Outcomes of hospitalised patients with hyperkalaemia at a South African tertiary healthcare centre

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Summary

Background Hyperkalaemia is a common electrolyte disorder in hospitalised patients. There is a lack of data from Africa on the prevalence, causes and outcomes of patients with hyperkalaemia. We aimed to identify the frequency of hyperkalaemia in hospitalised adults, and to identify any risk factors for in-hospital death.

Methods We conducted a retrospective cohort study of 1921 adult patients admitted to hospital with hyperkalaemia (potassium concentration ([K]) ≥ 5.5 mmol/L) over a one-year period during 2019. Multivariable logistic regression was performed to identify predictors of in-hospital mortality and multilinear regression was used to identify associations with the [K].

Findings We found an incidence rate of 3.7 cases per 100 patient-years. Nearly a third died during hospitalisation. Acute kidney injury (AKI) was common in patients who died (69.2% vs. 41.3%, P < 0.01). Age (odds ratio (OR) 1.02, 95% CI 1.01–1.03), [K] (OR 1.38, 95% CI 1.12–1.71), AKI (OR 3.13, 95% CI 2.19–4.47) and acute therapy (OR 1.93, 95% CI 1.40–2.66) were predictors of in-hospital death. AKI (r = 0.29, P < 0.01) and chronic kidney disease (r = 0.31, P < 0.01) were associated with the [K]. Fourteen percent of patients with hyperkalaemia were HIV positive with no difference in in-hospital death (P = 0.75).

Interpretation This is the largest study reporting on the epidemiology of hyperkalaemia in hospitalised adults from Africa. Hyperkalaemia in association with AKI was a strong predictor of in-hospital death. Late presentation to hospital may be a major factor contributing to poor outcomes.

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Introduction

In hospitalised patients, hyperkalaemia is a common electrolyte disorder which may cause life-threatening cardiac arrhythmias if not optimally treated. Variations in the reported incidence and prevalence of hyperkalaemia in hospitalised populations may be due to differences in the definitions of hyperkalaemia as well as in the populations studied. A recent, comprehensive systematic review reported an overall, global prevalence of 8.6% and an incidence of 5.1 cases per 100 person-years for hyperkalaemia, defined as a [K] ≥ 5.5 mmol/L in hospitalised patients. Few studies were identified from the African continent and none of the studies from Africa reported on the incidence of hyperkalaemia. CKD, an important public health problem which affects 10–15% of adults worldwide, is the most significant risk factor for the development of hyperkalaemia. In high-income countries (HICs), the main drivers of the CKD epidemic are non-communicable diseases (NCDs) like diabetes and hypertension. African countries also bear a large and increasing burden of NCDs.
effects, drugs in this class are frequently discontinued as a result of hyperkalaemia.\(^4\)

Hyperkalaemia has consistently been reported to be associated with an increased risk of death.\(^4\)–\(^6\) Few studies regarding the association between hyperkalaemia and mortality have been reported from Africa. A study from Rwanda reported an increased odds of death for hyperkalaemia in patients with AKI-requiring haemodialysis.\(^7\) A study from Ethiopia reported that hyperkalaemia was an independent predictor of in-hospital death in patients admitted to medical wards with AKI.\(^8\)

Although 70% of the world's human immunodeficiency virus (HIV) population lives in sub-Saharan Africa, there is a paucity of epidemiological data on hyperkalaemia in this population.\(^9\) Prevalence rates of 21% to 53% have been reported.\(^10\)–\(^13\) However, the true prevalence in hospitalised patients is unknown. Apart from NCDs in the HIV population, additional causes of hyperkalaemia are likely to be involved.

Due to the lack of epidemiological data from the African continent, we aimed to identify the frequency of hyperkalaemia in hospitalised adults, and to identify any risk factors for in-hospital death. Comparisons between HIV positive and negative patients were also performed as a secondary outcome.

