Patients with end-stage renal disease admitted to the intensive care unit: systematic review

N. Arulkumaran1*, N. M. P. Annear2 and M. Singer1

1 Bloomsbury Institute of Intensive Care Medicine, University College London, Cruciform Building, Gower Street, London WC1E 6BT, UK
2 Division of Medicine, University College London, Rayne Building, University Street, London WC1E 6JF, UK

* Corresponding author. E-mail: nish_arul@yahoo.com

Summary. The number of patients with end-stage renal disease (ESRD) is increasing worldwide, with a growing demand on healthcare services. A systematic review of the literature was performed to determine the requirement for intensive care unit (ICU) services, reasons for admission, predictors of mortality, and short- and long-term outcomes of ESRD patients admitted to ICU.

Sixteen studies were identified, comprising 6591 ICU admissions. Cardiovascular disease and sepsis accounted for the majority of admissions. Acute illness severity scores tend to overestimate mortality among ESRD patients. Critical illness associated with acute kidney injury (AKI) requiring renal replacement therapy (RRT) is associated with significantly higher hospital mortality compared with ESRD patients admitted to the ICU (odds ratio (OR) 3.9; 3.5–4.4; P<0.0001). However, hospital mortality of ESRD patients is less favourable compared with matched patients with mild AKI (OR 1.5; 1.4–1.6; P<0.0001). Although the mortality rate remains high shortly after hospital discharge, the duration of increased mortality risk is unclear. Patients with ESRD frequently benefit from ICU admission, despite chronic co-morbidity. Further studies are required to modify and validate existing illness severity scores for ESRD patients admitted to the ICU, and to establish the duration of increased mortality risk after discharge from ICU.

Keywords: intensive care; kidney, failure; renal

Editor’s key points

- This systematic review addresses the issue of outcome of patients with end-stage renal disease (ESRD) admitted to the intensive care unit (ICU).
- In the 16 identified studies, cardiovascular disease and sepsis accounted for the majority of the admissions.
- Compared to patients with acute kidney injury requiring renal replacement therapy, patients with chronic ESRD had a better ICU and hospital survival.
- Importantly, this review suggests that appropriately selected patients with ESRD frequently benefit from ICU admission.

The incidence and prevalence of chronic kidney disease (CKD) and end-stage renal disease (ESRD) are increasing appreciably, reflecting an increased prevalence of hypertension, type 2 diabetes mellitus, and an ageing population. The prevalence of CKD in the USA is ~13% among the adult population, while the incidence of patients reaching ESRD requiring renal replacement therapy (RRT) is 347.6 per million population per year. Patients with ESRD (defined as having an estimated glomerular filtration rate of <15 ml min⁻¹ 1.73 m⁻²) have significant co-morbidities and a greater mortality risk compared with an age-matched cohort. The relative risk for all-cause mortality, cardiovascular events, and hospitalization rates are 5.9, 3.4, and 3.1, respectively, relative to patients with normal renal function. Morbidity and mortality are predominantly related to cardiovascular disease and sepsis.

Despite the increase in numbers of patients with ESRD and its associated complications, better provision of care for these patients is associated with improved mortality rates. Consequently, a greater expectation of survival after critical illness drives an ever-increasing demand for ICU facilities. Illness severity scores have not been specifically evaluated to predict outcome in ESRD patients, since most scores allocate points for physiological and laboratory data that are usually outside the normal range in stable ESRD patients. Establishing the requirement for ICU services, predictors of mortality, and the short- and long-term outcomes among the ESRD population is therefore important.

We reviewed the literature to determine the epidemiology of patients with ESRD admitted to ICU, causes for admission, factors associated with mortality, and short- and long-term outcomes. The hospital mortality of ESRD patients was compared with patients with AKI requiring RRT and with patients with ‘mild renal injury’ admitted to the ICU.

