Chronic kidney disease rather than illness severity predicts medium- to long-term mortality and renal outcome after acute kidney injury

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ABSTRACT

Background. Acute kidney injury (AKI) requiring renal replacement therapy (RRT) continues to be associated with a hospital mortality of ~50%. Longer-term outcomes have been less well studied. We sought to determine the influence of ventilation and of underlying chronic kidney disease (CKD) on medium and long-term mortality and renal outcomes.

Methods. All patients requiring RRT for AKI in south west Scotland between 1 January 1994 and 31 December 2005 were followed prospectively. Survival of patients who were and were not ventilated and of those with and without underlying CKD was compared by odds ratio (OR), adjusting for age and sex. Renal outcomes were determined by interrogation of our biochemistry database.

Results. Three hundred and ninety-six patients with AKI received RRT. One hundred and seventy-six (44%) were ventilated and 98 (25%) had underlying CKD. Patients who required ventilation had a significantly worse 90-day survival than those who did not (OR 2.10 for death; 95% CI 1.34, 3.29) whereas underlying CKD did not predict such an early adverse outcome (OR 1.49; 95% CI 0.89, 2.50). By 5 years, patients who had been ventilated during the acute illness were no longer at increased risk (OR 0.79; 95% CI 0.38, 1.62) whereas the adverse effect of underlying CKD was statistically significant (OR 6.05; 95% CI 2.23, 16.5). Underlying CKD was also a strong predictor of the need for RRT during follow-up.

Conclusion. In an unselected series of patients with AKI requiring RRT, underlying CKD rather than illness severity predicted medium- to long-term mortality.

Keywords: acute kidney injury, acute on chronic kidney disease, renal outcomes, survival

INTRODUCTION

Acute kidney injury (AKI) is common, has multiple causes and is associated with high mortality [1]. It can be present at the time of admission or develop later in hospital. Most patients are managed by rehydration, withdrawal of nephrotoxic drugs, relief of urinary obstruction and treatment of sepsis. Some will require renal replacement therapy (RRT), which is undertaken on renal, medical high dependency or intensive care units (ICU) depending on the severity of illness. Admission to ICU generally requires AKI with at least one other organ failure.

A rapidly expanding evidence base suggests that short-term patient survival is adversely affected by the need for ventilation and by illness severity (summarized by Uchino [2]), whereas the presence of underlying chronic kidney disease (CKD) at the time of first RRT is not harmful and might even be protective [3-6]. The influence of illness severity and underlying CKD on medium- to long-term survival has been studied less frequently with reports suggesting that illness severity exerts less of an adverse effect [7] and that acute on CKD (A on CKD) predicts a significantly worse outcome with time [8, 9]. Renal outcomes have also been reported, although interpretation is complicated by studies that do not exclude patients with previous CKD from the subsequent cumulative incidence of CKD and end-stage renal disease (ESRD) [10].

Against this background, the aims of our study were to determine the influence of ventilation and of underlying CKD on short- and long-term survival in patients requiring RRT for...
We are particularly well placed to address these issues, given that RRT for AKI in south west Scotland is delivered by nephrologists rather than by intensivists, enabling us to document all cases of AKI in our hospital and not just those occurring on ICU and also because our patients had all been followed for a minimum of 5 years following their initial treatment.

**MATERIALS AND METHODS**

We conducted a prospective study of all patients receiving RRT for AKI in the south west of Scotland between 1 January 1994 and 31 December 2005. This was a single-centre study as Dumfries Infirmary is the only hospital in the catchment area to provide RRT. We included all patients who presented with acute on CKD unless they were already on regular haemodialysis or peritoneal dialysis. We defined CKD using the criteria adopted by Prescott [3]. If there was no previously recorded creatinine level, or the previously recorded creatinine level was <150 µmol/L within 3 months of the date of first RRT, then patients were designated as AKI. If imaging showed small kidneys or if underlying CKD was documented previously, they were considered to have A on CKD. Patients with an elevated creatinine recorded within 4 weeks of first RRT but not previously and who had no imaging available were allocated to our AKI group as were those with a diagnosis of vasculitis. Patients with ESRD already on RRT were excluded.

