End-stage kidney disease patients in the intensive care unit

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Introduction

Chronic kidney disease (CKD) is an important public health issue. In the US adult population, the prevalence of CKD is estimated at >13% (representing ~40 million), and has increased appreciably in recent years [1]. This increasing trend has been attributable to an ageing population, along with increasing rates of diabetes mellitus, hypertension and obesity [1–3]. This mounting burden of CKD is also projected to contribute to greater numbers of patients progressing to end-stage kidney disease (ESKD) and requiring maintenance renal replacement therapy (RRT). Data provided by the United States Renal Database System (USRDS) show that both the prevalence and incidence of ESKD have increased

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substantially in recent years [4]. This epidemic of ESKD has far-reaching clinical and economic implications, as patients with ESKD are more likely to develop cardiovascular morbidity; serious medical complications (i.e. gastrointestinal bleeding, nutritional deficiencies, infections) [5–9]; require hospitalization; consume greater health resources; and have higher associated costs of care [10]. The attributable costs of ESKD alone in the USA in 2005 were $21 billion, representing 6.4% of all Medicare expenditures [11].

As a consequence of this ESKD burden, greater numbers of these patients are likely to require support in an intensive care unit (ICU) setting. Previous observational studies have suggested that 0.9–6.8% of all patients admitted to ICU have a prior diagnosis of ESKD [8,12–18]. In a 10-year retrospective surveillance, Bell et al. similarly found that 10% of all patients receiving RRT in ICU had a prior diagnosis of ESKD [14]. Only two studies have approximated the proportion of ESKD patients who require ICU support. In a single-centre retrospective evaluation of 476 ESKD patients, Dara et al. found that 20% were admitted to ICU during the 3-year study period [7]. In a population-based study of 81 ICUs in Australia performed over a 3-month period, Uchino et al. identified all patients receiving RRT [19]. Of these 337 patients, 11.3% had a prior diagnosis of ESKD. By using Australian national census data, the authors estimated that 2% of all ESKD patients receive RRT in an ICU setting per year. For ESKD patients, this translates into an approximate 4-fold increase in the risk of development of critical illness prompting ICU admission and acute RRT [19].

There is a need for reliable and unbiased data on both the clinical course, short-term, and long-term outcomes of ESKD patients admitted to ICU. Such data are essential to better prognosticate, avoid biased perceptions and potentially prevent early and unjustified limitations on the intensity and duration of treatment of ESKD patients [19]. Regrettably, the clinical outcomes described from observational studies to date have not shown broad agreement [6–8,13–16,19] (Table 1). These inconsistencies are likely attributable to fundamental differences in study design (i.e. retrospective, secondary analyses), small sample size (i.e. seven out of nine studies included <100 patients), variable or lack of control group for comparison [i.e. use of non-ESKD, acute kidney injury (AKI) or both] and a relative paucity of long-term follow-up data on the consequences of how an episode of critical illness prompting ICU admission modifies morbidity and survival in ESKD patients.

Overall, most studies have interestingly described relatively low short-term ICU (range 9.0–28.3%) and hospital (14–45.3%) mortality rates for ESKD patients [6,8,15,19]. Following an episode of critical illness, 90-day and 6-month mortality rates have been estimated at 42 and 48%, respectively [8,14]. In a 3-year population-based surveillance, Bagshaw et al. described 1-year crude mortality for ESKD patients of 40% after ICU admission [13]. Studies have shown comparable mortality rates for ESKD patients admitted to ICU when compared to either non-ESKD critically ill [13,15] and AKI controls [19]. Yet, studies have also shown that critically ill ESKD patients have significantly lower mortality when compared to critically ill AKI patients [13,15]. Conversely, two studies have shown that ESKD patients have higher crude mortality when compared with non-ESKD critically ill controls [7,16]. In the largest observational study to date, using data from the Intensive Care National Audit and Research Centre (ICNARC) in the United Kingdom, Hutchison et al. captured 3420 ESKD patients admitted to 170 ICUs over a 10-year period [16]. This study found that ESKD patients had a similar mortality and duration of stay in ICU when compared with non-ESKD ICU admissions; however, they had markedly higher hospital mortality, a more prolonged duration of total hospitalization and a higher likelihood of re-admission to ICU [16]. These findings are supported by similar data describing an increased likelihood of post-ICU in-hospital death [7,19]. Finally, two studies suggest that the long-term survival of ESKD patients may be negatively modified by an episode of critical illness and ICU admission [6,14].

