

Risk factors and outcomes of sepsis-associated acute kidney injury in intensive care units in Johannesburg, South Africa

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Background. Sepsis-associated acute kidney injury (SA-AKI) has been shown to be a significant contributor to morbidity and mortality in both children and adults with critical illness. In sub-Saharan Africa, there is a lack of information on factors associated with development of SA-AKI and outcomes after intensive care unit (ICU) admission.

Objectives. To assess the rate of SA-AKI, factors associated with its development, and predictors of mortality at 90 days in critically ill patients admitted to the ICU with sepsis.

Methods. This was a prospective observational study conducted at two of the biggest teaching hospitals in Johannesburg, South Africa, from 15 February 2016 to 15 February 2020. The study included consecutive patients with confirmed sepsis who were admitted to the ICU within 24 hours of admission to hospital. The primary outcome of the study was development of SA-AKI (defined according to Kidney Disease Improving Global Outcome (KDIGO) criteria), and secondary outcomes were risk factors for SA-AKI and predictors of mortality at 90 days. Multivariate logistic regression analysis was employed to determine the factors associated with SA-AKI and 90-day mortality.

Results. In total, 327 critically ill patients with sepsis admitted to the ICUs were included in the study. The median (interquartile range) age was 39 (30 - 52) years, and 185 patients (56.6%) developed SA-AKI. Of these patients, blacks and whites comprised 91.0% and 6.1%, respectively, and the prevalent comorbidities were HIV/AIDS (19.3%), hypertension (14.2%) and diabetes mellitus (10.1%). Patients with SA-AKI were likely to be older and of male gender, and to have cardiovascular disease, malignancies, hypotension and a low serum albumin level. In multivariate analysis, the predictors of SA-AKI were age ≥ 55 years (odds ratio (OR) 2.43; 95% confidence interval (CI) 1.27 - 4.65), inotropic support (OR 3.61; 95% CI 2.18 - 5.96) and a low serum albumin level (OR 2.93; 95% CI 1.40 - 6.13). SA-AKI and need for inotropic support were respectively associated with 1.9-fold and 1.7-fold increased mortality at 90 days after ICU admission.

Conclusion. SA-AKI was found to be frequent in this study in two tertiary hospital ICUs in Johannesburg, and the need for inotropic support predicted mortality after ICU admission.

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Sepsis is a clinical condition in which the inflammatory response to an infection causes organ dysfunction distal to the primary site of infection.^[1] Sepsis-associated acute kidney injury (SA-AKI) has been shown to cause significant morbidity and mortality in both children and adults with severe illness.^[2,3] SA-AKI occurs in 35 - 70% of critically ill patients and increases both in-hospital morbidity and mortality.^[4] In the USA, a 22-year retrospective analysis of hospitalised patients from discharge records of non-federal acute care hospitals found that sepsis occurred at an annual rate of 13.7% of hospital admissions.^[5] In a single-centre retrospective cohort study in Asia in critically ill patients in the intensive care unit (ICU), the reported incidence of acute kidney injury (AKI) was nearly 55% and sepsis was the cause in 49% of cases.^[6] In a study in South Africa (SA) in HIV-positive patients, sepsis was the most common cause of AKI, in 60% of the patients,^[7] and in another study also conducted in SA in critically ill patients with AKI, ~41% of AKI was caused by sepsis.^[8]

There have been shown to be many risk factors for developing SA-AKI. In a meta-analysis that referenced 47 papers, it was noted that in patients diagnosed with sepsis or septic shock, hypertension, diabetes mellitus (DM), inotropic support and mechanical ventilation had 2.9-fold, 1.4-fold, 1.6-fold, 3.0-fold and 1.6-fold

odds ratios, respectively, for developing SA-AKI.^[9] In other studies, older age and low serum albumin levels (<35 g/L) were also found to be significant factors associated with SA-AKI.^[6,10] There are very few studies from Africa, and those that are available focused on elucidating the causes of AKI in critically ill patients and included SA-AKI as one of these causes.^[8,11]

For this reason, we conducted a study on SA-AKI in critically ill patients to determine the burden and associated risk factors in two tertiary centres in Johannesburg, SA. The study also investigated the influence of serum albumin, anaemia, underlying comorbidities and use of inotropes in critically ill patients admitted to ICUs in these two hospitals.