### Methods

We conducted a retrospective, cohort study of all adult patients (18-years-old or more) admitted with or who developed hyperkalaemia (potassium concentration ([K]) of ≥ 5.5 mmol/L) during hospitalisation from 1 January 2019 to 31 December 2019. The study was conducted at Tygerberg Hospital, a 1380-bed tertiary hospital in Cape Town, South Africa, which provides services to approximately 2.5 million people from the Western Cape province. Patients were identified from the database of the National Health Laboratory Service, the national reference laboratory. Exclusion criteria included haemolysed specimens, pseudohyperkalaemia (considered to be present in patients with normal kidney function and normal serum creatine phosphokinase (CPK) concentrations who were not taking drugs that interfere with the renal elimination of K, and who had a platelet count of more than 500 x 10\(^9\)/L or a white cell count of more than 100 x 10\(^9\)/L), patients receiving kidney replacement therapy (chronic dialysis and kidney transplantation), outpatients and patients with diabetic ketoacidosis (DKA). Patients with DKA were excluded since these patients have a total body depletion of K despite hyperkalaemia at presentation and the infusion of insulin is used to treat the DKA rather than the hyperkalaemia. Using a 95% confidence interval, a margin of error of 5%, a population proportion of hospitalised patients with hyperkalaemia of 10%, and a total inpatient population of 52,000, the estimated sample size was 138.
Data were extracted from patient electronic records. These included demographic data, and data on comorbid diseases including kidney disease, HIV infection, hypertension, diabetes mellitus and heart disease. Kidney disease was categorised into AKI and CKD. We used the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) criteria for AKI and CKD was defined as an estimated glomerular filtration rate (eGFR by the CKD-EPI equation) of less than 60 mL/min/1.73 m² for at least three months. We captured information pertaining to treatment with acute dialysis and the dialysis modalities used. We also reported on the subgroup of dialysed AKI patients admitted to the intensive care unit (ICU). Data were captured on the chronic prescription and use during hospitalisation of angiotensin-converting enzyme inhibitors (ACEi’s), angiotensin receptor blockers and spironolactone, trimethoprim (TMP) and non-steroidal anti-inflammatory drugs. Laboratory data included the serum potassium concentration, serum creatinine concentration, CD4 count and serum CPK concentrations. Outcomes data included the length of hospital stay (LOHS) and in-hospital death.

Data captured regarding the acute pharmacological management of the hyperkalaemia included the use of calcium salts, insulin and dextrose doses, beta-2 agonist nebulisations, diuretics, resins such as sodium polystyrene sulphonate, cathartics and dialysis. In addition, we also documented the frequency of capillary blood glucose monitoring following insulin-based therapy and extracted data on adverse events, particularly hypoglycaemia (defined as a glucose concentration of < 4 mmol/L), when insulin-based therapy was used.

The study was conducted in accordance with the Declaration of Helsinki. Permission to conduct the research was approved by the Health Research Ethics Committee (HREC) of Stellenbosch University (HREC study number 10988). A waiver of informed consent was granted by HREC due to the retrospective study design.

Role of funding
This study was self-funded. All authors had full access to the data and agreed with the decision to submit for publication.

Statistical analysis
Analyses were performed using Stata version 16.1 (StataCorp LLC, Texas, USA). We used the Shapiro—Wilk test of normality. Numerical data with a normal distribution were described using means and standard deviations while non-normal data were reported as median and interquartile ranges. Histograms, bar charts and box-and-whisker plots were used where appropriate. Chi-squared or Fisher’s exact tests were used to compare categorical variables. Student’s t-test was used to compare continuous variables and, where the data were not normally distributed, the Mann-Whitney U test was used. Multivariable logistic regression was performed to identify predictors of in-hospital mortality and included the following covariates: [K], age, male sex, HIV positive status, hypertension, diabetes, heart disease, CKD, all KDIGO stages of AKI, acute therapy for hyperkalaemia and RAASi therapy. Multilinear regression was used to identify associations with the [K] and included the following covariates: age, male sex, HIV positive status, hypertension, diabetes, heart disease, CKD, all KDIGO stages of AKI, RAASi therapy and TMP. Pearson correlation matrix and variance inflation factors were used to examine for potential multicollinearity. Kaplan-Meier survival analyses were performed, and associated log-rank tests were determined. We considered a P-value of less than 0.05 to be statistically significant and 95% confidence intervals (CI) were used.

Results
A total of 3183 records were screened. Patients were excluded because of missing data (n = 117), if they were outpatients, including those on chronic dialysis (n = 927), and if they had DKA (n = 34) or pseudohyperkalaemia (n = 184). Therefore, 1921 patients were included in the final analysis. Five hundred and fifty-five patients (28.9%) died during hospitalisation.

During 2019, the total adult admissions were 52243. Thus, the calculated incidence rate of adult patients with hyperkalaemia was 3.7 per 100 patient-years and the period prevalence was 3.7%.