We recorded the following baseline data for all patients: age, gender, causes of AKI, presence of underlying CKD, presence or absence of diabetes or malignancy, date of first RRT, urea and creatinine at time of first RRT and whether or not the patient required mechanical ventilation. All patients with single organ failure were treated on the renal or medical high dependency unit, whereas all those who needed mechanical ventilation were treated in ICU where they invariably required inotropic support. No elective patients who were mechanically ventilated for a short time post-operatively developed AKI in this study. This is likely to reflect the fact that our hospital does not undertake thoracic, renal or liver transplant surgery.

The causes of AKI were determined by case sheet review. We considered four main diagnostic groups, namely acute tubular necrosis (ATN), obstructive, inflammatory and other causes. ATN was either surgical or medical with medical causes further categorized as dry, septic, nephrototoxic or cardiorenal syndrome (CRS). We used the term CRS to describe patients with cardiac and renal failure that was not subsequently found to be due to bilateral renovascular disease.

We used the RIFLE (Risk, Injury, Failure, Loss, End Stage) classification of AKI. All patients included in the study had at least a 3-fold increase in serum creatinine or oliguria for 12 h (RIFLE class F). The indications for RRT were the classical ones, namely uremia, pulmonary oedema and hyperkalaemia resistant to conservative measures. Over 90% of the patients in this survey were treated by intermittent haemodialysis (IHD) rather than by continuous haemofiltration (CHF) because this is our unit’s preferred treatment modality. Occasional patients received both IHD and CHF. We performed IHD daily for 4–12 h per session according to the needs of the patient, reducing to alternate days as their clinical condition stabilized or improved. We followed all patients for a minimum of 5 years until death or until 1 January 2011. Estimated glomerular filtration rate (eGFR) was calculated at 1-, 5- and 10-year follow-up using the four variable Modification of Diet in Renal Disease formula. Record linkage with the Registrar General in Scotland meant that we were informed of the date of death for all patients even if they were no longer attending our clinic.

**Statistical methods**

We used unadjusted Kaplan–Meier survival curves to compare survival times from admission to death for different categories of patients. These were stratified separately by ventilation status and by the presence or absence of underlying CKD. We used logistic regression to calculate odds ratios after adjusting for age and sex, with survival status as the outcome. As the risk of death changed with time, separate analyses were done for two time periods, covering 0–90 days and 90 days to 5 years. In each case, the odds of survival was calculated over the time period. For the second time period, only those surviving beyond 90 days were considered. This approach was considered appropriate given non-constant ratio of risks over time for different levels of explanatory variables. SAS version 9.3 was used for the analysis.

**Ethical approval**

Our study was conducted to define and measure current care and involved routine interventions already in common use. We did not randomize or allocate patients to treatment groups. Our study met the criteria for service evaluation, and therefore, we did not seek approval from our research Ethics Committee, in keeping with our health board policy.

**RESULTS**

**Incidence**

Three hundred and ninety-six patients with AKI received RRT by IHD or haemofiltration during the study period. The population of south west Scotland at the mid-point of our survey was 147 000, giving a take on rate of 245 patients per million per year. The median age of our patients was 69 years, range 17–94 years. Two hundred and thirty-six (60%) were male, 98 (25%) had underlying CKD as defined and 176 (44%) were ventilated. Patients were followed up for a total of 950 patient years until death or 1 January 2011. Two hundred and twenty-three (56.3%) patients died within 90 days, 259 (65.4%) by 1 year and 311 (78.5%) by 5 years. Mean and median follow-up were 2.4 years and 43 days, respectively. All survivors were followed for a minimum of 5 years.

