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Incidence and outcomes of patients receiving chronic kidney replacement therapy (KRT) admitted to Scottish intensive care units between 2009 and 2019 – a national observational cohort study

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Abstract

Objectives: To determine the incidence and characteristics of intensive care unit (ICU) admissions in the Scottish population of patients treated with chronic kidney replacement therapy (KRT) over an 11-year period and determine factors associated with post ICU admission mortality.

Design: Retrospective observational cohort study.

Settings: We analysed admissions to Scottish intensive care environments between 1 January 2009 to 31 December 2019.

Patients: All patients receiving chronic KRT - including maintenance dialysis and kidney transplant - in Scotland.

Intervention: None

Measurements: Descriptive statistics and factors associated with mortality using logistic regression and Cox proportional hazard models.

Main Results: From 10,657 unique individuals registered in the Scottish Renal Registry over the 11-year study period and alive as of 1st January 2009, 1402 adult patients were identified as being admitted to a Scottish critical care setting. Between 2009 and 2019, admissions to ICU increased in a non-linear manner driven by increases in admissions for renal causes and elective cardiac surgery. The ICU admission rate was higher among patients on chronic dialysis than in kidney transplant recipients (59.1 versus 19.9 per 1000 person-years) but post-ICU mortality was similar (about 24% at 30 days and 40% at 1-year). Admissions for renal reasons were most common (20.9%) in patients undergoing chronic dialysis whilst kidney transplant recipients were most frequently admitted for pneumonia (19.3%) or sepsis (12.8%). Adjusted Cox PH models showed that receiving invasive ventilation and vasoactive drugs were associated with an increased risk of death at 30 days post ICU admission (HR=1.75, 95% CI 1.28-2.39 and 1.72, 95% CI 1.28-2.31 respectively).

Conclusions: With a growing population of kidney transplant recipients and the improved survival of patients on chronic dialysis, the number of ICU admissions are rising in the chronic KRT population. Mortality post ICU admission is high for these patients.

Keywords: Kidney failure, Kidney Replacement Therapy, Critical Care, Intensive Care Unit, Mortality

Key points:

Question: To determine the incidence and characteristics of intensive care unit admissions in patients on maintenance dialysis and kidney transplant recipients between 2009 and 2019 in Scotland.

Findings: This data linkage observational study showed an increasing number of admissions to ICU in Scotland between 2009 and 2019, mainly driven by increases in admissions for renal reasons and elective cardiac surgery. Post critical care death rate was high (24% at 30 days and 40% at 1-year) in both patients on maintenance dialysis and kidney transplant recipients and receiving invasive ventilation or vasoactive drugs were both associated with an increased mortality.

Meanings: With a growing prevalence of kidney transplant recipients and improved survival of patients on chronic dialysis, ICU admissions of chronic KRT patients have increased over the past decade with high post-critical care mortality rates.

Background

Global prevalence of chronic kidney disease (CKD) is rising due to an ageing population and an increasing prevalence of conditions identified as leading causes of CKD such as hypertension and diabetes mellitus. In Scotland, although the incidence of patients with kidney failure starting chronic kidney replacement therapy (KRT) has levelled out over the last two decades, the prevalence continues to rise due to improvements in survival. This population often presents with multiple comorbidities which can either cause CKD – such as pre-existing cardiovascular diseases, diabetes, hypertension, obesity - or complications of CKD - such as subsequent hypertension, cardio- and cerebrovascular diseases; increased incidence of critical illnesses such as gastrointestinal bleeding and sepsis; and increased mortality after surgical interventions (1, 2). Subsequently, patients on chronic KRT are more likely to require consideration for admission to a critical care environment (3, 4).

Previous studies have shown that 2 to 20% of patients on chronic KRT are admitted to an ICU annually (5-9), accounting for 1 to 9% of admissions to ICU (5, 7, 8, 10-13) and 10 to 12% of KRT provided in ICU (2, 3, 7, 14). This is in comparison to the general population who have annual admission rates of 0.2% (15). Previous studies have focused on comparing patients with chronic kidney failure receiving KRT to patients with acute kidney injury requiring KRT (9, 16-20). There is however a lack of contemporary data examining outcomes in patients on maintenance dialysis or with a kidney transplant admitted to ICU with a perception that outcomes are poor in these populations. Improving understanding of outcomes and factors associated with adverse outcomes can assist in decision making with regards to ICU admission in this vulnerable population.

