

ORIGINAL ARTICLE

An observational study of acute kidney injury in critically ill neonates at Chris Hani Baragwanath Academic Hospital, South Africa

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ABSTRACT

Background: Acute kidney injury (AKI) is common in critically ill, hospitalised neonates. Epidemiological data on AKI in children are scarce in South Africa. This study aimed to determine the incidence and outcomes of AKI in critically ill neonates.

Methods: This single-centre, prospective, observational study was conducted in the neonatal unit of the Chris Hani Baragwanath Academic Hospital, a tertiary-level hospital in Johannesburg, South Africa. Neonates with AKI, defined using the AKI Network criteria, were recruited over a three-month period in 2019. Risk factors and demographic data were collected for all study participants, who were followed up over the period to observe an outcome of either recovery or death.

Results: Fifty-one cases of AKI were identified, representing 7.8% of all admissions (95% CI 5.9–10.2%). The overall mortality of enrolled patients was 29.4% (95% CI 26.3–56.1%). Mortality was significantly associated with extremely low birth weight (OR 11.4, $p < 0.01$), umbilical catheterisation (OR 6.3, $p = 0.01$), sepsis (OR 5.4, $p = 0.01$), phototherapy (OR 4.4, $p = 0.03$) and prematurity ($p = 0.04$). The most frequent risk factor associated with AKI was intravenous nephrotoxic medication.

Conclusion: The incidence of AKI in our study was higher than expected. Further epidemiological and interventional studies are warranted to identify and improve the long-term outcome of AKI in the newborn in our setting.

Keywords: acute kidney injury; neonate; incidence; mortality.

INTRODUCTION

Acute kidney injury (AKI) is a condition characterised by the rapid decline in the ability of the kidneys to maintain homeostasis of water and electrolytes, resulting in a reduction of the glomerular filtration rate (GFR) and accumulation of nitrogenous waste [1]. The diagnosis of AKI poses many challenges, especially in the neonatal period. The diagnosis of AKI is difficult if a baseline serum creatinine value is not available. Prior to 2007, most neonatal studies defined AKI as a rise in serum creatinine (SCr) of $\geq 132 \mu\text{mol/L}$, but since then it was noted that even a small increase in SCr is associated with a poor outcome [2]. New criteria were then introduced, based

on SCr and urine output (UOP). Currently, there are three systems for classifying AKI in neonates, namely, the Acute Kidney Injury Network (AKIN) criteria, outlined in Table 1; neonatal Risk, Injury, Failure, Loss, End-stage (nRIFLE) criteria; and the neonatal Kidney Disease: Improving Global Outcomes (nKDIGO) criteria [3]. The classifications characterize AKI into stages based on an increase in SCr and a decrease in UOP [4]. The criteria proposed by AKIN define AKI based on the increase in SCr and the decrease in UOP. Three stages exist according to increasing severity from stage 1 to stage 3. The nRIFLE criteria, modified by Ackan-African et al., are

Table 1. AKIN classification.

	Stage	SCr/GFR criteria	UOP criteria
AKIN	1	SCr increase >26.5 $\mu\text{mol/L}$ or >1.5 – 2 times baseline	<0.5 mL/kg/h for 6 h
	2	SCr increase >2 – 3 times baseline	<0.5 mL/kg/h for 12 h
	3	SCr increase >3 times baseline or SCr >354 $\mu\text{mol/L}$ with acute increase >44.2 $\mu\text{mol/L}$	<0.3 mL/kg/h for 24 h or anuria for 12 h

SCr, Serum creatinine; GFR, glomerular filtration rate; UO, urine output; AKIN, acute kidney injury network.

based on the decrease in the estimated creatinine clearance and the urine output [4]. Three levels of kidney injury (risk, injury, failure) and two outcomes (loss of kidney function and end-stage kidney failure) have been graded according to the RIFLE criteria [4]. In 2013, the KDIGO clinical practice guidelines work-group proposed and published a definition combining AKIN and RIFLE aspects, thereby providing one tool used both in clinical practice and research [5]. Additionally, KDIGO classifications use a SCr rise in baseline level over 7 days, whereas AKIN includes similar rises in 48 hours.

