Comparison of patient survival in non-diabetic transplant listed patients
JP Traynor, PC Thomson, K Simpson, DT Ayansina, GJ Prescott and RA Mactier
On behalf of the Scottish Renal Registry, Walton Building, Glasgow Royal Infirmary, G4 0SF

Introduction. Haemodialysis (HD) and peritoneal dialysis (PD) have been used to treat patients with established renal failure (ERF) for over 40 years. However, it is still not known whether patients survive longer on one modality of dialysis compared to the other. We have tried to answer this question while avoiding the confounding effects of co-morbidity by including only patients listed for a renal transplant and excluding patients with a primary renal diagnosis (PRD) of diabetic nephropathy. Our assumption is that the remaining patients will have a similar level of health and could have chosen either modality of dialysis.

Methods. All adult patients without a PRD of diabetic nephropathy starting dialysis in Scotland for ERF between 01 January 1982 and 31 Dec 2006 and who were active on the renal transplant list at some point after the start of dialysis were included. We also noted patient age at start of dialysis, sex, PRD and level of renal function measured by 4-\(\nu\) MDRD formula before starting dialysis although the laboratory data were only available for 61.7% of the study cohort. Survival between the dialysis modalities was assessed using Kaplan-Meier plots and log-rank tests. Mann-Whitney U and Pearson’s Chi-square tests were used as appropriate for direct comparison of parameters between the PD and HD groups. Cox regression was used for multivariate modelling adjusting survival for patient age, sex and PRD.

Results. 3240 patients fulfilled our criteria. 1943 (60.0%) started with HD. There were significantly more males in the HD group (63.6% v 36.4% Chi-squared \(p < 0.001\)). There was no significant difference in age between the PD group (median age 46.8 years, quartiles 35.7, 56.6) and the HD group (median age 46.5 yrs, quartiles 33.3, 56.2, \(p = 0.093\)). There was no significant difference in level of residual renal function between PD and HD (median 5.5 v 5.4 mL/min/1.73m\(^2\), \(p = 0.298\)). A Kaplan-Meier plot showed no difference in survival between dialysis modalities at start of RRT (log rank \(p = 0.847\)). In the Cox regression model, dialysis modality at start of RRT was not a significant predictor of survival; hazard ratio = 0.99 (95% CI 0.82 to 1.20) after adjusting for age, sex and PRD. Only age at start of dialysis, hazard ratio = 1.05 (95% CI 1.04 to 1.06) and a PRD group of multi system disease, hazard ratio = 1.33 (95% CI 1.03 to 1.73) were found to significantly influence survival. However, when only patients who remained on the same dialysis modality were considered, over the whole study period there was a significantly lower hazard of death for patients on HD compared to those on PD (hazard ratio = 0.73, 95% CI 0.55 to 0.97; \(p=0.03\)) whilst during the first 12 months there was a survival advantage for patients staying on PD (\(p=0.045\)). Age at start of dialysis remained a significant predictor of death in both models.

Conclusion. This study shows that there was no survival advantage between initial dialysis modalities in non-diabetic patients who are deemed healthy enough for listing for a renal transplant. Over the whole period of follow up there was a small, but statistically significant, survival advantage for patients who remained on HD compared with patients who continued on PD, whilst in the initial 12 months of follow up there was a small and significant survival advantage on PD in comparison to HD.
Comparison of patient survival in non-diabetic transplant listed patients
JP Traynor, PC Thomson, K Simpson, DT Ayansina, GJ Prescott and RA Mactier
On behalf of the Scottish Renal Registry, Walton Building, Glasgow Royal Infirmary, G4 0SF

Introduction.
Haemodialysis (HD) and peritoneal dialysis (PD) have been used to treat patients with established renal failure (ERF) for over 40 years. However, it is still not known whether patients live longer on one modality of dialysis compared to the other. Many different studies have been conducted over the years. However, these have mostly been observational and have come to different conclusions and have often simply added to the uncertainty.

Some studies have shown a clear benefit for PD (1-3) whilst others have come to the converse conclusion (4). There are clearly a number of factors at play which affect the choice of modality such as co-morbidity (5) and the availability of dialysis facilities. One Canadian-based study by Murphy et al. suggested that the apparent survival advantage of PD was due to a lower burden of co-morbidity (6) whereas a US-based study by Sanabria et al. (7) found that patients on PD were poorer, more likely to be diabetic and have a higher degree of co-morbidity. Several studies have attempted to allow for co-morbidity but differing conclusions persist. Korevaar et al. found a hazard of death of 3.6 (0.8 to 15.4) for HD patients compared with patients on PD after adjusting for age, co-morbidity and primary renal disease (PRD) (8) while another European-based study by Van Manen et al. showed that the apparent survival advantage of PD disappeared after adjusting for baseline characteristics and co-morbidity (9).

