Incidence and outcomes of Acute Kidney Injury requiring renal replacement therapy

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Incidence and outcomes of Acute Kidney Injury requiring renal replacement therapy: a retrospective cohort study.

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Abstract

Background: Incidence of Acute Kidney Injury (AKI) requiring dialysis is rising globally and is associated with high mortality and morbidity.

Aim: To examine the incidence of AKI requiring renal replacement therapy (RRT) in the Tayside region of Scotland and the impact of RRT for AKI on morbidity, mortality and length of hospital stay.

Methods: 178 patients (>18 years of age) received acute RRT between 1 January 2012 and 31 December 2012 were retrospectively selected for inclusion into our longitudinal cohort study. Incidence rate was calculated. Length of hospital stay, likely cause of AKI, renal recovery and mortality data were collected for a, during a 1 year follow up period or until death. Chi-square testing was used to compare morbidity and mortality data between subgroups. RRT-free survival and time-until-event (death or RRT) analysis was performed using Kaplan-Meier plots. Cox-regression was used to examine associations between age, sex, diabetes and CKD on survival.

Results: Incidence of AKI requiring RRT was 430 per million population per year. Median length of hospital stay was 21 days. In-patient mortality was 36%, mortality at 90 days was 44% and at 1 year 54%. Median time from start of RRT until death or chronic RRT was 90 days (95% CI 14-166). 1-year cumulative RRT-free survival was 26% in the ward, 36% in HDU and 48% in ICU subgroups. Diabetes, gender and CKD at baseline did not affect RRT-free survival in our cohort. A quarter of the cohort regained full renal function and 15% of survivors were on a chronic dialysis programme at 1 year.

Conclusions: Our study has given a comprehensive summary of renal outcomes and mortality after a single episode of AKI requiring RRT. Our findings confirm that dialysis-dependent AKI is associated with increased length of hospital stay, high mortality and loss of renal function long term emphasizing the importance of recognition and prevention of AKI.

Keywords

Acute kidney injury

Renal replacement therapy

Clinical outcomes

Morbidity and mortality

Epidemiology

Background

Acute Kidney Injury (AKI) is commonly encountered by hospitalised as well as ambulatory patients with an acute illness. AKI is categorised by the Kidney Disease Improving Global Outcomes (KDIGO) AKI staging system [1]. Patients with AKI 1 and 2 sustain a moderate rise in serum creatinine or reduction in urine output over 12 hours. Patients with AKI 3 suffer a further reduction of urine output over 24 hours or anuria over 12 hours; a serum creatinine rise above 354 µmol/L or three times above their baseline value; or require renal replacement therapy (RRT). A large meta-analysis estimated the global burden of AKI in 2013 to be close to 50 million patients [2]. Recent studies demonstrated that AKI increases mortality rates, morbidity, progression to chronic kidney disease (CKD) and length of hospital stay [3-7]. Even a small rise in serum creatinine has been recognised as an important prognostic factor for worse clinical outcomes [6]. Mortality is especially high in the critical care setting, with rates of up to 80% if RRT is required [8]. Of surviving patients, 5-20% remain dialysis dependent at hospital discharge [5].

Accurate identification of patients at risk of developing AKI warrant an unambiguous definition, in order to improve outcomes through better prevention strategies and therapeutic interventions. Since the introduction of the KDIGO AKI staging system in 2012 [1,9] a steady increase in observational studies and systematic reviews have been performed, suggesting that the lack of global nomenclature historically has resulted in an underestimation of the impact of AKI on morbidity, mortality, hospital stay and medical costs [2,10,11].

The incidence of all-severity AKI in the UK is estimated to be as high as 620 per million population per year [12]. The most recent studies describing the burden of AKI on the National Health Service (NHS) in Scotland were conducted 10 years ago prior to the introduction of the KDIGO guidelines for AKI. A Scotland wide study performed in 2002 estimated the incidence of AKI requiring RRT to be 286 per million population [13]. An incidence of 252 per million population was estimated by the authors of a study done in the Grampian NHS board in 2003[4], which has a comparable population size and distribution as NHS Tayside

The objectives of our study were to examine the incidence of AKI requiring RRT in the geographical region covered by NHS Tayside and to describe the impact of RRT for AKI on length of hospital stay, mortality and morbidity.

