Residual renal function improves outcome in incremental haemodialysis despite reduced dialysis dose

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Abstract

Background and Methods. The importance of residual renal function is well recognized in peritoneal dialysis but its role in haemodialysis (HD) has received much less attention. We studied 650 incident patients in our incremental high-flux HD programme over a 15-year period. Target total $Kt/V$ urea (dialysis plus residual renal) was 1.2 per session and monitored monthly. Renal urea clearance (KRU) was estimated 1–3 monthly.

Results. KRU declined during the first 5 years of HD from $3.1 \pm 1.9$ at 3 months to $0.9 \pm 1.2$ ml/min/1.73 m² at 5 years. The percentage of patients with KRU $\geq 1$ ml/min at these

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time points was 85% and 31%, respectively. Patients with KRU ≥ 1 ml/min had a significantly lower mean creatinine (all time points), ultrafiltration requirement (all time points) and serum potassium (6, 12, 36 and 48 months). Nutritional parameters were also significantly better in respect to nPCR and serum albumin (6, 12, 24 and 36 months). Patients with KRU ≥ 1 ml/min had significantly lower erythropoietin requirements and erythropoietin resistance indices (12, 24, 36 and 48 months).

Mortality was significantly lower in patients with a KRU ≥ 1 at 6, 12 and 24 months after HD initiation, this benefit being maintained after correcting for albumin, age, comorbidities, HDF use and renal diagnosis. Our unique finding was that these benefits occurred despite those with KRU ≥ 1 ml/min having a significantly lower dialysis Kt/V at all time points.

Conclusion. The associations demonstrated suggest that residual renal function contributes significantly to outcome in HD patients and that efforts to preserve it are warranted. Comparative outcome studies should be controlled for residual renal function.

Keywords: haemodialysis; haemodialysis adequacy; mortality; outcomes; survival

Introduction

Residual renal function (RRF) is frequently present in those starting on a haemodialysis (HD) or peritoneal dialysis (PD) programme, but reduces over time. Over the past two decades, the importance of RRF has been increasingly recognized [1]. It contributes crucially to outcome in continuous ambulatory PD [2–5], but in HD it has received much less attention. Improved small solute clearance using a combination of large dialyzers, increased blood flow and treatment duration has allowed HD to be much less dependent on RRF.

There is a paucity of studies examining the effect of RRF on outcomes in HD patients. Suda et al. [6] found that serum albumin and protein catabolic rate were higher in HD patients with RRF. A small multivariate analysis by Shamlik et al. [7] found that having RRF was protective for death with a substantially reduced odds ratio of 0.44.

The mechanisms by which survival on HD may be improved by RRF are also little researched. One possible contributing factor is the additional renal contribution to clearance of middle [8] and larger molecules [9]. The clearance of these molecules is not measured by Kt/V urea. There may be more complex reasons why RRF may contribute beneficially to survival. Strong evidence already exists in PD that it has an effect on anaemia [10,11], nutrition [12,13], bone metabolism [14], blood pressure [15], salt and water retention, chronic hypervolaemia [16] and left ventricular hypertrophy [11]. If RRF does confer some intrinsic additional benefit that cannot be replaced by increasing dialysis dose, then efforts to preserve RRF may be warranted.

In determining the effect of RRF on HD outcomes, the confounding effect of dialysis dose needs to be considered. Many units adjust dialysis dose in relation to a target Kt/V urea, without reference to RRF. Therefore, patients with residual function have a higher overall level of urea clearance and any improvements in dialysis outcomes may be simply due to this. Our own practice has been to adjust dialysis using a two-pool kinetic model that also takes into consideration RRF. We adjust dose to deliver a Kt/V of 1.2 per dialysis session for three times weekly dialysis. All Kt/V targets are a composite of Kt/V_{dialysis} and Kt/V_{renal}. To calculate Kt/V_{renal} all patients with residual urine output perform a monthly inter-dialytic urine collection. Therefore, patients with a residual urea clearance will have their dialysis dose reduced by the equivalent amount. This technique is better suited for studying the effect of RRF. Since all patients have the same total delivered Kt/V target, outcome benefits for those with RRF will not be due to higher overall urea clearance, but instead the intrinsic difference between RRF and the equivalent dialyzer clearance. Using this technique to adjust dialysis dose allows the question to be addressed: is 1 ml/min of residual renal urea clearance (KRU) better for patient well-being than the equivalent dialyzer clearance? Using our incremental approach, it is possible to compare outcomes in those with and without RRF, with both groups having equal overall Kt/V. Any differences found between patients with and without RRF will have occurred despite those with residual function having a lower dialysis Kt/V.

In this study, we examined the relationship between RRF and a number of indices of HD patient outcome, including ultrafiltration requirement, blood pressure control, anaemia, bone metabolism, nutrition and survival.