There were no differences in age, sex, HIV-positive status or heart disease between patients who died in hospital and patients discharged alive; however, fewer patients who died had hypertension (45.9% vs. 56.0%, P < 0.01) or diabetes (22.9% vs. 30.0%, P < 0.01). Patients with in-hospital death had more kidney disease (86.6% vs. 67.2%, P < 0.01). AKI was the most common type of kidney disease in both groups but was higher in patients with in-hospital death (69.2% vs. 41.3%, P < 0.01). Compared to those who survived, more patients who died presented with KDIGO stage 3 AKI (56.8% vs. 41.4%, P < 0.01). Mortality was higher for dialysed AKI patients admitted to the ICU as compared to patients managed in the general wards (72.0% vs. 28.8%, P < 0.01). More patients who were discharged alive were prescribed RAASi therapy as chronic medication prior to hospitalisation as well as during hospitalisation (31.2% vs. 42.9%, P < 0.01) of which ACEi’s were the most common (27.6% vs. 38.3%, P < 0.01) (Table 1).

The median [K] was higher in patients who died during hospitalisation (6.0 [IQR 5.7–6.6] mmol/L vs. 5.8 [IQR 5.6–6.1] mmol/L, P < 0.01). Patients who died during hospitalisation also had a higher proportion of patients with [K]’s of 6 mmol/L or more. Although less
Table 1: Comparison of baseline characteristics of hyperkalaemic patients with in-hospital death vs. those discharged alive.

Abbreviations: IQR, interquartile range; HIV, human immunodeficiency virus; AKI, acute kidney injury; ICU, intensive care unit; RAASi, renin-angiotensin-aldosterone system inhibitor; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; TMP, trimethoprim; NSAIDs, non-steroidal anti-inflammatory drugs; ART, antiretroviral therapy; [K], potassium concentration; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; AKI, acute kidney injury; CPK, creatine phosphokinase; LOHS, length of hospital stay.

