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ORIGINAL ARTICLE

Outcomes of critically ill adult patients with continuous renal replacement therapy-requiring acute kidney injury in the Free State province of South Africa: the impact of HIV

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ABSTRACT

Background: Continuous renal replacement therapy (CRRT)-requiring acute kidney injury (AKI) in critically ill adult patients frequently occurs in the intensive care unit and is associated with high morbidity and mortality. There is a paucity of epidemiological data regarding CRRT-requiring AKI in sub-Saharan Africa.
Methods: We conducted a retrospective cohort study of all critically ill adult patients with CRRT-requiring AKI at Universitas Academic Hospital, Bloemfontein, during the period 1 July 2010 to 30 June 2014. The primary purpose was to determine the incidence of CRRT-requiring AKI. Secondary objectives were to record mortality, renal recovery and duration of CRRT.
Results: The number of patients with CRRT-requiring AKI was 87 (1.1%) of the 7 709 patients admitted to the ICU over this 4-year period. Of these, 37 (43%) were HIV infected. The median age was 56 years (43 years in the HIV-infected versus 64 years in the HIV-uninfected group ($P < 0.01$). The majority of the HIV-infected patients were Black (89%). Metabolic acidosis together with pulmonary oedema and oliguria were the main indications for dialysis. The overall mortality was 31% with most of the deaths (82%) occurring in the HIV-positive patients. These patients had a mortality rate of 60% versus 10% among the uninfected ($P < 0.01$. Multivariate logistic regression identified female sex and HIV infection as independent predictors of mortality. The median duration of CRRT was 3 days and renal recovery occurred in 26% of patients.
Conclusions: The incidence of CRRT-requiring AKI in critically ill adult patients at Universitas Academic Hospital was low. The overall mortality was relatively low when compared to that reported by others; however, it was relatively very high in the HIV-infected group.

Keywords: Acute kidney injury; continuous renal replacement therapy; critically ill adults, South Africa.

INTRODUCTION

Continuous renal replacement therapy (CRRT) was introduced into the intensive care (ICU) setting as early as the 1980s [1]. This was due to the need for effective renal replacement therapy (RRT) in patients who were often haemodynamically unstable and therefore unable to tolerate intermittent modalities of dialysis. As a result, CRRT has become the dialysis modality of choice for the treatment of AKI in critically ill adult patients with haemodynamic instability [2].

CRRT-requiring AKI in critically ill adult patients frequently occurs in the ICU, and is associated with high morbidity and mortality [3]. AKI is characterised by a rapid decline in kidney function and is signalled by a rising serum creatinine concentration and/or a reduction in urine output [4]. AKI has been reported to occur in up to 25% of ICU patients, depending on the definition, with ~6% requiring RRT [5-7]. The mortality rate of patients with multiple organ failure in the ICU approaches 50%, and

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increases to 80% when RRT is required [8,9]. The predominant cause of AKI in critically ill patients is acute tubular necrosis (ATN), usually resulting from sepsis [10]. This may result in life-threatening complications such as uraemia, volume overload, metabolic acidosis and hyperkalaemia that may require management with RRT.

RRT options in the ICU include intermittent haemodialysis (IHD), sustained low-efficiency daily dialysis (SLEDD), acute peritoneal dialysis and CRRT. The main difference between the intermittent and continuous forms of RRT is the duration; CRRT is delivered for 24 hours per day whereas IHD is usually given in 4-hour sessions. During CRRT, techniques that achieve solute clearance predominantly by convection require large volumes of ultrafiltration. A substantial amount of replacement fluid, given either by predilution or post-dilution relative to the dialyzer, is therefore required to maintain haemodynamic stability. Whereas CRRT may be preferred in haemodynamically unstable patients, a landmark randomised controlled trial (RCT) reported no difference in renal recovery, duration of RRT or mortality among patients receiving CRRT or IHD [11]. In a study conducted at a tertiary hospital in South Africa, the reported ICU mortality for medical patients with AKI was as high as 47.8% [12].