Methods

Patients

We retrospectively studied all patients who started HD at the Lister Renal Unit during a 15-year period between 1989 and 2005 (n = 650). Patients who had dialyzed for <3 months and previously had haemodialysis, peritoneal dialysis or renal transplantation were excluded. Additionally, patients who started dialysis in our unit and were transferred out to a different unit were excluded. The total number of exclusions from all these categories was 159. There were no other exclusions.

Haemodialysis programme

All patients were treated exclusively using high-flux membranes, predominantly polysulphone. Polyacrylonitrile and other biocompatible membranes were used in a small minority. During the earlier part of the study, dialyzers were reused for non-hepatitis positive patients but dialyzer reuse was zero after 2003. Bicarbonate was used exclusively as the buffer, and ultrapure water was used for dialysis and for the reuse procedure. Water quality was regularly monitored to ensure tight bacteriological standards. Dialysis fluid standards were <0.1 cfl/ml and <0.03 EU/ml. From 1993 a proportion of patients were treated by on-line haemodiafiltration (HDF), selection favouring those with poor renal function (KRU < 1 ml/min) and those with a large body size.

Dialysis adequacy and RRF

Dialysis was prescribed and monitored according to a target two-pool total Kt/V of 1.2 per dialysis session for three times weekly HD. Twice weekly HD was used in a small proportion of patients usually for a few months after dialysis initiation. These patients had a target Kt/V of 2.0 per session.

Total Kt/V urea (Kt/V_{urea}) per session was composed of delivered two-pool dialysis dose (Kt/V_{dialysis}) added to the interdialytic equivalent of continuous residual renal urea clearance (Kt/V_{renal}) using the method described by Gotch et al. [17]. This method aims to take into account the
In this equation, \( C_{\text{post}} \) is the post-dialysis serum urea (mmol/l) and \( C_{\text{pre}} \) was pre-dialysis serum urea (mmol/l). For outcome comparisons in this study, we corrected KRU measurements to 1.73 m² body surface area (KRU_{BSA}).

### Baseline characteristics

Baseline characteristics were collected for all patients in the study: age, height, weight at dialysis initiation, sex, cause of underlying renal disease, whether on HDF and dialysis initiation date. Comorbidity data were defined at dialysis initiation including diabetic status, known malignancy, ischaemic heart disease and peripheral vascular disease. Underlying renal disease was classified into seven groups (Table 1) by a senior nephrologist using clinical data including renal biopsy results.

### Definition of groups for comparison

The study population was subdivided by those with and without significant residual RRF at each time point. The level of KRU_{BSA} defining significant RRF was \( \geq 1 \) ml/min. For the analysis of survival, those with a KRU_{BSA} above and below this level at various time points following HD initiation were compared. In the survival analysis, RRF was also treated as a time-dependent variable.

### Outcome data

The following outcome data were collected at 6, 12, 24, 36, 48 and 60 months after dialysis initiation.

### Dialysis and renal adequacy

Biochemical markers of dialysis adequacy were \( Kt/V \) (dialysis and total), serum creatinine, urea and potassium. Serial KRU_{BSA} measurements were also determined as detailed above.

### Nutrition

Nutritional markers were serum albumin and normalized protein catabolic rate (nPCR). The following formula was used:

\[
nPCR = \frac{149.7 \cdot G/V + 0.17}{\text{mmol/kg/day}}
\]

where \( G/V = \frac{W_{\text{dry}}}{V_{\text{dry}}} + \frac{P_{\text{dry}}}{V_{\text{dry}}} \) and \( P_{\text{dry}} = \text{post-HD sodium urea (mmol/l)} \).

### Anemia and erythropoietin requirements

Serum haemoglobin and erythropoietin doses were collected. The erythropoietin resistance index (units/week/kg/g/dl) was calculated from peak erythropoietin dose (IU/week) divided by weight (kg) and haemoglobin level (g/dl).

### Fluid status

Interdialytic weight gain, ultrafiltration volumes and pre- and post-systolic blood pressures were collected.

### Survival

Patient survival was measured from the date of HD initiation to death.

### Statistical analysis

Statistical analysis was performed with SPSS v16.0.1. \( P \)-values of \( <0.05 \) were considered statistically significant.

Descriptive analysis was based on arithmetic means and standard deviations for normally distributed variables and percentages for those not. Baseline characteristics between those with and without significant RRF in the first 6 months of HD were compared. Demographics were compared using Fisher’s exact, Student’s independent samples’ \( t \)-tests and chi-squared tests as appropriate.

Decline in RRF was compared between males and females, diabetics and non-diabetics and those with or without adult polycystic kidney disease. KRU_{BSA} was compared at each time point using Student’s \( t \)-test. Nutritional, biochemical, fluid status and erythropoietin data were compared between those with and without significant RRF at 6-month intervals using Student’s independent samples’ \( t \)-test for normally distributed data and the Mann–Whitney \( U \)-test for non-parametric data.

