Survival and dialysis initiation: comparing British Columbia and Scotland registries

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Introduction

Survival on dialysis is used as a metric in all countries. International registries report survival on dialysis and allow for comparisons between countries.

Abstract

Background. Outcomes are a major metric for evaluating effectiveness of dialysis. Comparisons between different populations reveal significant variation. In addition, the question of optimal timing of dialysis start lacks robust data from which to generate conclusions.

Methods. This study compares dialysis survival in two geographically similar areas, Scotland and British Columbia, Canada (BC). The effect of eGFR at dialysis start on survival was also measured. Incident adult dialysis populations of Scotland (n = 3372) and BC (n = 3927), 2000–05 were compared. Mortality Hazard ratios (HR) were calculated using a Cox proportional hazards model. Multivariate analysis included pre-dialysis eGFR, registry, age, sex, dialysis modality, year of start, pre-dialysis haemoglobin and primary renal diagnosis.

Results. Median survival times from start of dialysis were 38 (35–40) and 44 (42–47) months in Scotland and BC, respectively, giving an unadjusted mortality HR, Scotland versus BC, of 1.20 (95% C.I. 1.12–1.29). BC patients started dialysis at a higher eGFR (8.9 ml/min/1.73 m²) than Scotland (7.5 ml/min/1.73 m²), and prior to modelling higher starting eGFR was associated with higher mortality (1 ml/min/1.73 m² increase, HR = 1.028; 95% C.I. 1.021–1.035). BC patients were also older and had more diabetic renal disease. In multivariate analysis, lower starting eGFR was associated with better survival, and Scotland had greater mortality than BC. General population mortality and transplantation rate had only minor influence.

Conclusions. Concepts of ‘late’ versus ‘early’ start dialysis based on eGFR alone may need modification given the complexity and confounding reasons for dialysis initiation.

Keywords: chronic kidney disease; dialysis initiation; eGFR; incident patients; survival

There continues to be debate on the appropriate timing of dialysis initiation. Many believe that early institution of dialysis results in improved outcomes based on data suggesting that those with no prior renal care, and those who present unexpectedly with end-stage renal disease and commence dialysis at very low GFR, have the worst survival. Thus, initiatives to encourage early referral and ‘earlier’ dialysis have been developed. Given the complexity of the clinical condition, however, and the various factors that influence the decision to start dialysis (biochemical, psychological, financial and social), there remains no specific set of circumstances that dictate when dialysis should begin.

The 1997, subsequently updated in 2001, Dialysis Outcomes Quality Initiative (DOQI) guidelines, based on expert opinion, recommended prompt initiation of dialysis at a Kt/V (urea) <2.0/week, equivalent to a GFR of 10.5 ml/min/1.73 m² [1]. The values were based on observational evidence that starting dialysis ‘late’, defined by lower eGFR, was associated with poorer nutritional state and appeared to increase morbidity and mortality [3–5]. Review of our current registry data would suggest that the median initiation level is substantially lower (6–8 ml/min/1.73 m²).

A study of renal centres in Europe compared 2-year survival stratified into three risk groups by age and comorbidity. They demonstrated superior survival in French and German centres compared with Scottish and Dutch centres [8]. An ERA-EDTA European analysis of patient data 1998–2002 reaffirmed a lower survival in the Scottish population. More recently, it has been demonstrated that much of the variation in outcomes can be explained by age and cause of renal disease (especially diabetes) [9]. However, no analysis has compared eGFR at the start of dialysis with survival between centres.

We report here an observational analysis comparing registry data for dialysis patients between Scotland, UK and British Columbia (BC), Canada. Although geographically distant from each other, Scotland and BC represent comparable populations, economies, infrastructures and healthcare systems. The proportion of patients requiring dialysis is similar (Table 1) [10–13]. The population of both is predominantly Caucasian, although BC has a substantial Oriental Asian minority (10%).
The primary objectives of this study were to compare survival on dialysis in the two populations, determine potential reasons for differences and determine the relationship of GFR at dialysis start with survival.

Subjects and methods

Two analytical datasets were created from the Scottish Renal Registry (SRR) and the BC Provincial Renal Agency Registry (BCPRA). The SRR, maintained by the Scottish Renal Association (SRA), contains demographic and outcome information on patients commencing RRT in each of 10 adult renal units in Scotland. The BCPRA maintains the ‘Patient Records, Outcome and Management Information System’ (PROMIS) providing demographic, laboratory and outcome information on all patients with kidney disease seen by provincial nephrology teams. Five health authorities with hospital- and satellite-based units provide information regularly to the registry. Use of SRR and PROMIS data was approved by the SRR steering committee and the BCPRA.