Lameire et al. [13] have pointed out that the incidence of AKI across the world is unknown due to under-reporting and regional disparities. Abraham et al. [14] reported a number of differences regarding the epidemiology of AKI in developing countries as compared to developed ones. In developed countries AKI commonly occurred in the elderly and was often due to nephrotoxic drug exposure whereas in developing countries AKI occurred at any age and was often due to infectious diseases such as malaria and diarrhoeal disease, often in the context of HIV infection. The incidence of CRRT-requiring AKI in developing countries may therefore be different from that reported by those in the developed world. Additional factors that may affect this include differences in clinical practice due to resource constraints. For example, patients with a very poor prognosis may not be admitted to the ICU and so may not receive RRT.

Since there is a paucity of epidemiologic data regarding CRRT-requiring AKI in sub-Saharan Africa, we conducted a study to determine the incidence of critically ill patients with CRRT-requiring AKI in the ICU and report here on their mortality rate and rate of renal recovery.

METHODS

This was a single-centre, retrospective cohort study describing the outcomes of critically ill adult patients who had CRRT-requiring AKI at Universitas Academic Hospital (UAH) in Bloemfontein, in the Free State province of South Africa.

Data were extracted from the charts of all adult patients ≥18 years old who were admitted to one of five ICUs at UAH and who had CRRT-requiring AKI during the period 1 July 2010 to 30 June 2014. UAH is the only public sector tertiary hospital in the Free State and operates five ICUs for adults with a total of 36 medical and surgical beds. Patients who received treatment for poisoning, treatment of AKI with other dialysis modalities and those with acute-on-chronic kidney disease were excluded. Chronic kidney disease (CKD) was defined by an estimated glomerular filtration rate of <60 mL/min/1.73 m^2 for more than 3 months and/or radiographic evidence suggesting CKD (mainly small kidneys on ultrasound scanning). An attending nephrologist selected the dialysis modality and supervised the prescription of CRRT.

Data extracted included age, sex, comorbid diseases, reason for admission to the ICU and the indication for RRT. Additional clinical data included surgical status, number of organ failures and APACHE II (Acute Physiology and Chronic Health Evaluation II) score, duration of CRRT, need for mechanical ventilation and assessment of survival and renal recovery up to 90 days after discharge from the ICU. Laboratory and physiological data included serum pH, serum potassium, serum urea and creatinine, daily urine output and haemodynamic status including mean arterial pressure (MAP) and pulse rate. Patients were regarded as haemodynamically unstable when MAP was ≤65 mmHg and/or they required vasopressor support.

Assessments of renal recovery and of mortality were made for the ICU stay, the post-ICU in-hospital stay, and for days 28 and 90. Patients who had improved to become independent of dialysis were considered to have recovered renal function.

Statistical analysis

Descriptive data were expressed as mean ± standard deviation, or median and interquartile range where data were not distributed normally. Chi-squared and Fisher's exact tests were used to compare categorical variables whereas the Wilcoxon rank-sum test was used to compare continuous variables between HIV-infected and -uninfected patients. Univariate and multivariate stepwise logistic regression was used to examine predictors of mortality. Statistical significance was set at $P < 0.05$. The data analysis was performed using STATA version 13.1.

Ethics approval

Permission to conduct this study was granted by the Research Ethics Committee of the Faculty of Health

Sciences at the University of the Free State (reference number 230408-011) as well as by the management of UAH.

RESULTS

A total of 7709 adult ICU admissions were recorded over the 4-year period of the study, of whom 87 had CRRT-requiring AKI, an incidence of 1.1%, or 11 per 1000 ICU admissions. Of these, 37 (43%) were HIV infected. Forty-eight (55%) were female. The median age was 56 years (IQR 41–67 years) with the HIV-infected patients being significantly younger (43 versus 64 years, $P < 0.01$). More than three-quarters were Black (67, 77%), of whom the majority (89%) were HIV-positive. See Table 1.