Survival was compared between those with a KRU_{BSA} above and below 1 ml/min using a Kaplan–Meier analysis at 6, 12, 24, 36, 48 and 60 months. Patients were censored for transplantation, conversion to PD or loss from the follow-up. In order to correct for the effect of confounding...
variables on survival, we used a Cox proportional hazards model comparing survival between those with a KRUBSA above and below 1 ml/min. Confounding variables included in the model were diabetic status, age, HDF use, serum albumin, underlying cause of renal disease, presence of malignancy, ischaemic heart disease and peripheral vascular disease. Patients in the HDF group were those who had >50% of their dialysis sessions as HDF throughout their dialysis career. In our model (Enter method, SPSS), survival and risk were calculated with respect to one of the factors, which was assigned a unitary risk of 1. For example, diabetics were compared to non-diabetics; the latter not being listed and having a unitary risk of 1. The Cox model was repeated using KRUBSA above or below 1 ml/min at all time points up to 5 years after HD initiation. Diabetic status, age, HDF use, serum albumin, underlying renal disease, presence of malignancy, ischaemic heart disease and peripheral vascular disease were similarly included in these models.

In order to assess whether the time-dependent variation decline in KRUBSA affected survival, we used a Cox proportional hazards model using KRUBSA as a time-dependent covariate, in addition to age, HDF use, serum albumin, previously described comorbidity variables and cause of underlying disease. Missing KRU data for subjects were replaced rather than excluding them from the analysis, as missing KRU measurements might not be completely at random. Missing KRU data were replaced using linear regression to estimate values based on other measurements for each subject (linear trend at point, SPSS).

The proportional hazards assumption was tested for each covariate using two methods: inclusion of interacting terms in the model (product for each subject (linear trend at point, SPSS)).

Results

Baseline characteristics

Baseline characteristics of the 650 patients included in the study are shown in Table 1. Although the demographics of the two groups were not significantly different, the group with a KRUBSA ≥ 1 ml/min had a significantly higher proportion with peripheral vascular disease \((P = 0.006)\) and diabetes \((P = 0.04)\), although there was no significant difference in the prevalence of diabetic nephropathy. There were also a significantly higher proportion of patients in the KRUBSA ≥ 1 ml/min group with congenital cystic kidney disease \((P = 0.04)\).

Decline of renal function with time

Decline in KRUBSA over time is shown in Figure 1. The mean KRUBSA fell from 3.08 ml/min (SD 1.87) at 3 months to 0.88 (SD 1.24) 60 months after HD initiation. Figure 2 shows the proportion of patients with a KRUBSA ≥ 1 ml/min at each time point after initiation of HD. Three months after the start of HD, 85.4% of patients had a KRUBSA ≥ 1 ml/min but this proportion declined to 58.1% at 2 years and 31.1% at 5 years.

Dialysis and renal adequacy parameters

Table 2 shows parameters of dialysis adequacy in those with KRUBSA above and below 1 ml/min at each time point. \(Kt/V\) dialysis urea was significantly different between groups at each time point \((P < 0.001)\) because overall \(Kt/V\) was used to define dialysis dose, a composite of \(Kt/V\) dialysis and \(Kt/V\) renal. Serum creatinine was lower in those with KRUBSA ≥ 1 ml/min at all time points, and serum potassium was lower at the 6, 12, 36 and 48 month points.

Nutrition and bone metabolism

Serum albumin and nPCR differed significantly between those with KRUBSA above and below 1 ml/min up to 36 months after HD initiation \((P\text{-value from }<0.001\text{ to }0.034, \text{ Table 3})\). Serum urea was significantly higher in those with KRUBSA ≥ 1 ml/min up to 24 months. Although mean serum phosphate was lower at all time points in those with a KRUBSA ≥ 1 ml/min, this was only statistically significant at 48 months \((P = 0.048)\). There was no significant difference in PTH between those with a KRUBSA above or below 1 ml/min.