Using SCr alone to diagnose AKI in neonates has its limitations. After birth, neonatal SCr reflects maternal levels and over weeks declines at varying rates, depending on gestational age, therefore changes in SCr may be difficult to interpret when evaluating AKI [6]. The postnatal decline in serum creatinine, due to changes in glomerular haemodynamics, is less marked in preterm neonates [7]. Non-invasive biomarkers of AKI, such as interleukin 8 and cystatin C, can predict AKI before SCr rises, but these tests are not widely available and have not been validated in paediatrics in our setting [5,6].

The risk of AKI is increased in neonates [8], with the pre-term infant particularly at risk due to incomplete nephrogenesis and immature tubular development [5]. AKI is common in critically ill, hospitalised neonates worldwide, with an incidence that ranges from 2.5% to 74.1% in the Assessment of Worldwide Acute Kidney Epidemiology in Neonates (AWAKEN) database [9]. It is associated with increased mortality and morbidity, increased risk for progression to chronic kidney disease and longer hospital stay [9]. The most common risk factor for AKI is sepsis. Other risk factors include hypovolemia secondary to dehydration, hypoxia secondary to respiratory distress syndrome, patent ductus arteriosus, asphyxia, renal venous thrombosis, nephrotoxic medications, intraventricular haemorrhage and necrotizing enterocolitis [1,8].

Multiple studies have reported the incidence of AKI together with risk factors and outcomes, especially in the high-income countries [10]. However, there are scarce epidemiological data on AKI in children in middle- and low-income countries, particularly in Africa. A review by Lameire et al. on AKI in children worldwide found only 21 African studies on paediatric AKI between 2000 and 2014 [10]. A systematic review of AKI in sub-Saharan Africa in 2016 identified 22 studies in children [11].

The study reported here aimed to identify the incidence and outcomes of AKI and observe the risk factors in critically ill neonates over a three-month period at Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto, South Africa.

METHODS

Study design

This single-centre, prospective, observational study was conducted over a three-month period in the neonatal intensive care unit (NICU) and transitional intensive care unit (TICU) of the tertiary-level Chris Hani Baragwanath Academic Hospital.

The study was performed in partial fulfilment of the Master of Medicine (MMed) degree at the University of the Witwatersrand, Johannesburg. Ethical clearance was obtained from the university's Human Research Ethics Committee (clearance certificate M180724).

Population and setting

Over the three-month period, between 1 June–31 July and 1 September–30 September 2019, patients admitted to the units were screened daily for AKI. Bedletters were reviewed daily to identify patients who had an abnormal serum creatinine as per blood tests requested by the attending doctors. Blood sampling was discontinued once a satisfactory reduction in SCr was observed by the attending physicians. Patients were recruited once consent was obtained.

Exclusion criteria included having the AKI diagnosis before the time of data collection, being aged older than 28 days, and having parents or guardians who did not provide consent. Demographic data were collected for all the study participants. Written informed consent was obtained from the parents or guardians.

The NICU at CHBAH is an 18-bed unit with approximately 50 admissions per month, whereas the TICU, which is a neonatal high-care unit with a 48-bed capacity including a six-bed surgical high-care facility, receives about 200 neonatal admissions per month. Patients 1000 g and above are offered invasive ventilation, while those weighing less than 1000 g are offered non-invasive ventilation.

Study patients were followed up within the three-month period until an outcome of either recovery or death was observed. If patients were recruited in June or July, they were followed until the end of July; if recruited in September, they were followed until 30 September.

Definitions

Neonatal AKI was diagnosed by the rise in serum creatinine and classified using AKIN criteria (Table 1). Urine output was not used as neonates typically have non-oliguric renal failure [6]. Additionally, urine measurement requires urinary catheterisation, which is invasive, and nappy weighing has proved to be inaccurate [2,7]. Patients were also enrolled if the baseline serum creatinine value was $\geq 132 \mu\text{mol/L}$ and classified into one of the AKIN stages based on the upper limit of the local neonatal SCr reference intervals obtained from the National Health Laboratory Service (NHLS). Spurious SCr results due to delays in specimen processing were not included in the analysis.

