Epidemiology and outcomes of renal replacement therapy: results from the ERA-EDTA registry
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Chapter 8

Pretransplant dialysis modality is likely not associated with patient and graft survival after kidney transplantation

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Summary

Background. Previous studies have found inconsistent associations between pre-transplant modality of dialysis and subsequent post-transplant survival. The aim of this study was to examine the relationship between pre-transplant dialysis modality and patient and graft survival after the first kidney transplantation.

Methods. We included 29,088 patients (age >20 years) from sixteen European national or regional renal registries who received a first kidney transplant between 1 January 1999 and 31 December 2008 and were on dialysis before transplantation for a period between 90 days and 10 years. We performed two types of analyses. Standard multivariable Cox regression was used to examine the association of individually assigned pre-transplant dialysis modality with post-transplant patient survival and graft survival. Secondly, to decrease confounding by indication through unmeasured factors we applied an instrumental variable method using the case-mix adjusted centre percentage of PD as instrumental variable.

Results. Standard analyses suggested that after adjustment for age, sex, primary renal disease, donor type, duration of dialysis, year of transplantation, and country, PD before transplantation was associated with better patient survival (HR (95% CI): 0.83 (0.76-0.91)) and better graft survival (HR (95% CI): 0.90 (0.84-0.96)) when compared to haemodialysis before transplantation. In contrast, the instrumental variable analysis showed that a 10% increase in the case-mix adjusted centre percentage of patients on PD was neither associated with post-transplant patient survival (HR (95% CI): 1.00 (0.97-1.04)) nor with graft survival (HR (95% CI): 1.01 (0.98-1.04)).

Conclusions. Results from standard Cox regression analyses using individually assigned pre-transplant dialysis modality may have suffered from confounding by indication. The instrumental variable method suggests that there is likely no association between pre-transplant dialysis modality and patient and graft survival after transplantation.
Introduction

While awaiting a donor kidney most ESRD patients need to initiate dialysis. There has been discussion if the choice of dialysis modality may affect prognosis of these patients. Studies examining the association between dialysis modality, i.e. haemodialysis (HD) or peritoneal dialysis (PD), before kidney transplantation, and patient and graft survival after transplantation have shown conflicting results [1-8]. Goldfarb-Rumyantzev et al. [1] studied the survival of 92,844 US kidney transplant recipients and concluded that patients on PD before transplantation had a 6% lower risk of death and a 3% lower risk of (death-censored) graft failure than HD patients. In contrast, Snyder et al. [2] studied the survival of 22,776 US kidney transplant recipients and reported that dialysis modality prior to transplantation was not associated with patient survival after transplantation, but that PD patients had a 15% increased risk of death-censored graft failure. On the other hand, other much smaller and therefore less powered studies (up to 3,464 patients) in different populations [3-8] reported that there was no association between dialysis modality prior to transplantation and the patient and graft survival after transplantation.

However, any association between dialysis modality before transplantation and the survival after transplantation potentially suffers from confounding by indication, as patients may have been selected to start with HD or PD because of observed or unobserved prognostic factors [9]. For example, in many countries patients on PD tend to be healthier than those on HD [10-12]. Previous studies addressed this problem by matching HD and PD patients for age and gender [3,4], or by adjustment for patient characteristics such as the presence of comorbidities [1,2]. However, these methods may insufficiently account for differences in health status. In observational studies the instrumental variable method is increasingly being used as an approach to reduce confounding by indication due to unmeasured factors [13-18]. Using this method patients are grouped by an organizational unit (the instrumental variable), rather than by the treatment assigned to each individual patient.

The aim of this study was to examine the association between pre-transplant dialysis modality and patient and graft survival after the first kidney transplantation in a large cohort of living and deceased donor kidney transplant recipients in Europe, using instrumental variable analysis.

