Nephrol Dial Transplant (2018) 33: 1411–1419
doi: 10.1093/ndt/gfy007
Advance Access publication 13 February 2018

ndt
Nephrology Dialysis Transplantation

Survival advantage of planned haemodialysis over peritoneal dialysis: a cohort study

Alicia Thiery[1], François Séverac[2,3], Thierry Hannedouche[4,5], Cecile Couchoud[6], Van Huyen Do[3], Aurélien Tiple[7], Clémence Béchade[8], Erik-Andre Sauleau[2,3,4] and Thierry Krummel[5] on behalf of the REIN registry

[1]Department of Public Health, Centre Paul Strauss, Strasbourg, France, [2]Department of Public Health, Strasbourg University Hospital, Strasbourg, France, [3]Biostatistical Laboratory, Laboratory ICube, University of Strasbourg, Strasbourg, France, [4]School of Medicine, University of Strasbourg, Strasbourg, France, [5]Department of Nephrology and Dialysis, Strasbourg University Hospital, Strasbourg, France, [6]Biomedicine Agency, Paris, France, [7]Department of Nephrology, Dialysis and Transplantation, Clermont-Ferrand University Hospital, Clermont-Ferrand, France and [8]Department of Nephrology, Dialysis and Transplantation, Caen University Hospital, Caen, France

Correspondence and offprint requests to: Thierry Krummel; E-mail: thierry.krummel@chru-strasbourg.fr

ABSTRACT

Background. Previous studies comparing the outcomes in haemodialysis (HD) with those in peritoneal dialysis (PD) have yielded conflicting results.

Methods. The aim of the study was to compare the survival of planned HD versus PD patients in a cohort of adult incident patients who started renal replacement therapy (RRT) between 2006 and 2008 in the nationwide REIN registry (Réseau Epidémiologie et Information en Néphrologie). Patients who started RRT in emergency or stopped RRT within 2 months were excluded. Adjusted Cox models, propensity score matching and marginal structural models (MSMs) were used to compensate for the lack of randomization and provide causal inference from longitudinal data with time-dependent treatments and confounders including transplant censorship, modality change over time and time-varying covariates.

Results. Among a total of 13 767 dialysis patients, 13% were on PD at initiation of RRT and 87% were on HD. The median survival times were 53.5 months or 4.45 years and 38.6 months or 3.21 years for patients starting on HD and PD, respectively. Regardless of the model used, there was a consistent advantage in terms of survival for HD patients: hazard ratio (HR) 0.76 [95% confidence interval (95% CI) 0.69–0.84] with the Cox model using propensity score; HR 0.67 (95% CI 0.62–0.73) in the Cox model with censorship for each treatment change; and HR 0.82 (95% CI 0.69–0.97) with MSMs. However, MSMs tended to reduce the survival gap between PD and HD patients.

Conclusion. This large cohort study using various statistical methods to minimize the bias appears to demonstrate a better survival in planned HD than in PD.

Keywords: dialysis, end-stage kidney disease, haemodialysis, peritoneal dialysis, survival

INTRODUCTION

Over 2 million people worldwide currently receive treatment with dialysis or a kidney transplant, and the prevalence of dialysis therapy for kidney failure is increasing at a much faster rate than population growth in most parts of the world [1]. Worldwide, nearly 90% of patients who require dialysis are maintained on haemodialysis (HD) and 10% on peritoneal dialysis (PD).

Over the past decades, several single-centre, multicentre and national-registry studies have compared the outcomes of end-stage renal disease (ESRD) patients treated with HD and PD. Despite the multitude of comparisons, the question remains whether any of the differences in outcomes are attributable to the dialysis modality or are a result of unmeasured differences in the characteristics of the patients who choose a given modality.

All observational studies comparing PD and HD, regardless of the statistical techniques used for matching patients, were inevitably affected by residual confounding owing to unmeasured baseline differences in the types of patients who choose PD over HD. Only a randomized controlled trial would enable answering the question as to whether it is best for a patient to begin on HD or PD, although there is some doubt that such a study would ever be performed. For comparing renal replacement therapy (RRT) modalities, blinding is impossible and randomization is difficult given that patients may not agree since the techniques may considerably affect their lifestyle [2].

Studies comparing HD versus PD have been retrospective in nature and the inherent biases may explain the conflicting

results regarding the survival differences between HD and PD. Some studies showed a benefit of PD [3–5], which was restricted most often to the first 2 years of treatment [6–8] or within specific populations lacking comorbidities [6, 9]. Other studies found either similar results [10–12] or an advantage for HD [13–17], specifically in older patients or those with congestive heart failure.

Of note, patient clinical patterns may differ according to both dialysis modality and local guidelines [12, 18, 19]. In addition, PD patients are heterogeneous and include on one hand a subgroup of young patients with few comorbidities who are more likely to receive a kidney transplant and, on the other hand, a subgroup of old or very old patients, some with heart failure and reduced life expectancy (indication bias) [12, 18]. Moreover, patients can change RRT modality, usually switching from PD to HD, resulting in further confounder bias [7, 20]. In the French REIN registry (Réseau Epidémiologie et Information en Néphrologie) for example, the mean duration of treatment by PD was 18 months [21].

Two other major biases have generally not been taken into account in previous studies: first, PD patients generally start RRT at a higher estimated glomerular filtration rate (eGFR) than HD patients, thereby falsely increasing the apparent survival (lead time bias or immortal time bias) [22, 23]; secondly, emergency initiation on a central venous catheter was generally restricted to HD and the harbinger of a worse prognosis [24, 25]. In the REIN registry, emergency initiation of RRT accounted for one-third of incident patients, and patients starting dialysis on a central venous catheter displayed an excess mortality rate of ∼10%, which would worsen the overall prognosis of HD patients [26], (A. Michel *et al.*, submitted for publication).