Methods

We performed a review of the literature using the National Centre for Biotechnology Information (NCBI) PubMed database using a combination of medical subject headings (MeSH), title, and abstract keywords. The search terms used were: ‘end stage renal failure’ or ‘end stage renal disease’ or ‘dialysis’ and ‘intensive care’ or ‘critical care’. Reviews, editorials, and individual case reports were excluded, as were...
publications based on the same data sets. CKD is defined by the National Kidney Foundation Disease Outcomes Quality Initiative (KDOQI) guidelines. Patients with an estimated GFR of $<15 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ are defined as having stage 5 CKD. We defined ESRD as patients with stage 5 CKD receiving chronic dialysis. Patients with stage 5 CKD not receiving dialysis were excluded. All other publications were included, irrespective of size, journal, or country of origin.

Epidemiology, causes for ICU admission, illness severity scores on ICU admission, and short- and long-term outcomes were assessed where reported. The $\chi^2$ tests were used to calculate the differences in survival between the groups, with data reported as odds ratio (OR; confidence intervals; $P$-value). Graphpad Prism Version 5.0 (GraphPad Software, Inc., CA, USA) was used to perform statistical analyses.

Results

Study selection

A total of 18 studies were identified. Two studies were excluded as data were extracted from the same ESRD population reported in other studies. The study by O’Brien and colleagues was excluded as it includes data extracted from the UK Intensive Care National Audit and Research Centre (ICNARC) database, as reported by Hutchison and colleagues. Furthermore, the study by O’Brien and colleagues focused primarily on patients with cirrhosis. Similarly, studies by Sood and colleagues and Strijack and colleagues included data from the same patient cohort. Since the study by Sood and colleagues was an analysis of long-term outcomes from the same patient cohort, it was excluded from analysis. However, results from the two excluded studies have been included in our discussion.

Epidemiology

The 16 studies included in this analysis describe a total of 6591 ICU admissions for patients with ESRD conducted in nine different countries (Table 1). Two were prospective case–control studies, four were prospective cohort studies, and the remaining 10 were retrospective cohort studies. Sample sizes varied from 28 to 3420 patients, while study periods ranged between 30 days and 10 yr. Where specified, the majority of patients were receiving haemodialysis (HD) rather than peritoneal dialysis (PD) as their mode of long-term RRT. A total of eight studies specified the mode of chronic RRT. Out of 580 patients, 71 (12%) were receiving PD and 509 (88%) were receiving HD. The mean patient ages were between 44 and 66 yr. 

ICU bed requirements were significantly greater among ESRD patients than the general population. A study of 476 ESRD patients followed over 7 yr reported that 20% required ICU admission. Compared with the general population, the risk of requiring ICU admission and RRT in the ESRD population was four-fold greater in the largest study which reviewed 276 731 ICU admissions between 1995 and 2004, 1.3% (3420) of whom were identified as having ESRD. This represents an ICU utilization rate of six admissions (32 bed-days) per 100 dialysis patient-years.

Causes for ICU admission

The most common causes for ICU admission were cardiogenic pulmonary oedema and sepsis, accounting for up to 24% and 20.5% of cases, respectively. However, when compared with patients with AKI requiring RRT, illness severity scores were either similar or lower among those with ESRD (Table 2). Factors predicting poor outcome include age, non-renal organ failure, infection, primary cardiac events. A further important reason for admission related to surgical diagnoses, ranging 9–27% of admissions.

Outcome predictors

Compared with ICU patients without acute kidney injury (AKI), illness severity scores were consistently higher among patients with ESRD. However, when compared with patients with AKI requiring RRT, illness severity scores were either similar or lower among those with ESRD (Table 2). Factors predicting poor outcome include age, non-renal organ failure, infection, primary cardiac events. The acute physiology and chronic health evaluation illness severity scores (APACHE II and APACHE III scoring systems), simplified acute physiology score (SAPS II), and sequential organ failure assessment (SOFA) score were used in 12, two, and two studies, respectively. Seven of the 10 studies using APACHE II had a higher predicted than actual ICU mortality rate. In six of these reports, this value exceeded the reported mortality by >10%. Similarly, actual hospital mortality was lower than that predicted in both studies using APACHE III scores and one of the two studies using SAPS II scores. The SOFA score accurately predicted mortality in one study and under-predicted mortality in another.