Despite this confusing background, two themes have emerged. The first of these is that patients starting with PD tend to have a better survival initially than those starting with HD but this trend is reversed with increasing time on dialysis (10) with 2 years appearing to be a point where the risk of death becomes higher for patients on PD (11-14). The second theme that has emerged is that for PD patients, the presence of diabetes is considered to increase the risk of death (15) particularly for those patients older than 50-55 years (4,16). The very recent paper by McDonald et al on patient outcomes in the Australia and New Zealand Registry illustrated this point and reported that patient survival rates on PD may be superior initially but become lower than HD after 12 months (17).

It is clear that there are complicated relationships between level of co-morbidity, primary renal disease and patient outcome which have clouded the issue of which modality, if any, confers better patient survival rates. In an attempt to negotiate this minefield, some authors have limited their study to those patients who were accepted for transplantation. The assumption is that this group of patients will represent the fittest cohort of our dialysis patients and therefore be free of most of the factors that
have confounded previous studies. These studies have shown no survival difference between the two modalities although the study cohorts used were generally very small (18-20).

Against this background, we undertook the current study which assessed survival between the two modalities for those patients who had been accepted for transplantation and did not have diabetic nephropathy as the PRD. By using data from the Scottish Renal Registry we were able to perform this analysis on a much larger cohort of patients than previous studies.

Materials and Methods

All adult patients starting dialysis in Scotland for ERF between 01 January 1982 and 31 December 2006 were included. Patients starting RRT before 1982 were excluded as PD was not fully established as a treatment modality until that time. The main analyses included only those patients who were active on the renal transplant list at some point after the start of dialysis and did not have a PRD of diabetic nephropathy. We also noted patient age at start of dialysis, sex, PRD and level of renal function measured by 4-v MDRD formula (21) before starting dialysis.

Survival between the dialysis modalities was assessed by Kaplan-Meier plots and log-rank testing. Survival was timed from start of dialysis until date of death and was censored for date of data retrieval (16 January 2008) and date of receiving a renal transplant. Survival was initially assessed for all patients starting RRT between 01 January 1982 and 31 December 2006 to indicate if our baseline data were consistent with published studies. Analyses were then restricted to those patients who were active on the renal transplant list at some point after the start of dialysis and did not have a PRD of diabetic nephropathy. To take account of improvements that have been made over the years to both modalities, we also assessed survival in 5-year cohorts. Mann-Whitney U and Pearson’s Chi-square tests were used as appropriate for direct comparison of parameters between the PD and HD groups. Survival was assessed for these patients and then for the subset of these patients who remained on the same dialysis modality. Multivariate analysis was by Cox regression modelling with survival of patients on dialysis modalities adjusted for age at onset of RRT, sex and PRD. SPSS for Windows version 16 (SPSS Inc., 233 S. Wacker Drive, Chicago IL, U.S.A.) was used for the analysis.

Results

A total of 9800 patients started dialysis for ERF during the period 01 January 1982 to 31 December 2006 of which 3761 (38.4%) were listed for renal transplantation and 1651 (16.8%) patients had a PRD of diabetic nephropathy. 3240 patients met our dual criteria of being accepted for transplantation and not having a PRD of diabetic nephropathy. Of these, serum creatinine values at the start of RRT were only available for 2000 patients (61.7%). The demographic characteristics of these patients at
the start of dialysis are shown in Table 1. 2139/3240 (66.0%) started with HD. There were significantly more males in the HD group (63.6% v 36.4% Chi-squared p < 0.001). There was no significant difference in age between the PD group (median age 46.8 years, quartiles 35.7, 56.6) and the HD group (median age 46.5 yrs, quartiles 33.3, 56.2, p = 0.093). There was no significant difference in level of residual renal function between PD and HD (median eGFR 5.5 v 5.4 mL/min/1.73m², p = 0.298), for those where eGFR was available.

Table 1. Patient demographics at the start of dialysis. Data are shown for all 3240 patients and expressed as median (quartiles) unless otherwise stated.

