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

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ABSTRACT

Background: Acute kidney injury (AKI) is a clinical syndrome in which the sudden loss of kidney function leads to kidney failure to maintain fluid hemostasis and electrolytes. Considering the increased hospitalization of patients in the neonatal intensive care unit (NICU), the prevalence of AKI due to common diseases, surgical procedures, various drugs, as well as the importance of long-term complications, this study aimed to determine the prevalence and related risk factors for the development of AKI in neonates admitted to NICU.

Methods: This descriptive cross-sectional study was conducted on 173 newborns admitted to Boo-Ali-Sina Hospital in Sari, Iran, during 2016-2018. Patients' demographic characteristics, clinical findings, laboratory results, clinical outcomes, and risk-related disease factors were recorded. Data were analyzed using SPSS software (version 16).

Results: The prevalence rate of AKI in infants admitted to Neonatal intensive care unit was 26.6%, consisting of 87% (n=40) prerenal, 8.7% (n=4) renal, and 2.2% (n=1) postrenal AKI cases. Furthermore, 6.4%, 9.2%, and 11% of the patients had grade 1, grade 2, and grade 3 AKI, based on RIFLE criteria. It should be mentioned that RDS, TTN, and seizure were the most common causes of hospitalization in the NICU. The most common laboratory disorders were acidosis, hyponatremia, anemia, and leukocytosis. Furthermore, anemia (89.1% vs. 19.7 %), hypernatremia (8.7% vs. 2.4%), and hyperkalemia (26% vs. 8%) were significantly greater in AKI than in the non-AKI group.

Conclusion: AKI was common in NICU, and accounted for about one-fourth of the admitted patients. The most common type of AKI was prerenal. The patients were equally distributed in all three stages. Eventually, anemia, hypernatremia, and hyperkalemia can be considered risk factors for AKI.

Keywords: Acute kidney injury, Neonatal intensive care unit, Renal insufficiency

Introduction

The neonatal period is an important and critical phase of life. Many long-term morbidities are due to organic disorders in this short period. Hypertension, chronic kidney dysfunction, nervous or developmental abnormalities, and many other disorders could occur due to pathologic events in the first weeks of life (1, 2). The neonatal intensive care unit (NICU) is a ward specialized in the care of ill or premature newborns who require proper medical management and kidney dysfunction is a prevalent daily problem in this unit (3). Acute kidney injury (AKI) is a clinical disorder with a sudden loss in kidney glomerular or tubular function and body hemostatic impairment (4). Alteration in kidney function leads to various and sometimes lethal complications, such as hyperkalemia, metabolic acidosis, and hypertension (3). It is worth mentioning that the incidence rate of AKI in NICU is estimated at 8-24% (5).

The AKI is characterized by the diminished urine output, reduction of glomerular filtration rate (GFR) leading to the rising of serum urea or creatinine levels, and a state of complication (6). Creatinine clearance (CrCl) is a measurable (and not necessarily most accurate) marker for GFR (7).

The prognosis of AKI differs based on the etiology and severity of the disorder. The most

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common causes of neonatal AKI are perinatal and neonatal events, such as hypoxic-ischemic events, hemorrhage, congenital heart diseases, sepsis, exposure to nephrotoxic agents, and other iatrogenic insults (2, 8). Based on pathophysiology, the AKI is classified as prerenal, intrinsic, or postrenal types. The severity of AKI is presented based on urine output and laboratory findings of renal function (8, 9).

There are different guidelines for the diagnosis and classification of AKI. RIFLE and Kidney Disease Improving Global Outcomes (KDIGO) are among two of the most notable guidelines (2). The RIFLE criteria modulated for children is entitled *pediatric* RIFLE (*P*RIFLE) and has an emphasis on urine volume and CrCl (3).

Prevention of AKI occurrence is the best strategy to manage the disorder and its complications (10, 11). Therefore, gaining knowledge about AKI risk factors is worthwhile. The incidence and risk factors of AKI were assessed in a tertiary NICU during two years in this study.