In addition to most studies not considering the aforementioned biases, many authors furthermore used statistical methods such as Log-rank and Cox models with limited adjustment on variables of interest such as age and comorbidities. Despite several model variations including different methods of censorship, bias control was generally limited [27].

The aim of the present study was to compare the survival of patients starting planned HD or PD in a large contemporary nationwide cohort of incident dialysis patients. We compared the performance of various models including classic Cox models, propensity score, a Cox model with time-dependent covariates to consider each treatment change as well as marginal structural models (MSMs) with a graphical adjustment method in order to compensate for the lack of randomization and to take into account the confounding factors including transplant censorship, modality change over time and time-varying covariates.

MATERIALS AND METHODS

Data extraction

Data were extracted from the REIN registry, an exhaustive national registry of patients with ESRD in France that has been running since 2002 [28]. In the registry were included all patients starting a first RRT including HD, PD and preemptive kidney transplant. Data on date of dialysis initiation, death, transplantation and change of treatment modalities, comorbidities, handicap, occupational activity and certain laboratory analyses were collected in the registry initially and thereafter on an annual basis. All patients who were at least 18 years old at the beginning of dialysis and who started dialysis between 1 January 2006 and 31 December 2008 were selected for the present analysis. Excluded were patients who were declared as starting dialysis in emergency (preregistered item in the registry database) or were weaned from dialysis for renal recovery within 60 days. Emergency treatment was retained whenever the first dialysis was performed within 24 h after an evaluation by a nephrologist due to a threatening medical condition including overhydration, severe hyperkalaemia or acidosis, poorly tolerated anaemia, pericarditis or uraemic encephalopathy. The presence of one among these criteria defined emergency treatment initiation, which also included acute decompensation despite early referral and regular follow-up by a nephrologist. Patients were censored at the date of the first kidney transplant, or at the date of their last follow-up. Considering the median lifetime of patients with ESRD, estimated at ∼5 years (United States Renal Data System register and REIN registry), a minimal follow-up period of 5 years was defined until 31 December 2013, the study end date.

Statistical analysis

Descriptive and univariate analyses. Social, demographic, clinical and biological characteristics at the initiation of dialysis were described by initial dialysis mode and for transplanted patients. For each group, quantitative variables are presented as their mean and standard deviations (SDs) and compared between dialysis modality groups with Student tests if following a Gaussian distribution (graphical assessment completed by Shapiro–Wilk tests when in doubt), or a Wilcoxon's rank test if following a non-Gaussian distribution. Similarly, for each group, the qualitative variables are described by their absolute numbers and percentages and subsequently compared using Pearson's χ^2 test.

'Classical' survival analyses (Model 1). In a first step, a graphical description of dialysis survival according to the initial dialysis method was performed using the Kaplan–Meier method with a Log-rank test for the study of gross survival. Thereafter, adjusted survival was studied using proportional hazard Cox models. This first analysis was performed by censoring the patient during the kidney transplant and also 2 months after the first change of treatment and with adjustment for potential confounding factors using a stepwise regression including age, chronic respiratory failure, coronary heart disease, cancer or diabetes. The proportionality of the risks was verified.

Survival analysis using propensity score (Model 2). In order to control for the numerous confounding factors, the relationship between the modality of dialysis and the initial characteristics of the patients was modelled by the propensity score approach. Propensity score was retrieved from predicted probabilities of being treated by PD or HD according to the patient's

initial characteristics in a logistic regression model. According to clinical expertise, the following variables that were significantly related to the treatment were included in the analysis [29]: gender, primary renal disease, being enrolled on a transplant waiting list, heart failure, occupational activity, diabetes, cancer, serum albumin, haemoglobin concentration, eGFR at initiation, age, a transport time of more than 1 h to reach a dialysis facility and deprivation index Fdep99. This latter index is estimated with the city of residence and is dependent on unemployed proportion, workers proportion, median wage and proportion of children >15 years old and out-of-school without vocational certificate or high school diploma [30]. Then, a propensity score matching approach using a maximum tolerated difference between matched subjects of 0.01 and a ratio 1:3 was performed in a Cox model in order to study survival [31]. This second analysis was performed by censoring the patient during the kidney transplant and also 2 months after the first change of treatment. Regarding the distribution of baseline covariates in the matching database by treated and untreated subjects, we added supplemental adjustment if necessary [32].

Survival analysis taking into account each treatment course, MSMs and combined selection methods for adjustment covariates. MSMs are based on a counterfactual approach that defines causality by comparing the observed event and the counterfactual event that would have been observed if contrary to the fact the subject had received a different exposure than the one actually received. MSMs have been developed to address the issue of time-varying confounding, using the inverse probability weights (IPWs). IPWs were estimated by combining the inverse probability of treatment weights (IPTWs) and inverse probability of censoring weights (IPCWs) [33, 34]. The IPTW (or IPCW) was computed from the ratio of the estimated probabilities of treatment (or censorship) using baseline covariates (numerator) to the estimated probabilities of treatment (or censorship) using baseline and time-dependent covariates (denominator). In this study, treatment was the dialysis modality and censorship was kidney transplantation.

For estimating IPTW, available data that were deemed as important for choice of dialysis modality were selected. Baseline covariates used in the analysis included occupational activity, age at the start of dialysis, primary renal disease, eGFR at initiation and gender. Time-dependent covariates included: diabetes, heart failure, cancer, serum albumin concentration, haemoglobin concentration, deprivation index (Fdep99), inscription on kidney transplant waiting list and travel time between home and dialysis facility.

For estimating IPCW, available data that were deemed as important for correlation with access to kidney transplantation were selected. Retained baseline covariates were: work activity, age at the start of dialysis, primary renal disease and eGFR at initiation. Retained time-dependent covariates were heart failure, coronary heart disease, arrhythmias, chronic respiratory failure, deprivation index (Fdep99) and RRT modality.