Methods

Design and study cohort

NHS Tayside board covers both rural and urban geographical areas in the east of Scotland with a population estimate of 412,000 persons in 2012. Acute RRT services in the Tayside region of Scotland are limited to Ninewells Hospital in Dundee. Depending on the clinical condition and therapeutic needs of the patient, intermittent haemodialysis (HD) or Sustained Low-Efficiency Dialysis (SLED) is provided in the intensive care unit (ICU). HD treatments are provided in medical and surgical high dependency units (HDU), coronary care unit (CCU) and the renal clinical inpatient unit, which will be referred to as 'Ward' in this paper. All HD and SLED

treatments are prescribed and supervised by members of the renal team and routinely recorded. All patients (>18 years of age) who received acute RRT in NHS Tayside between 1 January 2012 and 31 December 2012 were retrospectively selected for inclusion into our longitudinal cohort study.

Data collection

Approval from the local data protection officer was obtained to collate data from electronic and paper based patient records. Patients entered the cohort on the first day of dialysis and were followed up for 1 year or until death (if earlier). Patients [1]were excluded if receiving chronic haemodialysis or peritoneal dialysis. Likely cause of AKI ascertained by a renal physician for all patients and cause of death as documented by the clinician for the non-survivors was recorded.

Definitions

Baseline characteristics such as age, sex, diabetic status and CKD status were collated. The following audit measures were defined in accordance to the Renal Association Acute Kidney Injury guideline [8]. Baseline creatinine was defined as a stable recent serum creatinine measurement within 3 months of the index admission date. If such measurement was not available, a measurement within 1 year of the index date was accepted. KDIGO AKI staging criteria were used to define AKI stage at which RRT was initiated [1]. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula [14]. Baseline eGFR ≥60 ml/min was considered to represent preserved renal function. CKD stage 3, 4 and 5(ND), were defined as eGFR 30-59 ml/min, 15-29 ml/min and

<15 ml/min but not on dialysis respectively [15]. Complete renal recovery was defined by a return of serum creatinine within 20% of baseline value. Partial renal recovery at 90 days and 1 year were defined as a stable return of serum creatinine to a value more than 20% above the baseline value, but without the requirement of chronic RRT [8]. RRT-free survival was defined as survival without requiring chronic RRT.

Statistical analysis

For incidence calculations, a mid-point population estimate and median age in NHS Tayside were obtained from National Records of Scotland [16]. Incidence rate was defined as number of disease onsets divided by sum of the patient-time at risk. As this study dealt with a dynamic population (as patients may move in and out of NHS Tayside) the person-time was equal to the average population multiplied by the follow up time.

Descriptive statistics were used to summarise the renal function at baseline, discharge and during follow up (90 days and 1 year post start RRT). Those patients lost to follow up were excluded from analysis of outcome measures at 90 days and 1 year. Patients with missing data were excluded from analysis of the variable of interest only.

Chi-Square test was used to compare categorical data such as Community Acquired AKI (CA-AKI) vs Hospital Acquired AKI (HA-AKI), dialysis setting (ICU vs HDU vs ward) and death (Yes vs No) between patients with and without pre-existing CKD (Acute on Chronic Renal Failure (ACRF) vs AKI). Chi-square test was performed to compare in patients receiving RRT in ICU, HDU and the ward, between males and females,

diabetics and non-diabetics, in AKI a ACRF groups and between patients receiving HD or SLED in ICU. RRT-free survival and time-until-event (death or RRT) analysis was performed using Kaplan-Meier plots. Cox-regression was used to examine associations between age, sex, diabetes and CKD on survival. All statistical analyses were performed using SPSS version 21 (IBM, Armonk, NY), and $P<0.05$ was considered statistically significant.

Results

During the 12 month study period 178 cases requiring haemodialysis for AKI were identified. Two cases were excluded because of incorrectly recorded patient information. Five patients were lost to follow up at 90 days and 1 year, due to transfer to another health board after the acute phase of treatment.

The incidence of patients developing AKI that required RRT in NHS Tayside was calculated as 430 per million population per year.

Characteristics of AKI patients requiring RRT

Baseline characteristics of patients are shown in Table 1. Median age was 72 years (IQR 60-78). Median creatinine was 96 µmol/L (IQR 77-131) at baseline and 357 µmol/L (IR 258-483) at the start of RRT. Sixty-fife percent of patients had AKI stage 3 at the time of initiation of RRT.

Just over half of patients (53%) developed AKI prior to admission to hospital (CA-AKI). There was no difference in the development of CA-AKI vs HA-AKI between the patients with and without pre-existing CKD (χ^2 (1, n=174) = 1.289, p=0.26).