The aims of this study were to examine the incidence of ICU admission and survival of patients established on chronic KRT in Scotland between 2009 and 2019 and determine factors associated with post ICU admission mortality.

Methods

- **Study Design**

This observational cohort study comprised of all prevalent adult patients (≥18 years old) on chronic KRT via either maintenance dialysis or kidney transplantation in Scotland, who were admitted to a Scottish ICU or combined HDU/ICU at least 90 days after having initiated chronic KRT, from 1 January 2009 to 31 December 2019. Patients were followed up from their first ICU admission whilst on chronic KRT until time of death or until study end (right-censoring on 1st July 2020), whichever was sooner. All patients who started chronic KRT and were therefore registered in the SRR at least 90 days prior to admission to ICU were included in the cohort whilst ICU admissions prior to (or within less than 90 days of) chronic KRT initiation were excluded from analysis. Some patients had multiple admissions after being established on chronic KRT; in that case only their first admission during the study period was considered for analyses.

- **Data Sources**

The Scottish Renal Registry (SRR) and the Scottish Intensive Care Society Audit Group (SICSAG) datasets were linked using a unique patient identifier (Community Health Index or CHI) by the Public Health and Intelligence unit of Public Health Scotland. Details regarding the data sources are available in Supplementary Material S1.

- **Variables of interest**

Variables of interest are detailed in Supplementary Material S1.

- **Statistical analyses**

Baseline characteristics were summarised using means and standard deviations (SD) for normally distributed continuous data or medians and interquartile ranges (IQR) for non-normal data. Categorical data were summarised using percentages.

Kaplan-Meier curves were generated to estimate survival at different time points and to compare survival of patients by KRT modality and by APACHE diagnosis for critical care admission.

We also conducted multivariable analyses to identify risk factors associated with our primary outcomes [short- (30 days) and long-term (1 year) post-ICU admission mortality] using logistic and Cox PH regression models. To investigate factors associated with 1-year mortality we conducted a landmark analysis in which we only included patients who had survived at least 30 days (the acute phase) post ICU admission (N=1070). Both unadjusted and adjusted estimates were reported. In the adjusted models the age points were removed from the APACHE II score calculation so the impact of age could be assessed separately.

We then explored more specifically the association between interventions received during the ICU stay and 30-, 90- as well as 365-days mortality using a Cox PH model.

Unadjusted time trends of ICU admissions were evaluated by calculating the average number of admissions per month (globally and by APACHE diagnosis group) and visualised by fitting a LOcally wEighted Scatterplot Smoothing (LOESS) curve to the monthly data. Simultaneously we tracked changes in mean age of patients admitted to ICU over the study period. We also computed the ICU admission rate per 1000 person-years for each calendar year between 2009 and 2019 as well as for the overall 11-year study period. All analyses were stratified by chronic KRT modality since patients on maintenance dialysis and those with a kidney transplant represent different populations with distinct goals of care.

All data were analysed using the R statistical programming language (Version 3.6.2, Vienna, Austria).

Ethics approval and consent to participate: Access to the data were approved by the National Health Service Scotland Public Benefit and Privacy Panel for Health and Social Care (application number 1920-0078) which oversees studies accessing anonymized health care data held by the NHS Scotland (21). Information governance, confidentiality, and data protection were undertaken according to the Data Protection Act of 1998.

Results

From 10,657 unique individuals registered in the Scottish Renal Registry before 31st December 2019 and alive as of 1st January 2009, 1,402 unique patient admissions were identified with median follow-up of 2.19 years (IQR 1.81-2.58). Supplementary Figure 1 summarises the cohort study design in a flow chart. The ICU admission rate over the 11-year study period was around 3 times higher in patients on maintenance dialysis compared to that observed among kidney transplant recipients (59.1 versus 19.9 per 1000 person-years, Supplementary Table 1A and 1B).