Anaemia and erythropoietin requirements

There was no significant difference in serum haemoglobin between subjects with a KRUBSA above or below 1 ml/min at 6, 36, 48 and 60 months after dialysis initiation (Table 4). Those with a KRUBSA ≥ 1 ml/min had a significantly higher
Table 2. Dialysis adequacy parameters in those with a KRU_BSA ≥ or < 1 ml/min/1.73 m² BSA at each time point

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>6 m</th>
<th>12 m</th>
<th>24 m</th>
<th>36 m</th>
<th>48 m</th>
<th>60 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kt/V dialysis urea</td>
<td>KRU &lt; 1 mean</td>
<td>1.00</td>
<td>1.11</td>
<td>1.17</td>
<td>1.19</td>
<td>1.24</td>
<td>1.23</td>
</tr>
<tr>
<td></td>
<td>KRU ≥ 1 mean</td>
<td>0.82</td>
<td>0.84</td>
<td>0.89</td>
<td>0.94</td>
<td>0.94</td>
<td>0.96</td>
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<tr>
<td>df</td>
<td></td>
<td>546</td>
<td>457</td>
<td>339</td>
<td>226</td>
<td>159</td>
<td>100</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>KRU &lt; 1 mean</td>
<td>20.6</td>
<td>21.0</td>
<td>20.8</td>
<td>22.5</td>
<td>20.2</td>
<td>21.5</td>
</tr>
<tr>
<td></td>
<td>KRU ≥ 1 mean</td>
<td>22.4</td>
<td>22.4</td>
<td>22.7</td>
<td>22.0</td>
<td>21.4</td>
<td>21.7</td>
</tr>
<tr>
<td>df</td>
<td></td>
<td>593</td>
<td>463</td>
<td>342</td>
<td>229</td>
<td>159</td>
<td>100</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.007*</td>
<td>0.024*</td>
<td>0.009*</td>
<td>0.492</td>
<td>0.191</td>
<td>0.860</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>KRU &lt; 1 mean</td>
<td>815</td>
<td>844</td>
<td>867</td>
<td>914</td>
<td>849</td>
<td>845</td>
</tr>
<tr>
<td></td>
<td>KRU ≥ 1 mean</td>
<td>692</td>
<td>724</td>
<td>769</td>
<td>756</td>
<td>748</td>
<td>736</td>
</tr>
<tr>
<td>df</td>
<td></td>
<td>593</td>
<td>463</td>
<td>342</td>
<td>228</td>
<td>159</td>
<td>100</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>KRU &lt; 1 mean</td>
<td>5.13</td>
<td>5.19</td>
<td>5.22</td>
<td>5.37</td>
<td>5.36</td>
<td>5.31</td>
</tr>
<tr>
<td></td>
<td>KRU ≥ 1 mean</td>
<td>4.91</td>
<td>4.93</td>
<td>5.15</td>
<td>5.10</td>
<td>5.09</td>
<td>5.10</td>
</tr>
<tr>
<td>df</td>
<td></td>
<td>595</td>
<td>464</td>
<td>341</td>
<td>228</td>
<td>159</td>
<td>100</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.001*</td>
<td>0.001*</td>
<td>0.005*</td>
<td>0.027*</td>
<td>0.220</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05.

Table 3. Nutritional parameters in subjects with a KRU_BSA ≥ or <1 ml/min/1.73 m² BSA at each time point

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>6 m</th>
<th>12 m</th>
<th>24 m</th>
<th>36 m</th>
<th>48 m</th>
<th>60 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/l)</td>
<td>KRU &lt; 1 mean</td>
<td>34.8</td>
<td>35.4</td>
<td>35.1</td>
<td>34.7</td>
<td>34.5</td>
<td>34.4</td>
</tr>
<tr>
<td></td>
<td>KRU ≥ 1 mean</td>
<td>36.1</td>
<td>36.6</td>
<td>36.2</td>
<td>36.4</td>
<td>35.8</td>
<td>34.6</td>
</tr>
<tr>
<td>df</td>
<td></td>
<td>594</td>
<td>463</td>
<td>341</td>
<td>229</td>
<td>159</td>
<td>100</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.009*</td>
<td>0.017*</td>
<td>0.034*</td>
<td>0.005*</td>
<td>0.096</td>
<td>0.822</td>
</tr>
<tr>
<td>nPCR (g/kg/day)</td>
<td>KRU &lt; 1 mean</td>
<td>0.86</td>
<td>0.86</td>
<td>0.87</td>
<td>0.87</td>
<td>0.86</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>KRU ≥ 1 mean</td>
<td>0.95</td>
<td>0.95</td>
<td>0.95</td>
<td>0.94</td>
<td>0.92</td>
<td>0.92</td>
</tr>
<tr>
<td>df</td>
<td></td>
<td>521</td>
<td>428</td>
<td>321</td>
<td>208</td>
<td>148</td>
<td>89</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.002*</td>
<td>0.019*</td>
<td>0.053</td>
<td>0.616</td>
</tr>
<tr>
<td>Phosphate (mmol/l)</td>
<td>KRU &lt; 1 mean</td>
<td>1.87</td>
<td>1.82</td>
<td>1.88</td>
<td>1.92</td>
<td>1.82</td>
<td>1.77</td>
</tr>
<tr>
<td></td>
<td>KRU ≥ 1 mean</td>
<td>1.81</td>
<td>1.72</td>
<td>1.86</td>
<td>1.79</td>
<td>1.64</td>
<td>1.57</td>
</tr>
<tr>
<td>df</td>
<td></td>
<td>538</td>
<td>426</td>
<td>303</td>
<td>220</td>
<td>140</td>
<td>86</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.281</td>
<td>0.074</td>
<td>0.732</td>
<td>0.168</td>
<td>0.048*</td>
<td>0.100</td>
</tr>
<tr>
<td>PTH (pmol/l)</td>
<td>KRU &lt; 1 median (IQR)</td>
<td>21 (39)</td>
<td>17 (35)</td>
<td>21 (32)</td>
<td>29 (54)</td>
<td>27 (46)</td>
<td>35 (59)</td>
</tr>
<tr>
<td></td>
<td>KRU ≥ 1 median (IQR)</td>
<td>22 (34)</td>
<td>24 (30)</td>
<td>26 (50)</td>
<td>29 (49)</td>
<td>30 (49)</td>
<td>47 (50)</td>
</tr>
<tr>
<td>Total (n) with data</td>
<td></td>
<td>518</td>
<td>433</td>
<td>327</td>
<td>224</td>
<td>150</td>
<td>96</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.821</td>
<td>0.461</td>
<td>0.539</td>
<td>0.406</td>
<td>0.701</td>
<td>0.424</td>
</tr>
</tbody>
</table>