Methods

Study design, setting and population

This was a prospective observational study conducted in the ICUs of two tertiary teaching hospitals (Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBH)) in Johannesburg from 15 February 2016 to 15 February 2020. Ethical approval was obtained from the University of the Witwatersrand Human Research Ethics Committee

(ref. no. #M160901), and the study was conducted according to the Declaration of Helsinki. We recruited consecutive patients who were admitted to the multidisciplinary ICUs with a diagnosis of sepsis within 24 hours of admission to hospital. The inclusion criteria were adult patients aged ≥ 18 years with sepsis, and we excluded those with pre-existing kidney disease and those who did not give consent. CMJAH and CHBH are two of the largest hospitals in SA and are also the main teaching hospitals for the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg.

Study procedures

We evaluated the medical records and examined participants for risk factors for SA-AKI. Baseline information included age, gender, ethnicity, concomitant illness, including the Acute Physiology and Chronic Health Evaluation version II (APACHE II) score, need for assisted ventilation and inotropic support, and urine output. Baseline laboratory investigations that were recorded included a full blood count, kidney function, C-reactive protein and albumin levels and HIV status. Serum creatinine was analysed using Jaffe's reaction method and the estimated glomerular filtration rate using the modification of diet in renal disease equation.^[12]

Study definition and outcomes

Sepsis was defined according to the 2012 Surviving Sepsis guidelines,^[13] while SA-AKI was defined according to Kidney Disease Improving Global Outcomes (KDIGO) criteria.^[14] The primary outcomes of the study were the development of SA-AKI, the identification of associated risk factors, and 90-day mortality. The presence of hypertension, DM, malignancies and HIV was extracted from the patients' files, as was the APACHE II score.^[15] Hypoalbuminaemia was defined as a serum albumin level < 35 g/L.

Statistical analysis

Data were analysed using Stata version 13 (StataCorp, USA).

Continuous variables were expressed as means with standard deviations if normally distributed, and otherwise as medians with interquartile ranges (IQRs). Categorical variables were reported as percentages of the number of cases. The association of categorical variables with SA-AKI or mortality was performed using the χ^2 test. A Wilcoxon-Mann-Whitney test was employed to compare medians. Multivariate logistic regression analysis was employed to determine risk factors associated with development of SA-AKI and 90-day mortality. All factors that were significant at $p < 0.1$ in bivariate analyses were considered in a multivariate logistic regression analysis. The stepwise backward likelihood ratio variable selection method was used, with an enter probability of 0.05 and removal of 0.051. The unadjusted and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were reported.

Results

Baseline characteristics

After excluding 10 patients, 327 participants with sepsis were included in the study, and their characteristics are reported in Table 1. The median (IQR) age was 39 (32 - 52) years, 90.8% were black and 6.1% white, and 70.3% were male. The commonest underlying comorbidities were HIV/AIDS (19.3%), hypertension (13.2%) and DM (10.1%).

Rate of sepsis-associated AKI and associated factors

In total, 185 patients in the study (56.6%) developed SA-AKI. Patients with SA-AKI were likely to be male, to have DM, and to have underlying cardiovascular disease or a malignancy. Furthermore, they were likely to have a high APACHE II score, to be anaemic or hyperkalaemic, and to have a reduced bicarbonate level (Table 2). The sources of infections are shown in Table 3. In unadjusted analysis, age ≥ 55 years, male gender, inotropic support, DM, underlying malignancy, anaemia and hypoalbuminaemia (< 35 g/L) were found to be significantly associated with SA-AKI. In adjusted analysis, we

Table 1. Sociodemographic and clinical characteristics of intensive care unit patients with sepsis-associated AKI compared with those without

Characteristic	All (N=327), n (%)*	Sepsis, AKI (N=185), n (%)*	Sepsis, no AKI (N=142), n (%)*	p-value
Age (years), median (IQR)	39 (30 - 52)	45 (33 - 56)	35 (26 - 44)	0.001
Age ≥ 55 years	67 (20.5)	51 (27.6)	16 (11.3)	0.000
Male	230 (70.3)	121 (65.4)	109 (76.8)	0.026
Female	97 (29.7)	64 (34.6)	33 (23.2)	
Race				
Black	297 (90.8)	146 (88)	151 (94.4)	
White	20 (6.1)	14 (8.4)	5 (3.5)	
Indian	4 (2.0)	2 (1.2)	2 (1.4)	
Mixed race	6 (1.8)	4 (2.4)	1 (0.7)	
Comorbidities				
DM	33 (10.1)	24 (13.0)	9 (6.3)	0.049
Hypertension	43 (13.2)	29 (15.7)	14 (9.9)	0.123
Cardiovascular disease	11 (3.4)	10 (5.4)	1 (0.7)	0.019
HIV-positive	63 (19.3)	39 (21.1)	24 (16.9)	0.472
Malignancies	27 (8.3)	21 (11.4)	6 (4.2)	0.020
Drugs				
ACEIs	24 (7.3)	16 (8.7)	8 (5.6)	0.300
Diuretics	24 (7.3)	14 (7.6)	10 (7.0)	0.857
Inotropic use	134 (41.0)	102 (55.5)	32 (22.5)	< 0.001