Short-term outcome

The reported ICU mortality of ESRD patients ranged from 9% to 44% (Table 2). The mean ICU mortality was 21.4% and hospital mortality 34.5%. Six studies reported hospital mortality rates of ESRD patients and patients with AKI requiring RRT, including 3216 patients with AKI requiring RRT and 2182 patients with ESRD. There was a significantly increased risk of hospital mortality among patients with AKI requiring RRT (55%) compared with ESRD patients (24%) (OR 3.9; 3.5 – 4.4; $P<0.0001$). Similarly, the 90 day mortality among patients with AKI requiring RRT was significantly higher than ESRD patients, which was 56% and 38%, respectively (OR 2.1; 1.4 – 3.3; $P=0.0007$).

Although AKI is commonly stratified using the RIFLE or AKIN criteria, many studies included in this systematic review were published before the use of the RIFLE or AKIN...
### Table 1: Patient characteristics of ESRD patients admitted to intensive care units

<table>
<thead>
<tr>
<th>Study</th>
<th>Country of study</th>
<th>Number of ICU admissions</th>
<th>HDx:PD patients (%)</th>
<th>Mean age (yr)</th>
<th>Sex, F:M (%)</th>
<th>Study period</th>
<th>Study dates</th>
<th>Follow-up period</th>
<th>Single or multicentre</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bagshaw and colleagues&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Canada</td>
<td>92</td>
<td>Not specified</td>
<td>66.2</td>
<td>38:62</td>
<td>3 yr</td>
<td>1999–2002</td>
<td>1 yr</td>
<td>Multicentre</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Bell and colleagues&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Sweden</td>
<td>245</td>
<td>Not specified</td>
<td>&lt;49: 13% 50–69: 52% &gt;70: 21%</td>
<td>42:58</td>
<td>—</td>
<td>1995–2004</td>
<td>5 yr</td>
<td>Multicentre</td>
<td>Prospective</td>
</tr>
<tr>
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<td>199</td>
<td>Not specified</td>
<td>58</td>
<td>35:65</td>
<td>5 yr</td>
<td>1999–2004</td>
<td>2 yr</td>
<td>Multicentre</td>
<td>Retrospective</td>
</tr>
<tr>
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<td>57</td>
<td>Not specified</td>
<td>58</td>
<td>Not specified</td>
<td>10 months</td>
<td>2000–2001</td>
<td>—</td>
<td>Multicentre</td>
<td>Prospective</td>
</tr>
<tr>
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<td>93</td>
<td>100:0</td>
<td>66</td>
<td>42:58</td>
<td>5 yr</td>
<td>1997–2002</td>
<td>30 days</td>
<td>Single centre</td>
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</tr>
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<td>France</td>
<td>102</td>
<td>97:3</td>
<td>59</td>
<td>36:66</td>
<td>8 yr</td>
<td>2000–7</td>
<td>—</td>
<td>Single centre</td>
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<tr>
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<td>Not specified</td>
<td>57</td>
<td>39.8: 60.2</td>
<td>10 yr</td>
<td>1995–2004</td>
<td>—</td>
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<td>Retrospective</td>
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<tr>
<td>Juneja and colleagues&lt;sup&gt;19&lt;/sup&gt;</td>
<td>India</td>
<td>73</td>
<td>68.5:31.5</td>
<td>54</td>
<td>33:67</td>
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<td>30 days</td>
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<td>Not specified</td>
<td>2 yr</td>
<td>2009–2010</td>
<td>—</td>
<td>Single centre</td>
<td>Retrospective</td>
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<td>83:17</td>
<td>62</td>
<td>36:64</td>
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<td>1996–9</td>
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<td>Not specified</td>
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<td>40.4:59.6</td>
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<td>1989–1999</td>
<td>—</td>
<td>Multicentre</td>
<td>Retrospective</td>
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<td>Rocha and colleagues&lt;sup&gt;22&lt;/sup&gt;</td>
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<td>54</td>
<td>90.7:9.3</td>
<td>65</td>
<td>37:67</td>
<td>33 months</td>
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<td>Multicentre</td>
<td>Prospective</td>
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<td>104</td>
<td>77.23</td>
<td>57</td>
<td>48:52</td>
<td>5 yr</td>
<td>2001–6</td>
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<td>15:23</td>
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<td>2002</td>
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<td>46:54</td>
<td>8 yr 2 months</td>
<td>2002–2010</td>
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<td>Single centre</td>
<td>Retrospective</td>
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<td>Study</td>
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<tr>
<td>Bagshaw and colleagues</td>
<td>(1) No renal dysfunction (Cr &lt; 150 μmol litre(^{-1}))</td>
<td>APACHE II 29.7</td>
<td>APACHE II</td>
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<td>(2) Mild renal dysfunction (Cr 150–299 μmol litre(^{-1}))</td>
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<td>(1) 8.2</td>
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<td>(3) Moderate renal dysfunction (Cr &gt; 300 μmol litre(^{-1}))</td>
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<td>(2) 28.4</td>
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<td>(4) AKI requiring RRT</td>
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<td>(3) 26.3</td>
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<tr>
<td>Bell and colleagues</td>
<td>(1) ESRF patients outside ICU</td>
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<td>(4) 50</td>
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<td>(2) General population</td>
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<td>Clermont and colleagues</td>
<td>(1) ARF</td>
<td>APACHE III 64</td>
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<td>(2) No renal failure</td>
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<td>Juneja and colleagues</td>
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<td>Manhes and colleagues</td>
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<td>SOFA 8</td>
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<td>2) AKI with RRT</td>
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<td>Rocha and colleagues</td>
<td>AKI requiring RRT</td>
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<tr>
<td>Senthuran and colleagues</td>
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<td>APACHE II 24.8</td>
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**ITU LoS (days)**: Intensive Care Unit Length of Stay, **Hospital LoS (days)**: Hospital Length of Stay, **ITU mortality (%)**: Intensive Care Unit Mortality, **Hospital mortality (%)**: Hospital Mortality
criteria. Absolute values of serum creatinine were therefore used for analysis. Four studies included data on patients with ‘minimal’ renal injury, with the mean serum creatinine ranging from 103 to 184 μmol litre⁻¹ including 299742 patients with minimal renal injury and 4562 patients with ESRD. There was an increased hospital mortality rate among patients with ESRD patients (39%) compared with those with minimal renal injury (29%) admitted to the ICU (OR 1.5; 1.4–1.6; P<0.0001).