| Demographic data | In-hospital death | P-value |
|------------------|-------------------|---------|
|                  | Yes n% = 555 (28.9) | No n% = 1366 (71.1) |
| Age, median (IQR) | 55 (39–67) | 54 (37–66) | 0.22 |
| Male, n%          | 315 (56.8) | 744 (54.5) | 0.36 |
| Comorbidities, n% |                   |         |     |
| HIV, n%           | 78 (14.1) | 187 (13.7) | 0.75 |
| Hypertension, n%  | 255 (45.9) | 765 (56.0) | <0.01 |
| Diabetes mellitus, n% | 127 (22.9) | 410 (30.0) | <0.01 |
| Heart disease, n% | 79 (14.2) | 189 (13.8) | 0.86 |
| Kidney disease, n% | 482 (86.4) | 918 (67.2) | <0.01 |
| AKI, n%           | 384 (69.2) | 564 (41.3) | <0.01 |
| Stage 1           | 90 (23.4) | 213 (37.8) | <0.01 |
| Stage 2           | 76 (19.8) | 117 (20.8) |         |
| Stage 3           | 218 (56.8) | 233 (41.4) |         |
| Number of AKI patients dialysed, n% | 33 (2.4) | 44 (3.2) | 0.08 |
| Dialysis modality for AKI patients, n% |         |         |     |
| Intermittent haemodialysis | 27 (81.8) | 41 (93.2) | 0.26 |
| Slow low efficiency daily dialysis | 6 (18.2) | 3 (6.8) |         |
| Type of ward for dialysed AKI patients: |         |         |     |
| General ward      | 15 (2.7) | 37 (2.7) | <0.01 |
| ICU               | 18 (3.2) | 7 (0.5) |         |
| Dialysis modality for AKI patients in the ICU, n% |         |         |     |
| Intermittent haemodialysis | 16 (88.9) | 5 (71.4) | 0.13 |
| Slow low efficiency daily dialysis | 2 (11.1) | 2 (28.6) |         |
| Chronic kidney disease, n% | 96 (17.3) | 352 (25.8) | <0.01 |
| Drugs associated with hyperkalaemia, n% |         |         |     |
| Any RAASi         | 173 (31.2) | 586 (42.9) | <0.01 |
| ACEi              | 153 (27.6) | 523 (38.3) | <0.01 |
| ARB               | 26 (4.7) | 62 (4.5) | 0.89 |
| Spironolactone    | 32 (5.8) | 119 (8.7) | 0.03 |
| TMP               | 13 (2.3) | 48 (3.5) | 0.18 |
| NSAIDs            | 22 (4.0) | 67 (4.9) | 0.37 |
| Other drugs, n%   |                   |         |     |
| ART               | 43 (7.7) | 112 (8.2) | 0.74 |
| Loop diuretics    | 148 (26.7) | 389 (28.5) | 0.40 |
| Thiazide diuretics | 68 (12.3) | 228 (16.7) | 0.02 |
| Clinical and laboratory data |         |         |     |
| [K] (mmol/L, median (IQR) | 6.0 (5.7–6.6) | 5.8 (5.6–6.1) | <0.01 |
| [K] categories, n% |                   |         |     |
| 5.5–5.9 mmol/L    | 243 (43.8) | 892 (65.3) | <0.01 |
| 6.0–6.9 mmol/L    | 220 (39.6) | 370 (27.1) |         |
| ≥7.0 mmol/L       | 92 (16.6) | 104 (7.6) |         |
| Overall creatinine (µmol/L, median (IQR) | 242 (125–520) | 137 (83–29) | <0.01 |
| eGFR (CKD) (mL/min/1.73m²), median (IQR) | 8.7 (4.2–22.4) | 19.4 (6.9–36.2) | <0.01 |
| Creatinine (AKI) (µmol/L, median (IQR) | 268 (147–526) | 185 (124–409) | <0.01 |
| CD4 count (cells/mm³), median (IQR) | 140 (60–340) | 189 (79–376) | 0.23 |
| CPK (IU/L, median (IQR) | 2958 (518–7869) | 2171 (450–7718) | 0.73 |
| LOHS (days), median (IQR) | 2 (0–7) | 8 (3–16) | <0.01 |
patients with in-hospital death had CKD, their median eGFR was lower (8.7 [IQR 4.2–22.4] mL/min/1.73 m² vs. 19.4 [IQR 6.9–36.2] mL/min/1.73 m², P < 0.01). Also, median serum creatinine concentrations at presentation were higher in patients with AKI who died during hospitalisation (268 [IQR 147–526] µmol/L vs. 185 [IQR 124–409] µmol/L, P < 0.01). In-hospital death occurred soon after the diagnosis of hyperkalaemia (2 [IQR 0–7] days) (Table 1).

More patients who died during hospitalisation received acute therapies (37.5% vs. 18.2%, P < 0.01). However, there were no differences between groups regarding those treated with insulin and dextrose therapy, salbutamol nebulisation, intravenous sodium bicarbonate, sodium polystyrene sulfonate and acute dialysis. More patients with in-hospital death had capillary blood glucose monitoring (38.6% vs. 23.7%, P < 0.01) and had more documented hypoglycaemic events (13.1% vs. 4.0%, P < 0.01) (Table 2).

In-hospital death was associated with age (odds ratio (OR) 1.03), [K] (OR 1.01), and eGFR was lower (8.9 [IQR 7–10] mL/min/1.73 m² vs. 19.4 [IQR 6.9–36.2] mL/min/1.73 m², P < 0.01). In-hospital death was associated with age (odds ratio (OR) 1.03), [K] (OR 1.01), and eGFR was lower (8.9 [IQR 7–10] mL/min/1.73 m² vs. 19.4 [IQR 6.9–36.2] mL/min/1.73 m², P < 0.01).

Table 2: Acute therapies for hyperkalaemic patients with in-hospital death vs. those discharged alive.