Patients

Incident patients aged 18 or above starting dialysis for established ESRD between 1st January 2000 and 31st December 2005 were selected. The defin-ition of ESRD used by the SRA was based on the UK Renal Association and US Renal Data System.

1. A requirement of RRT for >90 days regardless of subsequent recovery (although date of first dialysis is noted).
2. In the event of recovery from RRT ≤90 days from onset, the diagnosis of ESRD remains if the patient returns to RRT within the subsequent 90 days.
3. In the event of death before ≤90 days of RRT, a diagnosis of ESRD can be made by nephrologists.

In BC, ESRD patients had a diagnosis of chronic kidney disease entered into the registry after being seen by the nephrology team and commencing dialysis. The criteria are the same as the SRA, except ‘1’, where in BC there is no minimum requirement for dialysis time to be classified as ESRD.

Recorded variables

Recorded variables were primary renal diagnosis (PRD), serum creatinine (sCr) and haemoglobin (Hb) measured <90 days before first dialysis, date of birth, sex and initial dialysis modality, haemodialysis (HD) or peritoneal dialysis (PD).

Objectives

The primary outcome was mortality, with censoring at 31 December 2006 or at the date a patient either received a transplant or was lost to follow-up. The other objective was to evaluate eGFR at dialysis start and compare these between registries, and also determine if eGFR impacted on survival.

Estimation of renal function

Pre-dialysis sCr was converted into GFR estimates using the original four-variable MDRD equation [14]. Predictions were based on unstandardized sCr:

\[
GFR = 186 \times sCr^{-1.154} \times \text{age}^{-0.203} \times 1.212 \times 0.724 \text{ if female}.
\]

Statistical analysis

Descriptive statistics are presented as mean with standard deviation or median with interquartile range, depending on the underlying distribution. Continuous and categorical variables were compared between registries using the t-test (parametric variables) or the Wilcoxon rank sum test (non-parametric variables) and the chi-square test, respectively. Patient survival was estimated using the Kaplan–Meier method; median survival time and 95% confidence interval are presented. Survival curves by registry were compared using the log-rank test.

Cox proportional hazards modelling was used to identify variables associated with mortality. We performed three sets of two models: one with all patients, and one including only patients who survived on dialysis longer than 90 days. The first set of models included age, gender, primary kidney disease, dialysis initiation year and initial dialysis modality. Primary kidney disease was classified in five categories. We conducted further standardization using age/sex/mortality rate data [15,16]. The second set, in addition to the above variables, included the last eGFR values before dialysis initiation. The eGFR values were classified in five groups. Missing eGFR values were included as one class. The third set adjusted for the last Hb value before dialysis start, classified in four groups, with missing values as one group. The interaction of registry parameter with other statistically significant covariates was tested by adding an interaction term to the models.

To explore the effect of GFR at dialysis initiation on survival, incident patients were classified into five groups according to GFR: 0–4.9 ml/min, 5–9.9 ml/min/1.73 m², 10–14.9 ml/min/1.73 m², 15 ml/min/1.73 m² or greater, and unavailable values. We used ANOVA or the Kruskal–Wallis test, where appropriate, to compare continuous variables by the GFR level. Categorical variables by the GFR group were compared using the chi-square test. Survival curves by the GFR level at dialysis initiation were compared using the log-rank test. Since we observed a significant difference between registries in time to transplant, as well as association of key parameters with both survival and probability of transplant, we performed a sensitivity analysis to explore the effect of transplantation on differential survival between registries. The sensitivity analysis did not censor patients when they received a transplant; we continued to follow up the patients until death, cohort exit or study end, and modelled transplantation as time-dependent covariate.

We used logistic regression to explore factors associated with the lowest GFR level at dialysis initiation. This modelling included the same set of the variables as above.

P-values of <0.05 from two-sided tests were considered statistically significant. All statistical analyses were performed using SAS, Version 9.1 (SAS Institute, NC, USA).

Results

Population characteristics

Using the databases described above, and limiting the period to all who commenced dialysis during the period 1 January 2000–31 December 2005, 3927 and 3372 adult patients starting dialysis were identified from the BCPRA and SRR, respectively. Of this cohort, 3037 and 2838 had an sCr recorded within 90 days before dialysis, respectively.