Recently, Rocha and colleagues have contributed to the growing body of literature evaluating the clinical course and outcomes of ESKD patients receiving RRT during an episode of critical illness [20]. These Brazilian investigators have conducted a 3-year multi-centre prospective

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### Table 1. Summary of observational studies describing outcome of critically ill ESKD patients admitted to ICU

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Study design</th>
<th>Controla</th>
<th>ICU mortality (%)</th>
<th>Hospital mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clermont et al. [15]</td>
<td>57</td>
<td>Prospective</td>
<td>No ESKD, AKI</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Uchino et al. [19]</td>
<td>38</td>
<td>Prospective</td>
<td>Matched AKI</td>
<td>18.4</td>
<td>37.5b</td>
</tr>
<tr>
<td>Dara et al. [7]</td>
<td>93</td>
<td>Retrospective</td>
<td>No ESKD</td>
<td>9</td>
<td>5.5</td>
</tr>
<tr>
<td>Manhes et al. [8]</td>
<td>92</td>
<td>Prospective</td>
<td>None</td>
<td>28.3</td>
<td>–</td>
</tr>
<tr>
<td>Bagshaw et al. [13]</td>
<td>92</td>
<td>Retrospective</td>
<td>No ESKD, AKI</td>
<td>16.3</td>
<td>8.2</td>
</tr>
<tr>
<td>Hutchison et al. [16]</td>
<td>3420</td>
<td>Prospective</td>
<td>Non ESKD</td>
<td>26.3</td>
<td>20.8</td>
</tr>
<tr>
<td>Bell et al. [14]</td>
<td>245</td>
<td>Retrospective</td>
<td>None</td>
<td>15</td>
<td>–</td>
</tr>
<tr>
<td>Senthuran et al. [6]</td>
<td>70</td>
<td>Retrospective</td>
<td>None</td>
<td>20</td>
<td>43d</td>
</tr>
</tbody>
</table>

ESKD = end-stage kidney disease; AKI = acute kidney injury; ICU = intensive care unit.

aIn all studies, control groups, when described, were critically ill patients admitted to ICU.
bRepresents 90-day mortality [14].
cRepresents 90-day mortality [14].
dCompared with AKI patients receiving RRT matched for age and severity of illness [20].
observational case–control study of 54 critically ill ESKD patients receiving RRT in an ICU setting (cases) and contrasted their outcomes with 54 age-, illness severity- and organ-failure-matched critically ill patients with AKI receiving RRT (controls). ESKD patients admitted to ICU for short-term post-operative monitoring or receiving emergent RRT for inadequate maintenance RRT (i.e. volume overload, hyperkalaemia) were excluded (n = 21). Consistent with previous studies, Rocha et al. found that an estimated 12% of all critically ill patients receiving RRT during the study period (n = 614) had a prior diagnosis of ESKD [14,19].

In their study, the majority of both ESKD and AKI patients had a primary septic diagnosis. However, there are some notable differences between the ESKD patients and matched AKI controls. For example, ESKD patients were far more likely to be admitted with gastrointestinal bleeding (15 versus 2%, \( P = 0.031 \)). In addition, ESKD patients were more likely to have ≥1 co-morbid illness (100 versus 82%, \( P = 0.003 \)), less likely to receive mechanical ventilation (26 versus 54%, \( P = 0.006 \)) and had trends for lower need for vasopressor therapy. Moreover, practically all ESKD patients initially received daily conventional intermittent RRT or sustained low-efficiency dialysis (83%), whereas those with AKI were far more likely to be started on continuous RRT (61%). ESKD patients also experienced markedly shorter durations of stay in both ICU (5 days versus 19 days, \( P < 0.001 \)) and hospital (13 days versus 28 days, \( P < 0.001 \)) and had strikingly higher crude ICU (80% versus 57%, \( P = 0.023 \)) and hospital (76% versus 50%, \( P = 0.01 \)) survival.