**Causes of AKI**

A clinical diagnosis of ATN was made in 207 of 298 (69.5%) patients presenting with AKI. Fifty-nine (28.5%) of these were surgical and 148 (71.5%) medical. Sepsis was the most common medical cause of ATN, being present in no fewer than 94 of 148 (64%) patients. Nephrotoxins contributed...
to ATN in 43 (29%) and dehydration in 34 (23%). Twenty-six (18%) patients had CRS. More than one cause of ATN was frequently present. Obstruction was the likeliest explanation for AKI in 9 (3%) and renal inflammation, i.e. patients with acute vasculitis or interstitial nephritis, in a further 20 (6.7%) patients. The other causes of AKI were a heterogeneous group accounting for 58 (19.5%) patients and comprising the following specific diagnoses: hepatorenal syndrome (16), severe acute pancreatitis (13), rhabdomyolysis (11), myeloma (5), HUS/TTP (4), lymphoma (3), bilateral renovascular disease (2), tumour lysis syndrome (2), atheroembolism (1) and malignant hypertension (1). Diabetes mellitus was present in 12% and malignancy in 17% patients though these were not usually the cause of the AKI.

**Patient survival**

Figures 1 and 2 show survival up to 90 days and from 90 days to 10 years for ventilated and non-ventilated (top panel) and acute versus acute on CKD (bottom panel) patients, respectively. Contrasting patterns of survival emerged. Ventilation was associated with a significantly worse 90-day survival (OR 2.10 for death; 95% CI 1.34, 3.29) whereas the presence of underlying CKD did not predict such an early adverse outcome (OR 1.49; 95% CI 0.89, 2.50) (Figure 1). During longer-term follow-up (90 days to 5 years), patients who had been ventilated during the acute illness were no longer at increased risk (OR 0.79; 95% CI 0.38, 1.62) whereas the adverse effect of underlying CKD became statistically significant (OR 6.05; 95% CI 2.23, 16.5) (Figure 2).

**Renal outcomes**

Renal outcomes for patients with AKI with and without underlying CKD, expressed as a percentage of survivors, are summarized in Table 1. Patients with AKI only had high rates of renal recovery with 5–10% requiring RRT at 1, 5 and 10 years. eGFR in patients with AKI only returned to normal (>60 mL/min) in 43–62% patients. CKD 3 (eGFR 30–59 mL/min) was present during follow-up in 31–43% of patients and CKD 4/5 in 3–8%. In contrast, 33–46% of A on CKD survivors required RRT at 1 and 5 years, and higher proportions of A on CKD survivors developed CKD class 4/5 during follow-up. No patient with A on CKD requiring RRT survived for 10 years; hence, it was not possible to analyse renal recovery at this time interval in our study (Table 1).
DISCUSSION

Our prospective single-centre cohort study of 396 patients with AKI requiring RRT has shown that patients who are ventilated at the time of their AKI requiring RRT have significantly lower survival at 90 days than those who are not ventilated. This is in keeping with the results of all studies of early outcome in which comparison of ventilation versus non-ventilation [2, 11], ICU versus non-ICU [3] and the impact of illness severity [2, 4, 11–13] has been assessed. By 5 years, patients who had been ventilated during the acute illness were no longer at increased risk. Only limited long-term comparisons with other studies are possible. Similar findings have been reported by Ahlstrom [14] and by Ng [6], but neither Frost [11], Schiif [15] nor Bihorac [16] attempted to examine the influence of illness severity on outcome in their 5-year follow-up study. Liano showed that survival of patients treated in ICU was significantly better than that of patients treated in other hospital areas (61 versus 24% at 10 years) (P < 0.001) although this benefit was not seen in multivariate analysis [7].