Methods

Data collection

Sixteen national or regional renal registries that annually submit individual patient data to the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA)
Registry, and had data available from 1999 to 2008, participated in this study, including the national registries of Austria, Denmark, England / Wales (United Kingdom), Finland, Greece, Norway, Scotland (United Kingdom), Sweden, The Netherlands, and the regional registries of Dutch and French speaking Belgium, and Asturias, Basque country, Cantabria, Catalonia and the Valencian region (together covering 35% of Spain). Details of the database and the methods used for data collection and data processing have been reported previously [19].

Patients satisfying the following criteria were included in the study cohort: 1) being on dialysis before transplantation for at least 90 days and no longer than 10 years; 2) receiving a first kidney transplant from a living or deceased kidney donor between 1 January 1999 and 31 December 2008; and 3) being older than 20 years of age at the time of first transplantation.

**Statistical analyses**

Differences in patient characteristics between groups were examined using the Chi-square test (for categorical variables) and Wilcoxon-Mann-Whitney test (for continuous variables). For both the analyses with patient survival and graft survival after transplantation, the date of transplantation was the starting point. For patient survival death was the event studied and reasons for censoring were loss to follow-up and the end of the follow-up period (31 December 2008 or five years after transplantation, whichever came first). For the graft survival the events studied were graft failure and patient death, and censored observations were loss to follow-up and the end of the follow-up period.

Primary renal diseases were defined according to the ERA–EDTA coding system [19] and classified into four groups. SAS 9.1 software was used for all statistical analyses.

**Standard analyses**

Although in this paper we considered the instrumental variable method as our primary analysis strategy we first analysed the data using ‘standard’ multivariable regression analysis to facilitate comparison with results from previous studies. All patients were stratified into “HD patients” and “PD patients” according to their dialysis modality at 90 days after dialysis initiation. This first dialysis modality was the primary predictor variable for survival after transplantation. We used the predominant dialysis modality (defined as modality used for more than 50% of the time on dialysis before transplantation), and the last dialysis modality before transplantation (defined as modality before transplantation that continued for at least 60 days) as additional predictor variables. Using Cox regression the survival analyses were adjusted for age at transplantation, sex, primary renal disease, duration of dialysis before transplantation, year of transplantation, donor type, and country.

**Instrumental variable analyses**

Differences in patient survival between PD and HD patients may arise from unmeasured
factors. To address the confounding by indication thereby introduced in the association between the pre-transplant dialysis modality and post-transplant patient and graft survival we used an instrumental variable approach [13,18,20,21]. Using this method one chooses a variable - the instrumental variable - that can be considered to be allocated to a patient at random, so independent of individual patient characteristics. The random allocation of this variable can be considered as a 'natural experiment'. In this study we chose the percentage of PD patients in the patient’s treatment centre as the instrumental variable. As patients tend to visit a treatment centre in the direct neighbourhood of their homes, in principle treatment centre can be considered to be allocated at random and serve as an instrumental variable. However, as being treated by a particular centre may still not be fully at random it is customary to still account for differences in case-mix between centres. Therefore, we adjusted the centre percentage of PD patients for centre case-mix. This required the following steps [13,14]. First, a logistic regression model was developed to predict the chance of PD for each patient based on their age at the start of RRT, sex, primary renal disease and country. Then for each centre the expected percentage of patients on PD was calculated as the average of all individual predicted chances for PD. Thereafter, we calculated the ratio between the observed percentage of patients on PD and the expected percentage of PD for each centre. This ratio can be considered as a measure for how often PD is provided relative to what would be expected based on the characteristics of the patient population in that centre. Thus, in centres with more PD than expected based on the patient population this ratio was higher than 1, and vice versa. This ratio was then multiplied by the overall percentage of patients on PD (34.8%), generating a case-mix adjusted percentage of patients on PD for each centre. We tested the assumptions [20] related to the use of the instrumental variable method: (1) the instrumental variable must be related to the treatment individually assigned; (2) the instrumental variable must be unrelated to observed and unobserved prognostic factors; and (3) the instrumental variable must be unrelated to outcome, except through pathways that operate via the treatment individually assigned.