Each dialysis pathway was taken into account with censorship at each change in treatment, with two models being created: in the first model (referred to as 'Model 3'), parameters of the Cox regression were estimated without the use of IPWs, whereas, in the second model ('Model 4'), IPWs were used in a weighted Cox regression.

Both models were adjusted using a combined covariates selection method based on directed acyclic graphs (DAG) in addition to the previous selection from clinical expertise. A DAG is a visual representation of the causal relationships believed to exist between variables of interest, including exposure, outcome and potential confounding variables [35–40]. After creating a diagram for the research question (clinically selected covariates, dialysis modality and survival), a set of rules described by Pearl, Shrier and Platt and based on a foundation of rigorous mathematics (d-separation) [40, 41], was applied to determine which of the measured variables must be controlled in the statistical analysis to produce an unbiased estimate of the effect for an exposure.

Each analysis was also performed without adjustment and results were compared with and without adjustment.

Missing data were not imputed although it was decided not to use covariates with more than 30% of unavailable data.

All analyses were performed using the R software (v3.2.2) (opensource, The R Foundation, www.r-project.org) with appropriate packages while DAG were created and analysed with DAGitty (v2.3) (@cran.r-project.org) [42].

RESULTS

Descriptive and univariate analyses

Among a total of 13 767 incident dialysis patients retained for analysis, 1748 (13%) were on PD at initiation of RRT and 12 019 (87%) were on planned HD. During follow-up, one quarter of PD patients switched to HD and only 1% changed from HD to PD (Figure 1). Characteristics of the patients at initiation of RRT are described in Table 1. Patients treated with PD globally were younger, started dialysis at a higher eGFR level, more often had a working activity and were more often on a transplant waiting list at dialysis initiation. In contrast, they were less frequently diabetic and less often experienced history of cancer, but more often had heart failure.

During follow-up, respectively 23.1% and 26.9% of the patients treated initially by HD and PD underwent a kidney transplant ($P < 0.001$).

'Classic' survival analyses

Over the follow-up period, there were 7181 deaths (52%), while the median survival time was 1627 days (4.45 years) for patients initially treated by planned HD and 1174 days (3.21 years) for patients originally receiving PD ($P < 0.001$). Crude mortality rates in both dialysis methods (PD, HD) are shown in Figure 2. Overall annual Kaplan–Meier survival is shown in Figure 3 and for discrete age groups in Supplementary data, Figures S1–S3.

In the first Cox model (Model 1), which included only the first modality of treatment and adjusted for the variables chosen by a stepwise regression method (age, cancer, diabetes, coronary disease and chronic respiratory insufficiency), the hazard ratio

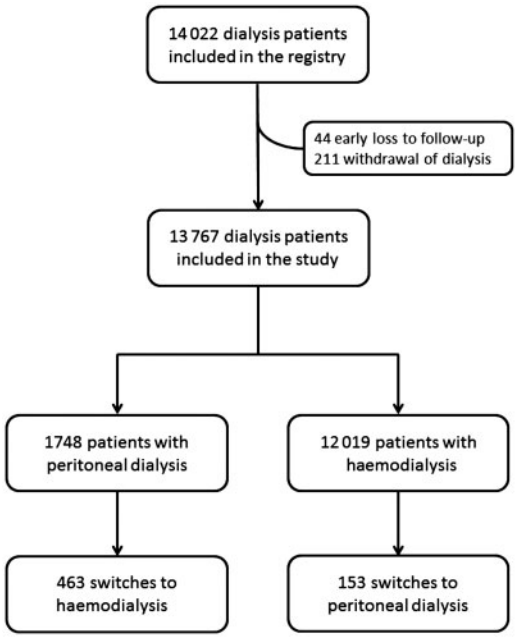

FIGURE 1: Flow chart of patients included in the study.

(HR) for survival was 0.76 [95% confidence interval (95% CI) 0.71–0.82] in favour of planned HD.

Survival analysis using a propensity score

The propensity scores, calculated for each of the 7523 patients for whom the data (variables significantly related to the treatment) were complete, averaged 0.85 (SD ± 0.06) in patients initially on planned HD and 0.82 (SD ± 0.08) in patients receiving PD. After matching, a total of 4193 patients were retained for analysis, of which 3088 patients were on HD and 1105 were on PD. The propensity scores averaged 0.83 (SD ± 0.06) in patients initially on planned HD and 0.82 (SD ± 0.07) in patients receiving PD (Figure 3).

In the Cox model adjusted for age, diabetes, coronary heart disease and chronic respiratory insufficiency, the HR for survival was 0.76 (95% CI 0.69–0.84) in favour of planned HD.

Survival analysis taking into account each treatment course without weighting

In the Cox model with censorship for each treatment change and adjusted for covariates obtained from the graphical method (age, eGFR at initiation, diabetes, respiratory failure, heart failure, cancer, transplant waiting list, stroke, primary renal disease, smoking status, peripheral vascular disease, handicap, cirrhosis) (Model 3), the HR for survival was 0.67 (95% CI 0.62–0.73) in favour of planned HD.

MSMs

In a further series of analyses, IPWs were calculated for all complete cases (8867 patients). Mean IPTWs and mean IPCWs were 1.07 (SD ± 1.85) and 0.99 (SD ± 0.16), respectively. The combined mean IPW was 1.06 (SD ± 1.91).

In the MSM (Model 4) adjusted for covariates obtained from the graphical method, the HR for survival was 0.82 (95% CI 0.69–0.97) in favour of planned HD.

Results from the different models with and without adjustment are summarized in Table 2.

DISCUSSION

In this nationwide cohort of incident dialysis patients comparing survival in planned HD and PD, we found that planned HD patients had a lower adjusted risk of death. Adjustment was made for known confounders including time-dependent covariates, modality switch and transplant censorship, with findings consistent across age ranges and presence or absence of specific comorbidities including diabetes, obesity and congestive heart failure.