Risk factors were defined using the CHBAH Neonatal Protocols of Nakwa et al. [12]. Sepsis was defined as confirmation of a microorganism on a positive blood culture. Hypotension was defined as a mean arterial pressure (MAP) of <10th percentile for age, gestation or birth weight, subsequently requiring inotropic support. Hypoxaemia was characterized by those neonates requiring supplemental oxygen. Asphyxia was defined as a 5-minute Apgar score of <5 or a blood gas test within 1 hour of life with a pH <7.0. Nephrotoxic medications noted were gentamicin, vancomycin, amphotericin B or colistin. Umbilical lines included a venous line and/or an arterial line. Surgical patients included all subspecialties except cardiothoracic surgery.

Extremely low birth weight (ELBW) was defined as a birth weight of less than 1000 g, very low birth weight (VLBW) in the range 1000–1499 g, low birth weight (LBW) between 1500–2499 g, and normal birth weight between 2500–3999 g. Prematurity was defined as a gestational age of less than 37 completed weeks at birth.

Although there are limitations when defining recovery of AKI, more so in the paediatric population, we used Forni et al. and defined full recovery as the absence of AKI criteria from baseline and partial recovery as a fall in AKI stage [13]. For those patients with an initial SCr of more than 132 $\mu\text{mol/L}$ and no baseline, partial recovery was defined as a reduction in SCr of at least 30% and full recovery as those whose SCr fell within normal neonatal SCr ranges. Outcome was either recovery or death. Final SCr was the last SCr record at death or recovery. Some patients went straight from having AKI to full recovery. Others achieved partial recovery and no further blood sampling was con-

ducted as per the instructions of the neonatologists in charge.

Serum creatinine was analysed by the National Health Laboratory Service using the enzymatic reaction method of the Roche/Hitachi Cobas C analyser. Serum creatinine was measured on day two of life, to remove the effect of maternal creatinine.

Statistical analysis

A sample size of 45 was estimated to be required to detect an incidence of 3% in a population of 10 000 live births if a 5% margin of error was accepted and a 95% confidence level. This sample size was recognised to be insufficient to explore risk factors and associations. Incidence and mortality rate were accompanied by a 95% confidence interval (95% CI). A value of $p < 0.05$ was considered statistically significant. Categorical variables were expressed as percentages and frequencies. Continuous variables, depending on the normality of distribution, were expressed as means \pm standard deviation (SD) or medians with interquartile range (IQR). Differences between categorical variables were calculated using the chi-squared test or Fischer's exact test. A univariate logistic regression was used for the association between risk factors and mortality, and results of the analysis were expressed as odds ratios with a 95% CI. STATA version V16 was used for all data analysis.

