: Presence of nurse specialized in PD in centers. C: Presence of PD referent nephrologist in centers. D: Surgical technique for catheter implantation. E: Type of catheter placed. F: *S. aureus* nasal screening. G: Prophylactic antibiotic administration prior to catheter insertion. H: Anti-staphylococcal antibiotic on exit site. I: Center classification according to a cluster of practices. PD = peritoneal dialysis.

TABLE 1  
Distribution of Practices Among PD Units

Practice	Number of centers using the technique as a reference (%)
<b>Catheter type</b>	
Swan neck, straight	14 (21.9)
Swan neck, coiled	10 (15.6)
Straight, straight	11 (17.2)
Straight, coiled	7 (10.9)
No standard	22 (34.4)
<b>Surgical technique</b>	
Laparoscopy	12 (18.8)
Open surgery	39 (60.9)
Trocart	1 (1.6)
No standard	12 (18.8)
<b>Prophylactic antibiotic use prior to catheter implantation</b>	
No antibiotic	27 (42.2)
Antibiotic	28 (43.8)
Vancomycin Other antibiotic	6 (9.4%)
No standard	22 (34.4%)
<b>Prophylactic <i>S. aureus</i> antibiotic use on exit-site site</b>	
None	47 (73.4)
Antibiotic	8 (12.5)
No standard	9 (14.1)
<b><i>S. aureus</i> nasal screening</b>	
None	31 (48.4)
Done	19 (29.7)
No standard	14 (21.9)
<b>Treatment modality</b>	
CAP	18 (28.1)
D	0 (0)
APD	46 (71.9)
No standard	
<b>Duration between catheter placement and first dressing</b>	
0 to 5 days	12 (18.8)
6 to 15 days	33 (51.2)
No standard	19 (19.7)
<b>Antiseptic for dressing</b>	
Chlorhexidine Alcohol	31 (48.4)
None	1 (1.6)
No standard	4 (6.3)
Unknown	11 (17.2)
	17 (26.6)

PD = peritoneal dialysis; CAPD = continuous ambulatory PD; APD = automated PD.

centers concerning the surgical technique: open surgery was standardly used in 39 centers (60.9%), “standardly” meaning that in each 1 of these 39 centers, more than 75% of the PD catheters were placed with open surgery technique (Figure 1D). More differences existed in the surgical approach: 31 centers (48.4%) did not have a standardized surgical approach, whereas a standardized approach was

used in the other centers (median approach in 11 centers [17.2%] and trans-rectal approach in 22 centers [34.4%]). The type of catheters placed was quite variable among centers (Figure 1E), and there was no standard type in 22 centers (34.4%).

#### ANTI-INFECTIOUS PROPHYLAXIS

Locations of the centers where *S. aureus* nasal screening was performed are presented in Figure 1F. Nineteen centers (29.7%) routinely screened for nasal *S. aureus*, whereas 31 (48.4%) did not. Frequencies at the center level are detailed in a barplot (Figure 2A).

The frequency of prophylactic antibiotic administration prior to catheter insertion is presented in Figure 2B. Twenty-eight centers (43.8%) used prophylactic antibiotics as a standard practice, whereas 27 (42.2%) did not. Among the 28 centers using prophylactic antibiotics, 6 (9.4%) administered vancomycin, and another unspecified antibiotic was used in 22 (34.4%). There was no standard practice concerning prophylactic antibiotic administration prior to catheter insertion in 9 centers (14.1%). Habits concerning the use of prophylactic antibiotic prior to catheter placement did not seem to correlate with geographical regions (Figure 1G).

An antibiotic cream or ointment was applied at the exit site in 8 centers (12.5%), whereas no antibiotic was used in 47 (73.4%). There was no standard for this practice in 9 centers (14.1%) (Figure 2C). The few centers that used a local antibiotic prophylaxis on the exit site were located in the same geographical area (Figure 1H).

We examined the change in prophylactic antibiotic use over time for each center. Graphically, no significant change was seen during the follow-up period (data not shown).

Chlorhexidine was the most frequently used antiseptic for dressing replacement in 31 centers (48.4%). One center (1.6%) used alcohol, and 4 (6.3%) did not use any antiseptic. Eleven centers had no standard practice, whereas the antiseptic used was unknown for the remaining 17 (26.6%).

First dressing replacement after the catheter placement was performed before day 5 in 12 centers (18.8%) and between day 6 and day 15 in 33 centers (51.2%). No standard was noted in 19 centers (19.7%).

#### PERITONEAL DIALYSIS MODALITY

In 18 centers (28.1%), the standard PD modality was CAPD, and 46 centers (71.9%) did not suggest a standard PD modality to their patients. One center (1.6%) used APD in greater than 75% of cases (Figure 2D).

#### ASSISTANCE FOR PD

In 6 centers (9.4%), more than 75% of the patients were autonomous for PD, whereas more than 75% of the patients benefited from a nurse assistance in 3 centers (Figure 2E).

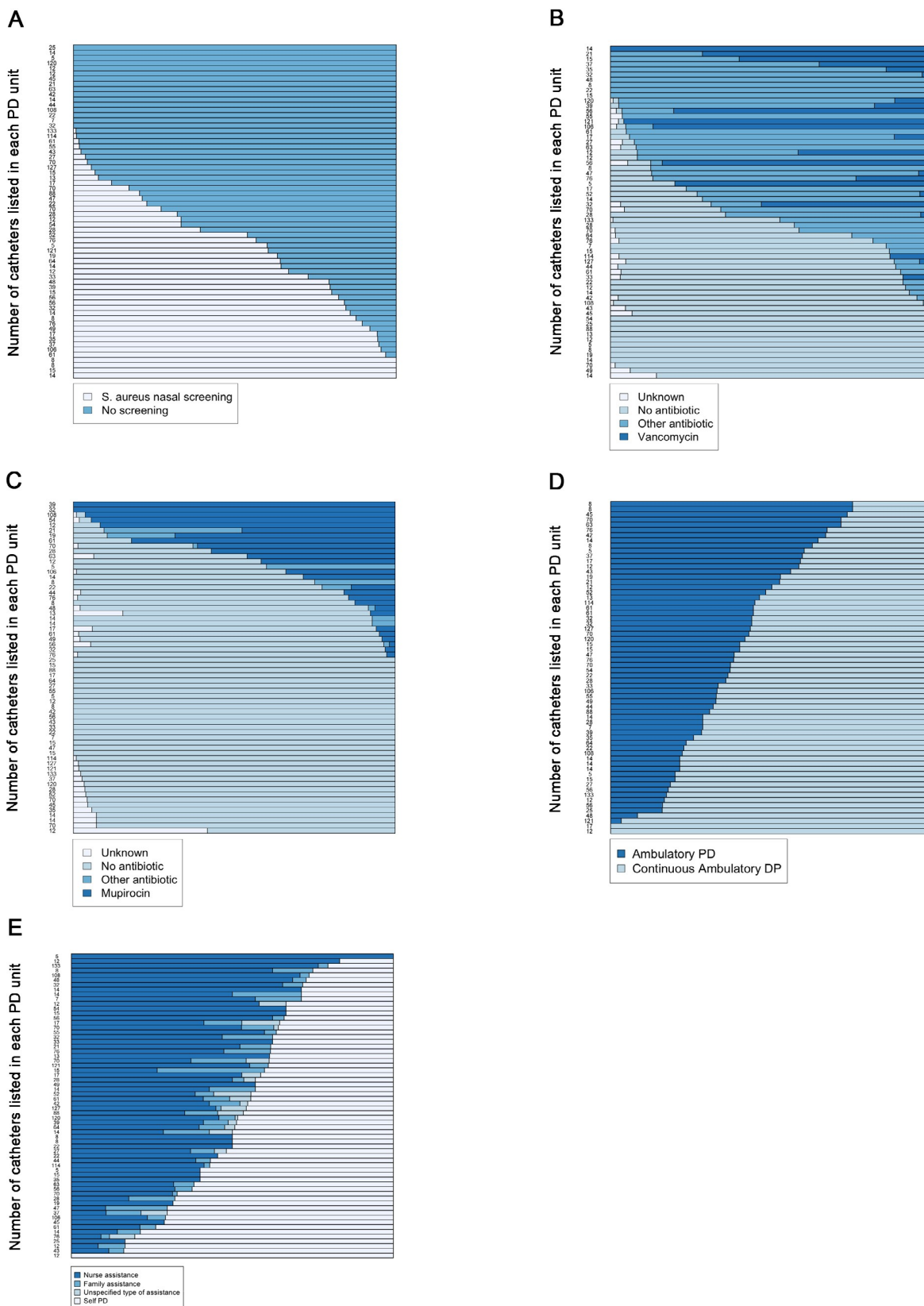


Figure 2 — Distribution of practice modalities across centers. Each horizontal line represents the rate of use of practice modalities in a given center. A: *S. aureus* nasal screening. B: prophylactic antibiotic administration prior to catheter insertion. C: Prophylactic antibiotic cream or ointment on the exit site. D: PD modality. E: Assistance for PD. PD = peritoneal dialysis.

## FACTORS ASSOCIATED WITH ADHERENCE TO GUIDELINES

We examined at the center level the existence of predictors of the adherence to guidelines. With a logistic regression model, we tried to explain the use of local prophylactic antibiotic use on the catheter exit site and administration of systemic prophylactic antibiotic prior to catheter placement with the following 4 explanatory covariates: presence of a nephrologist specialized in PD, presence of a PD-dedicated nurse, center size, and type of administrative structure. The only significant association was the higher rate of administration of prophylactic antibiotic prior to catheter placement in academic hospitals (odds ratio [OR] 0.13, confidence interval [CI] 95% 0.01 – 0.89). Results are shown in Table 2. There was no evidence of collinearity amongst examined variables.

## CLUSTERS OF PRACTICE

The practice dendrogram allowed us to gather practices typically associated within centers (Figure 3A). Practices represented by 16 leaves are gathered on nodes placed at different heights. The lower the node the closer the practices, meaning that if 2 practices are close on the dendrogram (low node), the use of the first practice is frequently associated with the use of the second one within a same center. On this dendrogram, it appears that 3 infection preventive practices (the use of prophylactic antibiotics prior to catheter placement, nasal screening of *S. aureus*, and administration of anti-staphylococcal local antibiotic prophylaxis) are used in a consistent way in the PD units. These infection preventive practices belonged to a same cluster, with the duration between catheter placement and first dressing, center characteristics such as the number of catheters placed, and the type of administrative structure. Practices associated with the antiseptic uses were grouped in another cluster. Surgical approach and choice for exit-site location were grouped in a third cluster. Surgical technique was potentially

associated with the presence of a specialized surgeon, the type of catheter placed, and 3 other practices: use of assistance for PD, person in charge for dressing, and PD modality.

In the center hierarchical clustering analysis, we identified 5 clusters of centers gathered according to the similarity of their practices (Figure 3B). In this second dendrogram, leaves represent the 64 centers, and the height of the nodes between 2 centers indicates how similar their practices are.

Thereafter, we mapped the cities according to their inclusion in 1 of these 5 clusters. At the country level, a clear geographical separation was not noted between clusters of practices. However, we can distinguish several nests with neighbor centers within the same cluster (Figure 11).

## DISCUSSION

We explored center-specific practices in France from the RDPLF and we found numerous disparities between PD units concerning these practices. The adherence to international guidelines was not homogenous, and surprisingly, the presence of a PD referent nephrologist or nurse specialized in PD within the PD unit was not associated with better adherence to guidelines. The size of the PD unit and the type of administrative structure were not associated with the prophylactic antibiotic use recommended by ISPD guidelines.

In a previous study from the RDPLF, we found that the use of systemic prophylactic antibiotic protected the individual against the risk of early peritonitis (OR 0.67, 95% CI 0.49–0.92). However, in a mixed logistic regression model with center as a random effect, this association lost significance (OR 0.73, 95% CI 0.48 – 1.09) indicated that the beneficial effect of prophylactic antibiotic use could be masked by a center effect (6).

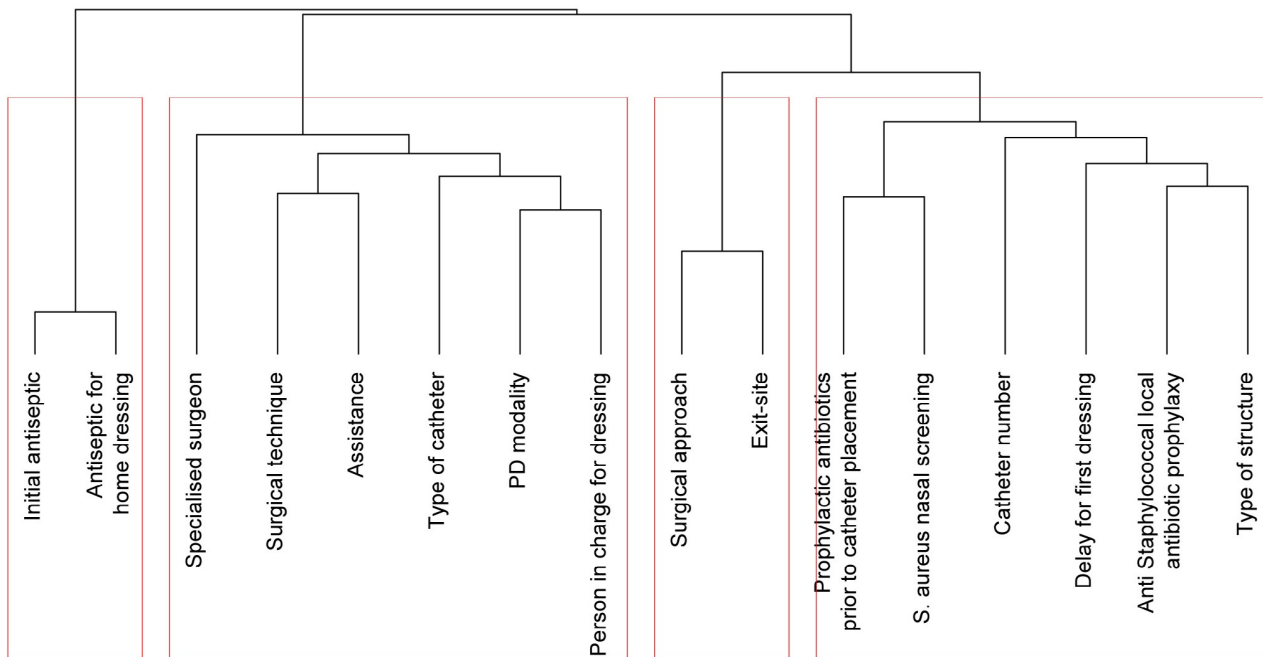
The interest of focusing on the center effect has been shown in previous works in North America, Australia, and New Zealand. A survey published in 2015 described PD practices in

TABLE 2  
Center-Specific Factors Associated with Prophylactic Antibiotic Use According to Guidelines

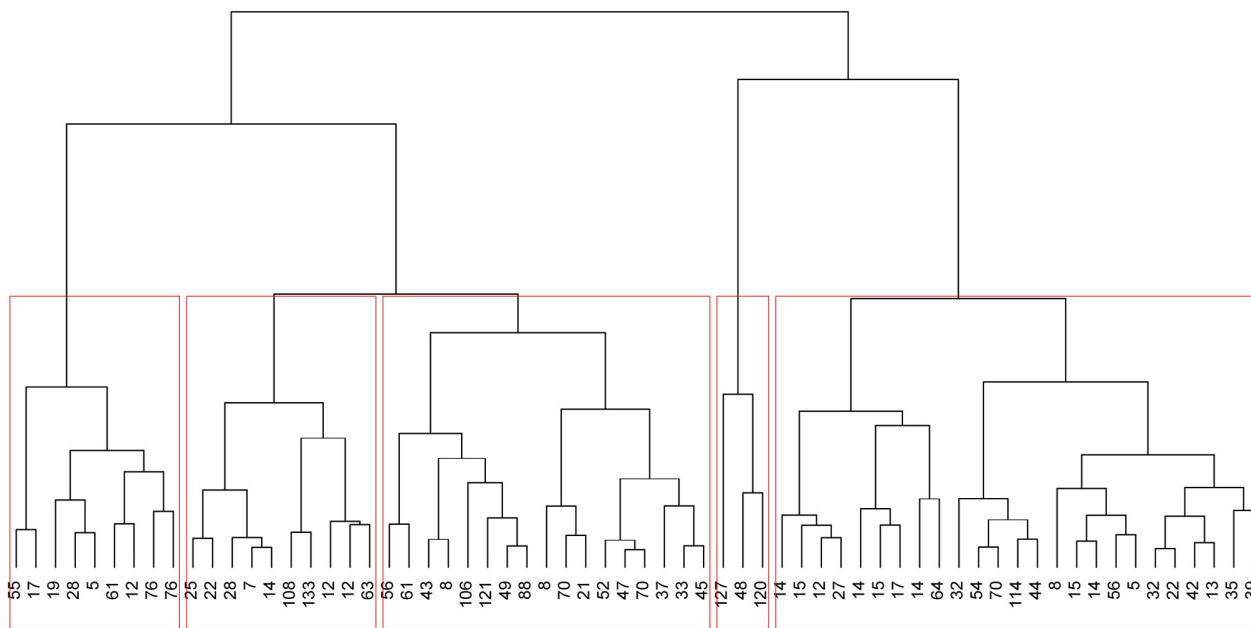
	Systemic prophylactic antibiotic prior to catheter insertion OR (95% CI)	Local prophylactic antibiotic on the exit site OR (95% CI)
Presence of a PD referent nephrologist	0.74 (0.26–2.09)	1.35 (0.36–4.85)
Presence of a PD dedicated nurse	2.62 (0.90–8.04)	0.69 (0.14–2.65)
Size of the PD unit (number of new patients per year)		
≤10	0.8 (0.23–2.65)	0.23 (0.01–1.37)
11–20	Reference	Reference
>20	0.89 (0.14–5.91)	0.43 (0.02–12.05)
Type of administrative structure		
Academic hospital	0.13 (0.01–0.89)	0.5 (0.08–4.05)
Community hospital	Reference	Reference
Non-profit center	4 (0.89–28.51)	1 (0.19–7.57)
Private center	1 (0.23–4.63)	0.7 (0.13–5.46)

OR = odds ratio; CI = confidence interval; PD = peritoneal dialysis.

**A**



**B**



**Numbers of catheters listed in each PD unit**

Figure 3 — Cluster analysis. A: clusters of center-specific practices. Height of the node between 2 leaves is a measurement of how practices are frequently associated within centers. B: Clusters of centers according to their practices. Height of the node between 2 centers is a measurement of the similarity of their practices.

51 North American PD centers (academic and non-academic, profit and not-for-profit, urban and community sites) and tried to characterize variability in practices. In total, 98% of centers routinely administered prophylactic antibiotics.

prior to PD catheter insertion, but the type of antibiotic differed: cefazolin in 78% of centers, vancomycin in 12% of centers, and cefazolin plus aminoglycoside in 10% of centers. Greater than 80% of units used a non-occlusive dressing



post-operatively, immobilized the catheter, and reported changes performed by a nurse using a sterile technique. In total, 80% of centers had at least 3 techniques available for catheter placement, and 95% used double-cuff catheters. In addition, 86% of centers had quality-improvement initiatives in place (11).

Variations in the use of antibiotic and antifungal prophylaxis for PD patients were assessed in a declarative study in Australia and New Zealand. According to guidelines and recommendations, 95.5% of 133 nephrologists who answered the survey prescribed prophylactic antibiotics prior to PD catheter insertion. In total, 59.4% prescribed mupirocin ointment at the exit site or intranasally and 69.9% prescribed a course of oral antifungal agents after an antibiotic treatment. In contrast to guideline recommendations, 63.9% routinely performed a screening for nasal *S. aureus* carriage and 88.4% treated *S. aureus* carriers with mupirocin cream or ointment (16).

We observed a substantially lower rate of prophylactic antibiotic use prior to PD catheter placement in the French centers than what is recommended by international guidelines (5). Our result seems reliable given that it was not obtained from a survey. We cannot surmise the reasons for the lack of adherence to recommendations from our data, but the reason has been considered in a previous work. In Australia and New Zealand, PD technique survival was lower than that in other parts of the world, and this lower survival rate was attributed to an increased incidence of peritonitis. In 2011, a prospective multicenter network study was designed to assess adherence to the Kidney Health Australia-Caring for Australasian with Renal Impairment (KHA-CARI) and ISPD guidelines in Australia and New Zealand. Eight PD units were selected, and their practices concerning peritonitis and exit-site-infection prevention were assessed together with infectious outcomes and identification of the barriers to following guideline recommendations. The authors found that guidelines were generally well known by practitioners; nevertheless, a wide variation in their application was noted. Non-adherence to guidelines was due to lack of protocols, a low staff-to-patient ratio, resistance by infectious disease staff to routinely provide mupirocin, and a lack of access to a specialized surgeon to perform catheter placement. Using Ishikawa diagrams, the authors proposed 3 levels of barriers to putting the guidelines into practice: healthcare providers, patients, and organizations (10). Implementation of guidelines into practice is known to be arduous. Various strategies should be used to target the 3 levels of barriers to change, such as educational interactive small group meetings, use of local opinion leaders, reminders, computerized decision support, financial interventions, performance feedback, and patient-mediated interventions (17). Continuous quality improvement programs should be set up in order to manage this process.

We identified patterns of practice in a cluster analysis. The mapping of centers according to their classification to 1 of the clusters allowed us to hypothesize that some geographical coherence may exist, which could be explained by the existence of “centers of influence” (Figure 11). Unfortunately, we have not been able to identify such centers. The hypothesis

that academic hospitals were leading-opinion centers could be incorrect concerning PD in France, but we could not verify this point because few academic centers contributed to the catheter modulus of the RDPLF (Figure 1A). Identifying the centers of influence is essential because if the effort to implement best practices is made in these facilities first, then it will likely spread quickly.

Quality improvement programs led to substantial improvement of the peritonitis rate in Australia and New Zealand (18). The ISPD guidelines recommend that each PD center have a continuous quality improvement program in place to reduce peritonitis rates (5). The existence of a PD quality improvement program was not present in our data, but maintaining such a program obviously requires a nurse specialized in PD. We believe that sufficient resources should be allocated to the centers to obtain and maintain nurses specialized in PD.

Several limitations exist in our study. Participation bias might occur, as our data are not exhaustive. Participation in the registry is voluntary, and we can imagine that centers participating in the RDPLF may have more involvement in PD than other centers and may have different practices. We did not consider practice change over time within centers. Studying this issue over a longer follow-up period would be of interest. Further information concerning which antibiotic was used as a prophylaxis prior to the catheter insertion would be relevant. Unfortunately, this information was not available in the registry. We do not know how many units recognize the existence of ISPD guidelines regarding systemic prophylactic antibiotics prior to catheter insertion and topical application of antibiotic ointment to the exit site. It would be of interest to assess the difference between the knowledge of the care provider and what is effectively done in the unit. The main strength of our study is that our data are collected from a reliable national registry and are truly representative of the center practices, with better accuracy than that of data obtained from a survey. We located the PD units and generated maps to explore relationships between practices and geographical proximity.

Variations exist in peritonitis rates across PD units in France. In the study by Bechade *et al.* on the risk of early peritonitis, the size of the center effect was assessed by the variance of the random effect, which was 0.33. This result indicates that the patients treated in the 14 centers with a random effect greater than 1 standard deviation above the mean had a relative risk of peritonitis higher than 1.39 (exponential function of 0.33) (7). The causes of these differences can be sought at the patient level. However, due to the existence of several clusters of practice across the territory, analyses of what occurs at the center level should also be considered. Moreover, center-level characteristics are largely modifiable practices. Reasons for non-adherence to guidelines should be sought, and an effort should be made to align practices to existing guidelines and to practices that have been proven efficient. This objective should be targeted by continuous quality improvement programs in the PD units. Our work is descriptive, so we cannot draw causal

conclusions. Our data shed light on several hypotheses to explore in further studies. In a forthcoming project, we will focus on the effect of center practices on PD patient outcomes, comparing the outcomes according to the clusters of practice that we have determined in this study.

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## DISCLOSURES

The authors have no financial conflicts of interest to declare.

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## IV. 4. Article 1

Lanot A, Bechade C, Verger C, Fabre E, Vernier I, Lobbedez T.

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International Seminar of Renal Epidemiology (ISRE)

« *Patterns of practices and risk of technique failure in peritoneal dialysis* »

RESEARCH ARTICLE

# Patterns of peritoneal dialysis catheter practices and technique failure in peritoneal dialysis: A nationwide cohort study

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## Abstract

### Introduction

Our objective was to assess whether clusters of centers with similar peritoneal dialysis (PD) catheter related practices were associated with differences in the risk of technique failure.

### Methods

Patients on incident PD in French centers contributing to the French Language PD Registry from 2012 to 2016 were included in a retrospective analysis of prospectively collected data. Centers with similar catheter cares practices were gathered in clusters in a hierarchical analysis. Clusters of centers associated with technique failure were evaluated using Cox and Fine and Gray models. A mixed effect Cox model was used to assess the influence of a center effect, as explained by the clusters.

### Results

Data from 2727 catheters placed in 64 centers in France were analyzed. Five clusters of centers were identified. After adjustment for patient-level characteristics, the fourth cluster was associated with a lower risk of technique failure (cause specific-HR 0.70, 95%CI 0.54–0.90). The variance of the center effect decreased by 5% after adjusting for patient characteristics and by 26% after adjusting for patient characteristics and clusters of centers in the mixed effect Cox model. Favorable outcomes were observed in clusters with a greater proportion of community hospitals, where catheters were placed via open surgery, first dressing done 6 to 15 days after catheter placement, and local prophylactic antibiotics was applied on exit-site.

### Conclusion

Several patterns of PD catheter related practices have been identified in France, associated with differences in the risk of technique failure. Combinations of favorable practices are suggested in this study.

## OPEN ACCESS

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**Data Availability Statement:** The RDPLF provides to every new patient an informative note explaining the use made of their data, and a consent form that must be signed. This note does not include a mention to full free access to the data on the Internet, but explains that the data will be made available to researchers in the field of PD. Therefore, data are kept by the RDPLF, and researchers in the field of PD can access them by submitting a query with a research protocol. No co-authorship is required to gain access to the data set of this study, neither to any other data from the

RDPLF. The RDPLF keeps archives of the dataset analyzed for this study. The person to contact for access to the dataset is Pr Max Dratwa, vice president of the RDPLF, through [max.dratwa@chubrugmann.be](mailto:max.dratwa@chubrugmann.be).

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## Introduction

One of the main challenges of peritoneal dialysis (PD) is to ensure the sustainability of the technique. Peritonitis is a leading cause of technique failure [1], [2], [3]. Individual risks factors for technique failure and peritonitis have been identified [4], [5], [6]. It has been demonstrated that a center effect explained by center characteristics influences the risks of peritonitis and technique failure [7], [8], [9]. This is a matter of concern since center characteristics are modifiable. PD practices are heterogeneous and variations observed between PD units contribute to the risk of peritonitis [10], [11], [12]. Consequently quality improvement programs at the center level are necessary [7], [13]. Identifying groups of centers with higher risks of peritonitis or technique failure is of importance if one wants to prioritize the action at the nationwide level. Furthermore practices may be interrelated and influence the patient outcomes.

We identified clusters of French PD centers that were grouped according to the proximity of their PD catheter related practices [10]. We hypothesize that these patterns of practices identified by a hierarchical analysis, may affect the patient outcome on PD. The objective of this study was to determine whether those clusters of centers with similar practices are associated with the risks of technique failure, peritonitis, and technique failure due to peritonitis.

## Materials and methods

### Study population

This was a retrospective study using data from the "catheter" section of the French Language Peritoneal Dialysis Registry (RDPLF) [14]. Eighty-seven centers provide data for the optional catheter section. Centers where fewer than 5 catheters were registered, and centers located in French overseas territories were excluded. Patients older than 18 years starting PD in France between 1 January 2012 and 31 December 2016 were included in the study. The end of study period was 3 February 2017.

### Definition of variables

**Individual characteristics (level 1 covariates).** Age, sex, weight, obesity (defined as a body mass index greater than 30 kg/m<sup>2</sup>), malnutrition (defined as a composite of BMI < 18.5 kg/m<sup>2</sup> or < 21 kg/m<sup>2</sup> for subjects older than 70 years old, and hypoalbuminemia, according to the pathology), causal nephropathy, existence of diabetes and its type of treatment, and modified Charlson comorbidity index, which is the Charlson comorbidity index after excluding the age subscore, were extracted from the registry.

**Center practices and clusters of centers (level 2 covariates).** Type of PD catheter, surgery technique, administration of antibiotic prophylaxis prior to catheter insertion, specialized surgeon for catheter placement, screening for nasal carriage of *S. aureus*, use of prophylactic nasal antistaphylococcal cream, use of local antistaphylococcal cream or ointment on the catheter emerging site, delay after catheter insertion for first dressing, type of antiseptic for dressing refraction, PD modality 3 months after dialysis initiation (automated peritoneal dialysis [APD] or continuous ambulatory peritoneal dialysis [CAPD]), assistance for PD (self-PD, family assistance, nurse assistance), type of administrative structure, and center size (number of catheters registered) were obtained from the database.

For each center, a practice was defined as being the center standard practice during the follow-up period whenever it was applied in 75% or more of the listed cases, from the individual data available in the registry.

A hierarchical clustering analysis using Ward's method was applied to determine five clusters of centers with similar practices [15]. Each practice is thought of as a specific dimension of

a virtual space, and the different modalities of the practice constitute the gradations along this dimension. A space of practices is therefore built, in which each center has a location according to its practices (S1 Fig). A Euclidian distance is defined in this virtual space and computed between the centers. Then, a dendrogram is built, joining centers with nodes at height proportional to the proximity of their practices. This allows the constitution of clusters of centers with similar practices. The number of clusters is determined graphically according to the semi-partial R-squared graph, to optimize the variability between clusters while minimizing complexity.

### Study outcomes

The primary outcome was PD technique failure, defined as a transfer to hemodialysis for longer than 2 months. Two events of interest were considered as secondary outcomes: first peritonitis episode for a given PD catheter, and technique failure due to peritonitis. A supplemental analysis was performed computing the risks for early or late technique failure (occurring respectively earlier or later than 3 months after the starting of PD). A composite outcome of technique failure and mortality was assessed to identify covariates potentially decreasing the risk of technique failure while increasing mortality.

### Statistical analysis

Categorical variables were described by their frequencies and percentages and continuous variables by their median and interquartile ranges. Differences of the distribution of practices among the clusters were evaluated using chi-squared tests. We examined for collinearity by assessing the generalized variance inflation factor.

### Survival analysis

**Cox modeling.** Kaplan-Meier survival curves were drawn, and log-rank tests were performed to determine whether the outcomes were different between the five clusters. Cox models were used to explore the association between the covariates and the events of interest: technique failure, first peritonitis episode, early and late technique failure. Considering the event technique failure due to peritonitis, other causes of technique failure would have been censored in a classical Cox model, overestimating the HR, so this event was not considered in the Cox model. Cause-specific HR with 95% confidence intervals (CI) were estimated. Regression splines were used to explore the effect of continuous variables and to choose their management in the models. Proportional hazard assumption was tested by visual inspection of Schoenfeld residual plots. Covariates were entered in the multivariate analysis when  $p < 0.20$  in the bivariate analysis, the cluster covariate was entered a priori since it was the covariate of interest.

**Fine and Gray modeling.** To avoid overestimating hazard rate, a competing risk analysis was performed, accounting for the risk of death, renal transplantation and other causes of technique failure [16]. The Fine and Gray model allows the estimation of the subdistribution HR, which is defined as the hazard of the event of interest in the presence of a competing event. The Fine and Gray modeling was used to explore the association between the covariates and all the outcomes of interest.

**Hierarchical analysis.** To assess the relevance of the approach with clusters of practices, we used a hierarchical analysis. A mixed-effect Cox model was used to estimate the influence of the clusters on the center effect for the two events: technique failure, and first peritonitis episode. An empty Cox model (model 0) with center as random effect was fitted to estimate the random effect. Individual characteristics (level 1 covariates) were included in the model

(model 1) to investigate whether the heterogeneity between centers was explained by the patient composition of the center. Cluster (level 2 covariates) was included in the model (model 2) to determine the magnitude of the clusters on the center effect. Model 1 and model 2 were compared with model 0 by analysis of variance (ANOVA). The proportional change in variance was calculated to estimate the contribution of the covariates in each model. Individual characteristics (level 1 covariates) were entered a priori in the multivariate analysis to improve the assessment of the center effect.

**Validation analysis.** We performed Cox and Fine and Gray analysis for each practice at the patients' level to assess the isolated effect of practices on technique failure risk. Results were compared with those found in the 4<sup>th</sup> cluster of centers.

The rate of missing data was < 3%. Given this very low rate, a complete case analysis was performed.

Statistical analyses were performed with R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria) including the *hclust*, *survival*, *cmprsk* and *coxme* packages.

The RDPLF provides an informative note to the patients, explaining the use made of their data, their rights to get an access to these data. Patients are informed of their right to oppose to the collection of their data without any consequence on their treatment. Nephrologists in the centers participating to the registry have the responsibility to give this note to any included patient, to obtain the patient's signature for agreement, and to keep this agreement in the medical records. The RDPLF has the approval of the French National Ethics Committee (*Commission nationale de l'informatique et des libertés, agreement number 542 668*) and fulfills the GDPR requests). This study took place within the framework of this authorization. All data analyzed were fully anonymized by the RDPLF, before we accessed them.

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [17].

## Results

### Patient characteristics (level 1 covariates)

Data concerning 2727 PD catheters placed in 2540 patients were included from 64 centers (Fig 1). The proportion of men was 1661/2727 (61%), median age was 68 years (first and third quartiles, 54 and 80), and median weight was 70.5 kg (first and third quartiles, 61 and 82). Of the 2727 patients 878 (35%) were diabetic.

### Center characteristics and clusters of practices (level 2 covariates)

There were 10 academic hospitals, 33 community hospitals, 12 nonprofit centers, and 9 private centers (Fig 2). The number of catheters placed and listed in each center ranged from 5 to 132 (median = 34, first and third quartiles = 15–61). No collinearity was detected between the practices with generalized variance index factors < 5.

Five clusters of centers have been identified, according to the similarity of their PD catheter related practices (Fig 3). Table 1 describes the distribution of patient characteristics among the five clusters of centers. Center characteristics and their distribution among the five clusters are given in Table 2 and illustrated in Fig 4.

### Events of interest

During the follow-up period, there were 604 technique failures, 755 peritonitis episodes occurring in 675 patients, and 81 cases of technique failure due to peritonitis. Survival curves are depicted on Fig 5.