Studies comparing the outcome of PD versus HD patients have yielded contrasting results worldwide [43]. These discrepancies may result from differences in initial clinical patterns, various biases unaccounted for in the analysis or inadequate adjustments.

Conflicting results from a North-American study by Lukowsky *et al.* have suggested that patient profiles may be different at dialysis initiation between countries [7, 12, 18, 19]. In France, as elsewhere in Europe (and according to European guidelines), young patients are more prone to receive PD as a bridge to rapid renal transplantation. However, this technique is also proposed to much older patients with a high comorbidity burden, especially diabetes and congestive heart failure, despite some reports suggesting that outcomes may be worse than in HD in these particular settings [15–17]. As a result, PD may be used in a higher proportion of patients (13% in our series between 2006 and 2008 and 11% in 2014) than in other countries (9% in the USA; 6% in the study by Lukowsky *et al.* [7]). It is therefore possible that, since PD use decreases in proportion, those who end up on this dialysis modality represent an even more selected population. Despite adjusting for a multitude of baseline characteristics, residual confounding in this observational study cannot be excluded. However, despite the bimodal age and comorbidity pattern distribution of PD in our cohort, we found consistent results after multiple adjustments including specific comorbidities that may have prompted the indication of PD (e.g. congestive heart failure).

Selection bias may also account for discrepancies across studies comparing outcomes of PD versus HD. Emergency dialysis initiation is admittedly associated with worse outcomes [24, 25], although is mostly confined to HD patients [26], (A. Michel *et al.*, submitted for publication). Intermixing patients with different initial clinical patterns may confuse the evaluation of survival, given that infections related to central venous access, metabolic consequences of malnutrition and anaemia, serious electrolytic disorders and pulmonary oedema are restricted to the HD subgroup. At odds with other studies, we took advantage of the fact that in the REIN registry, 'emergency initiation' is identified as a specific covariate and this subgroup of patients was therefore excluded from the analysis.

In our cohort, as in many previous reported studies [22, 23, 44], eGFR at initiation was higher in PD patients (+1.3 mL/min/1.73 m^2), a difference that can translate into several months of additional life expectancy, a phenomenon described as the lead time bias or immortal time bias [22]. The lead time

Table 1. Patient characteristics

Characteristics	PD *N* = 1748	HD *N* = 12 019	P
Age (years)	67.71 ± 16.47	67.13 ± 15.09	0.139
<50 years, *n* (%)	289 (16.5)	1687 (14.0)	<0.001
50–75 years, *n* (%)	711 (40.7)	5863 (48.8)	
>75 years, *n* (%)	748 (42.8)	4469 (37.2)	
Gender (female), *n* (%)	714 (40.8)	4441 (36.9)	0.002
Employment, *n* (%)			<0.001
Retired	1036 (67.5)	6721 (67.8)	
Employed or job search	298 (19.4)	1409 (14.2)	
Other	201 (13.1)	1776 (17.9)	
Nephropathy, *n* (%)			
Hypertension	475 (27.2)	3196 (26.6)	0.001
Diabetes	350 (20.0)	2688 (22.4)	
Chronic glomerulonephritis	240 (13.7)	1375 (11.4)	
APKD	113 (6.5)	952 (7.9)	
Pyelonephritis	66 (3.8)	497 (4.1)	
Vascular	29 (1.7)	144 (1.2)	
Other	248 (14.2)	1857 (15.5)	
Unknown	227 (13.0)	1310 (10.9)	
Kidney transplant waiting list, *n* (%)	219 (12.9)	1031 (8.7)	<0.001
Diabetes, *n* (%)	570 (33.4)	4329 (36.9)	0.006
Hypertension, *n* (%)	1368 (79.9)	9421 (80.6)	0.504
Tobacco, *n* (%)			
Non-smoking	1041 (65.2)	7080 (66.4)	0.033
Previously smoking	427 (26.7)	2580 (24.2)	
Smoking	129 (8.1)	1009 (9.5)	
Chronic respiratory disease, *n* (%)	138 (8.2)	1112 (9.6)	0.074
Heart failure, *n* (%)	505 (29.7)	2597 (22.3)	<0.001
Coronary disease, *n* (%)	392 (23.1)	2300 (19.8)	0.002
Arrhythmia, *n* (%)	339 (20.0)	1974 (17.0)	0.002
Myocardial infarction, *n* (%)	215 (12.7)	1051 (9.0)	<0.001
Peripheral vascular disease, *n* (%)	329 (19.4)	2197 (18.9)	0.646
Active malignancy, *n* (%)	98 (5.8)	1037 (8.9)	<0.001
Hepatitis B, *n* (%)	16 (1.0)	101 (0.9)	0.844
Hepatitis C, *n* (%)	20 (1.2)	205 (1.8)	0.111
Cirrhosis, *n* (%)	34 (2.0)	191 (1.6)	0.313
HIV, *n* (%)	7 (0.4)	83 (0.7)	0.219
Organ transplant (other than kidney), *n* (%)	18 (1.1)	129 (1.2)	0.864
Handicap, *n* (%)	459 (26.6)	3015 (25.7)	0.435
Mobility, *n* (%)			
Walks without help	1383 (84.6)	8415 (83.9)	0.648
Needs partial assistance	198 (12.1)	1238 (12.3)	
Totally dependent	54 (3.3)	375 (37)	
TIA or stroke, *n* (%)	190 (11.2)	1059 (9.1)	0.005
eGFR MDRD (mL/min/1.73 m^2)	10.5 ± 5.9	9.2 ± 5.2	<0.001
Serum albumin (g/L)	34.6 ± 6.2	34.35 ± 6.2	0.127
BMI (kg/m^2)	25.1 ± 4.6	25.8 ± 5.4	<0.001
Haemoglobin (g/dL)	11.0 ± 1.5	10.6 ± 1.6	<0.001
ESA, *n* (%)	1078 (62.3)	6279 (52.7)	<0.001
Travel duration >1 h, *n* (%)	75 (4.3)	278 (2.3)	<0.001
Deprivation index (Fdep99)	−0.25 ± 1.57	−0.18 ± 1.61	0.117
Dialysis withdrawal, *n* (%)	19 (1.1)	82 (0.7)	0.089

Any data not stated as being n (%) are mean ± SD.

