Original Article

The Incidence and Potential Risk Factors of Acute Kidney Injury in Neonatal Intensive Care Unit: Single Center Experience.

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Abstract

Introduction: Acute Kidney Injury (AKI) is associated with significant morbidity and mortality in newborns.
Aim of the study: This study aims to investigate the incidence, potential risk factors, and the outcomes of neonates diagnosed with AKI.
Methods: All admissions with AKI were recruited from neonatal intensive care unit at Cairo University Children's Hospital, during a six-month duration. The diagnosis of AKI was made based on n-RIFLE criteria. Data collected included maternal risk factors, gestational age, gender, birth weight, Apgar scores, vital signs, urine output, use of mechanical ventilation, and cause of admission. We reviewed the patients' investigations including complete sepsis profile, kidney function tests, urine analysis, and bedside abdominopelvic ultrasound.
Results: Of 1045 admissions, 101 patients (9.7%) developed AKI in the current study, with male sex predominance. Respiratory distress (RD) was the most common contributing factor of AKI (72.3%), followed by sepsis (14.9%). There was no statistically significant difference in incidence, severity, and mortality in patients with AKI as regards to gestational age, and weight at birth. The need for mechanical ventilation, and low APGAR score were significantly associated with high mortality (p=0.001, and p=0.02, respectively).
Conclusion: We concluded that, AKI is a common complication in neonates in the NICU with significant impact on morbidity and associated with many preventable risk factors. The incidence of mortality was significantly higher in patients with oliguria than those with non-oliguria. Every 1 mg % increase in creatinine/day increased mortality rate [OR = 1.393, 95% CI 0.78 to 2.49].

Key words: Acute kidney injury, Neonatal intensive care unit, n-RIFLE, Respiratory distress.

Running Title: The Incidence and Potential Risk Factors of Acute Kidney Injury in Neonatal Intensive Care Unit: Single Center Experience.

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INTRODUCTION

Acute kidney injury (AKI) is characterized as an acute (reversible) state of elevated serum creatinine that maybe associated with a decreasing urinary output (oliguria/anuria). The clinical presentation of AKI may vary from mild to complete renal failure, in which renal replacement therapy (hemodialysis or peritoneal dialysis) is essential [1]. The prevalence of AKI among the neonatal population is still unidentified but, global data demonstrate a variable incidence of 6%–24% in neonatal intensive care [2]. A commonly used definition of neonatal AKI, is a serum creatinine greater than 1.5 mg/dL. Oliguric AKI is characterized by a urine output lower than 1 mL/kg/h [3].

The RIFLE (Risk, Injury, Failure, Loss of function, End-stage kidney disease) score has been considered as a standardized classification of AKI, and is applicable to both adult and pediatric patients. Neonatal definition of AKI is a challenge, because of the unique renal pathophysiology of newborns, as they have immature kidneys [4]. Initially the glomerular filtration rate (GFR) in neonates is low, and gradually increases to the adult level at 12 months of age. The urine output is mainly regulated by tubular reabsorption, which is immature in newborns, so they have low GFR and polyuria [4].

AKI is a significant risk of morbidity and mortality, in critically ill infants. Generally non-oliguric AKI has a better prognosis than oliguric AKI. The mortality of neonates with oliguric AKI, may be as high as 60% and even higher in some neonatal disorders involving the cardiovascular (congenital heart disease), and renal (anomalies of the urinary tract and kidneys) systems [5]. Several studies of AKI in low birth weight, extremely LBW, sick near-term/term, and neonates with hypoxic ischemic insult, demonstrated a high prevalence of AKI which was associated with worsening outcomes [2].

Aim of the study

We aimed to assess the incidence of AKI, and its potential risk factors in neonates admitted to the NICU to help in future prevention of neonatal AKI.

METHODS

This cohort study was performed in the neonatal intensive care unit (NICU) at Cairo University Children's hospital, during a six-month duration. All neonates in the first 28 days of life, who were admitted to the NICU, were recruited. The study included 101 cases admitted to the NICU, and diagnosed as acute kidney injury (AKI), by neonatal RIFLE "Risk, Injury, Failure, Loss, End-Stage Kidney Disease" criteria, as described by Ricci and Ronco [6].