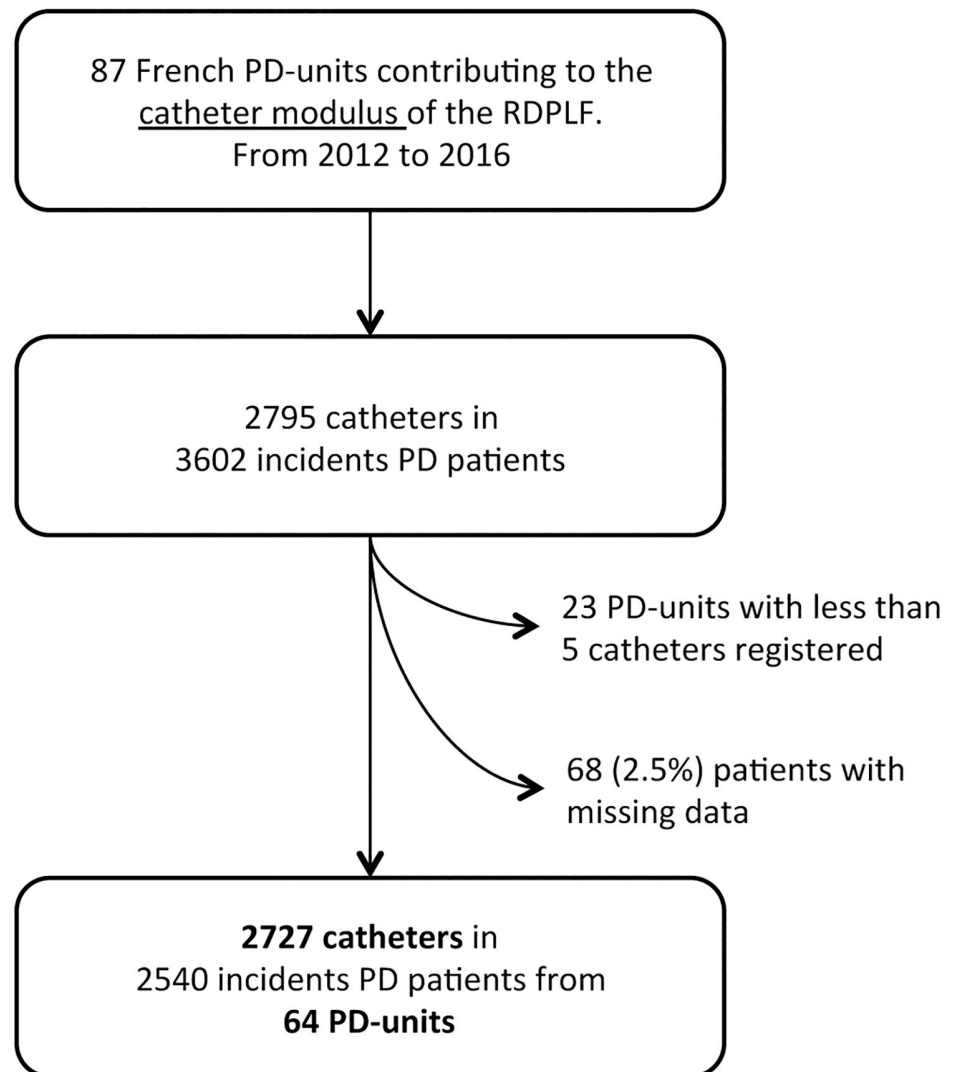


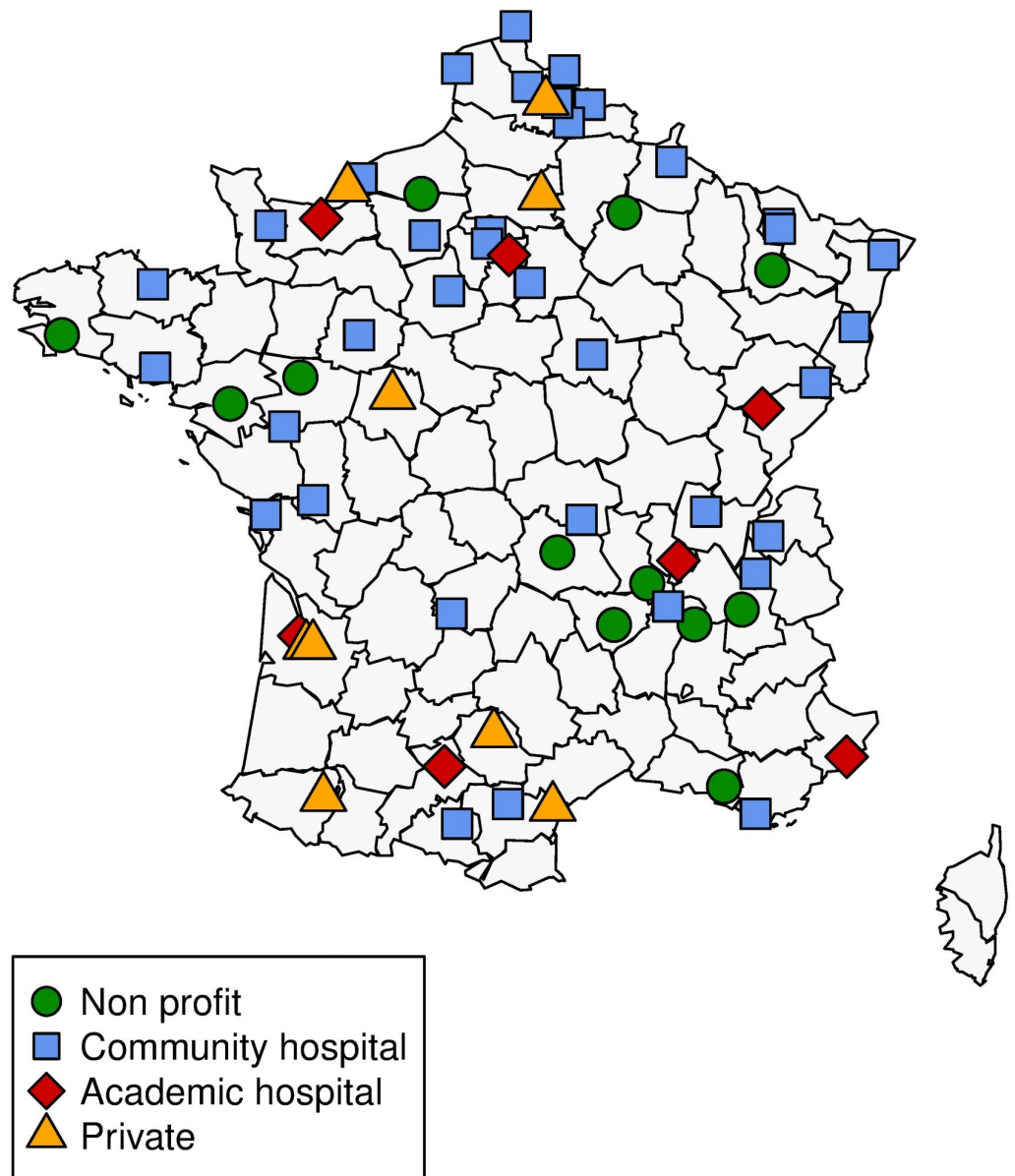
Fig 1. Flowchart.

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**Technique failure.** The absolute rate of survival free of technique failure censored for transplantation and death was 87% at one year during the follow-up period. In the bivariate analysis, covariates significantly associated with the risk of technique failure were sex, obesity, malnutrition, age, Charlson comorbidity index, and belonging to cluster number 4 in the Cox model, and obesity, malnutrition, age and belonging to cluster 4 in the Fine and Gray model (Table 3). In the multivariate analysis, covariates associated with the risk of technique failure were sex and age in the Cox model. In the Fine and Gray model obesity and age were associated with the risk of technique failure (Fig 6). Being treated in a PD-unit belonging to the fourth cluster was associated with a lower risk in the Cox model (cause specific-HR = 0.68, 95%CI 0.52–0.88) and in the Fine and Gray model (sub distribution-HR = 0.70, 95%CI 0.54–0.90). Making the distinction between early or late technique failures, we found that the clusters of centers were not associated with different risks of early technique failure (S1 Table and



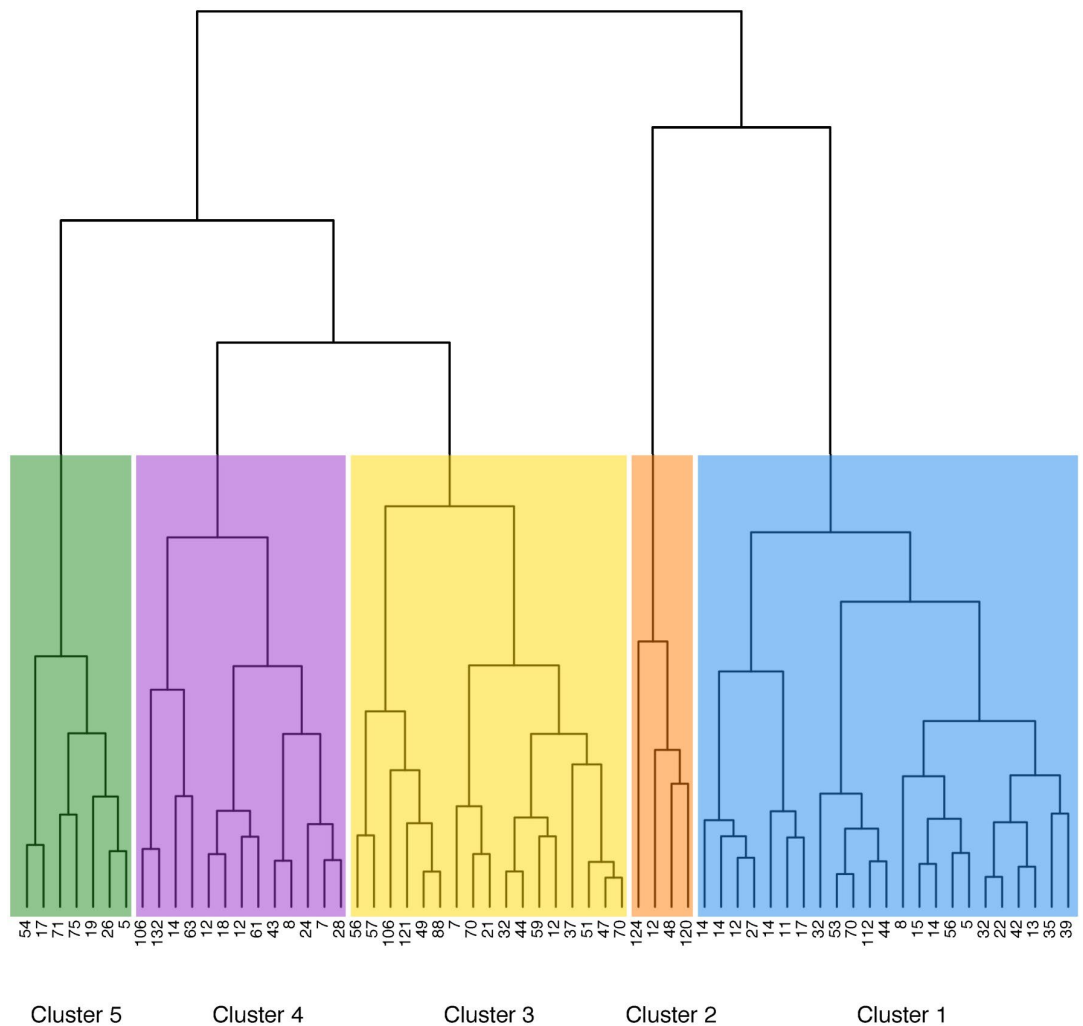
### Type of administrative structure



**Fig 2. Type of administrative structures.**

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*S2 Fig*). On the other side, cluster 4 was protective against the risk of late technique failure (sub distribution-HR 0.62; 95%CI 0.46–0.85) (*S1 Table* and *S4 Fig*). The results of the bivariate analysis concerning the composite outcome of technique failure and mortality are shown in *S2 Table*. Cluster 4 was still protective in the multivariate analysis, with the Cox model (cause



**Fig 3. Dendrogram defining the clusters of centers.** Each PD-center is represented by a black dot at the bottom of the dendrogram, with the number of catheter registered in it. In the virtual space of practices, distances between each center are computed. Centers are joined by nodes placed at a height that is proportional to the distance between the centers. Five clusters of centers are determined to optimize the variability between clusters while minimizing complexity.

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specific-HR 0.80; 95%CI 0.67–0.95), and the Fine and Gray model (subdistribution-HR 0.81; 95%CI 0.68–0.96) (S4 Fig).

**Peritonitis.** Of the 755 first episodes of peritonitis, 348 were due to Gram-positive cocci, 188 to Gram-negative bacilli, 18 to Gram-positive bacilli, 6 to fungi, and 195 to unidentified organism. The results of the bivariate analysis are given in Table 3. In the Cox multivariate analysis, there was no significant difference between the five clusters for the peritonitis risk neither in the Cox nor in the Fine and Gray model (S5 Fig).

**Technique failure due to peritonitis.** Taking into account the competing events with a Fine and Gray model, cluster 2 was associated with a greater risk of technique failure due to peritonitis in the bivariate analysis (Table 3) as in the multivariate analysis (sub distribution-HR 2.48, 95%CI 1.29–4.78) (S6 Fig).

**Table 1. Distribution of patient-level characteristics in the five clusters of centers.**

		Cluster 1 N = 701	Cluster 2 N = 304	Cluster 3 N = 927	Cluster 4 N = 528	Cluster 5 N = 267
Patient characteristics						
Sex: male (%)		427 (61)	197 (65)	538 (58)	336 (64)	163 (61)
Weight in kg	Median (IQR)	71 (62–82)	75 (62–86)	70 (60–80)	72 (63–84)	67 (59–77)
Obesity: N (%)		80 (11)	38 (12)	93 (10)	102 (19)	14 (5)
Malnutrition: N (%)		79 (11)	32 (11)	44 (5)	104 (20)	18 (7)
Age at PD initiation	Median (IQR)	71 (58–81)	66 (54–78)	65 (51–79)	73 (59–81)	67 (52–78)
Nephropathy: N (%)	Diabetic	156 (22)	55 (18)	187 (20)	94 (18)	31 (12)(38)
	GN	66 (9)	30 (10)	83 (9)	55 (10)	26 (10)
	Unknown	67 (10)	30 (10)	78 (8)	46 (9)	47 (18)
	TIN	31 (4)	16 (5)	35 (4)	21 (4)	15 (6)
	ADPKD	34 (5)	21 (7)	73 (8)	29 (5)	28 (10)
	Urologic	3 (0)	4 (1)	16 (2)	29 (5)	1 (0)
	Vascular	95 (14)	10 (3)	91 (10)	68 (13)	17 (6)
Diabetes: N (%)	Other	249 (36)	138 (45)	364 (39)	208 (39)	102 (38)
	Oral treatment	37 (5)	23 (8)	39 (4)	23 (4)	11 (5)
	Insulin	194 (30)	98 (29)	264 (29)	161 (31)	66 (21)
	Diet	22 (3)	12 (4)	35 (4)	25 (5)	14 (5)
Modified CCI	Median (IQR)	4 (2–5)	3 (2–5)	3 (2–5)	4 (2–5)	3 (2–5)

N: Number; IQR: Interquartile range; PD: Peritoneal Dialysis; GN: Glomerulonephritis; TIN: Tubulo interstitial nephropathy. ADPKD: Autosomic dominant polycystic kidney disease. IP: Intra peritoneal. SC: Sub cutaneous. CCI : Charlson Comorbidity Index

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### Hierarchical modeling

Considering technique failure, the SD of the random effect was 0.31 in model 0. This indicates that before any adjustments, the patients treated in centers with a random effect greater than 1 SD above the mean had a relative risk of technique failure higher than 1.36 (exponential of 0.31). The variance of the random effect decreased by 5% after adjusting for patient characteristics and by 26% after adjusting for patient characteristics and center clusters. Model 1 and model 2 were significantly different from model 0 according to ANOVA ( $p = 3.10^{-3}$  and  $p = 2.0 \times 10^{-3}$ , respectively). These results suggest that the clusters of practices explained a fifth of the center effect. Being treated in the fourth cluster was associated with a lower risk of technique failure (cause specific-HR 0.70, 95%CI 0.50–1.00) (Table 4).

### Differences of practices between the clusters

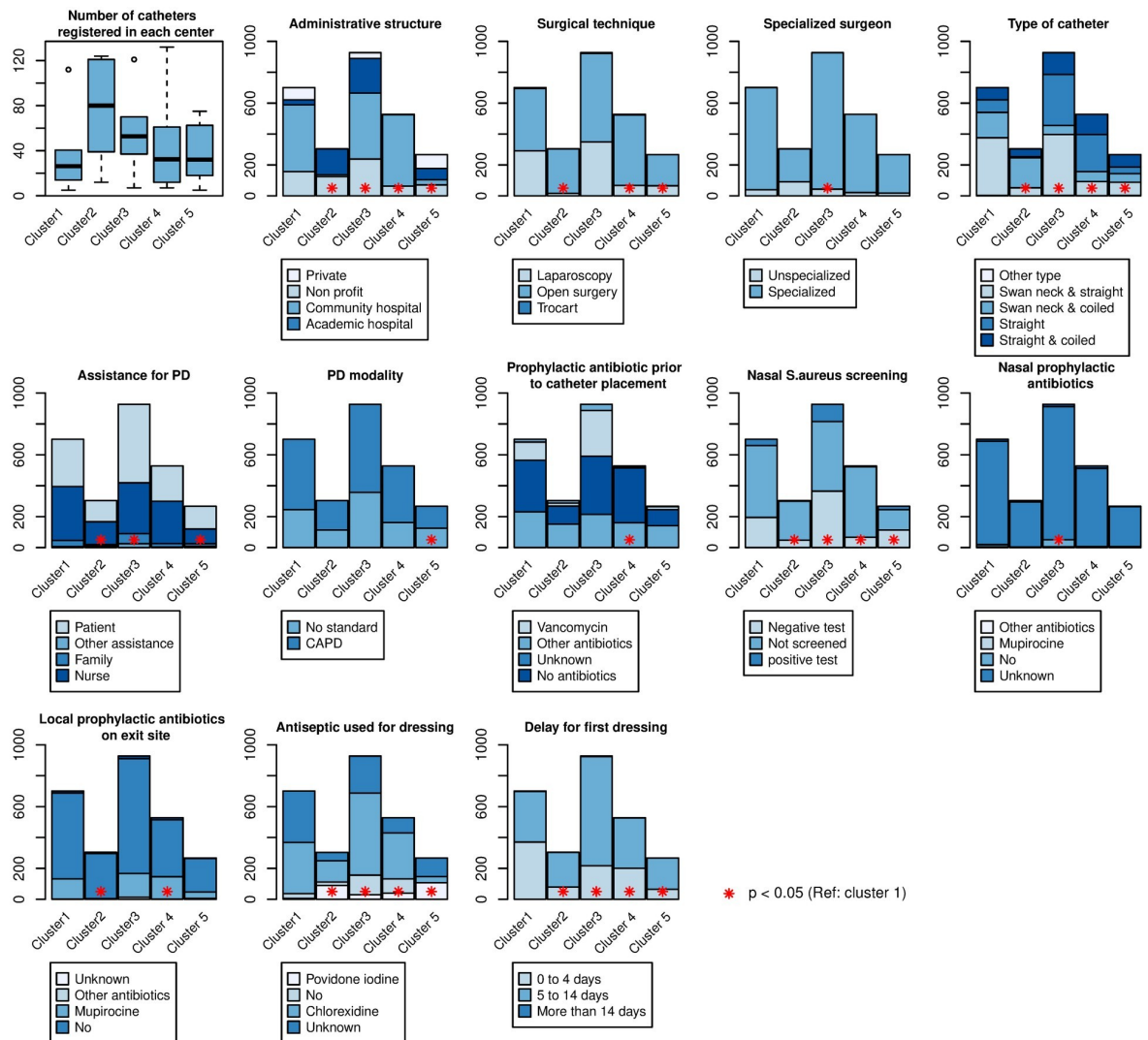
Compared with the first cluster, which was the reference, we found out that cluster 4 was protective against technique failure (cause specific-HR 0.68, 95%CI 0.52–0.88). In the centers from this cluster, there was a greater proportion of community hospitals, open surgery catheter placements, coiled catheters placed, use of local prophylactic antibiotics on exit-site, antiseptic use for dressing, and first dressing after catheter placement made between 5 and 14 days. On the other hand, there was fewer use of prophylactic antibiotic prior to catheter placement, and screening for nasal *S. aureus* presence. There was no difference on the covariates: use of assistance, PD modality, specialized surgeon for catheter placement (S5 Fig).

**Table 2. Distribution of center-level characteristics in the five clusters of centers.**

		Cluster 1 N = 701	Cluster 2 N = 304	Cluster 3 N = 927	Cluster 4 N = 528	Cluster 5 N = 267
Administrative structure	Non profit	157 (22)	124 (41)	238 (26)	63 (12)	71 (27)
	Community hosp.	432 (62)	12 (4)	427 (46)	462 (88)	33 (12)
	Academic hosp.	32 (5)	168 (55)	222 (24)	3 (1)	73 (27)
	Private	80 (11)	0	38 (4)	0	90 (34)
Catheters registered	Median (IQR)	22 (14–41)	84 (39–121)	51 (37–70)	24 (12–61)	26 (18–63)
Surgical technique for catheter placement	Laparoscopy	292 (42)	16 (5)	349 (38)	67 (13)	65 (24)
	Open surgery	403 (57)	287 (94)	573 (62)	456 (86)	202 (76)
	Trocart	6 (1)	1 (0)	5 (1)	5 (1)	0
Specialized surgeon		662 (94)	213 (70)	884 (95)	507 (96)	250 (94)
Catheter type	Swan neck—straight	374 (53)	52 (17)	394 (43)	91 (17)	85 (32)
	Swan neck—coiled	164 (23)	195 (64)	59 (6)	65 (12)	56 (21)
	Straight—straight	81 (12)	7 (2)	329 (35)	240 (45)	42 (16)
	Straight—coiled	80 (11)	50 (16)	142 (15)	131 (25)	81 (30)
	Other	2 (0)	0	3 (0)	1 (0)	3 (1)
Prophylactic antibiotics prior to catheter placement	Vancomycin	118 (17)	20 (7)	296 (32)	2 (0)	19 (7)
	Other antibiotics	231 (33)	152 (50)	215 (23)	161 (30)	141 (53)
	No antibiotic	334 (48)	116 (38)	376 (41)	355 (67)	104 (39)
	Unknown	18 (3)	16 (5)	40 (4)	10 (2)	3 (1)
Nasal S. aureus screening	Not screened	465 (66)	252 (83)	451 (49)	455 (86)	132 (49)
	Positive test	41 (6)	4 (1)	111 (12)	6 (1)	8 (21)
	Negative test	195 (28)	48 (16)	365 (39)	67 (13)	114 (43)
Nasal prophylactic antibiotics	No	669 (95)	292 (96)	861 (93)	506 (96)	258 (97)
	Mupirocine	14 (2)	3 (1)	46 (5)	5 (1)	5 (2)
	Other antibiotics	5 (1)	0	5 (1)	2 (0)	1 (0)
	Unknown	13 (2)	9 (3)	15 (2)	15 (3)	3 (1)
Local prophylactic antibiotics on exit-site	No	556 (79)	292 (96)	743 (80)	368 (70)	217 (81)
	Mupirocine	130 (19)	3 (1)	154 (17)	144 (27)	41 (15)
	Other antibiotics	2 (0)	1 (0)	13 (1)	2 (0)	6 (2)
	Unknown	13 (2)	8 (3)	17 (2)	14 (3)	3 (1)
Delay for first dressing	0 to 5 days	370 (53)	79 (26)	217 (23)	201 (38)	64 (24)
	6 to 15 days	328 (47)	224 (74)	706 (76)	325 (62)	203 (76)
	After day 16	3 (0)	1 (0)	4 (0)	2 (0)	0
Antiseptic used for dressing	No antiseptic	31 (4)	7 (22)	127 (14)	92 (17)	0
	Povidone iodine	6 (1)	89 (29)	29 (3)	40 (8)	107 (40)
	Chlorexidine	331 (47)	138 (45)	531 (57)	298 (56)	40 (15)
	Unknown	333 (48)	55 (18)	240 (26)	98 (19)	120 (45)
Assistance for PD	Family	40 (6)	9 (3)	65 (7)	22 (4)	17 (6)
	Nurse	349 (50)	147 (48)	329 (35)	274 (52)	95 (36)
	Patient	306 (44)	137 (45)	508 (55)	228 (43)	147 (55)
	Other assistance	6 (1)	11 (4)	25 (3)	4 (1)	8 (3)
PD modality	APD	246 (35)	114 (38)	357 (39)	162 (31)	125 (47)
	CAPD	455 (65)	190 (62)	570 (61)	366 (69)	142 (53)

Hosp: hospital. TAP: Transverse Abdominal Plane. APD: Automated peritoneal dialysis. CAPD: Continuous ambulatory peritoneal dialysis.

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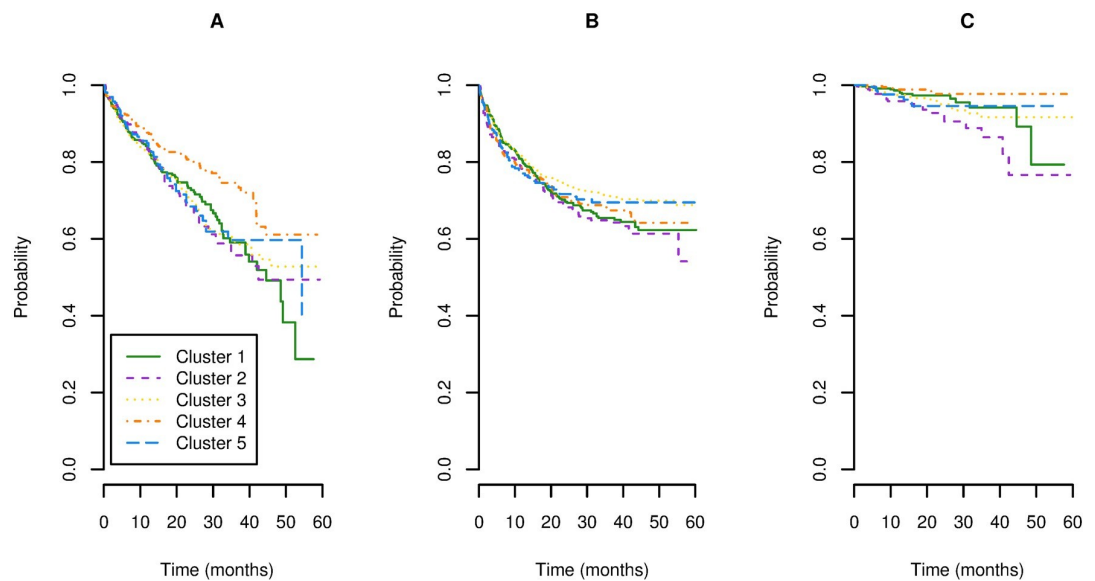


**Fig 4. Distribution of practices in the five clusters of centers.** The distribution of the modalities used for each practices is represented in the five clusters of centers. Statistically significant differences in the distribution of modalities with cluster 1 (taken as the reference) are marked with a red star.

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### Validation

Results of the bivariate Cox and Fine and Gray models at the patient’s level are shown in [S3 Table](#). In the competing risk analysis, several practices were protective against the risk of technique failure at the patient’s level: being treated in a community hospital compared to being treated in an academic hospital (sub distribution -HR 1.25, 95%CI 1.02–1.54), or a private center (sub distribution -HR 1.42, 95%CI 1.09–1.87), open surgery for catheter placement compared with laparoscopy (sub distribution -HR 0.78, 95%CI 0.49–0.92), and use of local prophylactic antibiotic on exit-site (sub distribution -HR 0.65, 95%CI 0.51–0.82). This is consistent with the practices of cluster 4, found to be protective against the risk of technique failure in the hierarchical analysis. Use of assistance for PD exchange was protective at the patient’s level (sub distribution -HR 0.68, 95%CI 0.58–0.80), whereas there was no significant difference



**Fig 5. Survival Kaplan-Meier curves according to the cluster of centers. 5A. Technique failure. 5B. Peritonitis.**

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in the clusters analysis. Practices with a greater risk for technique failure were use of APD (sub distribution -HR 1.34, 95%CI 1.15–1.57), and use of antiseptic for dressing (sub distribution -HR 1.66, 95%CI 1.19–2.31). Eventually, there was no difference according to the type of PD catheter used, delay for first dressing, prophylactic antibiotic use prior to catheter placement, nasal screening for *S. aureus*, and surgeon experience.

## Discussion

Using an ascendant hierarchical analysis, we defined five clusters of centers with similar patterns of PD catheter related practices [10]. Our study shows that the risk of technique failure and the risk of technique failure due to peritonitis were different in these five clusters. In the hierarchical analysis, the belonging to a given cluster explained partly the center effect associated with the risk of technique failure, as the variance of the random effect decreased by 26% after adjusting for both patient characteristics and center clusters.

One should wonder why clusters of centers were used instead of studying the effect of each given practice separately. Randomized trials are mandatory to determine the best practices to propose to PD patients, but unfortunately, due to the large numbers of eligible practices, it is unlikely that evidence will be produced for each practice. Moreover, interactions may exist between practices and may have a synergic effect on the outcomes. The cluster analysis could help to identify association of practices that could influence positively the patient outcome. Furthermore, the method of clustering centers could allow implementation of quality improvement programs in group of centers, to prioritize the action at a nationwide level especially when practices are modifiable.

Cluster identification could also lead to research about the effect of pattern of practices on the patient outcome. In support of this, in the pattern of practices of cluster 4, a greater proportion of patients received local prophylactic antibiotics on exit-site, a finding in line with the ISPD guidelines, [11]. In the PanThames study, the effect of local prophylactic antibiotic use on exit-site has been assessed in twelve English PD-units in 2012. Neither mupirocin nor gentamycin reduced the peritonitis rate [Panthames]. In the cluster 4, there were more catheters

**Table 3. Bivariate analysis for the three events of interest.** Results of the Cox and Fine and Gray models.

Model used	Technique failure		Peritonitis		Technique Failure due to peritonitis
	Cox	Fine and Gray	Cox	Fine and Gray	Fine and Gray
	Cs-HR (95%CI)	Sd-HR (95%CI)	Cs-HR (95%CI)	Sd-HR (95%CI)	Sd-HR (95%CI)
<b>Covariates</b>					
<b>Sex (Male)</b>	1.16 (0.99–1.37) <sup>ω</sup>	1.09 (0.93–1.08)	1.10 (0.95–1.28) <sup>ω</sup>	1.06 (0.88–1.28)	1.75 (1.07–2.85) <sup>ωω</sup>
<b>Obesity</b>	1.16 (0.92–1.46) <sup>ω</sup>	1.21 (0.97–1.52) <sup>ω</sup>	1.59 (1.31–1.93) <sup>ωω</sup>	1.70 (1.33–2.17) <sup>ωω</sup>	0.47 (0.19–1.15) <sup>ω</sup>
<b>Malnutrition</b>	0.81 (0.60–1.1) <sup>ω</sup>	0.70 (0.52–0.95) <sup>ωω</sup>	0.95 (0.74–1.20)	1.34 (1.02–1.77) <sup>ωω</sup>	0.47 (0.17–1.29) <sup>ω</sup>
<b>Age</b>	P < 0.001 <sup>ωω</sup>	P < 0.001 <sup>ωω</sup>	P = 0.03 <sup>ωω</sup>	P < 0.001 <sup>ωω</sup>	P = 0.22
<b>18–39</b>	Ref.	Ref.	Ref.	Ref.	Ref.
<b>40–59</b>	0.93 (0.71–1.22)	1.03 (0.79–1.34)	0.75 (0.59–0.97) <sup>ωω</sup>	1.02 (0.67–1.57)	2.04 (0.84–4.92) <sup>ω</sup>
<b>60–79</b>	0.71 (0.55–0.91) <sup>ωω</sup>	0.80 (0.62–1.03) <sup>ω</sup>	0.75 (0.59–0.94) <sup>ω</sup>	1.65 (1.13–2.43) <sup>ωω</sup>	1.50 (0.63–3.54)
<b>&gt; 80</b>	0.58 (0.44–0.78) <sup>ωω</sup>	0.58 (0.43–0.78) <sup>ωω</sup>	0.68 (0.53–0.88) <sup>ωω</sup>	2.21 (1.49–3.27) <sup>ωω</sup>	0.91 (0.35–2.37)
<b>Diabetes</b>	1.10 (0.93–1.29)	1.07 (0.91–1.27)	1.08 (0.93–1.25)	1.33 (1.10–1.61) <sup>ωω</sup>	0.92 (0.58–1.46)
<b>Nephropathy</b>	P = 0.29	P = 0.39	P = 0.28	P = 0.01 <sup>ω</sup>	P = 0.36
<b>Diabetic</b>	Ref.	Ref.	Ref.	Ref.	Ref.
<b>GN</b>	0.90 (0.66–1.21)	0.91 (0.67–1.23)	0.79 (0.59–1.05) <sup>ω</sup>	0.54 (0.36–0.82) <sup>ωω</sup>	1.97 (0.86–4.54) <sup>ω</sup>
<b>Unknown</b>	0.86 (0.64–1.17)	0.85 (0.63–1.16)	0.74 (0.55–0.99) <sup>ωω</sup>	0.77 (0.54–1.11) <sup>ω</sup>	1.20 (0.47–3.09)
<b>TIN</b>	0.76 (0.50–1.16)	0.78 (0.51–1.19)	1.11 (0.78–1.57)	0.79 (0.49–1.29)	2.76 (1.08–7.03) <sup>ωω</sup>
<b>ADPKD</b>	0.82 (0.58–1.15)	0.80 (0.57–1.10) <sup>ω</sup>	0.93 (0.69–1.27)	0.44 (0.27–0.73) <sup>ωω</sup>	1.67 (0.65–4.33)
<b>Urologic</b>	0.81 (0.40–1.66)	0.87 (0.42–1.79)	0.61 (0.29–1.30)	0.57 (0.22–1.47)	1.32 (0.17–10.28)
<b>Vascular</b>	0.64 (0.47–0.88) <sup>ωω</sup>	0.68 (0.50–0.94) <sup>ω</sup>	0.85 (0.64–1.12)	0.91 (0.65–1.27)	0.81 (0.28–2.32)
<b>Other</b>	0.85 (0.69–1.05) <sup>ω</sup>	0.81 (0.65–0.99) <sup>ωω</sup>	0.89 (0.73–1.09)	0.86 (0.67–1.10)	1.42 (0.72–2.81)
<b>Modified CCI</b>	P = 0.15 <sup>ω</sup>	P = 0.32	P = 0.93	P < 0.001 <sup>ωω</sup>	P = 0.79
<b>2–3</b>	Ref.	Ref.	Ref.	Ref.	Ref.
<b>4–5</b>	0.88 (0.73–1.06) <sup>ω</sup>	0.87 (0.73–1.05) <sup>ω</sup>	1.03 (0.88–1.22)	1.51 (1.23–1.86) <sup>ωω</sup>	0.84 (0.50–1.40)
<b>5–16</b>	1.10 (0.90–1.36)	1.00 (0.81–1.23)	1.00 (0.83–1.22)	1.48 (1.16–1.90) <sup>ωω</sup>	0.97 (0.55–1.73)
<b>Cluster</b>	P = 0.005 <sup>ωω</sup>	P = 0.04 <sup>ωω</sup>	P = 0.17	P = 0.01	P = 0.003 <sup>ωω</sup>
<b>Cluster 1</b>	Ref.	Ref.	Ref.	Ref.	Ref.
<b>Cluster 2</b>	1.05 (0.80–1.37)	1.03 (0.79–1.34)	1.11 (0.88–1.42)	0.95 (0.69–1.31)	2.51 (1.30–4.84) <sup>ωω</sup>
<b>Cluster 3</b>	1.00 (0.82–1.24)	1.00 (0.81–1.22)	0.85 (0.70–1.03)	0.78 (0.61–1.00) <sup>ω</sup>	1.32 (0.72–2.41)
<b>Cluster 4</b>	0.67 (0.51–0.86)	0.70 (0.54–0.90) <sup>ωω</sup>	1.00 (0.81–1.24)	1.20 (0.92–1.56) <sup>ω</sup>	0.46 (0.18–1.17)
<b>Cluster 5</b>	0.98 (0.74–1.32)	1.00 (0.75–1.33)	0.94 (0.72–1.23)	0.74 (0.51–1.08) <sup>ω</sup>	1.36 (0.60–3.09)

Cs-HR: Cause specific hazard ratio; sd-HR: sub distribution hazard ratio; p: global p-value; GN: Glomerulonephritis; CCI: Charlson comorbidity index; PD: peritoneal dialysis;

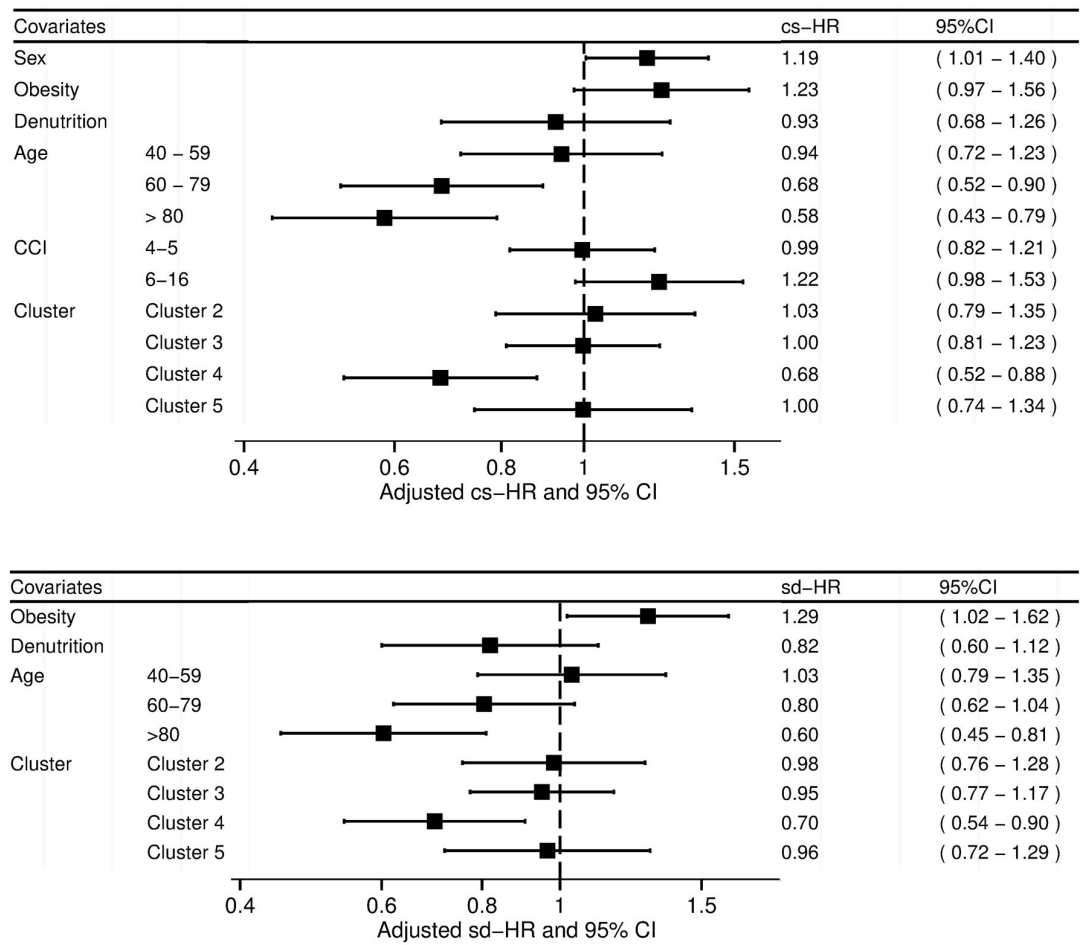
<sup>ω</sup>: p < 0.2;

<sup>ωω</sup>: p < 0.05

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placed via open surgery, and the delay for first dressing refection was between 6 to 15 days after surgery. These 2 practices have not shown their superiority in previous study to our knowledge. On the other hand, more patients in this cluster did not receive prophylactic antibiotic prior to catheter placement, whereas this practice is known to be protective against the peritonitis risk [18].