*P < 0.05, IQR = interquartile range, PTH = parathyroid hormone.

haemoglobin level at 12 months (P = 0.019), but conversely a lower Hb at 24 months (P = 0.020). Both weekly erythropoietin dose and erythropoietin resistance index were significantly higher at 12, 24, 36 and 48 months after dialysis initiation in those with a KRU < 1 ml/min (P varying from <0.001 to 0.005). This was despite there being no significant difference in CRP at any time point between groups.

Fluid status

There was a significantly higher mean ultrafiltration requirement on dialysis at every time point from 6 months to 5 years after dialysis initiation in those with a KRU_BSA < 1 ml/min (P-value varying from 0.04 to <0.001, t-test, Figure 3). There were no significant differences in mean pre-dialysis systolic and diastolic blood pressures between subjects with a KRU_BSA above or below 1 ml/min.

Survival

In the Kaplan–Meier survival analysis, we found a significantly better survival in subjects with a KRU_BSA ≥ 1 ml/min in the first 6 months of dialysis compared to those below this level (P = 0.002, log-rank test). The median survival was 55.7 months (95% C.I. 50.2–61.2) for the group with a KRU_BSA ≥ 1 ml/min in the first 6 months of HD and 38.8 months (95% C.I. 26.7–50.8) for those with <1 ml/min. Those with a KRU_BSA ≥ 1 ml/min at 12 months and at
RRF improves outcome in incremental haemodialysis despite reduced dialysis dose

Table 4. Parameters of anaemia and erythropoietin use in subjects with a KRU_{BSA} \geq 1 ml/min or <1 ml/min at each time point