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>HD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1101</td>
<td>2139</td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>519 (47.1)</td>
<td>778 (36.4)</td>
<td>p &lt; 0.001*</td>
</tr>
<tr>
<td>Male (%)</td>
<td>582 (52.9)</td>
<td>1361 (63.6)</td>
<td></td>
</tr>
<tr>
<td>Age at start of dialysis (years)</td>
<td>46.8 (35.7, 56.6)</td>
<td>46.5 (33.3, 56.2)</td>
<td>0.093</td>
</tr>
<tr>
<td>Median eGFR at start of dialysis (ml/min)</td>
<td>5.5 (4.4, 7.1)</td>
<td>5.4 (4.2, 7.0)</td>
<td>0.298</td>
</tr>
<tr>
<td>Primary renal diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Glomerulonephritis (%)</td>
<td>330 (30.0)</td>
<td>622 (29.1)</td>
<td></td>
</tr>
<tr>
<td>Interstitial nephropathies (%)</td>
<td>463 (42.0)</td>
<td>791 (37.0)</td>
<td></td>
</tr>
<tr>
<td>Multisystem diseases (%)</td>
<td>146 (13.3)</td>
<td>410 (19.2)</td>
<td></td>
</tr>
<tr>
<td>Diabetes (excluded)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Not known or other (%)</td>
<td>162 (14.7)</td>
<td>316 (14.7)</td>
<td>p &lt; 0.001*</td>
</tr>
</tbody>
</table>

Mann Whitney U test used in all cases except those marked with * where Pearson's Chi squared was used.

Survival was assessed using Kaplan-Meier plots. To demonstrate that our data were consistent with previous published studies, we first assessed survival for all patients who started RRT between 1982 and 2006 including those who were not accepted for transplantation and those with diabetic nephropathy. Figure 1 demonstrates an apparent survival benefit for patients starting on PD although this becomes less apparent with increasing time on dialysis (log rank p < 0.001).
Figure 1. Survival for all patients starting RRT between 01 January 1982 and 31 December 2006 (n = 9800). Survival was censored if patient was still alive when data were retrieved (16 January 2008) or for the date of receiving a renal transplant.

Figure 2 shows survival for those patients who started RRT between 01 January 1982 and 31 December 2006 but excluded those who were not accepted for transplantation or who had a PRD of diabetic nephropathy. This analysis demonstrates that the apparent survival advantage of PD disappears once the dataset has been limited to those without comorbidity serious enough to prevent them from being listed for transplant (log rank p = 0.847). This comparison was repeated within different eras of dialysis by stratifying into 5-year cohorts. A similar Kaplan-Meier plot was seen within each 5-year cohort (not shown) and no comparison of HD and PD showed any statistically significant differences.

Figure 2. Survival for all patients starting RRT between 01 January 1982 and 31 December 2006 but excluding those NOT accepted for transplantation and excluding those with a PRD of diabetic nephropathy (n = 3240). Survival was censored if patient was still alive when data were retrieved (16 January 2008) or for the date of receiving a renal transplant.
When survival was assessed using Cox regression and adjusting for patient sex, age, PRD and dialysis modality only patient age and PRD were significant predictors of death (Table 2).

**Table 2.** Cox regression analysis on patients starting RRT between 01 January 1982 and 31 December 2006 but excluding those NOT accepted for transplantation and excluding those with a PRD of diabetic nephropathy (n = 3240). Survival was censored if patient was still alive when data were retrieved (16 January 2008) or for the date of receiving a renal transplant.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD</td>
<td>0.99</td>
<td>0.82-1.20</td>
<td>0.905</td>
</tr>
<tr>
<td>Male</td>
<td>0.93</td>
<td>0.78-1.12</td>
<td>0.453</td>
</tr>
<tr>
<td>Age at Start of RRT</td>
<td>1.05</td>
<td>1.04-1.06</td>
<td>0.000</td>
</tr>
<tr>
<td>PRD Group 1 – Glomerulonephritis [Ref]</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PRD Group 2 – Interstitial disease</td>
<td>0.95</td>
<td>0.74-1.22</td>
<td>0.666</td>
</tr>
<tr>
<td>PRD Group 3 – Multisystem disease</td>
<td>1.33</td>
<td>1.03-1.73</td>
<td>0.028</td>
</tr>
<tr>
<td>PRD Group 4 – Unknown</td>
<td>1.27</td>
<td>0.96-1.68</td>
<td>0.091</td>
</tr>
</tbody>
</table>

Some patients are treated with more than one modality of dialysis in the course of their management. The reasons for changing dialysis modality vary and include patient choice as well as problems with the original mode of dialysis. It is very difficult to take these factors into account and so 2331 patients, who met our original inclusion criteria and who also remained on the same dialysis modality, were assessed separately to minimize any potential confounding effect arising from switching dialysis modality.