We found that cluster 4 was protective against the risk of late technique failure, whereas there was no association with the risk of early technique failure. We can hypothesize from these results that the protective effect observed in cluster 4 was mainly due to the use of local prophylactic antibiotics on exit-site, the absence of antiseptic use for dressing, and the absence of screening for nasal *S. aureus*, which have a sustained effect in time.



**Fig 6. Association between covariates and technique failure. Results of the multivariate Cox model (A) and Fine and Gray model (B).** The class of references are: female for the sex, 18–39 years old for the age, 2–3 for the modified Charlson comorbidity index, and cluster number 1 for the clusters of centers. CCI: modified Charlson Comorbidity Index, cs-HR: cause specific hazard-ratio, 95%CI: 95% confidence interval, sd-HR: subdistribution specific hazard-ratio.

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Substantial variations in the peritonitis rate are reported between countries but also within countries [19][11]. On the one hand, identifying clusters of centers with similar practices and poorer outcomes allows for a focus on centers with room for improvement because practices are modifiable. On the other hand, this method could identify units where outcomes are less favorable because of the patient characteristics.

Early peritonitis was associated with worse technique survival (HR 0.54, 95%CI 0.30–0.98) in a 10-year single-center study in Taiwan [1]. In another retrospective single-center study from China, peritonitis occurring in the first 6 months after starting PD was an independent risk factor for technique failure (HR 1.69, 95%CI 1.12–2.87) [20]. See et al. used the ANZDATA registry in a large observational study to describe the predictors and outcomes of early peritonitis. Among 3827 registered episodes of early peritonitis, 628 (16%) were followed by technique failure [4]. Other observational studies have tried to elucidate risk factors for peritonitis and poor outcomes [5] [21]. In all these studies, patient characteristics were very nearly the only variable tested, and few modifiable center-level characteristics were integrated



**Table 4. Hierarchical analysis for the primary outcome: Technique failure (multivariate analysis with a mixed effect Cox model).**

	Model 0 Empty model	Model 1 cs-HR (95%CI)	Model 2 cs-HR (95%CI)
Level 1 covariate			
Sex: Male	-	1.19 (1.00–1.41) <sup>ω</sup>	1.19 (1.01–1.42) <sup>ω</sup>
Obesity	-	1.23 (0.96–1.58)	1.25 (0.97–1.60)
Malnutrition	-	1.02 (0.74–1.40)	1.03 (0.75–1.43)
Age at PD initiation	-		
18–39		Ref.	Ref.
40–59		0.95 (0.72–1.26)	0.96 (0.73–1.28)
60–79		0.67 (0.5–0.89) <sup>ω</sup>	0.68 (0.51–0.91) <sup>ω</sup>
>80		0.60 (0.43–0.82) <sup>ω</sup>	0.60 (0.44–0.83) <sup>ω</sup>
Nephropathy			
Diabetic		Ref.	Ref.
GN		0.79 (0.55–1.15)	0.80 (0.55–1.16)
Unknown		0.84 (0.58–1.23)	0.84 (0.58–1.23)
TIN		0.69 (0.43–1.12)	0.69 (0.43–1.12)
ADPKD		0.74 (0.48–1.13)	0.74 (0.48–1.13)
Urologic		0.82 (0.38–1.79)	0.82 (0.38–1.78)
Vascular		0.73 (0.50–1.06)	0.74 (0.51–1.07)
Other		0.79 (0.59–1.06)	0.79 (0.59–1.06)
Diabetes	-	1.02 (0.78–1.33)	1.02 (0.78–1.33)
Modified CCI			
2–3	-	Ref.	Ref.
4–5		0.93 (0.75–1.16)	0.93 (0.75–1.16)
>5		1.07 (0.82–1.41)	1.06 (0.81–1.4)
Level 2 covariates	-		
Cluster			
Cluster 1	-	-	Ref.
Cluster 2			1.10 (0.72–1.68)
Cluster 3			1.07 (0.80–1.43)
Cluster 4			0.70 (0.50–1.00) <sup>ω</sup>
Cluster 5			1.00 (0.67–1.50)
Random effect			
Standard error (variance)	0.31 (0.1)	0.3 (0.09)	0.27 (0.07)
Standard error of the variance of the random effect	0–0.45	0–0.45	0–0.86
p-value (ANOVA)	-	0.003 <sup>ω</sup>	0.002 <sup>ω</sup>
PCV (%)	-	5	26

PD: Peritoneal Dialysis; GN: Glomerulonephritis; TIN: Tubulo interstitial nephropathy. ADPKD: Autosomic dominant polycystic kidney disease. CCI: Charlson Comorbidity Index. ICC: Intraclass correlation coefficient. ANOVA: analysis of variance. PCV: Proportional change in variance.

<sup>ω</sup>: p<0.05

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in the analysis. However, evidence has emerged that the peritonitis risk in PD is associated with modifiable center-specific characteristics [8] [22].

Few studies have focused on PD outcomes related to center-level characteristics. In a retrospective study analyzing 9100 episodes of peritonitis from the ANZDATA registry, Htay et al. showed that center-level characteristics substantially influenced PD peritonitis outcomes.

Centers with more than 29% of dialysis patients treated with PD had higher odds of cured peritonitis (odds ratio (OR) 1.21, 95%CI 1.04–1.40) and lower odds of catheter removal (OR 0.78, 95%CI 0.62–0.97), transfer to hemodialysis therapy (OR 0.78, 95%CI 0.62–0.97) and peritonitis relapse/recurrence (OR 0.68, 95%CI 0.48–0.98) [23]. In another retrospective multicentric study from the same team, 5813 episodes of technique failure were observed in 9642 incident patients on PD during a 10-year follow-up period. The cause of technique failure was infection in 1577 (27%) cases. Variation in the hazards of technique failure across centers was reduced by 28% after adjusting for patient-level characteristics and by an additional 53% after adjusting for center-level characteristics [24]. Guillouet et al. from our team determined in a previous study from the RDPLF data that center characteristics accounted for 52% of the variations in early PD failure and that center size was associated with the risk of early PD failure [9].

Peritonitis risk was not different between the five clusters. However, cluster 2 was associated with a greater risk of technique failure due to peritonitis. This reflects that peritonitis outcomes are not uniform between the centers. Htay et al. found that the variation in odds of peritonitis cure across Australian centers was 66% lower after adjustment for center-level characteristics [23]. Ways of treating peritonitis could be dissimilar, or transfer to hemodialysis could be considered earlier in some centers.

Taken together, these results argue that center experience and practices are more important than patient characteristics in determining major clinical outcomes in PD, such as technique failure and peritonitis outcome.

Quality improvement programs have already proven their efficacy in PD care. The overall rate of technique failure was significantly reduced in Australia and New Zealand after a 2009 national peritonitis prevention program [25]. Poor adherence to international guidelines was outlined in different countries [10] [12]. Implementation of changes in patient care is known to be arduous. Various strategies should be used to put guidelines into practice, such as educational interactive small group meetings, use of local opinion leaders and reminders, computerized decision support, financial intervention, performance feedback, and patient-mediated intervention [26]. It would be of interest to know whether a post-peritonitis re-training protocol exists in the PD-units, as advised by the ISPD [11].

Considering every practice of a PD unit and assessing the coherence of the whole program could be a further step toward improvement. The “clusters method” that we propose here does not give a definitive answer to what the more suitable practices are, but it adds significant information by identifying centers where poor outcomes should be more prone to improve, by evaluating and changing practices.

To our knowledge, this study is the first to propose a comparison of clinical outcomes among clusters of centers with similar practices. A large population of incident PD patients was included with very good quality data [14]. Robust statistical methodologies were used, allowing for an assessment of the adjustment of patient- and center-level characteristics and competing risks.

However, these strengths should be balanced against the study’s limitations, including the retrospective design and possibility of reporting bias. The use of registry data restricts the availability of clinical variables. Participation in the registry is voluntary, thus centers participating in the RDPLF may have more involvement in PD than other centers and may have different practices. Covariates declared in the registry, like specialization of the surgeon, were not defined in a standardized way, exposing to a declaration bias. The survival models used here do not allow handling for multiple events, which is a limitation considering the outcome peritonitis.

In conclusion, clusters of centers with similar patterns of practices can be identified in France. These patterns of practices are associated with significantly different risks of technique

failure. Belonging to a given cluster explained a significant part of the center effect associated with the risk of technique failure, and therefore combinations of profitable practices are suggested.

## Supporting information

**S1 Table. Early and late technique failure. Bivariate Cox and Fine and Gray analyses.** Early technique failure is defining as occurring earlier than 3 months after the starting of PD. Late technique failure is defining as occurring later than 3 months after the starting of PD. Cs-HR: Cause specific hazard ratio; sd-HR: sub distribution hazard ratio; p: global p-value; GN: Glomerulonephritis; TIN: tubulointerstitial nephritis; ADPKD: autosomic dominant polycystic disease; CCI: Charlson comorbidity index,  $\omega$ :  $p < 0.2$ ;  $\omega\omega$ :  $p < 0.05$ . (DOCX)

**S2 Table. Composite outcome of technique failure and mortality bivariate Cox and Fine and Gray analyses.** Cs-HR: Cause specific hazard ratio; sd-HR: sub distribution hazard ratio; GN: Glomerulonephritis; TIN: tubulointerstitial nephritis; ADPKD: autosomic dominant polycystic disease; CCI: Charlson comorbidity index,  $\omega$ :  $p < 0.2$ ;  $\omega\omega$ :  $p < 0.05$ . (DOCX)

**S3 Table. Validation analysis. Bivariate Cox and Fine and Gray analysis for technique failure according to practices.** Hosp: hospital, CAPD: Continuous Ambulatory Peritoneal Dialysis. APD: Automated Peritoneal Dialysis.  $\omega$ : p-value  $< 0.05$ . (DOCX)

**S1 Fig. Geometrical representation of a centre in the three-dimensional geographic space (A), and in the virtual space of practices (B).** In the geographical space, the dimensions are  $e_x$ ,  $e_y$ , and  $e_z$ , corresponding to the longitude, latitude and altitude. In the space of practices,  $e_1$  may be the use of prophylactic antibiotic prior to catheter insertion,  $e_2$  the type of catheter placed in the center, and each  $e_i$  a given practice. In this space of n-dimension, a metric is built and distances between centers are computed, allowing to gathering the centers according to their proximity in term of practice. (TIF)

**S2 Fig. Association between covariates and early technique failure (prior to 3 months after the starting of PD). Results of the multivariate Cox model (A), and Fine and Gray model (B).** The classes of references are: female for the sex, 2–3 for the modified Charlson comorbidity index, and cluster number 1 for the clusters of centers. CCI: modified Charlson Comorbidity Index, cs-HR: cause specific hazard-ratio, 95%CI: 95% confidence interval, sd-HR: subdistribution specific hazard-ratio. (PDF)

**S3 Fig. Association between covariates and late technique failure (later than 3 months after the starting of PD). Results of the multivariate Cox model (A), and Fine and Gray model (B).** The classes of references are: diabetic nephropathy for the nephropathy, female for the sex, 18–39 years old for the age, and cluster number 1 for the clusters of centers. GN: glomerulopathy, TIN: tubulo interstitial nephropathy, ADPKD: Autosomic dominant polycystic kidney disease, cs-HR: cause specific hazard-ratio, 95%CI: 95% confidence interval, sd-HR: subdistribution specific hazard-ratio. (PDF)

**S4 Fig. Association between covariates and composite outcome of technique failure and mortality. Results of the multivariate Cox model (A), and Fine and Gray model (B).** The classes of references are: female for the sex, 18–39 years old for the age, diabetic nephropathy for the nephropathy, 2–3 for the modified Charlson comorbidity index, and cluster number 1 for the clusters of centers. GN: glomerulopathy, TIN: tubulo interstitial nephropathy, ADPKD: Autosomic dominant polycystic kidney disease, CCI: modified Charlson Comorbidity Index, cs-HR: cause specific hazard-ratio, 95%CI: 95% confidence interval, sd-HR: subdistribution specific hazard-ratio.

(PDF)

**S5 Fig. Association between covariates and peritonitis. Results of the multivariate Cox model (A) and Fine and Gray model (B).** The classes of references are: female for the sex, 18–39 years old for the age, 2–3 for the CCI, and cluster number 1 for the clusters of centers. CCI: modified Charlson Comorbidity Index, cs-HR: cause specific hazard-ratio, 95%CI: 95% confidence interval, sd-HR: subdistribution specific hazard-ratio.

(PDF)

**S6 Fig. Association between covariates and technique failure due to peritonitis. Results of the multivariate Fine and Gray model.** The classes of references are cluster number 1 for the clusters of centers. CCI: modified Charlson Comorbidity Index, cs-HR: cause specific hazard-ratio, 95%CI: 95% confidence interval, sd-HR: subdistribution specific hazard-ratio.

(PDF)

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**Validation:** Clemence Bechade, Christian Verger, Emmanuel Fabre, Isabelle Vernier, Thierry Lobbedez.

**Visualization:** Antoine Lanot.

**Writing – original draft:** Antoine Lanot.

**Writing – review & editing:** Antoine Lanot.

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## IV.5. Discussion

Au cours de ce travail, nous avons exploré les pratiques de soins liées au cathéter en dialyse péritonéale, et leur influence sur le risque de transfert en hémodialyse. Nous avons utilisé une méthode de classification ascendante hiérarchique qui n'avait jamais été utilisée en dialyse à notre connaissance, et qui offre l'avantage de ne pas émettre d'hypothèse a priori sur l'effet des pratiques.

Nous avons mis en évidence l'hétérogénéité des pratiques de soins liées au cathéter de dialyse péritonéale dans les 64 centres français participant au module « cathéter » du RDPLF. Cinq groupes ou clusters de centres ont été constitués au sein desquels il existait une homogénéité de pratiques. Les possibilités de protocoles de soins en dialyse péritonéale sont nombreuses. Des essais cliniques randomisés multicentriques devraient permettre de qualifier les pratiques les plus bénéfiques aux patients afin de s'affranchir des effets des nombreux facteurs confondants. Malheureusement, peu d'essais de ce type sont actuellement disponibles et il paraît illusoire d'espérer que de tels essais puissent être réalisés pour chacune des pratiques de soins disponibles. Les interactions à prendre en compte entre ces pratiques sont encore plus nombreuses, et l'effet de ses interactions pourrait être synergique. La méthode de classification hiérarchique ascendante que nous avons utilisé pour la constitution de clusters de centres a rendu possible la détection d'ensemble de pratiques appliquées en pratique courante dans les centres de dialyse péritonéale. Cette méthode guidée par les données prend ainsi en compte les interactions des pratiques qui sont effectivement associées sans avoir fait d'hypothèse a priori.

A notre connaissance, seules deux études ont été menées en néphrologie qui mettaient à profit des méthodes de classification ascendante hiérarchique. Ces travaux cliniques ont fait l'analyse de caractéristiques cliniques, biologiques ou histologiques de

patients afin de préciser des classifications nosologiques estimées imparfaites dans le champs de la maladie glomérulaire [39], [40]. A notre connaissance, c'est la première fois qu'une approche de classification des pratiques de soins est proposée, et la recherche d'association avec un évènement clinique d'intérêt. Notre démarche se voit validée par le fait qu'un cluster de centres a été identifié dans lequel la survie technique de la dialyse péritonéale des patients était significativement plus longue.

Dans une analyse de survie multiniveaux, nous avons mis en évidence qu'il existait un effet centre tel que les patients des centres dont l'effet aléatoire était supérieur à un écart-type avaient un risque relatif de transfert en hémodialyse estimé à 1,36. La prise en compte dans le modèle multiniveaux des covariables individuelles et de l'appartenance à un cluster donné entraînait une diminution de 26 % de la variance de l'effet centre. Il est donc probant que des covariables spécifiques des centres ne sont pas mesurées dans nos modèles.

Ces résultats demanderaient à être consolidé avec la mise en œuvre d'un essai randomisé multicentrique dans lequel on comparerait plusieurs groupes de pratiques définies selon celles des différents clusters mis en évidence et/ou selon les recommandations édictées par les différentes sociétés savantes.



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## **V. PRATIQUES EDUCATIONNELLES EN DIALYSE PERITONEALE ET RISQUE D'INFECTION DU LIQUIDE DE DIALYSE**

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### **V.1 Introduction**

La dialyse péritonéale requiert un investissement particulier des patients ou de leurs proches qui deviennent acteurs de premier plan de leur prise en charge, a fortiori quand les soins sont réalisés sans l'intervention d'un infirmier au domicile. Cette situation d'autonomie est rendue possible après une période d'apprentissage de la réalisation des soins qui est proposée au sein des centres de dialyse. Cet apprentissage est déterminant, car la dialyse est un soin technique qui met en jeu des dispositifs technologiques parfois complexes.

Parmi les causes répertoriées d'arrêt de la dialyse péritonéale, l'infection péritonéale figure en tête de liste selon plusieurs études [22], [41], [42]. En outre, une proportion importante de ces infections péritonéales est liée à des germes manuportés, dont le respect des règles d'asepsie lors des manipulations devrait prémunir [43]. L'apprentissage de la réalisation des échanges de manière aseptique est un des items majeurs de la formation aux soins en dialyse péritonéale, afin de limiter le risque d'infection péritonéale [44].

Après avoir examiné la répartition des pratiques de soins liées aux cathéters et leur effet sur le risque de transfert en hémodialyse, nous nous sommes posé la question de l'impact des modalités d'apprentissage de la réalisation de la dialyse péritonéale chez les patients qui n'étaient pas assistés d'un infirmier.

La formation de patients (ou de leurs proches) adultes atteints d'IRCT doit être adaptée à plusieurs spécificités afin d'être efficace [45].

L'apprentissage de sujets adultes est plus efficace quand il suit les principes de l'andragogie, concept développé par Malcolm Knowles à partir des années 1950. Les piliers de ce mode d'apprentissage sont : la reconnaissance de l'autonomie des adultes, l'apprentissage basé sur les expériences et les erreurs, la pertinence de l'apprentissage, son côté pragmatique, le respect des apprenants, et l'orientation du contenu vers des résolutions de problèmes plutôt que l'apprentissage de protocoles [46].

Des supports de plusieurs natures sont utilisés dans la plupart des centres pour la formation des patients à la dialyse péritonéale : livrets, photos, films, simulation à la manipulation. Ces supports sont produits localement et leur contenu est varié. La production et l'utilisation de ces supports ne font pas l'objet de protocoles standardisés. Il a été montré que les patients atteints d'IRCT ont en moyenne un niveau d'éducation plus bas que celui de la population générale, et qu'ils sont plus fréquemment porteurs de troubles cognitifs [47], [48]. Les supports andragogiques doivent être adaptés à ces spécificités.

Nous avons cherché à caractériser l'effet de l'utilisation de différents supports pour l'apprentissage des soins de dialyse péritonéale dans la population des patients autonomes ou assistés d'un proche. L'évènement d'intérêt était le nombre d'infections péritonéales présenté par patient.

## V.2. Outils statistiques et méthodologie

Nous avons extrait les données du module « infirmier » du RDPLF. Quatre-vingt-quatorze centres participaient à ce module optionnel, et les patients assistés d'un infirmier pour la réalisation des soins de dialyse péritonéale étaient exclus.

### V.2.1. Modèle de comptage de hurdle

A la différence de l'évènement « transfert en hémodialyse », l'évènement « infection péritonéale » est susceptible de survenir plusieurs fois chez un même patient au cours du temps de suivi. La survie sans infection péritonéale est un évènement d'analyse pertinent, mais la répétition éventuelle des infections péritonéales est également digne d'intérêt. Nous avons donc cherché à prendre en compte ces deux aspects. La survie sans infection péritonéale peut-être évaluée à l'aide de modèles de survie tels que ceux de Cox ou Fine Gray précédemment utilisés dans nos travaux, mais cette modélisation ne rend pas compte de la répétition éventuelle des infections. Le décompte des infections présentées pour chaque patient est un processus classiquement analysé par un modèle de régression de Poisson. Deux hypothèses doivent être respectées pour l'utilisation licite d'un tel modèle : la première est que le nombre de patients n'ayant présenté aucun évènement ne soit pas surreprésenté, et la seconde est que la variance du nombre de répétitions des évènements soit égale à la moyenne. Ces deux hypothèses n'étaient pas vérifiées par nos données sur lesquelles nous avons constaté une surdispersion des non-zéros et un excès de zéros, aussi nous avons mis en place un autre type de modélisation.

Afin de surmonter les limites du modèle classique de Poisson, plusieurs solutions ont été développées pour modéliser les données de comptage. Dans les situations d'excès avec de zéros, l'utilisation de modèles ZIP (Zero Inflated Poisson) ou de modèles de hurdle de type Poisson est appropriée. En cas de surdispersion des non-zéros ajoutée à l'excès de zéros, un modèle ZINB (Zero Inflated Negative Binomial) ou un modèle de hurdle de type négatif binomial sont les mieux adaptés [49]. Les modèles « Zero Inflated » prennent en compte deux types de zéros : structureaux et d'échantillonnage, alors que les modèles de hurdle considèrent tous les zéros comme étant structurels [50]. Ce dernier cas correspondait à notre situation, et nous avons donc choisi de concevoir un modèle de hurdle négatif binomial.

Le modèle de hurdle ou modèle à barrière (*hurdle model*) est construit en deux parties : une partie « zéro » censurée à droite, dans laquelle est modélisé le risque de ne présenter aucun épisode d'infection, et une partie « compte » tronquée à gauche, qui modélise le nombre d'infections chez les patients qui en ont présenté au moins une (la barrière d'une première infection est franchie) [51]. Le principe du modèle est qu'en l'absence de survenue de l'évènement d'intérêt, la barrière (*hurdle*) de la partie de comptage tronquée à gauche n'est pas franchie, et alors la valeur zéro est observée. Sinon, la barrière du premier évènement est franchie et la partie comptage donne le nombre d'occurrence de la variable d'intérêt. Littéralement, pour la réalisation de la variable aléatoire  $Y_i$  associée à l'évènement « infection péritonéale », la fonction de masse de probabilité du modèle peut être définie ainsi pour le sujet  $i$  :

$$\Pr(y_i = j) = \begin{cases} \pi_i & \text{si } j = 0 \\ \frac{1 - \pi_i}{1 - g_i(0)} \cdot g_i(j) & \text{si } j > 0 \end{cases}$$

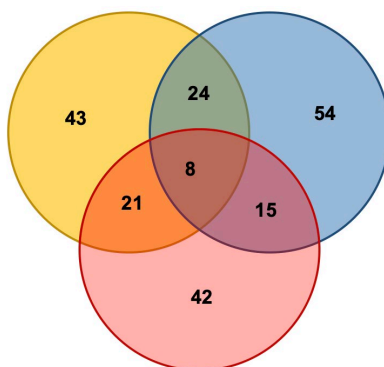
Avec  $\pi_i$  la probabilité de ne présenter aucune infection durant la période de suivi, qui suit une loi binomiale, et  $g_i$  la fonction de distribution du comptage chez les patients ayant présenté au moins une infection qui suit une loi négative binomiale tronquée à gauche en zéro. Le package *pcs/* permet d'implémenter ces modèles dans R [52].

La survie sans péritonite a également été modélisée à l'aide d'un modèle de Cox, dans le but de préciser les résultats de la partie zéro du modèle de hurdle.

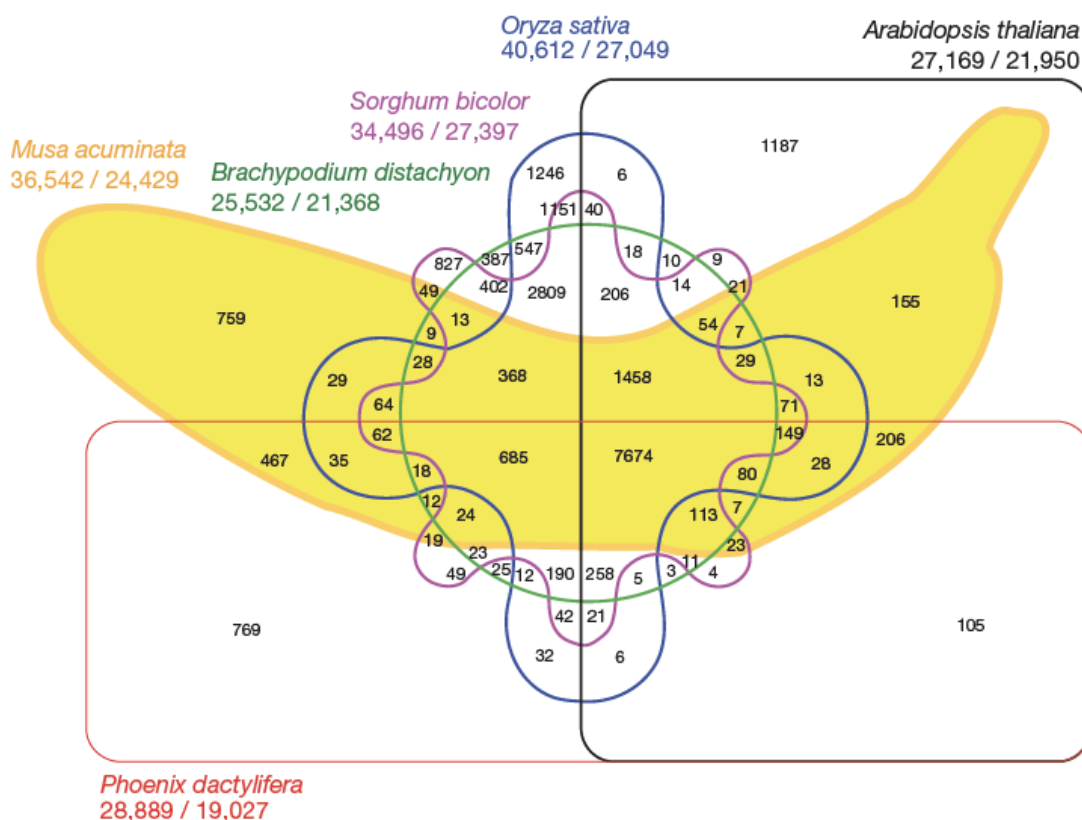
### **V.2.2. Visualisation de données : diagramme UpSet**

Les données extraites dont nous disposions comportaient sept covariables catégorielles relatives à l'utilisation de pratiques éducationnelles. Dans l'analyse univariée des données, nous avons souhaité décrire la distribution des pratiques éducationnelles, ainsi que la distribution de leurs intersections. La visualisation de ce type de résultats est habituellement proposée à l'aide d'un diagramme d'Euler, du nom du génial mathématicien suisse qui les introduisit au XVIII<sup>èm</sup> siècle. Dans ce type de diagramme et dans sa version adaptée dite de Venn, des formes plus ou moins circulaires représentent les ensembles et leurs intersections (figure 8a). L'information est lisible de manière intuitive pour trois ou quatre ensembles mais quand le nombre des ensembles représentés augmente, l'information devient rapidement confuse en raison du nombre d'intersections dont l'augmentation est exponentielle. En effet, le nombre d'intersections potentielles de  $N$  ensembles est  $2^N$ . Dans l'exemple du diagramme de Venn du génome de la banane moderne (figure 8b), 64 intersections sont représentées, et la taille des intersections n'est plus corrélée à la taille des effectifs représentés.

Figure 8. Diagrammes de Venn. 8a. Diagramme de Venn « classique » à 3 groupes.



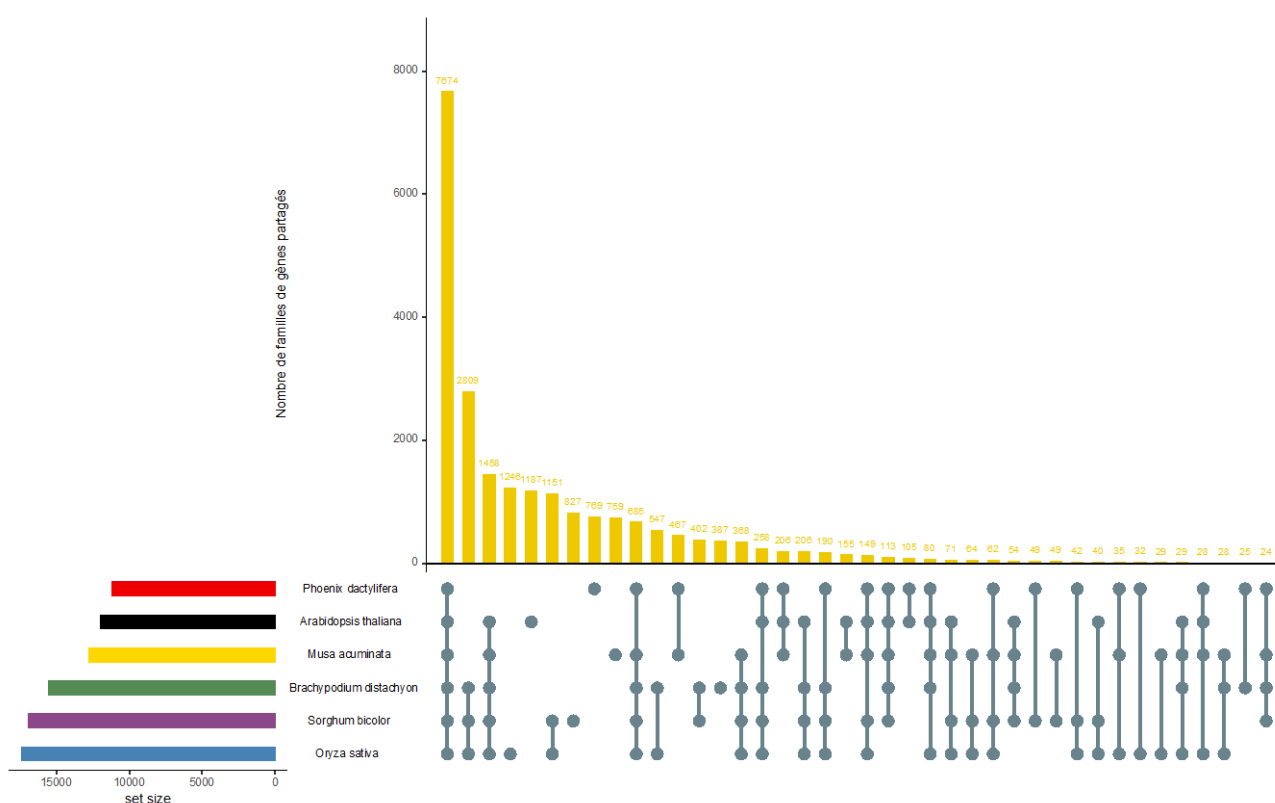
8b. Diagramme de Venn : distribution des familles de gènes issus de différentes variétés, partagés dans la banane moderne. D'après [53].