APKD, autosomic polycystic kidney disease; HIV, human immunodeficiency virus; TIA, transient ischaemic attack; eGFR MDRD, estimated glomerular filtration rate according to the Modified Diet in Renal Disease equation; BMI, body mass index; ESA, erythropoiesis-stimulating agent.

bias favouring an apparent increase in survival in PD patients was accounted for in our analysis by adjustment for eGFR at initiation.

In addition, and as suggested by Figure 2, survival rates tend to differ between modalities from 1 year of treatment onwards. This suggests a delayed switch from PD to HD in patients with method-related complications or failure [23].

In the present analysis, when comparing the dialysis survival of patients in a nationwide cohort, all analysis models (multivariate Cox model, propensity score, structural marginal model) yielded rather similar results, namely a better survival in patients treated with planned HD. The magnitude of the effect, however, differed somewhat among the models (from 20% to 40%), with the MSMs tending to blunt the differences in survival.

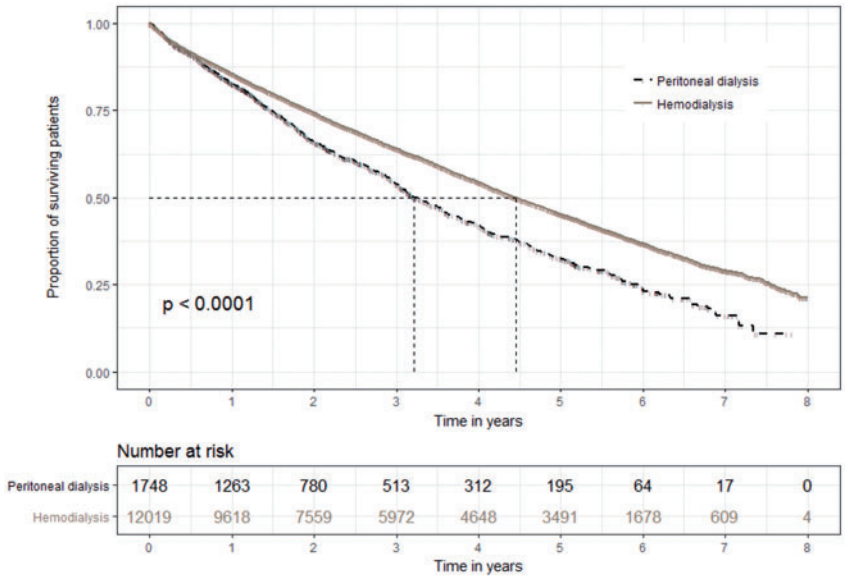

FIGURE 2: Kaplan–Meier survival curve analysis in patients receiving either PD or HD, considering censorship upon modality change.

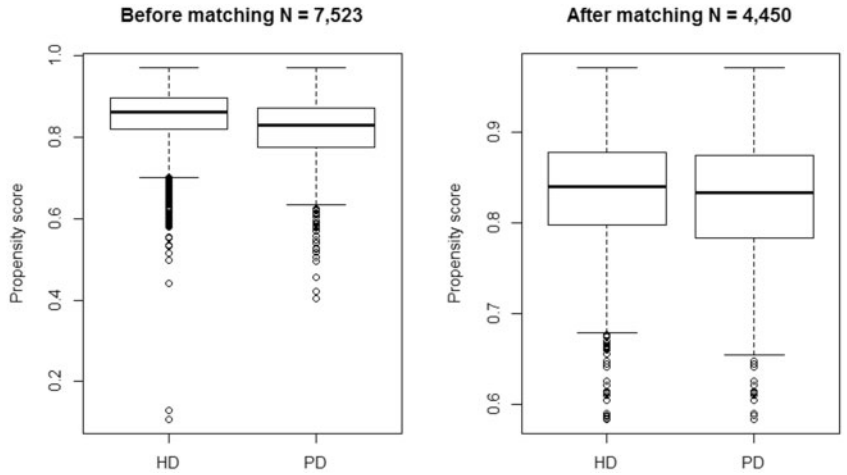

FIGURE 3: Boxplot of propensity scores among HD and PD patients.

The graphical method for adjustment used herein allowed keeping only covariates deemed as the most important from a clinical standpoint (Supplementary Material). For example, in our study, heart failure was retained but not coronary insufficiency or arrhythmia, which are surrogates, thereby suggesting that the graphical method was clinically relevant.

With regard to the propensity score, the matching method was retained since it is probably a more robust method for large cohorts. The propensity score was further used as adjustment or stratification by quintiles with results yielding similar conclusions.

MSM was used in the present study given that inverse probability weighting was thought to represent a better analytical tool for avoiding the potential bias with standard adjustment of a time-varying confounder affected by prior exposure [34].

In the structural marginal model, the methodological value of graphical methods was strengthened by the use of DAG, which take into account all potential confounding factors (and not only those derived from the collected database).

The use of MSMs altered the HR to some extent, alleviating the survival gap, although without changing the overall conclusion. This result can probably be explained by accounting for the variation in the patients' clinical characteristics over time, and further suggests that the clinical difference between dialysis modalities was accentuated over time.

The choice of the variables for calculating the inverse probability weights may prove difficult in those situations where the choice of dialysis modality is multifactorial. In our study, several variables potentially useful to better identify the indication of dialysis modality were not available (e.g. a history of peritonitis, abdominal surgery, patient hygiene conditions, malnutrition and volume overload). To compensate for this lack, the data as well as several scores and weights were used. It was found that, if a sufficient number of variables were used, the choice of one variable over another in the weight calculation did not significantly influence the outcome of the final Cox model.