Figure 3 shows the Kaplan-Meier plots comparing survival between modalities for these patients. Over the whole study period there was a significant difference in survival between modalities with the patients remaining on HD having better survival rates than patients staying on PD (Log rank p = 0.045).

Figure 3. Survival for all patients starting RRT between 01 January 1982 and 31 December 2006 and who remained on the initial dialysis modality. This analysis also excludes those patients NOT accepted for transplantation and excludes those with a PRD of diabetic nephropathy (n = 2331). Survival was censored if patient was still alive when data were retrieved (16/01/2008) or for the date of receiving a renal transplant.
A Cox model (Table 3) including patient sex, age, PRD, and dialysis modality for this subset of patients showed that HD had significantly lower hazards of death when compared with PD (Hazard ratio 0.73, 95% CI 0.55 to 0.97; \( p = 0.031 \)). The PRD was also no longer a significant predictor of mortality in this model.

The survival curves cross and so a log-minus log plot was used to check the assumption of proportional hazards required for Cox regression. This plot showed that the proportional hazards assumption held after 12 months, but was violated before this time. A separate multivariate analysis of the first 12 month period following the commencement of dialysis for these 2331 patients and adjusting for the same covariates showed that HD had significantly higher hazards compared with PD (Hazard ratio 2.94, 95% CI 1.02 to 8.45, \( p = 0.045 \)). Therefore, over the whole period of follow up in this subgroup of patients there is a small, but statistically significant, survival advantage on HD than PD, but initially there is a small and significant survival advantage on PD in comparison to HD.

Table 3: Cox regression analysis on patients who met the original inclusion criteria and also remained on the same dialysis modality (n=2331)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD</td>
<td>0.73</td>
<td>0.55-0.97</td>
<td>0.031</td>
</tr>
<tr>
<td>Male</td>
<td>1.05</td>
<td>0.82-1.34</td>
<td>0.715</td>
</tr>
<tr>
<td>Age at Start of RRT</td>
<td>1.05</td>
<td>1.04-1.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PRD Group 1 – Glomerulonephritis [Ref]</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PRD Group 2 – Interstitial disease</td>
<td>0.94</td>
<td>0.68-1.31</td>
<td>0.726</td>
</tr>
<tr>
<td>PRD Group 3 – Multisystem disease</td>
<td>1.10</td>
<td>0.78-1.56</td>
<td>0.589</td>
</tr>
<tr>
<td>PRD Group 4 – Unknown</td>
<td>1.23</td>
<td>0.86-1.76</td>
<td>0.254</td>
</tr>
</tbody>
</table>
Discussion
After several decades of treating patients with established renal failure with different dialysis modalities it is still uncertain whether one modality provides a survival advantage over the other. There are many potential confounding factors including patient co-morbidity and primary renal diagnosis. By selecting only those patients who were deemed fit enough for transplantation and excluding those who had diabetic nephropathy, we believe that we have identified a cohort of patients with similar co-morbidity and survival prognosis. By using the Scottish Renal Registry data we have ensured that we have studied a large number of patients.

Several interesting observations can be drawn from this single study. Firstly, the results shown in Figure 1 suggest that there is a survival benefit for patients starting on PD if the analysis is performed on all patients starting both dialysis modalities. Secondly, we have shown in Figure 2 that this apparent survival advantage of PD disappears after removing patients with serious co-morbidities by only including the dialysis patients who were accepted for transplant listing and excluding those with a PRD of diabetic nephropathy. A third important conclusion from this study is that patients remaining on PD appear to do better within the first year of commencing RRT but thereafter may have a lower survival rate than incident patients who commenced and remained on HD. These conclusions from three sets of analyses based on different subsets of a single study population may provide an explanation for the apparently contradictory conclusions reported in previous publications (1-9).

For several reasons, the initial dialysis modality may not remain either appropriate or possible for a patient resulting in a crossover of modalities. This is more pronounced in the direction of PD to HD and may be the main reason why initial dialysis modality has no influence on patient survival whereas differences in patient survival do become apparent in the subgroup of patients who remain on their initial dialysis modality.