SRR patients were younger, included fewer male patients and fewer patients with diabetes as primary kidney disease (Table 2). A larger percentage of BC patients had PD as...
1.73 m$^2$ eGFR prior to dialysis initiation
- 7.5 (5.8–10.0) vs 8.9 (6.4–12.0) < 0.0001

SRR patients had a significantly higher unadjusted mortality hazard ratio (HR = 1.20; 95% C.I. 1.12–1.29) than BC patients. The hazards ratio increased (HR = 1.34) after adjustments for patient demographic characteristics, population mortality rate and primary kidney disease (model 1, Table 3). The HR further increased (HR = 1.39) when eGFR levels prior to dialysis initiation were included in the model (model 2, Table 3). However, when Hb before commencement of dialysis was included in the model, the mortality HR fell to 1.36 for SRR patients versus BC patients (model 3, Table 3).

Overall, older age, primary kidney disease diagnoses other than glomerulonephritis (GN) and autoimmune diseases, higher starting eGFR, lower starting Hb and belonging to the SRR were associated with lower survival, while PD as initial dialysis modality and later year of dialysis start were associated with higher survival.

Given the differences in 30-day survival, which may have been related to differing definitions for ESRD, the analysis was repeated excluding patients surviving <90 days. Results remained the same: model 1 HR = 1.33 (95% C.I. 1.23–1.44); model 2 HR = 1.36 (95% C.I. 1.25–1.47); model 3 HR = 1.34 (95% C.I. 1.22–1.46).

**eGFR values at dialysis initiation and survival**

Higher starting eGFR was associated with a significant increase in the HR of death (HR per 1 ml/min/1.73 m$^2$ = 1.025; 95% C.I. 1.021–1.035, P < 0.0001). Using eGFR <5 ml/min/1.73 m$^2$ at dialysis start as a reference category (associated with best survival), each subsequent higher level of eGFR at dialysis initiation was associated with an increasingly higher HR for mortality: eGFR 5–10 ml/min/1.73 m$^2$ HR = 1.24 (95% C.I. 1.09–1.42; P = 0.0014), eGFR 10–15 ml/min/1.73 m$^2$ HR = 1.59 (95% C.I. 1.38–1.83; P < 0.0001), eGFR >15 ml/min/1.73 m$^2$ HR = 1.88 (95% C.I. 1.59–2.21; P < 0.0001), including patients without eGFR record at dialysis initiation HR = 1.46 (95% C.I. 1.26–1.68; P < 0.0001) (Figure 2).

This direction of the association of eGFR and survival was the same in both BC and SRR, as demonstrated by a statistically insignificant interaction term for the eGFR level by registry (P = 0.68) and a comparable HR of death (SRR eGFR HR per 1 ml/min/1.73 m$^2$ = 1.025; 95% C.I. 1.016–1.033 versus BC eGFR HR per 1 ml/min/1.73 m$^2$ = 1.028; 95% C.I. 1.021–1.035).

A large proportion of patients started dialysis with eGFR in the 5.0–9.9 ml/min/1.73 m$^2$ range, while fewer patients...
### Table 3. Survival models