Table 2. Summary of results from the various analysis models

Cox model		Comments	HR (95% CI)
'Classical' survival	Model 1	• Censoring 2 months after treatment change	
		• Variables used for adjustment: age, cancer, CRF, coronary disease and diabetes	0.76 (0.71–0.82)
		• Without adjustment	0.72 (0.67–0.78)
Propensity score matching	Model 2	• Censoring 2 months after treatment change	
		• Variables used for adjustment: age, diabetes, coronary disease and CRF	0.76 (0.69–0.84)
		• Without adjustment	0.74 (0.67–0.82)
Survival time-dependent covariates	Model 3	• Accounting for each treatment course	
		• Variables used for adjustment: age, eGFR at initiation, diabetes, CRF, heart failure, cancer, transplant waiting list, stroke, primary renal disease, smoking status, peripheral vascular disease, handicap, cirrhosis	0.67 (0.62–0.73)
		• Without adjustment	0.59 (0.54–0.64)
MSMs	Model 4	• With inverse probability weights	
		• Variables used for adjustment: age, eGFR at initiation, diabetes, CRF, heart failure, cancer, transplant waiting list, stroke, primary renal disease, smoking status, peripheral vascular disease, handicap, cirrhosis)	0.82 (0.69–0.97)
		• Without adjustment	0.75 (0.62–0.90)

CRF, chronic respiratory failure.

On more clinical grounds, we suggest several explanations to account for survival differences observed between planned PD and HD, which may be specific or not to our country practices. First, the length of technical survival in PD was relatively short (mean duration 18 months in the REIN registry) due to loss in peritoneal permeability, peritonitis or other complications related to PD techniques. Switch back to HD was relatively frequent but could have been decided too late, at the time when a complication had already occurred. Secondly, in France as in many other countries, the number of PD patients treated by facility is rather small, with a median number of 10 patients per centre, which may be associated with a lack of expertise or technical skills by the providers. Accordingly, the incidence rate of peritonitis was found to be significantly associated to centre size and organization, a finding that could be extrapolated to other complications and potentially to lesser outcomes [45, 46].

Several limitations of our study should be highlighted. All observational studies, the present being no exception, comparing PD and HD, regardless of the statistical techniques used for matching patients, are inevitably affected by residual confounding owing to unmeasured baseline differences in the types of patients who choose PD over HD.

Our results apply to our specific population and within the context of European practice patterns regarding indications of PD and patient profiles and may not be able to be extrapolated to other populations or other countries with different indication policies [23].

All-cause mortality was the sole endpoint analysed in this study with no additional data from specific causes of mortality, for instance, related to cardiovascular diseases.

Lastly, adjusted Cox models, propensity scores and MSM each have specific data requirements and subgroups extracted and analysed from the primary cohort were not strictly identical, although the large number of patients in each analysis would tend to yield very close patient profiles. Nevertheless, the survival superiority of planned HD was consistent across all models of analysis, although MSM, which more closely mimics a randomized trial, tended to reduce the survival gap between PD and HD patients.

Notwithstanding the above drawbacks, even if one modality could result in better survival than the other, the question remains as to whether this knowledge would have any clinical significance [43, 47]. The observational studies suggest that differences in risk between HD and PD may not be very large. Many patients with ESRD make decisions based more on immediate lifestyle preferences, e.g. willingness to stay at home and quality of life, rather than on differences in long-term survival [48, 49].

CONCLUSION

In a large nationwide cohort of incident patients, we compared the outcome of PD versus planned HD modalities by avoiding both the selection bias (emergency initiation) and the lead time bias (initiation at higher eGFR). In the adjusted Cox model accounting for modality switches and transplantation censorship, the HR for survival was 0.67 in favour of HD.

Counterfactual methods were also used based on the creation of pseudo-populations represented by weights that are used for survival analysis in MSMs to account for the variation of covariates over time. In the present study, these MSMs tended to reduce the survival gap between PD and HD patients as observed with adjusted Cox models and propensity scores (HR point estimate of 0.82 versus 0.67 and 0.76, respectively). Nevertheless, all models consistently demonstrated an advantage in terms of survival for patients treated with HD with no CI crossing 1, irrespective of the model.

Even if randomized trials comparing dialysis modalities may not be realistic, further studies are needed to optimize the care of PD patients and to determine the best timing of the transition to HD.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

ACKNOWLEDGEMENTS

We express our gratitude to all investigators and coordinators of the REIN registry. We also thank Pierre Pothier for editing the manuscript.

