The Scientific Journal of Medical Scholar

SJMS

Volume 1, Issue 4, July 2022

https://realpub.org/index.php/sjms

Online ISSN: 2833-3772

The Scientific Journal of Medical Scholar

Available online at Journal Website
https://realpub.org/index.php/sjms/index
Subject (Pediatrics)

Original Article

Acute Kidney Injury in the Neonatal Intensive Care Unit: Incidence and Risk Factors

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Article information

Submitted: April, 4th, 2022

Accepted: June, 19th, 2022

Published: July, 1st, 2022

DOI: 10.55675/sjms.v1i4.24

Citation: El-Samanoudy MIA, Elbakry EMT, Bakry HEK, Elkhraswy AM. **Acute Kidney Injury in the Neonatal Intensive Care Unit: Incidence and Risk Factors.** SJMS 2022; 1 (4) July: 89-93. DOI: 10.55675/sjms.v1i4.24

ABSTRACT

Introduction and Aim: Acute Kidney Injury (AKI) is a common medical problem, especially in neonatal intensive care unit. However, the reported incidences and associated risk factors are widely heterogenous and sometimes absent for developing countries. Thus, the current work designed to explore the incidence and potential risk factors of AKI for critically ill neonates.

Patients and methods: The current work was an observational prospective study, completed between March 2019 and March 2022. It included 459 newborns admitted to the NICUs at Al-Azhar University Hospital (New Damietta) and Damietta General Hospital (Ministry of Health, Damietta, Egypt). For all neonates, careful history and clinical examination were done and data was documented. Then, repeated creatinine measurements and arterial blood gas analysis were performed. Discharge or death was the primary end point of the study. Other comorbid conditions were the secondary outcome.

Results: The incidence of AKI was 92.2% and there was no significant difference between AKI and non-AKI regarding neonatal age, sex and mode of delivery. Patients with AKI had significantly lower gestational age, reduced birth weight, pH and HCO3. The serum creatinine showed significant increase during the first week of NICU admission in AKI than non-AKI groups, while basal values did not. Sepsis, nephrotoxic medications, hypoxic ischemic encephalopathy, umbilical catheter, duration of admission and mortality, all were significantly higher in AKI than non-AKI groups. Sepsis was reported among 44.8% and 27.7%, while mortality was reported for 20.9% and 4.9% of AKI and non-AKI groups, respectively. The duration of admission was 15.25±3.19 vs 9.50±2.21 days respectively.

Conclusion: AKI was relatively higher (29.2% of admitted neonates) and associated with prematurity and lower birth weight. Neonatal sepsis and exposure to nephrotoxic drugs were among the commonest predisposing factors for AKI.

Keywords: Neonatal; Acute Kidney Injury; Intensive Care Unit; Mortality; Sepsis.

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INTRODUCTION

Acute Kidney Injury (AKI) is commonly occurred in the neonatal intensive care unit. It is defined as a rapid deterioration of the kidney function, with inability to maintain adequate fluid, electrolyte balance, and overall homeostasis. It is manifested by elevated serum creatinine or reduction in urine output [1,2].

The neonatal kidney is susceptible to different endogenous and/or exogenous harmful effects, before or after delivery, due its physiological shortages associated with prematurity. Full term neonates are also exposed to these effects [3].

Physiological shortages among neonates include higher susceptibility to hypoperfusion, increased renin activity and vascular resistance, and reduced sodium reabsorption in the proximal renal tubules [4].

Youssef *et al*. [5] estimated the incidence of AKI to be 10.8% for neonates admitted to the Zagazig neonatal intensive care unit (NICU). The commonest was the pre-renal form. Mechanical ventilation and sepsis were the commonest risk factors. On the worldwide level, Hu Q, *et al*. [6] reported that, the incidence of neonatal AKI ranged between 8.4 to 63.3%. The risk factors with critically ill neonates include prematurity, low birth weight, lower 1- and 5- minutes Apgar scores, congenital malformations, jaundice, necrotizing enterocolitis, sepsis and mechanical ventilation

AKI is associated with a significant morbidity and mortality. Thus, early diagnosis and proper therapeutic inventions are associated with favorable outcome [7-10].