In the current study we reviewed all AKI cases records including, history, clinical examination, and investigations.

A. History: Antenatal history included, maternal gravidity, parity, maternal diseases (controlled or uncontrolled diabetes and/or hypertension), maternal infection, and antenatal maternal medication. Obstetric history included, gestational age, mode of delivery, premature rupture of membrane >18 hours, maternal pyrexia, obstructed labor, and anti-partum hemorrhage. Post-natal

history included, resuscitation data, and Apgar score at 1 and 5 minutes, drug administration at or soon after birth, volume depletion, cyanosis, and convulsions. Date of admission in the NICU, and cause of admission were reviewed. We reported all invasive maneuvers such as positive pressure ventilation, insertion of central lines, and peritoneal dialysis. All medication given to the neonate like antibiotics, non-steroidal anti-inflammatory drugs, inotropes, diuretics, and antihypertensive drugs were recorded.

B. Clinical examination of neonates emphasized on assessment of gestational age using Ballard score, reflexes, vital signs, urine output. A complete general examination was performed and included the cardiac, chest, abdomen, and nervous systems.

C. Investigation: We reviewed all laboratory records of cases with AKI (complete blood count, C-reactive protein, blood urea, cultures, creatinine, and estimated glomerular filtration rate (e-GFR), electrolytes, total and direct bilirubin, and urine analysis). GFR was estimated using Schwartz formula (K x height [cm]/plasma creatinine [mg/dL]), where k is a Constant (0.33 in preterm; 0.45 in full term infants) **[7].**

Statistical methods

Pre-coded data were tabulated by using Microsoft Office Excel Software Program 365. Pre-coded data were entered using the Statistical Package of Social Science Software program, version 25 (SPSS). Mean and standard deviation were used to identify quantitative variables, and were compared using the independent t test. Median and interquartile range were used to non-parametric values. Qualitative values were represented by percentage and frequency and were compared using the chi square test. P value was less than 0.05 were considered statistically significant.

Statement of ethics: The study was ethically conducted in compliance with the World Medical Association's Helsinki Declaration. The Institutional Review Board of Cairo University approved the study protocol (code: MS-17-2019).

RESULTS

A total of 1045 neonates were admitted to the NICU. 101 were diagnosed with AKI, at an estimated prevalence of 9.7%. Among them were 37 females (36.6%), and 64 males (63.4%), with a mean gestational age of 34.8 ±3.7 weeks. Low birth weight accounted for 49.5 % of admissions. The median age at admission was 2 (1-6) days, with a range of 1–21 days. Mean age of recruitment was 3days with range from 2 to 9 days. Respiratory distress (RD) was the major cause of admission, and its common causes in the current study were hyaline membrane disease (39.6%, n=40), congenital heart disease (27.72%, n=28), and persistent pulmonary hypertension (11.88%, n=12). Other causes of admission were neonatal infection (3.96%, n=4), neonatal jaundice (1.98%, n=2), hypoxic ischemic encephalopathy (HIE) (12.87%, n=13), and intestinal obstruction (0.99%, n=1). The mean duration of NICU stay was 16.9 ±9.7 days, and ranged between 2 to 45 days. About 29% died, and the rest improved and were

discharged home. Every 1 mg % increase in creatinine/day increased mortality rate [OR = 1.393, 95% CI 0.78 to 2.49], but this was not statistically significant ratio (P = 0.263).

The main maternal risk factors for developing AKI were diabetes mellitus (12.9%, n=13), hypertension (16.8%, n=17), urinary tract infection (5.9%, n=6), and others (6.9%, n=7). At 1 minute, the median Apgar score was 4 (2-6) with a range of 0-7. After 5 minutes, the median Apgar score was 6 (5-7), with a range of 1-9.

Normal blood pressure was observed in 54 cases (53.5%), hypotension that requires administration of inotropes was observed in 42 cases (41.6%) (dopamine in 62.4%, dobutamine in 44.6%, epinephrine in 18.8%, and norepinephrine in 10.9%). Only 5 cases were hypertensive, and required antihypertensive drugs. Not all patients with AKI in the study group were oligo-anuric, only 63.4% had oliguria or anuria.