AKI = acute kidney injury; IQR = interquartile range; DM = diabetes mellitus; ACEIs = angiotensin-converting enzyme inhibitors.
*Except where otherwise indicated.

Table 2. Clinical characteristics and laboratory parameters of intensive care unit patients with sepsis with and without AKI

Characteristic	All (N=327), n (%)*	Sepsis, AKI (N=185), n (%)*	Sepsis, no AKI (N=142), n (%)*	p-value
MAP <65 mmHg	12 (3.7)	10 (5.4)	2 (1.4)	0.056
Systolic BP (mmHg), median (IQR)	121 (109 - 138)	117 (106 - 133)	127 (113 - 142)	0.001
Diastolic BP (mmHg), median (IQR)	71 (60 - 83)	69 (60 - 80)	77 (66 - 88)	<0.001
Respiratory rate (breaths/min), median (IQR)	19 (12 - 25)	20 (15 - 26)	18 (14 - 24)	0.087
Temperature (°C), median (IQR)	36.9 (36.2 - 37.2)	36.8 (36.1 - 37.3)	37 (36.3 - 37.2)	0.692
Heart rate (bpm), median (IQR)	110 (93 - 126)	113 (95 - 127)	107 (89 - 125)	0.050
GCS, median (IQR)	7 (3 - 10)	6 (3 - 10)	8 (3 - 10)	0.877
SpO ₂ (%), median (IQR)	98 (95 - 100)	98 (94 - 99)	98 (96 - 100)	0.066
APACHE II score, median (IQR)	22 (17 - 28)	27 (22 - 32)	17.5 (13 - 20)	<0.001
Predicted death rate (%), median at enrolment (IQR)	42.4 (26.2 - 63.9)	60.5 (42.4 - 78)	26.6 (16.5 - 35.5)	<0.001
Fluid balance				
Input L/24 h, median (IQR)	1.9 (1.3 - 2.5)	1.94 (1.3 - 2.6)	1.9 (1.3 - 2.7)	0.624
Ventilation	273 (83.4)	152 (55.7)	121 (44.3)	0.462
Laboratory results				
WCC (× 10 ⁹ /L), median (IQR)	14 (9.8 - 20.2)	15 (9.7 - 21.7)	13.6 (9.4 - 18.5)	0.104
Hb (g/dL), median (IQR)	10.1 (8.3 - 12.6)	9.5 (8.1 - 12)	11 (8.9 - 12.9)	0.005
Anaemia (Hb <11 g/dL)	198 (60.6)	126 (63.4)	72 (36.4)	0.001
Platelet count (10 ⁹ /L), median (IQR)	181 (114 - 273)	180 (93 - 280)	187 (142 - 263)	0.229
Serum creatinine at enrolment (µmol/L), median (IQR)	142 (80 - 301)	271 (171 - 467)	79 (65 - 97)	<0.001
Urea at enrolment (mmol/L), median (IQR)	9.7 (5.3 - 19.4)	17.4 (11.1 - 21.1)	5.4 (4 - 6.9)	<0.001
Hypernatraemia (>145 mmol/L)	60 (18.4)	37 (20.0)	23 (16.2)	0.379
Hyperkalaemia (>5.5 mmol/L)	34 (10.4)	29 (15.7)	5 (3.5)	<0.001
Sodium (mmol/L), median (IQR)	140 (136 - 143)	140 (136 - 143)	140 (137 - 143)	0.774
Potassium (mmol/L), median (IQR)	4.4 (4 - 5)	4.6 (4 - 5.2)	4.3 (4 - 4.7)	0.001
Chloride (mmol/L), median (IQR)	102 (97 - 106)	101 (96 - 105)	103 (99 - 106)	0.004
Bicarbonate (mmol/L), median (IQR)	20 (16 - 24)	18 (14 - 21)	23 (20 - 25)	<0.001
CRP (mg/L), median (IQR)	215 (120 - 312)	238 (134 - 344)	189 (104 - 293)	0.001
Hypoalbuminaemia (<35 g/L)	287 (87.8)	172 (59.9)	115 (41.1)	0.001
Death at 90 days	127 (38.8)	88 (69.3)	39 (30.7)	<0.001

AKI = acute kidney injury; MAP = mean arterial pressure; BP = blood pressure; IQR = interquartile range; GCS = Glasgow Coma Score; SpO₂ = oxygen saturation; APACHE II = Acute Physiology and Chronic Health Evaluation version II; WCC = white cell count; Hb = haemoglobin; CRP = C-reactive protein.
*Except where otherwise indicated.