| Acute therapies | In-hospital death | P-value |
|-----------------|-------------------|---------|
|                 | Yes | No |
| Received acute therapy by in-hospital death, n% | 208 (37.5) | 249 (41.2) | <0.01 |
| [K] category, n% |     |     |
| 5.5–5.9 mmol/L | 53 (25.5) | 71 (28.5) | 0.70 |
| 6.0–6.9 mmol/L | 98 (47.1) | 111 (44.6) |     |
| ≥7 mmol/L | 58 (27.9) | 67 (26.9) |     |
| Calcium gluconate therapy, n% | 181 (87.0) | 216 (86.7) | 0.98 |
| Insulin therapy, n% | 176 (84.6) | 224 (90.0) | 0.06 |
| Insulin dose, n% |     |     |
| ≥10 units, n% | 170 (96.6) | 216 (96.4) | 0.52 |
| <10 units, n% | 8 (4.5) | 8 (3.6) | 0.47 |
| No. of insulin shifts, median (IQR) | 1 (1–1) | 1 (1–1) |     |
| 50% dextrose, n% | 183 (88.0) | 229 (91.9) | 0.09 |
| 50% dextrose volume, n% |     |     |
| 20 mL | 3 (1.6) | 7 (3.1) | 0.84 |
| 50 mL | 148 (80.9) | 185 (80.8) |     |
| 100 mL | 28 (15.3) | 35 (15.3) |     |
| 200 mL | 0 (0) | 1 (0.4) |     |
| Other* | 1 (0.5) | 1 (0.4) |     |
| Salbutamol, n% | 35 (16.8) | 30 (12.0) | 0.15 |
| Sodium bicarbonate, n% | 30 (14.4) | 25 (10.0) | 0.15 |
| Sodium polystyrene sulfonate, n% | 35 (16.8) | 52 (20.9) | 0.27 |
| Other cathartics, n% | 16 (7.7) | 35 (14.1) | 0.03 |
| Acute dialysis, n% | 27 (13.0) | 28 (11.2) | 0.57 |
| Capillary glucose monitoring, n% | 68 (38.6) | 53 (23.7) | <0.01 |
| Hypoglycaemic events, n% | 23 (13.1) | 9 (4.0) | <0.01 |

Abbreviations: [K], potassium concentration; IQR, interquartile range.

*Other: 200 mL 5% dextrose.

Figure 2 shows a regression analysis of the relationship between in-hospital death and the [K] after adjustment for age, sex, HIV positive status, hypertension, diabetes, heart disease, kidney disease, RAASI and TMP therapy. There was a progressive increase in the death rate within 24 hours of the hyperkalaemia diagnosis as the [K] range increased (Figure 3). AKI (Figure 4A), patients not prescribed RAASI therapy (Figure 4B), and acute therapy (Figure 4C) were associated with in-hospital death on Kaplan-Meier survival analysis; however, sex (log-rank P = 0.92), HIV positive status (log-rank P = 0.70), CKD (log-rank P = 0.72) and heart disease (log-rank P = 0.87) were not associated.

Regarding our secondary outcome, 13.8% (n = 265) of patients with hyperkalaemia were HIV positive. These patients were younger (39 [IQR 32–48] years vs. 55 (IQR 39–65) years, P < 0.01), mostly female (54.3% vs. 42.9%, P < 0.01), and had fewer NCDs (Table 4). Less HIV positive patients were using RAASI therapy (17% vs. 43.3%, P < 0.01); however, more received treatment with TMP (15.8% vs. 1.3%, P < 0.01). Regarding laboratory data, there were no differences between HIV positive and negative patients in [K], serum creatinine concentration at presentation or eGFR in CKD patients; however, the median creatinine concentration for patients with AKI was higher in the HIV positive group (368 [IQR 172–843] µmol/L vs. 225 (IQR 130–499) µmol/L, P < 0.01). There was no difference in in-hospital death between HIV positive and negative patients (29.4% vs. 28.4%, respectively, P = 0.75).

Discussion
This is the largest study to report on the frequency, risk factors, acute management, and mortality of hospitalised adult patients with hyperkalaemia from the African continent. We found a lower frequency of hyperkalaemia in hospitalised patients. A recent systematic review reported a prevalence of 8.6% and an incidence rate of 5.1 cases per 100 person-years for hospitalised patients when hyperkalaemia was defined as a [K] of more than or equal to 5.5 mmol/L.1 However, these frequencies included patients receiving kidney replacement therapy. No studies from the African continent reported on incidence, and only three reported on the prevalence of hyperkalaemia,13,15,16 ([K] ≥ 5.5 mmol/L), which was high at 36.7%. This is an overestimate since these studies were small and were convenience samples of patients at high risk for the development of
hyperkalaemia, such as patients with CKD, AKI, or a high burden of infectious disease. Our lower prevalence and incidence rates were probably the result of the inclusion all adult hospitalised patients, and the exclusion of patients with pseudohyperkalaemia, patients receiving kidney replacement therapy and patients with DKA.