**Long-term outcome**

Studies reporting long-term survival (at 1 yr and beyond) among ESRD patients requiring ICU admission are limited. There was a trend for an increased mortality rate within the first 1–6 months after ICU discharge, which subsequently diminished.

Sood and colleagues found that 62% and 52% of ESRD patients admitted to the ICU were alive at 6 and 12 months, respectively. Mortality rate was greatest up to 6 months after hospital discharge, with a relatively stable mortality rate thereafter. Similarly, Chapman and colleagues report the difference in long-term mortality between ESRD patients admitted to the ICU and matched ESRD controls was lost after patients who died within a month of ICU discharge were excluded. In this series, 31% of ESRD patients admitted to the ICU and 56% of ICU survivors were alive at 2 yr. In a series by Bagshaw and colleagues, mortality among ESRD patients had levelled off by 90 days, with a 64%, 61%, and 60% survival at 90 days, 6 months, and 1 yr, respectively. In this series, the presence of ESRD did not predict 1 yr mortality.

In contrast to these studies, a 5 yr follow-up study demonstrated that critical illness was associated with a lasting impact on long-term mortality rate among ESRD ICU patients compared with ESRD patients without any ICU admission. Although the majority of the deaths occurred in the first few weeks after ICU discharge, the relative risk of death was 2.86 during the first year of follow-up and 1.95 from the second year among ESRD patients admitted to the ICU compared with ESRD patients with no ICU admission. Long-term mortality was related to heart failure.