Baseline characteristics

Baseline patient characteristics are shown in Table 1. Most patients (62.9%) were undergoing hospital haemodialysis (HD), while 27.7% were kidney transplant recipients. The transplanted group were younger at the start of chronic KRT (42.0 years (SD 14.5) vs 52.1 years (SD 15.8)), more likely to be male (63.2% vs 57.4%), less deprived (21.7% vs 29.6% within first SIMD quintile), required a lower maximum level of care (level 3 care 79.9% vs 85.9%), had a longer median length of stay (14 versus 9 days) and were more likely to receive interventions. Table 2 presents the characteristics of the first ICU admission of patients on chronic KRT during the study period. In patients on maintenance dialysis, the most common APACHE diagnosis reason for admission to ICU was of renal origin (n=212 admissions, 20.9%) - which was mainly constituted of patients admitted for kidney transplant sugery (n=87/212) - followed by sepsis (n=94, 9.3%). Among kidney transplant recipients, the most frequent APACHE diagnoses were pneumonia (n=75, 19.3%) and sepsis (n=50, 12.8%), together accounting for nearly a third of all ICU admissions. Diagnoses included in the different APACHE groupings are presented in Supplementary Table 2A and 2B. The most common admission type was “emergency non-surgical”, characterizing more than half of all ICU admissions.

Time trends

Between 2009 and 2019, we recorded a total of 1,763 ICU admissions of non-unique patients on chronic KRT (maintenance dialysis: 1,266, transplant: 497). The prevalent chronic dialysis population remained stable between 2009 and 2019 (Supplementary Table 1A) whilst we noted an important increase in the kidney transplant population (from 2,205 individuals in 2009 to 3,352 in 2019, Supplementary table 1B). The number of ICU admissions of patients receiving chronic dialysis in Scotland increased in a non-linear fashion over the study period, from an average of 6.2 (SD 3.0) admissions per month in 2009 to 10.2 (SD 3.0) in 2019 (Figure 1A and Supplementary Table 3). A similar trend was observed in ICU admissions of kidney transplant recipients, from an average of 2.8 to 5.4 admissions per month between 2009 and 2019 (Supplementary Table 3). Consequently, the ICU admission rate only appeared to increase in the chronic dialysis population but remained stable among kidney transplant recipients (Supplementary Tables 1A and 1B, Supplementary Figure 2A and 2B). We noted an increase in admissions for cardiac surgery for both patients on maintenance dialysis (Supplementary Table 4, Figure 1B) and kidney transplant recipients. Almost all ICU admissions for cardiac surgery (100/104, 96%) were elective. We also observed an increase in admissions for renal causes in patients on chronic dialysis only (Supplementary Table 4). The age at admission of patients on chronic dialysis increased over time, from a mean of 52.9 years old (SD 14.9) in 2009 to 57.6 years old (SD 13.9) in 2019 (Supplementary Table 5). However, this trend was not observed among kidney transplant recipients.

Survival

Survival of patients on chronic dialysis was 76.7% (74.1 to 79.4) at 30 days after ICU admission, reducing to 70.8% (68.0 to 73.6) at 90 days and 58.9% (55.9 to 62.0) at one year (Table 2). Similar survival was observed in the kidney transplant group. Figure 3A and Table 2 depict post-ICU survival by chronic KRT modality showing no statistical difference overall (log rank test p=0.1) despite a higher median survival in kidney transplant recipients (3.15, 95% CI 2.15 - 4.38 versus 1.96, 95% CI 1.56-2.40). Critical care admissions by APACHE diagnosis, status at discharge (survival or death) and cause of death are represented in the Sankey diagram (Figure 2 and Supplementary Figure 3). Infections represented the main cause of death (36.8%) for kidney transplant recipients whilst patients receiving chronic dialysis were most likely to die from cardiovascular diseases (38.6%). Cancer-related deaths were more common among kidney transplant recipients than in maintenance dialysis patients (10.8% versus 3.6%) (Supplementary Table 6).