We found high in-hospital mortality of 29%. Another study reported a similar mortality rate of 30%.\(^\text{17}\) A large meta-analysis reported that the risk of all-cause mortality was increased by 22% when hyperkalaemia was defined as a \([K]\) of more than 5.5 mmol/L.\(^\text{18}\) Recently, researchers using a propensity-matched cohort reported 29% higher odds of short-term all-cause mortality following a single episode of hyperkalaemia. We also found a progressive increase in mortality rate within the first 24 hours of the hyperkalaemia diagnosis (Figure 3). This was similar to another study in patients with CKD.\(^\text{4}\) Interestingly, patients without CKD had a higher risk of death across all \([K]\) ranges as compared to patients with stage 5 CKD. We speculate that our high mortality may be related to late presentation since kidney function was more severe in patients who died. Factors that may contribute to this

| Potassium concentration (mmol/L) | Coefficient | Standard error | t | P-value | 95% CI          |
|---------------------------------|-------------|----------------|---|---------|----------------|
| Age (years)                     | -0.001      | 0.001          | -0.91 | 0.37   | -0.004 to 0.001 |
| Male sex                        | 0.01        | 0.04           | 0.18 | 0.86   | -0.07 to 0.08   |
| HIV positive                    | -0.02       | 0.05           | -0.35 | 0.73   | -0.12 to 0.08   |
| Hypertension                    | -0.02       | 0.06           | -0.37 | 0.71   | -0.13 to 0.09   |
| Diabetes                        | 0.02        | 0.05           | 0.36 | 0.72   | -0.08 to 0.12   |
| Heart disease                   | -0.08       | 0.06           | -1.34 | 0.18   | -0.20 to 0.04   |
| CKD                             | 0.31        | 0.06           | 5.61 | <0.01  | 0.20 to 0.42    |
| AKI                             | 0.29        | 0.04           | 6.59 | <0.01  | 0.20 to 0.38    |
| Any RAASi                       | -0.07       | 0.05           | -1.37 | 0.17   | -0.17 to 0.03   |
| Trimethoprim                    | -0.04       | 0.09           | -0.42 | 0.67   | -0.22 to 0.14   |

Table 3: Multilinear regression for predictors of the potassium concentration.

Abbreviations: HIV, human immunodeficiency virus; RAASi, renin-angiotensin-aldosterone system inhibitor; CKD, chronic kidney disease; AKI, acute kidney injury.
Figure 2. Regression plot of the association between in-hospital death and [K] after adjustment for age, sex, HIV, hypertension, diabetes, heart and kidney disease, RAASi and trimethoprim therapy.

Solid black line represents the mean in-hospital death. Dashed lines represent 95% confidence intervals. Abbreviation: [K], potassium concentration.

Figure 3. Death rate within 24 hours of hyperkalaemia diagnosis.

Abbreviations: [K], potassium concentration. [K] 5.5-5.9 mmol/L, n = 243; [K] 6.0-6.9 mmol/L, n = 220; [K] ≥ 7 mmol/L, n = 92.
include accessibility, affordability, and availability of health services on account of rural domicile, poor access to transport and seeking initial healthcare from traditional healers.

Kidney disease was more common in patients who died and was mainly related to AKI. AKI was also the strongest predictor of death on regression analysis and was associated with severity of the hyperkalaemia. In addition, AKI was more severe at the time of presentation in patients who died. This may be related to late presentation. With public sector acute dialysis services in the province centralised to only two major centres, healthcare workers at peripheral hospitals may delay referral until dialysis initiation is imminent. At our centre, dialysis is initiated at the discretion of the treating nephrologist. As a result of resource constraints, traditional indications for dialysis initiation are used. A randomized trial reported higher 60-day mortality in AKI patients when a more delayed strategy to dialysis initiation was used.19 Oliguria for more than three days and serum urea concentrations greater than 40 mmol/L were predictors of death. Since more patients who died had KDIGO stage 3 AKI at the time of admission, late presentation rather than lack of dialysis services is a major factor for delayed dialysis initiation at our centre.