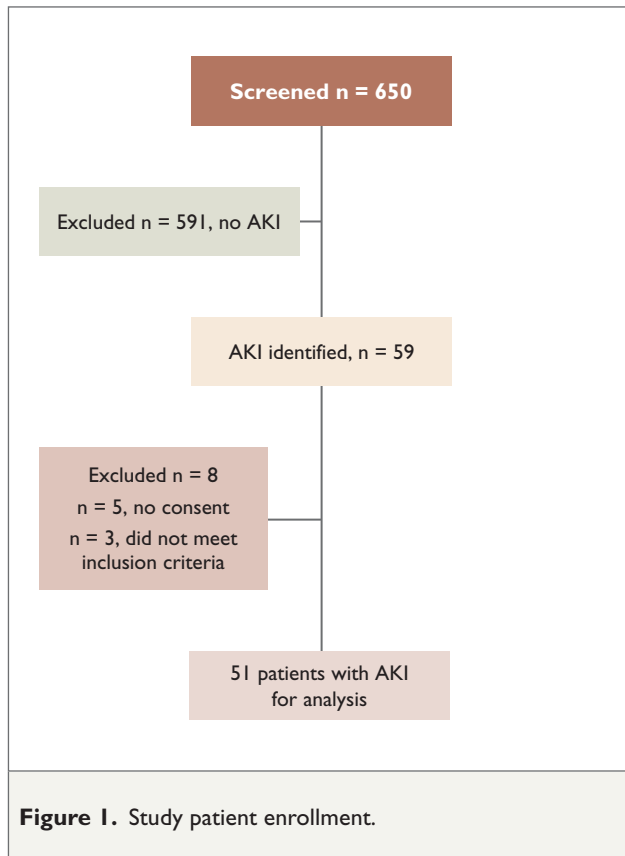
RESULTS

Incidence of AKI

Over the three-month duration of the study, 650 patients were screened as consecutive admissions to the TICU and NICU, and of these admissions 59 patients were diagnosed with AKI. Eight were excluded from the study: three did not meet the inclusion criteria, and consent was not obtained for five patients, so that 51 patients were used in the final analysis (Figure 1). The incidence of AKI in critically ill neonates at CHBAH over a three-month period was 7.8% (95% CI, 5.9–10.2%).

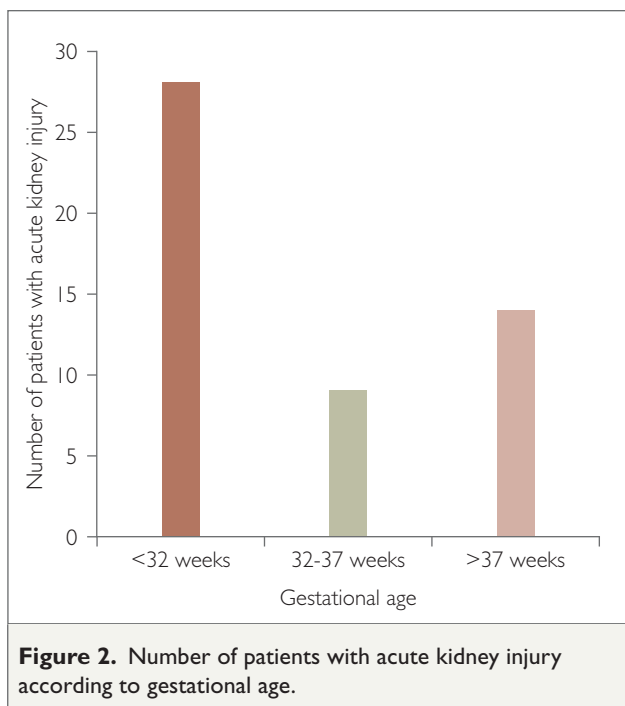
Patient characteristics

Table 2 summarizes patient characteristics. Of the 51 neonates enrolled, 27 (53%) were male. The median (IQR) gestational age was 32.0 (27–37) weeks, the median (IQR) birth weight was 1220 (905–2490) g. The mean (SD) serum creatinine at diagnosis was 142.9 (39.7) $\mu\text{mol/L}$. The median (IQR) final SCr at outcome was 71 (53–113) $\mu\text{mol/L}$. Of the 51 patients, 19 had an initial SCr of $\geq 132 \mu\text{mol/L}$ and were staged using the NHLS normal reference value for age. According to the AKIN criteria, 36 (71%) patients were classified as stage 1 AKI, 12 (24%) as stage 2, and three (6%) patients as stage 3 AKI. Eighteen (35%) of the patients were ELBW neonates and 37 (73%) were pre-