Table 3. Sources of infection

Source	All (N=327), n (%)	Sepsis, AKI (N=185), n (%)	Sepsis, no AKI (N=142), n (%)
Gastrointestinal	97 (29.7)	67 (36.2)	30 (21.1)
Other	96 (29.4)	68 (36.8)	28 (19.7)
Trauma	79 (22.9)	16 (8.7)	59 (41.6)
Respiratory	41 (12.5)	24 (13.0)	17 (12.0)
Neurological	10 (3.1)	3 (1.6)	7 (4.9)
Renal	3 (0.9)	3 (1.6)	0
Obstetrics and gynaecology	3 (0.9)	2 (1.0)	1 (0.7)
Cardiovascular	2 (0.6)	2 (1.1)	0

AKI = acute kidney injury.

found that age ≥55 years (OR 2.43; 95% CI 1.27 - 4.65; *p*=0.008), use of inotropes (OR 3.61; 95% CI 2.18 - 5.96; *p*<0.001) and the presence of hypoalbuminaemia (OR 2.93; 95% CI 1.40 - 6.13; *p*=0.004) increased the likelihood of SA-AKI, as shown in Table 4.

SA-AKI and mortality

The overall mortality at 90 days after ICU admission was 38.8%. In multivariate analysis, SA-AKI and inotropic support were associated with mortality at 90 days (OR 1.97; 95% CI 1.20 - 3.22; *p*=0.007 and OR

1.74; 95% CI 1.08 - 2.83; *p*=0.023, respectively), as shown in Table 5.

Discussion

Our study assessed the burden of SA-AKI and related risk factors and outcomes in the ICUs at two of the largest hospitals in SA. The study showed a high rate of SA-AKI in patients with sepsis at 56.6%, and the predictors were age ≥55 years, inotropic support, and the presence of low serum albumin (<35 g/L). The predictors of 90-day mortality were SA-AKI and need for inotropic support.

Table 4. Independent predictors of sepsis-associated AKI

Characteristic	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Age >55 years	2.04	1.04 - 4.01	0.039	2.43	1.27 - 4.65	0.008
DM	2.20	0.99 - 4.90	0.053	1.71	0.73 - 3.98	0.217
Malignancies	2.90	1.13 - 7.39	0.026	2.11	0.79 - 5.61	0.134
Inotropic support	3.49	2.10 - 5.80	<0.001	3.61	2.18 - 5.96	<0.001
Hypoalbuminaemia (<35 g/L)	2.79	1.30 - 5.97	0.008	2.93	1.40 - 6.13	<0.004

AKI = acute kidney injury; OR = odds ratio; CI = confidence interval; DM = diabetes mellitus.

Table 5. Independent predictors of mortality

Characteristic	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
SA-AKI	2.34	1.47 - 3.74	<0.001	1.97	1.20 - 3.22	0.007
Inotropic support	2.15	1.36 - 3.39	<0.001	1.74	1.08 - 2.83	0.023
Age >55 years	1.51	0.93 - 2.77	0.083	1.23	0.70 - 2.18	0.463
DBP	0.98	0.97 - 0.99	0.006	0.99	0.97 - 1.00	0.090
SBP	0.98	0.96 - 0.99	0.031	1.00	0.98 - 1.02	0.899

SA-AKI = sepsis-associated acute kidney injury; OR = odds ratio; CI = confidence interval; DBP = diastolic blood pressure; SBP = systolic blood pressure.