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
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<th>Model 2</th>
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<th>Model 3</th>
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<tbody>
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<td></td>
<td>Hazard ratio</td>
<td>95% Hazard ratio confidence limits</td>
<td>P-value</td>
<td>Hazard ratio</td>
<td>95% Hazard ratio confidence limits</td>
<td>P-value</td>
<td>Hazard ratio</td>
<td>95% Hazard ratio confidence limits</td>
<td>P-value</td>
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<td>SRR vs. BCPRA</td>
<td>1.336</td>
<td>1.244–1.435</td>
<td>&lt;0.0001</td>
<td>1.390</td>
<td>1.292–1.496</td>
<td>&lt;0.0001</td>
<td>1.363</td>
<td>1.259–1.476</td>
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<td>Age (per 5 years)</td>
<td>1.226</td>
<td>1.199–1.253</td>
<td>&lt;0.0001</td>
<td>1.220</td>
<td>1.194–1.247</td>
<td>&lt;0.0001</td>
<td>1.221</td>
<td>1.195–1.248</td>
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<td>Population mortality rate per 1000</td>
<td>0.999</td>
<td>0.998–1.001</td>
<td>0.3950</td>
<td>0.999</td>
<td>0.998–1.001</td>
<td>0.4355</td>
<td>0.999</td>
<td>0.998–1.001</td>
<td>0.5006</td>
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<td>Male sex</td>
<td>1.062</td>
<td>0.991–1.138</td>
<td>0.0866</td>
<td>1.039</td>
<td>0.969–1.114</td>
<td>0.2783</td>
<td>1.037</td>
<td>0.967–1.112</td>
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<td>Primary kidney disease, reference: GN/autoimmune diseases</td>
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<tr>
<td>Diabetes</td>
<td>1.824</td>
<td>1.602–2.076</td>
<td>&lt;0.0001</td>
<td>1.764</td>
<td>1.549–2.009</td>
<td>&lt;0.0001</td>
<td>1.769</td>
<td>1.553–2.015</td>
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<td>Polycystic/drug nephropathy/congenital</td>
<td>1.356</td>
<td>1.180–1.5588</td>
<td>&lt;0.0001</td>
<td>1.330</td>
<td>1.157–1.528</td>
<td>&lt;0.0001</td>
<td>1.354</td>
<td>1.178–1.556</td>
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<tr>
<td>Renovascular</td>
<td>1.417</td>
<td>1.232–1.631</td>
<td>&lt;0.0001</td>
<td>1.380</td>
<td>1.199–1.588</td>
<td>&lt;0.0001</td>
<td>1.391</td>
<td>1.209–1.601</td>
<td>&lt;0.0001</td>
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<td>Unknown</td>
<td>1.678</td>
<td>1.475–1.908</td>
<td>&lt;0.0001</td>
<td>1.643</td>
<td>1.444–1.869</td>
<td>&lt;0.0001</td>
<td>1.648</td>
<td>1.448–1.875</td>
<td>&lt;0.0001</td>
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<td>Dialysis initiation year, reference: 2000</td>
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<tr>
<td>2001</td>
<td>0.999</td>
<td>0.898–1.112</td>
<td>0.9915</td>
<td>1.008</td>
<td>0.904–1.123</td>
<td>0.8902</td>
<td>1.025</td>
<td>0.919–1.142</td>
<td>0.6612</td>
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<td>2002</td>
<td>0.998</td>
<td>0.895–1.114</td>
<td>0.9750</td>
<td>1.008</td>
<td>0.902–1.127</td>
<td>0.8886</td>
<td>1.023</td>
<td>0.915–1.144</td>
<td>0.6864</td>
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<td>2003</td>
<td>0.896</td>
<td>0.799–1.003</td>
<td>0.0573</td>
<td>0.907</td>
<td>0.807–1.020</td>
<td>0.1029</td>
<td>0.922</td>
<td>0.820–1.037</td>
<td>0.1759</td>
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<td>2004</td>
<td>0.885</td>
<td>0.782–1.001</td>
<td>0.0513</td>
<td>0.894</td>
<td>0.788–1.014</td>
<td>0.0813</td>
<td>0.915</td>
<td>0.807–1.039</td>
<td>0.1704</td>
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<td>2005</td>
<td>0.796</td>
<td>0.690–0.918</td>
<td>0.0017</td>
<td>0.784</td>
<td>0.679–0.905</td>
<td>0.0009</td>
<td>0.807</td>
<td>0.698–0.933</td>
<td>0.0039</td>
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<td>PD vs. HD</td>
<td>0.721</td>
<td>0.658–0.791</td>
<td>&lt;0.0001</td>
<td>0.727</td>
<td>0.662–0.798</td>
<td>&lt;0.0001</td>
<td>0.754</td>
<td>0.686–0.828</td>
<td>&lt;0.0001</td>
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<td>GFR at dialysis initiation, reference: GFR &lt;5 ml/min/1.73 m²</td>
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<tr>
<td>GFR not recorded</td>
<td>1.345</td>
<td>1.162–1.558</td>
<td>&lt;0.0001</td>
<td>1.345</td>
<td>1.142–1.584</td>
<td>0.0004</td>
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<td>GFR 5–10 ml/min/1.73 m²</td>
<td>1.145</td>
<td>1.002–1.309</td>
<td>0.0466</td>
<td>1.170</td>
<td>1.024–1.338</td>
<td>0.0214</td>
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<td>GFR 10–15 ml/min/1.73 m²</td>
<td>1.327</td>
<td>1.147–1.536</td>
<td>&lt;0.0001</td>
<td>1.371</td>
<td>1.185–1.587</td>
<td>&lt;0.0001</td>
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<td>GFR &gt;15 ml/min/1.73 m²</td>
<td>1.567</td>
<td>1.324–1.854</td>
<td>&lt;0.0001</td>
<td>1.648</td>
<td>1.391–1.951</td>
<td>&lt;0.0001</td>
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<td>Hb at dialysis initiation, reference: Hb ≥ 11 g/dl</td>
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<tr>
<td>Hb not recorded</td>
<td>1.196</td>
<td>1.059–1.350</td>
<td>0.0039</td>
<td>1.311</td>
<td>1.186–1.448</td>
<td>&lt;0.0001</td>
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<tr>
<td>Hb &lt;10.0 g/dl</td>
<td>1.083</td>
<td>0.956–1.225</td>
<td>0.2094</td>
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<td>Hb 10.0–10.9 g/dl</td>
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Hb, haemoglobin; HD, haemodialysis; PD, peritoneal dialysis; GN, glomerulonephritis.
started dialysis in ‘extreme’ eGFR groups (<5 and ≥15 ml/min/1.73 m²) (Table 4). The lowest dialysis initiation eGFR level was associated with younger age (OR per 5 years = 0.937, 95% C.I. 0.913–0.962; P < 0.0001), female sex (OR = 0.532, 95% C.I. 0.451–0.626; P < 0.0001), absence of diabetes (OR = 0.382, 95% C.I. 0.291–0.501; P < 0.0001), lower Hb levels (Hb <10 g/dl versus Hb ≥11 g/dl OR = 2.050, 95% C.I. 1.630–2.578; P < 0.0001) and earlier initiation year (2005 versus 2000 OR = 0.599, 95% C.I. 0.445–0.808; P = 0.0005), and it was more common in SRR patients. Diabetes, other/unknown/unrecorded, dyslipidaemia and initial dialysis modality were of insufficient power to detect a significant association with mortality. Beddhu et al. [7] following the outcome of USRDS (n = 2920) came to similar conclusions.