We have previously reported high in-hospital mortality rates for patients with AKI that was predominantly caused by infectious disease, trauma and pregnancy-related complications.20,21 Regardless of the cause, the abrupt loss of kidney function may be associated with a rapid rate of rise in the [K], which has been identified as a factor predisposing to cardiac arrhythmias and death.22,23

RAASi therapy use was less common among patients who died. An explanation for this may have been higher [K], which is frequently a rate-limiting factor for its use. However, since fewer were hypertensive, diabetic or had CKD, the prescription of RAASi therapy was less frequent. Therefore, despite continued RAASi therapy use in the face of hyperkalaemia, a mortality benefit was observed. This may highlight the importance of continuing RAASi therapy. A recent meta-analysis reported lower all-cause mortality and recurrent adverse kidney outcomes despite continued exposure to RAASi therapy after the onset of AKI.24 However, the risk of hyperkalaemia was higher when RAASi therapy was continued. Another study that investigated the association of RAASi therapy and all-cause mortality in patients with CKD reported a survival benefit in patients that continued RAASi therapy compared to those where therapy was discontinued.25 Hyperkalaemia was a common reason for its discontinuation. The decision to discontinue RAASi therapy may depend on several factors such as the rate at which hyperkalaemia evolves, the severity of hyperkalaemia, and associated comorbidities. We did not document the proportion of patients in which RAASi therapy was discontinued during hospitalisation. Novel potassium-binding resins, such as patiromer and sodium zirconium cyclosilicate, have allowed patients prone to hyperkalaemia to benefit from the continued use of RAASi-therapy.26,27 We do not have access to these novel resins. We speculate that access to these resins may have resulted in a lower

Figure 4. Kaplan-Meier survival analysis for the association between AKI (A), RAASi therapy (B) and acute therapy (C) and in-hospital death.

Abbreviations: AKI, acute kidney injury; RAASi, renin-angiotensin aldosterone system inhibitors; CI, confidence intervals.
Hypoglycaemia may occur up to six hours following insulin-based therapy.28 A systematic review found that hypoglycaemia may occur in as many as 18% of patients receiving insulin-based therapy for the treatment of hyperkalaemia and up to 30% when 25 g of dextrose is used.29 Since 90% of our cohort received treatment with 25 g dextrose, episodes of hypoglycaemia may have been missed.

Regarding the secondary outcome, approximately 14% of patients with hyperkalaemia were HIV positive. This proportion mirrors the national population prevalence of HIV infection of 13.1%.30 However, this proportion may be an underestimate since the HIV status was unknown in more than a third of our cohort. HIV-infected patients who died were younger,

| Demographic data          | HIV positive | HIV negative | P-value |
|---------------------------|-------------|--------------|---------|
| Age, median (IQR)         | 39 (32–48)  | 55 (38.5–64.5) | <0.01   |
| Male, %                   | 121 (45.7)  | 550 (57.1)    | <0.01   |
| Comorbidities, %          |             |              |         |
| Hypertension              | 6 (2.3)     | 549 (57.0)    | <0.01   |
| Diabetes mellitus         | 27 (10.2)   | 291 (30.2)    | <0.01   |
| Heart disease             | 16 (6.0)    | 136 (14.1)    | <0.01   |
| Kidney disease            | 180 (67.9)  | 701 (72.7)    | 0.11    |
| ARK                       | 135 (50.9)  | 468 (48.5)    | 0.48    |
| CKD                       | 44 (16.6)   | 232 (24.1)    | 0.01    |

| Drugs associated with hyperkalaemia, % | HIV positive | HIV negative | P-value |
|----------------------------------------|-------------|--------------|---------|
| Any RAASI                              | 45 (17.0)   | 418 (43.3)   | <0.01   |
| ACEi                                   | 42 (15.8)   | 382 (39.6)   | <0.01   |
| ARB                                    | 2 (0.7)     | 43 (4.5)     | <0.01   |
| Spironolactone                         | 7 (2.6)     | 85 (8.8)     | <0.01   |
| TMP                                    | 42 (15.8)   | 13 (1.3)     | <0.01   |
| NSAIDs                                 | 9 (3.4)     | 66 (6.8)     | 0.04    |
| Other drugs, %                         |             |              |         |
| ARVs                                   | 152 (57.4)  | N/A          | –       |
| Loop diuretics                         | 39 (14.7)   | 302 (31.3)   | <0.01   |
| Thiazide diuretics                     | 25 (9.4)    | 161 (16.7)   | <0.01   |