Studies evaluating AKI in NICUs are scarce, especially on the national level. Thus, it is of utmost importance to determine the incidence of AKI in NICUs and its associated factors. The current study designed to recognize the incidence and potential risk factors of neonatal AKI in two main hospitals (Al-Azhar University Hospital, New Damietta) and Damietta General Hospital (Ministry of Health, Damietta, Egypt).

PATIENTS AND METHODS

The present study was an observational prospective study. It carried out between March 2019 to March 2022. It included 459 newborns from those admitted to the NICUs at two healthcare facilities: Al-Azhar University Hospital (New Damietta) and Damietta General Hospital (Ministry of Health, Damietta, Egypt).

All neonates admitted to the NICUs were initially included. Then, those with any of exclusion criteria were excluded from the study. The exclusion criteria were congenital renal malformations or other major congenital anomalies, renal impairment of their mother or neonatal death before established diagnosis of AKI.

The AKI definition was established according to Zappitelli *et al*. [11], using the change in serum creatinine values and urine output. Persistent elevation of serum creatinine > 1.5 mg/dl, elevation of serum creatinine (≥ 0.3 mg/dl) within 48 h, or elevation by ≥ 1.5 to 1.9 of reference (the lowest prior) values within the 7 days, or reduced urine output to ≤ 1 mL/kg/hour.

Initially 591 neonates were included, 112 of them were initially excluded due to maternal renal impairment (62) and major congenital malformations (50), leaving a total of 479 neonates. Subsequently 15 were died within the first 48 hours and 5 guardians refused to participate in the study. Thus, the final number included in the study were 459. Acute kidney injury was confirmed for 134 neonates (29.2%). Figure (1) represented the flow chart of the study.

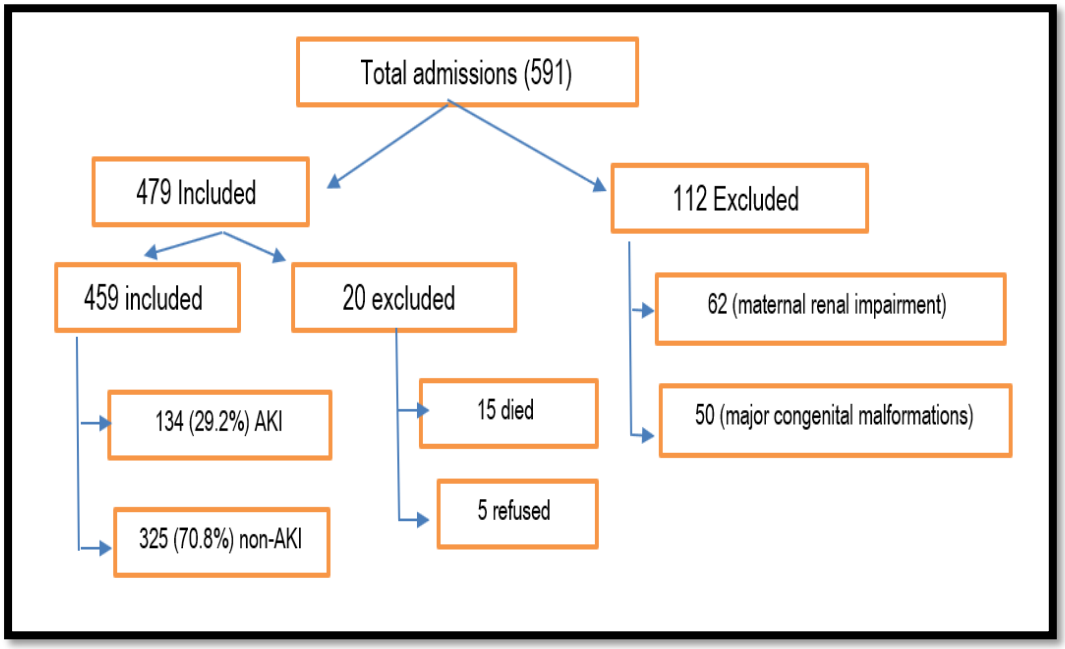

Figure (1): Flow chart of included neonates

For all neonates, careful history and detailed clinical examination were achieved and data were recorded. Then, repeated creatinine measurements were performed.

In addition, other laboratory investigations were performed. These include complete blood count (CBC), C-reactive protein (CRP), measurement of arterial blood gases and serum electrolytes (Na^+, K^+). For those with suspected neonatal sepsis, a blood culture was performed. Finally, an abdominal ultrasound was performed for all neonates with acute kidney injury.