Interestingly, despite careful matching for age, illness severity, number of failing organs, along with similar rates of sepsis, and a higher co-morbid illness burden, ESKD patients were far less likely to receive mechanical ventilation, need vasopressors or receive continuous RRT, and yet had significantly better observed clinical outcomes. These findings perhaps suggest that these case and control populations were fundamentally different, regardless of matching, by aspects not completely understood. Plausible explanations may include the following: illness severity scores used for matching fail to account for important unmeasured differences in acute physiology: ESKD patients respond differently to critical illness when compared to non-CKD patients present with AKI [19]; or there is a different approach for clinical management of ESKD patients, in terms of threshold for ICU admission and/or course in ICU, that is not otherwise captured or appreciated. While this study by Rocha et al. has helped expand our knowledge of the impact of critical illness on ESKD patients receiving RRT, when compared with matched critically ill AKI patients, it has notable limitations that should be considered when making inferences. Specifically, the sample size is small and certainly limits statistical power, and the study was performed as a secondary analysis. In addition, no detailed data on the pre-ICU status of ESKD patients (i.e. ESKD aetiology, duration of maintenance RRT, residual renal function, functional status) were provided. Likewise, no data were presented to expand our understanding of the long-term sequelae, such as quality of life or survival, of an episode of critical illness in an ESKD population.

In the end, however, there remain important unanswered questions about the ESKD population who experience an episode of critical illness prompting support in an ICU. No study to date has explored the hypothesis that ESKD patients may still be susceptible to AKI, particularly those with documented residual renal function. The development of novel serum and urinary biomarkers sensitive to AKI, such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1) or interleukin-18, may allow for the detection of super-imposed AKI in ESKD patients [21]. Observational data have clearly shown that residual renal function, defined by urinary clearance of creatinine and urea, can significantly contribute to the health and well-being of ESKD patients, in particular those receiving peritoneal dialysis (PD), by providing additional small-solute clearance, removal of middle-molecular-weight and/or uraemic toxins and contributing to maintenance of fluid and phosphate homeostasis [22]. More importantly, preservation of residual renal function, for both PD and haemodialysis patients, has been associated with improved nutritional status, lower prevalence of non-specific markers of inflammation and/or oxidative stress, attenuation of left ventricular remodelling and cardiovascular events, higher quality of life and improved survival [22–27]. No study has examined the presence or impact of loss of residual renal function in critically ill ESKD patients and how this might have modified the clinical course and outcome. For example, Rocha et al. reported that the median urine output for ESKD patients was 0 mL/day; however, at least 25% had a urine output exceeding ~200 mL/day, implying that a significant proportion might have had some residual renal function. As aforementioned, there is also clearly a need for additional investigation to evaluate how critical illness may modify the long-term outcome of ESKD patients, including not only survival, but also repeat hospitalizations, further risk of critical illness, quality of life, discharge disposition, measures of frailty and functional status. For example, Dara et al. found that 31% of ESKD patients surviving after an episode of critical illness to leave the hospital were discharged to either rehabilitation or nursing homes/long-term care facilities [7].

In summary, Rocha et al. have broadened our knowledge of the short-term outcomes of ESKD patients admitted to ICU; however, from their study, additional questions naturally arise. Future prospective studies should survey for residual renal function in ESKD patients admitted to ICU, examine for super-imposed AKI and loss of residual function and/or recovery. Importantly, future studies need to incorporate long-term clinical outcomes to better inform clinical decision making for ESKD patients experiencing critical illness.

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References


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