The most common pre-existing non-communicable diseases (NCDs) were hypertension (40%), diabetes mellitus (36%) and heart disease (33%). Liver disease and chronic obstructive pulmonary disease were present in 24% and 17%, respectively. These NCDs were found predominantly in the HIV-uninfected group. Most patients were from the medical ICU (53 patients, 26 HIV-infected) with the remainder being from the surgical ICU (34 patients, 11 HIV-infected). All the patients had community-acquired AKI. The most common causes of AKI included septic ATN (64%), followed by ischaemic ATN (35%) and nephrotoxic ATN (10%). These causes were not mutually exclusive and often more than one cause was present in a single patient.

The distribution of indications for the initiation of RRT is shown in Table 2. Sixty-nine patients (79%) were mechan-

Table 1. Baseline characteristics of included participants.

Demographic	All		HIV+		HIV-		P-value
Totals, n (%)	87	100	37	42.5	50	57.5	-
Age (years)	56	41–67	43	30–55	64	56–71	<0.01
Female, *n* (% of total)	48	55.2	23	62.1	25	50.0	0.26
Race, *n* (% of total)							
White	20	23.0	4	10.8	16	32.0	0.02
Black	67	77.0	33	89.2	34	68.0	
Comorbid diseases, *n* (% of total)							
Heart disease	29	33.3	7	18.9	22	44.0	0.01
Diabetes mellitus	31	35.6	11	29.7	20	40.0	0.93
Hypertension	35	40.2	11	29.7	24	48.0	0.09
Liver disease	21	24.1	8	21.6	13	26.0	0.64
COPD	15	17.2	2	5.4	13	26.0	0.01
Distribution of ICU admissions, *n* (% of total)							
Medical*	53	60.9	26	70.3	27	54.0	0.12
Surgical#	34	39.1	11	29.7	23	46.0	
Disease severity, vasopressor dependence & laboratory parameters							
Mechanical ventilation, n (% of total)	69	79.3	29	78.4	40	80.0	0.85
APACHE II score$	28	23–30	28	23–30	29	24–31	0.13
Oliguria, n (% of total)	60	69.0	21	56.8	39	78.0	0.03
Metabolic acidosis	7.20	7.12–7.30	7.24	7.18–7.31	7.19	7.11–7.27	0.11
Vasopressor dependence prior to CRRT, *n* (% of total)	40	46.0	18	48.6	22	44.0	0.67
Creatinine at CRRT initiation, µmol/L	362	267–450	340	272–423	387	267–463	0.45

Values expressed in a range refer to interquartile ranges; single values refer to percentage of the total population. COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ICU, intensive care unit; APACHE II score, Acute Physiology and Chronic Health Evaluation II score; CRRT, continuous renal replacement therapy. *Includes the coronary care unit, #Includes neurosurgery and cardiothoracic ICU, $Possible scores range from 0–71.

ically ventilated. The median APACHE II score was 28 (IQR 23–30). Sixty (69%) had oliguria and 40 (46%) had vasopressor dependence prior to CRRT initiation.

The median serum creatinine at CRRT initiation was 362 µmol/L (IQR 267–450 µmol/L). The median duration of CRRT was 3 days (IQR 2–4 days). The modality of CRRT in most patients (89%) was continuous venovenous haemodiafiltration (CVVHDF), with an average blood flow rate of 120 mL/min and a dialysate flow rate of 1000 mL/hour. The rest were treated with continuous venovenous haemodialysis (CVVHD). Anticoagulation was provided with unfractionated heparin to 65 patients (75%). This was the only anticoagulation available. The rest did not receive anticoagulation due to the risk of bleeding. Replacement fluid was administered pre-dilution to all patients, irrespective of bleeding risk, using normal saline at a rate of 200 mL/hour to reduce the risk of clotting of the dialyzer.