**Table 2. Acute kidney injury patient characteristics.**

Characteristic	Acute kidney injury (N = 51)
Male sex, n (%)	27 (52.9)
Birth weight (g), median (IQR)	1220.0 (905-2490)
<1000, n (%)	18 (35.3)
1000–1499, n (%)	10 (19.6)
1500–2499, n (%)	11 (21.5)
2500–4000, n (%)	12 (23.5)
Gestational age (weeks), median (IQR)	32.0 (27-37)
<26, n (%)	4 (7.8)
26–32, n (%)	24 (47.1)
>32–37, n (%)	9 (17.6)
>37, n (%)	14 (27.5)
Lowest pre-AKI creatinine (μmol/L), mean (SD)	107.4 (±43.2)
Diagnosis creatinine (μmol/L), mean (SD)	142.9 (±39.7)
Final creatinine (μmol/L), median (IQR)	71 (53-113)
AKI stage	
Stage 1, n (%)	36 (70.6)
Stage 2, n (%)	12 (23.5)
Stage 3, n (%)	3 (5.9)

AKI, acute kidney injury; SD, standard deviation; IQR, interquartile range.



mature. Figure 2 shows the distribution of gestational age, with 28 (55%) patients less than 32 weeks' gestation. The median (IQR) age at diagnosis of AKI was three (2–5) days. Forty-five (88%) patients developed AKI in the first week of life, three (6%) in the second week, two (4%) in the third week and one (2%) in the fourth week.

Outcomes

The end points of follow-up were defined as recovery or death: 36 (71%) patients recovered, and 15 (29%) died. All patient outcomes occurred within the three-month study period, including those identified late in the study. Follow-up was concluded at death, recovery or discharge. The median (IQR) follow-up time was six (5.0–11.0) days. The mean (SD) SCr value at recovery was 59.7 (18.2) μmol/L, and the median (IQR) SCr at death was 159 (116–213) μmol/L. The median (IQR) time to recovery was seven (5.0–11.5) days and the mean (SD) time to death was 6.1 (2.5) days.

Of those in stage 1 AKI, eight (22%) died, in stage 2 AKI six (50%) died, and in stage 3 AKI one patient (33%) died. The severity of AKI is an independent risk factor for poor outcome [6]. This could not be analysed in this study owing to the small sample size, with only three patients in stage 3.

Of the 36 babies in the recovery group, 29 (81%) made a full recovery and seven (19%) made a partial recovery. The overall mortality in the enrolled patients was 15 of 51 (29%). However, of those who died, five (33%) showed recovery of GFR before death. The cause of death in these patients was not directly related to AKI.

Of the 10 patients who died without renal recovery, seven (70%) had ELBW, one (10%) had severe intraventricular haemorrhage, one (10%) demonstrated severe hypoxic