Cox regression analyses were performed as described in the paragraph on standard analyses, except that the pre-transplant dialysis modality of each individual patient was substituted by the instrumental variable, i.e. the case-mix adjusted percentage of patients treated with PD on day 90 at the centre in which the patient was treated on day 90. Thus, these analyses did not examine the dialysis modality at day 90 for that individual patient per se, but instead they used the case-mix adjusted centre percentage of PD at day 90 as a patient characteristic for all dialysis patients in that centre. Only patients on dialysis in countries from which we received centre IDs and patients from centres that had at least 30 patients on dialysis and that had patients on both PD and HD were included in the instrumental variable analyses. Analyses were adjusted for patient’s individual age at transplantation, sex, primary renal disease, duration of dialysis before transplantation, year
of transplantation, and donor type, and accounted for effects of facility clustering using robust SE estimation techniques based on the sandwich estimator [22].

Additional analyses were performed stratified by year after transplantation to check whether the proportional hazards assumption was fulfilled. We also examined the presence of interaction between kidney donor source (deceased/living), year of transplantation, and dialysis modality in the association with patient and graft survival after transplantation.

Results

Standard analyses

In total 29,088 adults who received a first kidney transplant from a living (N=4,947) or deceased kidney donor (N=24,141) between 1999 and 2008 were included in the standard analyses. An overview of the baseline characteristics of these patients is shown in Table 1. Overall 34.8% of the patients were on PD on day 90 after dialysis initiation. When compared to HD patients, patients on PD were younger at the start of dialysis and at the time of transplantation, they were more often female, had a slightly different primary renal disease distribution and their time spent on dialysis before transplantation was approximately one month shorter.

Table 2 shows the unadjusted and adjusted hazard ratios for patient and graft survival resulting from the standard Cox regression analyses with PD as pre-transplant dialysis modality. After adjustment for relevant confounders the risk of post-transplant death for PD was 17% lower than that for being on HD (HR (95% CI): 0.83 (0.76-0.91)) and the risk of graft survival was 10% lower for PD patients (adjusted HR (95% CI): 0.90 (0.84-0.96)). Similar results were obtained with PD as either the predominant dialysis modality before transplantation or as the last dialysis modality before transplantation.

Instrumental variable analyses

To address confounding by indication Cox regression analyses used the instrumental variable as a patient characteristic, i.e. the case-mix adjusted percentage of PD patients at the centre in which the patient was treated on day 90, instead of the individual patient’s dialysis modality on day 90. Analyses were restricted to patients from national and regional renal registries with centre data available and who were treated in centres with more than 30 patients (N=19,755). The patients that were excluded in this way (N=9,333) had similar patient characteristics when compared to those remaining in the analyses. In total there were 228 centres with more than 30 dialysis patients that both had patients on HD and PD.

The median [interquartile range] of the case-mix adjusted centre percentage of patients on PD at day 90 was 43% [32-53%]. Table 3 provides an overview of the baseline characteristics of patients treated in centres with a case-mix adjusted percentage of patients
Table 1. Descriptive characteristics for all patients, and for patients on PD or HD on day 90 after dialysis initiation.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients</th>
<th>Dialysis modality at day 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, in years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>at start of dialysis, median [Q1-Q3]</td>
<td>48.5 [37.8-57.7]</td>
<td>46.7 [36.4-56.2]</td>
</tr>
<tr>
<td>at first transplantation, median [Q1-Q3]</td>
<td>51.3 [41.2-61.3]</td>
<td>49.3 [38.9-59.0]</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>males, %</td>
<td>63.3</td>
<td>60.6</td>
</tr>
<tr>
<td>females, %</td>
<td>36.7</td>
<td>39.4</td>
</tr>
<tr>
<td>Primary renal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>13.7</td>
<td>15.6</td>
</tr>
<tr>
<td>Hypertension / renal vascular disease, %</td>
<td>10.5</td>
<td>9.4</td>
</tr>
<tr>
<td>Glomerulonephritis, %</td>
<td>24.7</td>
<td>26.1</td>
</tr>
<tr>
<td>Other diseases, %</td>
<td>51.1</td>
<td>48.9</td>
</tr>
<tr>
<td>Kidney donor source</td>
<td></td>
<td></td>
</tr>
<tr>
<td>living donor, %</td>
<td>17.0</td>
<td>18.9</td>
</tr>
<tr>
<td>deceased donor, %</td>
<td>83.0</td>
<td>81.1</td>
</tr>
<tr>
<td>Time on dialysis before transplantation, in years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>in total, median [Q1-Q3]</td>
<td>2.2 [1.2-3.7]</td>
<td>2.1 [1.2-3.6]</td>
</tr>
<tr>
<td>on PD, median [Q1-Q3]</td>
<td>0.0 [0.0-1.1]</td>
<td>1.7 [0.9-2.8]</td>
</tr>
<tr>
<td>on HD, median [Q1-Q3]</td>
<td>1.3 [0.1-2.9]</td>
<td>0.0 [0.0-0.2]</td>
</tr>
</tbody>
</table>