Table 2. Indications for the initiation of renal replacement therapy.

Indications for RRT[#]	*n* (% of total)
Metabolic acidosis (pH < 7.2)	72 (82.6)
Pulmonary oedema	65 (74.7)
Oliguria	60 (69)
Hyperkalaemia	58 (66.7)
Anuria	37 (42.5)
Uraemia[*]	43 (39.2)

RRT, renal replacement therapy. [*]Acute cognitive impairment, altered level of consciousness or seizures, upper gastro-intestinal bleeding with gastritis and pericarditis that was not otherwise explained. [#] More than one indication was present in most patients.

Death was the outcome in 27 patients (31%). The overall mortality rates in the HIV-infected and -uninfected groups were 60% and 10%, respectively (P < 0.01). The ICU mortality was higher in the HIV-infected group (43% vs. 6%, P < 0.01). Three patient deaths (11%) occurred post-ICU while in hospital and the remaining five (19%) after hospital discharge. Multivariate logistic regression identified female sex and HIV as independent predictors of mortality (see Tables 3 and 4). The ICU in which the patient was managed (medical/surgical) was not predictive of mortality. Of the 53 patients admitted to the medical ICU, all 14 deaths occurred in HIV-infected patients. Of the 34 patients admitted to the surgical ICU, 13 deaths occurred, 8 of which occurred in HIV-infected patients.

Overall, renal recovery occurred in 23 patients (26%), with no significant difference by status of HIV infection. Ten patients (44%) had renal recovery during their hospital stay, seven (30%) recovered by day 28 and six more (26%) by day 90. The median serum creatinine concentration at the end of the study period for those who recovered kidney function was 130 µmol/L (IQR 125–130), with a median value of 127.5 µmol/L (IQR 118–130) in the HIV-infected group and 135 µmol/L (IQR 125–130) in the HIV-uninfected group (P = 0.25).

Table 3. Summary of outcomes.

Primary outcome	All patients		HIV+		HIV-		P-value
	n	% of total	n	% of group	n	% of group	
Patients with CRRT-requiring AKI	87	100	37	42.5	50	57.5	-
Overall mortality	27	31.0	22	59.5	5	10.0	<0.01
ICU	19	21.8	16	43.2	3	6.0	<0.01
In-hospital	3	3.4	2	5.4	1	2.0	0.55
Post-discharge	5	5.7	4	10.8	1	2.0	0.03
Overall renal recovery	23	26.4	7	18.9	16	32.0	0.17
ICU	10	11.5	2	5.4	8	16.0	0.18
Day 28	7	8.0	3	8.1	4	8.0	1.00
Day 90	6	6.9	2	5.4	4	8.0	0.69
Creatinine at end of study, µmol/L	130	125–140	127.5	118–130	135	125–140	0.25
Duration of CRRT, days	3.0	2-4	3.0	2-4	3.0	2-4	0.37

Values expressed in a range refer to interquartile ranges; single values refer to percentages. HIV, human immunodeficiency virus; ICU, intensive care unit; CRRT-requiring AKI, continuous renal replacement therapy-requiring acute kidney injury.

Table 4. Univariate and multivariate logistic regression analysis for predictors of mortality.

Univariate analysis	Odds ratio	P-value
Female sex	4.2	< 0.01
HIV infected	13.2	< 0.01
Multivariate analysis		
Female sex	4.9	0.01
HIV infected	14.4	< 0.01

HIV, human immunodeficiency virus.