Initiation of dialysis

Dialysis can be performed in ICU, HDU or the renal ward, depending on the disease severity of the patient. The majority (81%) of RRT was started in either ICU or HDU; 67 patients received RRT in ICU, of which 54 (81%) received SLED either as a single modality or in combination with HD. The remaining 13 patients (19%) in ICU received HD only. More patients who received their dialysis in ICU or HDU had preserved renal function prior to their admission as compared to the ward (67% vs 53% vs 39% for ICU, HDU and ward respectively, χ^2 (2, n=174) = 6.944, p=0.03).

Causes of AKI

Prevention of AKI warrants insight in the aetiology of the disease. AKI in our population was primarily caused by infection/sepsis syndrome (43%) or reduced renal perfusion due to volume depletion or hypotension (16%). A detailed overview of causes of AKI is presented in Supplementary Table 1.

In 37 cases (21% of total cohort) use of medication interacting with the renovascular system contributed to the development of AKI (Supplementary Figure 1 and Supplementary Table 3). Two thirds of these patients developed AKI in the community, 46% were on more than one interacting drug whilst developing AKI and 17 out of 37 patients (46%) were on inhibitors of the Renin-Angiotensin System. Intravenous contrast media use prior to the development of HA-AKI was identified in 11 cases. Non-Steroidal Anti Inflammatory Drugs, trimethoprim or metformin use prior to admission was associated with AKI in 12 cases.

Outcomes of AKI requiring RRT

The aim of our study was to describe the impact of RRT for AKI on length of hospital stay, mortality and morbidity. The median length of hospital stay was 21 days (IQR 9-38). Of the 176 patients included into our study, 64 patients (36%) died in hospital and an additional 8% died within the first 90 days after start of RRT. Total mortality after 1 year of follow-up was 54%. Further analysis of mortality data showed that 53% of the deaths within the first year were the result of infection/sepsis or cardiovascular causes (Supplementary Table 2).

In-hospital mortality rates for patients with AKI stage 1 or 2 at time of RRT initiation were 49% compared to 29% for patients with AKI stage 3. Ninety day mortality for both groups was 57% and 36% respectively.

In-hospital mortality, 90 day mortality and 1 year mortality rates were higher amongst those that received dialysis in ICU or HDU when compared with the ward (Figure 2). In-hospital mortality rates for the patients in ICU who received SLED alone or a combination of SLED and HD, were higher than for those that received HD only (SLED; 62%, HD+SLED; 25%, HD only; 39%, χ^2 (1, n=176) = 8.36, p=0.004).

Morbidity was defined as persistent loss of renal function, measured at three time points during follow up. At discharge, only 30% of all patients regained full renal function and 7% (n=13) remained dialysis dependent; six of these patients had CKD on admission. Of those that had a partial renal recovery on discharge (n=47), 39% died within the first year of follow up, one patient (2%) required chronic RRT.

At 1 year, 6% (n=11) of the patient cohort (which equals 15% of the survivors) was on a chronic dialysis programme and 25% (n=43) of all patients had a completely recovered renal function (Figure 2).

RRT-free survival

In practise the ultimate goal of emergency dialysis during an acute illness is to regain full level of fitness and renal function long term. The RRT-free survival in our cohort equates to this and is visible in figure 3A which depicts the time from first session of RRT until death or chronic RRT in our cohort. The median time from start of RRT until death or chronic RRT was 90 days (95% CI 14-166), six patients died on the day RRT was initiated. Thirty-nine percent of the cohort survived 1 year without requiring RRT. Median RRT-free survival was 132 days (95% CI 0-291) in the AKI group, 76 days (95% CI 0-155) in the ACRF group (Log rank testing not significant). Cumulative RRT-free survival at 90 days and 1 year did not differ for AKI and ACRF subgroups.

Median survival was 58 days in the subgroup dialysed in the ward (95% CI 4-112) and 57 days in the HDU-subgroup (95% CI 0-139) (Figure 3C). 1-year cumulative RRT-free survival was 26% in the ward, 36% in HDU and 48% in ICU subgroups. Diabetes, gender and CKD at baseline did not affect RRT-free survival in our cohort.

Discussion

Our study showed an incidence of AKI requiring RRT of 430 per million patients per year with an average length of hospital stay of 21 days per patient. In-hospital

mortality was 36% and 1 year mortality 54%. In-hospital mortality was higher amongst those who received RRT in intensive care or higher care settings as compared with the ward, with the highest mortality of 62% for those receiving SLED in ICU. One third of all patients had a completely recovered renal function on discharge and at 90 days post RRT. At 1 year, only 25% of the patient cohort had maintained their complete renal recovery, 6% were established on a chronic RRT programme.