Methods

This prospective descriptive study was performed from September 2016 to September 2018 in the NICU of Avicenna hospital, Sari, Iran. The NICU is a 17-bed referral tertiary care unit providing level II and III neonatal care. All neonates admitted to the NICU were enrolled for different clinical indications. All patients were monitored for daily urinary volume on all days of admission. The staff of the unit measured the volume of urine every six hours through direct assessment of collected urine, in case the patient has an indwelling catheter (based on clinical indications). The volume of urine in neonates who had not urinary catheters was estimated by the weight of their wet diapers. The difference between the weight of dry and wet diaper (in gram) was considered as urine volume (in milliliter). The diaper's weight was measured using a digital scale (ANDHT-500, Japan). Newborns who died within 24 hours of birth were excluded from the study.

Baseline and serial serum creatinine were collected at least twice a week. The serum creatinine (Cr) levels were measured using Jaffe method and presented in mg/dl. Based on reference values for serum creatinine in neonates, the upper limit of Cr was obtained at 0.5mg/dl according to the unit protocol. Given that in the first week of life the neonatal serum creatinine may reflect maternal creatinine, serum Cr≥1.5 mg/dl or Cr≥0.75 was considered as abnormally high in the first three days of life in order to avoid the effect of maternal creatinine. The severity of AKI was assessed based on *n*RIFLE criteria. The first three stages of *P*RIFLE (i.e. Risk, Injury and, Failure) are related to acute kidney insult. The stages refer to urine output of ≤0.5ml/kg/hr for 8hr, ≤0.5ml/kg/hr for 12hr and ≤0.3ml/kg/hr for 24hr (anuria for 12hr), respectively. Reduction of GFR to >25%, >50%, and >75% are the definition of risk, injury, and failure, respectively. Based on the persistence of failure there are two severe levels of *P*RIFLE, including Loss as the persistent failure of more than four weeks and ESRD as a persistent failure of more than three months (5, 9; Table1).

Table 1. Pediatric RIFLE criteria for AKI

Pediatric RIFLE	Creatinine	Urine output
Risk	Increased Cr×1.5 or GFR decreased >25%	UO<0.5ml/kg/hr For 8 hr
Injury	Increased Cr ×2 or GFR decreased>50%	UO<0.5ml/kg/hr For 12 hr
Failure	Increased Cr×3 or GFR decreased>75%	UO<0.3ml/kg/hr For 24 hr Or Anuria for >12hr
Loss	Persistent failure>4weeks	
End-stage	Persistent failure>3months	

The demographic characteristics were documented, including mode of delivery, gender, gestational age, and birth weight (BW)for all neonates. Moreover, the incidence of AKI, and potential risk factors for AKI were evaluated which included maternal-perinatal morbidities, underlying diseases, need for ventilator support, and exposure to nephrotoxic drugs. Biochemical, hematologic, and electrolyte measures in all patients were monitored based on the policy. Due to the patients' clinical condition, the diagnostic fluid challenge technique was used with or without furosemide for differentiation of prerenal failure. Furthermore, fraction excretion of sodium in the preferred index was employed to confirm prerenal failure in severe AKI cases.

The categorical and non-categorical variables are presented as percentages and mean±SD, respectively. Statistical analysis of the difference between groups was determined using t-test, Fisher's exact test, and one-way analysis of variance (ANOVA). Moreover, the chi-square test was used for qualitative data analysis, and nonparametric tests such as the Mann–Whitney, and Kruskal–Wallis tests were used for the variables without normal distributions. A p-value

of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (version16).

Results

Out of the total 173 neonates admitted to the NICU, 72 cases (41.6%) were female. The mean±SD age of the patients was 4.1±9.5 days. In total, 51 (29.5%) and 112 (70.5%) cases were full-term and preterm neonates, respectively. Moreover, 33 (19.1%) and 140 (80.9%) newborns were delivered through normal vaginal delivery and caesarian section, respectively. The BW ranged from 660 to 5400 grams with a mean±SD of 2434±898 grams. Respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), and surgical reasons were the first three most common indications for admission, respectively. In total, 57(33%) patients required ventilator support in the course of admission.