Q1 = 25th percentile, Q3 = 75th percentile, PD = peritoneal dialysis, HD = haemodialysis
Percentages are column percentages
NA: not applicable

on PD above and below the median (43%). It shows that, when compared according to case-mix adjusted centre percentage of PD, the patient groups were much more similar than when compared according to individual patient’s dialysis modality (as in Table 1): those treated in centres with a case-mix adjusted percentage of PD above the median were about one year younger at the start of dialysis and at the time of transplantation and only had a slightly higher percentage of glomerulonephritis as cause of renal failure. This suggests that indeed our instrumental variable functioned as a “pseudo-randomizer” [23].

Table 4 shows the hazard ratios for an increase of 10% in the case-mix adjusted centre percentage of PD. There was no association between the case-mix adjusted centre percentage of PD and patient survival after transplantation (HR per 10% increase of PD: 1.00 (0.97-1.04) and graft survival (HR per 10% increase of PD: 1.01 (0.98-1.04)). In addition, table 4 shows the hazard ratios for patients treated in centres with a case-mix adjusted percentage of patients on PD above versus below the median and hazard ratios
Table 2. Hazard ratios for patient and graft survival after transplantation in patients with PD as pre-transplant dialysis modality.

<table>
<thead>
<tr>
<th>Dialysis modality</th>
<th>Patient survival</th>
<th>Graft survival including death as event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N&lt;sub&gt;total&lt;/sub&gt;</td>
<td>N&lt;sub&gt;events&lt;/sub&gt;</td>
</tr>
<tr>
<td>PD at day 90, unadjusted</td>
<td>29.088</td>
<td>2.669</td>
</tr>
<tr>
<td>PD at day 90, adjusted *</td>
<td>29.088</td>
<td>2.669</td>
</tr>
<tr>
<td>PD predominant before Tx, adjusted *</td>
<td>29.088</td>
<td>2.669</td>
</tr>
<tr>
<td>PD prior to Tx, adjusted *</td>
<td>28.827</td>
<td>2.661</td>
</tr>
</tbody>
</table>

* Analysis adjusted for age at transplantation, sex, PRD distribution, donor type, duration on dialysis before transplantation, year of transplantation, and country

PD = peritoneal dialysis, Tx = transplantation

Comparing patients on dialysis in centres with a case-mix adjusted percentage of patients on PD in the second, third and fourth quartile with those in the lowest first quartile. Again there was no statistically significant association with patient and graft survival after transplantation. The first assumption regarding instrumental variable analysis - stating that the instrumental variable must be related to the treatment individually assigned - was fulfilled: the median of the case-mix adjusted centre percentage of PD was higher in patients who were on PD at day 90 than in patients who were on HD at day 90 (47% and 39% respectively, p<0.001). The second assumption – stating that the instrumental variable must be unrelated to observed and unobserved prognostic factors - was at least partially fulfilled: the differences in observed prognostic factors were substantially reduced if patients were compared on the basis of case-mix adjusted centre percentage of PD instead of on the basis of individual pre-transplant dialysis modality (Table 3 versus Table 1). The third assumption requires the case-mix adjusted centre percentage of PD to be unrelated to survival after transplantation, except through the individually assigned treatment under study. We have only few data to show that this is probably the case. However, kidney donor source (living versus deceased) could be considered as centre characteristic. As kidney donor source was equally distributed in patients treated in centres with case-mix adjusted centre percentages below and above the median, we assumed that also other centre practices, such as the provision of immunosuppressive regimens, followed a similar random distribution and are thus independent of the case-mix adjusted centre percentage of PD.