We have further shown that the presence of underlying CKD has no impact on early outcome, but that it exerts a significant adverse effect by 5 years. Others have found that A on CKD is either associated with lower mortality at 90 days [3, 4–6] or that it has no effect [2, 12, 13]. The reason usually advanced for a beneficial effect when this has been shown is that less severe injuries may induce AKI in patients with underlying CKD and so trigger the need for RRT, i.e. the patients require dialysis but are less ill [3, 5]. Assessment of the impact of underlying CKD on medium- to long-term outcome is compromised by the exclusion of CKD patients from many AKI cohorts [7, 14–16]. Bagshaw found no influence of underlying CKD on mortality at 1 year [17]. Ng showed that CKD predicted better patient survival at 1 year if treated on ICU but not if treated on a renal ward [6]. In contrast, results from the large North American databases suggest that medium- to long-term patient survival is indeed adversely affected by underlying CKD [8, 9]. Does this simply reflect the burden of co-morbid illness? Possibly, except that these patients’ prognosis may be even poorer than expected. When 1061 Kaiser Permanente patients with A on CKD requiring RRT were compared with 38 744 patients who had CKD without superimposed AKI, those with A on CKD had substantially higher mortality (19.7 versus 7.4%) at 6 months [18].

The design of our study also enabled us to assess renal outcomes in this consecutive series of AKI patients requiring RRT. Whereas it used to be thought that patients surviving an episode of AKI had a low risk of developing CKD, it is now recognized that AKI is an important risk factor for both CKD and ESRD [19]. Groups from Munich and Madrid have published a series of reports on the renal outcome of patients with ATN only. All of the German patients were treated on ICU and all received RRT [15, 20] whereas the Spanish studies included patients treated on renal wards and patients who did not receive dialysis [7, 21] (Table 2). Dialysis dependence expressed as a percentage of survivors was ~5% in both groups at 5–10 years. Schiff and colleagues have recently further shown that the risk of developing CKD in survivors of ATN requiring RRT is strongly related to the degree of renal recovery at hospital discharge [22]. Complete recovery was associated with zero risk of CKD whereas partial recovery was followed by progression to ESRD in 13% survivors during 10 years of follow-up. Our data are consistent with these studies and show in addition that the risk of both CKD and ESRD is very much greater in patients who have underlying CKD at the time of their AKI. A 20–25% dialysis dependence at 1 year has been recorded by researchers from Australia [7] and the UK [6], whose AKI cohorts included patients with A on CKD. Essentially, similar findings have also been reported by the large North American databases although the nature of these studies means that the results are not always based on individual patient data [8, 18, 23].

### Table 1. Renal recovery in patients with and without underlying CKD

<table>
<thead>
<tr>
<th>Year(s)</th>
<th>Alive</th>
<th>CKD 1 or 2 eGFR &gt;60 mL/min (%)</th>
<th>CKD 3 eGFR 30–59 mL/min (%)</th>
<th>CKD 4/5 eGFR &lt;30 mL/min (%)</th>
<th>RRT HD/PD/Tx (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>110</td>
<td>49 (44.5)</td>
<td>48 (43.6)</td>
<td>3 (2.7)</td>
<td>6 (5.5)</td>
</tr>
<tr>
<td>5</td>
<td>78</td>
<td>34 (43.6)</td>
<td>26 (33.3)</td>
<td>6 (7.7)</td>
<td>5 (6.4)</td>
</tr>
<tr>
<td>10</td>
<td>29</td>
<td>18 (62.1)</td>
<td>9 (31)</td>
<td>0 (0)</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td>A on CKD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>26</td>
<td>0 (0)</td>
<td>7 (26.9)</td>
<td>7 (26.9)</td>
<td>12 (46.2)</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>2 (33.3)</td>
<td>2 (33.3)</td>
<td>2 (33.3)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; A on CKD, acute on chronic kidney disease; RRT, renal replacement therapy; HD, haemodialysis; PD, peritoneal dialysis; Tx, transplant.