| Clinical and laboratory data           | HIV positive | HIV negative | P-value |
|----------------------------------------|--------------|--------------|---------|
| [K] (mmol/L), median (IQR)             | 5.8 (5.6–6.2) | 5.8 (5.6–6.3) | 0.81    |
| [K] categories, %                      |              |              |         |
| 5.5–6.9 mmol/L                         | 158 (59.6)   | 577 (60.0)   | 0.89    |
| 6.0–6.9 mmol/L                         | 81 (30.6)    | 284 (29.5)   | 0.31    |
| ≥7.0 mmol/L                            | 26 (9.8)     | 103 (10.7)   | 0.57    |
| Overall creatinine (µmol/L), median (IQR) | 174 (79–572) | 157 (91–414) | 0.38    |
| eGFR (KDOQ, mL/min/1.73m²), median (IQR) | 9.8 (3.7–31.3) | 15.3 (5.2–33.5) | 0.30    |
| Creatinine (AKI) (µmol/L), median (IQR) | 368 (172–843) | 225 (130–499) | <0.01   |
| CD4 count (cells/mm³), median (IQR)    | 181 (73–366) | N/A          | –       |
| LOHS from first hyperkalaemia (days), median (IQR) | 6 (2–14) | 7 (2–14) | 0.82   |
| In-hospital outcome                    |              |              |         |
| Died                                   | 78 (29.4)    | 274 (28.4)   | 0.75    |

Table 4: Comparison of baseline characteristics of hyperkalaemic patients with in-hospital death vs. those discharged alive by HIV status.

Abbreviations: IQR, interquartile range; HIV, human immunodeficiency virus; RAASI, renin-angiotensin-aldosterone system inhibitor; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; TMP, trimethoprim; NSAIDs, non-steroidal anti-inflammatory drugs; ART, antiretroviral therapy; [K], potassium concentration; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; AKI, acute kidney injury; CPK, creatine phosphokinase; LOHS, length of hospital stay.
predominantly female and had fewer NCDs. They were less likely to be prescribed RAASI therapy; however, more were using TMP, several of them being treated for *Pneumocystis jiroveci* pneumonia. Other diagnoses in the HIV-positive group included cervix carcinoma, lymphoma, Kaposi’s sarcoma and disseminated tuberculosis. There were no differences in mortality between HIV-positive and negative patients. Despite South Africa having the largest antiretroviral therapy (ART) programme in the world, patients continue to be diagnosed late as evidenced by the AIDS-defining diagnoses, low CD4 counts and the low proportion of patients using ART at admission. Again, the most common comorbidity in HIV patients associated with hyperkalaemia was AKI. Although there was no difference in the proportion of patients with AKI between the groups, the severity was greater in HIV patients, which might be related to late presentation.20

This is the largest study from the African continent to report on the frequency, risk factors, acute management, and mortality of hospitalised adult patients with hyperkalaemia. It is also the largest study describing the frequency, risk factors and outcomes of hyperkalaemia in patients with HIV infection. The exclusion of patients with pseudohyperkalaemia improved the accuracy of our findings. There were also some limitations. As a result of the retrospective design, there were missing data; however, data was considered to be missing completely at random since we were dependent on documents being scanned and placed onto the electronic platform. Since we used electronic data records, the quality of the available data varied. As a result of poor documentation, the underlying illness associated with AKI, which may have explained the strong association of AKI with in-hospital death, was not captured. We did not capture the prescription of beta-blocker therapy which may contribute to hyperkalaemia. Also, since this was a single-centre study, our findings may not be extrapolated beyond our clinical context.

In summary, this is the largest study reporting on the epidemiology of hyperkalaemia in hospitalised adult patients from Africa. Our in-hospital mortality was high. Hyperkalaemia in association with AKI was a strong predictor of in-hospital death. The prevalence of HIV was high but was similar to the national HIV prevalence. Late presentation to hospital may be a major factor contributing to poor outcomes, regardless of HIV status. Future prospective research should investigate whether earlier identification and treatment of patients with hyperkalaemia associated with AKI will improve outcome.

**Contributors**

MY Chothia: conceptualisation, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualisation, writing — original draft, and writing — review & editing. UMEC and MRD: conceptualisation, methodology, supervision, validation, writing — review & editing. AEZ: resources, validation, writing — review & editing. DM, NF, AW, EvV and TD: investigation, validation, writing — review & editing.

**Data sharing statement**

Deidentified individual participant data will be made available on request to the corresponding author, after fulfilling legal and regulatory requirements and with permission from the Health Research Ethics Committee of Stellenbosch University.

**Declaration of interests**

The authors declare that they have no competing interests.

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