Another factor that we have considered is whether changes in modality technique have changed survival over time. Part of the main study design was to exclude anyone starting RRT before 01 January 1982 as PD was not clearly established in Scotland until after this time. However, to investigate the difference over time we split the survival analysis after removing patients with serious co-morbidities into five 5-year cohorts. There was no significant survival difference between PD and HD during any of these 5-year cohorts.

We have not been able to quantify the proportion of patients with late referral and therefore unable to take this into account with our analyses. We do know that late referral affects a large proportion of
patients and that most of these are likely to start with hemodialysis. Metcalfe et al studied every single patient in Scotland who starting dialysis for end stage renal disease over a 12-month period (22). In this study it was found that 24.2% of patients starting during that year had less that 1 month of follow up by a nephrologist before starting dialysis. This figure rises to 34.9% if you include those patients who presented as acute renal failure but failed to recover. Those who had no planning prior to starting dialysis were 3.6 times more likely to die in the first 90 days of starting dialysis and those who presented as ARF were 8.9 times more likely to die. Thus, the failure to account for these patients may adversely affect the conclusions of this study and in particular introduce some bias against the HD group of patients. However, the impact of late referral will have the greatest effect on early survival and also these patients will have a greater degree of co-morbidity. However, the length of our follow up period coupled with our selection criteria should minimize any impact of late referral on this study.

Another source of potential bias in this study is lead-time bias where patients starting at a higher level of renal function may appear to have a better survival. This is a very important consideration in studies of patient survival after starting dialysis (23,24) and ideally should be factored into any analysis of survival. The fact that adequacy of PD depends to a greater extent on residual renal function means that patients may be started on PD earlier than in HD and this could introduce lead-time bias. This, in turn, might account for the initial better survival for PD. However, the PD and HD patients in this study started renal replacement therapy with a similar level of renal function and so any effect of lead-time bias in this study should be minimal. It should be also noted that we did not use the IDMS-traceable method of creatinine measurement, which would be preferable (25-27), as laboratories in Scotland have only been using this method routinely since 2007. In theory there may be small differences in methods of creatinine measurement among the laboratories that contributed data to the SRR but the range of levels of residual renal function observed in this study should not introduce significant bias arising from different methods of creatinine measurement.

The proportion of males is significantly greater in the group that started with HD than PD. The importance of this is not clear although it is worth stressing that this pattern is similar for the 9800 patients starting RRT in Scotland since 01 January 1982 where the male/female ratio was 1152/1166 and 4209/2973 for PD and HD respectively (Chi-squared p = 0.005). Thus the data in our study of those patients accepted for transplantation was representative of the male:female ratio of the wider dialysis population in Scotland. Also, in the 2004 SRR report there was no survival difference between males and females despite the better survival of females in the general population (28).

This is not the first study to compare patient survival on PD and HD in patients accepted for transplantation. We are aware of 3 other similar studies albeit with far fewer patients than our study.
Two of these studies compared patient survival after their renal transplant failed (17,18). Davies et al. studied 45 patients (28 PD; 17 HD) after transplant failure and found no difference in patient survival (18). De Jonge et al. similarly assessed survival in 51 patients after transplant failure (12 PD; 39 HD) and found no difference in survival (19). Mahalingasivam et al. have reported a similar study in dialysis patients accepted for listing for renal transplantation (20). As yet, this study has been published only as an abstract. However, as in our study, Mahalingasivam et al’s study of 830 patients showed that initial dialysis modality had no significant influence on survival rates in patients accepted onto the transplant list. Those who remained on PD, however, had significantly poorer survival compared with those who either remained on HD or switched from PD to HD (20).

One limitation of this study is that it is based on observational data. We agree that a prospective trial would be required to provide definitive answers to the questions posed in this manuscript. Analysis of prospectively collected registry data with complete follow up does not remove the potential bias introduced by non-randomised choice of RRT type but does circumvent the bias introduced in retrospective studies when patients with short survival are lost to follow up before registration.

**Conclusions**

This large national cohort study of incident adult dialysis patients provides an explanation for the previous conflicting reports of the effect of initial dialysis modality on patient survival. Analysis of patient survival in his national cohort has shown that there is an apparent survival advantage for PD if no adjustment is made for patient case-mix. However the choice of initial dialysis modality did not influence patient survival if multivariate analysis was restricted to the subgroup of patients who were accepted for transplantation and did not have diabetes mellitus as their PRD. A multivariate analysis of only those patients who remained on their initial dialysis modality suggested that HD over the whole study period had a small survival advantage over PD whereas during the first 12 months there was a small survival advantage in favour of PD.