Discussion

The median survival in these two cohorts was significantly different. The BCPRA had better survival than the SRR. Using a series of different models and adjusting for baseline general population mortality, we determined key variables important in predicting mortality and also refining the HR. The predictors of death were the same in both countries and included older age, male gender and diabetes. Those who started PD as their initial modality also had better outcomes. Paradoxically, higher eGFR at dialysis start predicted shorter survival, across both populations. Higher starting eGFR was also associated with older age, male sex and diabetes, which helps to explain the anomaly; however, the BCPRA patients started dialysis at a higher eGFR and had a greater proportion of older patients, male cohort and those with diabetes, but yet had better survival. This could not be explained by transplantation after commencing dialysis nor preemptive transplantation rates, which are similar.

Association between eGFR at dialysis initiation and survival

The correlation between higher eGFR at dialysis start and increased mortality is consistent with recent observational analyses, which have failed to show a benefit from ‘early’ (higher eGFR) start and hinted at a possible adverse association of high eGFR with mortality. Traynor et al. [2], looking specifically at a Scottish population, demonstrated a small survival disadvantage from an ‘early’ start. Our analysis extends those findings in two large cohorts with similar health care access. It is likely that those who start with higher eGFR are less well than those who tolerate a lower eGFR, and are therefore dialysed ‘earlier’. The concept of ‘early start’ by virtue of eGFR value may be flawed.

Others have investigated this counterintuitive relationship. Kazmi et al. [17] investigated a US cohort of 302 287 divided into ‘elderly’, ‘healthy’ and ‘general’ groups. They found a similar association between high starting eGFR and mortality, which, however, was only partially explained by increased comorbidity. Beddhu et al. [7] following the outcome of USRDS (n = 2920) came to similar conclusions.