The laboratory data of the neonates in the current study was listed in **Table 1**. CRP was positive in 73% of patients. Blood cultures were performed, and 47% cases had positive blood culture, with the main organism being Klebsiella in about half of the cases. Most neonates in the study had normal urine analysis. Only 5% had pyuria and 4% had microscopic hematuria. Urine cultures revealed Klebsiella.

In our study, 62.3 % of patients received aminoglycosides, and 44.5 % of them received vancomycin. About 79% of studied patients were mechanically ventilated, while 33 % of them had central venous catheter, and 34 % cases needed acute peritoneal dialysis for 48 hours; the main indication were volume overload not responding to diuretics &/or laboratory indications (hyperkalemia, interactable acidosis & uremia).

A comparison between survivors and non survivors in the current study using mean ±SD **Table 2**. There were significant variations demonstrated between the non survivors and survivors with regards to the Apgar score (at one and five minutes), the need for mechanical ventilation, blood pressure, and metabolic acidosis **Table 2.**

The median urine output in oliguric patients was 0.3 (0.1-1.28) ml/kg/h, while it was 2.3 (1.9-3.1) ml/kg/h in non-oliguric patients. Oliguric subjects had considerably higher urea and creatinine levels than non-oliguric patients **Table 3.** The median BUN/creatinine ratio in patients with oliguria was 42.5 (28-71.2), while it was 38 (28.5-63) in the others. The incidence of mortality was higher in patients with oliguria than those with non-oliguria**,** however, there were other risk factors such as sepsis, hypoxic ischemic encephalopathy, and respiratory distress **Table 3.** Mortality rate in patients who underwent peritoneal dialysis was 38.2% (n=13).

Low birth weight neonates were more liable to AKI (mainly oligo-anuric AKI), but the mortality rate was almost the same **Table 4.** The term neonates had significantly higher creatinine and urea, but lower urine output than preterm neonates. The incidence of renal risk and injury was higher in preterm neonates **Table 4.**

Table 1: Laboratory finding in the study group.

	Mean ± SD	Range
Hemoglobin (g/dL)	11.5 ± 3.3	4.1-21
Hematocrit (%)	33.7 ± 9.8	13-60
Platelets (× 10^3/mcL) [a]	150 (65-260)	9-590
TLC (× 10^3/ml) [a]	14(8.2-21)	1.7-56
I/T[a]	0.2(0.1-0.3)	0-0.5
pH	7.2 ± 0.1	6.9-7.5
HCO_3 (mEq/L)	18.4± 6.1	7.1-32
Base excess (mmol/L) [a]	-7(-11--4.5)	-19 – 8
Blood urea nitrogen (mg/dl)	41(25-77.5)	8.5-360
BUN/Creatinine ratio [a]	42(28-70)	9-170
Creatinine (mg/dl) [a]	1.1(0.8-1.4)	0.2-7.7
e-GFR (ml/min/1.73 m²)	9.1 ± 3.4	2.2-19.3
Serum sodium (mmol/l)	145.8 ± 15.1	112-190
Serum potassium (mmol/l)	5.4 ± 1.7	1.9-9
Serum calcium (mg/dl)	8 ± 1.3	5.5-12
Serum magnesium (mg/dl)	1.7 ± 0.5	0.5-4.6
Serum phosphorous (mg/dl)	5 ± 1.4	1.3-10

[a]Median (IQR); e-GFR: estimated glomerular filtration ratio; I/T: immature/total leucocyte ratio; TLC: total leucocyte count.