Gestational diabetes (12%), hypothyroidism (7%), and preeclampsia (4%) were the most common maternal, perinatal morbidities.

The AKI occurred in 46 (26.6%) patients, the majority 28(61%) of whom were male. There was no difference in gender between patients with AKI and those without AKI (P=0.73). The mean±SD age of the patients with and without AKI on admission was estimated at 2.7±5.7 and 4.6±10.5 days, respectively. Therefore, the patients with AKI were significantly younger (P=0.04). The AKI occurred in the course of admission in 17.6% of the term, and 30.3% of preterm infants, but the difference was not significant (P=0.085). In terms of BW; 50% of infants weighing below1500 gr had AKI. On the other hand, AKI was observed in 15% and 25% of infants with a BW of 1500-2500gr and above 2500gr, respectively, which indicates a significant difference (P=0.027).

On an etiological basis, 87% and 8.7% of AKI cases have been developed in the course of a pre-renal event and during renal insult, respectively. Only one case had a post renal obstruction.

Table 2 present the severity of AKI in the patients. The severe degrees of AKI were more common than milder ones.

Tables 3 and 4 tabulates the different laboratory findings in patients with AKI, compared to neonates with normal kidney function. As presented in Table 3, anemia, thrombocytosis, thrombocytopenia, hyponatremia, hyperkalemia, hypokalemia, acidosis, and hypocalcemia were more frequent in patients with AKI.

The laboratory findings in patients with different severity of AKI are presented in Table 5. Based on these findings, anemia, thrombocyte count disorders, hypo and hyperkalemia, hyponatremia, hypercalcemia, and acidosis were observed more frequently in infants with severe AKI.

Nearly all (98.3%) patients and all neonates with AKI had received at least one nephrotoxic agent (P=0.57). The high rate of nephrotoxin use was due to the administration of aminoglycosides as antimicrobial therapy for newborns. It is worth mentioning that, 24 (41%) patients with AKI and 22 (19%) cases without AKI had received at least a nephrotoxin other than aminoglycoside and that

Table 2. Presence and severity of AKI based on pRIFLE criteria

Severity of AKI	No	Percent
NO AKI	127	73.4
Risk	11	6.4
Injury	16	9.2
Failure	19	11
Total	173	100

Table 3. Common laboratory abnormalities in 173 neonates with and without AKI

Disorder	Neonates with AKI No (%)	Neonates without AKI No (%)	P-Value	Odds Ratio
Leukopenia	4 (32)	3 (2.4)	0.491	
Leukoctosis	17 (37)	45 (35.4)	0.854	
Anemia	41 (89.1)	25 (19.7)	<0.001	33
Thrombocytosis	5 (10.9)	3 (2.4)	0.019	5
Thrombocytopenia	22 (47.8)	17 (13.4)	<0.001	6
Hyponatremia	28 (60.9)	43 (33.9)	<0.001	3
Hypernatremia	4 (8.7)	3 (2.4)	.0.062	4
Hypokalemia	12 (26.1)	11 (8.7)	0.003	4
Hyperkalemia	9 (19.6)	2 (1.6)	<0.001	15
Alkalosis	5 (10.9)	19 (15)	0.492	
Acidosis	31 (67.4)	51 (40.2)	0.002	3
Hypocalcemia	12 (26.1)	15(11.8)	0.022	3
Hypercalcemia	1 (2.2)	0	0.096	
Hematuria	7 (24.1)	6 (25)	0.942	
Proteinuria	8 (27.6)	4 (16.7)	0.373	
Pyuria	6 (20.7)	7 (29.2)	0.475	