Table 4. Characteristics and outcomes by eGFR category

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;5 (n = 674)</th>
<th>5–9.9 (n = 3256)</th>
<th>10–14.9 (n = 1349)</th>
<th>≥15 (n = 596)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 59.9 (15.7)</td>
<td>62.4 (15.5)</td>
<td>65.8 (14.8)</td>
<td>66.2 (15.0)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Age &gt;75 years 129 (19.1%)</td>
<td>764 (23.5%)</td>
<td>429 (31.8%)</td>
<td>189 (31.7%)</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>Male sex 300 (44.5%)</td>
<td>1868 (57.4%)</td>
<td>861 (63.8%)</td>
<td>390 (65.4%)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Primary kidney disease</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Diabetes 97 (14.4%)</td>
<td>739 (22.7%)</td>
<td>397 (29.4%)</td>
<td>175 (29.4%)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Polycystic/drug nephropathy/congenital 147 (21.8%)</td>
<td>680 (20.9%)</td>
<td>233 (17.3%)</td>
<td>113 (19.0%)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Renovascular 87 (12.9%)</td>
<td>494 (15.2%)</td>
<td>245 (18.2%)</td>
<td>116 (19.5%)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>GN/autoimmune diseases 166 (24.6%)</td>
<td>553 (17.0%)</td>
<td>135 (10.0%)</td>
<td>53 (9.9%)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Other/unknown/unrecorded 177 (26.3%)</td>
<td>790 (24.3%)</td>
<td>339 (25.1%)</td>
<td>139 (23.3%)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Initial dialysis 115 (17.1%)</td>
<td>855 (26.3%)</td>
<td>329 (24.4%)</td>
<td>107 (18.0%)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>eGFR prior to dialysis initiation ml/min/1.73 m² 4.2 (3.7–4.6)</td>
<td>7.2 (6.1–8.4)</td>
<td>11.6 (10.6–12.9)</td>
<td>18.55 (16.3–23.0)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin g/dl 9.37 (1.98)</td>
<td>10.13 (1.75)</td>
<td>10.51 (1.77)</td>
<td>10.74 (1.91)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Median survival (months) 56 (49–68)</td>
<td>44 (42–47)</td>
<td>34 (32–37)</td>
<td>29 (26–34)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Transplanted during the follow-up 100 (14.8%)</td>
<td>392 (12.0%)</td>
<td>92 (6.8%)</td>
<td>24 (4.0%)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>
We represent comorbidity here using age and diabetes as PRD, because much other comorbidity clusters around these two variables. A comparison of dialysis survival in European centres [9] demonstrated that although comorbidities (diabetes, ischaemic heart disease, peripheral vascular disease, cerebrovascular disease and malignancy) are indeed associated with a poorer prognosis, adjustment conferred little additional change to HR estimates with prior adjustment for general characteristics, in particular age and PRD [9].

Comorbidity, as defined in any of these ways, appears unable to explain the poor prognosis with high eGFR starts. This may reflect a limitation in objective adjustment for comorbidity.

Previous studies, which described low eGFR as an indicator of reduced survival, will have included a higher proportion of patients with a sudden unexpected dialysis start [3–5]. The cohorts in this more recent study might have been expected to have a lower proportion of such patients; however, a previous study on the SRR population highlighted significant potential for improving survival with better pre-dialysis nephrology input [18]. Our study demonstrated improving median survival times in successive years (2000–2005) of initiation of dialysis in our data, and may still reflect subsequent improvements in pre-dialysis multidisciplinary input.

A total of 15.8% of SRR patients and 22.7% of BCPRA patients did not have an eGFR recorded in registry data. This incomplete data is a limitation to our study. Compared with eGFR < 5 ml/min/1.73 m², however, the HR of the unrecorded group was 1.345 (eGFR 5–10 ml/min/1.73 m² HR 1.17; 10–15 HR 1.371; > 15 ml/min/1.73 m² HR 1.648). Thus, the HR of the unrecorded group was well within the range of the various categories with a recorded pre-dialysis eGFR, suggesting that this group is likely to comprise a mix of patients from the other categories.

Despite using robust modelling techniques, our analysis demonstrates that a proportion of the variability remains unexplained, and that no amount of adjustment can replace randomization when assessing outcomes that are impacted by practice and intention. Conclusions of benefit in holding off dialysis while stable can only be tentative.

**International comparison**

Our second finding was significantly higher survival in the BCPRA versus SRR. This is present before and after multivariate modelling, which includes diabetes, but not other specific comorbidities such as cardiovascular disease. Significant differences are present after adjustment for demographic differences and in both modalities.

A recent study of RRT in Europe demonstrated the potential importance of considering the baseline general population mortality in between population analyses. Van Dijk et al. [19] demonstrated a significant effect on yearly death rates on dialysis, in some countries, of adding of this background mortality to adjustment for age, gender and diabetes. For their Scottish population, this resulted in significant reductions in relative risk of death [19].