Table 2: Comparison between survivors and non-survivors in the studied patients

	Outcome		P value
	Non-survivors (n=29)	Survivors (n=72)	
Gestational age(weeks)	34.3 ± 4.2	35 ± 3.4	0.61
Weight (kg)	2.2 ± 0.9	2.3 ± 0.8	0.48
Sepsis[a]	22 (75.9)	52 (72.2)	0.71
Mean blood pressure(mm/Hg)	46.1 ± 12.1	57 ± 13.7	**0.001***
Urine volume (ml/kg/h) [aa]	0.7 (0.1 - 1.3)	1.4 (0.3 - 2.3)	**0.01***
Urine output[a] Oliguria Non-oliguria	24 (82.8) 5 (17.2)	40 (55.6) 32 (44.4)	**0.01***
Mechanical ventilation[a]	27 (93.1)	52 (72.2)	**0.02***
Platelets (mg/dl) [aa]	120 (50 - 175)	185 (72 - 285)	**0.05***
I/T Ratio [aa]	0.2 (0.1 - 0.3)	0.2 (0.1 - 0.3)	0.860
PH	7.1 ± 0.1	7.2 ± 0.1	**0.001***
Base excess* (mmol/L) [aa]	-9 (-12 - -7)	-6.7 (-11 - -0.8)	**0.04***
Creatinine*(mg/dL) [aa]	1.9 (1.8 - 2.7)	1.9 (1.7 - 2.2)	0.07
e-GFR (ml/min/1.73 m²)	8.7 ± 3.3	9.2 ± 3.4	0.41
n-RIFLE[a] Risk Injury Failure	12 (41.4) 4 (13.8) 13 (44.8)	39 (54.2) 13 (18.1) 20 (27.8)	0.26
Apgar- 1 minute[aa]	2 (2 - 4)	4 (3 - 6)	**0.001***
Apgar- 5 minute	5 ± 1.9	6.4 ± 1.7	**0.001***

[a]Number (percent); [aa]Median (IQR); *significant p value; e-GFR: estimated glomerular filtration rate; I/T ratio: ratio between immature to total neutrophils.

NB: comparison of means using the independent t test and comparison of medians using the chi square test.

Table 3: Comparison between AKI patients presenting with oliguria and others with non-oliguria.

	Urine-volume		P value
	Oliguric (n=64)	Non-oliguric (n=37)	
Gestational age(weeks)	35.4 ± 3.7	33.6 ± 3.4	**0.005***
Respiratory distress[a]	43 (67.2)	33 (89.2)	**0.02***
Sepsis	46 (71.9)	28 (75.7)	0.68
Hypoxic-ischemic encephalopathy	19 (29.7)	4 (10.8)	**0.03***
Weight (kg)	2.5 ± 0.8	2.1 ± 0.7	**0.02***
Mean blood pressure (mmHg)	55.1 ± 15.2	51.7 ± 11.7	0.4
Total leucocyte count[a]	15.5 (9.5 - 22.5)	12 (7 - 18)	**0.04***
Urea (mg/dl) [a]	93.5 (56.5 - 190)	58 (45 - 105)	**0.01***
Creatinine (mg/dl) [a]	2 (1.8 - 3.2)	1.8 (1.5 - 1.9)	**<0.001***
Serum K (mg/dl)	5.8 ± 1.7	4.7 ± 1.4	**0.002***
pH	7.2 ± 0.1	7.2 ± 0.1	**0.004***
n-RIFLE[aa] Risk Injury Failure	23 (35.9) 9 (14.1) 32 (50)	28 (75.7) 8 (21.6) 1 (2.7)	**0.000***
Mortality[aa]	24 (37.5)	5 (13.5)	**0.010***

*Significant p values; [a]Median (IQR); [aa]number (percent); K: Potassium.
NB: comparison of means using the independent t test and comparison of medians using the chi square test.

Table 4: Comparison regarding blood pressure, kidney function tests, urine output, and n-RIFLE according to birth weight & gestational age.