Important differences in short and long-term post-ICU admission survival were observed across the various APACHE diagnosis groups (Supplementary Table 7A and 7B). Patients admitted for cardiac arrest presented with the highest APACHE scores and the lowest survival probabilities (30-day survival: 44.0%, 95% CI 34.6 - 56.0 for those on chronic dialysis and 20.0%, 95% CI 8.3 – 48 for kidney transplant recipients). Conversely, in patients on chronic dialysis, a "renal" APACHE diagnosis as reason for admission to critical care was associated with a better survival compared to other reasons for admission (30-day survival: 93.9%, 95% CI 90.7 – 97.1). This was however not the case for kidney transplant recipients. Figure 3B depicts the differential survival across the three most frequent APACHE diagnosis groups (renal, sepsis and cardiac arrest) among maintenance dialysis patients admitted to ICU.

Factors associated with short- and long-term mortality post ICU admission

Coefficients (along with their 95% CI) for candidate risk factors are presented in Supplementary Table 8 and Supplementary Figure 4 for 30-day mortality and in Supplementary Table 9 for 1-year mortality.

Of note, patients admitted for pneumonia, cardiac arrest, acute abdominal pathology or other cardiovascular reasons had a higher risk of both 30-day and 1-year mortality compared to those admitted for renal reasons. The APACHE II score was a consistent risk factor in unadjusted and adjusted analysis associated with both higher 30-day and 1-year mortality.

Receiving invasive ventilation and vasoactive drugs were associated with an increased risk of death (30-day mortality adjusted HR=1.75, 95% CI 1.28-2.39 and 1.72, 95% CI 1.28-2.31 respectively). This association showed a time-varying pattern and was most prominent in the first 30- and 90-days following admission (Table 3). However, there was no significant difference in survival of patients who received non-invasive ventilation compared to those who did not (30-day mortality adjusted HR=0.95, 95% CI 0.66-1.35).

Discussion

This study provides comprehensive data on all patients receiving chronic KRT admitted to critical care environments in Scotland over an 11-year study period. Between 2009 and 2019, 1,402 patients established on chronic KRT had at least one ICU admission. The ICU admission rate was 3 times higher in chronic dialysis patients compared to those with a kidney transplant (59.1 versus 19.9 per 1000 person-years) but mortality was similar. Renal diagnoses were the most common (20.9%) reason for admission in patients on maintenance dialysis and were associated with higher survival compared to other diagnoses whilst kidney transplant recipients were most frequently admitted for pneumonia (19.3%) or sepsis (12.8%). Patients admitted for cardiac arrest had the lowest survival overall. Receiving invasive ventilation or vasoactive drugs were both identified as risk factors for mortality post ICU admission, especially in the short-term.

The annual incidence of new patients initiating chronic KRT has stabilised over the last two decades in high income countries (22, 23) whilst survival has improved, especially in those undergoing maintenance dialysis (24). Our analysis showed an increasing number of kidney transplant recipients whilst the number of patients on maintenance dialysis has remained stable over the past decade in Scotland. This was reflected by an increasing number of ICU admissions for kidney transplantation in the chronic dialysis population between 2009 and 2019. Despite a stable population of patients treated with chronic dialysis, we found an increasing rate of ICU admissions over the 11-year study period in this subgroup which may be explained by the increasing age at time of admission to critical care that we reported. Although we could not assess this, the increasing prevalence of other risk factors such as diabetes and hypertension, is another hypothesis that may account for this trend.

Compared to other groups of patients with major comorbidities, the 1-year post-ICU admission mortality rate found in our cohort of patients with chronic KRT (41.1% in dialysis patients, 38.5% in kidney transplant recipients) appears similar to that found in a previous study investigating critically ill patients with solid cancer (46.2%) (25) - despite the latter only considering unplanned ICU admissions in contrast to our study where we also include elective admissions. According to another study, the comorbidities most strongly associated with 1-year mortality post critical illness were malignancy (HR=2.53) and need for chronic KRT (HR=1.79).(26)

We found that renal diagnoses were the most common reason for ICU admission in the chronic dialysis subgroup (20.9%), followed by admissions for sepsis (9.3%) and cardiac arrest (8.3%). Renal diagnoses as a reason for ICU admission does not appear commonly mentioned or studied in previous literature, but within our analysis was associated with improved survival compared to other APACHE diagnosis admission reasons in patients on maintenance dialysis. In our study, this may be explained by the fact that the top condition included in the renal APACHE diagnosis was kidney transplantation, an intervention reserved for fit patients with usually good outcomes. The presence of patients admitted due to missed dialysis sessions within this diagnosis group represents another hypothesis, as this can be easily resolved. (27) These hypotheses are in line with the fact that in our study, an APACHE renal diagnosis was not associated with better survival among kidney transplant recipients. In the transplant population, the most common reasons for admission to critical care were pneumonia and sepsis consistent with immunosuppressant medication. We also found infection to be the leading cause of death in this population. Although the risk of death from infection after kidney transplantation has dropped since the 1990s, it remains the main cause of non-cardiovascular death in this population (28-30).