Table 4. Laboratory tests in neonates with and without AKI

Lab test	Neonates with AKI (mean± SD)	Neonates without AKI (mean± SD)	P-Value
WBC	14473±7967	13420±5706	0.611
HB	14.4±3.7	15.5±2.8	0.076
PLT	208761± 112330	251194± 94637	<0.001
Cr	1.3±0.42	0.72±0.22	<0.001
BUN	61.70±54	21.36±14	<0.001
Na	136±7	136±5	0.294
K	4.7±1.1	4.7±0.7	0.866
PH	7.31±0.12	7.37±0.09	0.004
HCO3	23.5±7.4	23.4±5.5	0.755
Ca	8.5±1.0	8.7±0.9	0.267

Table 5. Common laboratory abnormalities in neonates with different severity of AKI

Disorder	RIFLE1	RIFLE2	RIFLE3	P-value
Leukopenia	1 (9.1)	0	1 (5.3)	0.477
Leukoctosis	4 (36.4)	6 (37.5)	7 (36.8)	0.998
Anemia	9 (81.8)	15 (93.8)	17 (89.5)	<0.001
Thrombocytosis	3 (27.3)	0	2 (10.5)	<0.001
Thrombocytopenia	4 (36.4)	10 (62.5)	8 (42.1)	<0.001
Hyponatremia	0	3 (18.8)	1 (5.3)	0.016
Hypernatremia	5 (45.5)	9 (56.2)	14 (73.7)	0.005
Hypokalemia	0	6 (37.5)	6 (31.6)	<0.001
Hyperkalemia	0	5 (31.2)	4 (21.1)	<0.001
Alkalosis	0	2 (12.5)	3 (15.8)	0.576
Acidosis	5 (45.5)	12 (75)	14 (73.7)	0.005
Hypocalcemia	0	0	1 (5.3)	0.043
Hypercalcemia	4 (36.4)	4 (25)	4 (21.1)	0.090
Hematuria	1 (20)	2 (20)	4 (28.6)	0.961
Proteinuria	1 (20)	3 (30)	2 (14.3)	0.732
Pyuria	1 (20)	5 (50)	2 (14.3)	0.099

this difference was significant (P=0.003).

In total, 18 (10.4%) neonates died, from whom 16 (34.8%) cases had AKI, and 2 (1.6%) cases had no evidence of AKI. The difference was statistically significant (P<0.001, OR=33). Gender and maturity had no impact on the incidence of death, however, the mortality rate was higher in a patient with lower BW (P<0.001). The mortality rate was 50%, 23%, 6.3%, and 5.4% in neonates with BW below 1000gr, between 1000-1500gr, between 1500-2500 gr, and 2500 gr or above, respectively. Moreover, The mortality rate was higher in patients who required a ventilator (P<001, OR=49), those with a history of transfusion (P<001, OR=24), or nephrotoxic agent use (P=0.001, OR=6). Some laboratory findings associated with higher mortality included thrombocytopenia (P<001, OR=5), anemia (P<001, OR=7), hyponatremia (P=004, OR=4), hypernatremia (P=004, OR=8), hypokalemia (P<0.001, OR=10), hyperkalemia (P=0.008, OR=4), and acidosis (P<0.001, OR=7).

Discussion

The AKI is a critical clinical problem in the NICU and is evident by the high morbidity rate in patients with AKI. Based on the results, 26.6% of admitted neonates in the NICU had some episodes of AKI. Prerenal conditions in 87% of cases were the most common etiology.

It is worth mentioning that sepsis, RDS, prematurity, and surgical complications were the most common indications of admission, similar to other studies (10, 12, 13).

Based on the results of a nested case-control study conducted by Askenazi, AKI was observed in 9 (16%) neonates out of 58 selected cases, all of whom had a BW of at least 2000gr (14). In a retrospective case-control study conducted by Ghobrial on 90 neonates admitted to a NICU of a tertiary care center, 30 cases had AKI (10). Overall, the incidence of AKI in the present study was obtained at 27%.

The significant difference observed in these studies in terms of the incidence rate of AKI can be due to the different definitions of AKI. In this study the RIFLE criteria were employed; however, Askenazi defined AKI as an acute rise in SCr (>0.3 mg/dL) within 48 hr or a persistent rise in SCr (≥1.7 mg/dL) for three days after the birth (14). Ghobrial also defined AKI grossly as increased serum creatinine or a reduction in urine output (<1mL/kg/h) (10).