Une façon simple et astucieuse de représenter les effectifs de plusieurs ensembles et de leurs intersections a été proposée en 2014 par une équipe de chercheurs de Harvard

dans le but d'améliorer la lisibilité [Lex, IEEE 2014]. Les diagrammes UpSet sont constitués d'une matrice dont chaque ligne est rattachée à un des ensembles étudiés, et dont chaque colonne porte l'information 0 ou 1 figurée par un point coloré définissant ainsi un agrégat d'ensembles. Un barplot supérieur permet la visualisation des effectifs de chaque agrégat d'ensemble, et un barplot latéral dans lequel chaque barre correspond à l'effectif des ensembles considérés. Un package R est disponible pour la création de diagramme UpSet [54] (Figure 9).

**Figure 9 : Diagramme UpSet de la distribution des familles de gènes issus de différentes variétés, partagés dans la banane moderne. D'après les données de [53].**



## V.3. Article 2

Bonnal H, Béchade C, Boyer A, Lobbedez T, Guillouët S, Verger C, Ficheux M, Lanot A.  
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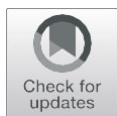
Baxter academy, en route vers l'expertise.

« *Information pré-dialyse et éducation thérapeutique en dialyse péritonéale* »




RESEARCH ARTICLE

Open Access



## Effects of educational practices on the peritonitis risk in peritoneal dialysis: a retrospective cohort study with data from the French peritoneal Dialysis registry (RDPLF)

Hélène Bonnal<sup>1,2</sup>, Clémence Bechade<sup>1,2</sup>, Annabel Boyer<sup>1,2</sup>, Thierry Lobbedez<sup>1,3</sup>, Sonia Guillouët<sup>1</sup>, Christian Verger<sup>3</sup>, Maxence Ficheux<sup>1</sup> and Antoine Lanot<sup>1,2\*</sup> 

### Abstract

**Background:** Peritoneal dialysis (PD) is a home-based therapy performed by patients or their relatives in numerous cases, and the role of patients' educational practices in the risk of peritonitis is not well assessed. Our aim was to evaluate the effect of PD learning methods on the risk of peritonitis.

**Methods:** This was a retrospective multicentric study based on data from a French registry. All incident adults assisted by family or autonomous for PD exchanges in France between 2012 and 2015 were included. The event of interest was the occurrence of peritonitis. Cox and hurdle regression models were used for statistical analysis to assess for the survival free of peritonitis, and the risk of first and subsequent peritonitis.

**Results:** 1035 patients were included. 967 (93%) received education from a specialized nurse. Written support was used for the PD learning in 907 (87%) patients, audio support in 221 (21%) patients, and an evaluation grid was used to assess the comprehension in 625 (60%) patients. In the "zero" part of the hurdle model, the use of a written support and starting PD learning with hands-on training alone were associated with a lower survival free of peritonitis (respectively HR 1.59, 95%CI 1.01–2.5 and HR 1.94, 95%CI 1.08–3.49), whereas in the "count" part, the use of an audio support and starting of PD learning with hands-on training in combination with theory were associated with a lower risk of presenting further episodes of peritonitis after a first episode (respectively HR 0.55, 95%CI 0.31–0.98 and HR 0.57, 95%CI 0.33–0.96).

**Conclusions:** The various PD education modalities were associated with differences in the risk of peritonitis. Prospective randomized trials are necessary to confirm causal effect. Caregivers should assess the patient's preferred learning style and their literacy level and adjust the PD learning method to each individual.

**Keywords:** Educational practices, Health literacy, Patient education, Peritoneal dialysis, Peritonitis

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## ABBREVIATIONS

PD: Peritoneal dialysis  
 CCI: Charlson comorbidity index  
 RDPLF: French Peritoneal Dialysis Registry  
 BMI: Body mass index  
 CAPD: Continuous ambulatory peritoneal dialysis  
 APD: Automated peritoneal dialysis

## Background

It is now well demonstrated that peritoneal dialysis (PD) delivers a high-quality treatment to patients presenting with end-stage renal disease. The survival of patients treated by PD is equivalent to the survival of those treated by hemodialysis, and several authors have shown that the technique is well tolerated and cost effective [1–3]. However, PD remains underused in several countries [4]. Peritonitis is a major cause of technique failure, and is one of the predominant factors limiting the extensive use of PD [5, 6]. The rate of peritonitis is highly variable worldwide, and within countries [7–9]. The risk of peritonitis depends on non-modifiable factors (age, sex, diabetes) and modifiable factors (anti-infectious prophylaxis, catheter care, assistance for PD) [10, 11]. It is important to accurately analyze the effect of modifiable factors, since they are the most relevant to decreasing the rate of peritonitis [12]. To our knowledge, there is a lack of data regarding the role of patients' educational practices in the peritonitis risk [13]. Recommendations for PD training were proposed by the ISPD in 2016, but the adherence to these guidelines is probably far from optimal in France and worldwide [3, 14]. The objective of our study was to describe the educational practices proposed to French patients treated by PD and to evaluate the effect of these currently applied educational practices on the risk of peritonitis.

## Methods

This was an observational retrospective study using data from the French Language Peritoneal Dialysis Registry (RDPLF). The registry includes several optional moduli, one of which is the “nurses' practices” modulus. Out of the 167 centers registered in the RDPLF, 94 participated to the “nurses' practices” modulus. All patients registered in the “nurses' practices” modulus of the RDPLF, starting PD between January 1, 2012 and December 31, 2015 were included in the study. The end of the observation period was December 31, 2016. Exclusion criteria were: assistance by nurse for PD exchanges, because the aim of the study was to assess the effect of educational practices dedicated to patients or their relatives, and age younger than 18 years when starting PD.

### Definition of variables

#### *Individual characteristics*

Age at PD initiation, the number of new patients per year

per center, sex, body mass index (BMI), diabetes mellitus, the causal nephropathy, the presence of illiteracy learning disability, manual disability, hearing or visual impairment were extracted from the registry. Comorbidities were assessed by calculating a modified Charlson score, which is the Charlson score after subtracting the age sub score, to evaluate the role of the comorbidities independently of the patient's age.

#### *Characteristics of centers and treatments*

PD modality (continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD)), PD assistance (self-PD or family assisted PD), a previous treatment before PD initiation (hemodialysis, renal transplantation or no replacement therapy), and the administrative type of center (non-profit, general, university or private hospital) in which the patient was treated were listed.

#### *Educational practices*

Data about the educational practices used during the learning of PD of the patients were retrieved: the timing of the education regarding the catheter placement, whether the education had been provided by a nurse specialized in PD, the use of audio or written support for PD learning which was respectively an audio file, or a printed booklet given to the patient to learn about, the assessment of the patients' knowledge and skills concerning PD with an evaluation grid, defined as a standard list of items used for assessment of the patients' knowledge and skills concerning PD prior or after the learning courses (of note, standardized within each center but not between all centers), the use of standard theoretical courses or adapted theoretical courses (adapted to the presumed preferred learning style of patients), and the start of learning with theory or with hands-on training.

#### *Events of interest*

The number of peritonitis for each patient was retrieved, with the declared cause, and the responsible germs.

#### *Statistical analysis*

Categorical variables were described by proportion and percentage, and continuous variables were described by their median value and first and third quartile. Overlapping of different educational practices were presented using an upset diagram [15].

All statistical models were performed at the individual levels. The event of interest was the first peritoneal infection after the start of PD. A survival analysis with a Cox proportional hazard model was assessed, to estimate the association between the covariates and the risk of first peritonitis. The proportional hazard assumption was tested graphically by inspection of the Schoenfeld

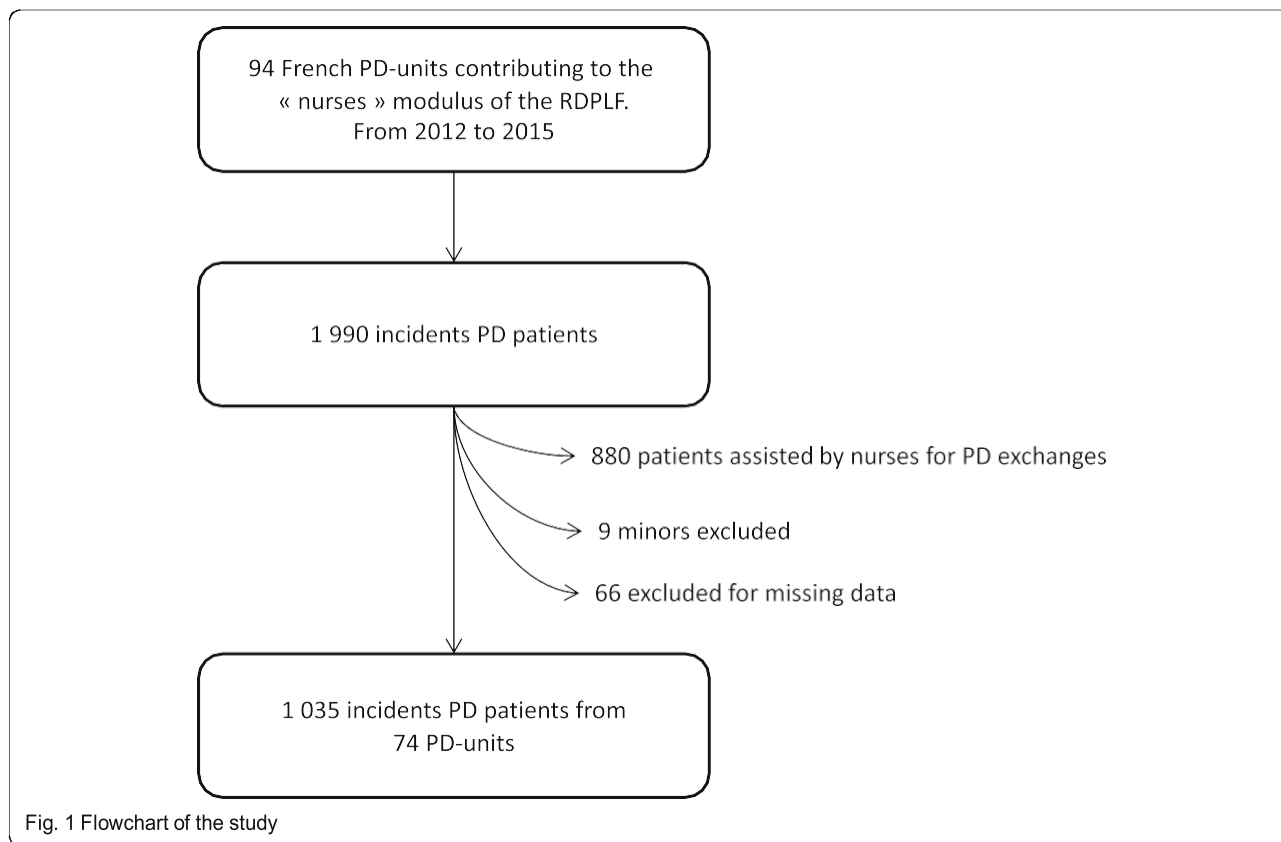


Fig. 1 Flowchart of the study

residual plots. The Cox model allows the assessment of the survival free of peritonitis, but does not consider the risks of multiples peritonitis cases. A classic Poisson regression model is commonly used to analyze count data, but it assumes that the number of patients with zero event is not overrepresented and that the variance of the distribution of the number of peritonitis cases is equal to the mean. Whenever these assumptions are violated, alternative models should be considered. Therefore, we used a hurdle model, which is built with two parts: a “zero count” rate ratio modeling the risk of presenting one peritonitis during the follow-up period, and a “count” rate ratio modeling the number of peritonitis during the follow-up period for the patients who have had a first episode. The exposure time to PD was used as an offset in both parts of the hurdle model.

Covariates associated with the risk of first peritonitis with  $p < 0.2$  in a bivariate analysis were entered in the multivariate analysis, and educational practices were entered a priori since they were the covariates of interest. The existence of collinearity between covariates was assessed by the generalized variance inflation factor.

In a sensitivity analysis, we assessed survival models focusing on the peritonitis due to handled germs (cocci Gram positive germs excluding *Enterococcus* and *Streptococcus agalactiae*), because this type of peritonitis

is mainly due to contamination while handling PD fluid exchange, and therefore, good education should be associated with a lower risk.

To describe the distribution of the different practices in the centers, we arbitrarily chose a cut-off of 75% to decide whether a practice was standardized or not in the PD center. In other words, whenever a practice was used in more than 75% of the registered cases of the center, the practice was estimated standardized in the center. This value of 75% was chosen because it was estimated sufficient to make sure that whenever a practice was used 75% or more of the time in a given center, it would not be due to chance, but it would be a standard practice of the center. In the center-level analysis (and only in this analysis), 22 centers were excluded because fewer than 5 patients were registered. The center-level analysis was strictly descriptive, and no statistical tests were performed at the center-level.

Fewer than 10% of the data were missing in the dataset. Therefore, we performed a complete case analysis.

Statistical analyses were performed with R 3.5.1 (R foundation for statistical computing) including the survival and lme4 packages.

The RDPLF has the approval of the French National Ethics Committee (*Commission nationale de l'informatique et des libertés*) with the agreement number 542668.

Table 1 Population's characteristics

	All patients (N = 1035)	
Covariates	Median (IQR)	
Age at PD initiation (years)	59 (45–69)	
BMI (kg/m <sup>2</sup> )	25 (22–28)	
	N	%
Sex (Male)	667	64
Diabetes	242	23
Nephropathy		
Polycystic kidney disease	124	12
Glomerulonephritis	227	22
Systemic disease	44	4
Diabetic nephropathy	129	12
Interstitial nephritis	60	6
Vascular	198	19
Uropathy	32	3
Other cause	100	10
Unknown	121	12
Previous treatment		
No RRT	770	74
Hemodialysis	197	19
Transplantation	19	7
PD modality (APD)	628	61
Modality of PD assistance		
Self PD	937	91
Family assisted PD	98	9
Type of center		
General hospital	487	47
Non profit	260	25
University hospital	181	17
Private	107	10
Charlson's score		
< 3	487	47
3	173	17
4	130	13
> 4	245	24
Functional impairment		
No impairment	857	83
Hearing impairment	41	4
Visual impairment	126	12
Hearing and visual impairment	11	1
Manual disability	46	4
Illiteracy	14	1
Learning disability	145	14

IQR Inter-quartile range, PD Peritoneal dialysis, BMI Body mass index, APD Automated peritoneal dialysis

and fulfills the GDPR requests. This study took place within the framework of this authorization. In the extracted dataset, information was anonymized by the RDPLF.

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [16].

## Results

During the study period, there were 1990 incident PD patients registered in the “nurses’ practices” modulus of the RDPLF, in 94 PD-units. A total of 880 patients were assisted by a nurse for PD exchange and were therefore excluded. Nine patients were excluded because they were under 18 years of age, and 66 were excluded because of missing data. Finally, data concerning 1035 patients from 74 PD units were analyzed (Fig. 1). The median follow-up time was 15.2 months. At the center level, the median number of incident PD patients per year was 5.6 (interquartile range (IQR) 3.4–9.4).

### Univariate analysis

#### Study population

The median age was 59 (IQR 45–69), and 667 (64%) patients were male. Of the 1305 patients included, 937 (91%) were autonomous and a family caregiver assisted 98 (9%) patients. The three main causes of nephropathy were glomerulonephritis in 227 (22%) patients, vascular nephropathy in 198 (19%) patients, and diabetic nephropathy in 129 (12%) patients. Two hundred and forty-two (23%) patients were diabetic. The median BMI was 25 kg/m<sup>2</sup> (IQR 22–28). Seven hundred and seventy (74%) patients were treated with neither dialysis nor renal transplantation before the PD initiation. One hundred and seventy-eight (17%) patients presented deafness and/or visual impairment, and 145 (14%) patients had learning disability. The characteristics of the population are displayed in (Table 1).

#### Educational practices

PD education was performed before catheter placement in 988 (95%) patients, and PD education was provided by a specialized nurse in 967 (93%) patients. The use of written support was widely spread in 907 (88%) patients. Theory and hands-on training were proposed simultaneously to start PD education in 666 (64%) patients. The distribution of educational practices at the patient's level is synthesized in (Table 2).

Table 2 also shows the distribution of educational practices standardly used at the center level (Table 2). A nurse specialized in PD provided the PD education to patients in every center. A written support was

Table 2 Distribution of educational practices at the patient's level and at the center's level

Covariates		All patients (N = 1035)		Number of centers (N = 53)	
				Practice used in more than 75% of cases in the center	
		N	%	N	%
Delay between education and catheter placement	More than 30 days prior	335	32.37	2	3.77
	Within 30 days	653	63.09	17	32.07
	After catheter placement	47	4.54	0	0
Education provided by specialized nurse	Yes	967	93.43	48	90.57
	No	68	6.57	1	1.89
Use of a written support	Yes	907	87.63	42	79.25
	No	128	12.37	3	5.66
Use of an evaluation grid	Yes	625	60.39	26	49.06
	No	410	39.61	16	30.19
Use of an audio support	Yes	221	21.35	2	3.77
	No	814	78.65	40	75.47
Theory learning	No	14	1.35	0	0
	Standardized	47	4.54	0	0
	Adapted	974	94.11	47	88.67
Education started with	Theory	269	25.99	5	9.43
	hands-on training	100	9.66	1	1.88
	Both hands-on training and theory	666	64.35	25	47.17

A practice was arbitrarily defined as standardized in a given center if the practice was used in more than 75% of the registered cases of the center

standardly used in 42 (79%) centers. Only two (4%) centers used an audio support during the PD education of their patients. The more frequent association pattern of educational practices was the use of an evaluation grid, use of a written support, learning provided by a PD-specialized nurse, starting with adapted theory and hands-on training, and learning started within a month prior to catheter placement. The frequencies of these associations are depicted on the (Fig. 2).

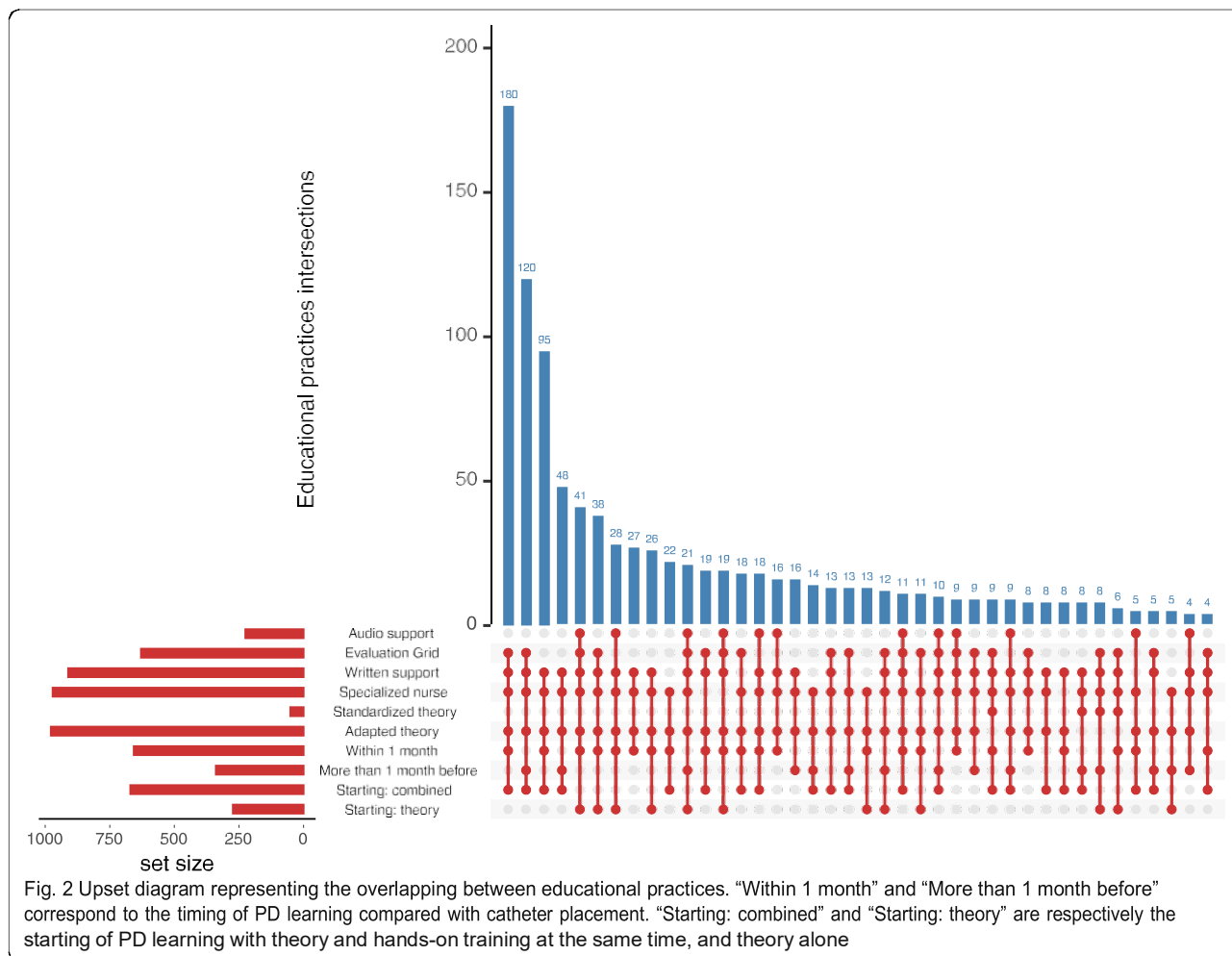
#### Characteristics of the peritonitis

There were 565 episodes of peritonitis occurring in 339 patients. The peritonitis rate during the study period was 0.34 episodes per patient per year at risk. One hundred and sixty-three (48%) peritonitis were due to Gram-positive cocci, and 80 (24%) were due to Gram-negative bacilli. Causes were registered for the first peritonitis only. The major registered cause was asepsis mistake in 108 (31.86%) cases of peritonitis, endogenous contamination in 47 (13.86%) cases, tunnel infection in 11 (3.24%) cases, mechanical issue in 11 (3.24%) cases, and unknown in 145 (42.77%) cases. Table 3 synthesizes the characteristics of peritonitis (Table 3). The proportions of peritonitis according to the educational practices are presented in Table 4, according to the number of peritonitis: 0, one or more than two (Table 4).

#### Cox model

##### Bivariate analysis

The results of the bivariate Cox model are shown in additional material (Additional file 1). The patient specific covariates that were significantly associated with the risk of peritonitis were: having a BMI between 25 and 30 kg/m<sup>2</sup> (HR 1.37, 95%CI 1.08–1.74), and between 30 and 35 kg/m<sup>2</sup> (HR 1.56, 95%CI 1.10–2.22) compared to the class of reference 18 to 25 kg/m<sup>2</sup>, having been treated with hemodialysis prior to PD compared to patients naive of prior extra renal epuration treatment (HR 1.48, 95%CI 1.15–1.91), a modified Charlson's score equal to 3 compared with a score of 2 as the reference (HR 1.38, 95%CI 1.04–1.83), and starting PD learning with hands-on training alone or in combination with theory (respectively HR 1.51, 95%CI 1.02–2.23 and HR 1.29, 95%CI 1.00–1.68). No significant association was retrieved between the risk of peritonitis and the other educational practices tested. The Kaplan Meier curve for peritonitis free survival is shown in (Fig. 3).



**Multivariate analysis**

The results of the Cox multivariate model are shown in (Fig. 4). Baselines covariates associated with a protective effect against peritonitis were being treated in a PD unit with ten or more incident patients per year (HR 0.55, 95%CI 0.36–0.84), presence of a hearing impairment (HR 0.35, 95%CI 0.16–0.75). Some other covariates were associated with a higher risk of peritonitis: BMI comprised between 25 and 30 kg/m<sup>2</sup> (HR1.37, 95%CI 1.07–1.75) or 30 and 35 kg/ m<sup>2</sup> (HR 1.51, 95%CI 1.06–2.17), having been treated with hemodialysis prior to PD (HR 1.58, 95%CI 1.21–2.05), and presenting a learning disability (HR 1.43, 95%CI 1.05–1.95). Two educational variables were significantly associated with a higher risk of peritonitis: use of a written support (HR 1.44, 95%CI 1.01–2.06) and starting education with hands- on training alone or combined with theory (respectively HR 1.6 95%CI 1.04–2.46 and HR 1.34, 95%CI 1.02–2.46).

**Hurdle model**

**Bivariate analysis**

In the “count” part of the hurdle model, starting PD between 30 and 49 years of age or between 50 and 64

years of age were associated with a higher risk of having further peritonitis after a first episode (respectively HR 5.13, 95%CI 1.36–19.33, and HR 4.39, 95%CI 1.18–16.40). On the other hand, being treated in a center with ten or more new patients per year (HR 0.36, 95%CI 0.14–0.97), having a BMI greater than 35 kg/m<sup>2</sup> (HR 0.04, 95%CI 0–0.37), and starting PD learning with theory and hands-on training concomitantly were protective (HR 0.36, 95%CI 0.14–0.92).

In the “zero” part of the hurdle model, male sex (HR 1.26, 95%CI 1.00–1.58), a BMI between 25 and 30 or between 30 and 35 kg/m<sup>2</sup> (respectively HR 1.34, 95%CI 1.05–1.71, and HR 1.59, 95%CI 1.11–2.27), previous treatment by hemodialysis (HR 1.55, 95%CI 1.19–2.01), a modified Charlson comorbidity index equal to 3 (HR 1.41, 95%CI 1.05–1.89), and starting PD education with hands-on training alone or in combination with theory (respectively HR 1.64, 95%CI 1.01–1.72 and HR 1.32, 95%CI 1.10–2.45) were significantly associated with the risk of presenting a first episode of peritonitis, whereas hearing impairment was protective (HR 0.44, 95%CI 0.21–0.93) (Additional file 2).

Table 3 Characteristics of the peritonitis

	All patients (N = 1315)	
	N	%
Number of peritonitis		
0	702	67.83
1	207	20
2	71	6.86
3	31	3
4	12	1.16
5 or more	12	1.16
Type of germ for first peritonitis		
Gram negative bacilli	80	23.60
Gram positive bacilli	17	5.01
Gram negative Cocci	1	0.29
Gram positive Cocci	163	48.08
Mycobacteria and unknown	78	23.01
Causes for first peritonitis		
Asepsis mistake	108	31.86
Endogenous contamination	47	13.86
Mechanical issue	11	3.24
Tunnel infection	11	3.24
Cat	6	1.77
Nosocomial	3	0.88
Icodextrine	2	0.59
Unknown	151	44.54

### Multivariate analysis

After adjustment in the “count” part of the hurdle model, a BMI greater than 35 kg/m<sup>2</sup> (HR 0.11, 95%CI 0.01–0.96), a previous treatment by hemodialysis (HR 0.11, 95%CI 0.01–0.96), use of an audio support for PD learning (HR 0.55, 95%CI 0.31–0.98) and starting PD education concomitantly with both hands-on training and theory (HR 0.57, 95%CI 0.33–0.96) were protective factors, whereas starting PD between 30 and 49 years of age (HR 3.2, 95%CI 1.07–9.51) was associated with a higher risk of presenting further peritonitis after a first episode (Fig. 5).

In the “zero” part of the multivariate hurdle model, previous treatment by hemodialysis (HR 1.9, 95%CI 1.33–2.73), a modified Charlson comorbidity index equal to 3 (HR 1.62, 95%CI 1.08–2.42), learning disability (HR 1.56, 95%CI 1.03–2.35), use of a written support for PD learning (HR 1.59, 95%CI 1.01–2.5), and starting PD education with hands-on training (HR 1.94, 95%CI 1.08–3.49) were significantly associated with the risk of presenting a first episode of peritonitis, whereas being treated in a center with ten or more new patient per year (HR 0.45, 95%CI 0.26–0.77), and the presence of hearing impairment were protective (HR 0.29; 95%CI 0.12–0.71) (Fig 5).

### Sensitivity analysis

One hundred and fifty-three peritonitis were due to handled germs. The results of the Cox multivariate analysis are shown in (Fig. 4). Starting PD education with hands-on training and theory at the same time was associated with a significantly higher risk of peritonitis due to manipulated germs (HR 1.58, 95%CI 1.02–2.46).

### Discussion

In this large observational study of patients autonomous or assisted by close relatives for PD care, we found that the use of a written support during PD learning and starting PD learning with hands-on training alone were associated with a lower survival free of peritonitis, whereas the use of an audio support and starting of PD learning with hands-on training in combination with theory were associated with a lower risk of presenting further episodes of peritonitis after a first episode.

PD is a home-based therapy; therefore, it is widely known that the patients and caregivers' education is essential to ensure a smooth running of the treatment. The best way to achieve this education is not well defined currently. However, several authors have tried to identify training methods to prevent peritonitis, and some protective factors have been pointed out. In Uruguay, Gadola et al. have shown that a PD education program based on the adult-learning principles was associated with a lower peritonitis rate (0.29 per patient-year vs 0.48 per patient-year with a previous PD education program,  $p < 0.05$ ) [17]. In a study from the Brazilian registry it was demonstrated that a cumulative training time greater than to 15 h was associated with significantly different peritonitis rates (0.26 per year at risk vs 0.32 per year at risk,  $p = 0.01$ ) compared with a cumulative training time of less than 15 h. Less than 1 h of training/day was associated with a higher incidence rate of peritonitis when compared with the intervals of 1–2 h/day ( $p = 0.03$ ). Training in the immediate 10 days after implantation of the catheter was associated with the highest peritonitis rate compared with training prior to catheter implantation (0.32 per year vs 0.28 per year) [18]. The location of PD training could have an impact on peritonitis rates, according to the results from a monocentric Spanish study where the peritonitis incidence decreased from 1 episode /24.5 patient/month to 1 episode /44.4 patient/month after having implemented the training sessions in the patient's home [19]. Hsu et al. demonstrated that a multidisciplinary predialysis education was associated with a longer peritonitis free survival (HR 0.59, 95%CI 0.43–0.81) [20].

Table 4 Proportion of peritonitis according to the different educational practice

Number of peritonitis	0 (N = 943)	1 (N = 236)	2 or more (N = 136)
Timing of education regarding catheter placement			
More than 30 days prior to catheter placement	225 (32%)	65 (31%)	45 (36%)
Within 30 days prior to catheter placement	444 (63%)	132 (64%)	77 (61%)
After catheter placement	33 (5%)	10 (5%)	4 (3%)
Education provider			
Non-specialized nurse	48 (7%)	13 (6%)	7 (6%)
Specialized nurse	654 (93%)	194 (94%)	119 (94%)
Use of written support	609 (87%)	182 (88%)	116 (92%)
Use of an evaluation grid	424 (60%)	125 (60%)	76 (60%)
Use of audio support	156 (22%)	40 (19%)	25 (20%)
Theory learning			
No	10 (1%)	3 (1%)	1 (1%)
Adapted learning	660 (94%)	191 (92%)	123 (98%)
Standardized learning	32 (5%)	13 (6%)	2 (2%)
First step of education			
Theory	194 (28%)	38 (18%)	37 (29%)
Hands-on training	63 (9%)	26 (13%)	11 (9%)
Theory and hands-on training	445 (63%)	143 (69%)	78 (62%)

HR Hazard ratio, 95% CI 95% Confidence interval, PD Peritoneal dialysis, BMI Body mass index, CAPD Continuous ambulatory peritoneal dialysis, APD Automated peritoneal dialysis

Learning PD theory and hands-on training can be challenging for some patients, and the PD learning programs should therefore be adapted to each patient. Several authors have shown that educational factors were associated with PD complications. In a large multicentric Brazilian observational study, Martin et al. showed that the patients' educational level was associated with the risk for survival free of peritonitis (illiteracy versus higher education level: HR 1.75, 95%CI 1.04–2.92, elementary versus higher education level: HR 1.64, 95%CI 1.06–2.54 and secondary versus higher education level: HR 1.57, 95%CI: 0.99–2.49) [21]. An association between lower education level and the risk for peritonitis (HR 1.45 95% CI 1.01–2.06,  $p = 0.0454$ ) was observed in a Taiwanese monocentric study in 2013 [22]. Kim et al. demonstrated similar results in a Korean population, where an education level of middle school or lower (academic year < 9) was associated with a significant risk for peritonitis (HR 1.61, 95%CI 1.10–2.36) [23]. Special attention could therefore be paid to the patients with lower education levels, who may need adapted learning styles. Assessing the knowledge and behavior in 191 Italian PD patients, Russo et al. found out that 47% of patients needed retraining, especially those in the early or late phase of PD therapy [24].