FUNDING

We did not receive any financial support for this study.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Jha V, Garcia-Garcia G, Iseki K. Chronic kidney disease: global dimension and perspectives. *Lancet* 2013; 382: 260–272
2. Korevaar JC, Feith GW, Dekker FW *et al.* Effect of starting with hemodialysis compared with peritoneal dialysis in patients new on dialysis treatment: a randomized controlled trial. *Kidney Int* 2003; 64: 2222–2228
3. Winkelmayer WC, Glynn RJ, Mittleman MA *et al.* Comparing mortality of elderly patients on hemodialysis versus peritoneal dialysis: a propensity score approach. *J Am Soc Nephrol* 2002; 13: 2353–2362
4. van de Luijtgaarden MW, Jager KJ, Segelmark M *et al.* Trends in dialysis modality choice and related patient survival in the ERA-EDTA Registry over a 20-year period. *Nephrol Dial Transplant* 2016; 31: 120–128
5. Collins AJ, Hao W, Xia H *et al.* Mortality risks of peritoneal dialysis and hemodialysis. *Am J Kidney Dis* 1999; 34: 1065–1074
6. McDonald SP, Marshall MR, Johnson DW *et al.* Relationship between dialysis modality and mortality. *J Am Soc Nephrol* 2009; 20: 155–163
7. Lukowsky LR, Mehrotra R, Kheifets L *et al.* Comparing mortality of peritoneal and hemodialysis patients in the first 2 years of dialysis therapy: a marginal structural model analysis. *Clin J Am Soc Nephrol* 2013; 8: 619–628
8. Kumar VA, Sidell MA, Jones JP *et al.* Survival of propensity matched incident peritoneal and hemodialysis patients in a United States health care system. *Kidney Int* 2014; 86: 1016–1022
9. Weinhandl ED, Foley RN, Gilbertson DT *et al.* Propensity-matched mortality comparison of incident hemodialysis and peritoneal dialysis patients. *J Am Soc Nephrol* 2010; 21: 499–506
10. Mehrotra R, Chiu YW, Kalantar-Zadeh K *et al.* Similar outcomes with hemodialysis and peritoneal dialysis in patients with end-stage renal disease. *Arch Intern Med* 2011; 171: 110–118
11. Chang YK, Hsu CC, Hwang SJ *et al.* A comparative assessment of survival between propensity score-matched patients with peritoneal dialysis and hemodialysis in Taiwan. *Medicine (Baltimore)* 2012; 91: 144–151
12. Quinn RR, Hux JE, Oliver MJ *et al.* Selection bias explains apparent differential mortality between dialysis modalities. *J Am Soc Nephrol* 2011; 22: 1534–1542
13. Bloembergen WE, Port FK, Mauger EA *et al.* A comparison of mortality between patients treated with hemodialysis and peritoneal dialysis. *J Am Soc Nephrol* 1995; 6: 177–183
14. Stack AG, Molony DA, Rahman NS *et al.* Impact of dialysis modality on survival of new ESRD patients with congestive heart failure in the United States. *Kidney Int* 2003; 64: 1071–1079
15. Sens F, Schott-Pethelaz AM, Labeeuw M *et al.* Survival advantage of hemodialysis relative to peritoneal dialysis in patients with end-stage renal disease and congestive heart failure. *Kidney Int* 2011; 80: 970–977
16. Kim H, Kim KH, Park K *et al.* A population-based approach indicates an overall higher patient mortality with peritoneal dialysis compared to hemodialysis in Korea. *Kidney Int* 2014; 86: 991–1000
17. Han SS, Park JY, Kang S *et al.* Dialysis modality and mortality in the elderly: a meta-analysis. *Clin J Am Soc Nephrol* 2015; 10: 983–993
18. Xue JL, Chen SC, Ebben JP *et al.* Peritoneal and hemodialysis: I. Differences in patient characteristics at initiation. *Kidney Int* 2002; 61: 734–740
19. Jaar BG. The Achilles heel of mortality risk by dialysis modality is selection bias. *J Am Soc Nephrol* 2011; 22: 1398–1400
20. Jaar BG, Plantinga LC, Crews DC *et al.* Timing, causes, predictors and prognosis of switching from peritoneal dialysis to hemodialysis: a prospective study. *BMC Nephrol* 2009; 10: 3
21. Couchoud C, Dantony E, Elsensohn MH *et al.* Modelling treatment trajectories to optimize the organization of renal replacement therapy and public health decision-making. *Nephrol Dial Transplant* 2013; 28: 2372–2382
22. Liu J, Weinhandl ED, Gilbertson DT *et al.* Issues regarding 'immortal time' in the analysis of the treatment effects in observational studies. *Kidney Int* 2012; 81: 341–350
23. Couchoud C, Bolignano D, Nistor I *et al.* Dialysis modality choice in diabetic patients with end-stage kidney disease: a systematic review of the available evidence. *Nephrol Dial Transplant* 2015; 30: 310–320
24. Perl J, Wald R, McFarlane P *et al.* Hemodialysis vascular access modifies the association between dialysis modality and survival. *J Am Soc Nephrol* 2011; 22: 1113–1121
25. Coentrao L, Santos-Araujo C, Dias C *et al.* Effects of starting hemodialysis with an arteriovenous fistula or central venous catheter compared with peritoneal dialysis: a retrospective cohort study. *BMC Nephrol* 2012; 13: 88
26. Couchoud C, Lassalle M, Jacquelinet C. REIN Annual report 2015 (in French). Agence de Biomédecine. https://www.agence-biomedecine.fr/IMG/pdf/rapport_rein_2015.pdf (19 January 2018, date last accessed)
27. Liem YS, Wong JB, Hunink MM *et al.* Propensity scores in the presence of effect modification: a case study using the comparison of mortality on hemodialysis versus peritoneal dialysis. *Emerg Themes Epidemiol* 2010; 7: 1
28. Couchoud C, Stengel B, Landais P *et al.* The renal epidemiology and information network (REIN): a new registry for end-stage renal disease in France. *Nephrol Dial Transplant* 2006; 21: 411–418
29. Brookhart MA, Schneeweiss S, Rothman KJ *et al.* Variable selection for propensity score models. *Am J Epidemiol* 2006; 163: 1149–1156
30. Rey G, Jougla E, Fouillet A, Hémon D. Ecological association between a deprivation index and mortality in France over the period 1997 - 2001: variations with spatial scale, degree of urbanicity, age, gender and cause of death. *BMC Public Health* 2009; 9: 33
31. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983; 70: 41–55
32. Austin PC. Goodness-of-fit diagnostics for the propensity score model when estimating treatment effects using covariate adjustment with the propensity score. *Pharmacoepidem Drug Safe* 2008; 17: 1202–1217
33. Dawid AP. Causal inference without counterfactuals. *J Am Stat Assoc* 2000; 95: 407–424
34. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000; 11: 550–560
35. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology* 1999; 10: 37–48
36. Textor J. Drawing and analyzing causal DAGs with DAGitty. 2015 [15 November 2015]. http://www.dagitty.net/manual-2.x.pdf (19 January 2018, date last accessed)
37. Breitling LP. dagR: a suite of R functions for directed acyclic graphs. *Epidemiology* 2010; 21: 586–587
38. Fosen J, Ferkingstad E, Borgan O *et al.* Dynamic path analysis-a new approach to analyzing time-dependent covariates. *Lifetime Data Anal* 2006; 12: 143–167
39. Weng HY, Hsueh YH, Messam LL *et al.* Methods of covariate selection: directed acyclic graphs and the change-in-estimate procedure. *Am J Epidemiol* 2009; 169: 1182–1190
40. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. *BMC Med Res Methodol* 2008; 8: 70
41. Pearl J. Causal diagrams for empirical research. *Biometrika* 1995; 82: 669–688
42. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology* 2011; 22: 745
43. Finkelstein FO, Levin NW. Dialysis: is it realistic to compare peritoneal dialysis and haemodialysis? *Nat Rev Nephrol* 2014; 10: 618–619
44. Wright S, Klausner D, Baird B *et al.* Timing of dialysis initiation and survival in ESRD. *Clin J Am Soc Nephrol* 2010; 5: 1828–1835
45. Bechade C, Guillouet S, Verger C *et al.* Centre characteristics associated with the risk of peritonitis in peritoneal dialysis: a hierarchical