The end point (primary outcome) of the current work was discharge of NICU or mortality during admission. The secondary outcomes included duration of NICU stay and other associated comorbidities (sepsis and others).

Ethical consideration:

The aim of the current work was explained for all parents or legal guardians. Then, an informed consent was signed. The study protocol was also reviewed and approved by the institutional review board of Damietta Faculty of Medicine (Damietta, Egypt) (IRB# 00012367-19-02-003).

Statistical analysis:

The statistical analysis related to the present study has been carried out using the statistical package for social sciences (SPSS) version 16 (SPSS Inc, Chicago, Illinois, USA). The statistical measurements were mean, standard deviation, relative frequency and percentages were used to represent continuous and categorical data respectively. Groups compared by students' independent samples student and Chi Square test, or equivalent tests, according to type of data and statistical situation. P value ≤ 0.05 was considered significant [12].

RESULTS

As regard general characteristics and laboratory findings of the studied cases, there was no significant difference between AKI and non-AKI groups as regard age, sex and mode of delivery. Patients with AKI had significantly lower gestational age, birth weight, pH and HCO_3 (Table (1).

The basal serum creatinine showed no significant difference between AKI and non-AKI groups. However, it significantly increased during the first week of NICU admission in AKI than non-AKI groups (Table 2).

Sepsis, nephrotoxic medications, hypoxic ischemic encephalopathy, umbilical catheter, duration of admission and mortality, all were significantly higher in AKI than non-AKI groups. Sepsis for example was reported among 44.8% and 27.7%, while mortality was reported for 20.9% and 4.9% of AKI and non-AKI groups, respectively. The duration of admission was 15.25± 3.19 vs 9.50 ± 2.21 days respectively (Table 3).

Table (1): **General characteristics and laboratory findings of the studied cases**

Variable		AKI group (n=134)	Non-AKI group (n=325)	P
Neonatal age at admission (days)		1.19±0.39; 1-2	1.23±0.43; 1-2	0.23
Gestational age (weeks)		35.92±1.61; 34-39	36.63±1.70; 34-40	***<0.001****
Gender	**Males**	54 (40.3%)	150 (46.2%)	0.25
	Females	80 (59.7%)	175 (53.8%)	
Mode of delivery	**NVD**	30 (22.4%)	100 (30.8%)	0.09
	CS	104 (77.6%)	225 (69.2%)	
Birth weight (kg)		2.45±0.34; 2-3.3	2.62±0.34; 2-3.40	***< 0.001****
pH		7.35±0.06	7.39±0.06	***< 0.001****
PCO_2(mmHg)		41.20±6.10	40.60±3.80	0.20
HCO_3(meq/l)		20.09±1.76	21.70±1.47	***< 0.001****
Sodium (meq/l)		139.0±1.14	140.3±1.26	0.12
Potassium (meq/l)		4.55±0.59	4.42±0.43	0.14
RBG (mg/dl)		73.30±9.47	74.50±10.28	0.21
Hemoglobin (g/dl)		14.98±1.50	14.60±1.17	0.25
Hematocrit (%)		44.80±2.06	43.50±2.50	0.16
Platelets (x10^3/cmm)		208.5±10.42	209.8±8.8	0.47
TLC (x10^3/cm^3)		15.13±2.04	15.33±2.9	0.41

* Indicates significant differences

Table (2): Comparison between AKI and non-AKI regarding serum creatinine and urine output

Variable	AKI group (n=134)	Non-AKI group (n=325)	P value
Basal creatinine (mg/dl)	0.84±0.27	0.87±0.37	0.13
Highest creatinine (mg/dl)	1.49±0.55	0.90±0.42	***< 0.001****
Creatinine at the third day (mg/dl)	1.10±0.42	0.60±0.20	***< 0.001****
Creatinine at the seventh day (mg/dl)	1.04±0.51	0.57±0.18	***< 0.001****
Urine output (ml/kg/h)	1.80±0.53	2.37±0.82	***< 0.001****