DISCUSSION

The incidence for CRRT-requiring AKI over the 4 years of the study was 1.1%, or 11 per 1000 ICU patients. This rate is relatively very low when compared to results in developed countries, where 80% of all ICU patients with AKI receive CRRT as the treatment modality [14]. In a multicentre study of more than 29 000 critically ill patients, 5.7% developed AKI during their stay in ICU of whom ~70% required RRT [9]. Another study reported that 37.2% of 500 critically ill patients required RRT [15]. A study from South India reported that a total of 69% of 1112 patients with AKI required RRT with the majority receiving IHD [16]. A study from Nigeria reported that 51% of 212 cases of AKI required RRT. All received IHD as the dialysis modality [17]. The latter two studies included all hospitalised patients with RRT requiring AKI. In a study reporting outcomes of critically ill HIV patients with AKI, 15% required CRRT [18]. The primary reason for the low incidence of CRRT at our institution is predominantly related to the high costs involved when using this modality. Also, many critically ill patients who have AKI will not be admitted to the ICU because the overall prognosis is thought to be poor. Thus, patients who may potentially benefit from CRRT will not receive it. However, it should be noted that the current study excluded patients who received other modalities of dialysis and was limited to ICU patients only.

The overall mortality of 31.0% is high but is much lower than that reported by others. A study conducted on medical ICU patients at Tygerberg Hospital in Cape Town, South Africa found that 17% of 46 patients with AKI required dialysis [12]. However, only 2 patients received CRRT. Other studies have reported mortality rates that range from 47–74% [2,19-21]. The median age of our cohort was 56 years, which was similar to that reported by others [2,19-21]. However, our HIV-infected group had a median age of 43 years. Despite their younger age, similar APACHE II scores and fewer comorbid NCDs, the mortality of those infected with HIV was relatively very high when compared to the uninfected group (60% vs. 10%, P < 0.01). HIV infection and female sex were identified as independent predictors of mortality. South Africa has the largest antiretroviral rollout programme in the world [22] but many patients are still unable to gain access to this life-saving treatment and present with AIDS-defining illnesses, which may explain the high mortality in this group. It is unclear why female sex was associated with mortality.

Most patients received CVVHDF, with an average blood flow rate of 120 mL/min and a dialysate flow rate of 1 000 mL/hour. A shortcoming of this study was that the effluent flow rate (EFR) was not recorded. Outcomes of critically ill patients have been linked to the dose of CRRT prescribed. In two large RCTs, critically ill patients were randomised to either low-intensity RRT with EFRs that ranged from 20–25 mL/kg/hour or higher intensity RRT with EFRs of 35–40 mL/kg/hour [11, 23]. The primary outcome, death, was no different in the two arms of these studies. It should be noted that the EFRs in the low-intensity arms of both RCTs were much higher than that achieved in usual clinical practice. An often-overlooked modality of CRRT in the ICU is peritoneal dialysis (PD). A study conducted in Brazil reported effective treatment of critically ill patients with AKI using high-volume PD [24]. In countries where contemporary modalities of CRRT are not available, high-volume PD may be a good alternative.

The median duration of CRRT was only 3 days. The interruption of treatment for radiological imaging or surgical procedures and for the replacement of clotted dialyzers may have had an effect on the delivered dose of RRT, and this may have affected outcomes [25].

Renal recovery occurred in only 26.4%. Despite being independent of dialysis, many had incomplete renal recovery at the time of last follow-up. It is possible that some may have had underlying CKD as many had NCDs such as diabetes and hypertension. It is also possible that AKI had resulted in CKD [26]. Regardless of such issues, the results are of concern, as many patients still remained dialysis-dependent. In the public healthcare sector of South Africa, due to resource constraints and rationing of RRT, many of these patients may not be accommodated on chronic RRT programmes [27].

Our study has some limitations. It was a relatively small, single-centre, retrospective investigation and therefore confounding and missing data may have affected the results. However, its strengths include the interesting comparisons of the outcomes between the HIV-infected and -uninfected groups.

CONCLUSION

The incidence of CRRT-requiring AKI in critically ill adult patients at UAH was very low and we had a relatively low overall mortality when compared to the rates reported by others. However, the mortality of the HIV-infected patients was very high. The low rates of renal recovery in those who survived adds to the numbers of patients requiring chronic RRT and increases the financial burden in a country with an already-constrained healthcare budget.

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Conflict of interest

None to declare.

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