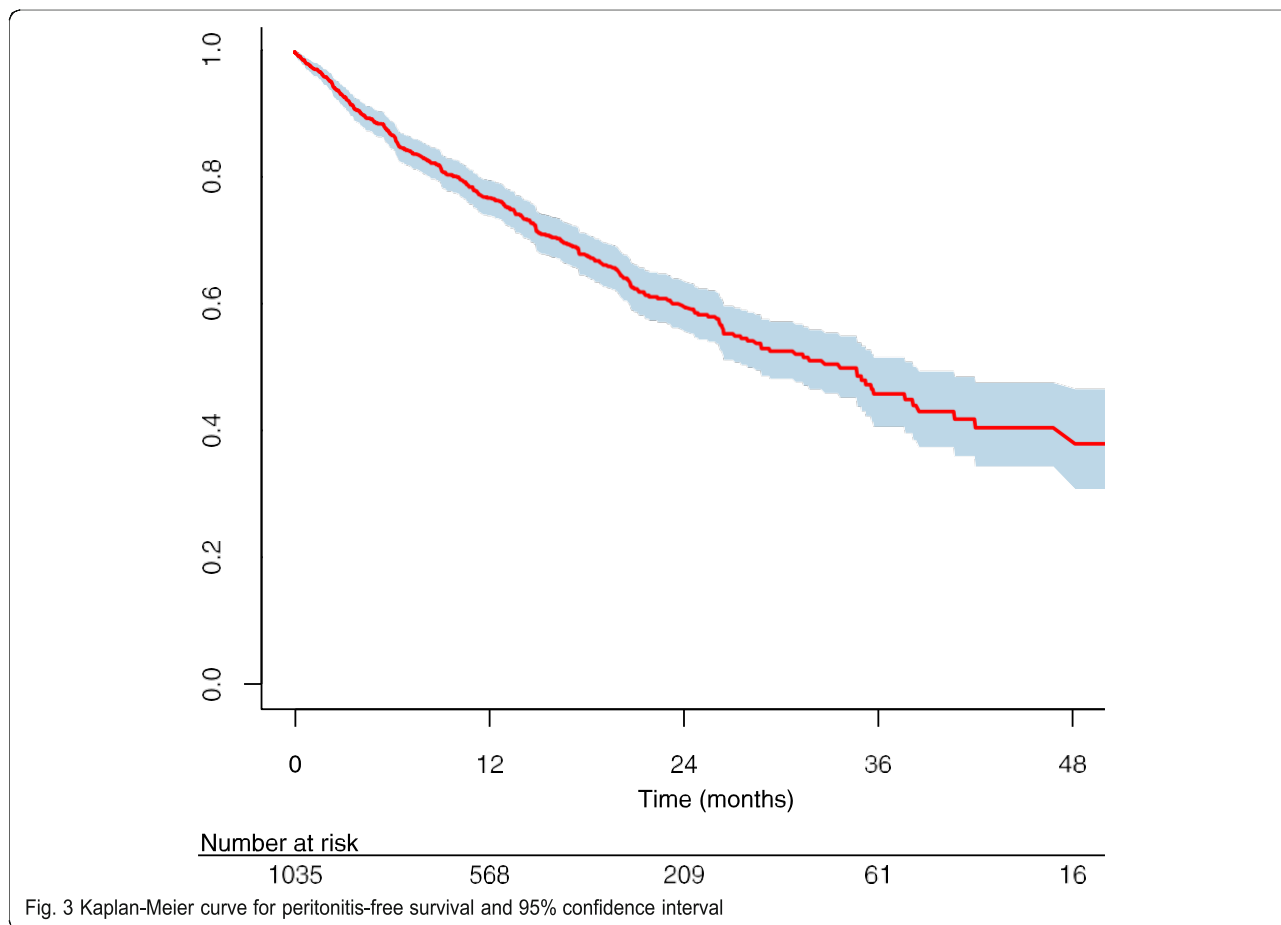
Congruently, we have found with the Cox model and the zero part of the hurdle model that hearing

impairment was associated with a lower risk of presenting a first episode of peritonitis (respectively HR 0.35, 95%CI 0.16–0.75 and HR 0.29, 95%CI 0.12–0.71). One might wonder how a disability could be protective. We make the hypothesis that in subjects with hearing impairments, the PD learning could be better individualized, with better adaptation to the abilities and learning patterns of the subjects. This protective effect however was not found in visual impaired patients, but it appears reasonable to think that a visual impairment is more disabling than a hearing one for realization of the PD exchange, due to the required dexterity.

The ISPD proposed recommendations for teaching PD to patients in 2016 [14]. These guidelines mainly advised basing the training programs on the principles of adult education, and proposed a five-day program of approximately 3 h per day. Suggestions were made to assess the patient's preferred learning style and to implement teaching style accordingly. The use of the VARK (Visual, Auditory, Read and write, and Kinesthetic) learning style questionnaire was proposed.

To our knowledge, the effect of the teaching medium on PD learning has not been studied. We tried to assess the effect of using several educational supports on the risk of peritonitis. We found the use of a written support to be associated with a lower survival free of peritonitis.





It has been shown that the information materials aimed at patients with chronic kidney disease are above the average patient’s literacy level, therefore many patients do not take advantage of the written supports provided, because they lack the skills required to understand them [25]. Moreover, we hypothesize that in some cases, written support may be provided to the patients with fewer explanations and/or fewer investments from the caring team in the learning process, therefore leading to poorer quality of the care. However, this result should be taken cautiously because it is not robust to the sensitivity analysis on handled germs peritonitis.

Patients who received audio support for PD learning experienced fewer recurrences after a first peritonitis episode. Notably, the use of audio support is not widespread in dialysis centers with only 2 centers using it as a standard feature, whereas written supports were used as standard features in 42 centers, as shown in Table 2. Therefore, we suppose that patients who benefit from audio learning may have been selected on some individual characteristics. This individualization of the educational support could be the explanation for this better outcome.

These results appear to be in line with the ISPD recommendations to assess the patient’s preferred learning style and to plan the education accordingly. No support may be universally better for PD learning. PD training programs should contain different supports to be able to deliver the best education for each given patient.

Starting PD learning with hands-on training was associated with shorter survival free of peritonitis. The combination of hands-on training and theory were associated with a lower risk of further peritonitis after a first episode whereas it was nearly significantly associated with a higher risk for first episode in the “zero” part of the hurdle model. This phenomenon has been called a “dissonant effect” by Lachenbruch [26]. A telling example is considering an antibiotic treatment, that could be effective in reducing the risk of carrying some specific bacteria, whereas it could be associated with the growth of these bacteria after a first infection, due to antibiotic resistance. A possible explanation for the tendencies observed here could be that patients who started PD learning with hands-on training get more confident earlier with a risk of being less attentive to the rules of asepsis. After a first complication, they should become more cautious and present fewer recurrence.

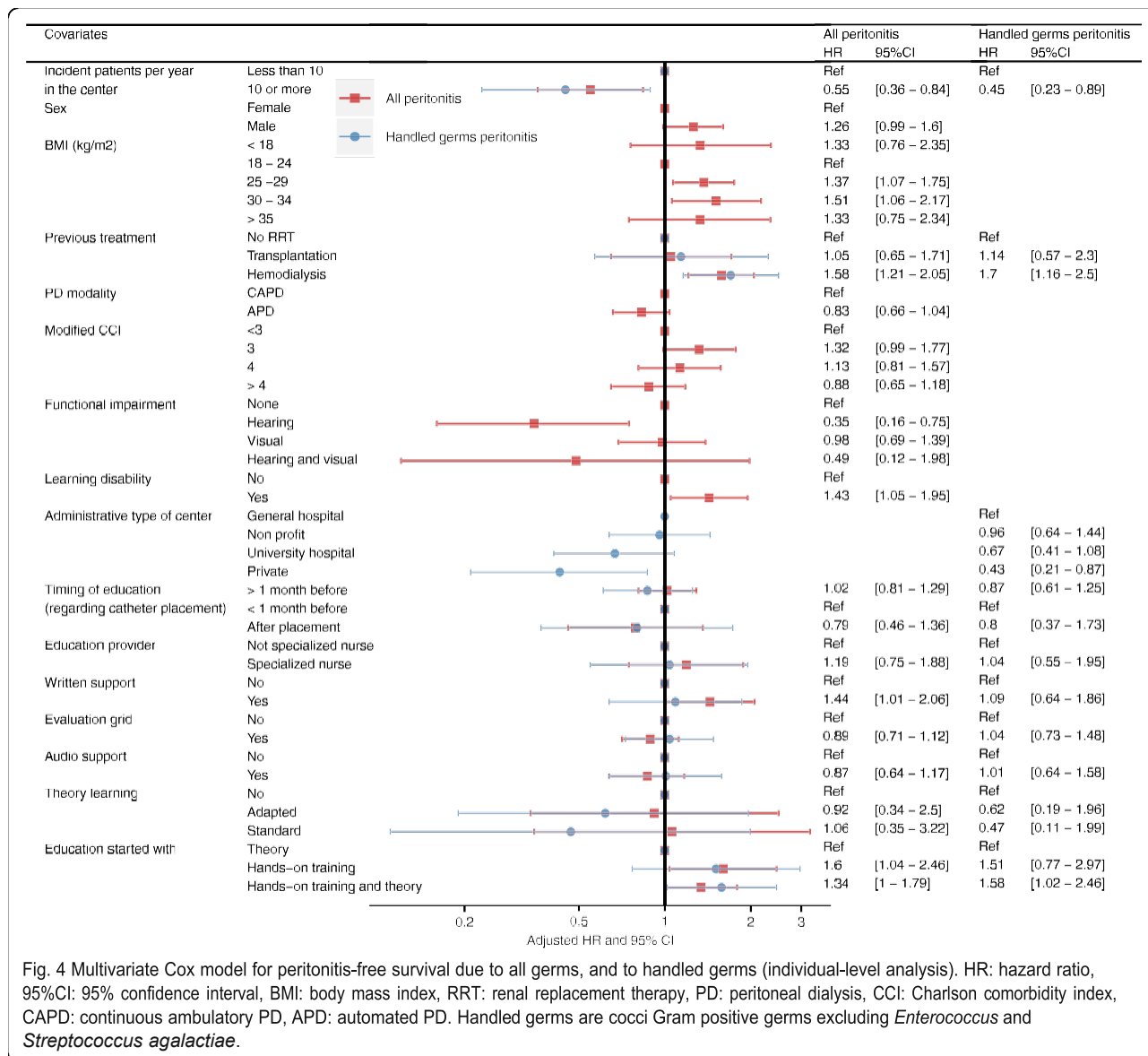


Fig. 4 Multivariate Cox model for peritonitis-free survival due to all germs, and to handled germs (individual-level analysis). HR: hazard ratio, 95%CI: 95% confidence interval, BMI: body mass index, RRT: renal replacement therapy, PD: peritoneal dialysis, CCI: Charlson comorbidity index, CAPD: continuous ambulatory PD, APD: automated PD. Handled germs are cocci Gram positive germs excluding *Enterococcus* and *Streptococcus agalactiae*.

It is worth noticing that counterintuitively, in the “count” part of the multivariate hurdle model, BMI greater than 35 kg/m2 was associated with a lower risk of presenting further peritonitis after a first episode. Obesity has been considered as a relative contra-indication to PD [27]. Therefore, we can hypothesize that nephrologists would be more likely to propose transfer to hemodialysis after a first peritonitis episode in obese patients, whereas they would have pursued the technique for non-obese patients. The protective effect against repeated peritonitis found here would in fact be biased by the presence of transfer to hemodialysis which is a competing event regarding peritonitis. This shorter time to transfer to hemodialysis therapy for obese patients has been reported in a 2017 American study [28].

Another worth commenting result was the higher risk for peritonitis of previous treatment by hemodialysis in the “zero” part of the multivariate hurdle model, whereas it was near significantly a protective effect in the “count” part. This dissonant effect can be explained by the fact that patients who experimented hemodialysis prior to PD might be transferred more easily than the others for several reasons: presence of a functional vascular access for hemodialysis, wish from the patient and/or the nephrologist to get back to a known dialysis modality. The lower survival risk free of peritonitis in patients previously treated with hemodialysis has already been found in a former study with data from the French registry, using a multivariate Cox model (cs-HR 1.15, 95%CI 1.03–1.29) [29]. In a Polish study, Liberek et al. have shown that patients treated with hemodialysis prior

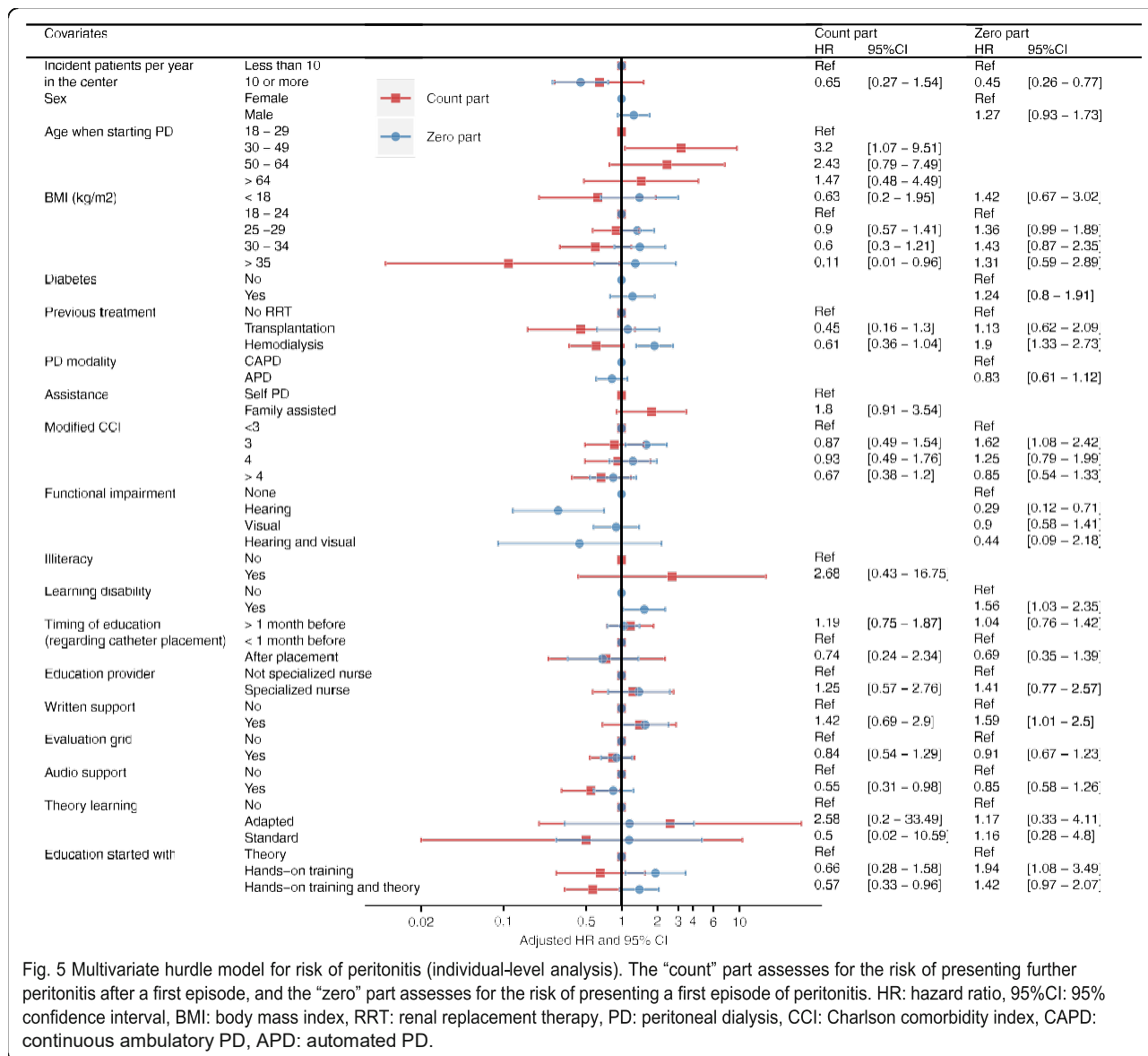


Fig. 5 Multivariate hurdle model for risk of peritonitis (individual-level analysis). The “count” part assesses for the risk of presenting further peritonitis after a first episode, and the “zero” part assesses for the risk of presenting a first episode of peritonitis. HR: hazard ratio, 95%CI: 95% confidence interval, BMI: body mass index, RRT: renal replacement therapy, PD: peritoneal dialysis, CCI: Charlson comorbidity index, CAPD: continuous ambulatory PD, APD: automated PD.

to PD had a significantly higher peritonitis rate compared with those in whom PD was the initial method of renal replacement therapy (0.86 vs 0.62 episode per year,  $p < 0.05$ ) [30]. Patients are transferred from hemodialysis to PD because of complications such as vascular access problems, hemorrhage risk, or cardiovascular condition making hemodialysis no more pursuable. In such patients, PD is not the modality of choice so their involvement may be poorer, explaining the higher peritonitis risk.

Our study is genuine due to the covariates we studied. We assessed the effect of modifiable factors, which is always relevant because the results of the study may have clinical implications. We used quality data extracted from a nationwide registry known for its quality. These strengths should be balanced with some limitations.

Some bias may exist due to the retrospective type of the study. The population is not representative of the whole French PD population because some PD centers did not participate in the “nurses’ practices” modulus in which the educational covariates were collected. Furthermore, we did not know how the methods of education for PD learning were chosen, which could have led to some selection bias. It would be of interest to assess and adjust the analysis on the educational and socioeconomic status of the patients, because these factors might interact with the educational method chosen and their effect.

### Conclusion

We have found that the modality of PD learning was associated with the risk of peritonitis in autonomous or family assisted PD patients. The use of a written

support and starting PD learning with hands-on training alone were associated with a lower survival free of peritonitis, whereas the use of an audio support and starting of PD learning with hands-on training in combination with theory were associated with a lower risk of presenting further episodes of peritonitis after a first episode. According to the ISPD guidelines, caregivers should assess the patient's preferred learning style and their literacy, to best adjust the PD learning program according to these preferences and skills, and offering individualized learning methods. Further interventional studies focusing on educational practices are needed to accurately determine the best practice in PD learning for patients.

## Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s12882-020-01867-w>.

Additional file 1 Table 1 Cox model for survival free of peritonitis. Bivariate analysis. Table showing the results of the bivariate Cox survival model for survival free of peritonitis.

Additional file 2 Table 2. Hurdle model for survival free of peritonitis. Bivariate analysis. Table showing the results of the bivariate hurdle model for the risk of peritonitis

### Acknowledgements

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### Authors' contributions

HB analyzed the data and drafted the work. CB designed the study and substantively revised the work. AB substantively revised the work. TL designed the work and substantively revised the work. SG substantively revised the work. CV acquired the data and provided intellectual content. MF substantively revised the work. AL designed the study, analysed and interpreted the data, and drafted the manuscript. All authors have read and approved the manuscript.

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### Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request after approval obtained from the RDPLF.

### Ethics approval and consent to participate

The RDPLF has the approval of the French National Ethics Committee (*Commission nationale de l'informatique et des libertés*) with the agreement number 542 668 and fulfills the GDPR requests. This study took place within the framework of this authorization.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interest.

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## V.4. Discussion

Au cours de ce deuxième travail, nous nous sommes concentrés sur un nouvel évènement d'intérêt : la survenue d'infections péritonéales. Cet évènement est une des causes les plus fréquentes de transfert en hémodialyse, et sa survenue est liée pour moitié des cas à des erreurs de manipulations. Il existe donc un rationnel pour faire l'hypothèse d'une association entre l'éducation à la dialyse péritonéale et la survenue d'infection péritonéale. Nous avons mis à profit des données originales concernant les supports et modalités pour la formation des patients autonomes ou de leurs proches. Il s'agissait de la première étude visant à évaluer l'effet de différents supports de formation sur l'efficacité de la dialyse péritonéale.

Dans la première partie de notre étude, nous avons montré à l'aide d'un modèle de Cox que l'utilisation de supports écrits pour l'apprentissage de la dialyse péritonéale et un début de formation par des cours pratiques sans théorie étaient associés à une survie sans péritonite moindre. De manière concordante, l'analyse de supports d'éducation imprimés utilisés dans des centres de néphrologie aux États-Unis, Royaume-Uni, et Australie a mis en évidence que le niveau de lisibilité de ces supports dépassait le niveau d'alphabétisation moyen des patients insuffisants rénaux chroniques auxquels ils étaient proposés [55]. Cependant, nos résultats étaient en faveur d'un effet bénéfique d'un début d'éducation par une partie théorique. La qualité des supports employés et leur adéquation avec les compétences des patients semblent donc primordiales.

L'étude de l'évènement « infection péritonéale » nous a conduit à l'utilisation de modèles spécifiques prenant en compte la répétition de l'évènement. L'analyse des résultats du modèle de hurdle est particulière en ce qu'elle comporte deux éléments : la partie zéro pour le risque de survenue d'une première infection péritonéale (ou son

complémentaire : l'absence d'infection péritonéale durant la période de suivi), et la partie compte qui modélise le risque de récurrence de péritonite chez les sujets qui ont passé la barrière d'un premier épisode. Cette particularité met à jour des effets à première vue paradoxaux. Nous avons ainsi observé que le fait d'avoir été traité par hémodialyse avant la dialyse péritonéale était associé à un risque plus élevé de survenue d'une première infection péritonéale dans le modèle zéro, mais que le risque de récurrence d'infection péritonéale n'était pas significativement différent, et même proche de la significativité pour un risque plus faible. A l'aide d'un modèle de survie de Cox, il avait déjà été montré chez les sujets âgés que la survie sans infection péritonéale était moindre en cas de traitement par hémodialyse avant la dialyse péritonéale [56]. Dans la partie « comptage » du modèle de hurdle, l'effet de la covariable « traitement par hémodialyse avant la dialyse péritonéale » était neutre, ce qui laisse supposer pour ces patients, que la récurrence d'infection péritonéale ne serait pas différente car mieux prévenue, ou bien que le retour en hémodialyse serait plus rapidement proposé en cas de récurrence d'infection. Nous avons mis en évidence le même type de résultat pour les patients avec un BMI > 35 kg/m<sup>2</sup> dont le risque de récurrence d'infection péritonéale était plus faible que chez ceux ayant un BMI entre 18 et 24 kg/m<sup>2</sup> alors qu'aucune différence significative n'existait pour le risque de première infection. Là encore, un biais de compétition d'évènement est probable avec des transferts en hémodialyse proposés plus fréquemment après une première infection chez les patients dont le BMI est > 35 kg/m<sup>2</sup>. Un tel effet différent d'une covariable entre les deux parties du modèle de hurdle a été décrit et qualifié de « dissonant » [57]. Ces résultats mettent en valeur un des intérêts de l'utilisation du modèle de hurdle.

Globalement, il ne semble pas y avoir de supériorité évidente de l'usage d'un type de support donné pour la formation sur le risque d'infection péritonéale. La flexibilité est certainement la clé de l'efficacité, afin de pouvoir adapter la formation proposée aux

patients. Une adaptation est nécessaire en fonction des capacités cognitives des patients, de leur littératie ou lettrure, mais également de leur mode d'apprentissage préférentiel. Les recommandations de 2016 de l'ISPD tiennent compte des travaux menés dans les domaines de l'andragogie et préconisent de pouvoir utiliser plusieurs supports pour la formation des patients ou aidants, et de s'adapter ainsi à leur mode d'apprentissage préférentiel [45]. Des questionnaires comme le VARK ont été développés afin de déterminer si les patients étaient plus réceptifs à une information visuelle (V), auditive (A), écrite (R pour *reader*) ou manuelle (K pour *kinetic*). Le VARK est utilisable en pratique clinique lors d'une consultation d'orientation au choix de technique de suppléance rénale.

Notre travail a porté sur l'efficacité de supports pour l'éducation des patients, et nous portons également une attention particulière aux media utilisés pour la transmission de notre propre message scientifique. Nous avons ainsi utilisé un diagramme UpSet dans le but de présenter les agrégats de pratiques et leurs effectifs d'une façon visuelle et aisément lisible. Cet outil est très simple de construction et également de lecture, mais à notre connaissance c'est la première fois que ce type de diagramme est utilisé dans le champ de la néphrologie.

La qualité du recueil des données est un point déterminant de la qualité des études observationnelles et en particulier à partir de données de registre. Le module « infirmier » du RDPLF réunit des covariables originales et c'est le seul registre qui réunit au niveau national les variables relatives à la formation des patients pour la dialyse péritonéale. Une limite de ces données tient à l'hétérogénéité des supports entre les différents centres pour un même medium, car chaque centre fabrique ses propres supports de formation sans protocole commun. La réalisation d'essais prospectifs dans lesquels seraient testés l'effet de supports homogènes ainsi que l'effet des interactions entre l'utilisation de ces supports apporterait des informations importantes pour la pérennité de la dialyse péritonéale chez



les patients autonomes ou assistés de leurs proches. Il existe une réelle attente de la part des patients et des aidants concernant l'amélioration de l'éducation à la dialyse en autonomie, comme cela a été récemment rapporté dans la première étude de PREMs (Patient-Reported Experience Measures) portant sur la dialyse à domicile aux Etats-Unis [58].

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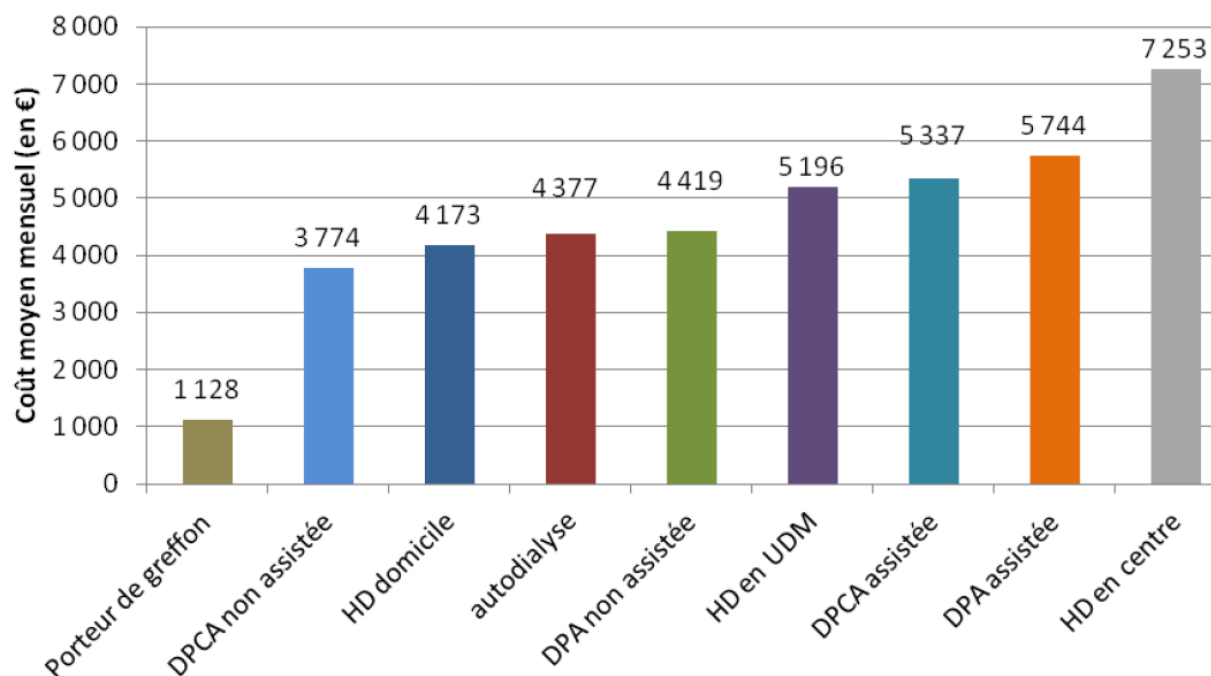
## **VI. EFFET DE L'ASSISTANCE POUR LA REALISATION DE LA DIALYSE PERITONEALE SUR LE RISQUE DE TRANSFERT EN HEMODIALYSE**

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### **VI.1. Introduction**

Les deux premières parties de notre travail ont porté sur l'effet de différentes pratiques de soins propres à la dialyse péritonéale : les pratiques de soins liées au cathéter, puis les pratiques liées à la formation des patients ou de leurs aidants proches. Dans cette troisième partie, nous avons souhaité nous intéresser à l'effet de l'assistance sur les différentes causes de transfert en hémodialyse. Le système de soins français prévoit le remboursement des soins d'assistance à domicile réalisés par un infirmier libéral pour la réalisation de la dialyse péritonéale. Si la France fait figure d'exception face aux autres pays dans lesquels le remboursement des soins n'est pas disponible, c'est bien entendu en premier lieu en raison du surcoût qui y est associé. Cette question du coût est centrale pour la mise à disposition du remboursement de l'assistance. Une évaluation médico-économique réalisée par la HAS rapportait qu'en France l'hémodialyse en centre était la modalité de traitement de l'IRCT la plus coûteuse chez des patients prévalents stables, devant les différentes modalités de dialyse péritonéale assistée (Figure 10). La part du coût total revenant aux soins infirmiers était de 26 % pour la dialyse péritonéale assistée et de 37 % pour la dialyse péritonéale continue ambulatoire [59].

**Figure 10. Coût moyen mensuel par modalité de traitement pour un patient prévalent stable (d'après [59])**



Il est donc important de pouvoir évaluer l'efficacité liée à cette mesure. Cette efficacité s'entend sur deux plans : l'effet de l'assistance sur l'élargissement de la population de patients à qui la dialyse péritonéale est proposée, et l'effet sur la survie de la technique. Un travail de notre équipe avait permis de montrer que le recours à l'assistance par un proche ou par un infirmier libéral était associé à un moindre risque de transfert en hémodialyse [60]. L'instauration au Royaume-Uni d'un service d'assistance a entraîné une augmentation de l'incidence des patients en dialyse péritonéale, surtout dans la frange de population des patients les plus âgés [61].

Les causes de transfert en hémodialyse des patients traités par dialyse péritonéale sont variées, et nous avons émis l'hypothèse que l'assistance pouvait être bénéfique spécifiquement dans le cas de certaines causes de transfert. L'identification de telles

causes préférentielles pourrait ainsi donner des arguments mécanistiques nécessaire pour retenir une causalité dans l'association entre recours à l'assistance et survie de la technique. En outre, on pourrait suggérer de proposer plus volontiers l'attribution d'une assistance chez les patients les plus à risque de présenter ces causes identifiées de transfert en hémodialyse. Les sept causes de transfert en hémodialyse que nous avons analysées étaient : les infections, l'insuffisance de dialyse, les dysfonctions de cathéter, les difficultés psycho-sociales, les péritonites sclérosantes encapsulantes, les autres causes en lien avec la dialyse péritonéale et les autres causes sans lien avec la dialyse péritonéale.

Nous avons souhaité étudier l'effet de l'assistance sur le risque des différentes causes de transfert en hémodialyse. L'évènement d'intérêt était le transfert en hémodialyse alors que le décès ainsi que la transplantation rénale étaient pris en compte en tant qu'évènements compétitifs.

## **VI.2. Outils statistiques et méthodologie**

Nous avons utilisé de nouveau pour ce travail des modèles de survie de Cox puis de Fine Gray afin de prendre en compte l'existence des risques compétitifs. Les modèles ont été réalisés en deux parties. Dans la première partie, l'évènement d'intérêt était le transfert en hémodialyse. Le décès et la transplantation rénale étaient deux évènements compétitifs. Dans la deuxième partie de l'étude, l'évènement d'intérêt était une des sept causes de transfert en hémodialyse, et les évènements compétitifs étaient le décès, la transplantation rénale, et les six autres causes de transfert en hémodialyse.

### **VII.2.1. Modèles de Cox et de Fine and Gray**

De manière similaire aux travaux réalisés dans notre premier article, nous avons utilisé des modèles de survie de Cox et de Fine Gray pour estimer les cs-HR et sd-HR associés à l'assistance pour le risque de transfert en hémodialyse et les risques compétitifs que sont la transplantation rénale et le décès.

### **VII.2.2. Données manquantes**

La base du RDPLF possède l'avantage d'une très bonne granularité et d'une excellente exhaustivité, grâce à une politique de veille et de rappel extrêmement proactive auprès des néphrologues. La base de données que nous avons exploitée comportait les données de 11 093 patients et moins de 2 % de données manquantes. Nous avons néanmoins souhaité limiter la perte d'information liée à ces données manquantes et pour cela nous avons utilisé une technique d'imputation multiple par équations en chaînes [62]. Cette technique repose sur l'hypothèse que les données manquantes sont distribuées aléatoirement. La structure des données manquantes est arbitraire, c'est-à-dire que chaque variable peut présenter des données manquantes de manière aléatoire. L'imputation multiple par équations en chaînes consiste à construire plusieurs jeux de données dans lesquelles les données manquantes sont remplacées par des valeurs simulées. Supposons que notre jeu de données comporte  $p$  variables  $(Y_i)_{i=1 \text{ à } p}$ . Les valeurs manquantes de  $Y_j$  sont notées  $Y_j^{NA}$  et les valeurs présentes  $Y_j^{obs}$ . Les valeurs imputées pour la variable  $Y_j$  sont calculées en fonction des valeurs de toutes les autres variables  $Y_j$  ( $j = 1 \text{ à } p \text{ et } j \neq i$ ) et de la

distribution théorique  $\theta_i$  de  $Y_i$ . Ainsi, pour le  $k$ -ième jeu d'imputation, la distribution de  $Y_i$  est déterminée en fonction des valeurs observées de la variable :  $Y_j^{obs}$ , et des valeurs observées et imputées sur les jeux précédents des autres variables  $Y_j$  ( $j = 1 \text{ à } p \text{ et } j \neq i$ ). Soit :

$$\theta_i^{*(k)} \approx P(\theta_i | Y_i^{obs}, Y_j^{(k-1)} \text{ (} j = 1 \text{ à } p \text{ et } j \neq i \text{)})$$

Une fois cette distribution déterminée, la variable  $Y_i^{*(k)}$  est imputée en prenant en compte : la distribution  $\theta_i^{*(k)}$ , les valeurs observées de la variable  $Y_i$ , et les valeurs observées et imputées des autres variables lors de l'imputation précédente :  $Y_j^{(k-1)}$ .

$$Y_i^{*(k)} \approx P(Y_i | Y_i^{obs}, Y_j^{(k-1)} \text{ (} j = 1 \text{ à } p \text{ et } j \neq i \text{)}, \theta_i^{*(k)})$$

La première imputation est réalisée à partir des données observées. Il s'agit donc d'un processus itératif à l'issue duquel  $N$  jeux de données complets sont créés. En pratique, il est conseillé de prendre  $N = 3 \text{ à } 10$ .

Pour chacun des jeux de données construits, l'estimateur de la quantité d'intérêt  $Q^{(k)}$  (souvent un coefficient de régression) est ensuite calculé à l'aide des techniques statistiques classiques.