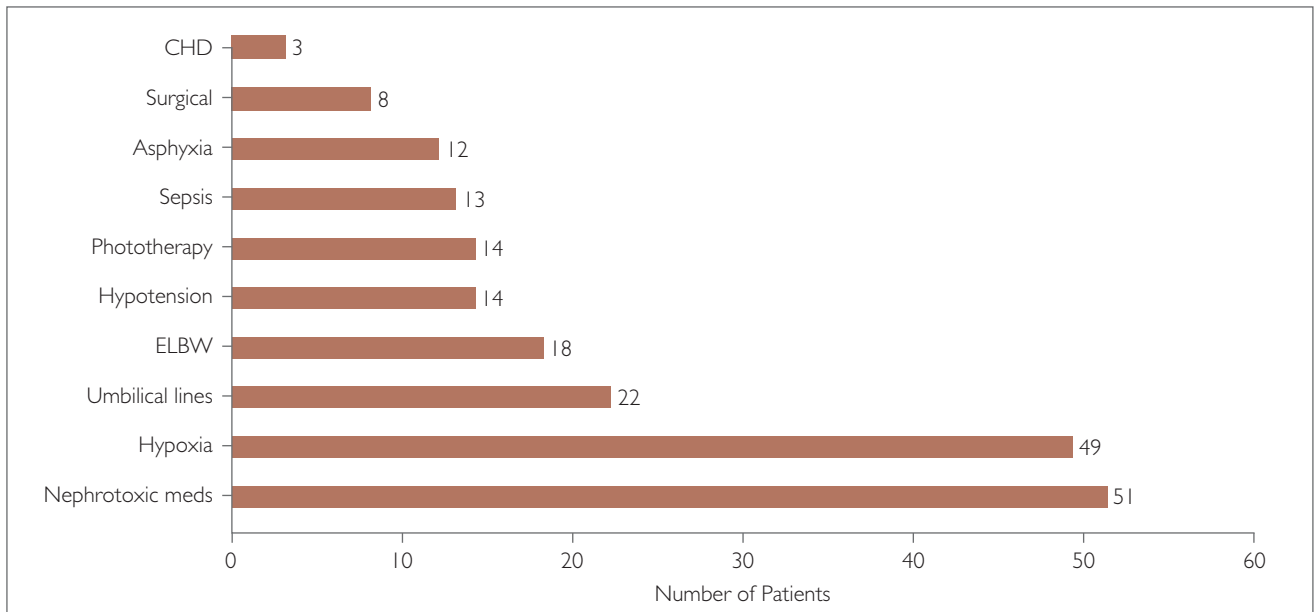


Figure 3. Patient risk factors for acute kidney injury.

CHD, congenital heart disease; ELBW, extremely low birth weight.

Table 3. Risk factors for mortality in neonates with acute kidney injury, by outcome group.

Risk factor	Recovered (N=36) n (%)	Died (N=15) n (%)	p value	Odds ratio, 95% CI
Sepsis	5 (13.9)	7 (46.7)	0.01	5.4 (1.4–21.7)
Hypotension	9 (25.0)	5 (33.3)	0.54	1.5 (0.4–5.6)
Hypoxia	35 (97.2)	15 (100)	1.00	N/A
Asphyxia	4 (11.1)	4 (26.7)	0.16	2.9 (0.6–13.7)
Nephrotoxic drugs	36 (100)	15 (100)	0.31	N/A
Umbilical lines	11 (30.5)	11 (73.3)	0.01	6.3 (1.6–24.0)
ELBW	7 (19.4)	11 (73.3)	0.001	11.4 (2.8–46.7)
Phototherapy	6 (16.7)	7 (46.7)	0.03	4.4 (1.1–16.7)
CHD	3 (8.3)	0 (0)	0.55	N/A
Surgical	6 (16.7)	0 (0)	0.16	N/A
Prematurity	23 (63.9)	14 (93.3)	0.04	7.9 (0.9–67.2)

ELBW, extremely low birth weight; CHD, congenital heart disease; N/A, unable to assess odds ratio as 100% of patients had the risk factor or there was very little difference between groups.

ischaemic encephalopathy and one (10%) died before dialysis could be initiated. The impact on mortality could not be assessed since there was no control group to compare. None of the patients received kidney replacement therapy.

Risk factors

All enrolled patients had more than one known risk factor identified. The most common risk factor associated with AKI was intravenous nephrotoxic medication, with gen-

tamicin being the most widely used. The second-most common risk factor was hypoxia, as 49 (96%) patients required supplementary oxygen at birth (Figure 3). The group that died had a mean (SD) of 5.1 (0.7) risk factors per patient compared to 3.4 (1.1) for those who recovered ($p < 0.001$). Table 3 summarizes the individual risk factors per outcome group. A univariate logistic regression was used for the association between all risk factors and mortality. The risk factors significantly associated with mortality were ELBW (OR 11.4, 95% CI 2.8–46.7, $p < 0.001$),

umbilical lines (OR 6.3, 95% CI 1.6–24.0, $p = 0.01$), sepsis (OR 5.4, 95% CI 1.4–21.7, $p = 0.01$), and phototherapy (OR 4.4, 95% CI 1.1–16.7, $p = 0.03$). Twelve (92%) of the 13 patients who received phototherapy were premature. More premature patients with AKI died than term neonates (38% vs 7%, $p = 0.04$).