The rate of SA-AKI in the ICU patients in our study was higher than that reported in previous studies.^[16] In a retrospective study of 19 579 patients conducted in Beijing, the rate of SA-AKI in patients with sepsis was 48.1%.^[17] Additionally, a review of ICU patients from Australia and New Zealand found a rate of 42.1%.^[18] A recent analysis of ICU data on patients with sepsis from the Medical Information for Intensive Care III (MIMIC-III) study in the USA found a rate of 40.0%.^[19] The high rate of SA-AKI in our study may be explained by the frequency of underlying comorbidities and the fact that almost three-quarters of the patients with SA-AKI were aged >55 years. Another relevant factor could be that a lack of resources relative to the developed world may mean that sicker patients are admitted. Critically ill patients are generally exposed to invasive monitoring devices and catheters and are frequently mechanically ventilated, both of which may predispose them to sepsis and therefore SA-AKI. Previous studies have also reported a positive link between SA-AKI and older age.^[17,20]

In the present study, age \geq 55 years correlated positively with SA-AKI, and this finding was comparable to previous studies.^[21,22] An analysis of 39 938 ICU patients in a large tertiary care university hospital system in the USA found that older patients had a higher incidence of AKI compared with those aged <55 years.^[23] In this study, patients aged >75 years had a rate of AKI 20% higher than those aged <55 years.^[23] The probable reason for this finding is that older age is associated with a greater likelihood of underlying comorbidities, as evidenced in the present study, where nearly 55% had comorbidities. Furthermore, there is evidence that elderly patients are more likely to have underlying age-related kidney damage.^[10]

The presence of a low serum albumin level had a positive association with development of SA-AKI in our study, a result consistent with previous studies.^[24,25] In patients undergoing coronary artery bypass grafting, the AKI group had slightly lower albumin levels compared with controls (39 g/L v. 40 g/L, respectively), and 45% of the patients with low albumin developed AKI.^[26] Similarly, in the MIMIC-III study of critically ill patients with sepsis, low albumin (<30 g/L) was associated with 1.33-fold increased odds of SA-AKI.^[19] The explanation is probably that albumin is a negative acute-phase reactant that correlates with severity of sepsis, and critically ill patients develop capillary leak with loss of albumin into the interstitium.^[27-29]

The need for inotropic support predicted SA-AKI and mortality in the present study. This finding has also been observed in a meta-analysis that included 42 studies of patients with sepsis,^[10] in which administration of vasopressor therapy was associated with a 3-fold increase in the odds of developing SA-AKI.^[10] This finding is likely to be related to the fact that patients on inotropes have had hypotensive episodes and have had more severe disease. In other studies, vasopressor use was also associated with an increased odds of mortality (OR 1.75).^[16] Studies have also shown that patients with sepsis who develop AKI are more likely to have required inotropic support compared with those with sepsis who have not developed AKI.^[16,22,30]

In the present study, SA-AKI was associated with mortality at least twice as high at 90 days as in patients with sepsis only (69.3% v. 30.7%), and SA-AKI was also associated with a 1.9-fold increase in the odds of death at 90 days. This finding is consistent with previous studies that have examined SA-AKI and its outcomes. In a multicentre retrospective review of data from the Australia and New Zealand Intensive Care Society Adult Patient Database, Bagshaw *et al.*^[18] observed a high ICU and hospital mortality rate in patients with SA-AKI at 30.0% and 20.0%, respectively, compared with those with AKI from other causes at 22.0% and 13.4%, and 13.0% and 7.5% in those with sepsis only.^[18] A study in SA that was limited to critically ill ICU patients also showed increased mortality in those with AKI v. those without (20.5% v. 2.3%).^[31]

This prospective study has shown important confirmatory findings relevant to a tertiary hospital in Africa. Although the sample size was adequate, there are some limitations. The sample was drawn from mixed ICUs at only two centres, which may mean that the data are not representative of other centres in Africa. Similarly, outcomes could have been influenced by specific management practices. Thirdly, vital information on renal replacement therapy and its mode and intensity was not collected, and dialysis could have had an influence on outcomes.

Conclusion

We have demonstrated that the rate of SA-AKI was high in our critically ill population, and that development of SA-AKI was associated with older age (>55 years), hypoalbuminaemia and need for inotropic support. SA-AKI has previously been shown to be a risk

factor for mortality. There is, however, a need to find new biomarkers that will identify patients at risk of developing SA-AKI, so that appropriate measures can be instituted early to improve outcomes. There is also a need for more studies from Africa to investigate and categorise the prevalence of SA-AKI in critically ill patients.

Declaration. The research for this study was done in partial fulfilment of the requirements for MDM's PhD degree in nephrology at the University of the Witwatersrand.

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Author contributions. MDM: conceptualised the research, collected data, participated in data analysis and write-up; CD, GP and GAR participated in conceptualisation, supervision, editing and review; JB: was involved in formal analysis, write-up and review of the research.

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Conflicts of interest. None.

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