Au cours de la troisième et dernière étape Les résultats sont ensuite regroupés ou « poolés » pour obtenir le résultat final qui intègre l'incertitude liée à la présence des données manquantes (Figure 11). Les règles de Rubin définissent le calcul pour l'obtention de l'estimateur global  $Q$  et de sa variance  $T$ .

$$Q = \frac{1}{N} \sum_{i=1}^N Q^{(j)}$$

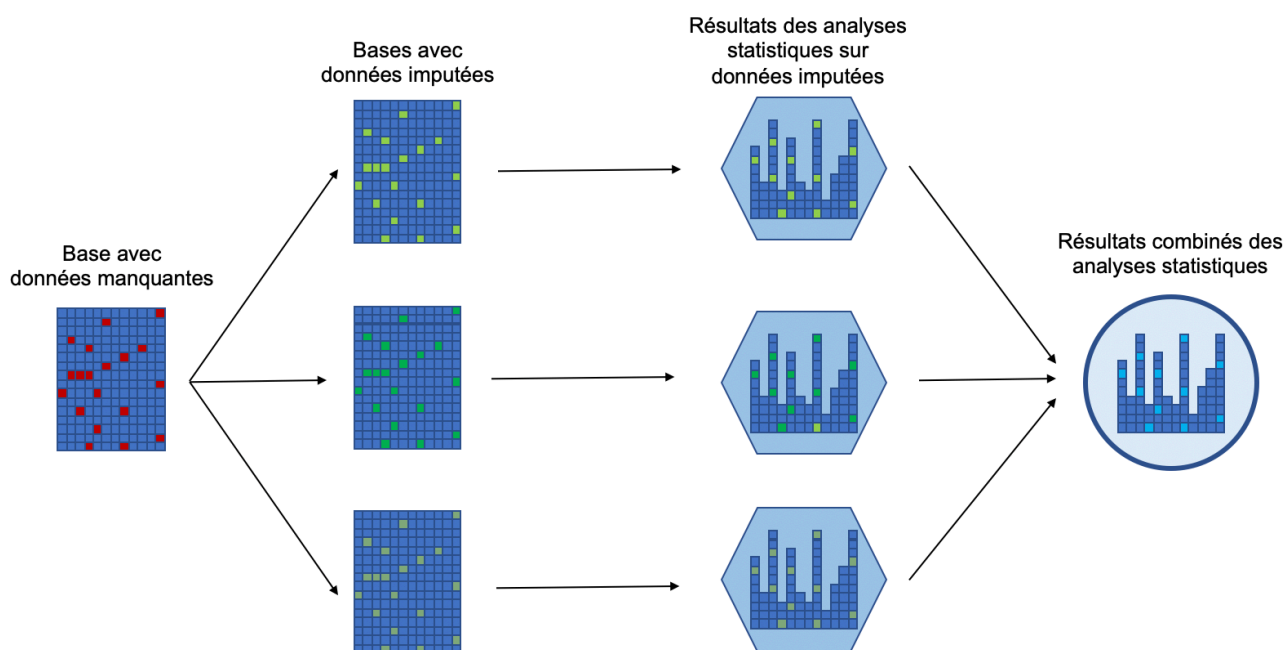
La variance T est calculée à partir de la variance intra-imputation U et de la variance inter-imputation B, avec :

$$B = \frac{1}{N-1} \sum_{i=1}^N [Q^{(j)} - Q]^2$$

$$U = \frac{1}{N} \sum_{i=1}^N U^{(j)}$$

ou finalement :  $T = U + \left(1 + \frac{1}{N}\right) B$

**Figure 11. Étapes de réalisation d'une imputation multiple par équations en chaînes.**



Des procédés d'imputations multiples sont implémentés dans les logiciels de calculs statistiques pour la plupart des modèles classiques. Nous avons utilisé le package mice dans R [63]. Le package mice ne permet pas l'utilisation directe de l'objet poolé dans les modèles de régression de Fine Gray. Il est nécessaire de définir comment extraire une

matrice de covariance des objets imputés. Les lignes de code suivantes dans R permettent cet ajustement :

```
vcov.crr <- function (object, ...) {  
    object$var  
}  
coef.crr <- function (object, ...) {  
    object$coef  
}
```

### **VII.2.3. Score de propension à trois groupes**

Nos travaux reposent sur l'utilisation de données de registres, c'est-à-dire de données observationnelles. En tant que telles, elles ne permettent pas de conclure à des liens de causalité car les associations mises en évidence peuvent être la conséquence de différents biais, et notamment de biais d'indications. Trois groupes de patients étaient considérés dans ce travail : les patients autonomes pour la réalisation de la dialyse péritonéale (désigné groupe « autonome » dans la suite), ceux assistés par un proche (groupe « famille »), et ceux assistés par un infirmier libéral (groupe « infirmier »). L'attribution de l'assistance dépend de l'autonomie et des comorbidités des patients et en conséquence, ces trois groupes de patients ont des caractéristiques différentes. Afin d'éviter un biais d'indication important, nous avons cherché à rendre ces trois groupes de patients comparables en calculant un score de propension pour appariement sur les caractéristiques des patients. L'objectif est ainsi de corriger les biais de sélection en contrôlant les différences observables entre les groupes de patients, et de se rapprocher



des conditions d'un essai randomisé. On garde bien à l'esprit cependant qu'il persiste des biais potentiels non mesurés dont seul un essai randomisé permet de se prémunir.

La première étape est le choix des variables à inclure dans le score de propension. Il est recommandé d'inclure toutes les variables disponibles corrélées à la fois avec le traitement et l'évènement d'intérêt [64].

Rosenbaum et Rubin ont défini en 1983 le score de propension comme étant la probabilité conditionnelle d'assignement à un traitement particulier étant donné un vecteur de covariables observées [65]. Ce score est donc pour le patient  $i$  :

$$PS_i = \Pr(T_i = 1 | X_i)$$

Où  $T_i$  est l'indicatrice associée à la présence du traitement chez le patient  $i$  et  $X_i$  le vecteur des covariables observées.

Classiquement, les scores de propension sont utilisés pour la comparaison de deux groupes de patients qui ont reçu ou non un traitement que l'on souhaite tester. Dans ce cas de figure, l'estimation du score de propension se fait à l'aide d'un modèle de régression logistique. Le score de propension est ensuite utilisé selon la méthode d'ajustement choisie : appariement, stratification, ajustement des covariables ou pondération. Nous avons choisi d'utiliser la méthode d'appariement sur le score de propension car c'est une des méthodes les plus performantes, la plus couramment utilisée dans la littérature médicale et qui peut-être implémentée dans les calculs de fonction de risques cumulés nécessaire pour l'utilisation de modèle de Fine Gray, ce qui n'est pas le cas des méthodes de pondération [66], [67].

Une particularité de notre travail est l'existence de trois groupes de traitement. Nous avons estimé trois scores de propension à l'aide de trois modèles de régression logistique. Nous avons pour cela utilisé le package Trimatch de R [68].

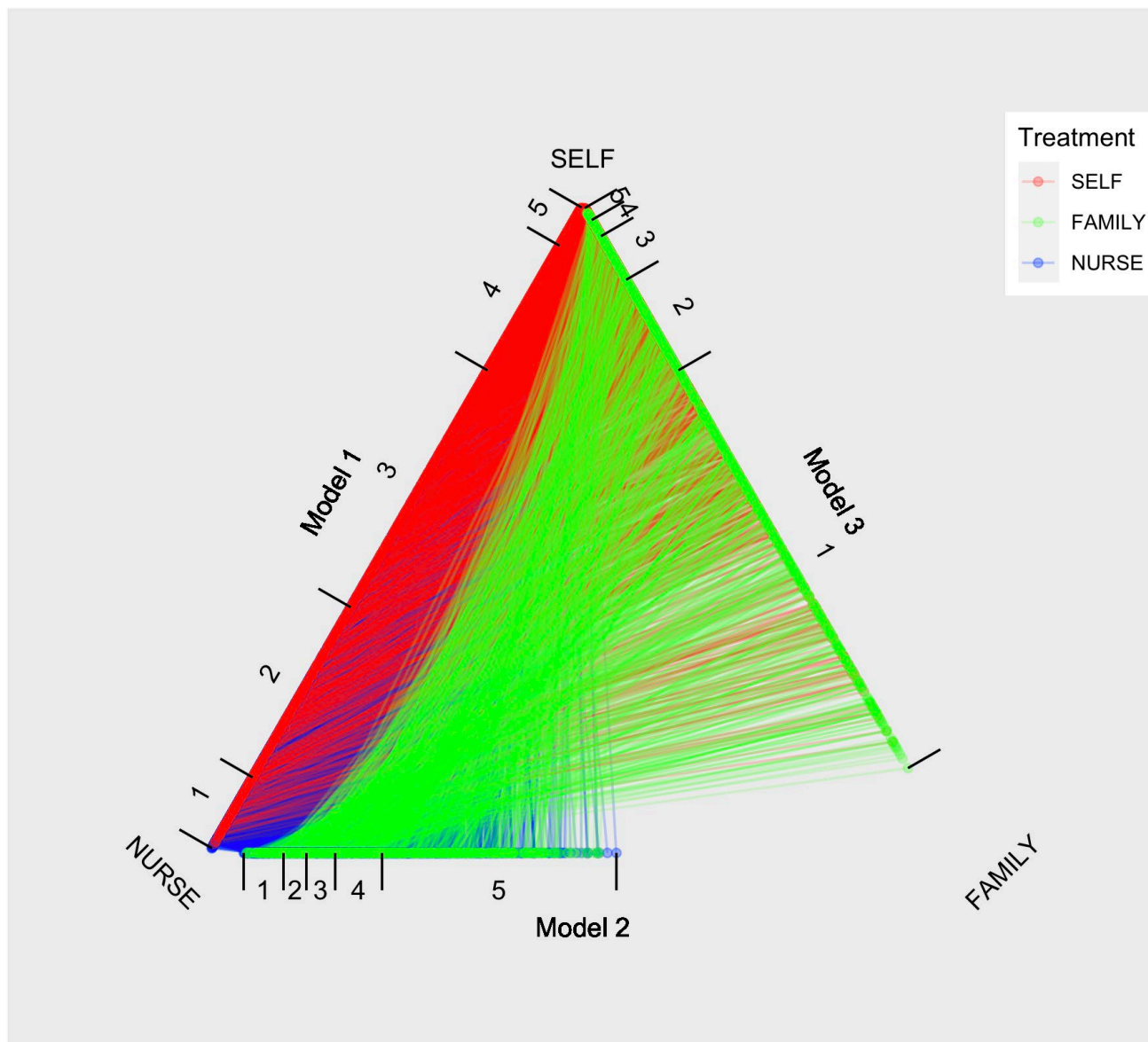
- Le premier score :  $PS_1$  ou  $PS_{A-I}$  estimait la probabilité d'être assisté par un infirmier par rapport à la référence : être autonome. Ce score est calculé dans les deux groupes de patients « infirmier » et « autonome ».

- Le deuxième score :  $PS_2$  ou  $PS_{F-I}$  estimait la probabilité d'être assisté par un infirmier par rapport à la référence : assistance par un proche. Le score  $PS_2$  est calculé dans les deux groupes de patients « infirmier » et « famille ».

- Le troisième score :  $PS_3$  ou  $PS_{A-F}$  estimait la probabilité d'être assisté par un proche par rapport à la référence : être autonome.  $PS_3$  est calculé dans les deux groupes de patients « autonome » et « famille ».

Deux scores de propension sont donc calculés pour chaque patient :  $PS_{A-I}$  et  $PS_{A-F}$  pour les patients autonomes,  $PS_{A-I}$  et  $PS_{F-I}$  pour les patients assistés par infirmier, et  $PS_{F-I}$  et  $PS_{A-F}$  pour les patients assistés par un proche.

Figure 12. Distribution des patients par quintiles pour chacun des trois scores de propension construits. Chaque patient se voit affecter deux scores de propension qui sont reliés par une ligne.



Une métrique est définie et trois distances standardisées sont ensuite créées.  $D_{A-I}$  est la distance entre les sujets suivant le calcul du  $PS_{A-I}$ .  $D_{F-I}$  est associée au  $PS_{F-I}$  et  $D_{A-F}$  est associée au  $PS_{A-F}$ . De manière commune, la distance est définie selon :

$$D(x, y) = \frac{|PS(x) - PS(y)|}{\sigma_{PS}}$$

L'appariement des triplets de patients est réalisé avec l'objectif de minimiser la somme des distances entre les scores de propension. Un seuil de distance minimum, appelé « caliper », est choisi. Il est habituellement recommandé de le choisir égal à 0,25 écart-type [69].

Trois matrices de distance sont élaborées : Pour toutes les paires de sujet x du groupe « autonome » et de sujets y du groupe « famille » :

$$D_{A-F}(x, y) = \frac{|PS_{A-F}(x) - PS_{A-F}(y)|}{\sigma(PS_{A-F})}$$

Pour toutes les paires de sujet x du groupe « autonome » et de sujets z du groupe « infirmier » :

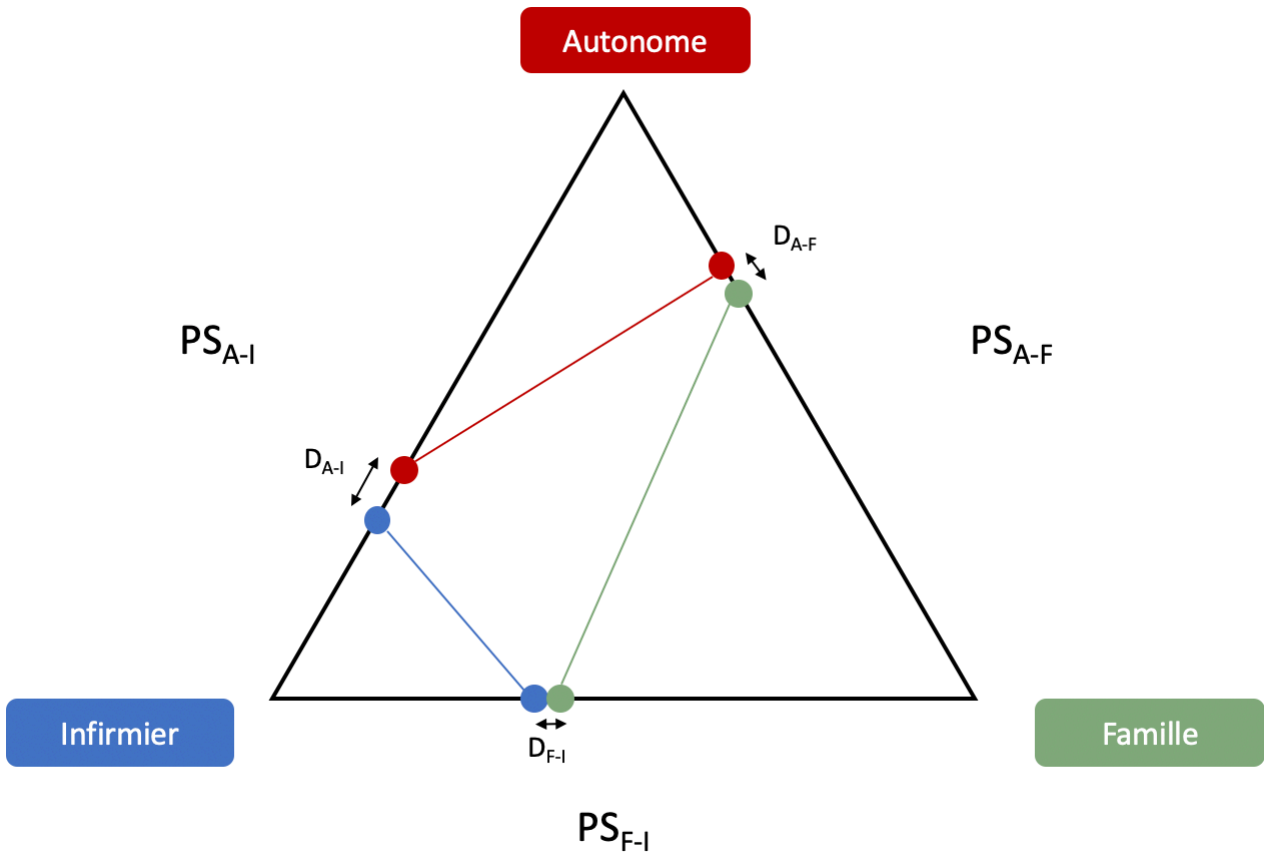
$$D_{A-I}(x, z) = \frac{|PS_{A-I}(x) - PS_{A-I}(z)|}{\sigma(PS_{A-I})}$$

Pour toutes les paires de sujet y du groupe « famille » et de sujets z du groupe « infirmier » :

$$D_{F-I}(y, z) = \frac{|PS_{F-I}(y) - PS_{F-I}(z)|}{\sigma(PS_{F-I})}$$

Les triplets {x, y, z} sont finalement choisis selon un critère de minimisation de la somme des distances :  $D_{A-F}(x, y) + D_{A-I}(x, z) + D_{F-I}(y, z)$  (figure 13).

Figure 13. Constitution des triplets. Critère de minimisation de la somme des distances  $D_{A-I} + D_{A-F} + D_{F-I}$



Différentes contraintes peuvent être imposées lors de la procédure d'appariement. Nous avons utilisé une méthode « one to N » dans laquelle nous avons imposé qu'il n'y ait pas de répétition des sujets issus des groupes assistés par infirmiers ou par la famille. Parmi les covariables sélectionnées pour le calcul des scores de propension, nous avons observé que deux caractéristiques étaient fortement associées à l'attribution de l'assistance, ainsi qu'au risque de transfert en hémodialyse, l'âge des patients et leur score de comorbidité de Charlson. Nous avons donc imposé un appariement exact sur ces deux variables pour la constitution des triplets.

Cette méthode a mené à la constitution d'un jeu de données appariées constitué de 484 dans le groupe « autonome », 640 dans le groupe « famille » et 640 dans le groupe « infirmier », soit un total de 1764 patients. On a pu contrôler l'équilibre de la distribution des covariables entre les trois groupes reconstitués après appariement. Cet équilibre des distributions est le garant de la qualité de l'appariement proposé. Le premier graphique donné en matériel supplémentaire de l'article permet ce contrôle.

Enfin, les modèles de survie de Cox et de Fine Gray ont pu être élaborés sur la cohorte appariée afin d'estimer les cs-HR et sd-HR.

## VI.3. Article 3

Lanot A, Bechade C, Boyer A, Ficheux M, Lobbedez T. Assisted peritoneal dialysis and transfer to haemodialysis: a cause-specific analysis with data from the RDPLF. *Nephrol Dial Transplant.* 2020;25:330-339

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Présentation en communication orale :

Lyon, le 5 juin 2019

Baxter academy, en route vers l'expertise.

« *L'échec technique en dialyse péritonéale* »

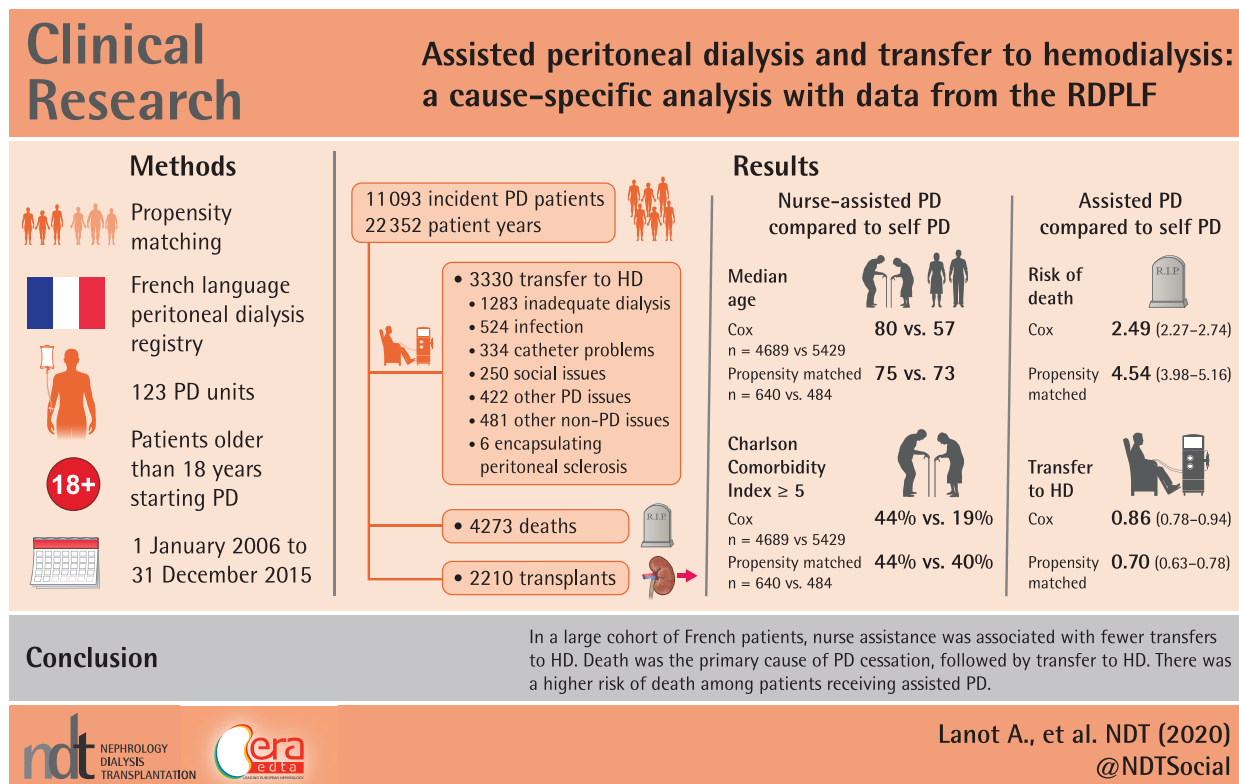
# Assisted peritoneal dialysis and transfer to haemodialysis: a cause-specific analysis with data from the RDPLF

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## GRAPHICAL ABSTRACT



## ABSTRACT

**Background.** Technique failure, defined as death or transfer to haemodialysis (HD), is a major concern in peritoneal dialysis (PD). Nurse-assisted PD is globally associated with a lower risk of transfer to HD. We aimed to evaluate the association between assisted PD and the risk of the different causes of transfer to HD.

**Methods.** This was a retrospective study using data from the French Language PD Registry of patients on incident PD from

2006 to 2015. The association between the use of assisted PD and the causes of transfer to HD was evaluated using survival analysis with competing events in unmatched and propensity score-matched cohorts.

**Results.** The study included 11 093 incident PD patients treated in 123 French PD units. There were 4273 deaths, 3330 transfers to HD and 2210 renal transplantations. The causes of transfer to HD were inadequate dialysis (1283), infection (524),



## KEY LEARNING POINTS

### What is already known about this subject?

- peritoneal dialysis (PD) is an efficient home dialysis technique, associated with superior quality of life, lower cost and equivalent survival compared with in-centre haemodialysis (HD). However, it remains underused partly because of a high rate of unwanted transfer to HD; and
- in countries where reimbursement for such care is available, nurse assistance for PD is associated with a lower risk of transfer to HD, but causation is speculative.

### What this study adds?

- nurse assistance for PD is associated with a lower risk of transfer to HD, especially due to inadequate dialysis; and
- this study is retrospective so conclusions should not be drawn on causality of the associations. However, the understanding of the mechanisms implied in the transfer to HD may help to understand the existence of a causal effect between the use of assistance for PD and nurse assistance.

### What impact this may have on practice or policy?

- The better outcomes associated with nurse assistance should encourage:
  - (i) decision makers to launch reimbursement programmes for nurse assistance in countries where it is not available yet; and
  - (ii) nephrologists to make PD widely available for ESRD patients, with help of a nurse assistance if estimated necessary.

catheter-related problems (334), social issues (250), other causes linked to PD (422), other causes not linked to PD (481) and encapsulating peritoneal sclerosis (6). Nurse-assisted PD patients were older and more comorbid. Assistance by nurse was associated with a higher risk of death [cause-specific hazard ratio (cs-HR) 2.49, 95% confidence interval (CI) 2.26–2.74], but with a lower risk of transfer to HD [subdistributionHR (sd-HR) 0.68, 95% CI 0.62–0.76], especially due to inadequate dialysis (cs-HR 0.83, 95% CI 0.75–0).

**Conclusions.** The lower risk of transfer to HD associated with nurse assistance should encourage decision makers to launch reimbursement programmes in countries where it is not available.

**Keywords:** assistance, competing events, peritoneal dialysis, survival analysis, technique failure

## INTRODUCTION

It is accepted that peritoneal dialysis (PD) is efficient, cost-effective in many countries and preserves the autonomy of

end-stage renal disease (ESRD) patients [1–3]. However, technique survival remains a major concern for ESRD subjects and for the nephrologists in charge of ESRD patients [4].

Technique failure can be defined by a composite endpoint of death or transfer to haemodialysis (HD). It has been suggested that death-censored technique failure and mortality should be reported separately to increase the amount of information [5]. Lan *et al.* [5] also recommend assessing the cumulative incidence of the individual causes of transfer to HD to allow action at the centre level. It has been reported in the literature that death was the primary cause of PD cessation and that transfer to HD was mainly due to infection, inadequate dialysis, social issues and catheter dysfunction [5–8]. Noteworthy, the term ‘failure’ has a negative connotation and according to the recent standardized outcomes in nephrology-PD (SONG-PD) findings, we preferred to use neutral or positively framed alternatives such as technique survival or cessation [9].

Nadeau-Fredette and Bargman recently suggested that if the objective is to increase PD survival, efforts must be made to act on modifiable risk factors of transfer to HD and to offer support to the more vulnerable patients treated by PD [10]. It has been demonstrated that patient age and comorbidity are associated with transfer to HD [11, 12].

In France, the costs of renal replacement therapy (RRT), including nurse-assisted PD, are fully covered by the healthcare insurance. In 2017 among the 45 538 French patients treated with dialysis, 1730 (3.8%) were on continuous ambulatory PD (CAPD) and 1093 (2.4%) on automated PD (APD) [13].

Nurse-assisted PD is mostly devoted to elderly and frail patients. We have previously shown that, compared with self-care PD subjects, nurse-assisted PD patients had a lower risk of transfer to HD [14]. The protective effect of assistance could act more specifically on some determined causes of transfer to HD. The mechanistic understanding of this effect could add arguments for causality.

This study was carried out to assess the association between the modality of assisted PD and the risks of the different causes of transfer to HD.

## MATERIALS AND METHODS

### Study population

This was a retrospective study of data from the French Language PD Registry (RDPLF) [15]. Patients >18 years starting PD in mainland France between 1 January 2006 and 31 December 2015 were included in the study. The end of the study period was 31 December 2017.

### Definition of variables

Sex, age at the start of PD, diabetes mellitus, underlying nephropathy, modified Charlson comorbidity index (CCI) (subtracting the age subscore from the CCI to evaluate the role of comorbidities independently of the patient’s age) and treatment prior to PD (HD, transplantation) were extracted from the database. Characteristics of the treatment, including PD modality (APD or CAPD) and suboptimal starting of PD after a period of <30 days on HD [16], were obtained from the registry.

Centre characteristics included centre experience, estimated by the number of incident patients per year during the study period dichotomized with a cut-off of 10 new patients per year by centre, centre administrative type and the presence of a nurse specialized in PD at the centre.

### Explanatory variables

The main explanatory variable was the modality of assisted PD (nurse-assisted PD and family-assisted PD). Self-care PD was used as the comparator.

### Event of interest and competing events

The event of interest was a transfer to HD for >2 months. The reason for transfer, which is a declarative variable collected in the registry, was extracted and classified into seven categories, adapted from those defined by Lan *et al.* [5]: infection, inadequate dialysis [inadequate solute clearance associated with uraemic syndrome or inadequate ultrafiltration (UF) associated with overhydration, or poor nutrition], dysfunction of PD catheter, social issues (patient preference, loss of assistance and geographic isolation), encapsulating peritoneal sclerosis (EPS), other causes linked with PD and other causes not linked with PD.

### Statistical analysis

Categorical variables are described by their absolute numbers and percentages, and continuous variables by their medians and interquartile ranges (IQRs). Curves of the cumulative incidence of each event were drawn.

The survival analysis was performed by multivariable Cox regression that provides cause-specific hazard ratios (cs-HR) and by multivariable Fine and Gray regression that provides subdistribution HR (sd-HR). All variables considered potentially relevant *a priori* were included in the multivariable models (assistance, age, sex, diabetes, causal nephropathy, modifies CCI, treatment prior to PD, suboptimal starter status, PD modality, administrative centre type, presence of a dedicated nurse and centre size). The uncertainty of the results was expressed with the 95% confidence interval (CI). For the cs-HR, the risk set decreases at each time point at which there is a cessation for another cause (events that are not the events of interest are censored), whereas for the sd-HR, the persons with cessation from another cause remain in the risk set. The Cox model measured the specific association between the variable and the event of interest, whereas the Fine and Gray model assessed the net association across all possible events [17–19]. In the first part of the analysis, transfer to HD was the event of interest, and while on PD, death and renal transplantation were the competing events. In the second part of the study, each cause of transfer to HD was the event of interest (one at a time), death and renal transplantation, and the other causes of transfer to HD were the competing events. Renal transplantation was not studied.

The analysis was performed with the full dataset and with a subset of patients matched on a propensity score for assistance for PD. Because the use of assistance for PD was dependent on patients' characteristics, propensity scores for the use of assistance for PD were calculated. Assistance is a three-level

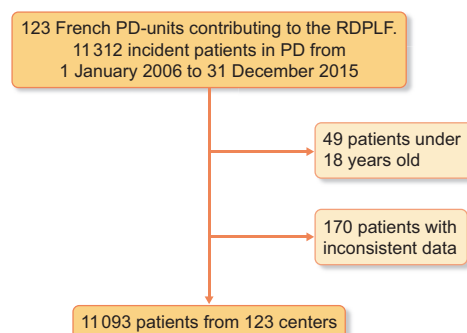


FIGURE 1: Flowchart of the study.

variable, therefore three propensity scores were calculated with logistic regressions, and distances between these propensity scores were computed. All available covariables were used as predictors to estimate the propensity scores, and a nearest-neighbour matching within a calliper of 0.25 SD to the propensity score was used to constitute the three groups of patients. An exact matching was required for the age and CCI, because these factors strongly predicted the use of assistance for PD. Covariables balance in the three groups before and after matching is represented in Supplementary data, Figure S1.

There were <2% missing data, which we assumed to be missing at random. We performed multiple imputations by chained equations, using five imputed data sets, a maximum of 10 iterations to impute missing values and achieve convergence of the models, and the predicting mean matching method for imputation.

We performed sensitivity analysis by running the different survival models using assisted PD as a binary variable. For this analysis, a propensity score was built using a classic logistic regression model including all listed covariables as predictors.

Statistical analyses were performed with R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

The RDPLF has the approval of the French National Ethics Committee (Commission nationale de l'informatique et des libertés). This study took place within the framework of this authorization.

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [20].

## RESULTS

### Univariable analysis

Data from 11 312 incident PD patients treated in 123 PD units were extracted; 219 subjects <18 years old or with inconsistent data were excluded from the original dataset, leaving 11 093 patients for the analysis with a total follow-up time of 22 352 patient-years (Figure 1). Assisted patients were older (median age was 80 years for nurse-assisted and 57 years for autonomous patients), had higher morbidity scores (44% had a modified CCI  $\geq 5$  in the nurse-assisted group and 19% in the self PD group) and were more frequently treated with CAPD (75% in the nurse-assisted group and 42% in the self PD group).

**Table 1. Characteristics of the population before and after matching by propensity score**

Characteristics	Self PD, <i>n</i> = 5429	Before matching Nurse, <i>n</i> = 4689	Family, <i>N</i> = 962	Self PD <i>N</i> = 484	After matching Nurse, <i>N</i> = 640	Family, <i>N</i> = 640
Age at PD start, median (IQR), years	57 (44–67)	80 (73–85)	75 (66–82)	73 (62–79)	75 (65–82)	76 (65–83)
Sex, <i>n</i> (%)						
Female	1927 (35.5)	2171 (46.3)	361 (37.5)	173 (35.7)	257 (40.2)	264 (41.2)
Diabetes, <i>n</i> (%)	1138 (21)	2020 (43.1)	446 (46.4)	191 (39.5)	289 (45.2)	260 (40.6)
Missing	16 (0.3)	13 (0.3)	13 (1.4)			
Nephropathy, <i>n</i> (%)						
Diabetic	698 (12.9)	1125 (24.0)	253 (26.3)	112 (23.1)	158 (24.7)	145 (22.7)
GN	1374 (25.3)	262 (5.6)	84 (8.7)	49 (10.1)	56 (8.8)	62 (9.7)
TIN	422 (7.8)	262 (5.6)	60 (6.2)	37 (7.6)	47 (7.3)	35 (5.5)
Other	43 (0.8)	33 (0.7)	12 (1.2)	6 (1.2)	4 (0.6)	11 (1.7)
PKD	628 (11.6)	101 (2.2)	27 (2.8)	23 (4.8)	22 (3.4)	23 (3.6)
Systemic	218 (4)	79 (1.7)	21 (2.2)	7 (1.4)	18 (2.8)	16 (2.5)
Unknown	588 (10.8)	603 (12.9)	113 (11.7)	52 (10.7)	80 (12.5)	79 (12.3)
Urologic	367 (6.8)	103 (2.2)	27 (2.8)	14 (2.9)	24 (3.8)	19 (3.0)
Vascular	1091 (20.1)	2121 (45.2)	365 (37.9)	184 (38.0)	231 (36.1)	250 (39.1)
Modified CCI, <i>N</i> (%)						
2	2652 (48.8)	758 (16.2)	157 (16.3)	100 (20.7)	118 (18.4)	118 (18.4)
3	979 (18.0)	902 (19.2)	155 (16.1)	92 (19.0)	118 (18.4)	118 (18.4)
4	747 (13.8)	935 (19.9)	169 (17.6)	101 (20.9)	123 (19.2)	123 (19.2)
≥5	1000 (18.4)	2060 (43.9)	470 (48.9)	191 (39.5)	281 (43.9)	281 (43.9)
Missing	64 (1.2)	47 (1)	24 (2.5)	–	–	–
Treatment prior to PD, <i>n</i> (%)						
No RRT	4135 (76.2)	3900 (83.2)	783 (81.4)	395 (81.6)	515 (80.5)	512 (80.0)
Transplantation	341 (6.3)	36 (0.8)	14 (1.5)	8 (1.7)	9 (1.4)	7 (1.1)
HD	941 (17.3)	746 (15.9)	165 (17.2)	81 (16.7)	116 (18.1)	121 (18.9)
Missing	25 (0.5)	20 (0.4)	13 (1)	–	–	–
Suboptimal starter, <i>n</i> (%)						
Yes	441 (8.1)	521 (11.1)	88 (9.1)	42 (8.7)	63 (9.8)	78 (12.2)
Missing	1 (0)	0	0	–	–	–
PD modality, <i>n</i> (%)						
CAPD	2265 (41.7)	3502 (74.7)	552 (57.4)	277 (57.2)	372 (58.1)	359 (56.1)
APD	3164 (58.3)	1187 (25.3)	410 (42.6)	207 (42.8)	268 (41.9)	281 (43.9)
Centre type, <i>n</i> (%)						
General hospital	2450 (45.1)	2321 (49.5)	484 (50.3)	238 (49.2)	304 (47.5)	300 (46.9)
University hospital	1206 (22.2)	877 (18.7)	196 (20.4)	97 (20.0)	128 (20.0)	132 (20.6)
Non-profit	1380 (25.4)	1048 (22.4)	198 (20.6)	112 (23.1)	140 (21.9)	148 (23.1)
Private	393 (7.2)	443 (9.4)	84 (8.7)	37 (7.6)	68 (10.6)	60 (9.4)
Dedicated nurse, <i>n</i> (%)						
Yes	3326 (61)	3153 (67)	642 (67)	314 (64.9)	410 (64.1)	411 (64.2)
Centre size, <i>n</i> (%)						
Large	3236 (59.6)	2933 (62.6)	555 (57.7)	288 (59.5)	385 (60.2)	394 (61.6)
Small	2193 (40.4)	1756 (37.4)	407 (42.3)	196 (40.5)	255 (39.8)	246 (38.4)

A centre is defined as 'small' if the number of incidental PD patients is <10/year. Dedicated nurse describes the presence of at least one nurse dedicated to PD care in the centre. *N*, number; GN, glomerulonephritis; TIN, tubulointerstitial nephritis; PKD, polycystic disease.

Overall, 1764 patients were matched in the propensity scoring approach: 484 in the autonomous group, 640 in the family assisted group and 640 in the nurse-assisted group (Table 1).