We performed a similar adjustment of the SRR and BCPRA using age- and sex-matched general population baseline mortality rates over the last 5 years (higher in Scotland) [15,16] to revise our HRs. This narrowed the gap in mortality; however, mortality risk remained significantly higher in the SRR.

Our sensitivity analysis demonstrates that these differences are independent of transplantation on dialysis. Additionally, preemptive transplantation rates were similar in the SRR and BCPRA. The absolute values were insignificant relative to study size and would have no bearing on the overall results, nor explain the differences.

Notably, IDMS traceable calibration for sCr assays was routinely available in BC for only the last 3 years of this study and not until after the study in Scotland; thus, calibration was not utilized to ensure consistency of data. At the high sCr values, we have reported, however, that any errors introduced by the lack of calibration are likely to be small.

Our data also appear to support longer survival on PD versus HD; however, modality was based on initial mode without consideration of subsequent changes or early deaths on dialysis. There is a selection bias of a presumably healthier group who had the preparation to begin RRT on PD. Furthermore, although decreasing Hb was associated with increasing HRs in the multivariate analysis, there was a little effect on the HRs for either eGFR category or registry affiliation of adding or removing the Hb value from the model.

**Lead time bias (LTB)**

Previously, it has been suggested that the benefits of ‘early’ dialysis are attributable to LTB, i.e. those starting dialysis earlier (with a higher eGFR) will appear to survive longer. Two previous studies have attempted to address this issue [2,6]. Arguments in favour of adjusting for LTB can be supported by Biblaki et al. who presented evidence of significant differences in starting eGFRs among renal centres in Scotland and higher starting eGFRs now than in the past (data presented at the SRA conference 2006). Adjustment for LTB on our data might attenuate some of the survival advantage of BC patients who appear to start dialysis with an eGFR 1–2 ml/min/1.73 m² higher. This would approximate to a delay of 2–4 months based on yearly decline in GFR off dialysis [6].

However, as higher eGFR correlated with decreased survival, the concept of LTB may not apply to this cohort. Patients start dialysis for other reasons including symptoms, comorbidity or acute deterioration from fluid overload or infection. These may be the very factors that impact on the long-term outcome, so mathematical adjustment while interesting may not be reflective of clinical practice.

In practice, once a patient’s eGFR reaches a critical value, e.g. 20 ml/min/1.73 m², the emphasis of chronic kidney disease management concentrates on patient symptoms and optimization of biochemistry in an attempt to alleviate the burden of illness. The absolute value of GFR, thus, becomes less important.

**A randomized trial**

Probably only a randomized controlled trial (RCT) could fully address the issue of LTB and early versus late start.
The Initiating Dialysis Early and Late (IDEAL) study in progress comparing eGFR 10–14 and 5–7 ml/min/1.73 m² starts will be of considerable interest and may enable a reinterpretation of our own results [20]. In an RCT, however, healthy dropouts from the early intervention group who want to delay dialysis longer would select more unstable or symptomatic patients with increased mortality risk. Thus, the IDEAL trial may encounter similar methodological concerns.

Conclusions

This analysis compares two population cohorts with respect to survival on dialysis and factors associated with survival. Survival was greater in BC than in Scotland, although the reasons are unclear. Importantly, using robust modelling, an association between increased mortality and higher eGFR at the initiation of dialysis was identified. These findings suggest that, in the absence of clinical indication, delaying dialysis is not associated with a deleterious outcome. Guidelines suggesting the detrimental effect of initiating dialysis ‘late’ may need to be reworded to include the concepts of associated symptoms and signs. In addition, more complex mathematical constructs which include the rate of progression, Hb, albumin and age may need to be developed to more accurately understand the impact of the uraemic milieu and avoid the over-simplicity of eGFR alone. Appropriately, 2006 updates of the NKF K/DOQI guidelines reflect the difficulty in making any recommendations on eGFR alone [21].

Acknowledgements. We are grateful to the SRR steering committee and the BC PRA for approving the use of registry data and to Alison Severn, Jamie Traynor and Simon Walker for comments on the manuscript.

Conflict of interest statement. KS is the Chair of the Scottish Renal Registry. AL is provincial executive director of the BC Provincial Renal Agency, BC PRA.

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Received for publication: 17.2.09; Accepted in revised form: 1.4.09