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>6 m</th>
<th>12 m</th>
<th>24 m</th>
<th>36 m</th>
<th>48 m</th>
<th>60 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dl)</td>
<td>KRU &lt; 1</td>
<td>10.6</td>
<td>10.7</td>
<td>11.3</td>
<td>11.2</td>
<td>11.0</td>
<td>11.4</td>
</tr>
<tr>
<td></td>
<td>KRU \geq 1</td>
<td>10.8</td>
<td>11.1</td>
<td>10.9</td>
<td>11.2</td>
<td>11.1</td>
<td>11.3</td>
</tr>
<tr>
<td>df</td>
<td></td>
<td>580</td>
<td>454</td>
<td>337</td>
<td>225</td>
<td>155</td>
<td>98</td>
</tr>
<tr>
<td>( P )</td>
<td></td>
<td>0.422</td>
<td>0.019*</td>
<td>0.020*</td>
<td>0.911</td>
<td>0.666</td>
<td>0.976</td>
</tr>
<tr>
<td>Erythropoietin dose (units/week)</td>
<td>KRU &lt; 1</td>
<td>8605</td>
<td>9432</td>
<td>10.368</td>
<td>10.844</td>
<td>11.128</td>
<td>10.454</td>
</tr>
<tr>
<td></td>
<td>KRU \geq 1</td>
<td>7893</td>
<td>7439</td>
<td>8130</td>
<td>8164</td>
<td>8231</td>
<td>8880</td>
</tr>
<tr>
<td>df</td>
<td></td>
<td>468</td>
<td>394</td>
<td>288</td>
<td>199</td>
<td>136</td>
<td>87</td>
</tr>
<tr>
<td>( P )</td>
<td></td>
<td>0.159</td>
<td>&lt;0.001*</td>
<td>0.003*</td>
<td>&lt;0.001*</td>
<td>0.005*</td>
<td>0.250</td>
</tr>
<tr>
<td>Erythropoietin resistance index</td>
<td>KRU &lt; 1</td>
<td>11.97</td>
<td>14.18</td>
<td>14.33</td>
<td>14.87</td>
<td>16.19</td>
<td>15.01</td>
</tr>
<tr>
<td></td>
<td>KRU \geq 1</td>
<td>10.49</td>
<td>9.98</td>
<td>11.06</td>
<td>11.03</td>
<td>11.34</td>
<td>12.37</td>
</tr>
<tr>
<td>(units/week per kg/dl)</td>
<td></td>
<td>440</td>
<td>386</td>
<td>284</td>
<td>197</td>
<td>132</td>
<td>85</td>
</tr>
<tr>
<td>( P )</td>
<td></td>
<td>0.057</td>
<td>&lt;0.001*</td>
<td>0.004*</td>
<td>0.003*</td>
<td>0.005*</td>
<td>0.276</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>KRU &lt; 1</td>
<td>8.4 (16)</td>
<td>9 (19)</td>
<td>9.7 (20)</td>
<td>9 (16)</td>
<td>15 (46)</td>
<td>14 (23)</td>
</tr>
<tr>
<td></td>
<td>KRU \geq 1</td>
<td>10 (18)</td>
<td>10 (16)</td>
<td>9.7 (15)</td>
<td>8.4 (25)</td>
<td>8.6 (18)</td>
<td>12 (56)</td>
</tr>
<tr>
<td>Total (n) with data</td>
<td></td>
<td>362</td>
<td>297</td>
<td>231</td>
<td>157</td>
<td>112</td>
<td>81</td>
</tr>
<tr>
<td>( P )</td>
<td></td>
<td>0.625</td>
<td>0.502</td>
<td>0.745</td>
<td>0.937</td>
<td>0.276</td>
<td>0.512</td>
</tr>
</tbody>
</table>

\*\( P < 0.05 \), IQR = interquartile range.

![Error Bars: +/- 2 SE](image)

Fig. 3. Mean ultrafiltration requirement per HD session in subjects with a KRU_{BSA} above or below 1 ml/min at each time point. Ultrafiltration was significantly lower in those with a KRU_{BSA} \geq 1 ml/min at every time point (\( P \)-value varying from 0.04 to <0.001, t-test).

24 months also had a survival advantage over those with lesser degrees of RRF at these time points.

In the Cox proportional hazards model (Figure 4), KRU_{BSA} level (\( \geq 1 \) or <1 ml/min at 6 months), age, serum albumin, predominant HDF use, malignancy and underlying renal disease category were all significant independent predictors of patient survival (Table 5). The risk of death was 31% less in the group with a 6-month KRU_{BSA} \geq 1 ml/min (hazard ratio 0.69, \( P = 0.01 \)); HDF use conferred a 48% reduction (hazard ratio 0.52, \( P < 0.001 \)). In the group defined as predominant HDF, the proportion of dialysis sessions delivered as HDF was 74% (SD 14%). In the HD group, 91% of sessions (SD 15%) were delivered as high-flux HD. A similar Cox model was repeated using KRU_{BSA} at 12, 24, 36, 48 and 60 months as a factor in the equation. KRU_{BSA} above or below 1 ml/min remained a significant predictor for death up to 24 months after dialysis initiation. Risk of death was 39% less in those with a KRU_{BSA} \geq 1 ml/min at 12 months (HR 0.61, 95% C.I. 0.45–0.82, \( P = 0.001 \)) and 40% less for a KRU_{BSA} \geq 1 ml/min at 24 months (HR 0.60, 95% C.I. 0.42–0.84, \( P = 0.003 \)).

Table 6 shows results of the Cox model designed to examine whether KRU remained a significant predictor for death after taking into account its time-dependent variation. KRU_{BSA} < 1 ml/min was a significant independent predictor of reduced survival.

![KRU 6 months after start of HD (ml/min)](image)

Fig. 4. Cox proportional hazards model comparing patient survival in subjects with a KRU_{BSA} \geq 1 ml/min in the first 6 months of HD, corrected for age, diabetes, HDF use, underlying renal disease, serum albumin, malignancy, ischaemic heart disease and peripheral vascular disease. KRU_{BSA} < 1 ml/min was a significant independent predictor of reduced survival.
Discussion

Contrary to a popular belief, RRF does not necessarily decline rapidly following the initiation of HD [18], though it may be affected by factors such as volume depletion, nephrotoxic drugs and radiocontrast agents [19]. In this study, we provide strong evidence that RRF ≥ 1 ml/min/1.73 m² BSA (KRUBSA) is associated with wide-ranging benefits that include reduced erythropoietin resistance, improved nutrition and reduced ultrafiltration requirements. Furthermore, RRF is a significant independent predictor of survival. These results are in keeping with previous studies in PD patients.