	Birth weight		P value	Term		P value
	Low birth weight (n=50)	Normal birth weight or macrosomia (n=51)		Preterm (n=50)	Full-term (n=51)	
Mean blood pressure(mmHg) [a]	50.1 ± 9.2	57.5 ± 16.9	**0.009***	50.42 ± 11.89	57.49 ± 15.36	**0.011***
Urine output(ml/Kg/h)	1.4 (0.7 - 2.1)	1.1 (0.1 - 1.9)	**0.02***	1.6 (0.8 - 2.2)	0.4 (0.1 - 1.4)	**0.003***
Urine volume[aa] Oliguria Non-oliguria	 27 (54) 23 (46)	 37 (72.5) 14 (27.5)	0.053	 24 (48) 26 (52)	 40 (78.4) 11 (21.6)	**0.002***
Urea (mg/dl)	77 (47 - 113)	100 (55 - 205)	**0.04***	77 (47 - 113)	98 (55 - 170)	0.059
Creatinine (mg/dl)	1.8 (1.7 - 2)	1.9 (1.8 - 3.5)	**0.002***	1.8 (1.7 - 1.9)	1.9 (1.8 - 3.5)	**0.002***
Bun/creatinine ratio	41 (28 - 70)	42 (28 - 70)	0.94	41 (28 - 65)	42 (28 - 70)	0.721
n-RIFLE Risk Injury Failure	31 (62) 10 (20) 9 (18)	20 (39.2) 7 (13.7) 24 (47.1)	**0.008***	32 (64) 10 (20) 8 (16)	19 (37.3) 7 (13.7) 25 (49)	**0.002***
Mortality[aa]	15 (30)	14 (27.5)	0.78	15 (30)	14 (27.5)	0.78

*Significant p values; [a]mean ± SD; [aa]number (percent).
NB: comparison of means using the independent t test and comparison of media

DISCUSSION

Acute Kidney Injury (AKI) is a fatal condition with poor outcomes. It is common in NICU patients and is linked to specific risk factors and neonatal renal functionality. The main risk factors for AKI in the study patients were respiratory distress (75%), sepsis (73%), CHD (55%), and hypoxic ischemic encephalopathy

(44%), which agrees with Liborio et al., who reported that the incidence of AKI secondary to a systemic illness or the use of nephrotoxic drugs was higher than that of primary renal disease [1].

Respiratory distress was observed in 75%, and about 79 % of these patients were mechanically ventilated (MV) in the current study. We observed that mechanically ventilated patients had higher mortality rates (34 %). Similarly, Bansal et al. noticed a positive correlation between mortality rates and MV, which may be a result of compromised renal blood flow (causing hypoxemia and/or hypercapnia), and barotrauma which stimulates the pulmonary inflammatory pathways resulting in secondary systemic inflammation [8]. Sepsis came as the second common risk factor 73.3% of the studied patients, in septic neonates, there are multifactorial mechanisms which may result in the development of AKI including; hemorrhage, heart failure, disseminated intravascular coagulation (DIC), and shock [9].

In the current study, the mean e-GFR was 8.3 (± 2.5) and (9.8 ± 3.9) ml/min/1.73 m², in preterm and full-term neonates, respectively (p=0.010). The mean e-GFR in low birth weight and normal birth weight were 8.6 ± 2.6 and 9.5 ± 3.9 ml/min/1.73 m², respectively (p=0.08). Key factors which play a role in determining GFR in neonates are gestational age and weight. GFR, at birth, is dependent on both the mass of the nephron, and the gestational age. The development of the kidney (nephrogenesis) continues until week 36 of gestation, and during this time, GFR can be adjusted using different intrauterine methods [10].

We studied prematurity as a risk factor of developing AKI. About 50 % of our patients were preterm, and this finding is in agreement with Youssef et al. who reported AKI in 59% of preterm neonates [11].

Given the weight of the studied neonates at birth, it was clear that low birth weight (LBW) neonates (33.7%) and extremely LBW (15.8%), had less severe AKI than others with normal birth weight (47.5%) and macrosomia (3%) (p=0.008), but no significant difference regarding mortality rate between them (p=0.77). This was not commensurate with Gane et al. who reported higher mortality in LBW [12]. It should be noted that despite measures such as therapeutic hypothermia, AKI is a common complication of perinatal asphyxia. Early identification of risk factors that increase the likelihood of an asphyxiated neonate developing AKI may be beneficial in limiting AKI-related complications and mortality [13].