modelling approach based on the data of the French Language Peritoneal Dialysis Registry. *Nephrol Dial Transplant* 2017; 32: 1018–1023
46. Duquennoy S, Bechade C, Verger C *et al*. Is peritonitis risk increased in elderly patients on peritoneal dialysis? Report from the French Language Peritoneal Dialysis Registry (RDPLF). *Perit Dial Int* 2016; 36: 291–296
47. Lee MB, Bargman JM. Survival by dialysis modality-who cares? *Clin J Am Soc Nephrol* 2016; 11: 1083–1087
48. Chanouzas D, Ng KP, Fallouh B *et al*. What influences patient choice of treatment modality at the pre-dialysis stage? *Nephrol Dial Transplant* 2012; 27: 1542–1547
49. Dahlerus C, Quinn M, Messersmith E *et al*. Patient perspectives on the choice of dialysis modality: Results from the Empowering Patients on Choices for Renal Replacement Therapy (EPOCH-RRT) study. *Am J Kidney Dis* 2016; 68: 901–910

Received: 31.8.2017; Editorial decision: 22.12.2017

Nephrol Dial Transplant (2018) 33: 1419–1427
doi: 10.1093/ndt/gfy041
Advance Access publication 26 March 2018

ORIGINAL ARTICLE

Systemic haemodynamics in haemodialysis: intradialytic changes and prognostic significance

Stefanie Haag[1], Björn Friedrich[2], Andreas Peter[1,3,4], Hans-Ulrich Häring[1,3,4], Nils Heyne[1,3,4] and Ferruh Artunc[1,3,4]

[1]Department of Internal Medicine, Division of Endocrinology, Diabetology, Vascular Disease, Nephrology and Clinical Chemistry, University Hospital Tübingen, Tübingen, Germany, [2]Nephrological Center, Leonberg, Germany, [3]Institute of Diabetes Research and Metabolic Diseases (IDM) of the Helmholtz Center Munich, University of Tübingen, Tübingen, Germany and [4]German Center for Diabetes Research (DZD), Tübingen, Germany

Correspondence and offprint requests to: Ferruh Artunc; E-mail: ferruh.artunc@med.uni-tuebingen.de

ABSTRACT

Background. Although haemodialysis (HD) leads to alterations of systemic haemodynamics that can be monitored using dilution methods, there is a lack of data on the diagnostic and prognostic significance of haemodynamic monitoring during routine HD.

Methods. In this multicentre study, we measured cardiac index (CI), access flow (AF) and central blood volume index (CBVI) during a single HD session in stable HD patients ($n = 215$) using the Transonic HD03 monitor (Transonic, Ithaca, NY, USA). Systemic CI (SCI) was defined as CI corrected for AF. In a subset of patients ($n = 82$), total end-diastolic volume index (TEDVI) and total ejection fraction (TEF) were derived from dilution curves. Data were correlated with clinical parameters, cardiac biomarkers and bioimpedance measurements (body composition monitor; Fresenius Medical Care, Homburg, Germany). Mortality was assessed prospectively after a median follow-up of 2.6 years.

Results. Median CI, CBVI and AF were 2.8 L/min/m^2 (interquartile range 2.4–3.4), 15 mL/kg (14.5–15.7) and 980 mL/min (740–1415), respectively, at the beginning of HD. At the end of HD, CI, CBVI and AF significantly fell by −10% (−22 to 3, $P < 0.0001$), −9% (−23 to 3, $P < 0.0001$) and −4% (−13 to 5, $P = 0.0004$), respectively. Peripheral resistance (PR) increased slightly ($P = 0.01$) and blood pressure fell by −6/−3 mmHg to 128/63 mmHg ($P < 0.0001$). Independent predictors of ΔCI were age and ultrafiltration rate, whereas AF, overhydration and PR were protective. TEF was strongly associated with mortality [area under the dilution curve 0.77, $P < 0.0001$], followed by TEDVI (0.72, $P = 0.0002$) and SCI (0.60, $P = 0.02$).

Conclusions. HD leads to a reduction of CI due to ultrafiltration. Haemodynamic monitoring identifies a significant number of HD patients with cardiac impairment that are at risk for increased mortality.

Keywords: cardiac index, haemodialysis, haemodynamics, prognosis, ultrasound dilution

INTRODUCTION

Haemodialysis (HD) patients suffer from high cardiovascular morbidity and mortality that is age-dependently increased 8- to 100-fold when compared with the general population [1–3]. Congestive heart failure with reduced systolic function is one of the most prominent determinants of cardiovascular mortality [4, 5]. It is associated with pump failure and sudden cardiac death [6, 7] and reflected by elevated levels of the cardiac biomarkers troponin and natriuretic peptides [8–10]. Cardiac