Assessment of interaction showed that any effect of dialysis modality before transplantation was not different in deceased or living donor kidney recipients, in different years of transplantation, or in different years of follow-up.
Table 3. Descriptive characteristics for all patients, and for patients treated in centres with case-mix adjusted percentages of PD above or below the median.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients</th>
<th>Patients on dialysis in centres with a case-mix adjusted percentage of PD &gt; median (43%)</th>
<th>Patients on dialysis in centres with a case-mix adjusted percentage of PD &lt; median (43%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, in years at start of dialysis, median [Q1-Q3]</td>
<td>48.2 [37.4-57.5]</td>
<td>47.7 [36.8-57.1]</td>
<td>48.6 [37.9-57.7]</td>
<td>0.001</td>
</tr>
<tr>
<td>Age, in years at first transplantation, median [Q1-Q3]</td>
<td>50.9 [40.1-60.4]</td>
<td>50.4 [39.6-60.0]</td>
<td>51.4 [40.4-60.6]</td>
<td>0.003</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>males, %</td>
<td>62.6</td>
<td>62.8</td>
<td>62.3</td>
<td>0.461</td>
</tr>
<tr>
<td>females, %</td>
<td>37.4</td>
<td>37.2</td>
<td>37.7</td>
<td></td>
</tr>
<tr>
<td>Primary renal disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>13.7</td>
<td>13.8</td>
<td>13.7</td>
<td>0.808</td>
</tr>
<tr>
<td>Hypertension / renal vascular disease, %</td>
<td>10.7</td>
<td>10.7</td>
<td>10.8</td>
<td>0.775</td>
</tr>
<tr>
<td>Glomerulonephritis, %</td>
<td>24.3</td>
<td>23.6</td>
<td>24.9</td>
<td>0.004</td>
</tr>
<tr>
<td>Other diseases, %</td>
<td>51.2</td>
<td>51.9</td>
<td>50.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Kidney donor source</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>living donor, %</td>
<td>19.3</td>
<td>19.4</td>
<td>19.2</td>
<td>0.727</td>
</tr>
<tr>
<td>deceased donor, %</td>
<td>80.7</td>
<td>80.6</td>
<td>80.8</td>
<td></td>
</tr>
<tr>
<td>Time on dialysis before transplantation, in years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in total, median [Q1-Q3]</td>
<td>2.2 [1.2-3.7]</td>
<td>2.3 [1.2-3.8]</td>
<td>2.2 [1.2-3.7]</td>
<td>0.006</td>
</tr>
<tr>
<td>on PD, median [Q1-Q3]</td>
<td>0.0 [0.0-1.5]</td>
<td>0.5 [0.0-1.9]</td>
<td>0.0 [0.0-1.0]</td>
<td>NA</td>
</tr>
<tr>
<td>on HD, median [Q1-Q3]</td>
<td>1.2 [0.0-2.7]</td>
<td>0.7 [0.0-2.4]</td>
<td>1.4 [0.3-2.9]</td>
<td>NA</td>
</tr>
</tbody>
</table>

Q1 = 25th percentile, Q3 = 75th percentile, PD = peritoneal dialysis, HD = haemodialysis
Percentages are column percentages
NA: not applicable

Discussion

Previous reports suggested that dialysis modality before the first kidney transplantation might influence both patient and graft survival after transplantation [1,2] with effects ranging from a 6% lower to a 15% higher risk of death for PD patients. With this study including 29,088 patients from Europe we examined the association of dialysis modality before the first kidney transplantation with patient and graft survival after transplantation. In standard analyses, with individual pre-transplant dialysis modality as a patient characteristic, PD before transplantation was associated with better patient survival and graft survival. However, this is potentially confounded by indication and standard analysis may fail to sufficiently account for differences in health status. In contrast, the instrumental variable method using the case-mix adjusted centre percentage of PD failed to show an association between the case-mix adjusted centre percentage of PD and post-transplant patient and
graft survival. This suggests that the results from standard analyses were confounded by indication and that there likely is no association.