### Causes of PD cessation

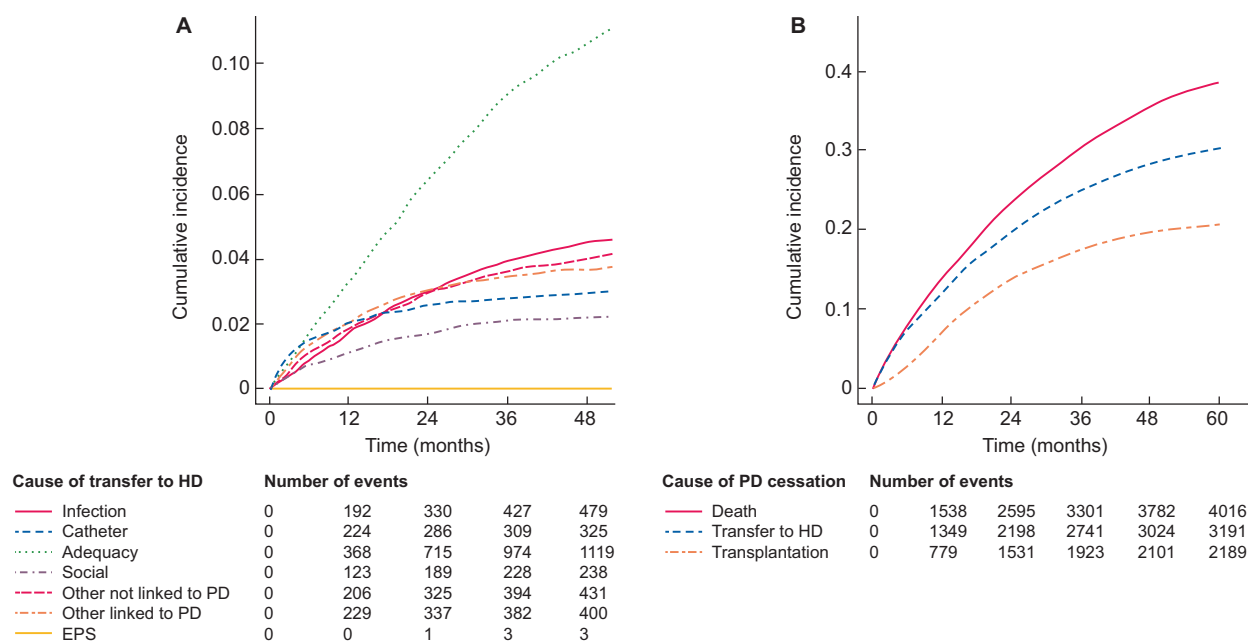
During the study period, there were 4273 deaths, 3330 transfers to HD and 2210 renal transplantations. The causes of transfer to HD were inadequate dialysis (1283), infection (524), mechanical issues (334), social issues (250), other causes linked to PD (422) and other causes not linked to PD (481). The cumulative incidence for the seven causes of technique cessation is illustrated in Figure 2A, and detailed for each modality of assistance in Supplementary data, Figure S2. Six cases of EPS causing technique cessation were observed during the follow-

up period. No statistical test was performed on this outcome because of its scarcity.

### PD technique cessation by death or by transfer to HD

Curves representing the cumulative incidence of each event are displayed in Figure 2B. The cumulative incidences according to the modality of assistance are shown in Supplementary data, Figure S3.

In the multivariable analysis assessed on the full dataset, nurse-assisted PD was protective against the risk of transfer to HD in both Cox and Fine–Gray (FG) models (cs-HR 0.83, 95% CI 0.75–0.91 and sd-HR 0.68, 95% CI 0.61–0.75, respectively). Regardless of the modality, assisted PD was associated with a higher risk of death (cs-HR 2.48, 95% CI 2.20–2.80 and sd-HR



**FIGURE 2:** Cumulative incidental risk curves. (A) for the seven causes of transfer to HD. (B) for the three competing events: death, transfer to HD and transplantation.

2.63, 95% CI 2.33–2.97 for family assistance and cs-HR 2.49, 95% CI 2.26–2.74 and sd-HR 2.70, 95% CI 2.45–2.99 for nurse assistance) (Figure 3A).

Analysis performed with the propensity-matched triplets dataset showed that compared with self-care PD, nurse-assisted PD was associated with a lower risk of transfer to HD (cs-HR 0.8, 95% CI 0.65–0.99 and sd-HR 0.62, 95% CI 0.50–0.77) and a higher risk of death (cs-HR 2.38, 95% CI 1.96–2.90 and sd-HR 2.70, 95% CI 2.24–3.25) (Figure 3B).

#### Transfer to HD for infection

The peritonitis rate was 0.33 episode per patient-year. In the FG multivariable analysis, nurse-assisted PD patients had a lower risk of transfer to HD due to infection (sd-HR 0.74, 95% CI 0.57–0.97). Nurse-assisted PD was not associated with a lower risk of transfer to HD when the analysis was performed with a Cox model (cs-HR 0.87, 95% CI 0.68–1.10) (Figure 4A).

In the propensity-matched dataset assistance was not associated with the risk of transfer to HD due to infection either in the Cox or in the FG models (Figure 4B).

#### Transfer to HD for inadequate dialysis

In the multivariable analysis, nurse-assisted PD was associated with a lower risk of transfer to HD due to inadequate dialysis in both Cox and FG models (cs-HR 0.63, 95% CI 0.54–0.74 and sd-HR 0.51, 95% CI 0.44–0.61, respectively) (Figure 4A). This result remained consistent when using the propensity-matched cohort for the analysis (cs-HR 0.60, 95% CI 0.41–0.87 and sd-HR 0.46, 95% CI 0.32–0.67) (Figure 4B).

#### Transfer to HD for catheter-related problems

In the multivariable analysis, family-assisted PD was associated with a lower risk of transfer to HD due to catheter-related

problems in the Fine and Gray modelling (sd-HR 0.57, 95% CI 0.34–0.93). When using a Cox model for the analysis, the effect estimate was quite similar but the association barely lost its statistical significance (cs-HR 0.63, 95% CI 0.39–1.03). Family-assisted PD was associated with a lower risk of transfer in the FG model when the analysis was performed with the propensity-matched cohort (sd-HR 0.47, 95% CI 0.19–0.91) (Figure 4).

#### Transfer to HD for social issue

There was no association between assisted PD modality and the risk of transfer to HD due to social issue (Figure 4).

#### Transfer to HD for other causes linked to PD

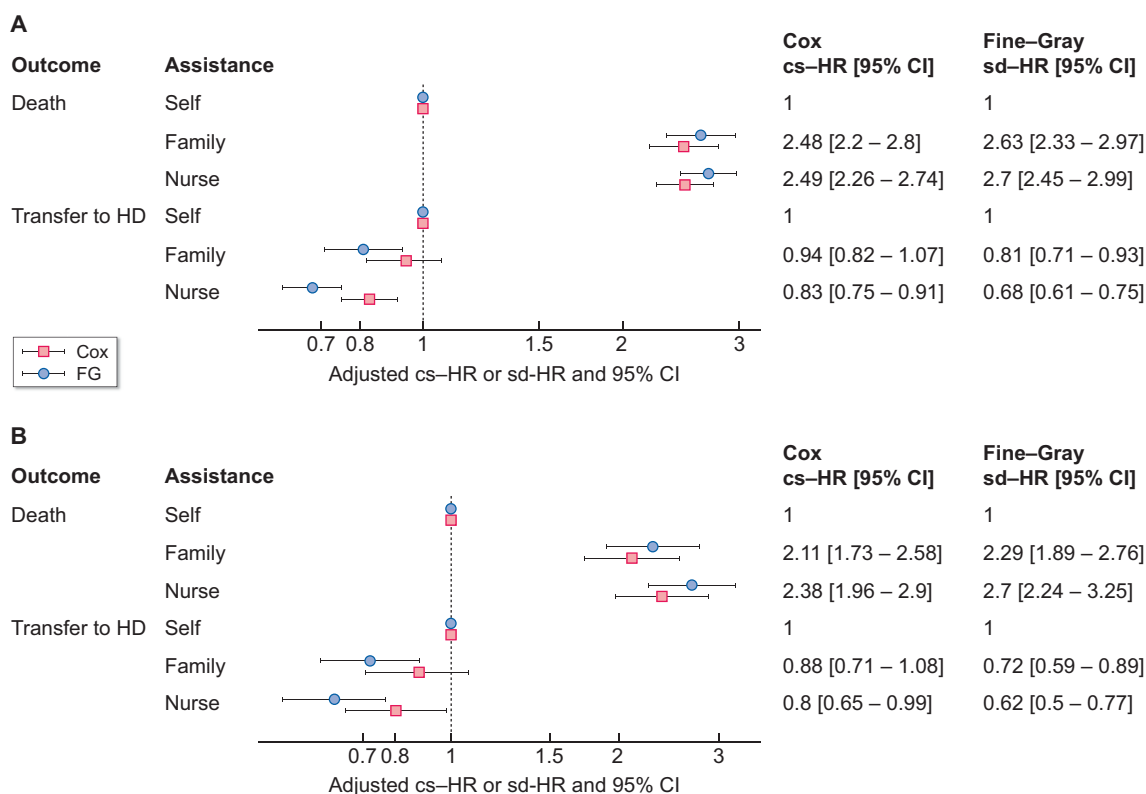
The risk of transfer to HD for other causes linked to PD was not significantly associated with family-assisted (cs-HR 0.96, 95% CI 0.65–1.4 and sd-HR 0.86, 95% CI 0.57–1.3) or nurse-assisted PD (cs-HR 0.87, 95% CI 0.66–1.15 and sd-HR 0.78, 95% CI 0.57–1.06) in the multivariable analysis performed with the full dataset (Figure 4A). With the propensity match dataset, the FG model showed that patients treated with nurse-assisted PD had a lower likelihood of transfer to HD (sd-HR 0.47, 95% CI 0.25–0.9) (Figure 4B).

#### Transfer to HD for other causes not linked to PD

No association was found in any of the multivariable models or in the propensity-matched cohort models between the assisted PD modality and the risk of transfer to HD due to other causes not linked to PD (Figure 4).

#### Sensitivity analyses

When considered as a binary variable (i.e. nurse or family assistance compared with no assistance) assistance



**FIGURE 3:** Effect of assistance on the risk of technique failure in FG and Cox survival analysis for the three competing events: death, transfer to HD and transplantation. (A) Multivariable models assessed on the unmatched cohort. (B) Models assessed on the propensity score-matched cohort. cs-HR and sd-HR are adjusted on age, sex, diabetes, causal nephropathy, modified CCI, treatment prior to PD, suboptimal starting of PD, PD modality, administrative centre type, presence of a dedicated nurse and centre size.

for PD was protective against transfer to HD in both Cox and FG models (cs-HR 0.86, 95% CI 0.78–0.94 and sd-HR 0.71, 95% CI 0.64–0.78). Assistance was associated with a lower risk of transfer to HD due to infection only in multivariable FG analysis (sd-HR 0.77, 95% CI 0.60–0.99), whereas the protective effect against transfer due to inadequate dialysis was consistent in both models (cs-HR 0.72, 95% CI 0.62–0.83 and sd-HR 0.59, 95% CI 0.50–0.68). No significant association was found with the four remaining causes of transfer to HD in the complete population (Table 2).

In the propensity-matched cohort, assistance was protective against the global risk of transfer to HD (cs-HR 0.70, 95% CI 0.63–0.78 and sd-HR 0.64, 95% CI 0.58–0.72), as against the risks of transfer due to infection (cs-HR 0.61, 95% CI 0.47–0.80 and sd-HR 0.59, 95% CI 0.45–0.77) and due to adequacy (cs-HR 0.54, 95% CI 0.45–0.64 and sd-HR 0.51, 95% CI 0.42–0.60) (Table 3).

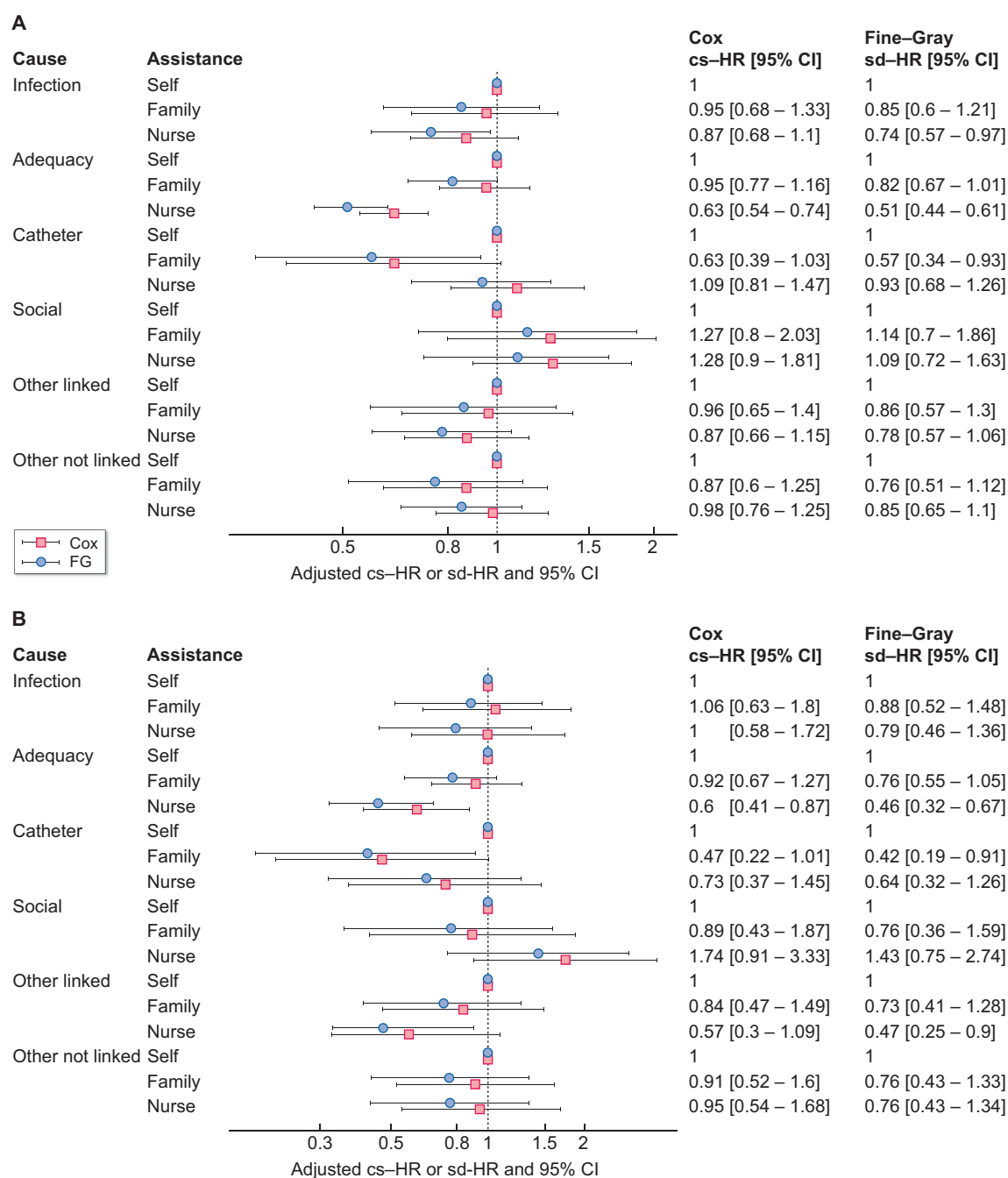
## DISCUSSION

In this large observational cohort of French patients, death was the primary cause of PD cessation, followed by transfer to HD.

Our study showed that patients treated by nurse- and family-assisted PD had a higher risk of death. To the best of our knowledge, the effect of assisted PD on patient survival has not

been evaluated to date. Even if there is no evidence, it is hard to believe that the association between death and nurse-assisted PD was causal. The association between assisted PD and the risk of death could be explained by a selection bias. Nevertheless, the propensity score approach showed that, whatever the modality of assistance, assisted PD was associated with a higher risk of death. However, propensity matching cannot reduce confounding attributable to unmeasured factors. For instance, disability and socioeconomic status, which could influence the risk of death, were not captured in the registry. It has been demonstrated that the utilization of assistance is decided by caregivers, based on their subjective evaluation, which could lead to selection bias [21]. Furthermore, the use of assisted PD could be a proxy of patient disability, which is a well-known risk factor of mortality [22].

Nurse-assisted PD was associated with a lower risk of transfer to HD, which was consistent with the result of a previous study from our team [13]. To our knowledge, only one study reported a lower risk of transfer to HD in assisted PD patients [23]. The lower risk of transfer to HD of assisted PD patients could reflect the nephrologist's willingness to avoid the transfer to HD of the oldest and most frail patients [24]. Patients with the shortest life expectancy may also have other priorities than transfer to HD [9]. Nevertheless, patient age, comorbidities were not associated with the risk of transfer to HD in our study (data not shown).



**FIGURE 4:** Effect of assistance on the risk of transfer. HD in FG and Cox survival analysis for the six competing events: transfer to HD due to infection, adequacy, catheter dysfunction, social issue, other causes linked with PD and other causes not linked with PD. (A) Multivariable models assessed on the unmatched cohort. (B) Models assessed on the propensity score-matched cohort.

In our work, the main cause of transfer to HD was inadequate dialysis followed by infection, whereas other studies have found infection to be the leading cause of transfer to HD [5–8].

Consistently in the different models developed, we found that assisted PD was associated with a lower risk of transfer to HD due to inadequate dialysis. Nephrologists must propose to their patients to increase the number of PD exchanges in CAPD, or to switch to APD in case of UF failure or to increase peritoneal clearance. These treatments reinforcements may be facilitated by the use of assistance in PD patients. In addition, in

France, private nurses are paid for the cyclor setup and line connections in APD and for one to four daily PD exchanges in CAPD. There is little difference in cost of treatments between nurse-assisted CAPD and nurse-assisted APD. This allows optimal PD prescription without any financial restrictions and may explain the lower risk of transfer to HD due to inadequate dialysis among the nurse-assisted PD patients. Notably, many more patients were treated with CAPD than APD in the nurse-assisted group. This finding is consistent with other studies from our team [20, 25]. One may speculate that the cyclor itself

**Table 2 Effect of assistance in multivariable Cox and FG survival models assessed on the unmatched population, with assistance considered as a binary variable**

Competing events	Cox cs-HR	95% CI	FG sd-HR	95% CI
Cause of PD cessation				
Death				
Self	Ref.		Ref.	
Assistance	2.49	2.27–2.74	2.69	2.44–2.96
Transfer to HD				
Self	Ref.		Ref.	
Assistance	0.86	0.78–0.94	0.71	0.64–0.78
Cause of transfer to HD				
Infection				
Self	Ref.		Ref.	
Assistance	0.88	0.70–1.10	0.77	0.60–0.99
Adequacy				
Self	Ref.		Ref.	
Assistance	0.72	0.62–0.83	0.59	0.50–0.68
Catheter				
Self	Ref.		Ref.	
Assistance	0.97	0.73–1.28	0.83	0.62–1.11
Social				
Self	Ref.		Ref.	
Assistance	1.25	0.89–1.72	1.10	0.75–1.61
Other linked to PD				
Self	Ref.		Ref.	
Assistance	0.89	0.68–1.15	0.79	0.59–1.07
Other not linked to PD				
Self	Ref.		Ref.	
Assistance	0.89	0.68–1.15	0.83	0.64–1.07

First part: analysis with the three competing events for PD cessation: death, transfer to HD and transplantation. Second part: analysis with the six competing events for transfer to HD.

may also induce anxiety in older subjects that could affect their quality of life and increase the risk of technique cessation [25].

We have previously reported that nurse-assisted PD was associated with a lower risk of infection in diabetic and elderly patients [26, 27]. In a study from Denmark, assisted PD patients had a lower risk of infection [28]. In our study, nurse-assisted PD was associated with a lower risk of transfer to HD due to infection only in the FG regression modelling. A high probability of presenting one of the competing events could explain the discrepancies between Cox and FG modelling. Due to the mechanism of the censoring, a higher risk of competing events in PD-assisted patients could explain the absence of direct association between nurse-assisted PD and the event of interest. A graphic explanation of this phenomenon is given in [Supplementary data, Figure S4](#). The cs-HR is better suited for studying the aetiology, whereas the sd-HR is used to predict the individual risk. Although there is no consensus on the best way to analyse competing risks, it is usually recommended to use both approaches [18, 19]. Of note in the sensitivity analysis, assisted PD (family or nurse assistance) was protective against transfer to HD due to infection for both Cox and FG modelling.

No significant association was found between the use of nurse-assisted PD or family-assisted PD and transfer to HD due to social cause or others causes not linked with PD. Family assistance was associated with a lower risk of transfer to HD

**Table 3 Effect of assistance in Cox and FG survival models assessed on the propensity-matched population, with assistance considered as a binary variable.**

Competing events	Cox cs-HR	95% CI	FG sd-HR	95% CI
Cause of PD cessation				
Death				
Self	Ref.		Ref.	
Assistance	4.54	3.98–5.16	6.82	6.01–7.74
Transfer to HD				
Self	Ref.		Ref.	
Assistance	0.70	0.63–0.78	0.64	0.58–0.72
Cause of transfer to HD				
Infection				
Self	Ref.		Ref.	
Assistance	0.61	0.47–0.80	0.59	0.45–0.77
Adequacy				
Self	Ref.		Ref.	
Assistance	0.54	0.45–0.64	0.51	0.42–0.60
Catheter				
Self	Ref.		Ref.	
Assistance	0.84	0.58–1.22	0.80	0.55–1.16
Social				
Self	Ref.		Ref.	
Assistance	1.15	0.77–1.72	1.10	0.73–1.64
Other linked to PD				
Self	Ref.		Ref.	
Assistance	0.88	0.64–1.20	0.84	0.61–1.15
Other not linked to PD				
Self	Ref.		Ref.	
Assistance	1.02	0.76–1.36	0.98	0.98–1.31

First part: analysis with the three competing events for PD cessation: death, transfer to HD and transplantation. Second part: analysis with the six competing events for transfer to HD.

due to catheter-related problems in FG models, but it was barely not significantly associated in the Cox models; however, the effect estimates are remarkably similar. A protective effect of family assistance against transfer to HD due to catheter-related problems could be explained by a better family environment with acceptable food and better health practices, limiting constipation and other causes of catheter dysfunction, and these subjects may be more patient and willing to cope with slower drains and more alarms [29–31].

Nurse-assisted PD was associated with a lower risk of transfer to HD due to miscellaneous causes linked to PD in the matched cohort, and only in the FG model. In the French healthcare system, the private nurse in charge of a PD patient is also reimbursed for home patient assessments and can contact the PD centre when required [32]. Consequently, it can be hypothesized that the nurse's assessments at the patient's home could prevent the transfer to HD in general.

The effect estimates of the different models assessed are quite similar whether competing events are included or not. Therefore, most of our findings do not seem to be predominantly influenced by the presence of competing events.

Denmark, Italy, Belgium, the Netherlands, Norway, Sweden, the Canary Islands, the UK, Canada, Brazil and China have developed assisted PD programmes to enhance PD access for elderly or non-self-sufficient patients [33]. However, assisted PD

programmes vary from one country to another, and the assisted PD modality (nurse or family) could differently influence the cause of transfer to HD; it is therefore of importance to understand how assisted PD could influence the outcome of PD. Our study showed that nurse-assisted PD and family-assisted PD operate differently on the causes of transfer to HD.

In the context of the global coronavirus disease 2019 (COVID-19) crisis, we could hypothesize that the use of assistance for PD could be a way to increase the use of home dialysis and to avoid in-centre HD exposure. However, one could raise concerns about the use of itinerant staff for nurse assistance. This question would deserve further studies.

Our study has a number of limitations. The retrospective nature of any registry study is associated with possible classification bias. The causes of PD technique cessation were declarative in the registry, which could lead to declaration bias. The matching on the propensity score led to a significant reduction in the number of patients and a decrease in statistical power. Additionally, propensity score use for matching has been the subject of recent criticism based on a paradoxical phenomenon that the use of this method can increase rather than decrease covariate imbalance [34]. Generalizability may not be appropriate to countries other than France, because the use of nurse assistance is largely conditional on national public funding.

In conclusion, in a country where assistance is covered by the national healthcare system, nurse- or family member-based assistance for PD exchange is associated with a lower risk of transfer to HD, especially due to dialysis adequacy. Nurse-assisted PD may decrease the risk of transfer to HD due to infection, but this finding needs further exploration. The benefits of assistance on the quality of life and the quality of treatment should be balanced with the costs of reimbursement, which could encourage decision makers to assume these costs [35].

## SUPPLEMENTARY DATA

Supplementary data are available at [ndt online](https://ndt.oup.com/ndt/advance-article/doi/10.1093/ndt/gyaa289/6032517).

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## AUTHORS' CONTRIBUTIONS

A.L. designed the study, analysed and interpreted the data, and drafted the manuscript. C.B., A.B. and M.F. analysed the data and provided intellectual content of critical importance. T.L. designed the study and interpreted the data.

## CONFLICT OF INTEREST STATEMENT

The authors have no relevant conflicts of interest to declare.

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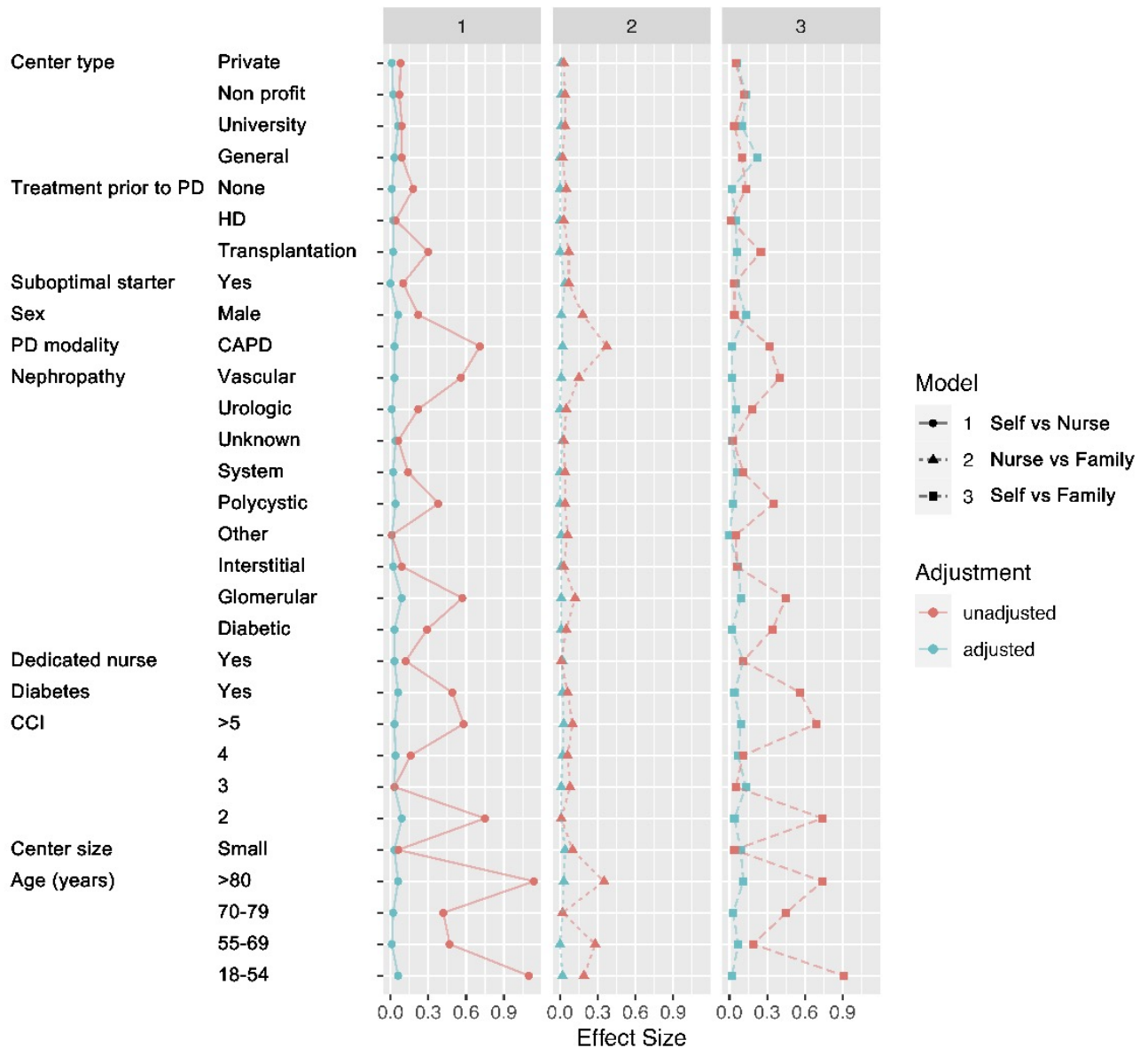


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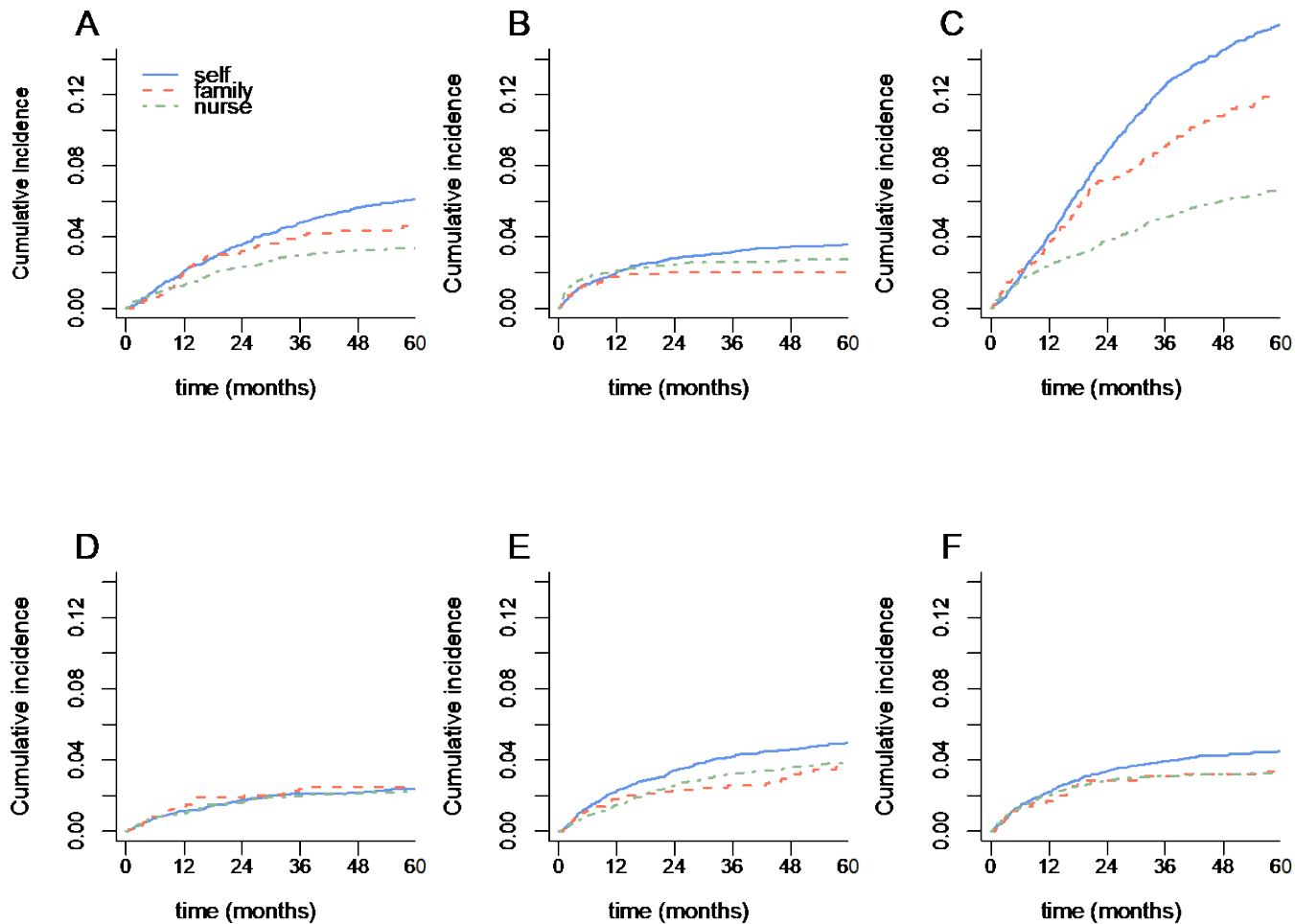
## SUPPLEMENTAL MATERIALS:

**Supplemental figure 1:** Effect sizes for the standardized differences before and after propensity score adjustment for covariables included in the three propensity scores that were used to match triplets of patients.



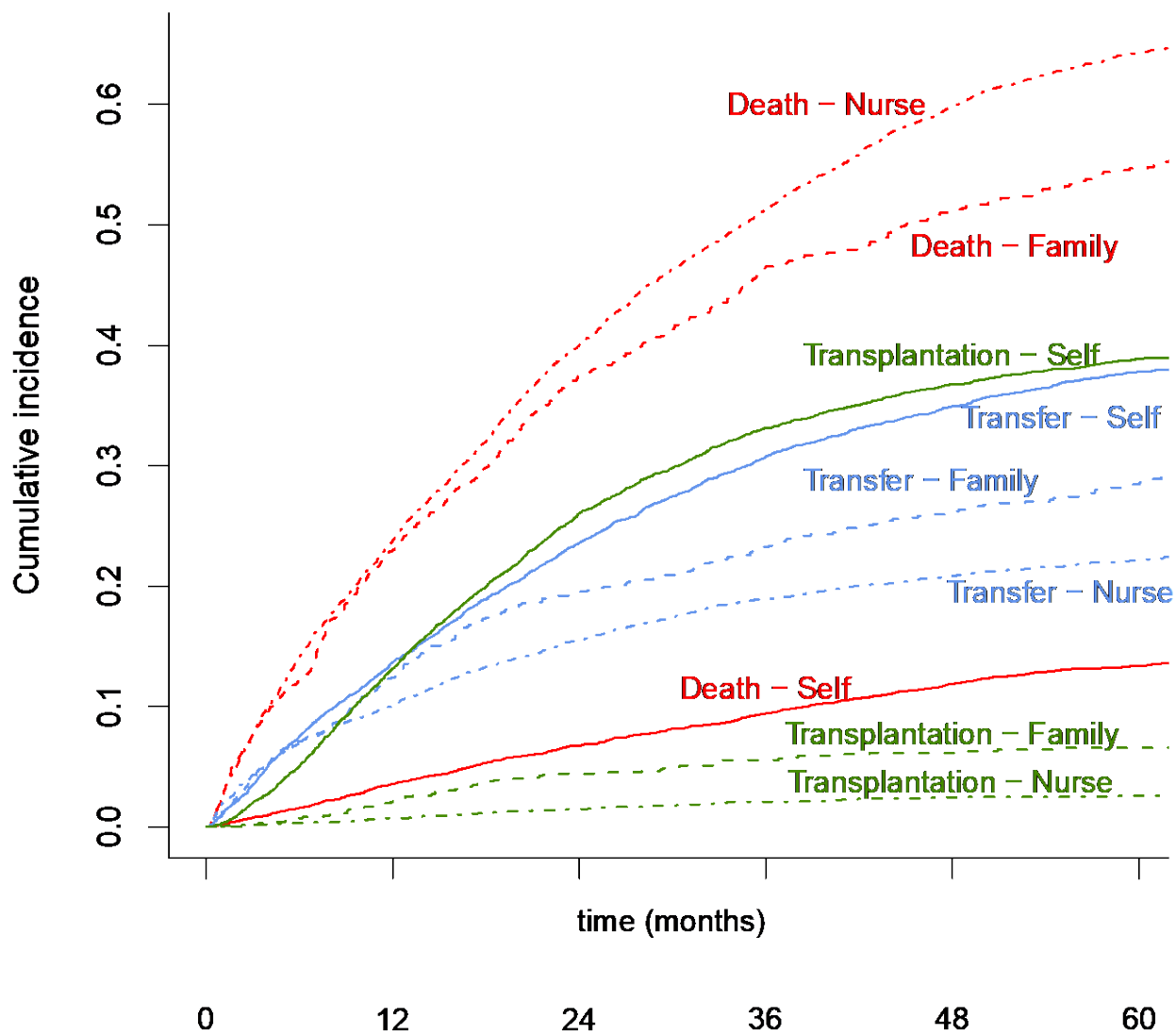
PD: peritoneal dialysis; HD: hemodialysis; CAPD: Continuous ambulatory peritoneal dialysis; CCI: Charlson comorbidity index

**Supplemental figure 2:** Cumulative incidental risk curves for the six main causes of transfer to hemodialysis according to the modality of assistance used.