In the current study, a low Apgar score was associated with a significant increase in mortality (p=0.001) but no significant worsening of AKI severity (p=0.25). In contrast, Mohkam et al. found no significant differences in Apgar scores between non-surviving and surviving AKI patients [4]. The mortality rate among patients with HIE was 21.7 % in the study population. This was similar to Bozkurt and Yucesoy study [13]. The kidney of a fetus is especially sensitive to certain gestational stressors such as, exposure to glucocorticoids, hypoxia, and malnutrition [14]. We reported AKI in

12%, 11%, and 6 % of neonates with maternal history of chronic hypertension, diabetes mellitus, and pregnancy induced hypertension, respectively.

The body of a neonate, particularly a preterm infant, has a higher water content than that of an adult, which, combined with immature development of the tubular system, explains why urinary output is much higher in this population [15] . In the current study, the mean urine output was 1.4 (±1.4) ml/kg/hour, with a range of anuria to 7.5 ml/kg/hour. Full-term neonates with AKI, on the other hand, had significantly lower urine output than preterm neonates (p= 0.003), owing to mature renal tubules that can reabsorb electrolytes, protein, and concentrate urine.

In our study, oliguric AKI was more frequent than non oliguric AKI, with 63% of patients being oliguric. This is in agreement with Mortazavi et al. [16]. Contrastingly, Youssef et al. reported that non-oliguric AKI was more frequent than oliguric AKI **[11]**. In our study of neonates with AKI, we discovered a link between mortality and oliguria, blood pressure, MV requirements, and Apgar scores (p=0.001, 0.001, 0.02, 0.001, respectively). There was no significant association with serum creatinine (p=0.072). This was comparable to Meher et al. [17].

A change in urine output is regarded as an important sign of AKI and has been linked to mortality in critically ill patients **[18].** The mortality rate was significantly higher in oliguric AKI than non-oliguric AKI (p=0.01), which could be due to factors such as volume overload, the need for MV, acid base imbalance (p=0.004), and electrolyte disturbances (p=0.002), which were all significantly higher in oliguric patients. There was a statistically significant difference in mean blood pressure between survivors and non-survivors (p=0.001), but a statistically insignificant difference between oliguric AKI and non-oliguric AKI (p=0.39) in the current study, which is consistent with previous research [4].

Antimicrobial medicines such as aminoglycosides and vancomycin have been linked to AKI. Aminoglycosides cause nephrotoxicity by blocking lysosomal phospholipase in the tubular epithelium, resulting in cell death, intra-renal vasoconstriction, and contraction of local mesangial and glomerular cells. Vancomycin produces nephrotoxicity by affecting energy-dependent renal reabsorption within proximal tubular cells, resulting in a change in mitochondrial function and eventual renal impairment **[19].**

Due to fluid overload or electrolyte imbalances, 34% of individuals in our study required peritoneal dialysis (PD). We chose PD because hemodialysis was not an option for this age group due to a lack of resources. The mortality rate among these patients was 37%. The kidney of a newborn is immature in terms of function. Due to physiological limits, treating renal illnesses such as AKI remains difficult, which is why renal replacement treatment, which has minimal evidence of long-term improvement, is more difficult to implement and may cause multiple difficulties in this group of patients [20].

CONCLUSION

There are multiple reasons why AKI is a serious condition with an increasing risk of mortality, and it is critical to detect AKI in newborns as soon as possible in order to avoid future complications and improve therapy, prognosis, and outcome. Long-term monitoring of neonates with AKI will be beneficial in determining if the patient advances to a condition of chronic kidney disease, which will aid in their management.

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AUTHORS' CONTRIBUTIONS

The submitted manuscript is the work of the author & co-author.
All authors have contributed to authorship, have read and approved the manuscript.
Conception and design of study: all authors
Acquisition of data: 2nd author
Analysis and/or interpretation of data: 1st and last author
Drafting the manuscript: all authors
Revising the manuscript critically for important intellectual content: 1st and last author
Approval of the version of the manuscript to be published: all authors

STATEMENTS

Ethics approval and consent to participate
The study was ethically conducted in compliance with the World Medical Association's Helsinki Declaration. This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of Cairo University and the Institutional Review Board of Cairo University approved the study protocol (code: MS-17-2019). Informed written consent was obtained in every case from their legal guardians.

Consent for publication
The contents and material of the manuscript have not been previously reported at any length or being considered for publishing elsewhere.

Availability of data and material
Done

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