**Discussion**

**Epidemiology**

Existing studies of ESRD patients admitted to the ICU provide a useful insight into their rates of admission and mortality. The rates of admission of ESRD patients to ICU are higher compared with the general population. Patients with ESRD undergoing RRT tend to have frequent and regular contact with healthcare services. This presents an opportunity for the nephrology team overseeing their RRT to establish, document, and review the patients’ values and attitudes to critical illness and end-of-life situations. This important information can facilitate difficult decision-making when considering ICU admission and defining goals in treatment, and emphasizes the importance of early communication between intensivists...
and the nephrology team overseeing a patient’s regular RRT.29

**Causes of admission**

Consistent with an enhanced cardiovascular risk among patients with ESRD,1-5 many studies have reported cardiogenic pulmonary oedema as the most common cause for ICU admission. In the largest series, ESRD patients were twice as likely as other patients to have had cardiopulmonary resuscitation before ICU admission.10 This is consistent with an increased prevalence of cardiac arrhythmias in this patient population.30 A number of ‘non-traditional’ risk factors associated with cardiovascular disease are also described, including left ventricular hypertrophy, rapid electrolyte shifts, QT prolongation, sympathetic over-activity, and arterial calcium–phosphate deposition.31

Sepsis accounted for a significant number of ICU admissions. Among ESRD patients, there is an increased incidence of sepsis and an increased risk of dying from infection; the adjusted relative risk of mortality from sepsis was reported as up to 100-fold higher than in the general population.32 Multiple factors are implicated in their increased susceptibility to sepsis. These include the presence of soluble plasma tumour necrosis factor receptors, anti-IL-1α autoantibodies, the accumulation of asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, defects in opsonization of pathogens, anaemia, vitamin, and trace element deficiencies, and aetiological factors responsible for the renal failure such as diabetes mellitus.33-36

The management of ESRD on the ICU requires special considerations, and involvement of nephrology services on the ICU is therefore crucial. The management of the ESRD patient on ICU is beyond the scope of this article and is detailed elsewhere in the literature.37

**Outcome predictors**

Illness severity scores and non-renal organ dysfunction were the most reported predictors of mortality in ICU patients with pre-existing ESRD. Although ESRD ICU non-survivors had higher illness severity scores than the survivors, the predicted mortality was greater than the actual mortality in most studies. Illness severity scores allocate points for physiological and laboratory data that often fall outside the physiological range in ESRD patients, which may account for this discrepancy. While the APACHE II score has been shown to under-predict mortality in critically ill patients with cirrhosis, critically ill ESRD patients had a lower mortality despite similar characteristics and higher APACHE II scores to patients with cirrhosis.3 Criteria that are directly applicable to ESRD patients remain elusive. Parameters of non-renal organ failure and the utility of the SOFA score require further validation of this cohort of patients.

Patients with ‘acutely reversible illness’ (such as acute pulmonary oedema due to inter-dialytic weight gain) may have a better prognosis than those with complex medical illnesses (such as cardiogenic pulmonary oedema). However, in a series by Halle and colleagues,18 the aetiology of acute pulmonary oedema did not affect survival rates. The authors themselves acknowledge the difficulty of drawing firm conclusions from a single-centre study of limited patient numbers.

Admission for a ‘medical’ as opposed to a surgical reason is associated with a worse outcome among ESRD patients.13-15 Surgical diagnoses accounted for 52–59% of all ICU admissions among ESRD patients. In the series by Chapman and colleagues,15 the 2 yr survival among ESRD patients was 77% for patients undergoing elective surgery, 61% for patients undergoing emergency surgery, and 41% patients admitted with a medical diagnosis. In this series, the relative risk of mortality among ESRD patients admitted with a medical diagnosis was twice that of ESRD patients admitted for a surgical diagnosis.15 This may reflect a low threshold for admitting ESRD patients to a high dependency environment after surgery. Such an approach is appropriate, given the significantly increased mortality rate among ESRD patients after major surgery, such as cardiac surgery.38 39

Among patients with any renal dysfunction, admission for a surgical as opposed to a medical reason was associated with a relative risk of mortality of 0.61 (0.52–0.73) for non-cardiac surgery and 0.04 (0.03–0.05) for cardiac surgery.13 There was no difference in mortality between ESRD patients undergoing elective and emergency surgery, although the number of patients in each group was relatively small.15

**Short-term outcome**

Critical illness associated with AKI requiring RRT is associated with a significant higher hospital mortality compared with ESRD patients admitted to the ICU (OR 3.9; 3.5–4.4; P<0.0001), reflecting acute organ dysfunction. However, survival of ESRD patients is less favourable compared with matched patients with mild AKI (OR 1.5; 1.4–1.6; P<0.0001). A significant number of patients with ESRD die in hospital shortly after ICU discharge10-15 and within 90 days.13 14 26 This may reflect a decreased physiological reserve and/or a susceptibility to relapse from their original critical illness. Small sample sizes, and differences in study design and in local service provision, may account for the variability in reported ICU mortality rates.