Our study data show a rise in annual incidence of 50% as compared with the Scottish incidence estimate from 2003 [13]. This is in line with results of a large American retrospective cohort study performed in 2013 [11] which reported an approximate 10% increase in incidence of AKI requiring RRT per annum since 2000. Interestingly, incidence has climbed despite increased global effort to improve prevention and management of AKI of all levels of severity. Ageing populations of the developed countries [11,17-19] may account for these increased rates due to an increase in prevalence of risk factors for the development of AKI such as cardiovascular disease, diabetes mellitus and CKD. One could also argue that the threshold to initiate RRT may have been lowered in recent years. However, our data suggest that there has been little change in local practice when commencing patients on RRT, with a median age of 72 years in our study cohort which is similar to that reported in the large Scottish cohort study in 2003 by Prescott et al [13].

In order to improve morbidity and mortality after AKI it is paramount to recognise the severity of the disease burden and to identify risk factors leading to less than complete recovery of renal function, dialysis dependence or death. A wide array of potentially modifiable risk factors for the development of AKI has been identified [20-23]. These include volume depletion/hypotensive state, surgery, sepsis/infection and use of contrast media and medication interacting with the renovascular system. Infection/Sepsis syndrome and extracellular fluid depletion were the two most common causes directly leading to AKI in our study. No differences in the cause of AKI between subgroups (CA-AK vs HA-AKI, ACRF vs AKI) were identified. AKI was caused by IV contrast in 11 patients (6%). A further 26 patients (15%) required RRT for AKI exacerbated by the use of antihypertensive medication, opioids or Non-Steroidal Anti Inflammatory Drugs, exacerbation of hyperkalaemia or acidosis (see Supplementary Table 3).

Timing of initiation of RRT has been subject of debate; two recent publications randomised critically ill patients with AKI stage 2 or 3 to early initiation (within six hours of documentation of AKI stage 3) or late initiation (after 72 hours of oliguria or when severe laboratory abnormalities such as hyperkalaemia, uraemia or acidaemia developed) of RRT [24,25]. *Gaudry et al.* reported no significant difference in 60 day mortality between the early-strategy group and the delayed strategy group, whereas *Zarbock* and colleagues recorded reduced 90 day mortality, length of hospital stay and duration of RRT in the early initiation group. In our heterogeneous cohort of patients receiving RRT in an Intensive Care, as well as High Dependency or Ward

setting 65% had AKI stage 3 when RRT was initiated (see table 1). As opposed to the survival advantage reported by *Zarbock et al.*[25], 90 day mortality was 36% in AKI stage 3 group, as compared to 57% in the combined AKI stage 1 and 2 group. Due to the retrospective design of our study and relatively small study size, our study was not powered to distinguish a significant difference in mortality between both groups. Life threatening complications of rapid onset AKI stage 1 or 2 such as hyperkalaemia, acidaemia and fluid overload are well known indications to start RRT before AKI stage 3 has developed, delaying RRT would be detrimental in these circumstances. This phenomenon might explain our reported in-hospital and 90 day mortality rates in the AKI 1 and 2 group.

In the literature, chronic RRT rates after admission for AKI vary widely; from 8-14% in mixed cohorts including patients with CKD and preserved renal function [26,27] to 49% in a CKD cohort [28]. Even a small reduction of renal function after an episode of AKI has been found to have major long-term effects on quality of life and health resources [7,29]. Moreover, patients with an acute illness, severe enough to cause dialysis dependent AKI are likely to lose significant muscle mass causing an overestimation of follow up eGFR. Consistent with previous research, our study provides further evidence of the increased risk of incomplete renal recovery and chronic dialysis dependence up to one year after a single episode of AKI requiring RRT.

Small retrospective dataset analyses have previously been done to assess the incidence and outcomes of CA-AKI and HA-AKI. AKI of all severities is found to develop more often in the community than in hospital, with percentages of CA-AKI ranging between 67% [30] and 79% [31,32]. In our RRT cohort 53% of the patients developed AKI in the community. Age, length of hospital stay, recovery rates of renal function and mortality rates were equal in HA-AKI and CA-AKI. This contrasts with a British retrospective analysis of renal outcomes post CA-AKI and HA-AKI published in 2014 [30], where the length of hospital stay was significantly longer and in-hospital mortality rates were higher in HA-AKI. A possible explanation for this discrepancy is that *Wonnacot et al* included AKI of all severities, with a high percentage of AKI stages 1 and 2.