We showed that receiving ventilation, and vasoactive drugs during admission was associated with increased mortality in individuals who are established on chronic KRT. This finding was most prominent in the first 30- and 90-days following critical care admission. A large 2018 retrospective cohort study found that increased duration of mechanical ventilation and vasoactive drug use during admission were both associated with decreased 1-year survival in patients who survived at least 30 days from ICU admission (31).

Strengths of our study include a national large study population over an 11-year study period collected across the whole Scottish population, making our results more widely generalisable. Data from the Scottish Renal Registry has 100% coverage, enabling capture of complete data on all individuals on chronic KRT in Scotland. This study also has limitations. It is based on observational data and is therefore limited by confounding and potential selection bias with individuals expected to have the best chance of survival admitted to critical care. This may explain why in our study, despite having a 3 times higher ICU admission rate, patients on maintenance dialysis presented a similar post-ICU survival to the generally fitter population of kidney transplant recipients. The results of our regression analyses simply aim to identify risk factors associated with post-ICU admission mortality and do not prove causality since residual confounding cannot be excluded from our design and models. It should also be noted that, in order to explore short and long-term outcomes post-ICU admission, our design sets the follow-up start date of each patient to the day of their first ICU admission during the 2009-2019 period. This in turn may be responsible of creating immortal time bias. It should also be noted that we have designed a cohort of prevalent chronic KRT patient and analyse their first admission to ICU during the study period (2009-2019). Consequently, for those who initiated chronic KRT prior to 2009, we may not have captured their first ICU admission since they started chronic KRT. Also, our study period is prior to the COVID-19 pandemic, a choice we made to avoid capturing patterns driven by the pandemic and remain able to compare trends over the years included. Finally, our data also lacks information on patients' co-morbidities and prescribing data.

Conclusions

With a growing prevalence of kidney transplant recipients and improved survival of patients on chronic dialysis, ICU admissions of chronic KRT patients have increased over the past decade, with a notable rise in those for elective cardiac surgery and renal reasons. Post-critical care mortality rates are high amongst patients on chronic KRT with large heterogeneity according to the different APACHE diagnoses at admission. Cardiovascular diseases and infections respectively represent the main causes of death post-ICU admission for patients on maintenance dialysis and kidney transplant recipients. With the aim to reduce post-ICU mortality, future prevention should take into account those specific vulnerabilities.

Declarations

Consent for publication: Not applicable.

Availability of data and materials: The data underlying this article cannot be shared publicly as they are held by Public Health Scotland. Data can be requested from the electronic Data Research and Innovation Service (eDRIS) team which are part of the Public Health Scotland through phs.edris@nhs.net

Author's contributions: JC, CW, MO, LD, AA, KB, ZC, NJ, WM, SM, VS, ES, JT, NL and SB contributed to the acquisition of the data. EL, HW and JC were responsible for the analysis of the data. SB was responsible for the conception of the work. EL and SB were responsible for the design of the study. All authors drafted the manuscript and approved the final version of the manuscript.

FIGURES LEGEND:

Figure 1A,B: Trends for monthly number of all critical care admissions (A) and admissions for cardiac surgery (B) in patients on maintenance dialysis, between 2009 and 2019. ICU=Intensive Care Unit

Figure 2. Sankey diagram depicting ICU admission reasons and outcomes for patients on maintenance dialysis. KRT=Kidney Replacement Therapy, GI=Gastrointestinal, CV=Cardiovascular, CHF=Chronic Heart Failure.

Figure 3A,B: Kaplan-Meier survival curves by chronic KRT modality (A) and in chronic dialysis patients admitted for renal reasons, sepsis or cardiac arrest (B)

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