In a prospective study conducted by Youssef

on 250 neonates admitted to the NICU, AKI was observed in 27 (10.8%) patients (15).

The incidence of AKI is influenced by gestational age and BW; therefore, heterogeneity of the population should be interpreted based on the maturity or BW. In this study, AKI developed in 50% of patients with BW of about 1500 grams. In a retrospective study conducted by Daga on 115 very low birth rate (VLBW; BW≤1500 gram) infants admitted to NICU, the AKI was developed in 26 (22.6%) neonates, according to RIFLE criteria (16). The results of a prospective study performed by Askenazi on 113 neonates with BW of ≤1200 gr or gestational age of <31wk, the incidence rate of AKI was estimated at 25%, based on the KDIGO criteria (17). In the present study, the incidence of AKI was not different in terms of gestational age, but it had a higher rate in VLBW infants. This difference can be attributed to the heterogeneity of our cases and the rate of small for gestational age neonates contributed to this result.

In a retrospective cohort study conducted in Taiwan, AKI occurred in 154(56%) cases out of 276 extremely low birth weight (ELBW, BW<1000 gr) infants (11). In the same line, based on the results of a retrospective study conducted by Maqsood, the incidence of AKI in all ELBW infants admitted to the NICU was 49% (110 out of 222), according to the KDIGO criteria (18). Similarly, the incidence of AKI in both VLBW and ELBW neonates was 50% in the present study.

In a multicenter study conducted by Jetton, 29.9% of all 2022 neonate admitted in 24 NICU centers had developed AKI, out of whom 281(14%), 143(7%), and 181(9%) had stage1, stage 2, and stage 3 AKI, respectively. (13). In the present study, the severity of stage 1, 2, and 3 AKI were 6.4%, 9.2%, and 11%, respectively. The higher incidence of severe AKI may be due to the presentation of disorders. The patients in this study were screened based on urine volume and measured according to the unit policy. Therefore, some cases of mild asymptomatic and presumably less clinically significant AKI may have been missed. However, severe cases of AKI can occur in a notable population of neonates.

In a retrospective study conducted by Elmas, out of a group of 105 preterm neonates, 21 (20%) had the criteria for AKI. In terms of severity, 9 (42.8%), 7(33.3%), and 5(23.8%) patients had stage 1, stage 2, and stage 3 AKI, respectively (7). In the same line, the results of a retrospective study conducted by Chowdhary on 483 admitted ELBW neonates revealed that AKI developed in 56% of the total 483 cases. The prevalence of stage1, 2, and 3 of AKI was 35%, 11%, and 9%, respectively based on the RIFLE criteria (8). The results of a study performed by Maqsood reported an incidence rate of 49% for 222 ELBW infants. It should be mentioned that, out of the total 222 ELBW infants, 39% (n=87) and 10% (n=23) of the cases had AKI stage 1 and stage 2 or 3 (18). Moreover, in a study conducted by Ferdaus, 44 neonates had AKI. The incidence rate of AKI stage1, 2, and 3, was estimated at 43.2%, 22.7%, and 34.1%, respectively, based on RIFLE criteria (19). In the present study, the incidence rate of stage 1, 2, and 3 AKI for VLBW neonates were estimated at 14%, 23%, and 14%, respectively. In addition, the incidence rate for ELBW neonates was obtained at 10%, 20%, and 20%, respectively.