Baseline co-morbidity influences decision making regarding intensity of treatment when dealing with an acutely unwell patient. A preserved baseline renal function was associated with dialysis in ICU, where pre-existing CKD was associated with dialysis on the ward. The mortality rate of patients who were dialysed on the ward rose considerably between discharge, 90 days and 1 year (6%, 24% and 41% respectively). An explanation for the rise in mortality within the first year potentially lies in the higher co-morbid state of this subgroup; CKD is widely recognised to be associated with increased all-cause mortality and kidney disease progression [33,34]. Eighty-one percent of the acute dialysis treatments were initiated in either ICU or HDU, which illustrates the disease severity of our patients requiring acute dialysis. SLED, modality of choice in patients with haemodynamic instability [35-37], was prescribed for 81% of patients in ICU. The majority of the patients in ICU and HDU

present with multi organ failure, and their in-hospital mortality was statistically significantly higher than for those patients in the ward (see Figure 1).

Our study has several strengths. It used a heterogeneous and representative cohort from the NHS Tayside area which centralises its RRT to one hospital with routine recording of all RRT provided. All AKI episodes were classified according to the KDIGO AKI staging system. Limitations include a relatively small cohort size with and short duration of follow up. We therefore could not establish the potential confounding effects of diabetes and the presence of proteinuria in our subgroup analyses. Studies with a larger sample size, formal disease severity scoring and longer follow-up time are warranted to establish the long term effects of AKI on progression towards RRT and death.

Conclusions

This observational study is the first British study to comprehensively characterise patients with stage 3 AKI requiring RRT since the implementation of the AKIN staging system in 2007. We have demonstrated a significant rise in annual incidence of AKI requiring RRT as compared with the Scottish estimate from 2003. Moreover, we have reported that within the first year after RRT a concerning 75% of patients died or lost a significant proportion of renal function, putting them at risk of developing CKD and death. Our study results emphasise the invaluable importance of early recognition, prevention and classification of AKI.

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Table 1: Characteristics of AKI patients requiring RRT

n = 176		
Age (years)	Median (IQR)	72 (60-78)
Sex (male)	n (%)	114 (65)
Diabetic (yes)	n (%)	43 (24)
Creatinine at baseline (umol/l)	Median (IQR)	96 (77-131)
Creatinine at start RRT (umol/l)	Median (IQR)	357 (258-483)
Renal function at baseline	n (%)	
Preserved renal function (eGFR >60 mL/min)		97 (56)
CKD stage 3 (eGFR 30-60 mL/min)		62 (36)
CKD stage 4 (eGFR 15-30 mL/min)		13 (7)
CKD stage 5ND (eGFR <15 mL/min)		2 (1)
KDIGO AKI stage at start RRT		
AKI stage 1 and 2 (creatinine up to 2.9 times baseline)		61 (35)
AKI stage 3 (creatinine >3 times baseline or creatinine > 354 umol/l)		114 (65)
Community-Acquired AKI (yes)	n (%)	94 (53)
Initiation of dialysis	n (%)	
ICU		67 (38)
HDU		75 (43)
Ward		34 (19)
Length of stay (days)	Median (IQR)	21 (9-38)

Median age in NHS Tayside: 42 years.
n; number of cases, IQR; interquartile range

Figure 1: Mortality according to location of dialysis

ICU = Intensive Care Unit, HDU = Higher Care Unit.* In-hospital mortality; $\chi 2$ ICU vs ward (1, n=109) = 13.928, p<0.001), $\chi 2$ HDU vs ward (1, n=109) = 16.46, p<0.001), HDU vs ICU ns.

^ Mortality at 90 days; $\chi 2$ ICU vs ward (1, n=100) = 4.01, p=0.05), $\chi 2$ HDU vs ward (1, n=108) = 8.79, p=0.003), HDU vs ICU ns.

+ Mortality at 1 year; ICU vs wardns ,

$\chi 2$ HDU vs ward (1, n=108) = 5.35, p=0.02), HDU vs ICU ns.

Figure 2: Renal recovery at 1 year follow-up

After 1 year follow-up, 54% of patients had died and 6% was established on a chronic dialysis programme. One quarter of patients had a fully recovered renal function, whereas the renal function of 13% of patients had not returned to its baseline.

n=174.

RRT; Renal Replacement Therapy. LTF; lost to follow up. Missing values n=2.

Figure 3: Survival Analyses

3A: Kaplan-Meier survival plot: time from first session of RRT until death or chronic RRT. RRT-free survival at 1 year is 39%. Whole cohort represented (n=176)

3B: Kaplan-Meier survival plot for AKI and ACRF subgroups. Median RRT-free survival time; 132 days for AKI group, 76 days for the ACRF group (log rank testing not significant)

3C: Kaplan-Meier survival plot by setting of dialysis. Median RRT-free survival time; 58 days in ward, 57 days in HDU