The NECOSAD study [20] suggested that the mortality benefit of a higher delivered Kt/V urea was attenuated in HD patients with a urine output >100 ml/day. Furthermore, RRF predicted survival to a greater extent than delivered Kt/V urea. However, in this study there was a higher mortality in patients with missing data so the survival data need to be interpreted with caution. While the DOPPS study [21] reported that diuretic use and RRF were both associated with lower mortality in HD patients, RRF was not formally measured and was defined by a questionnaire. Additionally, since the DOPPS study did not correct for the unmeasured Kt/V renal, the mortality benefit of RRF might be simply due to a higher overall Kt/V urea. Survival data from our study demonstrate that despite having a lower delivered Kt/V, patients with RRF have a significantly lower mortality.

Our finding that patients with a KRUBSA ≥ 1 ml/min had better survival despite having a reduced Kt/Vdialysistrongly suggests that a RRF of 1 ml/min KRUBSA provides more benefit to patient well-being than the equivalent dialyzer clearance. Our evidence supports the technique of incremental dialysis, though with certain caveats. Considerable variability exists between patients in the rate of decline of RRF [18], and regular measurement is required for this technique to be used effectively.

The beneficial effects of RRF may be due to enhanced middle molecule clearance [22–24], and RRF is certainly a major determinant of β₂-microglobulin levels [25–28]. Our data demonstrate improved nutritional parameters and reduced erythropoietin resistance, both of which were independent of CRP. Both these effects could result from enhanced removal of toxic middle molecules, and both could contribute to improved survival. Additionally, the reduced ultrafiltration requirement may confer survival benefits to those with RRF. Lower levels of left ventricular hypertrophy have previously been demonstrated in those with lower requirements for ultrafiltration [29], and ultrafiltration rate has been shown to be an independent predictor of survival [21].

Starting time bias is a possible mechanism underlying the benefits of RRF we have described, as has been discussed in relation to the similar benefits described in the PD context in the CANUSA study [5,30,31]. The contention is that patients initiating HD with lower KRU may be at a survival disadvantage having been uraemic for longer [32]. Set against this is the increased exposure of early starters on HD to dialysis-related complications and death. We cannot exclude lead-time bias as a contributor to the benefits of RRF.

Factors entered into the model are shown in column 1. Age, KRUBSA ≥ 1 ml/min at 6 months, serum albumin, HDF use and malignancy were all significant independent predictors of patient survival.

Table 5. Cox proportional hazards model of patient survival

<table>
<thead>
<tr>
<th>Wald statistic</th>
<th>Sig (P-value)</th>
<th>Hazard ratio</th>
<th>95% CI for hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-month KRU ≥ 1 ml/min</td>
<td>6.411</td>
<td>0.01</td>
<td>0.693</td>
</tr>
<tr>
<td>Diabetic status</td>
<td>1.047</td>
<td>0.306</td>
<td>1.210</td>
</tr>
<tr>
<td>Age</td>
<td>26.984</td>
<td>&lt;0.001</td>
<td>1.029</td>
</tr>
<tr>
<td>Albumin</td>
<td>9.805</td>
<td>0.002</td>
<td>0.959</td>
</tr>
<tr>
<td>HDF use</td>
<td>17.035</td>
<td>&lt;0.001</td>
<td>0.523</td>
</tr>
<tr>
<td>Malignancy</td>
<td>10.283</td>
<td>0.001</td>
<td>1.814</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>0.246</td>
<td>0.620</td>
<td>0.931</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>0.371</td>
<td>0.543</td>
<td>1.107</td>
</tr>
</tbody>
</table>

Table 6. Cox proportional hazards model examining the relationship of KRUBSA with patient survival after taking account of KRU variation with time

<table>
<thead>
<tr>
<th>KRUBSA TIME</th>
<th>Wald statistic</th>
<th>Significance (P-value)</th>
<th>Hazard ratio</th>
<th>95% CI for hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRUBSA TIME</td>
<td>4.787</td>
<td>0.029</td>
<td>0.932</td>
<td>0.875–0.993</td>
</tr>
<tr>
<td>Diabetic status</td>
<td>1.639</td>
<td>0.200</td>
<td>1.272</td>
<td>0.880–1.838</td>
</tr>
<tr>
<td>Age</td>
<td>27.736</td>
<td>&lt;0.001</td>
<td>1.030</td>
<td>1.019–1.041</td>
</tr>
<tr>
<td>Albumin</td>
<td>8.575</td>
<td>0.003</td>
<td>0.962</td>
<td>0.937–0.987</td>
</tr>
<tr>
<td>HDF use</td>
<td>18.377</td>
<td>&lt;0.001</td>
<td>0.508</td>
<td>0.373–0.692</td>
</tr>
<tr>
<td>Malignancy</td>
<td>10.888</td>
<td>0.001</td>
<td>1.841</td>
<td>1.281–2.645</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>0.292</td>
<td>0.589</td>
<td>0.925</td>
<td>0.698–1.227</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>0.165</td>
<td>0.684</td>
<td>1.070</td>
<td>0.773–1.481</td>
</tr>
</tbody>
</table>