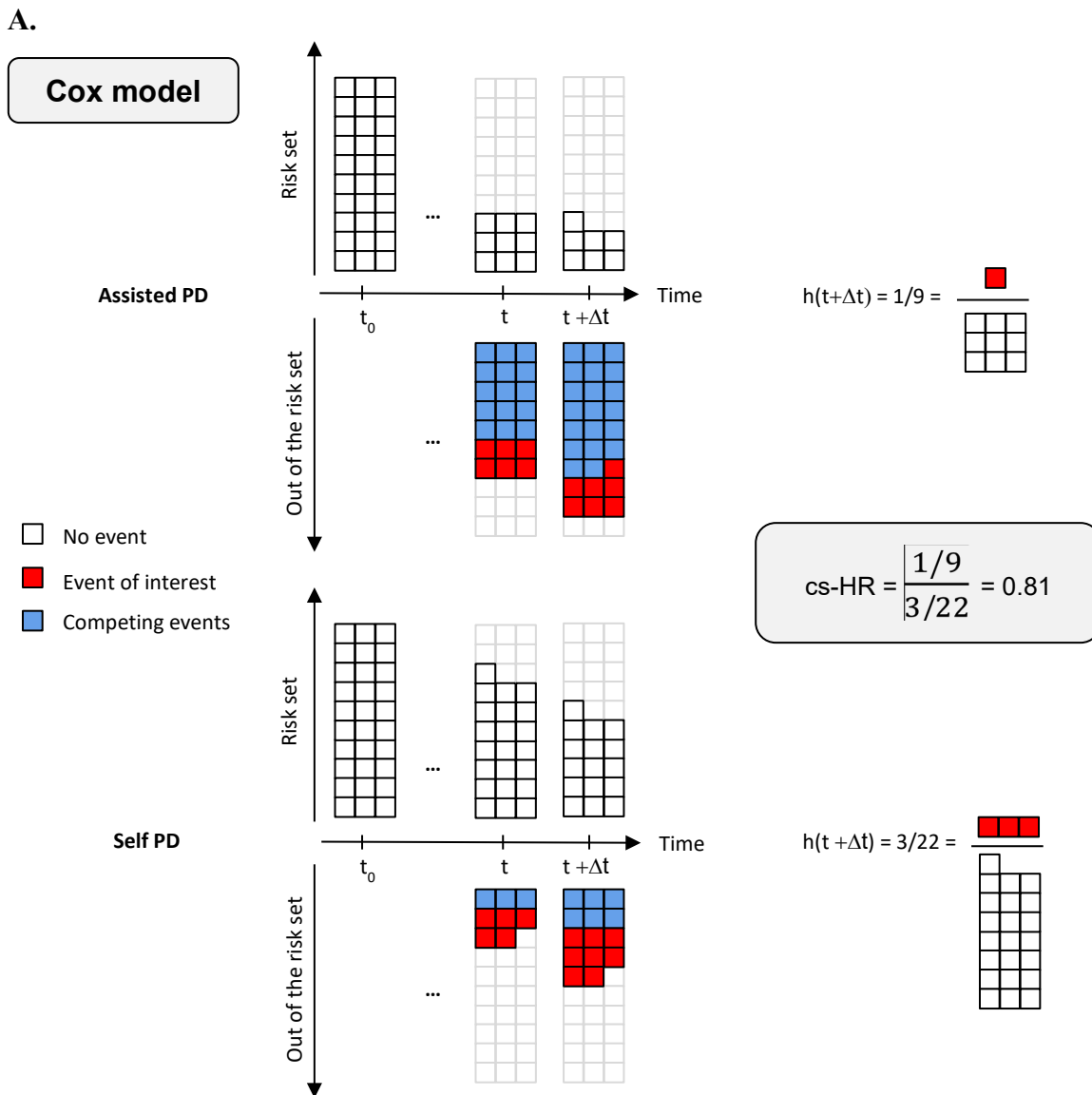


A: Transfer due to infection. B: transfer due to mechanical dysfunction. C: transfer due to inadequacy. D: transfer due to social issue. E: transfer due to other causes linked with PD. F: transfer due to other causes not linked with PD.

**Supplemental figure 3:** Cumulative incidental risk curves for the three competing events causing PD cessation according to the use of assistance.

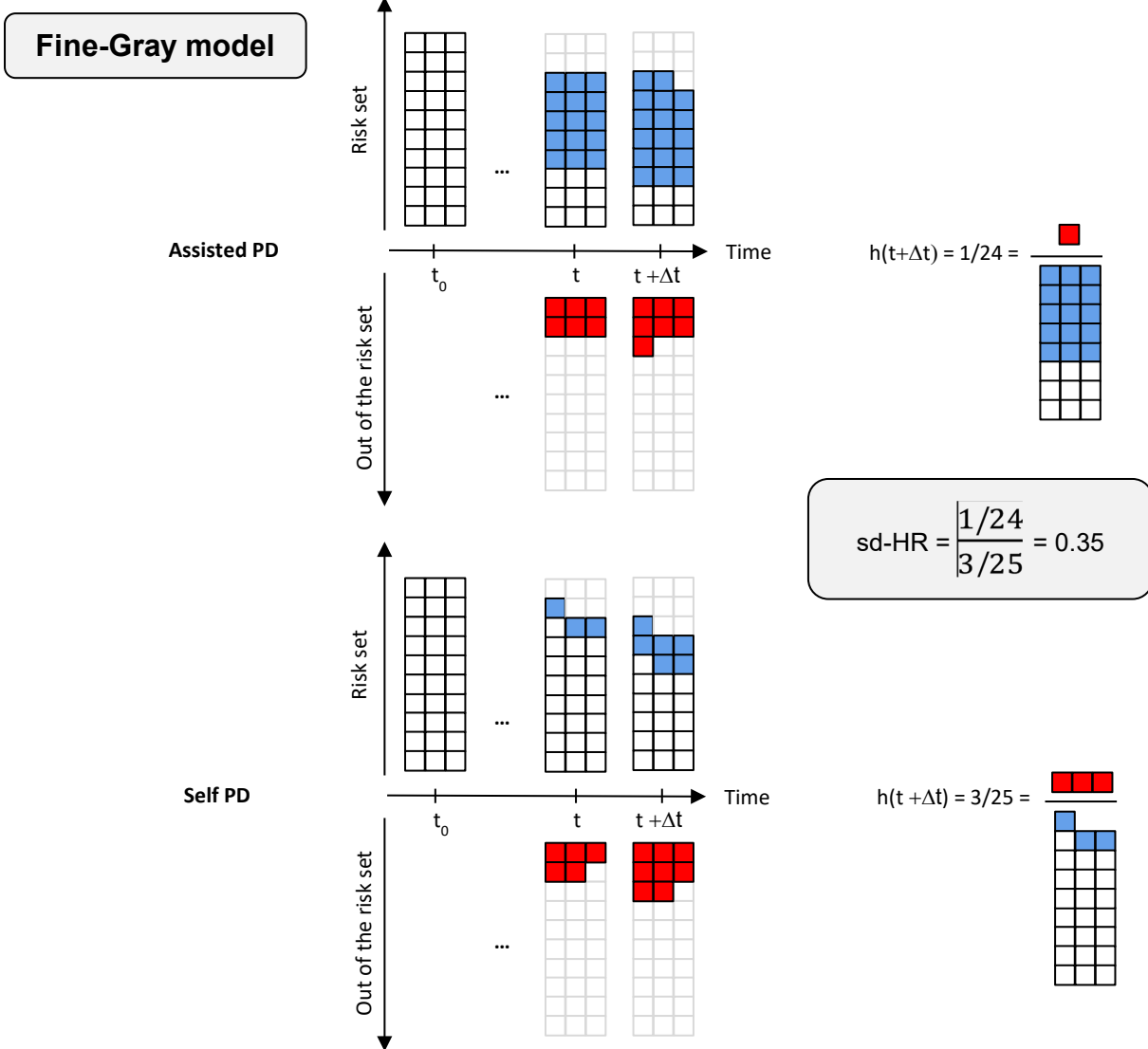


**Supplemental figure 4:** Visual representation of the assessment of A: cs-HR in Cox model and B: sd-HR in Fine-Gray model. Example of discrepancy between these two values.



Two groups of 60 patients are represented by 30 squares in the “assisted PD” group and 30 squares in the “Self PD” group. In the assisted group, at time “t”, 6 patients have presented the event of interest (red squares) and are censored for the later stages. Fifteen patients have presented one of the competing events (blue squares) and are also censored for the later stages and only  $30 - (6+15) = 9$  patients remain in the risk set. All these censored patients are excluded from the “risk set” for calculation of hazard rates. At time “t + Δt”, 1 new patient has experimented the event of interest. The hazard at time “t + Δt” in the “assisted PD” group is therefore  $1 / 9$ . In the same manner, in the “self PD” group, the hazard at time “t + Δt” is  $3/22$ . The cs-HR is the ratio of the hazards in the two group:  $\text{sc-HR} = 0.81$ .

B.



In the assisted group, at time “ $t$ ”, 6 patients have presented the event of interest (red squares) and are censored for the later stages. Fifteen patients have presented one of the competing events (blue squares) but unlike for the assessment of cs-HR, these patients are not censored, so  $30 - 6 = 24$  patients remain in the risk set. At time “ $t + \Delta t$ ”, one new patient has experimented the event of interest. The hazard at time “ $t + \Delta t$ ” in the “assisted PD” group is therefore  $1 / 24$ . In the same manner, in the “self PD” group, the hazard at time “ $t + \Delta t$ ” is  $3/25$ . The sd-HR is the ratio of the hazards in the two group:  $\text{sd-HR} = 0.35$ .

The difference in the calculation of cs-HR and sd-HR lie in the treatment of subjects who have experimented on of the competing events. In this example, numerous patients have experimented competing events in the “assisted PD” group compared to few in the “self PD” group. The consequence is a sd-HR substantially less than 1, whereas the cs-HR is just below 1.

## VI.4. Discussion

Au cours de ce troisième travail, nous nous sommes attachés à l'étude du rôle de l'assistance sur le risque de transfert en hémodialyse. Nous avons mis en évidence que le recours à l'assistance par un infirmier était associé à un moindre risque de transfert toutes causes confondues. Dans les différents modèles construits, l'effet de l'assistance était protecteur contre le risque de transfert en hémodialyse dû à une dialyse inadéquate. En revanche, les patients assistés par infirmier ou par un proche avaient un risque plus élevé de décès.

En plus de modèles de survie de Cox et Fine Gray que nous avons déjà utilisés précédemment, nous avons affiné nos outils d'analyse et avons utilisé un score de propension multiple. L'objectif de cette méthode est de limiter les biais de sélection inhérents aux études observationnelles, et particulièrement ici à un biais d'indication estimé important. La méthode de référence qui permet d'éliminer les biais de sélection est l'essai randomisé. Il paraît éthiquement très difficile de proposer la réalisation d'un essai dans lequel on tirerait au hasard l'attribution de l'assistance pour la dialyse péritonéale. L'utilisation d'une méthode utilisant un score de propension est donc tout naturellement indiquée ici.

Le score de propension a pour objectif de rendre comparable les groupes étudiés. Il est impossible de connaître le score de propension théorique réel car il existe toujours des caractéristiques non observées. Le score de propension calculé en pratique se base donc sur les covariables disponibles incluses dans son calcul. Un biais persiste donc toujours en raison de cette existence de facteurs confondants non mesurés. Nous avons trouvé que le risque de décès était plus important chez les patients assistés dans tous les modèles testés. Ce résultat ne doit pas être éludé mais mérite d'être discuté en détail. Selon nous, il

n'y a pas de rationnel susceptible d'expliquer un lien de causalité direct entre assistance et risque de décès. En revanche, on a pu remarquer que les caractéristiques des patients qui sont associées au recours à l'assistance sont des comorbidités associées à la mortalité, notamment l'âge et le score de Charlson. De nombreuses caractéristiques associées au risque de décès n'étaient pas incluses dans le calcul de notre score de propension, l'existence d'un handicap, d'addictions à des drogues, la consommation d'alcool ou le niveau socioéconomique pour n'en citer que quelques-unes. Toutes ces covariables sont sources de biais de confusion potentiels non mesurés. Ces hypothèses pourraient être explorées à l'aide d'une étude complémentaire par analyse de médiation dans laquelle on essaierait d'évaluer l'effet direct et l'effet indirect de l'utilisation de l'assistance sur le risque de décès des patients traités par dialyse péritonéale.

Nous avons montré que l'effet de l'assistance par un infirmier était surtout bénéfique contre le risque de transfert en hémodialyse dû à l'inadéquation de la dialyse péritonéale. On peut émettre plusieurs hypothèses sur les mécanismes expliquant ce résultat. Il est possible que les échanges réalisés par un infirmier soient plus efficaces, avec des drainages mieux réalisés. Ce temps de l'échange est en effet déterminant car l'insuffisance de drainage peut être source d'insuffisance d'ultrafiltration ou de mauvais renouvellement du dialysat, et donc d'efficacité de la dialyse. Il est également possible que l'assistance permette l'acceptation par les patients d'échanges supplémentaires en DPCA, associés à une augmentation de la dose de dialyse. Ce résultat est robuste puisque constant pour l'estimation des cs-HR des modèles de Cox et celle des sd-HR des modèles de Fine Gray, et qu'il est retrouvé dans les modèles multivariés ajustés sur la cohorte complète de patients comme dans les modèles calculés sur la cohorte formée par appariement au score de propension.



En France, les soins d'assistance par infirmier libéral au domicile sont pris en charge par la sécurité sociale. Cette singularité explique en partie la démographie des patients traités par dialyse péritonéale en France car grâce à cette prise en charge le traitement au domicile peut être proposé à des sujets âgés, porteurs de handicap ou isolés socialement. Ailleurs dans la plupart des pays du monde, la dialyse à domicile est surtout réservée aux sujets jeunes et autonomes [70]. L'assistance par infirmier libéral est l'option qui est mise en place en France, mais on peut signaler que certains pays ont développé d'autres types d'assistance, en faisant intervenir des travailleurs sociaux non infirmiers pour l'assistance à domicile. C'est le cas par exemple à Hong-Kong [70]. Nos résultats devraient, on l'espère, encourager les décideurs à mettre en place des dispositifs de remboursement de l'assistance pour les soins de dialyse péritonéale. De telles mesures pourraient entraîner une augmentation de l'incidence de la dialyse péritonéale en élargissant la population à qui cette technique est proposée, et également une augmentation de la prévalence en ciblant pour l'attribution de l'assistance les patients à risque de sous-dialyse. La réalisation d'études médico-économiques serait utile afin de quantifier le bénéfice apporté par l'usage de l'assistance en terme monétaire et en termes de QALI, grâce au bénéfice sur la survie technique qui permet d'éviter les surcoûts de l'hémodialyse en centre.

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## ***VII. Discussion générale***

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### **VII.1. Principaux résultats**

Nos travaux prennent ancrage dans la logique globale actuelle d'autonomisation des patients. La transplantation rénale est le meilleur traitement à proposer aux patients atteints d'IRCT, mais malheureusement tous les patients ne sont pas éligibles à ce traitement. Pour certains, les comorbidités sont telles qu'elles rendent les résultats d'une transplantation trop aléatoires, pour d'autres, des facteurs immunologiques interdisent l'accès à un greffon. Pour la majorité des patients, la dialyse est encore une étape incontournable qui peut durer plusieurs mois voire plusieurs années dans l'attente du précieux greffon. Il est donc encore nécessaire de s'intéresser à la dialyse et à ses différentes modalités.

Une importance croissante est apportée à la perception de la qualité des soins par les patients. La mesure des PROMS et PREMS (respectivement Patients-Reported Outcome Measures et Patient-Reported Experience Measures) s'inscrit ainsi dans cette optique [71]. Le poids des contraintes liées à l'IRCT et au traitement par dialyse est bien illustré par le terme de « fardeau », qui est le terme consacré dans la littérature scientifique pour qualifier les contraintes liées à la maladie chronique et ressenties par les patients [11]. Il est important de pouvoir proposer un choix entre plusieurs modalités aux patients afin de limiter la charge de ce fardeau. Quand un choix a été fait, l'équipe soignante doit se donner pour objectif de rendre possible le maintien de la technique choisie. L'arrêt de la dialyse péritonéale est donc un évènement primordial à considérer, comme cela a été souligné dans les études SONG-PD [Manera, AJKD 2020]. Le premier point à discuter concernant

cet évènement est sa dénomination, comme cela a clairement été signalé dans les témoignages de patients. Le terme d'échec technique devrait être banni en raison de sa connotation très négative. On préférera parler de survie technique ou de transfert de modalité.

Nous avons utilisé des données issues d'un registre national exhaustif. Il est très intéressant d'avoir de telles données afin de pouvoir établir des comparaisons avec les résultats obtenus dans d'autres pays. Une des grandes difficultés à l'établissement de comparaisons concernant l'analyse de la survie technique en dialyse péritonéale est la diversité des mesures rapportées. Nous avons utilisé une définition consistante de la survie technique, définie comme la durée depuis le début de la dialyse péritonéale jusqu'au transfert définitif en hémodialyse. Un transfert était considéré comme définitif après une durée de 2 mois sans reprise de la dialyse péritonéale. La définition australienne proposée en 2016 ne s'est pas imposée uniformément comme le prouvait la récente revue de littérature d'essais randomisés dans laquelle parmi 25 essais inclus sur le sujet, 17 définitions différentes étaient utilisées [21], [22]. Les termes de « survie technique », « transfert en hémodialyse », ou « échec technique » étaient utilisés et dans nombre d'études il n'était pas précisé si la définition incluait le décès ou la transplantation. La durée de transfert en hémodialyse nécessaire pour considérer l'évènement n'était précisée que dans 16% des cas. Le choix de cette durée est important car il conditionne les valeurs de survie estimée. Ainsi, dans l'étude de Lan en 2016 à partir du registre ANZDATA, la probabilité de revenir en dialyse péritonéale après un transfert en hémodialyse était de 24% quand le délai seuil de transfert adopté était de 30 jours, alors que cette probabilité était de 0,8% pour un délai seuil de transfert adopté de 365 jours [22]. Une approche standardisée a été suggérée en 2021 par une équipe canadienne pour rapporter les taux d'échec technique en dialyse péritonéale [73]. Il était proposé de considérer un transfert en

hémodialyse comme étant définitif après une période d'observation de 90 jours. Il sera souhaitable d'utiliser ce seuil lors des prochains travaux qu'on mettra en place.

Nos travaux ont débuté par l'étude d'une pratique de soins, en l'occurrence l'usage d'une antibioprophylaxie à la pose du cathéter de dialyse péritonéale, et de son effet sur le risque d'infection péritonéale précoce. L'importance de l'effet centre a bien été démontré, car la prise en compte de cet effet annulait l'effet statistiquement significatif de l'antibioprophylaxie sur le risque d'infection péritonéale. Nous avons alors souhaité analyser les pratiques de soins plus généralement et leurs répartitions au sein des centres de traitement. Pour cela, nous avons utilisé une méthode de classification des données par hiérarchie ascendante, sans a priori. Nous avons ainsi pu montrer que les pratiques de soins étaient hétérogènes entre les centres, mais qu'on pouvait déterminer des clusters de centres dont les pratiques étaient homogènes, et que le risque de transfert en hémodialyse était moins élevé dans un de ces clusters de centre. Ce résultat évoque la possibilité d'un effet de synergie entre l'association de certaines pratiques de soins dont l'effet pris individuellement ne serait pas significatif.

Les patients dont le choix se porte vers la dialyse péritonéale sont souvent motivés par la souplesse que leur autorise ce traitement. Cette souplesse est d'autant plus importante que la dialyse est réalisée en autonomie. L'autonomisation des patients nécessite un apprentissage préalable et nous nous sommes demandé dans quelle mesure cette phase d'apprentissage pourrait avoir un impact sur la survie de la technique. Nous avons choisi d'étudier l'infection péritonéale pour les raisons suivantes. D'une part, plus de la moitié des infections péritonéales sont le fait de germes Gram positifs [72]. Ces germes Gram positifs sont majoritairement manuportés. La prévention des erreurs de manipulation au cours des échanges et donc de l'apprentissage de la réalisation des échanges en asepsie est alors un élément crucial pour limiter le risque infectieux. D'autre part, l'infection

péritonéale a été décrite comme étant la première cause de transfert en hémodialyse [22]. Nous avons donc analysé l'effet des pratiques éducationnelles sur le risque d'infection péritonéale. De manière notable, l'usage de supports écrits était associé à une moins bonne survie sans péritonite alors que ce type de support est très répandu. Nos résultats concordent avec les recommandations internationales selon lesquelles il faut favoriser un apprentissage individualisé en s'adaptant aux préférences des patients.

Nous nous sommes intéressé au risque de survenue d'infection péritonéale au cours de certains de nos travaux car cet évènement est décrit comme la principale cause de transfert en dialyse et qu'il existait un rationnel en faveur d'une association avec certaines des variables que nous avons étudiées. Dans la dernière partie de cette thèse, nous avons cherché à analyser les déterminants de toutes les différentes causes du transfert en hémodialyse. Nous avons mis à profit les techniques statistiques acquises précédemment, à savoir l'imputation des données manquantes par équations chaînées et la gestion des risques compétitifs par évaluation des cs-HR et sd-HR. Ce travail nous a permis d'apprendre les techniques d'utilisation des scores de propension et d'appariement de groupes multiples. Nous avons montré qu'à la différence de précédentes études menées dans divers pays, en France, la première cause de transfert en hémodialyse était la sous-dialyse. Une originalité du système de soins français est de permettre l'utilisation large d'une assistance à domicile par un infirmier pour la dialyse péritonéale. Cette particularité nous a conduit à rechercher l'impact de l'assistance sur les différentes causes du transfert en hémodialyse. De manière consistante dans les différents modèles construits, l'assistance par infirmier était associée à un risque plus faible pour le transfert toutes causes confondues, ainsi que pour le transfert secondaire à la sous-dialyse. Il existait une association entre le recours à l'assistance et le risque de décès et nous pensons que ce point met en lumière une des limites de l'efficacité des scores de propension qui est

l'impossibilité de réduire les biais de confusion liés aux facteurs non mesurés. Seule la randomisation permet de dépasser cette limite de manière certaine.

## VII.2. Perspectives

Nos travaux ouvrent des pistes de réflexions multiples dans l'objectif d'améliorer la survie de la technique en dialyse péritonéale, et ainsi de permettre aux patients de rester traités avec la modalité de leur choix jusqu'à la transplantation rénale idéalement ou jusqu'au décès pour les patients qui ne pourraient pas bénéficier d'une transplantation.

Les associations de pratiques de soins bénéfiques contre le risque de transfert en hémodialyse pourraient être précisées afin de sélectionner un groupe de quelques pratiques dont on aimerait valider l'efficacité dans un essai randomisé.

L'éducation des patients pour la réalisation de la dialyse en autonomie est un domaine encore mal exploré. Notre étude est la première à avoir exploité les données du module « infirmier » du RDPLF. Ces données ont une très bonne granularité. On pourra notamment les utiliser pour explorer la survenue d'autres événements d'intérêts. Ces données sont une opportunité pour les infirmiers investis dans la recherche infirmière actuellement en plein essor.

Des travaux sont encore nécessaires pour explorer les effets de l'assistance selon le modèle français. La relation que nous avons confirmée entre l'usage de l'assistance et le décès mérite des analyses complémentaires dans le but de prouver que c'est bien la sélection des patients qui explique cette relation comme nous en faisons l'hypothèse. Il est important d'analyser plus en détail le lien entre le recours à l'assistance et le risque de décès. L'estimation des effets directs et indirects de l'assistance sur le décès par une

analyse de médiation devrait permettre d'éclaircir ce point en confirmant l'hypothèse de la présence de biais de confusion non mesurés.

Nous avons montré que la première cause de transfert en hémodialyse en France était la sous-dialyse. Parmi les différentes stratégies susceptibles de limiter spécifiquement ce risque, l'utilisation de la dialyse hybride pourrait être une solution adéquate. Il s'agit de la poursuite de la dialyse péritonéale associée à la réalisation d'une séance d'hémodialyse en centre par semaine. Cette modalité de traitement a fait preuve de résultats très encourageants au Japon où son utilisation est développée. Ainsi, par rapport à la dialyse péritonéale, la dialyse hybride est associée à une meilleure survie, une plus faible mortalité cardio-vasculaire, et un taux de transfert en hémodialyse plus faible [74]. Dans une étude transversale japonaise, la qualité de vie des patients traités par dialyse hybride était comparable à celle des patients traités par dialyse péritonéale, et supérieure à celle de ceux traités par hémodialyse [75]. Outre la limitation du risque de transfert en hémodialyse, on peut émettre l'hypothèse que cette modalité pourrait être une modalité de transition favorisant l'acceptabilité du transfert par les patients s'il devient nécessaire. De nombreux travaux restent à mener dans le champ de la transition entre les modalités de traitement par épuration extra-rénale.

Enfin, nous projetons d'étendre le champ de nos recherches à l'hémodialyse en centre en réalisant une étude sur une population de patients traités par toutes les techniques du domicile, dialyse péritonéale ou hémodialyse afin de mettre en lumière les caractéristiques globales associées à la survie des techniques du domicile. Nous avons pour cela le projet d'utiliser les données du registre REIN qui sont maintenant couplées au système national des données de santé (SNDS). Nous espérons pouvoir dégager des informations dont la portée sera double : définir les caractéristiques des patients correspondantes à divers risques de survie limitée en dialyse à domicile d'une part, et

déterminer des pratiques associées à une meilleure survie technique. Nous espérons que nos travaux contribueront à faire accroître la prévalence des techniques de dialyse à domicile pour l'amélioration de la qualité de vie des patients.



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## **IX. Valorisation des travaux de la thèse**

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### **VIII.1. Publications dans des journaux internationaux avec comité de lecture**

- Lanot A, Bechade C, Boyer A, Ficheux M, Lobbedez T. Assisted peritoneal dialysis and transfer to haemodialysis: a cause-specific analysis with data from the RDPLF. *Nephrol Dial Transplant*. 2020;25:330-339
- Bonnal H, Béchade C, Boyer A, Lobbedez T, Guillouët S, Verger C, Ficheux M, Lanot A. Effects of educational practices on the peritonitis risk in peritoneal dialysis: a retrospective cohort study with data from the French peritoneal dialysis registry (RDPLF). *BMC Nephrol* 2020;21:205
- Lanot A, Bechade C, Verger C, Fabre E, Vernier I, Lobbedez T. Patterns of peritoneal dialysis catheter practices and technique failure in peritoneal dialysis: a nationwide cohort study. *PLoS One* 2019 ;14 :e0218677

### **VIII.2. Communications orales**

- Réunion de formation continue de néphrologie aux Universités Catholiques de Louvain - Bruxelles / Visio le 15 janvier 2021 : « *Twitter et les réseaux sociaux pour les néphrologues* »
- Réunion commune de néphrologie Tenon – Pitié Salpêtrière, Paris le 22 janvier 2020 : « *Twitter pour le néphrologue* »
- 46<sup>èmes</sup> Séminaires Universitaires de Néphrologie - DP Star, Paris le 6 février 2020 : « *Clusters de pratiques en dialyse péritonéale et risque d'échec technique* »
- Congrès de la Société Française de Néphrologie Dialyse et Transplantation, Nancy le 05/10/2019. Session du Club des jeunes néphrologues : « *Twitter pour le néphrologue* »

- Congrès biennal : International Seminar of Renal Epidemiology (ISRE) à Paris le 12 juin 2019 : « Patterns of practices and risk of technique failure in peritoneal dialysis »
- Baxter Academy, Lyon 4 et 5 juin 2019 : « l'éducation thérapeutique en dialyse péritonéale »
- Baxter Academy, Lyon 4 et 5 juin 2019 : « l'échec technique en dialyse péritonéale ».
- Symposium du RDPLF à Montvillargène, le 26/04/2019 : « *comment soumettre un résumé à une revue à comité de lecture* »

### VIII.3. Autres publications pendant la durée de la thèse

- Lanot A, Kottler D, Béchade C. Prurit associé à la maladie rénale chronique. Néphrol Thérap 2021 [in press]
- Boyer A, Lanot A, Lambie M, Verger C, Guillouet S, Lobbedez T, Béchade C. Trends in Peritoneal Dialysis Technique Survival, Death, and Transfer to Hemodialysis: A Decade of Data from the RDPLF. Am J Nephrol. 2021;27:1-10
- Boyer A, Lanot A, Lambie M, Guillouet S, Lobbedez T, Béchade C. Trends in assisted peritoneal dialysis over the last decade: a cohort study from the French Peritoneal Dialysis Registry. Clin Kidney J. 2020;13:1003-1011
- Beaumier M, Ruet A, Boyer A, Lanot A, Guillouet S, Lobbedez T & Béchade C. Hand function assessment in peritoneal dialysis patients: a pilot study. J Nephrol 2020;34:483-491
- Boyer A, Bonnamy C, Lanot A, Guillouet S, Béchade C, Recorbet M. Comment prendre en charge une hernie abdominale en dialyse péritonéale. Nephrol Ther 2020 ;16 :164-170
- Boyer A, Gautier N, Comoiz F, Hurault de Ligny B, Aouba A, Lanot A. Néphropathie associée à une vascularite urticarienne hypocomplémentémique : présentation d'un cas clinique et revue de la littérature. Nephrol Ther 2020;16:124-135

- Lanot A, Verger C. Comment faire accepter un résumé ou abstract dans un congrès. Bulletin de la Dialyse à Domicile. 2019 ;2 :71-73
- Guillouët S, Boyer A, Lanot A, Ficheux M, Lobbedez T, Béchade C. Assessment for assisted peritoneal dialysis by peritoneal dialysis nurses: results of a cohort study. Am J Nephrol 2019;50:489-498
- Beaumier M, Rioult JP, Georges M, Brocheriou I, Lobbedez T, Lanot A. Mushroom Poisoning Presenting With Acute Kidney Injury and Elevated Transaminases. Kidney Int Rep 2019;4 :877-881
- Viron C, Lobbedez T, Lanot A, Bonnamy C, Ficheux M, Guillouët S, Béchade C. Simultaneous removal and reinsertion of the PD catheter in relapsing peritonitis. Perit Dial Int 2019 ;39 :282-288
- Fedi M, Falaise C, Lanot A, Von Kotze C, Robert T, Piétri L, Henri P, Delmotte N, Botta D, Verhelst D, Chambost H, Brunet P, Jourde-Chiche N. Prise en charge néphrologique des patients hémophiles A : difficultés diagnostiques et thérapeutiques illustrées par le cas de 2 patients. Néphrol Ther 2019;15:77-81

#### **VIII.4. Activités éditoriales et de reviewing**

Editeur associé de *Néphrologie et Thérapeutiques* depuis 2020

Activités de reviewing pour les journaux :

Peritoneal Dialysis International, BMC Nephrology, Néphrologie & Thérapeutiques, International Journal of Environmental Research and Public Health, Toxins, Journal of Clinical Medicine, Medicina, Antibiotics.

Profil publons : <https://publons.com/a/1635128/>

Membre du conseil scientifique du club des jeunes néphrologues



## **Survie technique en dialyse péritonéale**

Les traitements d'épuration extra-rénale imposent aux patients des contraintes importantes, et les modalités du domicile qui offrent pourtant une meilleure qualité de vie sont sous-utilisées au profit de l'hémodialyse en centre. La prévalence en dialyse péritonéale (DP) est faible en raison d'une incidence insuffisante, mais également d'une survie technique souvent limitée.

Notre objectif était de déterminer quels étaient les facteurs associés au risque de transfert vers l'hémodialyse en centre chez les patients traités par dialyse péritonéale en France à partir de données de registre.

Nous avons montré que si les pratiques de soins liées au cathéter de dialyse péritonéale étaient hétérogènes entre les centres, il existait des clusters de centres dont les pratiques étaient homogènes et que le risque de transfert en hémodialyse variait entre ces clusters. L'analyse des pratiques proposées pour l'apprentissage de la dialyse péritonéale en autonomie nous a montré qu'il ne semblait pas exister de support pédagogique unique associé à une diminution du risque d'infection péritonéale. Enfin, nous avons mis en lumière que l'assistance par infirmier à domicile en dialyse péritonéale était associée à une meilleure survie technique et tout particulièrement à un moindre risque de transfert en hémodialyse pour cause de sous-dialyse.

La compréhension de ce mécanisme de la survie technique en dialyse péritonéale est importante pour les patients. La liberté de choisir un traitement au domicile et la possibilité de la maintenir dans le temps sont des leviers d'amélioration de la qualité de vie et de l'autonomisation des patients.

**Mots-clés :** Dialyse péritonéale, dialyse à domicile, échec technique, infection péritonéale, éducation des patients

## **Peritoneal dialysis technique survival**

Dialysis is associated with a significant burden of care for patients, and home modalities, which offer a better quality of life, are underused in favor of in-center hemodialysis. The prevalence of peritoneal dialysis is low due to an insufficient incidence, but also often to a limited technique survival.

Our objective was to determine the factors associated with the risk of transfer to in-center hemodialysis in patients treated by peritoneal dialysis in France from registry data.

We showed that peritoneal dialysis care practices related to the catheter were heterogeneous between centers. However, clusters of centers with homogeneous practices were identified, and these clusters were associated with different risk of transfer to hemodialysis. The analysis of the practices used for autonomous peritoneal dialysis learning showed us that no single pedagogical support was associated with a decrease in the risk of peritoneal infection. Finally, we highlighted that the use of nurse assistance at home for peritoneal dialysis was associated with a better technique survival and especially with a lower risk of transfer to hemodialysis because of under-dialysis.

Understanding this mechanism of peritoneal dialysis technique survival is important for patients. The freedom to choose a treatment at home and the possibility to maintain it over time are levers for improving the quality of life and empowerment of patients.

**Keywords:** Peritoneal dialysis, home dialysis, technique failure, peritoneal infection, patient's education