* = significant

Table (3): Potential risk factors for AKI and outcome among studied cases

Variable	AKI group (n=134)	Non-AKI group (n=325)	P value
Sepsis	60 (44.8%)	90 (27.7%)	***<0.001****
Nephrotoxic medications	73 (54.5%)	80 (24.6%)	***<0.001****
HIE	28 (20.9%)	33 (10.2%)	***0.004****
Dehydration	21 (15.7%)	41 (12.6%)	0.20
Cardiovascular disease	29 (21.6%)	64 (19.7%)	0.70
Umbilical catheter	62 (46.3%)	65 (20.0%)	***<0.001****
Mechanical ventilation	42 (31.3%)	90 (27.7%)	0.43
Duration of admission	15.25±3.19	9.50±2.21	***< 0.001****
Mortality	28 (20.9%)	16 (4.9%)	***0.001****

HIE: Hypoxic ischemic encephalopathy; * = significant

DISCUSSION

The current study was designed to explore the incidence of acute kidney injury (AKI) in neonatal intensive care unit. It included all neonates admitted to the NICU of two centers for 3 consecutive years. The final analysis included 459 neonates, and the AKI was confirmed for 134 of them (29.2%). Those who developed AKI had significant lower gestational age, reduced birth weight, pH and HCO_3. In addition, neonates with AKI had significantly higher creatinine and lower urine output during their admission. AKI was also associated with significantly higher neonatal sepsis, hypoxic ischemic encephalopathy, the use of umbilical catheter, duration of admission and overall mortality. The overall mortality rate with AKI was 20.9% compared to 4.9% for neonates who did not develop AKI.

The incidence of AKI (29.2%) in the current work lies within values reported from different centers worldwide.

Jetton *et al.* [13] reported an incidence of 30.0% of AKI of the studied neonates. However, Bezerra *et al.* [14] reported a 20.0% incidence rate. The higher variability of incidence rate could be attributed to different criteria for AKI diagnosis and other contributing factors (e.g., higher incidence in low birth weight, prematurity, HIE and interventional treatment).

Our results are in line with previous studies linking prematurity and lower birth weight to high incidence of AKI. Carmody *et al.* [15] showed that AKI occurred in 40% of admitted neonates with 16.5% of had multiple episodes. AKI was associated with higher mortality and longer duration of stay. In another study included 932 premature neonates, the incidence of AKI was 38% and significantly increased with decreasing gestational age and birth weight [16]. Wu *et al.* [17] in a meta-analysis of more than 10000 neonates, reported that, the pooled AKI incidence was 25.0% with significantly higher mortality among those with AKI.

Neonatal AKI has been shown to occur commonly in with perinatal asphyxia (i.e., HIE) with an incidence 38 to 72% [18, 19]. A single center trial included 96 neonates with HIE submitted to therapeutic hypothermia, yielded a 38.0% incidence of AKI and associated with longer duration of NICU stay [20].

It is well-known that, critically ill neonates are frequently exposed to nephrotoxic medications during NICU stay, and it seems to be a preventable (modifiable) cause of AKI in older infants [21]. Rhone *et al.* [22] evaluated 107 neonates and reported that, 87% of those neonates received at least, one nephrotoxic drug during their admission (for example, gentamicin (86%), indomethacin (43%) and vancomycin (25%)), with a significant increase of nephrotoxic drug and duration of administration among AKI than non-AKI. Subsequently, Salerno *et al.* [23] evaluated the impact of nephrotoxic drug combinations in a database including 268 NICUs and 8,286 neonates with documented exposure. The AKI incidence was 17.0% with increased AKI incidence for those with longer duration of treatment.

The current work had some limitations, as the long-term outcome of neonatal AKI had not been evaluated. However, it was beyond the scope of the current study. Thus, it is highly recommended to be investigated in the future studies. On the other side, the nature of the study (prospective), careful data documentation, inclusion of two centers, with the higher sample

included are strengths of the current work.

Conclusion: The current work shed light on the magnitude of AKI in NICU and its associated and possible risk factors. AKI was relatively higher and associated with prematurity and lower birth weight. Neonatal sepsis and exposure to nephrotoxic drugs were among the commonest predisposing factors for AKI.

Conflict of Interest: None

Financial Disclosure: None to be disclosed.

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The Scientific Journal of Medical Scholar

SJMS

Volume 1, Issue 4, July 2022

https://realpub.org/index.php/sjms

Online ISSN: 2833-3772