**Long-term outcome**

Critical illness is associated with the increased long-term mortality among the general population. Between 2 and 4 yr after discharge, patients discharged from the ICU have an increased mortality rate of 3.3- to 3.4-fold above the general population.40 61 Consistent with this, Bell and colleagues14 found an increased mortality rate among ESRD ICU patients compared with ESRD patients not admitted to the ICU (relative risk of death was 2.86 during the first year of follow-up and 1.95 from the second year), with risk factors for long-term mortality related to age and heart failure. However, the three other long-term studies including a total of 910 ESRD patients admitted to the ICU found that
the increased risk of death did not extend beyond 1–6 months of ICU discharge. Differences in the long-term mortality may relate to differences in ICU admission and discharge policies, and differences in baseline patient characteristics between the ESRD populations. This is reflected in the difference in 1 yr survival between these studies, which Bell and colleagues reported as 35% in contrast to 60% and 52% as reported by Bagshaw and colleagues and Sood and colleagues, respectively. Further studies are required to evaluate the long-term survival of ESRD patients admitted to the ICU.

Limitations

The main limitation of this review is that there is an inherent bias in the data presented, as ESRD patients with limited comorbidities and reversible acute illness would have been admitted to ICU for treatment. Criteria for referral to ICU, or acceptance by the ICU team, may be highly variable. Similarly, the number of ICU beds in relation to the size of the population varies between countries, and admission policies may vary. Furthermore, the criteria to offer chronic HD vary between different countries depending on available healthcare resources. These factors may account for at least some of the variation in reported mortality data. This limits how generalizable the data are to ESRD patients who would be considered for ICU admission.

Another major limitation relates to the quality of the existing studies. Ten of the 16 studies are retrospective observational studies, whereas just two are prospective case–control studies. Sample sizes are relatively small in most series with less than half the studies including more than 100 patients. Further multicentre prospective studies with a control group of patients need to be carried out to better ascertain the patient characteristics and outcomes of ESRD patients admitted to the ICU.

The majority of these studies do not distinguish between HD and PD patients. Such a distinction could impact upon causes of admission to ICU and outcomes; for example, ESRD patients undergoing chronic PD or HD via a central venous catheter have a greater long-term mortality after ICU discharge compared with ESRD patients who undergo chronic dialysis via an arteriovenous fistula.

A further limitation of this study was the heterogeneity in the diagnostic categories used in the different papers. For instance, chest sepsis may have been described as ‘respiratory failure’ or as ‘sepsis’. As such, it is not possible to unify the causes of admission to ICU and draw any firm conclusions from the different studies.

As with all epidemiological studies, extrapolating data to inform management of individual patients has limitations. Long-term survival data cannot fully inform decisions and the acceptability of ICU care to an individual is hugely variable. The quality of life and associated morbidity in patients with ESRD subsequent to ICU discharge is undetermined. Nonetheless, the studies reviewed provide a useful insight into reasons for admission and outcomes from the ICU.

Conclusion

Despite the heterogeneity in the size and design of the published studies, patients with ESRD requiring ICU admission appear to have a favourable short- and long-term outcome compared with those admitted with AKI requiring RRT. Critical illness among ESRD patients is commonly related to an increased risk of cardiovascular disease and sepsis. Illness severity scores tend to overestimate mortality among ESRD patients admitted to the ICU, requiring the modification and validation of illness severity scores. The long-term survival, duration of increased mortality risk, and quality of life after an episode of critical illness needs to be evaluated.

Patients with ESRD should be given full consideration for ICU care if required. Ideally, these issues will have already been discussed with patients and their relatives, as part of advanced care planning, and this information should be communicated promptly to intensivists.

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