Previous papers suggested reasons why dialysis modality before the first kidney transplantation might influence both patient and graft survival after transplantation [1,2]. However, for each of these potential reasons the data in the literature are inconsistent.

For example, it has been hypothesized that residual renal function may be better preserved in PD patients [24,25], and consequently PD patients may have a higher GFR at the moment of kidney transplantation. Nevertheless, two studies examining the association of eGFR of the recipient’s own kidney before transplantation with patient and graft survival after pre-emptive kidney transplantation did not find any relationship [26,27].

Also, it has been suggested that the occurrence of infections after transplantation may differ between PD and HD patients. Studies, however, reported conflicting results.

### Table 4

Hazard ratios for patient and graft survival after transplantation with the case-mix adjusted percentage of patients treated with PD on day 90 after the start of dialysis at a centre as instrumental variable.

<table>
<thead>
<tr>
<th>Patient survival</th>
<th>Graft survival including death as event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N&lt;sub&gt;total&lt;/sub&gt;</td>
</tr>
<tr>
<td>Case-mix adjusted percentage PD per centre, per 10% increase, adjusted *</td>
<td>19.755</td>
</tr>
<tr>
<td>Case-mix adjusted percentage PD per centre, above versus below median (43%), adjusted *</td>
<td>19.755</td>
</tr>
<tr>
<td>Case-mix adjusted percentage PD per centre, Q2 versus Q1, adjusted *</td>
<td>9964</td>
</tr>
<tr>
<td>Case-mix adjusted percentage PD per centre, Q3 versus Q1, adjusted *</td>
<td>9848</td>
</tr>
<tr>
<td>Case-mix adjusted percentage PD per centre, Q4 versus Q1, adjusted *</td>
<td>9933</td>
</tr>
</tbody>
</table>

* Analysis adjusted for age at transplantation, sex, PRD distribution, donor type, duration on dialysis before transplantation, and year of transplantation, and accounted for facility clustering.

PD = peritoneal dialysis

Q1: patients on dialysis in centres with case-mix adjusted percentage of PD patients within the lowest quartile (reference); Q2: patients on dialysis in centres with case-mix adjusted percentage of PD patients within the second quartile; Q3: patients on dialysis in centres with case-mix adjusted percentage of PD patients within the third quartile; Q4: patients on dialysis in centres with case-mix adjusted percentage of PD patients within the highest quartile.
abdominal, bloodstream, and wound site infections after transplantation. On the other hand, Miemois-Foley et al. [29] reported less bacterial infections in PD patients after transplantation and Yang et al. [8] reported less hepatitis infections in PD patients after transplantation, and a similar rate of other infections in HD and PD patients.

In addition, delayed graft function (DGF) after transplantation, which is a predictor for graft failure [30], was suggested to be higher for HD patients [31-33], possibly due to a worse hydration status of HD patients. However, other studies did not find a difference between HD and PD patients with regard to the risk of DGF after transplantation [8,34].

Furthermore, the development of post transplant diabetes mellitus (PTDM) may be associated with the pre-transplant treatment modality due to the glucose load resulting from PD. However, also in this case results were conflicting. Whereas Madziarska et al. [35] and Seffi et al. [36] reported higher rates of PTDM in former PD patients, Courivaud et al. [37] reported similar rates of PTDM between those who were on HD or PD before transplantation.