KRUBSA remained a significant predictor for death in this model with a unitary 1 ml/min KRUBSA conferring a reduction in the risk of death of 7% (hazard ratio 0.93, CI 0.88–0.99). HDF use, serum albumin and malignancy remained significant independent predictors of survival. KRUBSATIME = KRUBSA as a time-dependent covariate.
we have described, but question its clinical relevance. In our study, the decision to initiate HD was made on the basis of clinical features including uraemic symptoms, volume overload, hyperkalaemia and acidosis. Patients initiating HD with higher RRF may have a higher burden of comorbidity as seen in our table of baseline characteristics (Table 1). However, the survival benefit associated with RRF existed in our data even after correction for these comorbidities. Furthermore, our Cox proportional hazards model that used KRU as a time-dependent covariate demonstrated that higher KRU was associated with improved survival after taking account of changes in KRU with time after HD initiation. The important issue is that even months and years after dialysis initiation, the presence or absence of RRF is an important factor that needs to be taken into account in clinical decision making.

Several further criticisms may be made of our study. The retrospective design resulted in data being collected over a 15-year period of time during which HD practice changed undoubtedly. The demographics of the incident dialysis population also altered during this period, although we attempted to correct for this in our multivariate analysis. Additionally, when comparing survival of patients with and without RRF it is important to control for factors that are associated with RRF, but not directly affected by this, which may have an independent impact on survival. We selected known confounding factors to correct in the multivariate analysis but other unknown variables may exist. Incorporating haemodiafiltration use as a covariate in the survival analysis was necessary as it may be a predictor of survival and was introduced during the study period for selected patients having low RRF. The substantial survival benefit for patients treated predominantly with haemodiafiltration should therefore be interpreted with caution. Although we defined significant renal function in a binary way (KRU_BSA ≥ 1 ml/min), it may be more appropriate to look at outcomes related to RRF measured as a continuous variable. However, we used this definition of RRF because it is clear and widely applicable.

Our selection of KRU_BSA to measure RRF was pragmatic. Urea clearance underestimates insulin clearance by ~20% and creatinine clearance overestimates by a similar amount [33], so many authors advise the mean of creatinine and urea clearance to measure RRF. The ‘gold standard’ methods of insulin and EDTA clearance are not suited for serial frequent measurement as part of routine clinical practice in an incremental HD programme. Urea clearance is simple to perform, can be safely repeated for serial measurements and formed as part of our routine adequacy monitoring. Urea clearance is recommended for both dialyzer and residual renal clearance in the NKF K/DOQI guidelines for HD adequacy [34]. Our use of the technique precedes the European guidelines that suggest combining urea and creatinine clearance to estimate GFR [35].

Combining residual renal and dialyzer urea clearance is not straightforward because residual clearance is continuous and more efficient. Several methods have been suggested to combine these clearances. We selected the method described by Gotch et al. [17] that converts residual renal clearance into an intermittent equivalent, in effect dividing the weekly residual urea clearance by the number of dialysis sessions to give a per-session residual renal clearance. The higher efficiency of residual urea clearance is taken into account using a factor J (see methods). More recently alternative techniques have been suggested that involve the conversion of intermittent dialyzer clearance to its continuous equivalent [36–38].

Maintaining RRF in HD patients is likely to require a modification to our approach to drug therapy and avoidance of nephrotoxic agents. Increasing evidence now exists that use of angiotensin-converting enzyme inhibitors [39], angiotensin II receptor blockers [40] and calcium channel blockers [41] are associated with a reduced risk of RRF loss and one may postulate that this may be due to the anti-proteinuric effects [42]. The degree to which blood pressure control should be exerted using aggressive ultrafiltration to the detriment of RRF is still a subject of debate [1,43].

In summary, we present an analysis of outcomes, including survival, in patients on HD with and without significant RRF. Our finding of wide-ranging benefits confirms that RRF is important not only in PD, but also in HD. All these benefits occur despite those with RRF having a lower delivered HD dose. In addition, the survival benefit conferred by RRF persists after correction for confounding factors. We have also demonstrated a survival benefit associated with predominant HDF use but the selection bias means this should be interpreted with caution. We suggest that this is strong evidence that efforts should be made to maintain RRF in HD. Furthermore, in view of these findings, comparative outcome studies should be controlled for the presence of RRF.

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Conflict of interest statement. None declared.

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