The laboratory findings in a recent study showed that there was a significant statistical difference between the patients with AKI, and the controls in terms of pH and potassium level (10). A study conducted by Elmas showed that serum uric acid is significantly higher, and calcium levels are lower in patients with AKI, compared to those without AKI. Moreover, intubation and ventilator assistance, sepsis, and some antibiotic consumption were significantly prominent in premature neonates with AKI(20). Furthermore, the results of a study conducted by lee showed that ventilator and inotropic use, as well as preeclampsia, are risk factors for the development of AKI (11). Furthermore, the results of a study performed by Daga demonstrated that infants with AKI were more likely to become mechanically ventilated, and exposed to prenatal nonsteroidal anti-inflammatory drugs (16). The findings of the present study showed that anemia, thrombocyte, sodium and potassium abnormalities, acidosis, and hypocalcemia are significantly higher in neonates with AKI. It is worth mentioning that anemia and hyperkalemia had the highest odds ratio, and all of the mentioned items had a significant relation to the severity of AKI.

The mortality rate of the AKI patients in the study conducted by Ferdaus was 27% (19). The results of the study performed by Jetton revealed that infants with AKI had a higher mortality rate (9.7%), compared to those without AKI (1.4%). In terms of AKI stage, the mortality rate was higher for infants with stage 3 AKI, compared to those with stage 2 or 1 (13).

The results of a cohort study conducted by El-Badawy revealed that, out of 100 critically ill NICU neonates, 21 (51.2%) cases with AKI and 9

(15.2%) cases without AKI died. The most common risk factors for AKI included sepsis, nephrotoxic drug administration, and shock (21). In the present study, the death rate was significantly higher in neonates with AKI, compared to those without AKI (34.8% vs. 1.6%). It is worth mentioning that the need for ventilator support was the most potent risk factor (OR=49). Other significant mortality risk factors included blood product transfusion, thrombocytopenia, anemia, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, acidosis, and the history of nephrotoxic agent use.

The mortality and risk factors were different in neonates with lower BW. Elmas reported a mortality rate of 61.9% for premature infants with AKI (20). Lee reported a mortality rate of 20% and 2% for VLBW neonates with AKI and those without AKI(11). The findings of this study revealed that the death rate was lower in neonates with higher BW. Neonates with BW below 1000 grams had the highest mortality rate (50%).

The results of a prospective study conducted by Doaa et al. over six-month revealed that 10.8% of neonates admitted in NICU had AKI with a male sex preference similar to the present study. The higher AKI incidence in male newborns may be due to their susceptibility to some prenatal disorders, such as RDS. Moreover, prerenal failure was the most common form of AKI in the patients that were in line with the findings of the current study. Therefore, the early detection of prerenal failure risk factors, such as sepsis, asphyxia, as well as the early treatment of the contributing conditions will be useful in the reduction of AKI in neonates (22).

In a prospective cohort study performed by Shalaby, the incidence rate of AKI was 56% in a NICU in Saudi Arabia. Moreover, lower birth weight and gestational age were risk factors of AKI; although, KIDGO criteria were employed. Moreover, AKI was associated with an increased risk of mortality, similar to the present study. The difference in the incidence of AKI may be attributed to different definitions and the criteria employed (23). Similarly, exposure to nephrotoxic medications was another risk factor in their study (23). It is worth mentioning that the duration of nephrotoxic agent therapies and aminoglycosides administration modalities (continuous or intermittent, once, twice, or multiple daily dosing) should be selected with caution. These modalities affected renal accumulation, kinetics, and nephrotoxicity in patients. It seems that the use of extended interval doses causes lower nephrotoxicity in newborns, compared to the conventional doses. On the other hand, except in LBW infants, a combination of vancomycin and aminoglycoside should be replaced with an alternative combination in neonates whenever possible.

Limitations

Regarding the limitations of the present study one can refer to the referral NICU in this study that accepted all critically ill patients from the region. Therefore, the present findings may not be indicative of other levels of NICU, such as level I for which the clinical practice may be different. Furthermore, all neonates were not followed up after discharge. Accordingly, the findings of this study cannot be considered as long-term outcomes.

Conclusion

AKI is a relatively common event in NICU, and can develop in at least one-fourth of resident neonates. Moreover, intubated/ ventilator assisted neonates and those with lower birth weight have a higher incidence of AKI and mortality.

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Conflicts of interest

The authors confirm that there is no conflict of interest regarding the publication of this study.

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