Also graft thrombosis has been put forward as potential explanation. Both Ojo et al. [38] and Palomar et al. [39] reported a higher incidence of graft thrombosis after transplantation among PD patients. They proposed possible mechanisms including increased levels of various coagulation factors in PD patients, as well as a higher risk of haemoconcentration in PD patients as opposed to HD patients. On the other hand, Pérez Fontán et al. [40] reported that PD is not a risk factor for graft thrombosis after transplantation.

Finally, it has been speculated that immunologic differences between HD and PD patients may play a role in graft survival after transplantation. It has been shown that HD patients have elevated levels of natural killer cells and production of cytokines [41,42] although the mechanisms through which this could influence survival after transplantation are unclear.

**Standard analyses**

When considering the results of our standard analyses using individual pre-transplant dialysis modality as a patient characteristic our results were in line with those from the largest US based study (N=92,844) by Goldfarb-Rumyantzev et al. [1], who found a patient survival benefit (HR PD (95% CI): 0.94 (0.91-0.97)) for transplant recipients who had PD as last dialysis modality before transplantation. On the other hand, another large US study (N=22,776) by Snyder et al. [2] reported that dialysis modality prior to transplantation was not associated with patient survival after transplantation (HR PD (95% CI): 0.95 (0.85-1.06)).

Our patient-based analyses of graft survival using pre-transplant dialysis modality as a patient characteristic revealed a lower risk of graft failure for PD patients, which was in line with the results of Goldfarb-Rumyantzev et al. [1] (HR PD (95% CI): 0.97 (0.94-1.00)), but not with the results of Snyder et al. [2] who reported a higher risk of graft failure for PD patients (HR (95% CI): 1.15 (1.04-1.26)). However, a difference in post-transplant outcome
or any other outcome between HD and PD patients may result from confounding by indication as patients on PD tend to be healthier than those on HD [10-12]. The conflicting results of our standard analyses and instrumental variable analyses regarding patient survival suggest that the adjustment in the standard multivariable analyses for age at transplantation, sex, primary renal disease, donor type, duration on dialysis before transplantation, year of transplantation, and country may have been insufficient to largely eliminate differences in health status between patients on PD and HD. Only randomization of dialysis modality may fully prevent this form of selection bias, but randomization for dialysis modality is extremely difficult [43], and information from randomized trials are currently not available.

**Instrumental variable analyses**

One way to simulate random assignment in observational studies is the use of an instrumental variable. In this study we used the case-mix adjusted centre percentage of PD patients. The allocation of a centre to a patient may be considered as a natural experiment, as patients tend to visit a centre in their direct neighbourhood. The case-mix adjusted centre percentage of PD may be viewed as a measure for how often PD is provided relative to what would be expected based on the characteristics of the patient population in that centre. Thus, the allocation of a centre to a patient where PD is provided relatively frequently, and where the patient has a higher probability of starting dialysis with PD independent of the patient’s age, gender and primary renal disease, may be considered as random. In this way the effects of confounding by indication may have been substantially reduced.

**Limitations of the study**

The case-mix adjustment of the centre percentage of PD was based on relatively few variables. Patient co-morbidity for example could not be taken into account. A previous study, however, has shown that once age, gender and primary renal disease are included in models for patient survival on RRT, co-morbidity may add relatively little to the variance in mortality [44]. As for other unobserved prognostic factors, the instrumental variable approach has increased the likelihood that they were more evenly distributed between patient groups.

**Conclusions**

Using instrumental variable analysis, a method that in observational studies is used to approximate randomisation of treatment, we found that patients in centres where PD was provided more frequently had a similar patient and graft survival when compared to patients treated in centres in which PD was provided less frequently. This suggests that there is no
association between pre-transplant dialysis modality and patient and graft survival after transplantation. However, as instrumental variable approaches may still not fully correct for confounding by indication, we cannot exclude the possibility that pre-transplant PD may effect survival after kidney transplantation. Nevertheless, we cannot think of any biological hypothesis why it would do so. We therefore conclude that previous studies as well as our own standard analyses using individual pre-transplant dialysis modality as a determinant for outcomes after transplantation may have suffered from confounding by indication and that there is likely no association between pre-transplant dialysis modality and patient and graft survival after transplantation.
References