### Table 2. Medium- to long-term outcome of acute kidney injury in adults

<table>
<thead>
<tr>
<th>Year of study</th>
<th>Number of patients</th>
<th>Age (mean)</th>
<th>Male (%)</th>
<th>Type of AKI</th>
<th>A on CKD (%)</th>
<th>ICU (%)</th>
<th>RRT (%)</th>
<th>Survival (%)</th>
<th>Dialysis dependence (% survivors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ponte 1977–92</td>
<td>413</td>
<td>64.4 (65)</td>
<td>66.4</td>
<td>ATN only</td>
<td>0</td>
<td>0</td>
<td>48.2</td>
<td>1 year: 40.2</td>
<td>1 year: 1 5 years: 32.2</td>
</tr>
<tr>
<td>Schiff 1990–91</td>
<td>425</td>
<td>65 (66)</td>
<td>66</td>
<td>ATN only</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>5 years: 36</td>
<td>5 years: 5 10 years: 22.3</td>
</tr>
<tr>
<td>Bagshaw 1999</td>
<td>240</td>
<td>66 (median)</td>
<td>68</td>
<td>ATN only</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>1 year: 35</td>
<td>1 year: 1 5 years: 25</td>
</tr>
<tr>
<td>Ng 2004–07</td>
<td>481</td>
<td>65.3 (mean)</td>
<td>62.0</td>
<td>All</td>
<td>18.8</td>
<td>10.2</td>
<td>100</td>
<td>5 years: 36</td>
<td>5 years: 5 10 years: 22.3</td>
</tr>
</tbody>
</table>

**Notes:**
- SC ≥ 150 µmol/L for at least 6 months before ICU admission.
- SC ≥ 150 µmol/L within 90 days.

**References:**
- Frost [11], Schiff [15] and Bihorac [16] attempted to examine the influence of illness severity on outcome in their 5-year follow-up study.
- Liano showed that survival of patients treated in ICU was significantly better than that of patients treated in other hospital areas (61 versus 24% at 10 years) (P < 0.001) although this benefit was not seen in multivariate analysis [7].
Our study has strengths and limitations. We believe we may be among the first to report patient survival and renal outcomes in an unselected cohort of patients with AKI including A on CKD, all of whom received RRT, who were treated both on and off ICU and whose average follow-up exceeded 5 years. Also, our observations were based on examination of individual patient data and are therefore likely to be more accurate than those derived from administrative codes. We considered analysing our data using a proportional hazards model but decided that the non-constant hazard function for the time-to-event data, namely that the risk of death changes with time, would violate the assumption of the model. We considered other models, for example a parametric survival model with a Weibull non-constant hazard function, but felt this would be hard to interpret and would not add anything to the overall message of this paper. As this was an observational study, we must also acknowledge the risk of residual confounding, namely that our findings might be explained by factors not controlled for in the analysis. We only adjusted for age and sex: a more complex multivariate analysis was beyond the scope of our dataset and would have been problematic because of the issue relating to the non-constant hazard function. Any resulting analysis would still be susceptible to bias from unmeasured confounders. Our other main limitation was that our high mortality meant our assessment of renal outcomes was compromised because it was based on only a small number of survivors, particularly among patients with A on CKD.

In conclusion, our single-centre study of 396 patients with AKI requiring RRT has shown that illness severity determined short-term but not long-term survival and that the risk of ESRD in survivors was ~5% at 5 years in those who did not have underlying CKD. In contrast, when AKI requiring RRT occurred in patients with underlying CKD, underlying CKD influenced medium- to long-term but not short-term survival and 33–46% of patients required RRT during follow-up. The very high long-term mortality of patients with A on CKD who require RRT means that larger studies will be required for more precise assessment of renal outcomes in this important patient group.

**ACKNOWLEDGEMENT**

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**AUTHORS’ CONTRIBUTION**

C.I. and M.F. had the idea for the study; K.D., S.R. and A.A. were involved in data collection; R.F. provided statistical support; C.I. and M.F. wrote the first draft and all six authors contributed to the final version.

**CONFLICT OF INTEREST STATEMENT**

None declared.

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