DISCUSSION

The incidence of AKI in critically ill neonates varies and has been reported to differ at multiple centres [9], with Momtaz et al. recording an incidence as low as 1.5% in their study [1] and Shalaby et al. reporting an incidence as high as 54% in a tertiary NICU in Saudi Arabia, a high-income country, using the nKDIGO classification [8]. The difference in incidence varies according to the population studied and definitions used [8,14], therefore we need a consensus regarding the definition of neonatal AKI. Shalaby et al. and Bolat et al. documented mortalities of 28% and 23.8% in Turkey and Saudi Arabia, respectively, among neonates with AKI [8,14], similar to our findings. The AWAKEN study documented a mortality rate as low as 9.7% but this could be explained by the inclusion of multiple centres including high-income countries [9]. This U-shaped distribution of AKI incidence, with higher rates at extremes of gestation, is similar to the AWAKEN study [9].

Patients were diagnosed with AKI using the SCr criteria from the AKIN classification or, using the definition prior to 2007, a SCr value $\geq 132 \mu\text{mol/L}$. The latter definition was adopted to include patients who did not have a baseline serum creatinine.

In our study, neonates were particularly at risk of developing and dying from AKI in the first week of life. Meticulous attention should be paid to limiting the risk factors during this time.

Since all babies enrolled in our study were exposed to multiple known risk factors, a logistic regression was used to determine variables associated with mortality, and identified patients with ELBW, umbilical line catheterisation, sepsis and phototherapy to be at an increased risk of death. Other studies documented similar associations with sepsis and ELBW [8,9,15]. Sepsis is a risk factor for mortality due to vasodilatation and hypotension [6]. Umbilical catheterisation may result in renal vascular thrombosis [1,6,15]. Although phototherapy as a risk factor is not well documented, its association with dehydration due to insensible water loss has been proposed [5,6]. In our study, the association between phototherapy and death may be confounded by prematurity because almost all patients who received phototherapy were premature. Premature neonates with AKI were more likely to die than those delivered

at term, even after recovery of kidney function. It is well known that prematurity is an independent risk factor for mortality [8]. Although nephrotoxic medication was the most frequent exposure variable, it was not associated with mortality in our study. This was likely due to the unit's policy of measuring drug levels and limiting empirical antibiotic use to 48 hours, where possible.

Of note, congenital anomalies of the kidney and urinary tract (CAKUT) were not diagnosed in any of the patients enrolled in our study. This may be underestimated due to the low rate of antenatal ultrasounds and possible delays in postnatal ultrasounds [16]. Okoronkwo et al. reported CAKUT in 20% of patients referred over a 10-year period to the paediatric renal unit at Charlotte Maxeke Johannesburg Academic Hospital [17]. The short study period in our case may have contributed to the absence of underlying CAKUT in this cohort. In addition, not all patients with CAKUT develop AKI [18,19].

This investigation documents the incidence of AKI in critically ill neonates in South Africa, and reports on the risk factors and outcomes in this study population. It identifies risk factors as areas of intervention for further studies to improve the outcome in this group. However, limitations are noted. The shortcomings of serum creatinine in diagnosing AKI are universal, and if we had been able to use urine output to identify AKI we may have observed a higher incidence rate. The lack of local published incidence rates, and paucity of studies from developing countries, resulted in underestimation of the sample size. We used an incidence rate of 3% based on studies from mainly developed countries [1,2,3,8,9]. Using the incidence rate from our study, the calculated sample size would be 110 patients. The small sample size limited the statistical analysis of risk factors. Another limitation is the lack of long-term follow-up to assess outcome, particularly progression to chronic kidney disease.

Despite these limitations, this study can form the basis of future investigations by applying the incidence rates, risk factors and outcomes in critically ill neonates with AKI.

CONCLUSION

AKI affected 7.8% of critically ill neonates at CHBAH during a three-month period, with 71% of cases recovering and 29% dying in-hospital. The incidence of AKI in the neonate may be reduced by addressing the risk factors associated with AKI. More epidemiological and interventional studies are needed to identify and improve the long-term outcome of AKI in the newborn in our setting.

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Conflict of interest

The authors declare that they have no conflict of interest.

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